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OPTION
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TITLE

Metals debenzylation of tetrazoles, and high convergent straightforward stereoselective synthesis of (+)-C(9a)-Epiepiquinamide

By: Benlahrech Meriem

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This thesis work is dedicated

*To my **father's** memory, your love always lives in my heart. May Allah grant you Jannah Firdaws.*

*To my **Mother** and my **Stepfather**, who have always loved me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve.*

*To my husband, **Mohamed**, who has been a constant source of support and encouragement and helping . I am truly thankful for having you in my life.*

*To my brothers **Ahmed, Zakaria, Lotfi, Radouan**.*

*To my sister **Nani** and her husband **Abdou** and the little angel **Fadila**.*

*To my uncles **Abderahmane, Ahmed .***

To my aunts .

To my parents in law.

Their unconditional support and encouragements to pursue my interests.

*To my Extended family and friends **Aisha, Zineb, Hadjer,...** for always supporting me.*

To all those who believe in me and pried for my success.

"I have not failed 700 times. I have not failed once.
I have succeeded in proving that those 700 ways will not work.
When I have eliminated the ways that will not work, I will find the way that will work."
Thomas Edison.

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Technical notes

During our work we used the following equipment:

All chemicals were commercially available (Acros, Aldrich).

Chromatography

TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain and UV. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and different eluents.

Low-resolution electron impact (EI) mass spectra were obtained at 70eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and high resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apparatus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatograph (UPLC) model Waters ACQUITY H CLASS.

Melting points

All melting points were measured in open end glass capillary tubes on a Buchi 535melting point apparatus and are uncorrected.

Infra-Red spectrometry

IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer.

Nuclear Magnetic Resonance spectrometry (NMR)

NMR spectra were recorded with a Bruker AC-300 and a Bruker 500-AVANCE IIIHD, using $CDCl_3$ or CD_3OD as solvents, and TMS as internal standard.

Polarimeter

Optical rotations were measured on a Perkin Elmer 341 polarimeter.

Abbreviations

Chromatography and spectroscopy

J	Couling constant
ddd	double double doublet
MS/GC	Gas chromatography/mass spectrometry
IR	infrared spectroscopy
m	Multiplet
NMR	nuclear magnetic resonance
s	singlet
TMS	Tetramethylsilane
TLC	thin layer chromatography
UPLC	Ulta-high pressure liquid chromatograph

Units and physical constant

δ	Chemical shift
^{o}C	degree celsius
E_q	Equivalent
Δ	heating
h	Hour
Mol%	Molar percent
Mp	Multing point
ppm	Part per million
rt	Room temperature

Other abbreviations

AcOH	Acetic acid
MeCN	Acetonitrile
Bn	Benzyl
DCM	dichloromethane
DCC	N.N'-Dicyclohexylcarbodiimide

DiBAL-H	Diisobutylaluminium hydride
DPPA	Diphenylphosphorylazide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
EWG	Electron withdrawing group
ee	Enatiomeric excess
LHMDS	Lithium hexamethyldisilazide
MsCl	Mesyl chloride
Ph	Phenyl
py	Pyridine
R	radical
R	Rectus mean right
S	Sinister mean left
t-Bu	Tert-Butyl
TBAF	Tetra-n-butylammoniumflouride
OTBDMS	O-tert-butyldimethylsilyl
TBDPSCl	Tetra-butyl(chloro) diphenylsilane
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
Trityl	Triphenylmethyl chloride

Contents

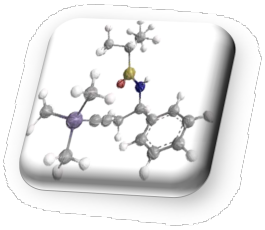
Chapter IV: Magnesium-promoted debenzylation of tetrazoles

Part II: ***Use of N-butylsulfnylimine In synthesis of (+)-C (9a)-epiepiquinamide***

Chapter five: N-butylsulfnylimine

Chapter sixe: synthesis of (+)-*C(9a)-epi*epiquinamide

General introduction



General introduction

The synthesis of natural products continues to be one of the most exciting and good-studied areas of organic chemistry. Natural products and their analogues continue to be the greatest source of potential new pharmaceuticals. The application of new methodologies is vital to the goals of natural product. When we speak about total synthesis we have to speak also about protecting group.

A protecting group is inserted onto a molecule by chemical modification of a functional group to block its reactivity that otherwise may lead to undesired reactions under the experimental conditions needed. Chemoselectivity is thus obtained. Protecting groups are important to strategies in multistep organic synthesis.

Our laboratory has developed in recent years a line of research devoted mainly to: The use of metals in deprotection of functional groups like alcohol[1] and tetrazoles[2] with different protecting groups.

In the continuity of this work, the study that we want to undertake in the framework of this thesis has for main objective the deprotection of benzyl group from protectecd tetrazoles using metals Zn, Mg, In.

The benzyl group has been deprotected in multi-step organic synthesis with a variety of reaction conditions, including catalytic hydrogenolysis.[3]

Tetrazoles as a group of heterocyclic compounds are reported to have a wide spectrum of biological activities such as antifungal,[4] antibacterial[5] analgesic,[6] anti-inflammatory,[7] antiulcer;[8] and antiviral,[9] antihypertensive[10] activities. Then, 5-substituted-1H-tetrazoles can Function as carboxylic acid surrogates,[11] lipophilic spacers and specialty explosives[12] and

[1] Behloul, C.; Chouti, A.; Guijarro, D.; Foubelou, F.; Najera, C.; Yus, M. *Tetrahedron,* **2016**, 7939
[2] Behloul, C.; Bouchelouche, K.; Guijarro, D.; Najera, C.; Yus, M. *Synthesis,* **2014**, 2065.
[3] (a) Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chem. Fr.,***1973**, 2147. (b) Jacobsen, S. M.; Smith, W. E. *Inorg. Chim. Acta*, **1985**, *98*, 63. (c) Sanchez, I. H.; Larraza, M. I.; Rojas, I.; Brena, F. K.; Flores, H. J.; Jankowski, K. *Heterocycles,* **1985**, *23*, 3033. (d) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc*. **1978**, *100*, 545.
[4] Sangal, S. K.; Ashok Kumar, A. *J. Indian Chem. Soc*. **1986**, *63*, 351.
[5] Okabayashi, T.; Kano, H.; Makisumi, Y. *Chem. Pharm. Bull.* **1960**, *8*, 157.
[6] Maxwell, J. R.; Wasdahl, D. A.; Wolfson, A. C.; Stenberg. I.; *J. Med. Chem.* **1984**, *27*, 1565.
[7] Shukla, J. S.; Ahmed, J.; Saxena, S. *J. Indian Chem. Soc.* **1979**, *41*, 70.
[8] Ray, S. M.; Lahiri, S. C. *J. Indian Chem. Soc.* **1990**, *67*, 324.
[9] Witkowski, J. K.; Robins, R. K.; Sidwell, R.W.; Simon, L. N.; *J. Med. Chem.* **1972**, *15*, 1150.
[10] Fig dor, S. K.; Von Wittenau, M. S. *J. Med. Chem.* **1967**, *10*, 1158.
[11] Singh, H.; Chala, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K.; *Prog. Med. Chem.* **1980**, *17*, 151.

precursors of a variety of nitrogen containing heterocycles in coordination chemistry, and information recording systems in materials ligands.

In contrast, the epiquinamide is a quinolizidine alkaloid that was isolated from the skin of Ecuadoran frog in 2003. Primary studies concerning its biological activity indicated that this compound displayed strong and selective activities against nicotinic acetylcholine receptors. However, further more neatly undertaken studies shown that (+)-epiquinamide was inactive and (-)-epibatidine alkaloid,[13] which was isolated also from the same source, was responsible for the biological activity due to contamination in the first studies.

The synthesis of (+)-epiquinamide and its stereoisomers has attracted much attention because these compounds could show potential pharmacological activity.[14] Different synthetic approaches have been reported to access epiquinamide in an enantioselective or racemic[15] form. Most of the enantioselective syntheses are based on the chiral pool approach starting from monosaccharides[16] or aminoacids[17] and also by chiral auxiliaries.[18] Or a catalytic enantioselective procedure is involved .[19]

The work is organized around two main themes:

The first part of this work debenzylation of tetrazoles using indium and zinc, magnesium in mild reaction condition with a comparative study, we started from preparation of tetrazoles and protected theme with benzyl groups « chapter one », then deprotection of tetrazoles using indium « chapter two », after that debenzylation of tetrazoles using zinc « chapter three » and finally with Mg « chapter four ».

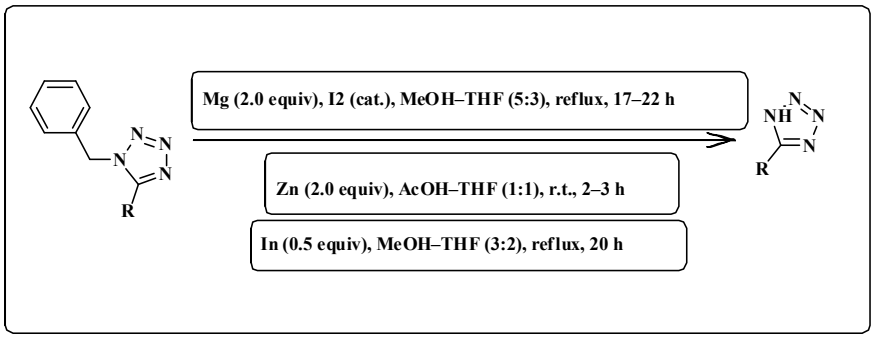
[12] Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I.V. *Targets Heterocyclic Syst.* **1999**, *3*, 467.
[13] Spande, T.F.; Garrafo, H.M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc*., **1992**, *114*, 3475.
[14] Rajesh, U. C.; Gupta, A.; Rawat Curr, D.S. *Org.Synth,* **2014**, *11*, 627.
[15] Fitch, R. W.; Sturgeon, G. D.; Patel, S. R.; Spande, T. F.; Garraffo, H. M.; Daly, J. W.; Blaauw, H. R. *J. Nat. Prod*., **2009**, *72*, 243.
[16] Sangsuwan, W.; Kongkathip, B.; Chuawong, P;Kongkathip, N. *Tetrahedron, **2017**, 73*, 7274.
[17] (a)Wijdeven, M. A.; Botman, P. N.; Wijtmans, M. R.; Schoemaker, H. E.; Rutjes, J. T.; Blaauw, R. H.*Org.Lett*.,2005, 7, 4005 ; (b) Huang, P.Q.;Guo, Z.Q.; Ruan, Y. P. *Org. Lett.*, **2006**, *8*, 1435.
[18] Voituriez, A.; Ferreira, F.; Pérez-Luna,A. ; Chemla, F. *Org. Lett.*, **2007**, *9*, 4705.
[19] (a)Chandrasekhar,S.; Parida, B. B. ; Rambabu, C. *Tetrahedron Lett.*, **2009**, *50*, 3294 ; (b) Ahuja, B. B. ;Emmanuvel, L.; Sudalai, A. *Synlett,* **2016**, *27*, 1699.

The second part is reserved for the synthesis of (+)-C(9a)-epiepiquinamide, we started by synthesis of N-*tert*-butane sulfinyl imine as staring material « chapter five », than in « chapter six » a synthesis of (+)-C(9a)-epiepiquinamide.

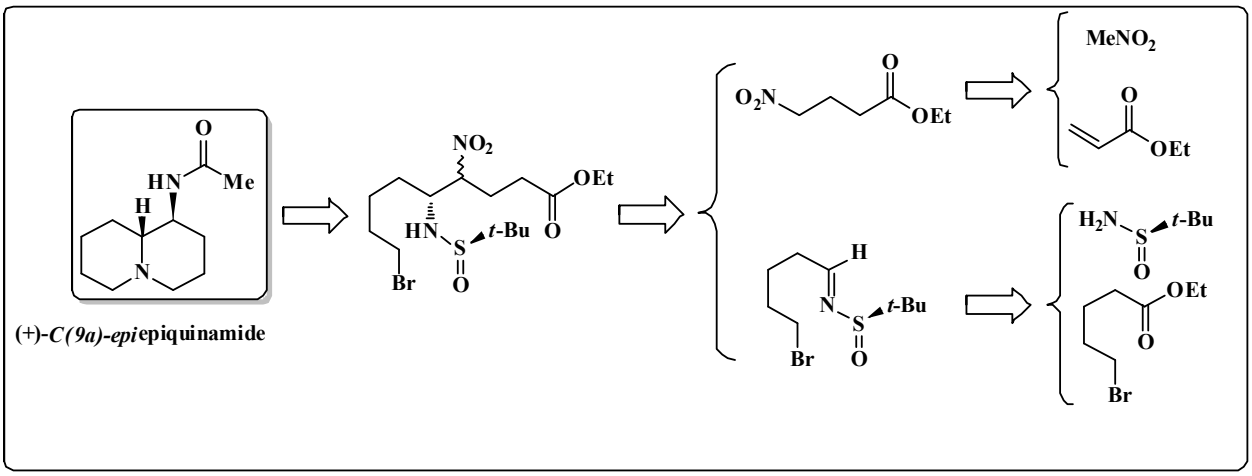
Finally, this thesis will be closed by a conclusion.

The work carried out during this thesis was the subject of two publications issued: ***An International Journal for Reviews and Communications in Heterocyclic Chemistry*** and ***Synthesis***, the copies of which are annexed.

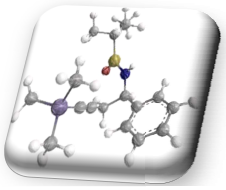
Our work is summarizing below



Our retrosynthentic analysis for the preparation of (+)-*C(9a)-epi*epiquinamide is depicted below

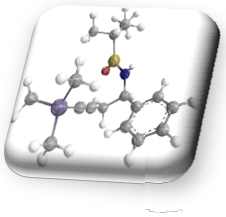


Part I
Indium, magnesium, and zinc-mediated debenzylation of protected 1H-tetrazoles.



Chapter I

Protection of tetrazoles



I.1 Generality of protecting group

Protecting groups are used in synthesis to block the characteristic chemistry of a functional group temporally. The choice of protecting groups is critical, there are seven tactical considerations which define how effectively a protecting group will best fulfil its assigned strategic role of shielding a functional group from destruction (or reaction with another functional group).

1. The protecting group should be easily and efficiently introduced.

2. It should be cheap or readily available.

3. It should be easy to characterise and avoid.

4. It should be stable to chromatography.

5. It should be stable to widest possible range of reaction conditions.

6. It should be removed selectivity and efficiently under highly specific conditions.

7. The by-products of the deprotection should be easily separated from the substrate.

The protection of heterocycles such as pyrroles,[20] imidazoles,[21] tetrazoles[22] and indoles[23] has been a widely studied topic due to the importance of nitrogen heterocycles[24] in biological systems. Amide, carbamate and sulfonamide groups work very well in protection/deprotection because of the increased acidity of the aromatic amines when compared to simple amines. This allows for easy protection and deprotection of the heterocycle. However, the lability of these protecting groups may lead to problems later in the synthesis. For this reason, there have also been investigations in to the use of very stable protecting groups such as *N*-alkyl or *N*-aryl derivatives, with these derivatives. However, deprotection can be difficult and may require forcing conditions for removal.

[20] Handy, S.T.; Sabatini, J.J.;Zhang, Y.;Vulfova, I. *Tetrahedron lett*. **2004**, *45*, 5057.
[21] Lipshutz, B.H.; Vaccaro.; Huff, B. *Tetrahedron lett*.**1986**, *27*, 4095.
[22] Behloul, C.; Bouchelouche, K.; Guijarro, D.; Najera, C.; Yus, M. *Synthesis*. **2014**, 2065.
[23] Baran, P.S.; Guerrero,C.A.; Corey, E. *Org. Lett*.**2003**, *5*, 1999.
[24] Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl*. Compd. **2007**, *43*, 1.

I.1.1 Amino protecting groups

I.1.1.1 Carbamate

Carbamates have been applied for the protection of the amine function. In fact, the lone pair of electrons carried by the nitrogen is unreactive and is involved in mesmeric with carbamate, and it is then possible to make functional facilities without touching the nucleophilic character of the amine.

- ***t-butoxycarbonyl Boc***

The impact of *tert*-butyl carbamate was due to their stability under various reaction conditions as nucleophilic attacks, mild alkaline treatments and catalytic hydrogenation.[25]

✓ Formation

For the protection using $(Boc)_2O$ there are many methods we can mention. For example: the utilisation of catalytic amount of $ZrCl_4$ (10 mol%) in acetonitrile at room temperature, The reaction times are very short and the yields are generally high (**Figure I.1).**[26]

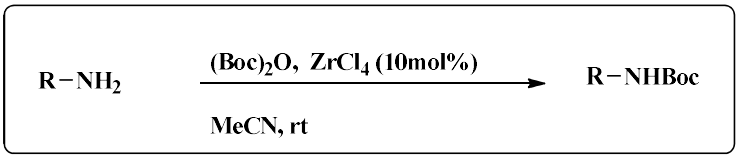
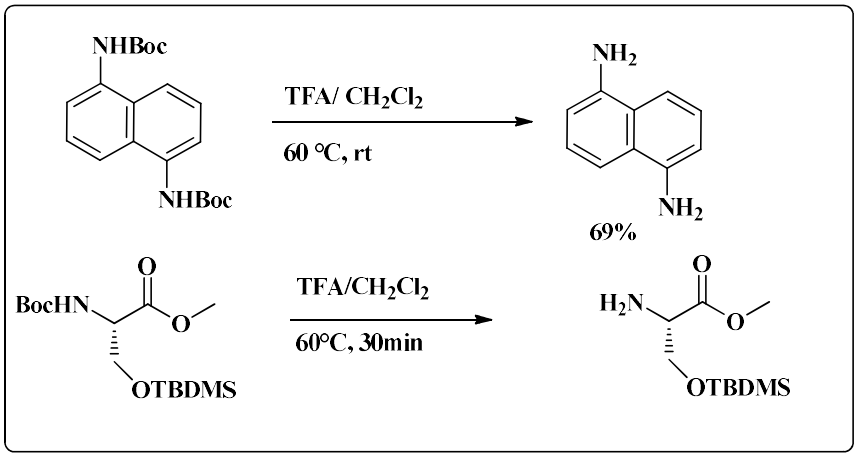


Figure I.1

✓ Cleavage

The deprotection of N-Boc are doing by acid treatment and is rapidly accomplished using 5 equivalents of TFA at 60 °C for 30min.[27] The selectivity of the N-Boc deprotection method is approved by the conservation of the OTBDMS ethers (**Scheme I.1**).

[25] a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Chemistry*; Wiley: New York, **1999**; b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, **1994**.
[26] Sharma, G. V. M.; Goverdhan Reddy, Ch.; RadhaKrishna, P. *Tetrahedron Letters*. **2004**, *45*, 6963.
[27] a) Kunz, H.; Waldmann, H. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; E, W. Eds.; Pergamon: Oxford, **1991**; Vol. *6*; p. 631 ; b) Albericio, F. *Peptide Science,* **2000**, *55*, 123 ; c) Schelhaas, M.; Waldmann, H. *Angew. Chem. Int*. Ed. Engl, **1996**, *35*, 2056 ; d) Lalonde, A.; Chan, T. *Synthesis*. **1985**, 817. Jarowicki, k.; Kocienski, P. *J. Chem. Soc. Perkin. Trans.1*. **1998**, 4005.



Scheme I.1

I.1.1.2 Amide

- ***Acetamide***

The preparation of acetamide by using acetic anhydride or acetyl chloride and amine with or without addition of a base. The disadvantage of these reagents is that they are quite reactive and thus often are insufficiently selective.[28]

✓ Formation

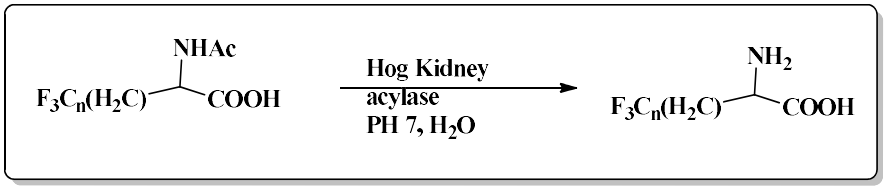
Kurlkarni et al. have developed a new way of chemoselective acylation of aliphatic, aromatic and cyclical amines. That is performed with acetic acid in the presence of Y-Zeolite (**Scheme I.2).**[29]

Scheme I.2

[28] Masamune, S.; Lu, L. D. L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc*. **1982**, *104*, 5523-5526.
[29] Seebach, D.; Chow, H. F.; Jackson, R. F. W.; Sutter, M. A.; Thaisrivong, S.; Zimmermann, J. *Liebigs. Ann. Chem.***1986**, 1281-1308.

✓ Cleavage

In general, acetamides as good as any other alkyl and aryl amides are relatively difficult to hydrolyze and often need more forcing conditions to attain hydrolysis. The use of Hog Kidney acylas was performed with a significant enantioselective resolution (**Scheme I.3**).[30]



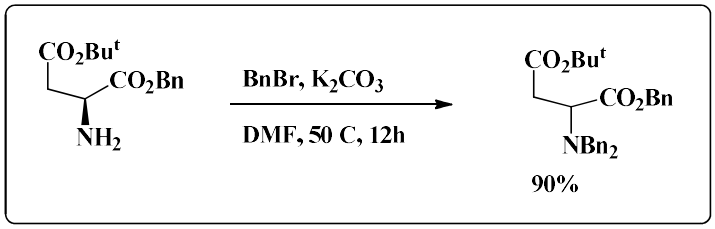
Scheme I.3

I.1.1.3 Benzyl and diphenyl and Trityl groups

Benzyl groups are important protecting group for amines, and they are particularly useful when a substrate is to be objected to strong organometallic reagents or metal hydrides which might attack a carbamate. Benzylamines are not generally cleaved by Lewis acids under mild reaction conditions.[31]

- ***Formation***

The easiest method for alkylation of amines with benzylic halides, is that primary amines can alkylate twice to give the *N, N*-dibenzyl derivative using K_2CO_3as base (**Scheme I.4).**[32]

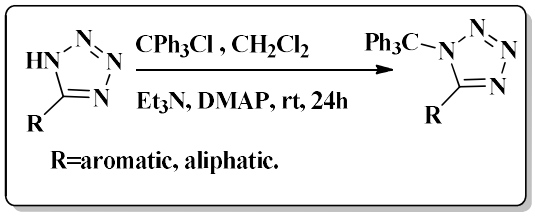


Scheme I.4

The trityl and diphenyl groups are an important and useful protecting group for amines and amino acids. For instant trityl group a very efficient[33] because its bulkiness causes the nitrogen atom to be much less reactive as a nucleophile. An easy treatment is to remove the

[30] Kocienski, P. J.; Brown, R. C. D.; Pommier, A.; Procter, M.; Schmidt, B., *J. Chem. Soc. Perkin Trans. I*. **1998**, 9.
[31] Greene, T. W.;Wurts,P.G.M.*Protective groups in organic synthesis*, 3rd ed.; Wiley:New York; **1999**, 570.
[32] De Ninno, M. P. *Synthesis* .**1991**, 583.
[33] (a) Bodanzky, M.; Onetti,O.*A. peptide synthesis; Interscience*: New York, **1966.** (b)Bodanzky, M. *Principles of peptide synthesis,* 2nd ed; Springer: New York, **1993**, 88.

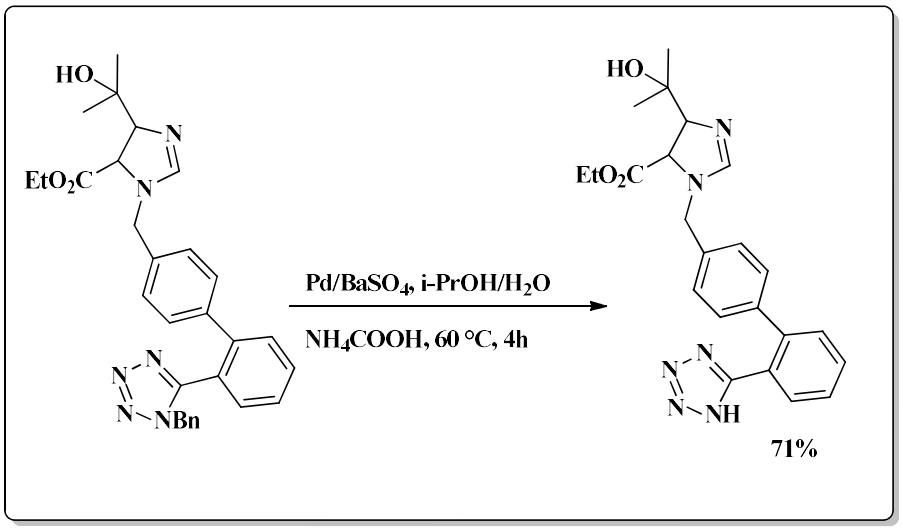
trityl protecting group with an aqueous acidic solution[34]. But some side-reactions have been observed under these conditions, such as the elimination of tritylamine during detritylation of some tritylated amines.[35] For example: tetrazoles can be protected by using trityl groups in DCM, and triethyl amine with DMAP as base (**Scheme I.5).**



Scheme I.5

- ***Cleavage***

The trityl group is quite voluminous and is not resistant to strong acidic conditions which have limited its practical use in the synthesis of tetrazole derivatives. [36] The debenzylation protocol permit the stable and comparatively small benzyl group as the protecting group, and thus would considerably improve the atom economy and expand the reach of the reactions in the synthesis of tetrazole derivatives (**Scheme I.6).**



Scheme I.6

I.2 Generality of tetrazoles

Chemistry of tetrazole over the past few years has been increasing speedily because the wide range of applications, mostly as a result of the role played by this heterocyclic

[34] Greene, T.W.; Wuts,P.G.M.*Protective groups in organic synthesis*,3rd ed.; Wiley:New York; **1999**, 583.
[35] Sharna, S. K.;Songster,M.F.; Colpitts. T. L.; Hegyes, P.; Barany, G.;Castellino, F.J.*J. Org.Chem*.**1993**, *58*, 4993.
[36] Rao,N.S.;Babu,S.*Org.Commun*, **2011**, 105.

functionality in medicinal chemistry as these offer a more favourable pharmacokinetic profile and a metabolically stable surrogate for carboxylic acid functionalities.[37] Particularly, by the expanded incorporation of the tetrazole functionality in to angiotensin II antagonist structures (sartans) (**Figure I.2**). This functionality acts important role as lipophilic spacers, ligands, precursors of a variety of nitrogen containing heterocycles in coordination chemistry[38,39] and in material sciences including photography, information recording systems, and explosives.

The Tetrazoles are characterized by a five membered, doubly unsaturated ring consisting of one carbon and four nitrogen atoms CN_4H_2. They are unknown in nature (**Figure I.3).**

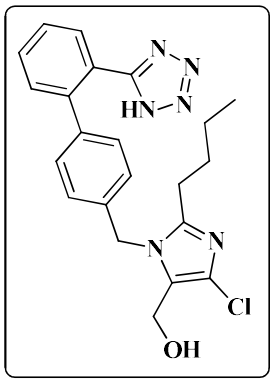


Figure I.2

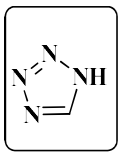


Figure I.3

I.2.1 Synthetic approach for the synthesis of tetrazoles

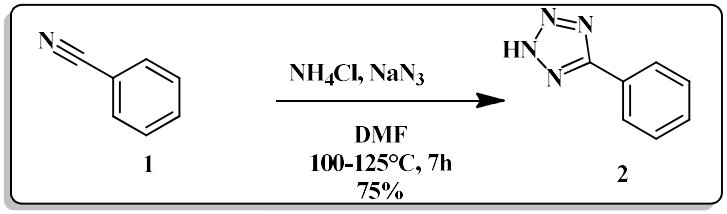
Several methods have been reported in literature during the past few years for the synthesis of tetrazoles.[40]

In general, the most direct method of the synthesis of 5-substituted 1H-tetrazoles is [2+3] the cycloaddition between nitriles and azides. Sodium azide (NaN_3) has been used as an inorganic azide source in combination with an ammonium halide as the additive employing dipolar aprotic solvents.[41,42] However the method suffers from disadvantages of use of

[37] (a) Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd*. **2007**, *43*, 1.
[38] Huisgen, R.; Sotuer, J.; Sturn, H. J.; Mark Graf*, J. H. Chem. Ber*. **1960**, *93*, 2106
[39] Moderhack, D. J. Prakt. *Chem*. **1988**, *340*, 687.
[40] (a) Wittenberger, S. J.; Donner, B. G. *J. Org. Chem*. **1993**, *58*, 4139; (b) Duncia, J.V.; Pierce, M. E.; Santella, J. B.*J. Org. Chem***. 1991**, *56*, 2395; (c) Smith, R. D.;Duncia, J. V.; Lee, R. J.; Christ, D. D.; Chiu, A. T.; Carini, D. J.; Herblin, W. F.; Timmermans, P. B.; Wexler, R. R. *Methods Neurosci*. **1993**, *13*, 258; (d) Buehlmayer, P.; Criscione, L.; Fuhrer, W.; Furet, P.; DeGasparo, M.; Stutz, S.; White bread, S. *J. Med. Chem*. **1991**, *34*, 3105.
[41] (a) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst*. **1999**, *3*, 467; (b) Koldobskii, G. I.; Ostrovskii, V. A.*Usp. Khim*. **1994**, *63*, 847.

expensive and toxic metals, strong Lewis acids and the *in-situ* generation of hydazoic acid which is highly toxic and explosive in nature (Synthesis of tetrazoles analogues of amino acids). Various inorganic azide salts, trimethyl silyl, trialkyl tin and organoaluminium azides have been introduced because of their comparatively less explosive behaviour (sometimes prepared in situ) which have the added advantage of being soluble in organic solvents under homogeneous conditions.

Lofquist and Finnegan.[43] has been found fifteen years ago, the reaction of nitriles with the ammonium and trialkyl ammonium azides in organic solvents to be a general method to give good yields of 5-substituted tetrazoles. The reactive azide species is prepared *in situ* by reaction of sodium azide and the appropriate ammonium or trialkyl ammonium chloride (**Scheme I.7**).



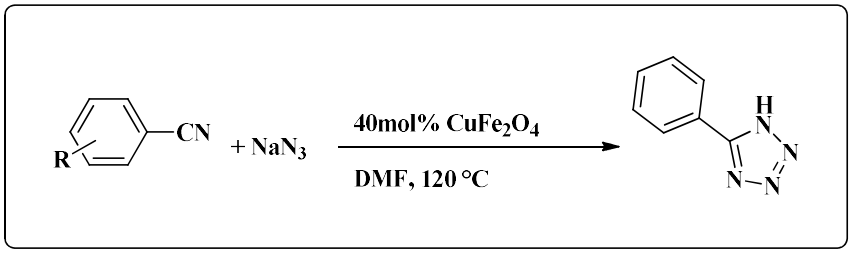
Scheme I.7

Sharpless and al at the end of 2001, in which a method was described for the synthesis of tetrazoles from nitriles in water as a solvent.[44] This method utilizes a 1:1 ratio of sodium azide and zinc (II) bromide as reagents, and is works at temperatures ranging from reflux to 170 °C. Electron poor aromatic nitriles reach completion at reflux after a few days, where as electron-rich aromatic species and unactivated aliphatic nitriles require higher temperatures with the use of a sealed glass pressure reactor. Nevertheless, the protocol minimizes the risk of liberating hydrazoic acid, and usually a simple acidification is all that is necessary to provide the pure tetrazole products. Several additives have been reported for azide-nitrile addition process such as Bronsted or Lewis acids or stoichiometric amounts of Zn(II) salts.

[42] (a) Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc*. **1958**, *80*, 3908; (b) Lieber, E.; Enkoji, T. *J. Org. Chem*. **1961**, *26*, 4472; (c) Bernstein, P. R.; Vacek,E. P. *Synthesis,* **1987**, 1133; (d) Koguro, K.; Oga, T.; Mitsui, S.; Orita, R. *Synthesis.***1998**, 910; (e) Jursic, B. S.; Leblanc, B. W. *J. Heterocycl. Chem*. **1998**, *35*, 405; (f)Alterman, M.; Hallberg, A. *J. Org. Chem*. **2000**, *65*, 7984; (g) Shie, J. J.; Fang, J. M. *J.Org. Chem.***2007**, *72*, 3141; (h) Roh, J.; Artamonova, T. V.; Vavrova, K.;Koldobskii, G. I.; Hrabalek, A. *Synthesis*. **2009**, 2175; (i) Schmidt, B.; Meid, D.;Kieser, D. *Tetrahedron*. **2007**, *63*, 492.
[43] Finnegan, W. G.; Henry, R. A.; Lofquist, R. *J. Am. Chem. Soc***. 1958**, *80*, 3908.
[44] He, J.; Li, B.; Chen, F.; Xu, Z.; Yin, G. J. Mol. *Catal. A: Chem.***2009**, *304*, 135.

Several heterogeneous catalysts, nanocrystalline ZnO, Zn/Al[45] Zn hydroxyapatite[46] and Cu_2O,[47] tungstate salts[48] have been reported for the synthesis. They have the advantage of ease of production and ready separation of large quantities of product.

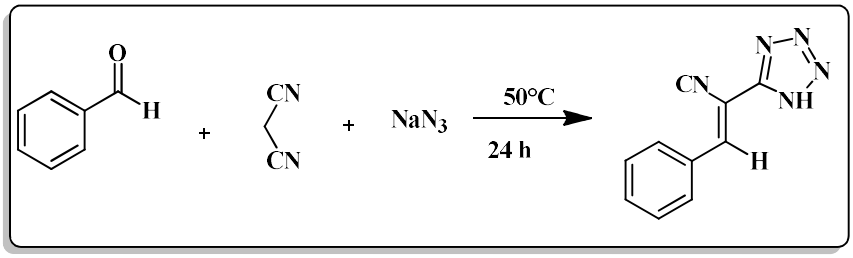
Sreedhar *el al.* in 2011 has been reported for the synthesis of 5-substituted *1H*-tetrazoles using $CuFe_2O_4$ nanoparticles.[49] The catalyst was magnetically separated and reused five times without significant loss of catalytic activity (**Scheme I.8**).



Scheme I.8

The protocols for the synthesis of 5-substituted 1H-tetrazoles have some disadvantages, such as the use of toxic metals, strong Lewis acid, expensive reagents, low yield, drastic reaction conditions, water sensitivity and the presence of hydrazoic acid, which is toxic and explosive. In addition, all of the known methods use organic solvents, in particular, dipolar aprotic solvents, such as DMF. The need of new tetrazolium derivatives using simple and safe process is an interesting target for investigation. Despite continuous research for the synthesis of tetrazoles and development of new multi-component reactions,Tisseh *et al*. reported a novel, facile, eco-friendly andone-pot process for synthesis of 5-substituted 1H-tetrazoles via a domino Knoevenagel condensation and 1,3 dipolar cycloaddition reaction. The selection of the condition of reaction is crucial important for successful synthesis. The three-component reaction of benzaldehyde, malononitrile and sodium azide as a simple model substrate was investigated in different solvents without any catalyst. It was found that water is the best solvent with respect to reaction yield. This effect can be attributed to the strong hydrogen bond interaction at the organic-water interface, which stabilizes the reaction intermediate.[50] They performed the model reaction using different quantities of reagents in water. The best result was obtained with a 1:1:2 ratio of benzaldehyde, malononitrile and sodium azide (**Scheme I.9**).

[45] Kantam, M. L.; Shiva Kumar, K. B.; Raja, K. P. *J. Mol. Catal. A: Chem.***2006**, *247*, 186.
[46] Kantam, M. L.; Balasubrahmanyam, V.; Shiva Kumar, K. B.*Synth. Commun***. 2006**, *36*, 1809.
[47] Jin, T.; Kitahara, F.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett*. **2008**, *49*, 2824.
[48] He, J.; Li, B.; Chen, F.; Xu, Z.; Yin, G. J. Mol. *Catal. A: Chem.***2009**, *304*, 135–138.
[49] Kantam, M. L.; Shiva Kumar, K. B.; Sridhar, C. *Adv. Synth. Catal*. **2005**, *347*, 1212.
[50] Tisseh, Z. N.; Dabiri, M.; Nobahar, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron,* **2012**, *68*, 1769.

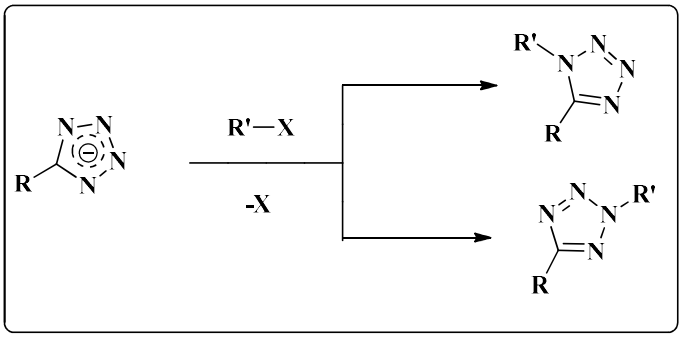


Scheme I.9

I.2.2 Functionalization of 5-tetrazoles

5-Substituted tetrazole are precious intermediates in the synthesis of more complex compounds. Tetrazole rings can differently be kept, changed into other cycles, or eliminated. As a result of their π electron systems and the presence of a lone pair in every nitrogen, 5-Substituted tetrazole react with a wide range of electrophiles. 5-Substituted tetrazole can be protonated, functionalized, or coordinated. Substitution of 5-Substituted tetrazole is the most common and effective method for the preparation of 1,5- and 2,5-disubstituted tetrazoles.[51] There are many alternative ways to prepare 1,5-disubstituted tetrazoles,[52]usually from the corresponding amides,[53] but for the preparation of 2,5-disubstituted tetrazoles, substitution on the 5-Substituted tetrazole is the only possible method. As well as a wide range of alkyl substituents, aryl, acyl, silyl, vinyl, sulfonyl, phosphoryl, and other similar groups can be introduced onto the tetrazole ring,[54]reactions between 5-Substituted tetrazole and electrophiles have been widely searched, with special attention to the underlying mechanisms. Substitutions of 5-Substituted tetrazole are usually carried out in aqueous or alcoholic alkaline solutions, in aprotic organic solutions in the presence of a base, or under phase-transfer catalysis conditions. Depending on the reaction conditions, 5-Substituted tetrazole can act as free tetrazolate anions, ion pairs, or hydrogen-bonded complexes with nitrogen bases. The main problem of 5-Substituted tetrazole substitution lies in its low and hardly influence able regioselectivity. Alkylation of a tetrazolate anion, either with or without a substituent in the 5-position, almost always leads to a mixture of both 1- and 2- alkyltetrazole isomers in various ratios (**Scheme I.10**).

[51] Koldobskii,G. I.; Kharbash,R. B. *Russ. J. Org. Chem.* **2003**, *39*, 453.
[52] M. Spulak, R. Lubojacky, P. Senel, J. Kunes, M. Pour, *J. Org.Chem.* **2010**, *75*, 241–244.
[53] a) Katritzky, A. R.; Cai, C. M.; Meher, N. K. *Synthesis*. **2007**,1204.; b) Artamonova, T. V.; Zhivich, A. B.; Dubinskii,M. Y. Koldobskii,G. I. *Synthesis***1996**, 1428.
[54] Ostrovskii, V. A.; Koren, A. O.; *Heterocycles,* **2000**, *53*, 1421.



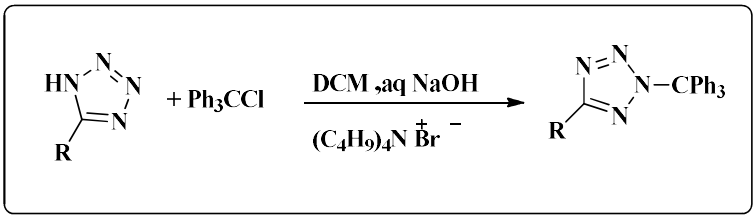
Scheme I.10

Other functionalizations, such as arylation and acylation, forward in the same way.[55] The ratio of isomers formed during the reaction depends on the reaction temperature and the properties of the substituent at the 5-position, in particular with regard to steric retardation. Higher reaction temperatures lead to increased amounts of 1-isomers, whereas electron-accepting properties of substituents at the 5-position increase the amounts of 2-isomers. Bulky substituents, either R or R' or their combination, direct the substitution to the 2-position of the tetrazole ring. The effect of the solvent can be illustrated by the alkylation of 5-phenyltetrazolate anion with dimethylsulfate in acetonitrile, in which increasing amounts of water in acetonitrile led to decreased reaction rates as a result of greater solvation of the substrate by water molecules.[56] Several substitutions on the tetrazole ring that display high or nonstandard regioselectivity are summarized below.

- **Alkylation of 5-STs**

Tritylation of a 5-Substituted tetrazole is the noblest substitutions on the tetrazole ring. The triphenylmethyl group is the fundamental protecting group of 5-Substituted tetrazole and is used in the synthesis of more complex structures such as Losartan and its analogues.[5758] Alkylation of 5-Substituted tetrazole with triphenylmethyl chloride (**Scheme I.11**) resulted in the formation only of the 2-isomers, regardless of the substituents at the 5-position. Phase-transfer catalysis is often used for these reactions.[5960]

[55] a) Koldobskii, G. I.; *Russ. J. Org. Chem*. **2006**, *42*, 469.;b) Bang-Andersen, B.; Lenz,S. M.; Skjaerbaek, N.; Soby, K. K.; Hansen, H. O.; Ebert,B.; Bogeso, K. P.; Krogsgaard-Larsen,P.*J. Med. Chem.***1997**, *40*, 2831.
[56] Agarkova, L. N.; Ostrovskii,V. A.; Koldobskii, G. I.; Erusalimskii,G. B. *Zh. Org. Khim*.**1982**, *18*, 1043.
[57] a) Larsen, R. D.; King, A. O.; Chen, C. Y.; Corley, E. G.; Foster, B. S.; Roberts, F. E.; Yang, C. H.; Lieberman, D. R.; Reamer,R. A.; Tschaen, D. M.; Verhoeven, T. R.; Reider,P. J. *J. Org. Chem*. **1994**, *59*, 6391.; b) Smith, G. B.; Dezeny,G. C.; Hughes, D. L.; King,A. O.; Verhoeven,T. R. *J. Org. Chem*.**1994**, *59*, 8151.
[58] Yoo, S. E.; Lee, S. H.; Kim, S. K. *Bioorg. Med. Chem.* **1997**, *5*, 445.
[59] Myznikov, L. V.; Artamonova, T. V.; Bel'skii, V. K.; Stash, A. I.; Skvortsov, N. K.; Koldobskii,G. I. *Russ. J. Org. Chem.* **2002**, *38*, 1360.
[60] Huff, B. E.; LeTourneau, M. E.; Staszak,M. A.; Ward,J. A. *Tetrahedron Lett*. **1996**, *37*, 3655.



Scheme I.11

It is not surprising that tritylation of 5-Substituted tetrazole proceeded only at the 2-position of the tetrazole ring. However, in the case of unsubstituted tetrazole this reaction still displayed a high regioselectivity even without steric control of the process.[61] Tritylation of a 5-Substituted tetrazole or of unsubstituted tetrazole should probably proceed through the S*N*1 mechanism. In this case, the limiting stage consists of triphenylmethyl chloride ionization to provide a triphenylmethyl cation, characterized by high thermodynamic stability. At the same time, the more stable the carbocation is, the higher its selectivity to one of the two competing nucleophilic centers will be.[62] This is most likely the reason why these reactions proceeded with high regioselectivity, even in the case of unsubstituted tetrazole. In many cases, the existence of ionic pairs, associated to greater or lesser extents, in the reaction medium must be considered. However, the influence of these associates on the reaction rates or regioselectivity is not still clearly understood, although many examples have shown that the regioselectivity is controlled in the same manner as in the case of the tetrazolate anion.[63] In substitution reactions, 5-Substituted tetrazole are often employed as ammonium salts. It was found that in aprotic solvents, these salts existed in the form of hydrogen-bonded complexes (**Figure I.4**).[64]These complexes had lower aromaticities than highly aromatic tetrazolate anions due to the hydrogen-bonded nitrogen in the 1-position of the tetrazole ring. It was disputed that the existence of such a complex would orient the electrophile to double bonding between N_2 and N_3 of the tetrazole ring, and not to the plane of the tetrazole, as in the case of the tetrazolate anion.

[61] Ostrovskii, V. A.; Ivanova, N. V.; Malin, A. A.; Shcherbinin, M. B.; Poplavskii, V. S.; Studentsov, E. P. *Zh. Org. Khim*. **1993**, *29*, 2333.
[62] Bethell,D. V. *Gold, Carbonium ions, an introduction,* AcademicPress, London, New York, **1967.**
[63] Titova, I. E.; Poplavskii, V. S.; Ostrovskii, V. A.; Erusalimskii, G. B.; Tereshchenko, G. F.; Koldobskii, G. I. *Zh. Org. Khim.* **1987**, *23*, 1082.
[64] a) Tsentovskii, V. M.; Bashkirtseva,V. Y.; Yevgenyev, M. I.; Ivanova, Z. P.; Poplavskii, V. S.; Ostrovskii, V. A.; Koldobskii,G. I. *Khim. Geterotsikl. Soedin*. **1983**, 1556.; b) Poplavskii, V. S.; Titova, I. E.; Ostrovskii, V. A.; Koldobskii,G. I. *Zh.Org. Khim*. **1989**, *25*, 2182.

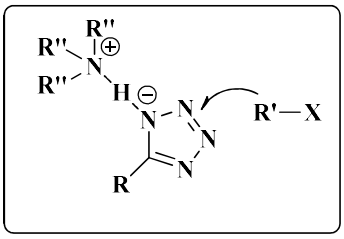
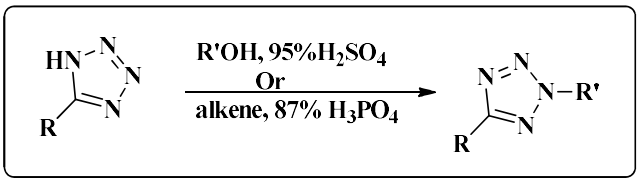


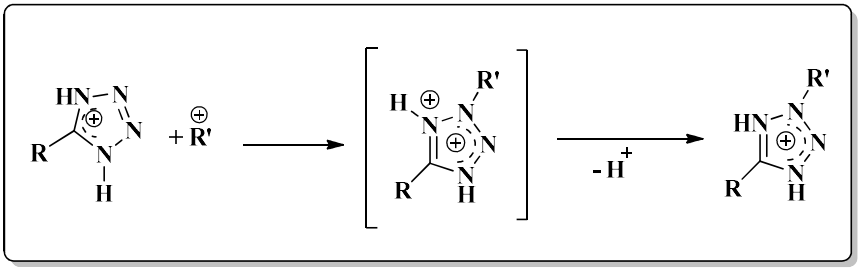
Figure I.4.

A completely different mechanism of substitution occurred in strongly acidic media. Reactions between 5-Substituted tetrazole and secondary or tertiary aliphatic alcohols[65] or alkenes,[66,67] in sulfuric acid produced only 2-alkylated products. No 1-isomers were detected in the reaction mixtures, regardless of the substituents at the 5-position in the tetrazole ring (**Scheme I.12**).



Scheme I.12

One possible explanation for this is that although 5-Substituted tetrazole are weak bases (for example: p*K*BH+ = –1.8 for 5-methyl-1*H*-tetrazole and p*K*BH+ = –9.3 for 5-nitro-1*H*-tetrazole),[68] they are protonated in strong mineral acid solutions. The nitrogen at the 4-position is protonized preferentially, resulting in a 1*H*,4*H*-tetrazolium cation of type (**Scheme I.13**).[69] The electrophilic attack of a carbocation, formed from alcohol or olefin, could be directed only to N_2 or N_3 of the tetrazolium cation, leading exclusively to 2,5-disubstituted tetrazoles .



Scheme I.13

[65] Koren, A. O.; Gaponik, P. N. *Khim. Geterotsikl. Soedin.* **1990,** 1643.
[66] Koren, A. O.; Gaponik, P. N. *Khim. Geterotsikl. Soedin*. **1991**, 1280.
[67] Gaponik, P. N.; Voitekhovich, S. V.; Klyaus, B. C. *Russ. J. Org. Chem*. **2004**, *40,* 598.
[68] Ostrovskii, V. A.; Koldobskii,G. I.; Shirokova, N. P.; Poplavskii,V. S. *Khim. Geterotsikl. Soedin*. **1981**, 559.
[69] a) Koldobskii, G. I.; Ostrovskii,V. A. *Khim. Geterotsikl. Soedin.***1988**, 579.; b) Mo, O.; Depaz, J. L. G.; Yanez, M.*J. Phys. Chem*. **1986**, *90*, 5597.; c) Ostrovskii, V. A.; Erusalimskii,G. B.; Shcherbinin,M. B. *Zh*. *Org. Khim.* **1993**, *29*, 1297.

I.3 Objective

For the synthesis of tetrazole derivatives, proper selection of the N-protecting group has been a significant challenge. For instance, most of the syntheses of sartan have been conducted by using a labile and easy-to-remove trityl group as the protecting group[70]. However, the trityl group is relatively voluminous and is not resistant to strong acidic conditions[71]. For this reason we would like to use a benzyl like protecting group with variety of substituted tetrazoles, in this context we prepared a tetrazoles using two methods as starting material and protect theme with Benzyl group (**Figure I.5)**.

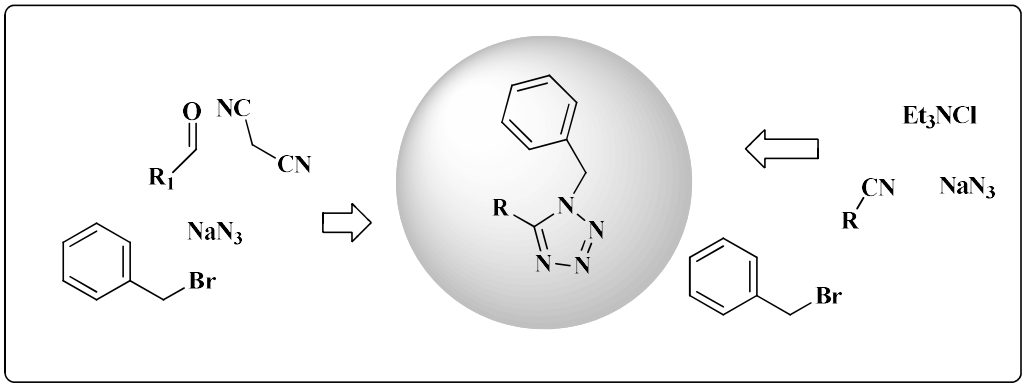


Figure I.5

I.4 Results and discussion

I.4.1 Synthesis of tetrazoles

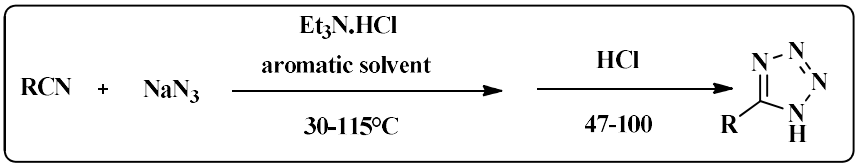
I.4.1.1 Synthesis of tetrazoles from nitril and amine salt

A variety of tetrazoles were prepared through reactions of sodium azide with corresponding nitriles in aromatic solvent in the presence of an amine salt. The mixture was heated to 110°C for 17-30 h with stirring. The product was extracted with water and the aqueous layer was acidified with HCl affording to the expected tetrazoles with higher purity in greater yield after filtration. This method has several advantages: the reaction produces no by-products due to side reaction; the reaction takes place rapidly. Another characteristic is its

[70] (a)Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B. III; Wells, G. J.; Wexler, R. R.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. M. W. M. *J. Med. Chem*. **1991**, *34*, 2525. (b)Bernhart, C. A. ; Perreaut, P. M. ; Ferrari, B. P. ; Muneaux, Y. A.; Assens, J.-L. A.; Clément, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E.; Vignal, M.-A.; Gougat, J.; Guiraudou, P. R.; Lacour, C. A.; Roccon, A.; Cazaubon, C. F.; Brelière, J.-C.; Le Fur, G.; Nisato, D. *J. Med. Chem.* **1993**, *36*, 3371. (c)Kubo, K.; Kohara, Y.; Yoshimura, Y.; Inada, Y.; Shibouta, Y.; Furukawa, Y.; Kato, T.; Nishikawa, K.; Naka, T. *J. Med. Chem*. **1993**, *36*, 2343. (d)Wexler, R. R.; Greenlee, W. J.; Irvin, J.D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. *J. Med. Chem*. **1996**, *39*, 625. (e)Kurup, A.; Garg, R.; Carini, D. J.; Hansch, C. *Chem. Rev*. **2001**, *101*, 2727.

[71] Rao,N.S.;Babu, S. *Org. Commun*, **2011**, 105.

simple workup procedures, through which products of excellent purity can be easily isolated (**Scheme I.14)**



Scheme I.14

The simplicity of the synthesis of tetrazoles permit us to synthesize several products have the same form with a difference in the radical which is varied between aromatic and alkyl nitriles. The reaction conditions and the physical properties of synthetic products are summarizing in (**Table II.1)**.

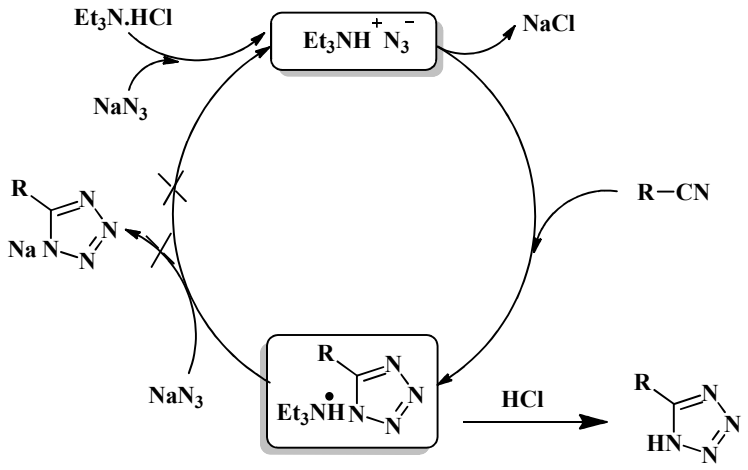
Table II.1: Synthesis of 5-substituted tetrazoles(2a-2e).

Entry	Product	R	Time (h)	Mp (°C)	Solvent	Yield (%)
1	**2a**	Ph	17-30	215-216	Toluene	41
2	**2b**	$PhCH_2$	17	123-124	-	25
3	**2c**	$4\text{-}NO_2C_6H_4$	20	146-147	-	32
4	**2d**	$CHPh_2$	17-30	165-166	-	27
5	**2e**	2-pyridyl	17-30	208-210	-	27

❖ ***Proposed mechanism***

Koguro *et al*. reported a variant by using triethyl amine hydrochloride in toluene. In this procedure, the authors proposed that the intermediate complex $[Et_3N \cdot HN_3]$ is first ionized as Et_3NH^+ and N_3^-, then, each of these react with the triple bond of the nitrile group to produce**,** when an aromatic solvent such as toluene is used, both the cation and the anion are not solvated, and the reaction thus proceeds smoothly **(Scheme I.15)**.[72]

[72] K. Koguro, T. Oga, S. Mitsui, R. Orita, *Synthesis*. **1997**, 910.



Scheme I.15

All tetrazole products were identified by spectroscopic methods usual IR, ^{1}H NMR and ^{13}C NMR.

I.4.1.1 Spectroscopic Study

- ***^{1}H NMR Spectroscopy***

We note in the spectrum of this compound **2a** the three aromatic protons resound at [7.55-7.62] ppm as multiplet (m), and two other resound at [8.01-8.1]ppm as multiplet (m) (**Figure I.6).** The results of the all compounds are summarizing in the (**Table I.2)**.

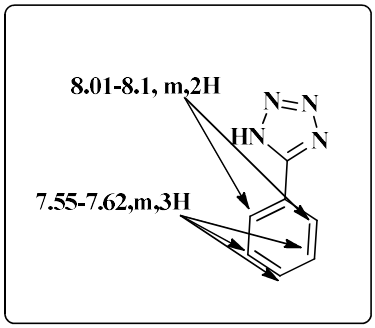


Figure I.6

Table I.2: [1]HNMR for compounds (2a-2e).

Compounds	CH	CH_2	CH_3	H_{arom}
2a				7.55-7.62, m, 3H 8.01-8.10, m, 2H
2b		4.31, s		7.25-7.37, m, 5H
2c				8.29-8.33, m, 2H 8.43-8.46,m ,2H
2d	5.97,s			7.11-7.48, m, 10H
2e				7.54-7.75, m, 1H 8.04-8.19, m, 1H 8.27,dd,3.8Hz, 1H

❖ ***[13]C NMR Spectroscopy***

Spectral analysis of the compound **2a** shows the existence of a weak magnetic field signal at 155.3 ppm corresponding to the tetrazole ring. The aromatic carbons appear in the usual area between [124.1 -131.3] ppm (**Figure I.7**)**.** The results of the all compounds are summarizing in the (**Table I.3).**

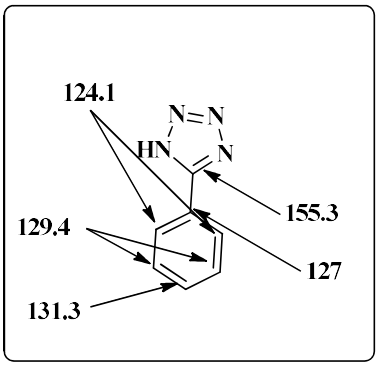


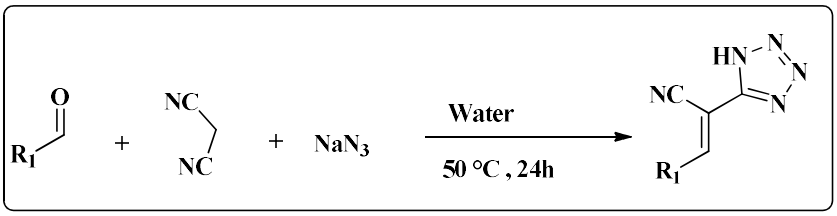
Figure I.7

Table I.3: ^{13}C NMR for compounds (2a-2e).

Compounds	CH	CH_2	CH_3	C_{arom}
2a	---	---	---	124.1-127-131.3-155.3
2b	---	29.0		127.1-128.7-128.8-136-155.3
2c	---	32.2	25.8	125-128.6-131-149.1-155.8
2d	46.2	---	---	127.65-128.9-129.15-140.5-158.5
2e				123-126.5-138.65-144.1-150.5-155.3

I.4.1.2 Synthesis of tetrazoles with knoevenagel reaction

We prepare the tetrazole via multi-component domino Knoevenagel condensation/ 1,3dipolar cycloaddition, this method is safe process to prepare a new tetrazoles without using any toxic metal or organic solvent, for these reaction, malononitrile was used with aldehyde with sodium azide in water for 24h at 50 °C (**Scheme I.15),** our results are summarized in **(Table I.4).**



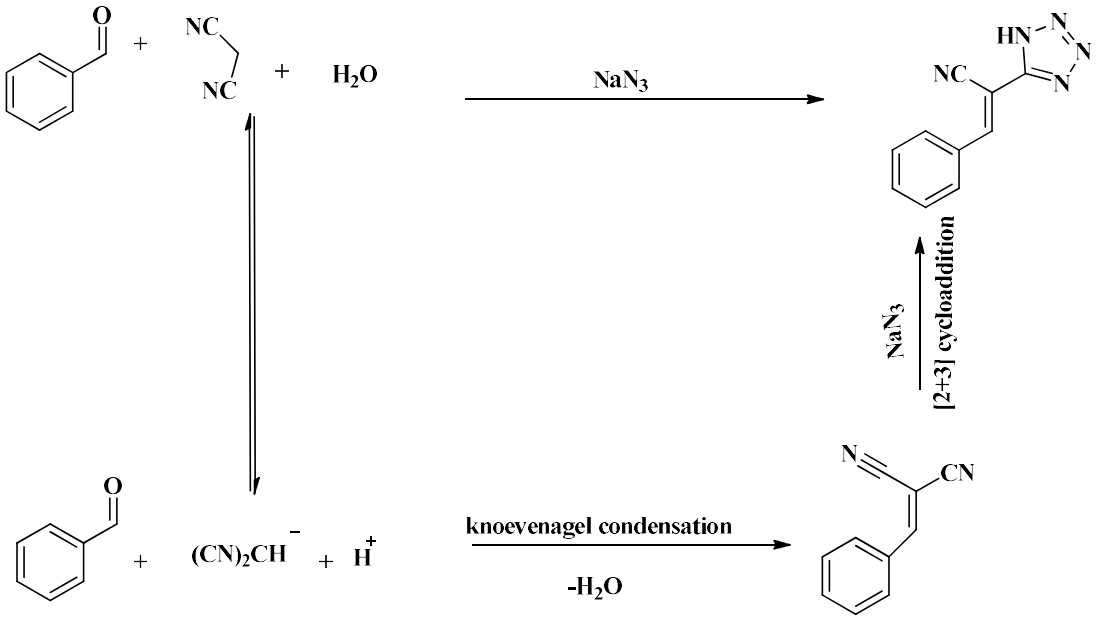
Scheme I.15

Table I.4: condition and results of preparation of tetrazoles.

Entry	Product	R	Time (h)	Mp (°C)	Solvent	Yield (%)
6	**6f**	(*E*)-C(CN)=CH(4-HOC_6H_4)	24	159-161	Water	94
7	**7g**	(*E*)-C(CN)=CHPh	20	168-170	-	51
8	**8h**	(*E*)-C(CN)=CH(4-ClC_6H_4)	25	158-160	-	75
9	**9i**	(*E*)-C(CN)=CH(4-$MeOC_6H_4$)	23	76-78	-	88
10	**10j**	(*E*)-C(CN)=CH(3-MeO-4-OHC_6H_3)	25	88-89	-	75

❖ **Proposed mechanism**

The formation of tetrazole can be rationalized by initial formation of 2-benzylidenemalononitrile through a knoevenagel condensation reaction of benzaldehyde and malonitrile .after wards the intermediate undergoes [2+3] cycloaddition reaction with the sodium azide. Although the role of water as reaction medium and its mechanism is not clear, this one pot reaction with regards to the observation of Sharpless et al, might take place of organic substrates with water in a heterogeneous system.



Scheme I.16

❖ **Spectroscopic study**

➢ ***^{1}H NMR Spectroscopy***

We note in the spectrum of this compound **2f**, the four protons of the aromatic ring are observed in the range[6.99-7.97] ppm whose multiplicity varies between two doublets (d): the first at 6.98 ppm with coupling constant *J*= 8.3 Hz, while the second at 7.97 ppm with coupling constant *J*= 8.3 Hz. And we have vinylic proton appear at 8.23 as a Singlet (**Figure I.8).** The results of the all compounds are summarizing in the (**Table I.5).**

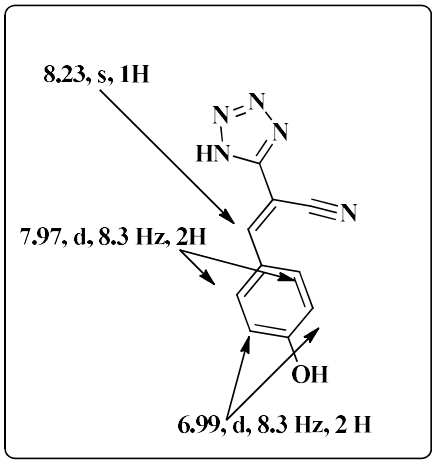


Figure I.8

Table I.5: ^{1}H NMR for compounds (2f-2j).

Compounds	**CH**	**CH_2**	**CH_3**	**H_{arom}**
2f				6.99, d, 8.3Hz , 2H 7.96, d ,8.3Hz, 2H 8.23, s, 1H 10.68, s, 1H
2g				7.58-7.63, m, 3H 8.00-8.15, m, 2H 8.42,d,3.6Hz, 1H
2h				7.62-7.72, m, 2H 8.05, d, 8.6, 2H 8.41, s, 1H
2i			3.85,s	7.14, d, 8.6Hz, 2H 8.01, d, 8.6Hz, 2H 8.25, s, 1H

	3.88,s	7.00, d, 8.3Hz, 1H
2j		7.53, d, 8.4,1H
		7.75, s, 1H
		8.22, s, 1H

- ***^{13}C NMR Spectroscopy***

Spectral analysis of the compound **2f** shows the existence of a weak magnetic field signal at 155.6 ppm corresponding to the carbon in beta position of acrylonitrile groups and at 148 ppm corresponding to the tetrazole ring. The aromatic carbons appear in the usual area between [116.75-133.1] ppm, to the carbon of nitrile group appear at 116.3 ppm and the carbon of alpha position in 91.9 ppm **(Figure I.9).** The results of the all compounds are summarizing in the (**Table I.6).**

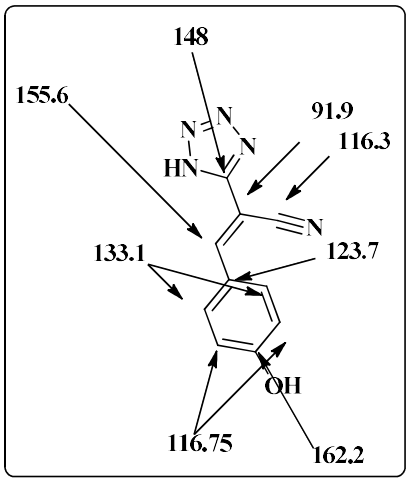


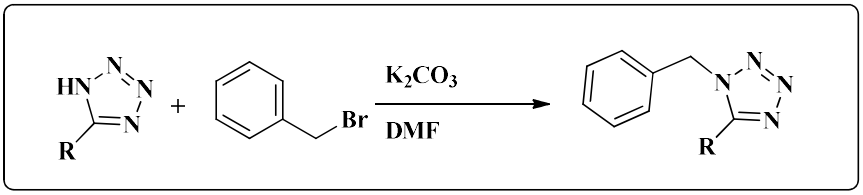
Figure I.9

Table I.6: ^{13}C NMR for compounds (2f-2j).

Compounds	CH	CH_2	CH_3	C=CCN	CN	C_{arom}
2f				91.9-155.6	116.3	91.9-116.75-123.7-133.1148.8-162.2
2g				97.4-155.9	115.8	129.6-130-130.3-132.6-148.8
2h				98.1-147.3	115.8	129.15-129.8-131.5-131.9-137.3
2i			56.1	93.9-155.9	115.35	116.6-125.3-132.6-148.05-163
2j			56	91.9-151.1	113.2	116.4-116.8-124-126.3-148.2-148.9-155.75

I.4.2 Protection of tetrazoles

We protect the tetrazoles using K_2CO_3 as base and benzyl bromide in DMF as solvent of the reaction (**Scheme I.17).**



Scheme I.17

Table I.7: Results

Entry	Product	R	Time (h)	Mp (°C)	Yield(%)
1	**1a**	Ph	overnight	78-80	77
2	**1b**	$PhCH_2$	-	140-142	80
3	**1c**	4-$NO_2C_6H_4$	-	76-78	66
4	**1d**	$CHPh_2$	-	133-135	84
5	**1e**	2-pyridyl	-	75-78	88
6	**1f**	(E)-C(CN)=CH(4-HOC_6H_4)	-	160-162	77
7	**1g**	(*E*)-C(CN)=CHPh	-	190-192	67
8	**1h**	(*E*)-C(CN)=CH(4-ClC_6H_4)	-	170-172	45
9	**1i**	(*E*)-C(CN)=CH(4-$MeOC_6H_4$)	-	76-78	60
10	**1j**	(*E*)-C(CN)=CH(3-MeO-4-OHC_6H_3)	-	170-172	63

❖ **Spectroscopic Study**

➢ ***^{1}H NMR Spectroscopy***

We note in the spectrum of the compound **1a** a singlet peak at 5.85 ppm corresponding to CH. Also the eight aromatic protons resound at [7.23-7.5] ppm as multiplet (m), the two other protons resound at 8.13 ppm as doublet of doublet with coupling constants =7.5,2.3 Hz, (**Figure I.10).** The results of the all compounds are summarizing in the (**Table I.8).**

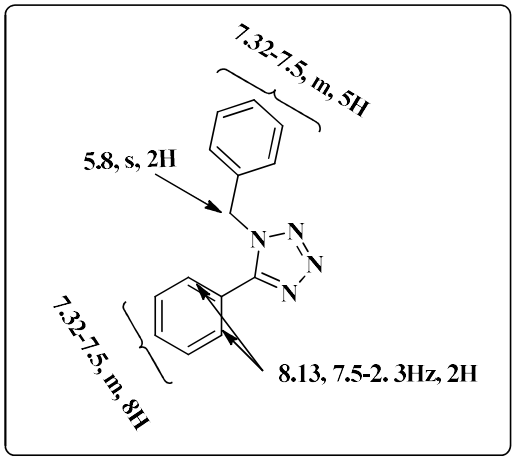


Figure I.10

Table I.8: ^{1}H NMR for compounds.

Compounds	CH	CH_2	CH_3	H_{arom}
1a		5.8, s, 2H		7.32-7.5, m, 8H 8.13, dd, 7.5-2.3 Hz, 2H
1b		4.2, s, 2H 5.68, s, 2H		7.18-7.37, m,10H
1c		5.84, s, 2H		7.33-7.52, m, 5H 8.3-8.33, m, 4H
1d	5.35-5.37, m, 1H	5.35-5.37,m,2H		7.00-7.18,m, 9H 7.19-7.38,m,6H
1e		6.25, s, 2H		7.82-7.92, m, 1H 8.33, d, 7.9Hz, 1H 8.74, s, 1H
1f	5.78, s, 1H	5.13, s, 2H		7.05, d, 8.9Hz, 2H 7.33-7.46, m, 5H 7.97, d,8.8Hz, 2H 8.2, s, 1H
1g		5.8, s, 2H		7.33-7.51, m, 8H 7.91-8.02, m, 2H 8.29, s, 1H
				7.32-7.53, m, 7H

1h	5.8, s, 2H		7.91, d, 8.6Hz, 2H 8.24, s, 1H
1i	5.79, s, 2H	3.87, s, 3H	6.98,d,8.9Hz,2H 7.36-7.47,m,5H 7.97,8.8Hz,2H 8.2,m,1H
1j	5.23,s,2H	3.96, m, 3H	5.78, s, 1H 6.94, d, 8.5Hz, 1H 7.38-7.43, m, 6H 7.79, s, 1H 8.17, s, 1H

- ***^{13}C NMR Spectroscopy***

Spectral analysis of the compound **1a** shows the existence of a weak magnetic field signal at 165 ppm corresponding to the carbon of tetrazole ring. The aromatic carbons appear in the usual area between [126.9-133.4] ppm**.** The appearance of CH_2 peak at 56.8 ppm**, (Figure I.11).** The results of the all compounds are summarizing in the (**Table I.9)**.

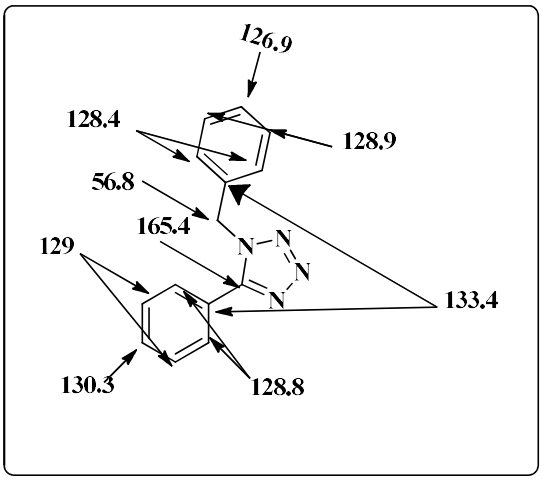


Figure I.11

Table I.9: ^{13}C NMR for compounds.

Compounds	CH	CH_2	CH_3	CH=CCN	CN	C_{arom}
1a		56.8				126.9-128.4-128.8-128.9-129-130-133.4-165.4
1b		31.9-56.6				126.9-128.4-128.6-128.8-128.9-129-133.35-136.7-165.9
1c		57.2				124.2-127.7-128.5-129.1-129.2-132.9-133.2-148.85-163.6

1d	46.55	51.1			127.5-127.8-128.6-128.9-129.2-133.15-138.1-156.2
1e		52.6			124.5-125.5-128.3-128.4-128.7-134.8-137.5-144.7-149.3-151.6
1f		52.6	95.3-146.7	116.2	125.45-127.5-128.5-129.1-132.4-132.8-136-161.8
1g		57.2	98.6-161.8	115.6	128.6-129.1-129.2-129.3-130.1-132.1-132.2--147.3
1h		57.3	99.1-161.6	115.3	128.6-129.1-129.25-129.5-130.8-131.3-132.7-138.2-145.7
1i	55.6	57.4	95.2-162.25		114.6-116.2-125.2-127.9-128.5-129.1-129.2-132.3-132.9-146.8-162.7
1j	56.1	57.1	95.3-151.6	113	116.2-125.7-127.2-128.1-128.5-128.7-132.8-136.1-147-149.6-151.6-162.1

I.5 Conclusion

The benzylation of tetrazoles by a simple alkylation under mild reaction condition, having good purity for the next and important step with moderate to good yields.

I.6 Experimental part

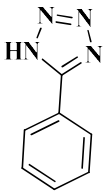
I.6.1 Description of experimental I.4.1

I.6.1.1 General Procedure for the preparation of tetrazoles 2a-e

A mixture of the corresponding nitrile (50 mmol), NaN_3 (65 mmol) and $Et_3N{\cdot}HCl$ (150 mmol) in toluene (100 mL) was stirred at 110 ºC for 17-30 h (TLC monitoring). After cooling at rt, the mixture was extracted with water (100 mL) and the aqueous phase was acidified with 36% HCl. The solid formed was filtered, washed with water (3 × 10 mL) and dried under reduced pressure to give products **2a-e**.

Yields, physical and spectroscopic data follow.

Synthesis of 5-Phenyl-1H-tetrazole **(2a)**

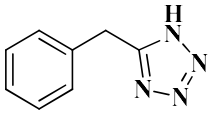


(2a)

Following the general procedure, the reactionof benzonitrile (5.15g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2a** as a white solid.

- Yield: 3.0 g (41%).
- Mp: 215−216 ºC.
- IR (KBr): 3333, 2588, 2511, 1055, 925, 789, 643, 619 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-d_6): δ 7.55−7.62 (m, 3H), 8.01−8.10 (m, 2H).
- ^{13}C NMR (101 MHz, DMSO-d_6): δ 124.1 (CH), 127.0 (C), 129.4, 131.3 (CH), 155.3 (C).
- H RMS (ESI): calculated for $C_7H_6N_4(M^+)$ 146.0592, found 146.0598.

Synthesis of 5-Benzyl-1H-tetrazole **(2b)**

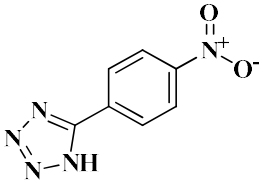


(2b)

Following the general procedure, the reaction of 2-phenylacetonitrile (5.85g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2b** as a white solid.

- Yield: 2.0 g (25%).
- Mp: 123−124 ºC.
- IR (KBr): 2949,2864, 2709, 1073, 961, 835, 694, 608 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-d_6): δ 4.31 (s, 2H), 7.25−7.37(m, 5H).
- ^{13}C NMR (101 MHz, DMSO-d_6): δ 29.0 (CH_2), 127.1, 128.7, 128.8 (CH), 136.0, 155.3 (C).
- HRMS (ESI): calculated for $C_8H_8N_4(M^+)$ 160.0749, found 160.0748.

Synthesis of 5-(4-Nitrophenyl)-1H-tetrazole **(2c)**

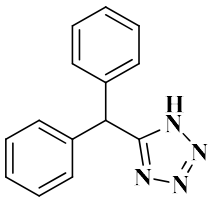


(2c)

Following the general procedure, the reactionof 4-nitrobenzonitrile (7.4 g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2c** as a green solid.

- yield: 2.9 g (32%).
- mp: 146−147 ºC.
- IR (KBr): 3453, 2543, 1018, 988, 978, 851, 702, 634 cm^{-1}.
- ^{1}H NMR (400 MHz, DMSO-*d*6): δ 8.29−8.33 (m, 2H), 8.43−8.46 (m, 2H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 125.0, 128.6 (CH), 131.0, 149.1, 155.8 (C).
- HRMS (ESI): calculated for $C_7H_5N_5O_2$ (M^+) 191.0443, found 191.0452.

Synthesis of 5-Benzhydryl-1H-tetrazole **(2d)**

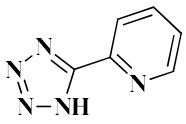


(2d)

Following the general procedure, the reaction of 2,2-diphenylacetonitrile (9.55 g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2d** as a white solid.

- Yield: 3.0 g (27%)
- Mp: 165−166 ºC
- IR (KBr): 3360, 2680, 1082, 990, 845, 695, 617 cm^{-1}.
- ^{1}H NMR (400 MHz, DMSO-*d*6): δ 5.97 (s, 1H), 7.11−7.48 (m, 10H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 46.2 (CH), 127.65, 128.9, 129.15 (CH), 140.5, 158.5 (C).
- HRMS (ESI): calculated for $C_{14}H_{12}N$ (M^+-N_3) 194.0970, found 194.0954.

Synthesis of 2-(1H-Tetrazol-5-yl)pyridine **(2e)**



(2e)

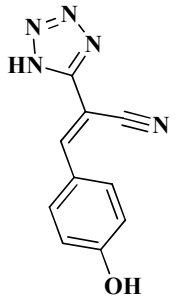
Following the general procedure, the reaction of picolinonitrile (5.2g, 50 mmol), NaN_3 (3.9 g, 65 mmol) and an amine salt (8.22 g, 150 mmol) in toluene at 110°C gave **2e** as a Brown solid.

- yield: 3.0 g (27%).
- mp: 208−210 ºC.
- IR (KBr): 3091, 2650, 1539, 1114, 975, 899, 695, 615 cm–^{1}.
- ^{1}H NMR (400 MHz, DMSO-*d*6): δ 7.54−7.75 (m,1H), 8.04−8.19 (m, 1H), 8.27 (dd, *J* = 7.4, 3.8 Hz, 1H), 8.84 (t, *J* = 4.3 Hz, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 123.0, 126.5, 138.65 (CH), 144.1 (C), 150.5 (CH), 155.3 (C).
- HRMS (ESI): calculated for $C_6H_5N_3$ (M^+-N_2) 119.0483, found 119.0491.

I.6.1.2 General Procedure for the preparation of tetrazoles 2f-j

A mixture of the corresponding carbonyl compound (1 mmol), malononitrile (1 mmol) and NaN_3 (2 mmol) in water (5 mL) was stirred at 50 ºC until the starting materials were consumed (TLC monitoring). The reaction mixture was filtered and to the filtrate was added 2N HCl (30 mL) so a precipitate was formed. The solid was filtered and dried in a drying oven to furnish the expected tetrazoles **2f-j**. Yields, physical and spectroscopic data follow.

Synthesis of (*Ɛ*)-3-(4-Hydroxyphenyl)-2-(1H-tetrazol-5-yl)acrylonitrile (**2f**)

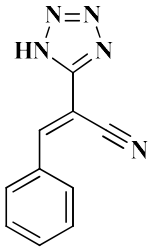


(2f)

Following the general procedure, the reactionof4-hydroxy benzaldehyde(0.6g, 5 mmol), NaN_3 (0.66 g, 10 mmol) and an malonitrile (0.32 g, 05mmol) in Water (10 mL)at 50°C gave **2f** as a white solid.

- yield: 0.20 g(94%).
- mp: 159−161 ºC.
- IR (KBr): 3330, 2642, 1509, 1411, 988, 821, 653, 604 cm^{-1}.
- ^{1}H NMR (400MHz, DMSO-*d*6): δ 6.99 (d, *J* = 8.3 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 8.23 (s, 1H), 10.68 (br s, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 91.9 (CN), 116.3 (C), 116.75 (CH), 123.7 (C), 133.1 (CH), 148.8, 155.6, 162.2 (C).
- HRMS (ESI): calculated for $C_{10}H_6NO$ (M^+-HN_4) 156.0449, found 156.0452.

***Synthesis of (E)-3-Phenyl-2-(1H-tetrazol-5-yl) acrylonitrile*(2g)**

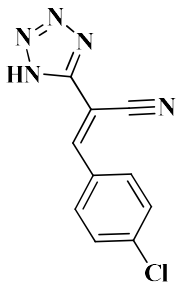


(2g)

Following the general procedure, the reaction of benzaldehyde (0.5g, 5 mmol), NaN_3 (0.66 g, 10 mmol) and an malonitrile (0.32 g, 05 mmol) in Water (10 mL) at 50°C gave **2g** as a Pale yellow solid.

- yield: 0.10 g (51%).
- mp: 168−170 ºC.
- IR (KBr): 3310, 2641, 1570, 1477, 982, 848, 669, 608 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 7.58−7.63 (m, 3H), 8.00−8.15 (m, 2H), 8.42 (d, *J* = 3.6 Hz, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 97.4 (CN), 115.9 (C), 129.6, 130.0, 130.3, 132.6 (CH), 148.8, 155.9 (C).
- HRMS (ESI): calculated for $C_{10}H_6N_3$ (M^+−HN_2) 168.0562, found 168.0566.

***Synthesis of (E)-3-(4-Chlorophenyl)-2-(1H-tetrazol-5-yl)acrylonitrile* (2h)**

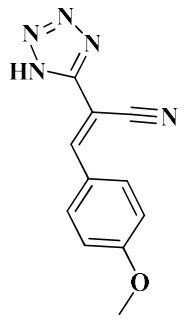


(2h)

Following the general procedure, the reaction of 4-chlorobenzaldehyde (0.7g, 5 mmol), NaN_3 (0.66 g, 10 mmol) and an malonitrile (0.32 g, 05mmol) in Water (10 mL) at 50°C gave **2h** as a white solid.

- yield: 0.16 g (75%).
- mp: 158−160 ºC.
- IR (KBr): 3158, 2359, 1585, 1497, 930, 810, 691, 623 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 7.62−7.72 (m, 2H), 8.05 (d, *J* = 8.6 Hz, 2H), 8.41 (s, 1H)
- ^{13}C NMR (101 MHz, DMSO*d*6): δ 98.1 (CN), 115.8 (C), 129.15, 129.8 (CH), 131.5 (C), 131.9 (CH), 137.3, 147.3 (C).
- HRMS (ESI): calculated for $C_{10}H_5ClN_2$ (M^+−HN_3) 188.0141, found 188.0140.

***Synthesis of (Ɛ)-3-(4-Methoxyphenyl)-2-(1H-tetrazol-5-yl)acrylonitrile* (2i)**

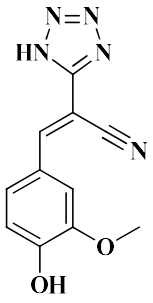


(2i)

Following the general procedure, the reaction of 4-methoxybenzaldehyde (0.7g, 5 mmol), NaN_3 (0.66 g, 10 mmol) and a malonitrile (0.32 g, 05mmol) in Water (10 mL) at 50°C gave **2i** as a Green solid.

- yield: 0.20 g (88%).
- mp: 76−78 ºC.
- IR (KBr): 3120, 2773, 1589, 1462, 954, 864, 651, 604 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 3.85 (s, 3H), 7.14 (d, *J* = 8.6 Hz, 2H), 8.01 (d, *J* = 8.6 Hz, 2H), 8.25 (s, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 56.1 (CH3), 93.9 (CN), 115.35 (CH), 116.6 (C), 125.3, 132.6 (CH), 148.05, 155.9, 163.0 (C).
- HRMS (ESI): calculated for $C_{10}H_9N_3O$ (M^+-CN_2) 187.0746, found 187.0733.

***Synthesis of (Ɛ)-3-(4-Hydroxy-3-methoxyphenyl)-2-(1H-tetrazol-5-yl) acrylonitrile* (2j)**



(2j)

Following the general procedure, the reaction of 4-hydroxy-3-methoxybenzaldehyde (0.76g, 5 mmol), NaN_3 (0.66 g, 10 mmol) and a malonitrile (0.32 g, 05mmol) in Water (10 mL) at 50°C gave **2j** as a Green solid.

- yield: 0.16 g (75%).
- mp: 88−89 ºC.
- IR (KBr): 3121, 2225, 1574, 1458, 998, 844, 644, 620 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 3.88 (s, 3H), 7.00 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 8.22 (s, 1H).

- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 56.0 (CH3), 91.9 (CN), 113.2, 116.4 (CH), 116.8 (C), 124.0, 126.3, (CH), 148.2, 148.9, 151.9, 155.75 (C).
- HRMS (ESI): calculated for $C_{10}H_6N_3O$ ($M^+-N_2CH_3O$) 184.0511, found 184.0537.

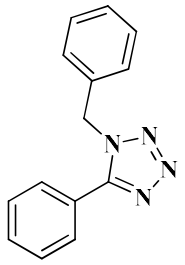
I.6.2 Description of experimental I.4.2

I.6.2.1 General Procedure for the benzylation of tetrazoles 2

A mixture of the corresponding tetrazole **2** (1 mmol), benzyl bromide (1 mmol) and K_2CO_3 (2 mmol) in DMF (5 mL) was stirred a 0 ºC until the conversion was complete (TLC monitoring). The reaction mixture was filtered and to the filtrate was added water (15 mL) and extracted with EtOAc (3 × 10 mL) and dried over Na_2SO_4. After evaporation of the solvent (15 Torr) the resulting residue was purified by recrystallization (EtOH) to give tetrazoles **1**.

Yields and physical and spectroscopic data follow.

Synthesis of 1-Benzyl-5-phenyl-1H-tetrazole **(1a)**

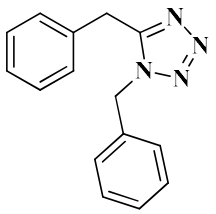


(1a)

Following the general procedure, the reaction of tetrazoles **2a** (0.5g, 5 mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5mmol) in DMF (5 mL) at 0°C gave **1a** as a white solid.

- yield: 0.18 g (77%).
- mp: 78−80 ºC.
- IR (KBr): 1651, 1274, 979, 854, 773, 615 cm^{-1}.
- ^{1}H NMR (400 MHz, DMSO-*d*6): δ 5.80 (s, 2H), 7.32−7.50 (m, 8H), 8.13 (dd, *J* = 7.5, 2.3 Hz, 2H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 56.8 (CH2), 126.9, 128.4, 128.8, 128.9, 129.0, 130.3 (CH), 133.4, 162.7, 165.4 (C).
- HRMS (ESI): calculated for $C_{14}H_{12}N_4$ (M^+), 236.1062, found 236.1051.

***Synthesis of 1,5-Dibenzyl-1H-tetrazole*(1b)**

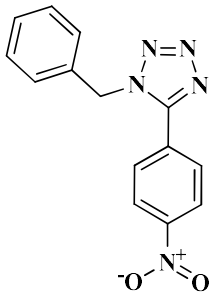


(1b)

Following the general procedure, the reaction of tetrazoles **2b** (0.5 g, 5 mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5mmol) in DMF (5 mL) at 0°C gave **1b** as a white solid.

- yield: 0.2 g (80%).
- mp: 140−142 ºC.
- IR (KBr): 1604, 1278, 976, 854, 693, 601 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 4.21 (s, 2H), 5.68 (s, 2H), 7.18−7.37 (m, 10H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 31.9, 56.6 (CH2), 126.9, 128.4, 128.6, 128.8, 128.9, 129.0 (CH), 133.35, 136.7, 165.9 (C).
- HRMS (ESI): calculated for $C_{14}H_{12}N_3$ (M^+−CH_2N) 222.1031, found 222.1027.

***Synthesis of 1-Benzyl-5-(4-nitrophenyl)-1H-tetrazole* (1c)**

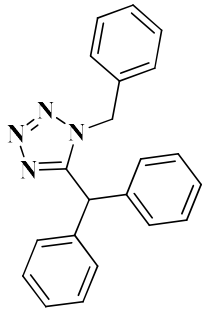


(1c)

Following the general procedure, the reaction of tetrazoles **2c** (0.95g, 5 mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5mmol) in DMF (5 mL) at 0°C gave **1c** as a green solid.

- yield: 0.18 g (66%).
- mp: 76−78 ºC.
- IR (KBr): 1604, 1282, 965, 852, 651, 601 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 5.84 (s, 2H), 7.33−7.52 (m, 5H), 8.30−8.33 (m, 4H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 57.2 (CH2), 124.2, 127.7, 128.5, 129.1, 129.2 (CH), 132.9, 133.2, 148.85, 163.6 (C).
- HRMS (ESI): calculated for $C7H_5N_5O_2$ (M^+) 191.0443, found 191.0452.

Synthesis of 5-Benzhydryl-1-benzyl-1H-tetrazole **(1d)**

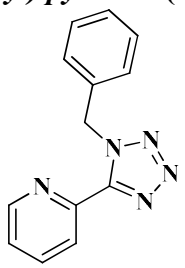


(1d)

Following the general procedure, the reaction of tetrazoles **2d** (1.18g, 5mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5mmol) in DMF (5 mL) at 0°C gave **1d** as a white solid.

- yield: 0.27 g (84%).
- mp: 133−135 ºC.
- IR (KBr): 1598, 1254, 953, 890, 688, 608 cm^{-1}
- ^1H NMR (400 MHz, DMSO-*d*6): δ 5.35−5.37 (m, 3H), 7.00−7.18 (m, 9H), 7.19−7.38 (m, 6H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 46.55 (CH), 51.1 (CH2), 127.5, 127.8, 128.6, 128.9, 129.2 (CH), 133.15, 138.1, 156.2 (C).
- HRMS (ESI): calculated for $C_{21}H_{18}N_4$ (M^+) 326.1531, found 326.1522.
-

Synthesis of 2-(1-Benzyl-1H-tetrazol-5-yl) pyridine **(1e)**

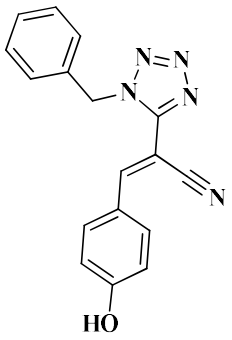


(1e)

Following the general procedure, the reaction of tetrazoles **2e** (0.73g, 5mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5mmol) in DMF (5 mL) at 0°C gave **1e** as a green solid.

- yield: 0.20 g (88%).
- Mp: 75−77 ºC.
- IR (KBr): 1589, 1263, 999, 876, 690, 601 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 6.25 (s, 2H), 7.19−7.52 (m, 6H), 7.82−7.92 (m, 1H), 8.33 (d, *J* = 7.9 Hz, 1H), 8.74 (s, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 52.6 (CH2), 124.5, 125.5, 128.3, 128.4, 128.7 (CH), 134.8 (C), 137.5 (CH), 144.7 (C), 149.3 (CH), 151.6 (C).
- HRMS (ESI): calculated for $C_{13}H_9N_3$ ($M^+-N_2H_2$) 207.0796, found 207.0792.

Synthesis of (E)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-hydroxyphenyl) acrylonitrile (**1f**)

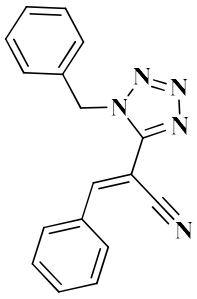


(1f)

Following the general procedure, the reaction of tetrazoles **2f** (1.06g, 5mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5mmol) in DMF (5 mL) at 0°C gave **1f** as an orange solid.

- yield: 0.23 g (77%).
- mp: 160−162 ºC.
- IR (KBr): 2360, 1511, 1439, 1261, 997, 895, 672, 614 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 5.13 (s, 2H), 5.78 (s, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 7.33−7.46 (m, 5H), 7.97 (d, *J* = 8.8 Hz, 2H), 8.20 (s, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 52.6 (CH2), 95.3 (CN), 115.5 (CH), 116.2, 125.45 (C), 127.5, 128.5, 129.1, 132.4 (CH), 132.8, 136.0 (C), 146.7 (CH), 161.8 (C).
- HRMS (ESI): calculated for $C_{17}H_{11}N_O$ ($M^+-N_4H_2$) 245.0841, found 245.0829.

Synthesis of (*E*)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-phenylacrylonitrile **(1g)**



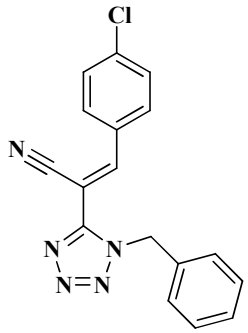
(1g)

Following the general procedure, the reaction of tetrazoles **2g** (0.98g, 5mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5 mmol) in DMF (5 mL) at 0°C gave **1g** as a green solid.

- yield: 0.19 g (67%).
- mp: 190−192 ºC.
- IR (KBr): 2332, 1596, 1443, 1211, 973, 856, 697, 605 cm^{-1}.
- ^1H NMR (400 MHz, DMSO-*d*6): δ 5.80 (s, 2H), 7.33−7.51 (m, 8H), 7.91−8.02 (m, 2H), 8.29 (s, 1H).

- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 57.2 (CH2), 98.6 (CN), 115.6 (C), 128.6, 129.1, 129.2, 129.3, 130.1, 132.1 (CH), 132.2 (C), 147.3 (CH), 161.8 (C).
- HRMS (ESI): calculated for $C_{17}H_{13}N_5$ (M^+) 287.1171, found 287.1148.

Synthesis of (Ɛ)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-chlorophenyl) acrylonitrile **(1h)**

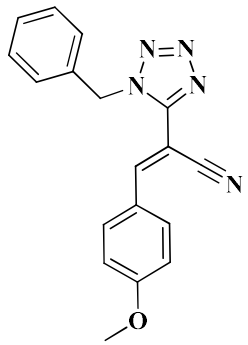


(1h)

Following the general procedure, the reaction of tetrazoles **2h** (1.15g, 5 mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5 mmol) in DMF (5 mL) at 0°C gave **1h** as a green solid.

- yield: 0.14 g (45%).
- mp:170−172 ºC.
- IR (KBr): 2224, 1588, 1474, 1211, 962, 833, 687, 616 cm^{-1}.
- ^{1}H NMR (400 MHz, DMSO-*d*6): δ 5.80 (s, 2H), 7.32−7.53 (m, 7H), 7.91 (d, *J* = 8.6 Hz, 2H), 8.24 (s, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 57.3 (CH2), 99.1 (CN), 115.3 (C), 128.6, 129.1, 129.25, 129.5 (CH), 130.8 (C), 131.3 (CH), 132.7, 138.2 (C), 145.7 (CH), 161.6 (C).
- HRMS (ESI): calculated for $C_{17}H_{12}ClN_5$ (M^+) 321.0781, found 321.0775.

Synthesis of (Ɛ)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-methoxyphenyl) acrylonitrile **(1i)**



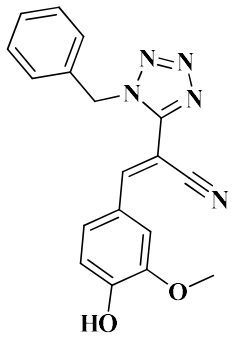
(1i)

Following the general procedure, the reactionoftetrazoles **2i** (1.13g, 5 mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5mmol) in DMF (5 mL) at 0°C gave **1i** as a green solid.

- yield: 0.19 g (60%).

- mp: 76−78 ºC.
- IR (KBr): 2221, 1594, 1497, 1217, 970, 825, 683, 613 cm^{-1}.
- ^{1}H NMR (400 MHz, DMSO-*d*6): δ 3.87 (s, 3H), 5.79 (s, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 7.36−7.47 (m, 5H), 7.97 (d, *J* =8.8 Hz, 2H), 8.20 (s, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 55.6 (CH3), 57.4 (CH2), 95.2 (CN), 114.6, 116.2, 125.2 (C), 127.9, 128.5, 129.1, 129.2, 132.3 (CH), 132.9 (C), 146.8 (CH), 162.25, 162.7 (C).
- HRMS (ESI): calculated for $C_{18}H_{15}N_5O$ (M^+) 317.1277, found 317.1268.

***Synthesis of (*Ɛ*)-2-(1-Benzyl-1H-tetrazol-5-yl)-3-(4-Hydroxy-3-methoxyphenyl acrylonitrile* (1j)**



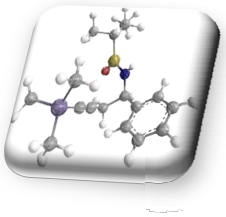
(1j)

Following the general procedure, the reaction of tetrazoles **2j** (1.21 g, 5 mmol), K_2CO_3 (1.35 g, 10 mmol) and Benzyl bromide (0.55 g, 5 mmol) in DMF (5 mL) at 0°C gave **1j** as a green solid.

- Yield: 0.20 g (63%).
- Mp: 170−172 ºC.
- IR (KBr): 2225, 1512, 1426, 1253, 939, 801, 671, 603 cm^{-1}.
- ^{1}H NMR (400 MHz, DMSO-*d*6): δ 3.96 (s, 3H), 5.23 (s, 2H), 5.78 (s, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 7.38−7.43 (m, 6H), 7.79 (s, 1H), 8.17 (s, 1H).
- ^{13}C NMR (101 MHz, DMSO-*d*6): δ 56.1 (CH3), 57.1 (CH2), 95.3 (CN), 113.0 (CH), 116.2 (C), 125.7, 127.2, 128.1, 128.5, 128.7 (CH), 132.8, 136.1 (C), 147.0 (CH), 149.6, 151.6, 162.1 (C).
- HRMS (ESI): calculated for $C_{18}H_{15}NO_2$ (M^+-N_4) 277.1103, found 277.1085.

ChapterII

Debenzylation of tetrazoles using indium



II.1 Introduction

The discovery of the remarkable reactivity of the indium in organometallic reaction inside organic media,[73] or aqueous media.[74] Several research groups are interested in using indium metal in aqueous media as it is not touched by water or by air.[75] Other aspects of indium (0) or indium (III) chemistry were recently described.[76] Organometallic species may be applied when any indium (0) or indium (I) is introduced into a carbon–halogen bond[77], but in most cases, indium (0), acting as a reducing agent, may induce a radical intermediate.[78] Indium (III) in the presence of various hydrides may increasethe power of the reducing agent, thereby allowing space for new reactivates.[79] Indium (III) salts are water-tolerant additives and this property has resulted in an increase in the interest of using things such as Lewis acids in catalytic processes.[80] This chapter focuses on the recent advances of indium-promoted reduction agent, whatever the oxidation state of indium.

II.2 The oxidation states of indium

The indium has a first ionization potential almost as low as that of the alkali metals, much lower than that of magnesium, tin, or zinc. Is also inert to water and its lack of toxicity[2] Otherwise, the advantage of indium, compared to aluminium, lies in its low propensity to form oxides in air. Indium powder, when placed in a Schlenk tube for half an hour under gentle stirring and vacuum, gives pleasing results in terms of reactivity, so that further activation is often unnecessary. A new protocol that uses granular indium metal as a cheaper form of indium was recently introduced, but mild heating was then desired, [81] (**Table II.1)** gives the ionization potential values of some common metals.[82]

Table II.1: First ionisation potential of some metals

Metal	Potential (eV)
Lithium	5,39
Sodium	5,12
Magnesium	7,65
Aluminium	5,98
Indium	5,79
Tin	7,43
Zinc	9,39

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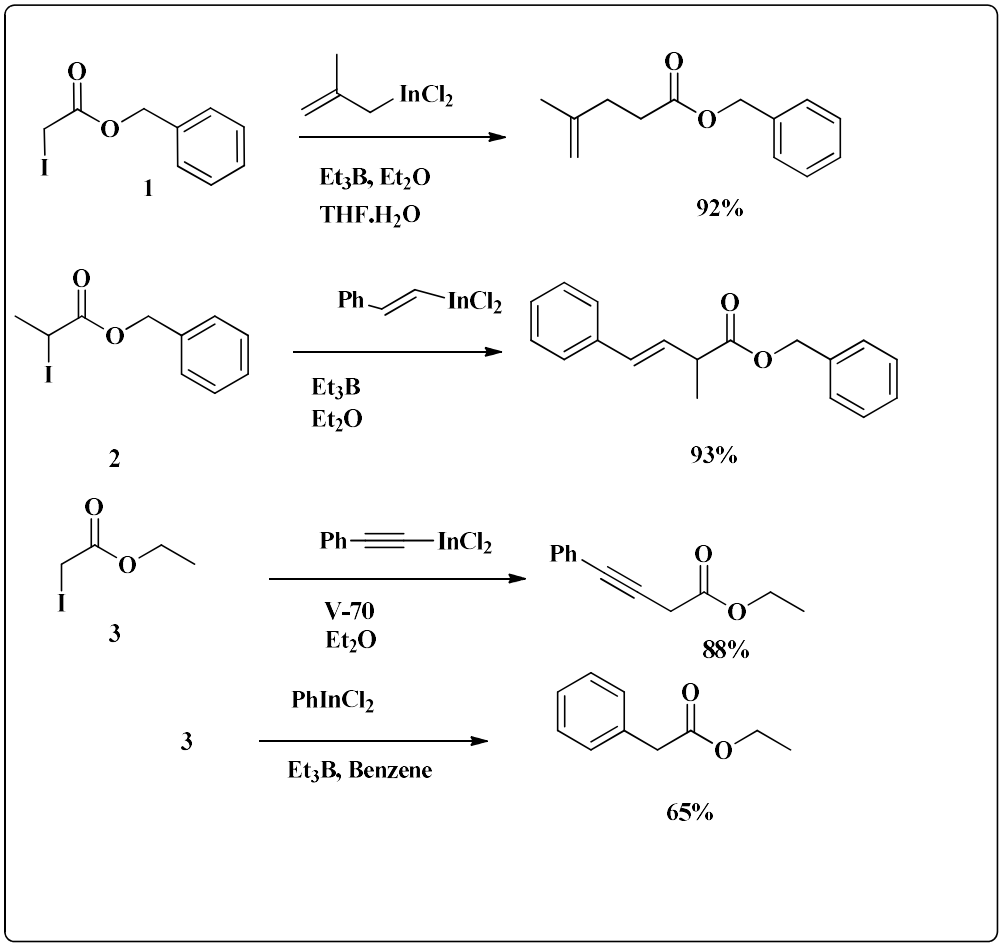
II.3 Radical Reactions

The low ionization potential of indium, promoted single-electron processes.

II.3.1 Radical substitutions Initiated by Triethylborane

The Triethylborane form ethyl radical in the presence of dioxygen was exploited in the radical indium mediated substitution of α-halo carbonyl compounds[83]. Transmetalation of Grignard reagents with indium (III) chloride provide allylindium reagents than transferred their allyl moiety to α-iodo (or α-bromo) amides or esters such as **1** in aqueous tetrahydrofuran solution. With alkenylindium reagents, the reaction was carried out in diethyl ether. Starting from an ester such as **2**, the stereochemistry of alkenylindiums was essentially retained, so that the E/Z configurational ratio of the product was approximately that of the starting alkenyl bromide. In the same way, phenylethynylindium dichloride and phenylindium dichloride were added to α-iodo esters such as **3**. In all these reactions, dichloroindium (II) radical was used as an efficient radical mediator (**Scheme II.1**).

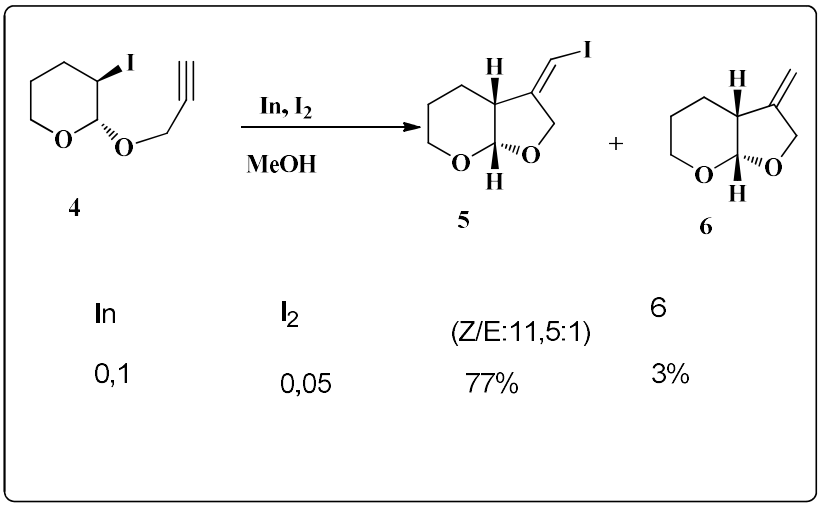


Scheme II.1

[83] Marshall, J. A.; Grant, C. M. *J. Org. Chem*. **1999**, *64*, 8214.

II.3.2 Radical Cyclizations

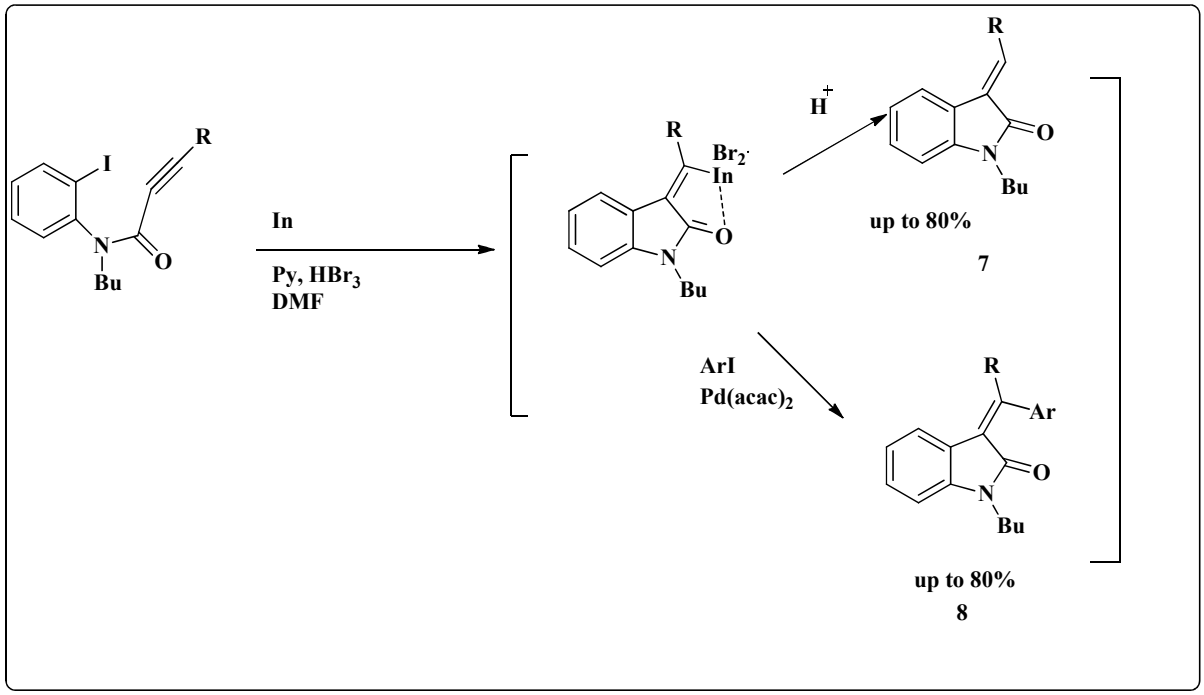
The activation of indium with iodine to produce indium (I), indium (II) and indium (III) salts in aromatic solvents under reflux.[84] A radical process can be initiated by indium as Low-Valente. For example: treatment of iodoalkynes such as **4** with a catalytic amount of indium (0.1 equiv) and iodine (0.05 equiv) promoted an atom transfer 5-exo cyclization to give the five-membered alkenyl iodide products such as **5.**[85] With an excess of indium, cyclization was followed by reduction of the alkenyl iodide to give **6** (**Scheme II.2**). When the starting alkyne contained a leaving group at the propargylic position, allelic products were produced selectively.[86]



Scheme II.2

With alkenes bearing leaving groups at the allylic position, the 5-exo cyclization was accompanied by the elimination of these groups. In some cases, the indium–molecular bromine couple turned out to be more efficient than the indium–molecular iodine couple for inducing the radical cyclization. Another example is the pyridinium tribromide ($Py{\cdot}HBr_3$) could be used instead of molecular bromine.[87] Such conditions were used in the 5-exo radical cyclization of iodo-ynamide leading to the vinylindium intermediate, which could be quenched by a proton to give **7** or which could, after addition of aryl iodide, undergo a palladium-catalyzed cross-coupling reaction to afford **8**, (**Scheme II.3**).

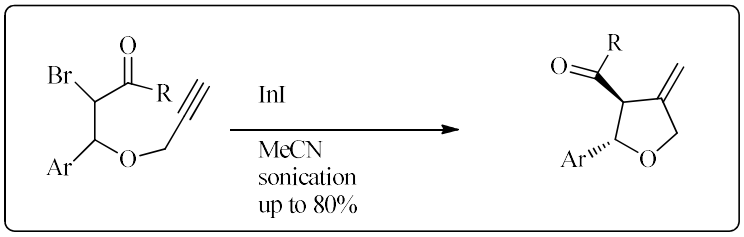
[84] Peppe, C.; Tuck, D. G.; Victoriano, L. *J. Chem. Soc*., *Dalton Trans*. **1982**, 2165.
[85] A. Srikrishna, T. J. Reddy and R. Viswajanani, *Tetrahedron*, **1996**, *52*, 1631.
[86] Rahman,M. A.; Fraser-Reid,B. *J. Am. Chem. Soc*., **1985**, *107*, 5576.
[87] Diab, Y.; Laurent, A.; Mison, P. *Tetrahedron Lett.* **1974**, *15*, 1605.



Scheme II.3

II.3.3 Indium (I) as a radical initiator

Indium (I) was used as a radical initiator to promote intramolecular cyclization of δ-bromoalkynes, indium (I) iodide was used in a stoichiometric amount under sonication, and gave mount to a vinylindium intermediate according to a mechanism similar to that observed with the stoichiometric indium–iodine or indium–bromine protocol. After hydrolysis, the corresponding substituted 4-methylenetetrahydrofurans were obtained in yields ranging from 62% to 80% (**SchemeII.4**). [88]



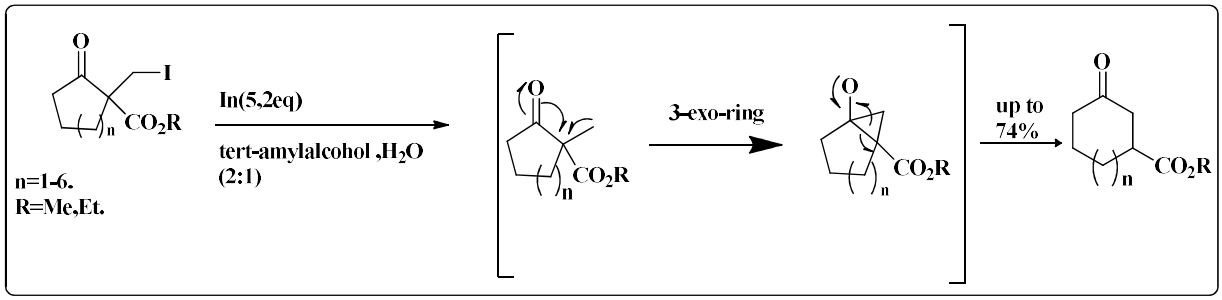
Scheme II.4

II.3.3 Indium (0) as a Radical Initiator

Indium was used as a radical initiator in aqueous media to promote intermolecular alkyl addition to oxime and hydrazone carbon–nitrogen double bonds and to electron deficient

[88] Tafesh, A. M.;Weiguny,J. *Chem. Rev*. **1996**, *96*, 2035.

carbon–carbon double bonds.[89] The reaction gave good yields with five equivalents of secondary alkyl iodides in the presence of seven equivalents of indium in aqueous methanol or dichloromethane–water mixtures. Another example of single-electron processes initiated by indium was the one-carbon ring expansion of the α-iodomethyl cyclic β-keto esters in aqueous *tert*-amyl alcohol at reflux; the primary radical formed by reduction of the iodide underwent a 3-exo-trig cyclization and a subsequent b-cleavage to afford product (**Scheme II.5**).[90]



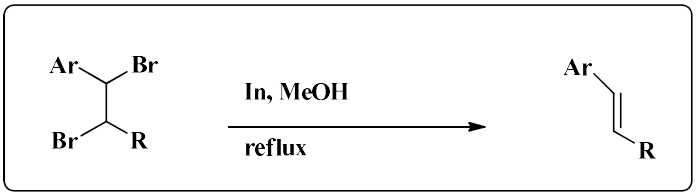
Scheme II.5

II.4 Indium metal as a reducing agent in organic synthesis

II.4.1 Stereoselective Debromination of vic-Dibromides

Debromination of olefins is an important process in organic synthesis, but bromination generally proceeds slowly and stereospecifically to give high yields of dibromides, debromination in the synthesis often proves more difficult. This is primarily because the efficiency of the process is highly dependent on the stereoselectivity of the debromination step and on the compatibility of the reagent with the carbon-carbon double bond formed and other functionalities present in the substrates. Many reagents,[91] including metals such as Zn, Mg, and Sm, have been reported in the literature to be effective in this reaction, but most of them are associated with limitations concerning selectivity and compatibility. It has been discovered,[92] that aryl-substituted vic-dibromides undergo smooth debromination to produce the corresponding (E)-alkenes when treated with indium metal in MeOH (**Scheme II.6).**

[89] Fischer.; Sheihet,L. *J. Org. Chem*., **1998**, *63*, 393.
[90] Scheuerman,R. A.;Tumelty, D.*Tetrahedron Lett.* **2000**, *41*, 6531.
[91] Chan, T. H.; Isaac,M. B. *Pure Appl. Chem*., **1996**, *68*, 919.
[92] Moody, C. J.Pitts,M. R. *Synlett,***1998**, *10*, 282.

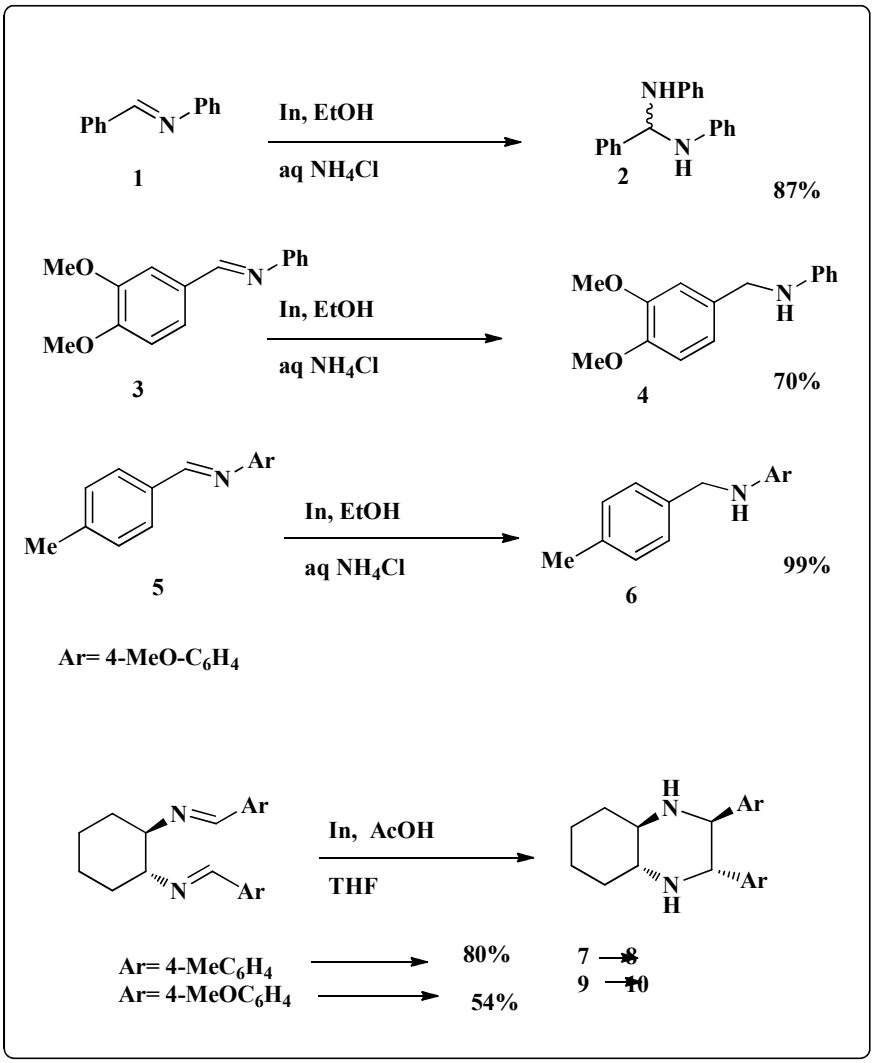


Scheme II.6

II.4.2 Reductive coupling of imines

Kalyanam and Rao. found that indium was very effective in the reductive coupling of imines (the aza-pinacol coupling) to give 1,2-diamines.[93] They are reported in the literature the treatment with indium powder in ethanolic aqueous ammonium chloride, N-benzylideneaniline gave the diamine as a mixture of (+)/(-) and meso-isomers in good yield[32]. The same product could be obtained, although a lower yield (52%) by heating aniline and benzaldehyde in the presence of indium. Attempted extension of the reaction to the imines **3** and **5** resulted in simple reduction of the C=N bond (**Scheme II.7**). However, the imine coupling reaction could be effected intramolecularly. Thus the bis-imines **7** and **8** derived from trans-1,2 diaminocyclohexane were treated with indium in THF in the presence of acetic acid, the addition of the stronger acid being based on related electrochemical coupling of imines reported by Shono et al.[94] The resulting decahydroquinoxalines **8** and **10** were formed in good yield as single diastereomers, assigned as the all-equatorial isomers (**Scheme II.7**).

[93] Ranu, B. C. ; Dutta, P.; Sarkar, A. *J. Chem. Soc., Perkin Trans. I*, **1999**, *113*, 92-140.
[94] Greene, T. W.; Wuts,P. G. M. *Protective Groups in Organic Synthesis*, 3rd Edition, John Wiley & Sons Inc., New York, **1999**



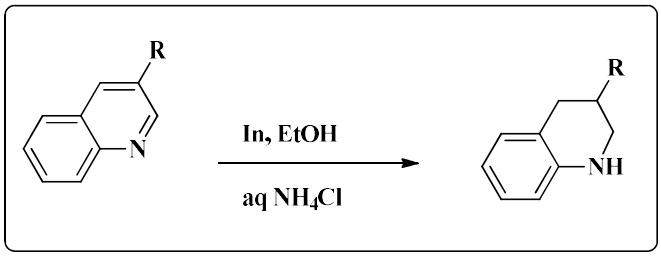
Scheme II.7

II.4.3 Reduction of benzo-fused nitrogen heterocycles

The important selective reduction of the heterocyclic ring in benzo-fused heterocyclic compounds such as quinolines and isoquinolines uses a number of methods for this transformation. This includes catalytic hydrogenation or transfer hydrogenation, alkali metals such as sodium or lithium, diborane, sodium borohydride in the presence of nickel(II) chloride, lithium triethylborohydride or sodium cyanoborohydride.[95] Resulting tetrahydro derivatives turn as useful synthetic intermediates.[96] It was determined to investigate indium use in the reduction of a range of heterocyclic compounds. The reduction of a quinolinewas carried out by simply heating the substrate with indium powder in aqueous ethanol containing ammonium chloride, and gave, after chromatography, the corresponding 1,2,3,4-

[95] Keinan, E.;Greenspoon. *in Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I.; E, W. Eds.; Pergamum, Oxford, **1991**, vol. *8*, 523.
[96] Jarowicki, K.; Kocienski,P. *J. Chem. Soc*., *Perkin Trans. I,* **2000**, 2495

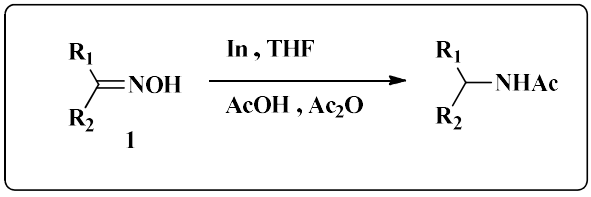
tetrahydroquinolines in a modest to good yield (**Scheme II.8**), attempts to vary the reaction conditions, for example: the use of THF–AcOH in place of aqueous systems, usually resulted in lower yields. A number of functional groups are tolerated including alkyl, aryl, alkoxy, and acetylamino. Although the yield from 6-chloroquinoline was low, and 6-aminoquinoline was recovered unchanged. 2-Chloroquinoline, in which the halide is activated was reduced to 1,2,3,4-tetrahydroquinoline in 79% yield.



Scheme II.8

II.4.4 Reduction of oximes

Oximes are one of important substrates for reduction by indium despite the fact that they are generally more resistant to reduction than imines. The oximes were either commercially available or obtained from the corresponding carbonyl compound by standard methods; in cases where the oxime was obtained as an E/Z-mixture, no attempt was made to separate such mixtures. For example: oxime **1** was therefore chosen for reduction by indium metal. The reduction was carried out by simple heating of α-oximino carbonyl compound in THF containing 4 equivalents of acetic acid and 2.5 equivalents of acetic anhydride, and a suspension of 4 equivalents of indium powder. The reactions were complete in less than 30 minutes for compounds in which the C=N bond was rendered more reactive by the presence of two carbonyl groups, and within 18 hours for monocarbonyl compounds, and gave the N-acetyl amines in a good to excellent yield (**Scheme II.9**).[97]

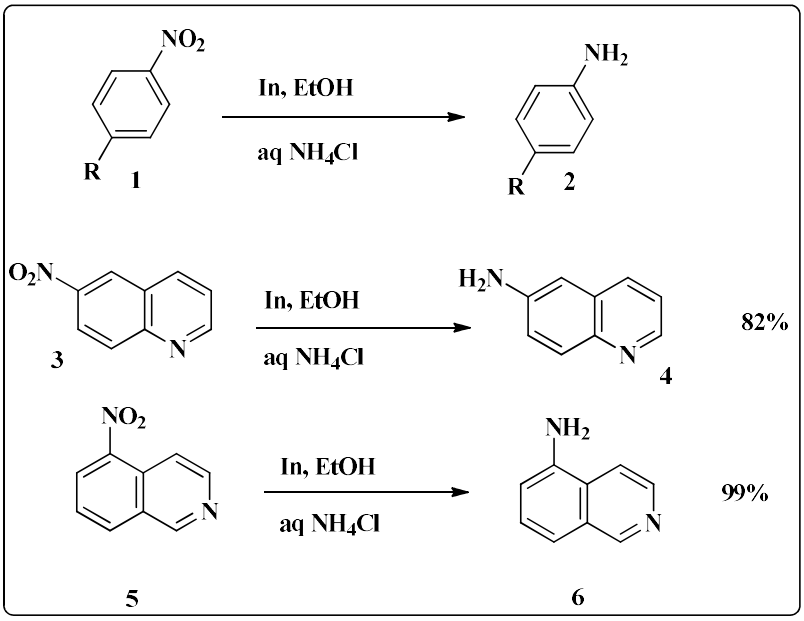


Scheme II.9

[97] E. Keinan and N. Greenspoon, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, **1991**, vol. *8*, 523.

II.4.5 Reduction of nitro compounds

The reduction of aromatic nitro compounds has been developed many methods some of them are incompatible with other functional groups in the molecule. This is a new method for the nitro group reduction continue to be developed as a search of the recent literature shows.[98] For example: the reduction of aromatic nitro compounds **1** proceeded easily on heating the substrate with indium powder in aqueous ethanolic ammonium chloride. The reactions are easy to carry out, and are usually complete within 1–3 hours. They give the corresponding aniline **2** in good to excellent yield. Other nitro compounds were also investigated. The reduction of 6-nitroquinoline **3** and 5-nitroisoquinoline **5** in 82 and 99% yield.The reduction of these nitro compounds is summarised in (**Scheme II.10).**



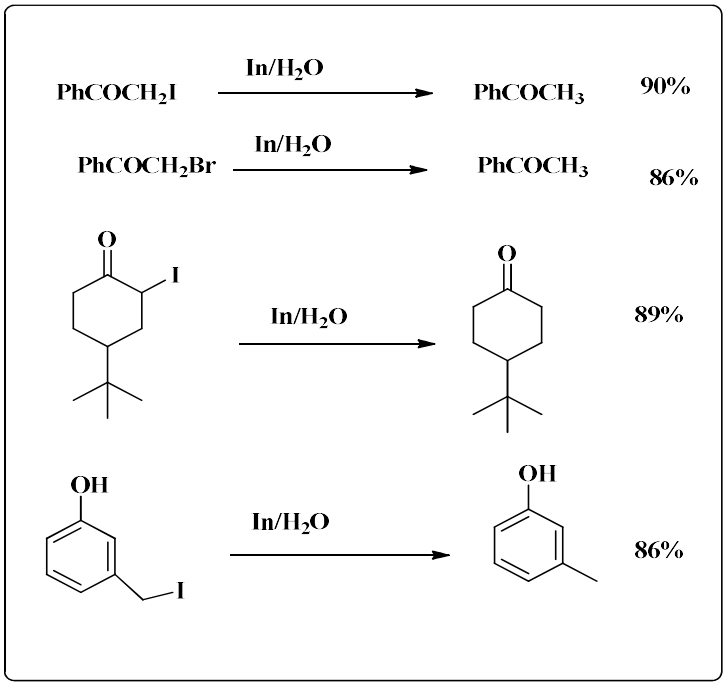
Scheme II.10

II.4.6 Reduction of α-halocarbonyl compounds and benzyl halides by In/H_2O

It was discovered that the reduction of α-halocarbonyl compounds by indium metal proceeds very efficiently in water under sonication.[99] A wide range of structurally diverse α-iodo and α-bromo ketones and esters have been reduced according to this procedure to provide the corresponding dehalogenated carbonyl compounds. The results are reported in (**Scheme II.11**). The reactions of the bromo compounds were found to be slow compared to those of the iodo compounds. The reduction of α-halocarbonyl compounds and benzyl halides

[98] Fournier, F.; Berthelot,J.; Basselier,J.-J. *Tetrahedron*, **1985**, *41*, 5667
[99] Ranu, B. C.; Dutta, P.; Sarkar,A. *J. Chem. Soc., Perkin Trans.1,* **1999**, 1139.

by indium is of great significance with regard to the potential of indium metal as a reducing agent.



Scheme II.11

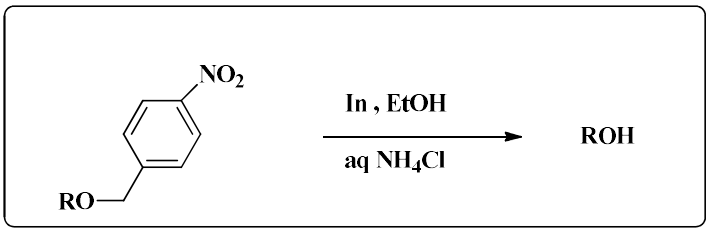
II.4.7 Deprotection of 4-nitrobenzyl ethers and esters

The 4-nitrobenzyl protecting group has seen use in the protection of alcohols, thiols, amines (as the 4-nitrobenzyl carbamates), and carboxylic acids.[100] [101] For example: 4-nitrobenzyl esters are much more stable to acidic hydrolysis than other benzyl esters, and are recommended for glutamic acid and aspartic acid side chain protection in solid-phase peptide synthesis. Such protecting groups have also seen extensive use in the β-lactam field. Methods of deprotection include: Na_2S or $Na_2S_2O_4$ reduction, catalytic hydrogenolysis, TBAF, or oxidative cleavage with alkaline hydrogen peroxide. Electrochemical methods have also been used, especially for the unmasking of alcohols, either direct electrolytic reduction, or oxidative electrolysis following initial chemical reduction of the nitro group. Despite the undoubted usefulness of the 4-nitrobenzyl protecting group, many of the methods of deprotection are not compatible with the presence of other functionality or protecting groups.

A series of alcohols, phenols and acids was protected as their corresponding 4-nitrobenzyl ethers and esters. A variety of standard methods was used for the protection step with no attempt to optimise the yields. The ethane-1,2-diol derivatives were used to explore

[100] Greene,T. W.; Wuts,P. G. M. *Protective Groups in Organic Synthesis*, 3rd Edition, John Wiley & Sons Inc., New York, **1999.**
[101] Jarowicki, K.; Kocienski,P. *J. Chem. Soc., Perkin Trans. 1*, **2000**, 2495.

the compatibility of other alcohol protecting groups. The deprotection reactions were carried out using indium metal under the usual aqueous conditions. Simple extractive work-up involving acid–base wash to remove the 4-toluidine by-product gave the deprotected material in good yield (**Scheme II.12).**[102]

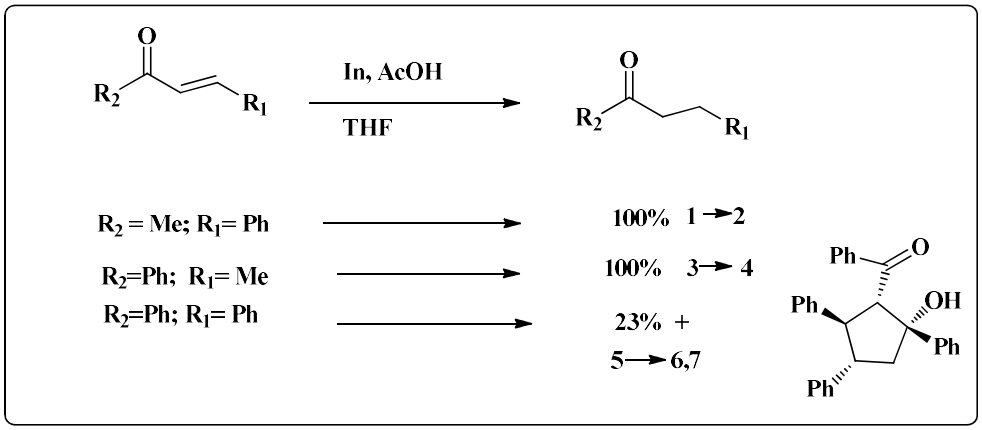


Scheme II.12

II.4.8 Reduction of conjugated alkenes

The reduction of conjugated alkenes, particularly α,β-unsaturated carbonyl compounds, was studied mostly in an organic synthesis.[103] The method of choice often involve electron transfer from appropriate metals. These have been investigated in the reduction of conjugated alkenes. The reaction was investigated using simple α, β-unsaturated ketones, and although the usual aqueous conditions were unsatisfactory, reduction using indium in THF in the presence of acetic acid was successful. Thus benzylideneacetone **1** and 1-phenylbut-2-en-1-one **3** were reduced to the corresponding ketones **2** and **4** in quantitative yield. However, when chalcone **5** was submitted to the same conditions, only 23% of the corresponding ketone **6** was formed. The major product being the cyclopentane derivative **7** (59%) formed as a single diastereomer (**Scheme II.13**). Such 'dimers' have been noted previously in the reduction of chalcone using samarium diiodide, [104] zinc [105] or electrochemistry,[106] and their stereochemistry and mechanism of formation discussed.[40] It is likely that the indium mediated reaction follows a similar pathway initiated by single electron transfer from the metal to the conjugated system.

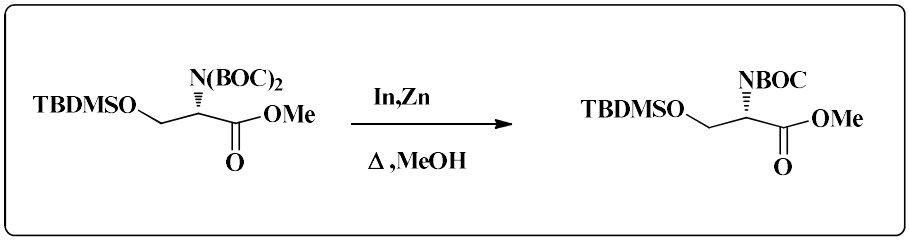
[102] Kocienski, P. J. *Protecting Groups*, Thieme, Stuttgart, **1994.**
[103] Keinan, E.; Greenspoon, N. in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, **1991**, vol. *8*, 523.
[104] Cabrera, A.; Lagadec, R. L.; Sharma, P.; Arias, J. L.; Toscano, R. A.; Velasco, L.; Gaviño, R.; Alvarez,C.; Salmón,M. *J. Chem. Soc., Perkin Trans. I,* **1998**, 3609.
[105] Mirek,J.; Gaweda,M.;Kawalek,B. *Pol. J. Chem*., **1981**, *55*, 987.
[106] Fournier,F.; Berthelot,J.; Basselier,J.-J. *Tetrahedron,* **1985**, *41*, 5667.



Scheme II.13

II.4.9 Indium mediated facile cleavage of the butoxycarbonyl group from di-*t*-butoxycarbonyl group from di-*t*-butylimidodicarbonate

They have demonstrated a novel and highly efficient protocol for the selective removal of the *t*-BOC group from N-BOC protected amides using indium or zinc metal under mild conditions. Due to its high chemoselective efficiency and simplicity, this method may find wide applications in solid-phase peptide synthesis (**Scheme II.14**).[107]



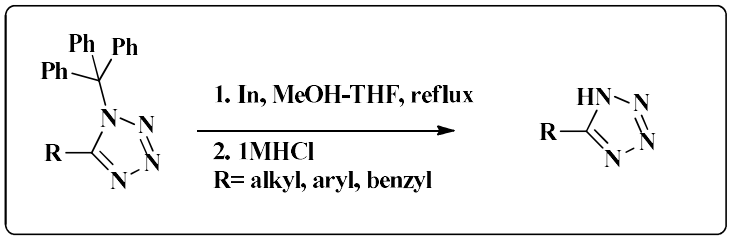
Scheme II.14

II.4.10 Reduction of trityl group from protected tetrazoles

Detritylation of tetrazole N-trityl-protected sartan derivatives to produce the free N-H bonds was carried out under different conditions: hydrogenolysis in the presence of Pt/C (5%) or with aqueous NaOH in MeOH. Surprisingly, in the last case, the removal took place without any side reaction and in excellent yields. Our research group has already reported the removal of the trityl unit in different functional groups using an arene catalyzed lithiation all those reactions performed at -78^{0}C in excellent yields.[3] In the course of developing deprotection methods of any protecting group, they attempt to remove the trityl unit using different electron transfer sources, Such as lithium, sodium, samarium, and indium (**Scheme**

[107] Yadav, J. S.; Reddy, B. V. S.; Reddy, K.S.; Reddy, K.B. *Tetrahedron Lett*. **2002**, *43,* 1549.

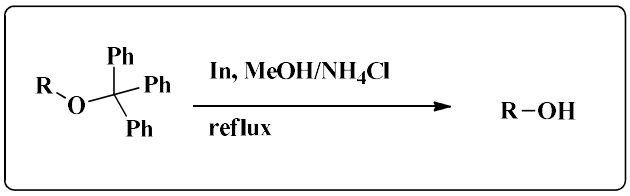
II.15). Present a very efficient method for detritylation of protected tetrazole using indium as electron source.[108]



Scheme II.15

II.4.11 Reduction of trityl groups from protected alcohol

The reduction of primary, secondary, allylic and benzylic trityl ethers using indium powder in MeOH/NH_4Cl led to produce the trityl-oxygen bond, gave the corresponding alcohols in good to excellent yield under very mild reaction conditions. The detritylation process could successfully be extended to mono and detritylation diols this methodology represents a new and efficient detritylation procedure under mild reaction condition (**SchemeII.16**).[109]



Scheme II.16

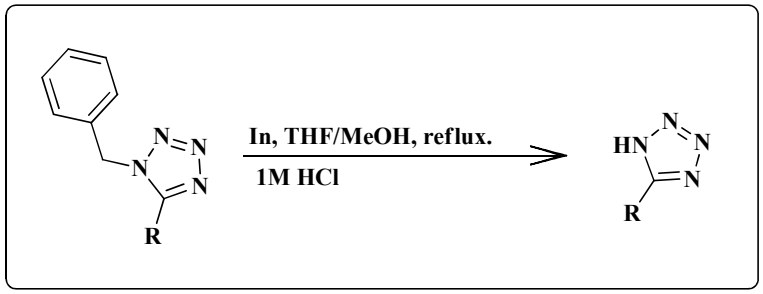
II.5 Objective

The N-benzyl (Bn) group has been sparingly utilized as a protecting group for nitrogen containing heterocycles. The small number of procedures available for debenzylation may be the reason for the synthetic chemist's aversion to its use. The most common method of removal is through the use of hydrogenolysis. Recently, indium has been demonstrated to be an efficient and promising metal to mediate organic reactions in aqueous media.[110] The

[108] Behloul.; Bouchelouch, K.; Guijarro, D.;Foubelo, F.;Nàjera, C.;Yus,M.*synlett,* **2015**, 2399.
[109] Behloul.; Chouti, A.;Guijarro, D.;Foubelo, F.; Nàjera, C.; Yus, M.*tetrahedron,* **2016**, 2399.
[110] (a) Loh, T. P.; Chua, G. L. *Chem. Commun.***2006**, 2739. (b) Cintas, P. *Synlett,* **1995**, 1087. (c) Podlech, J.; Maier, T. C. *Synthesis,* **2003**, 633. (d) Nair, V.; Ros, S.; Jayan; C, N.; Pillai, B. S. *Tetrahedron,* **2004**, 60, 1959. (e) Ranu, B. C. *Eur. J. Org.Chem.* **2000**, 2347. (f) Auge, J.; LubinGermain, N.; Uziel, J. *Synthesis,* **2007**, 1739.

utilization of indium species as radical initiator via SET (single electron transfer) process in several organic transformations has been reported by Naito et al.[111,112]

The application of indium metal reductive removal of the benzyl group from the nitrogen atom of several protected tetrazoles under mild reaction conditions is discussed below (**Equation 1**).



Equation1

II.6 Results and discussion

The aim of determining the best reaction conditions for the removal of the benzyl group bonded to the nitrogen in different tetrazoles, we took 5-phenyl-1-benzyl-1Htetrazole (1a) as the model compound. Unfortunately, no reaction occurred when tetrazole **1a** was treated with indium metal (1:1 molar ratio) in a mixture of MeOH and THF (2:1 volume ratio) at 0 ºC for 24 h. However, total conversion was observed when this reaction mixture was heated at reflux temperature for 20 h, 5-phenyl-1H-tetrazole **2a** being isolated in 95% yield after column chromatography purification (**Table II.2, entry 1**). In absence of indium the cleavage did not take place under the same reaction conditions. On the other hand, indium was partially consumed during the reaction, before the acidic hydrolysis. In order to broaden the scope of this indium-mediated debenzylation, we applied the same reaction conditions to different 5-substituted tetrazoles. Debenzylation of tetrazoles benzylic (1b and 1d) substituents at 5-position occurred also in high yields (**Table II.2**, entries 2,

[111] (a) Miyabe, H.; Naito, T. *Org. Biomol. Chem*. **2004**, *2*, 1267. (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron,* **2004**, *60*, 4227. (c) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.***2002**, *4*, 131. (d) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun. 2002*, 1454. (e) Huang, T.; Keh, C. C. K.; Li, C. *J. Chem. Commun*. **2002**, 2440. (f) Sugi, M.; Sakuma, D.; Togo, H. *J. Org. Chem*. **2003**, *68*, 7629. (g) Jang, D. O.; Cho, D. H. *Synlett,***2002**, 631. (h) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Chem. Eur. J*. **2008**, *14*, 1875. (i) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett*. **2003**, *5*, 3835. (j) Shen, Z. L.; Loh, T. P. *Org. Lett*. **2007**, *9*, 5413.

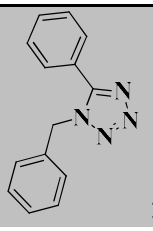
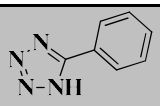
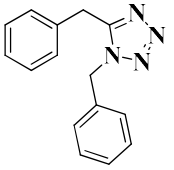
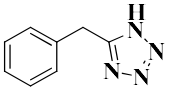
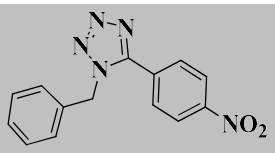
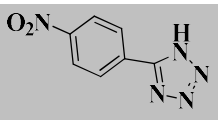
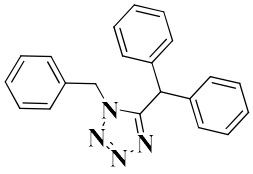
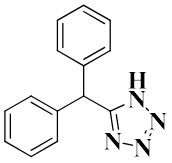
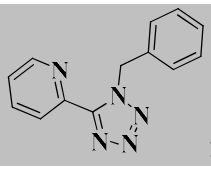
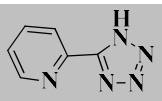
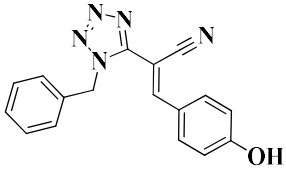
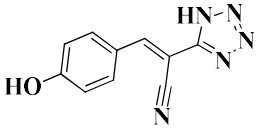
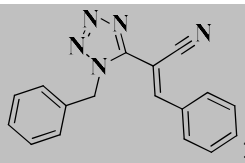
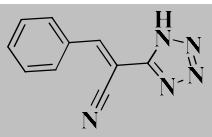
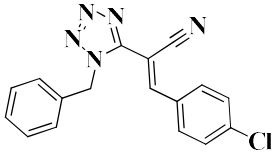
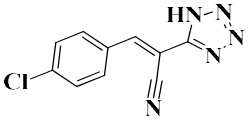
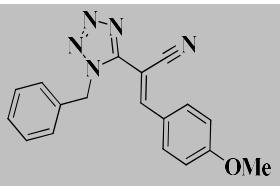
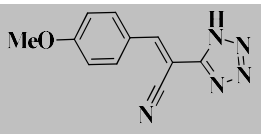
[112] (a)Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett*. **2002**, *43*, 4585. (b) Yanada, R.; Obika, S.; Nishimori, N.; Yamauchi, M.; Takemotoa, Y. *Tetrahedron Lett*. **2004**, *45*, 2331. (c) Bhatti, N. H.; Salter, M. M. *Tetrahedron Lett*. **2004**, *45*, 8379. (d) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2007**, *47*, 2859. (e) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem*. **2004**, *69*, 2417.

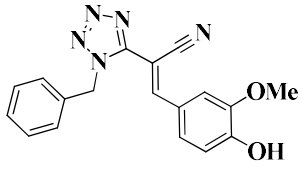
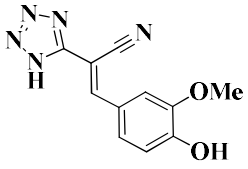
4,).Heteroaromatic2-pyridyl substituent at 5-position gave 5-(2-pyridyl)-1H-tetrazole (2e) in 88% yield (**Table II.2, entry 5**).

Treatment of benzyl tetrazole in the presence of a double bond and nitrile with the same reaction conditions afforded the corresponding deprotected tetrazoles in moderate yields without affecting the double bond and reduction of nitrile (entries 6–10).

The progress of the reactions was monitored in all cases by TLC. Once the reaction went to completion, final hydrolysis with 1M HCl led to the corresponding tetrazoles **2**. After hydrolysis, benzyl and the tetrazoles products were extracted together with EtOAc and then easily separated by column chromatography. The starting Bn-tetrazoles **1** were prepared by reaction of the corresponding tetrazole **2** with benzyl bromide in the presence of Carbonate de potassium. All of these compounds were characterised by comparison of their physical and spectroscopic data with authentic samples.

Table II.2. Indium-Mediated Cleavage of the Benzyl Group from Protected 1H-Tetrazoles.

Entry	Substrate	Time(h)	Product	Yield(%)
1	 1a	20		95
2	 1b	20		80
3	 1c	20		76
4	 1d	20		80
5	 1e	20		88
6	 1f	20		50
7	 1g	20		60
8	 1h	20		51
9	 1i	20		55

10		1j	20		53

❖ **Mechanistic study**

Concerning a possible reaction mechanism, we presume that a single electron transfer (SET) takes place from the metal to the starting tetrazole **1** cleaving the benzyl–nitrogen bond to give a benzyl radical **I** and the heterocyclic anion **II**, both stabilized by delocalization (**Figure II.1**). Benzyl radical **I** decomposes by a hydrogen atom abstraction to give toluene,[113] mean while the hydrolysis of heterocyclic anion **II** leads to the formation of deprotected tetrazole **2**. A similar mechanism could be also involved in the detritylation of protected tetrazoles.[114]

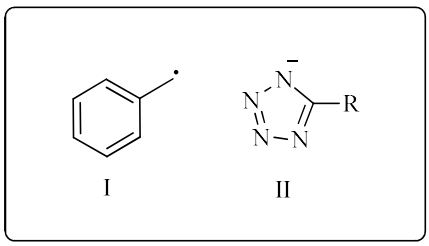


Figure II.1

II.7 Conclusion

These studies have shown that indium metal can mediate a range of synthetically useful, selective reductions. The reactions are usually high yielding, are easy to carry out, usually avoiding the need for exclusion of air or moisture or any other special precautions, and involve simple work-up and product isolation.

[113] Boyle, W. J.; Bunnett, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 1418.
[114] (a) Yus, M.; Behloul, C.; Guijarro, D. *Synthesis,***2003**, 2179. (b) Behloul, C.; Guijarro, D.; Yus, M. *Synthesis,* **2004**, 1274. (c) Behloul, C.; Bouchelouche, K.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis,* **2014**, *46*, 2065. (d) Behloul, C.; Bouchelouche, K.; Guijarro, D.; Foubelo, F.; Nájera, C.; Yus, M. *Synlett,* **2015**, *26*, 2399. (e) Behloul, C.; Bouchelouche, K.; Hadji, Y.; Benseghir, S.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis,***2016**, *48*, 2455. (f) Behloul, C.; Chouti, A.; Guijarro, D.; Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron,* **2016**, *72*, 7937. (g) Behloul, C.; Chouti, A.; Chabour, I.; Bey, H. B.; Guijarro, D.; Foubelo, F.; Nájera, C.; Yus, M. *Tetrahedron Lett.* **2016**, *57*, 3526.

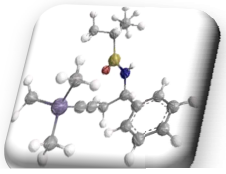
II.8 Experimental part

II.8.1 General procedure

A mixture of the corresponding tetrazole 2 (0.1 mmol) and indium powder (58 mg, 0.5 mmol) in MeOH (6 mL) and THF (4 mL) was refluxed until the starting material disappeared (20 h). After cooling at rt. 1M HCl (0.5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and evaporated (15 Torr).The resulting residue was recrystallized to give pure products **2**, which were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2**.

ChapterIII

Reductive removal of the benzyleprotecting group from tetrazoles by zinc metal



III.1 Introduction

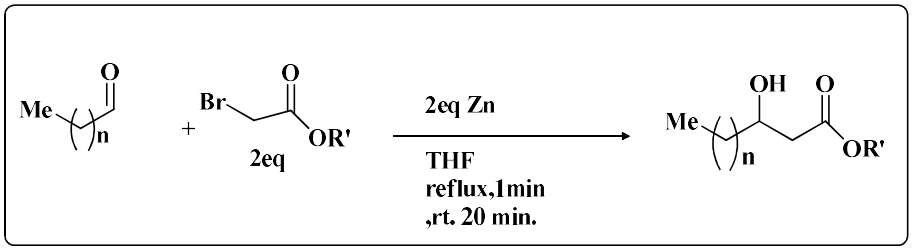
The **24**th most abundant element in the earth's crust is zinc. Since the discovery of pure zinc metal in the **18**th century, the basic application of zinc metal is as materials. Because zinc salts are abundant, cheap, non-toxic, and exhibit environmentally benign properties, organic chemists have been interested in using zinc salts as catalysts in organic synthesis during the last three decades.[115]

III.2 Zinc as catalyst in organic chemistry

III.2.1The reformetsky reaction

The converting of α-haloester and an aldehyde or ketone to a β-hydroxyester using zinc metal followed by an acid work-up is called the Reformatsky Reaction. The reaction starts with oxidative addition of the zinc metal to the carbon-halogen bond of the α-haloester. Two of the resulting compounds coordinate together forming a dimer, which then undergoes a rearrangement to give two molecules of O-zinc emulates. The oxygen of the aldehyde or ketone reagent then coordinates to the zinc and another rearrangement follow by the two reagents with a carbon-carbon bond. An acid work-up then cleaves the zinc-oxygen bond to give the final β-hydroxyester product and a zinc(II) salt.[116]

Sailer et al. they use reformatsky reaction for the preparation of the medium-chain-length β-hydroxy esters in good yield. From this work, it will be used as the basis for more investigation of hydroxyalkanoate polymers as potential feedstock for biofuel production. (**Scheme III.1).**



Scheme III.1

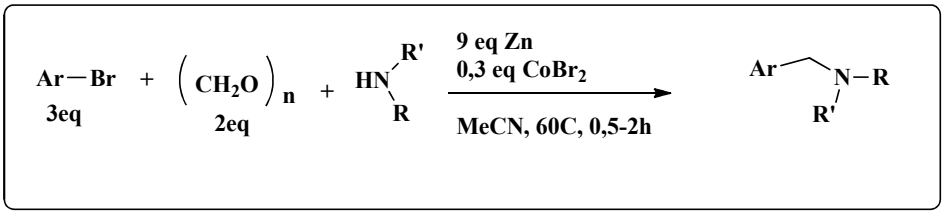
III.2.2 Mannich reaction

Mannich reaction is a condensation of an amine and an enolizable carbonyl compounds reacts to give some amino methylated products. This reaction is also called amino

[115] Mann, J. B.; Meek, T. L.; Allen, L. C. *J. Am. Chem. Soc.* **2000**, *122*, 2780.
[116] Reformatsky, S. Ber. Dtsch. *Chem. Ges.***1887**, *20*, 1210–1211.

alkylation. The product obtained in this reaction is α -amino carbonyl compound which is also called Mannich base.

Three-component mannich reaction of aromatic halides, amines, and paraformaldehyde. This procedure, which involves the formation *insitu* of arylzinc reagents. This allows the straightforward synthesis of a range of functionalized tertiary benzylamines(**Scheme III.2).**[117]

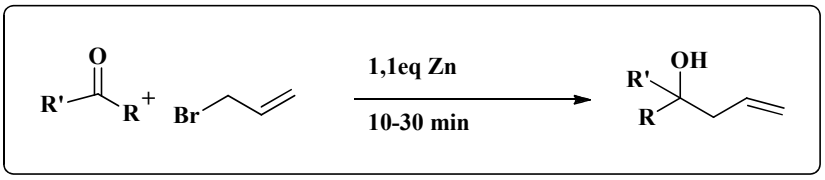


Scheme III.2

III.2.3 Barbier type reaction

The Barbier reaction is an organic reaction between an alkyl halide and a carbonyl group as an electrophilic substrate in the presence of magnesium, aluminium, zinc, indium, tin or its salts. The reaction product is a primary, secondary or tertiary alcohol. The reaction is similar to the Grignard reaction but the critical difference is that the Barbier reaction is a one pot synthesis when a Grignard reagent is prepared separately before addition of the carbonyl compound.

Wang et al. describe a rapid and efficient procedure for the solvent free synthesis of homoallylic and homopropargyl alcohols has been achieved by Zinc –mediated barbier-type reaction of carbonyl compounds at room temperature (**Scheme III.3).**[118]



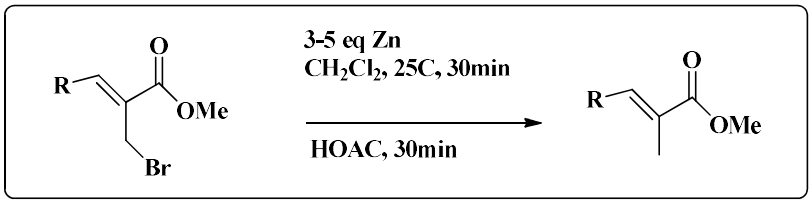
Scheme III.3

[117] Le Gall,E.; Decompte, A.; Martens, T.; Troupel,M.*Synthesis*, **2010**, 249.
[118] Wang, J-I.; Jia, X.; Meng,T.; Xina,L. *Synthesis,***2005**, *17*, 2838.

III.3 Zinc as reduction agents

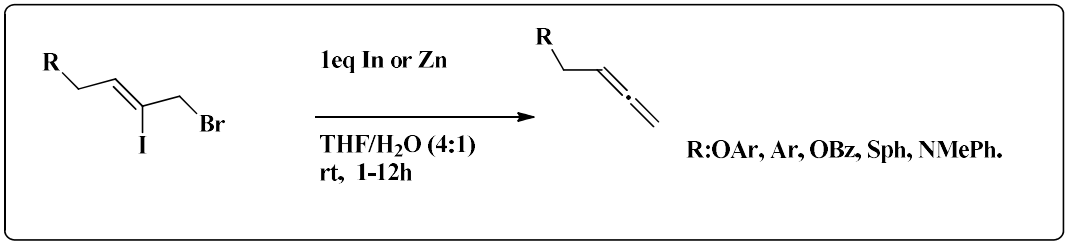
III.3.1 Reduction of halides

Alkyl and alkenyl halides are easily reduced with zinc under several reaction conditions. Allylic bromides can be reduced to the corresponding olefins by a number of methods, including simple and inexpensive reaction conditions employing metallic zinc in acidic medium. For example: (E)-2-Methylacrylates are prepared in good yield and high stereoselectivity by zinc favored reduction of 2-(bromomethyl)alkenoates derived from Baylis–Hillman adducts (**Scheme III.4).**[119]



Scheme III.4

Lin et al. prepared various allenylmethyl arylether and monosubstituted allenes dehalogenation reactions of vicinal dihalides in an aqueous solvent, using zinc or indium the yield between good to excellent (**Scheme III.5).**[120]



Scheme III.5

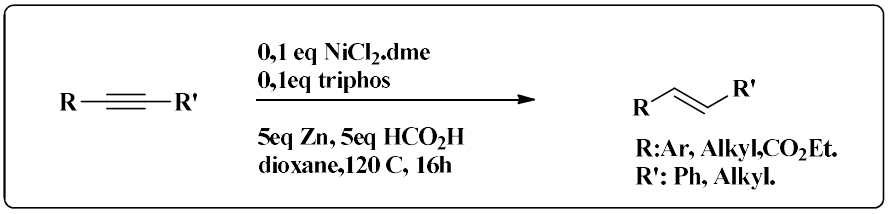
III.3.2 Reduction of defluorination

The reductive defluorination of perfluoroarenes is a potentially favourable process to partially fluorinated arenes wich are valuable starting compounds for synthesis but significantly less accessible than perfluoroarenes. They have found that aqueous ammonia is a good medium permiting the selective reductive defluorination of polyfluoroarenes functional derivatives by zinc at room temperature.[121]

[119] Fernandes, L. Bortoluzzi, A.J.; Sa,M.M.*Tetrahedron,***2004**, *60*, 9983
[120] Lin, M.-H.; Hung, S.-F.; Lin, L.-Z.; Tsai, W.-S.; Chuang, T.-H. *J. Org. Chem*. **2011**, *76*, 8518.
[121] Laev, S. S.; Shteingarts,V.D.*Journal of fluorine chemistry*. **1998**, *91*, 21.

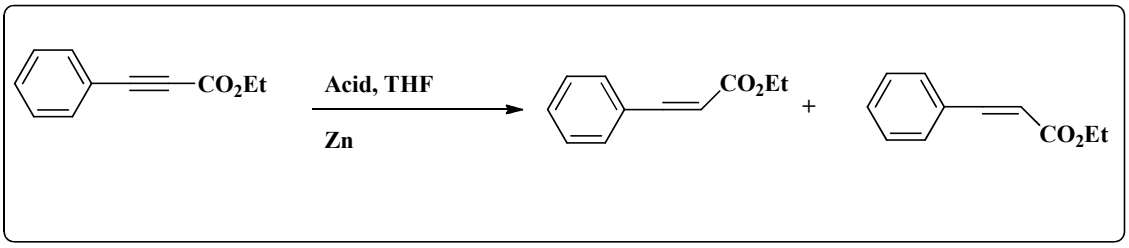
III.3.3 Reduction of alkyne to alkenes

A nickel-catalyzed can be used to both internal and terminal alkynes using formic acid and Zn as the terminal reductants has been developed. In the case of internal alkynes, the (E)- or (Z)-olefin isomer can be reached selectively under the same reaction conditions by including of a triphos ligand(**Scheme III.6).**[122]



Scheme III.6

The reduction of ethyl phenylpropiolate to the corresponding cinnamate ester can be stereochemically controlled by changing the proton source in the reaction in dissolving zinc metal process. The results of this study, however, cannot be understood.[123] (**Scheme III.7).**



Scheme III.7

III.3.4 Reduction of nitro group

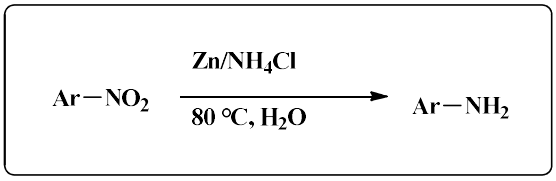
There are a diversity of methods for the reduction of nitro compounds reported in the literature; the most popular being catalytic hydrogenation [124] and metal-mediated reduction.[125] Conventional reductions nitroarenes using zinc metal need an organic solvent, corrosive reagents such as NH_3, conc. HCl, aq. NaOH, high temperatures, prolonged reaction times and moreover use substantial amounts of zinc metal. Although reduction in an aqueous medium employing 7.25 equiv of Zn at 80 °C was reported recently.[126]

The reduction of nitroarenes to the corresponding amines is an important transformation since many aromatic amines exhibit biological activities and find a multitude

[122] Schabel, T.; Belger, Ch.;Plietker,B. *Org. Lett*. **2013**, *44*, 2858.
[123] Kaufman, D.; Johnson, E.; Mosher,M. D. *Tetrahedron Letters*. **2005**, *46*, 5613.
[124] Tafesh, A. M.; Weiguny, *J. Chem. Rev*. **1996**, *96*, 2035–2052.
[125] (a) Martin, E. L. *Org. Synth*. **1943**, Coll. Vol. II, 501–503; (b) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem*. **2001**, *66*, 919–924; (c) Brady, E. D.; Clark, D. L.; Keogh, D. W.; Scott, B. L.; Watkin, J. G. *J. Am. Chem. Soc*. **2002**, *124*, 7007–7015; (d) Moody, C. J.; Pitts, M. R. *Synlett*,**1998**, 1028.
[126] Tsukinoki, T.; Tsuzuki, H. *Green Chem*. **2001**, *3*, 37–38.

of industrial applications, these include being intermediates for the synthesis of dyes, pharmaceuticals, and agricultural chemicals.

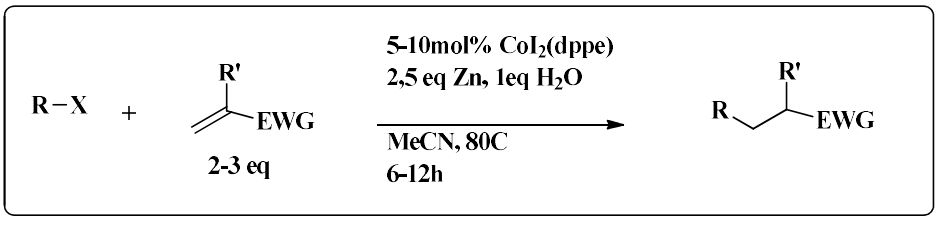
The reduction of Nitroarenes to the corresponding anilines using zinc metal and NH_4Cl in water without any organic solvent at 80 °C with a simple procedure at low cost, in high yields. The process is strong enough to reduce sterically hindered 2,6-dimethylnitrobenzene and is chemoselective for nitro groups; ester, amide and halide substituents on aromatic rings are unaffected[127](**Scheme III.8).**



Scheme III.8

III.3.5 Reduction coupling

The reduction coupling reaction of alkyl halides with electron-withdrawing alkenes (CH_2 =CR_1EWG, EWG) electron-withdrawing group) in the presence of water and zinc powder in acetonitrile, catalyzed by cobalt to give the corresponding Michael-type addition product (RCH_2, CR_1EWG). The methodology is pliable such that unactivated primary, secondary, and tertiary alkyl bromides and iodides and various conjugated alkenes including acrylates, acrylonitrile, methyl vinyl ketone, and vinylsulfone all successfully participate in this coupling reaction. For the alkyl halides used in the reaction, the iodides generally gave better yields compared to those of the corresponding bromides. It is a unique method employing CoI_2dppe, zinc, and alkyl halides, affording conjugate addition products in high yields. Mechanistically, the reaction appears to follow an oxidative addition driven route rather than the previously reported radical route[128] (**Scheme III.9).**

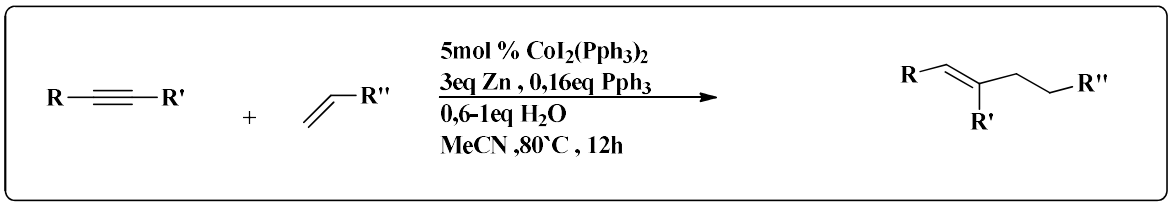


Scheme III.9

[127] Schabel, T.; Belger, Ch.;Plietker,B. *Org. Lett*. **2013**, *44*, 2858.
[128] Shukla, P.; Hsu, Y-Ch.; Cheng,Ch-H.*J. Org. Chem*. **2006**, *71*, 655.

III.3.6 Reduction coupling of alkynes with alkenes

The systems of Cobalt/Zn indeed catalyze the reductive coupling of activated alkenes with alkynes in the presence of water to give substituted alkenes with very high regio- and stereoselectivity in excellent yields. Whereas the intermolecular reaction of acrylates, acrylonitriles, and vinyl sulfones with alkynes takes place in the presence of $CoI_2(PPh_3)_2$/Zn, the reaction of enones and enals with alkynes requires the use of the CoI_2 (dppe)/Zn/ZnI_2 system. The intramolecular reductive coupling of activated alkenes (enones, enals, acrylates, and acrylonitriles) with alkynes also works efficiently. Furthermore, a variety of cyclic lactones and lactams were prepared using this methodology. Possible mechanistic pathways are proposed based on a deuterium-labeling experiment carried out in the presence of D_2O.[129] (**Scheme III.10).**

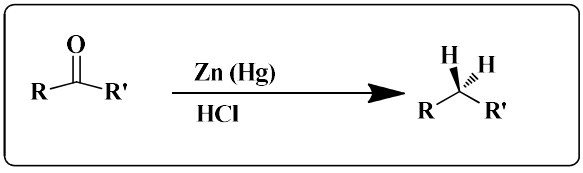


Scheme III.10

III.3.7 Clemensen reduction

The reduction of ketones to the corresponding alkanes using amalgamated zinc and hydrochloric acid has been widely employed in organic synthesis, and as a degradative step in structure elucidation, since clemmensen reported the reaction in 1913 (**Scheme III.11).**

The reduction of aldehyde or ketone to an alkane is called by Clemmensen reduction using amalgamated zinc and hydrochloric acid. The mechanism for it is not yet fully understood and there are two popular proposals. The "Carbanionic mechanism", where the zinc attacks the protonated carbonyl directly, and the "Carbenoid mechanism", which is a radical process and the reduction happens on the surface of the zinc metal.[130]

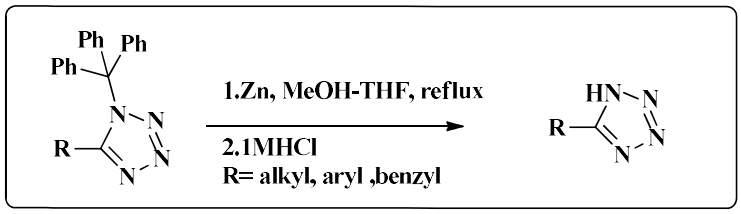


Scheme III.11

[129] Chang, H-T.; Jayanth, T.T.; Wang, Ch-Ch.; Cheng,Ch-H. *J.Am. Chem. Soc*. **2007**, *129*, 12.
[130] (a)Clemmensen, E. *Ber. Dtsch. Chem. Ges*. **1913**, *46*, 1837; (b) Clemmensen, E. *Ber. Dtsch. Chem. Ges*. **1914**, *47*, 51.; (c) Clemmensen, E. *Ber. Dtsch. Chem. Ges*. **1914**, *47*, 681.

III.3.8 Reduction of tetrazoles using zinc

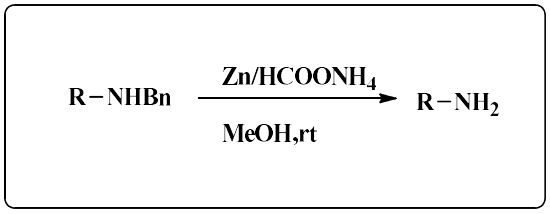
Behloul et al. described a practical and low-cost method for the detritylation of 1-titryltetrazoles using zinc in methanol .This procedure is versatile and efficient in the deprotection of several protected tetrazoles bearing aliphatic, aromatic, and heteroaromatic substituents, as well as some functional groups, without decomposition of the tetrazole ring[131] (**Scheme III.12).**



Scheme III.12

III.3.9 Reduction of benzyl group

Gorwda chenne et al. describe a selective deprotection of several N-Bzl amino derivatives to the corresponding amines with ammonium formate and commercial zinc dust. Many other reducible or hydrogenolysable substituents such as halogens, methoxy, phenol, ester, acid, ethene, and Boc groups are unaffected (**Scheme III.13).**[132]



Scheme III.13

III.4 Objective

The use of metals such zinc,[133] and indium[134]as catalysts for the transfer reduction reactions was reported from our laboratory. The utility of Zinc as low-cost metal for the selective hydrogenolysis of some commonly used trityle tetrazoles synthesis was also reported.

There are no reports on the use of other low-cost metal as catalyst for the transfer hydrogenolysis of N-Bzl derivatives.

[131] Behloul, C.; Bouchelouche,K.; Hadjia, Y.; Benseghira, S.; Najera, C.; Yus, M. *Synthesis,* **2016**, *48*, 2455.
[132] Srinivasa, G. R.; Narendra Babu, S. N.; Lakshmi,C.; Channe Gowda,D. *Synthetic Comunications,* **2004**, *34*, 1831
[133] Behloul, C.; Bouchelouche,K.; Hadjia, Y.; Benseghira, S.; Najera, C.; Yus, M. *Synthesis,***2016**, *48*, 2455.
[134] Behloul, C.; Bouchelouche, K.; Guijarro, D.; Najera, C.; Yus, M. *Synthesis*, **2014**, 2065.

In this context, we wish to report the conventional hydrogenolysis of N-Bzl derivatives by using zinc dust and acetic acid in THF (**Scheme III.14**).

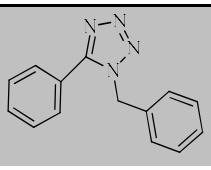
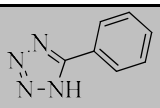
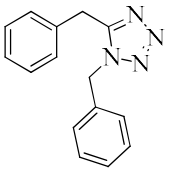
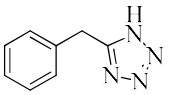
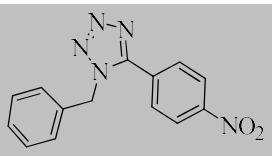
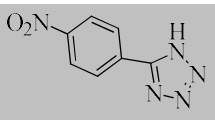
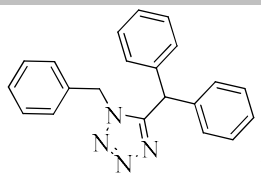
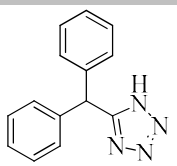
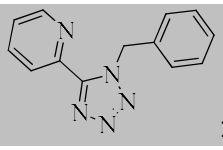
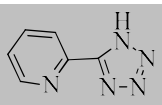
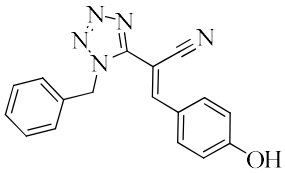
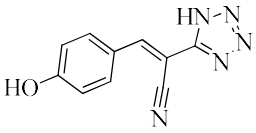
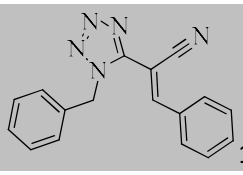
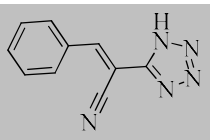
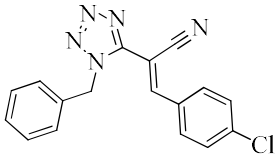
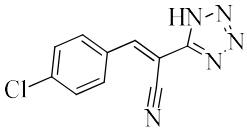
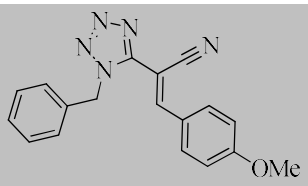
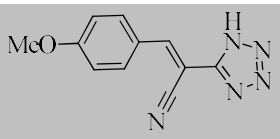
Scheme III.14

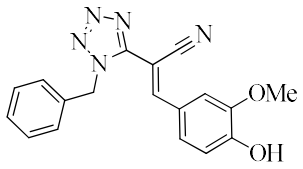
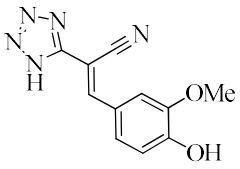
III.5 Results and discussion

Our results are shown in (**Table III.1)**, in a typical procedure, reaction is initiated by addition of zinc dust to a solution of the benzyle tetrazole in acetic acid /THF.

The reaction following by TLC they take from 1-4h (entries 1–5). In the presence of a double bond and nitrile with the same reaction conditions afforded the corresponding deprotected tetrazoles in moderate yields without affecting the double bond and reduction of nitrile (entries 6–10). The reactions were subjected to an aqueous workup and the crude products were purified by recrystallization. All of these compounds were characterised by comparison of their physical and spectroscopic data with authentic samples.

Table III.1: Zinc promoted an efficient and facile debenzylation of protected tetrazoles

Entry	Substrate	Time(h)	Product	Field(%)
1	 1a	2		88
2	 1b	2		87
3	 1c	2		80
4	 1d	2		84
5	 1e	2		88
6	 1f	3		60
7	 1g	3		64
8	 1h	3		68
9	 1i	3		58

10		1j	3		61

III.6 Conclusion

We have demonstrated the zinc-mediated smooth reduction of Benzyl tetrazoles to their corresponding in the presence of Acetic acid, the advantages include a safe reaction medium, high selectivity, low reaction time, easy product isolation.

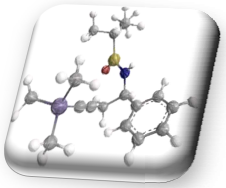
III.7 Experimental part

III.7.1 General procedure for the zinc-promoted debenzylation of tetrazoles 1

To a stirred solution of the corresponding tetrazole **1** (2.5 mmol) in THF (1.0 mL) at rt. zinc dust (5 mmol) was added and stirring was continued for 30 additional minutes. The resulting suspension was cooled with an ice-water bath and glacial acetic acid (1.0 mL) was added slowly. The cooling bath was removed and the final mixture was stirred for further 1-3 hours and then filtered. The collected solids were washed with H_2O (3 × 10 mL) and CH_2Cl_2 (3 × 15 mL). The organic phase was separated, washed with H_2O (2 × 10 mL), sat $NaHCO_3$ (3 × 10 mL) and brine (3 × 15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure (15 Torr). The resulting residue was purified by recrystallization to give pure compounds **2**, which were characterized by comparison of their physical and spectroscopic data with pure samples of **2**.

ChapterIV

Magnesium-promoted debenzylation of tetrazoles



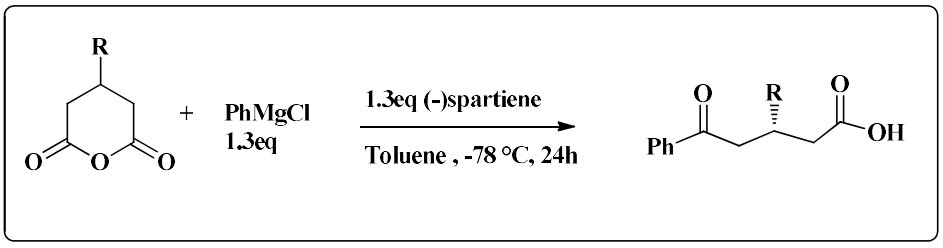
IV.1 Introduction

Magnesium is found linked as carbonates, silicates, chlorides, sulphates and different oxides (natural abundance = 2%) in the earth's crust. The water concentration of magnesium averages1.3mg/L.[135] Magnesium cations take part in various biological processes. The produce of organomagnesium compounds was first reported in 1859. After that several essay were made to prepare dialkyl magnesium compounds and investigate their reactivity (in 1900), their synthetic potential as he was working on the optimization of the Barbier reaction.[136]

IV.2 Magnesium as catalyse in organic chemistry

IV.2.1 Grignard reaction

The addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol. Grignard Reagents are also used in the following important reactions: The addition of an excess of a Grignard reagent to an ester or lactone gives a tertiary alcohol in which two alkyl groups are the same, and the addition of a Grignard reagent to a nitrile produces an unsymmetrical ketone via a metalloimine intermediate. They have reported that (-)-sparteine-bound Grignard reagents effectively desymmetrizecyclic anhydrides to make ketoacids in very good enantiomeric excess (**Scheme IV.1).**[137]



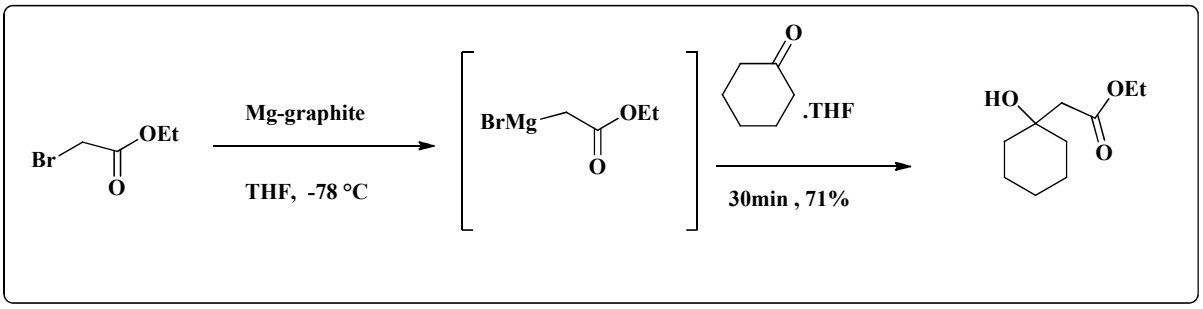
Scheme IV.1

[135] Dudev, T.; Lim, C. *Chem. Rev.* **2003**, *103*, 773.
[136] Grignard, V. *Compt. Rend. Acad. Sci.* **1900**, *130*, 1322.
[137] a) Willis,M. C. *J. Chem. Soc. Perkin Trans. I.* **1999**, 1765; b) Lo,T.-L. Symmetry: *A Basis for Synthesis Design*, Wiley-Interscience, New York, **1995**, chap. 1.3; c) Magnuson,S. R. *Tetrahedron,* **1995**, *51*, 2167.

IV.2.2 Reforematsky reaction

Magnesio-reformatsky reaction are similar to Grignard preparations, employing magnesium instead of Zinc, were essentially limited to bromo-*t*-butyl ester, and bromo arylacetamides, as in Grignard reaction, self-condition is an undesirable side reaction. This disadvantage can be up by the extraordinary reactivity of zinc/silver-graphite. Importantly, magnesio-reformatsky reactions can be also carried out with magnesium–graphite.[138]

The metal has high reactivity reagent permits reactions with ethyl α-halogens alkanoates, at -78°C to give the corresponding magnesio-ester enolate, which can react with a variety of substrates (**Scheme IV.2**). In general, yields are moderate to good, although lower than those of classical reformatsky reactions using activated zinc.



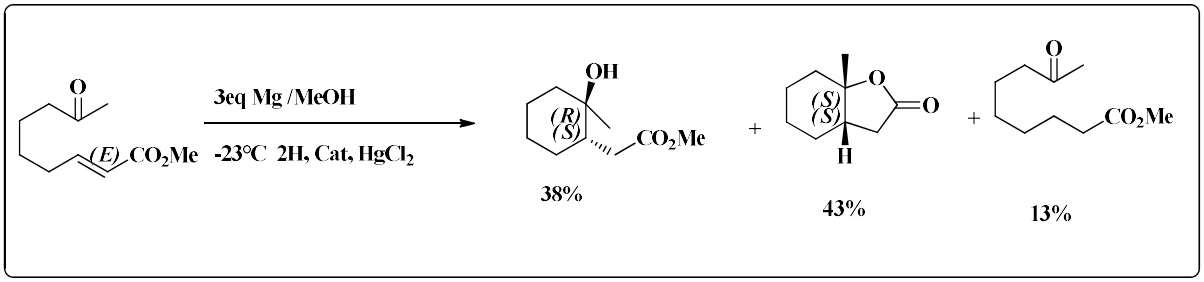
Scheme IV.2

IV.3 Magnesium as reduction agents

IV.3.1 Reductive Cyclization

The intramolecular addition of carbon radical to multiple bonds by radical cyclization have been demonstrated as useful implement in organic synthesis.[139] The cyclization reaction of ketones tied to α,β-unsaturated esters proceeded slowly when the substrates were treated with 3 equiv of magnesium in dry methanol in the presence of a catalytic amount of $HgCl_2$ at -23°C for 3h (**Scheme IV.3**). The cyclization gave mixtures of *trans* and *cis*-isomers in excellent yields along with trace amounts of simple reduction products.

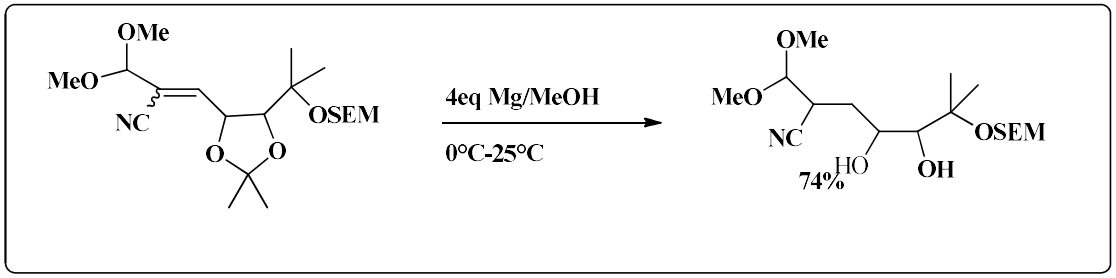
[138] Cintas,Ac*tivated metals in organic synthesis,* **1993.**
[139] Curran, D. P.; Poter, N. A.;Giese, B. *Stereochemistry of Radical Reactions*: concepts, guidelines, and synthetic application; VCH, Weinheim; **1995** pp. 23-101.



Scheme IV.3

IV.3.2 Reductive Cleavage

Kandil *et al*, describe the use of Mg/MeOH for reduction cleavage, in the course of the synthesis of aggregation pheramone (+)-lineatin.[140] Unexpected reductive cleavage of the dioxolanyl group was observed in trying to reduce the olefinic double bond of an α,β-unsaturated nitrile. Probably reductive cleavage first gave β,γ-unsaturated nirile, which was thereafter isomerized into α,β-unsaturated nitrile after having been catalyzed with Mg (OMe). Then the conjugated double bond was further reduced to afford the saturated product (**Scheme IV.4**).

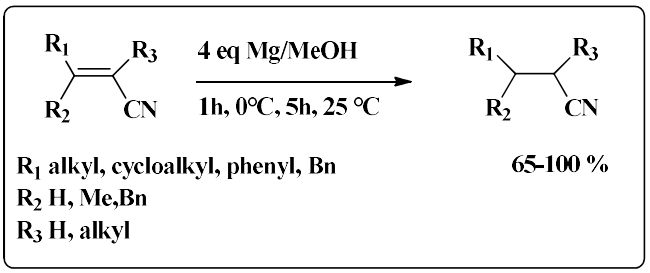


Scheme IV.4

IV.3.3 Conjugated Double Bond Reduction

The reduction of conjugated double bond of α,β- unsaturated ketone using Mg has reported in 1929by Zechmeister and Rom.[141] In 1973 another investigation reported the first employment for the reduction of α,β-unsaturated nitrile to its saturated analogue.[142] Soon after reduction of several α,β-unsaturated nitriles with excess amounts of Mg (40 equiv) in MeOH at room temperature a number of different types of α,β-unsaturated nitriles were reduced in high yields (**Scheme IV.5**).[143]

[140] Kandil, A. A.;Slessor,K.N. *J. Org. Chem*. **1985**, *50*, 5649.
[141] (c) Zechmeister, L.; Rom, P. J. *LiebigsAnn. Chem.* **1929**, *486*, 117.
[142] (a) Corey, E. J.; Watt, D. S. *J. Am. Chem.* Soc. **1973**, *95*, 2303.
[143] (b) Profitt, J.A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*,127.

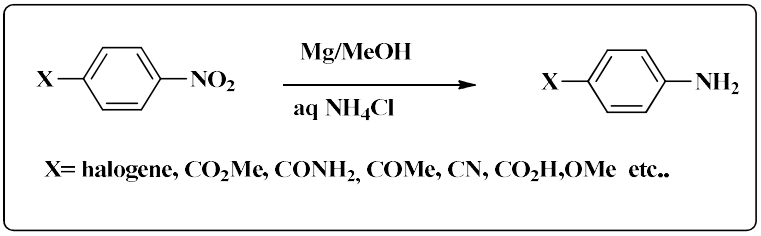


Scheme IV.5

IV.3.4 Reduction of Functional Groups

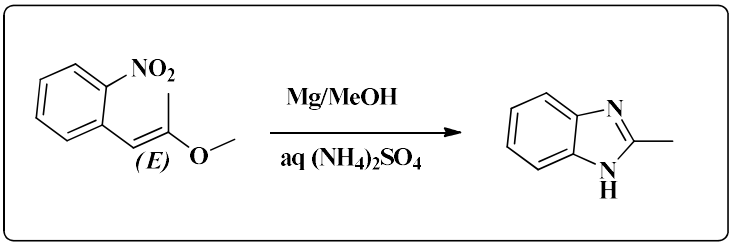
❖ **Reduction of Nitro group**

The aromatic nitro compounds can be reduce to azoxy compounds in moderate yields (30~90%) with Mg metal in a mixed solvent of methanol and a small amount of saturated aqueous NH_4Cl solution (**Scheme IV.6**).[144] The various reducing agents used to reduce nitroarenes to azo compounds, often used is a mixture of Zn and NaOH.[145] Sometimes $Zn/AcOH/Ac_2O$,[146] Sn (II) in a basic media,[147] Na-Pb alloy,[148]or Ti/EtOH[149] were used for the reduction of aromatic nitro compounds to azoxy derivatives. The uses of Mg in large excess, oriented the azoxy compounds to be reduce in hydrazines. They also obtained azo or hydroxylamine derivatives depending at reaction conditions, (mainly the amount of Mg used). Azoxy compounds were reduced under control to the corresponding azo products with Mg in boiling ethanol in quantitative yields.[150] Further reduction to amine could be achieved by employing a rather different reaction condition using ammonium sulfate as a promoter (**SchemeIV.7**).[151]



Scheme IV.6

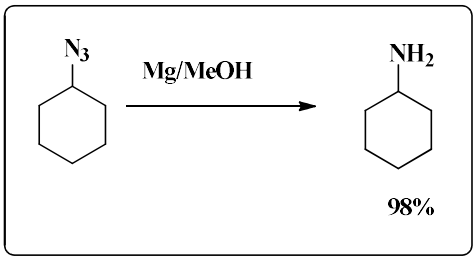
[144] (a) Zechmeister, L.; Rom, P. *Chem. Ber.* **1926**, *59B*, 567. (b) Zechmeister, L.; Truka, J. *Chem. Ber.* **1926**, *63B*, 2883.
[145] (a) Shinkai, S.; Nakaji, T.; Ogawa, T.; Shigematsu, K.; Manabe, O.*J. Am. Chem. Soc.* **1981**, *103*, 111. (b) Shine, H. J.; Chamness, J. T. *J. Org. Chem*. **1963**, *28*, 1232. (c) Newbold, B. T. *J. Chem. Soc*. **1961**, 4260. (d) Blackadder, D. A.; Hinshelwood. C. *J. Chem. Soc*. **1957**, 2898.(e) Radell, J.; Spialter, L.; Hollander, J. *J. Org. Chem*. **1956**, *21*, 1051. (f) Badger, G. M.; Lewis, G. E. *J. Chem. Soc.* **1953**, 2147. (g) Meisenheimer, J.; Witte, K. *Chem. Ber*. **1903**, *36*, 4153.
[146] Cullen, E.; L'Ecuyer, P. Can. *J. Chem*. **1961**, *39*, 862.
[147] Sandler, S. R.; Karo, W. *Organic Functional Group Preparation ;*2nd ed. Academic Press, New York, **1986**, vol. II p422.
[148] Tabei, K.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.***1967**, *40*, 1538.
[149] McKillop, A.; Raphael, R. A.; Taylor, E. C. *J. Org. Chem*. **1970**,*35*, 1670.
[150] Joshua, C. P.; Ramdas, P. K. *Synthesis,* **1974**, 873.
[151] (a) Prajapati, D.; Borah, H. N.; Sandhu, J. S.; Ghosh, A. C. *Synth.Commun*. **1995**, *25*, 4025. (b) Harizi, A.; Zantour, H. *Synth. Commun*. **2002**, *32*, 387.



Scheme IV.7

❖ **Reduction of Azide**

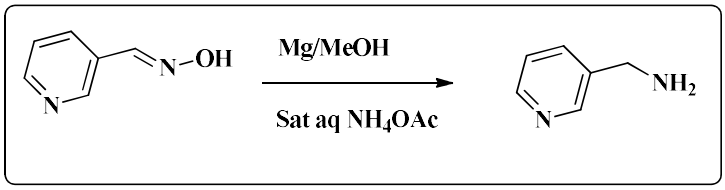
The reduction of azides to the corresponding amines in the presence of Mg/MeOH are described by Maiti et al, in 1988 (**Scheme IV.8**).[152]



Scheme IV.8

❖ **Reduction of imine**

The Mg reduces various aromatic aldimines to corresponding saturated primary or secondary amines.[153] Oxime was also reduced into amine in the presence of saturated aqueous NH_4OAc (**Scheme IV.9**).[154]



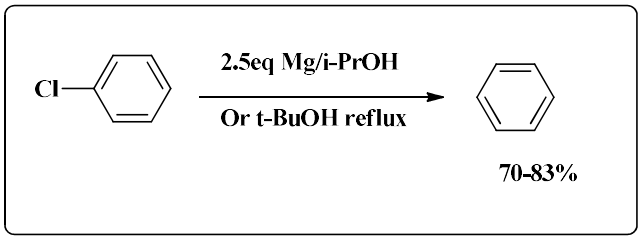
Scheme IV.9

❖ **Reduction of halide**

Mg in absolute methanol at room temperature reduce aryl halides, but fluorides are reduced with excess Mg in boiling alcohols such as isopropanol or *tert*-butanol

[152] Maiti, S. N.; Spevak, P.; Reddy, A. V. N.; Synth. *Commun.* **1988**, *18*, 1201.
[153] Khurana, J. M.; Gogia, A.; Bankhwal, R. K. *Synth. Commun*. **1997**, *27*, 1801.
[154] Sugden, J. K. *Chem. Ind.***1969**, 260.

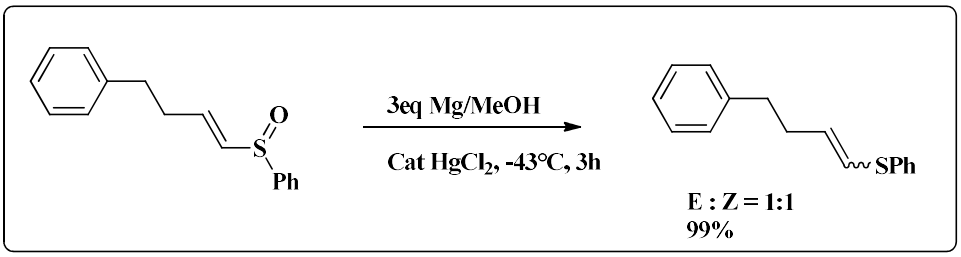
(**SchemeIV.10**).[155]Under this reaction condition, secondary and tertiary halides undergo elimination to give olefin as the major product.[156]



Scheme IV.10

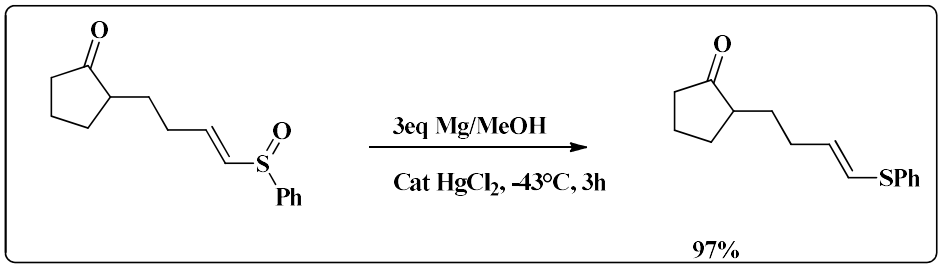
IV.3.5 Deoxygenation

There are various reagents known for deoxygenation of sulfoxides.[157] Deoxygenation proceeded slowly with Mg /MeOHof sulfoxide,[158]*N*-oxide,[159] phosphine oxide.[160] E and *Z* isomers of alkenylphenyl sulfoxides were subjected to the standard conditions to give the corresponding sulfides in quantitativeyields (**Scheme IV.11-IV.12**). Complete isomerisation occurred to give the identical product mixture of 1:1 *E* and Z sulfides from each of the substrates (**Scheme IV.12**). On the other hand, geometry of double bond was kept completely in keto sulfoxide (**Scheme IV.11**).



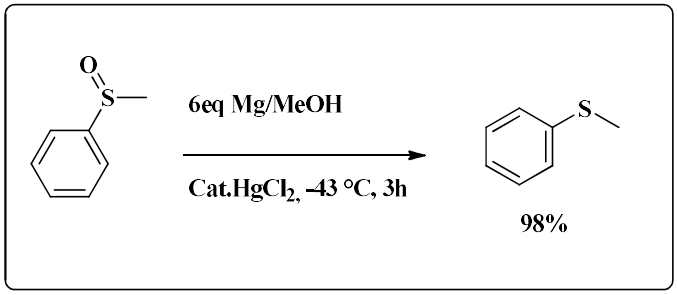
Scheme IV.11

[155] Hutchins, R. O.; Suchismita; Zipkin, R. E.; Taffer, I. M. *Synth. Commun.* **1989**, *19*, 1519.
[156] (a) Bryce-Smith, D.; Wakefield, B.; Blues, E. T. *Proc. Chem. Soc*. **1963**, 219. (b)Bryce-Smith, D.; Wakefield, B. J. *Org. Synth*. **1967**, *47*, 103. (c) Cahiez, G. ; Bernard, D.; Normant, J. F. *J. Organomet. Chem.***1976**, *113*, 107. (d) Orsini, F. ; Pelizzoni, F. ; Forte, M. *Gazz. Chim. Ital.* **1986**, *116*.
[157] (a) Bartsch, H.; Erker, T. *Tetrahedron Lett*. **1992**, *33*, 199. (b) Balicki, R *Synthesis,* **1991**, 155.
[158] Hutchins, R. O.; Suchismita; Zipkin, R. E.; Taffer, I. M.; Sivakumar, R.; Monaghan, A.; Elisseou, E. M. *Tetrahedron Lett*. **1989**, *30*, 55.
[159] (a) Joshua, C. P.; Ramadas, P. K. *Synthesis,***1974**, 873. (b) Yoshida, T.; Nishiyachi, M.; Nakashima, N.; Murase, M.; Kotani, E. *Chem. Pharm. Bull.* **2002**, *50*, 872. (c) Murase, M.; Wadanabe, K.; Yoshida, T.; Tobinaga, S. *Chemiphar. Bull.* **2000**, *48*, 81.
[160] (a) Rhomberg, A.; Tavs, P. *Monatsh. Chem.* **1967**, *98*, 105. (b) Teichmann, H.; Jatkowski, M.; Hilgetag, G. *Angew.Chem.***1967**, *79*, 379. (c) Nesterov, L. V.; Mutalapova, R. I. *Tetrahedron Lett.* **1968**, *9*, 51.



Scheme IV.12

On the other hand, the reduction of alkyl phenyl sulfoxides (**Scheme IV.12**) was so slow at low temperatures that excess amounts of Mg (6 equiv) and prolonged reaction time (5 h) were required to complete the reaction. However, the yields of the corresponding sulfides are nearly quantitative.



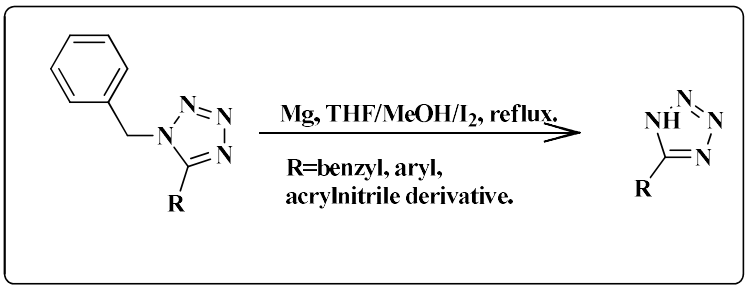
Scheme IV.13

IV.4 Objective

Among electron transfer reactions using Mg metal, reactions in protic solvents have not been fully exploited in comparison with reactions in aprotic solvents such as Grignard reaction,[161] pinacol coupling,[162] and low valent transition metal complex reactions.[163]Utility of Mg/MeOH as an electron transfer reagent has appeared in literature rather periodically since the ability of Mg/MeOH to reduce functional groups such as nitro, oxime, ketone and halogen. We are interested in using Mg as a source of electron transfer for one of the important heterocycle tetrazoles.

[161] Silrerman, G. S.; Rakita, P. E. Kirk-Othmer, *Encyclopaedia of Chemical Technology*, **1994**, vol *12,* (Wiley-Interscience, New York 4th ed.) pp. 768-786.
[162] (a) Bruch, M.; Jun, Y. M.; Luedtke, A. E.; Schneider, M.; Timberlake, J. W. *J. Org. Chem*. **1986**, *51*, 2969. (b) Mundy, B. P.; Bruss, D. R.; Kim, Y.; Larsen, R. D.; Warnet, R. J. *Tetrahedron Lett*. **1985**, *26*, 3927. (c) Rupp, H.; Schwarz, W.; Musso, H. *Chem. Ber*. **1983**, *116*, 2554. (d) Mundy, B. P.; Kim. Y.; Warnet, R. *J. Heterocycles.* **1983**, *20*, 1727. (e) Mundy, B. P.; Srinivasa, R.; Kim, Y.; Dolph, T.; Warnet, R. J.(f) Bhushan, V.; Chandrasekaran, S. *Chem. Lett*. **1982**, 1537. (g) Pons, J. M.; Zahara, J. P.; Santelli, M *Tetrahedron Lett*. **1981**, *22*, 3965. (h) Eaton, P. E.; Jobe, P. G.; Nyi, K. *J. Am. Chem. Soc*. **1980**, *102*, 6636. (i) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260.
[163] (a) Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chem. Fr*. **1973**, 2147. (b) Jacobsen, S. M.; Smith, W. E. *Inorg. Chim. Acta.* **1985**, *98*, L63. (c) Sanchez, I. H.; Larraza, M. I.; Rojas, I.; Brena, F. K.; Flores, H. J.; Jankowski, K.; *Heterociclos.* **1985**, *23*, 3033. (d) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc*. **1978**, *100*, 545.

We describe the deprotection of benzyl protected tetrazoles with Mg, this methodology merit should be emphasized in its economy, versatility, and easy handling, compared to its equivalent metal reagent[164] (**Equation1).**



Equation 1

IV.5 Results and discussion

Starting from 5-phenyl-1-benzyltetrazole (1a) we explored a range of reaction condition (**Table IV.1)**. the use of Magnesium at room temperature in Methanol, THF or Ethanol as well as a mixture of MeOH/THF (2:1) or methanol under reflux didn't lead to cleavage after 24hours (1-5) However, under reflux in MeOH/THF, the expected product 2a was obtained in 40% yields than we added tiny of iodine to the mixture we increase the yield to 93% (**TableIV.1).**

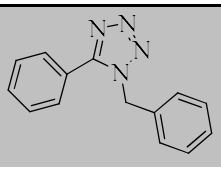
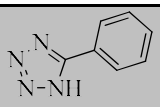
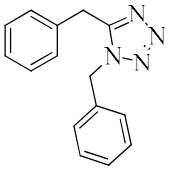
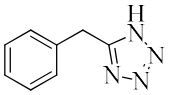
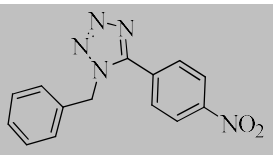
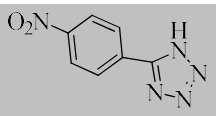
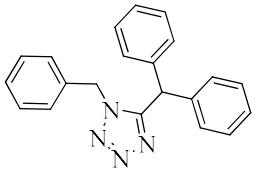
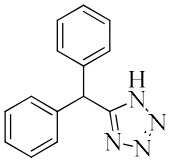
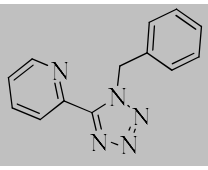
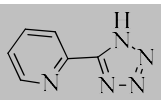
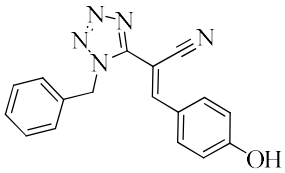
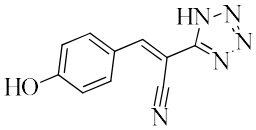
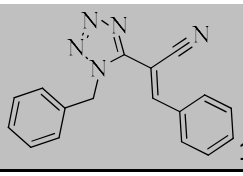
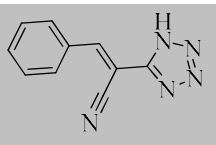
Our results are shown in (**Table IV.2**) In a typical procedure, reaction is initiated by addition of magnesium turnings and a crystal of iodine to a solution of the benzyle tetrazole in warm methanol/ THF (2 :1).Following disappearance of the starting material, and show the expected tetrazole in good yields reaction take from 1-26h (entries 1–5). In the presence of a double bond and nitrile with the same reaction conditions, afforded the debenzylation tetrazoles in moderate yields without affecting the double bond and reduction of nitrile (entries 6–10). The reactions were subjected to an aqueous workup and the crude products were purified by flash chromatography. All of these compounds were characterised by comparison of their physical and spectroscopic data with authentic samples.

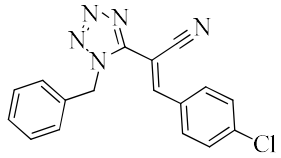
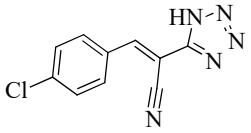
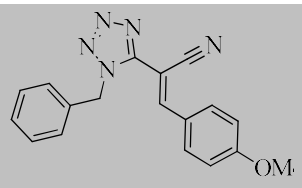
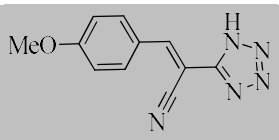
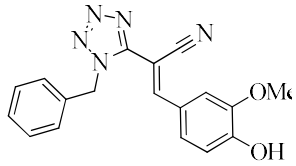
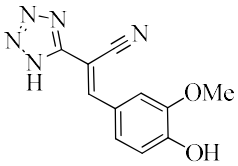
[164] Pasupathy, K. *Synlett Lett*. **2003**, *12,* 1942.

Table IV.1: Assayed condition for Mg-promoted cleavage of (1a) for 24h

Entry	Solvent	Temperature(C°)	Yields (%)
1	MeOH	rt	0
2	THF	rt	0
3	EtOH	rt	0
4	MeOH/THF	rt	0
5	MeOH/THF	reflux	40
6	MeOH/THF/I_2	reflux	93

Table IV.2. Magnesium-Mediated Cleavage of the Benzyl Group from Protected 1H-Tetrazoles.

Entry	Substrate	Time(h)	Product	Yield(%)
1	 1a	22		93
2	 1b	22		85
3	 1c	22		80
4	 1d	22		84
5	 1e	22		90
6	 1f	17		56
7	 1g	17		69

8	 1h	17		58	
9	 1i	17		60	
10	 1j	17		59	

IV.6 Conclusion

In conclusion Mg/MeOH is a reagent of choice for electron transfer reagent for versatile organic reactions. It is a simple to use, inexpensive, and an environmentally benign reagent compared to other methods.

IV.7 Experimental part

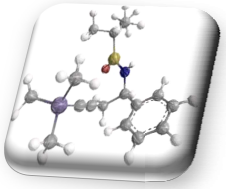
IV.7.1 General procedure for the magnesium-promoted debenzylation of tetrazoles 1

To a solution of the corresponding tetrazole **1** (1 mmol) in MeOH (5 mL) and THF (3 mL) was added a freshly scratched Mg turnings (48 mg, 2 mmol) and a tiny crystal of iodine. The reaction was refluxed until the starting material was consumed (17-22 h) and then the reaction was cooled to 0°C and diluted with ether (5 mL) and 10% aqueous NH_4Cl. The mixture was stirred until it became clear and then separated. The combined ether extracts (2 × 5 mL) were dried over Na_2SO_4 and evaporated (15 Torr) to give a residue that was purified by recrystallization in EtOH, to afford the pure deprotected tetrazoles **2**. They were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2**.

Part II

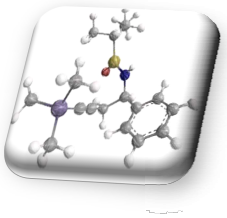
Use of N-butylsulfnylimine

in synthesis of (+)-C (9a)-Epiepiquinamide



Chapter V

N-butylsulfnylimine



V.1 Generality of imine

Imines are important nitrogen-containing compounds due to their note worthy electrophilicity, that are widely distributed in nature and show polyvalent pharmacological activities[165][166]. Many methods for imine formation have been reported in organic synthesis because of the importance of imines in the fields of chemistry[167] and biology.[168][169]

The procedures of two important sulfinimines, N-p-toluenesulfinimines and N-*tert*-butanesulfinimines, have been developed by Davis[170] and Ellman[171] respectively. The two important sulfinimines have been proved as potential intermediates for the organic syntheses of amine derivatives.

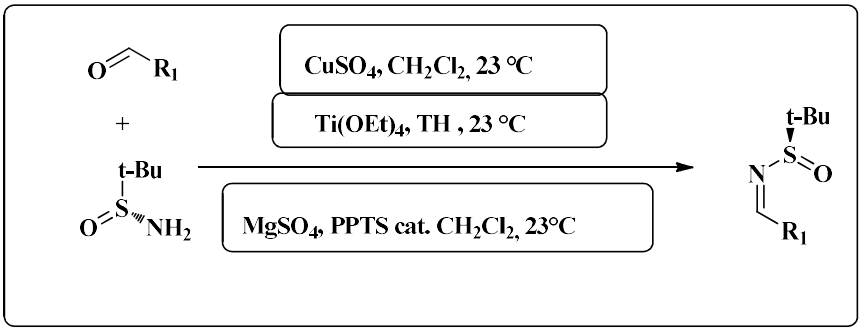
The imines are usually obtained from condensation of aldehydes and amines. The Enantiomerically pure N-(*tert*-butylsulfinyl) imines have shown to be very versatile substrates for the asymmetric synthesis of chiral primary amines.[172] Chiral primary amines are a very interesting class of compounds because they are present in many natural and biologically active products and also form part of pharmaceuticals and agrochemicals. The chiral and electron-withdrawing sulfinyl group plays a dual role as an activating and a stereo directing group and has an advantage in that it can be easily removed from the reaction products leading to the free primary amines.[173]

V.2 Synthesis and reactivity of N-butylsulfnylimine

There are several methods available to prepare these kind of aldimines, which are mainly based on the direct condensation of aldehydes with optically pure 2-methylpropane-2-sulfinamide in the presence of an activating and dehydrating agent such as copper(II) sulfate, magnesium sulfate/pyridinium p-toluenesulfonate, titanium(IV) alkoxid [174] , [175]

[165] Liu, G.; Cogan, D. A.;Ellman, J.A. *J. Am. Chem. Soc*. **1997,** *119*, 9913.
[166] Ferreira, F.; Botuha, C.; Chemla, F.; Perez-Luna, A. *Chemical Society Reviews*, **2009**, *38*, 1162.
[167] Hua, D.H.; Lagneau, L.; Wang, H.; Chen. J.*Tetrahedron,* **1995**, *6,* 349.
[168] Sun, P.; Weinreb, M. S.; Shang, M.*Journal of Organic Chemistry*, **1997**, *62*, 8604.
[169] Leca, D.; Fensterbank, L.; Lacote, E.;Malacria, M.*J. Organic Letters*, **2002**, *4*, 4093.
[170] Davis, F.A. *Journal of Organic Chemistry*, **2006**, *71*, 8993.
[171] Robak, M.A.T.; Herbage, M. A.; Ellman,*J.A.Chemical Review,* **2010,** *110*, 3600.
[172] Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626.
[173] Yamada, K.; Tomioka, K. *Chem. Rev*. **2008**, *108*, 2874.
[174] a) Adachi, S.; Moorthy, R.; Sibi, M. P. *Copper-Catalyzed Asymmetric Synthesis* (Eds.:Alexakis, A.; Krauser, N.; Woodward, S.), Wiley-VCH, Weinheim, **2014**, 283.; b) Takemoto, Y.; Miyabe, H. *Catalytic Asymmetric Synthesis* 3rd Ed. (Ed.: I. Ojima), John Wiley & Sons, *Hoboken,* **2010**, 227.; c) Moberg, C.; Wingstrand, E. *Synlett***, 2010**, 355; d) Shibasaki, M.; Matsunaga, S.; Kumagai, N. *Acid Catalysis in Modern Organic Synthesis* (Eds.: Yamamoto, H.; Ishihara, K.), Wiley-VCH, Weinheim, **2008**, 635.

cesiumcarbonate,[176] ytterbium(III) triflate,[177] or potassium hydrogensulfate.[178]Another method based on the activation of the sulfinamide, instead of the aldehyde, has also been reported.[179] Less reactive ketones usually require more drastic conditions to transform them into the corresponding N-(tert-butylsulfinyl) ketimines [$Ti(OEt)_4$[180]or $Ti(OPri)_4$[181] being the activating agents of choice in these cases]. From chiral tert-butanesulfinamide and arylmethyl alcohols, benzylthiol, dibenzyl ether, thioether, or disulfide in the presence of KO^tBu under air atmosphere are also reported (**Scheme V.1).**[182]

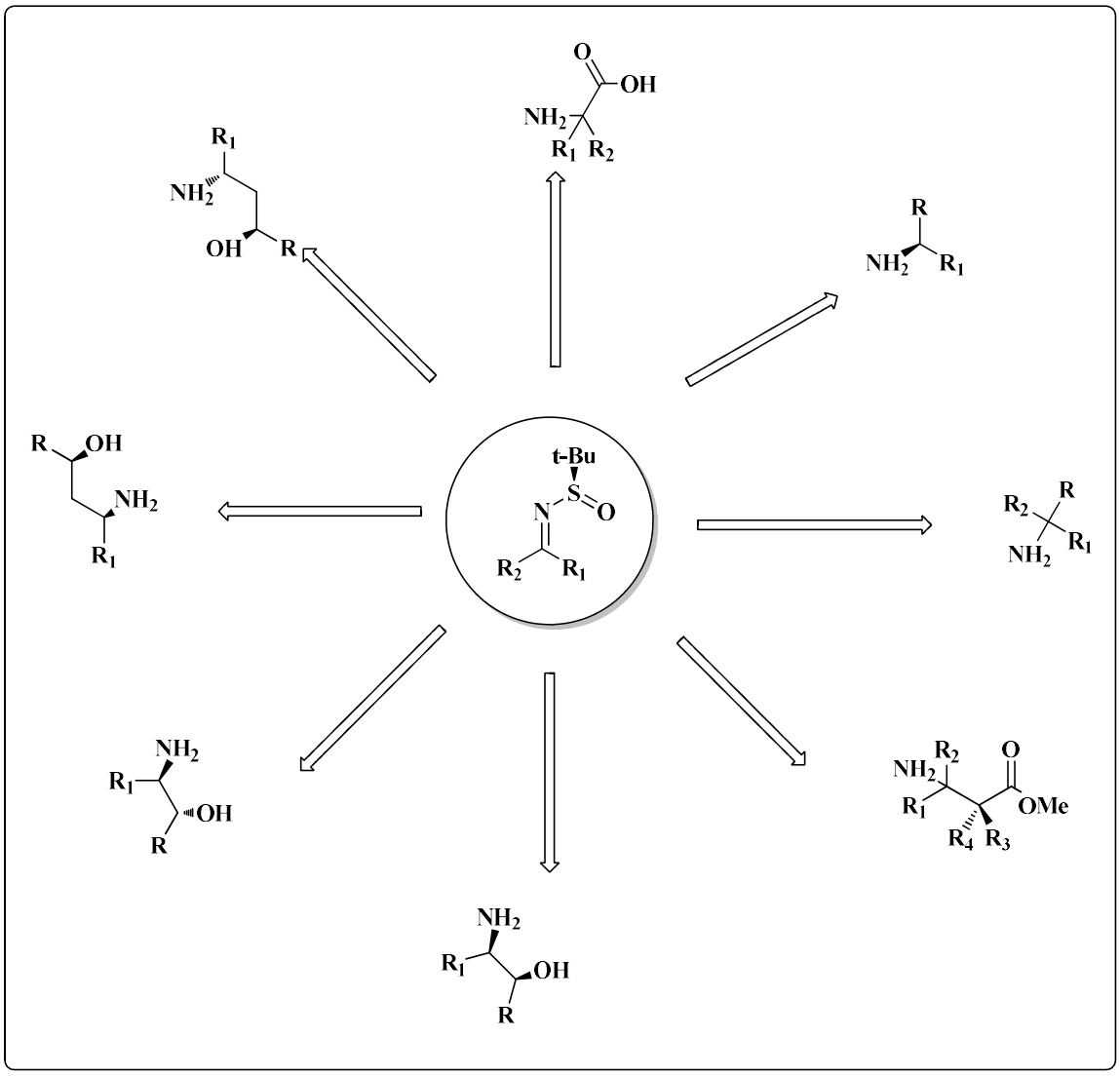


Scheme V.1

From these investigations, the N-*tert*-butanesulfinimines have been used by Ellman and other research groups in asymmetric synthesis. Specifically, the addition nucleophilic of different organometallic species to N-*tert*-butanesulfinimines has been subject to numerous studies and, therefore, in recent years a large number of publications have focused on the stereoselective synthesis of different compounds of great interest, such as sin and anti- 1,2- or 1,3-amino alcohols,[183,184] branched amines and α, α-diramified[185] and α- or β-amino acids and

[175] a) Nakajima, M. in Comprehensive Chirality, Vol. 4 (Eds.: Carreira, E. M.; Yamamoto, H.), Elsevier E. V., Amsterdam, **2013**, 198.; b) Denmark, S. E.; Fujimori, S. Modern Aldol Reactions (Ed.: Mahrwald, R.), Wiley-VCH, Weinheim, **2005**, pp. 229-326.
[176] Paull, D. H.; Abraham, C. J.; Scerba, M. T.; Alden-Danforth, E.; Lectka, T. *Acc. Chem. Res*. **2008**, *41*, 655.
[177] a) Shaw, A. K. J. Ind. Chem. Soc. **2013**, *90*, 1557; b) Gademann, K. *Asymmetric Synthesis* II (Eds.: M. Christmann, S. Brase), Wiley-VCH, Weinheim, **2012**, pp. 317-322; c) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem. Rev*. **2013**, *113*, 5595; d) Hiersemann, M.; Jaschinski, T. *Comprehensive Chirality*, Vol. 2 (Eds.: Carreira, E. M.; Yamamoto, H.), Elsevier E. V., Amsterdam, **2012**, pp. 625-647.
[178] (a) Ferreira, F.; Botuha, C. ; Chemla, F.; Perez-Luna,A. *Chem. Soc. Rev*. **2009**, *38*, 1162. (b) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 3600.
[179] Davis, F, A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.*, **1974**, *96*, 5000.
[180] (a) Annunzaita, R. ; Cinquini, M. ; Cozzi, F. *J. Chem. Soc*., *Perkin Trans. 1,***1982**, 339. (b) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Portonovo, P. S. *Tetrahedron Lett.*, **1993**, *34*, 6229. (c) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M.; Reddy, G. V.; Portonovo, P. S.; Zhang, H.; Fanelli, D.; Reddy, R. T.; Zhou, P.; Carroll, P. J. *J. Org. Chem*., **1997**, *62*, 2555.
[181] (a) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. *J. Org. Chem.*, **1996**, *61*, 440. (b) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem*., **1995**, *60*, 7037. (c) Davis, F. A.; Zhou, P; Reddy, G. V. *J. Org. Chem*., **1994**, *59*, 3243.
[182] X.LV,Y.Zhoi,A.Zhang;L. Zhou; Q.Zeng,*journal of Toxicological Environmental chemistry*, **2015**, 17, 486.
[183] (a) Zhong, Y.-W. Et al.*J. Am. Chem. Soc*. **2005**, *127*, 11956; (b) Evans, J. W.; Ellman, J. A.*J. Org. Chem*. **2003**, *68*, 9948; (c) Tang, T. P. et al. *J. Org. Chem.***2001**, *66*, 3707. (d) Barrow, J. C. et al. *Tetrahedron Lett.* **2001**, *42*, 2051.
[184] (a) Kochi, T. et al. *J. Am. Chem. Soc.***2003**, *125*, 11276; (b) Kochi, T. et al. *J. Am. Chem. Soc.* **2002**, *124*, 6518.
[185] (a) Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 268. (b) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **1999**, *64*, 1278.

esters. [186] Some researchers have used N-*tert*-butanesulfinimines as intermediates in the synthesis of antibiotics, compounds biologically active and other complex natural products, in the synthesis of chiral ligands [187] less common is the use directly of N-*tert*-butanesulfiniminesas ligands in asymmetric catalytic transformations (**Scheme V.2**).[188]



Scheme V.2

[186] (a) Avenoza, A. et al. *Synthesis,* **2005**, 575. (b) Naskar, D. et al. *Tetrahedron Lett.* **2003**, *44*, 8865. (c) Jacobsen, M. F.; Skrydstrup, T. *J. Org. Chem.***2003**, *68*, 7122; (d) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **2002**, *67*, 7819; (e) Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **1999**, *64*, 12.
[187] Kato, T. et al. *Tetrahedron: Asymmetry,* **2004**, *15*, 3693.
[188] (a) Schenkel, L. B.; Ellman, J. A. *J. Org. Chem.* **2004**, *69*, 1800; (b) Schenkel, L. B.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 545; (c) Owens, T. D. et al. *J. Org. Chem.* **2003**, *68*, 3.

V.3 Characteristics of N-*tert*-butanesulfinyl imines

During the last decade, the use of N-*tert*-butanesulfinimines[16] as precursors of chiral amines, has experienced a great development. The reason is that the *tert*-butanesulfinyl group has special features that differentiate it from the rest:

- The two enantiomers of N-*tert*-butanesulfinamide can be prepared on a large scale in enantiomerically pure form, being affordable commercially at reasonable prices.
- The direct condensation of *tert*-butanesulfinamide with a wide range of aldehydes and ketones take place with high yields under mild reaction conditions, obtaining N-*tert*-butansulfinyl aldimines and ketimines respectively. These are less sensitive to hydrolysis than most N-alkyl, aryl, acyl or carbamoyl imines.
- N-*tert*-butanesulfinyl imines are more electrophilic than typical N-alkyl or aryl imines due to charge density positive localized in the sulfur atom. This electrophilicity allows the addition of numerous nucleophiles, such as organometallic reagents from magnesium, lithium, zinc, silica, indium, cerium and boron, carbaniones stabilized as enolates; nucleophiles other than carbon such as phosphorus, boron, tin and silica, as well as, different hydrides.
- The *tert*-butanesulfinyl group, besides being chiral, allows the coordination of metals, providing high diastereoselectivities in reactions of addition.
- The tert-butanesulfinyl group acts as a protective group attenuating the nucleophilicity of the amine. It is also stable in different conditions of reaction, such as the presence of strong bases, nucleophiles and a large variety of transition metals in catalyzed processes.
- The deprotection of the *tert*-butanesulfinyl group is easily carried out with hydrogen chloride in methanol, generating the corresponding hydrochloride of the amine with almost quantitative yields.

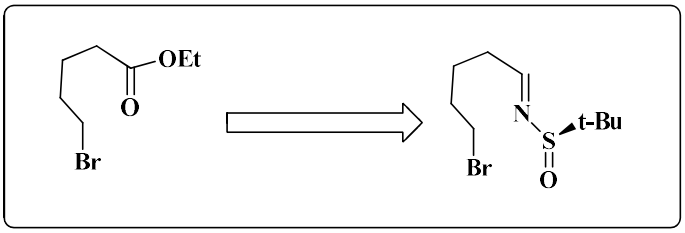
V.4 Objective

In 1996 **García Ruano** described the first synthesis of enantiomerically pure *N-tert*-butanesulfinylimines using diacetone-D-glucose (DAG).[189] However, this method is not practical when it is destined to work on a large scale, it requires chromatographic separations.

We have prepared chiral *N-tert*-butanesulfinyl imine as starting material, the reaction

[189] Garcia Ruano, J. L.; Fernandez, I.; Catalina, M. del Prado; Cruz, A. A. *Tetrahedron: Asymmetry*, **1996**, *7*, 3407.

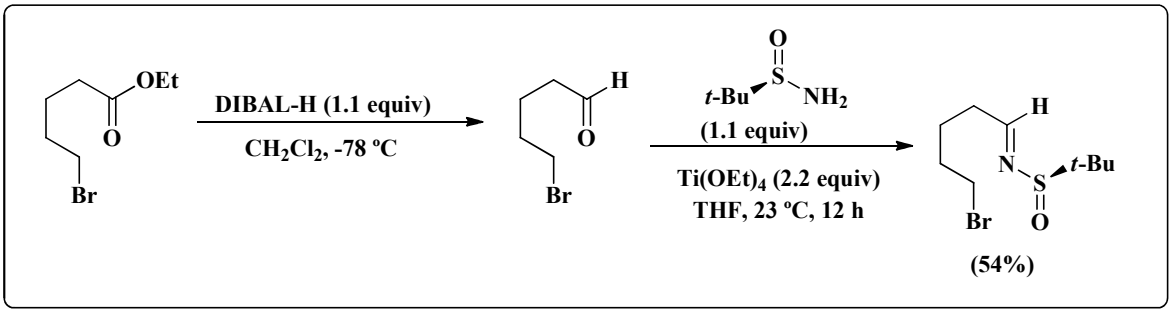
is simple, first we apply the reduction of ester to aldehyde, then condensation to have the desired product (**Scheme V.3).**



Scheme V.3

V.5 Results and discussion

Reduction of the ester ethyl 5-bromopentanoate with DIBAL-H in dichloromethane at -78 ºC for 3 hours led to 5-bromopentanal, which was condensed with (R_S)-*tert*-butanesulfinamide in the presence of titanium tetraethoxide at room temperature for 12 hours, to give the expected chiral *N-tert*-butanesulfinyl imine in 54% overall yield (**Scheme V.4**).

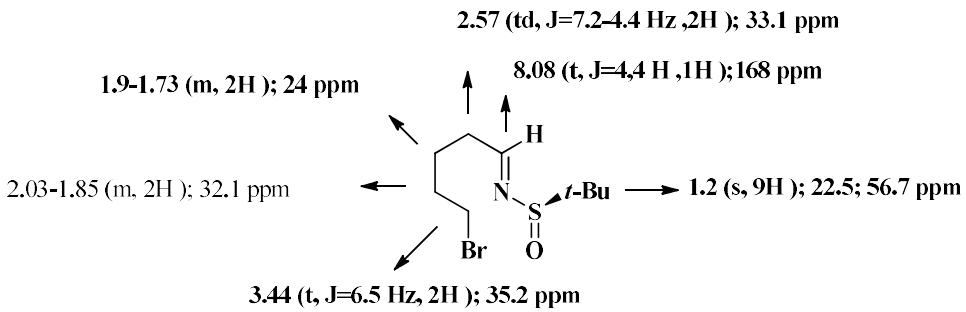


Scheme V.4

The imine was identified by spectroscopic methods usual including infrared spectroscopy and ^{1}H NMR, ^{13}C NMR.

- ***^{1}H NMR and ^{13}C NMR Spectroscopy***

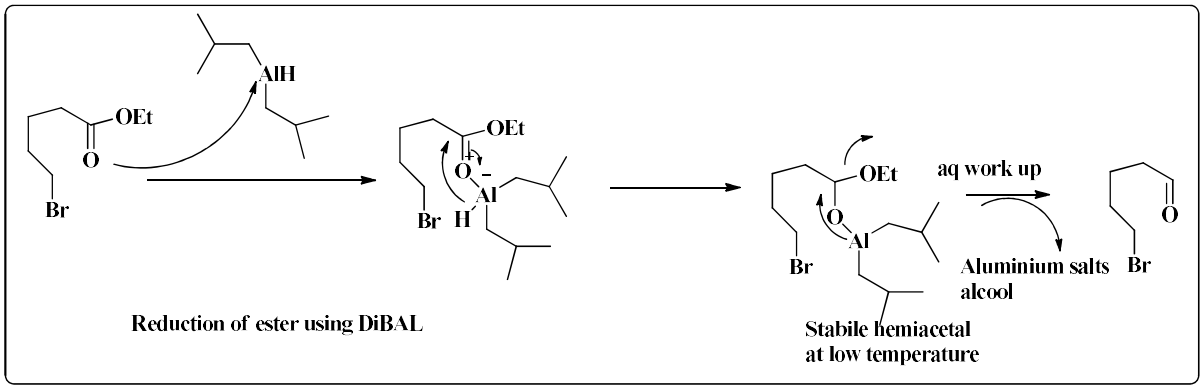
We have made the imine from reduction of 5-bromopentanal, the proton of imine 1H which resonate in the low field 8.08ppm as triplet with 168ppm corresponding to the carbon of imine, the identification of the product is summarized in the picture below.



- ***Proposed mechanism***

1. Reduction of ester

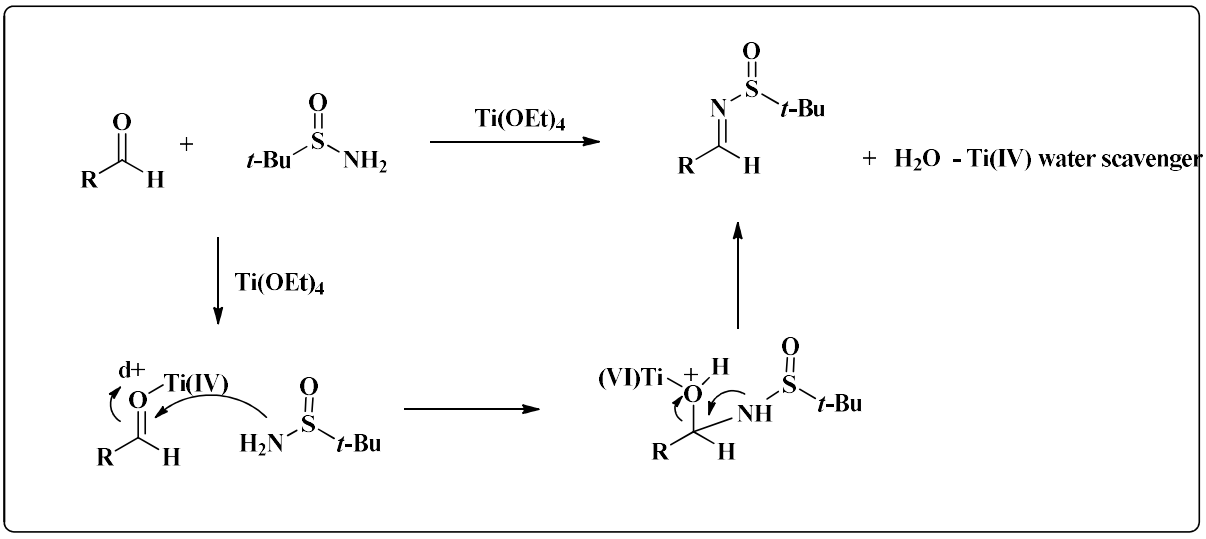
DIBAL is an "electrophilic" reductant. The first step in the reaction is coordination of a lone pair from the carbonyl oxygen (a nucleophile) to the aluminium (electrophile). It is only after coordinating to its carbonyl host that DIBAL delivers its hydride to the carbonyl carbon, resulting in formation of a neutral hemiacetal intermediate that is stable at low temperatures. Quenching of the reaction then breaks down the hemiacetal, resulting in isolation of the aldehyde (**Scheme V.5**).



Scheme V.5

2. Condensation of aldehyde

The condensation of the aldehyde using titanium tetraethoxide as Lewis acid which activates the aldehyde to the attack of *t*-butanesulfinamide (t-BuSONH$_2$). In order to promote the formation of the imine, it is also a water scavenger. Otherwise, t-butanesulfinamide it is not a good nucleophile, the mechanismdescribes in **(Scheme V.6).**



Scheme V.6.

V.6 Conclusion

A practical synthetic protocol of chiral N-(*tert*-butylsulfinyl) imines. In the presence of Titanium tetraethoxide, converted to chiral N-(*tert*-butylsulfinyl) imines. This reaction involves a two-step, the reduction of ester to give aldehyde catalyzed by DiBAL-H, and further condensation of aldehydes and tert-butanesulfinamide to give chiral N-(tert-butylsulfinyl) imines.

V.7 Experimental part

V.7.1 General Procedure for reduction of ester

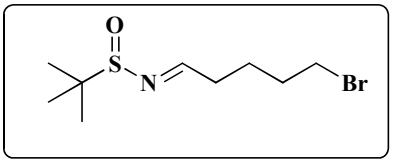
To a solution of ethyl 5-bromopentanoate (1.045 g, 0.817 mL, 5.0 mmol) in dry CH_2Cl_2 (9.0 mL) a solution of DIBAL-H in toluene (4.60 mL, 5.5 mmol)was addedat -78 ºC. The mixture was stirred for 3 h at the same temperature, quenched with 1M HCl (5.0 mL) and allowed to reach room temperature. Then, the resulting mixture was hydrolyzed with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL), dried over anhydrous MgSO4 and evaporated (15 Torr).

V.7.2 General procedure for condensation of aldehyde

The resulting residue was 5-bromopentanal (0.529 g, 3.2 mmol) and it was pure enough to be used in the next reaction step. Thus, a mixture of (*R*)-*tert*-butanesulfinamide **(**0.428 g, 3.5 mmol), 5-bromopentanal (0.529 g, 3.2 mmol), and $Ti(OEt)_4$ (1.596 g, 1.465 mL, 7.0 mmol) in THF (5.0 mL) was stirred for 12 h at room temperature. Then, the resulting mixture was hydrolyzed with brine (8 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure product **(**0.713 g, 2.66 mmol, 54% overall yield).

Yields, Physical and spectroscopy data:

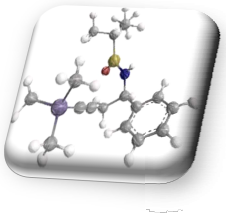
(R_S)-*N*-(*tert*-Butanesulfinyl)-5-bromopentan-1-imine



- Yellow oil;
- $[\alpha]^{20}_{D}$ -171.3 (*c* 1.01, CH_2Cl_2);
- IR (film) 2956, 1622, 1456, 1362, 1252, 1230, 1183, 1082, 732, 644 cm^{-1};
- ^1H NMR (300 MHz, $CDCl_3$) δ 8.08 (t, *J* = 4.4 Hz, 1H), 3.44 (t, *J* = 6.5 Hz, 2H), 2.57 (td, *J* = 7.2, 4.4 Hz, 2H), 2.03-1.85 (m, 2H), 1.90-1.73 (m, 2H), 1.20 (s, 9H);
- ^{13}C NMR (75 MHz, $CDCl_3$)δ 168.8 (CH), 56.7 (C), 35.2 (CH_2), 33.1 (CH_2), 32.1 (CH_2), 24.0 (CH_2), 22.45 (CH_3);
- LRMS (EI) *m/z* 213 (M^+-C_4H_8, 17%), 211 (M^+, 17), 84 (8), 70 (8), 57 (100), 55 (9), 43 (41), 41 (26).

Chapter VI

Synthesis of (+)-*C(9a)*-Epiepiquinamide



VI.1 Introduction

Ecuadoran frog skin is an important source of interesting biologically-active alkaloids.[190]

In 2003, Daly et al. isolated novel quinolizidine alkaloids epiquinamide[191] (1) along with known alkaloids epibatadine[192] (2) from the methanolic skin extracts of an Ecuadoran frog, Epipedobates tricolor (**Figure VI.1**).

The compound (+)-Epiquinamide (1) has been reported to possess nicotinic agonistic activity and considered as a lead compound for a new nicotinic agent. Due to the low availability of the isolated product, many research groups have synthesized this alkaloid as a single enantiomer[193] and a racemic mixture[194] in order to identify its absolute configurations and examine the biological activities. Several asymmetric compounds including amino acids,[195] cyclic amines,[196] and a reduced monosaccharide were employed as chiral starting materials.

In 2009, the reinvestigation of its biological activity revealed that (+)-epiquinamide and its stereoisomers are inactive to α4β2 nicotinic receptor subtypes up to 100 mM.[197] The activity previously discovered is due to the contamination with epibatidine in the isolation steps.

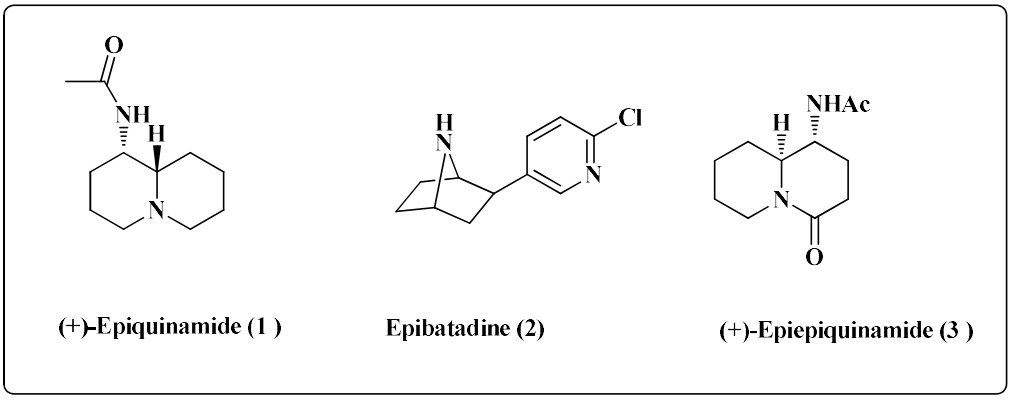


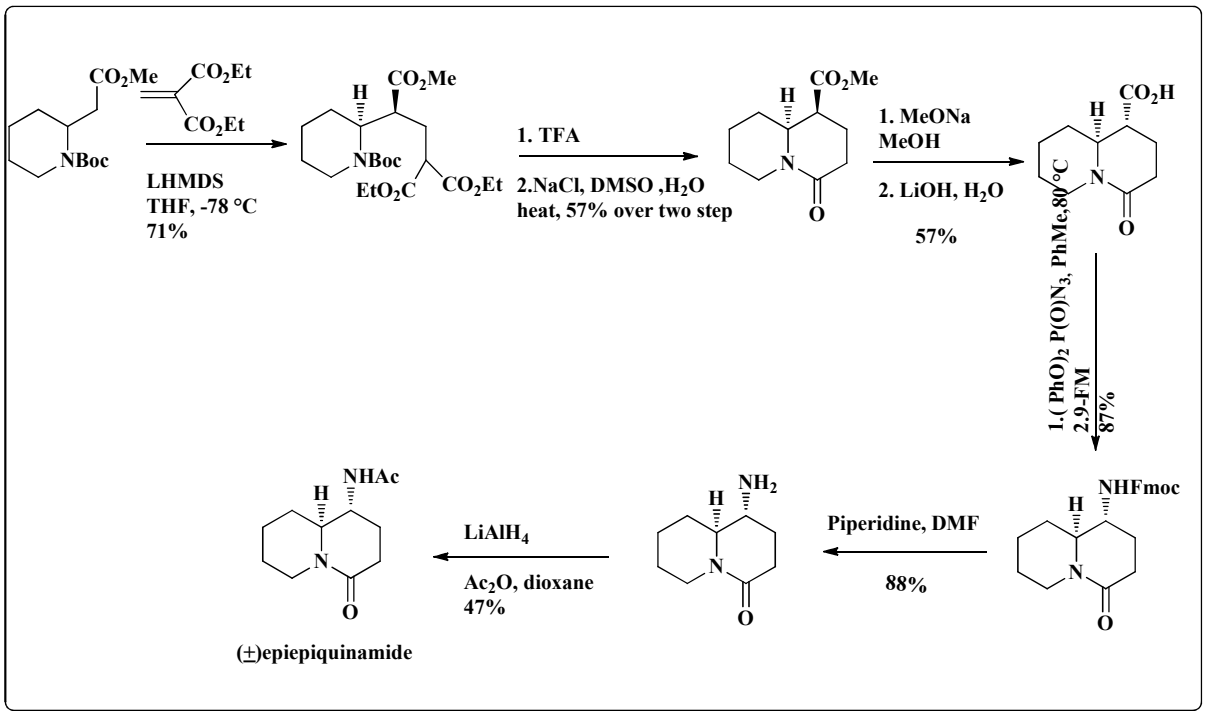
Figure VI.1

[190] Daly, J. W.; Spande, T. F.; Garraffo, H. M**.** *J. Nat. Prod.* **2005**, *68*, 1556.
[191] Fitch, R. W.; Garraffo, H. M.; Spande, T. F.; Yeh, H. J. C.; Daly, J. W. *J. Nat. Prod.* **2003**, *66*, 1345.
[192] (a) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc*. **1992**, *114*, 3475–3478; (b) Daly, J. W. Cell Mol. Neurobiol. **2005**, *25*, 513.; (c) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.***2005**, *68*, 1556.
[193] (a) Suyama, T.L.; Gerwick,W. H. *Org Lett*. **2006**, *8*, 4541.; (b) Tong, S.T.; Barker,D. *Tetrahedron Lett*. **2006**, *47*, 5017.; (c) Wijdeven, M. A.; Wijtmans, R.; Van den Berg, R. J. *Org Lett.* **2008**, *10*, 4001.; (d) Ghosh, S.; Shashidhar, J. *Tetrahedron Lett*. **2009**, *50*, 1177.; (e) Srivastava, A. K.; Das, S. K.; Panda, G.; *Tetrahedron*. **2009,** *65*, 5322.; (g) Airiau, E.;Spangenberg, T.; Girard, N.; Breit, B.;Mann, A. *Org Lett*. **2010**, *12*, 528.
[194] Kanakubo, A.;Gray, D.; Innocent, N.; Wonnacott, S.;Gallagher, T. *Bioorg Med Chem Lett*. **2006**, *16*, 4648.
[195] (a) Wijdeven, M. A.; Botman, P. N.;Wijtmans, R.; Schoemaker, HE.; Rutjes, F.P.; Blaauw., R.H. *Org Lett.***2005**, 7, 4005.; (b) Kise, N.;Fukazawa, K.; Sakurai, T. *Tetrahedron Lett.* **2010**, *51*, 5767.
[196] Pinho, V. D.; Procter, D. J.; Burtoloso, A.C. *Org Lett*. **2013**, *15*, 2434.
[197] Fitch, R.W.; Sturgeon, G. D.;Patel, S. R. *J. Nat Prod.* **2009**, *72*, 243.

VI.3 Synthesis of isomers epiquinamide

The first synthesis of epiquinamide was reported in 2005 by Blaauw and co-workers.[198] This was an asymmetric route leading to the (1S, 9aS) -(+)-1, but no biological data for this single enantiomer were reported. The ability to measure the optical rotation of natural **1**, which would have aided correlation of Blaauw's synthetic product to the natural product, was presumably limited by the small amount (a total of 240 lg of 14) that was isolated. More recently, Huang[199] has reported an entry to the enantiomeric series that is (1R, 9aR)-(-)-1, but again no biological data for this enantiomer were reported.

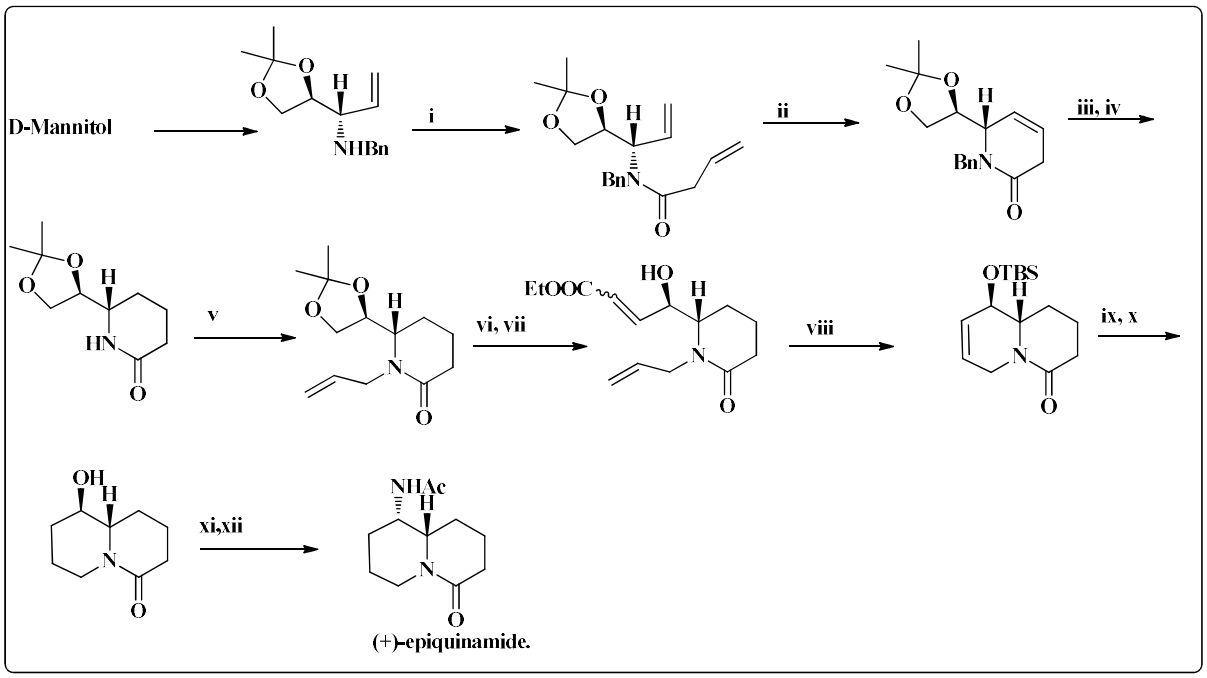
Kanakubo et al.[200] report a quite different synthetic approach to (±)-1 that is also readily adapted to the construction of the C(1) epimer of **1**, C(1)-epiepiquinamide **3**. The synthesis of (±)-epiquinamide **1** and (±)-C (1)-epiepiquinamide **3** based on the use of a Curtius rearrangement to introduce the C (1) amino residue. In a competition binding assay for [3H] epibatidine binding to rat brain membranes neither (±)-1 nor (±)-3 showed any significant level of nicotinic activity (**Scheme VI.1)**



Scheme VI.1

[198] Wijdeven, M. A.; Botman, P. N. M.; Wijtmans, R.;Schoemaker, H. E.; Rutjes, F. P. J. T.; Blaauw, R. H. *Org.Lett***. 2005**, *7*, 4005.
[199] Huang, P.-Q.; Guo, Z.-Q.; Ruan, Y.-P. *Org. Lett***. 2006,***8*, 1435.
[200] Kanakubo, K.; Gray, D.; Innocent, N.; Wonnacott, S.; Gallagher, T.*journal Bioorganic and Medicinal Chemistry Letters*, **2006**, *16*, 4648.

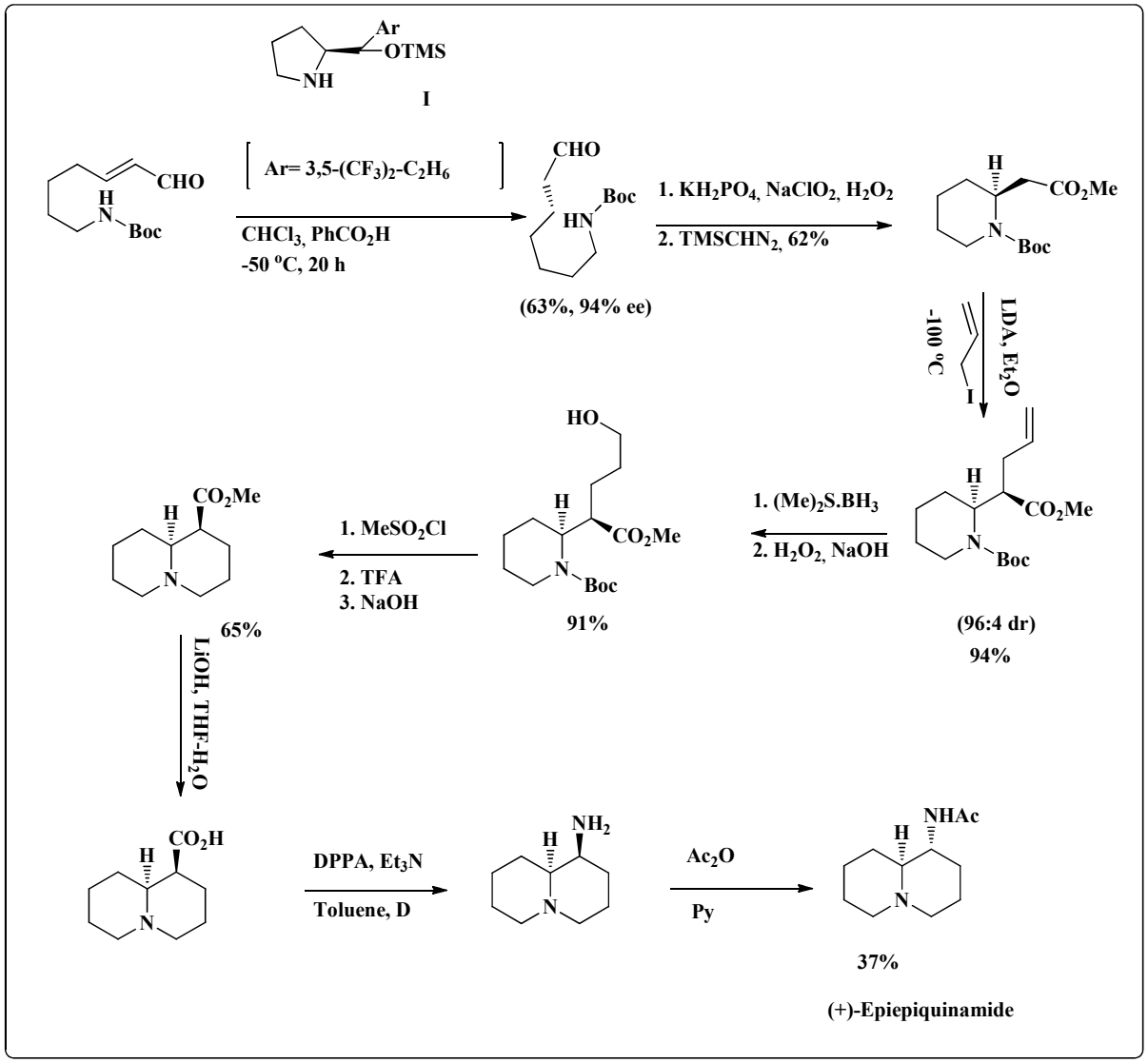
In 2008 Ghosh et al.[201] described the total synthesis of (+)-epiquinamide, the key step includes a ring-closing metathesis reaction to construct both the six member rings. D-Mannitol was used as a chiral pool material (**Scheme VI.2).**



Scheme VI.2:Reagents and conditions: (i) 3-butenoic acid, isobutylchloroformate, NMM, THF, 0 _C to rt, 8 h, 87%; (ii) 5 mol % Grubbs' 1st generation catalyst, CH2Cl2, 50°C, 5 h,92%; (iii) H2, Pd–C, MeOH, rt, 0.5 h, 90%; (iv) Li, liq. NH3, THF, -78 °C, 1 h, 64%; (v) NaH, ally bromide, DMF, 0 _C to rt, 2 h, 83%; (vi) (a) CSA, MeOH, rt, 4 h, 77%; (b) TBSOTf, 2,6-lutidine, CH2Cl2, 0 °C, 0.5 h, 96%; (c) HF–Py, THF, rt, 14 h, 86%; (vii) (a) DMP, CH2Cl2, 0 °C to rt, 1.5 h; (b) Ph3PCHCOOEt, CH2Cl2, rt, 1 h, 84% over two steps; (viii) 10 mol %Grubbs' 1st generation catalyst, CH_2Cl_2, 50°C, 24 h, 71%; (ix) Pd–C, H2, MeOH, 0.5 h, 90%; (x) TBAF, THF, rt, 7 h, 89%; (xi) (a) Ms–Cl, Et3N, CH2Cl2, 0.5 h; (b) NaN_3, DMF, 100 °C, 24 h, 50% over two steps; (xii) (a) $LiAlH_4$, THF, reflux, 24 h; (b) Ac_2O, 1 N NaOH, dioxane, 2 h, 79% over two steps.

Fustero et al.[202] uses an organocatalytic for synthesis of quinolizidine alkaloids, (+)-epiepiquinamide, as the key step, an enantioselective intramolecular aza-Michael reaction (IMAMR) catalyzed by Jørgensen catalyst,[203] affording the common precursor with high enantioselectivity. This compound was subsequently transformed into the three alkaloids in a highly diastereoselective form (**Scheme VI.3).**

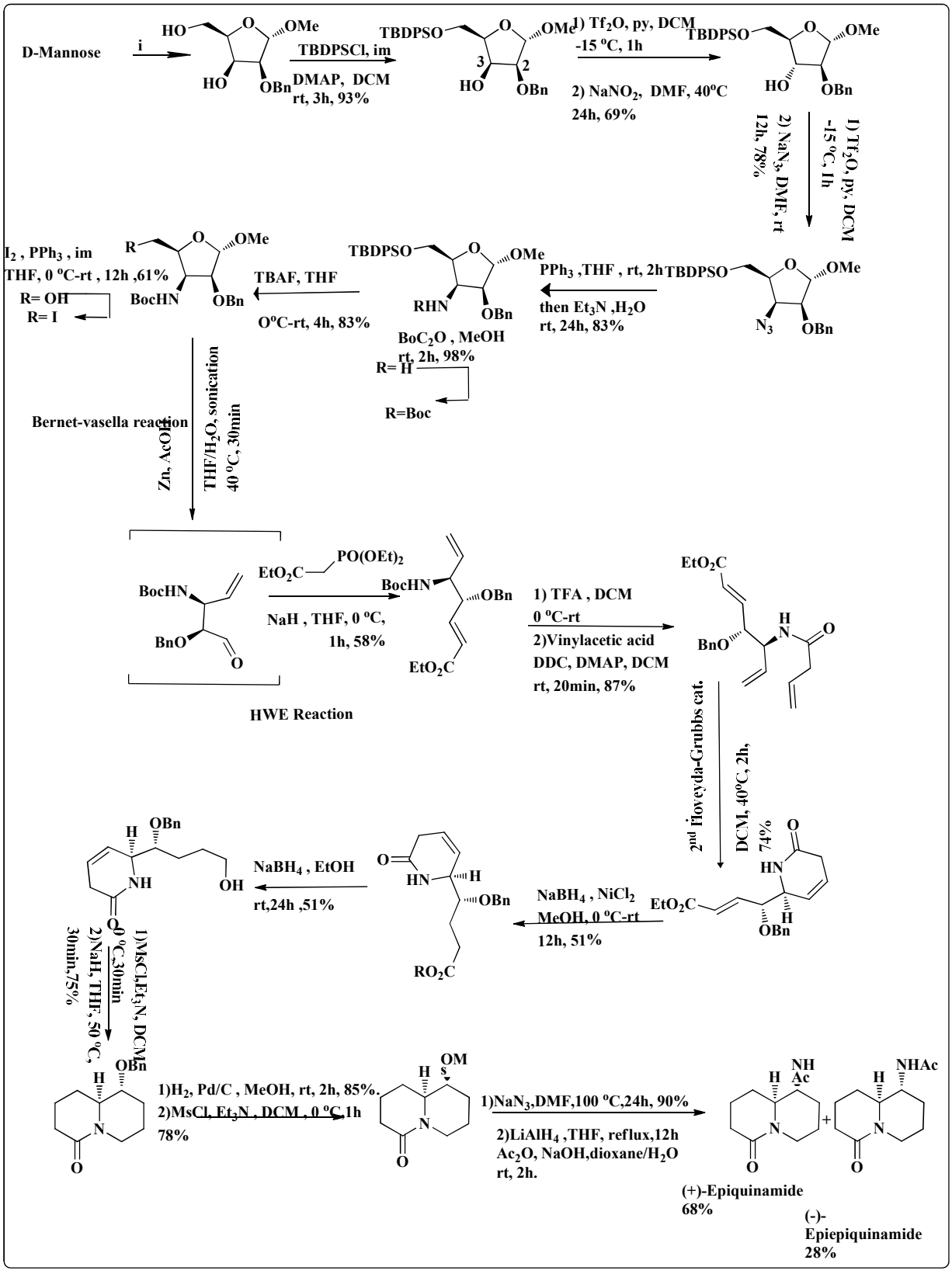
[201] Ghosh. S;Shashidhar.J.,*Tetrahedron Letters,* **2008**, *50*, 1177.
[202] Fustero, S.; Moscardo, J.; Sanchez-Rosello, M.; Flores, S.; Guerola.M,del pozo, C. *Tetrahedron*, **2011**, *67*, 7412.
[203] Carlson, E. C.; Rathbone, L. K.; Yang, H.; Collet, H. D.; Carter, R. G. *J. Org. Chem*. **2008**, *73*, 5155.



Scheme VI.3

Sangsuwan et al.[204] describes a total synthesis of (+)-epiquinamide and (-)-epiepiquinamide starting from a 3,5-dihydroxyfuranoside synthon derived from D-mannose. The methods Bernet-Vasella reaction followed by Horner-Wadsworth-Emmons (HWE) reaction to provide a new chiral building block diene as the key steps. The bicyclic framework of this quinolizidine was constructed by using ring-closing metathesis, selective reduction of ester and intramolecular nucleophilic substitution-cyclization (**Scheme VI.4).**

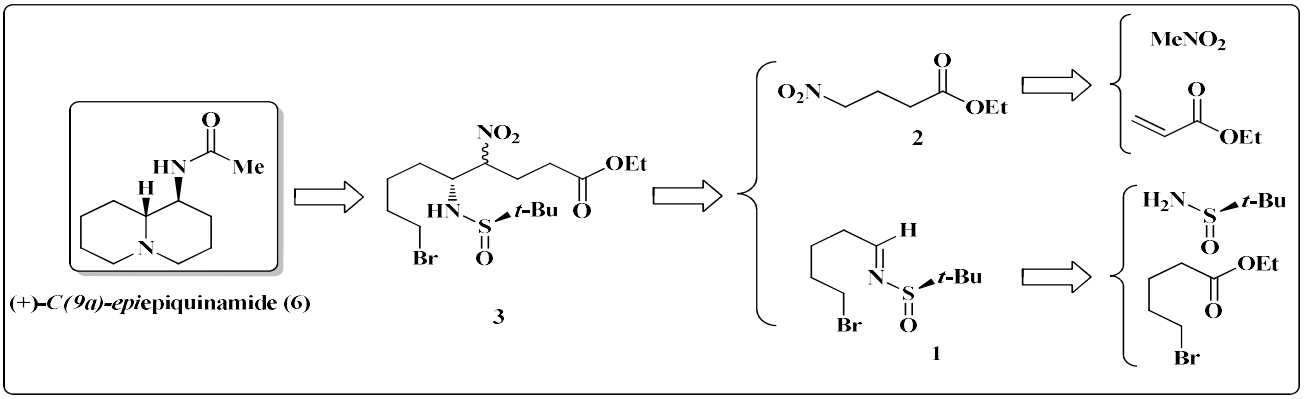
[204] Sangsuwan.W;KongKathip. B.;Chauwong. P;Kongkathip.N. *Tetrahedron.* **2017**, *52*, 7274-7281.


D-Mannose
i
TBDPSCl, im
DMAP, DCM
rt, 3h, 93%
1) Tf2O, py, DCM
-15 °C, 1h
2) NaNO2, DMF, 40°C
24h, 69%
1) Tf2O, py, DCM
-15 °C, 1h
2) NaN3, DMF, rt
12h, 78%
PPh3 ,THF , rt, 2h
then Et3N ,H2O
rt, 24h, 83%
TBAF, THF
O°C-rt, 4h, 83%
I2 , PPh3 , im
THF, 0 °C-rt , 12h ,61%
R= OH
R= I
BoC2O , MeOH
rt, 2h, 98%
R= H
R=Boc
Bernet-vasella reaction
Zn, AcOH
THF/H2O, sonication
40 °C, 30min
NaH , THF, 0 °C,
1h, 58%
HWE Reaction
1) TFA , DCM
0 °C-rt
2)Vinylacetic acid
DDC, DMAP, DCM
rt, 20min, 87%
2nd Hoveyda-Grubbs cat.
DCM, 40°C, 2h,
74%
NaBH4 , NiCl2
MeOH, 0 °C-rt
12h, 51%
NaBH4 , EtOH
rt,24h ,51%
1)MsCl,Et3N, DCM
0 °C,30min
2)NaH, THF, 50 °C,
30min,75%
1)H2, Pd/C , MeOH, rt, 2h, 85%.
2)MsCl, Et3N , DCM , 0 °C,1h
78%
1)NaN3,DMF,100 °C,24h, 90%
2)LiAlH4 ,THF, reflux,12h
Ac2O, NaOH,dioxane/H2O
rt, 2h.
(+)-Epiquinamide
68%
(-)-
Epiepiquinamide
28%

Scheme VI.4

VI.4 Objectif

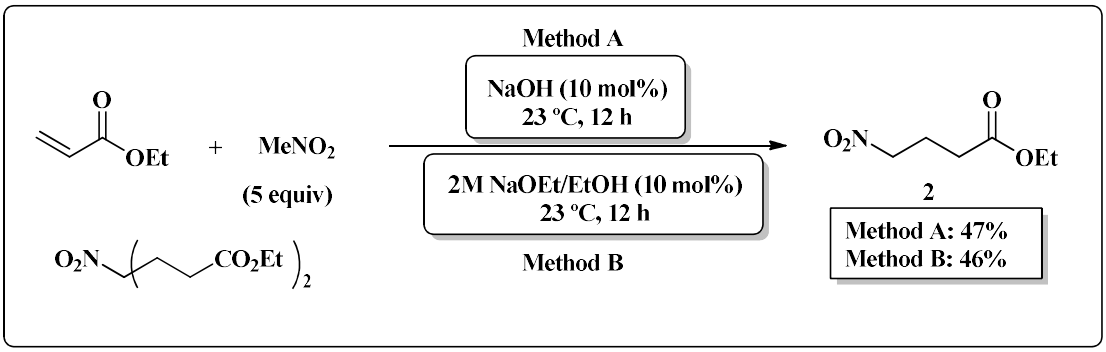
We find new synthetic to (+)-*C(9a)-epi*epiquinamide based on the diastereoselective aza-Henry reaction of ethyl 4-nitrobutanoate and a chiral *N-tert*-butanesulfinyl imine. Our retrosynthetic analysis for the preparation of (+)-*C(9a)-epi*epiquinamide is drawn on (**Scheme VI.5).**



Scheme VI.5

VI.5 Results and discussion

The preparation of ethyl 4-nitrobutanoate (**2**) from ethyl acrylate and nitromethane, under basic conditions. When the reaction was carrying out in the presence of 0.1 equivalents of sodium hydroxide at 0 to 23 ºC for 12 hours, the expected ethyl 4-nitrobutanoate (**2**) was obtained in 47% yield (Method A, **Scheme VI.6**). Nearly the same yield was obtained under the same reaction conditions by using a 2M solution of sodium ethoxide in ethanol as a base (Method B, **Scheme VI.6**). The second method looks more interesting for scaling up the process. In addition, diethyl 4-nitroheptanedioate was always formed as a side reaction product in yields varying from 18 to 24%, which results from a double conjugate addition of one molecule of nitromethane to the α, β-unsaturated ester**,** although working with a large excess of nitromethane (5 equivalents) (**Scheme VI.6**).



Scheme VI.6

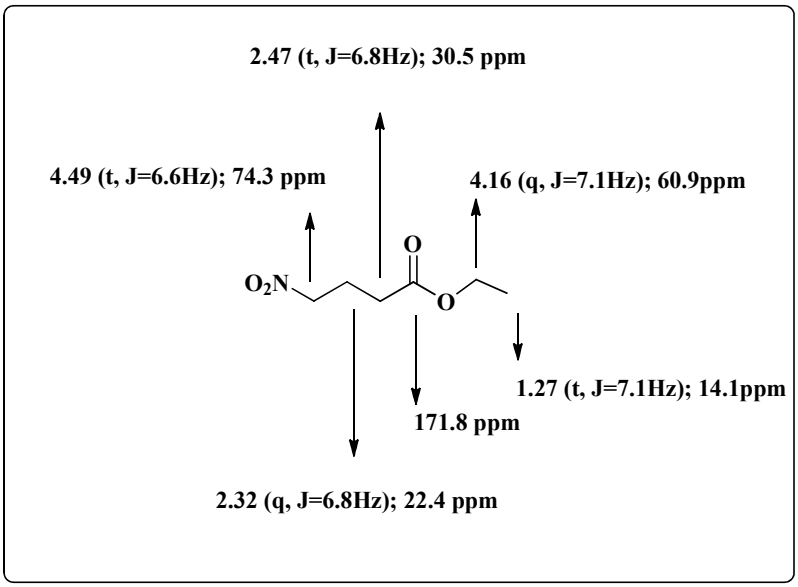
The compound **2** was identified by spectroscopic methods usual including infrared spectroscopy and ^{1}H NMR, ^{13}C NMR.

❖ *^{1}H NMR and ^{13}C NMR Spectroscopy*

The H^{1}NMR spectra of the compound **2** were measured in $CDCl_3$ solution, the protons of this compound appear with different multiplicity as follows:

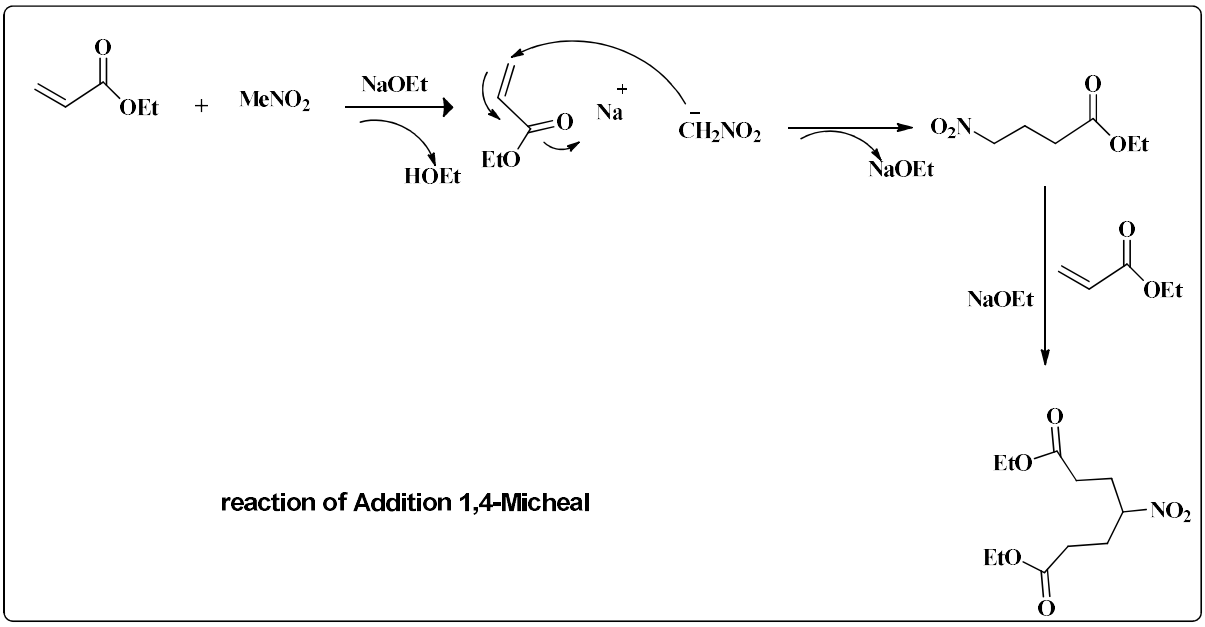
- Triplet (t) belongs to protons methyl and resonate at 1.27 ppm with coupling constant *J*=7.1Hz.
- Quadruple (q) with integration of 2 H at 4.16 ppm with coupling constant *J*= 7.1Hz.
- Triplet (t) with integration 2H at 2.47 ppm corresponding to CH_2CO, with coupling constant *J*= 7.1Hz.
- Quadruple (q) with integration 2H at 2.32 ppm corresponding to CH_2CH_2CO, with coupling constant *J*= 6.8Hz.
- Triplet at 4.49 ppm corresponding to NO_2CH_2 with coupling constant *J* = 6.6 Hz.

The spectrum of ^{13}C NMR showed the appearance of peak at 14.1 ppm refers to methyl group, and four signals at 22.4, 30.5, 60.9, 74.3 ppm corresponding to CH_2CH_2, CH_2CO, CH_2O, CH_2NO_2 respectively, and also a carbonyl group at 171.8 ppm, our results are summarized in picture blow.



❖ ***Proposed mechanism***

The Michael Addition is thermodynamically controlled; the reaction donors are nitromethane, and the acceptors are activated olefins such as acrylate compounds. Picture below describes the mechanism (**Scheme VI.7).**

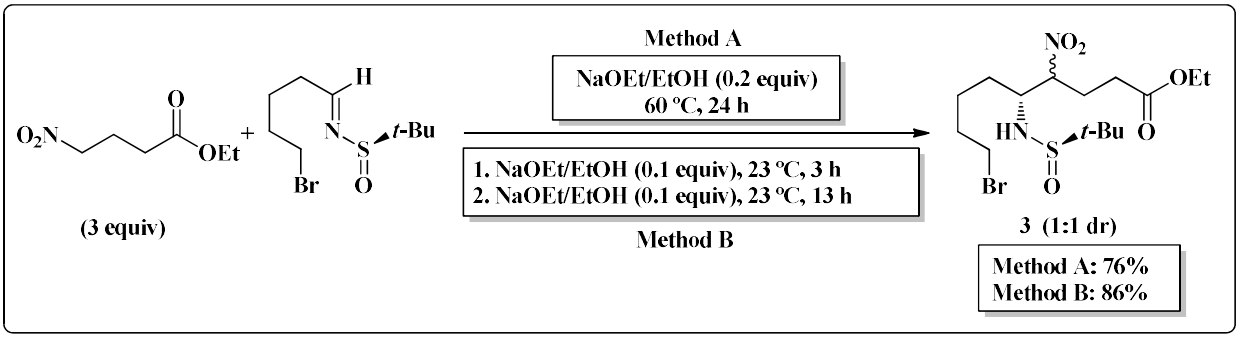


Scheme VI.7

The second step was the addition of nitroester **2** to imine with aza-Henry reaction, the preparation of imines is described in the last chapter, the Compound **3** was obtained in moderate yields working with 3 equivalents of the nitro ester in the presence of 0.2 equivalents of sodium hydroxide as a base, at 40 °C for 24 hours. Higher yield was obtained when 0.2 equivalents of a 2M solution of sodium ethoxide in ethanol was used at 60 ºC for 24 hours (**Scheme VI.8**).

Fortunately, yield was considerably improved when 0.1 equivalents of sodium ethoxide were added to the reaction mixture first, and after 3 hours, another 0.1 equivalents of the same base were also added, working at room temperature for 13 additional hours.

These reactions proceeded with almost total facial diastereoselectivity considering the addition to the imine functional group. Concerning the second stereogenic centre, the one bearing the nitro group, an almost 1:1 mixture of primers were always obtained, because a rapid epimerization occurs working under basic conditions due to the acidic character of the proton on that stereocenter. Concerning the stereochemical pathway of the addition of nitro compounds to chiral *N-tert*-butanesulfinyl imines, we always found that the attack of the nucleophile occurs predominantly to the *Si*-face of the imine with *R* configuration at the sulfur atom of the sulfinyl group.



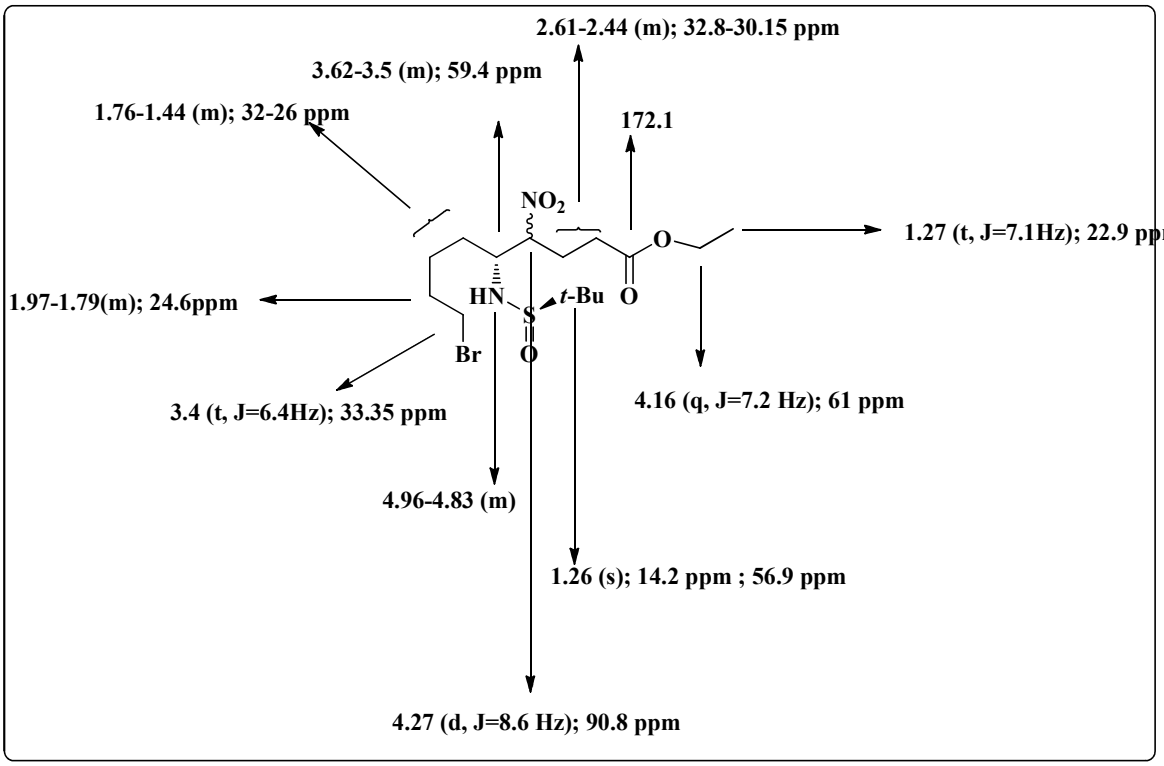
Scheme VI.8

The compound **3** was identified by spectroscopic methods usual including infrared spectroscopy and ^{1}H NMR, ^{13}C NMR, DEPT.

❖ *^{1}H NMR and ^{13}C NMR Spectroscopy*

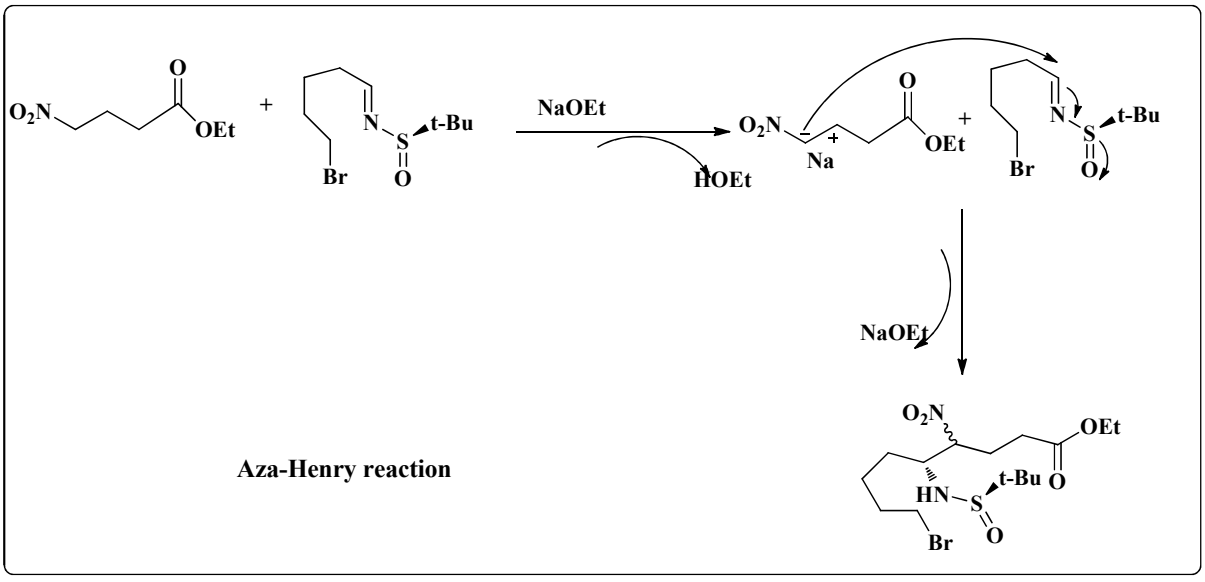
The NMR spectra of the compound **3** were measured in $CDCl_3$ solution, the spectrum of proton shows in low field a doublet at 4.27ppm with coupling constant *J*=8.6Hz corresponding to proton chiral $CHNO_2$and also we have multiplet in the range [3.62-3.5] ppm corresponding to chiral proton CHNH.

From the ^{13}C NMR of the compound with comparison with DEPT spectra, we have quaternary carbon at 172.1 ppm, and six carbon methylene, and two carbon methane, and four carbon methyl. The results are summarized in picture blow.



❖ *Proposed mechanism*

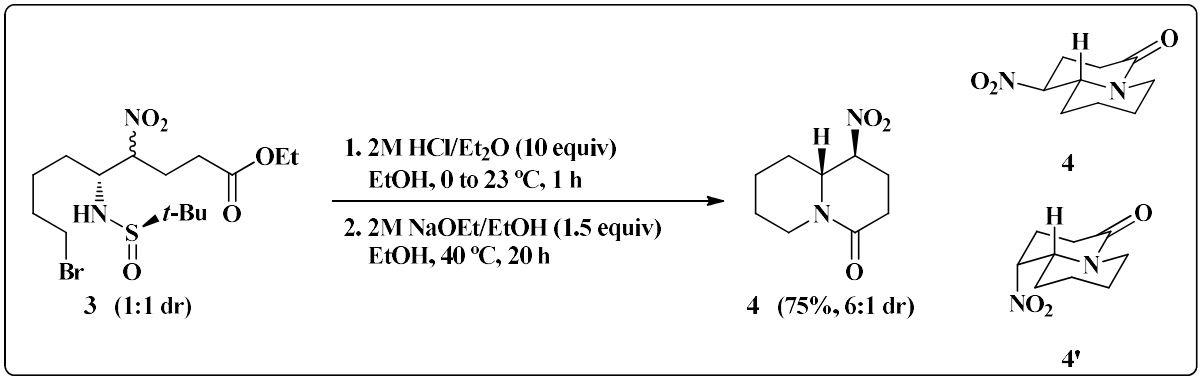
The Henry reaction is base–catalyzed reaction between nitroalkane and aldehyde or ketones. In our cas, the reaction between imine and nitroalkane in the presence of sodium ethoxide. The mechanism of reaction described in (**Scheme VI.9).**



Scheme VI.9

In the Third step, the quinozinile system was obtained from a double cyclization involving the amine group resulting onto desulfinylation of compound. Removal of the *tert*-butane sulfinyl group was easily achieved by treatment with a 2M solution of hydrogen chloride in diethyl ether, in ethanol as solvent, and it was completed after 1 hour. Then, treatment of the resulting ammonium salt with sodium ethoxide in ethanol at 40 ºC for 20 hours led to the formation of nitroquinilizidone **4** in 75% overall yield (**Scheme VI.10**). In this double cyclization, the free amine participated in an intramolecular *N*-alkylation involving the C-Br bond and lactam formation with the ester group.

More importantly, quinolizidine derivative **4** was formed as 6:1 mixture of diastereoisomers, even though compound **3** was isolated in a 1:1 dr. This experimental result can be explained because epimerization occurs rapidly under basic conditions, and isomer **4** with a *trans*-fused quinolizidine core in a chair-chair conformation, with the nitro group in an equatorial orientation, is thermodynamically more stable than isomer **4'**.



Scheme VI.10

The compound **4** was identified by spectroscopic methods usual including infrared spectroscopy and ^{1}H NMR, ^{13}C NMR, DEPT.

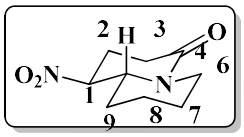
❖ *^{1}H NMR and ^{13}C NMR Spectroscopy*

The NMR spectra of the compound **4** were measured in $CDCl_3$ solution, the isomer **4** with a trans-fused quinolizidine core in a chair-chair conformation with the nitro group in an equatorial orientation, is thermodynamically more stable than isomer **4'**.

In the ^{1}HNMR of the compound in low field, H_1 resonate at 4.85-4.73 ppm as multiplet are deshielded compared with same carbon in the starting material compound **3**.

We can see the disappearance of t-Bu in the zone of strong fields 1.27 ppm. We have also the H_{10} resonate at 4.58-4.5 ppm as multiplet characterised the compound.

From the ^{13}C NMR of the compound with comparison with DEPT spectra, we have quaternary carbon at 166.5ppm, six carbon methylene, and two carbon methine. our results are summarized in (**Table.VI.1**) blow.



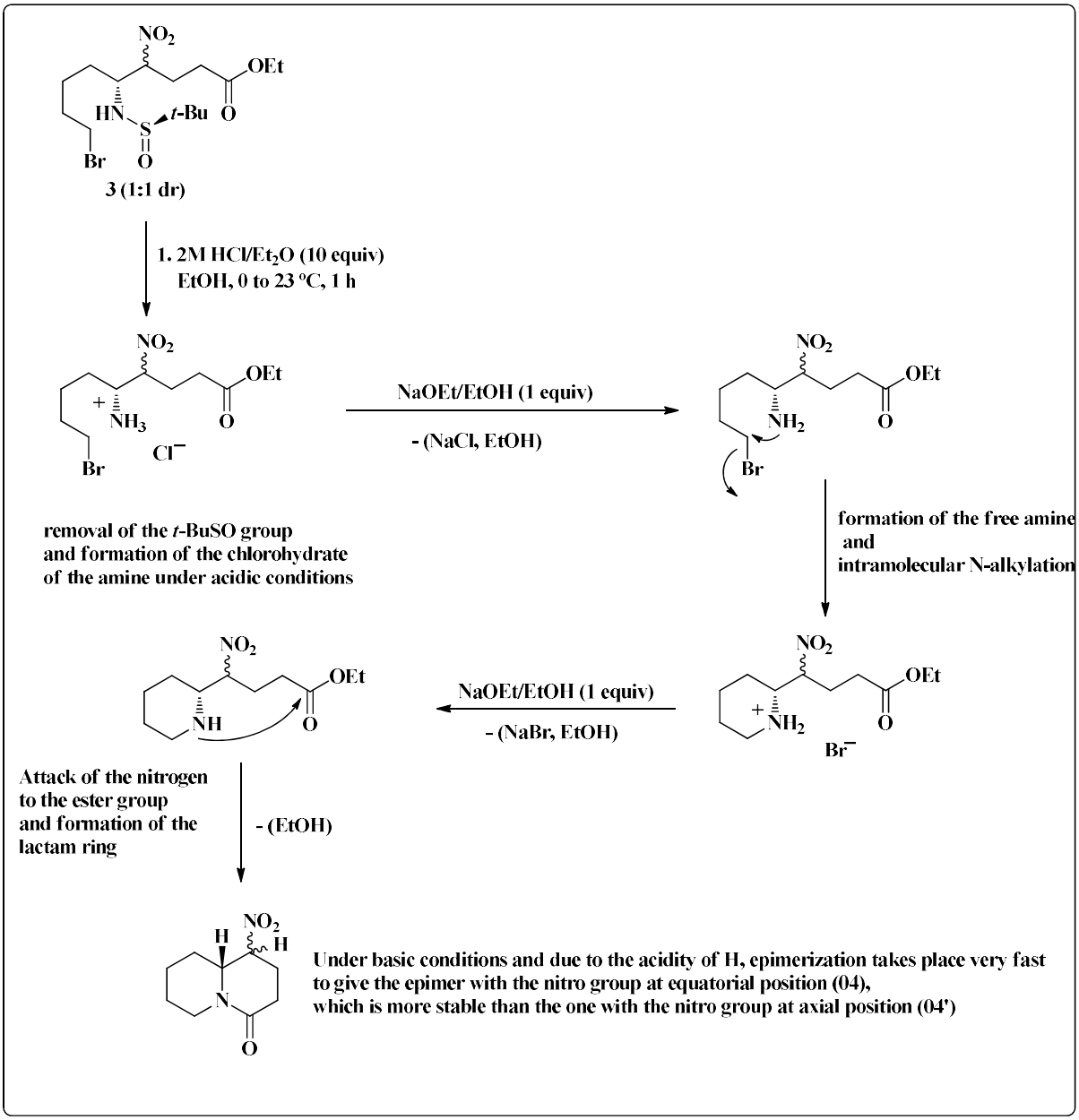
4

Table VI.1: NMR parameters of compound **4**

site	δ_c(ppm)	δ_H(ppm)	Multiplicity	*J*(Hz)
1	84.9	4.85-4.73	m	
2a	28.4	2.59-2.41	m	
2e		2.39-2.27	m	
3a	32	2.39-2.27	m	
3e		2.59-2.41	m	
4	166.5			
6a	43.2	4	ddd	11.7,5.1,2.5
6e		2.59-2.41	m	
7a	24.3	1.78-1.69	m	
7e		1.52-1.35	m	
8a	23.9	1.52-1.35	m	
8e		1.68-1.54	m	
9a	24.8	2.03-1.92	m	
9e		1.91-1.82	m	
10	58.3	4.58-4.5	m	

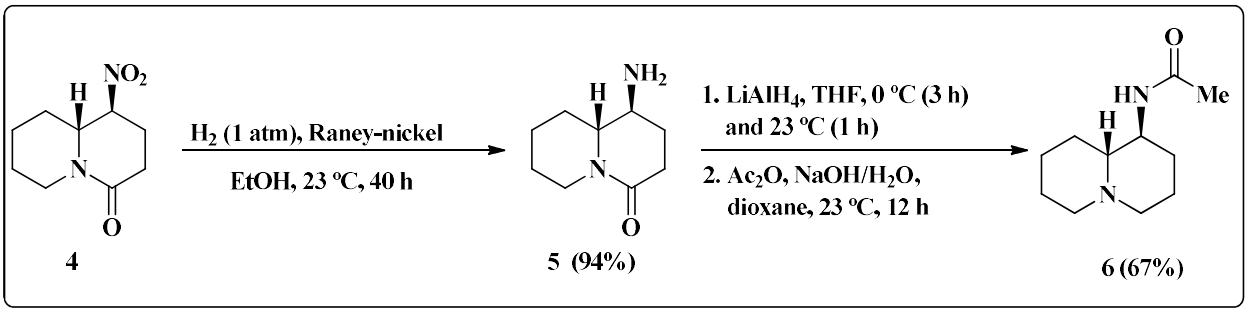
- ***The Proposed mechanism***

A double cyclization of the compound **3** take place with removal of *t*-butylsulfinyl group using HCl, (**Scheme VI.11)** illustrates the mechanism in detail.



Scheme VI.11

In the Last steps, the reduction of the nitro group to the amino group, the reduction of the lactam to give a bridge trialkyl amine derivative, and final acetylation of the primary amine. Reduction of nitro group in compound **4** was achieved in almost quantitative yield with hydrogen (1 atm) and Raney-nickel in ethanol at room temperature for 40 hours. Primary amine derivative **5** was isolated in 94% yield (**Scheme VI.12**). Reduction of lactam **5** with lithium aluminium hydride provide the corresponding aminoquinolizidine, which was further *N*-acetylated to provide the expected (+)-*C(9a)-epi*epiquinamide (**6**)in 67% yield.



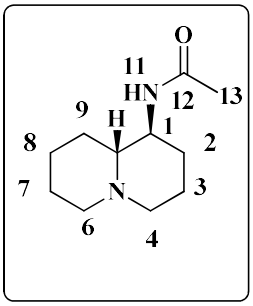
Scheme VI.12.

The compound **6** was identified by spectroscopic methods usual including infrared spectroscopy and ^{1}H NMR, ^{13}C NMR, DEPT.

❖ *^{1}H NMR and ^{13}C NMR Spectroscopy*

In the ^{1}H NMR spectrum of the compound **6**, in low field H_1resonate at 3.68ppm as ddd compared with the starting material the chemical shifts deshielded, the spectrum show the apparition of two proton at 2.31-2.2 ppm as multiplet of C_4, which means that the reduction is done.

The appearance of CH_3 at 1.93 as singlet from acetylation of the primary amine. From the ^{13}C NMR of the compound in comparison with DEPT spectra, we have quaternary carbon at 172.7ppm of the acyl group, and seven carbon methylene, two carbon methine, and one methyl. Our results are summarized in (**Table VI.2**) blow.



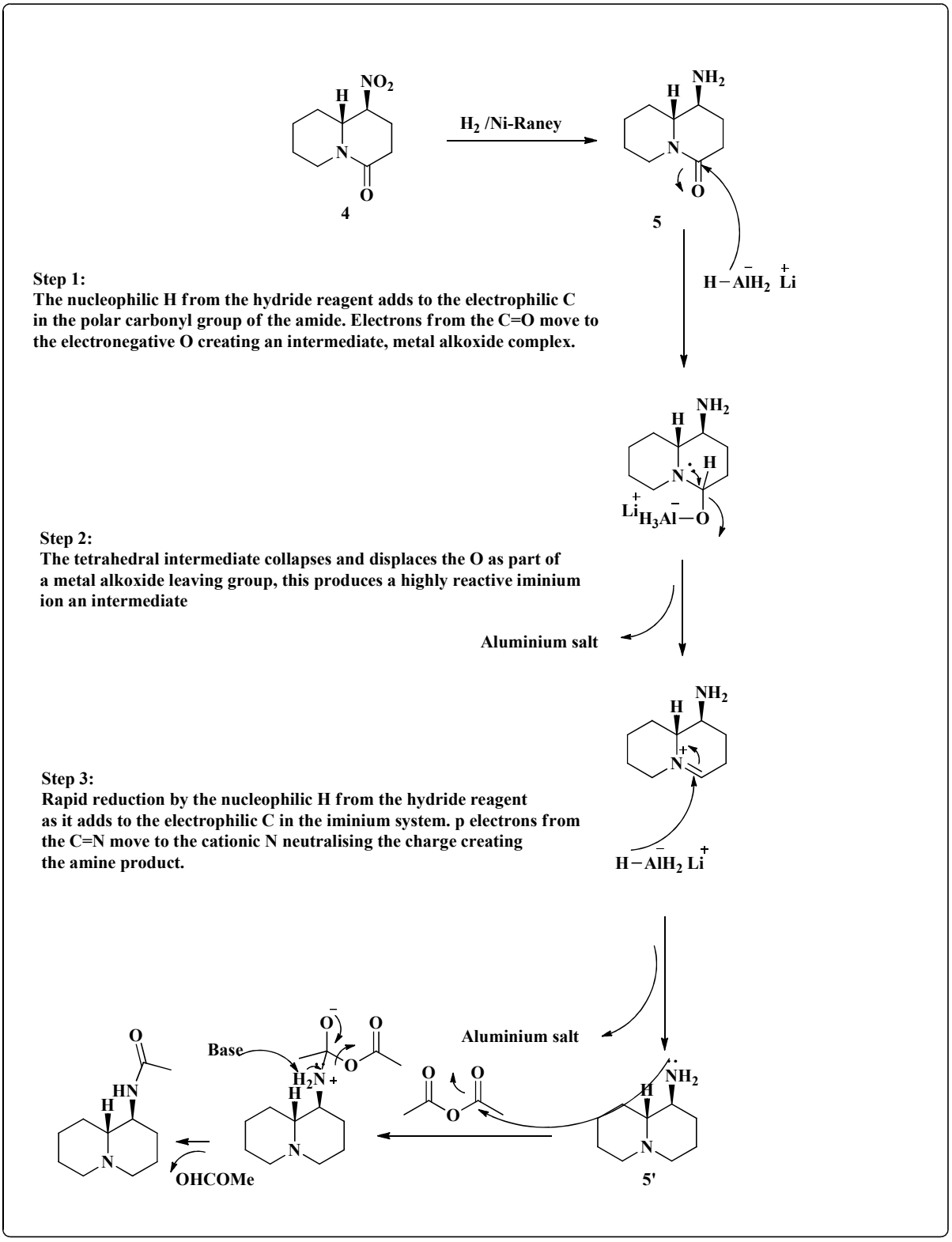
6

Table VI.2: NMR parameters of compound **6**

site	δ_c(ppm)	δ_H(ppm)	Multiplicity	*J*(Hz)
1	68	3.68	ddd	11.9,9.9,4.3
2a	32	1.84-1.78	m	
2e		1.77-1.67	m	
3a	29.4	1.77-1.67	m	
3e		1.77-1.67	m	
4	57.2	2.31-2.2	m	
6a	56.6	1.93-1.9	m	
6e		1.9-1.87	m	
7a	24.4	1.66-1.57	m	
7e		1.41-1.27	m	
8a	24.8	1.41-1.27	m	
8e		1.41-1.27	m	
9a	26	1.41-1.27	m	
9e		1.26-1.18	m	
10	51.8	2.93-2.85	m	
11		3.01-2.94	m	
12	172.7			
13	22.7	1.93	s	

❖ ***Proposed mechanism***

At first, Catalytic hydrogenation with Raney nickel effectively reduce nitro group in compound **4** to amine **5**, then reduce the amide group of the compound **5** to amine using lithium aluminium hydride as catalyst. The mechanism of action is shown in (**Scheme VI.13)** to give the intermediair 5'. Finally, the acetylated of amine in dioxane using acetic anhydride gives the corresponding (+)-C(9a)-Epiepiquinamide (6).


NO2
H
N
O
4
H2 /Ni-Raney
NH2
H
N
O
5
H − AlH2 Li
Step 1:
The nucleophilic H from the hydride reagent adds to the electrophilic C in the polar carbonyl group of the amide. Electrons from the C=O move to the electronegative O creating an intermediate, metal alkoxide complex.
NH2
H
N
H
Li H3Al − O
Step 2:
The tetrahedral intermediate collapses and displaces the O as part of a metal alkoxide leaving group, this produces a highly reactive iminium ion an intermediate
Aluminium salt
NH2
H
N
H − AlH2 Li
Step 3:
Rapid reduction by the nucleophilic H from the hydride reagent as it adds to the electrophilic C in the iminium system. p electrons from the C=N move to the cationic N neutralising the charge creating the amine product.
Aluminium salt
Base
O
HN
H
N
OHCOMe
H2N
5'

Scheme VI.13

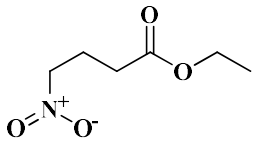
VI.5 Conclusion

We can expect to witness in the future more applications of these methodologies for the synthesis of natural products with increasing complexity.

VI.6 Experimental part

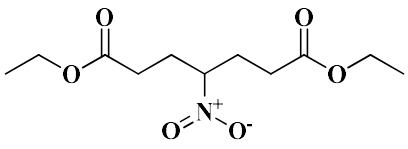
Synthesis of ethyl 4-nitrobutanoate (2) and diethyl 4-nitroheptanedioate (2')

To a solution of ethyl acrylate (**7**) (1.00 g, 1.09 mL, 10.0 mmol) in nitromethane (3.052 g, 2.76 mL, 50.0 mmol) a 2M solution of NaOEt in EtOH (0.50 mL, 1.0 mmol) was added at 0 ºC. The reaction mixture was stirred for 12 h and the system was allowed to reach room temperature. Then, the resulting mixture was hydrolyzed with H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous MgSO4 and evaporated (15 Torr). The resulting residue was purified by distillation under vacuum to give pure compound **9** (0.676 g, 4.60 mmol, 46%) and the undistilled residue was passed through a path of silica gel with hexane to give pure compound **10** (0.548, 2.10 mmol, 21%). Physical and spectroscopic data follow.



Ethyl 4-nitrobutanonate (2)

- Colourless oil
- bp 156-158 ºC (20 Torr)
- R_f 0.46 (hexane/EtOAc: 3/1)
- IR (film) 2983, 2946, 2908, 1728, 1550, 1435, 1376, 1177, 1027 cm^{-1}
- ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (t, *J* = 6.6 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 2.47 (t, *J* = 6.8 Hz, 2H), 2.32 (quint, *J* = 6.8 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H)
- ^{13}C NMR (75 MHz, $CDCl_3$)δ 171.8 (C), 74.3, 60.9, 30.5, 22.4 (CH_2), 14.1 (CH_3)
- LRMS (EI) *m/z* 116 (M^+-CH_3O, 35%), 100 (9), 88 (11), 69 (10), 59 (100).

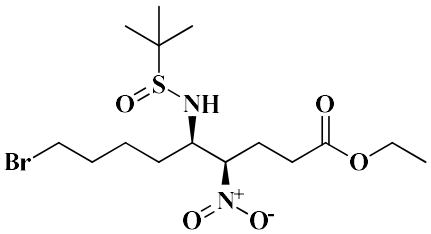


Diethyl 4-nitroheptanedioate (2')

- Colourless oil
- R_f 0.44 (hexane/EtOAc: 3/1).
- IR (film) 2983, 2941, 2910, 1729, 1548, 1445, 1375, 1322, 1252, 1182, 1097, 1028 cm^{-1}
- ^1H NMR (300 MHz, $CDCl_3$) δ 4.70-4.61 (m, 1H), 4.15 (t, J = 7.15 Hz, 4H), 2.41-2.35 (m, 4H), 2.27-2.12 (m, 4H), 1.26 (t, J = 7.15 Hz, 6H).
- ^{13}C NMR (75 MHz, $CDCl_3$)δ 171.8 (C), 86.7 (CH), 60.9, 30.2, 28.7 (CH_2), 14.2 (CH_3)
- LRMS (EI) *m/z* 216 (M^+-C_2H_5O, 26%), 185 (10), 170 (51), 169 (62), 157 (22), 141 (97), 123 (100), 113 (52), 111 (28), 99 (48), 95 (50), 85 (15), 71 (81), 67 (42), 60 (16), 55 (63)
- HRMS (ESI): Calculated for $C_9H_{14}NO_5$ (M^+-C_2H_5O) 216.0872, found 216.0879.

Synthesis of compound 3 by diastereoselective coupling of ethyl 4-nitrobutanoate (2) and chiral imine 1

To a mixture of ethyl 4-nitrobutanoate (**2**) (1.450 g, 9.0 mmol), and chiral imine **1** (0.805 g, 3.0 mmol) a 2M solution of NaOEt in EtOH (0.15 mL, 0.2 mmol) was added at room temperature and was stirred for 3 h. Then a 2M solution of NaOEt in EtOH (0.15 mL, 0.2 mmol) was also added and the resulting reaction mixture was stirred at the same temperature for 13 additional hour. The resulting mixture was hydrolyzed with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous MgSO4, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compound **15** (1.100 g, 2.57 mmol, 86%). Physical and spectroscopic data follow.



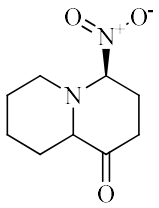
(4*R,5*R*, *RS*)-Ethyl 9-bromo-*N*-(*tert*-butanesulfinyl)-5-amino-4-nitrononanoate (3)**.

- Mixture of diastereoisomers (1:1); colourless oil
- R_f 0.47 (hexane/EtOAc: 1/1)
- IR (film)3421, 3230, 2960, 2869, 1732, 1625, 1549, 1457, 1367, 1303, 1184, 1055, 911 cm^{-1}.

- ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96-4.83 (m, 2H), 4.27 (d, *J* = 8.6 Hz, 1H), 4.21 (d, *J* = 9.8 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 4H), 3.62-3.50 (m, 2H), 3.40 (t, *J* = 6.4 Hz, 4H), 2.61-2.14 (m, 8H), 1.97-1.79 (m, 4H), 1.76-1.44 (m, 8H), 1.27 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 6H), 1.26 (s, 9H).
- ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 172.05 (C), 90.8, 89.8 (CH), 61.0, 61.0 (CH_2), 59.4, 58.5 (CH), 56.9, 56.8 (C), 33.35, 33.3, 32.8, 32.05, 32.0, 30.6, 30.15, 29.9, 26.0, 25.2, 24.6, 24.5 (CH_2), 22.9, 22.8, 14.2 , 14.2 (CH_3).
- LRMS (EI) *m/z* 385 (M^+-C_2H_5O, 2%), 383 (2%), 232 (10), 230 (8), 213 (8), 162 (14), 116 (27), 93 (8), 67 (9), 57 (100), 55 (16), 41 (26).
- HRMS (ESI): Calculated for $C_{15}H_{28}{}^{79}BrN_2O_5S$ (M^+) 427.0902, found 427.0905.

Synthesis of nitroquinolizidinone 4 from compound 3 through an intramolecular double cyclization

To a solution of compound **3** (0.601 g, 1.40 mmol) in EtOH (15 mL) a 2M solution of HCl in in Et_2O (7.0 mL, 14.0 mmol) was added at 0 ºC. The reaction mixture was allowed to reach room temperature and stirred for 1 h. After that, all volatiles were removed under vacuum (15 Torr) and the resulting residue was dissolved in EtOH (100 mL). A 2M solution of NaOEt in EtOH (1.05 mL, 2.1 mmol) was added to this ethanolic solution, and the reaction mixture was stirred at 40 ºC for 20 h. Then, EtOH was removed under vacuum (15 Torr), and the resulting residue was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (100 mL), and brine (15 mL), and extracted with EtOAc (3 × 25 mL). The organic layer was dried over anhydrous MgSO4, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compound **16** (0.208 g, 1.05 mmol, 75%). Physical and spectroscopic data follow.



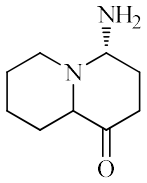
(4*S*)-4-Nitrohexahydro-2*H*-quinolizin-1(6*H*)-one (4).

- Brow-orange liquid.
- $[\alpha]^{20}_{D}$ +6.3 (*c* 1.01, CH_2Cl_2).

- R_f 0.48 (CH_2Cl_2/MeOH: 18/1).
- IR (film) 2941, 2858, 1635, 1547, 1470, 1444, 1421, 1377, 1363, 1343, 1272, 1198, 914 cm^{-1}.
- ^1H NMR (300 MHz, $CDCl_3$) δ 4.85-4.73 (m, 1H), 4.58-4.50 (m, 1H), 4.00 (ddd, *J* = 11.7, 5.1, 2.5 Hz, 1H), 2.59-2.41 (m, 3H), 2.39-2.27 (m, 2H), 2.03-1.92 (m, 1H), 1.91-1.82 (m, 1H), 1.78-1.69 (m, 1H), 1.68-1.54 (m, 1H), 1.52-1.35 (m, 2H).
- ^{13}C NMR (75 MHz, $CDCl_3$)δ 166.5 (C), 84.9, 58.3 (CH), 43.2, 32.0, 28.4, 24.8, 24.3, 23.9 (CH_2).
- LRMS (EI) *m/z* 198 (M^+, 1%),152 (20), 151 (100), 150 (17), 136 (25), 123 (12), 122 (27), 108 (16), 97 (12), 82 (12), 67 (12), 55 (27).
- HRMS (ESI): Calculated for $C_9H_{14}NO$ (M^+-NO_2) 152.1075, found 152.1065.

Synthesis of aminoquinolizidinone 5 by reduction of nitrocompound 4

To a solution of nitro compound **4** (0.071 g, 0.356 mmol) in EtOH (3.0 mL) commercially available Raney nickel (0.812 g, 0.3 mL, 50% slurry in water) was added and the mixture was vigorously stirred at room temperature in hydrogen atmosphere (1 atm) for 40 h. The resulting suspension was filtered through a short pad of Celite with EtOH (40 mL) and concentrated in vacuo (15 Torr). The residue was pure compound **5**(0.056 g, 0.333 mmol, 94%). Physical and spectroscopic data follow.



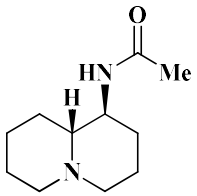
(4*S*)-4-Aminohexahydro-2*H*-quinolizin-1(6*H*)-one (5)

- Brow-orange oil.
- $[\alpha]^{20}_D$ -9.0 (*c* 1.06, CH_2Cl_2).
- R_f 0.12 (CH_2Cl_2/MeOH: 18/1).
- IR (film) 3282, 2931, 2856, 1709, 1621, 1467, 1443, 1421, 1272, 1172, 837 cm^{-1}.
- ^1H NMR (300 MHz, $CDCl_3$) δ 4.82-4.69 (m, 1H), 3.04-2.91 (m, 1H), 2.94-2.83 (m, 1H), 2.62-2.31 (m, 5H), 2.12-1.82 (m, 3H), 1.78-1.61 (m, 2H), 1.56-1.28 (m, 3H).

- ^{13}C NMR (75 MHz, $CDCl_3$)δ 168.5 (C), 64.4, 51.9 (CH), 42.8, 32.0, 30.1, 28.3, 25.15, 24.3(CH_2).
- LRMS (EI) *m/z* 168 (M^+, 35%), 125 (21%), 97 (82), 84 (100), 83 (36), 82 (9), 56 (28), 55 (16).
- HRMS (ESI): Calculated for $C_9H_{16}N_2O$ (M^+) 168.1263, found 168.1265.

Synthesis of (+)-*C(9a)-epi*epiquinamide (6) from aminoquinolizidinone 5

To a solution of aminoquinolizidinone **5** (0.0747 g, 0.44 mmol) in dry THF (10 mL) was added $LiAlH_4$ (0.0479 g, 1.20 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 3 h, and at room temperature for 1 h. After that, H_2O (0.44 mL), K_2CO_3 (0.44 g, 11.5 mmol) and H_2O (0.44 mL) were successively added. The gray solid was filtered off and washed with EtOAc (30 mL). The filtrate was concentrated in vacuo (15 Torr) to provide a colourless oil which was then dissolved in dry dioxane (4.0 mL). A 1M solution of NaOH (4.4 mL, 4.4 mmol) was added followed by Ac_2O (0.225 g, 0.212 mL, 2.2 mmol). The reaction mixture was stirred at room temperature for 12 h. After that, it was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer wasdried over anhydrous MgSO4, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 9/1) to yield pure compound **6** (0.058 g, 0.296 mmol, 67%). Physical and spectroscopic data follow.

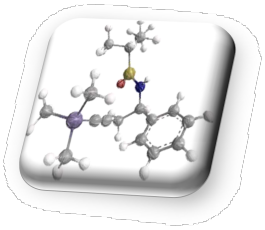


(+)-*C(9a)-Epi*epiquinamide (6).

- White solid.
- mp 124-126 ºC (hexane/CH_2Cl_2).
- $[\alpha]^{20}_D$ +2.4 (*c* 0.63, CH_2Cl_2).
- R_f 0.12 (CH_2Cl_2/MeOH: 18/1).
- IR (KBr) 3280, 2929, 2853, 1639, 1557, 1444, 1372, 1310, 1122, 1113, 1023 cm^{-1}.

- ^{1}H NMR (500 MHz, CD_3OD) δ 3.68 (ddd, *J* = 11.9, 9.9, 4.3 Hz, 1H), 3.01-2.94 (m, 1H), 2.93-2.85 (m, 1H), 2.31-2.20 (m, 2H), 1.93 (s, 3H), 1.93-1.90 (m, 1H), 1.90-1.87 (m, 1H), 1.84-1.78 (m, 1H), 1.77-1.67 (m, 3H), 1.66-1.57 (m, 1H), 1.41-1.27 (m, 4H), 1.26-1.18 (m, 1H).
- ^{13}C NMR (126 MHz, CD_3OD) δ 172.7 (C), 68.0 (CH), 57.2, 56.6 (CH_2), 51.8 (CH), 32.0, 29.4, 26.0, 24.8, 24.4 (CH_2), 22.7 (CH_3).
- LRMS (EI) *m/z* 138 (M^+-C_2H_4NO, 11%), 137 (100), 136 (40), 122 (11), 83 (31), 70 (11), 55 (10), 43 (12).
- HRMS (ESI): Calculated for $C_9H_{15}N$ (M^+-C_2H_5NO) 137.1206, found 137.1204.

General conclusion



General Conclusion

The main objective of the work presented in this manuscript is part of a research line development mainly oriented to cleavage of protecting groups in the synthesis of natural products by simple safe methods in mild reaction condition.

The synthesis of (+)-*C(9a)-epi*epiquinamideis tuning in laboratory of Alicante.

Our practice is based on the role of metals as agent in the mild reaction conditions, which has proven effective in many reactions. At the time of assessment, taking into account the results presented in this thesis, we can consider that the objective that we have assigned is reached.

We have presented general information on methods of introduction and cleavage of various protecting groups on amine functional group in the bibliographic status of the subject.

Our work allows us the synthesis of starting materials tetrazoles bearing various benzylic substituents in the 5-position by reaction of sodium azide with the corresponding nitriles in the presence of an amine and also by knoevelage condensation to have varieties of tetrazoles then benzylated on N1 by reaction with benzyl bromide, giving protected tetrazoles in good yields.

We report the use of metals In, Mg, Zn to perform the removal of the benzyl protecting group from tetrazoles under very mild conditions.

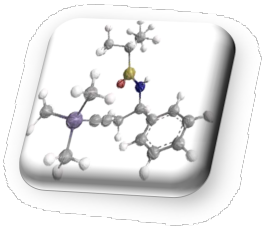
The results have shown that the use of metals (Zn, In, Mg) in the removal of carbon-nitrogen bond is very effective with high yields and reduced reaction time affording to the corresponding starting materials.

We reported also the synthesis of (+)-C (9a)-epiepiquinamide, we started by generality of synthesis of N-*tert*-butane sulfinyl imine as key of this transformation, than we have presented general information of (+)-C(9a)-epiepiquinamide as alkaloide with method of synthesis .

The synthesis of (+)-C(9a)-epiepiquinamide, based on the diastereoselective aza-Henry reaction of ethyl 4-nitrobutanoate and a chiral *N-tert*-butanesulfinyl imine, this method allow as to synthesis this alkaloid with a good yield and purity.

The yields are good for the most products, all prepared products have been identified by the usual spectroscopic methods (^{1}H NMR, ^{13}C NMR), and also by using elemental analysis and the mass spectrometry (**MS**).

Abstract



Abstract

This manuscript encloses two principal parts:

In the first part,

We report the use of three metals for debenzylation of protected tetrazoles: indium, magnesium and zinc, comparing the process of using metals, and taking into account financial aspects, the use of zinc show to be the most effective for substrates non-sensitive to acidic conditions. For substrates sensitive to acid, magnesium or indium metal can be used, can we say that zinc being preferable considering reaction conditions and metal prices.

In the second part,

We have synthesis from commercially available compounds, the (+)-C(9a)-epiepiquinamide the reaction was carried out in six synthetic operations starting from a diastereoselective aza-Henry reaction of a chiral N-*tert*-butanesulfinyl imine and ethyl 4-nitrobutanoate, the configuration of the sulfur atom of the sulfinyl group determining the configuration of C(9a) stereocenter in this transformation.

Key Words: Protected, (+)-*C(9a)-epi*epiquinamide, alkaloid, aza-Henry, *N-tert*-butanesulfinyl imine.

Résume

Ce manuscrit renferme deux parties principales:

Dans la première partie,

Nous rapportons l'utilisation de trois métaux pour la débenzylation de tétrazoles protégés: l'indium, le magnésium et le zinc, en comparant le processus d'utilisation des métaux et en tenant compte des aspects financiers, l'utilisation du spectacle de zinc comme étant la plus efficace pour les substrats insensibles aux acides conditions. Pour les substrats sensibles aux acides, le magnésium ou l'indium peuvent être utilisés, peut-on dire que le zinc est préférable compte tenu des conditions de réaction et du prix des métaux.

Dans la deuxième partie,

Nous avons synthèses par des composés commerciale, le (+) - C (9a) -épiépiquinamide. La réaction a été effectuée dans six opérations de synthèse à partir d'une réaction aza-Henry diastéréosélective d'un N-tert-butanesulfinylimine et du 4-nitrobutanoate d'éthyle chiraux. , la configuration de l'atome de soufre du groupe sulfinyle déterminant la configuration du stéréocentre C (9a) dans cette transformation.

Mots Clés : Protégés, (+)-*C(9a)-epi*epiquinamide, alcaloide, aza-Henry, *N-tert*-butanesulfinyl imine.

الـــمـــلخـــص

يتضمن هذا العمل جزئين أساسيين:

في الجزء الأول ،

أوجـدنا الطـرق العمليـة لإزالـة مجموعـة البنزيـل مـن تيـتراوزول المحميـة باسـتخدام معـادن الإنـديوم ، الجوانـب الماليـة والمغنيسـيوم والزنـك ، ومقارنـة عمليـة اسـتخدام المعـادن ، ومـع الأخـذ فـي الاعتبـار فـإن اسـتخدام الزنـك هـو الأكـثر فعاليـة للمركبـات غـير الحساسـة للحموضـة، بالنسـبة للمركبـات الحساسـة مـن الحموضـة يفضـل اسـتعمال المغنسـيوم أو معـدن الإنـديوم ، يمكننـا القـول أن الزنـك احسـن مـن ناحيـة ظـروف التفاعـل وأسـعار المعـادن

في الجزء الثاني ،

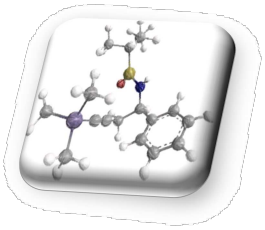
خـلال مركبـات تجاريـة ،بتركيـب ابيكناميـد لقـد قمنـا مـن.

تـم تنفيـذ التفاعـل فـي سـت عمليـات تركيبيـة تبـدأ بتفاعـل أزاءهـنري بيـن ترسـيبوتيل سـلفينيل ايميـن(+) و إيثيـل 4ءنيتروبوتـانوا ت

تكـوين ذرة الكبريـت لمجموعـة سـولفينيل الـتي تحـدد تكـوين سـي ا (9) مـركز فـراغي فـي هـذا التحـول

مفاتيح اللفظ :تيتراوزول المحمية , (+) ايبكناميد ,ازاءهنري, ترسيبوتيل سلفينيل ايمين.

ANNEX



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HIGHLY CONVERGENT STRAIGHTFORWARD STEREOSELECTIVE SYNTHESIS OF (+)-*C(9a)-EPI*EPIQUINAMIDE

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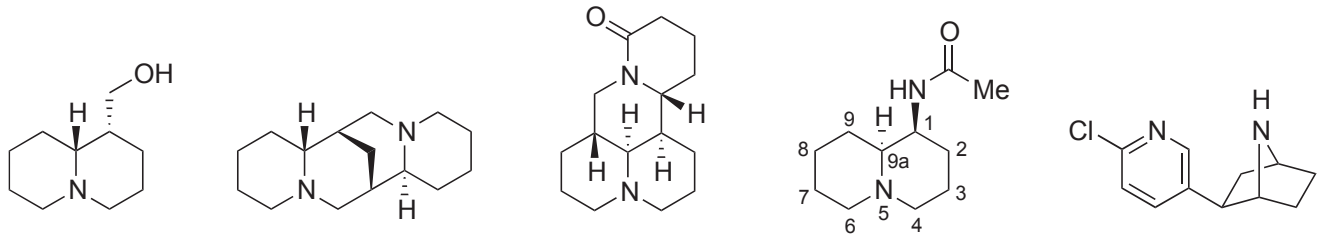
Abstract – The total synthesis of (+)-*C(9a)-epi*epiquinamide has been achieved starting from ethyl 5-bromopentanoate, (R_S)-*tert*-butanesulfinamide, nitromethane, ethyl acrylate and acetic anhydride. The diastereoselective coupling of ethyl 4-nitrobutanoate and a chiral *N*-*tert*-butanesulfinyl imine, along with a double cyclization involving a primary amine through an intramolecular *N*-alkylation and lactam formation, are key steps of this synthesis.

Alkaloids with the quinolizidine structural motif were isolated from different plants and, in a lesser extension, from animal sources too.[1] Quinolizidine alkaloids are abundant in the family Leguminosae, especially in the genus *Lupinus*,[2] and are biosynthesized through the cyclization of a unit of cadaverine, which derives from amino acid L-lysine upon decarboxylation.[3] These natural products exhibit broad pharmacological actions, performing as antipyretics, antibiotics and antivirals.[4] They function as chemical defense compounds in plants against pathogens and herbivorous animals.[5] For instance, (-)-lupidine (**1**) exhibits immunostimulatory activity[6] and inhibit also cholisnesterases (Figure 1). The tetracyclic bis-quinolizidine (-)-sparteine (**2**) is an antiarrhythmic agent[7] and has also found wide application in asymmetric synthesis as a chiral ligand involving organolithium compounds (Figure 1).[8] A mixture of quinolizidine alkaloids, among them (+)-sophoridine (**3**), were present in *Sophora flavescens* root, which is

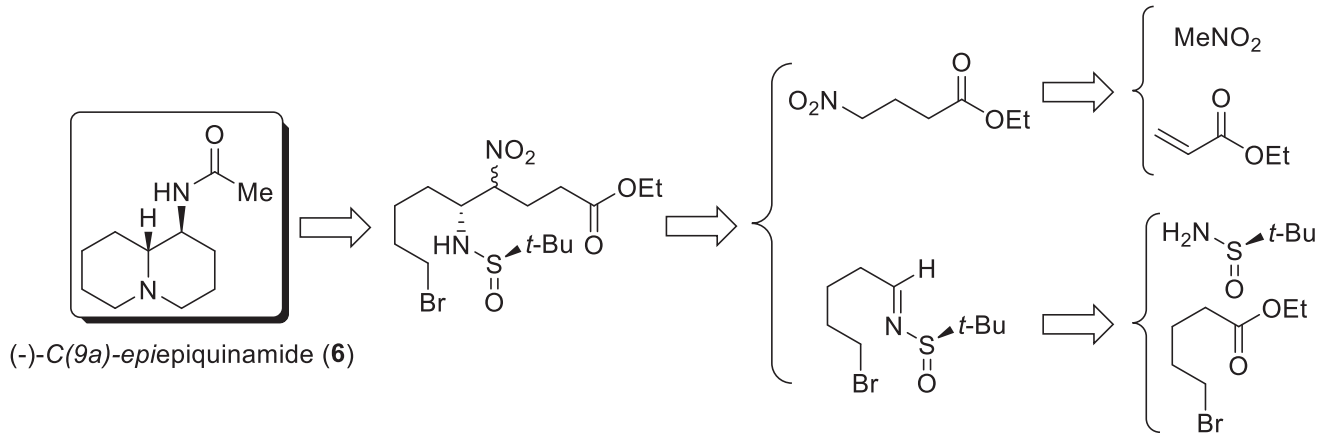
used in traditional Chinese medicine as antipyretic and diuretic agent (Figure 1).[9] On the other hand, (+)-epiquinamide (**4**) is a quinolizidine alkaloid which was isolated from the skin of Ecuadoran frog *Epipedobates tricolor* in 2003.[10] Primary studies regarding its biological activity indicated that this compound displayed potent and selective activities against nicotinic acetylcholine receptors. However, further more carefully undertaken studies shown that (+)-epiquinamide (**4**) was inactive and (-)-epibatidine alkaloid (**5**),[11] which was isolated also from the same source, was responsible for the biological activity due to contamination in the first studies (Figure 1).[12]



(-)-lupinine (**1**) (-)-sparteine (**2**) (+)-sophoridine (**3**) (-)-epiquinamide (**4**) (-)-epibatidine (**5**)

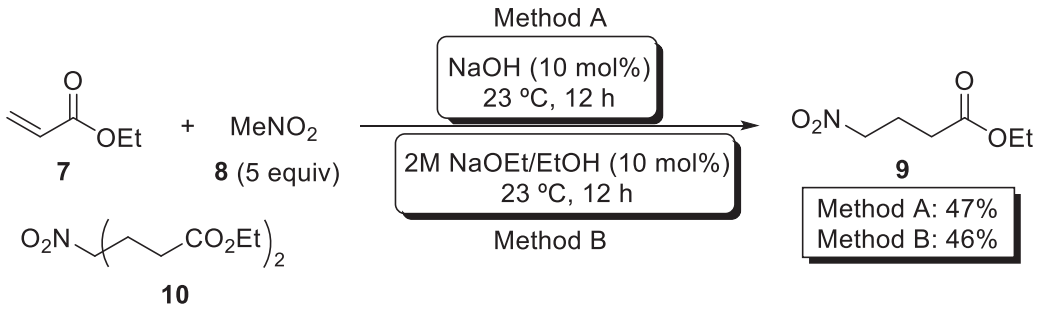
Figure 1

In spite of these results, the synthesis of (+)-epiquinamide (**4**) and its stereoisomers has attracted much attention because these compounds could display potential pharmacological activity.[13] Different synthetic approaches have been reported to access epiquinamide in an enantioselective or racemic[12,14] fashion. Most of the enantioselective syntheses are based on the chiral pool approach starting from aminoacids[15] or monosacharides,[16] and also by means of chiral auxiliaries.[17] There are also examples where at one step of the synthesis either a resolution of a racemate (enzymatic[18a] or with a chiral reagent[18b]) or a catalytic enantioselective procedure is involved.[19] Continuing our interest in the use of *N-tert*-butanesulfinyl imines[20] as electrophiles, and being aware of the potential interest of epiquinamide stereoisomers with regard to biological activity, we decided to explore new synthetic pathways to access to (+)-*C(9a)-epi*epiquinamide (**6**) in an enantioenriched form, based on the diastereoselective aza-Henry reaction of ethyl 4-nitrobutanoate and a chiral *N-tert*-butanesulfinyl imine. Our retrosynthentic analysis for the preparation of (+)-*C(9a)-epi*epiquinamide (**6**) is depicted on Scheme 1.



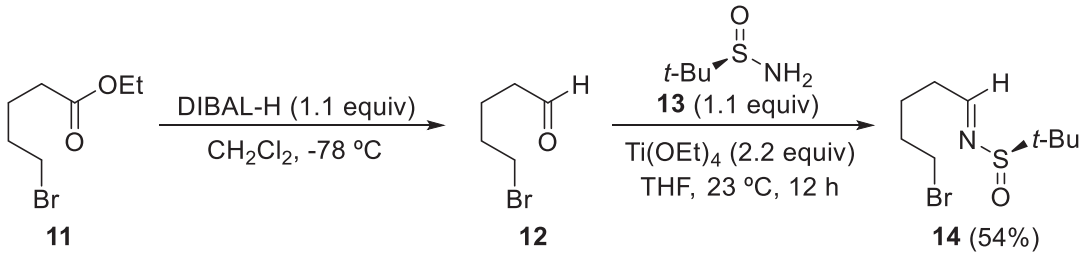
Scheme 1

The first building block of this convergent strategy was prepared from ethyl acrylate (**7**) and nitromethane (**8**), working under basic conditions. When the reaction was performed in the presence of 0.1 equivalents of sodium hydroxide at 0 to 23 ºC for 12 hours, the expected ethyl 4-nitrobutanoate (**9**) was obtained in 47% yield (Method A, Scheme 2).[20t] Almost the same yield was reached working under the same reaction conditions but using a 2M solution of sodium ethoxide in ethanol as a base (Method B, Scheme 2). The second method looks more interesting for scaling up the process. In addition, diethyl 4-nitroheptanedioate (**10**) was always formed as a side reaction product in yields ranging from 18 to 24%, which results from a double conjugate addition of one molecule of nitromethane (**8**) to the α,β-unsaturated ester **7**, in spite of working with a large excess of nitromethane (5 equivalents). Importantly, no additional solvent, apart from the reagents, was needed in this transformation (Scheme 2).



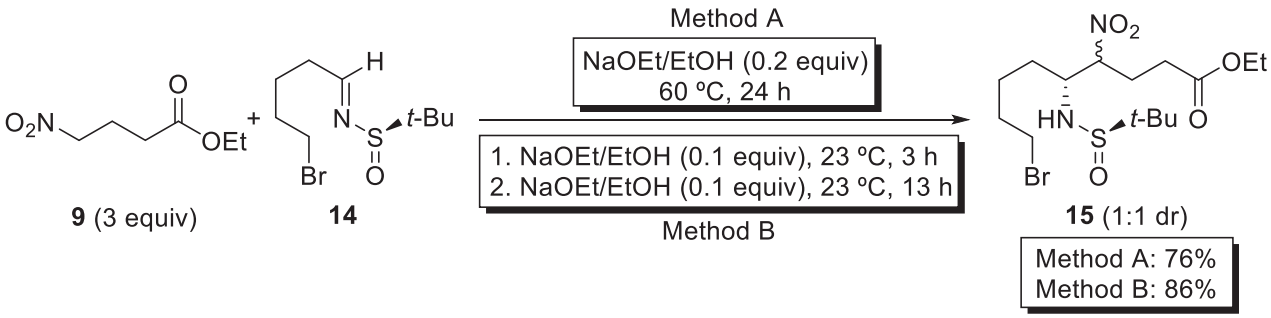
Scheme 2

The second building block was prepared starting from commercially available ethyl 5-bromopentanoate (**11**). Reduction of the ester **11** with DIBAL-H in dichloromethane at -78 ºC for 3 hours led to 5-bromopentanal (**12**),[21] which was condensed with (*R*S)-*tert*-butanesulfinamide (**13**) in the presence of titanium tetraethoxide at room temperature for 12 hours, to give the expected *N*-*tert*-butanesulfinamide **14** in 54% overall yield (Scheme 3).



Scheme 3

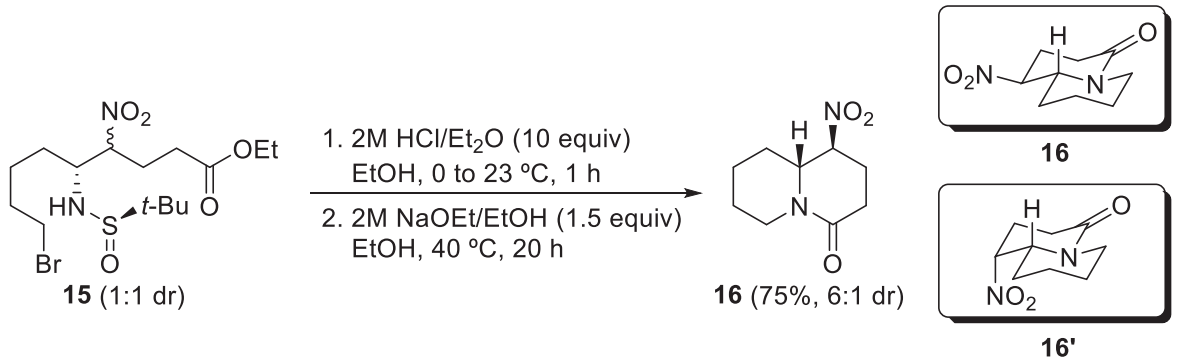
The key step of this synthesis is the diastereoselective coupling of nitro ester **9** and chiral sulfinyl imine **14**. We previously reported the aza-Henry reaction of ethyl 4-nitrobutanoate (**9**) with chiral *N-tert*-butanesulfinyl imines. Compound **15** was obtained in moderate yields working with 3 equivalents of the nitro ester **9** in the presence of 0.2 equivalents of sodium hydroxide as a base, at 40 ºC for 24 hours.[20t] Higher yield was obtained when 0.2 equivalents of a 2M solution of sodium ethoxide in ethanol was used at 60 ºC for 24 hours (Scheme 4). Fortunately, yield was considerably improved when 0.1 equivalents of sodium ethoxide were added to the reaction mixture first, and after 3 hours, another 0.1 equivalents of the same base were also added, working at room temperature for 13 additional hours (Scheme 4). These reactions proceeded with almost total facial diastereoselectivity considering the addition to the imine functional group. Regarding the second stereogenic center, the one bearing the nitro group, an almost 1:1 mixture of epimers were always obtained, because a rapid epimerization occurs working under basic conditions, due to the acidic character of the proton on that stereocenter. Concerning the stereochemical pathway of the addition of nitrocompounds to chiral *N-tert*-butanesulfinyl imines, we always found that the attack of the nucleophile occurs predominantly to the *Si*-face of the imine with *R* configuration at the sulfur atom of the sulfinyl group.[20r,20t]



Scheme 4

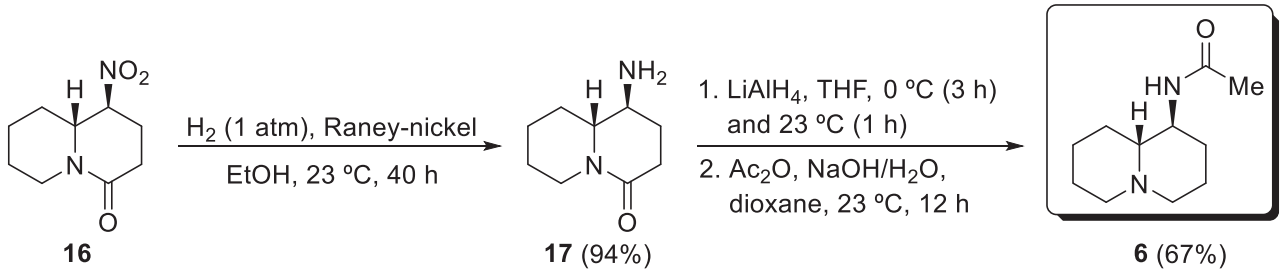
Construction of the quinozinile system was envisioned as arising from a double cyclization involving the amine group resulting upon desulfinylation of compound **15**. Removal of the *tert*-butanesulfinyl group

was easily achieved by treatment with a 2M solution of hydrogen chloride in diethyl ether, in ethanol as solvent, and it was completed after 1 hour. Further treatment of the resulting ammonium salt with sodium ethoxide in ethanol at 40 ºC for 20 hours, led to the formation of nitroquinolizidinone **16** in 75% overall yield (Scheme 5). In this double cyclization, the free amine participated in an intramolecular *N*-alkylation involving the C-Br bond and lactam formation with the ester group. Importantly, quinolizidine derivative **16** was formed as 6:1 mixture of diastereoisomers, although compound **15** was isolated in a 1:1 dr. This experimental result can be explained because epimerization occurs rapidly under basic conditions, and isomer **16** with a *trans*-fused quinolizidine core in a chair-chair conformation, with the nitro group in an equatorial orientation, is thermodynamically more stable than isomer **16'**.



Scheme 5

Last steps of the synthesis comprise the reduction of the nitro group to the amino group, the reduction of the lactam to give a bridge trialkylamine derivative, and final acetylation of the primary amine. Reduction of nitro group in compound **16** was achieved in almost quantitative yield with hydrogen (1 atm) and Raney-nickel in ethanol at room temperature for 40 hours. Primary amine derivative **17** was isolated in 94% yield (Scheme 6). Reduction of lactam **17** with lithium aluminium hydride provide the corresponding aminoquinolizidine, which was further *N*-acetylated to provide the expected (+)-*C(9a)-epi*epiquinamide (**6**) in 67% yield (Scheme 6).



Scheme 6

In summary, a straightforward enantioenriched synthesis of (+)-*C(9a)-epi*epiquinamide (**6**) was carried out in six synthetic operations starting from commercially available compounds. A diastereoselective aza-Henry reaction of ethyl 4-nitrobutanoate and a chiral *N-tert*-butanesulfinyl imine is the key step of the synthesis, the configuration of the sulfur atom of the sulfinyl group determining the configuration of C(9a) stereocenter in this transformation. Target (+)-*C(9a)-epi*epiquinamide (**6**) was obtained in a 18.7% overall yield, considering the lowest yield of the two equally long linear sequence of this convergent synthesis.

EXPERIMENTAL

All chemicals were commercially available (Acros, Aldrich). TLC was performed on Merck silica gel 60 F_{254}, using aluminum plates and visualized with phosphomolybdic acid (PMA) stain. Chromatographic purification was performed by flash chromatography using Merck silica gel 60 (0.040-0.063 mm) and different eluents. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on Agilent GC/MS-5973N apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and high resolution mass spectra (HRMS-ESI) were obtained on a Waters LCT Premier XE apparatus equipped with a time of flight (TOF) analyzer and the samples were ionized by ESI techniques and introduced through an ultra-high pressure liquid chromatograph (UPLC) model Waters ACQUITY H CLASS. IR spectra were measured (film) with a Nicolet Impact 510 P-FT Spectrometer. NMR spectra were recorded with a Bruker AC-300 and a Bruker 500-AVANCE IIIHD, using $CDCl_3$ or CD_3OD as solvents, and TMS as internal standard. Optical rotations were measured on a Perkin Elmer 341 polarimeter.

Synthesis of ethyl 4-nitrobutanoate (9) and diethyl 4-nitroheptanedioate (10)

To a solution of ethyl acrylate (**7**) (1.00 g, 1.09 mL, 10.0 mmol) in nitromethane (3.052 g, 2.76 mL, 50.0 mmol) was added a 2M solution of NaOEt in EtOH (0.50 mL, 1.0 mmol) at 0 ºC. The reaction mixture was stirred for 12 h and the system was allowed to reach room temperature. Then, the resulting mixture was hydrolyzed with H_2O (20 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was purified by distillation under vacuum to give pure compound **9** (0.676 g, 4.60 mmol, 46%) and the undistilled residue was passed through a path of silica gel with hexane to give pure compound **10** (0.548, 2.10 mmol, 21%). Physical and spectroscopic data follow.

Ethyl 4-nitrobutanonate (9).[22]- Colourless oil; bp 156-158 ºC (20 Torr); R_f 0.46 (hexane/EtOAc: 3/1); IR ν (film) 2983, 2946, 2908, 1728, 1550, 1435, 1376, 1177, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (t, J = 6.6 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 2.47 (t, J = 6.8 Hz, 2H), 2.32 (quint, J = 6.8 Hz, 2H),

1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 74.3, 60.9, 30.5, 22.4 (CH_2), 14.1 (CH_3); LRMS (EI) *m/z* 116 (M^+-OC_2H_5, 35%), 100 (9), 88 (11), 69 (10), 59 (100).

Diethyl 4-nitroheptanedioate (10).[23]- Colourless oil; R_f 0.44 (hexane/EtOAc: 3/1); IR ν (film) 2983, 2941, 2910, 1729, 1548, 1445, 1375, 1322, 1252, 1182, 1097, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70-4.61 (m, 1H), 4.15 (t, J = 7.2 Hz, 4H), 2.41-2.35 (m, 4H), 2.27-2.12 (m, 4H), 1.26 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 86.7 (CH), 60.9, 30.2, 28.7 (CH_2), 14.2 (CH_3); LRMS (EI) *m/z* 216 (M^+-OC_2H_5, 26%), 185 (10), 170 (51), 169 (62), 157 (22), 141 (97), 123 (100), 113 (52), 111 (28), 99 (48), 95 (50), 85 (15), 71 (81), 67 (42), 60 (16), 55 (63); HRMS (ESI): Calculated for $C_9H_{14}NO_5$ (M^+-C_2H_5O) 216.0872, found 216.0879.

Synthesis of chiral imine 14 from ethyl 5-bromopentanoate (11) and (*R*)-*tert*-butanesulfinamide (13)

To a solution of ethyl 5-bromopentanoate (**11**) (1.045 g, 0.817 mL, 5.0 mmol) in dry CH_2Cl_2 (9.0 mL) was added a solution of DIBAL-H in toluene (4.60 mL, 5.5 mmol) at -78 ºC. The mixture was stirred for 3 h at the same temperature, quenched with 1M HCl (5.0 mL) and allowed to reach room temperature. Then, the resulting mixture was hydrolyzed with H_2O (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was 5-bromopentanal (**12**) (0.529 g, 3.2 mmol) and it was pure enough to be used in the next reaction step. Thus, a mixture of (*R*)-*tert*-butanesulfinamide **(13)** (0.428 g, 3.5 mmol), 5-bromopentanal (**12**) (0.529 g, 3.2 mmol), and $Ti(OEt)_4$ (1.596 g, 1.465 mL, 7.0 mmol) in THF (5.0 mL) was stirred for 12 h at room temperature. Then, the resulting mixture was hydrolyzed with brine (8 mL), extracted with EtOAc (3 × 10 mL), dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure product **14** (0.713 g, 2.66 mmol, 54% overall yield). Physical and spectroscopic data follow.

(*R*s)-*N*-(*tert*-Butanesulfinyl)-5-bromopentan-1-imine (14).[20y]- Yellow oil; $[\alpha]^{20}_D$ -171.3 (*c* 1.01, CH_2Cl_2); R_f 0.32 (hexane/EtOAc: 3/1); IR ν (film) 2956, 1622, 1456, 1362, 1252, 1230, 1183, 1082, 732, 644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (t, J = 4.4 Hz, 1H), 3.44 (t, J = 6.5 Hz, 2H), 2.57 (td, J = 7.2, 4.4 Hz, 2H), 2.03-1.85 (m, 2H), 1.90-1.73 (m, 2H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (CH), 56.7 (C), 35.2 (CH_2), 33.1 (CH_2), 32.1 (CH_2), 24.0 (CH_2), 22.5 (CH_3); LRMS (EI) *m/z* 213 (M^+-C_4H_8, 17%), 211 (M^+, 17), 84 (8), 70 (8), 57 (100), 55 (9), 43 (41), 41 (26).

Synthesis of compound 15 by diastereoselective coupling of ethyl 4-nitrobutanoate (9) and chiral imine 14

To a mixture of ethyl 4-nitrobutanoate (**9**) (1.450 g, 9.0 mmol), and chiral imine **14** (0.805 g, 3.0 mmol) was added a 2M solution of NaOEt in EtOH (0.15 mL, 0.3 mmol) at room temperature and was stirred for 3 h. Then a 2M solution of NaOEt in EtOH (0.15 mL, 0.3 mmol) was also added and the resulting reaction mixture was stirred at the same temperature for additional 13 h. The resulting mixture was hydrolyzed with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was washed with brine (2 × 10 mL), dried over anhydrous $MgSO_4$, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compound **15** (1.100 g, 2.57 mmol, 86%). Physical and spectroscopic data follow.

(4*R,5*R*,*R*s)-Ethyl 9-bromo-*N*-(*tert*-butanesulfinyl)-5-amino-4-nitrononanoate (15)**.- Mixture of diastereoisomers (1:1); colourless oil; R_f 0.47 (hexane/EtOAc: 1/1); IR ν (film) 3421, 3230, 2960, 2869, 1732, 1625, 1549, 1457, 1367, 1303, 1184, 1055, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96-4.83 (m, 2H), 4.27 (d, J = 8.6 Hz, 1H), 4.21 (d, J = 9.8 Hz, 1H), 4.16 (q, J = 7.2 Hz, 4H), 3.62-3.50 (m, 2H), 3.40 (t, J = 6.4 Hz, 4H), 2.61-2.14 (m, 8H), 1.97-1.79 (m, 4H), 1.76-1.44 (m, 8H), 1.27 (s, 9H), 1.27 (t, J = 7.1 Hz, 6H), 1.26 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 172.05 (C), 90.8, 89.8 (CH), 61.0, 61.0 (CH_2), 59.4, 58.5 (CH), 56.9, 56.8 (C), 33.4, 33.3, 32.8, 32.1, 32.0, 30.6, 30.2, 29.9, 26.0, 25.2, 24.6, 24.5 (CH_2), 22.9, 22.8, 14.2 , 14.2 (CH_3); LRMS (EI) *m/z* 385 (M^+-OC_2H_5, 2%), 383 (2%), 232 (10), 230 (8), 213 (8), 162 (14), 116 (27), 93 (8), 67 (9), 57 (100), 55 (16), 41 (26); HRMS (ESI): Calculated for $C_{15}H_{28}{}^{79}BrN_2O_5S$ (M^+) 427.0902, found 427.0905.

Synthesis of nitroquinolizidinone 16 from compound 15 through an intramolecular double cyclization

To a solution of compound **15** (0.601 g, 1.40 mmol) in EtOH (15 mL) was added a 2M solution of HCl in in Et_2O (7.0 mL, 14.0 mmol) at 0 ºC. The reaction mixture was allowed to reach room temperature and stirred for 1 h. After that all volatiles were removed under vacuum (15 Torr) and the resulting residue was dissolved in EtOH (100 mL). A 2M solution of NaOEt in EtOH (1.05 mL, 2.1 mmol) was added to this ethanolic solution, and the reaction mixture was stirred at 40 ºC for 20 h. Then, EtOH was removed under vacuum (15 Torr), and the resulting residue was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (100 mL), and brine (15 mL), and extracted with EtOAc (3 × 25 mL). The organic layer was dried over anhydrous $MgSO_4$, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, hexane/EtOAc) to yield pure compound **16** (0.208 g, 1.05 mmol, 75%). Physical and spectroscopic data follow.

(4*S*)-4-Nitrohexahydro-2*H*-quinolizin-1(6*H*)-one (16).- Brow-orange liquid; $[\alpha]^{20}_D$ +6.3 (*c* 1.01, CH_2Cl_2); R_f 0.48 (CH_2Cl_2/MeOH: 18/1); IR ν (film) 2941, 2858, 1635, 1547, 1470, 1444, 1421, 1377, 1363, 1343, 1272, 1198, 914 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85-4.73 (m, 1H), 4.58-4.50 (m, 1H),

4.00 (ddd, J = 11.7, 5.1, 2.5 Hz, 1H), 2.59-2.41 (m, 3H), 2.39-2.27 (m, 2H), 2.03-1.92 (m, 1H), 1.91-1.82 (m, 1H), 1.78-1.69 (m, 1H), 1.68-1.54 (m, 1H), 1.52-1.35 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5 (C), 84.9, 58.3 (CH), 43.2, 32.0, 28.4, 24.8, 24.3, 23.9 (CH_2); LRMS (EI) *m/z* 198 (M^+, 1%), 152 (20), 151 (100), 150 (17), 136 (25), 123 (12), 122 (27), 108 (16), 97 (12), 82 (12), 67 (12), 55 (27); HRMS (ESI): Calculated for $C_9H_{14}NO$ (M^+-NO_2) 152.1075, found 152.1065.

Synthesis of aminoquinolizidinone 17 by reduction of nitrocompound 16

To a solution of nitro compound **16** (0.071 g, 0.356 mmol) in EtOH (3.0 mL) was added commercially available Raney nickel (0.812 g, 0.3 mL, 50% slurry in water) and the mixture was vigorously stirred at room temperature in hydrogen atmosphere (1 atm) for 40 h. The resulting suspension was filtered through a short pad of Celite with EtOH (40 mL) and concentrated in vacuo (15 Torr). The residue was pure compound **17** (0.056 g, 0.333 mmol, 94%). Physical and spectroscopic data follow.

(4*S*)-4-Aminohexahydro-2*H*-quinolizin-1(6*H*)-one (17).- Brow-orange oil; $[\alpha]^{20}_D$ -9.0 (*c* 1.06, CH_2Cl_2); R_f 0.12 (CH_2Cl_2/MeOH: 18/1); IR ν (film) 3282, 2931, 2856, 1709, 1621, 1467, 1443, 1421, 1272, 1172, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82-4.69 (m, 1H), 3.04-2.91 (m, 1H), 2.94-2.83 (m, 1H), 2.62-2.31 (m, 5H), 2.12-1.82 (m, 3H), 1.78-1.61 (m, 2H), 1.56-1.28 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 64.4, 51.9 (CH), 42.8, 32.0, 30.1, 28.3, 25.2, 24.3 (CH_2); LRMS (EI) *m/z* 168 (M^+, 35%), 125 (21%), 97 (82), 84 (100), 83 (36), 82 (9), 56 (28), 55 (16); HRMS (ESI): Calculated for $C_9H_{16}N_2O$ (M^+) 168.1263, found 168.1265.

Synthesis of (+)-*C(9a)-epi*epiquinamide (6) from aminoquinolizidinone 17

To a solution of aminoquinolizidinone **17** (0.0747 g, 0.44 mmol) in dry THF (10 mL) was added $LiAlH_4$ (0.0479 g, 1.20 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 3 h, and at room temperature for 1 h. After that, H_2O (0.44 mL), K_2CO_3 (0.44 g, 11.5 mmol) and H_2O (0.44 mL) were successively added. The gray solid was filtered off and washed with EtOAc (30 mL). The filtrate was concentrated in vacuo (15 Torr) to provide a colourless oil which was then dissolved in dry dioxane (4.0 mL). A 1M solution of NaOH (4.4 mL, 4.4 mmol) was added followed by Ac_2O (0.225 g , 0.212 mL, 2.2 mmol). The reaction mixture was stirred at room temperature for 12 h. After that, it was hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried over anhydrous $MgSO_4$, and evaporated (15 Torr). The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 9/1) to yield pure compound **6** (0.058 g, 0.296 mmol, 67%). Physical and spectroscopic data follow.

(+)-*C(9a)-Epi*epiquinamide (6).- White solid, mp 165-168 ºC (dec.; hexane/CH_2Cl_2); $[\alpha]^{20}_D$ +2.4 (*c* 0.63, CH_2Cl_2); R_f 0.12 (CH_2Cl_2/MeOH: 18/1); IR ν (KBr) 3280, 2929, 2853, 1639, 1557, 1444, 1372, 1310, 1122,

1113, 1023 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 3.68 (ddd, *J* = 11.9, 9.9, 4.3 Hz, 1H), 3.01-2.94 (m, 1H), 2.93-2.85 (m, 1H), 2.31-2.20 (m, 2H), 1.93 (s, 3H), 1.93-1.90 (m, 1H), 1.90-1.87 (m, 1H), 1.84-1.78 (m, 1H), 1.77-1.67 (m, 3H), 1.66-1.57 (m, 1H), 1.41-1.27 (m, 4H), 1.26-1.18 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 172.7 (C), 68.0 (CH), 57.2, 56.6 (CH_2), 51.8 (CH), 32.0, 29.4, 26.0, 24.8, 24.4 (CH_2), 22.7 (CH_3); LRMS (EI) *m/z* 138 (M^+-C_2H_4NO, 11%), 137 (100), 136 (40), 122 (11), 83 (31), 70 (11), 55 (10), 43 (12); HRMS (ESI): Calculated for $C_9H_{15}N$ (M^+-C_2H_5NO) 137.1206, found 137.1204.

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Synthesis C. Behloul et al. Paper

Indium-, Magnesium-, and Zinc-Mediated Debenzylation of Protected 1*H*-Tetrazoles: A Comparative Study

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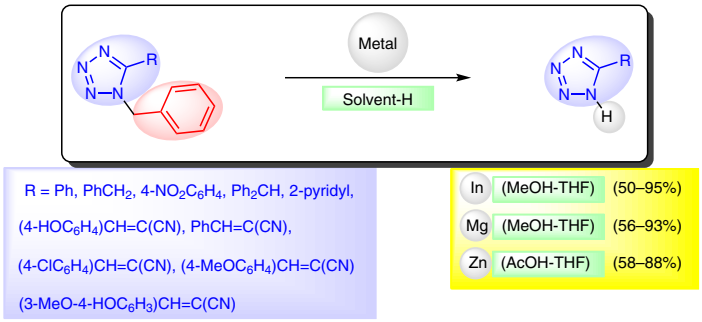
Dedicated to Professor Vicente Gotor on the occasion of his retirement



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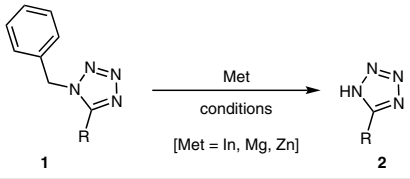
Abstract 5-Substituted 1-benzyltetrazoles are easily debenzylated to give the corresponding deprotected tetrazoles using dissolved metals under protic conditions: Mg/MeOH, In/MeOH, or Zn/$MeCO_2H$ are the procedures of choice for this transformation.

Key words debenzylation, magnesium, indium, zinc, tetrazoles

The benzyl moiety is commonly used in synthetic organic chemistry as protecting group for heteroatoms (O, S, N), mainly due its easy introduction and inherent stability.[1] Concerning the corresponding deprotection, the hydrogenolysis has been widely used in multistep organic synthesis, particularly for the debenzylation of *N*-benzylamines,[2] benzyl ethers,[3] benzyl esters,[4] and benzyl carbamates.[5] This methodology has also been used for the debenzylation of nitrogen-containing heterocycles.[6] Among this group of compounds are tetrazoles, which represent an important structural motif as an aromatic carboxylic acid surrogate in medicinal chemistry since many pharmaceuticals contain this unit.[7] On the other hand, in the last few years we have been interested in developing new methodologies based on dissolved metals (lithium, zinc, and indium). Thus, we have reported detritilations,[8] depivaloylations,[9] deacylations,[10] desilylations,[11] deallyloxy- and debenzyloxycarbonylations,[12] and the reductive removal of the Boc group.[13] In this article, we report the use of indium, magnesium, and zinc metals for the debenzylation of protected tetrazoles under protic conditions to the corresponding 5-substituted tetrazoles under mild reaction conditions.

Tetrazoles **2a–e**, precursors of the starting materials **1a–e**, were prepared by the standard procedure[14] by reacting the corresponding nitrile with sodium azide under reflux in toluene. For tetrazoles **2f–j** the corresponding carbonyl compound, malononitrile, and sodium azide were reacted in water at 50 °C.[15]

The benzylation of tetrazoles **2** was performed by treatment of 1*H*-tetrazoles with benzyl bromide in DMF and using potassium carbonate as base.[16] Once compounds **1** were prepared, the corresponding debenzylation was carried out using indium, magnesium, or zinc as the metallic component according to the general Scheme 1.

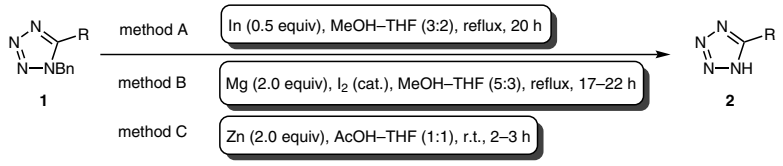


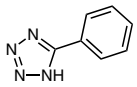
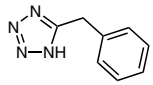
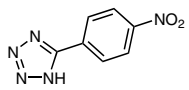
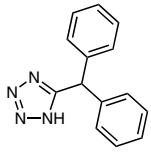
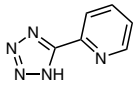
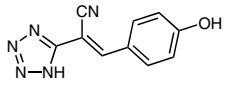
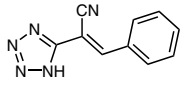
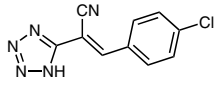
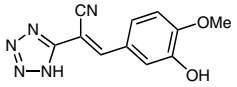
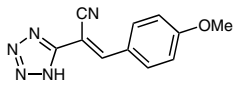
Scheme 1 Debenzylation of compounds **1**; for R groups, see Table 1

Indium-Promoted Debenzylation of Tetrazoles 1 (Method A)

Synthetic methodologies based on indium metal have shown to be very versatile and productive,[17] especially concerning electron transfer processes,[8d,f] which led us to apply this metal to the debenzylation of compounds **1**. When the tetrazole **1a** was treated with indium metal (1:0.5 molar ratio) in a mixture of methanol and THF at 0 °C for 24 hours no reaction was observed. However, total conversion occurred when the same reaction mixture was refluxed for 20 hours (Table 1, entry 1). These conditions were applied to a series of tetrazoles **1b–j**, some of them bearing functional groups such as nitro (**1c**; entry 3), pyridyl (**1e**; entry 5), a

Table 1 Debenzylation of Tetrazoles **1** with Indium, Magnesium, or Zinc



Entry	Starting material	R	Tetrazole product	Structure	A (In)	B (Mg)	C (Zn)
1	**1a**	Ph	**2a**		95	93	88
2	**1b**	$PhCH_2$	**2b**		80	85	87
3	**1c**	4-$O_2NC_6H_4$	**2c**		76	80	80
4	**1d**	Ph_2CH	**2d**		80	84	84
5	**1e**	2-pyridyl	**2e**		88	90	88
6	**1f**	(*E*)-C(CN)=CH(4-HOC_6H_4)	**2f**		50	56	60
7	**1g**	(*E*)-C(CN)=CHPh	**2g**		60	69	64
8	**1h**	(*E*)-C(CN)=CH(4-ClC_6H_4)	**2h**		51	58	68
9	**1i**	(*E*)-C(CN)=CH(4-$MeOC_6H_4$)	**2i**		55	60	58
10	**1j**	(*E*)-C(CN)=CH(3-MeO-4-HOC_6H_3)	**2j**		53	59	61

[a] Isolated yield after recrystallization based on the starting material **1**.

conjugate cyano group (**2g–j**; entries 7–10), chlorine (**2h**; entry 8), or phenolic OH (**2j**; entry 10), thus indicating that this methodology tolerates several functionalities.

Magnesium-Promoted Debenzylation of Tetrazoles 1 (Method B)

Although the mixture of magnesium and methanol has been used for the hydrogenation of double bonds,[18] as far as we know it has been reported to be useful only for the debenzylation of benzyl ethers.[19] In Table 1, the results from the deprotection of tetrazoles **1** with magnesium in methanol are shown. Treatment of the starting material **1a** with

magnesium in methanol or in mixture of methanol and THF at room temperature did not produce the expected debenzylated tetrazoles **2a** after 24 hour. However, after refluxing the former mixture (MeOH–THF 2:1) for 22 hours, a 40% yield of **2a** was obtained. An important increase in the yield was obtained (93%) when a flake of iodine was added to the reaction mixture (Table 1, entry 1). As it can be seen from Table 1, this methodology is also compatible with the same functionalities shown in Table 1.

Zinc-Promoted Debenzylation of Tetrazoles 1 (Method C)

Zinc metal in combination with a proton source can also be useful as dissolving metal for electron transfer reactions.[8e] Thus, by treating protected tetrazoles **1** with zinc metal and acetic acid in THF at room temperature, the corresponding debenzylated products **2** were isolated after 2–3 hours. Also in this case several functionalities were compatible with the reaction conditions used in the deprotection, as it can be seen in Table 1.

Discussion

In general, debenzylation of substituted tetrazoles with indium, magnesium, or zinc metals works properly, especially for non-functionalized compounds **1**, giving the expected deprotected tetrazoles in isolated yields over 80%. However, for highly functionalized tetrazoles **1f–j** containing a conjugate nitrile, isolated yields decrease to 50–70% due to secondary reactions and/or partial decomposition of the starting material/product under the assayed reaction conditions. Concerning the reaction conditions, whereas Zn works at room temperature, In and Mg need refluxing in THF–MeOH for the reaction to proceed. The reaction times for Zn reductions (2–3 h) were significantly shorter than those for In and Mg deprotections (17–22 h).

Concerning a possible reaction mechanism, we presume that a single electron transfer (SET) takes place from the metal to the starting tetrazole **1** cleaving the benzyl–nitrogen bond to give a benzyl radical **I** and the heterocyclic anion **II**, both stabilized by delocalization (Figure 1). Benzyl radical **I** decomposes by a hydrogen atom abstraction to give toluene,[20] meanwhile the hydrolysis of heterocyclic anion **II** leads to the formation of deprotected tetrazole **2**. A similar mechanism could be also involved in the detritylation of protected tetrazoles.[8]

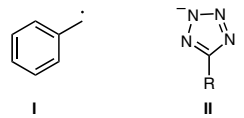


Figure 1 Proposed radical intermediates in the metal debenzylation of tetrazoles **1**

Considering the obtained results, and taking into account reaction conditions and the price of metals,[21] we consider that zinc would be the metal of choice for compounds that are not sensitive to acetic acid. For acid sensitive compounds, probably magnesium would be the best metal to be used in debenzylation of protected tetrazoles due to reaction times, yields, and metal price.

From the results shown here, we can conclude that the debenzylation of 1-benzyl 5-substituted tetrazoles **1** can be performed with indium/methanol, magnesium/methanol, and zinc/acetic acid, in general in good yields to the corresponding tetrazoles **2**. Comparing the three procedures, and taking into account financial aspects, the use of zinc seems to be the most effective for substrates non-sensitive to acidic conditions. For substrates sensitive to acid, magnesium or indium metal can be used, the first one being preferable considering reaction conditions and metal prices.

General Information

FTIR spectra were obtained with a Nicolet Impact 400D spectrophotometer using KBr pellets. NMR spectra were recorded with a Bruker AV400 (400 MHz for 1H and 100 MHz for ^{13}C), DMSO-d_6 as solvent and TMS (δ = 0.00 ppm, 1H) and DMSO-d_6 (δ = 2.50 ppm, ^{1}H and δ = 39.75 ppm, ^{13}C) as internal standards; chemical shifts are given in δ (ppm) and coupling constants (*J*) in Hz. High-resolution mass spectra (HRMS) were carried out in a Agilent 7200, in the electrospray ionization mode (ESI) using a TOF analyzer. All reagents used for the synthesis of tetrazoles **2** and *N*-benzyltetrazoles **1** were commercially available and used without any further purification.

Tetrazoles 2a–e;[14] General Procedure

A mixture of the corresponding nitrile (50 mmol), NaN_3 (65 mmol) and $Et_3N{\cdot}HCl$ (150 mmol) in toluene (100 mL) was stirred at 110 °C for 17–30 h (TLC monitoring). After cooling to r.t., the mixture was extracted with H_2O (100 mL) and the aqueous phase was acidified with aq 36% HCl. The solid formed was filtered, washed with H_2O (3 × 10 mL), and dried under reduced pressure to give the corresponding product **2a–e**.

5-Phenyl-1*H*-tetrazole (2a)[8c]

White solid; yield: 3.0 g (41%); mp 215–216 °C.

IR (KBr): 3333, 2588, 2511, 1055, 925, 789, 643, 619 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55–7.62 (m, 3 H), 8.01–8.10 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 124.1 (CH), 127.0 (C), 129.4, 131.3 (CH), 155.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_7H_6N_4$ (M^+): 146.0592; found: 146.0598.

5-Benzyl-1*H*-tetrazole (2b)[8c]

White solid; yield: 2.0 g (25%); mp 123–124 °C.

IR (KBr): 2949, 2864, 2709, 1073, 961, 835, 694, 608 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.31 (s, 2 H), 7.25–7.37 (m, 5 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 29.0 (CH_2), 127.1, 128.7, 128.8 (CH), 136.0, 155.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_8H_8N_4$ (M^+): 160.0749; found: 160.0748.

5-(4-Nitrophenyl)-1*H*-tetrazole (2c)[22]

Green solid; yield: 2.9 g (32%); mp 146–147 °C.

IR (KBr): 3453, 2543, 1018, 988, 978, 851, 702, 634 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29–8.33 (m, 2 H), 8.43–8.46 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 125.0, 128.6 (CH), 131.0, 149.1, 155.8 (C).

HRMS (ESI): *m*/*z* calcd for $C_7H_5N_5O_2$ (M^+): 191.0443; found: 191.0452.

5-Benzhydryl-1*H*-tetrazole (2d)[8c]

White solid; yield: 3.0 g (27%); mp 165–166 °C.

IR (KBr): 3360, 2680, 1082, 990, 845, 695, 617 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.97 (s, 1 H), 7.11–7.48 (m, 10 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 46.2 (CH), 127.65, 128.9, 129.15 (CH), 140.5, 158.5 (C).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}N$ ($M^+ - N_3$): 194.0970; found: 194.0954.

2-(1*H*-Tetrazol-5-yl)pyridine (2e)[22]

Brown solid; yield: 3.0 g (27%); mp 208–210 °C.

IR (KBr): 3091, 2650, 1539, 1114, 975, 899, 695, 615 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.54–7.75 (m, 1 H), 8.04–8.19 (m, 1 H), 8.27 (dd, *J* = 7.4, 3.8 Hz, 1 H), 8.84 (t, *J* = 4.3 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 123.0, 126.5, 138.65 (CH), 144.1 (C), 150.5 (CH), 155.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_6H_5N_3$ ($M^+ - N_2$): 119.0483; found: 119.0491.

Tetrazoles 2f–j;[15] General Procedure

A mixture of the corresponding carbonyl compound (1 mmol), malononitrile (1 mmol), and NaN_3 (2 mmol) in H_2O (5 mL) was stirred at 50 °C until the starting materials were consumed (TLC monitoring). The reaction mixture was filtered and to the filtrate was added aq 2 N HCl (30 mL) until a precipitate was formed. The solid was filtered and dried in a drying oven to furnish the expected tetrazoles **2f–j**.

(*E*)-3-(4-Hydroxyphenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2f)[23]

White solid; yield: 0.20 g (94%); mp 159–161 °C.

IR (KBr): 3330, 2642, 1509, 1411, 988, 821, 653, 604 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.99 (d, *J* = 8.3 Hz, 2 H), 7.96 (d, *J* = 8.3 Hz, 2 H), 8.23 (s, 1 H), 10.68 (br s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 91.9 (CN), 116.3 (C), 116.75 (CH), 123.7 (C), 133.1 (CH), 148.8, 155.6, 162.2 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_6NO$ ($M^+ - HN_4$): 156.0449; found: 156.0452.

(*E*)-3-Phenyl-2-(1*H*-tetrazol-5-yl)acrylonitrile (2g)[23]

Pale yellow solid; yield: 0.10 g (51%); mp 168–170 °C.

IR (KBr): 3310, 2641, 1570, 1477, 982, 848, 669, 608 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.58–7.63 (m, 3 H), 8.00–8.15 (m, 2 H), 8.42 (d, *J* = 3.6 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 97.4 (CN), 115.9 (C), 129.6, 130.0, 130.3, 132.6 (CH), 148.8, 155.9 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_6N_3$ ($M^+ - HN_2$): 168.0562; found: 168.0566.

(*E*)-3-(4-Chlorophenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2h)[24]

White solid; yield: 0.16 g (75%); mp 158–160 °C.

IR (KBr): 3158, 2359, 1585, 1497, 930, 810, 691, 623 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.62–7.72 (m, 2 H), 8.05 (d, *J* = 8.6 Hz, 2 H), 8.41 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 98.1 (CN), 115.8 (C), 129.15, 129.8 (CH), 131.5 (C), 131.9 (CH), 137.3, 147.3 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_5ClN_2$ ($M^+ - HN_3$): 188.0141; found: 188.0140.

(*E*)-3-(4-Methoxyphenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2i)[24]

Green solid; yield: 0.20 g (88%); mp 76–78 °C.

IR (KBr): 3120, 2773, 1589, 1462, 954, 864, 651, 604 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3 H), 7.14 (d, *J* = 8.6 Hz, 2 H), 8.01 (d, *J* = 8.6 Hz, 2 H), 8.25 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.1 (CH_3), 93.9 (CN), 115.35 (CH), 116.6 (C), 125.3, 132.6 (CH), 148.05, 155.9, 163.0 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_9N_3O$ ($M^+ - CN_2$): 187.0746; found: 187.0733.

(*E*)-3-(4-Hydroxy-3-methoxyphenyl)-2-(1*H*-tetrazol-5-yl)acrylonitrile (2j)[24]

Green solid; yield: 0.16 g (75%); mp 88–89 °C.

IR (KBr): 3121, 2225, 1574, 1458, 998, 844, 644, 620 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.88 (s, 3 H), 7.00 (d, *J* = 8.3 Hz, 1 H), 7.53 (d, *J* = 8.4 Hz, 1 H), 7.75 (s, 1 H), 8.22 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.0 (CH_3), 91.9 (CN), 113.2, 116.4 (CH), 116.8 (C), 124.0, 126.3, (CH), 148.2, 148.9, 151.9, 155.75 (C).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_6N_3O$ ($M^+ - N_2CH_3O$): 184.0511; found: 184.0537.

Benzylation of Tetrazoles 2;[16] General Procedure

A mixture of the corresponding tetrazole **2** (1 mmol), benzyl bromide (1 mmol), and K_2CO_3 (2 mmol) in DMF (5 mL) was stirred a 0 °C until the conversion was complete (TLC monitoring). The reaction mixture was filtered and to the filtrate was added H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and after evaporation of the solvent (15 Torr) the resulting residue was purified by recrystallization (EtOH) to yield tetrazoles **1**.

1-Benzyl-5-phenyl-1*H*-tetrazole (1a)[25]

White solid; yield: 0.18 g (77%); mp 78–80 °C.

IR (KBr): 1651, 1274, 979, 854, 773, 615 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.80 (s, 2 H), 7.32–7.50 (m, 8 H), 8.13 (dd, *J* = 7.5, 2.3 Hz, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.8 (CH_2), 126.9, 128.4, 128.8, 128.9, 129.0, 130.3 (CH), 133.4, 162.7, 165.4 (C).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}N_4$ (M^+): 236.1062; found: 236.1051.

1,5-Dibenzyl-1*H*-tetrazole (1b)[26]

White solid; yield: 0.2 g (80%); mp 140–142 °C.

IR (KBr): 1604, 1278, 976, 854, 693, 601 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.21 (s, 2 H), 5.68 (s, 2 H), 7.18–7.37 (m, 10 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 31.9, 56.6 (CH_2), 126.9, 128.4, 128.6, 128.8, 128.9, 129.0 (CH), 133.35, 136.7, 165.9 (C).

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{12}N_3$ ($M^+ - CH_2N$): 222.1031; found: 222.1027.

1-Benzyl-5-(4-nitrophenyl)-1*H*-tetrazole (1c)[25]

Green solid; yield: 0.18 g (66%); mp 76–78 °C.

IR (KBr): 1604, 1282, 965, 852, 651, 601 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.84 (s, 2 H), 7.33–7.52 (m, 5 H), 8.30–8.33 (m, 4 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.2 (CH_2), 124.2, 127.7 128.5, 129.1, 129.2 (CH), 132.9, 133.2, 148.85, 163.6 (C).

HRMS (ESI): *m*/*z* calcd for $C_7H_5N_5O_2$ (M^+): 191.0443; found: 191.0452.

5-Benzhydryl-1-benzyl-1*H*-tetrazole (1d)

White solid; yield: 0.27 g (84%); mp 133–135 °C.

IR (KBr): 1598, 1254, 953, 890, 688, 608 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.35–5.37 (m, 3 H), 7.00–7.18 (m, 9 H), 7.19–7.38 (m, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 46.55 (CH), 51.1 (CH_2), 127.5, 127.8, 128.6, 128.9, 129.2 (CH), 133.15, 138.1, 156.2 (C);

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{18}N_4$ (M^+): 326.1531; found: 326.1522.

2-(1-Benzyl-1*H*-tetrazol-5-yl)pyridine (1e)[27]

Green solid; yield: 0.20 g (88%); mp 75–77 °C.

IR (KBr): 1589, 1263, 999, 876, 690, 601 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.25 (s, 2 H), 7.19–7.52 (m, 6 H), 7.82–7.92 (m, 1 H), 8.33 (d, *J* = 7.9 Hz, 1 H), 8.74 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 52.6 (CH_2), 124.5, 125.5, 128.3, 128.4, 128.7 (CH), 134.8 (C), 137.5 (CH), 144.7 (C), 149.3 (CH), 151.6 (C).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_9N_3$ ($M^+ - N_2H_2$): 207.0796; found: 207.0792.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-hydroxyphenyl)acrylonitrile (1f)[28]

Orange solid; yield: 0.23 g (77%); mp 160–162 °C.

IR (KBr): 2360, 1511, 1439, 1261, 997, 895, 672, 614 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.13 (s, 2 H), 5.78 (s, 1 H), 7.05 (d, *J* = 8.9 Hz, 2 H), 7.33–7.46 (m, 5 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 8.20 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 52.6 (CH_2), 95.3 (CN), 115.5 (CH), 116.2, 125.45 (C), 127.5, 128.5, 129.1, 132.4 (CH), 132.8, 136.0 (C), 146.7 (CH), 161.8 (C).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{11}NO$ ($M^+ - N_4H_2$): 245.0841; found: 245.0829.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-phenylacrylonitrile (1g)[29]

Green solid; yield: 0.19 g (67%); mp 190–192 °C.

IR (KBr): 2332, 1596, 1443, 1211, 973, 856, 697, 605 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.80 (s, 2 H), 7.33–7.51 (m, 8 H), 7.91–8.02 (m, 2 H), 8.29 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.2 (CH_2), 98.6 (CN), 115.6 (C), 128.6, 129.1, 129.2, 129.3, 130.1, 132.1 (CH), 132.2 (C), 147.3 (CH), 161.8 (C).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{13}N_5$ (M^+): 287.1171; found: 287.1148.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-chlorophenyl)acrylonitrile (1h)

Green solid; yield: 0.14 g (45%); mp 170–172 °C.

IR (KBr): 2224, 1588, 1474, 1211, 962, 833, 687, 616 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 5.80 (s, 2 H), 7.32–7.53 (m, 7 H), 7.91 (d, *J* = 8.6 Hz, 2 H), 8.24 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 57.3 (CH_2), 99.1 (CN), 115.3 (C), 128.6, 129.1, 129.25, 129.5 (CH), 130.8 (C), 131.3 (CH), 132.7, 138.2 (C), 145.7 (CH), 161.6 (C).

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}ClN_5$ (M^+): 321.0781; found: 321.0775.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-methoxyphenyl)acrylonitrile (1i)

Green solid; yield: 0.19 g (60%); mp 76–78 °C.

IR (KBr): 2221, 1594, 1497, 1217, 970, 825, 683, 613 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.87 (s, 3 H), 5.79 (s, 2 H), 6.98 (d, *J* = 8.9 Hz, 2 H), 7.36–7.47 (m, 5 H), 7.97 (d, *J* = 8.8 Hz, 2 H), 8.20 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 55.6 (CH_3), 57.4 (CH_2), 95.2 (CN), 114.6, 116.2, 125.2 (C), 127.9, 128.5, 129.1, 129.2, 132.3 (CH), 132.9 (C), 146.8 (CH), 162.25, 162.7 (C).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}N_5O$ (M^+): 317.1277; found: 317.1268.

(*E*)-2-(1-Benzyl-1*H*-tetrazol-5-yl)-3-(4-Hydroxy-3-methoxyphenyl)acrylonitrile (1j)

Green solid; yield: 0.20 g (63%); mp 170–172 °C.

IR (KBr): 2225, 1512, 1426, 1253, 939, 801, 671, 603 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.96 (s, 3 H), 5.23 (s, 2 H), 5.78 (s, 1 H), 6.94 (d, *J* = 8.5 Hz, 1 H), 7.38–7.43 (m, 6 H), 7.79 (s, 1 H), 8.17 (s, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 56.1 (CH_3), 57.1 (CH_2), 95.3 (CN), 113.0 (CH), 116.2 (C), 125.7, 127.2, 128.1, 128.5, 128.7 (CH), 132.8, 136.1 (C), 147.0 (CH), 149.6, 151.6, 162.1 (C).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}NO_2$ ($M^+ - N_4$) 277.1103; found: 277.1085.

Indium-Promoted Debenzylation of Tetrazoles 1; General Procedure

A mixture of the corresponding benzylated tetrazole **1** (0.1 mmol) and In powder (58 mg, 0.5 mmol) in MeOH (6 mL) and THF (4 mL) was refluxed until the starting material disappeared (20 h). After cooling to r.t., aq 1 M HCl (0.5 mL) was added and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and evaporated (15 Torr). The resulting residue was recrystallized to give the corresponding pure product **2**. All the products were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2** (Table 1).

Magnesium-Promoted Debenzylation of Tetrazoles 1; General Procedure

To a solution of the corresponding benzylated tetrazole **1** (1 mmol) in MeOH (5 mL) and THF (3 mL) was added freshly scratched Mg turnings (48 mg, 2 mmol) and a tiny crystal of I_2. The reaction mixture was refluxed until the starting material was consumed (17–22 h) and

then cooled to 0 °C. The mixture was diluted with Et_2O (5 mL) and 10% aq NH_4Cl was added. The mixture was stirred until it became clear and then separated. The process was repeated once again and the combined Et_2O extracts (2 × 5 mL) were dried (Na_2SO_4) and evaporated (15 Torr) to give a residue that was purified by recrystallization in EtOH, to afford the corresponding pure deprotected tetrazole **2**. All the products were fully characterized by comparison of their physical and spectroscopic data with pure samples of **2** (Table 1).

Zinc-Promoted Debenzylation of Tetrazoles 1; General Procedure

To a stirred solution of the corresponding benzylated tetrazole **1** (2.5 mmol) in THF (1.0 mL) at r.t. was added Zn dust (5 mmol) and stirring was continued for an additional 30 min. The resulting suspension was cooled with an ice-water bath and glacial AcOH (1.0 mL) was added slowly. The cooling bath was removed and the final mixture was stirred for further 1–3 h and then filtered. The collected solids were washed with H_2O (3 × 10 mL) and CH_2Cl_2 (3 × 15 mL). The organic phases were separated, combined, and washed with H_2O (2 × 10 mL), sat. aq $NaHCO_3$ (3 × 10 mL), and brine (3 × 15 mL). After drying (Na_2SO_4), and filtration, the solvent was evaporated under reduced pressure (15 Torr). The resulting residue was purified by recrystallization to give the corresponding pure compound **2**. All the products were characterized by comparison of their physical and spectroscopic data with pure samples of **2** (Table 1).

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610170.

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