Synthesis of enamines and their bromination

A dissertation

Submitted in fulfillment

For the Degree of

Master of Science in Chemistry

By

Vasundhara Thakur

Under the supervision of

Dr. Niranjan Panda

Department of Chemistry

National Institute Of Technology, Rourkela

ODISHA, INDIA

CONTENTS

Acknowledgement

I would like to thanks Prof. Niranjan Panda, for his guidance, ever encouraging words of wisdom and for taking such an active interest in my project. His never ending zeal for research was an inspiration to bring the best out of me.

It is my great pleasure to acknowledge to Prof. Braja Gopal Mishra, Head of the Department and all faculty and staff members of Department of Chemistry National Institute of Technology, Rourkela for their help which made this research work a success.

I would like to express my deep appreciation and thanks to Mr. Ashish Kumar Jena for his encouragement, unforgettable support and unaccountable help throughout this project.

I extend my thanks to Ms. Swapna Sarita Mahapatra and my entire laboratory colleague for their friendlier and helping nature which made my stay comfortable in the lab.

I also wish to thank all of my friends for making my stay in this institute a memorable experience.

Last but not the least I would like to thank my parent and my family members for standing by me all along and for all the support and loving care given to me.

Vasundhara Thakur

Department of Chemistry

National Institute of Technology

Odisha, India.

CERTIFICATE

This is to certify that the dissertation entitled," Synthesis of Enamines and their bromination" submitted by Vasundhara Thakur as a project work requirement for the award of Master of Science in Chemistry during the period of August 2010- April 2011 in the Department of Chemistry, National Institute of Technology, Rourkela. The work done by her in my laboratory following the reported procedure is for her training purpose.

Date:

Dr. Niranjan Panda

Supervisor

Associate Professor,

Department of Chemistry

National Institute of Technology

Rourkela-769008

INTRODUCTION

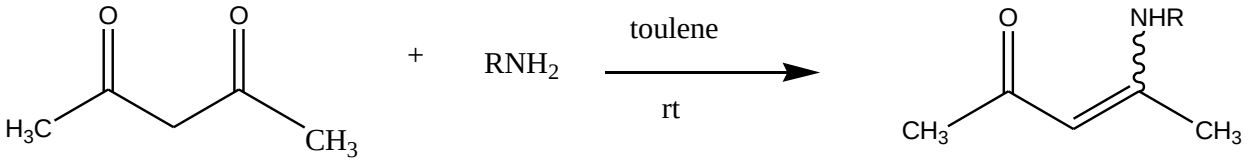
Enamines represent an important class of reactive intermediates in organic synthesis. They have high impacts as synthons for synthesis of various heterocyclic and biologically active [1] analogues including anticonvulsant [2], anti-inflammatory (p-arylamidoacrylic acids) [3] and anti-tumor agents. [4] Enamines are frequently used as a potential building block to access several types of heterocyclic ring systems such as 1,4-dihydropyridines, pyrroles, oxazoles, pyridinones, quinolines, dibenzodiazepines, tetrahydrobenzoxazines, tetronic acids, azasteroids, (1H)-pyridin-2-one, pyrazolo-[1,5-α]- pyrimidine and isoxazole derivatives, which are well-known as anti-inflammatory, antitumor, antibacterial, and anti convulsant activities. Enamines are also used to form volatile chelate metal complexes with $PdCl_2$ in amine medium to form palladiuim β-ketoiminate. [5] Realizing the wide spectrum of usage of enamines, there is a quest for the development of simple and high yielding process for the synthesis of various enamines.

Here some of the important methods for the synthesis of enamine are presented.

1) *Reaction of 1, 3-dicarbonyl compounds with amines.*

1, 3-dicarbonyl compounds such as acetyl acetone, ethyl acetoacetate etc. reacts with ammonia and/or amine, leads to the enamines. These enamines are usually the isomeric mixture of E and Z-isomers at room temperature. [6]

Scheme- 1



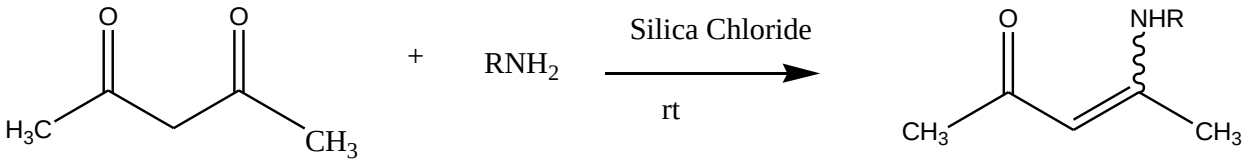
4-amino-3-penten-2-one

2) *Enamination in heterogeneous medium using silica chloride*

Heterogeneous catalysts like silica chloride (a modified silica gel), are used for various organic synthesis. In 2006, K. V. Srinivasan [7] reported that variety of aliphatic and aromatic

amines including ammonium acetate, were condensed with various 1, 3-dicarbonyl compounds like ethyl acetoacetate, acetyl acetone etc. in presence of heterogeneous silica chloride lead to the enamine at ambient temperature. They have also suggested the plausible mechanism for the

Scheme-2



4-amino-3-penten-2-one

reaction which is shown below (Figure 1). The Si-Cl bond is labile and can give rise to Lewis acid centers on silica. The Cl is easily displaced selectively by the acetyl oxygen of 1, 3-dicarbonyl compounds by a nucleophilic substitution reaction generating a cationic center on the carbonyl carbon, which is easily attacked by the nucleophilic primary amines to form the imine which after tautomerisation forms the enaminone.

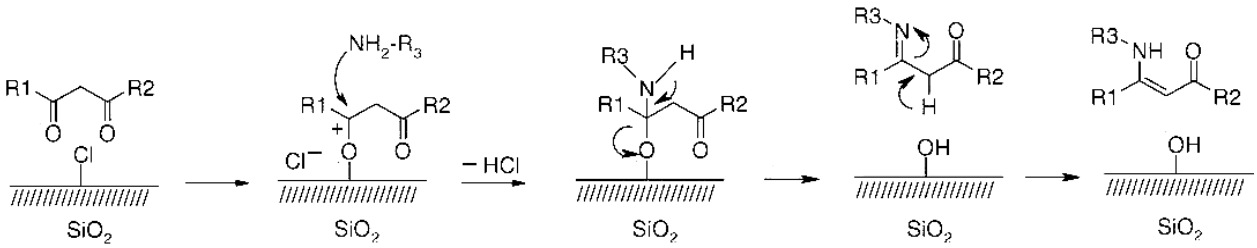
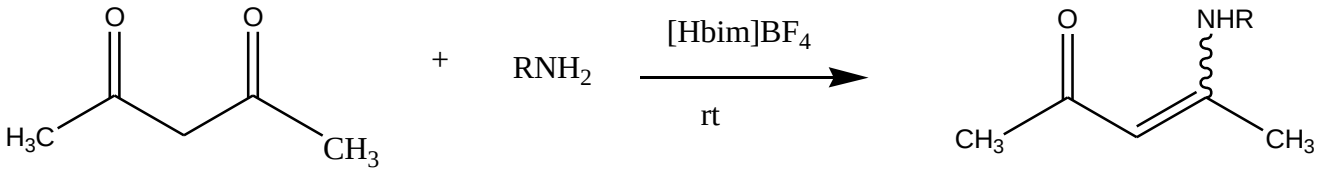


Figure-1

3) *Enamination in a homogeneous medium using ionic liquid.*

Ionic liquids such as 1-*n*-butylimidazolium [Hbim] series were also utilized for the synthesis of enamines. For example, reaction of aniline with acetyl acetone in presence of [Hbim] BF4 leads to 4-phenylamino-pent-3-en-2-one. This catalyst was also utilized for the synthesis of enamines from both acyclic and cyclic 1, 3-dicarbonyl compounds. [7, 8]

Scheme-3

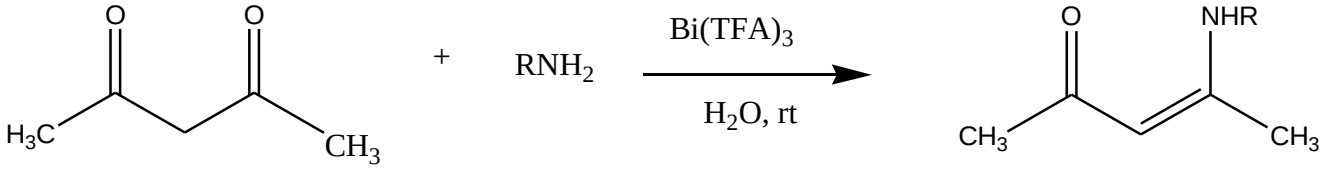


4-amino-3-penten-2-one

4) *Bismuth (III) trifluoroacetate mediated synthesis.*

In 2004, Khosropour et al reported the catalytic activity of bismuth (III) trifluoroacetate in β-enaminone synthesis. [9] They found that the reactions are environmental friendly and proceeded smoothly at room temperature and the products were obtained in excellent yields. Both activated and weakly activated anilines also form enaminones in nearly quantitative yields. The low cost and the low toxicity of the catalyst and media, make this procedure environmentally acceptable.

Scheme-4

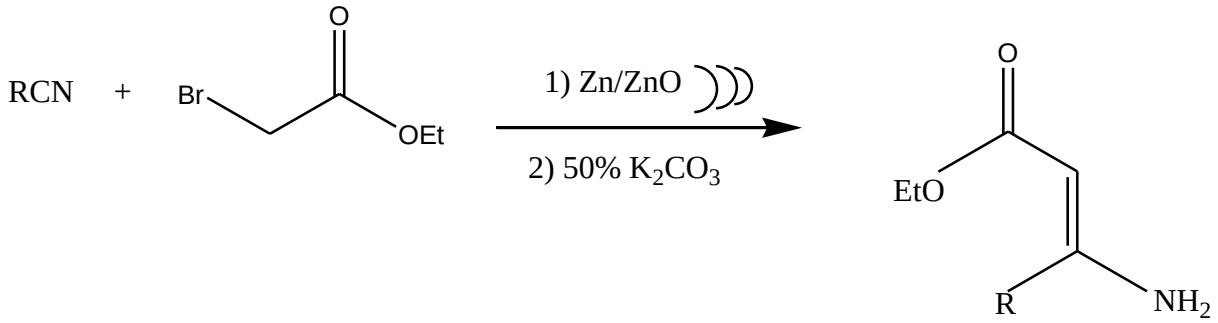


4-amino-3-penten-2-one

5) From nitriles by sonochemical method.

Nitriles on reaction with α-bromoester in presence of zinc/zinc oxide powder under sonochemical conditions which are presented in Scheme 5. Alkyl as well as aryl nitriles also gave the enamine under the same condition and this process is found to be very useful. [10]

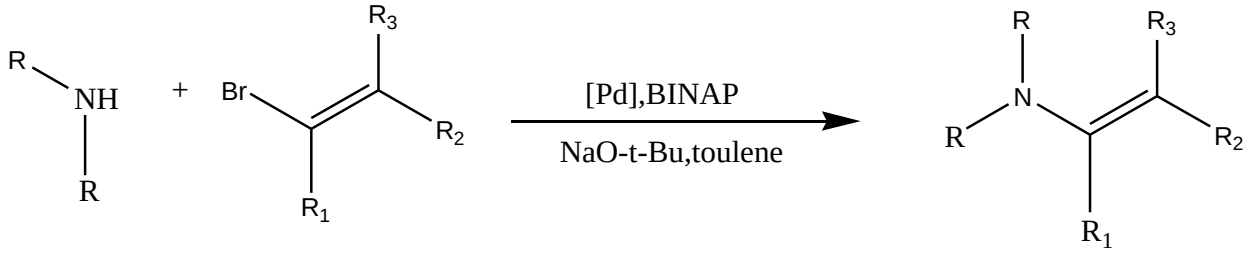
Sheme-5



6) By coupling reaction.

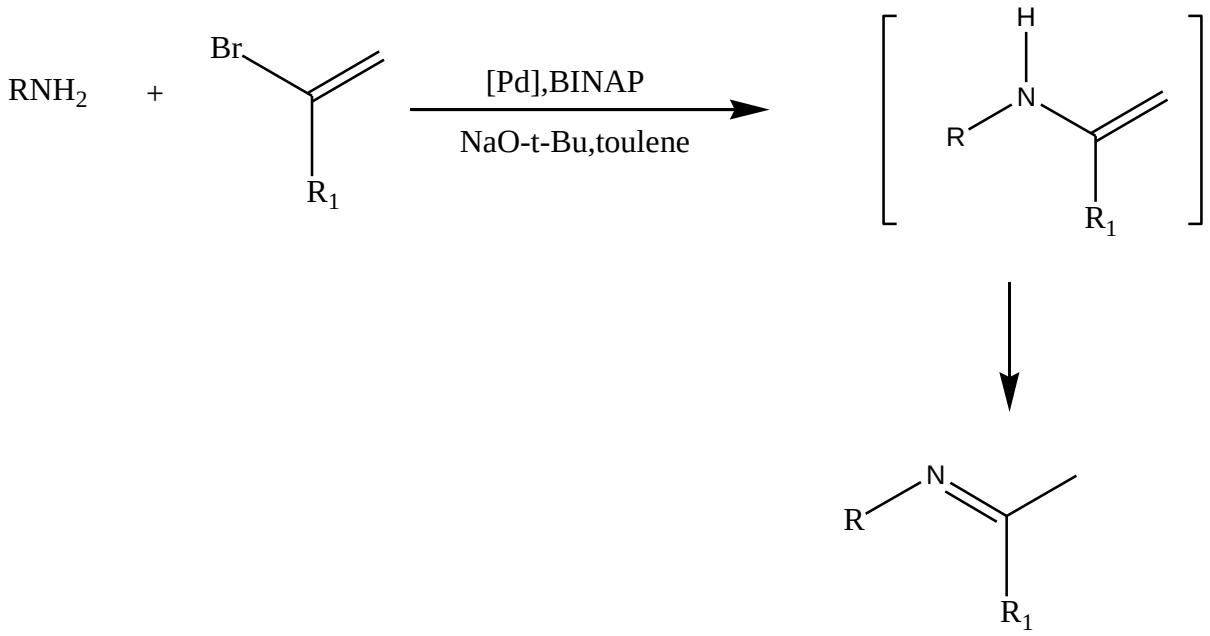
Barluenga et al reported for the first time on the cross-coupling of alkenyl bromides and non-aromatic secondary amines leads to the enamines (Scheme 6). [11] They showed that 0.5 mol % of both $Pd(OAc)_2$ and $Pd_2(dba)_3$ were active enough for the cross-coupling reaction in presence of ligands such as BINAP and biphenyl monophosphine. It may be noteworthy that both stereo-(Z/E) and regiochemistry (internal/external) of the vinyl bromides were retained throughout the coupling process. Another significant feature of this method was the mildness of the work-up, which was required due to the sensitivity of enamines towards acids and water.

Scheme-6



In a subsequent study it was shown that couplings of primary amines such as anilines and benzylamines yielded, after tautomerisation, the corresponding imines. The reaction time was short (15 min) and the catalyst loadings relatively low (0.1 mol% of palladium). [11] The overall transformation is shown in Scheme- 7.

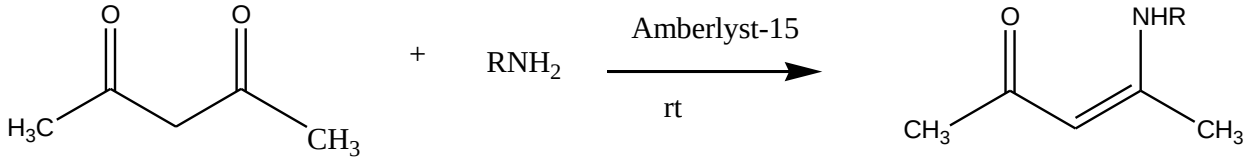
Scheme-7



7*) Amberlyst-15 mediated synthesis*.

In 2011, Narsaiah et al reported the catalytic activity of Amberlyst-15 in β-enaminones synthesis. The β-dicarbonyl compounds readily react with variety of amines in the presence of Amberlyst -15 to produce β-enaminones in quantitative yields. [12] These reactions are applicable to wide range of substrates and are carried out at ambient temperature as presented in Scheme-8.

Scheme-8



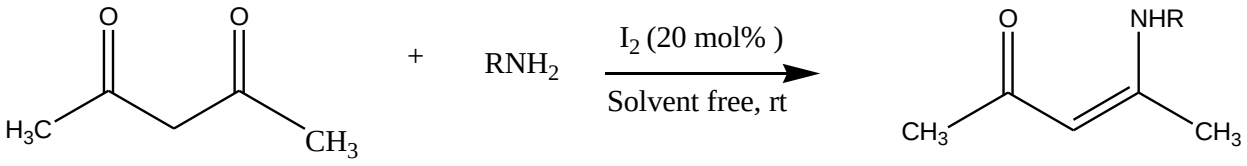
4-amino-3-penten-2-one

8) *I_2 mediated enamine synthesis*

Barua et al in 2005, have demonstrated a very mild and efficient method for conversion of the β-dicarbonyl compounds to β -enaminones in the presence of amines using a catalytic amount of iodine at room temperature within few minutes under solvent-free conditions as presented in scheme-9. [13] The yields of the products are quite good in comparison to other methods

reported in the literature. This method is widely accepted because; iodine is a less expensive, easily available, and environmentally friendly catalyst.

Scheme-9



4-amino-3-penten-2-one

As for the mechanism of this reaction, they believe that the enol or enolates form of A reacts with iodine and drives the reaction toward formation of the iodinated product B. The lone pair on nitrogen of the amine then undergoes nucleophilic addition to the more active carbonyl to give species C. The I^- ion present in the reaction mixture then picks up iodine with dehydration driven by more stabilized product with liberation of iodine to give the desired product as shown in figure-3.

Mechanism

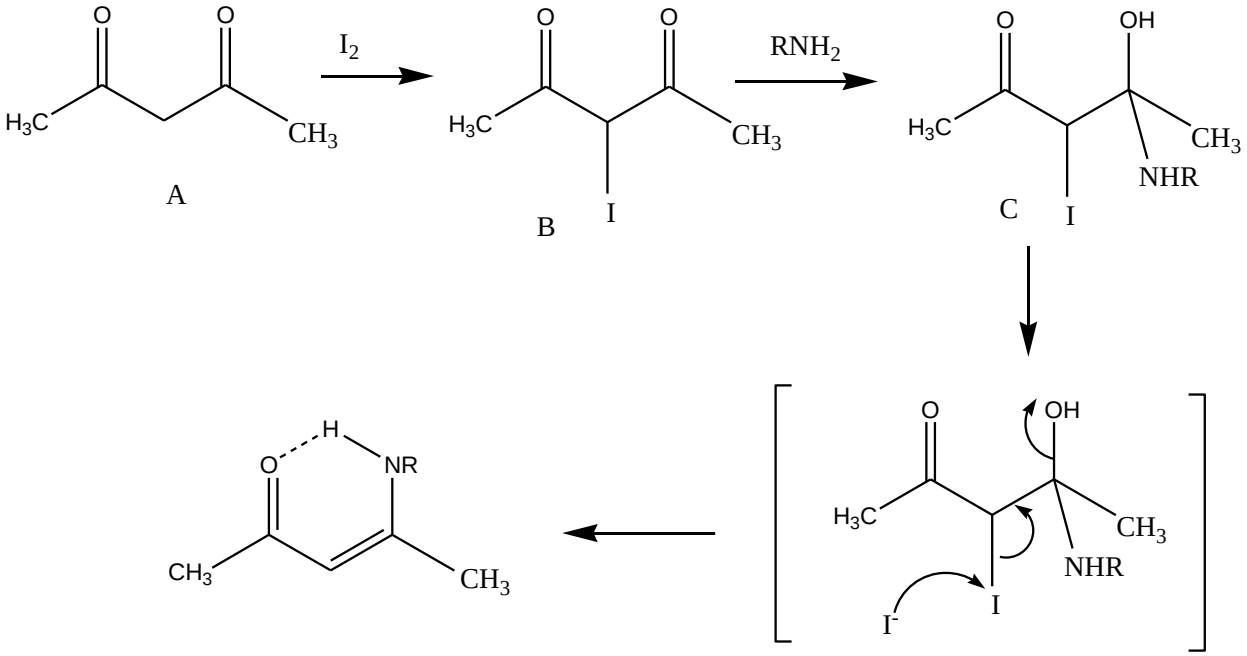


Figure-3

BROMINATION OF ENAMINES

The conventional method used for the bromination of enamino compounds is with the use of NBS/MeOH, Br_2/CCl_4 or BrCN [14, 15] which gives rise to different products such as mono and di- bromination with variable yields and show dependence on nature of N- substituted and reaction condition.

Braibante et al have reported in 2001 [16], that the selective bromination of enamine such as ethyl 3-amino- butenoate is done with NBS supported on K-10 (montomorillonite). When this reaction was performed without using solid support MeOH or other solvent, the isolation of product was difficult. The use of NBS/K-10 has advantages over the traditional procedures is the decreased reaction time of 5 hr and also the workup is simple.

According to them, the isolation of required product is simplified because the succinimide formed during the reaction is adsorbed into the support and the filtration is sufficient. This is method is successfully applied to β- amino-α, β unsaturated ketone and ester respectively resulting in α-brominated compounds.

Thus they concluded that, the use of NBS as brominating agent with β-enamino ketones gives only substituted product. The use of elementary bromine (Br_2/Et_2O or CH_2Cl_2) with the enamines gives the mixture of substituted products.

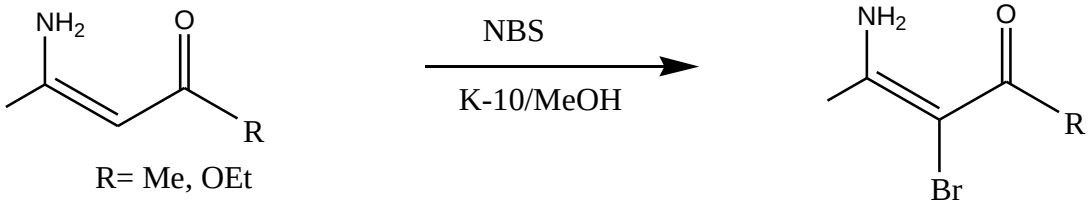


Figure-2

Thus the use of NBS/K-10 method for the bromination of β-enaminones compared with other system employed, resulted in regioselective synthesis of α-bromoenaminones. The solid support of K-10 also facilitated these reactions. [16]

Under this project work we have synthesized several enamines from 1, 3-dicarbonyl compound following the procedure reported elsewhere. Additionally, we brominated the 2-aminocrotonate using the procedure reported by *Braibante et al.* [16]

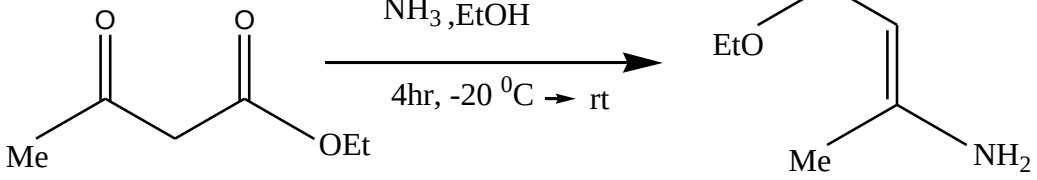
Synthesis of Enamines from 1, 3-dicarbonyl compounds.

General procedure for synthesis of enamines from 1, 3-dicarbonyl compounds.

1) 15 ml of 1, 3 dicarbonyl compounds is taken in a RB and dissolved in 20 ml of ethyl alcohol over the magnetic stirrer. Then the temperature is cooled to -20º C .To this 50 ml of conc. NH_3 or methylamine is added drop wise respectively and stirred for about 4-5 hrs. White ppt is formed just after 5 mins. The excess solvent is evaporated through vacuum. Using separating funnel, the compound separated using dichloromethane (DCM). The organic layer is collected and dried with $NaHSO_4$.The excess solvent is again evaporated. The compound was characterized by taking TLC, IR absorption measurement and NMR data.

a) Following the above mentioned procedure, we have prepared, Ethyl-3-aminobut-2-enoate by condensing ethyl acetoacetate with conc. NH_3 in ethyl alcohol at required condition, as presented in Scheme -10. The compound was characterized by taking TLC, IR absorption measurement and NMR data. The yield of compound is 70%.

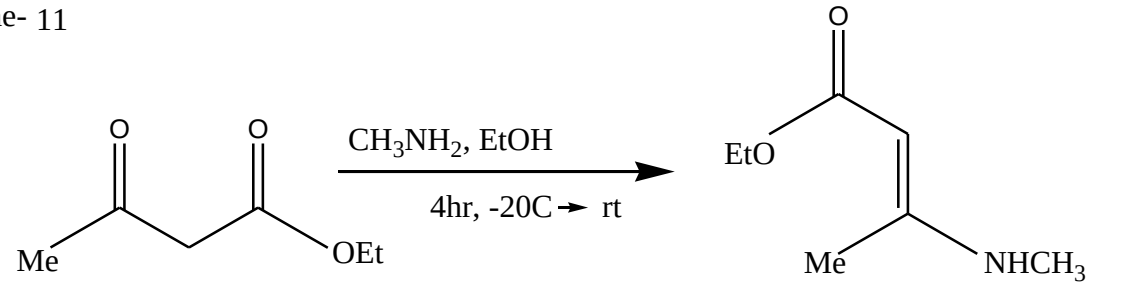
Scheme-10



Ethyl-3-aminobut-2-enoate

b) The same above mentioned procedure is followed to prepare Ethyl-3-methylaminobut-2-enoate, by condensing ethyl acetate with conc. methylamine in ethyl alcohol at required condition, as presented in Scheme -11. The compound was characterized by taking TLC, IR absorption measurement and NMR data. The yield of compound thus obtained is 90%.

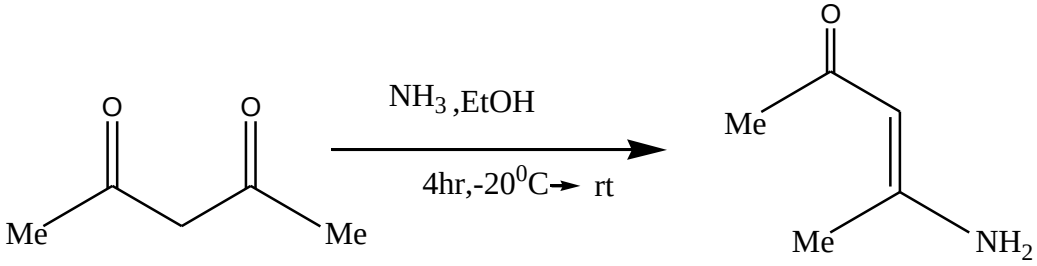
Scheme- 11



Ethyl-3-methylaminobut-2-enoate

c) 4-aminopent-3-en-2-one is also prepared by condensing acetyl acetone with conc. NH_3 in ethyl alcohol at required condition, as presented in Scheme -12, following the same procedure as used for the ethyl acetate. The yield of compound obtained is 90%. The compound was characterized by taking TLC, IR absorption measurement and NMR data.

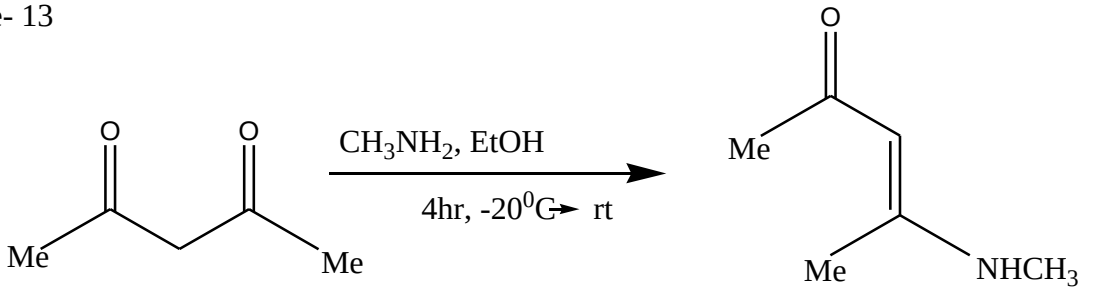
Scheme- 12



4-aminopent-3-en-2-one

d) Similarly, acetyl acetone can also be condensed with concentrated methylamine to prepare 4-methylaminopent-3-en-2-one, following the above mentioned procedure, at the required reaction conditions as represented in scheme-13. The compound was characterized by taking TLC, IR absorption measurement and NMR data. The yield of compound thus obtained is 80%.

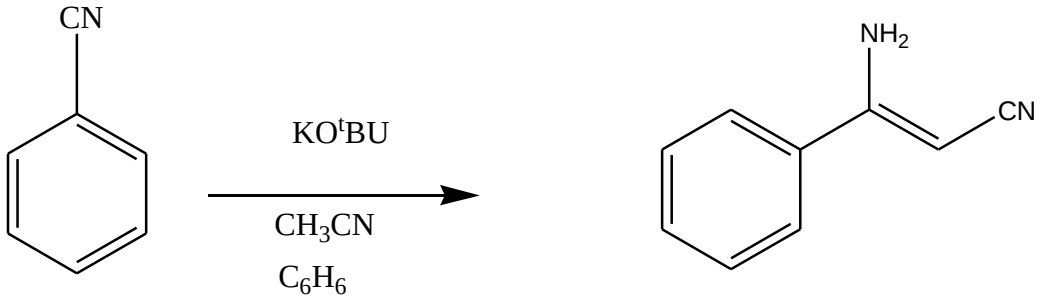
Scheme- 13



4-methylaminopent-3-en-2-one

2) 9.7 mmol (1 gm) of benzonitrile is added in 25 ml of benzene. To this 19.5 mmol of acetonitrile was added followed by addition of KO^tBu (2.5 gm or 41.7 mmol). The mixture was stirred for 24 hrs at 20 C. Using separating funnel, the compound separated with diethyl ether followed by addition of 2% $NaHCO_3$ (10 ml). The organic layer was separated and washed with brine solution (5 ml) and then dried with $NaHSO_4$.The excess solvent is evaporated in vacuum. The compound was characterized by taking TLC, IR absorption measurement and NMR data. [17]. The yield of the compound is 45%.

Scheme-14

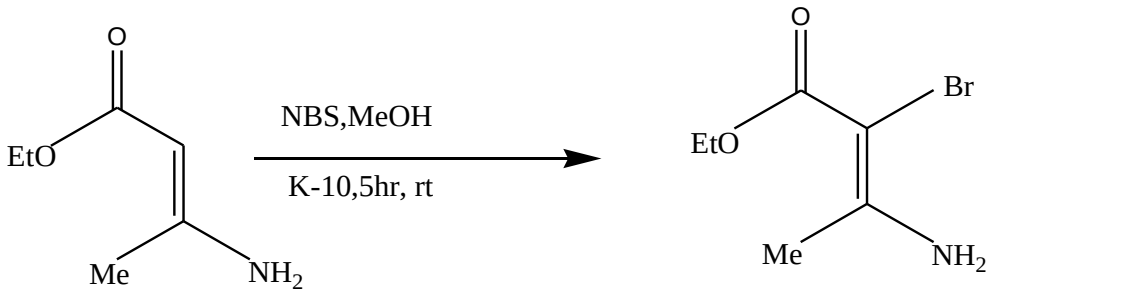


1-Amino-1-Phenylacrylonitrile

3) Braibante et al have reported in 2001, [16] the selective bromination of enamine such as ethyl 3-amino- butenoate with NBS supported on K-10 (montomorillonite).We have followed this method for mono-bromination of the enamines.

N-Bromosuccinimide (4.52 mmol) was suspended in MeOH (8 ml) and added to ethyl 3-amino butenoate (3.8 mmol) or 500mg, and dispersed in K-10 (1.16 g). The mixture was stirred at room temperature for 5 -6 hrs. After completion of the reaction (TLC/ CH_2Cl_2), the product was extracted by washing the K-10 with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ (13 ml).Dried with $NaHSO_4$. Filtered and the solvent was removed under vacuum to yield the crude product. Solid compound were recrystallised from di-isopropyl ether. [16]. The yield of compound was found to be 20%.

Scheme-15



Ethyl-3-amino-2-bromobut-2-enoate

CONCLUSION

We have synthesized various enamines from 1, 3-dicarbonyl compounds with ammonia and/or amines with azeotropic removal of water. The enamines thus formed, can be further used to synthesize heterocyclic compounds by cross coupling reactions which has various applications in the field of drug and pharmaceuticals. Bromination of these enamines is also carried out in presence of NBS/MeOH in solid support K-10 at α –position following the procedure reported by Braibante and co workers.

REFERENCES

1) (a) Gielen,H.; Li,V.M., Rosentreter,U.;Schlemmer,K.;Fitzgerald,H.;Nash,K.; *Chem. Abstr*. **2003**,139.

(b)Charushin,V.N.; Mochulskaya,N.N.; Andreiko,A.A.; Filyakova,V.I.; Kodess,M.I.; Chupakhin,O.N.; *Tetrahedron Lett.* **2003**, *44*, 2421.

(c) Savarin,C.G.; Murry,J.A.; Dormer,P.G. *Org. Lett*., **2002**, 4, 2071.

2)Natalie,D.E.; Donna,S.C.; Khurana,M.; Noha,N.S.; James,P.S.;Sylvia,J.H.;Abraham,N.; Robert,S.T.; Jacqueline,A.M.; *Eur. J. Med. Chem*.,2003,*38*, 49.

3) Dannhardt,G.; Bauer,A.; Nowe,U.; *J. Prakt. Chem*., 1998,340, 256.

4) Boger,D.L.; Ishizaki,T.; Wysocki,J.R.; Munk,S.A.; Kitos,P.A.; Suntornwat,O.; *J. Am. Chem. Soc*.,**1989**,*111*, 6461.

5) Zharkova,G.I.; Stabnikov ,P.A.; Baidina,I.A.; *Polyhedron*, **2009**,*28*, 2307–2312.

6) Valduga, C. J.; Squizani, A.; Braibante, H. S.; Braibante, M. E. F. *Synthesis* **1998**, 1019.

7) Gholap,A.R.; Chakor,N.S.; Daniel,T.; Srinivasan, V.K.; *Journal of Molecular Catalysis A: Chemical* **2006**, *245*, 37–46.

8) R. Sheldon, *Chem. Communication*. **2001**, 2399.

9) Khosropour,A.R.; Khodaei,M.M.; and Kookhazadeh,M.; *Tetrahedron Lett.* **2004**, *45*, 1725.

10) Lee,A.S.; and Cheng,R.Y.; *Tetrahedron letters*, **1997**, *38*, 443-446.

11) Barluenga,J.; Ferna´ndez,M.A.; Aznar, F.; and Valde´s, C,;Chem.Commun., **2002**, 2362.

12)Narsaiah,A.V.;Reddy,A.V.;Reddy,B.V.S.;andYadav,J.S.; *The Open Catalysis Journal*, **2011**, *4*, 43-46.

13) S.Gogai, R. Bhuyan, N.C. Barua, Synthetic Communications, **2005**, *35*, 2811–2818 .

14) Jirkovsky,I.; *Can. J. Chem*. **1974,**55.

15) Alberola,A.; Andres,C.; Ortega,G.A.; Pedrosa,R.; *synth. Commun*. **1986**, *16*, 1161.

16) Braibante ,M.E.F.; Braibante,H.S.; da Roza,J.K. *Synthesis*,**2001**,13,1935-1937.

17) de Paulis, T.; Hemstapat, K.; Chen, Y.; Zhang, Y. *J. Med. Chem.* **2006**, *49*, 3332.

.