CHAPTER – I

A Brief Review On Multicomponent Reactions

CHAPTER I

A BRIEF REVIEW ON MULTICOMPONENT REACTIONS:

1.1 INTRODUCTION:

Reaction is nothing else but the conversion of reactant to product. Reactant or substrate is an organic compound which is undergoing structural or functional group change. Most of organic reactions can be placed in one of four classes.

1) Substitution reactions
2) Addition reactions
3) Elimination reactions
4) Rearrangement reactions

According to number of reactant or component used in reaction they are classified as,

1) One component reactions (mostly self condensation reaction)
2) Two component reactions (quite common, reaction between two substrates)
3) Multicomponent reactions (using more than two substrates)

In recent years, multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because these reactions increase the efficiency by combining several operational steps without isolation of intermediates or changes in the reaction conditions. This principle therefore, is highly efficient in terms of time as well as resources. Thus, multicomponent reactions are of special types of synthetically useful organic reactions, which give complex reaction products from mixing of three or more simple starting materials, in one pot. Due to their operational simplicity to furnish the desired products in

excellent yields multicomponent reactions have attracted much attention of synthetic organic chemists.[1]

In multicomponent reactions, product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equillibria which all finally flow into an irreversible step yielding the product. The challenge is to conduct multicomponent reactions in such a way that the network of pre-equilibrated reactions channel into the main product and do not yield side products to an appreciable extent. The result is obviously dependent upon the reaction conditions such as, choice of solvent, reaction temperature, catalyst selected, concentration of the components used as well as the kind of starting materials and functional groups in them. Such considerations are of particular importance in connection with the design and discovery of novel multicomponent reactions. Furthermore, multicomponent reactions also serve as comer stones of both combinatorial chemistry and diversity oriented synthesis and thus have played a central role in the development of modern synthetic methodology for pharmaceuticals and in drug discovery research. Together with target oriented synthesis, combinatorial chemistry expands structural variations in a lead compound of interest. Diversity oriented synthesis is helpful in exploring large areas of chemical structure space in search of new bioactive small molecules that might not be identified by conventional natural product screening assays.

Despite the spectacular investment in and organic growth of combinatorial chemistry as a platform technology within the pharmaceutical industry, during 1980s and 1990s, a few new multicomponent reactions were discovered or developed by corporate research laboratories. Most combinatorial libraries were assembled using traditional, tried and true processes such as Biginelli (1891), Hantzsch (1882), Mannich (1912), Passerini (1921), Strecker (1850), Ugi, (1959) etc reactions. However, judging from numerous recent reports, interest has now

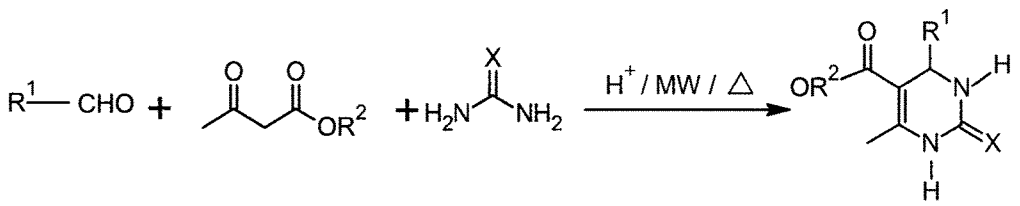
intensified within academic laboratories in the development of new MCRs as basis for complexity generating strategies for the synthesis of small molecules.

In following few paragraphs we have taken a brief account of various multicomponent reactions of general synthetic importance.

1.2 Types of Multicomponent reactions:

1.2.1 Biginelli Reaction:

Dihydropyrimidin-2(1H)-ones, Biginelli compounds, are widely used in pharmaceutical industry as calcium channel blockers, α-antagonists, and antihypertensive, antitumor as well as anti-inflammatory agents.[2-4] The rational and well defined approach towards the synthesis of Biginelli compounds involves a one pot three component condensation between an aldehyde, an active methylene compound, usually a β-keto ester and urea or thiourea in the presence of an acid catalyst or under the influence of thermal / MW dielectric heating in absence of a catalyst. (Scheme 1)



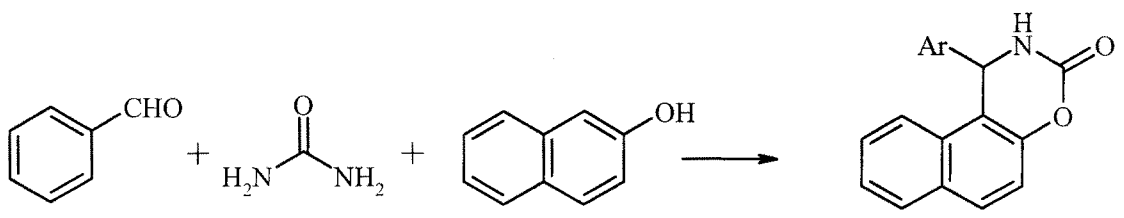
X = O / S; R^1 = Ph, alkyl, etc.; R^2 = Me, Et, etc.

Scheme 1

The reaction was originally introduced by P. Biginelli [5] almost a century ago however, owing to the importance of these compounds in pharmaceutical

industry, the interest in the synthesis of these compounds has rejoiced and more than hundred reports have appeared in the journals of international repute describing the synthesis as well as biological activities of these compounds. Most of the developed protocols involve the use of either Lewis / Bronsted acid catalyst while a catalyst as well as solvent free protocol has been reported by Ranu et al.[6] The only drawback of this protocol being the necessity of elevated temperature (100°C). From our laboratory we have reported a solvent-free protocol operable at ambient temperature for the synthesis of these compounds using anhydrous magnesium sulfate as a mild Lewis acid catalyst as well as water scavenger.[7] In this protocol we have demonstrated that the removal of water formed in this condensation reaction is one of the driving forces of this reaction. Quite recently, Karade et al [8] have demonstrated the use of scolecite as a novel, heterogenous and reusable catalyst in the synthesis of Biginelli compounds.

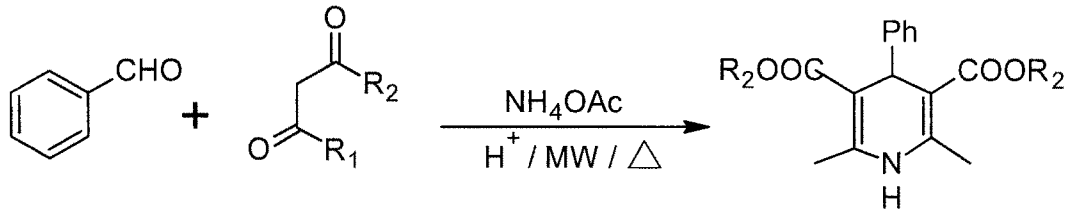
Like Biginelli compounds, aromatic condensed oxazinone derivatives are important class of heterocyclic compounds which also exhibit important biological properties.[9] e.g. naphthalene based 1,3-oxazin-3-ones have been reported as antibacterial agents.[10] Bazgir et al[11] have reported the synthesis of these compounds by one pot three component condensation between an aldehyde, urea and β-naphthol. The main drawback of the protocol being lower yields and essentiality of elevated temperature. (Scheme 2)



Scheme 2

1.2.2 Hantzsch reaction:

1,4-Dihydropyridine (DHPs) moiety is a common feature of many biologically active compounds that have not alone exhibits vasodilator and bronchodilator activity but are associated with antitumor, antidiabetic and other biological activities[12]. The synthesis of 1,4-DHPs basically involves simple three component condensation between an aldehyde, active methylene compound viz. a β-ketoester or a β-diketone , and ammonium acetate as a source of ammonia, again in presence of an acid catalyst or under thermal / MW or other energy source, in absence of any catalyst [13] (Scheme 3)

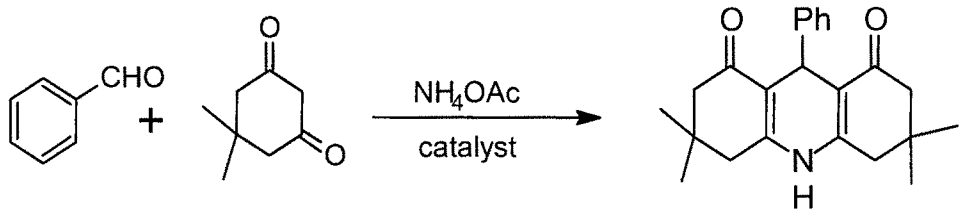


R_1= alkyl ; R_2 = OMe / OEt, alkyl

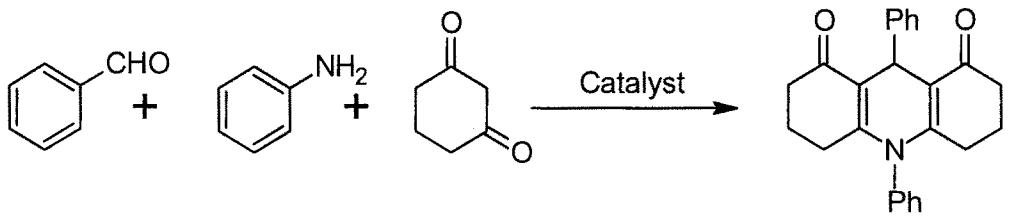
Scheme 3

From mechanistic view point, Bronsted / Lewis acid can act as a catalyst while at elevated temperature ammonium acetate liberates ammonia and acetic acid. The former gets utilized as a third component of the reaction while acetic acid acts as Bronsted acid catalyst. A logical extension to this concept was to use two equivalents of active methylene compound other than alkyl acetoacetate e.g. dimedone / cyclohexane 1, 3-dione, which under the similar reaction conditions furnished acridinenones, instead of 1,4-DHPs[14] which are also known for their biological activities. [15] (Scheme 4) In place of ammonium acetate, as a source of

amine quite recently Chandrasekhar et al[16] reported the synthesis of similar acridinedenones via. three component condensation between an aldehyde, aniline and cyclohexane-1,3-dione using Tris(pentafluoro-phenyl)borane as a catalyst. (Scheme 5)

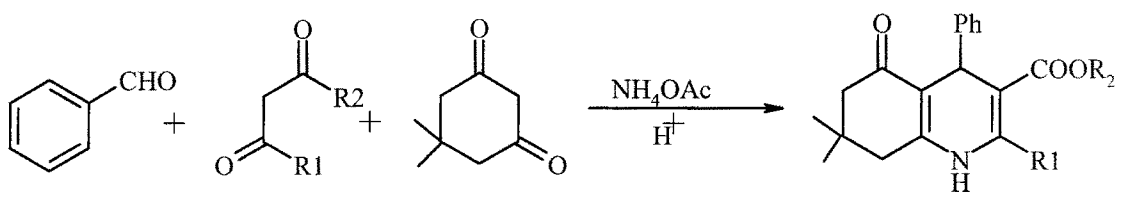


Scheme 4



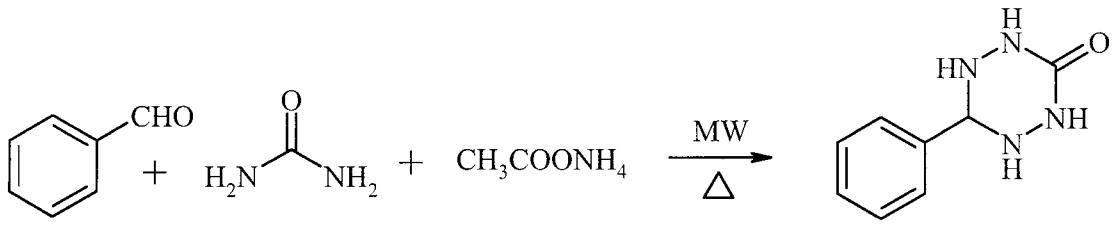
Scheme 5

Further extension to this concept was to use two different active methylene compounds e.g. dimedone and ethyl acetoacetate / 1,3 diketone, instead of using two equivalents of a single active methylene compound in this condensation. This condensation furnishes polyhydroquinoline as a final product[17]. (Scheme 6)



Scheme 6

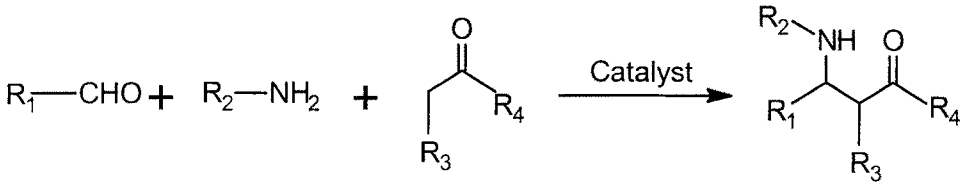
Alike 1,4-dihydropyridines 1,2,4,5-tetrazenes represent an important class of heterocyclic compounds that not alone find applications in synthetic organic chemistry but are now under investigation for their effectiveness against cancer by national cancer Institute, USA.[18a] There are only a limited number of reports on the synthesis of this class of compounds. Classically 1,2,4,5-tetrazenes are synthesized by a one-pot three component condensation between an aldehyde, urea and ammonium acetate.[18b] (Scheme 7)



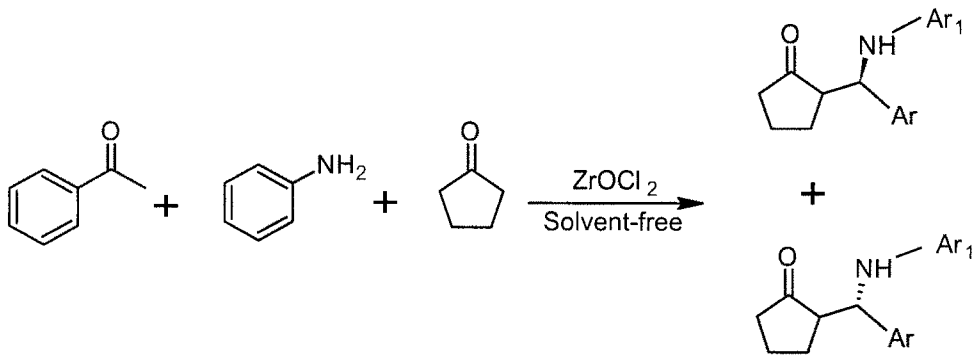
Scheme 7

1.2.3 Mannich reaction:

Mannich reaction is among the most important C – C bond forming reactions leading to β-amino carbonyl compounds which are important structural motifs present in many natural products as well as pharmaceuticals[19]. The reaction basically involves one-pot condensation between an amine and two different carbonyl compounds in presence of either an acid or a base catalyst. In a view to design the catalyst of better selectivity as well as reusability Han et al[20] have reported [Bmim]$^+$ [HSO_4]$^-$ as acidic ionic liquid catalyst which also serves as a reusable reaction medium. (Scheme 8) Zhao et al[21] have reported $ZrOCl_2$ as a Lewis acid catalyst for this reaction which proceeds under solvent-free condition. (Scheme 9)

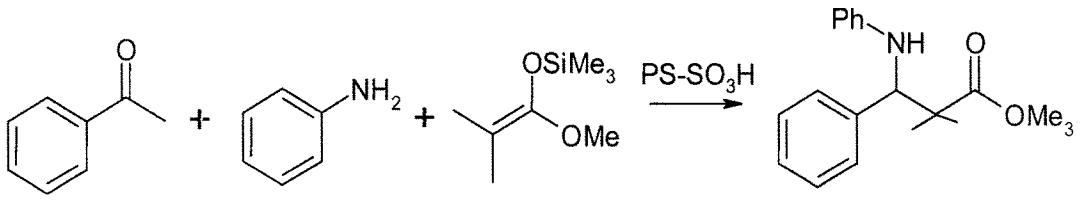


Scheme 8

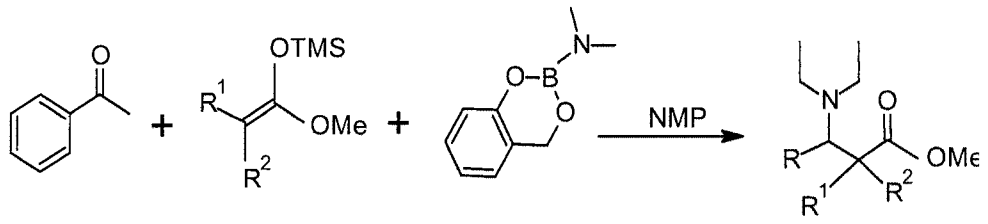


Scheme 9

In this three component condensation reaction, instead of using ketone as a source of carbonyl compound (third component) the use of silyl acetal was reported by Kobayashi et al.[22] (Scheme 10) while instead of using amine directly, the use of aminoborane as a highly effective iminium ion generator was reported by Suginome et al.[23] (Scheme 11)

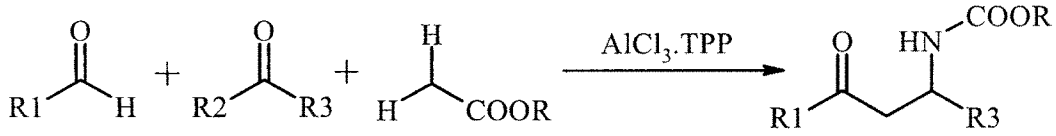


Scheme 10



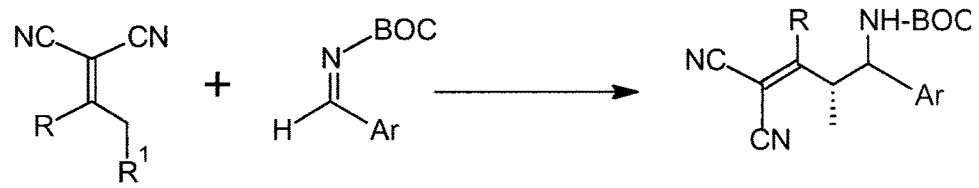
Scheme 11

Further extension to this reaction was the use of carbamate as an amine equivalent. Xu et al[24] have reported a three component condensation between an aldehyde, ketone and a carbamate using aluminium chloride supported on triphenyl phosphine as a catalyst to furnish N-protected β-aryl-β-aminoketones (Scheme 12)



Scheme 12

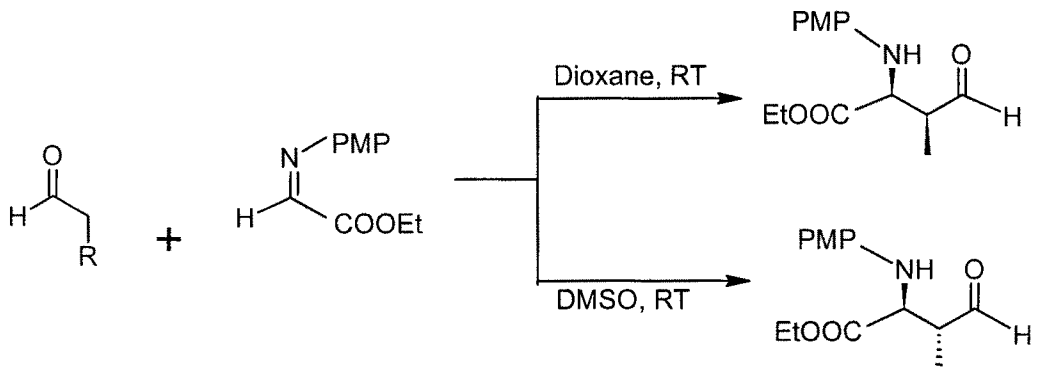
Mannich reaction with N-protected amines has no longer remained new, however, the condensation between N-BOC imine with α, α'-dicyanoolefins has been reported by Liu et al[25] using a chiral catalyst. (Scheme 13)



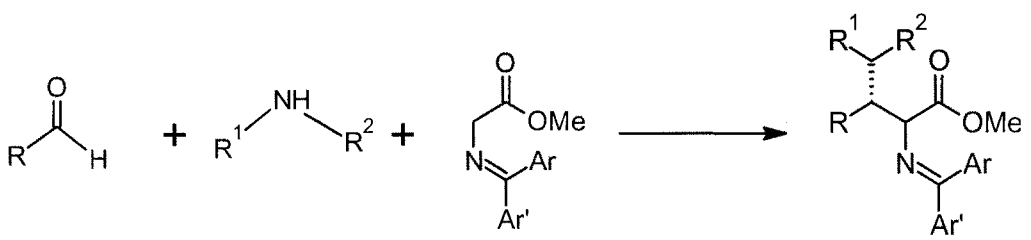
Scheme 13

First asymmetric Mannich reaction between an aldehyde and an imine (derived from ethyl glyoxate and 4-methoxyaniline) using (s)-proline as a naturally occurring chiral catalyst was reported by Cordova et al[26]. Interesting feature of this reaction is the diastereoselectivity. In two different organic solvents

two different diastereomers were obtained (Scheme 14). A Lewis acid catalyzed Mannich reaction between aliphatic aldehyde, secondary amine and glycine derivative is known to afford α, β-diaminoester derivatives with very high diastereoselectivity.[27] (Scheme 15)

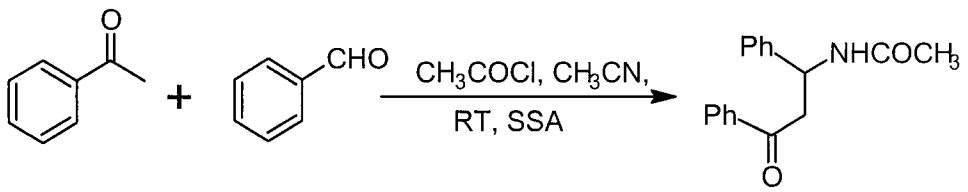


Scheme 14



Scheme 15

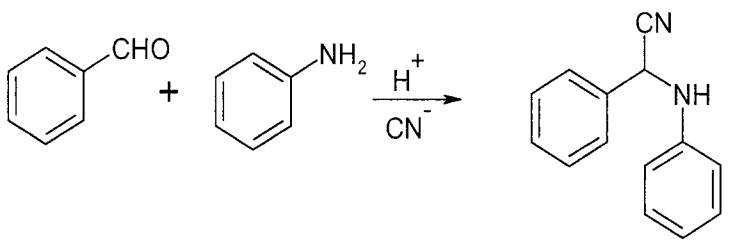
An alternative route towards the synthesis of β-acetaamidoketones is Dakin West reaction which involves one pot condensation between an aldehyde, ketone and acetyl chloride in acetonitrile as the reaction medium and a Bronsted acid as a catalyst e.g. silicasulfuric acid.[28] (Scheme 16)



Scheme 16

1.2.4 Strecker reaction:

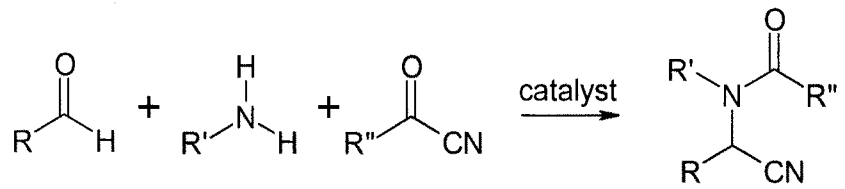
The reaction involving a three component condensation between an aldehyde, amine and cyanide ion source in presence of an acid catalyst leading to α-aminonitrile is known as Strecker reaction.[29] (Scheme 17)



Scheme 17

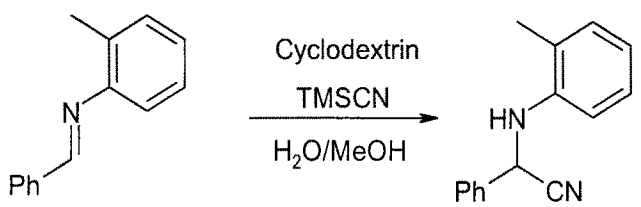
As a cyanide ion source, Strecker has originally proposed the use of hydrocyanic acid, however due to its inherent toxicity it is difficult in handling. Many other cyanide ion sources viz trimethylsilyl cyanide (TMSCN), tributyltin cyanide, diethylphosphino cyanidate, acetone cyanohydrins etc. have been examined and amongst these trimethyl silyl cyanide was proved to be the best cyanide ion source. [30, 31] *(This reaction has been discussed in much detail in the next chapter of the thesis)*

As a modification to strecker reaction, one pot three component synthesis of N-acyl aminonitriles has been reported by Pan et al. [32] (Scheme 18)



Scheme 18

Several modified protocols have been reported for the synthesis of α-aminonitriles however, an environmentally benign and highly efficient protocol was reported by Surendra et al[33] using β-cyclodextrin as a catalyst in aqueous medium. (Scheme 19)

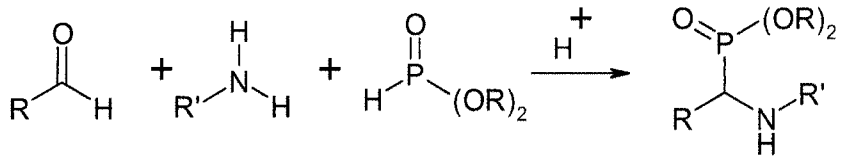


Scheme 19

1.2.5 Kabaschink reaction:

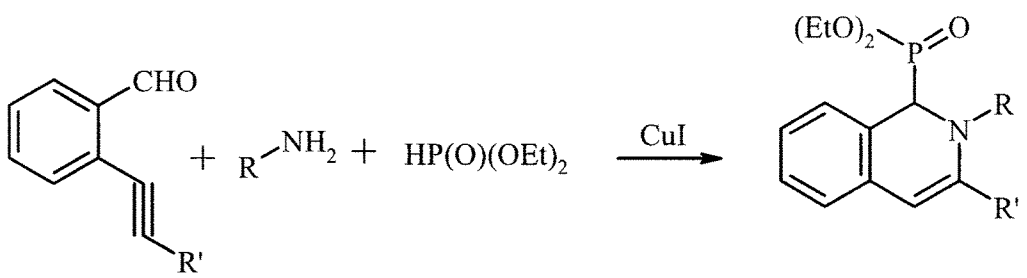
Aminophosphonates are phosphorous analogous of amino acid esters and those are also of significant biological importance.[34] The synthetic strategies leading to α- aminophosphonates are quite analogous to that for α-aminonitriles except in this case three component condensation is carried out between aldehyde, amine and dialkyl/ trialkyl phosphite as a nucleophile, again in the presence of an acid catalyst. (Scheme 20) From our laboratory, we have demonstrated the usefulness of sulfamic acid as an environmentally benign, highly economical and

commercially available catalyst in the synthesis of both α-aminonitriles as well as α-aminophosphonates.[35]



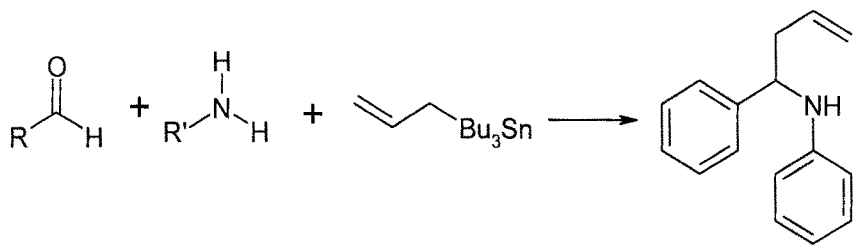
Scheme 20

The use of resulting α-aminophosphonates as nucleophile was reported by Wu et al.[36] It is well presented that, the transition metal / Lewis acid catalyzed cyclization of alkynes possessing nucleophile in its close proximity to triple bond is an important process in organic synthesis. Based upon this concept, the synthesis of 2,3-disubstituted-1,2-dihydroisoquinolin-1-yl phosphates has been reported by Wu et at [36] (Scheme 21)



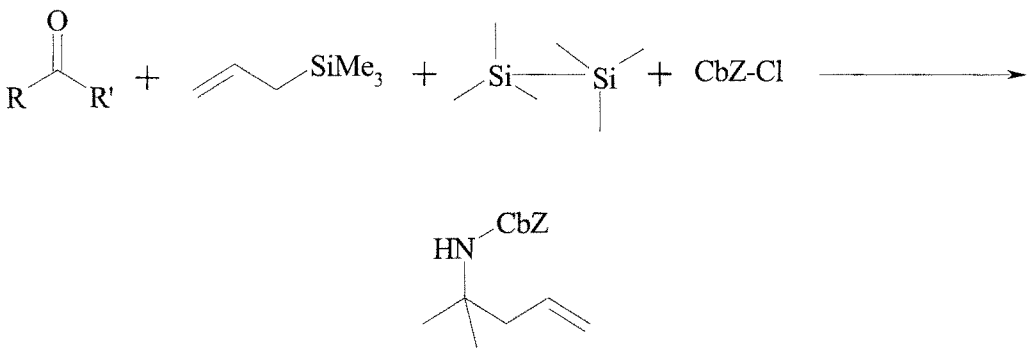
Scheme 21

Synthesis of α-aminonitriles as well as α-aminophosphonates basically involves the generation of an aldimine as an intermediate which upon attack of either cyanide ion or a phosphate nucleophile leads to α-aminonitrile or α-aminophosphonate, respectively. Taking clues from this, synthesis of homoallylic amine was planned; wherein *insitu* generated imine upon attack of allyl tri-n-butyl stanane furnishes respective homoallylic amine in presence of variety of acid catalyst[37]. (Scheme 22)



Scheme 22

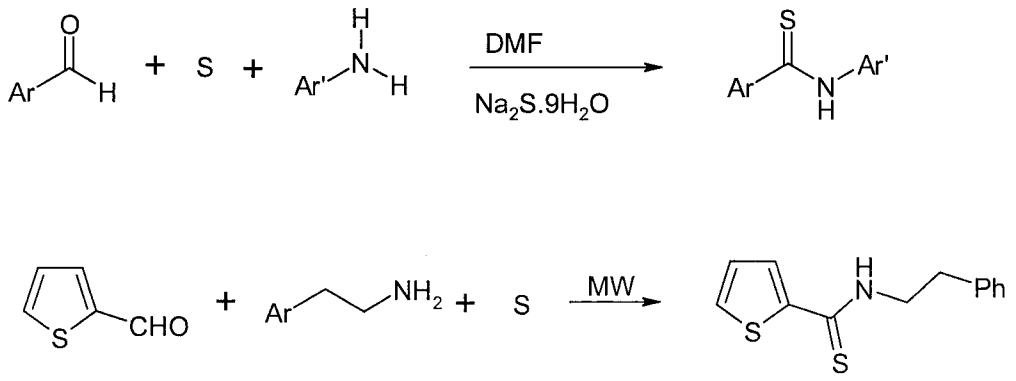
As an extension to this, Das et al have reported an efficient four component reaction between a carbonyl compound, benzyl chloroformate, hexamethyldisilazane and allyl trimethyl silane leading to CBZ-protected homoallylic amine.[38] (Scheme 23)



Scheme 23

1.2.6 Willgerodt reaction:

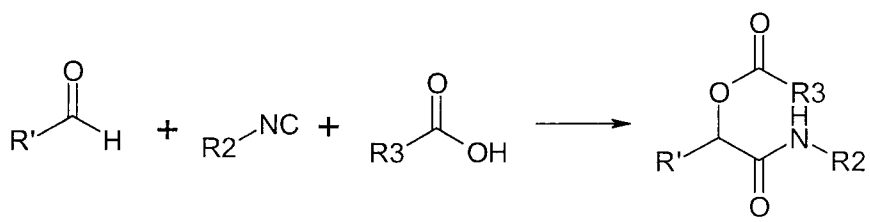
The reaction between an aromatic aldehyde, aniline and elemental sulphur (or a convenient source of elemental sulphur e.g. $Na_2S.9H_2O$) in the presence of a base catalyst is known as Willgerodt reaction. Instead of anilines one may use aqueous ammonia.[39] (Scheme 24)



Scheme 24

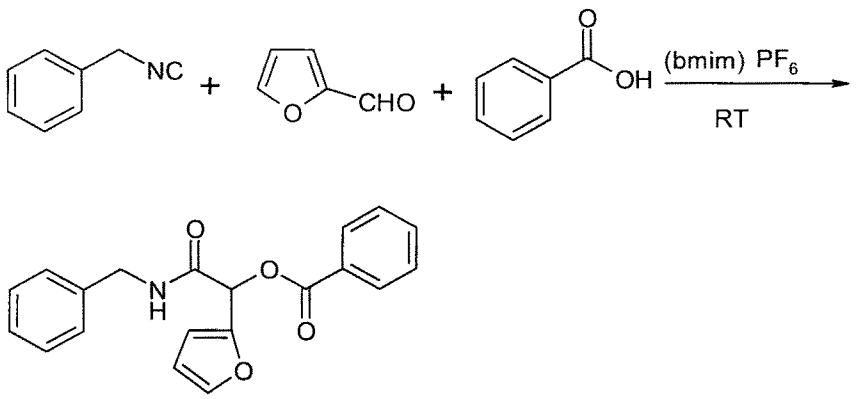
1.2.7 Passerini reaction:

It is the reaction that involves condensation between an aldehyde, isocyanide and carboxylic acid leading to α-acyloxy amide. (Scheme 25)

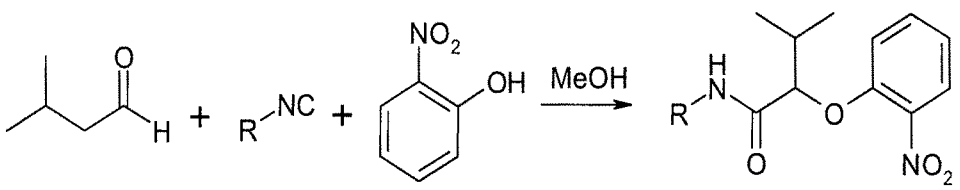


Scheme 25

The reaction can also be carried out in non conventional organic solvents like polyethylene glycol or a reusable ionic liquid [40] *viz* (Bmim) PF_6. (Scheme 26) In modified Passerini reaction, instead of carboxylic acid (as a third component) the use of sufficiently acidic phenol as a third component was described by Kaim et al.[41] (Scheme 27)



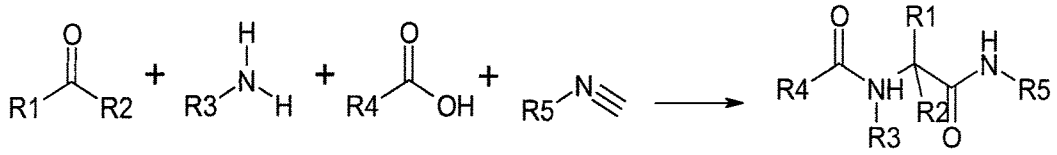
Scheme 26



Scheme 27

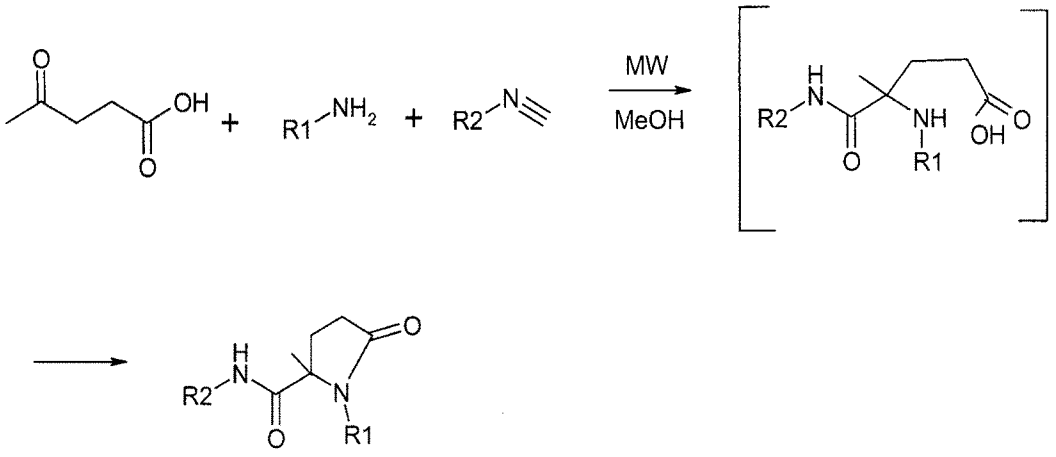
1.2.8 Ugi reaction:

It is another multicomponent reaction involving the condensation between the ketone/aldehyde, amine, isocyanide and carboxylic acid to yield bisamide.[42] This highly exothermic and rapid reaction proceeds under catalyst free condition with very high atom economy. (Scheme 28)



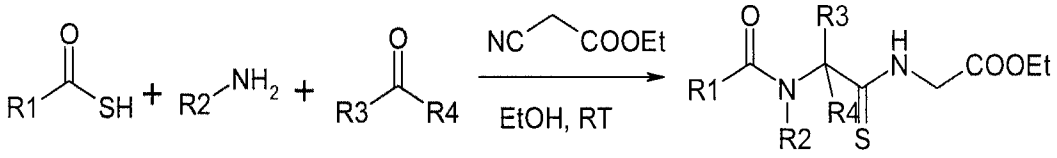
Scheme 28

Instead of using carboxylic acid, equally acid ortho/para to nitro phenols can also be used. [43] The utility of this reaction leading to β-lactum derivatives was demonstrated by Tye et al.[44] (Scheme 29) who first of all explored the possibility of using levulinic acid in this reaction as it can serve as a source of carbonyl as well as carboxylic acid group. The reaction leads to the formation of β-lactum derivatives.



Scheme 29

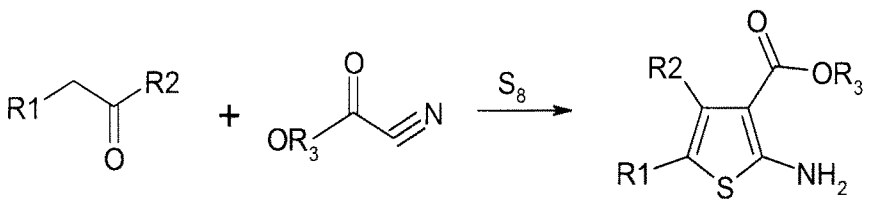
Further extension to Ugi reaction was as regards the use of thio acids as an acid component.[45] (Scheme 30)



Scheme 30

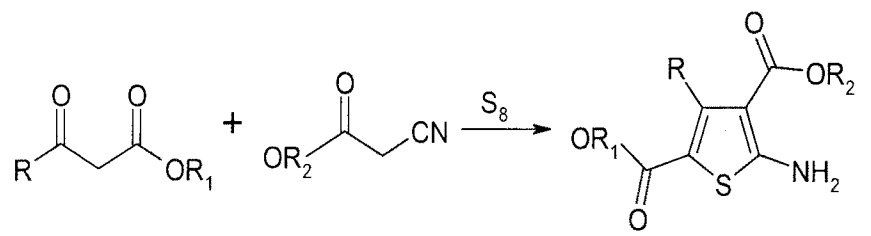
1.2.9 Gewald reaction:

Another multicomponent reaction which uses elemental sulphur as one of the component is, Gewald reaction which involves condensation between an aldehyde/ketone, α-cyanoester and elemental sulfur leading to polysubstituted 2-aminothiophene derivatives. (Scheme 31)



Scheme 31

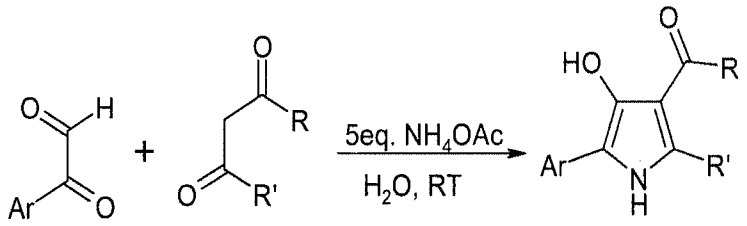
The resultant thiophene derivatives serve as key templates for structural diversification and semi-automated laboratory synthesis. [46] (Scheme 32)



Scheme 32

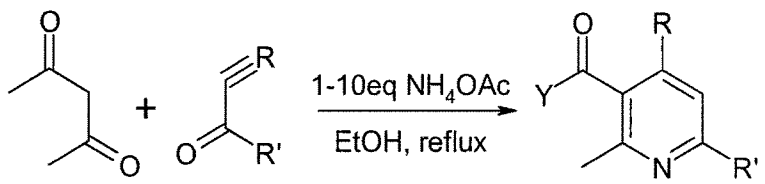
1.2.9 Other reactions:

A) (i) Various 2-alkyl-5-aryl-(1H)-pyrrole-4-ol derivatives have been synthesized by three component condensation between a β-dicarbonyl compounds, arylglyoxals and ammonium acetate[47]. (Scheme 33)



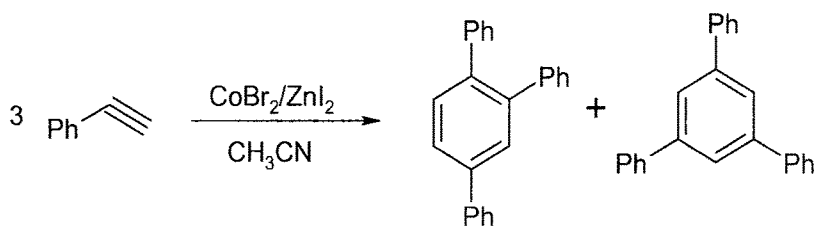
Scheme 33

(ii) Based upon similar concept, the reaction between a β-diketone, alkynone and ammonium acetate leads to polysubstituted pyridines.[48] (Scheme 34)



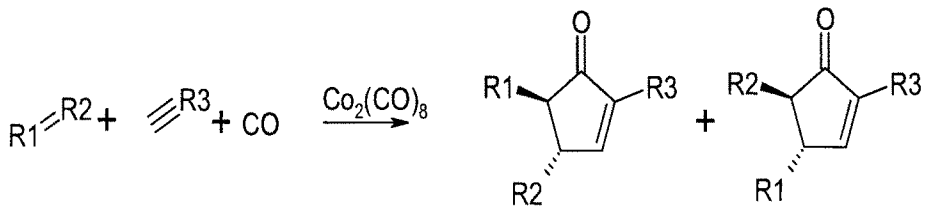
Scheme 34

B) (i) An alkyne trimerisation leading to benzene derivatives is a pseudo pericyclic reaction involving 2+2+2 cyclization. The reaction typically needs a transition metal catalyst e.g. $CoBr_2$, ZnI_2, etc. [49] (Scheme 35)



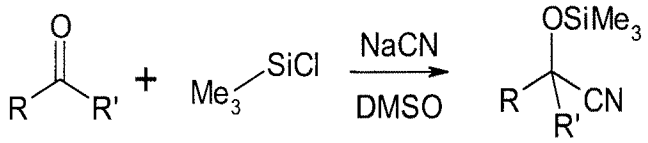
Scheme 35

(ii) Pauson- Khand reaction is a 2+2+1 cycloaddition reaction between an aldehyde, alkene and carbon monoxide to form α, β-cyclopentenone again in the presence of a transition metal catalyst. [50] (Scheme 36)



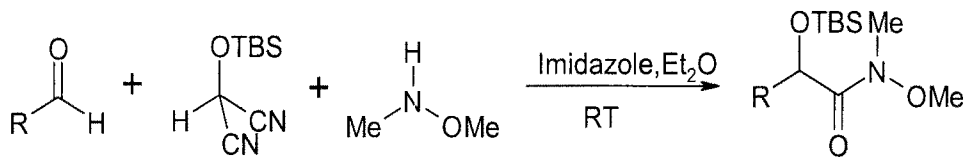
Scheme 36

C) (i) The reaction between ketones, sodium cyanide and chlorotrialkyl silane in DMSO medium leads to trialkyl silyl protected cyanohydrins.[51] (Scheme 37)



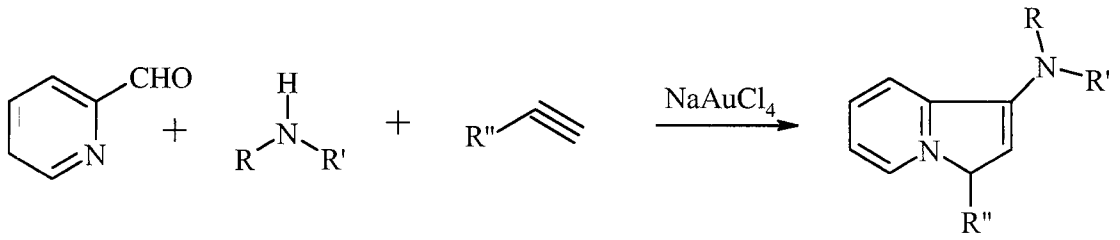
Scheme 37

(ii) Another one pot reaction leading to α-silyloxy-weinreb amides involves aldehyde, masked acyl cyanide reagent and N, O-dimethyl hydroxyl amine.[52] (Scheme 38)



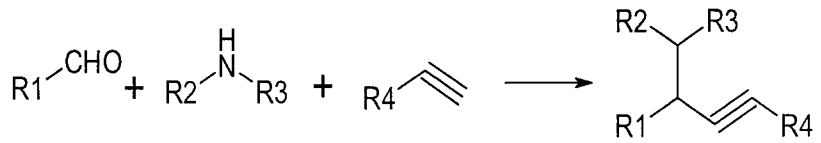
Scheme 38

D. (i) In another multicomponent reaction or cycloisomerization reaction condensation is effected between a heteroaryl aldehyde, amine and an alkyne to furnish aminoindolizines.[53] (Scheme 39)



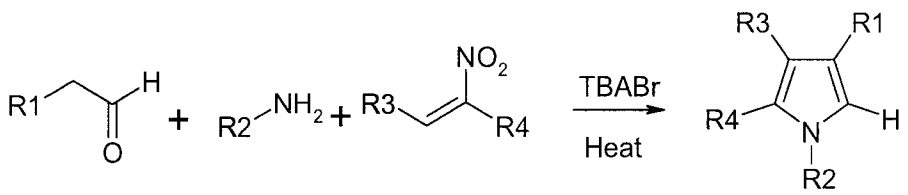
Scheme 39

(ii) A three component coupling between an aldehyde, alkyne and an amine can be employed in the synthesis of proparagylic amines with Ag-dodecatungstophosphate. [54] (Scheme 40)



Scheme 40

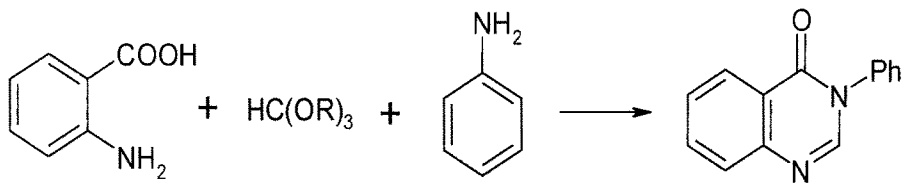
E. A three component condensation between a carbonyl compound, an amine and nitroalkene leading to substituted pyrrole has been reported by Ranu et al.[55] (Scheme 41)



Scheme 41

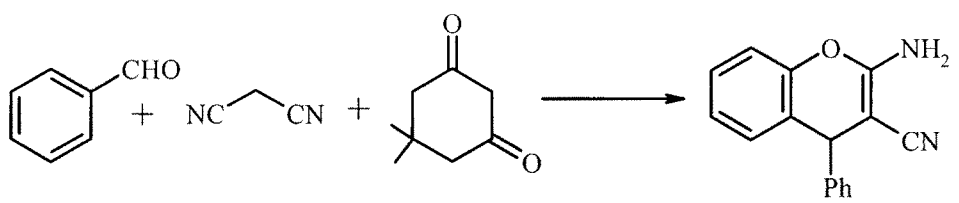
F. 4(3H)-Quinazolines constitutes a class of fused heterocycles having a wide range of biological activities [56] and can be synthesized by a three component condensation between anthranilic acid, an ortho ester and an amine in presence of

an acid catalyst. The reaction probably proceeds via initial formation of N-formylated product. [57] (Scheme 42)



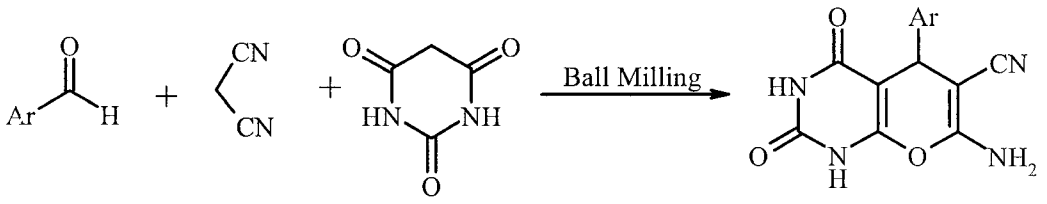
Scheme 42

G. In recent years polyfunctionlized benzopyranes have attracted much attention due to their pharmacological properties as well as due to their presence in many natural products.[58, 59] The reaction between an aldehyde, malononitrile and cyclic 1,3-diketone leads to the formation of benzo(b) pyran derivatives.[60] (Scheme 43)

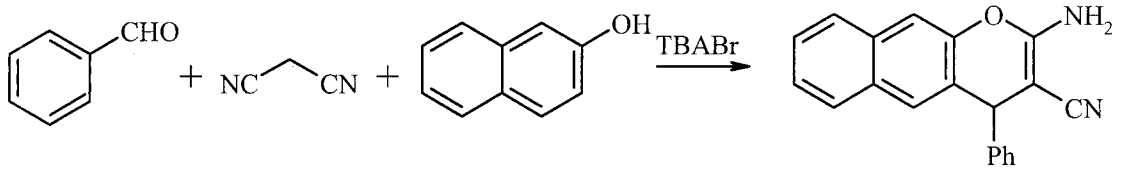


Scheme 43

Instead of using cyclohexane 1,3-dione/dimedone as an active methylene compound, Jamal et al[61] have demonstrated the use of barbituric acid as another active methylene compound. The reaction between an aldehyde, malononitrile and barbituric acid and catalyst as well as solvent free condition was shown to furnish pyrano (2,3-)pyrimidine-2,4(1H,3H)-diones. (Scheme 44) Further extension to this was reported by Jin et al[62] who has used β-naphthol as the third component in the synthesis of benzopyran derivatives. The synthesised benzopyranes are of importance in the synthesis of cosmetics, pigments [63] and biodegradable agrochemicals. [64] (Scheme 45)

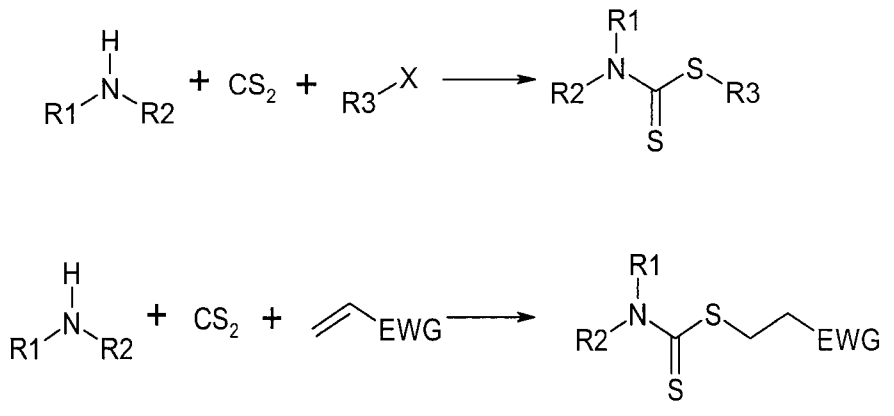


Scheme 44



Scheme 45

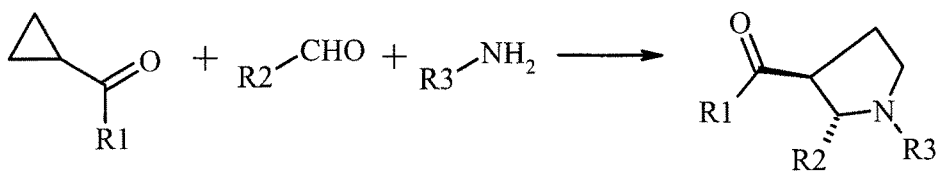
H. From mechanistic view there are two different methods for the preparation of dithiocarbamates as depicted below involving either alkylation of thiolate anion or thia-michel addition to conjugated alkenes.[65,66] (Scheme 45)



Scheme 46

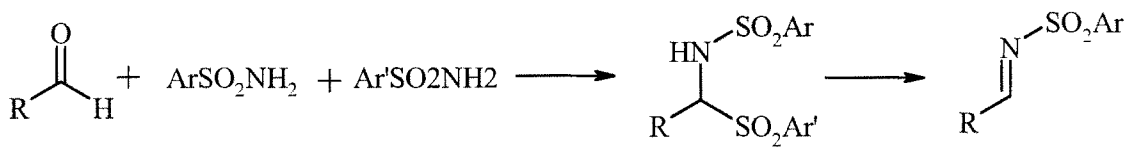
I. Olsson and co-workers [67] have disclosed a new method for the synthesis of substituted pyrrolidone derivatives by a three component condensation between cyclopropyl ketones, aldehydes and primary amines using MgI_2 as a catalyst. The

same protocol was further extended by Hung et al.[68] for the synthesis of pyrrolidone derivatives. (Scheme 47)



Scheme 47

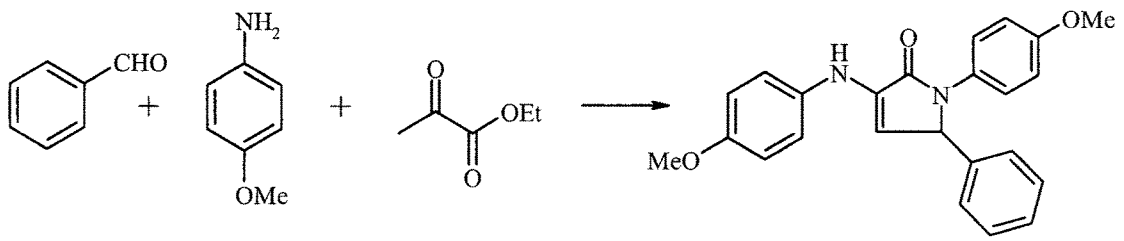
J. Imines bearing N-substituted electron withdrawing groups are useful intermediates in organic synthesis.[69] Sulfonyl imines have been importance in last decade.[70] Direct condensation between sulfanamides with carbonyl compounds offers a straight forward route for these compounds. However, it can not be used due to the weak nucleophilicity of sulfanamides and this necessities the use of a Lewis acid catalyst / harsh reaction conditions.[71,72] Due to these limitations, Li et al.[73] have developed a one pot procedure for the synthesis of sulfonyl imines by condensation between an aldehyde, sulfanamides and an alkyl sulfinate. (Scheme 48)



Scheme 48

K. 1,5-Dihydro-2H-pyrrole-2-ones and particularly their 3-amino substituted derivatives are interesting type of lactum that are found in many natural products and exhibit prominent biological properties. [74,75] Such derivatives have been

prepared by Cheng et al[76] with three component condensation between an aldehyde, an amine and a pyruvate ester. (Scheme 49)



Scheme 49

1.3 Remarks:

By virtue of their synthetic potential, inherent atom efficiency, convergent nature, ease of implementation and high atom economy, multicomponent reactions have attracted much attention in these days. The ability to synthesize small drug molecules with several degrees of structural diversity is the other noteworthy feature of multicomponent reactions.

In last few pages, although we have taken a brief account of multicomponent reactions, we are well aware that it is just the tip of an iceberg. Furthermore, each of the above discussed reaction may constitute a matter of an indepent article for discussion and that is simply beyond our scope and after all that is not the aim of this thesis.

Amongst many muticomponent reactions, we have focused our attention on Strecker reaction for the synthesis of α-aminonitriles which is described in the second part of the thesis.

References:

1 (a) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L.

Acc. Chem. Res. **2003**, *36*, 899-907.

(b) Zhu, J.

Eur. J. Org. Chem. **2003**, *7*, 1133-1144.

(c) Hulme, C.; Gore, V.

Curr. Med. Chem. **2003**, *10*, 51-80.

(d) Domling, A.

Curr. Opin. Chem. Biol. **2002**, *6*, 306-313.

2. (a) Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta,G.; Dimarco, J. D.; Gougoutas, J.Z.; Hedberg, A. O.; Malley, M.; McCarthy, J. P.

J. Med. Chem. **1995**, *38*, 119.

(b) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.;Swanson, B.N.; Gougoutas, J.; Schwartz, Z. J.; Smillie, K.M.; Malley, M.

J. Med. Chem. **1990**, *33*, 2629.

3. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

4. Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; De Brosse, C.; Mai, S.; Truneh, A.; Carte, B.

J. Org. Chem. **1995**, *60*, 1182.

5. (a) Biginelli; P.

Ber **1891**, *24*, 1317, 2962.

(b) Biginelli; P.

Gazz. Chim. Ital. **1893**, *23*, 360.

6. B. C. Ranu, A. Hajra, S. S. Dey,

Org. Process Res. Dev. **2002**, *6*, 817.

7. D. M. Pore, U. V. Desai; T. S. Thopate, P. P. Wadgaonkar

Aust. J. Chem. **2007**, *60*, 435–438.

8. Shinde, S. V.; Jadhav, W. N.; Lande, M. K.; Gadekar, L. S.; Arbad, B. R.; Kondre, J. M., Karade, N. N.

Catal. Lett., **2008**, *125*, 57-61.

9. (a)Patel, M.; Mchugh, R. J.Jr.; Cordova,B. C.

Bioorg. Med. Chem. Lett., **1999**, *9*, 3221.

(b) El-Shafei, H. A.; Badr-Eldin, S. M.

Egypt J. Microbiol., **1994**, *27*, 353.

(c) Sugimoto, H.; Yonaga, M.; Karibe, N.; Limura, Y.

Eur. Patent Appl. Ep. **1992**, *468*, 187. (*Chem. Abstr.*, **1992**, *116*, 235643).

10. Latif, N.; Mishrity, N.; Assad, F. M.

Aust. J. Chem., **1982**, *35*, 1037.

11. Bazgir, A.; Delbari, A. S.; Dabiri, M.

Synlett, **2007**, *5*, 821-823.

12. Mauzeral, D.; Westheimer, F. H.

J. Am. Chem. Soc. **1955**, *77*, 2261.

13. Zolfigol, M. A.; safaiee, M.

Synlett **2004**, *5*, 827.

14. Tu, S.-J.; Lu, Z.; Shi, D.; Yao, C.; Gao, Y.; Guo, C.

Synth. Commun. **2002**, *32(8)*2181.

15. (a)Janis, R. A.; Silver, P. J.; Triggle, D. J.;

Adv. Drug Res. **1987**, *16,* 309.

(b) Bossert, F.; Vater, W.

Med. Res. Rev. **1989**, *9*, 291.

16. Chandrasekhar, S. Rao, S. Y.; Sreelakshmi, L.; Mahipal, B.; Reddy, C. R.

Synlett **2008**, *11*, 1737.

17. Zhang, X.-Lan.; Sheng, S.- Ri; Liu, X.- Liang; Liu, X.-Ling

ARKIVOC **2007**, *xiii*, 79.

18. (a) Ferwanah, A.R.S.; Awadallah, A. M. Private Communication, 2003.

(b) Gopalkrishan, M.; Sureshkumar, P.; Thanusu, J.; Kanagarajan, V.

J. Enzyme Inh. And Med. Chem., **2008**, *23(1)*, 87-93.

19. (a) Blicke, F.F.*Org. React.* **1942**, *1*, 303;

(b) Kleinnamann, E. E. in *Comprehensive Organic synthesis*, ed. B.M. Trost, Pergamon, New York, **1991**, *Vol. 2*, ch. 4.1.

20. Zhao, G.; Jiang, T.; Gao, H.; Han, B.; Huang, J.; Sun, D

Green Chem., **2004**, *6*, 75-77.

21. Eftekhari-sis, B.; Abdollahifar, A.; Hashemi, M.M.; Zhao, G.

J.Org. Chem., **2006**, 5152-5157.

22. Iimura, S.; Nobutou, D.; Manabe, K.; Kobayashi, S.

Chem. Comm., **2003**, 1644-1645.

23. Suginome, M.; Uehlin, L.; Murakami, M.

J. Am. Chem. Soc., **2004**, *126*, 13196-13197.

24. Xu, L.-W.; Xia, C.-G.; Li, L.

J.Org. Chem., **2004**, *69*, 8482-8484.

25. Liu, T.-Y.; Cui, H. –L.; Long, J.; Li, B. –I, Wu, Y.; Ding, L. –S.; Chen, Y.

J. Am. Chem. Soc., **2007**, *129*, 1878-1879.

26. Cordova, A.; Watanade, S.; Tanaka, F.

J. Am. Chem. Soc., **2002**, 124(9), 1866-1867.

27. (a)Salter, M.M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S.

Org. Lett., **2006**, *8*, 3533-3536.

28. Khodaei, M. M.; Khosropour, A. R.; Fattahpour, P.

Tetrahedron Lett., **2005**, *46*, 2105-2108.

29. Strecker, A.

Ann. Chem. Pharm., **1950**, *75*, 27.

30. Harusawa, S.; Hamada, Y.; Shioiri, T.

Tetrahedron Lett., **1979**, *20*, 4663.

31. Paraskar, A. S.; Sudali, A.

Tetrahedron Lett., **2006**, *47*, 5759.

32. Pan, S. C.; List, B.

Synlett, **2007**, 318-320.

33. Surendra, K.; Krishnaveni, N. S.; Mahesh, A.; Rao, K. R.

J. Org. Chem., **2006**, *71*, 2532-2534.

34 (a) Kafarski, P.; Lejczak, B.

Phosphorus Sulfur Silicon Relat. Elem.**1991**, 63, 1993.

(b) Allen, M.C.; Fuher, W.; Tuck, B.;.; Wade, R ; Wood, J. M.

J. Med. Chem. **1989,** *32*, 1652.

(c) Baylis, E.K.; Campbell, C.D.; Dingwall, J.G.

J. Chem. Soc., Perkin Trans. I **1984**, 2845.

(d) Benkovic, S.J.; Hirschmam, R.

Tetrahedron Lett. **1994**, *35*, 6856.

(e) Hassal, C.H.; HahnAntibiotics, E. F. vol. VI, Springer, Berlin, 1983,p. 11.

35. Mitragotri, S.D.; Pore, D.M.; Desai, U.V.; Wadgaonkar, P.P.

Catal. Commun. **2008,** *9*, 1822–1826.

36. Wu, J.; Wang, B.; Ding, Q.

Tetrahedron **2007**, *63*, 12166-12171.

37. Das, B.; Ravikanth, B.; Thirupati, P.; Vittalrao, B.

Tetrahedron Lett. **2006**, *47,* 5041-5044.

38. Das, B.; Venkateswarla, K.; Mahender, G.; Mahender, J.

Tetrahedron Lett. **2005**, *46*, 3041.

39. (a) Okamoto, K.; Yamamoto, T.; Kanbara, T.

Synlett, **2007**, 2687-2690.

(b) Zubruyev, O. I.; Stiasni, N.; Kappe, C.O.

J. Comb. Chem., **2003**, *5*, 145-148.

40. Andrade, C. K. Z.; Takada, S. C. S.; Suarez, P.A.Z., Alves, -M. B.

Synlett **2006**, 1539-1541.

41. Kaim, L. El.; Gizolme, M.; Grimaud, L.

Org. Lett., **2006**, *8*, 5021-5023.

42. Ugi, I.; Domling, A.; Werner, B.

J. Heterocycl. Chem., **2000**, *37*, 647.

43. Kaim, L. El.; Oble, J.; Grimaud, L.

Angew, Chem. Int. Ed., **2005**, *44*, 7961-7964.

44. Tye, H.; Whittaker, M.

Org. Biomol. Chem., **2004**, *2*, 813-815.

45. Kazamaier, U.; Ackermann, S.

Org. Biomol. Chem., **2005**, *3*, 3184-3187.

46. Gewald, K.; Schinke, E.; Bottcher, H.

J. Am. Chem. Soc. **1966**, *99*, 94-100.

47. Khalili, B.; Jajarmi, P.; Ettekhari-sis, B.; Hasheri, M.M.

J. Org. Chem., **2008**, *73*, 2090-2095.

48. Xiong, X.; Bagley, M.C.; Chapaneri, K.

Tetrahedron Lett., **2004**, *45*, 6121-6124.

49. Hilt, G.; Vogler, T.; Hess, W.; Galbiati, F.

Chem. Comm., **2005**, *(II)*, 1474-1475.

50. Pauson, P. L.; Khand, I. U.

Acadamic Sci., **1977**, *295*, 2.

51. Cabirol, F.L.; Lim A. E. C.; Hanefuld, U.; Sheldon, R. A.; Lyapkalo, I.M.

J. Org. Chem., **2008**, *73*, 2446-2449.

52. Nemoto, H.; Ma, R.; Moriguchi, H., Kawamura, T.; Kamiya, M.

J. Org. Chem., **2007**, *72*, 9850-9853.

53. Yan, B.; Liu, Y.

Org. Lett., **2007**, *9*, 4323-4326.

54. Reddy, K. M.; Babu, N. S.; Suryanarayana, I.; SaiPrasad, P. S.; Lingaiah,

Tetrahedron Lett., **2006**, *47*, 7563-7566.

55. Ranu, B. C.; Dey, S. S.

Tetrahedron Lett., **2003**, *44*, 2865-2868.

56. Wolfe, J. F.; Rathman, T. L.; Sleevi, M. C.; Compbell, J. A.;

Greenwood, T. D.

J. Med. Chem., **1990**, *33*, 161.

57. Das, B.; Banerjee, J.

Chem. Lett., **2004**, *33(8)*, 960.

58. (a)Foye, W. O.

Principi di chimica Farmaceutica Piccin; Padova: Italy, **1991**, 416.

(b) Andreami, L. L.; Lapi, E.

Boll. Chim. Farm., **1960**, *99*, 583.

(c) Bonsignore, L.; Loy, G.; Secci, D.

Eur. J. Med. Chem. **1993**, *28*, 517.

59. (a)Hatakeyama, S.; Ochi, N.; Numata, H.; Takano, S.

J. Chem. Soc. Chem. Commun., **1988**, 1202.

(b) Cingolant, G. M.; Pigini, M.

J. Med. Chem., **1969**, *12*, 531.

60. Pore, D. M.; Desai, U. V.; Undale, K. A.; Dongare, B. B.

Cat. Lett. **2009**, *132 (1-2),* 104-108.

61. Mashkouri, S.; Jamal, R. N.

Molecules **2009**, *14*, 474.

62. Jin, T. S.; Xia, J. C.; Wang, S, J.; Li, T. S.; Song, X. R.

Synlett, **2003**, *13*, 2001-2004.

63. Ellis, G. P., Weissberger, A.; Taylor, E. C.

The Chemistry of heterocyclic compounds, In Chromenes, Chromanes and chromeones, **1977**, 13.

64. (a)Hafez, E. A. A.; Elnagdi, M. H.; Elagamey, A. G. A.

Heterocycles, **1987**, *26*, 903.

(b) Abdel Galil, F. M.; Raid, B. Y.; Elnagdi, M. H.

Chem. Lett. 1982, 1123.

65. Li, R.-Tuo; Ding, P.-Yu; Han, Mei; Cai, M.-Shen

Synth. Commun. **1998**, *28(2)*, 295.

66. (a) Azizi, N.; Ebrahimi, F.; Aakbari, E., Aryanasab, F.; Saidi, M. R.

Synlett, **2007**, 2797-2800.

67 Olsson, R.; Gustafsson, M.; Bertozzi, F.

Org. Lett., **2002**, *4*, 3147-3150.

68. Huang, W.; O'Donell, M.M.; Bi, G.; Liu, J.; Yu, L.; Baldino, C. M.; Bell, A. S.; Underwood, T. J.

Tetrahedron Lett., **2004**, *45*, 8511-8514.

69. (a) Bloch, R.

Chem. Rev., **1998**, *98*, 1407-1438.

(b) Kobayashi, S.; Ishitani, H.

Chem. Rev., **1999**, *99*, 1069-1094.

(c) Miyabe, H.; Ueda, M.; Naito, T.

Synlett, **2004**, 1140-1157.

70. (a) Weinreb, S. M.

Top. Curr. Chem., **1997**, *190*, 131-184.

(b) Enders, D.; Reinhold, U.

Tetrahedron Asymmetry, **1997**, *8*, 1895-1946.

71. (a) Mckay, W. R.; Proctor, G. R.

J. Chem. Soc., Perkin. Trans, **1981**, *1*, 2435-2442.

(b) Jennings, W. B.; Lovely C. J.

Tetrahedron Lett., **1988**, *29*, 3725-3728.

(c) Davis F. A.; Thimmareddy R.

J. Am. Chem. Soc., **1989**, *111*, 5964-5965.

72. (a) Albrecht R.; Kresze G.

Chem. Ber., **1964**, *97*, 490-493.

(b) Davis F. A.; Kaminski, J. M.; Kluger, E. W.

J. Am. Chem. Soc., **1975**, *997*, 7085-7091.

(c) Davis F. A.; Lamendola, J.; Nadir, Jr. U., Kluger, E. W.;

Sedergran, T. C.

J. Am. Chem. Soc., **1980**, *102*, 2000-2005.

73. Li, Z.; Ren, X.; Wei, P.; Wan, H.; Shi, Y.; Ouyang, P.

Green Chem., **2006**, *8*, 433-436.

74. (a)Gein, V. L.; Popav, A. V.; Kolla, V. E.; Popova, N. A.

Pharm. Chem. J., **1993**, *27*, 343.

(b) Gein, V. L.; Popav, A. V.; Kolla, V. E.; Popova, N. A.

Pharmazie, **1993**, *48*, 107.

75. (a) Wu, Y. C.; Liu, L., Wang, D.; Chen, Y. J.

J. Heterocyl. Chem., **2006**, *43*, 949.

(b) Palacios, F.; Vicario, J.; Aparicio, D.

Eur. J. Org. Chem. **2006**, 2843.

76. Li, X; Deng, H.; Luo, S.; Cheng, J. P.

Eur. J. Org. Chem., **2008**, 4350-4356.