RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.2, No.3 (2009), 662-676
ISSN: 0974-1496
CODEN: RJCABP

REVIEW ARTICLE

RECENT PROGRESS IN THE CHEMISTRY OF DIHYDROPYRIMIDINONES

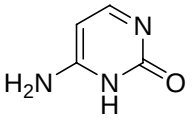
I. T. Phucho, A. Nongpiur, S. Tumtin, R. Nongrum and R. L. Nongkhlaw*
Department of Chemistry
North Eastern Hill University, Shillong, Meghalaya, India
Email: rlnongkhlaw@nehu.ac.in

ABSTRACT

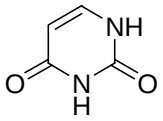
This review elaborates the collective synthetic studies of a known group of Dihydropyrimidinones and their reactions. Their mechanistic studies as well as their important bioactivities have been discussed together with the synthesis of special groups of substances. The scope and limitation of the classical procedure and the synthetic applications of the catalytic variant of Biginelli reaction are also briefly summarized in this review.
Keywords: dihydropyrimidinone, Biginelli compound**.**

INTRODUCTION

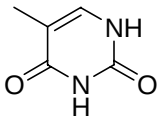
Pyrimidinones or Dihydropyrimidinones (DHPMs) are well known for their wide range of bioactivities and their applications in the field of drug research have stimulated the invention of a wide range of synthetic methods for their preparation and chemical transformations. Out of the five major bases in Nucleic acids three are pyrimidine derivatives which comprises of Cytosine (**1**) which is found in DNA and RNA, Uracil (**2**) in RNA and Thymine (**3**) in DNA. Because of their involvement as bases in DNA and RNA, they have become very important in the world of synthetic organic chemistry. Aryl-substituted 3, 4-dihydropyrimidin-2(*1H*)-one and their derivatives are an important class of substances in organic and medicinal chemistry.



1
cytosine



2
uracil

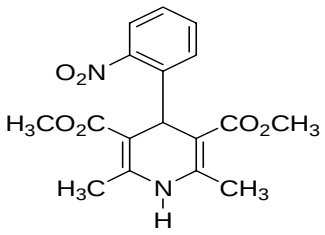


3
thymine

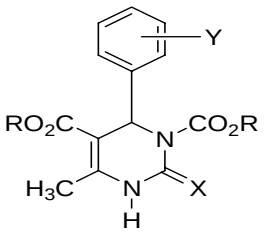
Several alkaloids containing the dihydropyrimidine core unit have been isolated from marine sources, which also exhibit interesting biological properties[1]. Most notably, among these are the batzelladine alkaloids, which were found to be potent HIV gp-120-CD4 inhibitors. The scope of this pharmacophore has been further widen with their identification of 4-(3-hydroxyphenyl)-2-thione derivative **4** called monastrol[2] as a novel cell-permeable molecule for the development of new anticancer drugs. Monastrol (**4)** has been identified as a compound that specifically affects the cell-division (mitosis) by a new mechanism which does not involve tubulin targeting. It has been established that the activity of **4** consists of the specific and reversible inhibition of the motility of the mitotic kinesis, a motor protein required for spindle bipolarity.

Trimethoprim (**5**) is a type of drug with a pyrimidine core which attacks the folic acid metabolism of bacteria and is often used as antibacterial agents [3].

4-aryl-1,4-dihydropyridines (DHPs) of the nifedipine type [4] (e.g. **6**) were first introduced into clinical medicine in 1975 and are still the most potent group of calcium channel modulators available for the treatment of cardiovascular diseases.[5] Dihydropyrimidines of type **7** show a very similar pharmacological profile, and in recent years, several related compounds were developed (*e.g* **7**) that are equal in potency and duration of antihypertensive activity to classical and second-generation dihydropyridine drugs.[6]



6
Nifedipine



7

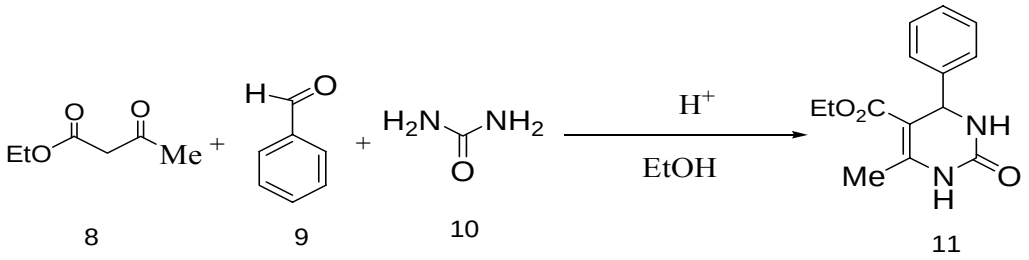
R= Alkyl,
Y= NO_2, CF_3
X= O, S, NH

The major aim of this review is to provide examples for the synthesis of the known groups of Dihydropyrimidinones. In some cases, the mechanistic studies of the synthesized compounds, their reactions with different reagents and their transformations are included. Their most important bioactivities together with the synthesis of special groups of substances are also discussed. In this review we would like to briefly summarize the mechanistic data as well as the scope and limitation of the classic procedure, and describe the synthetic applications of the catalytic variant of Biginelli reaction.

The first synthesis of dihydropyrimidinones was reported by Biginelli[7] in 1893, however, the synthetic potential of this heterocyclic synthesis remained unexplored for quite some time. In the 1970's interest gradually increased, and the scope of the original cyclocondensation reaction shown in scheme **1** was gradually extended by variation of all the building blocks, allowing access to a large number of multifunctionalized dihydropyrimidines of type **11**. Since the late 1980's, a tremendous increase in activity has again occurred, as evident by the growing number of publications and patents on the subject. This is mainly due to the fact that the multifunctionalized dihydropyrimidine scaffold ("Biginelli compounds") represents a heterocyclic system of remarkable pharmacological efficiency. Since then several reviews on synthesis and chemical properties of pyrimidinones have been published. The search for new and efficient methods for the synthesis of pure compounds has been an active area of research in organic synthesis. From a modern point of view, Biginelli protocol is obviously very attractive for combinatorial chemistry and has been rarely used for parallel synthesis, a new avenue could be connected with an elaboration of catalytic procedures. Here we present the essential summary of important characteristics of this reaction.

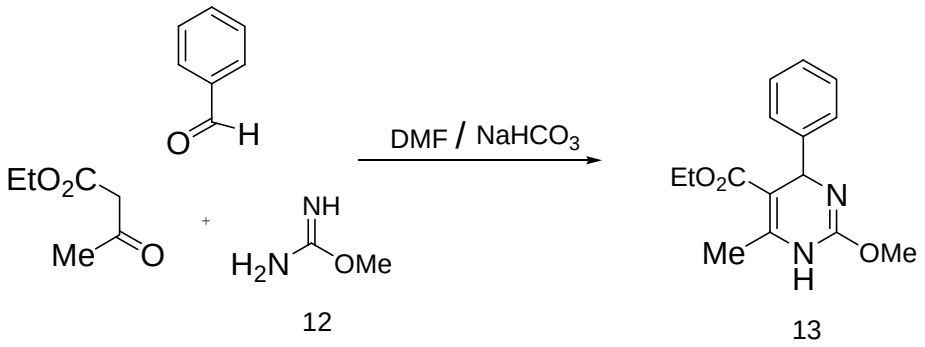
Synthetic methodologies for dihydropyrimidinones

In 1893, P Bigenelli reported on the acid catalyzed cyclo-condensation reaction of ethyl acetoacetate (**8**), benzaldehyde (**9**), and urea (**10**). The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of hydrochloric acid at reflux temperature. The product of this novel one-pot, three components synthesis that precipitated on cooling of the reaction mixture was identified as 3,4-dihydropyrimidin-2*(1H)*-one (**11**) and this reaction is known as "Biginelli reaction", or "Biginelli Condensation", or as "Biginelli dihydropyrimidine synthesis". [7] ***(Scheme-1).***



Scheme 1. Classical biginelli synthesis of DHPMs

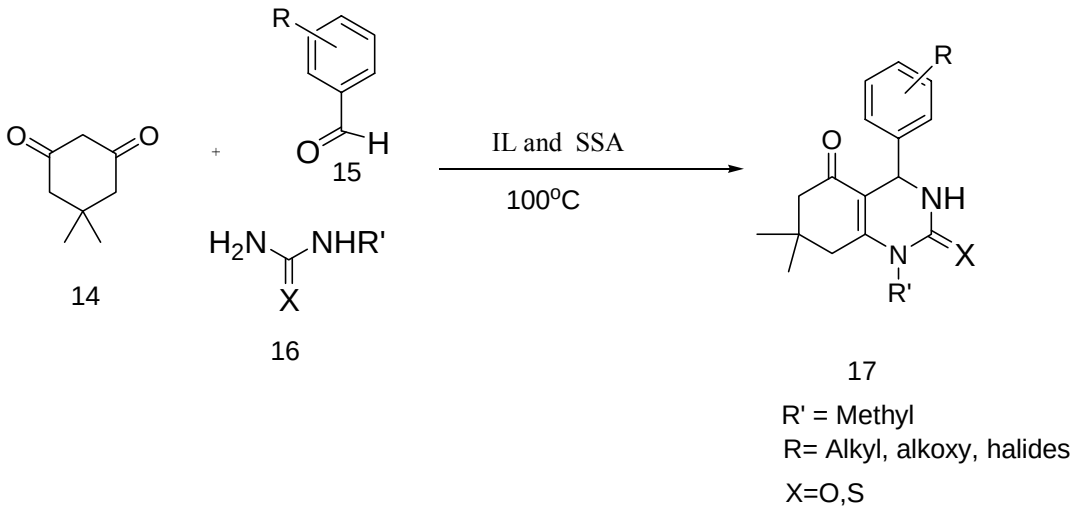
Since then a number of improved variants employing new reagents, catalyst, methodologies and technique have emerged. Numerous synthetic method for the preparation of these compounds have been reported using $InCl_3$,[8] lanthanide triflate,[9] BF_3•OEt_2,[10] PPE,[11a] KSF clay,[11b] $LaCl_3$,[12] H_2SO_4,[13] ceric ammonium nitrate (CAN),[14] $Mn(OAc)_3$,[15] ion-exchange resin,[16] $InBr_3$,[17] $FeCl_3$,[18] $CdCl_2$,[19] 1-n-butyl-3-methyl imidazolium tetrafluoroborate,[20] ytterbium triflates,[21] $SiO_2/NaHSO_4$,[22] $BiCl_3$,[23] $LiClO_4$,[24] $ZrCl_4$,[25] $Cu(OTf)_2$,[26] $Bi(OTf)_3$,[27] LiBr,[28] NH_4Cl,[29] $SnCl_2.2H_2O$,[30a] $AlCl_3/KI$,[30b] $CoCl_2$ /$MnCl_2$,[30c] $AlCl_3/AlBr_3$,[30d] P_2O_5,[31] $BiOClO_4.xH_2O$,[32] $CaCl_2$,[33a] 1,3-Dibromo-5,4-dimethylhydantoin,[33b] zinc tetrafluoroborate.[33c]
C O Kappe reported the synthesis of 2-methoxy-1,4-dihydropyrimidines (**13**) which was obtained by condensation of ethylacetoacetate, O-methylisourea (**12**) and an appropriate aldehyde.[34] ***(Scheme-2).***



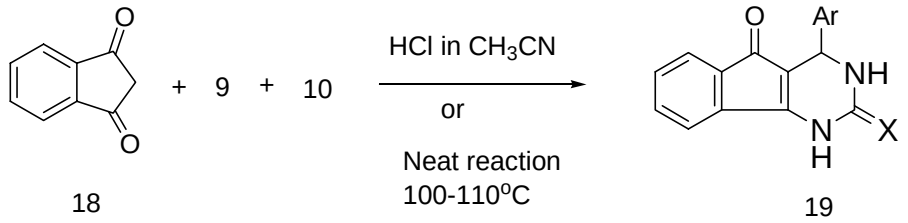
Scheme 2

Recently, for novel Biginelli-like scaffold syntheses,[35a] the use of common open-chain β -dicarbonyl compounds has been extended to cyclic β -diketones,[35b] β-ketolactones,[35c] cyclic β –diesters[35d] or β –diamides[35e-g], benzocyclic ketones and α–ketoacids[35g]. Shabani *et al* synthesized biginelli type (**17**) compound by the reaction of 5,5-dimethyl-1,3 cyclohexanedione **14** and aldehydes **15** with urea (**16)**, *N*-methylurea or thiourea (**16)** using 1-butyl-3-methylimidazolium bromide [bmim]Br as an ionic liquid (IL) in conjunction with a solid acid catalyst, silica sulfuric acid (SSA).[36] ***(Scheme-3).***

The above reaction (scheme **3**) is the modification of the earlier report of Perumal *et al*[30f] where HCl in acetonitrile was used instead of ionic liquid in SSA and the use of indane-1,3-dione (**18**) gives 4-aryl-indeno-[1,2-d] pyrimidine (19) which was found that solvent-free and catalyst-free reaction at 100-110°C gave better yield than those catalysed by HCl. ***(Scheme-4).***



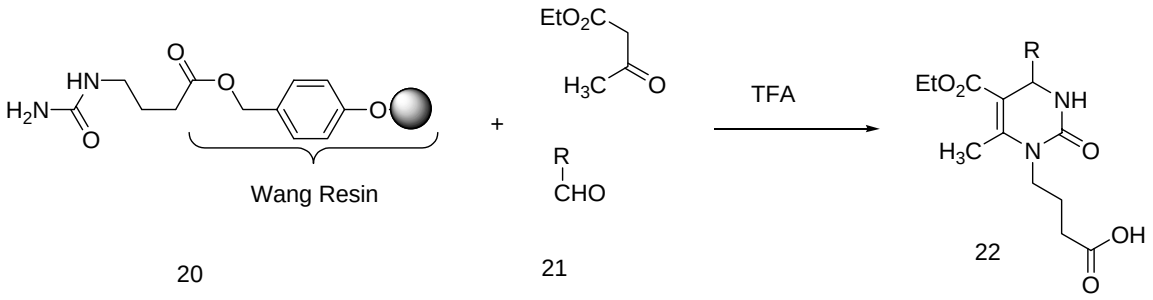
Scheme 3



Scheme 4

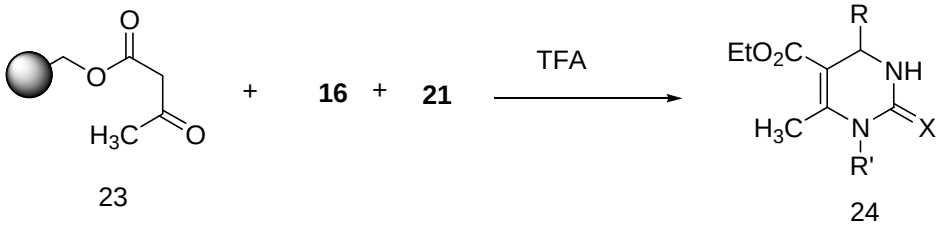
Kappe and Stadler reported the automated microwave-assisted synthesis of dihydropyrimidines utilizing $Yb(OTf)_3$.[37] They prepared a forty-eight compounds library within time span of twelve hour which includes a variety of aldehydes, *N*-substituted ureas, and carbon acids. Solid-phase synthesis provided another method for accessing a diverse collection of dihydropyrimidines. The use of a large excess of reagents in solid-phase synthesis resulted in high yield products. Also, non-resin bound by-products formed could be easily washed away, eliminating the need for further purification. A variety of polymer-supported building blocks have been explored, including attachment of the linker to the urea and β-keto ester components. Wipf and Cunningham provided the first example of a solid-phase Biginelli reaction using a resin bound urea **20** (Scheme **5a**).[38] Formation of the dihydropyrimidine and cleavage from the resin with TFA produced the N-1 substituted products **22.**

Kappe and co-workers further explored the scope of the solid-phase application by using a β-keto ester immobilized reagent **23** (scheme **5b**).[39] This strategy yielded 5-carboxylic acid dihydropyrimidines **24** upon cleavage from the resin, as well as N-1 unsubstituted compounds. In another application, Kappe utilized a polymer bound thiuronium salt **25**[40] (scheme **5c**). After completion of the Biginelli reaction, the resin bound dihydropyrimidines **26** was cleaved under different conditions to yield dihydropyrimidines (**27)**, thiopyrimidines (**39)**, or 2-iminodihydropyrimidines (**28**). These solid-phase methods allow for the synthesis of diverse dihydropyrimidines in high yield and purity, with a potential for automation.



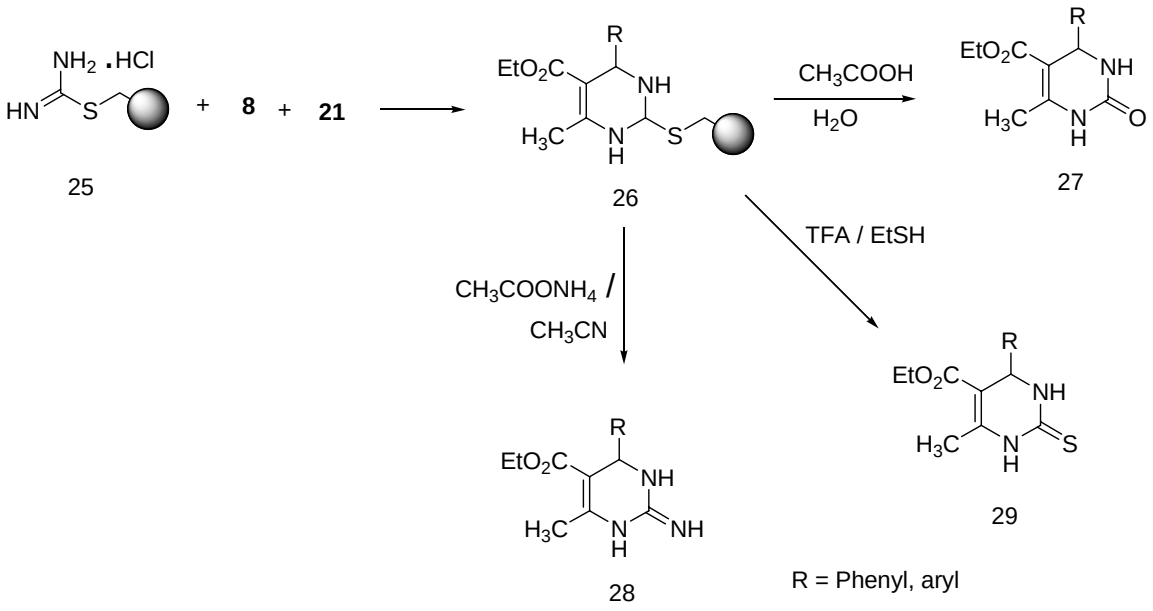
20 21 22

Scheme 5a



23 24

Scheme 5b

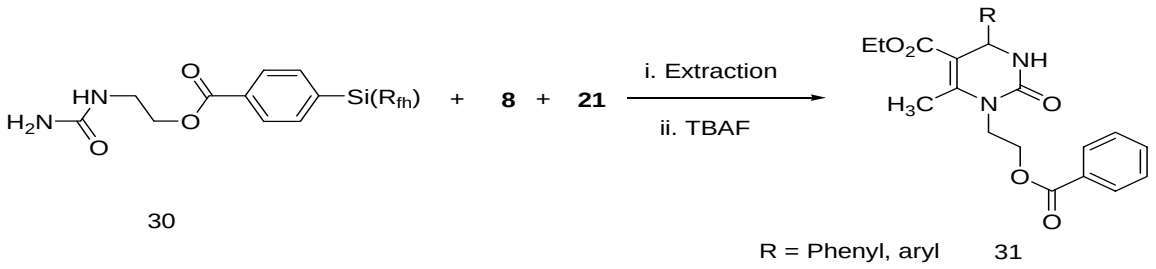


25 26 27 28 29

Scheme 5 c

Curran and coworkers[41] adapted fluorous-phase chemistry towards the synthesis of dihydropyrimidines. These strategies are based on the high ability of fluorinated compounds mix with the fluorinated solvents. The reaction mixture was purified by a liquid-liquid extraction method since the by-products were not soluble in the fluorinated solvent. Curran has prepared fluorinated ureas **30**, which underwent the Biginelli reaction and were cleanly extracted into fluorinated hexanes. Desilylation affords N-1 substituted dihydropyrimidines **31**. The yields for the fluorous-phase reaction are comparable to reactions

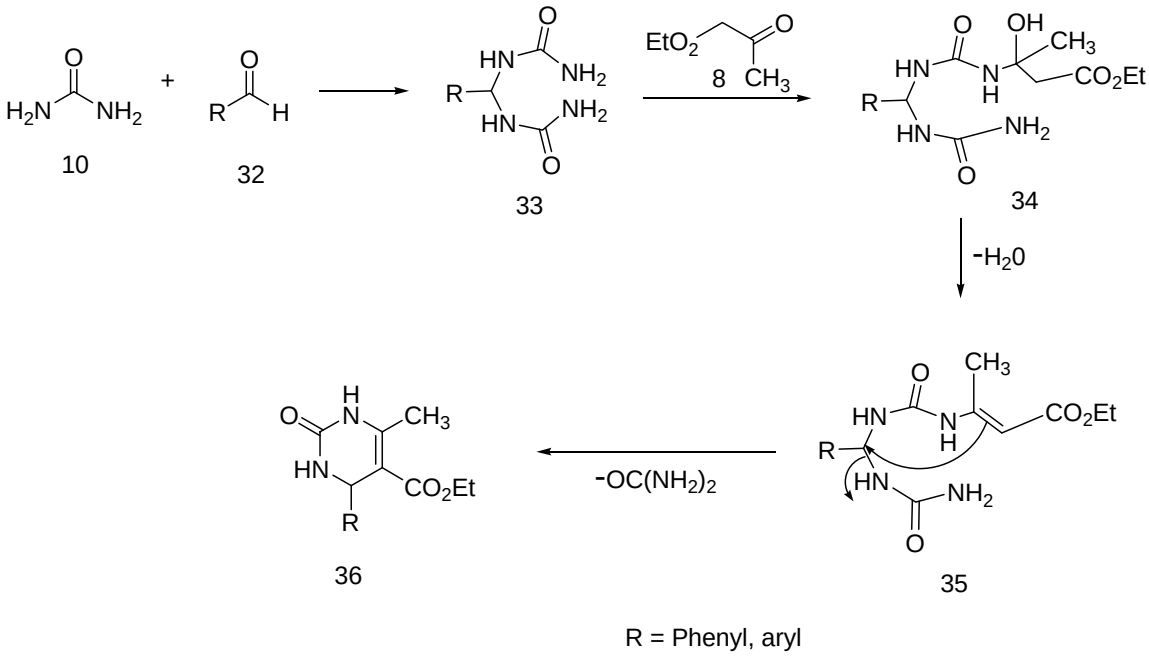
preformed under standard Biginelli reaction conditions (Scheme-6). However, the fluorous methodology required the synthesis of fluorinated ureas and the use of expensive fluorinated solvents.



Scheme 6

Mechanistic Studies

Forty years after Biginelli's initial report, the first mechanism for the synthesis of DHPMs (Biginelli reaction) were conducted by Folkers and Johnson 1n 1933.[42]



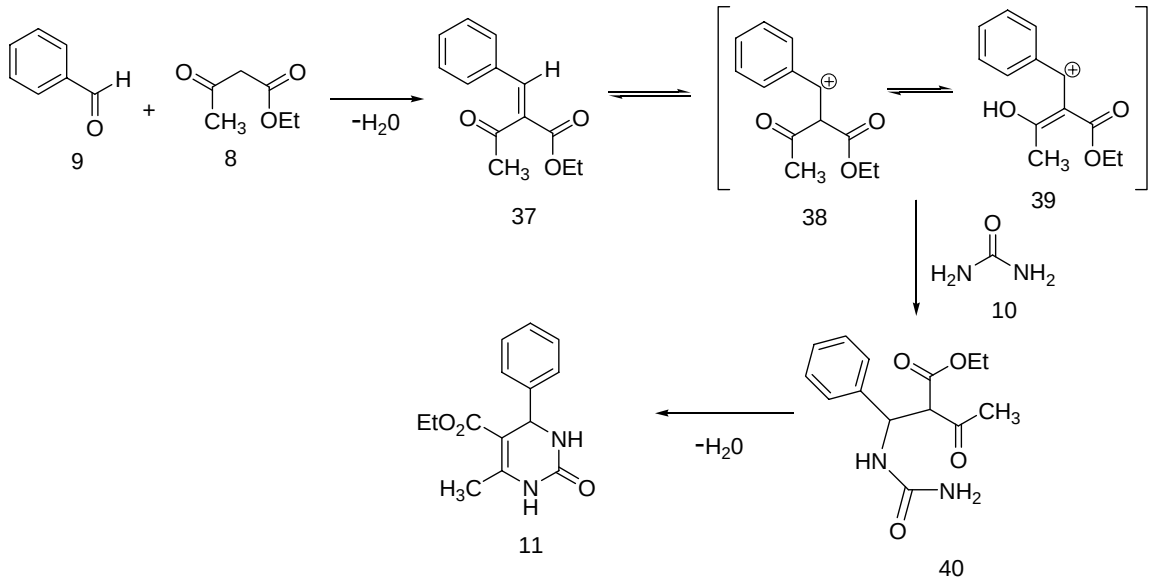
Scheme 7. Folker and Johnson mechanism

Four possible combinations of the three reaction components were examined for the generation of dihydropyrimidine **36** (Scheme-7):

A. the intermolecular reaction between benzaldehyde, ethyl acetoacetate, and urea,
B. the combination of ethyl acetoacetate and benzal bisurea,
C. the reaction of benzaldehyde and ethyl β-carbamidocrotonate, and
D. The reaction of ethyl α-benzalacetoacetate and urea.

Folkers and Johnson based their mechanistic conclusions on the reaction yields and visual observation. They proposed that the simultaneous combination of the three components in **A** was improbable. **D** was ruled out on the basis of the low reaction yields (2%). In contrast, **B** and **C** gave high yields of **36** (80%).

The authors noted that **B** may undergo fragmentation of the benzal-bisurea, regenerating the three reaction components, which may then form the product by another pathway. Further, the authors posit that the β-carbamidocrotonate in **C** hydrolyzes to the original three reaction components. Therefore, they concluded that **36** is likely formed from the cyclization of **35**, which was generated from either **B** or **C**.
Again in 1973, a second mechanistic proposal was suggested by Sweet and Fissekis, forty years after Folkers' pioneering work.[43]



Scheme 8. Sweet and Fissekis Mechanism

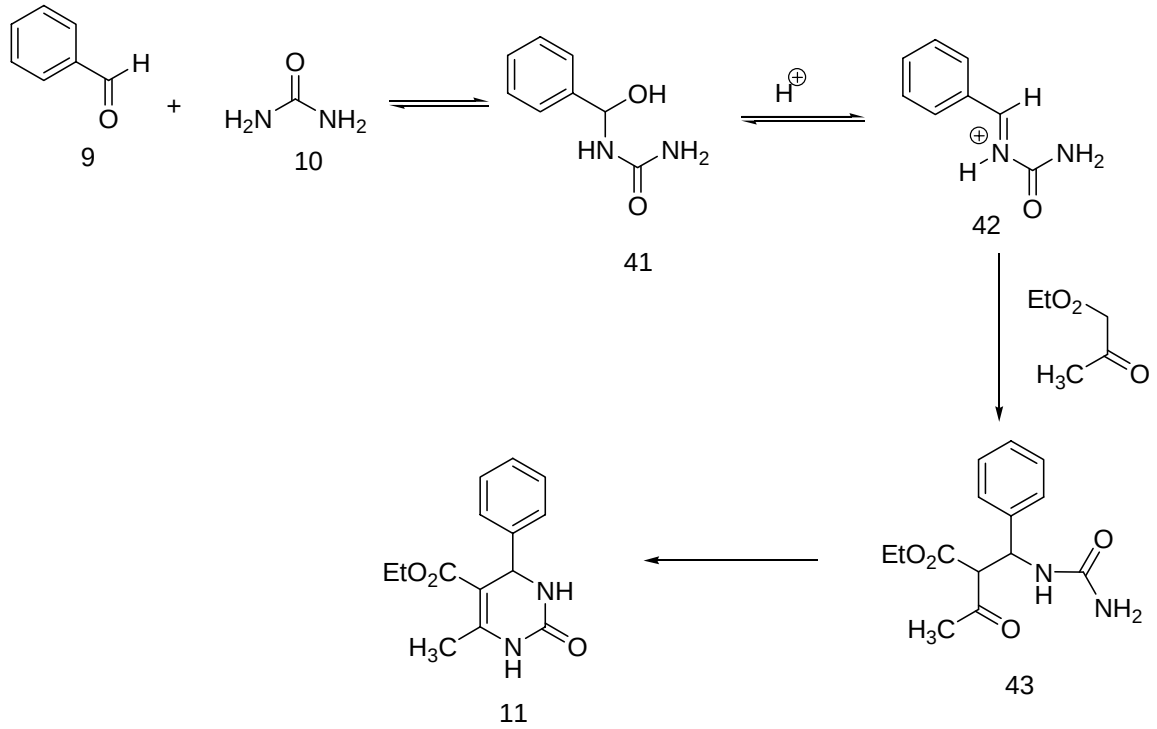
The proposal involved an aldol condensation between benzaldeyde and ethyl acetoacetate to form a stabilized carbenium ion (**38 and 39)**. Trapping with *N*-methylurea gave **40**, which cyclized to form **11** (Scheme **8**). The observation that independently prepared **37** reacted with urea under acidic conditions to generate **11** provided evidence in support of this mechanism. Evidence against this mechanism was provided by Kappe[44], who found that reaction of **37** with *N*-methylthiourea produces thiazine and not *N*-methyl dihydropyrimine **11**, which was the observed product under standard Biginelli conditions (catalytic amounts of HCl, refluxing ethanol).

Kappe further explored the mechanism of the Biginelli reaction using NMR spectroscopy and trapping experiments. He proposed the formation of *N*-acyliminium **42** from benzaldehyde and urea via an unobservable (1H NMR) hemiaminal **41**(Scheme **9**). Interception of **42** with the enol tautomer of ethyl acetoacetate gave **43**, the precursor to dihydropyrimidine **6**. Kappe suggested that the first step, formation of **41**, is rate limiting, thus preventing the observation of intermediates **42** and **43** by NMR. Kappe's proposal is currently the accepted mechanism for the Biginelli reaction.

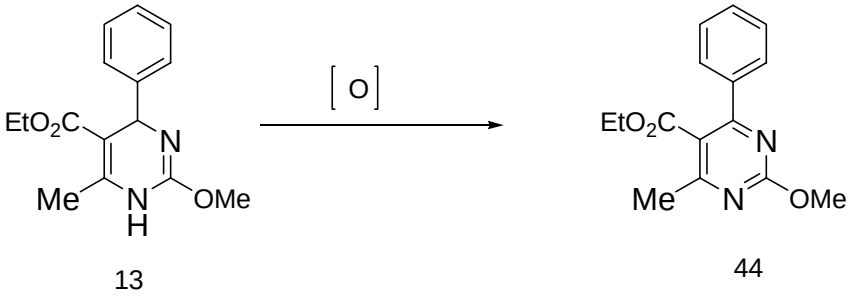
Some Reactions

Reaction of DHPMs has been researched extensively and its further reactions are still in progress till today. We herein highlight only some selected important reactions of DHPMs with different reagents and under different reaction conditions as reported by different authors.

The production of heteroaromatics by oxidative dehydrogenation is of fundamental importance in organic synthesis. Conversion of DHPMs to pyrimidines is rather difficult as reported by C O kappe in 1993,[45] where they could not disclosed any practical reaction procedure, However when the carbonyl group at C-2 is alkylated, the DHPMs can be easily oxidized to pyrimidines by treatment with pyridine hydrochloride.



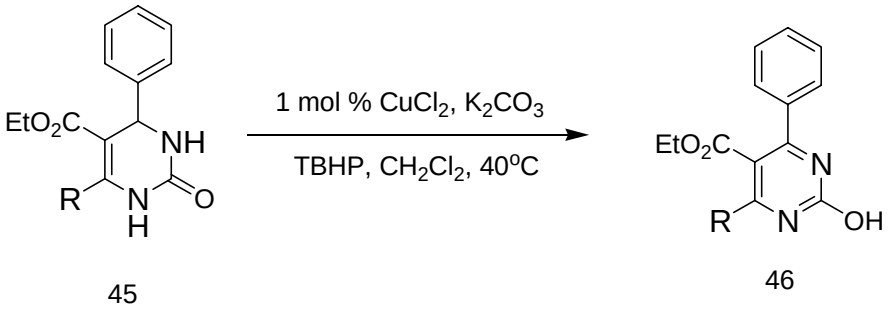
Scheme 9. Kappe Mechanism



Scheme 10

Certain oxidants for oxidation of pyrimidinones to pyrimidines have also been reported which include HNO_3,[46a] DDQ,[46b] CAN,[46c] and Pd/C[46d] as well as electrochemical oxidation[46e]. None of these oxidations are ideal, particularly for scale-up, due to their safety profile and/or difficulty in product isolation. Yamamoto *et al* [46f] have reported a mild and practical procedure for oxidative dehydrogenation of

DHPMs with catalytic amounts of a Cu salt, K_2CO_3, and tert-butylhydroperoxide (TBHP) as a terminal oxidant.

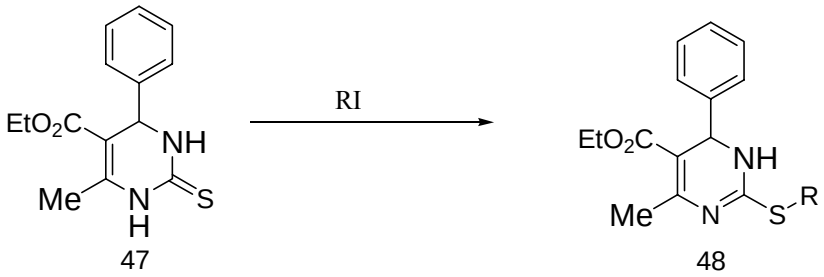


45 46

Scheme 11

A preliminary screening of terminal oxidants for metalcatalyzed systems revealed that the use of *tert*-butylhydroperoxide (TBHP) is crucial for this oxidative dehydrogenation. Upon further survey of optimal catalysts, Cu^{I} or Cu^{II} salts were found to be the most effective

Depending on the reagent employed for the reaction, DHPMs can be alkylated or arylated at various positions, for example; *S*-methylated compound of DHPMs (**48**) can be obtained in excellent yield by reaction of alkyl iodide with dihydropyrimidinethione (**47**) in refluxing methanol.[47] S-methylated DHPMs (**48**) can also be synthesized alternatively by replacing urea in Biginelli reaction with *S*-methylisothiourea.

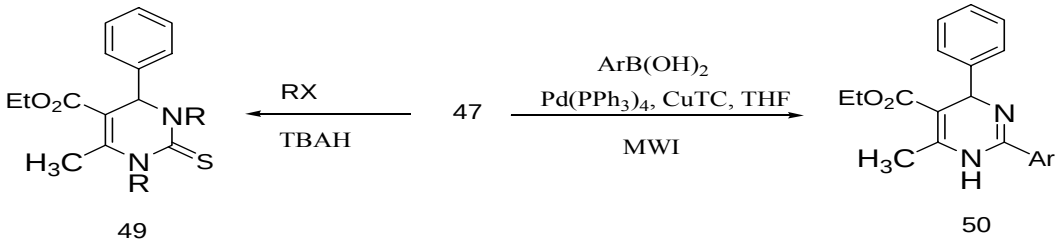


47 48

R = Alkyl

Scheme 12

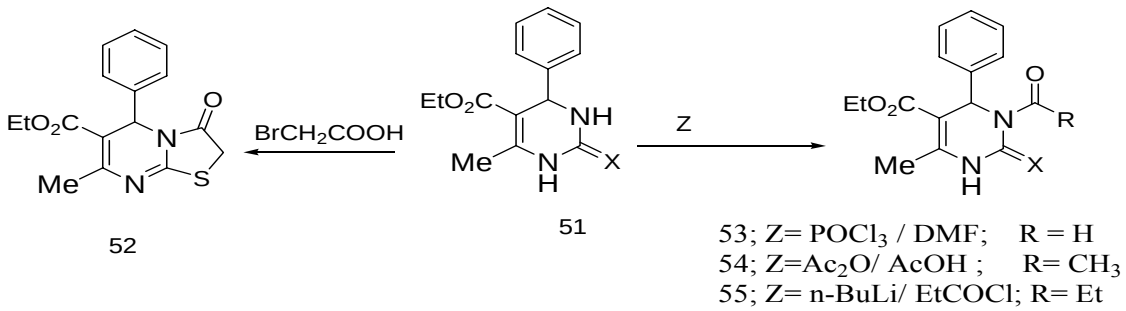
Kappe and Lenger[48] have reported the arylation of DHPMs at C-2 when arylboronic acid is used in presence of Pd(0) catalyst under microwave irradiation (scheme 10). According to Zhang *et al*[49], alkylation takes place at N-1 and N-3 in presence of tetra-n-butylammonium hydroxide (TBAH).



49 50

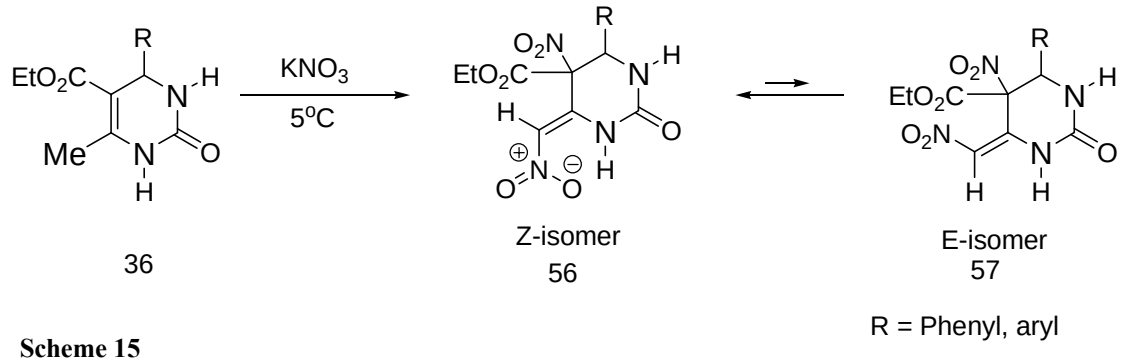
Scheme 13

DHPMs can be formylated[47] at N-3 when reacted with Dimethyl formamide in presence of $POCl_3$. In the same manner acylation also takes place at N-3 when treated with appropriate reagents.[50]



Scheme 14

Reaction of DHPMs with potassium nitrate in concentrated sulfuric acid results in the possible formation of two isomer 4,5-dinitromethylidene-5-pyrimidinecarboxylate, which in solid state the intramolecular hydrogen-bonded *Z* isomer is preferred[47], whereas in solution it exist in both *Z* and *E* forms, depending on the solvent used. In more polar solvents such as DMSO, around 10% of the *E* isomer was observed, whereas in less polar solvents such as acetone only *Z* isomer was observed.

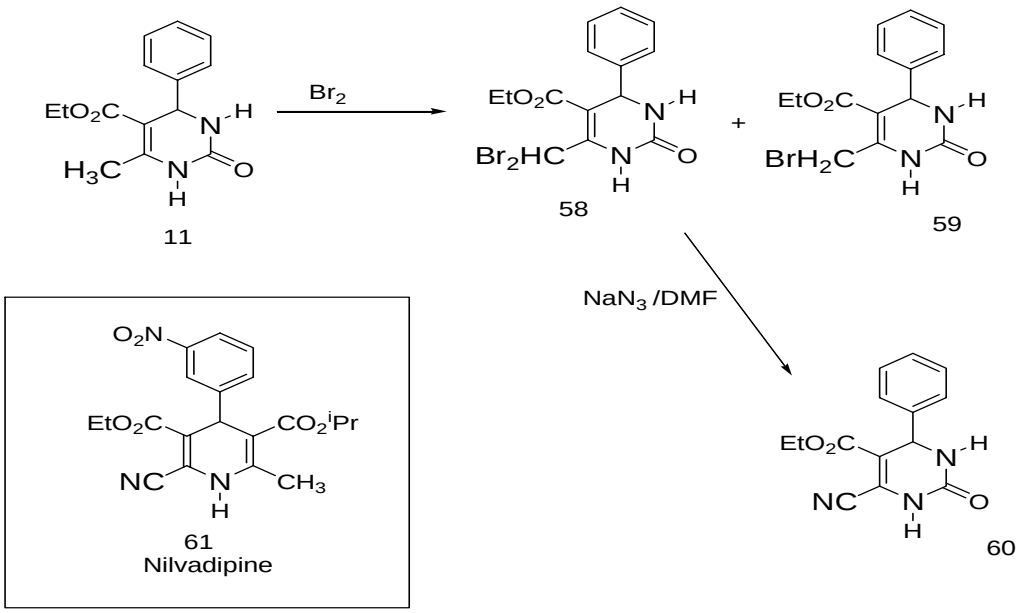


Scheme 15

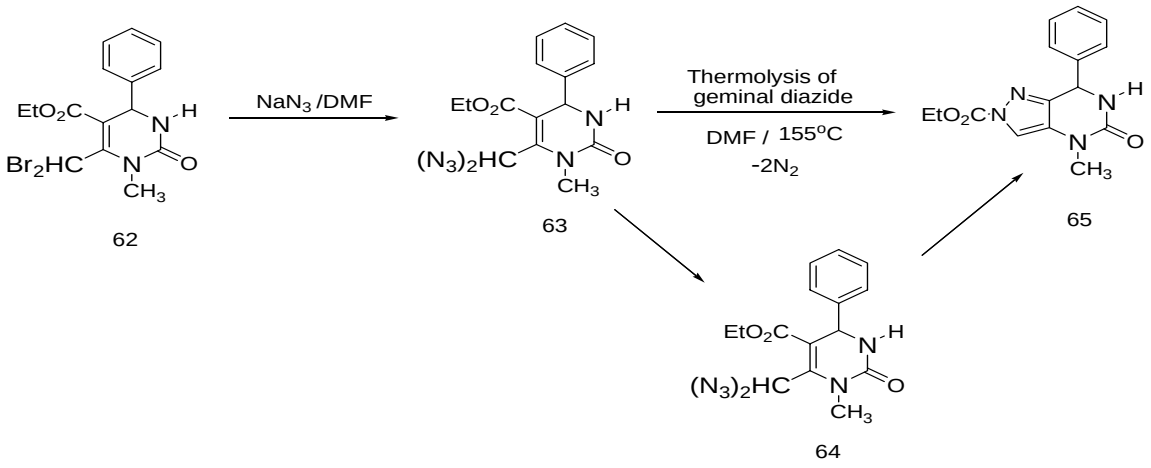
Bromination of C-6 methyl group in DHPMs can be achieved by reacting DHPMs with elemental bromine which gives mono-bromomethyl pyrimidine (**59**) and dibromo-methyl pyrimidine (**58**) derivatives.[51] By further reaction of **58** with sodium azide in DMF at 35°C, 6-cyano-pyrimidine (**60**) is formed in high yield which can be considered as a structural analogue of the dihydropyridine calcium channel antagonist nilvadipine (**77**)

However when the N-1 methyl analogue of **58** is treated with the same reagents in DMF, the unexpected diazido derivatives (**63**) is formed which on further heating in DMF at 155°C produces Pyrazolo(4,3-d)pyrimidine (**65**) by thermolysis of germinal diazide. The possible mechanism of transformation was reported by kappe where diazide decomposes to vinyl diazo derivatives which undergo spontaneous 1,5-electrocyclization to 3H-pyrazole (**64**) and subsequent migration of the ester substituent from the tetrahedral carbon to N-2 (Alphen-Hüttel rearrangement) yields pyrazolo[4,3-d]pyrimidine (**65**). The position of the ester group at N-2 was established by an X-ray analysis which confirms the structure of pyrazolo(4,3-d)pyrimidine **65.**[52]

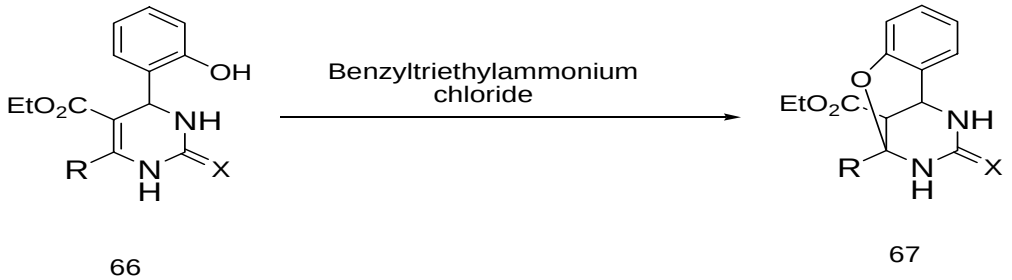
The presence of substituent on the ring of DHPMs also influence the rate of formation of product, for example the condensation product of DHPMs (**66**) from 2-hydroxybenzaldehyde, when treated with benzyltriethylammonium chloride isomerise to tricyclic compound (**67**), the formation of the isomerized product was confirmed by IR, NMR and mass spectra as reported by Bose *et al*.



Scheme 16



Scheme 17



Scheme 18

Application:

1. Dihydropyrimidinone derivatives are known to possess calcium antagonistic action[53] in the cardiovascular systems which have attracted much synthetic attention. Calcium antagonists inhibit the influx of calcium ions through plasma membrane channels and thus dilate vascular smooth muscle and alleviate the force of cardiac muscle contraction. Some calcium antagonists such as nifedipine and verapamil have been used as antihypertensive agents. However, nifedipine and verapamil have a serious disadvantage in the treatment of hypertension. Since their plasma half-lives are relatively short, these drugs must be administered repeatedly to achieve enough clinical efficacy, and the multiple dosages lower compliance. Therefore, the afore mentioned drugs were replaced by dihydropyrimidines which is suitable for Calcium Antagonists with Potent and long-lasting Vasodilative, hypotensive or antihypertensive activity.[54]
2. The biological significance of pyrimidines is well established as this scaffold has been positioned as a privileged molecule *i.e.* having a wide spectrum of biological activity like antiviral,[55] anticancer[56] and several others.[57] The clinically important antiretroviral agents like AZT, DDC, and DDI possess the pyrimidine **1a** scaffold. Another related framework of the **1b** type is also very easily accessible *via* MCR involving urea, active methylene compounds and aldehydes in the presence of a catalyst as originally reported by Biginelli. In recent years, type **1b** pyrimidine scaffold has been under intensive investigation[45] as it has a very broad pharmacological profile such as calcium channel blockers[58], antihypertensive agents[59] (these can be considered as aza-analogues of clinically used drugs[60] like niguldipine, felodipine, nifedipine) and alpha-1a-antagonists. [61]
3. Additionally, DHPM unit is also present in the natural marine alkaloids batzelladine A and B which are the first low molecular weight natural products to inhibit the binding of HIV gp 120 to CD4 cells[62] that may have potential application in the treatment of AIDS.
4. Parlato *et al*[63] synthesized various dihydropyrimidinone derivatives by modification of the substituents in virtually all the six positions of the pyrimidine nucleus which provided with interesting activity against HIV, ASFV, Sendai virus and Rubella virus. Besides these, substituted pyrimidine derivatives have been used as antihypertensive agents, anticancer agents (Monastrol), antimalarial agents, anti-inflammatory agents and also used as calcium channel blockers,neuropeptide γ-antagonists and α-1a-antagonists. [64]

CONCLUSION

The chemistry of Dihydropyrimidines has been synthesized as early as 1893s, but the most considerable advances in both the synthetic methodologies and the biological evaluation of these derivatives have been made in the last decade. Although several strategies and methodologies have been applied to achieve conveniently the synthesis of these compounds, further research must, however, be undertaken in order to design and develop efficient, practical, and scalable synthetic routes to some of these compounds and their analogues for biological and preclinical studies. The challenge for prospective research in this area of synthetic organic chemistry involves the optimization of known procedures on the one hand, and the development of new useful synthetic approaches on the other. In particular, future work should be directed to develop effective processes involving different reaction conditions and employing different catalyst, which should be designed to reduce or eliminate the use and generation of hazardous substances, whenever possible, the utilization of the atom-economy concept of all materials used in the process which should be conducted at favorable condition. It also important to note that good strategies for the catalyst–product separation and the catalyst recycling should be established for industrial application.

REFERENCES

1. D. Subhas Bose, M. Sudharshan, and S. W. Chavhan, *Arkivoc,* (**iii**) 228, (2005).
2. T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber and T. J. Mitchison, *Science*, **286**, 971(1999).
3. J. Clayden, N. Greeves, S. Warren and P. Wother, Organic chemistry, oxford university press, 1180 (2006).
4. C. O. Kappe, *J. Org. Chem.*, **62,** 3109 (1997).
5. (a) R. A. Janis, P. J. Silver and D. J. Triggle, *Adv. Drug. Res.*, **16**, 309 (1987). (b) F. Bossert and W. Vater, *Med. Res. Rev.*, **9**, 291 (1989).
6. (a) K. Atwal, G. C. Rovnyak, J. Schwartz, S.Moreland, A. Hedberg, J. Z. Gougoutas, M. F. Malley and D. M. Floyd, *J. Med. Chem.*, *33*, 1510 (1990). (b) K. S. Atwal, G. C. Rovnyak, S. D. Kimball, D. M. Floyd, S. Moreland, B. N. Swanson, J. Z. Gougoutas, J. Schwartz, K. M. Smillie and M. F. Malley, *J. Med. Chem.*, **33**, 2629 (1990). (e) M. Negwer, *Organic-Chemical Drugs and their Synonyms*, Akademie Verlag: Berlin, 2558 (1994**)**. (h) K. S. Atwal, S. Moreland, *Bioorg. Med. Chem. Lett.*, **1**, 291 (1991).
7. (a) P. Biginelli, *Chem Ber,* **24**, 1317 (1891). (b) P. Biginelli, *Chem Ber.,* **24**, 2962 (1891) (c) P. Biginelli, *Gazz. Chim. Ita.,l* **19**, 212 (1889). (d) P. Biginelli, *Gazz. Chim. Ital.,* **23**, 360 (1893).
8. F. Bigi, S. Carloni, B. Frulanti, R. Maggi and G. Sartori, *Tetrahedron Lett.*, **40**, 3465 (1999).
9. J. Lu, Y. Bai, Z. Wang, B. Yang and H. Ma, *Tetrahedron Lett.,* **41**, 9075 (2000).
10. E. H. Hu, D. R. Sidler and U. H. Dolling, *J. Org. Chem.,* **63**, 3454 (1998).
11. (a) C. O. Kappe & S. F. Falsone, *Synlett.,* 718(1998). (b) C. O. Kappe, D. Kumar & R. S. Varma, *Synthesis,* 1799 (1999).
12. B. C. Ranu, A. Hajra and U. Jana *J. Org. Chem.,* **65**, 6270 (2000).
13. Y. Ma, C. Qian. L. Wang and M. Yang, *J. Org. Chem.,* **65**, 3864 (2000)**.**
14. J. C. Bussolari & P. A. McDonnell, *J. Org. Chem.,* **65**, 6777 (2000).
15. J. S. Yadav, K. B. Reddy, K. S. Raj and A. R .Prasad, *J. Chem. Soc, Perkin Trans* **1**, 1939 (2001).
16. K. A. Kumar, M. Kasthuraiah, C. S. Reddy and C. D. Reddy, *Tetrahedron Lett.,* **42**, 7873 (2001).
17. J. S. Yadav, B. V. Subba Reddy, C. Venugopal and T. Ramalingam, *Synthesis,* **9**,1341 (2001).
18. N. Y. Fu, Y. F. Yuan, Z. Cao, J. T. Wang and C. Peppe, *Tetrahedron*, **58**, 4801 (2002).
19. C. M. Adharvana and Syamasundar K, *J. Mol. Catalysis – A,* **221**, 137 (2004).
20. A. Dondoni & A. Massi, *Tetrahedron Lett.,* **42**, 7975 (200).
21. G. Maiti, P. Kundu and C. Guin, *Tetrahedron Lett.,* **44**, 2757 (2003).
22. H. Salehi and X. G. Qing, *Synn Comm,* **34**, 171 (2004).
23. J. Peng & Y. Deng, *Tetrahedron Lett.,* **42**, 917 (2001).
24. K. Ramalinga, P. Vijayalakshmi & T. N. B. Kaimal, *Synlett,* 6, 863 (2001).
25. J. Lu & Y. Bai, *Synthesis,* **4**, 466 (2002).
26. Ch. V. Reddy, M. Mahesh, T. R. Babu and V. N. Reddy, *Tetrahedron Lett.,* 43, 2657 (2002).
27. A. S. Prabhakar, Dewkar and A. Sudalai, *Tetrahedron Lett.,* **44**, 3305 (2003).
28. R. A. Srisnivas, R. Varala, M. M. Alam and, *Syn. lett.,* **1**, (2003).
29. L. Wang, C. Qian, H. Tian and M. A. Yun, *Syn. Comm.,* **33**, 1459 (2003).
30. (a) S. Kumar, A. Saini & J. S. Sandhu, *Indian J. Chem.,* **43B**, 1485 (2004). (b) *ibid,* **44B**, 762 (2005). (c) *ibid,* **45B**, 684 (2006). (d) *ibid*, **46B**, 1690 (2007). (e) Z. T. Wang, L. W. Xu, C. G. Xia & H. Q. Wang, *Tetrahedron Lett,* **45**, 7951(2004). (f) P. Shanmugan, C. Sabastein, & P. T. Perumal, *Indian J Chem,* **45B**, 135-140(2004); (g) A. Shaabani, A. Sarvary, Rahmati and A. H. Rezayan *, Letters in Organic Chemistry,* **4**, 68 (2007).
31. M. B. Deshmukh, V. Anbhule, Prashant, S. D. Jadhev , A. R. Mali, S. S. Jagtap and A. Deshmukh, *Indian J. Chem.,* **46B**, 1545 (2007).
32. Y. T. Reddy and P. N. Reddy, *Indian J. Chem.,* **44B**, 1304 (2005).

33. (a) A. K. Misra, A. Geetanjali & Madhusudan, *Indian J. Chem.,* **43B**, 2018 (2004). (b) M. A. Alibek, Z. Zaghaghi, *Chemical papers* **63(1)**, 97 (2009). (c) S. K. Kundu, A. Majee & A. Hajra *Indian J. Chem.,* **48B**, 408 (2009).
34. J. J. Vanden Eynde, N. Audiart, V. Canonne, S. Michel, Y. van Haverbeke and C. O. Kappe, *Heterocycles*, *45*, 1967 (1997).
35. (a) C.O. Kappe, *Acc. Chem. Res.,* **33**, 879 (2000). (b) M. Yarim, S. Sarac,.; F.S. Kilic, K. Erol, *Farmaco,* **58**, 17 (2003). (c) G. Byk, H.E. Gettlieb, J. Herscovici, F. J. Mirkin, *Comb. Chem*., **2**, 732 (2000). (d) A. Shaabani, A. Bazgir, H. R. Bijanzadeh, *Mol. Diver.,* **8**, 141 (2004). (e) J. L. Mokrosz,. M.H. Paluchowska, E. Szneler and B. Drozdz, *Arch. Pharm*., (Weinheim, Germany), *322*, 231 (2003). (f) V.P. Mamaev, V.P. Borovik, *Izobret. Prom. Obraztsy Tovarnye Znak,* 45, 24 (1968); *Chem. Abstr*., , *69*, 96790f (1968); (g) V. P. Borovik, V. P. Mamaev, *Khim. Farm. Zh*., **4**, 32 (1970); *Chem. Abstr*., , *72*, 111411r(1970), (h) M. M. Abelman, S. C. Smith and D. R. James, *Tetrahedron Lett*., **44**, 4559 (2003).
36. Ahmad Shaabani, Afshin Sarvary, Abbas Rahmati and Ali Hossein Rezayan *Letters in Organic Chemistry,* **4**, 68 (2007).
37. A. Stadler and C. O. Kappe, *J. Comb. Chem.*, **3**, 624 (2001).
38. P. Wipf and A. Cunningham., *Tet. Lett.*, **36**, 7819 (1995).
39. M. G. Valverde, D. Dallinger, and C. O. Kappe, *Synlett*, **6,** 741(2001).
40. C. O. Kappe,. *Bioorg. Med. Chem. Lett.*, **10**, 49 (2000).
41. A. Studer, P. Jeger, P. Wipf, and D. P. Curran, *J. Org. Chem.*, **62**, 2917 (1997).
42. Folkers and K. Johnson, T. B. *J. Am. Chem. Soc.*, **55**, 3784 (1933).
43. Sweet and F. Fissekis, J. D. *J. Am. Chem. Soc.*, **95**, 8741 (1973).
44. C. O. Kappe, *J. Org. Chem.*, **62**, 7201 (1997).
45. C. O. Kappe, *Tetrahedron*, **49**, 6937 (1993).
46. (a) A. Puchala, F. Belaj, J. Bergman, and C. O. Kappe, *J. Heterocycl. Chem.*, *38,* 1345 (2001). (b) M. Watanabe, H. Koike, T. Ishiba, T. Okada, S. Seo, and K. Hirai, *Bioorg. Med. Chem.*, ***5***, 437 (1997). (c) A. Matsushima, M. Oda, Y. Kawachi, Chika, J. PCT WO 03/006439 A1(d) C. O. Kappe, P. Roschger, *J. Heterocycl. Chem.*, *26*, 1555-1560(1989). (e) Kadis, V.; Strandins, J.; Khanina, E. L.; Duburs, G. *Electrochim. Acta* **1989**, *34*, 899-904 (f) K. Yamamoto, Y Grace Chen, and F. G. Buono, *Org. Lett*., Vol. 7, No. 21, (2005)
47. C. O. Kappe, *Molecule*, **3**, 1 (1998).
48. Alenka Lengar, and C. Oliver Kappe *Org. Lett.*, , 6 (5), 771 (2004).
49. Zhang Zhi-li , Z. Shou-xin , W. Xiao-wei , WANG Hong-tao, Chen Yan-li and LIU Jun-yi, *Chem. Res. Chinese U*., **22(4),** 4 5 1 4 5 4(2006).
50. K. Singh and S. Singh, *Tet. Lett.*, **47**, 8143 (2006).
51. (a) C. O. Kappe, *Liebigs Ann. Chem.*, 505 (1990). (b) C. O. Kappe,. *Tetrahedron*, *49*, 6937 (1993).
52. C. O. Kappe and G. Färber, *J. Chem. Soc., Perkin Trans. 1*, 1342 (1991).
53. H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, and K. Aisaka, *J. Med. Chem*., **32** (10), 2399(1989).
54. K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg and B. C. O'Reilly *J. Med. Chem.*, **34** (2), 806 (1991).
55. (a) R. Neumann and R. Morten, *Drugs of Todays*, **21**, 133 (1998). (b) R. K. Robin, *Chem Eng News*, 28(1986).
56. (a) F. Focher, D. Ubiali, M. Pregnolato, C. Zhi, J. Bambio, G. E. Wright and S. Spadri, *J. Med. Chem.*, 42, 2601 (2000). (b) A. Matsuda, H. Hattori, M. Tanaka and T. Sasaki, *Bioorg MedChem Lett*, 6, 1887 (1996).
57. (a) H. Sherman & A. M. Kaplan, *Toxicol Appl Phermacol*, **34**, 189 (1975). (b) S. J. Stewart, *AU Patent* **2001**, 720032; *Chem. Abstr.*, 134, 67474 (2001). (c) G. D. Daves Jr, R. K. Robins and C. C. Cheng, *J. Org. Chem.*, **26**, 5256 (1961).

58. J. Stoltefuss, H. Boeshagen, M. Schramm and G. Thomas, *Chem. Abstr.*, 101, **1984**, 55110v (Bayer AG) *Ger Offen DE*, 3234 684(1984).
59. H. Cho, M. Ueda, K. Shima, A. Mizuno, M. Hayashimatsu, Y. Ohnaka, Y. Takeuchi, M. Hamaguchi, K. Aisaka, T. Hidaka, M. Kawai, M. Takeda, T . Ishihara, K. Funahashi, F. Satah, M. Morita and T. Noguchi, *J Med Chem*, 32, 2399 (1989).
60. F. Bossert and W. Vater, *Med. Res. Rev.*, **9**, 291 (1989).
61. (a) C. O. Kappe, *Acc Chem Res*, 879(2000). (b) C. O. Kappe, *Molecules* ,1 (1998). (c) B. Jauk, T. Pernant and C. O. Kappe, *Molecules*, 227 (2000).
62. A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freger, C. Debrossi, S. Mai, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertzbery, R. K. Johnson, J. W. Westley and B. C. M. Potts, *J Org Chem,* 60, 1182 (1995).
63. M. C. Parlato, C. Mugnaini, M. L. Renzulli, F. Corelli and M. Botta, *Arkivoc*, 5, 349 (2004).
64. (a) K. S. Atwal, G. C. Rovnyak, B. C. O' Reilly and J. Schwartz, *J. Org. Chem.*, **54**, 5898(1989). (b) C. O. Kappe, W. M. F. Fabian and M. A. Semones, *Tetrahedron*, **53**, 2803 (1997).

(Received: 22 July 2009 Accepted: 25 July 2009 RJC-415)
