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Ammonium acetate in acetic acid: A versatile chemical mixture in organic synthesis

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Ammonium acetate in acetic acid is an alternative source of ammonia gas. The beauty of this chemical mixture is it is inexpensive, fairly soluble in water, commercially available, very safe and can handle easily. Moreover the mixture is nontoxic and eco-friendly in nature. This chemical mixture is easily biodegradable. It is widely used mixture as buffer for analytical purpose. Literature reveals that many organic reactions involve this NH_4OAc/HOAc combination. The mixture has been extensively used for the synthesis of heterocycles (pyridine, triazole, oxazole, thiazole, acridine derivatives, isoindole derivatives, phenazine derivatives, dihydrofuran, pyrimidine), N-acetylation of anilines and secondary amine. Also this mixture catalyzed the highly regio- and stereoselective ring enlargement reaction of cyclopropane derivatives to 2,3-dihydrofuran derivatives. NH_4OAc/HOAc mixture is used as additives for the epoxidation of alkene.

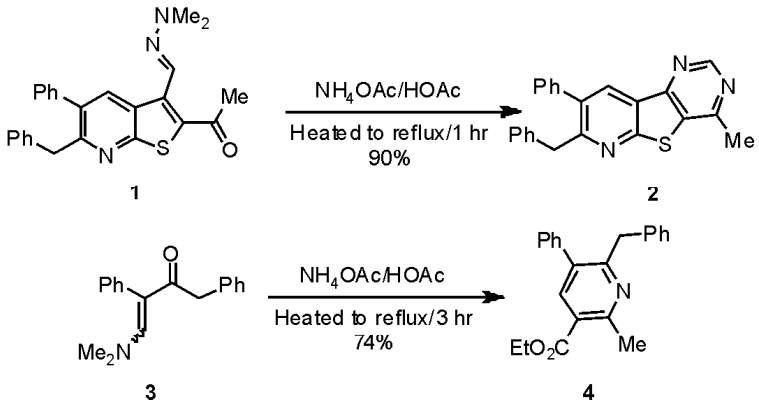
Keywords: NH_4OAc/HOAc, ammoniating agent, heterocycles, pyridine, triazole, oxazole, N-acetylation.

Introduction

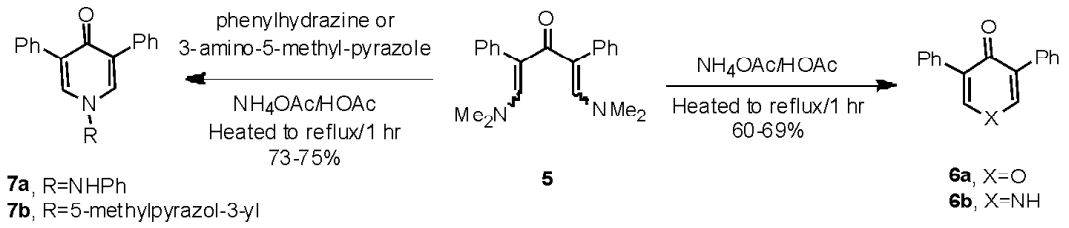
Mohammed Hilmy Elnagdi and coworkers were interested to synthesize the densely functionalized, biologically active heteroaromatic compounds[1] using readily available and cheap starting materials. They reported the synthesis of 7-benzyl-4-methyl-8-phenyl pyrido[2′,3′:2,3] thieno[4,5-*d*]pyrimidine (**2**) and 6-benzyl-2-methyl-5-phenylnicotinic acid ethyl ester (**4**) from *N*,*N*-dimethyl-formamidine derivative (**1**) and the enaminone intermediate (**3**) respectively using the ammonium acetate in acetic acid which shown in the Scheme 1.

Also they reported the synthesis of 3,5-diphenyl-pyran-4-one (**6a**), 3,5-diphenyl-1*H*-pyridin-4-one (**6b**) and 1,3,5-trisubstituted pyridin-4-ones (**7a,b**) from the intermediate compound dienaminone (**5**) shown in the Scheme 2.

G. W. V. Cave and C. L. Raston, reported[2] the synthesis of bipyridine, a supramolecular building block, in chiral and achiral form in a solvent-free condition involving Michael addition followed by treatment with ammonium acetate in acetic acid of the appropriate starting material with better yield. Literature revealed that bipyridine known to complexed with various metal ions. Specially pinene and camphor con-



Scheme 1



Scheme 2

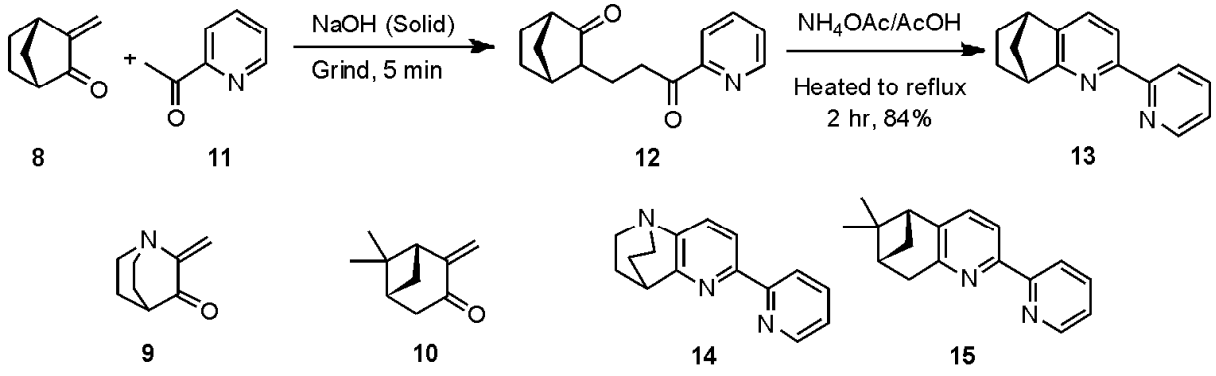
taining complexes can form supramolecular helicates. The conventional methods for the synthesis of bipyridine have some limitation e.g. harsh reaction condition, multi step process, generating considerable amount of waste, time consuming protocol, low atom efficiency, low to moderate yield and use of volatile solvent and so on. The methodology reported by Cave and Raston is more benign. They report "one pot" more benign protocol for the synthesis of bipyridine in chiral and achiral form.

They started their synthesis of the achiral bipyridine (**13**) with 2-acetylpyridine and 3-methylen-2-norbornone grinding with solid NaOH to get the 1,5-diketo derivative (**12**). Then heated to reflux the diketo derivative with ammonium acetate in presence of acetic acid which shown in Scheme 3. Similarly 2-methylene-3-quinuclidinone (**9**) and pinocarvone (**10**) converted into the corresponding achiral bipyridine (**14**) and chiral bipyridine (**15**) respectively in good yield.

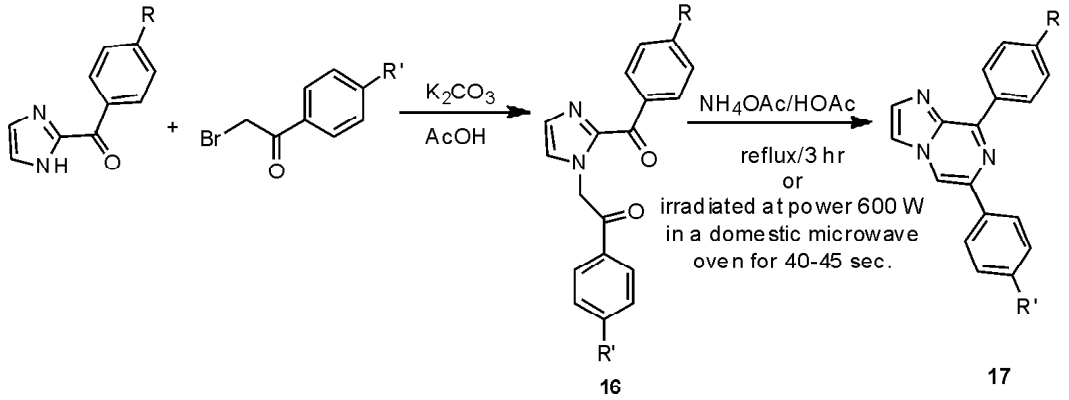
The heterocyclic compound containing imidazo[1,2-*a*]pyrazine ring system shows good biological activity, such as anticancer and antimicrobial activities. Besides that this ring containing compound has antihypertensive, antibroncospastic and inotropic activities on the cardiovascular system. Also the well known chemiluminescent, luciferin contain this imidazo[1,2-*a*]pyrazine ring system. Being inspired by the highly biological activity of this ring system Seref Demirayak and coworker synthesize[3] 6,8-diarylimidazo[1,2-*a*]pyrazine derivatives (**17**) from 1-(2-aryl-2-oxoethyl)-2-aryloylimidazole derivatives (**16**) in presence of ammonium acetate in acetic acid by either reflux or microwave irradiation method shown in Scheme 4. They also investigate the anticancer activities of the synthesized compounds which show noticeable anticancer activity.

One of the procedures for protection of amino group is acetylation. In this method the amino group is converted into the N-acetyl derivative. There are so many methods reported in the literature for the N-acetylation of amino group. But many of the methods have certain drawback. A group of chemist from India reports the convenient, cost-effective and mild procedure for the acetyl protection of amino group in good yield. Secondary amines and differently substituted anilines are acetylated[4] in presence of ammonium acetate in acetic acid medium under refluxing condition shown in Scheme 5.

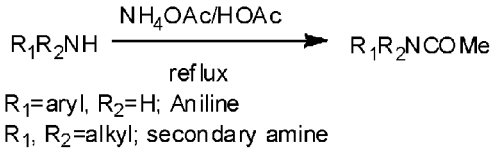
Many biologically important natural alkaloids containing 2-pyridone nucleus which played vital role in heterocyclic



Scheme 3



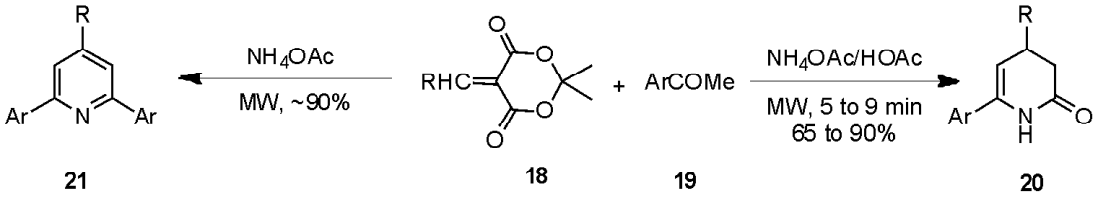
Scheme 4



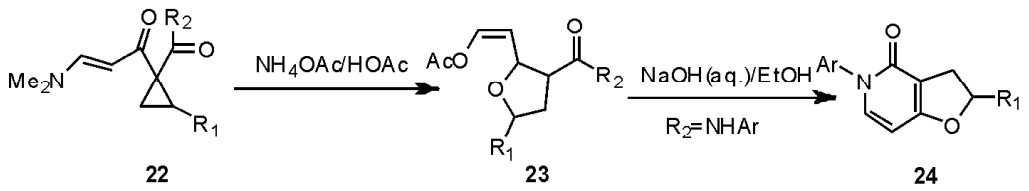
Scheme 5

chemistry. As for example functionalized 2-pyridone derivatives exhibit promising bioactivity and it is extensively used as synthetic intermediate in pharmaceutical and agrochemical research. Of the 2-pyridone family, 4,6-diaryl-2-pyridones are known as effective LTB_4 antagonists. Tu *et al*. reported[5] the synthesis of 3,4-dihydro-4,6-diaryl-2-pyridones through an efficient three-component reaction assisted by microwave irradiation. The compound Meldrum's acid (**18**) was irradiated in microwave with appropriate aromatic ketone (**19**) in presence of ammonium acetate in acetic acid and obtained the 2-pyridone derivative (**20**) shown in Scheme 6. 3:4 mass ratio of the ammonium acetate and acetic acid gave the best result. They did the same reaction in absence of acetic acid and obtained 2,4,6-triarylpyridine derivative (**21**) instead of 2-pyridone derivative in excellent yield.

Dewen Dong and coworker reported[6] a convenient and efficient route to 2,3-dihydrofuran derivative (**23**) from 1-dimethylaminopropenoyl-1-carbamoyl/benzoyl cyclopropanes (**22**) catalyzed by ammonium acetate (0.1 equivalent) in acetic acid with good regio- and stereoselectivity. On further synthetic transformation of the 2,3-dihydrofuran derivative in presence of NaOH (aq.) in EtOH yielded 5-aryl-2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-ones (**24**). The transformations are shown in the Scheme 7.



Scheme 6



Scheme 7

To optimize the reaction condition they used organic acid i.e. acetic acid at room temperature and found no reaction. When the same reaction was refluxing with AcOH it occurs. It requires long reaction time and yield was not satisfactory. Surprisingly addition of small quantity of ammonium salt such as ammonium acetate boosts the reaction. Intractable mixture was observed when DMF was used instead of AcOH as solvent. In Ac_2O at 100°C after 24 h no product was found. Addition of several drops of water, the reaction proceeds and yielded mixture which containing the ring enlarged dihydrofuran. This indicates the acetate anion may involve in the ring enlargement reaction.

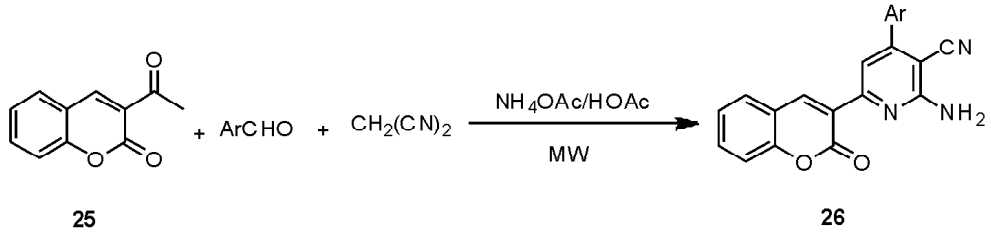
NH_4OAc/HOAc mixture acts as additives for the epoxidation of alkene[7] along with H_2O_2 and 5-chloro-7-iodo-8-quinolinolatomanganese(III) catalyst. The efficiency of the catalyst was relatively low in absence of the additives e.g. epoxidation of styrene.

A group of chemists from China report the facile synthesis of pyridine derivatives[8] in one-pot using multicomponent reaction under microwave irradiation. Under microwave irradiation 3-acetylcoumarin (**25**), aromatic aldehydes, malononitrile, and ammonium acetate in acetic acid produced a series of 2-amino-6-(2-oxo-2*H*-chromen-3-yl)-4-pyridine-3-carbonitriles (**26**) in very short time with good yield. The reaction shown in Scheme 8.

Ranjan G. Patel and coworkers reported one pot cyclocondensation reaction for the synthesis of number of 3-(2,6-diphenyl-4-pyridyl)hydroquinolin-2-one compounds (**30**) from 2-chloro-3-formyl quinolines (**27**) under microwave irradiation (Scheme 9)[9] in presence of ammonium acetate in acetic acid. The compound (**30**) consists of two biologically active moieties. One is pyridine and the other is quinoline. The yield was high and synthesized compounds shows moderate to good antimicrobial activity.

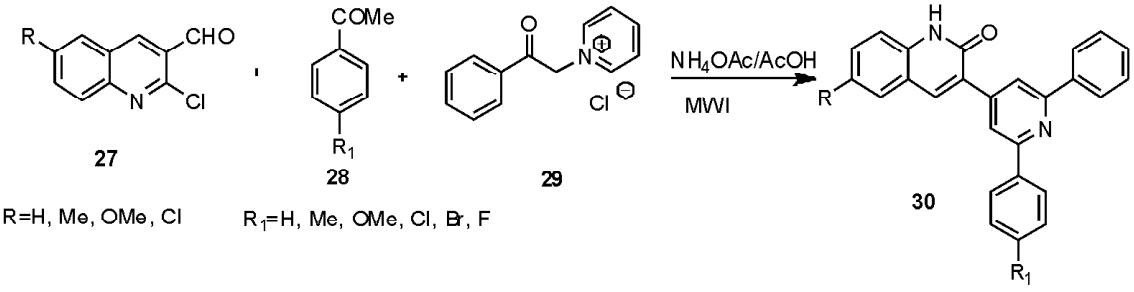
Similarly Dinker I. Brahmbhatt and coworkers report the synthesis[10] of 4-aryl-2,6-di(coumarin-3-yl)pyridines (**33**) (Scheme 10) under the Kröhnke reaction conditions in presence of ammonium acetate in acetic acid mixture. The beauty of their synthesis is that they synthesized symmetrically as well as asymmetrically 2,6-dicoumarinyl substituted pyridines. The synthesized compounds were screened for antimicrobial activity but did not exhibit good activity.

1-(2-Aryl-2-oxoethyl)-2-aryloylbenzimidazoles (**37**) were synthesized[11] on reaction with 2-aryloylbenzimidazole derivatives (**36**) and 2-bromoacetophenones in acetone. 1-(2-Aryl-2-oxoethyl)-2-aryloylbenzimidazoles were treated with ammonium acetate in acetic acid to get the 1,3-diarylpyrazino[1,2-*a*]benzimidazole derivatives (**38**) shown in Scheme 11. Anticancer studies of these compounds exhibit promising result.



25 26

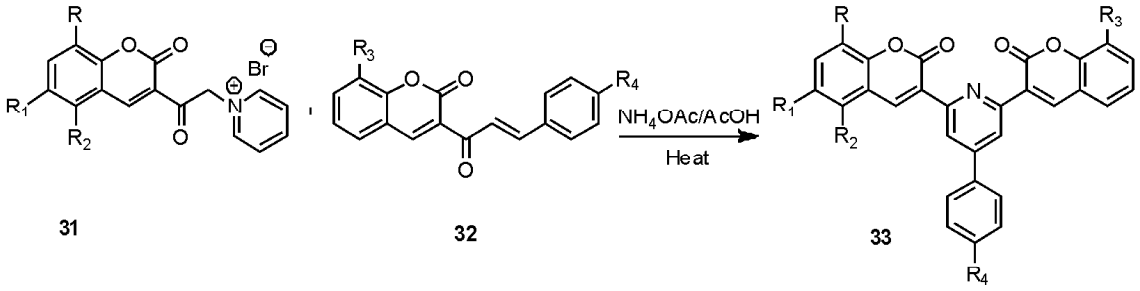
Scheme 8



27 28 29 30

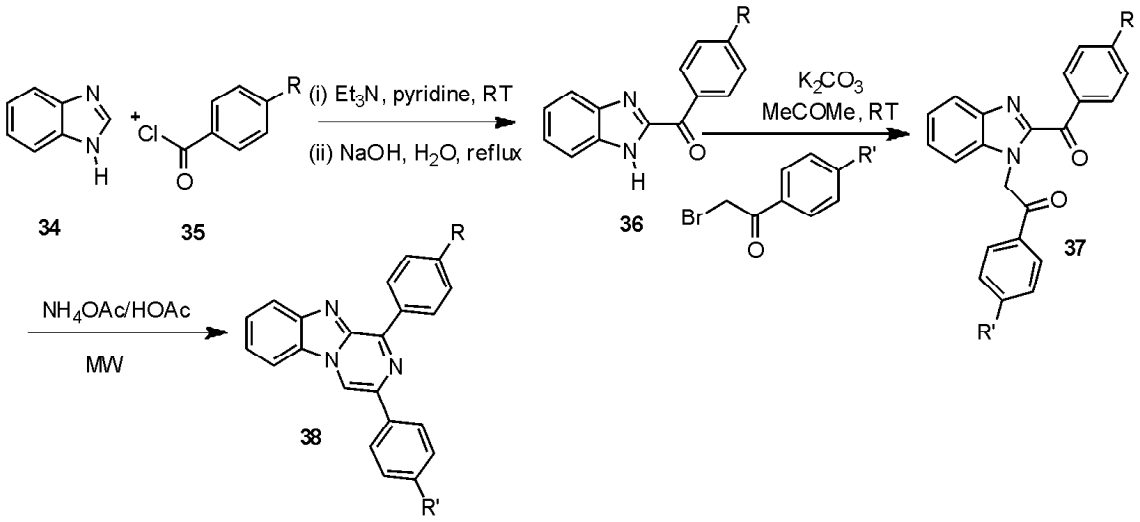
R=H, Me, OMe, Cl R_1=H, Me, OMe, Cl, Br, F

Scheme 9



31 32 33

Scheme 10

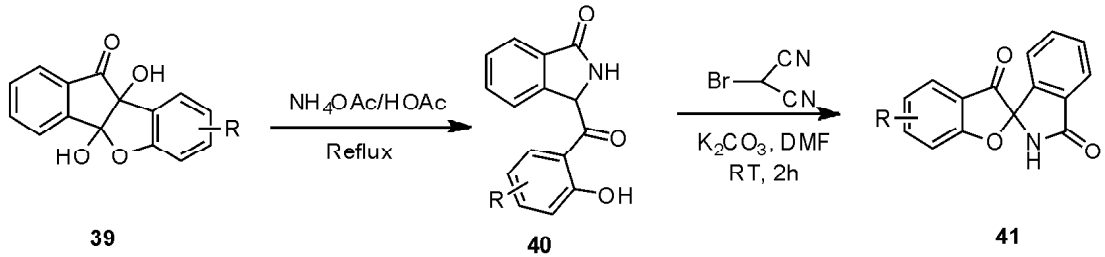


34 35 36 37 38

Scheme 11

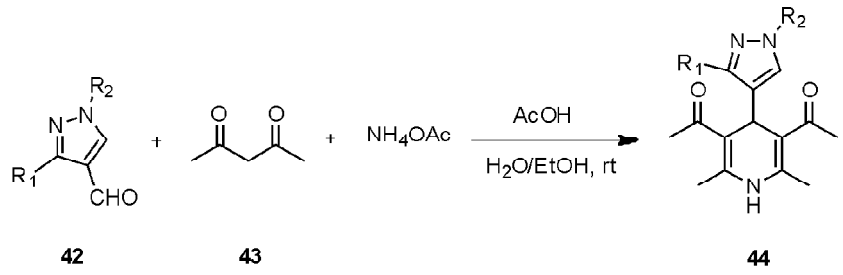
Pramanik and coworkers successfully developed an efficient short method[12] for the synthesis of potentially bioactive 3*H*,3′*H*-spiro[benzofuran-2,1′-isoindole]-3,3′-diones (**41**). Ninhydrin adducts of phenols (**39**) were reflux with ammonium acetate in acetic acid to obtained a new class of compounds 3-(2′-hydroxybenzoyl)-2,3-dihydroisoindol-1-ones (**40**) in very good yield (Scheme 12). Most of the synthesized compounds were decompose while purifying using coloumn chromatography. However they were able to purify some of them. On treatment with monobromomalononitrile these compounds (**40**) provides their target compound 3*H*,3′*H*-spiro[benzofuran-2,1′-isoindole]-3,3′-diones (**41**).

Manickam Pramesh and coworkers reported[13] the synthesis of 1,4-dihydropyridine (DHPs) derivatives (**44**) by



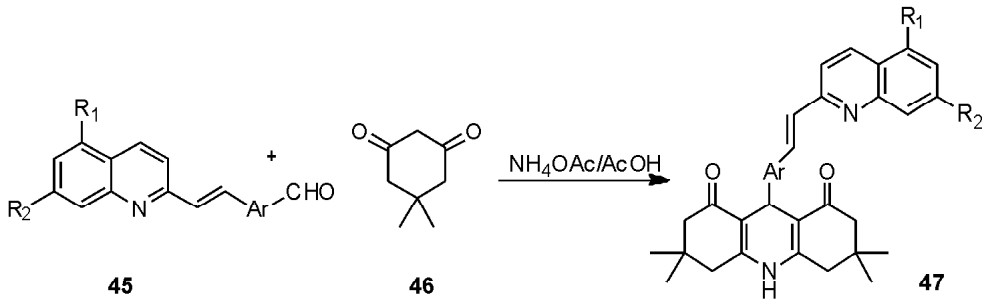
39 40 41

Scheme 12



42 **43** **44**

Scheme 13



45 **46** **47**

Scheme 14

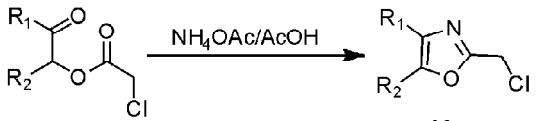
Hantszch method shown in Scheme 13. DHPs are nothing but a six membered cyclic ring compound which contain one nitrogen atom and it is a good calcium channel blocker. Because of its pharmaceutical and biological properties e.g. inhibition of human cytochrome P450 enzyme, angiotensine-converting enzyme inhibition and blood pressure control on chronic, non diabetic nephropathies it has attract considerable interest for its synthesis. Pramesh *et al.* synthesise 1,4-dihydropyridine (DHPs) derivatives using pyrazole aldehyde (**42**), 1,3-diketone (**43**) and ammonium acetate and in presence of catalyst. They have screened several catalysts and found that acetic acid is the best catalyst for their reaction. Also they used different solvent system and comes up with the best result in water:ethanol (40:60) mixture.

Li *et al.* reported the synthesis and crystal structure of acridine derivatives[14] using one pot multi component reaction. They report the synthesis of 9(10*H*)-acridone derivatives (**47**) in a single pot three component reaction (Scheme 14) of styrylquinoline aldehydes (**45**), dimedone (**46**) and ammonium acetate in acetic acid.

Frederick A. Luzzio and coworkers reported the synthesis[15] of 2-chloromethyl-4,5-disubstituted oxazoles (**49**) on treatment of chloroacetyl esters (**48**) of symmetrical and non-symmetrical acyloins (Scheme 15) in presence of ammonium acetate and acetic acid.

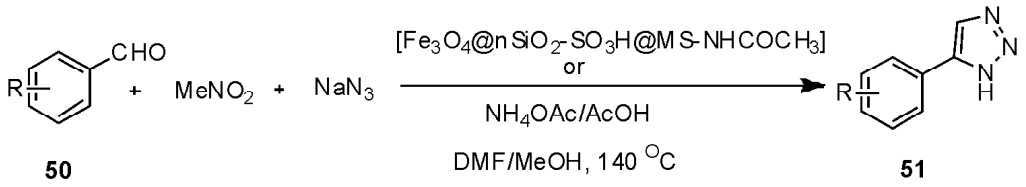
Qionglin Liang and Hong-Bin Sun reported[16] the synthesis of 5-aryl-1*H*-1,2,3-triazoles (**51**) using core-shell-shell-structured heterogeneous [Fe_3O_4@nSiO_2-SO_3H@MS-$NHCOCH_3$ (n = nonporous, MS = microporous SiO_2)] as well as homogeneous AcOH/NH_4OAc catalyst in DMF/MeOH (5:1) solvent mixture which shown in the Scheme 16. They have shown that heterogeneous catalyst is more efficient compare to homogeneous catalyst. They heated the mixture of substituted aromatic aldehyde (**50**), nitroalkane and sodium azide in the DMF/MeOH solvent mixture with both the catalysts system mentioned separately above and obtained the substituted triazole derivatives in good yield.

Jain and coworkers reported[17] the synthesis of 4-methyl-



48 **49**

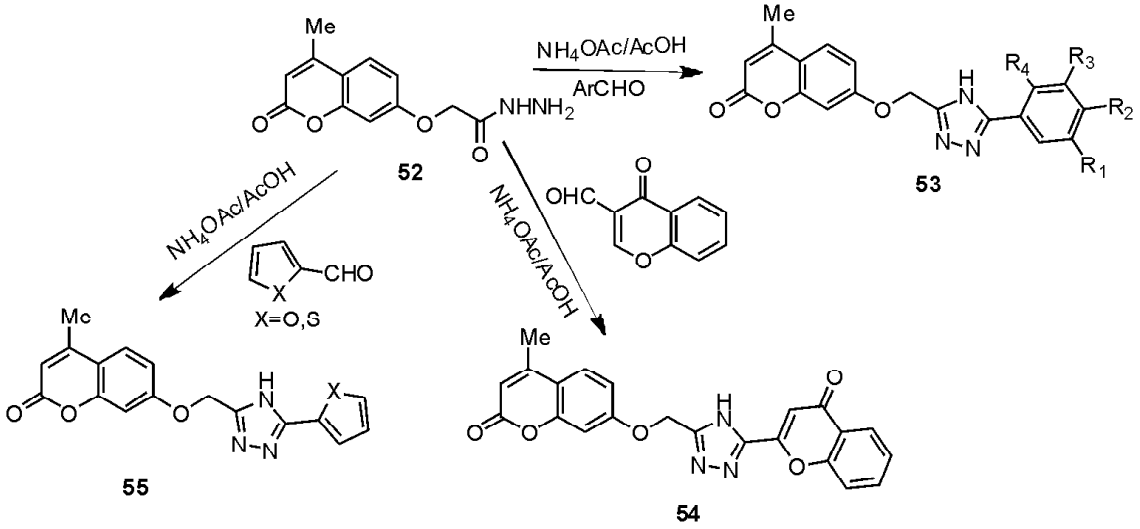
Scheme 15



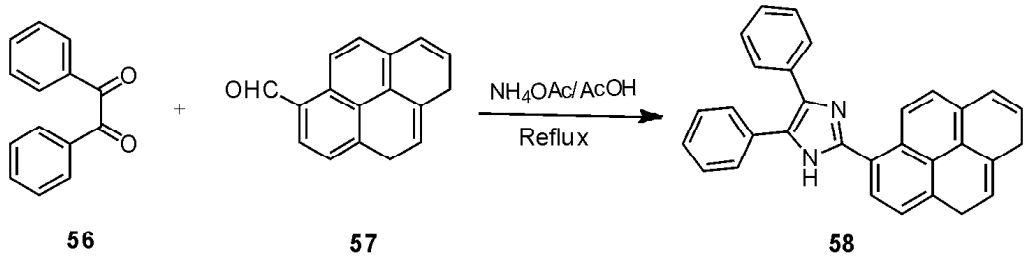
Scheme 16

7-((5-aryl-4*H*-1,2,4-triazol- 3-yl)methoxy)-2*H*-benzopyran-2-ones (Scheme 17) using the starting material 7-hydroxy-4-methyl-2*H*-benzopyran-2-one. They first synthesise 7-yloxyacetohydrazide (**52**) in two steps from 7-hydroxy-4-methyl-2*H*-benzopyran-2-one. Then the synthesized compound 7-yloxyacetohydrazide (**52**) was treated with aromatic or heterocyclic aldehydes and ammonium acetate in acetic acid to get the triazole derivatives (**53**, **54**, **55**). They screened the compounds *in vitro* for antimicrobial and antifungal activities. The compounds show promising activity against the bacteria and fungi.

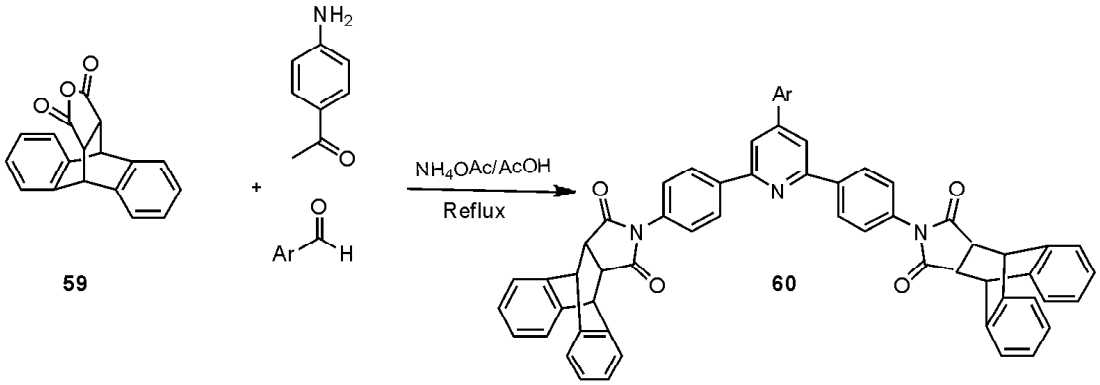
Khan and Asiri reported[18] one pot synthesis of a deep blue light-emitting highly fluorescent pyrene-imidazole dye i.e. 4,5-diphenyl-2-(pyren-1-yl)-1*H*-imidazole (DPI) chromophore (**58**). The title compound (**58**) was obtained by refluxing pyrene-1-carboxaldehyde (**57**) and benzil (**56**), ammonium acetate in acetic acid shown in Scheme 18. Depending on the polarity of the solvent used they were calcu-



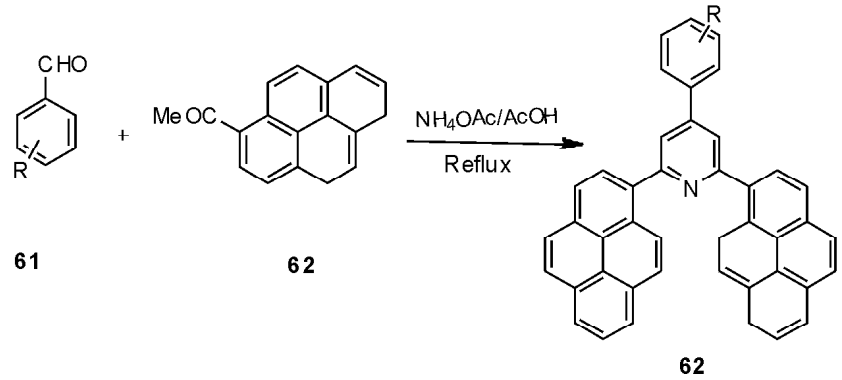
Scheme 17



Scheme 18



Scheme 19



Scheme 20

late (theoretically and experimentally) the physicochemical as well as photophysical parameter of the DPI chromophore. Critical micelle concentration (CMC) of some surfactant [e.g. cetyl trimethyl ammonium bromide (CTAB) and sodium dodecyl sulfate (SDS)] can be determined by using this DPI chromophore.

Mahmoud Abdi and coworkers reported[19] the synthesis of 2,4,6-triaryl pyridines derivatives (**60**) via four component one pot method. To obtain the target they reflux the mixture of 4-amino acetophenone, dibenzobarallene (**59**), various aromatic aldehyde and ammonium acetate in acetic acid (Scheme 19).

Mohammad Shaker and coworkers reported[20] the facile one pot synthesis of 4-aryl-2,6-di(pyren-1-yl)pyridines (**62**). Refluxing the mixture of arylalaldehydes (**61**), 1-acetylpyrene (**62**) and ammonium acetate in acetic acid obtained the target molecule (Scheme 20).

Conclusion

In conclusion it has been found that NH_4OAc in AcOH mixture is a safe, cheap and environmentally benign ammoniating agent. We have seen that this unique mixture has been extensively used for the synthesis of variety of biologically important heterocycles. Also this mixture is effective in stereoselective ring enlargement, epoxydation of alkene and N-acetylation reaction of aniline and secondary amine. There are scopes to use this mixture to synthesize differently substituted bioactive heterocycles which are not included in this review. This mixture can do wonders in the era of Organic Chemistry.

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