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A New Greeen Protocol for the Synthesis of Substituted Imidazoles Using Ammonium Fluoride as Catalyst

Arun S.*[1] and Shinu V.S. [2]

[1]Department of Chemistry, Christ College, Irinjalakuda, Thrissur, Kerala, India.
[2]Department of Chemistry, St.Joseph's College,Devagiri, Kozhikode, Kerala State, India.

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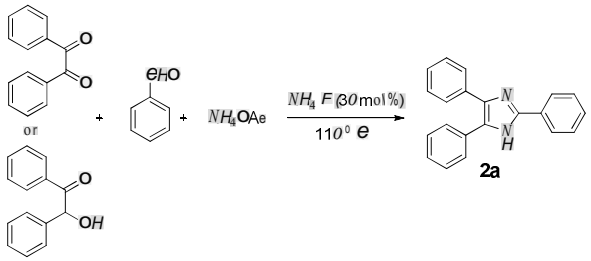
Abstract: We report an efficient, mild and rapid approach for the synthesis of 2,4,5-trisubstituted imidazoles via condensation of a representative 1,2-diketone (benzil or benzoin) with aromatic aldehydes and ammonium acetate by using NH_4F as a new and highly effective catalyst under solvent free conditions. Non corrosiviness, safe, low waste, easy for separation, short time, high yield and environmentally benign are some of the advantages of this methodology.

Key Words: imidazoles, Ammonium Fluoride, *Catalyst*

Introduction

Multicomponent reactions (MCRs) have drawn great interest enjoying an outstanding status in modern organic synthesis and medicinal chemistry because they are one-pot processes bringing together three or more components and show high atom economy and high selectivity (D'Souza and Muller, 2007; Domling, 2006; Setamdideh *et al.,* 2011). MCRs have great contribution in convergent synthesis of complex and important organic molecules from simple and readily available starting materials, and have emerged as powerful tools for drug discovery (Tempest, 2005; Kalinski *et al.,* 2008). The imidazole nucleus is a fertile source of biologically important molecules. Compounds containing imidazole moiety have many pharmacological properties and play important roles in biochemical processes. They are well known as inhibitors of P38MAP kinase, fungicides, herbicides, anti-inflammatory agents, antithrombotic agents, plant growth regulators and therapeutic agents. In addition, they are used in photography as photosensitive compounds. Some substituted triary-limidazoles are selective antagonists of the glucagons receptor and inhibitors of IL-1 biosynthesis (Gadekar *et al.,* 2009).



Scheme 1. NH_4F catalysed synthesis of 2,4,5-triphenyl-1H imidazole under conventional heating conditions

Radziszewskiand Jaapand Robinson, proposed the first synthesis of the imidazole core in 1882, starting from 1,2-dicarbonyl compounds, aldehydes and ammonia to obtain 2,4,5- triphenylimidazole. There are several methods for the synthesis of 2,4,5-triarylimidazoles using $ZrCl_4$, zeolites HY/silica gel, $NaHSO_3$, sulphanilic acid, iodine, ceric ammonium nitrate, oxalic acid, ionic liquids and also by microwave irradiation using acetic acid. Each of the above methods for this reaction has its own merits, while some of the methods are plagued

* Corresponding author
E-mail: arunkalazans@gmail.com

Table 1. Optimisation one-pot synthesis of trisubstistute imidazoles under classical heating conditions

Entry	NH_4F (mol%)	T(^{0}e)	Time(min)	yield(%)
1.	10	100	60	42
2.	10	110	60	55
3.	10	120	60	55
4.	10	130	60	62
5.	20	120	60	75
6.	30	110	60	95
7.	30	120	60	86
8.	40	110	60	85

Benzil (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (5 mmol)

by the limitations of poor yield, longer reaction time, difficult work-up and effluent pollution (Gadekar *et al.,* 2009). Therefore, the development of a new mild method to overcome these disadvantages still remains a challenge for organic chemists. One of the aims we have in mind is to introduce a new catalyst for synthesis of 2,4,5-trisubstituted imidazoles with cost effectiveness and mild condition in high yields. In this perspetive, we demonstrated the solvent-free synthesis of 2,4,5-trisubstituted imidazoles using ammonium fluoride (NH_4F) as a catalyst under classical heating (Scheme 1).

Thus we examined the substituted aromatic aldehydes to establish the catalytic importance of NH_4F for this reaction. Aromatic aldehydes undergo this one-pot multicomponent synthesis with Benzil or Benzoin and ammonium acetate to afford 2,4,5-trisubstituted imidazoles in good yields.

Results and discussion

Several methods are used in the synthesis of these trisubstitutedimidazoles and their derivatives. In addition, the synthesis of these heterocycles has been usually carried out in polar organic solvents such as ethanol, methanol, acetic acid, DMF and DMSO leading to complex isolation and recovery procedures. These processes also generate waste containing catalyst and solvent, which have to be recovered, treated and disposed of. The toxicity and volatile nature of many organic solvents, particularly chlorinated hydrocarbons that are widely used in huge amounts for organic reactions have posed a serious threat to the environment.Thus, design of solvent-free catalytic reaction has received tremendous attention in recent times in the area of green synthesis (Tanaka *et al.*,2000; Kidwai *et al.,* 2006; Safari *et al.,* 2010; Sangshetti *et al.*,2008).

Efficiency of this reaction is mainly affected by the amount of catalyst,

Table 2. Optimisation one-pot synthesis of trisubstistute imidazoles under classical heating conditions

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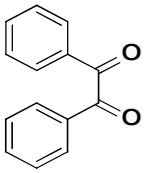
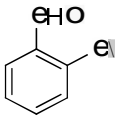
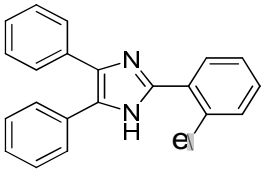
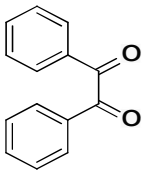
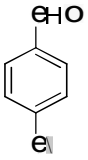
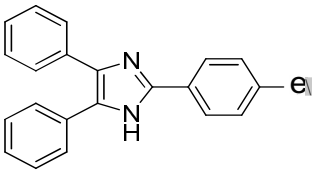
			96
			93

temperatureand reaction time. For getting the best conditions, initially we started the condensation of benzil (1mmol), benzaldehyde (1 mmol) and ammonium acetate (5 mmol) in the presence of ammonium fluoride (1 mmol, 10 mol %) as a catalyst at 100^{o}C for 1h, which led tolow yield (50%) of 2,4,5- trisubstituted imidazole. To enhance the yield of thedesired product the temperature of the reaction was increased to 130^{0}C. With increasing the temperature, the productivity of the reaction increased but was not very high, yet. Then, it was thought worthwhile to carry out the reaction in the iu presence of higher amount of the catalyst. As indicated in Table 1, Maximum yield was obtained (95%) when the reaction was loaded with 30 mol % of the catalyst at the 110 ^{0}C. A further increasing of catalyst loading does not affect the yield (entry 6, Table 1).

After optimizing the conditions, we applied the catalyst for synthesis of trisubstitutedimidazoles by using substituted aromatic aldehydes under solvent-free classical heating conditions to

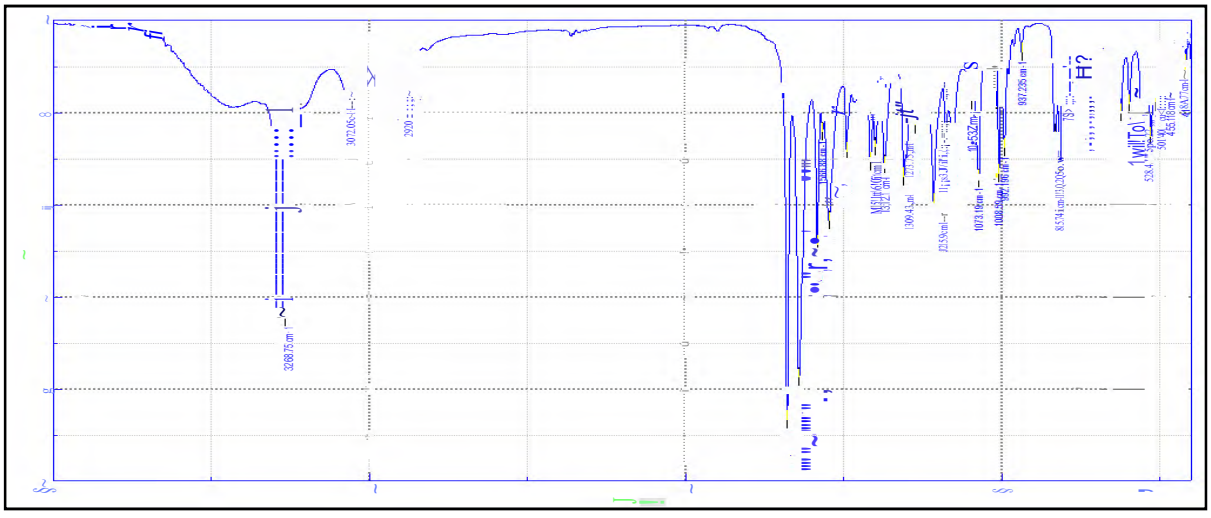


Fig. 1. FTIR spectra of compound 2,4,5-Triphenyl-1H-imidazole **2a**

establish the catalytic importance of NH_4F for this reaction (Table 2).

Generally, the synthetic procedure involves stirring the mixture of aldehyde (1 mmol), benzil (1 mmol), ammonium acetate (5 mmol) and ammonium fluoride (30 mol %) for 45-60 min at 110 ^{0}C. The corresponding results are given in Table 2. We found that the reaction proceeded very efficiently irrespective of their substitution on aryl ring of aldehyde. Also due to direct use of benzoin rather than benzil in the synthesis of imidazoles a significant improvement in the synthesis toward the greener chemistry is represented. We have repeated the reaction with benzoin instead of benzil and the desired product has been efficiently produced. When we used benzoin instead of benzil, the reaction time increased and also the yield of the reaction decreased partially. Possible mechanism for the NH_4F catalysed synthesis of trisubstitutedimidazoles has been proposed in scheme 1.

Thus we have developed a convenient and efficient process for the solvent-free synthesis of trisubstitutedimidazoles through the three-components coupling of benzil or benzoin, aldehydes and ammonium acetate using NH_4F as a catalyst. Reaction profile is very clean and no side products are formed. The synthesized imidazoles have been characterized on the basis of FT-IR studies. We believe that this procedure is convenient, economic, and a user-friendly.

Conclusion

In summary, we presented an efficient, mild and rapid approach for the synthesis of 2,4,5-trisubstituted imidazoles via condensation of a representative 1,2-diketone(benzil or benzoin) with aromatic aldehydes and ammonium acetate, by using NH_4F as a new and highly effective catalyst under solvent-free conditions. Non-corrosiveness, safe, low waste, easy for separation, short time, high yields and environmentally benign are some of the advantages of this methodology.

Experimental

Materials

Chemical reagents were purchased from the Merck Chemical Company in high purity. All the materials were of commercial grade reagent.

General procedure for synthesis of 2,4,5-trisubstitutedimidazoles under conventional heating conditions

A mixture of aldehyde (1 mmol), benzil or benzoin (1 mmol), ammonium acetate (5 mmol) and ammonium fluoride (3 mmol, 30 mol %) as a catalyst in a 20 ml glass tube was stirred at 110^{o}C for 45-75 min. After completion of the reaction, the reaction was cooled to room temperature and solid materials washed with water and the solvent was evaporated to give the crude product. For further purification it was recrystallized from ethanol to afford pure product.

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