

A New Insight on the Synthesis of 2,4,5-Triaryl-1H-imidazoles in the Absence of Catalyst

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Abstract The new results concerning synthesis of some 2,4,5-triaryl-1H-imidazoles in the absence of any additive, as catalyst, is presented. Moreover, we modified the experimental route for the isolation and purification of the un-reacted benzyl, as initial reactant, from products at the end of the reaction.

Keywords Tri-aryl-imidazole, Multi-component, Synthesis, Green

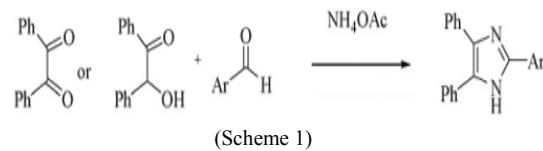
1. Introduction

Imidazole containing compounds have widespread applications in organic synthesis and in pharmaceutical research. Substituted imidazoles are known as inhibitors of P38MAP kinase[1], fungicides and herbicides[2], plant growth regulators[3], and therapeutic agents[4]. Furthermore, they are of interest due to their herbicidal, analgesic, fungicidal, anti-inflammatory, and antithrombotic activities[5]. There are several methods in the literature for the synthesis of 2,4,5-triaryl-1H-imidazoles from benzil/benzoin, aldehydes and ammonium acetate using different catalyst such as zeolite HY/silica gel[6], ZrCl₄[7], NiCl₂.6H₂O[8], iodine [9], sodium bisulfite[10], acetic acid[11], and NH₄OAc[12] (Scheme 1). However, these methods require prolonged reaction time, exotic reaction condition and high cost of catalysts and. Therefore, development of new strategies for the preparation of 2,4,5-triaryl-1H-imidazole derivatives would be highly desirable.

The art of performing efficient chemical transformation coupling three or more components in a single operation by a catalytic process avoiding stoichiometric toxic reagents large amounts of solvents and expensive purification techniques represents a fundamental target of the modern organic synthesis. Accordingly, multi-component condensation reactions provided an especially attractive synthesis method for fast and effective generation of products. The use of solid acid catalysts[13] has attracted a vast importance in organic synthesis due to their several advantages including operationally simplicity, no toxicity, reusability, low cost, and ease of isolation after completion of the reaction.

Potassium dihydrogen phosphate (KH₂PO₄) as a buffer,

neutralizing agent, and yeast food also applied as an efficient heterogeneous acid catalyst[14,15]. Potassium dihydrogen phosphate has been found as a mild and effective catalyst in synthesis of 2,4,5-Triaryl-1H-imidazoles under reflux. Preparation of 2,4,5-triaryl-1H-imidazoles needs at least 2 mole of ammonium acetate against each mole of benzyl. However, reported catalytic procedures used 4-8 mole of NH₄OAc per each mole of diketone or benzil. Recently, we found that this reaction is mainly catalyzed by >8 mol ratio of NH₄OAc and led to >70% of the corresponding imidazoles.



2. Experimental

All starting materials were purchased commercially and were used as received. All products were characterized by comparison of their spectral and physical data with those reported in the literature. Silica gel 60 (70—230 mesh) was used for column chromatography. Progress of the reactions was monitored by TLC. Infrared spectra were recorded (KBr pellets) on a 8700 Shimadzu Fourier Transform spectrophotometer. ¹HNMR spectra were recorded on a Bruker AVANCE 300-MHz instrument.

A mixture of benzaldehyde (10 mmol), benzyl (10 mmol), ammonium acetate (20 mmol), were refluxed with stirring in ethanol for 40 min. The mixture was cooled and cold water was added and the residue washed with hot petroleum benzene to afford the pure product. The pure product, if needed, could be obtained by re-crystallization from ethanol-water mixture. All products were identified by means of IR and ¹H NMR spectroscopy and/or comparison of their melting points with those reported in the literature.

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3. Results and Discussion

In continuation of our research program on the use of simple inorganic non-toxic catalysts, we report herein the efficacy of KH_2PO_4 as catalyst. In this study the multi-component reaction strategy for the synthesis of 2,4,5-triaryl-1H-imidazole by using benzil/benzoin, various substituted aldehydes and ammonium acetate in presence of KH_2PO_4 as catalyst, in ethanol at reflux condition is introduced.

Preparation of the title compound has been reported with different amounts of ammonium acetate. For example in the synthesis of this compound with $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ and Sodium Bisulfite, the mol ratio of benzaldehyde, benzyl and ammonium acetate has been 2.4:2:8 and with Phosphomolybdcic acid 2.4:2:6[4,5]. Table 1 shows some catalytic systems using different amounts of NH_4OAc .

Table 1. Synthesis of 2,4,5-triphenyl-1H-imidazole with different amounts of ammonium acetate in presence of various catalysts

Catalyst	Benzyl (mmol)	NH_4OAc (mmol)	Time (min)	Yield (%)	Ref.
KH_2PO_4	10	20	40	93	3
$\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$	10	40	30	97	4
Sodium bisulfite	10	40	30	98	5
Phosphomolybdcic acid	10	30	45	97	6
Boric acid ($\text{B}(\text{O}_3\text{H}_3)$)	1	3	30	98	7

We performed this reaction with different mmols of ammonium acetate without using any additive to study the role of this initial substrate as catalyst. The results have been presented in Table 2.

Table 2. Synthesis of 2,4,5-triphenyl-1H-imidazole with benzaldehyde(10 mmol), benzyl(10 mmol) and different amounts of ammonium acetate without catalyst in ethanol under reflux for 40 min

Mol ratio of benzyl: NH_4OAc	NH_4OAc (mmol)	Yield(%)
1: 2	20	26
1: 3	30	45
1: 4	40	58
1:5	50	77

These results show that increasing the amount of ammonium acetate, as catalyst, accelerates rate of the reaction. It is found that ammonium acetate converts to ammonia and acetic acid during the reaction. It seems that the produced acid, catalyzes the reaction.

According to the above findings, performing the reaction with 1:4 mol ratio of benzyl:ammonium acetate, without

catalyst, led to ~60% yield. So, we believe that the observed efficiency for the previously reported catalytic systems is mainly due to the presence of high molar ratio of ammonium acetate in the reaction medium and presence of catalyst only slightly affected the yield%.

We repeated the synthesis of 2,4,5-triphenyl-1H-imidazole according to the publication of Joshi *et al*[16]. A mixture of benzaldehyde (10 mmol), benzyl (10 mmol), ammonium acetate (20 mmol), and potassium dihydrogen phosphate (5 mol %) were refluxed with stirring in ethanol for 40 min. Despite the reported yield, 93%, we gained just 32% under the same reaction conditions. After several attempts, we found that the high reported yield% is due to the presence of the unreacted benzyl, as the starting material, accompanying with the desired product. The reported experimental procedure reported by Joshi *et al.* has been inefficient to separate benzyl from the corresponding products. We separated the desired product from benzyl by dissolving the reaction mixture in hot petroleum benzene. This experimental procedure was carried out for some other catalysts under the same time and circumstances. The results have been summarized in Table 3.

Table 3. Synthesis of 2,4,5-triphenyl-1H-imidazole with benzaldehyde(10 mmol), benzyl(10 mmol), ammonium acetate (20 mmol) catalyzed by 5 mol% of different catalysts in the same time (40 min) in ethanol at reflux

catalyst	Yield% (obtained)	Yield% (reported)	Ref.
KH_2PO_4	32	93	16
$\text{NH}_4\text{H}_2\text{PO}_4$	35	-	-
NaH_2PO_4	32	99	17
KHSO_4	25	-	-
Na_2HPO_4	33	-	-

These catalysts showed almost the same reactivity pattern in this reaction. Unfortunately, it seems that many of the yield% reported previously are uncorrected and should be repeated exactly.

4. Conclusions

In conclusion, this report illustrated the new findings on the synthesis of some 2,4,5-triaryl-1H-imidazoles in the absence of any additive as catalyst. Moreover, the modified experimental route for the isolation and purification of the un-reacted benzyl, as initial reactant, from products at the end of the reaction was studied.

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