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Chinese Chemical Letters 21 (2010) 429–432

CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Potassium dihydrogen phosphate catalyzed one-pot synthesis of 2,4,5-triaryl-1*H*-imidazoles

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Received 26 August 2009

Abstract

A simple and efficient method has been developed; benzil/benzoin undergoes smooth condensation with various substituted aldehyde and ammonium acetate in the presence of potassium dihydrogen phosphate (KH_2PO_4) under mild reaction conditions to afford the corresponding trisubstituted imidazole in excellent yields. The method for synthesis of product, the reaction mixture was reflux in ethanol for 40–90 min. The present method is simple, efficient, and cost-effective.

Keywords: Potassium dihydrogen phosphate (KH_2PO_4); 2,4,5-Triaryl-1*H*–imidazole; Benzil; Benzoin; Aldehyde; Ammonium acetate

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Recently interest in imidazole-containing structures stems from their widespread occurrence in molecules have been exhibits significant activity and their use in synthetic chemistry. Substituted imidazoles are well known as inhibitors of P38MAP kinase [1], fungicides and herbicides [2], plant growth regulators [3], and therapeutic agents [4]. In addition, they are of interest due to their herbicidal, analgesic, fungicidal, antiinflammatory, and antithrombotic activities [5]. Trifenagre [6] is a 2,4,5-triaryl-1*H*-imidazole that reduces platelet aggregation in several animal species and humans. Despite their importance have been developed from pharmacological, industrial, and synthetic points of view, recently, there are several methods reported in the literature for the synthesis of 2,4,5-triaryl-1*H*-imidazoles from benzil/benzoin, aldehydes and ammonium acetate using different catalyst such as zeolite HY/silica gel [7], $ZrCl_4$ [8], $NiCl_2{\cdot}6H_2O$ [9], ionic liquid [10], iodine [11], sodium bisulfite [12], acidic Al_2O_3 [13], acetic acid [14], NH_4OAc [15], $Yb(OTf)_3$[16]. However, these methods require prolonged reaction time, exotic reaction condition and high cost of catalysts and. Thus, the development of a new method for the synthesis of 2,4,5-triaryl-1*H*-imidazoles derivatives would be highly desirable.

Accordingly multi-component condensations (MCCs) constitute an especially attractive synthesis strategy for rapid and efficient generation of products due to the fact that the products are formed in a single step and also the diversity could be achieved simply by varying the reacting components. The use of solid acid catalysts [17] has gained 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.

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1001-8417/$ – see front matter
doi:10.1016/j.cclet.2009.11.012

Potassium dihydrogen phosphate (KH_2PO_4) was a buffer, neutralizing agent, yeast food also emerged as an efficient heterogeneous acid catalyst [18,19]. Potassium dihydrogen phosphate was found to be mild and effective catalyst in synthesis of 2,4,5-Triaryl-1*H* -imidazoles at reflux condition and commercial availability of this catalyst provides clean conversion; greater selectivity and easy workup make this protocol practical and economically attractive.

1. Experimental

All chemicals were purchased from Merck, Aldrich and Rankem chemical companies and used without further purification. The uncorrected melting points of compounds were taken in an open capillary in a paraffin bath. The progresses of the reactions were monitored by thin layer chromatography (TLC). IR spectra were recorded on PerkinElmer FT spectrophotometer in KBr disc.^{1}H NMR spectra were recorded on an 400 MHz FT–NMR spectrometer in $CDCl_3$ and DMSO-d6 as a solvent and chemical shift values are recorded in units (δ) relative to tetramethylsilane (Me_4Si) as an internal standard (Scheme 1).

2. General procedure of synthesis of substituted imidazole

A mixture of substituted aldehyde (10 mmol), benzil/benzoin (10 mmol), ammonium acetate (20 mmol), and potassium dihydrogen phosphate (5 mol %) were reflux with stirring in ethanol. The progress of reaction was monitored by TLC and after completion of reaction the mixture was cooled and ice-cold water was added (2 × 25 mL) and the residue crystallized from ethanol to afford the pure product.

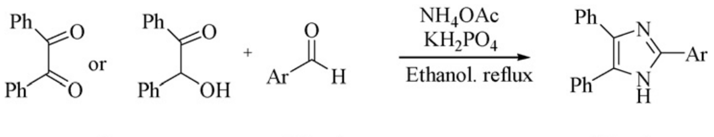
- **3d:** IR (KBr, cm^{-1}): 3450 (N–H), 1600 (C = C), 1580 (C = N) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10–7.60 (m, 10H, 2 C_6H_5), 7.35 (d, 2H, *J* = 10 Hz), 7.85 (d, 2H, *J* = 10 Hz) 11.86 (s, NH). EIMS (*m/z*): 331 (M + 1). 333 (M + 3).
- **3g:** IR (KBr, cm^{-1}): 3405 (N–H), 1597 (C = C), 1562 (C = N). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.28 (s, 3H), 7.21–7.49 (m, 10H, $2C_6H_5$), 7.22 (d, 2H, *J* = 7.3 Hz), 7.92 (d, 2H, *J* = 7.4 Hz), 12.56 (s, NH). EIMS (*m/z*): 327 (M + 1).
- **3l:** IR (KBr, cm^{-1}): 3400 (N–H), 1580 (C = N), 1515 (NO_2), 1335 (NO_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.15–7.70 (m, 10H, $2C_6H_5$), 7.90–8.25 (d, 4H, *J* = 9 Hz), 11.45 (s, 1H, N–H). EIMS (*m/z*): 342 (M + 1).

3. Result and discussion

As a part of our program [23] aimed at developing useful novel, selective and synthesis methods based on the use of functionalized KH_2PO_4 as catalysts. In this report, we have studied using the multi-component reaction (MCR) strategy for the synthesis of 2,4,5-triaryl-1*H*-imidazole by using benzil/benzoin, various substituted aldehydes and ammonium acetate in presence of KH_2PO_4 as catalyst, in ethanol at reflux condition.

We have initially studied the catalytic efficiency of potassium dihydrogen phosphate for the synthesis of 2,4,5 triphenyl-1*H*-imidazole (Table 3 entry **3a**) using benzil, benzaldehyde and ammonium acetate in different solvents and various mol% of KH_2PO_4 (Scheme 1).

To determine the role of catalyst, on the model reaction the same reaction was carried in the absence of catalyst. The desired product was not observed after long reaction time (2–3 h), this indicates that the catalyst exhibits a high catalytic activity in this transformation and the employ of 5 mol% of the catalyst was enough to endorse the reaction. The elevated amount of the catalyst did not progress the yield. The best result was obtained with 5 mol % of KH_2PO_4 the results are summarized in (Table 1, entries 1–7).



Scheme 1. Synthesis of substituted 2,4,5-triaryl-1*H* -imidazoles.

Table 1
Effect of KH_2PO_4 on the synthesis of 2,4,5-triphenyl-1*H* –imidazole **3a**.[a].

Entry	Catalyst (mol%)	Time (min)	Yield[b] (%)
1	0	40	–
2	1	40	24
3	2	40	36
4	3	40	58
5	4	40	80
6	5	40	93
7	6	40	93

[a] Reaction condition: Reaction of benzaldehyde (10 mmol) with benzil (10 mmol) and ammonium acetate (20 mmol) in presence of KH_2PO_4 in ethanol at reflux.

[b] Isolated yield.

Table 2
Effect of solvent on the synthesis of 2,4,5-triphenyl-1*H* –imidazole **3a**.[a].

Entry	Solvent	Time (min)	Yield[b] (%)
1	Water	40	–
2	Toluene	40	20
3	Dichloromethane	40	33
4	Methanol	40	72
5	Acetonitrile	40	78
6	Ethanol	40	93

[a] Reaction condition: Reaction of benzaldehyde (10 mmol) with benzil (10 mmol) and ammonium acetate (20 mmol) in presence of KH_2PO_4 (5 mol %) at reflux.

[b] Isolated yield.

The effect of different solvents like water, toluene, dichloromethane, methanol, acetonitrile, and ethanol are shown in (Table 2 entries 1–6). It was found that ethanol stands out as the solvent of choice, with its fast conversion, high yield and low toxicity. The presence of electron donating groups on the aldehyde resulted in the corresponding products in low yields and the reaction was sluggish, however the presence of electron-withdrawing groups afforded the corresponding trisubstituted imidazole in shorter reaction time with higher yields. Also, there was no effect of benzoin/ benzil on reaction give corresponding products in good yields.

Table 3
Synthesis of 2,4,5-triaryl-1*H* –imidazole **3**(**a**–**n**) catalyzed by KH_2PO_4 (5 mol %) in ethanol at reflux.[a].

Entry	Ar-CHO	Time (min)		Yield (%)[b]		MP (°C)
		Benzil	Benzoin	Benzil	Benzoin	
3a	Benzaldehyde	40	55	93	90	277–278[20]
3b	2-Chlorobenzaldehyde	45	50	92	91	195–197[20]
3c	2-Napthaldehyde	50	60	92	90	241–242[23]
3d	4-Chlorobenzaldehyde	40	55	94	91	260–262[20]
3e	4-Hydroxybenzaldehyde	50	65	90	88	268–269[20]
3f	4-Methylbenzaldehyde	50	60	88	90	230–232[20]
3g	4-Methoxybenzaldehyde	50	60	90	86	229–230[20]
3h	3,4-Dimethoxy benzaldehyde	55	70	92	89	219–221[20]
3i	4-Bromobaenzaldehyde	55	65	89	85	260–262[21]
3j	4-Flurobenzaldehyde	40	50	91	87	189–190[20]
3k	Furan-2-carbaldehyde	55	70	90	86	200–201[20]
3l	4-Nitrobenzaldehyde	35	40	92	89	200–202[20]
3m	Thiopenealdehyde	55	65	90	90	260–261[20]
3n	4-(Dimethylamino)benzaldyde	55	60	90	86	257–258[20]

[a] All the products were characterized by ^1H NMR and mass spectroscopy and compared with previously reported data [20–22].

[b] Isolated yield.

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aryl/heteroaryl aldehydes with benzil/benzoin and ammonium acetate in the 5 mol% of catalyst KH_2PO_4 in ethanol at 70 °C and the results are shown in Table 3. The results of synthesized compounds were compared (MP, MS, NMR, and IR) with compounds that were reported in the literature. This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds.

In conclusion, the present procedure using potassium dihydrogen phosphate as catalyst provides an efficient one-pot synthesis of 2,4,5 trisubstituted-1*H*-imidazole in ethanol at reflux conditions. The advantages of this procedure are operational simplicity, wide substrate scope, and high yields. In many cases, the products crystallized directly from the reaction mixture having high purity. We believe that this method presents a practical alternative to existing procedures for the synthesis of 2,4,5 trisubstituted-1*H*-imidazole.

Acknowledgments

The authors are thankful to University Grants Commission, New Delhi, for financial support and to the Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, for his valuable support and laboratory facilities.

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