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ORIGINAL PAPER

A greener route for the one-pot synthesis of 1,2,4,5-tetraarylated imidazoles

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Abstract An efficient synthesis of various tetraarylated imidazoles using anhydrous $FePO_4$ as a catalyst by four-component condensation of benzil (or benzoin), aldehydes, amines, and ammonium acetate in refluxing ethanol is described.

Keywords 1,2,4,5-Tetraarylated imidazoles · Iron(III) phosphate · One-pot synthesis

Introduction

The imidazole ring system is one of the most important substructures found in a large number of natural products and pharmacologically active compounds [1–5], and members of this class of compounds are known to inhibit NO synthase and have antifungal, antimycotic, antibiotic, antiulcerative, antibacterial, antitumor, and CB_1 receptor antagonistic activities [6, 7]. Various substituted imidazoles act as inhibitors of p38 MAP kinase [8] and B-Raf kinase [9], glucagon receptor antagonists [10], plant growth regulators [11, 12], therapeutic agents [1], and also pesticides [13, 14]. Accordingly, a number of synthetic methods have been reported for the construction of this important structure. In 1882, Radziszewski [15] and Japp and Robinson [16] reported the first synthesis of highly substituted imidazoles from 1,2-dicarbonyl compounds, different aldehydes, and ammonia.

A number of methods have been also developed for the synthesis of 1,2,4,5-tetraarylated imidazoles. The syntheses of 1,2,4,5-tetraarylated imidazoles are carried out by four-component condensation of a 1,2-diketone or β-hydroxyketone with an aldehyde, primary amine, and ammonium acetate using microwaves [17], molecular iodine [18], $HClO_4$–SiO_2 [19], heteropolyacid [20, 21], silica gel/$NaHSO_4$ [22], L-proline [23], $FeCl_3{\cdot}6H_2O$ [24], $BF_3{\cdot}SiO_2$ [25], and silica-supported Wells–Dawson acid [26]. In addition, they can also be accessed by the condensation of a 1,2-diketone with an aryl nitrile and primary amine under microwave irradiation [27], by hetero-Cope rearrangement [28], and by N-alkylation of triarylated imidazoles [29]. These methods are suitable for certain synthetic conditions; however, many of these procedures are associated with one or more disadvantages such as expensive reagents, longer reaction times, tedious work-up procedure, low selectivity, and large amounts of catalysts which would eventually result in the generation of large amounts of toxic waste.

In this paper we present a novel, mild, and efficient method for the synthesis of tetraarylated imidazoles using benzil (or benzoin), aldehyde, aniline, and ammonium acetate in the presence of $FePO_4$ as a catalyst (Scheme 1). Benzoin participated in the condensation with aldehyde, amine, and ammonium acetate in the presence of $FePO_4$ to give the corresponding tetraarylated imidazoles, but the yields were found to be low (20–40%). The role of $FePO_4$ is probably in promoting the aerial oxidation of benzoin to benzil [30], followed by formation of tetraarylated imidazoles in low yield.

In addition to the cases mentioned above, $FePO_4$ is a relatively cheap, safe, and available reagent [31] that has also been employed for the selective oxidation of CH_4 to CH_3OH [32] and benzene to phenol [33], one-pot synthesis of dihydropyrimidinones and -thiones [34], and as a catalyst in the synthesis of triarylated imidazoles [35]. Therefore, in connection with our research [36–38] on the

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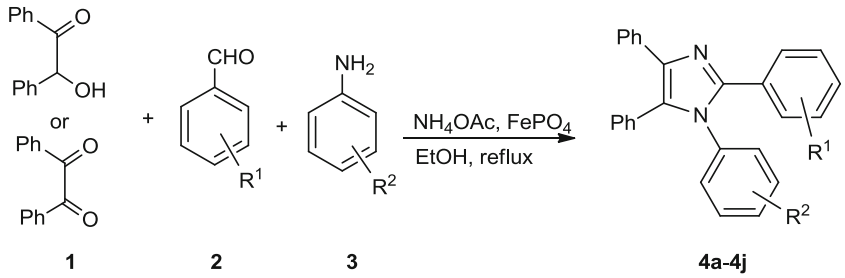
Scheme 1



R^1 = H, 4-CH_3, 3-NO_2, 4-NO_2, 4-$N(CH_3)_2$, 2-CH_3, 2-CH_3O, 2-CH_3, 4-OH, 3-OH
R^2 = H, 4-CH_3, 4-CH_3O

development of simple and efficient methods for the synthesis of various heterocyclic compounds, herein we present iron(III) phosphate as a green, reusable, recyclable, environmentally safe, inexpensive, and commercial catalyst for the synthesis of 1,2,4,5-tetraarylated imidazoles.

Results and discussion

The typical procedure for preparing 1,2,4,5-tetraarylated imidazoles involves heating a mixture of ammonium acetate (ammonia source) in an ethanolic solution of benzil, benzaldehyde, and aniline, and this system was used as a model reaction to optimize the reaction conditions. Among the tested catalysts, 10 mol% $FePO_4$ promoted the facile formation of product **4a** in high yield (Table 1).

The four-component condensation of benzil, benzaldehyde, aniline, and ammonium acetate was also performed in the absence of $FePO_4$ under reflux; however, the yield of **4a** was low (10%).

The effect of temperature was investigated by carrying out the model reaction in ethanol and at different temperatures in the presence of this catalyst (room temperature, 50 °C, and 80 °C). The results Table 2 show that the yield increased as the reaction temperature was raised. Therefore, all reactions were carried out in refluxing ethanol.

To explore the applicability of this method, the same reaction conditions were applied to the synthesis of 1,2,4,5-tetraarylated imidazoles via the one-pot, four-component condensation of benzil (or benzoin) (1 mmol), aldehyde (1 mmol), primary arylamine (1 mmol), and ammonium acetate (1 mmol) as depicted in Scheme 1.

The substrate scope of the reaction was then evaluated using a variety of structurally diverse aldehydes and primary arylamines (Table 3). The cyclocondensation of benzyl or benzoin with various aromatic aldehydes bearing electron-withdrawing groups (such as nitro) or electron-releasing groups (such as methyl, hydroxyl, mono- or dimethoxy groups), substituted anilines, and ammonium acetate was carried out in the presence of $FePO_4$ as a catalyst. The yields of products (**4a**–**4j**) obtained were good to excellent without formation of any side products such as 2,4,5-triarylated imidazoles, oxidized products of anilines, aldehydes etc., which are normally observed under the influence of strong acids. The results obtained with the current method are listed in Table 3. In each case, the reaction profile is clean and this one-pot, four-component procedure presents some improvements and advantages over existing methods. One of the major advantages is the isolation and purification of the products, which are achieved by simple washing and crystallization of the crude products.

A plausible mechanism [39] for the synthesis of the tetraarylated imidazoles involves the formation of intermediate **A** by the reaction of a $FePO_4$-activated aldehyde [35], primary amine, and ammonium acetate (Scheme 2). Intermediate **A** condenses with benzil to form intermediate **B**, which in turn liberates a water molecule to form the tetraarylated imidazole.

To check the reusability of the catalyst, the condensation of benzaldehyde, benzil, aniline, and NH_4OAc to provide

Table 1 Catalytic activity evaluation for the synthesis of 1,2,4,5-tetraphenylimidazole (**4a**)

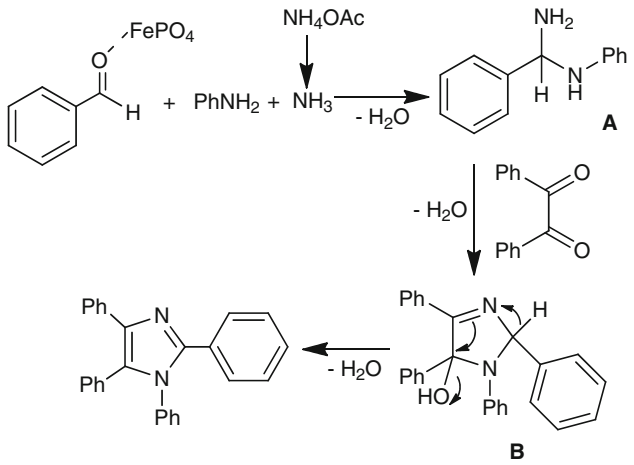
Entry	$FePO_4$/mol%	Time/h	Yield/%
1	0	24	10
2	5	10	75
3	7	8	80
4	10	5	90
5	15	4.5	91

Table 2 Synthesis of 1,2,4,5-tetraphenylimidazole (**4a**) in the presence of $FePO_4$ in ethanol at different temperatures

Entry	Temp/°C	Time/h	Yield/%
1	25	24	30
2	50	10	50
3	80	5.0	90

Table 3 Synthesis of 1,2,4,5-tetraarylated imidazoles using benzil (or benzoin), ammonium acetate, aromatic aldehydes, and arylamines catalyzed by 10 mol% $FePO_4$ (see Scheme 1)

Product	R^1	R^2	Time/h		Yield/%		M.p./°C
			Benzoin	Benzil	Benzoin	Benzil	Found (reported)
4a	H	H	5.5	5	40	90	218–219 (219–220 [21])
4b	4-CH_3	H	8.5	7	30	90	160–162 (155–157 [21])
4c	3-NO_2	4-CH_3	8.5	8	35	96	223–225 (218–220 [21])
4d	4-NO_2	4-CH_3	8	7.5	30	94	150–152 (151–153 [21])
4e	4-$N(CH_3)_2$	H	7.5	7	20	88	254–256 (256–259 [21])
4f	2-CH_3	4-CH_3	6.5	6	25	90	254–256 (–)
4g	2-CH_3O	4-CH_3O	5.5	5	40	85	164–166 (–)
4h	2-CH_3	4-CH_3O	5.5	5	40	86	256–257 (–)
4i	4-OH	4-CH_3	6.5	6	30	90	303–305 (280 [21])
4j	3-OH	4-CH_3	7.5	7	25	82	229–230 (230–232 [21])



Scheme 2

the tetraarylated imidazoles under the conditions described with $FePO_4$ as a catalyst was run for four consecutive cycles. The corresponding imidazole was obtained in 90, 88, 85, and 83% isolated yields, which proved the efficiency of the catalyst for multiple usages.

Conclusion

This method not only affords the products in excellent yields but also avoids the problems associated with catalyst cost, handling, safety, and pollution. $FePO_4$ is an eco-friendly catalyst for a variety of organic transformations. It is nonvolatile, recyclable, nonexplosive, easy to handle, and thermally robust. In view of the emerging importance of this heterogeneous catalyst, we aim to explore the use of $FePO_4$ as a recyclable catalyst for the synthesis of other five- and six-membered heterocyclic compounds.

Experimental

Melting points were measured by using the capillary tube method with an Electrothermal 9200 apparatus. IR spectra were recorded on a Perkin Elmer FT-IR spectrometer scanning between 4,000 and 400 cm^{-1}. The products were characterized by ^1H NMR and ^{13}C NMR spectra recorded on a Bruker DRX-300 NMR instrument. GC/MS spectra were recorded on an Agilent 6890 GC Hp-5 (capillary 30 m × 530 μm × 1.5 μm, operating at 70 eV). Anhydrous $FePO_4$ and the other starting materials were purchased from Merck. All melting points compared satisfactorily with those reported in the literature [21].

Preparation of 1,2,4,5-tetraarylated imidazoles: typical procedure

A 50-cm^3 round-bottom flask was charged with benzil (or benzoin) (2 mmol), aromatic aldehyde (2 mmol), aniline (2 mmol), ammonium acetate (2 mmol), and $FePO_4$ (10 mol%) followed by 5 cm^3 of ethanol. The mixture was then stirred and refluxed until the reaction was completed (TLC). The mixture was then cooled to room temperature and filtered to remove and recover the catalyst. The filtrate was dried to afford crude product. The crystalline pure product was obtained by further recrystallization from water/ethanol (10:1).

1-(2,4-Dimethylphenyl)-2-(4-methylphenyl)-4,5-diphenyl-1H-imidazole (**4f**, $C_{30}H_{26}N_2$)
Yield 90%; IR (KBr): $\bar{\nu}$ = 3,062 (C–H), 1,603 (C=C), 1,580 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 7.26–7.35 (m, 17H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.2 (N–C=N), 138.5, 136.0, 135.0, 131.5, 129.0, 127.5, 126.0, 124.5, 123.0, 122.2 (Ar, C=C), 24.5, 17.5, 15.3 (CH_3) ppm; GC-MS: *m/z* (%) = 414 (3).

2-(2-Methoxyphenyl)-1-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazole (**4g**, $C_{29}H_{24}N_2O_2$)
Yield 85%; IR (KBr): $\bar{\nu}$ = 3,062 (C–H), 1,601 (C=C), 1,583 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.42 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 6.62–6.64 (d, 2H, Ar, J = 8.8 Hz), 6.69–6.72(d, 1H, Ar, J = 8.3 Hz), 6.83–6.86 (d, 2H, Ar, J = 8.8 Hz), 6.97–7.02 (dd, 1H, Ar, J = 7.5,7.8 Hz), 7.13–7.26 (m, 11H, Ar), 7.29–7.37 (dd, 1H, Ar, J = 7.8, 7.5 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.5 (CH_3O–C), 144.2 (N–C=N), 138.5, 137.0, 135.5, 129.0, 127.0, 125.0, 123.0, 122.0, 121.0, 115.0, 114.0 (Ar, C=C), 56.2 (CH_3O) ppm; GC/MS: m/z (%) = 432 (3).

1-(4-Methoxyphenyl)-2-(2-methylphenyl)-4,5-diphenyl-1H-imidazole (**4h**, $C_{29}H_{24}N_2O$)
Yield 86%; IR (KBr): $\bar{\nu}$ = 3,061 (C–H), 1,603 (C=C), 1,581 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 6.61–6.64 (d, 2H, Ar, J = 8.6 Hz), 6.79–6.82 (d, 2H, Ar, J = 8.9 Hz), 7.12–7.58 (m, 14H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5 (CH_3O–C), 144.2 (N–C=N), 138.5, 136.0, 130.0, 129.0, 127.0, 126.0, 125.0, 123.0, 122.0, 115.2 (Ar, C=C), 56.2 (CH_3O), 17.5 (CH_3) ppm; GC/MS: m/z (%) = 416 (2).

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