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Multicomponent, one-pot synthesis and spectroscopic studies of 1-(2-(2,4,5-triphenyl-1*H*-imidazol-1-yl)ethyl)piperazine derivatives

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Abstract

A simple, highly versatile and efficient synthesis of 1,2,4,5-tetrasubstituted imidazoles is achieved by four-component cyclocondensation of benzil, an aromatic aldehyde, aminoethylpiperazine and ammonium acetate using sulphated yttria as a catalyst in ethanol. The synthesized compounds are characterized through IR, ^{1}H and ^{13}C NMR and HR-MS.

Keywords: 1,2,4,5-Tetrasubstituted imidazoles; Sulphated yttria; SO_4^{2-}/Y_2O_3; Multi-component reaction

1. Introduction

Multicomponent reactions (MCRs) are atom economical and highly useful protocols in modern synthetic organic chemistry. MCRs have great advantages, such as short reaction time, low cost, low energy consumption, high yield and easy purification processes without isolation of intermediates [1]. Development of new MCRs and improvement of known MCRs are popular areas of research; one such reaction is imidazole synthesis using the MCR strategy. Over recent years, imidazole scaffolds have become a vital class of important heterocycles due to their abundance in natural products and their extensive use in medicinal chemistry [2,3].

Imidazole scaffolds are particularly well known for their anticancer [4], antifungal [5] and antibacterial activities [6]. On the other hand, highly substituted imidazole derivatives possess good photophysical properties, which result in their potential applications to material chemistry, such as in organic electroluminescent devices (OLED) [7]. In addition, imidazole derivatives were utilized as ligands in metal-catalyzed reactions [8] and as fluorescent probes [9]. Therefore, a variety of synthetic routes has been devised for the synthesis of imidazole analogues [10]. Imidazole ring systems show a variety of pharmaceutical activities [11–13] and play crucial roles in biochemical processes. It appears that the highly substituted imidazoles could have novel therapeutic activities [14], and they constitute an essential moiety in a number of therapeutic agents, fungicides, herbicides [15] and plant-growth regulators [16] in addition to being known as inhibitors of p38 MAP kinase [14]. Furthermore, a recent report indicates that imidazoles are potent inhibitors of protein–protein interactions [17].

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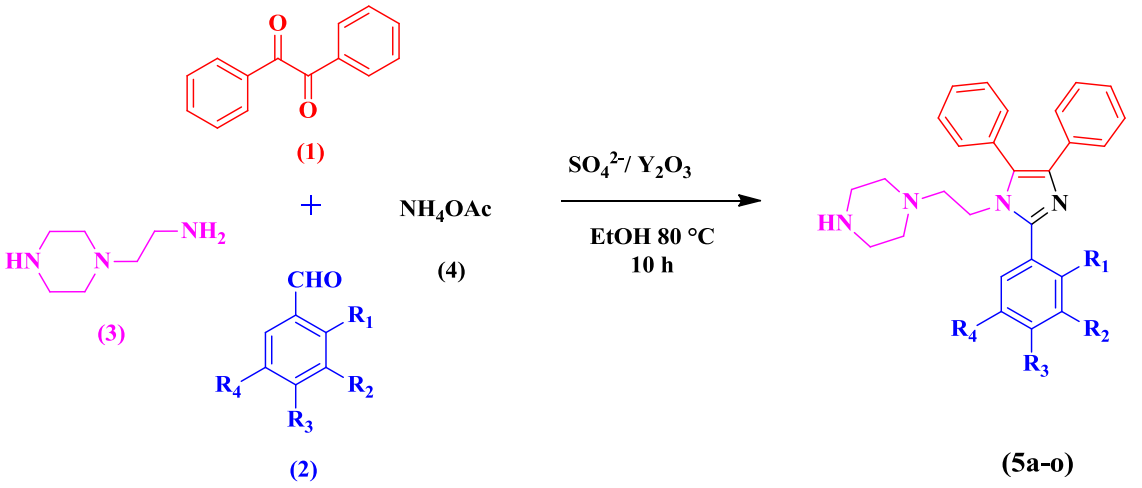


Scheme 1. Synthesis of 1,2,4,5-tetrasubstituted imidazole derivatives.

Numerous methods have been reported for the synthesis of 1,2,4,5-tetrasubstituted imidazoles by four-component condensation of 1,2-diketone with an aldehyde, a primary amine and ammonium acetate using a heteropolyacid [18], $BF_3{\cdot}SiO_2$ [19], silica gel/$NaHSO_4$ [20] or $HClO_4$–SiO_2 [21], ionic liquids [22], L-proline [23], $ZrCl_4$ [24], $InCl_3{\cdot}3H_2O$ [25], $K_5CoW_{12}O_{40}{\cdot}3H_2O$ [26], molecular iodine [27], silica sulphuric acid [28], $NiCl_2{\cdot}6H_2O/Al_2O_3$ [29], $Yb(OTf)_3$ [30] selectfluor [31] $H_2SO_4{\cdot}SiO_2$ [32] and CAN [33]. In this study, we report a facile, efficient and eco-friendly one-pot process for the synthesis of 1,2,4,5-tetrasubstituted imidazoles **5a–o** through a four-component condensation reaction of benzil **1**, substituted benzaldehyde **2**, aminoethylpiperazine **3** and ammonium acetate **4** in the presence of sulphated yttria (SO_4^{2-}/Y_2O_3), as an efficient and reusable catalyst in ethanol (Scheme 1). Currently, sulphated metal and mixed metal oxides have gained substantially more recognition for their significant catalytic activity than metal and mixed metal oxides due to their higher number of acid sites and larger surface area, which result in enhanced catalytic activity [34].

2. Materials and methods

2.1. Chemicals and analysis

The chemicals were purchased from Merck, Fluka and Aldrich chemical companies. The melting points were recorded in an open capillary tube and were uncorrected. The ^1H and ^{13}C NMR spectra of the synthesized compounds using $CDCl_3$ as the solvent were recorded on a Bruker Avance 400 or 500 MHz NMR spectrometer. The ^1H NMR and ^{13}C NMR were referenced to TMS as an internal standard and the central line of $CDCl_3$, respectively. IR spectra were recorded using a JASCO FT/IR-5300 spectrometer. High-resolution mass spectra (HRMS) were recorded using electrospray ionization on a Bruker Maxis instrument. Column chromatography was performed using silica gel (100–120 mesh).

2.2. General procedure for preparation of 1-(2-(2,4,5-triphenyl-1H-imidazol-1-yl)ethyl)piperazine (5a–o)

In a 50 mL round bottom flask, a mixture of benzil (1 mmol), aromatic aldehyde (1 mmol), aminoethylpiperazine (1 mmol), ammonium acetate (2 mmol) and SO_4^{2-}/Y_2O_3 (50 mg) [35] was stirred and refluxed at 80 °C in ethanol (20 mL) for 10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the volume of the reaction mixture was reduced, diluted with cold water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure. The crude products were subjected to purification by column chromatography with silica gel (100–120 mesh size) using 20% methanol in ethyl acetate as the eluent to yield 1,2,4,5-tetrasustituted imidazoles (**5a–5o**).

2.2.1. 1-(2-(2,4,5-triphenyl-1H-imidazol-1-yl) ethyl)piperazine (5a)

Yield 1.784 g (93%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 500 MHz) δ 2.02 (s, 4H, $(CH_2)_2NH$), 2.23 (t, $J = 7.5$ Hz, 2H, CH_2), 2.4 (s, 1H, NH), 2.64 (t, 4H, $(CH_2)_2N$), 4.03 (t, $J = 7.5$ Hz, 2H, CH_2), 7.12–7.73 (m, 15H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 41.88, 45.62, 54.07, 58.36, 126.31, 126.83, 128.08, 128.35, 128.67, 128.79, 128.96, 129.14, 129.29, 129.58, 131.09, 131.35, 131.37, 134.50, 137.75, 147.96; HRMS (ESI): calculated for $C_{27}H_{28}N_4$ $[M+H]^+$ 409.2387; found 409.2391.

*2.2.2. 1-(2-(4,5-diphenyl-2-(p-tolyl)-1H-imidazol-1-yl)ethyl)piperazine (**5b**)*

Yield 1.845 g (93%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (s, 4H, $(CH_2)_2NH$), 2.24 (t, $J = 7.0$ Hz, 3H, CH_3), 2.42 (s, 2H, CH_2), 2.66 (t, $J = 4.5$ Hz, 4H, $(CH_2)_2N$), 4.02 (t, $J = 7.5$ Hz, 2H, CH_2), 7.12–7.48 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.40, 41.85, 45.69, 54.22, 58.34, 126.26, 126.84, 127.42, 127.81, 128.05, 128.34, 128.51, 128.73, 129.10, 129.14, 129.33, 129.44, 129.91, 131.01, 131.11, 131.43, 134.51, 137.62, 138.90, 148.06, HRMS (ESI): calculated for $C_{28}H_{30}N_4$ $[M+H]^+$ 423.2544; found 423.2587.

*2.2.3. 1-(2-(2-(4-bromophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5c**)*

Yield 2.102 g (92%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 4H, $(CH_2)_2NH$), 2.24 (t, $J = 7.0$ Hz, 2H, CH_2), 2.71 (t, $J = 5.0$ Hz, 4H, $(CH_2)_2N$), 4.02 (t, $J = 7.0$ Hz, 2H, CH_2), 7.14–7.63 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.11, 45.31, 53.66, 58.21, 123.30, 126.49, 126.83, 128.13, 128.35, 128.93, 129.20, 129.27, 129.93, 130.23, 130.67, 130.75, 130.97, 131.03, 131.11, 131.89, 131.97, 134.22, 138. 11, 146.80; HRMS (ESI): calculated for $C_{27}H_{27}BrN_4$ $[M+H]^+$ 487.1492; found 487.1498.

*2.2.4. 1-(2-(2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5d**)*

Yield 1.891 g (91%). Yellow solid, mp 96–98 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.05 (s, 4H, $(CH_2)_2NH$), 2.24 (t, $J = 7.5$ Hz, 2H, CH_2), 2.68 (t, $J = 4.5$ Hz, 4H, $(CH_2)_2N$), 4.02 (t, $J = 7.5$ Hz, 2H, CH_2), 7.14–7.71 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.10, 45.73, 54.33, 58.38, 126.45, 126.57, 126.82, 128.12, 128.35, 128.91, 129.01, 129.18, 129.27, 129.80, 129.90, 130.43, 130.54, 130.98, 131.07, 131.16, 134.28, 135.03, 138.03, 146.77; HRMS (ESI): calculated for $C_{27}H_{27}ClN_4$ $[M+H]^+$ 443.1997; found 443.2001.

*2.2.5. 1-(2-(2-(4-fluorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5e**)*

Yield 1.822 g (91%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 500 MHz) δ 2.05 (s, 4H, $(CH_2)_2NH$), 2.24 (t, $J = 7.0$ Hz, 2H, CH_2), 2.68 (t, $J = 4.5$ Hz, 4H, $(CH_2)_2N$), 4.01 (t, $J = 7.5$ Hz, 2H, CH_2), 7.15–7.72 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.96, 45.61, 54.13, 58.33, 115.67, 115.84, 126.41, 126.80, 128.11, 128.14, 128.35, 128.86, 129.17, 129.26, 129.61, 130.99, 131.07, 131.20, 131.24, 131.27, 134.33, 137.81, 146.97; HRMS (ESI): calculated for $C_{27}H_{27}FN_4$ $[M+H]^+$ 427.2293; found 427.2298.

*2.2.6. 1-(2-(2-(4-nitrophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5f**)*

Yield 1.853 g (87%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.13 (s, 4H, $(CH_2)_2NH$), 2.25 (t, $J = 7.2$ Hz, 2H, CH_2), 2.71 (s, 4H, $(CH_2)_2N$), 4.07 (t, $J = 6.8$ Hz, 2H, CH_2), 6.15–8.34 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.59, 44.07, 52.08, 57.85, 123.98, 126.84, 128.21, 129.24, 129.34, 129.63, 130.58, 130.91, 131.10, 133.80, 137.48, 139.06, 145.51, 147.64; HRMS (ESI): calculated for $C_{27}H_{27}N_5O_2$ $[M+H]^+$ 454.2238; found 454.2243.

*2.2.7. 1-(2-(2-(4-methoxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5g**)*

Yield 1.896 g (92%). Yellow solid, mp 99–101 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.09 (s, 4H, $(CH_2)_2NH$), 2.17 (d, $J = 6.5$ Hz, 2H, CH_2), 2.70 (s, 4H, $(CH_2)_2N$), 3.80 (t, $J = 4.5$ Hz, 3H, OCH_3), 3.95 (d, $J = 6.0$ Hz, 2H, CH_2), 6.53–7.57 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.88, 43.30, 50.72, 55.35, 57.46, 114.09, 114.17, 123.44, 126.37, 126.84, 126.88, 128.08, 128.78, 129.09, 129.18, 129.25, 130.50, 130.59, 130.89, 131.03, 131.21, 134.32, 137.57, 147.93, 160.18, 177.98; HRMS (ESI): calculated for $C_{28}H_{30}N_4O$ $[M+H]^+$ 439.2493; found 439.2498.

*2.2.8. 4-(4,5-diphenyl-1-(2-(piperazin-1-yl)ethyl)-1H-imidazol-2-yl)-N,N-dimethylaniline (**5h**)*

Yield 1.931 g (91%). Red gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01 (d, $J = 2.8$ Hz, 4H, $(CH_2)_2NH$), 2.23 (t, $J = 7.6$ Hz, 2H, CH_2), 2.40 (s, 1H, NH), 2.63 (t, $J = 4.4$ Hz, 4H, $(CH_2)_2N$), 2.97 (s, 6H, $(NCH_3)_2$), 3.99 (t, $J = 7.6$ Hz, 2H, CH_2), 6.75–7.54 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.37, 41.80, 45.70, 54.20, 58.30, 112.05, 118.73, 126.08, 126.82, 128.00, 128.58, 129.04, 130.06, 131.13, 131.69, 134.75, 137.28, 148.63, 150.71; HRMS (ESI): calculated for $C_{29}H_{33}N_5$ $[M+H]^+$ 452.2809; found 452.2815.

*2.2.9. 1-(2-(2-(3-fluorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5i**)*

Yield 1.722 g (86%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 500 MHz) δ

2.04 (s, 4H, $(CH_2)_2NH$), 2.22 (t, $J = 7.0$ Hz, 2H, CH_2), 2.65 (t, $J = 4.0$ Hz, 4H, $(CH_2)_2N$), 4.02 (t, $J = 7.0$ Hz, 2H, CH_2), 7.09–7.48 (m, 14H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.07, 45.52, 54.06, 58.31, 115.74, 115.91, 116.28, 116.46, 124.84, 124.86, 126.39, 126.75, 128.05, 128.88, 129.15, 129.92, 130.23, 130.29, 131.03, 131.11, 133.35, 133.42, 134.26, 137.98, 146.54, 146.56; HRMS (ESI): calculated for $C_{27}H_{27}FN_4$ $[M+H]^+$ 427.2293; found 427.2298.

*2.2.10. 1-(2-(2-(3-bromo-4-fluorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5j**)*

Yield 2.108 g (89%). white solid, mp 110–112 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.08 (s, 4H, $(CH_2)_2NH$), 2.14 (d, $J = 6.0$ Hz, 2H, CH_2), 2.66 (s, 4H, $(CH_2)_2N$), 3.88 (d, $J = 6.0$ Hz, 2H, CH_2), 7.00–7.92 (m, 13H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.24, 43.44, 51.16, 57.56, 60.26, 109.24, 109.41, 116.63, 116.80, 126.51, 126.73, 128.08, 128.83, 128.87, 128.99, 129.22, 129.72, 129.78, 129.90, 130.76, 130.82, 134.02, 134.26, 138.06, 145.40, 158.25, 160.24, 170.95,; HRMS (ESI): calculated for $C_{27}H_{26}BrFN_4$ $[M+H]^+$ 505.1398; found 505.1403.

*2.2.11. 2-bromo-4-(4,5-diphenyl-1-(2-(piperazin-1-yl)ethyl)-1H-imidazol-2-yl)phenol (**5k**)*

Yield 2.147 g (91%). Yellow solid, mp 160–162 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 4H, $(CH_2)_2NH$), 2.17 (s, 2H, CH_2), 2.71 (s, 4H, $(CH_2)_2N$), 3.97 (s, 2H, CH_2), 6.89–7.77 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.69, 30.94, 43.40, 50.50, 111.23, 127.10, 128.23, 129.29, 130.76, 133.83, 137.50, 147.40; HRMS (ESI): calculated for $C_{27}H_{27}BrN_4O$ $[M+H]^+$ 503.1441; found 503.1447.

*2.2.12. 1-(2-(2-(3,4-dichlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5l**)*

Yield 1.946 g (87%). Yellow solid, mp 115–117 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.21 (s, 6H, $(CH_2)_2NH$) and CH_2), 2.82 (s, 4H, $(CH_2)_2N$), 3.97 (d, $J = 4.5$ Hz, 2H, CH_2), 7.10–7.86 (m, 13H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.31, 42.84, 49.98, 51.79, 57.34, 126.70, 126.87, 127.94, 128.17, 129.14, 129.32, 130.18, 130.63, 130.81, 130.84, 131.01, 132.94, 133.26, 133.81, 138.38, 145.44; HRMS (ESI): calculated for $C_{27}H_{26}Cl_2N_4$ $[M+H]^+$ 477.1608; found 477.1615.

*2.2.13. 1-(2-(2-(2,3-dichlorophenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5m**)*

Yield 1.852 g (90%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.21–2.27 (m, 6H, $(CH_2)_2NH$) and CH_2), 2.82 (s, 4H, $(CH_2)_2N$), 4.0 (t, $J = 6.8$ Hz, 2H, CH_2), 7.04–7.87 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.33, 43.13, 50.53, 50.93, 51.57, 57.48, 126.73, 126.87, 127.17, 128.19, 128.79, 129.15, 129.33, 130.16, 130.72, 130.81, 130.89, 131.03, 132.99, 133.32, 133.84, 138.45, 145.48; HRMS (ESI): calculated for $C_{27}H_{26}Cl_2N_4$ $[M+H]^+$ 477.1608; found 477.1615.

*2.2.14. 1-(2-(2-(3,5-dimethoxyphenyl)-4,5-diphenyl-1H-imidazol-1-yl)ethyl)piperazine (**5n**)*

Yield 1.826 g (83%). Yellow gummy solid (after column chromatography). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 4H, $(CH_2)_2NH$), 2.25 (t, $J = 7.6$ Hz, 2H, CH_2), 2.72 (s, 4H, $(CH_2)_2N$), 3.95 (d, $J = 8.4$ Hz, 6H, $(OCH_3)_2$), 4.02 (t, $J = 7.6$ Hz, 2H, CH_2), 6.93–7.52 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.76, 52.96, 55.99, 56.09, 110.98, 112.72, 121.62, 126.33, 126.83, 128.06, 128.77, 129.14, 129.34, 131.05, 149.08; HRMS (ESI): calculated for $C_{29}H_{32}N_4O_2$ $[M+H]^+$ 469.2599; found 469.2603.

*2.2.15. 1-(2-(4,5-diphenyl-2-(3,4,5-trimethoxyphenyl)-1H-imidazol-1-yl)ethyl) piperazine (**5o**)*

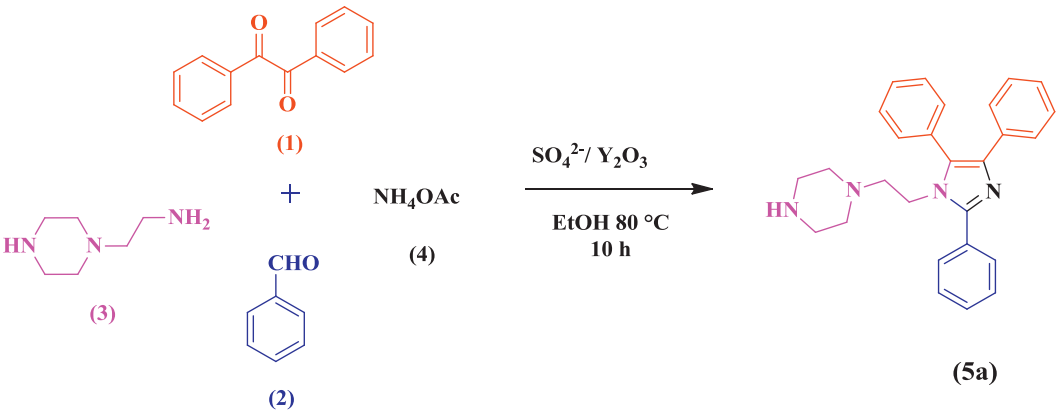
Yield 2.107 g (90%). Yellow solid, mp 62–64 °C. ^1H NMR ($CDCl_3$, 500 MHz) δ 2.11 (s, 4H, $(CH_2)_2NH$), 2.21 (d, $J = 5.0$ Hz 2H, CH_2), 2.72 (s, 4H, $(CH_2)_2N$), 3.81–3.86 (m, 9H, $(OCH_3)_3$), 3.98 (d, $J = 5.0$ Hz, 2H, CH_2), 6.82–7.46 (m, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.02, 43.06, 43.10, 50.40, 50.47, 56.33, 57.55, 60.34, 60.93, 106.59, 126.45, 126.47, 126.82, 128.06, 128.91, 129.20, 129.42, 130.88, 131.01, 134.08, 137.61, 138.87, 147.75, 153.37; HRMS (ESI): calculated for $C_{30}H_{34}N_4O_3$ $[M+H]^+$ 499.2704; found 499.2709.

3. Results and discussion

We began our investigation with the condensation reaction of benzil (1 mmol), aminoethylpiperazine (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (2 mmol) in ethanol at 80 °C in the absence of catalyst for 10 h, and no product formation was observed (Table 1, entry 1). Next, we performed the reaction in the presence of catalysts, such as *p*-toluenesulphonic acid (PTSA), ceric ammonium nitrate (CAN), acetic acid (AcOH) and L-proline.

The multicomponent condensation reaction to synthesize 1,2,4,5-tetrasubstituted imidazoles was performed at 80 °C using 5 mol% and 10 mol% PTSA in ethanol, and we obtained only 24% and 20% yields, respectively, in 10 h (Table 1, entries 2 and 3, respectively). Further investigation was performed using

Table 1
Optimization of the reaction condition for compound **5a**.[a]



Entry	Catalyst	Catalyst loading (mol%)	Temperature (°C)	Time (h)	Yield[b] (%)
1	No catalyst	–	80	10	–
2	PTSA	5	80	10	24
3	PTSA	10	80	10	20
4	CAN	5	80	10	47
5	CAN	10	80	10	43
6	AcOH	5	80	10	51
7	AcOH	10	80	10	50
8	l-proline	5	80	10	63
9	l-proline	10	80	10	60
10	SO_4^{2-}/Y_2O_3 (5 wt%)	–	80	10	93

[a] Reaction scale: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), **4** (2 mmol).
[b] Isolated yield.

5 mol% and 10 mol % CAN as a catalyst for the condensation reaction over 10 h, yielding only 47% and 43% of products, respectively (Table 1, entries 4 and 5, respectively).

The same condensation reaction was performed at 80 °C using 5 mol% and 10 mol% AcOH, yielded the corresponding substituted imidazole in 51% and 50% yields, respectively, after 10 h (Table 1, entries 6 and 7, respectively). The same condensation reaction was attempted using 5 mol% and 10 mol% of L-proline as a catalyst for 10 h, yielding only 63% and 60%, respectively (Table 1, entries 8 and 9, respectively). From these results, we concluded that the mentioned catalysts are moderately efficient for this condensation reaction.

To enhance the yield of the MCR, sulphated yttria (SO_4^{2-}/Y_2O_3) was used as a catalyst, and the results revealed that the reaction was complete within 10 h and yielded the corresponding imidazole in 93% yield (Table 1, entry 10). This result proved that when sulphated yttria is used as the catalyst, the product yield was nearly doubled compared with the previously used catalysts.

The scope and efficiency of the method was explored under optimized conditions. For this purpose, various aromatic aldehydes were condensed with benzil, aminoethylpiperazine and ammonium acetate under a conventional heating method, and the results are given in Table 3. An increased yield of products was observed with aromatic aldehydes containing electron-releasing groups compared with electron-withdrawing substituents in the aromatic ring.

Among the various catalysts used for the synthesis of 1,2,4,5-tetrasubstituted imidazoles, sulphated yttria showed better catalytic efficiency (Table 1). One of the major advantages of this protocol is the easy isolation and purification of the products achieved by column chromatography.

The structure and morphology of the catalyst are important parameters because they control the catalytic activity. The surface morphology of sulphated yttria was analyzed by SEM techniques. The SEM images at two different levels of magnification are shown in Fig. 1a and b. Generally, the SEM images showed agglomerated "flaky or platy" morphology (Fig. 1a and b). Excessive particle growth up to the micrometre size was also observed in both of the magnifications.

Transmission electron microscopic (TEM) analysis also reveals the catalytic activity of the prepared material.

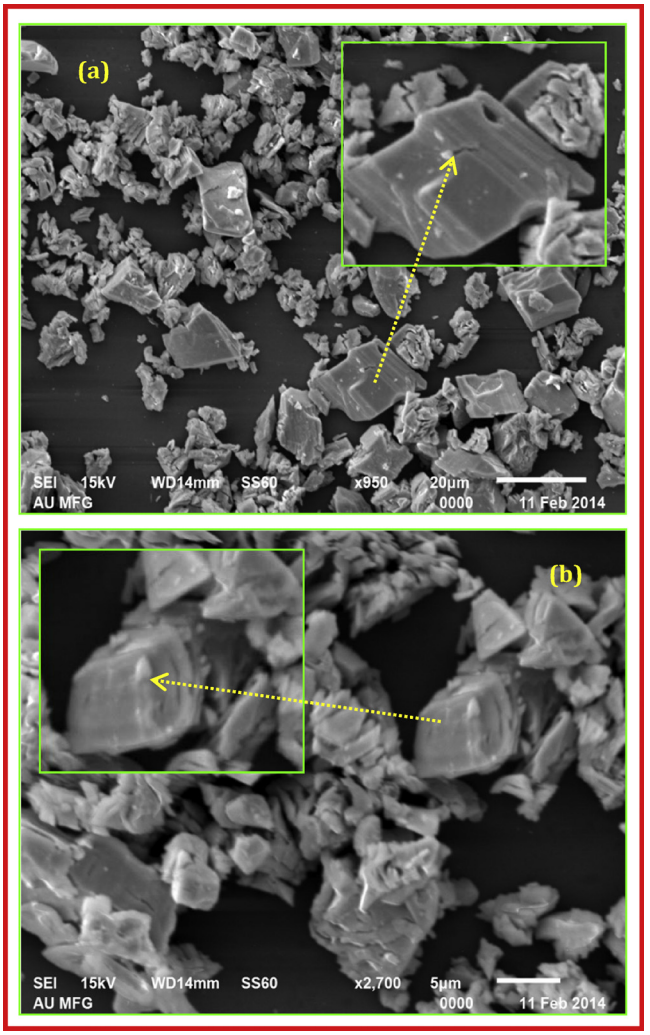


Fig. 1. SEM images of SO_4^{2-}/Y_2O_3.

TEM images of sulphated yttria at different magnifications in certain locations are shown in Fig. 2a–d. Due to accumulation or amassing, the sulphate and Y_2O_3 particles cannot be discerned in all of the magnifications. The sizes of the particles are over the range of 3–100 nm.

X-ray diffractograms of the commercially available Y_2O_3 and prepared SO_4^{2-}/Y_2O_3 are shown in Fig. 3. The 2θ values of the prepared SO_4^{2-}/Y_2O_3 at 20.35°, 29.02°, 33.62°, 35.76°, 39.83°, 43.34°, 48.38°, 53.10°, 57.49°, 60.38°, 71.09° and 78.57° correspond to the (2 2 1), (2 2 2), (4 0 0), (4 1 1), (3 3 2), (1 3 4), (4 4 0), (6 1 1), (6 2 2), (4 4 4), (8 0 0) and (6 2 2) diffraction planes of cubic Y_2O_3 [JCPDS No. 65-3178] [36] (Fig. 3a). All of the diffraction peaks of SO_4^{2-}/Y_2O_3 perfectly matched the cubic phase of Y_2O_3 (Fig. 3b). Therefore, the crystallographic phase of the prepared SO_4^{2-}/Y_2O_3 was confirmed as the cubic Y_2O_3 form in the prepared catalyst. The addition of sulphuric acid during the formation of SO_4^{2-}/Y_2O_3 does not change the cubic phase of Y_2O_3. The diffraction peaks of SO_4^{2-}/Y_2O_3 are sharp and strong, which indicates the highly crystalline nature of SO_4^{2-}/Y_2O_3. The Scherrer formula employed for the precise calculation of the crystallite sizes of SO_4^{2-}/Y_2O_3 is as follows:

$$\Phi = \frac{K\lambda}{\beta \cos\theta}$$

where Φ is the crystallite size, λ is the wavelength of the X-ray used, K is the shape factor, β is the full line width at the half-maximum height of the main intensity peak, and θ is the Bragg angle. From this equation, the average crystallite size of SO_4^{2-}/Y_2O_3 was found to be 4.8 nm.

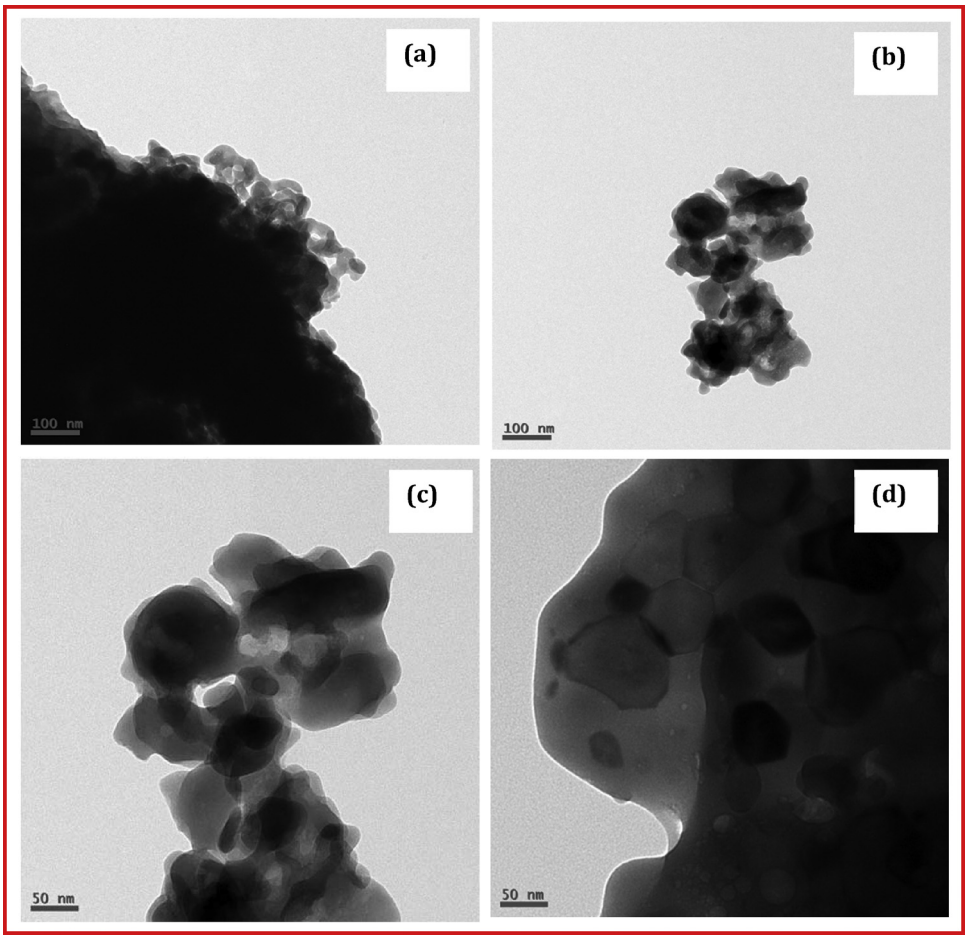


Fig. 2. TEM images of SO_4^{2-}/Y_2O_3 (a) 100 nm, (b) 100 nm, (c) 50 nm and (d) 50 nm.

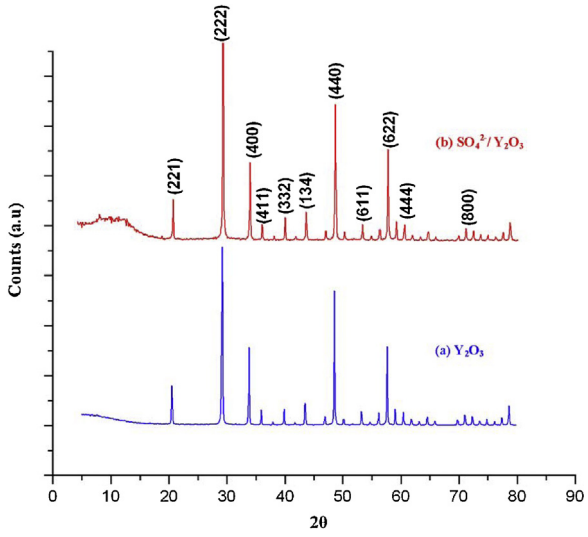


Fig. 3. PXRD images of SO_4^{2-}/Y_2O_3.

While evaluating the influence of different solvent systems for the SO_4^{2-}/Y_2O_3-catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles, the role of solvents, such as water, methanol, ethanol, *iso*-propanol, *tert*-butanol, acetonitrile, dichloromethane and chloroform, was examined. Among these solvents, ethanol was found to be the best medium to obtain optimum yields (Table 2). All of the synthesized products were characterized by IR, HR-MS, ^{1}H and ^{13}C NMR spectra. The numbering of compound **5a** is shown in Fig. 4.

In the ^{1}H NMR spectrum of compound **5a** (Fig. S5), in addition to the aromatic proton signal at 7.12–7.72 ppm with 15 protons, the NH proton signal of the piperazine ring appears as a broad singlet at 2.44 ppm. In the higher frequency region, one triplet appeared at 4.03 ppm that is assigned to the methylene protons of the C6 carbon. Methylene protons of the C7 carbon appeared at 2.23 ppm as a triplet. There are two signals at 2.64 and

Table 2
Synthesis of compound **5a** using SO_4^{2-}/Y_2O_3 in different solvents.

Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	Solvent free	80	10	40
2	Water	80	10	No reaction
3	Methanol	80	10	89
4	Chloroform	80	10	58
5	Acetonitrile	80	10	84
6	Dichloromethane	80	10	36
7	*tert*-butanol	80	10	54
8	*iso*-propanol	80	10	67
9	Ethanol	80	10	93

[b] Yields refer to isolated products.

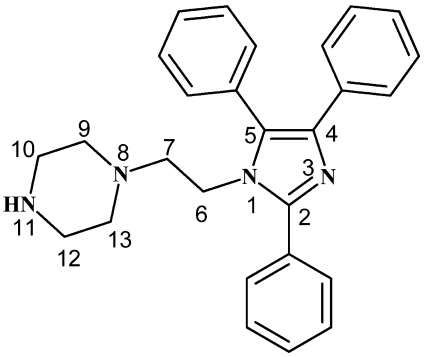


Fig. 4. Numbering of compound **5a**.

2.02 ppm with eight protons. Of these two signals, one deshielded signal appearing as a triplet at 2.64 ppm is assigned to two sets of methylene protons attached to N8, whereas the shielded signal appearing as a singlet at 2.02 ppm is due to the remaining two sets of methylene protons connected to N11.

In the ^{13}C NMR spectrum of compound **5a** (Fig. S5), the signal appearing at 147.96 ppm is unambiguously assigned to the imino carbon of the imidazole ring. The aromatic carbon signals appeared in the region of 137.75–126.31 ppm. The signals observed at 58.36 and 41.88 ppm are assigned to methylene carbons C7 and C6, respectively, and the signal observed at 54.07 ppm is due to methylene carbons C10 and C12 connected to N11. The methylene carbons C9 and C13 connected to N8 appeared at 45.62 ppm.

To determine the reusability of the catalyst, the reaction mass was cooled to room temperature, and the catalyst was filtered and washed with ice-cold methanol and then dried. The recovered catalyst was used in four successive cycles, furnishing the corresponding imidazole with 92%, 90%, 87% and 78% isolated yields as shown in Table 4. It was observed that the yields of tetrasubstituted imidazoles diminished slightly after every cycle.

Table 3
SO_4^{2-}/Y_2O_3 catalyzed synthesis of 1,2,4,5-tetrasubstituted imidazoles.[a]

Entry	R_1	R_2	R_3	R_4	Product	Time	Yield[b]
a	H	H	H	H	5a	10	93
b	H	H	CH_3	H	5b	10	93
c	H	H	Br	H	5c	10	92
d	H	H	Cl	H	5d	10	91
e	H	H	F	H	5e	10	91
f	H	H	NO_2	H	5f	10	87
g	H	H	OCH_3	H	5g	10	92
h	H	H	N-$(CH_3)_2$	H	5h	10	91
I	H	F	H	H	5i	10	86
j	H	Br	F	H	5j	10	89
k	H	Br	OH	H	5k	10	91
l	H	Cl	Cl	H	5l	10	87
m	Cl	Cl	H	H	5m	10	90
n	H	OCH_3	H	OCH_3	5n	10	83
o	H	OCH_3	OCH_3	OCH_3	5o	10	90

[a] Benzil:benzaldehyde:aminoethylpiperazine:NH_4OAc (1 mmol:1 mmol:1 mmol:2 mmol).
[b] Isolated yield.

Table 4
Recyclability of SO_4^{2-}/Y_2O_3 catalyst.

Cycles	Yield (%)	Catalyst recovered (%)
Native	93	96
1	92	94
2	90	92
3	87	91
4	78	90

4. Conclusions

We developed a simple and efficient one-pot methodology for the synthesis of tetrasubstituted imidazoles catalyzed by SO_4^{2-}/Y_2O_3. The advantages of this method are the high conversion, simple operation, cost efficiency, easy work up and recyclability of the catalyst.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:10.1016/j.jtusci.2014.12.001.

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