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COVALENTLY BONDED SULFONIC ACID MAGNETIC GRAPHENE OXIDE PROMOTED SYNTHESIS OF 1,2,4,5-TETRASUBSTITUTED IMIDAZOLES

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Abstract
Covalently bonded sulfonic acid magnetic graphene oxide (Fe_3O_4@GO-Pr-SO_3H), has been used as a catalyst for the synthesis of 1,2,4,5-tetrasubstituted imidazoles by the one-pot, four-component thermal reaction of benzil with aromatic aldehydes, primary amines, and ammonium acetate under solvent-free conditions. The catalyst was prepared according to a previously published literature procedure using inexpensive and readily available starting materials, and subsequently characterized by FT-IR, X-ray diffraction spectroscopy, and pH analysis. The results showed that Fe_3O_4@GO-Pr-SO_3H exhibited high catalytic activity towards the synthesis of 1,2,4,5-tetrasubstituted imidazoles, with the desired products being formed in good to high yields. Furthermore, the catalyst was recyclable and could be reused at least three times without any discernible loss in its catalytic activity. Overall, this new catalytic method for the synthesis of 1,2,4,5-tetrasubstituted imidazoles provides rapid access to the desired compounds following a simple work-up procedure, and avoids the use of harmful organic solvents. This method therefore represents a significant improvement over the methods currently available for the synthesis of tetrasubstituted imidazoles.

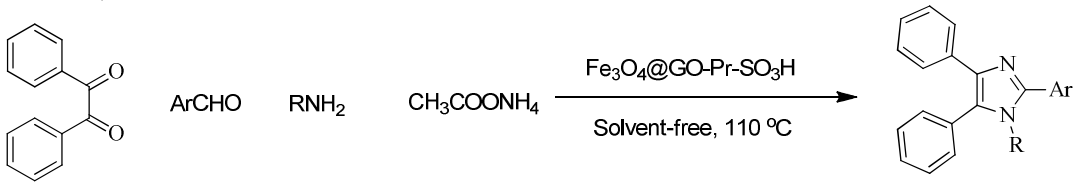
Keywords: 1,2,4,5-tetrasubstituted imidazoles, fast synthesis, Fe_3O_4@GO-Pr-SO_3H, reusability.

Introduction

The imidazole ring system is an important nitrogen containing substructure that plays an important role in numerous biochemical processes, and this system can be found in a large number of natural products and pharmacologically active compounds[i]. Multisubstituted imidazoles are biologically active, and several compounds containing systems of this type have been reported to possess interesting biological properties, including antibacterial[ii], analgesic[iii] and glucagon receptor antagonism[iv] activity. Several substituted imidazoles have also been reported as inhibitors of p38 MAP kinase[v] and B-Raf kinase[vi]. Furthermore, recent advances in green chemistry and organometallic catalysis have extended the application of imidazoles as ionic liquids[vii] and N-heterocyclic carbenes[viii]. Despite the availability of a wide variety of synthetic routes for the construction of imidazoles, very few methods exist for the

synthesis of 1,2,4,5- tetrasubstituted imidazoles. These compounds are generally synthesized via the four-component reaction of 1,2-diketones or α- hydroxyketones with aldehydes, primary amines, and ammonium acetate in the presence of a catalyst such as $K_5CoW_{12}O_{40}.3H_2O$[ix], $NH_4H_2PO_4/Al_2O_3$[x], Brönsted acidic ionic liquid[xi], BF_3-SiO_2[xii], carbon-based solid acid[xiii], $NaHSO_4/SiO_2$[xiv], $H_6P_2W_{18}O_{62}.24H_2O/SiO_2$[xv], $FeCl_3$/montmorillonite K10 under microwave irradiation[xvi], and p-dodecylbenzenesulfonic acid[xvii]. 1,2,4,5-Tetrasubstituted imidazoles can also be accessed by the hetero-Cope rearrangement or the N-alkylation of trisubstituted imidazoles[xviii]. However, some of these synthetic methods have been limited in terms of their application because of poor yields or their requirement for expensive catalysts, long reaction time, and tedious isolation procedures. With this in mind, there is therefore an urgent need for the development of a new environmentally friendly method using an inexpensive catalyst with high catalytic activity for the synthesis of 1,2,4,5-tetrasubstituted imidazoles.

The current presentation is the development of our earlier studies of reusable catalysts for the synthesis of organic compounds[xix-xxxi], and as a result of global interest in the ongoing research towards the development of environmentally friendly methods for the synthesis of organic compounds especially compounds that are frequently used in current pharmaceutical industry, we report herein facile and efficient green synthesis of 1,2,4,5-tetrasubstituted imidazoles with short reaction time by the one-pot, four-component thermal reaction of benzil with aromatic aldehydes, primary amines, and ammonium acetate under solvent-free conditions using Fe_3O_4@GO-Pr-SO_3H, as heterogeneous catalysts with high catalytic activity (Scheme 1).



Scheme 1. Synthesis of 1,2,4,5-tetrasubstituted imidazoles in the presence of Fe_3O_4@GO-Pr-SO_3H under solvent-free condition.

Experimental section

Chemicals and apparatus

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature[xxxii]. Melting points were recorded using a Stuart SMP3 melting point apparatus. The FT-IR spectra of the products were obtained with KBr disks, using a Tensor 27 Bruker spectrophotometer. The ^{1}H NMR (400 MHz) spectra were recorded using Bruker spectrometers.

General experimental procedure

A mixture of benzil **1** (1 mmol), aromatic aldehyde **2** (1 mmol), primary amine **3** (1 mmol), ammonium acetate **4** (1 mmol), and catalyst (0.08 g) was heated in the oil bath at 110 °C for 14–21 min. Upon completion of the reaction, as determined by thin-layer chromatography (TLC), the mixture was diluted with hot ethanol and then filtered to remove the catalyst. The catalyst was then washed with a small portion of hot ethanol (10 ml), and the combined filtrates were concentrated in volume (by half) and allowed to stand at room temperature until precipitation occurred. The resulting precipitate was collected by filtration, and recrystallized from ethanol to give compounds 5a–5i in high yields (Scheme 1).

^{1}H NMR & FT-IR data:

1,2,4,5-Tetraphenyl-1H-imidazole (5a): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 6.5 Hz, 2H, arom-H), 7.15-7.20 (m, 2H, arom-H), 7.22-7.37 (m, 12H, arom-H), 7.45-7.53 (m, 2H, arom-H), 7.65 (d, *J* = 7.2 Hz, 2H, arom-H); IR (KBr, cm^{-1}): υ 3050, 1598, 1496, 1479, 1441, 1394, 1073, 1025, 763, 694.

2-(4-Chlorophenyl)-1,4,5-triphenyl-1H-imidazole (5b): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05-7.10 (m, 2H, arom-H), 7.13-7.18 (m, 2H, arom-H), 7.23-7.37 (m, 11H, arom-H), 7.42 (d, *J* = 8.8 Hz, 2H, arom-H), 7.61-7.66 (m, 2H, arom-H); IR (KBr, cm^{-1}): υ 3057, 1597, 1496, 1478, 1446, 1410, 1084, 1027, 836, 766, 696.

2-(4-Nitrophenyl)-1,4,5-triphenyl-1H-imidazole (5c): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 6.8 Hz, 2H, arom-H), 7.17 (dd, *J* = 7.8, 1.2 Hz, 2H, arom-H), 7.23-7.44 (m, 9H, arom-H), 7.60-7.68 (m, 4H, arom-H), 8.13 (d, *J* = 9.2 Hz, 2H, arom-H); IR (KBr, cm^{-1}): υ 3059, 1598, 1522, 1498, 1340, 1110, 854, 767, 697.

2-(2-Thienyl)-1,4,5-triphenyl-1H-imidazole (5d): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (t, *J* = 3.6 Hz, 1H, arom-H in thienyl), 7.15-7.34 (m, 12H, arom-H), 7.38-7.48 (m, 3H, arom-H), 7.64 (d, *J* = 7.2 Hz, 2H, arom-H); IR (KBr, cm^{-1}): υ 3051, 1595, 1496, 1478, 1444, 1419, 1072, 1024, 850, 767, 694.

1-Benzyl-2-(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (5e): ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (s, 2H, CH_2), 6.80-6.90 (m, 2H, arom-H), 7.15-7.50 (m, 13H, arom-H), 7.62 (t, *J* = 8.4 Hz, 4H, arom-H); IR (KBr, cm^{-1}): υ 3060, 2920, 1600, 1499, 1479, 1448, 1356, 1073, 1089, 835, 692.

1-Benzyl-2-(4-methylphenyl)-4,5-diphenyl-1H-imidazole (5f): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 5.14 (s, 2H, CH_2), 6.80-6.90 (m, 2H, arom-H), 7.15-7.45 (m, 13H, arom-H), 7.55-7.65 (m, 4H, arom-H); IR (KBr, cm^{-1}): υ 3026, 2926, 1600, 1483, 1451, 1385, 1394, 1073, 1026, 827, 767, 702.

1,2-Bis(4-chlorophenyl)-4,5-diphenyl-1H-imidazole (5g): ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (d, *J* = 8.4 Hz, 2H, arom-H), 7.15 (d, *J* = 6.8 Hz, 2H, arom-H), 7.20-7.35 (m, 10H, arom-H), 7.39 (d, *J* = 8.4 Hz, 2H, arom-H), 7.60 (d, *J* = 7.2 Hz, 2H, arom-H); IR (KBr, cm^{-1}): υ 3057, 1603, 1489, 1443, 1416, 1091, 1017, 840, 722, 696.

1,2-Bis(4-methylphenyl)-4,5-diphenyl-1H-imidazole (5h): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 6H, $2CH_3$), 6.95 (d, *J* = 7.6 Hz, 2H, arom-H), 7.05-7.45 (m, 14H, arom-H), 7.62 (d, *J* = 7.6 Hz, 2H, arom-H); IR (KBr, cm^{-1}): υ 3023, 2941, 1600, 1515, 1480, 1444, 1072, 1026, 821, 776, 700.

2-(4-Bromophenyl)-1-methyl-4,5-diphenyl-1H-imidazole (5i): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.52 (s, 3H, NCH_3), 7.15-7.30 (m, 3H, arom-H), 7.40-7.60 (m, 7H, arom-H), 7.65 (s, 4H, arom-H); IR (KBr, cm^{-1}): υ 3048, 1602, 1500, 1479, 1447, 1400, 1376, 1073, 833, 695.

Results and discussion

Characterization of the catalyst

To begin our study, the Fe_3O_4@GO-Pr-SO_3H catalyst was prepared according to the literature procedure[xxxii]. The Fe_3O_4@GO-Pr-SO_3H was characterized by FT-IR, X-ray diffraction (XRD), Raman spectrum, and pH analysis.

The FT-IR spectrums of Fe_3O_4, GO, Fe_3O_4@GO, and Fe_3O_4@GO-Pr-SO_3H are shown in Figure 1, curves a-d, respectively. Spectrums c and d shows peaks at 3000-3100 that can be attributed to the presence of aromatic C-H bonds in the both of Fe_3O_4@GO and Fe_3O_4@GO-Pr-SO_3H. Also, the broad band at 3200-3500 cm^{-1} in the both materials can be assigned to the presence of hydroxyl groups of Fe_3O_4 and GO. Because of the presence of sulfonic acid groups, this band has significant intense in the Fe_3O_4@GO-Pr-SO_3H curve compared to the Fe_3O_4@GO that can be considered as evidence for the sulfonation of the surface through

mercapto-propyl-trimethoxysilane (MPTMS) as well the peaks observed at 1056, 1421 and 1636 cm^{-1} can be related to the functionalization of Fe_3O_4@GO with sulfonic acid groups linked by MPTMS[xxxiii] [33]. Aliphatic peaks of Fe_3O_4@GO-Pr-SO_3H can be seen at 2900-300 cm^{-1}. The two peaks at 461 and 589 cm^{-1} can be attributed to Fe-O bonds of Fe_3O_4[xxxiv] [34].
The XRD patterns of the Graphene oxide (GO), Fe_3O_4, and Fe_3O_4@GO-Pr-SO_3H are presented in Figure 2, patterns a-c, respectively. According to the XRD p atterns of the GO and Fe_3O_4, it can be seen that the XRD diagram of the Fe_3O_4@GO-Pr-SO_3H shows peak intensities equal to (220), (311), (400), (422), (511), and (440) corresponds to Fe_3O_4 and also broad peak related to the GO that can be attributed to the presence of Fe_3O_4 nanoparticles between GO sheets. Broadening of related GO sheets can be explained by accepting the claim that GO Nano-sheets are pillared by Fe_3O_4 nanoparticles.
The density of the -SO_3H groups was measured using NaOH (0.08 N) as titrant by acid-base potentiometric titration. The amount of PO_3H_2 in the catalyst was 3.23 mmol/g.

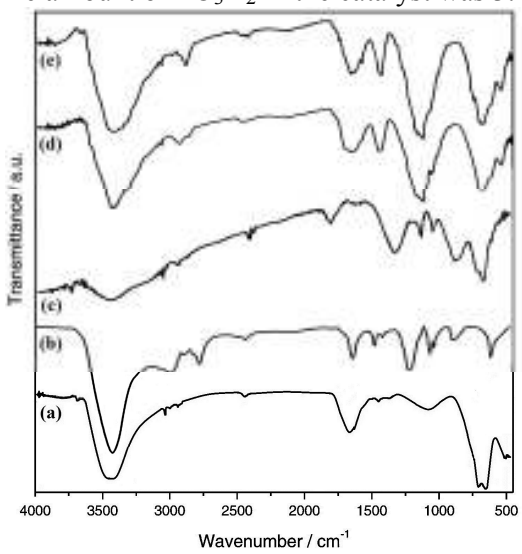


Figure 1. FT-IR spectra of (**a**) Fe_3O_4, (**b**) GO, (**c**) Fe_3O_4@GO, (**d**) Fe_3O_4@GO-Pr-SO_3H (fresh), (**e**) Fe_3O_4@GO-Pr-SO_3H (fourth run).

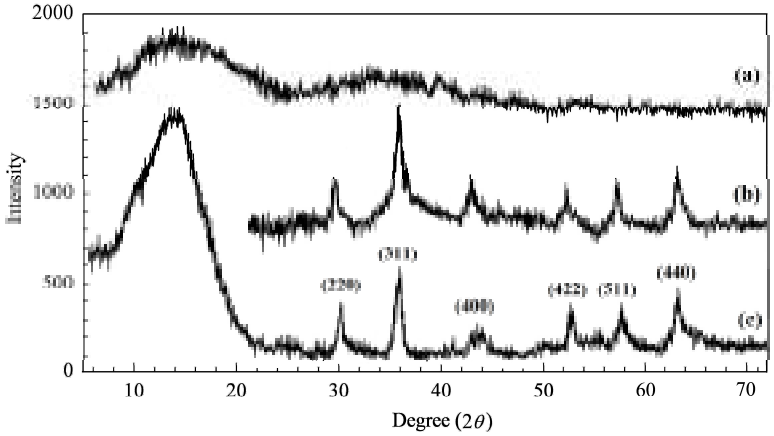


Figure 2. XRD patterns of (**a**) GO, (**b**) Fe_3O_4, (**c**) Fe_3O_4@GO-Pr-SO_3H.

Evaluation of catalytic activity of Fe_3O_4@GO-Pr-SO_3H towards the reaction
The catalytic activity of Fe_3O_4@GO-Pr-SO_3H was evaluated in the synthesis of 1,2,4,5-tetrasubstituted imidazoles. The synthesis of compound 5b by the four-component reaction of benzil (1 mmol) with 4-chlorobenzaldehyde (1 mmol), aniline (1 mmol), and

ammonium acetate (1 mmol) was initially selected as a model reaction to optimize the reaction conditions. Several reaction parameters were evaluated during this optimization stage, including the loading of the Fe_3O_4@GO-Pr-SO_3H catalyst, the temperature of the reaction, and the reaction solvent (Table 1). It is clear from the results shown in Table 1 that the shortest reaction time and best yield were achieved under solvent-free conditions (Table 1, entry 8). These results also revealed that the loading of the catalyst and the reaction temperature had a significant impact on the yield of compound 5b when the reaction was conducted under solvent-free conditions. For example, the reaction gave a very low yield of the product when it was conducted in the absence of the catalyst at 110 °C (Table 1, entry 1), and gave no product when it was conducted in the presence of the catalyst at room temperature (Table 1, entry 2). These results therefore highlighted the importance of the catalyst loading and reaction temperature on the success of the reaction. Increases in the amount of the catalyst and reaction temperature up to 0.08 g and 110 °C, respectively, led to an increase in the yield of the product 5b, although further increases in these parameters did not lead to further improvements in the product yield or reaction time (Table 1, entries 9-11). With the optimized conditions in hand, we proceeded to explore the scope of Fe_3O_4@GO-Pr-SO_3H catalyzed reacting of **1** and **4** with a range of other aromatic aldehydes **2** and primary amines **3** (Table 2). As shown in Table 2, the Fe_3O_4@GO-Pr-SO_3H catalyst efficiently catalyzed the condensation reactions of **1**, **2**, **3**, and **4** to give the desired products **5a**–**5i** in high yields over relatively short reaction time. It is noteworthy that the products could be readily separated from the catalyst, making this method especially useful for the synthesis of a wide range of 1,2,4,5- tetrasubstituted imidazoles.

We also used the model reaction under optimized reaction conditions to evaluate the reusability of the Fe_3O_4@GO-Pr-SO_3H catalyst. After completion of the reaction, the catalyst was recovered as described in the experimental section. The separated catalyst was washed with hot ethanol and subsequently dried at 50 °C under vacuum for 1 h before being reused in a similar reaction. The catalyst could be used at least four times without significant reduction in its activity (91, 90, 90, 89 % yields in first to fourth use, respectively) which clearly demonstrates the practical reusability of this catalyst.

Table 1: Synthesis of compound **5b** in the presence of Fe_3O_4@GO-Pr-SO_3H nanoparticles as catalysts under various reaction conditionsa

Entry	Catalyst (g)	Solvent	*T*/°C	Time (min)	Isolated yield (%)
1	----	----	110	100	37
2	0.08	----	r.t.	100	---
3	0.04	----	110	60	58
4	0.04	----	120	60	57
5	0.06	----	110	37	64
6	0.06	----	120	40	66
7	0.08	----	90	30	86
8	**0.08**	**----**	**110**	**25**	**91**
9	0.08	----	120	25	92
10	0.1	----	110	25	92
11	0.1	----	120	25	90
12	0.15	----	110	25	91
13	0.08	H_2O	Reflux	60	82
14	0.08	EtOH	Reflux	60	79
15	0.08	MeOH	Reflux	60	71
16	0.08	CH_3CN	Reflux	60	65
17	0.08	CH_2Cl_2	Reflux	60	43

Table 2: Synthesis of 1,2,4,5-tetrasubstituted imidazoles **5a–5i** using the Fe_3O_4@GO-Pr-SO_3H catalyst.

Entry	Ar	R	Product	Time/ min	Isolated yield(%)	Melting point (°C)	
						Found	Reported
1	C_6H_5	C_6H_5	**5a**	21	89	214–216	213–216[xxx]
2	4-ClC_6H_4	C_6H_5	**5b**	17	91	152–154	153–155[xxx]
3	4-$O_2NC_6H_4$	C_6H_5	**5c**	14	90	190–191	191–193[xxx]
4	2-thienyl	C_6H_5	**5d**	16	93	144–246	242–244[xxx]
5	4-ClC_6H_4	$C_6H_5CH_2$	**5e**	20	94	161–163	160–162[xxx]
6	4-MeC_6H_4	$C_6H_5CH_2$	**5f**	15	92	169–171	168–170[xxx]
7	4-ClC_6H_4	4-ClC_6H_4	**5g**	14	95	190–192	189–192[xxx]
8	4-MeC_6H_4	4-MeC_6H_4	**5h**	16	89	192–194	192–194[xxx]
9	4-BrC_6H_4	Me	**5i**	17	93	199–201	200–202[xxx]

Mechanistically, it is possible that the catalyst could acts as Brönsted acid related to the –SO_3H groups and therefore promote the necessary reactions. The catalyst would play a significant role in increasing the electrophilic character of the electrophiles in the reaction.

Conclusions

In this paper we developed the synthesis of 1,2,4,5-tetrasubstituted imidazoles in the presence of Fe_3O_4@GO-Pr-SO_3H as a highly effective heterogeneous catalyst by the one-pot, four-component thermal reaction of benzil with aromatic aldehydes, primary amines, and ammonium acetate under solvent-free conditions. This method provided these products in high yields over short reaction time, following a facile work-up process. The catalyst is inexpensive and easily obtained, stable and storable. Also, easy magnetic separation makes this catalyst attractive in view of green chemistry and catalysis science.

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