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Nanomagnetically Modified Sulfuric Acid (γ-Fe_2O_3@SiO_2-OSO_3H): An Efficient, Fast, and Reusable Catalyst for Greener Paal–Knorr Pyrrole Synthesis

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Abstract Paal–Knorr pyrrole synthesis was performed in the presence of superparamagnetic nanoparticles of modified sulfuric acid (γ-Fe_2O_3@SiO_2-OSO_3H) as an efficient and magnetically separable catalyst. Recovery of the catalyst was simple using a magnet, allowing its reuse without significant loss of its catalytic activity (over five cycles).

Keywords Superparamagnetic nanoparticles · Paal–Knorr pyrrole synthesis · Sulfuric acid · Magnetically separable catalyst · Reusability

1 Introduction

An important class of heterocyclic compounds are pyrroles. They have different biological activity and show broad applications in the field of medicine and drug [1, 2]. Moreover, the pyrrole moiety is found in many naturally occurring compounds [3]. Although in recent years a variety of methods have been developed for the synthesis of pyrroles, the Paal–Knorr synthesis remains the most useful preparative method. To date, numerous homogeneous and heterogeneous catalytic system have been used to promote the reaction of 2,5-hexanedione with amines such as $UO_2(NO_3)\cdot 6H_2O$ [4], Nano sulfated zirconia [5], [HMIM]HSO_4 ionic liquid [6], p-TSA [7], $SbCl_3/SiO_2$ [8], K10 [9], montmorillonite KSF [10], $Sc(OTf)_3$ [11], Silica sulfuric acid [12], $Bi(NO_3)_3\cdot H_2O$ [13], Vitamin B1 [14], $RuCl_3$ [15], PS/$GaCl_3$ [16], $SnCl_2\cdot H_2O$ [17], xanthan sulfuric acid [18], zirconium phosphonate [19], and $BiCl_3/SiO_2$ [20]. Ultrasonic [21] or microwave irradiation [22] method for this purpose has been reported too. Recently deep eutectic solvents were used for the Paal–Knorr reactions [23]. Apart from the high temperatures, prolonged reaction times and tedious work-up, difficulty in separating the catalyst from the reaction mixture as well as recycling of it is the main disadvantage of almost all previously reported methods. Thus, green, efficient, and easily recyclable catalytic systems are still required for this reaction.

With the appearance of magnetic nanoparticles and their entrance into the catalyst field, the difficulty in separation of catalyst from the reaction mixture was greatly improved. Therefore the design of catalytic systems based on magnetic nanoparticles became a hot topic in the field of organic synthesis [24]. The main feature of magnetic nanoparticles is that by applying an external magnetic field, they can be dispersed or aggregated which allows for the facile separation and recycling of immobilized catalysts on the nano-sized supports.

We have reported the preparation of γ-Fe_2O_3@SiO_2-OSO_3H and its application as a highly efficient and magnetically separable catalyst for the synthesis of aminoimidazopyridine skeletons [25]. In continuation of our interest in using magnetic nanoparticles as a catalyst support [26–29], herein we report a green and environmentally benign catalytic system based on a magnetic support for the preparation of pyrrole derivatives via condensation reaction of 2,5-hexanedione with amines.

2 Results and Discussion:

As shown in Scheme 1, the synthesis of 2,5-dimethyl-*N*-phenyl pyrrole was chosen as our model reaction to optimize the reaction conditions.

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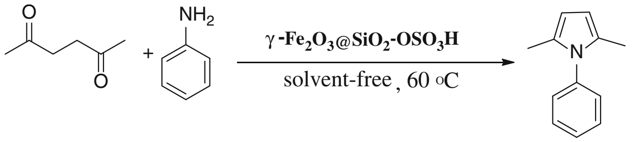


Scheme 1 Synthesis of 2,5-dimethyl-*N*-phenyl pyrrole

The first reaction was performed in CH_2Cl_2 as solvent, in the presence of 20 mg of catalyst, and at room temperature. After 10 h of reaction time, only 40 % of product was found (Table 1, entry 1). To improve the efficiency of the reaction, first, the solvent effect was investigated. To this end, some organic solvents as well as solvent-free conditions was examined (Table 1, entries 2–5) and as can be seen in this table, in solvent-free condition the reaction proceeded more efficiently than with other solvents. By increasing the amount of the catalyst to 30 mg, no difference was made in the reaction yield. On the contrary, the reduction in catalyst loading to 10 mg gave rise to a significant drop of yield (Table 1, entries 6 and 7). Finally, the role of the temperature was probed. It was observed that increasing the temperature to 60 °C enhances the yield by a significant amount. By elevating the temperature up to 80 °C, the yield remained unchanged (Table 1, entries 8 and 9). After passing 24 h of reaction time in the absence of catalyst, a 90 % efficiency was obtained which it indicates that the presence of catalyst is essential for increasing the reaction rate (Table 1, entry 10).

Therefore, the optimum conditions for this reaction were as follows: 20 mg of catalyst at 60 °C under solvent-free condition. Having established optimum conditions, a series of pyrroles was synthesized by reacting various amines with 2,5-hexanedione in the presence of γ-Fe_2O_3@SiO_2-OSO_3H in order to showcase the broad scope and generality of this method.

Table 1 Results of screening the conditions

Entry	Solvent	Catalyst (mg)	Temp. (°C)	Time (h)	Yield (%)[a]
1	CH_2Cl_2	20	r.t	10	40
2	CH_3OH	20	r.t	10	55
3	*n*-Hexane	20	r.t	10	20
4	Toluene	20	r.t	10	25
5	Solvent-free	20	r.t	5	70
6	Solvent-free	30	r.t	5	70
7	Solvent-free	10	r.t	5	50
8	Solvent-free	20	60	3	90
9	Solvent-free	20	80	3	90
10	Solvent-free	–	60	24	90

Reaction conditions: 2,5-hexanedione (0.5 mmol), aniline (1 mmol)

[a] Isolated yield

Generally speaking, different derivatives of aniline and benzyl amine were well coupled with 2,5-hexanedione to give the corresponding pyrrole. Among these derivatives, 4-methoxy benzyl amine was the fastest response (Table 2, entry 8). In contrast, for chlorinated aniline derivatives the reaction time was longest (Table 2, entries 9 and 10). The reaction conditions were also used to di-amino substrates, in giving bipyrrole compounds in good yields (Table 2, entries 11–14 and 16).

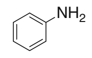
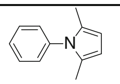
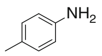
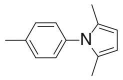
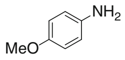
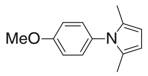
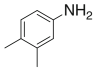
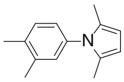
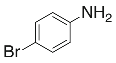
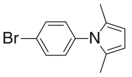
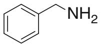
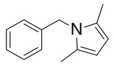
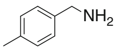
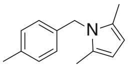
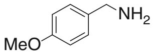
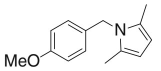
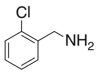
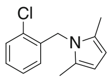
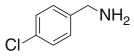
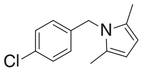
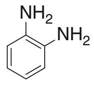
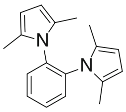
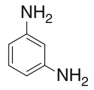
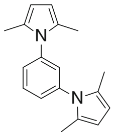
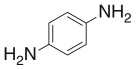
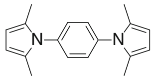
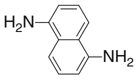
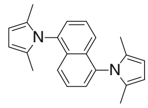
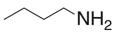
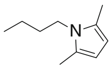
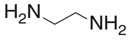
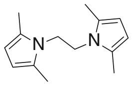
The reusability of the catalyst was also tested in the reaction between 2,5-hexanedione and aniline. When the stirring was stopped, CH_2Cl_2 was add to the reaction. Then, the catalyst was adsorbed onto the surface of the stir bar. The nanoparticles were then washed with H_2O and Et_2O respectively, air-dried and used directly for the next reaction without further purification. The γ-Fe_2O_3@SiO_2-OSO_3H nanoparticles could be recovered and reused five times without any significant loss of catalytic activity (Fig. 1).

3 Experimental

3.1 Catalyst Preparation

The maghemite (γ-Fe_2O_3) nanoparticle was synthesized by a chemical co-precipitation technique of ferric and ferrous ions in alkali solution [25c]. $FeCl_2 \cdot 4H_2O$ (1.99 g) and anhydrous $FeCl_3$ (3.25 g) were dissolved in water (20 mL) separately, followed by the two iron salt solutions being mixed under vigorous stirring (800 rpm). A NH_4OH solution (0.6 M, 200 mL) was then added to the stirring mixture at room temperature, immediately followed by the addition of a concentrated NH_4OH solution (25 %, w/w, 30 mL) to maintain the reaction pH between 11 and 12. The resulting black dispersion was continuously stirred for 1 h at room temperature and then heated to reflux for 1 h to yield a brown dispersion. The magnetic nanoparticles were then purified by a repeated centrifugation (3,000–6,000 rpm, 20 min), decantation, and redispersion cycle three times, until a stable brown magnetic dispersion (pH 9.4) was obtained. Coating of a layer of silica on the surface of the γ-Fe_2O_3 nanoparticles was achieved by premixing (ultrasonic) a dispersion of the purified nanoparticles (8.5 %, w/w, 20 mL) obtained previously with methanol (80 mL) for 1 h at 40 °C. Concentrated ammonia solution as added, and the resulting mixture was stirred at 40 °C for 30 min. Subsequently, tetraethyl orthosilicate (TEOS, 1.0 mL) was charged to the reaction vessel, and the mixture was continuously stirred at 40 °C for 24 h. The silica-coated nanoparticles were collected by a permanent magnet, followed by washing three times with EtOH, diethyl ether and drying at 100 °C in vacuum for 24 h.

Table 2 Preparation of various pyrroles in the presence of γ-Fe_2O_3@SiO_2-OSO_3H

Entry	Amine	Product	Time(h)	Yield(%)[a]
1			3	90
2			3	88
3			3	89
4			3	90
5			3	78
6			5	80
7			0.5	88
8			15 min	80
9			12	78
10			12	78
11			3	75
12			3	70
13			3	72
14			4	60
15			2	90
16			2	90

Reaction conditions: 2, 5-hexanedione (0.5 mmol), amine (1 mmol), catalyst (20 mg), 60 °C

[a] Isolated yield

Chlorosulfonic acid (1 g) was added drop-wise at room temperature (over 15 min) to a suspension of 1 g γ-Fe_2O_3@SiO_2 in Et_2O (50 mL) while dispersed by sonication. The mixture was stirred for 5 h and then concentrated and the residue was washed three times with Et_2O, air-dried to obtain γ-Fe_2O_3@SiO_2-OSO_3H. The loading of impregnated acid measured by back titration (0.60 mmol g^{-1}).

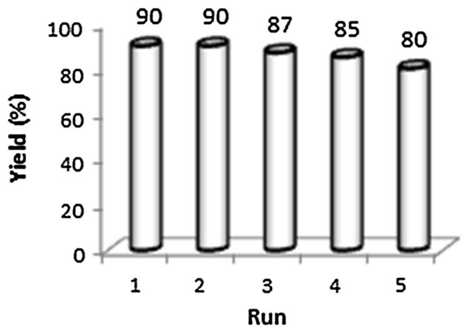


Fig. 1 Reusability of the γ-Fe_2O_3@SiO_2-OSO_3H catalyst in the synthesis of 2,5-dimethyl-*N*-phenyl pyrrole. Reaction time 3 h

3.2 General Procedure for the Synthesis of Pyrroles

To a solution of amine (1 mmol) and 2,5-hexanedione (0.5 mmol) at 60 °C, γ-Fe_2O_3@SiO_2-OSO_3H (20 mg) was added. The mixture was allowed to stirring at this temperature for a period time specified in Table 2. The reaction was monitored by TLC (8:1 hexane/EtOAc). After completion of the reaction, 10 mL CH_2Cl_2 was added and catalyst was removed by using an external magnet. Evaporation of the solvent under reduced pressure gave the products. Further purification was achieved by thin layer chromatography using n-hexane/EtOAc as the solvent system to afford the pyrroles. For all known pyrroles, the spectral data matched that reported in the literature, while for the new pyrroles, the spectral data was consistent with the anticipated product.

3.2.1 Spectral Data for New Compounds:

3.2.1.1 1-(3,4-Dimethylphenyl)-2,5-dimethyl-1H-pyrrole (Table 2, entry 4) Isolated yield = 90 %; yellow oil; IR cm^{-1}: 2924, 2859, 1614, 1506, 1452, 1411, 1340, 1020; ^{1}H NMR (250 MHz,$CDCl_3$) δ 2.01(s,6H, $2CH_3$), 2.28 (s, 3H, CH_3), 2.30 (s, 3H, CH_3) 5.87 (s, 2H, pyrrolics), 6.91 (s, 1H, CH of Ar), 6.91–6.96 (m, 2H, 2CH of Ar), 7.18 (d, 1H, $^3J = 7.7$ Hz, CH of Ar); MS (EI, 70 eV): *m/z* (%) = 199 (M^+, 100), 143 (7), 83.(34).

3.2.1.2 2,5-Dimethyl-1-(4-methylbenzyl)-H-pyrrole (Table 2, entry 7) Isolated yield = 88 %; yellow oil; IR cm^{-1}: 2923, 2855, 1653, 1580, 1456, 1383, 1022; ^{1}H NMR (250 MHz,$CDCl_3$) δ 2.16 (s, 6H, $2CH_3$), 2.34 (s, 3H, CH_3), 4.99 (s, 2H, CH_2), 5.88 (s, 2H, pyrrolics), 6.80 (d, 2H, $^3J = 7.2$ Hz, 2CH of Ar), 7.12 (d, 2H, $^3J = 7.5$ Hz, 2CH of Ar); MS (EI, 70 eV): *m/z* (%) = 199 (M^+, 100), 108 (36).

3.2.1.3 1-(2-Chlorophenyl)-2,5-dimethyl-1H-pyrrole (Table 2, entry 9) Isolated yield = 78 %; yellow oil; IR cm^{-1}: 2925, 2855, 1650, 1572, 1518, 1407, 1343, 1038; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.11(s, 6H, $2CH_3$), 5.03 (s, 2H, CH_2), 5.89 (s, 2H, pyrrolics), 6.24 (d, 1H, $^3J = 7.0$ Hz, CH of Ar), 7.10–7.21 (m, 2H, 2CH of Ar), 7.37 (d, 1H, $^3J = 7.25$ Hz, CH of Ar); MS (EI, 70 eV): *m/z* (%) = 219 (M^+, 22), 125 (50), 91 (100).

3.2.1.4 1-(4-Chlorophenyl)-2,5-dimethyl-1H-pyrrole (Table 2, entry 10) Isolated yield = 78 %; yellow oil; IR cm^{-1}: 2925, 2880, 1653, 1490, 1405, 1349, 1092, 1016; ^{1}H NMR (250 MHz,$CDCl_3$) δ 2.17 (s, 6H, $2CH_3$), 5.01 (s, 2H, CH_2), 5.92 (s, 2H, pyrrolics), 6.85 (d, 2H, $^3J = 8.25$ Hz, 2CH of Ar), 7.30 (d, 2H, $^3J = 8.50$ Hz, CH of Ar); MS (EI, 70 eV): *m/z* (%) = 219 (M^+, 67), 127 (85), 89.(100).

4 Conclusion

In conclusion, we have shown that sulfonic acid supported on magnetite nanoparticles can act as a novel, effective and heterogeneous catalyst for the one-pot synthesis of pyrroles from commercially available starting materials. Various amines were condensed with 2,5-hexanedione to give the corresponding products in high yields. Recovery of the catalyst was simple using a magnet, allowing its reuse without significant loss of its catalytic activity (over five cycles).

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