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Nanomagnetically modified sulfuric acid (γ-Fe_2O_3@SiO_2-OSO_3H): an efficient, fast, and reusable green catalyst for the Ugi-like Groebke-Blackburn-Bienaymé three-component reaction under solvent-free conditions

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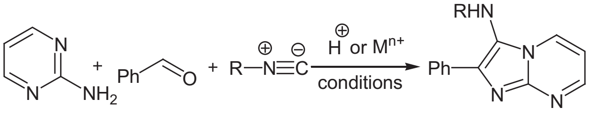
ABSTRACT

Superparamagnetic nanoparticles of modified sulfuric acid (γ-Fe_2O_3@SiO_2-OSO_3H) represent a straightforward and green catalyst for the rapid synthesis of aminoimidazopyridine skeletons via the Ugi-like Groebke-Blackburn-Bienaymé three-component reaction. The γ-Fe_2O_3@SiO_2-OSO_3H catalyst could be recovered and reused in five reaction cycles, giving a total TON = 453. The products were prepared under solvent-free conditions without any additives.

The 'greening' of global chemical processes has became a major issue in the chemical industry and biology both in terms of selection of reactions and for the study of solvent and catalyst effects.[1] Solvent-free approaches show useful versatility and minimize the formation of waste.[2] On the other hand, the development of new strategies for recycling catalysts, which minimizes the consumption of auxiliary substances, energy, and time required in achieving separations can result in significant economic and environmental benefits.[3]

Much attention has been directed toward the fabrication of magnetic nanoparticles because they have both fundamental and practical values due to their potential applications in chemical and materials science.[4] The strategy of magnetic separation, taking advantage of magnetic nanoparticles, is typically more effective than filtration or centrifugation as it prevents loss of the catalyst.[4,5] Magnetic separation of supermagnetic nanoparticles is simple, economical, and promising for industrial applications. From both economic and environmental viewpoints, organic reactions under solvent-free conditions using recoverable catalysts have gained significant attention.[5,6]

Combinatorial methods using multicomponent reactions (MCRs) have been closely examined as a convenient solution for the synthesis of diverse classes of compounds.[7,8] Of pivotal importance in this area are the isocyanide-based MCRs such as the versatile Ugi reactions.[9] Aminoimidazo[1,2-*a*]pyridines, which represent an important class of pharmaceutical compounds, exhibit a wide spectrum of biological activities.[9–11] Several isocyanide-based three-component reactions (3-CRs) have been reported for the synthesis of these compounds by condensation of an aldehyde, an isocyanide, and 2-aminoazine in the presence of a Brønsted acid such as AcOH,[12] $HClO_4$,[13] *p*-toluenesulfonic acid,[14] cellulose sulfuric acid,[15] or Lewis acids such as $Sc(OTf)_3$,[16] $MgCl_2$,[17] $SnCl_2$,[18] $ZrCl_4$,[19] and $ZnCl_2$[20] via the Groebke-Blackburn-Bienaymé reaction (Scheme 1). However, many of these methods suffer from drawbacks such as low yields of products, long reaction times, harsh reactions conditions, tedious work-ups leading to the generation of large amounts of toxic metal-containing waste, the



Scheme 1. Ugi-type Groebke-Blackburn-Bienaymé 3-CR.

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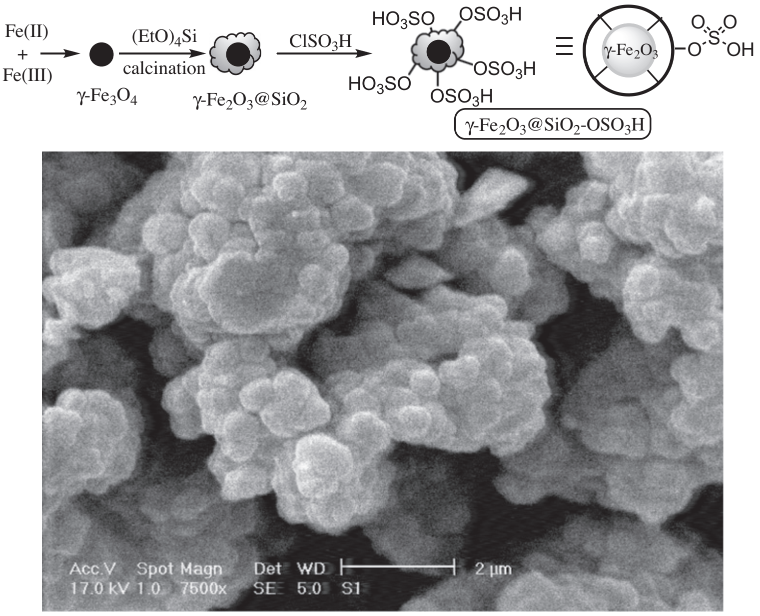


Figure 1. Schematic representation of the procedure for the synthesis of γ-Fe_2O_3@SiO_2-OSO_3H nanoparticles and its SEM image.

Table 1
Study of the solvent and temperature on the model reaction. The bold values selected as optimum value for next study

Solvent	Temp (°C)	Time (h)	Yield (%)
H_2O	rt	0.5	<10
H_2O	rt	1	13
H_2O	50	0.5	20
EtOH	rt	0.5	<10
EtOH	30	0.5	20
MeOH	rt	0.5	<10
CH_2Cl_2	rt	0.5	<10
Solvent-free	rt	0.5	38
Solvent-free	35	0.5	64
Solvent-free	rt	1	58
Solvent-free	**35**	**1**	**92**

Table 2
Optimization of the model reaction under solvent-free conditions. The bold values selected as optimum value for next study

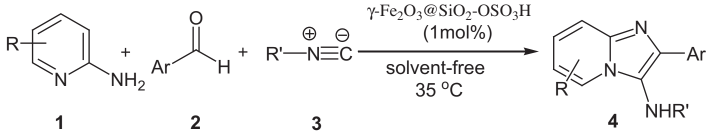
Cat. (mol %)	Temp (°C)	Time (h)	Yield (%)
0.5	35	0.5	58
0.5	35	1	76
1	rt	0.5	40
1	rt	1	53
1	**35**	**1**	**92**
1	45	1	90
2	rt	1	58
2	35	1	92
2	50	1	94
3	rt	1	62
5	rt	1	66
5	35	1	93

Table 3
Recyclability study on the synthesis of model compound **4a**

Run[a]	1	2	3	4	5
Yield% **4a**	92	93	92	90	86[b]

[a] Time of the reaction was 60 min.
[b] After 90 min.

Table 4
One-pot synthesis of imidazo[1,2-*a*]pyridines **4**

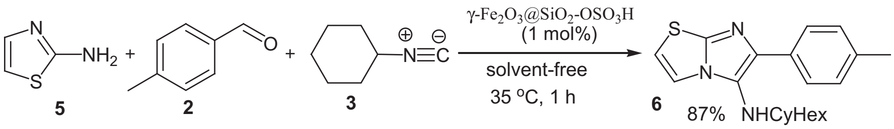


Product	R	Ar	R′[a]	Time[b] (min)	Yield[c] (%)
4a	H	C_6H_5	*c*-Hex	60	92
4b	H	4-NO_2-C_6H_4	*c*-Hex	45	94
4c	H	4-Cl-C_6H_4	*c*-Hex	45	94
4d	H	3-NO_2-C_6H_4	*c*-Hex	45	93
4e	H	C_6H_5	^{t}Bu	60	90
4f	6-CH_3	C_6H_5	*c*-Hex	70	87
4g	6-CH_3	4-Cl-C_6H_4	*c*-Hex	60	90
4h	6-CH_3	3-NO_2-C_6H_4	*c*-Hex	60	90
4i	6-CH_3	4-NO_2-C_6H_4	*c*-Hex	60	88
4j	6-CH_3	4-NO_2-C_6H_4	^{t}Bu	60	86
4g	5-CH_3	C_6H_5	*c*-Hex	70	85
4k	5-CH_3	4-Cl-C_6H_4	*c*-Hex	60	86

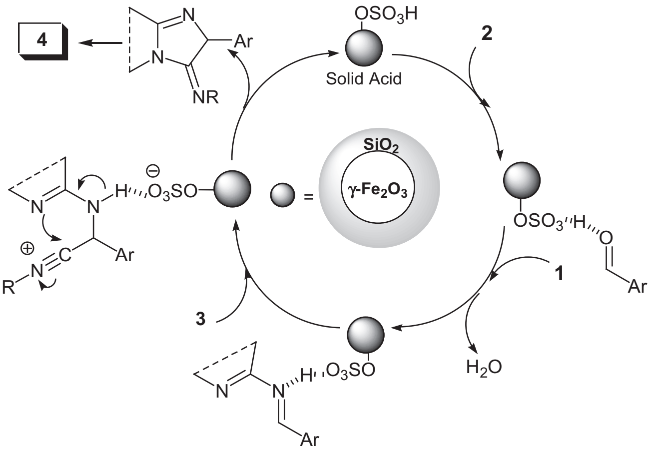
[a] *c*-Hex (cyclohexyl).
[b] Optimized time.
[c] Isolated yield.

requirement for an inert atmosphere, and the use of stoichiometric or relatively expensive reagents.[12–20] As a result, the development of new synthetic methods for this purpose remains an attractive goal.

Recently, we developed methods for the synthesis of biologically interesting heterocycles via multicomponent reactions.[21–28] The challenge in this field was developing efficient and rapid green methods. Based on our earlier success in the preparation of magnetic nanoparticles as catalysts,[6,21–23] combined with our achievements in this area, in this Letter, we present the results of an extended investigation on the activity of the SO_3H functionalized magnetic nanocatalyst,[21] γ-Fe_2O_3@SiO_2-OSO_3H, as a green catalyst in Ugi-like Groebke-Blackburn-Bienaymé reactions leading to the formation of aminoimidazole derivatives without the requirement for any solvent, salt, or additive. We have developed a synthetic method for the preparation of 3-aminoimidazo[1,2-*a*]pyridines via the three-component condensation of an aldehyde, 2-amino-



Scheme 2. The use of γ-Fe_2O_3@SiO_2-OSO_3H for the synthesis of aminoimidazothiazole **6**.



Scheme 3. A plausible mechanism for the Ugi-like MCR using γ-Fe_2O_3@SiO_2-OSO_3H.

pyridine, and an isocyanide using SO_3H-functionalized magnetic iron oxide as the catalyst.

The maghemite nanoparticles (γ-Fe_2O_3, Fig. 1) were synthesized by a chemical co-precipitation technique using ferric and ferrous ions.[21–23] Based on our previous reports,[6,21–23] coating a layer of silica on the surface of the γ-Fe_2O_3 nanoparticles and then functionalization of the iron oxide with a sulfonic acid group were achieved by treatment with tetraethyl orthosilicate [$(EtO)_4Si$, TEOS] followed by chlorosulfonic acid (0.60 mmol g^{-1} $-SO_3H$ loading, see Supplementary data).

In order to investigate the catalytic activity and application of γ-Fe_2O_3@SiO_2-OSO_3H in the Ugi-like multicomponent synthesis of imidazopyridines,[4,29] we examined its efficiency in a model reaction between 2-aminopyridine, benzaldehyde, and cyclohexyl isocyanide. Due to the fact that the solvent may play an important role in this process, various solvents were screened. The model reaction was examined in methanol, ethanol, and water using 2% mol of γ-Fe_2O_3@SiO_2-OSO_3H (Table 1). However, when the reaction was run under solvent-free conditions, the product was obtained in 92% yield at 35 °C in 1 h; the yield increased sharply when the temperature was raised from room temperature to 35 °C.

Next, the model reaction of 2-aminopyridine with benzaldehyde and cyclohexyl isocyanide under solvent-free conditions was carried out using different amounts of γ-Fe_2O_3@SiO_2-OSO_3H as the catalyst (Table 2). A very high yield of 3-aminoimidazo[1,2-*a*]pyridine (92%) was obtained with 1 mol % of the catalyst. A further increase in the amount of catalyst (up to 5 mol %) and of the reaction temperature did not have any significant effects on the product yield or reaction time.

The possibility of recycling the magnetic catalyst was also studied. When the reaction was complete, the catalyst was easily separated from the product by applying a magnet to the exterior of the reaction vessel. As illustrated in Table 3, the catalyst could be reused without any significant loss in the yield over five runs. After the fifth run the turnover number (TON) was 453.

To demonstrate the diversity of the γ-Fe_2O_3@SiO_2-OSO_3H nanocatalyst and to expand the scope of the process, the optimized conditions were applied to a series of substrates **1**, **2**, and **3** as shown in Table 4.

The catalytic activity of γ-Fe_2O_3@SiO_2-OSO_3H in the Ugi-like Groebke-Blackburn-Bienaymé three-component synthesis of an aminoimidazothiazole was also studied under the optimized conditions. The yield of the designed product **6** was 87% after 1 h (Scheme 2).

Although we have not established the exact mechanism for this reaction in the presence of γ-Fe_2O_3@SiO_2-OSO_3H in an experimental manner, a possible explanation for the synthesis of 3-aminoimidazo[1,2-*a*]pyridines **4**, based on an isocyanide-based multicomponent reaction[12–20,30–32] is proposed in Scheme 3.

In summary, covalent functionalization of sulfuric acid onto magnetic γ-Fe_2O_3@SiO_2 nanoparticles has successfully been achieved. An extensive and systematic study identified γ-Fe_2O_3@SiO_2-OSO_3H as a heterogeneous, green, and reusable catalyst for the synthesis of aminoimidazopyridines via an Ugi-like (isocyanide-based) three-component reaction. A variety of annulated aminoimidazoles are accessible under mild conditions using this method. This rapid, green method in which the catalyst can be recycled might serve as an interesting alternative to other synthetic methods. The aminoimidazole products are of potential synthetic and pharmaceutical interest.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.075.

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29. To a mixture of 2-aminopyridine (1 mmol) and benzaldehyde (1 mmol) was added γ-Fe_2O_3@SiO_2-OSO_3H catalyst (0.067 g, 1 mol %) under solvent-free conditions at room temperature. The mixture was then allowed to stir for 5 min. The isocyanide (1.2 mmol) was added and the mixture was stirred at 35 °C for the appropriate amount of time (Table 4). The mixture was cooled and CH_2Cl_2 (4 mL × 3) was added. The catalyst was recovered magnetically by attaching a general magnet to the exterior of the reactor vessel. The CH_2Cl_2 was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel using EtOAc–*n*-hexane (2:1) as the eluent to afford the aminoimidazopyridine product **4** in high purity. All the isolated products gave satisfactory spectral and physical data. The isolated catalyst could be recycled, see Supplementary data for details.
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