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Magnetic, Acidic, Ionic Liquid-Catalyzed One-Pot Synthesis of Spirooxindoles

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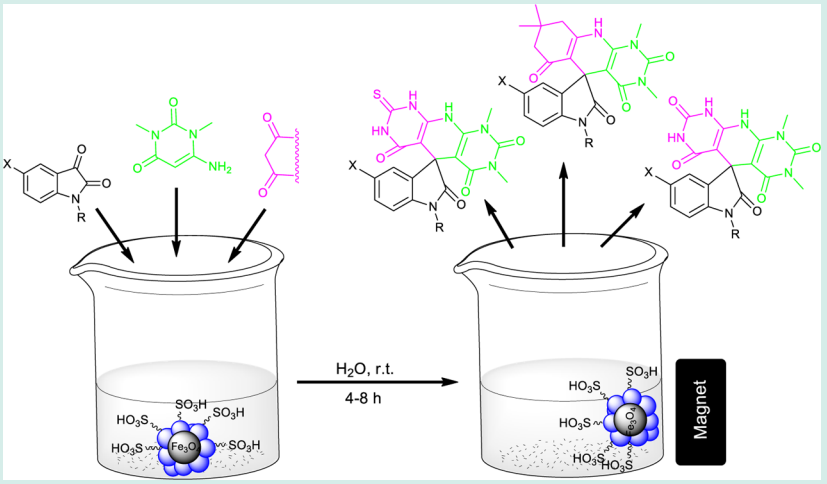
Supporting Information



ABSTRACT: Magnetic, supported, acidic ionic liquid was synthesized and identified as an efficient catalyst for the one-pot synthesis of novel spirooxindole derivatives at mild conditions and in good yields. Three component reaction of wide variety of substituted isatins, 1,3-dimethyl-2-amino uracil, and barbituric acid, thiobarbituric acid, and dimedon as 1,3-dicarbonyl compounds gives the target compounds. Operational simplicity, low cost, high yields, environmental friendliness, wide applicability and reusability and easy recovery of the catalyst using an external magnet are the key features of this methodology.

KEYWORDS: *multicomponent reaction, spirooxindole, magnetic catalyst, supported acidic ionic liquid*

1. INTRODUCTION

In recent years, there has been considerable growth of interest in the synthesis of spirooxindole derivatives (Figure 1) because of the wide-ranging biological activity associated with them such as antibacterial, antifungal, antiinflammatory, and antipyretic activities.[1] On the other hand, a large number of pyrimidine derivatives consist of barbituric acid and 2-amino-uracil have attracted great interest for their biological activities and applications in medicine and therapeutics.[2] In this context, the synthesis of this important ring system fused with spirooxindole remains a topic of current interest. Various methods for the preparation of spirooxindole derivatives have been reported.[3,4] However, to the best of our knowledge, some of these methods suffer from tedious synthetic routes, long reaction time, drastic reaction conditions, toxicity, corrosiveness, cost, as well as unreusability of catalyst. Therefore, there is still a need for versatile, simple, and environmentally friendly processes.

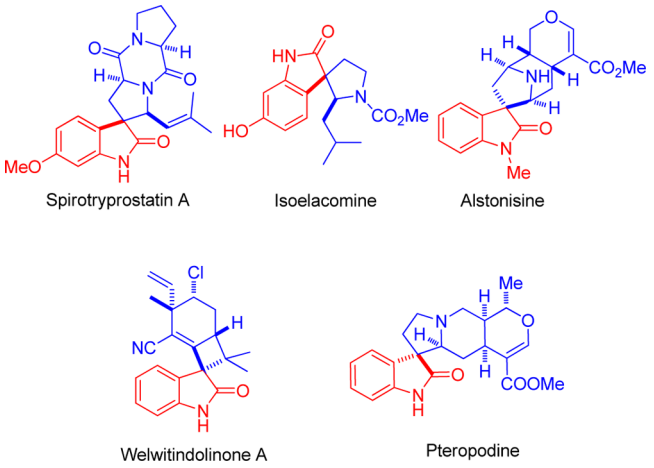


Figure 1. Representatives of spirooxindole-containing compounds.

Recently, ionic liquids (IL), especially acidic types, have attracted increasing interest in organic synthesis, because they can provide green and efficient media for organic reactions.[5] In

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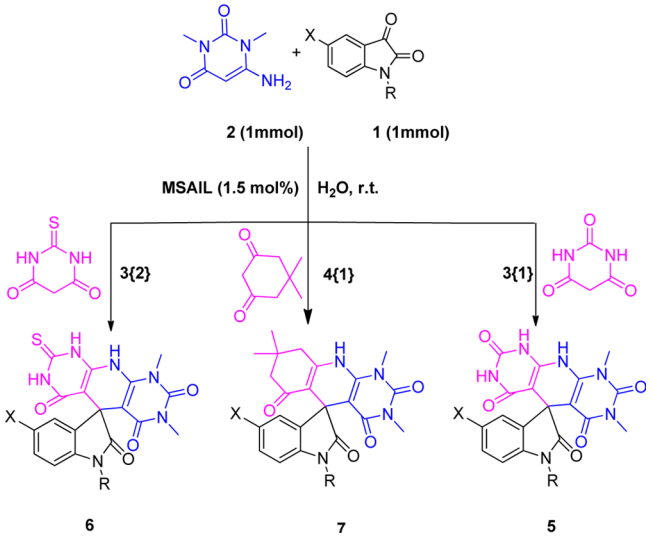
Scheme 1. Various Synthesized Spirooxindoles in the Presence of MSAIL



parallel with the use of ILs in organic transformations, they also have been used as reaction medium for multicomponent reactions (MCRs).[6] The MCRs are an attractive synthetic strategy, because the complex products are formed in single step and diversity can be achieved simply by varying the reaction components.[7]

On the other hand, heterogeneous catalysis is generally preferred to homogeneous catalysis mainly because of the easy recovering and possible recycling of the catalyst, simple experimental procedures, and minimization of chemical wastes as compared to the liquid phase counterparts. It seems that magnetic nanoparticles (MNP) can be a good candidate as a support material for heterogeneous catalysts, because of easy synthesis, high surface area, facile separation by magnetic forces, and low toxicity and cost.[8] According to these attractive properties, many MNP supported catalysts have been designed and widely applied as novel magnetically separated catalysts in traditional metal catalysis,[9,10] organocatalysis,[11] and even enzyme catalysis.[12] In this work, for combining the benefits of ILs and heterogeneous magnetic catalysts, we reveal a new nanometer scale, magnetic, supported, acidic ionic liquid (MSAIL), which can be used for different organic functional group transformations as a catalyst in green processes. Therefore, in continuation with our interest in developing efficient and environmental benign synthetic methodologies,[13] we focused our attention on a simple, green, and efficient method for synthesis of biological active spirooxindole derivatives from a wide variety of isatin, 1,3-dimethyl-2-amino uracil, and different 1,3-dicarbonyl compounds in high yields and short reaction time (Scheme 1). Lower cost, operational simplicity, high yields, and the possibility of easy recovering of the catalyst are the most advantages of this method. To the best of our knowledge, this is the first report on the synthesis of these spiro pyrimido pyrimidine derivatives in the presence of magnetic ionic liquid.

However, very recently, Das et al.[14] have reported a PEG-OSO_3H mediated one-pot three-component domino coupling of 1,3-diketo compounds, 6-aminouracil/4-aminocoumarin, and isatin/5-bromoisatin under thermal conditions to afford highly substituted uracil and coumarin fused spirooxindole derivatives. But the set of reactants used in this method is quite small (only isatin and 5-bromo isatin) and in contrast to the easy separation of a magnetic, supported catalyst by a magnetic force, the separation of PEG-OSO_3H catalyst from the product needs filtration and H_2O evaporation under reduced pressure.

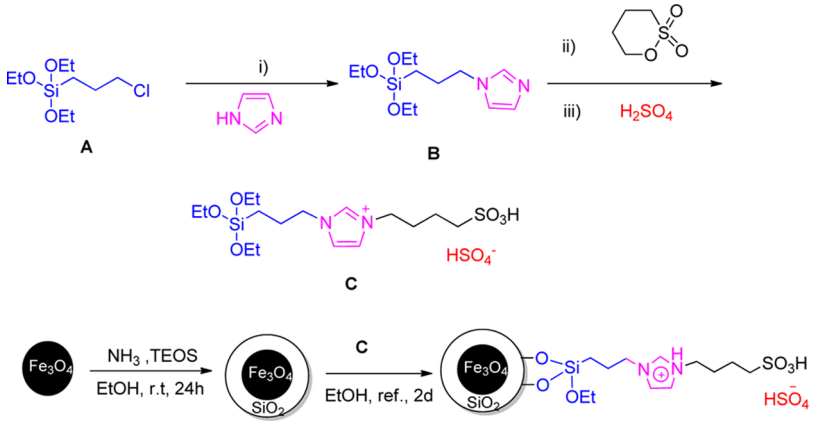
2. RESULTS AND DISCUSSION

Catalyst Preparation. New MSAIL as a catalyst was prepared based on the following procedure (Scheme 2, see the Supporting Information). The magnetic catalyst was characterized using some different microscopic and spectroscopic techniques such as transmission electron microscopy (TEM), scanning electron microscopy (SEM), and FT-IR. The number of H^+ site of MSAIL determined by acid−base titration was 0.85 ± 0.05 mequiv·g.[1] (see the Supporting Information, Figures 1−3).

Optimization of Reaction. To show the merit of MSAIL as a catalyst in organic synthesis, we first applied this catalyst for multicomponent reaction. The reaction of isatin, 1,3-dimethyl-2-amino uracil, and barbituric acid affording spirooxindole was examined in the presence of different catalysts and solvents. The results of the optimized conditions are summarized in Table 1.

During our optimization studies, when the reaction was carried out in the absence of catalyst the reaction was

Scheme 2. Different Steps for the Synthesis of MSAIL[a]



[a](i) toluene, reflux, 24 h; (ii) toluene, rt, 8h; (iii) ethanol, 30 min.

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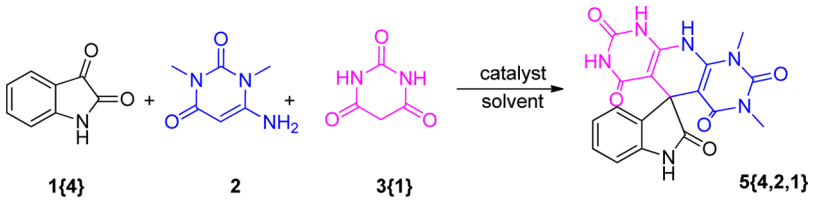
Table 1. Combined Effects of Solvents and Catalysts on the Multicomponent Reaction between Isatin, Barbituric Acid, and 1,3-Dimethyl-2-amino Uracil[a]



1{4} 2 3{1} 5{4,2,1}

entry	condition[a]	cat.[b]	time (h)	yield (%)[c]
1	EtOH (reflux)		24	trace
2	EtOH (reflux)	CH_3COOH	24	39
3	MeCN (reflux)	$FeCl_3$	24	45
4	MeCN (reflux)	$AlCl_3$	24	50
5	H_2O (reflux)	*p*-TSA	13	75
6	H_2O (reflux)	SSA	10	75
7	EtOH (reflux)	$H_3PMo_{12}O_{40}$	10	70
8	H_2O (reflux)	nano-Fe_3O_4	24	trace
9	H_2O (reflux)	nano-Fe_3O_4.SiO_2	24	trace
10	EtOH (reflux)	[MIMPSA][HSO_4]	12	65
11	EtOH (reflux)	nano-MSAIL	8	75
12	MeOH(reflux)	nano-MSAIL	8	75
13	DMF (reflux)	nano-MSAIL	10	75
14	H_2O (reflux)	nano-MSAIL	5	75
15	**H_2O (rt)**	**nano-MSAIL**	**5**	**89**

[a]Reaction conditions: isatin(1 mmol), barbituric acid (1 mmol), 1,3-dimethyl-2-amino uracil (1 mmol). [b]1.5 mol % of catalysts was used. [c]Isolated yield.

Table 2. Effect of Catalyst Amount on the Reaction between Isatin, Barbituric Acid, and 1,3-Dimethyl-2-amino Uracil[a]

entry	amount of cat. (mg)	yield (%)
1	40	38
2	45	65
3	**50**	**89**
4	55	89
5	60	90

[a]Reaction conditions: isatin (1 mmol), barbituric acid (1 mmol), 1,3-dimethyl-2-amino uracil (1 mmol), H_2O (1 mL), catalyst (MSAIL), rt, 5h.

incomplete even after 24h under reflux in ethanol and nearly no product was obtained (Table 1, entry 1). When different solid catalysts such as $FeCl_3$, $AlCl_3$, *p*-TSA, SSA, and $H_3PMo_{12}O_{40}$ were used, their effect was only moderate (Table 1, entries 3−7). By using a typical acidic IL [MIMPSA][HSO_4] 65% yields of the product were obtained after 12h, respectively (Table 1, entry 10). In comparison with [MIMPSA][HSO_4], MSAIL increased the yield to 75% in a shorter reaction time (Table 1, entry 11). This is presumed to occur due to the adsorption of reactants on the surface of the nanomagnetic support, increasing the local concentration of reactants around the active sites of the MSAIL and effectively promoting the reaction. Decreasing the reaction temperature to ambient increased the yield to 89% after 5h.

The efficiency of the supported catalyst was found to be solvent dependent with water being the best. The catalyst concentration, which afforded the best yields, was 1.5 mol % (Table 2). Increasing the amount of catalyst did not change the yield dramatically, whereas reducing it significantly decreased the product yield.

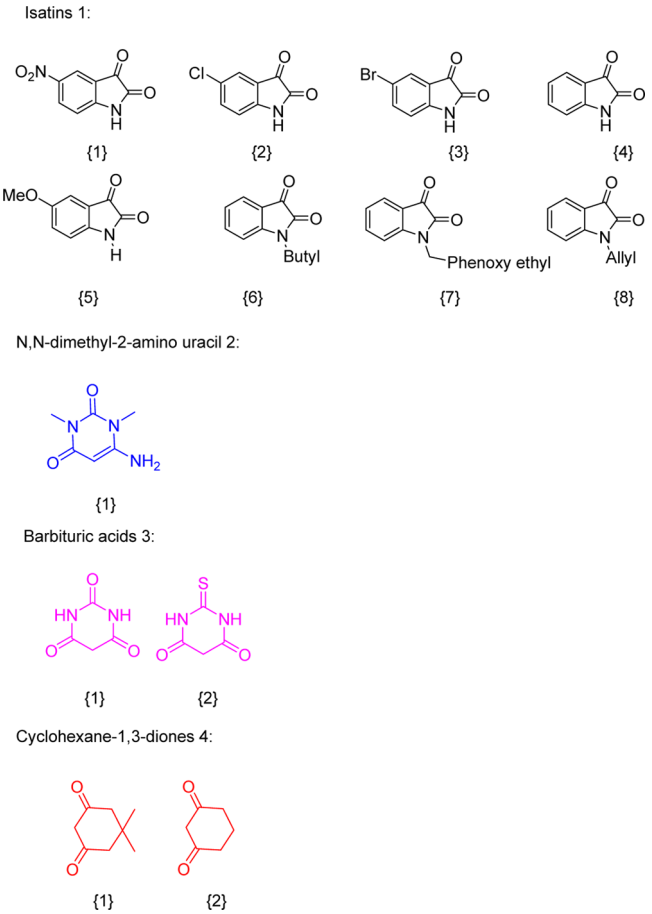


Figure 2. Diversity of reagents.

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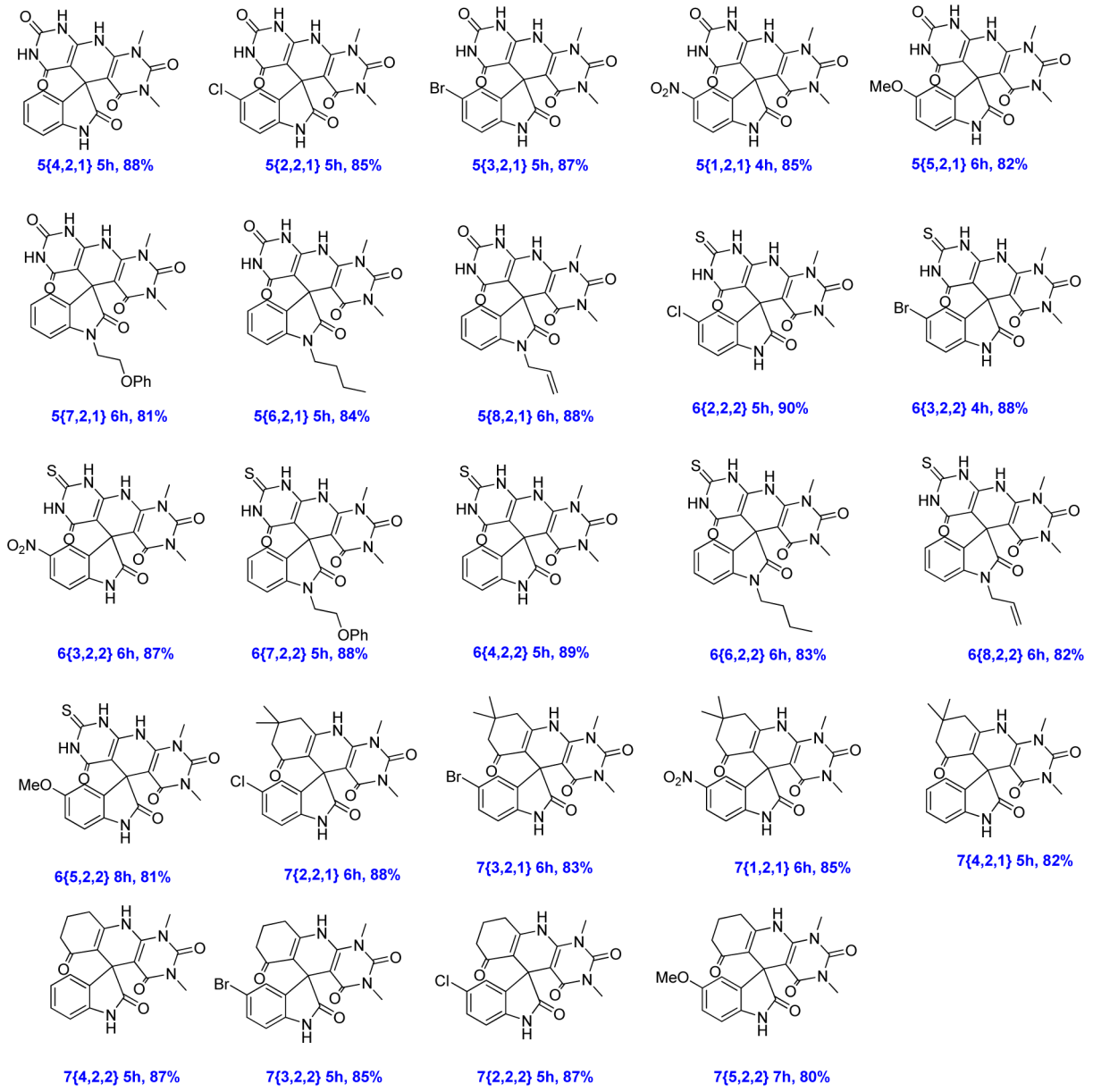

Figure 3. Synthesized spirooxindoles in the presence of MSAIL.

The methodology was evaluated by using 1,3-dimethyl 2-amino uracil, isatin derivatives, and different 1,3-dicarbonyl groups such as barbituric acid, thiobarbituric acid and dimedon as nucleophiles (Scheme 1, Figure 2), under similar conditions (50 mg MSAIL, H_2O, room temp.) to explore the scope of the procedure reported in Figure 3.

The reactions proceeded smoothly and the desired spirooxindole products from a diverse set of substrates were obtained in good yields (Figures 2 and 3). Isatins with electron-withdrawing groups as well as electron-donating substituents underwent this one-pot conversion to give the corresponding spirooxindols in good yield (Figure 3); however, the reaction time of isatins with electron-rich groups was longer than those of with electorn-withdrowing group, which is probably because of the lower reactivity of the isatins with electron-rich groups.

The structure of final adducts are compatible with the mechanistic proposal depicted in Scheme 3 in which after the protonation of isatin by our catalyst, a molecule of uracil would be added affording intermediate **I** after dehydratation. In a subsequent step a molecule of barbituric acid would suffer a conjugated addition over **I** rendering intermediate **II**, which after condensation would afford main product.

To shed light on the above proposed mechanism, when the reaction of 2-amino-uracil with isatin was carried out for 1 h, the intermediate 6-imino-1,3-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidene) dihydro-pyrimidine-2,4-dione (**I**) was isolated and characterized by spectroscopic methods. Then, the intermediate (**I**) was converted to intermediate 5-[3-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro pyrimidin-5-yl)-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-2,4,6-trione (**II**) after attacking enolate of nucleophileand followed by cyclization afforded the corresponding spiro-compound (Scheme 3).

To show an additional advantage of our developed catalytic system we explored the recycling of catalyst MSAIL, which was able to be recycled simply via attaching an external magnet after completion the reaction and washed with ethyl acetate, dried under vacuum and reused in a subsequent reaction. Nearly quantitative catalyst (up to 98%) could be recovered from each

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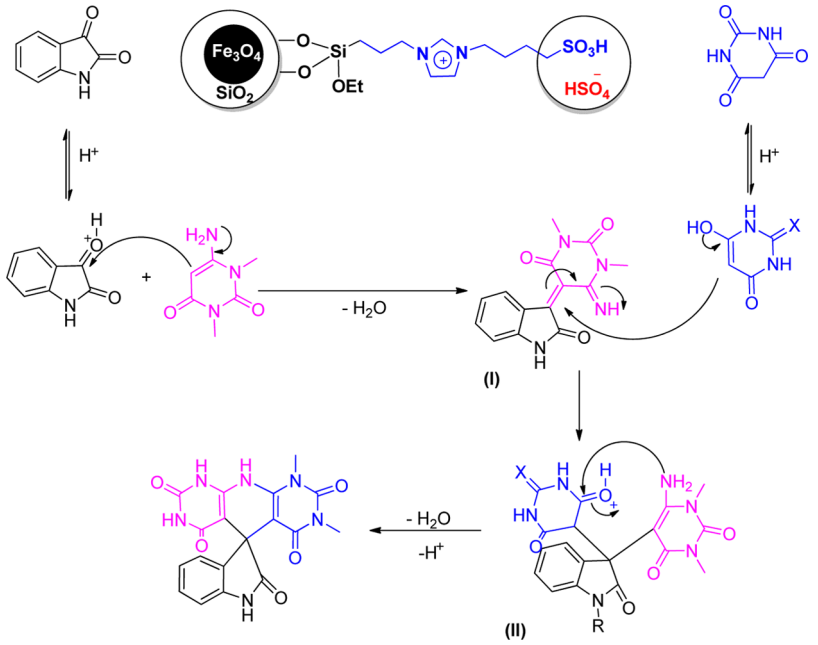
Scheme 3. Proposed Mechanism for the Multicomponent Reaction Using MSAIL Catalyst



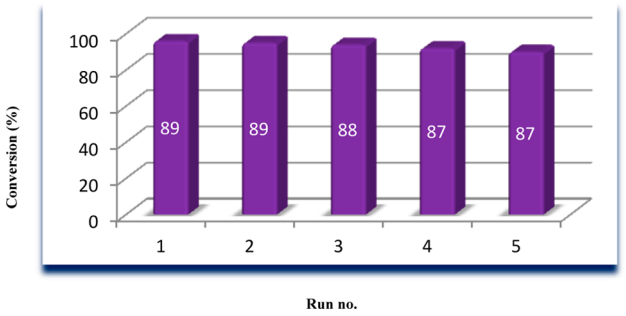


Figure 4. Catalytic recovery times of MSAIL catalyst for fifth runs.

run. In a test of five cycles, the catalyst could be reused without any significant loss of catalytic activity (Figure 4).

When using a supported catalyst, there is a possibility that the active species might migrate from the solid support to the liquid phase, since the leached active ones become responsible for the good catalytic activity. To explore the catalyst leaching, the reaction of isatin (2 mmol), 1,3 dimethyl-2-amino uracil (2 mmol) and dimedone (2 mmol) catalyzed by MSAIL was carried out at room temperature. When the reaction time reached 2.5h, hot ethanol (20 mL) was added and the MSAIL was easily removed using a magnetic force. The solution was averagely divided into two parts (P1 and P2). The corresponding product of P1 was obtained with a 40% yield. Moreover, the solution of P2 was reacted under the above conditions for another 2.5h to afford the product in 41% yield, which was similar to P1 and less than normal (82%, Figure 3, entry 15). Therefore, these above results convinced us that the leaching of MSAIL was negligible in the catalytic process.

3. CONCLUSION

In conclusion, we successfully developed a novel MNP supported acidic IL and used it in a one-pot three-component condensation of isatin with 1,3-dimethyl-2-amino uracil and 1,3-dicarbonyl compounds to prepare spirooxindole derivatives in excellent yields (up to 90%). Moreover, the catalyst could be readily separated by use of a magnetic force and reused without any significant loss of catalytic activity after five runs. Besides the synthesis of spirooxindole derivatives, such an environmentally benign catalyst should find a wider application in various acid-catalyzed reactions, which is an ongoing project.

4. EXPERIMENTAL PROCEDURES

General Considerations. All chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. For recorded ^{1}H NMR spectra we used a Bruker (250 MHz) Avanc DRX in pure deuterated DMSO-d_6 and $CDCl_3$ solvents with tetramethyl silane (TMS) as the internal standard. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at 70 eV. FT-IR spectroscopy (Shimadzu FT-IR 8300 spectrophotometer), was employed for characterization of the compounds. The scanning electron micrograph for MSAIL catalyst was obtained by SEM instrumentation (SEM, XL-30 FEG SEM, Philips, at 20 kV). Melting points were determined in open capillary tubes in a Barnstead Electrothermal 9100 BZ circulating oil melting point apparatus. The reaction monitoring was accomplished via TLC on silica gel PolyGram SILG/UV254 plates.

General Procedure for the Synthesis of Spirooxindoles Derivatives from Isatin Using MSAIL. An equimolar mixture of isatin (1 mmol), 1,3-dimethyl-2-amino uracil (1 mmol), barbituric acid (1 mmol) and 1.5 mol % MSAIL in H_2O (1 mL) was stirred at room temperature. Completion of the reaction was monitored by TLC. All the reactions were invariably complete in 4−8 h. Upon completion of the reaction, 5 mL of ethyl acetate was added to the reaction mixture. The spirooxindole derivatives were dissolved in ethyl acetate and the catalyst was separated magnetically from the product solution, washed with ethyl acetate, and used for subsequent cycles after drying under vacuum. Pure products were afforded by evaporation of the solvent, followed by recrystallization from ethanol or by column chromatography on silica gel using ethyl acetate/hexane as the eluent.

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1′,3′-Dimethyl-1′*H*-spiro[indoline-3,5′-pyrido-[2,3d:6,5d′]dipyrimidine]2,2′,4′,6′,8′ (3′*H*, 7′*H*, 9′*H*,10′*H*)-pentaone (5{*4,2,1*}). White crystals (yield = 96%); mp >300 °C. IR (solid film, cm^{-1}): 3754, 3286, 3109, 2302, 1750, 1685, 1620, 1543, 1432, 1157, 964, 867, 763.^{1}H NMR (250 MHz, DMSO-d_6): δ 2.15 (s, 3H, CH_3); 3.00 (s, 3H, CH_3); 6.63−7.19 (complex, 4 arom. H); 8.88 (S, NH, D_2O exchangeable); 11.67 (s, NH, D_2O exchangeable), 11.88 (s, NH, D_2O exchangeable), 12.08 (s, NH, D_2O exchangeable).^{13}C NMR (62.5 MHz, DMSO-d_6): δ 26.1, 32.5, 56.7, 117.2, 121.3, 123.3, 126.8, 128.9, 134.0, 145.3, 150.0, 150.9, 152.7, 155.8, 159.5, 173.8, 180.5. MS (m/z): 395 $[M + H]^+$. Anal. Calcd. for $C_{18}H_{14}N_6O_5$: C, 54.82; H, 3.58; N, 21.31; Found: C, 54.70; H, 3.45; N, 20.85.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data of catalyst and product, and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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