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ORIGINAL PAPER

N-Sulfonic acid modified poly(styrene-co-maleic anhydride): an efficient and recyclable solid acid catalyst for the synthesis of a wide range of spiropyrans

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Abstract *N*-Sulfonic acid modified poly(styrene-co-maleic anhydride) as a recyclable solid acid catalyst efficiently catalyzed the one-pot three-component synthesis of spiropyran derivatives through a simple, convenient, and cost-effective approach in good yields and selectivity.

Keywords Heterogeneous catalyst · Multicomponent reactions · Poly(styrene-co-maleic anhydride) · Polymer-supported catalyst · Recyclable solid acid catalyst

Introduction

In modern organic chemistry, considerable effort is being made on the design of strategies and protocols leading to provide structurally diverse and complex molecules, which are preferably, biologically active. Multicomponent reactions (MCR) have become popular for constructing complex molecules because of using, protocols involving less environmental impact, maintaining higher atom-economy and if possible the recyclability and reusability of the appropriate catalysts [1].

Spiro compounds as a well-known class of biologically active molecules are present in many naturally occurring substances. It has found out; when indoles which are present in many natural products, pharmaceuticals, and agrochemicals [2] involve in these spiro nuclei enhance the biological activity to a significant extent. Powerful cytostatic alkaloids like spirotryprostatins and pteropodines are some distinguished examples of spiroindoles [3]. Condensed spirooxindole compounds with 4H chromenes provided pharmacologically active systems with immense importance due to their diuretic, spasmolitic, anticoagulant, anticancer, and antinaphylactic activities [4]. Due to importance and value mentioned above, the facile, green and heterogeneously catalyzed synthesis of these moieties especially the nitrile substituted 4*H* chromenes which are effective drugs in human neurodegenerative disorders [5] via multicomponent condensation is desirable.

A variety of catalysts such as piperidine [6], triethanolamine [7], L-proline [8], ethylenediaminediacetic acid [9], triethylamine [10], porcine pancreas lipase [5], 1-*N*-butyl-3-methyl-imidazolium tetrafluoroborate [11], sodium octadecanoate [12], $InCl_3$ [13], nanocrystalline MgO [14] were applied for the synthesis of spiro[4*H*-pyran-oxindole] derivatives, which each shows at least one drawback, such as harsh reaction conditions, long reaction times, low yields, complicated, tedious work up procedure, and technical complexity. Therefore, further development on the environmental and economical impact of the reaction is of interest and still in much demand.

Scientific interest for the development of heterogeneous catalysts for fine chemical synthesis has become a major area of research because of their simple recovery and reusability, as well as their potential for incorporation in MCRs. Heterogeneous solid acid catalysts as efficient, easy recyclable and recoverable, non-corrosive and environmental friendly catalysts in organic reactions are extensively used in academia and applicable in industry. Nowadays, more than 100 transformations catalyzed by over 103 solid acids are doable in large scale levels [15–21].

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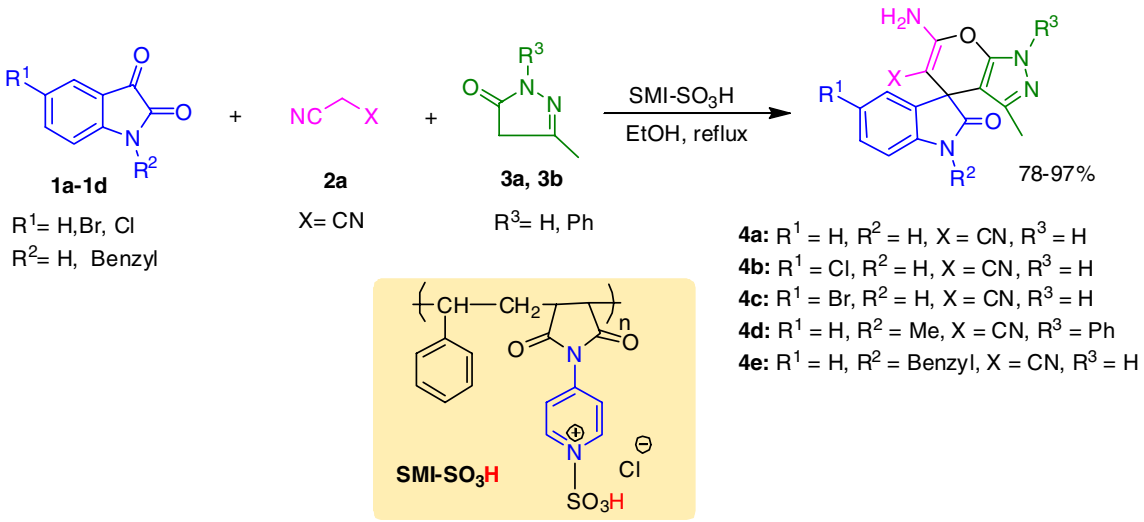


Scheme 1 Synthesis of spirooxindole derivatives **4a**–**4e**

In the course of our studies on the modification and use of heterogeneous solid acid catalyst in organic transformations [22–27], and in continuation of our interest in the synthesis of biologically heterocyclic systems via MCRs [28–31] herein we wish to report a simple and efficient method for the syntheses of a series of spirooxindoles with fused tetrahydro chromene derivatives via the condensation reaction of isatin, with different nitrilo active methylene components, and various reagents including α-methylencarbonyl in the presence of *N*-sulfamic acid modified poly(styrene-co-maleic anhydride) catalyst (SMI-SO_3H) as an efficient and recyclable solid acid catalyst which has been recently synthesized in our laboratory [32].

Experimental

General

N,*N*-Dimethylformamide (DMF) and triethylamine (TEA) were distilled and kept over 4 Å molecular sieve before use. The other reagents were purchased from Aldrich and Merck in high-grade quality and used as received (except SMA). SMA used in this study is KARABOND SAM and its general formula is $[(C_8H_8)_{0.6}\ (C_4H_2O_3)_{0.4}]_n$ with anhydride/imide content = 40 %, M_n = 86,666 (g/mol), M_w = 182,000 and M_w/M_n = 2.1.

The ^{1}H NMR and ^{13}C NMR spectra were recorded, using Bruker Ultrashield 400 and 100 MHz, respectively, Advance instrument, with DMSO-d_6 used as solvent. Proton resonances are designated as singlet (s), doublet (d), triplet (t) and multiplet (m). FTIR spectra were recorded using KBr disks on FT-IR Bruker Tensor 27 instrument in the 500–4,000 cm^{-1} region. The vibrational transition frequencies are reported in wave numbers (cm^{-1}). Band intensities are assigned as weak (w), medium (m), and strong (s). All yields refer to isolated products.

Catalyst synthesis

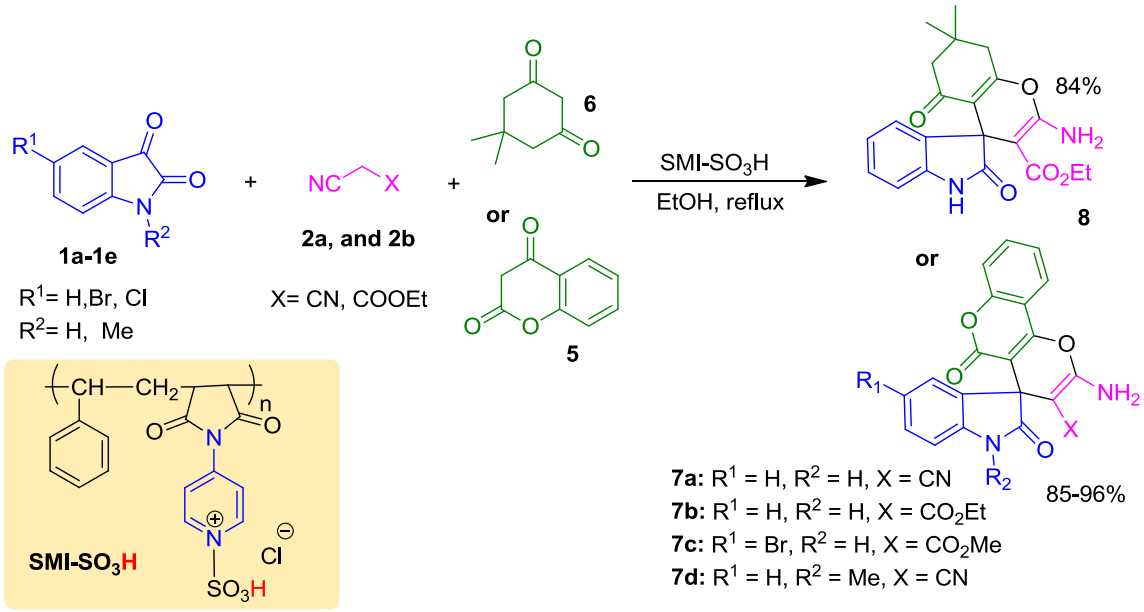
SMI-SO_3H was synthesized according to our previous work [32] and applied to the aforementioned MCRs as the catalyst.

Synthesis of spirooxindoles (**4a**–**4e**): general procedure

For the preparation of spiropyran derivatives (**4a**–**4e**), a mixture of isatin derivatives **1a**–**1d** (1 mmol), malononitrile (1 mmol), pyrazole **3a** and **3b** (1 mmol) and 0.03 g of catalyst SMI-SO_3H in ethanol (3 mL) was refluxed for an indicated time (see Table 4). After completion of the conversion, as monitored by TLC (*n*-hexane:EtOAc = 1:1), the solid heterogeneous catalyst was easily filtrated. The recovered catalyst was washed with acetone and dried under reduced pressure in 70 °C for 3 h and stored for another consecutive reaction to run. It can be used at least 6 times in all the reaction, above with no appreciable loss of activity. The filtrate was concentrated to solidify and the crude products were purified by recrystallization from aqueous ethanol to afford the title compounds and their physical data were compared with those of authentic samples (Scheme 1).

Synthesis of spirooxindole derivatives 7a–7d and 8: general procedure

Isatin derivatives **1a**–**1d** (1 mmol), different nitrilo active methylene components **2a** and **2b** (1 mmol), and 4-hydroxy



Scheme 2 Synthesis of spirooxindole derivatives **7a**–**7d** and **8**

coumarin (1 mmol) or dimedone (1 mmol) were reacted under similar optimized reactions, in presence of 0.03 g of catalyst and 3 mL of solvent at reflux condition, to afford spirooxindole derivatives **7a**–**7d** and **8** and their physical data were determined (Scheme 2).

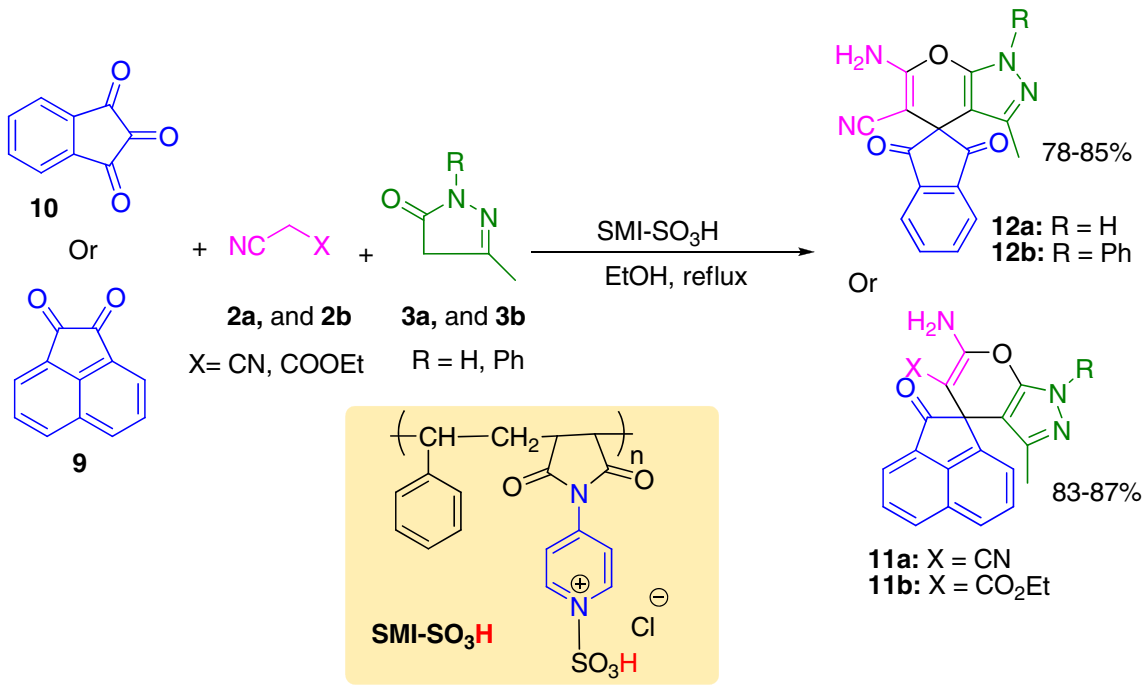
Synthesis of spiropyrans derivatives **11a**, **11b**, **12a** and **12b**: general procedure

Similar three-component reaction, in the presence of 0.03 g of catalyst and 3 mL of solvent at reflux condition, acenaphthenequinone (1 mmol) or ninhydrin (1 mmol) reacted with nitrilo active methylene compounds **2a** and **2b** and (1 mmol) pyrazolone **3a** and **3b** (1 mmol) to provide the spiropyrans derivatives **11a**, **11b**, **12a** and **12b** and their physical data were determined (Scheme 3). The physical and spectral (melting point (Mp), IR, and ^{1}H NMR) data for the derivative **12b** as a new compound is as follows:

6′-amino-3′-methyl-1,3-dioxo-1′-phenyl-1,3 dihydro-1′H-spiro[indene-2,4′-pyrano [2,3c] pyrazole]-5′-carbonitrile (***12b***): Yellow powder, Mp: 264–266 °C, IR (KBr, ν, cm^{-1}): 3,559, 3,366, 3,319, 3,188, 2,197, 1,712, 1,657, ^{1}HNMR (400 MHz, DMSO-d_6): δ (ppm) = 1.1 (s, 3H, CH_3), 7.2–7.4 (m, 4H, Ar–H), 7.5 (s, 2H, NH_2), 7.9–8.1 (m, 5H, Ar–H).

Results and discussion

In our previous research, SMI-SO_3H catalyst was successfully synthesized and applied as an efficient catalyst in different MCRs, requiring acidic conditions [32]. In continuation of our ongoing research program on the development of new catalysts and technologies for the synthesis of biologically active heterocycles [22–27], herein we wish to extend the applicability of SMI-SO_3H catalyst in the promotion of the facile and clean synthesis of spirooxindoles with fused tetrahydro chromene. For the optimization of the reaction condition, initially, the condensation of isatin (**1a**), malononitrile (**2a**), and 3-methyl-1*H*-pyrazol-5-one (**3a**) which could be catalyzed by SMI-SO_3H was selected as a model reaction. At first, the effect of different solvents on the reaction times and yields of the product **4a** was examined (Table 1) and ethanol was selected as the solvent of choice. The optimization of the amount of the catalyst and reaction temperature indicated that the best result is achievable in the presence of 0.03 g of catalyst at reflux condition (Table 2). We investigated the effectiveness of the catalyst by comparing the reaction in 0.03 g of different appropriate catalysts. From the result in Table 3, the superior activity of our catalyst was vividly observed. It was found, more efficient even than silica perchloric acid as an excellent acidic catalyst [33] and commercially available Amberlyst-15 catalyst which has many applications in organic transformations [34]. To evaluate the scope and limitations of this methodology, we extended this optimized conditions for the preparation of spirooxindoles **4a**–**4e** by condensation reaction of isatin derivatives (**1a–1d**), malononitrile (**2a**) and pyrazols **3a** and **3b** (Scheme 1). The selected derivatives (**4a**–**4d**) were known and their melting point data were compared with those of authentic samples and found to be identical (Table 4) [35, 36].



Scheme 3 Synthesis of spiropyrans derivatives **11a**, **11b**, **12a** and **12b**

Table 1 Synthesis of **4a** in presence of different solvents

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	H_2O	Reflux	1.1	73
2	CH_3CH_2OH	Reflux	0.3	88
3	CH_3CN	Reflux	1.5	31
4	DMF	Reflux	1	42
5	CH_2Cl_2	Reflux	3.3	27
6	–	100	2	69

1 mmol (**1a**), 1 mmol (**2a**) and 1 mmol (**3a**) in presence of 0.03 g of catalyst and 3 mL of solvent

[a] Refers to the isolated yield

Table 2 Synthesis of **4a** in presence of different amount of catalyst and temperature

Entry	Catalyst (g)	Temperature (°C)	Time (h)	Yield[a] (%)
1	0.01	Reflux	1.1	42
2	0.02	Reflux	1	58
3	0.03	Reflux	0.3	88
4	0.04	Reflux	0.3	89
5	0.03	R.T.	3	30
6	0.03	50	1.5	42

1 mmol (**1a**), 1 mmol (**2a**) and 1 mmol (**3a**)

[a] Refers to the isolated yield

Table 3 Synthesis of **4a** in presence of different catalysts at refluxed condition

Entry	Catalyst	Time (h)	Yield[a] (%)
1	Silica perchloric acid	0.3	70
2	$AlCl_3$-HSO_4	4	43
3	SMI-SO_3H	0.3	88
4	Dawson	6	25
5	Amberlyst-15	0.4	55
6	–	24	–

1 mmol (**1a**), 1 mmol (**2a**) and 1 mmol (**3a**) in presence of 0.03 g of catalyst and 3 mL of EtOH

[a] Refers to the isolated yield

Table 4 Synthesis of spirooxindole derivatives **4a**–**4e** under optimized conditions

Entry	Product	Time (min)	Yield[a] (%)	Mp (°C)/Lit. Mp [references]
1	**4a**	20	88	281–283/279–280 [35]
2	**4b**	25	97	240–241/239–240 [35]
3	**4c**	25	92	282–283/282–283 [35]
4	**4d**	30	87	220–222/219–220 [35]
5	**4e**	45	78	213–214/210 [36]

1 mmol (**1a**–**1d**), 1 mmol (**2a**), 1 mmol (**3a**, **3b**) in the presence of 0.03 g catalyst and 3 ml EtOH at reflux conditions

[a] Refers to the isolated yield

Table 5 Synthesis of spirooxindole derivatives **7a–7d** and **8** under optimized conditions

Entry	Product	Time (min)	Yield[a] (%)	Mp (°C)/Lit. Mp [references]
1	**7a**	30	88	252–253/250 [37]
2	**7b**	30	85	206–208/210 [37]
3	**7c**	40	96	285–287/285–286 [38]
4	**7d**	30	87	241–242/244 [37]
5	**8**	40	84	256–257/258–260 [39]

1 mmol (**1a–1d**), 1 mmol (**2a, 2b**), 1 mmol (**5** or **6**) in the presence of 0.03 g catalyst and 3 ml EtOH at reflux conditions

[a] Refers to the isolated yield

Table 6 Synthesis of spiropyrans derivatives **11a**, **11b**, **12a** and **12b** under optimized conditions

Entry	Product	Time (min)	Yield[a] (%)	Mp (°C)/Lit. Mp [references]
1	**11a**	90	83	229–231/227–230 [40]
2	**11b**	115	87	210/210–211 [40]
3	**12a**	45	78	251–253/250–252 [41]
4	**12b**	50	85	264–266

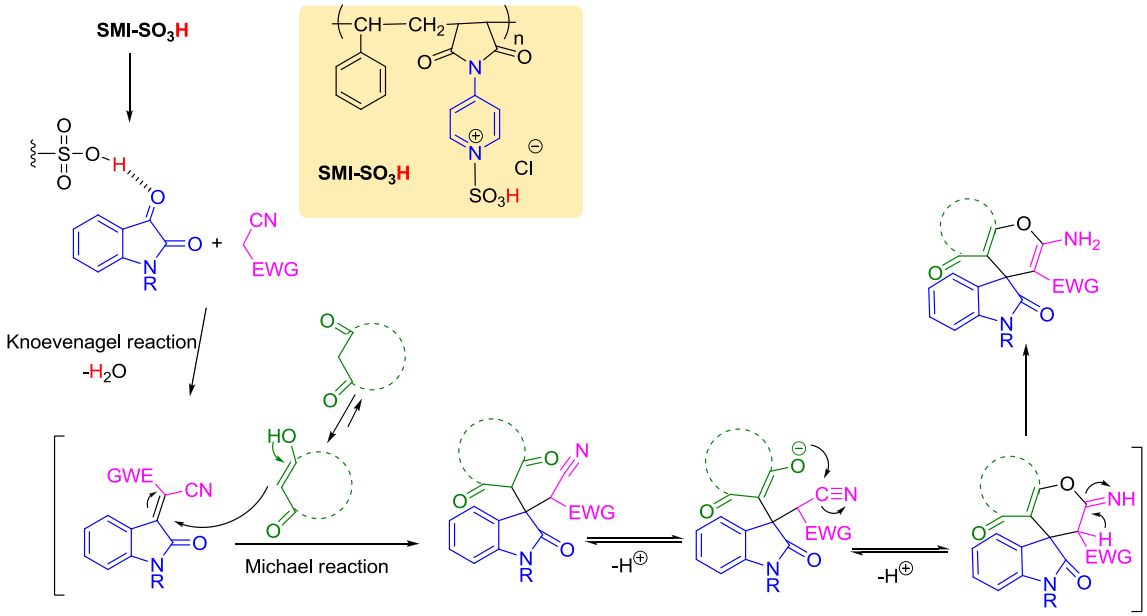
1 mmol (**1a–1e**), 1 mmol (**2a**, **2b**), 1 mmol (**5** or **6**) in the presence of 0.03 g catalyst and 3 ml EtOH at reflux conditions

[a] Refers to the isolated yield

Encouraged by these results, we turned our attention to study the reactivity of an equimolar quantity of isatin derivatives (**1a–1e**), different nitrolo active methylene components (**2a** and **2b**), and 4-hydroxy coumarin (**5**) or dimedone (**6**) under the obtained optimized reaction conditions (Scheme 2). We found out that using SMI-SO_3H acid catalyst makes this method extremely simple and suitable to provide a variety of spiropyrans (**7a–7d** and **8**) in a single-step process. The selected synthesized derivatives (**7a–7d** and **8**) were known and their melting point data were compared with those of authentic compounds and found to be identical (Table 5) [37–39].

To further explore the potentiality of this process in the heterocyclic synthesis, we used this approach for the synthesis of spiropyrans. Acenaphthenequinone (**9**) and ninhydrin (**10**) were reacted with pyrazolone derivatives **3a** and **3b** (Scheme 3). The reaction proceeded under similar conditions and afforded the corresponding spiro-acenaphthylene derivatives in excellent yields and selectivity (Table 6). Thus, using this catalyst provides an efficient route to access spiropyrans. The synthesized derivatives (**11a**, **11b**, **12a**) were known and their melting point data were compared with those of the authentic samples and found to be identical (Table 6) [40, 41]. In addition, spectra data of new compound **12b** conformed its structure.

The plausible mechanism for the formation of spirooxindole **7a–7d** and **8** involves the activation of isatin by SMI-SO_3H as an acid catalyst to generate α,β-unsaturated dicyano adduct which is subsequently subjected to the 1,4-addition of 1,3-dione. This adduct undergoes intramolecular cyclization through [1, 3] -sigmatropic proton shift of the iminopyrans which leads to the formation of a 2-amino-4*H*-pyran ring system. Because of the higher electrophilicity and lower steric



Scheme 4 The possible mechanism for the preparation of spirooxindole **7a–7d** and **8** with SMI-SO_3H

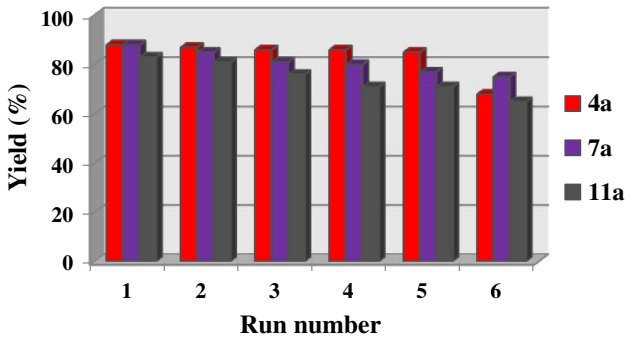


Fig. 1 The recyclability of the SMI-SO_3H in the preparation of **4a**, **7a**, and **11a**

hindrance of the nitrile group toward nucleophilic addition, the nucleophilic addition of enolic oxygen occurs preferably to nitrile rather than to the ester group, when both nitrile and ester groups are present, providing the desired 2-amino-4*H*-pyran with high regioselectivity (Scheme 4).

Because of green chemistry viewpoint, the recyclability and reusability of the catalyst was carried out for the synthesis of **4a**, **7a** and **11a** compounds in each selected multi-component reaction. Upon completion of the reaction, the catalyst was simply recovered by simple filtration, washing with acetone and drying at 70 °C for 3 h and reused for another fresh reaction run. The results clearly showed that the catalyst could be efficiently recovered and recycled even after 6 cycles without suffering any significant drop in its catalytic activity or the yield of reaction (Fig. 1).

Conclusions

In conclusion, we have successfully developed an interesting mild three-component one-pot process with sequential Knoevenagel/Michael/cyclization reactions, catalyzed by SMI-SO_3H as a solid acid for the efficient synthesis of diverse spiropyrans in good yields and high regioselectivity. The catalyst not only plays a crucial role in the progress of the reactions regarding the rate and yields of the products, but with it, the common problems in the recovery and reuse of the catalysts is also circumvented. This catalyst system could be easily separated from the reaction mixture almost, quantitatively, in high purity and being directly reused after simple extraction, for several times with no noticeable loss of activity, concluding from the comparison of the yield of products for each run.

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