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Solvent-free multicomponent reactions using the novel *N*-sulfonic acid modified poly(styrene-maleic anhydride) as a solid acid catalyst

Majid. M. Heravi*, Elaheh Hashemi, Yahya Shirazi Beheshtiha, Khadijeh Kamjou, Maryam Toolabi, Nastaran Hosseintash

Department of Chemistry, School of Science, Alzahra University, Vanak, Tehran, Iran

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ABSTRACT

A new *N*-sulfonic acid based on the polymer-support as a solid acid catalyst is prepared by the reaction of the modified poly(styrene-*alt*-maleic anhydride) with neat chlorosulfonic acid. 4*H*-Pyrimido[2,1-b]benzothiazole derivatives, tetrasubstituted imidazoles and benzoxanthenones as selected solvent-free multicomponent reactions were successfully synthesized using this catalyst. These eco-friendly protocols offer several advantages such as green and cost-effective procedures with excellent yield, shorter reaction time, simpler work-up, recovery, and reusability of metal-free solid acid heterogeneous catalyst along with tolerance of a wide range of functional groups.

1. Introduction

Assembling several molecules into the product in one reaction step is as a result of the convergent character of multi-component reactions (MCRs) which often give excellent chemo- and regioselective products. These simple, atom economy and time-saving methods make that an important procedure in the synthesis of biologically active compounds such as drugs and agricultural chemicals [1,2].

Increasing the importance of heterocyclic compounds in the field of pharmaceuticals and industrial chemicals has increased the development of simple, elegant and facile methodologies for their synthesis. MCRs reactions remain the most efficient synthetic transformation to produce heterocyclic compounds [3,4].

Using the eco-friendly reusable heterogeneous catalysts such as solid acids instead of conventional, toxic and polluting traditional homogeneous Brönsted and Lewis acid catalysts is currently in much demand. Solid acids have many advantages over liquid acids in organic reaction catalysis such as their efficiency, easy recyclability and recoverability, operational simplicity, non-corrosive and environmental friendly nature. These benefits make them efficient catalysts in industry and there are more than 100 industrial transformations using over 103 solid acids at the end of the last century [5–11]. Although, among various supports that can be used for the preparation of the above mentioned catalysts [12–15], silica and zeolite are the more extensively used [16–21], 'leaching' in these supported catalysts leads to loss of activity and they are also thermally unstable above 120 °C in their acid form. Consequently, the synthesis of new support like polymers for the preparation of solid acid catalysts that addresses these drawbacks is enviable [22–25].

Poly(styrene-*co*-maleic anhydride) (SMA) as a commercially available copolymer with reactive anhydride groups, which are susceptible to be modified with different nucleophilic reagents, is an attractive candidate support for design of different reagents [26–31] and catalyst [32]. In the course of our studies on the modification and use of heterogeneous solid acid catalyst in organic transformations [33–38], and in continuation of our interest in synthesis of biologically heterocyclic systems via MCR [39–42] herein we attempted the reaction SMA with 4-aminopyridine and discovered the capability of new modified support in synthesis of new *N*-sulfamic acid modified poly(styrene-maleic anhydride) catalyst. In addition, for the development of environmentally benign chemical methods in which heterogeneous recyclable catalysts are used under solvent-free conditions, we examined the efficiency of this heterogonous catalyst in some solvent-free multicomponent reactions.

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* Corresponding author. Fax: +98 21 88041344.
E-mail address: mmh1331@yahoo.com (Majid.M. Heravi).

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2. Experimental

2.1. Materials

N,*N*-Dimethylformamide (DMF) and triethylamine (TEA) were distilled and kept in 4 Å molecular sieve before use. The other reagents were not purified before use and were purchased from Aldrich and Merck with high-grade quality (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.

2.2. Equipments

The ^{1}H NMR and ^{13}C NMR spectra were recorded by 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 500–4000 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). The scanning electron micrographs of the catalyst surface were recorded using Lecia Cambridge S 360 SEM instrument. Thermogravimetric analysis (TGA/DTG) data were recorded on a Setaram instrument (Caluire, France) at a heating rate of 10 °C/min under nitrogen atmosphere. All yields refer to isolated products.

2.3. Catalyst synthesis

The chemical modification of SMA (**1**) was performed in two steps according to Lee et al. optimized reactive condition [43]. 1.00 g SMA, 1.54 g 4-aminopyridine (**2**) and 15 mL dry DMF were added into a 100-mL glass reactor and then N_2 gas was charged into the reactor and sealed. The reactor was placed into a thermostatic oil-bath on the oscillator and the reactive mixture was oscillated until the reagents dissolved in DMF and kept oscillating at 35 °C for 3.5 h. After that, 0.6 mL acetic anhydride, 0.33 g sodium acetate and 0.3 mL triethylamine were added into the reactor by syringe (Scheme 1). The temperature was continuously raised to 75 °C and oscillating for another continued for 3.5 h. The reaction mixture was cooled to room temperature, and was poured slowly into 300 mL of vigorously stirring methanol. A fiber-like precipitated polymer was repeatedly washed with methanol, collected by filtration and dried under reduced pressure at 70 °C to constant weight. For further purification, the SMI polymer (**3**) was re-precipitated twice.

Chlorosulfonic acid (0.23 mL as a >97% standard solution) was added to a suspension of powdered (0.5 g) SMI in 10 mL dry CH_2Cl_2 over a period of 5 min. The mixture was stirred at room temperature for 6 h then dichloromethane was removed under reduced pressure. The solid powder was dried under vacuum at 65 °C for 4 h to afford SMI-SO$_3$H (0.719 g) as a light-yellow powder (Scheme 1).

IR spectrum of SMI (υ_{max}: cm^{-1}): 3209.61 (br), 2928.77 (br), 1783–1705 (s), 1665.01 (s), 1564.80 (s), 1415.83 (s), 1252.92 (w), 1192.59 (w), 1102.29 (w), 763.60 (s).

IR spectrum of SMI-SO$_3$H (υ_{max}: cm^{-1}): 3208.56 (br), 1721.25 (s), 1655.39 (s), 1531.21 (m), 1288.53 (s), 1175.34 (s), 1069.94 (s), 1007.23 (s), 884.56 (s), 850.87 (s), 578.35 (s).

2.4. Catalytic reactions

2.4.1. General procedure for the synthesis of 4H-pyrimido[2,1-b]benzothiazole derivatives (*8a–g*)

A mixture of the ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), and 2-aminobenzothiazole (1 mmol) in the presence of SMI-SO$_3$H (0.08 g) was stirred at 100 °C in an oil bath. Completion of the reaction was monitored by TLC. After that, the mixture was cooled to room temperature, then hot ethanol was added and the solid heterogeneous catalyst was easily filtrated. The obtained catalyst was washed with acetone and dried under reduced pressured in 70 °C for 3 h and stored for another consecutive reaction run. The filtrate was concentrated to solidify and the crude product **8a** was purified by re-crystallization from aqueous ethanol in 72% yield. The selected benzothiazole derivatives (**8b–g**) were similarly synthesized and their physical data were determined (Scheme 2).

The physical and spectral (melting point (Mp), IR, ^{1}H NMR, and Mass) data for the new derivatives **8b** and **8c** are as follow:

Ethyl-2-methyl-4-(4-chlorophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (8b, $C_{20}H_{17}ClN_2SO_2$): Mp 86–88 °C; IR (υ_{max}, cm^{-1}): 3390, 1699, 1670, 1588, 1496, 744; ^{1}H NMR: δ_H 1.21 (t, 3H, CH_2CH_3), 2.32 (s, 3H, CH_3), 4–4.09 (m, 2H, OCH_2), 6.48 (s, 1H, CH), 7.17–7.20 (t, 1H, ArH), 7.28–7.48 (m, 6H, ArH), 7.73–7.75 (d, 1H, Ar–H) ppm; MS (*m*/*z*): 384 (M^+), 355, 311, 273, 245, 199, 175, 134.

Ethyl-2-methyl-4-(3-nitrophenyl)-4H-pyrimido[2,1-b][1,3]benzothiazole-3-carboxylate (8c, $C_{20}H_{17}N_3SO_4$): Mp 222–224 °C; IR (υ_{max}, cm^{-1}): 3073,2981, 1656, 1581, 1505, 748; ^{1}H NMR: δ_H 1.21 (t, *J* = 7 Hz, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.99–4.13 (m, 2H, OCH_2), 6.7 (s, 1H, CH), 7.18–8.10 (m, 7H, ArH), 8.36 (s, 1H, ArH) ppm; MS (*m*/*z*,%): 395 (M^+), 366, 322, 273, 245, 199, 175, 134.

2.4.2. General procedure for the synthesis of 1,2,4,5-tetrasubstituted imidazoles (*12a–m*)

A mixture of benzil (1 mmol), benzaldehyde (1 mmol), aniline (1 mmol), ammonium acetate (1 mmol) and 0.03 g of SMI-SO$_3$H was stirred in an oil-bath (90 °C). After the completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature. The reaction mixture was soluble in warm absolute ethanol and separated from the catalyst which was insoluble in Ethanol. The recovered catalyst was washed with acetone and dried under reduced pressured in 70 °C for 3 h and stored for another consecutive reaction run. The pure product **12a** was obtained by re-crystallization of the reaction mixture from ethanol (85% yield). By the application of this reaction condition, other imidazole derivatives (**12b–m**) were synthesized and their physical data were determined (Scheme 3).

2.4.3. General procedure for the synthesis of benzoxanthenones (*15a–g*)

A heterogeneous mixture of β-naphthol (1.0 mmol), benzaldehyde (1.0 mmol), dimedone (1.0 mmol) and SMI-SO$_3$H (0.07 g) is heated at 80 °C in an oil bath under solvent-free condition. The progress of the reaction was monitored by TLC. After the completion of the reaction, the product was extracted with hot ethanol and the catalyst was easily filtered. The filtered catalyst is washed with acetone, dried under reduced pressure, and reused for successive runs. The filtrate is concentrated and the crude product **15a** is re-crystalized from ethanol to give 78% yield. Some selected benzoxanthenones (**15b–g**) were prepared in the similar way and their physical data were compared with those of authentic samples (Scheme 4).

3. Results and discussion

3.1. Preparation and characterization of the SMI-SO$_3$H catalyst

The high concentration and reactivity of the cyclic anhydride groups of SMA make this polymer as an ideal support in organic synthesis [26–31]. In continuation of Nàjera and co-workers