J. Chem. Sci. Vol. 124, No. 2, March 2012, pp. 501–508.

Solid-supported sulfonic acid-containing catalysts efficiently promoted one-pot multi-component synthesis of β-acetamido carbonyl compounds

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MS received 3 July 2011; revised 26 September 2011; accepted 7 October 2011

Abstract. Silica-functionalized sulfonic acid (SFSA) and sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO_3H) efficiently catalysed one-pot multi-component condensation of enolizable ketones or alkyl acetoacetates with arylaldehydes, acetonitrile and acetyl chloride to afford the corresponding β-acetamido ketone or ester derivatives in high to excellent yields and in relatively short reaction times. Moreover, in this work, some novel β-acetamido carbonyl compounds (i.e., one complex structure) are synthesized.

Keywords. Solid-supported catalysts; silica-functionalized sulfonic acid (SFSA); sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO_3H); enolizable ketone; β-acetamido ketone; β-acetamido ester.

1. Introduction

Multi-component reactions (MCRs) are sometimes viewed as subdiscipline of organic chemistry; actually this topical field transcends any narrow classification and pervades essentially all chemistry. In fact, in MCRs, besides the multi-step reaction and sequential synthesis of target molecule, the desired product can also be obtained in one-pot reaction of three or more starting compounds.[1] Speed, diversity, efficiency, and environmental amiability are some of the key features of this class of reactions.[1]

β-acetamido ketone or ester derivatives are useful building blocks for a number of biologically and pharmaceutically valuable compounds. They can be used as precursor for synthesis of various antibiotics,[2] β-amino acids,[3] 1,3-amino alcohols,[4] δ-lactams,[5] as well as biologically attractive compounds such as nikkomycins or neopolyoxins.[4,6] Generally, the one-pot multi-component condensation of enolizable ketones with aromatic aldehydes, acetonitrile and acetyl chloride have been used as a most common synthetic route towards β-acetamido carbonyl compounds. Some catalysts have been employed to promote this transformation, e.g., $CoCl_2$,[7] sulfamic acid,[8] $SnCl_2.H_2O$,[9] 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis(tetrafluoroborate) {selectfluor™},[10] $Zr(HSO_4)_4$,[11] $Mg(HSO_4)_2$,[11] $La(OTf)_3$,[12] ZnO,[13] $ZrOCl_2.8H_2O$,[14] $K_5CoW_{12}O_{40}.3H_2O$,[15] $CeCl_3.7H_2O$,[16] and sulfated zirconia.[17] However, the reported protocols for the synthesis of β-acetamido ketones/esters suffer from one or more of the following drawbacks: (i) low yields, (ii) long reaction times, (iii) the use of large amount of catalyst, (iv) the use of toxic or expensive catalysts, (v) tedious work-up procedure, (vi) harsh reaction conditions, and (vii) performing of the reaction under certain special conditions. Thus, search for finding efficient, safe and inexpensive catalysts for the preparation of β-acetamido ketones/esters is still relevant.

In recent years, the use of solid-supported catalysts has gained considerable attention both in industrial and academia research due to their unique properties such as enhanced reactivity as well as selectivity, efficiency, straightforward work-up, and the eco-friendly reaction

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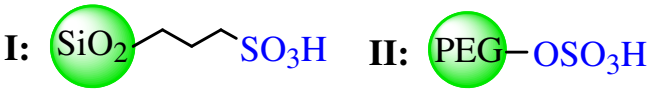


Figure 1. The structure of silica-functionalized sulfonic acid (SFSA, **I**) and sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO_3H, **II**).

conditions.[18] In this type of catalysts, various solid-supports have been used, including porous inorganic oxides such as silica, and organic polymers such as polyethylene glycol, because of their high surface areas and well-defined structures.[18] One useful example of silica-supported catalysts is silica-functionalized sulfonic acid (SFSA) in which the reactive centers are highly mobile similar to that of homogeneous catalysts (figure 1),[18e–k] and has been used as an efficient acidic catalyst for some organic transformations such as acetalization of carbonyl compounds,[18e] thioacetalization of carbonyl compounds,[18f] synthesis of benzimidazoles,[18g] preparation of 3,4-dihydropyryimidinones,[18h] synthesis of 1,4-dihydropyridines,[18i] brominatation of carbonyl compounds,[18j] and brominatation of phenols, alkoxy arenes and anilines.[18k] Polyethylene glycols (PEGs) are another type of solid-supports which are inexpensive, readily functionalized, environmentally benign and commercially available polymeric matrixes with their molecular weight is >2000 Da.[18l,m] Moreover, high reactivity, lack of diffusion phenomena, and analytical simplicity (advantageous features of homogeneous solution chemistry) besides the ready isolation and purification of products (advantageous features of solid phase methods)[18m] introduce PEGs as an important group of polymeric supports for the preparation of polymer-supported catalysts. Sulfuric acid-modified polyethylene glycol-6000 (PEG-OSO_3H) is an interesting case of PEG-supported catalysts that functionalized by sulfonic acid groups, and has been successfully used for synthesis of 3,4-dihydropyrimidones,[18n] triazolo[1,2-a]indazole-triones and spiro triazolo[1,2-a]indazole-tetraones,[18o] thiocyanohydrines,[18p] acylals,[18q] *bis*(indolyl) methanes,[18r] and poly-substituted quinolines.[18s]

Considering the above points, we report here new catalytic applications of SFSA and PEG-OSO_3H in the synthesis of β-acetamido ketones and esters *via* the one-pot multi-component condensation of enolizable ketones/alkyl acetoacetates with aromatic aldehydes, acetonitrile and acetyl chloride at room temperature (scheme 1).

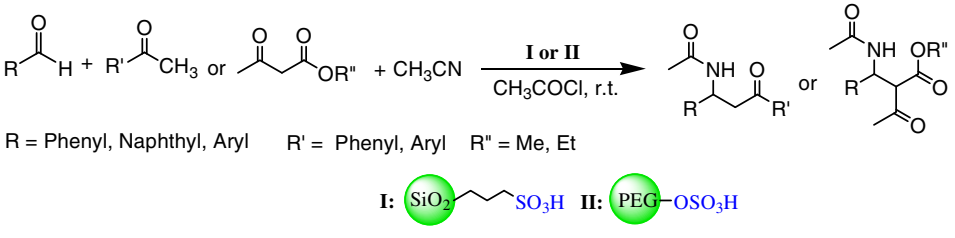
2. Experimental

2.1 *General*

All chemicals were purchased from Merck or Fluka Chemical Companies. All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm). Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

2.2 *General procedure for the synthesis of β-acetamido carbonyl compounds*

To a mixture of compounds consisting of enolizable ketone or alkyl acetoacetate (1 mmol), arylaldehyde (1 mmol), acetonitrile (3 mL) and acetyl chloride (0.3 mL) in a 10 mL round-bottomed flask, was added SFSA (0.05 g) or PEG-OSO_3H (0.15 g, 0.025 mmol, 2.5 mol%), and the resulting mixture was stirred at room temperature. After completion of the reaction, as monitored with TLC, crushed ice (10 mL) was added to the reaction mixture and stirred thoroughly. On solidification, the crude product was filtered, dried, and purified by short column chromatography on silica gel



Scheme 1. The synthesis of β-acetamido ketones/esters from enolizable ketones/alkyl acetoacetates, aldehydes, acetonitrile and acetyl chloride using SFSA and PEG-OSO_3H.

eluted with EtOAc/*n*-hexane (1/4). **Note:** Compounds **8**, **9**, **10**, **17**, **20**, **21**, **22**, **23**, **25**, **26** and **2a** are new.

3. Results and discussion

Initially, the silica and polymer-supported SO_3H-containing catalysts (SFSA and PEG-OSO_3H) were prepared according to the reported procedures.[18f,o], To examine the applicability of the catalysts in the synthesis of *β*-acetamido carbonyl compounds, the multicomponent condensation of 4-bromoacetophenone (1 mmol) with benzaldehyde (1 mmol), acetonitrile (3 mL) and acetyl chloride (0.3 mL) was selected as a model reaction, and studied in the presence of different amounts of SFSA as well as PEG-OSO_3H at room temperature. The results are summarized in table 1. As it is shown in table 1, 0.15 g (2.5 mol%) of PEG-OSO_3H or 0.05 g of SFSA efficiently catalysed the reaction, and produced the product in high yields and in short reaction times (table 1, entries 3 and 8). Increasing the amounts of the catalysts showed no substantial improvement in the yields. Moreover, it was observed that the reaction did not proceed at all in the absence of SFSA or PEG- OSO_3H (table 1, entry 1).

To recognize the role of silica as well as polyethylene glycol skeletons of the catalysts in the reaction, the condensation between 4-bromoacetophenone, benzaldehyde, acetonitrile and acetyl chloride was checked using SO_3H residues of the catalysts without solid supports (H_2SO_4 and $ClSO_3H$) as well as solid supports (SiO_2 and PEG-6000) separately, in which significant decrease in the yields, and increase in the reaction times were observed (table 2, entries 2–6). Furthermore, the reaction was examined in the presence of H_2SO_4 together with SiO_2, H_2SO_4 together with PEG wherein the reaction times were longer, and the yields were lower than SFSA or PEG-OSO_3H (table 2, entries 7 and 8). These results confirmed that supporting the SO_3H group on silica or PEG-6000 significantly increased the efficacy of the catalysts.

Table 1. Effect of different amounts of the catalysts on the reaction of 4-bromoacetophenone (1 mmol) with benzaldehyde (1 mmol), acetonitrile (3 mL) and acetyl chloride (0.3 mL) at room temperature.

Entry	Catalyst	Catalyst Amount (g)	Time (h)	Yield[a] (%)
1	None	-	12	No reaction
2	SFSA	0.01	3	45
3	SFSA	0.05	1.5	90
4	SFSA	0.1	1.5	86
5	SFSA	0.2	1.5	88
6	PEG-OSO_3H	0.05	6	68
7	PEG-OSO_3H	0.1	3	84
8	PEG-OSO_3H	0.15 (2.5 mol%)	1.75	92
9	PEG-OSO_3H	0.2	1.75	92

[a]Isolated yield.

Table 2. Study of the role of silica as well as polyethylene glycol skeletons of the catalysts on the reaction.

Entry	Catalyst	Catalyst amount	Time (h)	Yield[a] (%)
1	SFSA	0.05 g	1.5	90
2	PEG-OSO_3H	0.15 (2.5 mol%)	1.75	92
3	H_2SO_4	2.5 mol%	7	36
4	$ClSO_3H$	2.5 mol%	7	23
5	SiO_2	0.05 g	10	11
6	PEG-6000	0.15 g (2.5 mol%)	10	15
7	H_2SO_4/SiO_2	2.5 mol%/0.05 g	7	40
8	H_2SO_4/PEG-6000	2.5 mol%/0.15 g	7	46

[a]Isolated yield.

In another study, generality and efficiency of SFSA and PEG-OSO_3H in the synthesis of *β*-acetamido carbonyl compounds were explored under the optimized reaction conditions by the reaction of different enolizable carbonyl compounds with a broad range of structurally and electronically diverse arylaldehydes, acetonitrile and acetyl chloride. The results are given in table 3. As it can be seen in table 3, all enolizable carbonyl compounds (acetophenone and its derivatives bearing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic rings, and alkyl acetoacetates) as well as arylaldehydes (benzaldehyde and its derivatives possessing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic rings) afforded the desired *β*-acetamido carbonyl compounds in high to excellent yields and in short reaction times. Moreover, the method worked well when 2-naphthaldehyde and anthracene-9-carbaldehyde were used instead of benzaldehydes (table 3, compounds **9**, **10**, **13**, **17**, **21**–**23**, **25** and **26**). In the reaction of *p*-aminoacetophenone with 2-naphthaldehyde (or anthracene-9-carbaldehyde), acetonitrile and acetyl chloride, the corresponding *N*-acylated *β*-acetamido ketones were obtained (table 3, compounds **22** and **23**).

Interestingly, the condensation of *p*-bromoacetophenone (3.2 equiv.) with a *tris*-aldehyde (1 equiv.), acetonitrile (6 mL) and acetyl chloride (0.9 mL) in the presence of SFSA as well as PEG-OSO_3H at room temperature afforded complex compound **2a** in 85 and 88% yields within 2.5 and 2.25 h, respectively

Table 3. The synthesis of β-acetamido ketones and esters *via* the condensation of enolizable ketones or alkyl acetoacetates with aldehydes, acetonitrile and acetyl chloride.

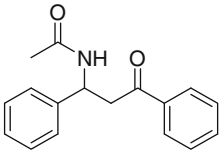
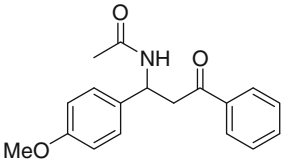
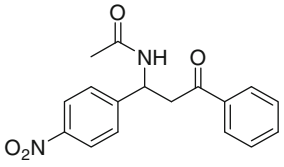
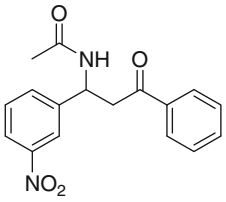
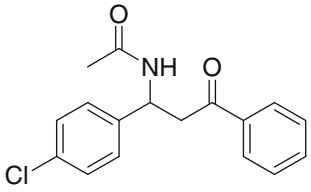
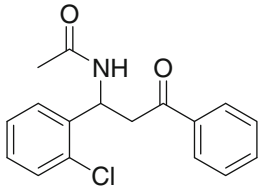
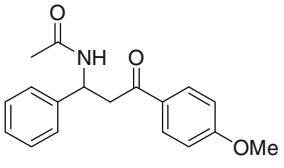
Entry	Product	SFSA Time (h)/Yield[a] (%)	PEG-OSO_3H Time (h)/Yield[a] (%)	M.p. ˚C (lit.)
1		1.75/91	2/93	101–103 (104–106)[25]
2		1.5/88	1.5/89	109–111 (110–112)[26]
3		2.5/83	2.5/86	151–152 148–149)[30]
4		2.75/84	3/88	120–123 (119–121)[30]
5		1.5/89	1.5/90	157–159 (156–158)[30]
6		2.25/86	2.5/84	158–160 (155–157)[33]
7		1.25/88	1.75/85	127–129 (130–132)[33]

Table 3. (continued)

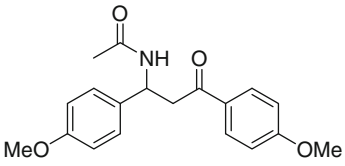
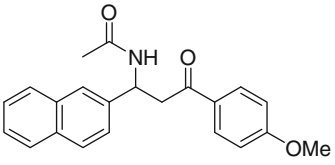
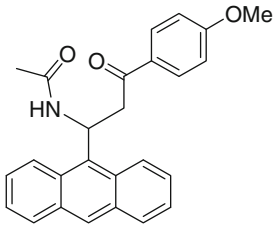
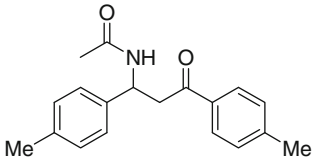
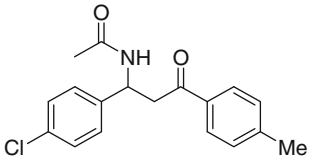
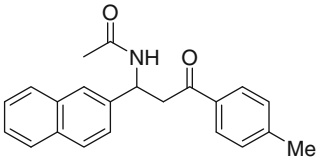
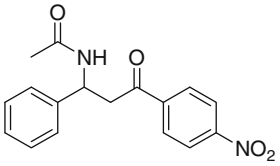
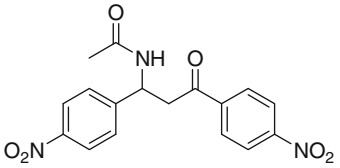
Entry	Product	SFSA Time (h)/Yield[a] (%)	PEG-OSO_3H Time (h)/Yield[a] (%)	M.p. ˚C (lit.)
8		0.75/93	1.0/91	124–127[b]
9		1.75/89	1.75/90	108–110[b]
10		3/80	3.5/84	138–140[b]
11		1.25/85	1.75/81	118–119 (-)[18]
12		1.5/90	2/90	130–132 (-)[18]
13		2.25/83	3/85	111–112 (112–114)[26]
14		2.5/84	2.5/89	75–77 (74–76)[33]
15		3/80	2.75/86	185–188 (187–188)[25]

Table 3. (continued)

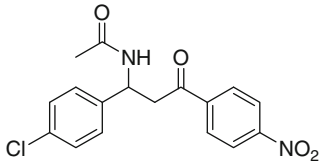
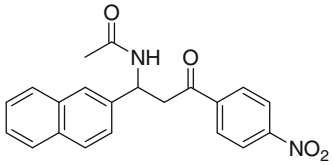
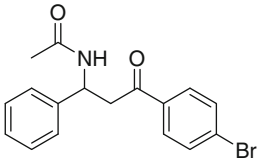
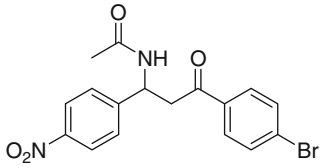
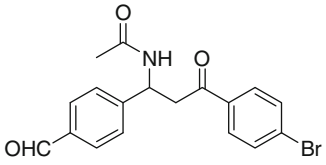
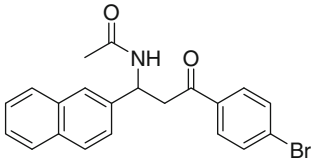
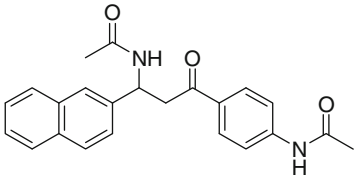
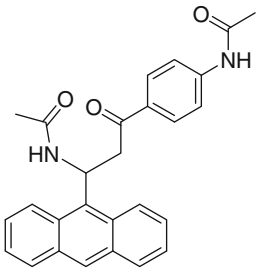
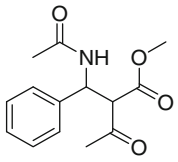
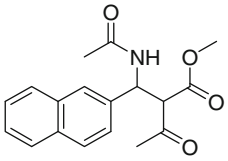
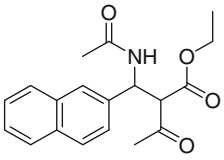
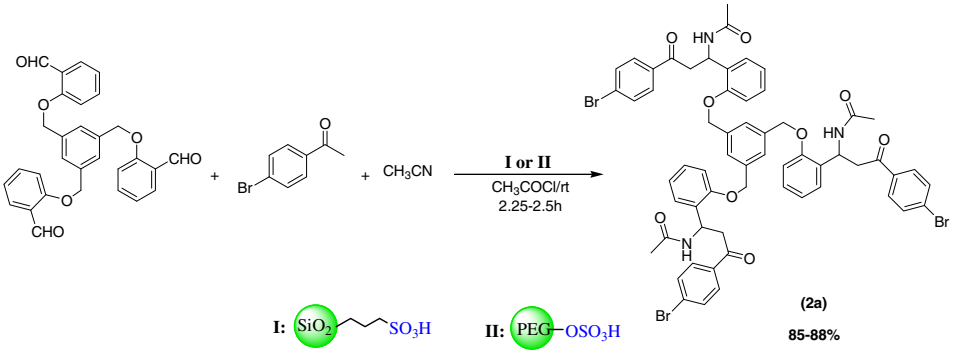
Entry	Product	SFSA Time (h)/Yield[a] (%)	PEG-OSO_3H Time (h)/Yield[a] (%)	M.p. ˚C (lit.)
16		2.5/81	3/86	114–116 (116–118)[26]
17		2.5/82	2.75/84	165–166[b]
18		1.5/90	1.75/92	100–101 (98–100)[26]
19		2.25/81	2/87	162–163 (-)[18]
20		2/85	1.75/88	104–105[b]
21		1.5/87	1.5/89	138–140[b]
22		2/88	1.25/80	168–174[b]
23		3.25/79	3.75/81	166–167[b]

Table 3. (continued)

Entry	Product	SFSA Time (h)/Yield[a] (%)	PEG-OSO_3H Time (h)/Yield[a] (%)	M.p. ˚C (lit.)
24		2.25/88	2.25/86	140–142 (140–141)[25]
25		2/89	2.25/89	138–139[b]
26		1.75/85	2/90	149–152[b]

[a]Isolated yield. [b]This compound is new.



Scheme 2. The synthesis of complex compound **2a**.

(scheme 2). For the first time, we have reported the synthesis of this class of β-acetamido ketones.

4. Conclusion

In conclusion, we have introduced the new applications of SFSA and PEG-OSO_3H in organic synthesis. In this work, we have successfully used them for the preparation of β-acetamido ketone/ester derivatives from enolizable ketones or alkyl acetoacetate, arylaldehydes, acetonitrile and acetyl chloride. The promising points for the application of the solid-supported catalysts in the reaction are efficiency, generality, high yields, relatively short reaction times, mild conditions, cleaner reaction profile and simplicity.

Supporting information

Spectral data for compound entries 7–23 and entries 25, 26 are given as supplementary material (www.ias.ac.in/chemsci).

Acknowledgements

The authors gratefully acknowledge the partial support received from the Research Affairs Office of Bu-Ali Sina University (Grant number 32-1716 entitled development of chemical methods, reagents and molecules), and Center of Excellence in Development of Chemical Method (CEDCM), Hamedan, I.R. Iran.

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