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Journal of Molecular Catalysis A: Chemical 276 (2007) 226–229
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Sulfamic acid as a cost-effective catalyst instead of metal-containing acids for the one-pot synthesis of β-acetamido ketones

Majid M. Heravi [a,*], Leila Ranjbar [a], Fatemeh Derikvand [a], Fatemeh F. Bamoharram [b]

[a] *Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran*
[b] *Department of Chemistry, Islamic Azad University, Mashhad Branch, Mashhad, Iran*

Received 28 April 2007; received in revised form 23 June 2007; accepted 5 July 2007
Available online 10 July 2007

Abstract

An efficient and improved procedure for the synthesis of β-acetamido carbonyl compounds is developed using sulfamic acid (SA) as a reusable, green catalyst at room temperature.

Keywords: Multicomponent reactions; MCRs; Sulfamic acid; β-Acetamido ketone

1. Introduction

β-Acetamido ketones are versatile intermediates, in that their skeletons exist in a number of biologically or pharmacologically active compounds [1,2]. They could easily be converted to 1,3-amino alcohols [3], which are utilized for the synthesis of several antibiotics [4].

β-Acetamido ketones are usually prepared through acylation of β-aminoketones [5], Michael addition to α,β-unsaturated ketones [6] or photoisomerisation of phthalimides [7].

The best-known route for the synthesis of these compounds is the one-pot condensation of an aldehyde, an enolisable ketone, acetyl chloride and acetonitrile, originally reported by Iqbal and co-workers.

A few catalysts including $CoCl_2$ [8], cobalt(II) acetate supported on polyaniline [9], Montmorillonite K10 Clay [10], SiO_2–H_2SO_4 [11], triflate salts [12], zeolite [13], iodine [14], $BiCl_3$ generated in situ from BiOCl and acetyl chloride [15], $ZrOCl_2{\cdot}8H_2O$ [16a], iron(III) chloride [16b], and heteropoly-acids [17] have already been applied for the synthesis of β-acetamido ketones, using this method. Although some of these methodologies are efficient and provide the practical means for the synthesis of β-acetamido ketones, some of the reported methods suffer from drawbacks such as longer reaction times, tedious work up, higher temperatures, expensive catalysts, lower yields and requiring an inert atmosphere.

In recent years considerable emphasis has been placed on improvement in environmental impact of industrial processes. Solid acids can play a significant role in the development of cleaner technologies [18]. Most of the used solid acid catalysts are metal-containing and are not green, so environmental pollution has limited their practical usage in a large scale and they should be replaced by a suitable one.

Sulfamic acid (SA) is a nonvolatile, inexpensive, and non-corrosive common inorganic acid. It is a white crystalline solid with outstanding physical and chemical properties and is commercially available. Due to its zwitter-ionic property, this heterogeneous catalyst could be readily recycled and reused through a simple filtration and washing. SA has emerged as a substitute for conventional acidic catalysts in different areas of organic synthesis. In recent years, it has been used as an efficient catalyst for acid catalyzed reactions, viz. acetalization [19], esterification [20], acetylation of alcohols and phenols [21], nitrile formation [22], tetrahydro-pyranylation of alcohols [23] and transesterification of β-ketoesters [24]. Moreover, some important organic transformations, including the Biginelli condensation [25], the Beckmann rearrangement [26], inter- and intramolecular imino Diels–Alder reaction [27] and very recently the pechmann condensation [28a], etc. [28b,c,d] have been carried out in the presence of SA.

* Corresponding author. Fax: +98 2188047861.
E-mail address: mmh1331@yahoo.com (M.M. Heravi).

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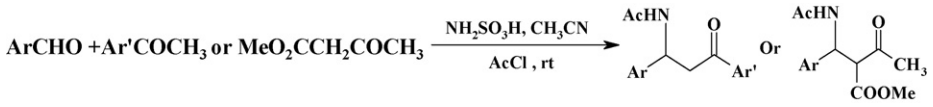
doi:10.1016/j.molcata.2007.07.010



Scheme 1.

Table 1
Optimization of the reaction condition in the synthesis of β-acetamido-β-phenyl-propiophenone in CH_3CN over SA

Entry	mol%	Temperature (°C)	Time (min)	Yield (%)[a]
1	0	25	720	0
2	2.5	25	85	70
3	5	25	85	90
4	10	25	85	90
5	5	80	85	80
6	5	25	24 h	50

[a] Yields were analyzed by GC.

Based on our previous studies on the use of heterogenous catalysts for carrying organic reactions [29–35] and in continuation of our investigations on the synthesis of β-acetamido ketones/esters [17], herein we wish to report a mild and efficient approach for the synthesis of these compounds using sulfamic acid (SA) as a reusable, green catalyst at room temperature (Scheme 1).

2. Results and discussion

Initially, benzaldehyde has been used to react with acetophenone and acetyl chloride over different catalytic amounts of sulfamic acid in acetonitrile (reactant as well as solvent), at 25 °C and under refluxing condition, in order to optimize the reaction conditions (model reaction) (Table 1).

The best catalytic activity of SA was optimized to be 5 mol% and any excess of the catalyst, beyond this proportion (10%), did not show any further increase in the conversion and yield.

Further prolongation of the reaction time and increasing the temperature seems to be ineffective for the improvement of the reaction. Thus, in a model experiment, when benzaldehyde (1.1 equiv.) was reacted with acetophenone (1 equiv.) and acetyl chloride (3 equiv.) in the presence of SA (5 mol%) in acetonitrile (3 mL) at room temperature, the corresponding β-acetamido ketone was obtained after 85 min in 90% yield (Table 1, entry 3).

We also examined the efficiency of benzoyl chloride instead of acetyl chloride in this reaction, but our attempts were failed to generate the corresponding β-acetamido ketones even after 24 h. When acetyl chloride was replaced by trimethyl silyl chloride (3 equiv.) the full conversion was not attained even after prolonged times (Table 2, entry 2).

The mechanism may be involving the formation of an enolate, which attacks the activated aldehyde to provide the corresponding β-acetoxy ketone 1, which can be converted to the final product by treatment with acetonitrile (Scheme 2); therefore acetyl group of the products has been derived from MeCN. This has been proven by carrying out the reaction with PhCN instead of MeCN in dichloromethane as solvent, which afforded the corresponding β-benzamido ketone in good yield (Table 2, entry 15).

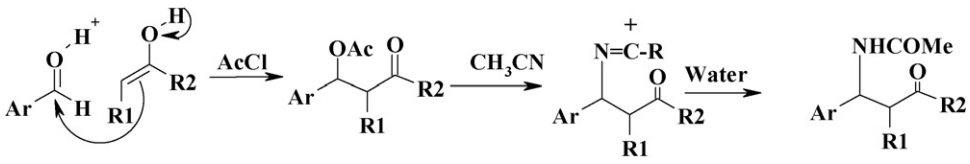
To test the recyclability, after completion of the model reaction, the catalyst was filtered off, washed with diethyl ether and activated at 70 °C for 2 h and used in another reaction with the same substrates. There was no significant change in the activity and selectivity after two cycles (90, 87 and 85% of product after three runs).

Under optimized conditions, a variety of aromatic aldehydes and ketones/β-ketoesters have been utilized for the preparation of β-acetamido ketones/esters and all products were obtained

Table 2
One-pot synthesis of β-acetamido ketones using catalytic amount of NH_2SO_3H

Entry	Ar	R1	R2	Time (min)	Yield (%)[a]	m.p. (°C)	
						Found	Reported [ref.]
1	H	H	Ph	85	90	104–105	102–104 [10]
2	H	H	Ph	120	48[b]		
3	4-Cl	H	Ph	137	90	149–150	146–148 [8]
4	4-Br	H	Ph	130	93	162–164	–
5	4-CH_3O	H	Ph	120	90	109–110	110–112 [16]
6	3-NO_2	H	Ph	102	89	119–121	112–115 [10]
7	4-NO_2	H	Ph	120	71	155–156	148–149 [10]
8	H	H	4-$NO_2C_6H_5$	130	75	70–71	74–76 [17a]
9	4-NO_2	H	4-$NO_2C_6H_5$	135	70	186–187	187–188 [7]
10	H	H	4-CH_3 OC_6H_5	68	92	127–129	130 [16]
11	H	CH_3	Ph	90	91	169–171	174 [16]
12	4-Cl	CH_3	Ph	50	83	163–164	162–164 [16]
13	H	$COOCH_3$	CH_3	90	60	135–136	129–131 [8]
14	4-Cl	$COOCH_3$	CH_3	120	62	137–140	130–132 [8]
15	3-NO_2	H	Ph	240	69[c]	191–192	194–195 [16]

[a] Yields were obtained using GC analysis.
[b] Using Me_3SiCl instead of AcCl.
[c] Using PhCN instead of MeCN in dichloromethane.



Scheme 2.

Table 3
Comparison of the catalyst effects in the synthesis of β-acetamido-β-phenyl-propiophenone

Entry	Cat. (mol%)	Time (h)	Temperature (°C)	Yield (%)	Reference
1	Silica sulfuric acid (78)	65 min	80	91	[11]
2	$Bi(OTf)_3$ (10)	30	RT	69	[12]
3	$Sc(OTf)_3$ (10)	30	RT	82	[12]
4	Montmorillonite K-10 (2 g)	7	70	80	[10]
5	NH_2SO_3H (5)	85 min	RT	90	This work

in good to excellent yields, averaging 70–93% (Table 2). In the case of methylacetoacetate, lower yields of the products were achieved. It may be due to the more stability of its enolate than those related to the acetophenone derivatives (Table 2, entries 13 and 14).

In these reactions α,β-unsaturated carbonyl compounds were obtained as by products in very low yields and prolongation of reaction time increase the amount of these by products (2–10%). Subsequent work showed that β-acetamido ketones, for example, β-acetamido β-phenyl-propiophenone in this condition converted to chalcone after 24 h in 33% yield. It showed that increasing the reaction time caused to elimination of acetamido group from the product and increased by products, so control of reaction time is very important in this reaction (Table 1, entry 6).

A mixture of chalcone (1 equiv.), acetyl chloride (3 equiv.) and NH_2SO_3H (5 mol%) in acetonitrile (5 mL) failed to produce any β-acetamido ketone after 12 h.

In order to show the merit of this method in comparison to those reported, we compared the results of the synthesis of β-acetamido-β-phenyl-propiophenone in the presence of silica sulfuric acid, $Bi(OTf)_3$, $Sc(OTf)_3$, Montmorillonite K-10 and NH_2SO_3H, with respect to the catalysts amounts, reaction times and temperatures and yields of the products (Table 3). It seems that Bronsted acids catalyze the reaction better than Lewis acids. It could be due to the creation of a bulky intermediate with Lewis acid catalysts.

3. Conclusion

In conclusion, we have demonstrated an alternative and simple procedure for the synthesis of β-acetamido ketones using sulfamic acid as an eco-friendly, reusable, inexpensive and efficient catalyst. High yields, relatively short reaction times, simplicity of operation and easy work-up procedure are some advantages of this protocol.

4. Experimental

All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical. Yields were obtained using GC analysis. All yields are referred to area% of the peak of the desired product from GC spectroscopy.

4.1. Synthesis of β-acetamido ketone and esters: general procedure

At room temperature, sulfamic acid (0.05 mmol, 5 mg) was added to a solution of aldehyde (1.1 mmol) and ketone or methylacetoacetate (1 mmol) and acetyl chloride (3 mmol) in acetonitrile (3 mL). The resulted mixture was stirred for appropriate time (determined by TLC) and then filtrated. The filtered catalyst could be washed with ether (3× 5 mL) and activated at 70 °C for 2 h, and reused in another cycle. The filtrate was poured into ice water, which resulted in precipitation of the desired β-acetamido ketone. The precipitated solid was filtered and washed with diethylether. The pure product was obtained by recrystallization from $EtOH/H_2O$.

4.2. Selected spectroscopic data

Entry 5, Table 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 3.36–3.42 (dd, J = 6.4, 17.2 Hz, 1H), 3.69–3.75 (dd, J = 5.6, 17.2 Hz, 1H), 3.74 (s, 3H), 5.47–5.51 (m, 1H), 6.64–6.66 (d, J = 7.2 Hz, 1H), 6.80–6.84 (m, 2H), 7.23–7.25 (d, J = 8.8 Hz, 2H), 7.41–7.45 (t, J = 7.8 Hz, 2H), 7.53–7.57 (t, J = 7.6 Hz, 1H), 7.88–7.91 (d, J = 8 Hz, 2H). IR (KBr): 3310, 1690, 1650, 1550, 1510, 1240, 1030, 760, 690 cm^{-1}.

Entry 6, Table 2: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (s, 3H), 3.49–3.57 (dd, J = 5.5, 17.6 Hz, 1H), 3.78–3.86 (dd, J = 5, 17.6 Hz, 1H), 5.64–5.71 (m, 1H), 6.96–6.99 (br d, J = 8.1 Hz, 1H), 7.45–7.53 (m, 3H), 7.57–7.62 (t, J = 7.3 Hz, 1H), 7.70–7.73 (d, J = 7.5 Hz, 1H), 7.89–7.92 (br d, J = 7.2, 2H), 8.09–8.12 (d, J = 8.2 Hz, 1H), 8.24 (br s, 1H). FT-IR (KBr): 3292, 3068, 2245, 1690, 1647, 1523, 1351, 990, 755, 685 cm^{-1}.

Entry 9, Table 2: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.1 (s, 3H), 3.56–3.64 (dd, J = 5.9 and 12 Hz, 1H), 3.87–3.94 (dd, J = 4.79 and 12 Hz, 1H), 5.66–5.73 (m, 1H), 6.63–6.66 (br d, J = 7.44 Hz, 1H), 7.52–7.57 (t, J = 7.94, 1H), 7.73–7.75 (d, J = 7.64, 1H), 8.07–8.1 (d, J = 8.62 Hz, 2H), 8.13–8.16 (d, J = 8.33, 1H), 8.24

(s, 1H), 8.32–8.35 (d, $J = 8.52$, 2H). FT-IR (KBr): 3274, 3068, 1691, 1643, 1534, 1348, 1098, 854, 736 cm^{-1}.

Acknowledgement

MMH is thankful to presidential office for the partial financial support through grant 84186.

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