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A simple and efficient one-pot synthesis of β-acetamido carbonyl compounds using sulfated zirconia as a heterogeneous recyclable catalyst☆

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Abstract

Sulfated zirconia has been employed as an efficient recyclable catalyst for the preparation of various β-acetamidoketones or esters at room temperature. The process involves the one-pot multicomponent reactions of aromatic aldehydes, enolizable ketones or β-ketoesters and acetonitrile in the presence of acetyl chloride.

Keywords: Aromatic aldehyde; Enolizable ketone; Acetonitrile; Acetyl chloride; Sulfated zirconia; β-Acetamidoketone

The multicomponent one-pot synthesis is highly important because of their wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery [1]. β-Acetamido carbonyl compounds are useful building blocks for a number of biologically and pharmaceutically valuable compounds [2]. These are precursors of 1,3-amino alcohol [3] present in antibiotic nikkomycins or neopolyoxines [4]. Generally, this type of compounds is prepared by the Dakin–West reaction [5]. A variety of catalysts including $CoCl_2$ [6], montmorillonite K-10 [7], $Cu(OTf)_3/Sc(OTf)_3$ [8], silica sulfuric acid [9], BiOCl [10], $CeCl_3{\cdot}7H_2O$ [11], $ZrOCl_2{\cdot}8H_2O$ [12], I_2 [13] and heteropoly-acids [14] have been employed for the synthesis of β-acetamido carbonyl compounds. All of these methods while offering some advantages, also suffer from different drawbacks such as the use of expensive catalysts, longer reaction times, high temperature and low yields.

In continuation of our work [13,15] on the development of useful synthetic methodologies, we have investigated a mild and suitable method for the preparation of β-acetamido ketones or esters by multicomponent reactions of an aromatic aldehyde, acetonitrile, an enolizable ketone or β-ketoester and actyl chloride in the presence of sulfated zirconia as a heterogeneous recyclable catalyst (Scheme 1).

Different aromatic aldehydes having electron-donating as well as electron—withdrawing substituents underwent the reaction smoothly. The convesion was complete at room temperature within 1–3 h and the products were obtained in excellent yields (Table 1). 1,3-Diketones (ethyl acetoacetate and methyl acetoacetate) were also applied in the reaction to afford the corresponding β-acetamido ketoesters in good yields with high diastereoselectivities. The structures of the products were established from their spectral (^{1}H NMR and MS) and analytical data. In the case of ketoesters or propiophenones (Table 1) both *anti*- and *syn*-products were formed (confirmed by ^{1}H NMR). In most of the cases, *anti* isomer was the major product. In the ^{1}H NMR spectrum, the coupling constant between H-2 and H-3 for *anti* isomer is nearly 6 Hz while for a *syn* isomer is nearly 3 Hz [6]. Thus, both the *anti* and *syn* isomers could be identified properly. Moreover, all the prepared β-acetamido carbonyl compounds (Table 1) are known compounds [8–14] and their ^{1}H NMR data agreed well with those reported earlier.

The catalyst, sulfated zirconia [16], a solid acid, works under heterogeneous conditions. In recent years, this catalyst has gained much importance in laboratories and industries because of its good catalytic activity, super-acidity, non-toxicity, low cost and wide range of applications in organic synthesis

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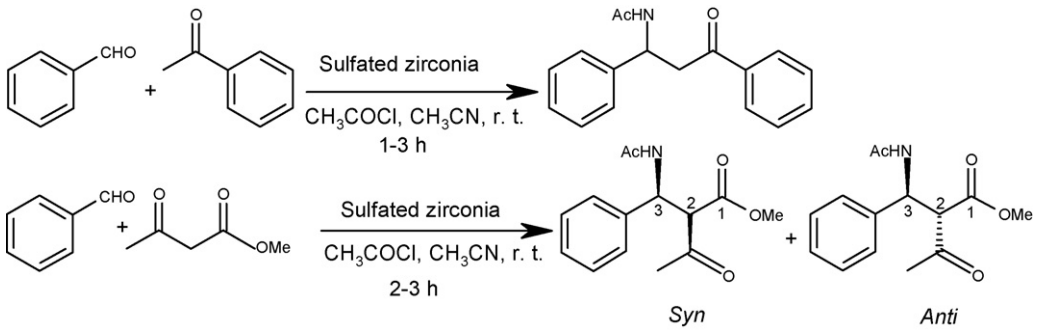
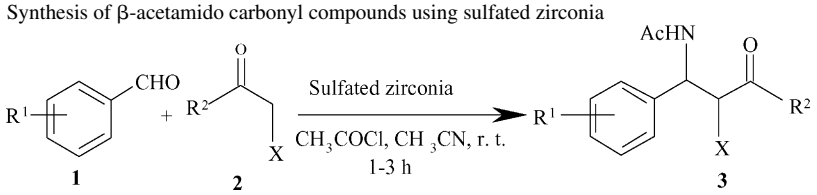


Scheme 1.

Table 1
Synthesis of β-acetamido carbonyl compounds using sulfated zirconia



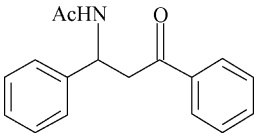
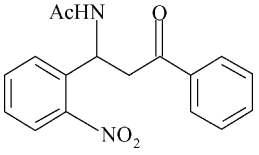
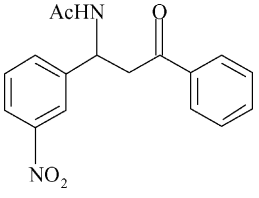
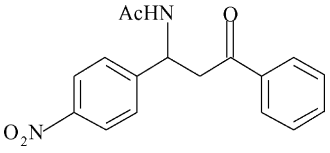
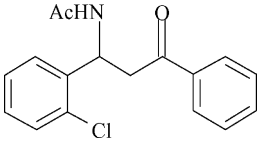
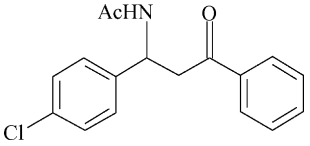
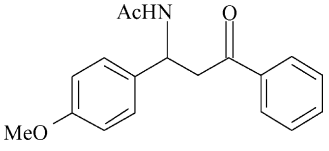
Entry	R^1	X	R^2	Product (**3**)	Isolated yield (%)[a]	*Syn–anti*[b]
a	H	H	Ph		95	–
b	2-NO_2	H	Ph		89	–
c	3-NO_2	H	Ph		87	–
d	4-NO_2	H	Ph		90	–
e	2-Cl	H	Ph		91	–
f	4-Cl	H	Ph		94	–
g	4-MeO	H	Ph		95	–

Table 1 (*Continued*)

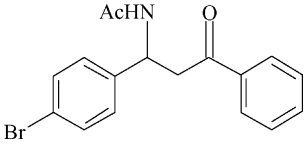
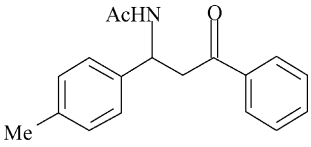
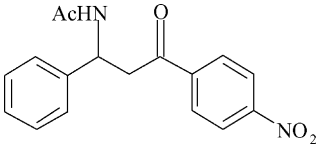
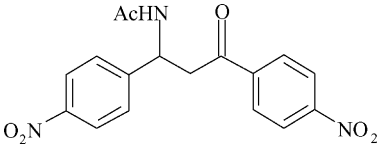
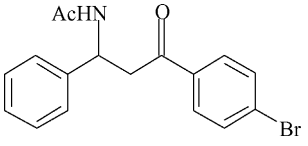
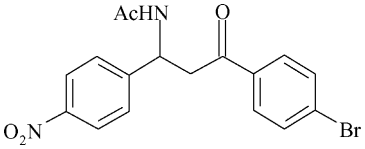
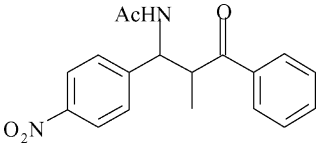
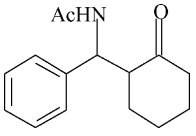
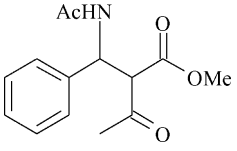
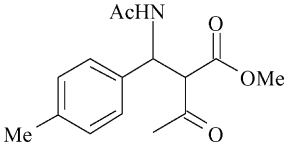
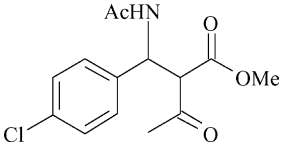
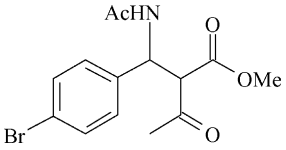
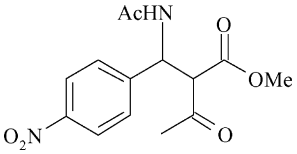
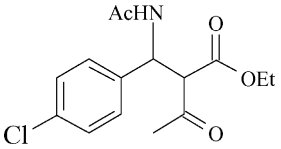
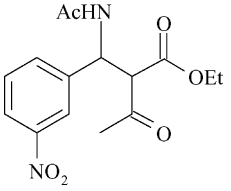
Entry	R^1	X	R^2	Product (**3**)	Isolated yield (%)[a]	*Syn–anti*[b]
h	4-Br	H	Ph		93	–
i	4-Me	H	Ph		94	–
j	H	H	$4\text{-}NO_2C_6H_4$		78	–
k	$4\text{-}NO_2$	H	$4\text{-}NO_2C_6H_4$		84	–
l	H	H	$4\text{-}BrC_6H_4$		87	–
m	$4\text{-}NO_2$	H	$4\text{-}BrC_6H_4$		76	–
n	$4\text{-}NO_2$	Me	C_6H_5		82	20:80
o	H	H	$C_6H1_{10}O$		72	–
p	H	COOMe	Me		80	20:80
q	4-Me	COOMe	Me		84	28:72
r	4-Cl	COOMe	Me		82	25:75

Table 1 (*Continued*)

Entry	R^1	X	R^2	Product (**3**)	Isolated yield (%)[a]	*Syn–anti*[b]
s	4-Br	COOMe	Me		84	30:70
t	4-NO_2	COOMe	Me		81	32:68
u	4-Cl	COOEt	Me		86	35:65
v	3-NO_2	COOEt	Me		88	38:62

[a] The structures of the products (which are known compounds [6–14]) were established from their spectral (^{1}H NMR and MS) and analytical data.
[b] Ratio of the *syn* and *anti* isomers (by ^{1}H NMR).

[17]. Sulfated zirconia catalyzes many reactions under simple conditions in the liquid phase as well as in the vapour phase. Generally, this type of catalysts offer several advantage such as short reaction times, mild reaction conditions, high selectivity and the ease of work-up procedure.

In conclusion, we have developed a mild and simple method for the preparation β-acetamido ketones or estrers using sulfated zirconia as a heterogeneous catalyst. The major advantages of this protocol include short reaction times, mild reaction conditions, easy work-up procedure and reusability of the catalyst.

1. Experimental

1.1. General procedure for the synthesis of β-acetamido ketones or esters

A mixture of aromatic aldehyde (1 mmol), acetophenone or β-ketoester (1 mmol), acetyl chloride (2 mmol) and catalytic amount of sulfated zirconia in acetonitrile (5 ml) was stirred at room temperature. After completion of the reaction as indicated by TLC, 10 ml of DCM was added to the reaction mixture and the catalyst was recovered by filtration. The organic portion was poured onto water (20 ml) and extracted with CH_2Cl_2 (3 ml × 10 ml) the combined organic layer was concentrated under vacuo and the product was purified by silica gel column chromatography eluted by an ethyl acetate and hexane (1:1) mixture to afford pure β-acetamido ketone or ester in good yield. The wet catalyst was recycled and no significant change in activity was observed after three cycles.

The spectral and analytical data of some representative β-acetamido carbonyl compounds are given below:

Compound **3d**—^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.15 (2H, d, J = 8.0 Hz), 7.86 (2H, d, J = 8.0 Hz), 7.60–7.42 (5H, m), 6.98 (1H, d, J = 6.0 Hz), 5.60 (1H, m), 3.79 (1H, dd, J = 12.0, 2.0 Hz), 3.46 (1H, dd, J = 12.0, 3.0 Hz), 2.02 (3H, s); FABMS: *m/z* 313 $[M+H]^+$; Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.13; N, 8.97%. Found: C, 65.41; H, 5.22; N, 8.92%.

Compound **3l**—^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.80 (2H, d, J = 8.2 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.42–7.10 (5H, m), 6.8 (1H, d, J = 6.2 Hz), 5.41 (1H, s), 3.82 (1H, dd, J = 8.20, 10.05 Hz), 3.42 (1H, dd, J = 8.20, 10.05 Hz), 2.15 (3H, s); FABMS: *m/z* 346, 348 $[M+H]^+$; Anal. Calcd. for $C_{17}H_{16}NO_2Br$: C, 58.95; H, 4.62; N, 4.05%. Found: C, 58.89; H, 4.60; N, 4.13%.

Compound **3q** (*anti*)—^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.21–7.05 (4H, m), 6.90 (1H, d, J = 9.3 Hz), 5.72 (1H, m), 4.06 (1H, d, J = 5.90 Hz), 3.70 (3H, s), 2.32 (3H, s), 2.18 (3H, s) 2.05 (3H, s); FABMS: *m/z* 278 $[M+H]^+$; Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.98; H, 6.86; N, 5.05%. Found: C, 64.92; H, 6.91; N, 5.10%.

Compound **3v** (*anti*)—^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.21 (1H, d, J = 8.0 Hz), 8.11 (1H, d, J = 8.0 Hz), 7.23 (1H, t, J = 8.0 Hz), 7.57–7.50 (2H, m), 5.82 (1H, dd, J = 8.5, 5.8 Hz), 4.21–4.06 (3H, m), 2.22 (3H, s), 2.01 (3H, s), 1.20 (3H, t, J = 7.0 Hz); FABMS: *m/z* 323 $[M+H]^+$; Anal. Calcd. for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.56; N, 8.66%. Found: C, 55.96; H, 5.52; N, 8.62%.

Acknowledgments

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