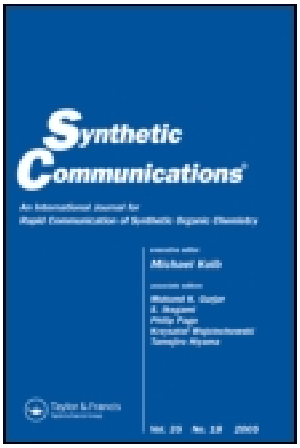

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Abstract: Silica-supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) efficiently catalyzes the four-component reaction of aryl aldehydes, enolisable ketones, acetyl chloride, and acetonitrile to form the corresponding β-acetylamino ketones at room temperature. The catalyst is inexpensive and ecofriendly and works under heterogeneous conditions.The present methodology offers several advantages such as excellent yields, simple procedure, short reaction times (1–3 h), and mild conditions.

Keywords: β-acetylamino ketones, heterogeneous catalyst, short reaction times, silica-supported sodium hydrogen sulfate

Heterogeneous catalysts have attracted attention in recent years because of economic and environmental considerations. The catalyst are generally inexpensive and easily available and can be conveniently handled and removed from the reaction mixture, thus making the experimental procedure simple and ecofriendly. Recently, we have utilized different heterogeneous catalysts successfully for various chemical transformations.[1] This prompted

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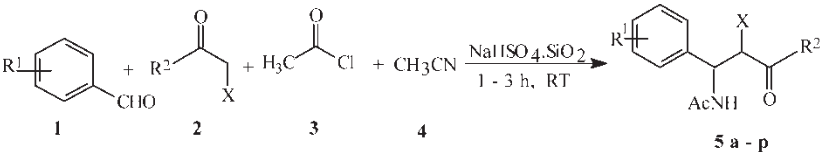
us to use silica-supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) for multicomponent coupling. As a part of our ongoing green technology program,[2] we disclose here a more practical, one-pot, green alternative for the synthesis of β-acetylamino ketones (Scheme 1).

β-Acetylamino ketones are usually prepared through acylation of β-amino ketones,[3] Michael addition to α,β-unsaturated ketones,[4] or photoisomerization of phthalimides.[5] The most interesting reaction for the synthesis of these compounds is multicomponent coupling involving aldehyde, enolisable ketone, acetyl chloride, and acetonitrile as first reported by Bahulayan and coworkers.[6] The multicomponent reactions leading to the formation of β-acetylamino ketones can be catalyzed by $CoCl_2$,[6b] cobalt(II) acetate supported on polyaniline,[6c] monmorillonite K10,[6a] and bismuth oxychloride.[6c] β-Acetylamino ketones have also been synthesized using $Cu(OTf)_2$, Zn(II), Bi(III), Sn(II), Sc(III), triflates, BF_3, $CuCl_2$, $BiCl_3$, $LaCl_3$, $LiClO_4$, $InCl_3$,[7a] H_2SO_4/SiO_2,[7b] and zeolite Hβ (reported as a reusable catalyst).[8] Recently, heteropoly acids (HPAs) have been reported[9] as solid green Brønsted acids for a one-pot synthesis of β-acetylamino ketones by the Dakin–West reaction. However, the reported procedures have disadvantages.

In a typical procedure, the reaction of enolisable ketone, acetyl chloride, and acetonitrile with various aromatic aldehydes in presence of $NaHSO_4 \cdot SiO_2$ proceded smoothly at room temperature in 1–3 h to afford excellent yields of β-acetylamino ketones (Table 1). The major advantages of this is that $NaHSO_4 \cdot SiO_2$ could conveniently be prepared[10] from the readily available ingredients in very short reaction times (1–3 h) and the isolation of the products can be isolated without chromatography, affording β-acetylamino ketones in high purity. It is noteworthy that the reported $CoCl_2$-catalyzed reaction, even though carried out at room temperature, required longer periods (i.e., 5 days) and also required a nonaqueous workup.[6b] The use of montmorillonite K10 required a high temperature (70°C).[6a] Polyaniline-supported cobalt (II) acetate required a nitrogen atmosphere.[6c] Zeolite Hβ–catalyzed reaction, even though carried out at room temperature, required 8–12 h,[8] does not require an inert atmosphere, is reusable, and has an aqueous workup, but our protocol has several advantages, as it does not need an inert atmosphere or a high temperature, involves an aqueous workup, and above all requires very short reaction times (1–3 h). The reaction involving acetophenone gave products with only one asymmetric



Scheme 1.

Table 1. Synthesis of β-acetylamino ketones at room temperature using $NaHSO_4 \cdot SiO_2$

No.	R^1	X	R^2	Time (h)	*Syn/anti*	Yield (%)[a]
5a	H	H	Ph	3.0	—	88
5b	2-Cl	H	Ph	1.0	—	90
5c	4-Cl	H	Ph	1.5	—	93
5d	2,4-di Cl	H	Ph	2.0	—	96
5e	4-Br	H	Ph	1.0	—	97
5f	2-NO_2	H	Ph	3.0	—	78
5g	3-NO_2	H	Ph	3.0	—	76
5h	4-OCH_3	H	Ph	1.0	—	81
5i	2-OH	H	Ph	3.0	—	78
5j	2,3,4-tri OCH_3	H	Ph	3.0	—	76
5k	4-CN	H	Ph	2.0	—	80
5l	4-CH_3	H	Ph	1.5	—	83
5m	H	CH_3	Ph	2.0	5:95	72
5n	H	$COOCH_3$	CH_3	3.0	20:80	70
5o	4-Br	$COOCH_3$	CH_3	3.0	13:87	75
5p	4-Cl	$COOCH_3$	CH_3	3.0	10:90	73

[a] Yields refer to pure products, and all products, were characterized by a comparision of their physical data and ^1H NMR and IR spectral data with those of authentic samples.

center (**5a–i**). The reaction involving propiophenone (**5m**) and methyl acetoacetate (**5n**), however, led to diastereomeric mixtures. The ratio of these diastereomers was determined by ^1H NMR spectroscopy. As can be seen from Table 1, the major diastereomer was *anti* in all cases.

In conclusion, this article describes a convenient and efficient process for the synthesis of β-acetylamino ketones through the four-component coupling of various aromatic aldehydes, enolisable ketone, acetyl chloride, and acetonitrile using $NaHSO_4 \cdot SiO_2$ as a solid support at room temperature. The present methodology offers very attractive features such as reduced reaction times, higher yields, and economic viability of the catalyst when compared with conventional method as well as with other catalysts and will have wide scope in organic synthesis. This simple procedure combined with ease of recovery and reuse of the catalyst makes this method economical benign, and a waste-free chemical process for the synthesis of β-acetylamino ketones. We believe that this procedure is convenient, economic, and a user-friendly process for the synthesis of β-acetylamino ketones.

TYPICAL PROCEDURE

To a stirred mixture of $NaHSO_4 \cdot SiO_2$ (100 mg) in acetonitrile (2.5 mL), an aldehyde (106 mg), an enolisable ketone (120 mg), and acetyl chloride

(0.4 mL) were added. The reaction mixture was stirred at room temperature for 1–3 h. The mixture was filtered to remove the catalyst, and the filtrate was poured into ice-cold water. The precipitated solid was filtered (entry **a** was not precipitated immediately), dried, washed with petroleum ether 60–80°C to remove any residual starting material, and dried. All products were characterized by their physical constants and spectral data compared with those for authentic samples.

REPRESENTATIVE SPECTRAL DATA

Compound **5a**: Mp 102–103°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05 (s, 3H, Ac), 3.30 (dd, 1H, $J = 6.5$ & 9.6 Hz), 3.65 (dd, 1H, $J = 6.6$ & 9.7 Hz), 5.55 (m, 1H), 6.85 (brs, 1H), 7.40 (d, 5H, $J = 9.4$ Hz), 7.85 (d, 5H, $J = 9.1$ Hz); IR (KBr, cm^{-1}) 3250, 3035, 1665, 1630, 1570, 1265, 1087. Compound **5d**: Mp 168–170°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.01 (s, 3H, Ac), 3.35 (dd, 1H, $J = 6.6$ & 9.9 Hz), 3.70 (dd, 1H, $J = 6.8$ & 10.0 Hz), 5.70 (m, 1H), 7.05 (brs, 1H), 7.30 (s, 1H), 7.45 (m, 5H), 7.55 (d, $J = 9.6$ Hz, 1H), 7.80 (d, 1H, $J = 9.4$ Hz); IR (KBr, cm^{-1}) 3282, 3080, 1688, 1651, 1548, 1232, 753. Compound **5f**: Mp: 190–192°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.07 (s, 3H, Ac), 3.33 (dd, 1H, $J = 6.8$ & 9.8 Hz), 3.77 (dd, 1H, $J = 7.0$ & 10.0 Hz), 5.56 (m, 1H), 6.85 (brs, 1H), 7.18–7.55 (m, 4H); IR (KBr, cm^{-1}) 3295, 3035, 1652, 1460, 1220, 680, 585. Compound **5j**: Mp: 152–154°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.05 (s, 3H, Ac), 3.35 (dd, 1H, $J = 6.8$ & 10.0 Hz), 3.75 (dd, 1H, $J = 6.8$ & 9.9 Hz), 3.85 (s, 9H, OCH_3), 5.40 (m, 1H), 6.55 (s, 2H), 6.78 (brs, 1H), 7.45 (t, 2H), 7.60 (t, 1H), 7.90 (d, 2H, $J = 9.5$ Hz); IR (KBr, cm^{-1}) 3272, 3075, 2942, 1690, 1557, 1230, 1123, 752, 682; Compound **5m**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.04 (s, 3H, Ac), 2.18 (s, 3H, CH_3) 3.80 (s, 3H, OCH_3), 4.08 (d, 1H, $J = 6.0$ Hz), 5.75 (dd, 1H, $J = 8.6$ & 5.5 Hz), 6.80 (brs, 1H), 6.95 (d, 2H, $J = 9.0$ Hz), 7.26 (d, 2H, $J = 9.2$ Hz); IR (KBr, cm^{-1}) 3275, 1745, 1720, 1660, 1515.

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