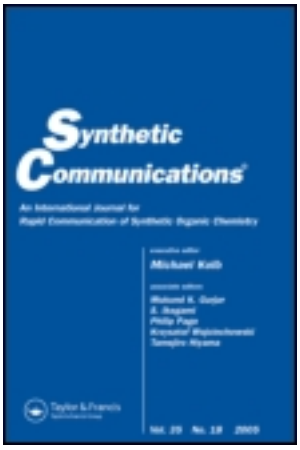

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Silica Sulphuric Acid: An Efficient and Recyclable Catalyst for the Synthesis of β-Acetamido Ketones in Single Pot

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Silica Sulphuric Acid: An Efficient and Recyclable Catalyst for the Synthesis of β-Acetamido Ketones in Single Pot

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Abstract: An efficient method has been developed for the synthesis of β-acetamido ketones by a multicomponent condensation route using sulphuric acid on silica gel as an inexpensive catalyst. Catalyst was recycled without loss of activity.

Keywords: Acetonitrile, acetophenones, acetyl chloride, aromatic aldehydes, silica sulphuric acid

INTRODUCTION

Solid acid catalysts play a prominent role in organic synthesis under heterogeneous conditions. The importance of these catalysts is growing because of their ecofriendly nature as attention is directed toward the development of clean and green technologies for important organic molecules to promote environmental safety. In general, solid acid catalysts are mainly based on clay[2–10] and silica.[11] In terms of convenience, silica-based catalysts are inexpensive, easy to prepare, and insoluble in most of the organic solvents, which means they have the advantage of recovery and recycle from various reactions. Therefore, silica sulphuric acid is extensively studied and found useful in many reactions such as nitration of aromatic compound,[11a]

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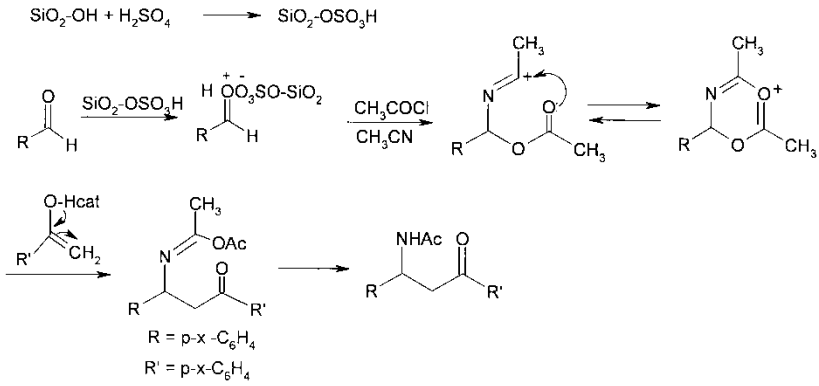
oxidation of thiols to disulphides,[11b] three component Biginelli reaction,[11c] and so on. Based on these facts, we propose to use silica sulphuric acid as a catalyst for multicomponent condensation reaction. Earlier studies to obtain β-acetamido ketones mainly used cobalt (II) chloride[12] as catalyst; however, search for an efficient and economically viable catalyst for complex reactions is ongoing among chemists. It is prerequisite that the catalyst should activate aldehyde, acetonitrile, and enolisable ketone one after the other to facilitate the reaction in a multicomponent reaction. In our findings, we identified silica sulphuric acid as a suitable catalyst for preparation of β-acetamido ketones by multicomponent condensation reaction in a single pot and are report our results here for the first time.

In a typical reaction, the enolizable ketone (acetophenone) was reacted with various aldehydes in presence of acetyl chloride in acetonitrile medium using silica sulphuric acid as a catalyst. The catalyst is the source of protons, which protonates aldehyde and acetonitrle to form a six-membered transition state. Subsequently, a nucleophile of enolizable ketone attacks methine carbon and forms β-acetamido ketones. The formation of silica–sulphuric acid and probable mechanism for multicomponent condensation is schematically drawn below in Scheme 1.

The role of substituents in enolizable ketone (acetophenone) and aldehydes on the rate of reaction and yield of products is studied in detail. In the case of enolizable ketone, it is found that the electron-withdrawing groups in para position enhances the rate of reaction and yield in comparison to electron-donating groups. We attribute this to the electron-withdrawing groups in para position promoting enolization of active methyl group to facilitate the reaction, resulting high yield and low reaction time. In the case of aldehydes, electron-withdrawing groups in para position promote reaction whereas electron-releasing groups are detrimental to the reaction. It is confirmed when the reaction is carried out with aldehydes that have



Scheme 1.

electron-releasing groups such as CH_3, OCH_3, and $N(CH_3)_2$ and there is no reaction. The catalyst is recovered and recycled four times for compound **3a** and found to have no loss of activity. The reaction is drawn in Scheme 2 and the number of compounds prepared in this study have been tabulated in Table 1.

In conclusion, an efficient method for multicomponent condensation using an inexpensive catalyst has been demonstrated for further applications in the synthesis of a number of interesting molecules of high value.

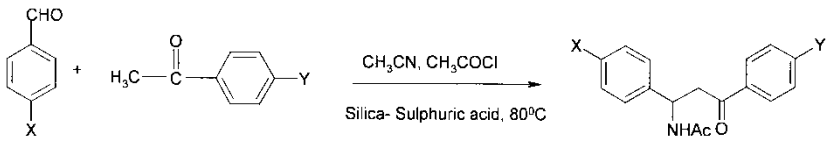
EXPERIMENTAL

Melting points were determined in open-glass capillaries on a Mettler FP51 melting point apparatus and are uncorrected. IR spectra were recorded on FT-IR Schimadzu Perkin-Elmer 1310 infrared spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini (200 MHz) spectrometer and tetramethylsilane (TMS) was used as the internal standard. ^{13}C NMR spectra recorded on Varian Gemini (50 MHz) spectrometer. Mass spectra were recorded on a VG-micromass 7070H instrument 70 ev.

General Procedure for the Synthesis of β-Acetamido Ketones (3)

A freshly prepared, dried solid silica sulphuric acid[11a] (0.4 g) was added to a stirred solution of substituted aromatic aldehyde (1.8 mmol), substituted acetophenone (1.8 mmol), and acetyl chloride (1.5 mL) in acetonitrile (2.5 mL). The reaction mixture was heated to 80°C and stirred for 2–5 h at the same temperature. After completion of the reaction, the solid catalyst was filtered off and the filtrate was concentrated under reduced pressure to afford the crude product as residue. It was purified by the column chromatography method using 100–200 mesh silica gel as stationery phase and ethylacetate–n-hexane (35 : 65) as eluents.

3a: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, $J = 7.3$ Hz, 2H), 7.58–7.20 (m, 8H), 6.77 (d, J = 8.9 Hz, 1H), 5.56 (dd, J = 5.7 and 13.4 Hz, 1H), 3.77 (dd, J = 5.2 and 16.9 Hz, 1H), 3.43 (dd, J = 6.1 and 16.9 Hz, 1H), 2.0 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 198.5, 169.45, 140.8, 133.46, 128.6,



1 2 3

Scheme 2.

Table 1. Reaction time and yields of β-acetamido ketones **(3)**

Entry	X	Y	Time (h)	Yield (%)	Mp (°C)
3a	H	H	4	75	104–106
3b	NO_2	H	2.5	86	151–153
3c	F	H	3.0	89	109–111
3d	H	Cl	3.0	87	114–115
3e	NO_2	Cl	2.0	89	125–127
3f	F	Cl	2.5	88	108–110
3g	H	CH_3	5.0	76	121–123
3h	F	CH_3	4.5	78	104–106
3i	NO_2	CH_3	4.0	69	Liquid

All the compounds gave satisfactory elemental data.

128.07, 127.3, 126.4, 49.8, 43.14, 23.37; IR (KBr) $Vmax/cm^{-1}$, 3423, 1772, 1659, 1500, 1374, 1295, 1188, 1023, 704, 585. MS (m/z): 266 (M-1), 208, 179, 162, 120, 107, 106, 77, 50. Anal. calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.29; H, 6.37; N, 5.11.

3b: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, $J = 8.4$ Hz, 2H), 7.89 (d, J = 9.6 Hz, 2H), 7.62–7.46 (m, 5H), 7.02 (d, J = 9.0 Hz, 1H), 5.66 (s, 1H), 3.80 (dd, J = 4.8 and 17.6 Hz, 1H), 3.50 (dd, J = 5.2 and 17.6 Hz, 1H), 2.0 (s, 3H); ^{13}C NMR (75 MHz, CDCl3 + DMSO) δ 195.38, 168.93, 147.34, 137.3, 135.4, 132.5, 132.49, 127.8, 127.7, 127.1, 127.05, 123.35, 44.83, 42.89, 21.76; IR (KBr) $Vmax/cm^{-1}$: 3310, 1686, 1645, 1580, 1513, 1352, 1300, 751. MS (m/z): 311(M^+), 295, 270, 194, 175, 165, 151, 129, 120, 105, 102, 90, 68, 54. Anal. calcd. for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 9.00. Found: C, 65.19; H, 5.08; N, 8.95.

3c: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.00 (d, 1H, NH), 7.90 (d, J = 7.2 Hz, 2H, aromatic H), 7.22–7.60 (m, 5H, aromatic H), 6.90–7.00 (m, 2H, aromatic H), 5.40 (q, H, methine H), 3.60 (dd, J = 4.9 and 15.2 Hz, 1H, CH_2), 3.30 (dd, J = 5.8 and 15.7 Hz, 1H, CH_2), 1.85 (s, 3H, CH_3). IR (KBr) $Vmax/cm^{-1}$, 294, 3065, 2362, 1688, 1646, 1546, 1368, 1204, 760, 687. MS (m/z): 284(M^+), 242, 105, 77, 43. Anal. calcd. for $C_{17}H_{16}FNO_2$: C, 71.56; H, 5.65; N, 4.90. Found: C, 71.52; H, 5.59; N, 5.10.

3d: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.10 (d, 1H, NH), 7.90 (d, J = 7.8 Hz, 2H, aromatic H), 7.25–7.45 (m, 7H, aromatic H), 5.35 (q, 1H, methine H), 3.55 (dd, J = 5.1 and 17.4 Hz, 1H, CH_2), 3.25 (dd, J = 7.2 and 18.1 Hz, 1H, CH_2), 1.85 (s, 3H, CH_3). IR (KBr)$Vmax/cm^{-1}$: 3289, 3068, 2369, 1690, 1650, 1558, 1380, 1208, 754, 668. MS (m/z): 301 (M^+), 259, 139, 106, 77, 43. Anal. calcd. for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64. Found: C, 67.71; H, 5.29; N, 4.68.

3e: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.25 (d, 1H, NH), 8.10 (d, J = 8.1 Hz, 2H, aromatic H), 7.85 (d, J = 10.2 Hz, 2H, aromatic H), 7.57 (d, J = 9.1 Hz, 2H, aromatic H), 7.55 (d, J = 8.6 Hz, 2H, aromatic H), 7.40

(d, J = 10.6 Hz, 2H, aromatic H), 5.45 (q, 1H, methine H), 3.60 (dd, J = 5.2 and 16.1 Hz, 1H, CH_2), 3.30 (dd, J = 6.4 and 17.3 Hz, 1H, CH_2), 1.85 (s, 3H, CH_3). IR (KBr)$Vmax/cm^{-1}$: 3310, 3066, 2369, 1686, 1645, 1580, 1380, 1209, 760, 656. MS (m/z): 346 (M^+), 304,139,43. Anal. calcd. for $C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.35; N, 8.07. Found: C, 58.91; H, 4.33; N, 8.17.

3f: ^{1}HNMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.10 (d, 1H, NH), 7.92 (d, J = 8.6 Hz, 2H, aromatic H), 7.30–7.50 (m, 4H, aromatic H), 6.90–7.05 (m, 2H, aromatic H), 5.40 (q, 1H, methine H), 3.60 (dd, J = 5.4 and 16.8 Hz, 1H, CH_2), 3.30 (dd, J = 6.8 and 18.6 Hz, 1H, CH_2), 1.85 (s, 3H, CH_3). IR (KBr)$Vmax/cm^{-1}$: 3296, 3067, 2370, 1689, 1651, 1549, 1372, 1209, 758, 690. MS (m/z): 320 (M^+), 278, 139, 106, 77, 43. Anal. calcd. for $C_{17}H_{15}ClFNO_2$: C, 63.85; H, 4.72; N, 4.38. Found: C, 63.92; H, 4.69; N, 4.41.

3g: ^{1}HNMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.10 (d, 1H, NH), 7.75 (d, J = 9.9 Hz, 2H, aromatic H), 7.15–7.35 (m, 7H, aromatic H), 5.35 (q,1H, methine H), 3.49 (dd, J = 6.4 and 19.2 Hz, 1H, CH_2), 3.20 (dd, J = 7.4 and 18.9 Hz, 1H, CH_2), 2.35 (s, 3H, CH_3), 1.80 (s, 3H, CH_3). IR (KBr)$Vmax/cm^{-1}$: 3423, 3071, 2961, 1772, 1659, 1500, 1374, 1295, 1188, 1023, 704, 585. MS (m/z): 282 (M^+), 239, 223, 147, 106, 43. Anal. calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.80; N, 4.97. Found: C, 76.79; H, 6.86; N, 5.01.

3h: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.05 (d, 1H, NH), 7.80 (d, J = 12.1 Hz, 2H, aromatic H), 7.20–7.40 (m, 4H, aromatic H), 6.90–7.05 (m, 2H, aromatic H), 5.40 (q, 1H, methine H), 3.58 (dd, J = 4.8 and 18.2 Hz, 1H, CH_2), 3.30 (dd, J = 7.8 and 19.0 Hz, 1H, CH_2), 2.40 (s, 3H, CH_3), 1.90 (s, 3H, CH_3). IR (KBr)$Vmax/cm^{-1}$: 3290, 3065, 2958, 2362, 1688, 1646, 1546, 1367, 1202, 758, 685. MS (m/z): 299 (M^+), 257, 191, 119, 43. Anal. calcd. for $C_{17}H_{18}FNO_2$: C, 71.06; H, 6.31; N, 4.87. Found: C, 71.12; H, 6.39; N, 4.91.

3i: ^{1}H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 8.40 (d, 1H, NH), 8.0 (d, J = 8.1 Hz, 2H, aromatic H), 7.75 (d, J = 10.2 Hz, 2H, aromatic H), 7.55 (d, J = 9.8 Hz, 2H, aromatic H), 7.15 (d, J = 10.6 Hz, 2H, aromatic H), 5.58 (q, 1H, methine H), 3.62 (dd, J = 4.6 and 18.9 Hz, 1H, CH_2), 3.35 (dd, J = 4.9 and 16.2 Hz, 1H, CH_2), 2.30 (s, 3H, CH_3), 1.90 (s, 3H, CH_3). IR(KBr) $Vmax/cm^{-1}$: 3310, 3071, 2959, 1686, 1645, 1586, 1513, 1352, 1300, 751. MS (m/z): 284 (M^+), 165, 77, 43. Anal. calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.55; N, 8.58. Found: C, 66.29; H, 5.61; N, 8.49.

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