PCC/SiO_2–H_2SO_4: a convenient system for *in situ* oxidative β–acetamidoketone formation from aromatic alcohols and silyl ethers

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A convenient and efficient one-pot multicomponent synthesis of β-acetamidoketones from aromatic alcohols and silyl ethers in the presence of acetylchloride and a combination of PCC and silica gel supported sulfuric acid is described.

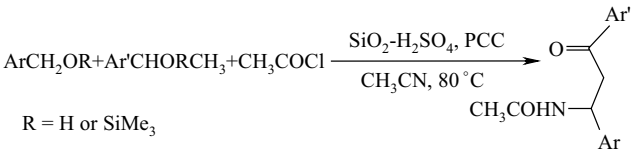
Keywords: β-acetamidoketones, one pot synthesis, PCC, SiO_2–H_2SO_4, alcohols

One of the strategies for the combination of economy with environmental improvement in modern organic synthesis is the multicomponent reaction (MCR). This process consists of two or more synthetic steps, which are performed without isolation of any intermediates thus reducing time and saving energy and raw materials. There have been tremendous developments in the coupling of three or more components in a single operation and great efforts have been and still are being made to develop new multicomponent reactions.[1] MCRs are powerful tools in the modern drug discovery process and allow the fast, automated and high throughput generation of organic compounds.[2] β-Acetamidoketones are versatile intermediates for the synthesis of building blocks for natural nucleoside peptide antibiotics. Their structure also exists in a number of biologically or pharmacologically important compounds.[3,4] The procedure proposed by Iqbal and coworkers[5,6] for the formation of β-acetamidoketones includes the condensation of an aryl aldehyde, acetophenone and acetyl chloride in acetonitrile in the presence of $CoCl_2$ or montmorillonite K-10 clay. Very recently, Ghosh *et al.*[7] reported multi-component routes leading to β-acetamidoketones using BiOCl in the presence of acetyl chloride as a precursor of $BiCl_3$. Due to the importance of β-aceamidoketones in the synthesis of some biologically and pharmacologically compounds, the introduction of new and efficient methods for this multi-component reaction is still needed.

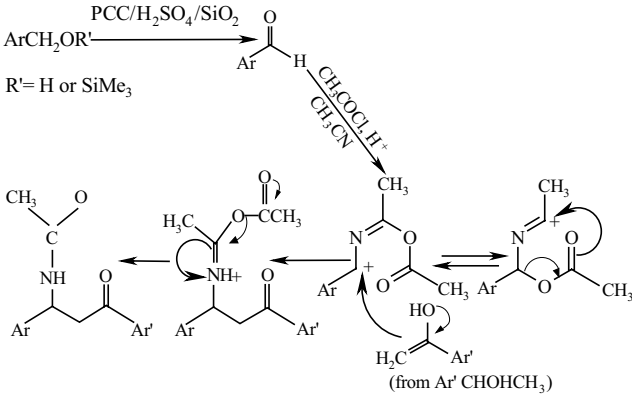
As part of our programme aiming at developing new methods for the preparation of 1,3-aminols and in continuation of our interest in the synthesis of β-acetamido ketones,[8] β–enaminones[9] and performance of MCRs,[10] we now describe an efficient, and high yielding protocol for the synthesis of the title compounds from alcohols and silyl ethers in the presence of acetyl chloride and pyridinium chlorochromate (PCC) and silica gel supported sulfuric acid (Scheme 1).

There is current interest research in heterogeneous systems due to their importance in industry.[11] Heterogeneous systems have many advantages such as simple experimental procedures, mild reaction conditions and minimisation of chemical wastes as compared to their liquid phase counterparts.[12] In continuation of our studies on the application of inorganic acid salts,[13] we examined the effectiveness of a combination of SiO_2–H_2SO_4 and PCC as an oxidising agent. Initially we studied the reaction of benzyl alcohol with methyl phenyl carbinol and acetyl chloride with PCC and SiO_2–H_2SO_4 in acetonitrile as a model reaction. The reaction took place at 80 °C for 75 min to afford the corresponding β-acetamido-ketone in 75% yield. A series of other *in situ* oxidation–multicomponent reactions from alcohols were attempted and the results are shown in Table 1.

Benzyl alcohols and methyl phenyl carbinols underwent smooth transformation to the corresponding β-acetamidoketones, without over-oxidation of any alcohols



Scheme 1



Scheme 2

to carboxylic acids, in high to excellent yields and in relatively short reaction times (< 100 min). Aryl alcohols and methyl aryl carbinols with electron-releasing or electron-withdrawing groups also reacted efficiently. The reactions of *ortho*-substituted benzyl alcohols afforded high yields of the desired β–acetamido ketones (Table 1, entries 2 and 7). However, the synthesis could not be achieved in the absence of the PCC and SiO_2–H_2SO_4 system. We found that aliphatic alcohols do not give the corresponding β–acetamidoketones under corresponding conditions.

In addition, the direct reactions of the corresponding silyl ethers under the similar conditions were also examined and the similar results were obtained after the one pot oxidative deprotection coupling reaction (see Table 1).

A possible mechanism for the formation of β-acetamido-ketones from alcohols or silyl ethers and acetyl chloride in acetonitrile in the presence of PCC/H_2SO_4–SiO_2 is shown in Scheme 2.

In conclusion, we have demonstrated a new, straightforward and efficient method for the oxidative one-pot synthesis of β-acetamido ketones from alcohols and silyl ethers and acetyl chloride using PCC/SiO_2–H_2SO_4 as an oxygen and moisture tolerant and inexpensive reagent. The other advantages are low reaction times and operation under relatively mild reaction conditions. This procedure has the merits that the intermediate aldehydes do not need isolation.

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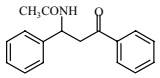
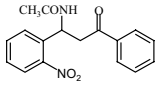
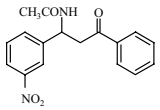
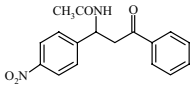
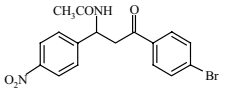
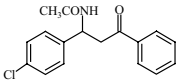
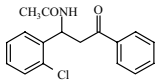
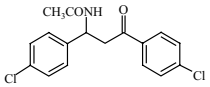
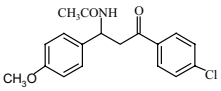
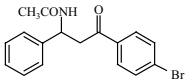
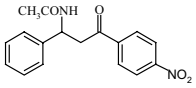
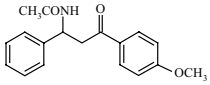
Table 1 One pot condensation of: (A) alcohols and (B) silyl ethers with acetyl chloride and acetonitrile by PCC/silica sulfuric acid

A: Alcohols				B: Silyl ethers			
Entry	Ar/Ar'	Time(min)/ Yield (%)	Product	Mp (°C)	Entry	Ar/Ar'	Time (min)/ Yield (%)
1	C_6H_5/C_6H_5	75/75		99–101 (102–104)11	1	C_6H_5/C_6H_5	70/75
2	$2\text{-}NO_2C_6H_4/C_6H_5$	75/80		189–190 2 (190–191)11		$2\text{-}NO_2C_6H_4/C_6H_5$	70/85
3	$3\text{-}NO_2C_6H_4/C_6H_5$	85/77		113–114 (112–115)11	3	$3\text{-}NO_2C_6H_4/C_6H_5$	80/80
4	$4\text{-}NO_2C_6H_4/C_6H_5$	90/70		149–150 (148–149)11	4	$4\text{-}NO_2C_6H_4/C_6H_5$	85/77
5	$4\text{-}NO_2C_6H_4/4\text{-}BrC_6H_4$	75/75		115–118	5	$4\text{-}NO_2C_6H_4/4\text{-}BrC_6H_4$	80/80
6	$4\text{-}ClC_6H_4/C_6H_5$	65/78		149–150 (150)13	6	$4\text{-}ClC_6H_4/C_6H_5$	70/80
7	$2\text{-}ClC_6H_4/C_6H_5$	70/85		136–138 (135–136) 13	7	$2\text{-}ClC_6H_4/C_6H_5$	85/85
8	$4\text{-}ClC_6H_4/4\text{-}ClC_6H_4$	75/70		141–143	8	$4\text{-}ClC_6H_4/4\text{-}ClC_6H_4$	75/73
9	$4\text{-}CH_3OC_6H_4/4\text{-}ClC_6H_4$	70/77		97–99 (110–112)13	9	$4\text{-}CH_3OC_6H_4/4\text{-}ClC_6H_4$	95/80
10	$C_6H_5/4\text{-}BrC_6H_4$	80/85		98–100	10	$C_6H_5/4\text{-}BrC_6H_4$	90/80
11	$C_6H_5/4\text{-}NO_2C_6H_4$	100/80		103–106	11	$C_6H_5/4\text{-}NO_2C_6H_4$	85/70
12	$C_6H_5/4\text{-}CH_3OC_6H_4$	75/80		109–111 (110–112)13	12	$C_6H_5/4\text{-}CH_3OC_6H_4$	80/78

[a]All products were characterised by IR, ^{1}H NMR and ^{13}C NMR spectroscopy. [b]Isolated yields.

Experimental

Preparation of silica gel supported sulfuric acid as catalyst

Concentrated (98%) sulfuric acid (1 ml) was stirred with a suspension of silica gel (Merck Kiesegel 60G, 70–230 mesh, 4 g) in acetonitrile (20 ml) for 30 mins. Evaporation of the solvent at 45°C for 1 h, afforded a white powder 5.85 g. The amount of the impregnated acid (3 mmol per gram of the supported) was determined by titration with 0.1 M sodium hydroxide in the presence of phenolphthalein.

General experimental procedure

In a 25 ml round-bottomed flask a mixture of aryl alcohol or trimethylsilyl aryl ether (1 mmol), methyl aryl' carbinol or 1-aryl'-1-trimethylsilyloxyethane (1 mmol), acetyl chloride (0.6 ml) and acetonitrile (3 ml) was stirred for the appropriate time at 80°C in the presence of H_2SO_4/SiO_2 (0.5 or 0.4 g) and pyridinium chlorochromate (1 mmol). The progress of the reaction was monitored with TLC. On completion, the reaction mixture was filtered and the filtrate poured into 50 ml ice-water. The solid product formed was filtered washed with ice-water and recrystallised from ethyl acetate/*n*-heptane to give the pure product in 70–85% yields.

Spectroscopic data for the entries **4**, **5**, **6**, **8**, **9**, **10**, **11** *and* **12**. (For AA'XX' systems in ^{1}H NMR, $J^* = J_{23} + J_{25}$)

4: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 3.50 (dd, J = 7.3, 9.1 Hz, 1H), 3.80 (dd, J = 7.3, 9.1 Hz, 1H), 5.65–5.74 (m, 1H), 7.00 (s, 1H), 7.50 (m, 7H), 8.20 (m, J^* = 9.1 Hz, 2H).

5: IR ν_{max}/cm^{-1} (KBr): 3260, 3042, 1690, 1644, 1585, 1542, 1353, 1077, 1008, 820; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 3H), 3.47 (dd, J = 7.4, 11.0 Hz, 1H), 3.84 (dd, J = 7.4, 11.0 Hz, 1H), 5.64–5.75 (m, 1H), 7.02 (s, 1H), 7.50 (m, J^* = 8.2 Hz, 2H)7.60 (m, J^* = 8.2 Hz, 2H), 7.83 (m, J^* = 9.1 Hz, 2H), 8.25 (m, J^* = 9.1 Hz, 2H);^{13} C NMP (50 MHz, $CDCl_3$): δ 197.4, 170.2, 148.7, 147.6, 135.3, 132.7, 130.0, 129.8, 127.8, 124.3, 49.6, 43.0, 23.7; MS: *m/z* 390 (2), 349 (8), 347 (9), 185 (95), 183 (100), 164 (22), 155 (40), 150 (28), 105 (24), 77 (25), 73 (20), 57 (22), 43 (76); Anal. Calcd. For $C_{17}H_{15}BrN_2O_4$: C, 52.2; H, 3.9; N, 7.2. Found: C, 52.2; H, 4.0; N, 7.2.

6: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 3.49 (dd, J = 7.8, 10.9 Hz, 1H), 3.83 (dd, J = 7.8, 10.9 Hz, 1H), 5.55–5.76 (m, 1H), 7.08–7.26 (m, 5H), 7.41–7.59 (m, 3H), 7.94 (m, J^* = 9.1 Hz, 2H).

8: IR ν_{max}/cm^{-1} (KBr): 3264, 3056, 1670, 1635, 1584, 1292, 1088, 885, 825; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.08 (s, 3H), 3.40 (dd, J = 7.3, 10.9 Hz, 1H), 3.82 (dd, J = 7.3, 10.9 Hz, 1H), 5.45–5.60 (m, 1H), 7.32 (s, 1H), 7.47 (m, J^* = 9.1 Hz, 4H), 7.91 (m, J^* = 9.1 Hz, 4H); ^{13} C NMR (50 MHz, $CDCl_3$): δ 197.3, 170.5, 140.6, 139.7, 135.1, 133.8, 129.9, 129.5, 129.3, 128.4, 49.9, 43.6, 23.5; MS: *m/z* 335 (10), 296 (1), 294 (5), 292 (9), 155 (10), 153 (44), 141 (38), 139 (100), 113 (14), 111 (36), 77 (10), 75 (26), 43 (66); Anal. Calcd.

For $C_{17}H_{15}Cl_2NO_2$: C, 60.7; H, 4.5; N, 4.2. Found: C, 60.8; H, 4.6; N, 4.3.

9: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.10 (s, 3H), 3.35 (dd, *J* = 7.3, 8.2 Hz, 1H), 3.70–3.90 (m, 4H), 5.45 (θ, *J* = 5.5 Hz, 1H), 6.60 (δ, *J* = 7.2 Hz, 1H), 7.15 (m, *J** = 9.1 Hz, 2H), 7.32 (m, *J** = 9.1 Hz, 2H), 7.44 (m, *J** = 8.9 Hz, 2H), 7.75 (m, *J** = 8.9 Hz, 2H).

10: IR ν_{max}/cm^{-1} (KBr): 3296, 3060, 1690, 1675, 1644, 1545, 1395, 1372, 1072, 995, 816, 759, 695; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (s, 3H), 3.44 (dd, *J* = 7.5, 10.9 Hz, 2H), 3.82 (dd, *J* = 7.5, 10.9 Hz, 2H), 5.65–5.80 (m, 1H), 6.85 (br, 1H), 7.25–7.42 (m, 5H), 7.62 (m, *J** = 9.2 Hz, 2H), 7.80 (m, *J** = 9.2 Hz, 2H); ^{13} C NMR (50 MHz, $CDCl_3$): δ 197.8, 170.3, 140.9, 135.7, 132.6, 130.1, 129.2, 128.1, 127.0, 122.8, 50.6, 43.7, 23.6; MS: *m/z* 345 (6), 304 (8), 302 (9), 185 (70), 183 (76), 120 (67), 106 (78), 77 (26), 43 (100); Anal. Calcd. For $C_{17}H_{16}BrNO_2$: C, 59.0; H, 4.7; N, 4.05. Found: C, 59.0; H, 4.7; N, 4.25.

11: (This is formally a tentative characterisation in view of the carbon analysis.) IR ν_{max}/cm^{-1} (KBr): 3280, 3045, 1665, 1624, 1588, 1548, 1351, 1290, 1080, 992, 825, 756, 695; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.11 (s, 3H), 3.48 (dd, *J* = 6.8, 8.9 Hz, 1H), 3.82 (dd, *J* = 6.8, 8.9 Hz, 1H), 5.65 (q, *J* = 5.6 Hz 1H), 6.65 (d, *J* = 7.1 Hz 1H), 7.52–7.62 (m, 5H), 8.05 (m, *J** = 9.2 Hz, 2H), 8.62 (m, *J** = 9.2 Hz, 2H); ^{13} C NMR (50 MHz, $CDCl_3$): δ 196.7, 169.7, 150.4, 140.9, 140.3, 129.2, 128.8, 127.9, 126.6, 123.9, 50.2, 44.2, 23.3; MS: *m/z* 312 (5), 269 (32), 150 (49), 120 (60), 106 (100), 104 (58), 43 (87); Anal. Calcd. For $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.2; N, 9.0. Found: C, 64.0; H, 5.2; N, 8.90.

12: ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.14 (s, 3H), 3.80 (dd, *J* = 7.8, 9.1 Hz, 1H), 3.65–3.85 (m, 4H), 5.50 (θ, *J* = 5.5 Hz, 1H), 6.70 (δ, *J* = 7.2 Hz, 1H), 6.85 (m, *J** = 10.0 Hz, 2H), 7.30 (m, *J** = 10.0 Hz, 2H), 7.44–7.90 (m, 5H).

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