SHORT PAPER

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Solvent-free three-component condensation reaction of aromatic ketones with aliphatic amines and formaldehyde[†]

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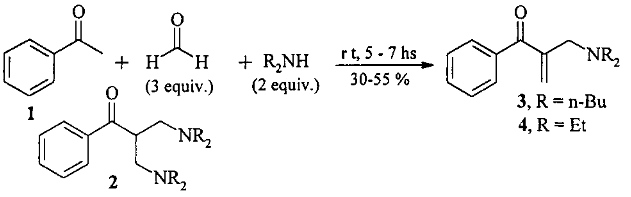
A solvent-free procedure for the synthesis of several 1-aryl-2-(dialkylaminomethyl)-prop-2-en-1-ones **3** (**a–e**) and **4** (**a–e**) is reported. Reaction of arylmethyl ketones with formaldehyde and dialkylamines, such as diethyl- or dibutylamines at room temperature in silica gel produce **3** and **4** with moderate yields.

There is a considerable interest in the development of synthetic protocols that utilize solvent-free reactions on inorganic solids due to their inexpensive, recylable and environmentally benign nature.[1–3]

The synthesis of 1-aryl-2-(dialkyaminomethyl)prop-2-en-1-ones **3** and **4**, is of interest due to their application in medicinal chemistry.[4] There have been reports of the synthesis of 1-aryl-2-(dialkyaminomethyl)prop-2-en-1-ones. **3** or **4**, with low yield or formation of mixture.[5,6] Heber *et al*. reported the synthesis of **4** from arylmethyl ketones, paraformaldehyde and dimethylamine in dimethylformamide with moderate yields of 40–50%, involving a prolonged purification procedure.[5]

In continuation of our recent studies on Mannich type reactions in lithium perchlorate etherial solution[7] and solvent-free reactions, [8,9] we now wish to report the reaction of arylmethyl ketone **1** with formaldehyde and dialkylamines. This produced compounds **3** or **4** in solvent-free procedure in moderate yields. The methyl group in the aryl ketone is reactive and the hydrogen atoms readily undergo electrophilic replacement. In general, condensation of the active methyl group in acetophenone with formaldehyde and dimethylamine produces dimethylaminopropiophenone, in an example of a Mannich reaction.[10] In contrast with the above produce, we found that the solvent-free reaction of one equivalent of arylmethyl ketone, **1**, three equivalent of formaldehyde and two equivalent of dialkylamine, such as diethyl- or dibuthylamines, on silica gel, produced compounds **3** or **4** in moderate yields (30–78%) at room temperature. Scheme 1 One can envision the formation of **3** or **4** via the intermediate **2**. Table 1 shows the products and their isolated yields.



Scheme 1

General procedure for the preparation of 1-aryl-2-(dialkyaminomethyl)prop-2-en-1-ones, **3** and **4**: Arylmethol ketone, **1**, (1 mmol) was mixed with silica gel (2.0 g) in a mortar. Then formaldehyde (0.18 g, 3 mmol, 37% in H_2O), and dialkylamine (2 mmol) were added and mixed. The mixture was placed into a flask with a cap, and stirred for 5–7 hours at room temperature. Then ether (20 ml) was added. After filtration and the removal of the solvent at the reduced pressure, the product was isolated. Further purification of the crude reaction mixture on silica gel column gave the pure product. All new compounds were characterized by ^{1}HNMR, ^{13}CNMR, IR and MS. Chemical ionization (CI) high-resolution mass spectra (HRMS) were obtained using *iso*-butane as the ionizing source. All compounds afforded satisfactory analysis.

In conclusion, we developed a reliable, environmentally benign, synthetically very simple, and a solvent-free procedure for the preparation of Mannich product **3** and **4** with moderate yields for about 5 hours.

Selected spectroscopic data. **3a** (62%), viscose oil; ^{1}H NMR ($CDCl_3$); δ 0.71–1.32 (m, 14H), 2.32 (t, *J* = 6.8 Hz, 4H), 3.31 (s, 2H), 5.53 (s, 1H), 5.95 (s, 1H), 7.23–7.74 (m, 4H), ^{13}C NMR ($CDCl_3$): 13.78 (CH_3), 20.30 (CH_2), 29.14 (CH_2), 53.66 (CH_2), 55.61 (CH_2), 124.96 (CH_2), 128.16 (CH), 130.57 (CH), 135.65 (C), 138.36 (C), 146.35 (C), 196.39 (C). IR (neat); ν, 1684, 1592 cm^{-1}.

3b. (78%), m.p. 260°C (decompose); ^{1}H NMR ($CDCl_3$): δ 0.70–1.32 (m, 14H), 2.31 (t, *J* = 6.9Hz, 4H), 3.33 (s, 2H), 5.64 (d, *J* = 1.0 Hz, 1H), 6.04 (d, *J* – 1.0 Hz, 1H), 7.75–8.34 (m, 4H). ^{13}C NMR (CDC13): 13.77 (CH_3), 20.32 (CH_2), 28.92 (CH_2), 53.69 (CH_2), 54.17 (CH_2), 123.16 (CH_2), 128.79 (CH), 129.84 (CH), 142.0 (C), 145.91 (C), 149.48 (C), 198.43 (C). IR (KBr): ν 1692, 1530, 1363 cm^{-1}. HRMS calcd. for $C_{18}H_{26}N_2O_3$ (M^+) 319.022, found 319.1946.

3c. (68%) viscous oil; ^{1}H NMR ($CDCl_3$); δ 0.73–1.30 (m, 14H), 2.35 (t, *J* = 7.1 Hz, 4H), 3.32 (s, 2H), 5.60 (s, 1H), 5.96 (s, 1H), 7.32–7.85 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 13.72 (CH_3), 20.27 (CH_2), 29.20 (CH_2), 53.66 (CH_2), 55.58 (CH_2), 124.75 (CH_2),127.77 (CH), 129.12 (CH), 131.62 (CH), 137.38 (C), 146.55 (C), 198.21 (C). IR (neat) cm^{-1}: 3438, 1667, 1583: MS *m/z* (%), 273 (M^+, 11), 230 (100), 188 (37), 142 (45), 105 (94), 77 (73). IR (neat): ν, 1667, 1583 cm^{-1} $_1$. HRMS calcd for $C_{18}H_{27}NO$ (M^+) 274.2171, found 274.2133

3d. (68%), b.p. 180–182°C (670 mmHg); ^{1}H NMR ($CDCl_3$): δ 0.81–1.55 (m, 14H), 2.44 (t, *J* = 7.0 Hz, 4H), 3.34 (s, 2H), 5.55 (s, 1H), 5.90 (s, 1H), 7.34–7.65 (m, 4H). **3e**. m.p. 230–232 °C; IR (KBr): ν, 1669, 1590, cm^{-1}.

4a. (30%), b.p. 200–201°C (670 mmHg); ^{1}H NMR ($CDCl_3$): 0.91 (t, *J* = 7.1 Hz, 6H), 2.43 (q, *J* = 7.1 Hz, 4H), 5.44 (s, 2H), 5.52 (s, 1H), 5.92 (s, 1H), 7.23–7.75 (m, 4H). MS: *m/z* (%), 139 (100), 111 (48),. IR (KBr): ν, 1662, 1592, 1100 cm^{-1}. HRMS calcd for $C_{14}H_{18}NOCl$ (M^+) 252.1155, found 252.1102.

4b. 50%), m.p. 130–131°C; ^{1}H NMR (CDC1$_3$): δ 0.93 (t, *J* = 7.0 Hz, 6H), 2.44 (q, *J* = 7.0 Hz, 4H), 3.36 (s, 2H), 5.62 (s, 1H), 6.02 (s, 1H), 7.76–7.29 (m, 4H)./ MS: *m/z* (%), 262 (M^+,

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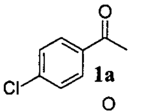
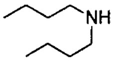
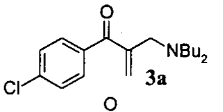
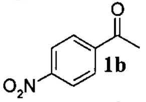
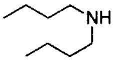
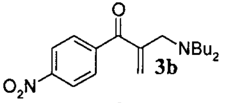
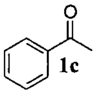
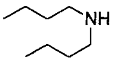
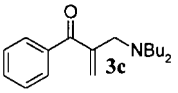
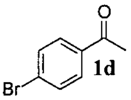
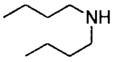
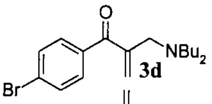
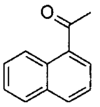
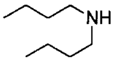
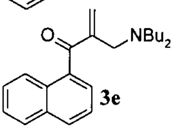
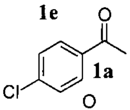
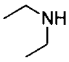
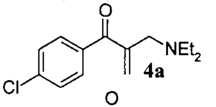
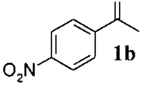
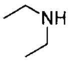
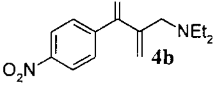
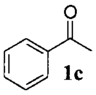
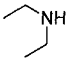
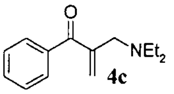
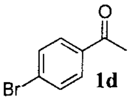
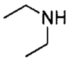
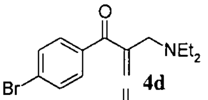
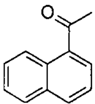
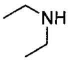
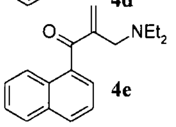
* To receive any correspondence.

[†] This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Yield of 1-aryl-2-(dialkylaminomethyl)prop-2-en-1-ones

Entry	Aromatic keton	Aliph. amine	Product	%Yield[a] (time, h)
1	 **1a**		 **3a**	62(5)
2	 **1b**		 **3b**	78(4)
3	 **1c**		 **3c**	68(7)
4	 **1d**		 **3d**	68(5)
5	 **1e**		 **3e**	55(7)
6	 **1a**		 **4a**	30(5)
7	 **1b**		 **4b**	50(7)
8	 **1c**		 **4c**	54(7)
9	 **1d**		 **4d**	35(5)
10	 **1e**		 **4e**	45(7)

[a]Isolated yields.

14), 247 (62), 243 (53), 150 (72), 104 (58), 86 (100). IR (KBr): ν, 1692, 1607, 1530, 1353 cm^{-1}. HRMS calcd for $C_{14}H_{18}N_2O_3$ (M$^+$) 263.1396, found 263.1395.

4c[11]. (54%), b.p. 160–162°C (670 mmHg); ^{1}H NMR ($CDCl_3$): δ 1.03 (t, *J* = 7.1 Hz, 6H), 2.42 (q, *J* = 7.1 Hz, 4H), 3.45 (s, 2H), 5.62 (s, 1H), 5.96 (s, 1H), 7.33–7.85 (m, 5H). ^{13}C NMR ($CDCl_3$): 11.62 ((CH_3), 46.99 (CH_2), 54.33 (CH_2), 125.40 (CH_2), 127.95 (CH), 129.31 (CH), 132.04 (CH), 137.50 (C), 146.33 (C), 194.50 (C). MS *m/z* (%), 217 (10), 200 (65), 105 (80), 86 (100), 77 (83).

4d. (35%), mp 78–80°C ^{1}H NMR ($CDCl_3$): δ 0.91 (t, *J* = 7.0 Hz, 6H), 2.42 (q, *J* 7.0 Hz, 4H), 3.33 (s, 2H), 5.65 (s, 1H), 5.90 (s, 1H), 7.32–7.65 (m, 4H),. IR (KBr): ν, 1676, 1584, 1076 cm^{-1}. HRMS calcd for $C_{14}H_{18}NOBr$ (M$^+$) 296.0650, found 296.0645.

4e. (45%), viscose oil; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, *J* = 7.1 Hz, 6H), 2.63 (q, *J* = 7.1 Hz, 4H), 3.42 (s, 2H), 5.92 (s, 1H), 6.00 (s, 1H), 7.42–8.23 (m, 7H), HRMS calcd for $C_{18}H_{22}NO$ (M$^+$) 269.1701, found 268.1701.

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