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A New Method for the Construction of α-Diazoketones

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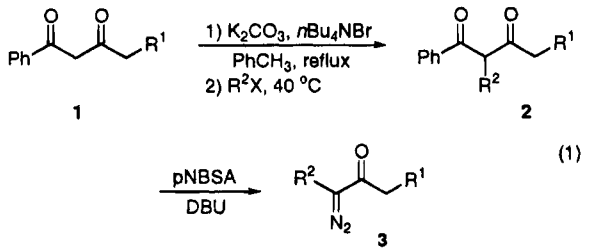
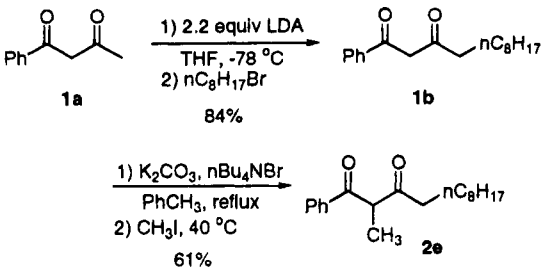
α-Diazoketones **3** undergo a variety of useful reactions, making them valuable synthetic intermediates.[1,2] Unsymmetrical α-diazoketones have been prepared[3ab] by condensing the requisite acid chloride with a diazoalkane. As diazoalkanes are difficult to prepare and to purify, we have now developed an alternative method for the regioselective construction of α-diazoketones, based on the alkylation of benzoylacetone **1** (R = H). We now report the key observation that diazo transfer[3,4] to a diketone **2** proceeds with selective *debenzoylation*[5] to provide the desired unsymmetrical α-diazoketone **3** (eq 1).



(1)

α-Alkylation of benzoylacetone (**1a**) using potassium carbonate in the presence of tetra-*n*-butylammonium bromide in toluene[6] produced a variety of α-substituted diketones **2**, as shown in Table 1. Alternatively, benzoylacetone may be γ-alkylated as its dianion[7] to provide diketone **1b**, which is then α-alkylated to provide a new unsymmetrical diketone **2e** (eq 2).



(2)

Various methods of debenzoylation/diazo transfer were then attempted, including the often-successful combination of NaH and methanesulfonyl azide[3b] in a variety of solvents, but with mediocre results. The use of *p*-nitrobenzenesulfonyl azide (*p*-NBSA)[8] and DBU,[9] however, produced α-diazoketones **3** in much higher yields (*cf.* Table 1).[10] In summary, we have developed a new method for the regioselective construction of unsymmetrical α-diazoketones using the inexpensive benzoylacetone as a precursor. This opens the way for the exploration of synthetic applications of these versatile intermediates.

Experimental Section[11]

Preparation of 1-Benzoyl-2-undecanone (1b). To a solution of 4.4 mmol of LDA [prepared from 0.62 mL (4.4 mmol) of diisopropylamine and 1.93 mL (4.4 mmol, 2.28 M solution in hexanes) of n-BuLi] in 4 mL of anhydrous THF at −78 °C under nitrogen was added dropwise a solution of 0.386 g (2.4 mmol) of benzoylacetone in 2 mL of anhydrous THF. The mixture was then warmed to −20 °C and stirred for 3 h, after which 0.38 mL (2.2 mmol) of *n*-bromooctane was added dropwise over 10 min, and the mixture was then slowly warmed to rt and stirred for 12 h. The mixture was then diluted with 20 mL of saturated aqueous NH_4Cl and extracted twice with 8 mL portions of ethyl acetate. The combined organic extracts were then washed with 15 mL of brine solution, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was then chromatographed to produce **1b** as a colorless, partially enolic oil (0.462 g, 84%). TLC R_f (10% ethyl acetate/petroleum ether) = 0.50; ^1H NMR (250 MHz, $CDCl_3$) δ 7.88 (d, 2H, J = 7.0 Hz), 7.60–7.40 (m, 3H), 6.17 (s, 0.92H), 4.08 (s, 0.16H), 2.58 (t, 0.08H, J = 7.3 Hz), 2.42 (t, 0.92H, J = 7.3 Hz), 1.75–1.60 (m, 2H), 1.45–1.05 (m, 2H), 0.88 (t, 3H, J = 6.3 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 196.9, 183.3, 135.0, 39.1, 31.8, 29.4, 29.3, 29.2 (2), 25.7, 22.6; down: 132.1, 128.4, 126.9, 95.9, 14.0; IR (film) 3058, 2836, 1614, 1574, 1264, 1080, 762, 689 cm^{-1}; EI MS m/z (rel intensity) 274 (M^+, 1), 162 (41), 161 (17), 147 (38), 120 (12), 105 (100), 77 (26), 69 (61), 55 (14); HRMS (calcd for $C_{18}H_{26}O_2$) 274.1933, found

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(3) For reviews of diazoketone preparation, see: (a) Regitz, M.; Mass, G. In *Diazo Compounds: Properties and Synthesis*, Academic Press: New York, 1986. (b) Taber, D. F. *Comprehensive Organic Synthesis*; Pattenden, G., Ed., Pergamon Press: Oxford, 1991; Vol. 3, p 1045. For more recent reagents for diazo transfer, see: (c) Ghosh, S.; Datta, I. *Synth. Commun.* **1991**, *21*, 191. (d) McGuiness, M.; Shechter, H. *Tetrahedron Lett.* **1990**, *31*, 4987. (e) Kumar, S. M. *Synth. Commun.* **1991**, *21*, 2121.

(4) Formylation is the most common method for α-methylene activation: (a) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610. (b) Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077. (c) For the use of trifluoracetylation, see Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

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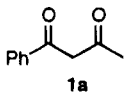
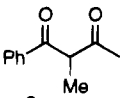
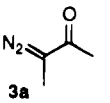
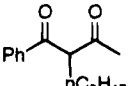
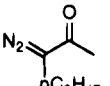
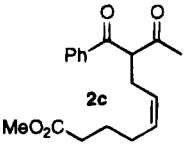
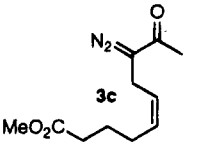
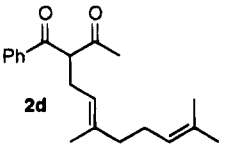
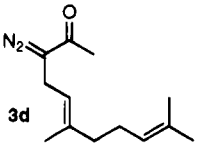
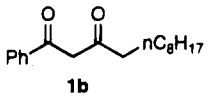
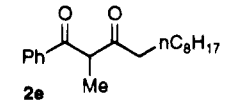
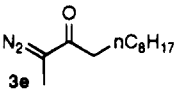
(9) For the use of DBU to promote diazo transfer, see: Koteswar Rao, Y.; Nagarajan, M. *J. Org. Chem.* **1989**, *54*, 5678.

(10) In some cases the use of MsN_3 instead of *p*-NBSA is advantageous due to the ease of removal of MsN_3 and $MsNH_2$ versus *p*-NBSA and *p*-nitrobenzenesulfonamide from the crude reaction mixture (see ref 3b).

(11) For a summary of general experimental procedures see: Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

0022-3263/95/1960-2283$09.00/0

Table 1. α-Alkylation and Diazo Transfer of Diketones 1

Entry	Diketone	Alkylation Product	Yield (%)	Diazoketone	Yield (%)
1	 **1a**	 **2a**	77	 **3a**	72
2	**1a**	 **2b**	59[a]	 **3b**	70
3	**1a**	 **2c**	90	 **3c**	83
4	**1a**	 **2d**	72	 **3d**	63
5	 **1b**	 **2e**	61	 **3e**	70

[a] This reaction was performed using 10 mol % nBu$_4$NI.

274.1925. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79%; H, 9.55%. Found: C, 78.80%; H, 9.84%.

3-Benzoyl-2-butanone (2a). A mixture of 8.88 g (64.3 mmol) of anhydrous, powdered K_2CO_3, 0.052 g (0.16 mmol) of n-Bu$_4$NBr and 2.34 g (14.4 mmol) of benzoylacetone in 30 mL of anhydrous toluene under nitrogen was heated at reflux for 3.5 h. The mixture was then cooled to 40 °C for the dropwise addition of 1.00 mL (16.1 mmol) of iodomethane. The mixture was then stirred at 40 °C for an additional 18 h. The mixture was cooled to 0 °C and filtered, and the residue was washed twice with 100 mL portions of petroleum ether. The combined filtrate was concentrated, and the residue was chromatographed to produce **2a** as a yellow oil (1.96 g, 77%). TLC R_f (5% ethyl acetate/petroleum ether) 0.32; bp 80 °C/1 mmHg; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 7.0 Hz), 7.65–7.35 (m, 3H), 4.49 (q, 1H, J = 6.9 Hz), 2.15 (s, 3H), 1.45 (d, 3H, J = 6.8 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 133.1, 128.4, 128.1, 55.6, 27.7, 13.0; down: 204.3, 197.0, 135.5; IR (film) 3063, 2987, 1722, 1674, 1596, 1449 cm^{-1}; EI MS m/z (rel intensity) 176 (M$^+$, 1), 134 (9), 133 (15), 105 (100), 77 (53), 51 (21); HRMS (calcd for $C_{11}H_{12}O_2$) 176.0837, found 176.0833.

3-Benzoyl-2-undecanone (2b): TLC R_f (20% ethyl acetate/petroleum ether) = 0.64; bp 120 °C/1 mmHg; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.92 (d, 2H, J = 7.1 Hz), 7.51–7.37 (m, 3H), 4.39 (t, 0.9 Hz, J = 7.0 Hz), 3.88 (t, 0.1 Hz, J = 7.0 Hz), 2.36 (s, 0.3H), 2.07 (s, 2.7H), 2.00–1.82 (m, 2H), 1.30-1.05 (m, 12H), 0.79 (t, 3H, J = 6.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 133.4, 128.6, 128.4, 63.2, 27.6, 13.8; down: 204.1, 196.3, 136.4, 31.6, 29.3, 29.1, 29.0, 28.9, 27.5, 22.4; IR (film) 3063, 2925, 1723, 1678, 1597, 1448, 1357 cm^{-1}; EI MS m/z (rel intensity) 162 (M$^+$, 21), 133 (13), 105 (100), 77 (30), 55 (10); HRMS (calcd for $C_{18}H_{26}O_2$) 274.1933, found 274.1845.

Methyl (*Z*)-8-Benzoyl-9-oxo-5-decenoate (2c): TLC R_f (20% ethyl acetate/petroleum ether) = 0.35; bp 150 °C/1 mmHg; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 5.1 Hz), 7.65–7.35 (m, 3H), 5.45–5.25 (m, 2H), 4.47 (t, 1H, J = 7.2 Hz), 3.66 (s, 3H), 2.73 (t, 2H, J = 6.9 Hz), 2.30 (t, 2H, J = 7.4 Hz), 2.15 (s, 3H), 2.11 (m, 2H), 1.67 (m, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 203.1, 195.7, 173.4, 136.0, 32.8, 26.4, 26.0, 24.1; down: 133.3, 131.0, 128.4, 128.2, 125.7, 62.0, 50.9, 28.0; IR (film) 3008, 2951, 1732, 1676, 1596, 1448 cm^{-1}; EI MS m/z (rel intensity) 302 (M$^+$, 1), 259 (5), 227 (5), 161 (13), 140 (34), 105 (100), 77 (52); HRMS (calcd for $C_{18}H_{22}O_4$) 302.1516, found 302.1518. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50%; H, 7.33%. Found: C, 71.24%; H, 7.29%.

(*E*)-3-Benzoyl-6,10-dimethylundeca-5,9-dien-2-one (2d): TLC R_f (5% ethyl acetate/petroleum ether) = 0.18; bp 150 °C/1 mmHg; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 7.0 Hz), 7.65–7.40 (m, 3H), 5.10–4.95 (m, 2H), 4.46 (t, 1H, J = 7.2 Hz), 2.70 (t, 2H, J = 7.2 Hz), 2.15 (s, 3H), 2.05–1.85 (m, 4H), 1.62 (s, 3H), 1.61 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 203.9, 196.2, 138.0, 136.4, 131.2, 39.4, 27.6, 26.2; down: 133.4, 128.6, 128.5, 123.8, 119.8, 62.9, 28.0, 25.4, 17.5, 15.9; IR (film) 3061, 2922, 1722, 1681, 1597, 1448 cm^{-1}; EI MS m/z (rel intensity) 298 (M$^+$, 2), 255 (6), 161 (9), 105 (100), 77 (36), 69 (31); HRMS (calcd for $C_{20}H_{26}O_2$) 298.1933, found 298.1943.

2-Benzoyl-3-dodecanone (2e): TLC R_f (10% ethyl acetate/petroleum ether) = 0.38; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (d, 2H, J = 7.3 Hz), 7.65–7.40 (m, 3H), 4.49 (q, 1H, J = 7.1 Hz), 2.55–2.30 (m, 2H), 1.52 (m, 2H), 1.44 (d, 3H, J = 6.9 Hz), 1.30–1.05 (m, 12H), 0.86 (t, 3H, J = 6.3 Hz); ^{13}C (62.9 MHz, $CDCl_3$) δ up: 133.5, 128.8, 128.6, 56.2, 14.0, 13.5; down: 207.1, 197.3, 136.1, 40.6, 31.8, 29.3, 29.2 (2), 28.9, 23.5, 22.6; IR (film) 2926, 1712, 1678, 1596, 1450 cm^{-1}; EI MS m/z (rel intensity) 288 (M$^+$, 1), 134 (81), 133 (16), 105 (100), 77 (40), 71 (16), 57 (22); HRMS (calcd for $C_{19}H_{28}O_2$) 288.2089, found 288.2094. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12%; H, 9.78%. Found: C, 78.85%; H, 9.81%.

3-Diazobutan-2-one (3a). To a solution of 1.82 g (10.3 mmol) of diketone **2a** in 40 mL of anhydrous CH_2Cl_2 at 0 °C under nitrogen was added 3.09 mL (20.7 mmol) of DBU, followed by the dropwise addition of a solution of 4.71 g (20.7 mmol) of p-NBSA in 10 mL of anhydrous CH_2Cl_2. The mixture was warmed to rt and stirred for 1 h, after which the solvent was removed *in vacuo*. The product was isolated by fractional distillation (87–89 °C/90 mmHg) to produce **3a** as a yellow oil (0.73 g, 72%). The spectral data of **3a** were identical to the known compound:[12] ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.96 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 24.5, 7.4; down: 190.8; IR (film) 2929, 2072, 1638, 1328, 1296 cm^{-1}.

(12) (a) Regitz, M.; Menz, F. *Chem. Ber.* **1961**, *101*, 2622. (b) Diels, O.; Pflaumer, K. *Ber. Dtsch. Chem. Ges.* **1915**, *58*, 223.

3-Diazoundecan-2-one (3b). TLC R_f (20% ethyl acetate/petroleum ether) = 0.55; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.32 (t, 2H, J = 7.6 Hz), 2.23 (s, 3H), 1.46 (m, 2H), 1.40–1.15 (m, 10H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 191.1, 67.3, 31.7, 29.1, 29.0, 28.7, 27.0, 22.5, 22.2; down: 25.3, 14.0; IR (film) 2926, 2066, 1644, 1367, 1330 cm^{-1}; EI MS m/z (rel intensity) 168 ($M^+ - N_2$, 3), 125 (6), 112 (21), 97 (65), 84 (21), 71 (28), 69 (100), 55 (93); HRMS (calcd for $C_{11}H_{20}O$) 168.1512, found 168.1514.

Methyl (Z)-8-Diazo-9-oxo-5-decenoate (3c): TLC R_f (20% ethyl acetate/petroleum ether) = 0.21; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.43 (m, 1H), 4.13 (q, 2H, J = 7.1 Hz), 3.08 (d, 2H, J = 7.4 Hz), 2.28 (t, 2H, J = 2.8 Hz), 2.25 (s, 3H), 2.12 (m, 2H), 1.70 (m, 2H), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 190.0, 173.4, 66.7, 32.9, 26.1, 24.3, 19.7; down: 132.5, 123.4, 51.1, 25.1; IR (film) 2951, 2071, 1736, 1639, 1330 cm^{-1}; EI MS m/z (rel intensity) 196 ($M^+ - N2$, 3), 164 (6), 122 (33), 107 (25), 95 (100), 85 (21), 79 (44), 55 (23); HRMS (calcd for $C_{11}H_{16}O_3$) 196.1094, found 196.1099.

***(E)*-2-Diazo-6,10-dimethylundeca-5,9-dien-2-one (3d)**: TLC R_f (5% ethyl acetate/petroleum ether) = 0.12; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.20–5.00 (m, 2H), 3.05 (d, 2H, J = 7.5 Hz), 2.24 (s, 3H), 2.05 (m, 4H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (62.9 MHz, CDCl3) δ up: 190.5, 140.1, 131.6, 67.4, 39.4, 26.3, 20.4; down: 123.6, 117.2, 25.5 (2), 17.5, 15.9; IR (film) 2923, 2069, 1642, 1366, 1326 cm^{-1}; EI MS m/z (rel intensity) 192 ($M^+ - N_2$, 3), 149 (4), 124 (27), 109 (42), 81 (57), 69 (100); HRMS (calcd for $C_{13}H_{20}O$) 192.1509, found 192.1514.

2-Diazo-3-dodecanone (3e): TLC R_f (10% ethyl acetate/petroleum ether) = 0.57; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.46 (t, 2H, J = 7.3 Hz), 1.95 (s, 3H), 1.63 (m, 2H), 1.40–1.10 (m, 12H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ up: 194.8, 62.0, 37.7, 31.8, 29.6, 29.3 (2), 29.2 (2), 24.8, 22.6; down: 14.0, 8.0; IR (film) 2925, 2067, 1644, 1463, 1283 cm^{-1}; EI MS m/z (rel intensity) 182 ($M^+ - N_2$, 2), 112 (35), 97 (38), 84 (18), 69 (100), 55 (63); HRMS (calcd for $C_{12}H_{22}O$) 182.1672, found 182.1671.

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Supplementary Material Available: ^{1}H and ^{13}C spectra for compounds **1b**, **2a–e**, and **3b-e** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.

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