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A Simple Preparation of α-Diazo Esters

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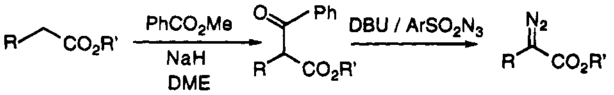
α-Diazo esters are valuable intermediates for organic synthesis.[1–3] Despite this, no general procedure for diazo transfer[4–6] to the α-methylene of an ester has been developed.[7] We, and others,[2c] have found that formylation does not lead to successful diazo transfer. We now report that *benzoylation*[6] followed by diazo transfer is much more successful (**1** → **2** → **3**).

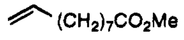
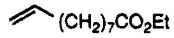
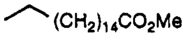
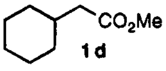
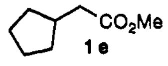


1 **2** **3**

Initially, we carried out diazo transfer by using excess NaH and adding the sulfonyl azide to the benzoylation reaction mixture. We have found, however, that the overall yield for diazo transfer is a little better if the intermediate benzoyl ester is purified. Diazo transfer is then effected with DBU[8] and 4–nitrobenzenesulfonyl azide.[7] This protocol worked well for each of the examples we have so far tried (Table 1).

This procedure for diazo transfer to the α-methylene of an ester should make α-diazo esters readily available as intermediates for organic synthesis.

Table 1. Benzoylation and Diazo Transfer

entry	ester	benzoylation yield (%)	diazo transfer yield (%)	overall yield (%)
1	 **1a**	91	81	74
2	 **1b**	98	90	88
3	 **1c**	85	80	68
4	 **1d**	83	97	81
5	 **1e**	84	92	77

Experimental Section[9]

Methyl 2-Benzoyl-10-undecenoate. NaH (0.92 g, 60% in mineral oil, 23 mmol, 4 equiv) was washed twice with petroleum ether and then suspended in 20 mL of DME. To this suspension at 0 °C was added 1.14 g of methyl 10-undecenoate (5.76 mmol, 1 equiv) in 2 mL of DME. After 10 min at 0°, 1.19 g of methyl benzoate (8.7 mmol, 1.5 equiv) in 2 mL of DME was added. After 1 drop of methanol was added, the mixture was heated to reflux for 8 h. The reaction was quenched by cautiously adding aqueous 1 N HCl, to pH = 4. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the methyl 2-benzoyl-10-undecenoate (1.6 g, 92% yield) as a colorless oil: TLC R_f (10% ethyl acetate/petroleum ether) = 0.51. ^1H NMR (δ): 8.01 (dd, *J* = 7.0 Hz, 1.6 Hz, 2H), 7.56 (dt, *J* = 7.2 Hz, 1.3 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 5.79 (m, 1H), 4.96 (m, 2H), 4.33 (t, *J* = 7.1 Hz, 1H), 3.68 (s, 3H), 1.97 (m, 4H), 1.29–1.33 (m, 10H). ^{13}C NMR (δ) up: 194.9, 170.3, 136.1, 114.0, 33.5, 29.2, 29.0, 28.9, 28.8, 28.7, 27.4; down: 138.8, 133.3, 128.6, 128.4, 53.8, 52.1. IR (cm^{-1}): 2927, 2855, 1724, 1687, 1640, 1597, 1581, 1448, 1435, 1231. MS (*m/z*, %): 191 (3), 178 (17), 146 (5), 105 (100). HRMS: calcd ($C_{19}H_{26}O_3$) 302.188, obsd 302.187. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.34; H, 8.64.

Methyl 2-Diazo-10-undecenoate. DBU (0.304 mL, 2 mmol, 2.1 equiv) was added to a solution of methyl 2-benzoyl-10-undecenoate (288 mg, 0.95 mmol, 1 equiv) in 2 mL of CH_2Cl_2 at 0 °C. After 10 min, 466 mg of 4-nitrobenzenesulfonyl azide (2 mmol, 2.1 equiv) in 2 mL of CH_2Cl_2 was added. The mixture was warmed to rt and stirred for 30 min, and then aqueous 0.5 M phosphate buffer (pH = 7.0, 3 mL) and 4 mL of distilled water were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give methyl 2-diazo 10-undecenoate (173 mg, 81% yield) as a yellow oil: TLC R_f (10% ethyl acetate/petroleum ether) = 0.64. ^1H NMR (δ): 5.79 (m, 1H), 4.98 (m, 1H), 4.92 (m, 1H), 3.75 (s, 3H), 2.3 (t, *J* = 7.3 Hz, 2H), 2.03 (m, 2H), 1.48 (m, 2H), 1.5 (m, 8H). ^{13}C NMR (δ) up: 170.0, 114.1, 33.6, 29.0, 28.9, 28.7, 28.5, 27.5, 22.9; down: 138.9, 51.7. IR (cm^{-1}): 2928, 2856, 2079, 1699, 1437, 1351, 1306, 1190, 1138. MS (*m/z* %): 165 (15), 139 (5), 136 (15), 113 (44), 95 (54), 81 (100). HRMS: calcd ($C_{12}H_{20}O_2N_2$) 196.146, obsd 196.146.

Ethyl 2-benzoyl-10-undecenoate: TLC R_f (5% ethyl acetate/petroleum ether) = 0.36. ^1H NMR (δ): 7.96 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.54 (m, 1H), 7.43 (t, *J* = 7.0 Hz, 2H), 5.76 (m, 1H), 4.90 (m, 2H), 4.24 (t, *J* = 7.1 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 3H), 1.99 (m, 4H), 1.29 (m, 10H), 1.12 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (δ) up: 195.4, 170.0, 136.3, 114.1, 61.2, 33.7, 29.3, 29.1, 28.9,

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[1] For general reviews of the use of α-diazo esters and α-diazo ketones in synthesis, see (a) Doyle, M. P. in *Homogeneous Transition Metal Catalysts in Organic Synthesis*; Moser, W. R., Slocum, D. W., Eds.; ACS Advanced Chemistry Series 230; American Chemistry Society, Washington, D. C., 1992; Chp. 30. (b) Taber, D. F. *Comprehensive Organic Synthesis*; Pattenden, G., Ed., Pergamon Press: Oxford, 1991, Vol. 3, p 1045.

[2] A diazo group α to a carbonyl can be converted into a variety of other functional groups, including (a) Alkene: Hudlicky, T.; Olivo, H. F.; Natchus, M. G. *J. Org. Chem.* **1990**, *55*, 4767. (b) Haloalkene: Buckley, D. J.; Kulkowit, S.; McKervey, A. *J. Chem. Soc. Chem. Commun.* **1980**, 506. (c) Ether: Aller, E.; Cox, G. C.; Miller, D. J.; Moody, C. J. *Tetrahedron Lett.* **1994**, *35*, 5949. (d) Thioether: McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1982**, *23*, 2509. (e) Ammonium ylide: West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1993**, *115*, 1177. (f) Oxonium ylide: Padwa, A.; Chinn, R. L.; Zhi, L. *Tetrahedron Lett.* **1989**, *30*, 1491. (g) Sulfonium ylide: Kido, F.; Sinha, S. C.; Abiko, T.; Yoshikoshi, A. *Tetrahedron Lettt.* **1989**, *30*, 1575. (h) Silyl: Andrey, O.; Landais, Y.; Planchenault, D. *Tetrahedron Lett.* **1993**, *34*, 2927. (i) Acyl: Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258. (j) Alkylidene: Herrmann, W. A.; Wang, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1641.

[3] For the first observation of the efficient cyclization of simple α-diazo esters, see Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436.

[4] The current method of choice[2c] for the preparation of an α-diazo ester requires prior preparation of the corresponding α-keto ester.

[5] For an overview of diazo transfer chemistry, with a detailed discussion of reaction mechanisms, see (a) Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic Press: Orlando, 1986. (b) Askani, R.; Taber, D. F. *Comprehensive Organic Synthesis*; E. Winterfeldt, Ed.; Pergamon: Oxford, 1991; Vol. 6, p 103.

[6] (a) For benzoylation of a *ketone* followed by diazo transfer, see Metcalf, B. W.; Jund, K.; Burkhart, J. P. *Tetrahedron Lett.* **1980**, *21*, 15. (b) More recently, trifluoroacetylation has been used to activate ketones for diazo transfer: Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959.

[7] Evans, seeking azide tranfer, reported occasional partial conversion of an ester enolate to the α-diazo ester: Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011.

[8] For the use of DBU to promote diazo transfer, see Koteswar Rao, Y.; Nagarajan, M. *J. Org. Chem.* **1989**, *54*, 5678.

[9] For general experimental procedures, see Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

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28.8, 27.5; down: 139.0, 133.3, 128.6, 128.5, 54.3, 13.9. IR (cm^{-1}): 2927, 2855, 1738, 1688, 1448, 1231, 1183. MS (*m/z* %): 316.5 (0.05), 205 (1), 192 (15), 146 (3), 105 (100). HRMS: calcd ($C_{20}H_{28}O_3$) 316.204, obsd 316.203.

Ethyl 2-diazo-10-undecenoate: TLC R_f (5% ethyl acetate/petroleum ether) = 0.49. ^{1}H NMR (δ): 5.80 (m, 1H), 5.02 (m, 2H), 4.92 (1H), 4.21 (q, J = 7.2 Hz, 3H), 2.30 (t, J = 7.1 Hz, 2H), 2.03 (m, 2H), 1.50 (m, 2H), 1.30 (m, 8H), 1.27 (t, J = 7.2 Hz, 3H). ^{13}C NMR (δ) up: 167.6, 114.1, 60.6, 33.7, 29.0, 28.9, 28.8, 28.6, 27.5, 22.9; down: 139.0, 14.4. IR (cm^{-1}): 2979, 2928, 2856, 2080, 1695, 1464, 1446, 1394, 1371, 1303, 1172, 1131, 910, 739. MS (*m/z* %): 210 (1), 181 (5), 165 (31), 136 (24), 120 (9), 95 (100). HRMS: calcd ($C_{13}H_{22}O_2N_2$) 210.162, obsd 210.164.

Methyl 2-benzoylstearate: TLC R_f (10% ethyl acetate/petroleum ether) = 0.44. ^{1}H NMR (δ): 7.99 (dd, J = 8.2, 1.6 Hz, 2H), 7.59 (m, 1H), 7.47 (t, J = 7.0 Hz, 2H), 4.33 (t, J = 7.1 Hz, 1H), 3.70 (s, 3H), 2.00 (m, 2H), 1.26 (m, 28H), 0.9 (t, J = 7.6 Hz, 3H). ^{13}C NMR(δ) up: 195.0, 170.4, 136.2, 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 29.0, 27.5, 22.6; down: 133.3, 128.6, 128.4, 53.9, 52.2, 14.0. MS (*m/z* %): 297 (1), 233 (1), 178 (22), 146 (4), 120 (7), 105 (100). HRMS: calcd ($C_{26}H_{42}O_3$) 402.314, obsd 402.313.

Methyl 2-diazostearate: TLC R_f (10% ethyl acetate/petroleum ether) = 0.57. ^{1}H NMR (δ): 3.75 (s, 3H), 2.30 (t, J = 7.2 Hz, 2H), 1.50 (m, 2H), 1.26 (m, 26H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (δ) up: 168.3, 141.5, 32.3, 30.4, 30.1, 30.0, 29.9, 29.8, 29.7, 29.4, 29.1, 28.0, 23.4, 23.1; down: 52.1, 14.5. IR (cm^{-1}): 2942, 2854, 2360, 2341, 2079, 1701, 1466, 1437, 1351, 1305, 1190, 1135. MS (*m/z* %): 296 (3), 265 (5), 213 (5), 199 (12), 151 (2), 113 (100). HRMS: calcd ($C_{19}H_{36}O_2N_2$) 296.271, obsd 296.271.

Methyl 2-benzoyl-2-cyclohexylacetate: TLC R_f (10% ethyl acetate/petroleum ether) = 0.35. ^{1}H NMR (δ): 8.01 (dd, J = 8.3 Hz, 1.6 Hz, 2H), 7.58 (m, 1H), 7.47 (t, J = 7.0 Hz, 2H), 4.21 (d, J = 9.7 Hz, 1H), 3.66 (s, 3H), 2.41 (m, 1H), 1.67 (m, 5H), 1.30 (m, 2H), 1.17 (m, 2H), 1.12 (m, 1H). ^{13}C NMR (δ) up: 194.2, 169.1, 136.9, 31.0, 30.6, 25.9, 25.8; d: 133.2, 128.5, 128.2, 59.8, 51.8, 38.1. IR (cm^{-1}): 2925, 2853, 1741, 1687, 1596, 1581, 1448, 1434, 1341, 1320, 1285, 1242, 1191, 1158, 1131, 1097, 1053, 1000. MS (*m/z* %): 261 (1), 229 (3), 178 (47), 146 (16), 115 (3), 105 (100). HRMS: calcd ($C_{16}H_{20}O_3$) 260.141, obsd 260.141.

Methyl 2-diazo-2-cyclohexylacetate: TLC R_f (10% ethyl acetate/petroleum ether) = 0.49. ^{1}H NMR (δ): 3.75 (s, 3H), 2.36 (m, 1H), 1.86 (m, 5H), 1.36 (m, 2H), 1.18 (m, 3H). ^{13}C NMR (δ) up: 31.2, 26.4, 26.0; down: 138.5, 52.0, 32.0. IR (cm^{-1}): 2930, 2854, 2123, 2074, 1698, 1436, 1370, 1339, 1303, 1276, 1226, 1187, 1145, 1098, 1006. MS (*m/z* %): 154(100), 139(12), 123-(70), 111(63), 95(72), 79(74). HRMS: calcd ($C_9H_{14}O_2N_2$) 154.102, obsd 154.099.

Methyl 2-benzoyl-2-cyclopentylacetate: TLC R_f (10% ethyl acetate/petroleum ether) = 0.35. ^{1}H NMR (δ): 8.02 (dd, J = 8.3 Hz, 1.6 Hz, 2H), 7.59 (m, 1H), 7.48 (t, J = 7.7 Hz, 2H), 4.20 (d, J = 10.3 Hz, 1H), 3.67 (s, 3H), 2.74 (m, 1H), 1.86 (m, 2H), 1.61 (m, 4H), 1.36 (m, 1H), 1.04 (m, 1H). ^{13}C NMR (δ) up: 194.1, 163.3, 136.3, 30.6, 30.3, 24.5, 24.3; down: 133.0, 128.3, 128.1, 58.9, 51.7, 39.6. IR (cm^{-1}): 2954, 2870, 1738, 1682, 1597, 1580, 1448, 1434, 1359, 1326, 1270, 1219, 1148, 1022, 1001. MS (*m/z* %): 246 (1), 215 (3), 192 (9), 155 (2), 146 (2), 120 (2), 105 (100). HRMS: calcd ($C_{15}H_{18}O_3$) 246.126, obsd 246.126.

Methyl 2-diazo-2-cyclopentylacetate: TLC R_f (10% ethyl acetate/petroleum ether) = 0.50. ^{1}H NMR (δ): 3.76 (s, 3H), 2.79 (m, 1H), 1.96 (m, 2H), 1.66 (m, 4H), 1.38 (m,2H). ^{13}C NMR (δ) up: 170.0, 140.1, 31.3, 25.0; down: 52.1, 33.8. IR (cm^{-1}): 2957, 2871, 2078, 1700, 1437, 1260, 1107. MS (*m/z* %): 140 (72), 125 (9), 109 (82), 107 (39), 95 (3), 70 (100). HRMS: calcd ($C_8H_{12}O_2N_2$) 140.084, obsd 140.086.

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Supplementary Material Available: ^{1}H and ^{13}C spectra for compounds **2a**–**e** and **3a**–**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; see any current masthead page for ordering information.

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