Synthesis of Monosubstituted 1,3,4-Oxadiazolidine-2,5-diones

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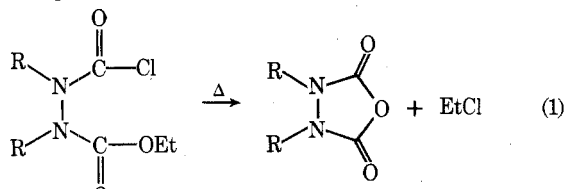
Monosubstituted 1,3,4-oxadiazolidine-2,5-diones **7** (diazasuccinic anhydrides), desired by us as precursors of cyclic diacylhydrazyl radicals, have never been reported. Although structurally simple, they cannot be prepared by the routes that suffice for the synthesis of disubstituted analogues **2**, themselves only recently prepared. Hurd and Cesark[1] found that pyrolysis of 2-carbethoxy-1,2-dialkylhydrazinecarbonyl chlorides **1** [R = CH_3, CH_3CH_2, $(CH_3)_2CH$] at 140–180 °C



(1)

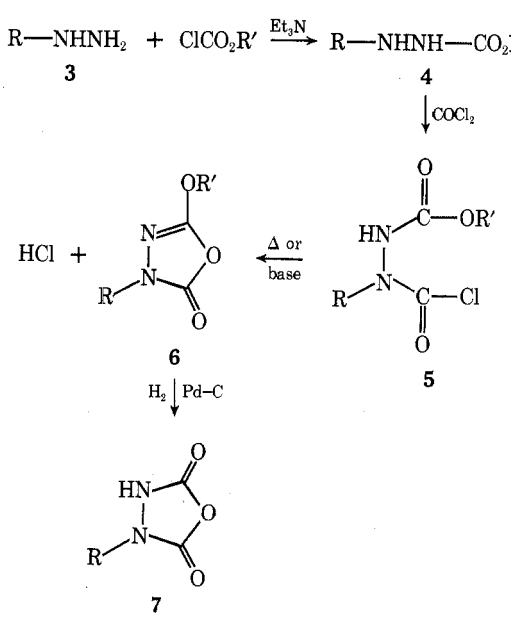
1 **2**

provides dialkyl diazasuccinic anhydrides (**2**) in quantitative yields (eq 1). Henderson and Zweig[2] reported that diphenyldiazasuccinic anhydride **2** (R = C_6H_5) could be made in 35% yield by the copper(II)-catalyzed pyrolysis of the corresponding hydrazinecarbonyl chloride (**1**).

Pyrolysis of 2-carbethoxy-1-phenylhydrazinecarbonyl chloride (**5d**) afforded, not the desired monosubstituted diazasuccinic anhydride, but Δ^2-1,3,4-oxadiazolin-5-one **6d**, via the loss of hydrogen chloride.[3] Unsurprisingly, attempts to remove the ethyl groups from this product by either acid- or base-catalyzed hydrolysis were unsuccessful, resulting instead in ring cleavage. Replacement of the ethyl group with benzyl, it was felt, would allow the latter to be removed under potentially mild conditions. Pyrolysis of carbobenzyloxyhydrazinecarbonyl chloride **5e** affords hydrogen chloride and a gum in which none of the desired oxadiazolinone could be detected (NMR). Base-induced cyclization of **5e** with ethyldiisopropylamine provides oxadiazolinone **6e** in high yield. Hydrogenolysis (palladium on carbon) occurs rapidly to give oxadiazolidinedione **7a** in good yield. Phenyldiazasuccinic anhydride **7a**, a crystalline solid, turns yellow and decomposes after a few months at room temperature. α-Cumylhydrazinecarbonyl chloride **5f** did not cyclize when treated with ethyldiisopropylamine. However, treatment of **5f** with lithium diisopropylamide affords, after workup, a brown semisolid product, from which analytically pure α-cumyloxadiazolinone **6f** was obtained chromatographically. Hydrogenolysis of **6f** affords oxadiazolidinedione **7b** (22%), as a white solid that began to decompose within a week at 25 °. Similarly, *tert*-butyloxadiazolinone **6g** was made by lithium diisopropylamide treatment of *tert*-butylhydrazinecarbonyl chloride **5g**. Hydrogenolysis of **6g** affords a white solid that was shown by NMR to be a 1:1 mixture of *tert*-butyloxadiazolidinedione **7c** and *tert*-butylhydrazine (**3c**). Presumably, hydrolytic decomposition of the diazasuccinic anhydride via loss of carbon dioxide gives rise to *tert*-butylhydrazine. A solid containing ca. 85% of oxadiazolidinedione **7c** was obtained by washing the impure solid with 1:1 benzene–pentane. Within a few days at room temperature, the diazasuccinic anhydride had partially decomposed as judged by an increase in relative size of the *tert*-butylhydrazine NMR signals.

These monosubstituted diazasuccinic anhydrides decompose on standing at room temperature. However, the benzyloxyoxadiazolinone precursors **6** are appreciably more stable to storage at room temperature.

Scheme I



3 **4** **6** **5** **7**

a, R = Ph
b, R = PhC(Me)$_2$
c, R = *t*-Bu
d, R = Ph; R′ = Et
e, R = Ph; R′ = $PhCH_2$
f, R = PhC(Me)$_2$; R′ = $PhCH_2$
g, R = *t*-Bu; R′ = $PhCH_2$

Experimental Section

Benzyl 3-Phenylcarbazate (4e). After cooling a solution of phenylhydrazine (**3a**, 50.8 g, 0.471 mol) and triethylamine (49.6 g, 0.491 mol) in THF (960 ml) to −5 °C in an ice–acetone bath, a solution of benzyl chloroformate (82.15 g, 0.482 mol) in THF (480 ml) was added with mechanical stirring at a rate that maintained a temperature below 0 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature. Filtration and concentration of the filtrate in vacuo afforded 116.59 g of a brown-red solid. Recrystallization from ethanol provided 69.18 g (0.286 mol, 60.6%) of a white solid: mp 94.5–96.5 °C; ir ($CHCl_3$) 3420 and 3380 (NH), 3035 (CH), 1742 (C=O), 1607, 1500, 1482, 1240 (C–O), 1180, 790, and 700 cm^{-1}; NMR ($CDCl_3$) 5.08 (s, 2, OCH_2Ph), 5.51 (s, 1, PhNHN), and 6.4–7.6 ppm (m, 11, C_6H_5 and CONHN); mass spectrum (70 eV) *m/e* (rel intensity) 242 (15, M^+), 108 (6), 107 (61), 93 (5), 92 (12), 91 (100), 77 (17), 65 (14), 51 (7), and 39 (7).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.23; H, 5.76; N, 11.67.

Benzyl 3-α-Cumylcarbazate (4f). α-Cumylcarbazate **4f** was prepared from α-cumylhydrazine[4] (**3b**, 25.66 g, 0.171 mol) and benzyl chloroformate (30.2 g, 0.177 mol) in a manner similar to that used to prepare phenylcarbazate **4e**. The crude solid product was purified (three times) by dissolution in carbon tetrachloride and precipitation by pentane addition to afford a white solid: mp 51–52 °C; ir ($CHCl_3$) 3440, 3380, and 3320 (NH), 3020 and 2995 (CH), 1730 (C=O), 1455, 1380 (CMe_2), 1374 (CMe_2), 1255 (C–O), 1175, 1152, 788, and 705 cm^{-1}; NMR ($CDCl_3$) 1.42 [s, 6, $C(CH_3)_2$], 3.82 (s, 1, CNHN), 5.06 (s, 2, $PhCH_2O$), 5.84 (s, 1, NNHCO), and 7.1–7.6 ppm (m, 10, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 284 (4, M^+), 166 (9), 120 (12), 119 (100), 92 (8), 91 (77), 79 (7), 77 (8), 65 (9), 41 (13), and 28 (9).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.59; H, 6.93; N, 9.87.

Benzyl 3-*tert*-Butylcarbazate (4g). *tert*-Butylcarbazate **4g** (14.52 g, 65.3 mmol) was prepared in 65% yield from *tert*-butylhydrazine[5] (**3c**, 8.82 g, 100 mmol) and benzyl chloroformate (17.10 g, 100 mmol) in a manner analogous to that used to prepare phenylcarbazate **4e**. The crude yellow product was washed with pentane to afford an off-white solid, mp 73.5–76.5 °C. An analytical sample was recrystallized from benzene: mp 74–76 °C; ir ($CHCl_3$) 3435, 3395, and 3210 (NH), 3025 and 2980 (CH), 1723 (C=O), 1470, 1442, 1395 (CMe_3), 1369 (CMe_3), 1258 (C–O), 1150, and 702 cm^{-1}; NMR ($CDCl_3$) 1.05 [s, 9, $C(CH_3)_3$], 5.11 (s, 2, $PhCH_2O$), and 7.32 ppm (s, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 222 (9, M^+), 92 (9), 91 (100), 87 (41), 65 (8), 56 (69), 41 (9), 29 (5).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.59; H, 8.11; N, 12.66.

2-Carbethoxy-1-phenylhydrazinecarbonyl Chloride (5d). To a stirred solution of phosgene (37.7 g, 0.381 mol) in anhydrous ether (40 ml) at 0 °C was added a solution of ethyl 3-phenylcarbazate[6] (**4d**, 13.52 g, 0.075 mol) in anhydrous ether (100 ml), causing a solid to form. While being stirred at 30 °C overnight, this solid dissolved. Addition of pentane caused the product to precipitate as a white solid. Recrystallization from 1:1 benzene–cyclohexane afforded 14.76 g (0.061 mol, 81.1%) of a white solid: mp 96.5–98 °C; ir (KBr) 3270 (NH), 2990 (CH), 1755 (C=O), 1497, 1290, 1255, 1118, 1056, 819, 751, and 703 cm^{-1}; NMR ($CDCl_3$) 1.24 (t, 3, J = 7 Hz, OCH_2CH_3), 4.18 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 7.2–7.5 (m, 5, C_6H_5), and 8.28 ppm (s, 1, CONHN); mass spectrum (70 eV) *m/e* (rel intensity) 244 (8, M + 2), 242 (26, M^+), 179 (9), 170 (11), 169 (8), 136 (5), 135 (25), 119 (12), 108 (8), 107 (100), 106 (11), 105 (19), 91 (17), 79 (8), 78 (11), 77 (81), 65 (5), 64 (9), 63 (6), 51 (22), 29 (62), 28 (5), and 27 (11).

Anal. Calcd for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.57; Cl, 14.61; N, 11.54. Found: C, 49.72; H, 4.38; Cl, 14.91; N, 11.54.

2-Carbobenzyloxy-1-phenylhydrazinecarbonyl Chloride (5e). A solution of phenylcarbazate **4e** (52.56 g, 0.215 mol) in THF (150 ml) was treated with a solution of phosgene (63.3 g, 0.64 mol) in THF (300 ml) in a manner similar to that used to prepare carbethoxyhydrazinecarbonyl chloride **5d**. Removal of the solvent at reduced pressure gave 67.24 g of a light yellow solid. Recrystallization from carbon tetrachloride afforded 54.59 g (0.179 mol, 83.3%) of a white solid: mp 104–106 °C; ir ($CHCl_3$) 3410 (NH), 3040 and 2965 (CH), 1758 (C=O), 1495, 1283, 1240, and 700 cm^{-1}; NMR ($CDCl_3$) 5.16 (s, 2, $PhCH_2O$), 7.30 (s, 5, $C_6H_5CH_2$), 7.35 (s, 5, C_6H_5N), and 7.68 (s, 1, CONHN); mass spectrum (70 eV) *m/e* (rel intensity) 306 (1.2, M + 2), 304 (4.8, M^+), 224 (5), 197 (5), 92 (9), 91 (100), 77 (9), and 65 (7).

Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; Cl, 11.63; N, 9.19. Found: C, 58.68; H, 4.32; Cl, 11.90; N, 9.17.

2-Carbobenzyloxy-1-α-cumylhydrazinecarbonyl Chloride (5f). A solution of α-cumylcarbazate **4f** (16.27 g, 57.2 mmol) in THF (115 ml) was treated with a solution of phosgene (13.2 g, 133 mmol) in THF (30 ml) in a manner similar to that used to prepare phenylhydrazinecarbonyl chloride **5d**. Removal of the solvent at reduced pressure gave a viscous brown oil which afforded, after vacuum drying, 23.60 g (119%) of a brown gum that could not be induced to crystallize or further purified: NMR ($CDCl_3$) 1.59 [s, $C(CH_3)_2$], 1.73 [s, $C(CH_3)_2$], 5.19 (s, $PhCH_2O$), 7.0–7.6 (m, C_6H_5), and 7.86 ppm (s, CONHN).

2-Carbobenzyloxy-1-*tert*-butylhydrazinecarbonyl Chloride (5g). A solution of *tert*-butylcarbazate **4g** (9.92 g, 44.6 mmol) in THF (45 ml) was treated with a solution of phosgene (9.4 g, 95 mmol) in THF (45 ml) in a manner analogous to that used to prepare **5d**. Concentration in vacuo and vacuum drying afforded 12.80 g (100.7%) of an off-white solid. Recrystallization from carbon tetrachloride afforded a white solid: mp 95–96.5 °C; ir ($CHCl_3$) 3410 (NH), 3035 and 2985 (CH), 1754 (C=O), 1483, 1398 (CMe_3), 1368 (CMe_3), 1246, 1200 (C–O), 1044, 1025, and 697 cm^{-1}; NMR ($CDCl_3$) 1.31 and 1.41 [2 s, 9, $C(CH_3)_3$], 5.15 (s, 2, $PhCH_2O$), and 7.09 ppm (s, 5, C_6H_5); mass spectrum 70 eV) *m/e* (rel intensity) 286 (weak, M + 2), 284 (weak, M^+), 228 (3), 92 (9), 91 (100), 65 (6), 57 (52), 41 (9), and 29 (6).

Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; Cl, 12.45; N, 9.84. Found: C, 54.95; H, 5.92; Cl, 12.92; N, 9.81.

2-Ethoxy-4-phenyl-Δ²-1,3,4-oxadiazolin-5-one (6d). Phenylhydrazinecarbonyl chloride **5d** was heated at 150 °C until gas evolution ceased. The cooled melt was recrystallized from ethanol to afford oxadiazolinone **6d** as white needles: mp 67.5–69 °C; ir ($CHCl_3$) 3000 (CH), 1798 (C=O), 1662 (C=N), 1505, 1390, 1375, 1355, 955, and 888 cm^{-1}; NMR ($CDCl_3$) 1.46 (t, 3, J = 7 Hz, OCH_2CH_3), 4.43 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), and 7.05–7.85 (m, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 207 (7, M^+), 206 (50), 178 (53), 134 (18), 105 (19), 92 (10), 91 (100), 77 (70), 64 (11), 51 (26), 29 (50), and 27 (17).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.08; H, 4.90; N, 13.60.

2-Benzyloxy-4-phenyl-Δ²-1,3,4-oxadiazolin-5-one (6e). A solution of carbobenzyloxyhydrazinecarbonyl chloride **5e** (54.59 g, 0.179 mol) and ethyldiisopropylamine (27.20 g, 0.21 mol) in THF (680 ml) was stirred at 30 °C. After 1 h, a solid had begun to form; stirring was continued for an additional 1.5 h. The reaction mixture was washed with 5% hydrochloric acid, 10% sodium bicarbonate, and saturated sodium chloride, and dried over anhydrous magnesium sulfate. Filtration and concentration provided 48.34 g of crude product as an off-white solid. Recrystallization from ethanol furnished 36.59 g (0.136 mol, 76.2%) of a slightly off-white solid: mp 86–88.5 °C; ir ($CHCl_3$) 3080, 3045, and 2965 (CH), 1798 (C=O), 1663 (C=N), 1508, 1377, 1359, 939, 909, and 701 cm^{-1}; NMR ($CDCl_3$) 5.29 (s, 2, $PhCH_2O$), and 7.0–7.9 ppm (m, 10, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 268 (3, M^+), 92 (10), 91 (100), 77 (5), and 65 (7).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.86; H, 4.38; N, 10.40.

2-Benzyloxy-4-α-cumyl-Δ²-1,3,4-oxadiazolin-5-one (6f). A solution of lithium diisopropylamide was prepared at 0 °C from a solution of diisopropylamine (7.05 g, 69.8 mmol) in anhydrous ether (75 ml) and ethereal methyllithium (33.4 ml of 2 M, 66.8 mmol). When the effervescence had stopped, the solution was stirred for 15 min at 0 °C and then cooled to below −60 °C in a dry ice–acetone bath. A solution of α-cumylhydrazinecarbonyl chloride **5f** (23.60 g, 68.1 mmol) in THF (150 ml) was added to the ethereal lithium diisopropylamide at a rate that maintained the temperature below −60 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature and then stirred for 2 h. This solution was washed with 5% hydrochloric acid, 10% sodium bicarbonate, and saturated sodium chloride, and dried over anhydrous magnesium sulfate. Filtration and concentration gave 18.85 g of a brown semisolid, that was chromatographed on silica gel with chloroform. Collection and concentration of the mobile yellow band afforded a light yellow solid. After vacuum drying, 13.79 g (44.4 mmol, 64.3%) of product was obtained: mp 57.5–60 °C; ir ($CHCl_3$) 3035 and 2995 (CH), 1790 (C=O), 1675 (C=N), 1423, 1396 (CMe_2), 1374 (CMe_2), 1355, 1322, 940, 902, and 700 cm^{-1}; NMR ($CDCl_3$) 1.95 [s, 6, $C(CH_3)_2$], 5.10 (s, 2, $PhCH_2O$), 7.25 and 7.29 (2 s, 10, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 119 (31), 92 (8), 91 (100), 65 (8), and 41 (9).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.87; H, 5.97; N, 9.25.

2-Benzyloxy-4-*tert*-butyl-Δ²-1,3,4-oxadiazolin-5-one (6g). A solution of *tert*-butylhydrazinecarbonyl chloride **5g** (2.85 g, 10.0 mmol) in anhydrous ether (20 ml) was treated with ethereal (15 ml) lithium diisopropylamide (10.2 mmol) as described for α-cumyloxadiazolinone **6f**. After workup, 2.43 g of a yellow solid was obtained. Washing with pentane afforded 2.33 g (9.4 mmol, 93.9%) of a white solid: mp 78–80 °C; ir ($CHCl_3$) 3035 and 2990 (CH), 1786 (C=O), 1653 (C=N), 1423, 1354, 1320, 932, 910, and 697 cm^{-1}; NMR ($CDCl_3$) 1.48 [s, 9, $C(CH_3)_3$], 5.22 (s, 2, $PhCH_2O$), and 7.38 ppm (s, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 248 (1, M^+), 92 (8), 91 (100), 65 (7), and 57 (10).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.35; N, 11.40.

3-Phenyl-1,3,4-oxadiazolidine-2,5-dione (7a). A solution of phenyloxadiazolinone **6e** (5.15 g, 19.2 mmol) in ethyl acetate (95 ml) was shaken with 5% palladium on carbon (100 mg) in a Parr apparatus under an atmosphere of hydrogen (20 psi). After 15 min, hydrogen uptake had ceased. Filtration and concentration of the filtrate at reduced pressure furnished 3.37 g of a tan solid. Recrystallization from ethyl acetate gave 2.92 g (16.4 mmol, 85.4%) of an off-white solid: mp 150–155 °C dec; ir (KBr) 3450 and 3170 (NH), 2940 (CH), 1853 and 1763 (C=O), 1510, 1365, 982, 957, 843, and 760 cm^{-1}; NMR (acetone-d_6) 7.1–7.7 (m, 5, C_6H_5) and 8.60 ppm (s, 1, CONHN); mass spectrum (70 eV) *m/e* (rel intensity) 179 (5), 178 (46, M^+), 135 (10), 134 (100), 106 (40), 105 (47), 92 (20), 91 (100), 78 (39), 77 (86), 65 (33), 64 (55), 63 (20), 52 (19), 51 (42), 50 (17), 44 (61), 39 (22), 38 (12), and 28 (18).

Anal. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.72. Found: C, 53.89; H, 3.32; N, 15.95.

3-α-Cumyl-1,3,4-oxadiazolidine-2,5-dione (7b). A solution of α-cumyloxadiazolinone **6f** (1.56 g, 5.0 mmol) in ethyl acetate (25 ml) was shaken overnight with 5% palladium on carbon (25 mg) under an atmosphere of hydrogen (25 psi). Filtration and concentration under reduced pressure provided 1.17 g of a light yellow solid. When washed with carbon tetrachloride, 0.70 g of an off-white solid remained. Recrystallization from benzene afforded 0.24 g (1.1 mmol, 21.8%) of a white solid: mp 94–95 °C dec; ir ($CHCl_3$) 3370 (NH), 3030 and 3000 (CH), 1850 and 1780 (C=O), 1338, 962, and 708 cm^{-1}; NMR ($CDCl_3$) 1.84 [s, 6, $C(CH_3)_2$], 6.7 (s, 1, CONH), and 7.38 (s, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 220 (weak, M^+), 120 (11), 119 (72), 118 (7), 117 (5), 103 (5), 91 (37), 79 (7), 77 (8), 51 (5), 44 (100, CO_2), 41 (15), 39 (5), and 28 (11).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.24; H, 5.59; N, 12.75.

3-*tert*-Butyl-1,3,4-oxadiazolidine-2,5-dione (7c). A solution of *tert*-butyloxadiazolinone **6g** (1.24 g, 5.0 mmol) in ethyl acetate (25 ml) was shaken overnight with 5% palladium on carbon (25 mg) under an atmosphere of hydrogen (20 psi). Filtration and concentration under reduced pressure afforded a yellow oil, which upon shaking with carbon tetrachloride formed a slurry. After filtration and washing (carbon tetrachloride) 0.48 g (3.0 mmol, 60%) of a white solid, mp ca. 91 °C, was obtained; NMR shows this solid to be contaminated by an

equal molar amount of *tert*-butylhydrazine. Repeated washing with 1:1 benzene–pentane afforded a solid that was 85% pure (NMR): mp 90–92 °C dec; NMR ($CDCl_3$) 1.11 (s, *tert*-butylhydrazine) and 1.40 ppm (s, **7c**).

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 46.17; H, 6.65; N, 18.69.

Acknowledgments. This work has been partially supported by the Alfred P. Sloan Research Foundation and the National Institutes of Health (GM 14518).

Registry No.—**3a,** 100-63-0; **3b,** 3178-39-0; **3c,** 32064-67-8; **4d,** 6233-02-9; **4e,** 40887-05-6; **4f,** 60103-93-7; **4g,** 60103-94-8; **5d,** 60103-95-9; **5e,** 60103-96-0; **5f,** 60103-97-1; **5g,** 60103-98-2; **6d,** 3711-77-1; **6e,** 60103-99-3; **6f,** 60104-00-9; **6g,** 60104-01-0; **7a,** 60104-02-1; **7b,** 60104-03-2; **7c,** 60104-04-3; benzyl chloroformate, 501-53-1; phosgene, 75-44-5; ethyldiisopropylamine, 7087-68-5; lithium diisopropylamide, 4111-54-0.

References and Notes

(1) C. D. Hurd and F. F. Cesark, *J. Am. Chem. Soc.*, **89,** 1417 (1967).
(2) W. A. Henderson, Jr., and A. Zweig, *J. Chem. Soc., Chem. Commun.*, 169 (1972).
(3) Hurd and Cesark[1] proposed that a cyclization of this type might occur when the unsubstituted carbethoxyhydrazinecarbonyl chloride is pyrolyzed. However, no product from this type of cyclization was reported.
(4) C. G. Overberger and A. V. DiGiulio, *J. Am. Chem. Soc.*, **80,** 6562 (1958).
(5) P. A. S. Smith, J. M. Clegg, and J. Lakritz, *J. Org. Chem.*, **23,** 1595 (1958).
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New Syntheses of β,β-Dimethoxy Esters and Ketones by Conjugate Addition of Methanol to Some Activated Alkynes

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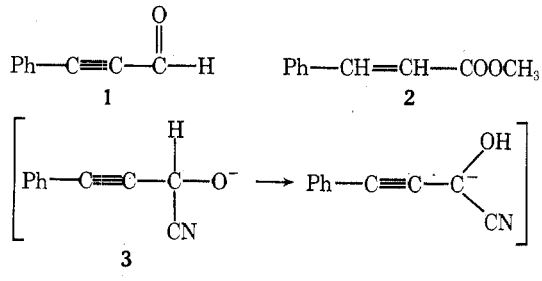
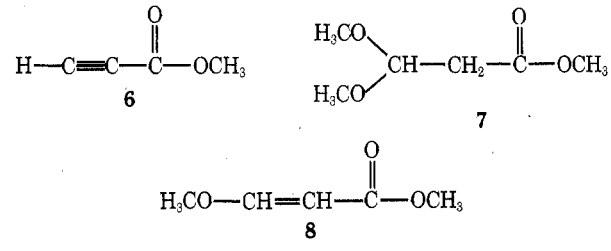
We have previously reported[2,3] that cyanide ion catalyzes the addition of the elements of one molecule of methanol to α,β-acetylenic aldehydes such as 3-phenyl-2-propynal (**1**), which yield a 1:1 mixture of *cis*- and *trans*-methyl 3-phenyl-2-propenoate (**2**). Others have also described[4,5] reactions of this type. A key step envisaged in the proposed[2] mechanism for this reaction is the prototropic shift of the aldehydic proton in the intermediate **3** (formed by nucleophilic attack of cyanide ion on the carbonyl group of **1**). A test of this mechanism might be made using α,β-acetylenic esters and ketones **4**, which possibly could provide the hydrocyanated product **5**. This report provides the answer to this query, at least for a few representative cases.

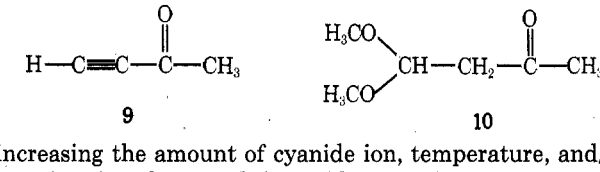


However, no product related to **5** was observed. Instead, the reaction of methyl 2-propynoate (**6**) with excess methanol using 1.2 molar equiv of sodium cyanide provided methyl 3,3-dimethoxypropanoate (**7**) as the major product (75%). When 0.1 molar equiv of sodium cyanide was used, a mixture was obtained that was predominantly ester **7** along with a lesser amount of methyl 3-methoxypropenoate (**8**). Relative yields were estimated from the infrared spectrum of the mixture. When the reaction was carried out in the presence of acetic acid, the ir spectrum of the crude reaction mixture showed the presence of a large amount of unsaturated ester **8** together with some ester **7**. The structure of ester **7** was established by comparison of boiling point and spectroscopic data with those of an authentic sample. Since the ester **7** is easily accessible by our method and has a potential aldehydic group present, it ought to be a useful bifunctional synthetic intermediate.



A possible mechanism for the conversion of ester **6** to **7** involves Michael addition of two molecules of methanol (presumably initiated by methoxide ion, generated by the reaction of sodium cyanide and methanol) in two steps via unsaturated ester **8**. The fact that olefinic ester **8** (prepared independently[6] by the reaction of **6** with methanol in the presence of triethylamine) on treatment with cyanide ion in methanol under these conditions also gives ester **7** supports the proposed mechanism.

It was of interest to investigate the extension of this reaction to α,β-acetylenic ketones. Treatment of commercially available 3-butyn-2-one (**9**) with 0.05 molar equiv of sodium cyanide in methanol at −10 °C for about 10 min gave 1,1-dimethoxy-3-butanone (**10**) in 88% yield; clearly, two molecules of methanol added to **9**. These reaction conditions are critical;



increasing the amount of cyanide ion, temperature, and/or reaction time decreased the yield of **10**. The structure of ketone **10** was established by the identity of its ir spectrum with that of a commercial sample of 1,1-dimethoxy-3-butanone.

When the cyanide ion catalyzed addition reaction of methanol was carried out with 4-phenyl-3-butyn-2-one (**11**), a mixture of products was formed as indicated by the ir and NMR spectra of the crude product. Attempts to obtain a single product by variation of reaction conditions were not fruitful. It appeared that the nucleophilic nature of cyanide ion could have caused side reactions. We therefore tried next the poorly nucleophilic weak base, carbonate ion. It was gratifying to find that carbonate ion catalyzed addition of methanol to ketone **11** occurred smoothly at 0 °C to afford 1-phenyl-1,1-dimethoxy-3-butanone (**12**) in 86% yield. Expectedly, the carbonate ion also catalyzed the addition of methanol to methyl prop-2-ynoate (**6**), and 3-butyn-2-one (**9**)