The Chemistry of Acylals. Part III. Cyanohydrin Esters from Acylals with Cyanide Reagents

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EXPERIMENTAL

General: ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM 200 spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as an internal standard. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet and q = quartet. IR spectra were recorded on a Perkin-Elmer model 1310 spectrometer. Flash chromatography was performed on Silica gel 60 (230-400 mesh) from Merck using either hexane : ethyl acetate 95 : 5 or hexane : ethyl acetate 90 : 10 as eluent. Thin layer chromatography (TLC) was carried out on Silica 60 F_{254} from Merck. Analytical gas chromatography (GC) was performed on a Hewlett Packard 5720 A gas chromatograph equipped with a 4-m packed column (15% SP-2100 on Supelcoport); FID detection was applied and a HP 3380 A integrator was connected to the instrument. The sonication experiments were performed in a Bandelin Sonorex Super RK 255 H laboratory cleaner with a 320 W effect. THF was distilled from sodium/benzophenone. Mass spectra were obtained on a VG Fisons 7070E Micromass spectrometer operated in the EI mode at 70 eV.

*Synthesis of acylals (**2**)*. Aldehydes (**1**) were converted to acylals on a 18-450 mmol scale following literature procedures.[1,2] The physical and spectroscopic properties of most acylals have been reported previously[1] whereas those of the remaining acylals are as follows.

Ethylidene diacetate (**2f**). Acetic anhydride (69.5 g, 0.68 mol) and ethanal (20.0 g, 0.45 mol) gave **2f** (43.3 g, 65%) as a colourless liquid, b.p. 68-70 ^{o}C/10 mmHg (lit.[3] 54-56 ^{o}C/10 mmHg); ν_{max} (neat) 2995, 2920, 1745, 1440, 1370, 1240, 1100, 1005, 945, 655 cm^{-1}; δ_H 7.47 (1 H, t, *J* 5.5 Hz), 2.70 (6 H, s), 2.10 (3 H, d, *J* 5.5 Hz); δ_C 168.9, 88.5, 20.9, 19.5.

Ethylidene dipropanoate (**2g**). Propanoic anhydride (44.0 g, 0.34 mol) and ethanal (10.0 g, 0.23 mol) gave **2g** (31.6 g, 80%) as a colourless liquid, b.p. 116-117 ^{o}C/22 mmHg (lit.[4] 87-89 ^{o}C/10 mmHg); ν_{max} (neat) 2960, 2920, 1735, 1440, 1360, 1190, 1070, 915, 865 cm^{-1}; δ_H 6.88 (1 H, q, *J* 6.1 Hz), 2.35 (4 H, q, *J* 7.5 Hz), 1.47 (3 H, d, *J* 6.1 Hz), 1.14 (6 H, t, *J* 7.5 Hz); δ_C 172.1, 88.1, 27.1, 19.3, 8.5.

2-Butenylidene diacetate (**2i**). Acetic anhydride (43.2 g, 0.42 mol) and crotonaldehyde (20.0 g, 0.28 mol) gave **2i** (39.8 g, 82%) as a colourless liquid, b.p. 96-98 ^{o}C/11 mmHg; ν_{max} (neat) 2920, 1740, 1430, 1360, 1230, 1200, 950 cm^{-1}; δ_H 7.08 (1 H, m), 6.10-5.99 (1 H, m), 5.62-5.58 (1 H, m), 2.08 (6 H, s), 1.79-

1.74 (3 H, m); δ_C 168.4, 132.9, 124.4, 89.5, 20.6, 17.3; ; *m/z* (EI) 131 (2), 130 (27), 129 (13), 114 (2), 113 (27), 112 (3), 103 (4), 87 (6), 71 (100), 70 (26), 69 (77), 61 (13); HRMS (EI): M^+-$AcO^·$, found 113.0572. $C_6H_9O_2$ requires 113.0602.

Cyclohexylidene diacetate (**2j**). Acetic anhydride (10.8 g, 0.106 mol) and cyclohexanecarbaldehyde (8.00 g, 71 mmol) gave **2j** (13.7 g, 60%) as a colourless liquid, b.p. 146-148 °C/13 mmHg (lit.[5] 131-133 °C/10 mmHg); ν_{max} (neat) 2920, 2840, 1750, 1440, 1365, 1235, 1200, 1110 cm^{-1}; δ_H 6.62 (1 H, d, *J* 5.2 Hz), 2.07 (6 H, s), 1.81-1.65 (6 H, m),1.27-1.10 (5 H, m); δ_C 168.7, 92.1, 40.6, 26.5, 25.8, 25.2, 20.4.

Butylidene dicrotonate (**2k**). Crotonic anhydride (6.94 g, 45 mmol) and butanal (2.16 g, 30 mmol) gave **2k** (5.96 g, 88%) as a colourless liquid, b.p. 99-102 °C/1 mmHg; ν_{max} (neat) 2950, 1725, 1640, 1430, 1245, 1155, 1090, 980 cm^{-1}; δ_H 7.03-6.85 (2 H, m), 6.76 (1 H, t, *J* 5.5 Hz), 5.80-5.71 (2 H, m), 1.92-1.87 (6 H, m), 1.85-1.68 (2 H, m), 1.42 (2 H, sextet, *J* 7.5 Hz), 0.97 (3 H, t, *J* 7.5 Hz); δ_C 162.7, 144.5, 122.3, 89.8, 35.3, 17.7, 16.7, 13.7; *m/z* (EI) 155 (2), 142 (2), 141 (8), 128 (2), 127 (2), 126 (24), 95 (2), 71 (62), 70 (27), 69 (100); HRMS (EI): M^+-$CH_3CH{=}CHCOO^·$, found 141.0890. $C_8H_{13}O_2$ requires 141.0915.

Hexylidene dihexanoate (**2l**). Hexanoic anhydride (48.1 g, 0.22 mol) and hexanal (15.0 g, 0.15 mol) gave **2l** (35.4 g, 75%) as a pale yellow liquid, b.p. 137-138 °C/0.7 mmHg. ν_{max} (neat) 2940, 2910, 2840, 1745, 1450, 1370, 1235, 1085, 980 cm^{-1}; δ_H 6.81 (1 H, t, *J* 5.6 Hz), 2.31 (4 H, t, *J* 7.2 Hz), 1.77-1.66 (2 H, m), 1.62-1.55 (4 H, m), 1.37-1.24 (14 H, m), 0.89 (9 H, m); δ_C 171.8, 90.4, 34.1, 33.3, 31.4, 31.3, 24.5, 23.2, 22.5, 22.4, 13.9; *m/z* (EI) 200 (1), 199 (7), 158 (1), 100 (7), 99 (100), 98 (3), 87 (6), 73 (16), 71 (18); HRMS (EI): M^+-$CH_3(CH_2)_4COO^·$, found 199.1741. $C_{12}H_{23}O_2$ requires 199.1698.

Benzylidene dicrotonate (**2n**). Crotanoic anhydride (20.0 g, 0.13 mol) and benzaldehyde (13.8 g, 0.13 mol) gave **2n** (28.4 g, 84%) as a white crystalline solid, m.p. 45-47 °C; ν_{max} (CCl_4) 3030, 2985, 1735, 1650, 1440, 1290, 1250, 1095, 1000, 970 cm^{-1}; δ_H 7.68 (1 H, s), 7.49-7.44 (2 H, m), 7.34-7.29 (3 H, m), 7.04-6.93 (2 H, m), 5.92-5.74 (2 H, m), 1.97-1.75 (6 H, m); δ_C 162.5, 145.0, 136.2, 128.9, 128.0, 126.5, 122.1, 89.1, 17.8; *m/z* (EI)192 (2), 191 (5), 175 (3), 174 (2), 138 (3), 106 (6), 105 (40), 77 (10), 70 (5), 69 (100); HRMS (EI): M^+- $CH_3CH{=}CHCOO^·$, found 175.0746. $C_{11}H_{11}O_2$ requires 175.0759.

Benzylidene dihexanoate (**2o**). Benzaldehyde (10.6 g, 0.10 mol) and hexanoic anhydride (32.1 g, 0.15 mol) gave **2o** (24.1 g, 75%) as a pale yellow liquid, b.p. 153-156 °C/2 mmHg; ν_{max} (neat) 3030, 2950, 2920, 2880, 1755, 1450, 1205, 1160, 700 cm^{-1}; δ_H 7.72 (1 H, s), 7.47-7.54 (2 H, m), 7.35-7.42 (3 H, m), 2.37 (4 H, t, *J* 7.7 Hz), 1.57-1.71 (4 H, m), 1.22-1.36 (8 H, m), 0.88 (6 H, t, *J* 6.4 Hz); δ_C 171.4, 135.6, 129.4, 128.3, 126.5, 89.3, 33.9, 30.9, 24.1, 22.1, 13.7.

Reactions of acylals with potassium cyanide in DMSO. In a typical experiment a dry, nitrogen-filled, 50-mL, round-bottomed flask was charged with an aliphatic acylal (4.94 mmol), and a mixture of KCN (0.33 g, 5.04 mmol, 1.2 eqv.) and dry DMSO (10 mL) was added. The reaction was completed by stirring overnight, at room temperature to 80 °C for the aromatic acylals and at room temperature for the aliphatic acylals. Work-up was carried out by addition of H_2O (50 mL) and extraction with Et_2O (3 x 30 mL). The combined etheral extracts were washed with H_2O (5 x 50 mL). Drying ($MgSO_4$), filteration, and concentration under vacuum afforded spectroscopically pure products as pale yellow liquids.

Two reactions deviated slightly from the general procedure, *viz*. those of **2f** and **2g**, which required 1.25 eqv. of KCN and a reaction time of 48 hours to give satisfactory results.

Physical and spectroscopic properties of the cyanohydrin esters formed and isolated are as follows.

1-Cyanoethyl acetate (**3f**). Ethylidene diacetate (1.00 g, 6.84 mmol) and potassium cyanide (0.49 g, 7.52 mmol) gave **3f** [6] (0.68 g, 87%) as a colourless liquid when isolated by flash chromatography; ν_{max} (neat) 2980, 1745, 1360, 1210, 1090 cm^{-1}; δ_H 5.37 (1 H, q, *J* 6.9 Hz) , 2.13 (3 H, s), 1.63 (3 H, d, *J* 6.9 Hz); δ_C 169.0, 117.3, 57.0, 20.1, 18.4.

1-Cyanoethyl propionate (**3g**). Ethylidene dipropanoate (1.00 g, 5.74 mmol) and potassium cyanide (0.41 g, 6.31 mmol) gave **3g** (0.60 g, 82%) as a colourless liquid when isolated by flash chromatography; ν_{max} (neat) 2980, 1750, 1450, 1160, 1095 cm^{-1}; δ_H 5.40 (1 H, q, *J* 6.9 Hz), 2.41 (2 H, q, *J* 7.5 Hz), 1.64 (3 H, d, *J* 8.3 Hz), 1.18 (3 H, t, *J* 7.5 Hz); δ_C 172.6, 117.7, 57.2, 27.1, 18.8, 8.7.

1-Cyanohexyl acetate (**3h**). Hexylidene diacetate (1.00 g, 4.95 mmol) and potassium cyanide (0.39 g, 5.93 mmol) gave **3h** (0.76 g, 91%) as a pale yellow liquid when isolated by flash chromatography; ν_{max} (neat) 2960, 2940, 2860, 1750, 1460, 1370, 1220 cm^{-1}; δ_H 5.31 (1 H, t, *J* 6.7 Hz), 2.13 (3 H, s), 1.84-1.95 (2 H, m), 1.43-1.54 (2 H, m), 1.21-1.40 (4 H, m), 0.91 (3 H, t, *J* 5.6 Hz); δ_C 168.8, 116.6, 60.8, 31.9, 30.6, 23.9, 22.0, 20.0, 13.5.

1-Cyano-2-butenyl acetate (**3i**). 2-Butenylidene diacetate (1.00 g, 5.80 mmol) and potassium cyanide (0.45 g, 6.97 mmol) gave **3i** [3] (0.64 g, 80%) as a yellow liquid isolated by flash chromatography; ν_{max} (neat) 2920, 1740, 1655, 1430, 1360, 1205, 1010 cm^{-1}; δ_H 5.97-6.08 (1 H, m), 5.62-5.66 (1 H, m), 5.37-5.49 (1 H, m), 2.07 (3 H, s), 1.64-1.68 (3 H, m); δ_C 168.8, 135.4, 121.1, 115.5, 61.2, 20.2, 17.4.

1-Cyanocyclohexyl acetate (**3j**). Cyclohexylidene diacetate (1.00 g, 4.14 mmol) and potassium cyanide (0.31 g, 4.75 mmol) gave **3j** [7] (0.70 g, 92%) as a colorless liquid when eluted with hexane : ethyl acetate 95 : 5; ν_{max} (neat) 2920, 2845, 1750, 1445, 1365, 1220, 1030 cm^{-1}.[4] δ_H 5.17 (1 H, d, *J* 5.9 Hz), 2.14 (3 H, s), 1.69-1.93 (6 H, m), 1.10-1.33 (5 H, m); δ_C 169.0, 115.9, 65.3, 39.7, 27.8, 27.6, 25.5, 25.1, 25.0, 20.1.

In addition to **3l** 20 mg (4%) of cyclohexanecarbaldehyde was isolated.

1-Cyanobutyl crotonate (**3k**). Butylidene dicrotonate (1.00 g, 4.42 mmol) and potassium cyanide (0.42 g, 6.45 mmol) gave **3k** (0.32 g, 43%) as a pale yellow liquid when isolated by flash chromatography; ν_{max} (neat) 2960, 2865, 1725, 1650, 1435, 895, 750 cm^{-1}; δ_H 7.04-7.19 (1 H, m), 5.82-5.92 (1 H, m), 5.40 (1 H, t, *J* 6.7 Hz), 1.83-1.97 (5 H, m), 1.46-1.64 (2 H, m), 1.00 (3 H, t, *J* 7.3 Hz); δ_C 164.0, 147.4, 120.5, 116.8, 60.3, 34.0, 17.8, 17.6, 13.0.

1-Cyanohexyl hexanoate (**3l**). Hexylidene diacetate (1.00 g, 3.18 mmol) and potassium cyanide (0.25 g, 3.82 mmol) gave **3l** (0.65 g, 91%) as a pale yellow liquid when isolated by flash chromatography; ν_{max} (neat) 2940, 2910, 1740, 1450, 1150, 1100 cm^{-1}; δ_H 5.33 (1 H, t, *J* 6.7 Hz), 2.38 (2 H, t, *J* 7.6 Hz), 1.73-1.95 (2 H, m), 1.54-1.69 (2 H, m), 1.42-1.50 (2 H, m), 1.28-1.35 (8 H, m), 0.87-0.94 (6 H, m); δ_C 171.9, 116.9, 60.7, 35.1, 33.4, 32.0, 30.9, 30.7, 24.1, 24.0, 22.1, 22.0, 13.7.

1-Cyanododecyl acetate (**3m**). Dodecylidene diacetate (1.00 g, 3.49 mmol) and potassium cyanide (0.27 g, 4.19 mmol) gave **3m** (0.87 g, 97%) as a pale yellow liquid when isolated by flash chromatography; ν_{max} (neat) 2920, 2850, 1750, 1460, 1370, 1240, 1030 cm^{-1}; δ_H 5.31 (1 H, t, *J* 6.7 Hz), 2.14 (3 H, s), 1.81-1.95 (2 H, m), 1.42-1.53 (2 H, m), 1.17-1.40 (16 H, m), 0.88 (3 H, t, *J* 6.8 Hz); δ_C 169.1, 116.8, 61.0, 35.1, 32.0, 31.7, 29.3, 29.2, 29.1, 29.07, 28.6, 24.3, 22.5, 20.2, 13.9.

*Treatment of **2** with trimethylsilyl cyanide in the presence of titanium(IV) chloride.* The acylals were reacted on a 3.5 - 5.0 mmol scale. In a typical experiment a 50-mL, nitrogen-filled round-bottom flask was charged with acylal in CH_2Cl_2 (5 mL) and trimethylsilyl cyanide (TMSCN) (1.10 eqv). The reaction mixture was cooled to -78 °C with a dry ice-acetone bath, and titanium(IV) chloride (1.10 eqv.) was added with stirring. The mixture was allowed to reach room temperature and was stirred at this temperature for 2 hrs. H_2O (50 mL) was added, and the products were extracted with Et_2O (3 x 30 mL). The combined extracts were washed with H_2O (2 x 50 mL), dried ($MgSO_4$), filtered and concentrated under vacuum. The crude products were subjected to further purification by flash chromatography if necessary.

The results of the reactions with a number of acylals are summarized in Table 4.

Physical and spectroscopic properties of the cyanohydrin esters formed and isolated, but not reported above are as follows.

Cyano(phenyl)methyl acetate (**3a**). Benzylidene diacetate (0.50 g, 2.40 mmol), TMSCN (0.26 g, 2.64 mmol) and $TiCl_4$ (0.50 g, 2.64 mmol) gave **3a**[7] (0.39 g, 93%) as a colorless liquid; ν_{max} (neat) 1745, 1360, 1205, 750, 690 cm^{-1}; δ_H 7.54-7.41 (5 H, m), 6.40 (1 H, s), 2.13 (3 H, s); δ_C 168.6, 131.5, 130.1, 128.9, 127.6, 115.9, 62.6, 20.1.

Cyano(4-methylphenyl)methyl acetate (**3b**). 4-Methylbenzylidene diacetate (0.50 g, 2.25 mmol), TMSCN (0.25 g, 2.47 mmol) and $TiCl_4$ (0.43 g, 2.47 mmol) gave **3b**[8] (0.32 g, 75%) as pale yellow crystals, m.p. 46-47 °C; ν_{max} (neat) 1745, 1365, 1210, 1010, 805 cm^{-1}; δ_H 7.42-7.38 (2 H, m), 7.26-7.21 (2 H, m), 6.36 (1 H, s), 2.37 (3 H, s), 2.12 (3 H, s); δ_C 168.7, 140.4, 129.6, 128.6, 127.6, 116.0, 62.5, 21.0, 20.2.

In addition chloro(4-methylphenyl)acetonitrile (80 mg, 21%) was obtained as pale, yellow crystals, m.p. 33-34 °C; ν_{max} (CCl_4) 1530, 1240, 1200, 1190, 995, 965 cm^{-1}; δ_H 7.40-7.44 (2 H, m), 7.22-7.26 (2 H, m), 5.52 (1 H, s), 2.38 (3 H, s); δ_C 140.7, 129.9, 127.4, 116.0, 43.9, 21.1; *m/z* (EI) 167 (5 M^+), 165 (15 M^+), 150 (2), 147 (2), 145 (2), 132 (3), 131 (14), 130 (10), 103 (18), 91 (9), 77(10); HRMS (EI): M^+, found 167.0291. $C_9H_8{}^{37}ClN$ requires 167.0315.

Cyano(4-methoxyphenyl)methyl acetate (**3c**). 4-Methoxybenzylidene diacetate (1.00 g, 4.20 mmol), TMSCN (0.46 g, 4.62 mmol) and $TiCl_4$ (5 drops) gave **3c**[9] (0.75 g, 87%) as a pale yellow liquid; ν_{max} (neat) 1730, 1490, 1010, 940, 810 cm^{-1}; δ_H 7.47-7.43 (2 H, m), 6.96-6.93 (2 H, m), 6.35 (1 H, s), 3.83 (3 H, s), 2.14 (3 H, s); δ_C 167.7, 160.8, 129.4, 124.1, 115.5, 114.2, 62.1, 54.8, 20.0.

Cyano(4-chlorophenyl)methyl acetate (**3d**). 4-Chlorobenzylidene diacetate (0.50 g, 2.06 mmol), TMSCN (0.23 g, 2.32 mmol) and $TiCl_4$ (0.39 g, 2.06 mmol) gave **3d**[9] (0.23 g, 53%) as a colourless oil; ν_{max} (neat) 3060, 2910, 1735, 1475, 1210 cm^{-1}; δ_H 7.47-7.37 (4 H, m), 6.39 (1 H, s), 2.16 (3 H, s); δ_C 168.5, 136.2, 131.6, 129.2, 129.0, 115.6, 61.9, 20.1.

In addition chloro(4-chlorophenyl)acetonitrile (160 mg, 42%) was obtained as a colorless liquid; ν_{max} (neat) 1535, 1220, 1190, 990, 970, 680cm^{-1}; δ_H 7.34-7.51 (4 H, m), 5.56 (1 H, s); δ_C 136.4, 131.1, 130.1, 128.2, 115.5, 43.2. The compound decomposed before the mass spectrum was run.

Cyano(4-nitrophenyl)methyl acetate (**3e**). 4-Nitrobenzylidene diacetate (0.50 g, 1.97 mmol), TMSCN (0.22 g, 2.17 mmol) and $TiCl_4$ (0.41 g, 2.17 mmol) gave **3e** (0.42 g, 96%) as light yellow crystals, m.p. 108-109 °C (lit.[10] 110-112 °C); ν_{max} (CCl_4) 1750, 1525, 1340, 1250, 1200, 1000 cm^{-1}; δ_H 8.20-8.30 (2 H, m), 7.60-7.75 (2 H, m), 6.47 (1 H, s), 2.17 (3 H, s); δ_C 168.5, 148.7, 137.9, 128.5, 124.1, 115.0, 61.5, 20.1.

Cyano(phenyl)methyl crotonate (**3n**). Benzylidene dicrotonate (0.51 g, 1.92 mmol), TMSCN (0.21 g, 2.11 mmol) and $TiCl_4$ (0.40 g, 2.11 mmol) gave **3n** (0.36 g, 96%) as a colourless oil; ν_{max} (neat) 3030, 2940, 1710, 1635, 1420, 1150, 1090, 730, 690 cm^{-1}; δ_H 7.03-7.14 (5 H, m), 6.47 (1 H, s), 5.82-5.90 (1 H, m), 1.84-1.88 (3 H, m); δ_C 163.7, 148.0, 131.6, 129.9, 128.8, 127.4, 120.2, 116.0, 62.3, 17.8.

Cyano(phenyl)methyl hexanoate (**3o**). Benzylidene dihexanoate (0.50 g, 1.56 mmol), TMSCN (0.17 g, 1.71 mmol) and $TiCl_4$ (0.33 g, 1.71 mmol) gave **3o** (0.33 g, 91%) as a colorless oil when isolated by flash chromatography (hexane : ethyl acetate 90 : 10); ν_{max} (neat) 2940, 2920, 2850, 1745, 1450, 1145, 755, 695 cm^{-1}. δ_H 7.41-7.55 (5 H, m), 6.43 (1 H, s), 2.40 (2 H, t, *J* 8.1 Hz), 1.58-1.69 (2 H, m), 1.25-1.36 (4 H, m), 0.88 (3 H, t, *J* 6.5 Hz); δ_C 171.5, 131.7, 130.1, 129.0, 127.6, 116.0, 62.4, 33.4, 30.8, 24.1, 22.0, 13.6.

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