A Superior and General Synthesis of Enantioenriched 2-Oxathianyl Ketones

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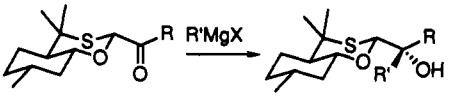
Introduction

Recently, the bicyclic 2-oxathianyl ketones 1 (Eliel's ketones) have found considerable utility for the enantioselective synthesis of α-hydroxycarbonyl derivatives 2 (R = alkyl or H, X = H or OH) which are synthons of a variety of chiral, highly enantiomerically enriched compounds (eq 1).[1,2]



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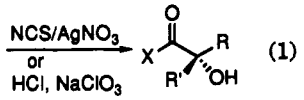
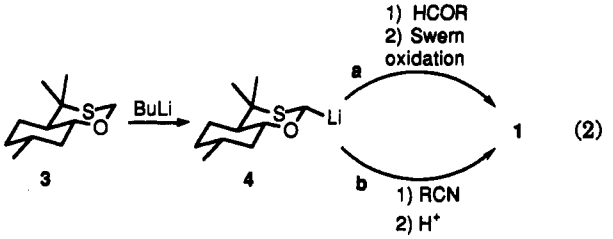


(1)

2

The key intermediates 1 have been prepared by two routes (eq 2). The first involves a two-step process that



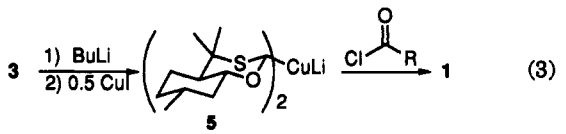
3 4 (2)

includes a nucleophilic addition of 4, the lithio derivative of oxathiane 3,[3] to an aldehyde followed by Swern oxidation of the resulting alcohol to the desired ketone 1 (eq 2, route a).[2a] A simpler one-step method employs a nucleophilic addition of 2-lithio oxathiane 4 to appropriate nitriles followed by acidic hydrolysis (eq 2, route b).[4,5]

However, both methods have limitations. Thus, in route a, the intermediate alcohol needs to be isolated and the subsequent Swern oxidation proceeds in good yields only if experimental conditions are very carefully controlled. Furthermore, route b is not general and affords high yields only with nitriles devoid of α-protons because of competition between nucleophilic addition and proton abstraction. Route b also fails (or gives very poor yields) with heterocyclic and α,β-unsaturated nitriles.[4]

Results and Discussion

As a consequence of the above, a more general, one-step synthesis of 1 was developed employing coupling with much less basic cuprate reagents. This approach involves conversion of the 2-lithio oxathiane 4 to the corresponding lithium cuprate 5 which is then coupled with acid chlorides[6] to afford 1 in generally excellent (82–97%) yields with no evidence for α-proton abstraction (eq 3). Results for a



(3)

variety of structural types are presented in Table I and illustrate the generality of the process in that alkyl, including those bearing α-protons (entries 1–7), aromatic (entry 8), α,β-unsaturated (entries 9, 10), and heterocyclic (entries 11, 12) acid chlorides all gave consistently good yields. The only negative result was observed with trichloroacetyl chloride which gave a complex mixture possibly due to competing coupling with the alkyl halide.

Other features of note include the observation that the cuprate 5 maintained the same strong stereochemical (equatorial) orientation as the lithio derivative in formation of 1 and no evidence for the axial diastereomer was obtained. Also, unlike most reported cuprate transfers,[6,7] the couplings were stoichiometric in that both 2-oxathianyl groups were utilized so that excess cuprate was not required.[6]

Experimental Section

General Information. Melting points are uncorrected. Mass spectra (electron impact) were recorded at 70 eV as *m/e*. Proton and carbon-13 NMR spectra were recorded in $CDCl_3$ on a 250-

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(2) (a) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 2943. (b) Ko, K-Y.; Frazee, W. J.; Eliel, E. L. *Tetrahedron* **1984**, *40*, 1333. (c) Frye, S. V.; Eliel, E. L. *J. Org. Chem.* **1985**, *50*, 3402. (d) Frye, S. V.; Eliel, E. L. *Tetrahedron Lett.* **1985**, 3907. (e) Frye, S. V.; Eliel, E. L. *Croat. Chim. Acta* **1985**, *58*, 647. (f) Ohwa, M.; Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 2599. (g) Ko, K.-Y.; Eliel, E. L. *J. Org. Chem.* **1986**, *51*, 5353. (h) Ohwa, M.; Eliel, E. L. *Chem. Lett.* **1987**, 41. (i) Eliel, E. L.; Alvarez, M. T.; Lynch, J. E. *Nouv. J. Chem.* **1986**, *10*, 749. (j) He, X.-C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979. (k) Cervantes-Cuevas, H.; Joseph-Nathan, P. *Tetrahedron Lett.* **1988**, 5535. (l) Kaulen, J. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 462. (m) Bai, X.; Eliel, E. L. *J. Org. Chem.* **1991**, *56*, 2086. (n) Eliel, E. L.; Frye, S. V.; Hortelano, E. R.; Chen, X.; Bai, X. *Pure Appl. Chem.* **1991**, *63*, 1591.

(3) Synthesis: Eliel, E. L.; Lynch, J. E.; Kume, F.; Frye, S. V. *Org. Synth.* **1987**, *65*, 215.

(4) Eliel, E. L.; Bai, X.; Abdel-Magid, A. F.; Hutchins, R. O. *J. Org. Chem.* **1990**, *55*, 4951.

(5) Recently, α-alkoxy, α-alkylthio, and α-dimethylamino derivatives of 1 have been successfully prepared by the reaction of the lithio oxathiane 4 with corresponding α-substituted esters. In some of these cases both axial and equatorial diastereomers were obtained; see: Bai, X.; Eliel, E. L. *J. Org. Chem.* **1992**, *57*, 5162.

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(7) Typically, large excesses of dialkyl cuprates are recommended (e.g. 6-fold in alkyl group, ref 6a) and only one of the two substituents is transferred because the organometallic that remains (RCu) is much less reactive. However, exceptions have been reported which allow groups transfer from RCu reagents. These include systems in which sulfur ligands [i.e. mercaptide (ref 8a), thienyl (ref 8b)] are incorporated (mixed cuprates), mercaptide anion is generated in the reaction of R_2CuLi (ref 8c), or the reactions of RCu are performed in dimethyl sulfide solvent (ref 8d). Perhaps in the present case the oxathianyl group behaves as a sulfide ligand and promotes transfer of the second group.

(8) (a) Posner, G. H.; Whitten, C. H.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788. Posner, G. H.; Whitten, C. H. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. *VI*, p 248. (b) Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyn, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437. Malmberg, H.; Nilsson, M.; Ullenius, C. *Tetrahedron Lett.* **1982**, *23*, 3823. (c) Posner, G. H.; Brunelle, D. J. *J. Chem. Soc., Chem. Commun.* **1973**, 907. (d) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425.

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Table I. Reaction of Lithium Bis(oxathianyl)cuprate 5 with Carboxylic Acid Chlorides in THF at −78 °C to Oxathianyl Ketones 1 (eq 3)

entry	acid chloride	R of 1	% yield of 1[a]
1a	CH_3COCl	CH_3	92
1b	$CH_3(CH_2)_{12}COCl$	$CH_3(CH_2)_{12}$	97
1c	$(CH_3)_2CH(CH_2)_2COCl$	$(CH_3)_2CH(CH_2)_2$	90
1d	c-$C_6H_{11}COCl$	c-C_6H_{11}	96
1e	$PhCH_2COCl$	$PhCH_2$	91
1f	p-$ClPhOCH_2COCl$	p-$ClPhOCH_2$	84
1g	$(CH_3)_3CCOCl$	$(CH_3)_3C$	86
1h	PhCOCl	Ph	87
1i	PhCH=CHCOCl	PhCH=CH	82
1j	CH_3CH=CHCOCl	CH_3CH=CH	93
1k	2-furanyl-COCl	2-furanyl	90
1l	2-Cl-pyridyl-5-COCl	2-Cl-5-pyridyl	87

[a] Yields are for isolated products purified by flash chromatography.

MHz FT-NMR spectrometer. IR spectra were obtained on an FT instrument. Unless otherwise indicated, reagents purchased commercially were used without further purification. Dry THF was obtained by distillation from sodium–benzophenone under a nitrogen atmosphere.

General Procedure for Oxathianyl Ketones: Methyl Oxathianyl Ketone 1a (R = CH_3). A two-necked, 25-mL flask, equipped with an argon bubbler, a magnetic stirring bar, and a rubber septum was charged with 1,3-oxathiane **3** (200 mg; 1.0 mmol) and 15 mL of dry THF, and the flask was cooled with an ice–water bath. To this cooled, well-stirred solution was slowly injected 2.5 M *n*-butyllithium solution in hexanes (0.44 mL; 1.10 mmol). After stirring for 10 min, CuI powder (100 mg; 0.55 mmol) was added in one portion and stirring was continued for 10 min at 0 °C. The resulting dark solution was then cooled to −78 °C and freshly distilled acetyl chloride (100 μL; 1.50 mmol) was added dropwise via a syringe. The reaction was stirred at −78 °C for 30 min, allowed to warm to room temperature, and quenched immediately by addition of 5 mL of saturated aqueous NH_4Cl. The mixture was transferred into a separatory funnel, diluted with 20 mL of diethyl ether and separated. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. The product, methyl oxathianyl ketone **1a**, was isolated in 92% yield (220 mg) by flash chromatography (silica gel) using 5% ethyl acetate in hexanes as eluent. The ^1H NMR spectrum was identical with that reported.[2c]

Tridecanyl Oxathianyl Ketone 1b (R = $(CH_2)_{12}CH_3$). Using the procedure described above, 400 mg (97%) of pure product **1b** was obtained from the reaction of oxathiane **3** (200 mg; 1.0 mmol) and myristoyl chloride (370 mg; 1.50 mmol) after isolation by flash chromatography (1% ethyl acetate in hexanes): ^1H NMR δ 5.45 (s, 1 H), 3.43 (dt, J = 4.3, 10.4 Hz, 1 H), 2.63 (t, J = 7.4 Hz, 2 H), 1.46 (s, 3 H), 1.29 (s, 3 H), 1.25 (s, broad, 8 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.88 (t, J = 6.6 Hz, 3 H), and others; ^{13}C NMR δ 205.2 (C), 82.4 (CH), 76.8 (CH), 50.2 (CH), 43.8 (C), 41.4 (CH_2), 37.9 (CH_2), 34.5 (CH_2), 31.9 (CH_2), 31.3 (CH), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_3), 29.1 (CH_2), 24.2 (CH_2), 23.1 (CH_2), 22.6 (CH_2), 22.4 (CH_3), 22.0 (CH_3), 14.1 (CH_3); IR (neat, film) 2923, 2852, 1722 (s, C=O), 1460, 1372, 1151, 1090, 1068 cm^{-1}; MS m/e (rel abund) 412 (M^+ + 1, 0.3), 411 (M^+, 0.5), 211 (16), 199 (100), 137 (63), 95 (29), 81 (53). Anal. Calcd for $C_{25}H_{46}O_2S$: C, 73.11; H, 11.29. Found: C, 73.35; H, 11.43.

Isopentyl Oxathianyl Ketone 1c [R = $(CH_2)_2CH(CH_3)_2$]. Using the procedure described above, 270 mg (90%) of pure **1c** was obtained from oxathiane **3** (1.0 mmol) and 4-methylvaleroyl chloride (1.5 mmol) after isolation by flash chromtography (5% ethyl acetate in hexanes): ^1H NMR δ 5.45 (s, 1 H), 3.43 (dt, J = 4.4, 10.3 Hz, 1 H), ^{13}C NMR δ 205.5 (C), 82.5 (CH), 76.8 (CH), 50.2 (CH), 43.8 (C), 41.4 (CH_2), 35.9 (CH_2), 34.5 (CH_2), 31.9 (CH_2), 31.3 (CH), 29.3 (CH_3), 27.6 (CH), 24.2 (CH_2), 22.3 (CH_3), 22.0 (CH_3); IR (neat, film) 2996, 2870, 1723 (s, C=O), 1462, 1386, 1366, 1150, 1068, 1009 cm^{-1}; MS m/e (rel abund) 300 (M^+ + 1, 10), 299 (M^+, 74), 199 (100), 137 (68), 95 (19), 81 (21). Anal. Calcd for $C_{17}H_{30}O_2S$: C, 68.41; H, 10.13. Found: C, 68.38; H, 10.16.

Cyclohexyl Oxathianyl Ketone 1d (R = C_6H_{11}). Using the procedure described above, 300 mg (97%) of purified **1d** was obtained from oxathiane **3** (1 mmol) and cyclohexanecarbonyl chloride (1.5 mmol) after isolation by flash chromatography (5% ethyl acetate in hexanes). The ^1H and ^{13}C NMR spectra were identical with those reported.[2b]

Benzyl Oxathianyl Ketone 1e (R = CH_2Ph). Using the procedure described above, 290 mg (91%) of pure **1e** was obtained from oxathiane **3** (1 mmol) and phenylacetyl chloride (1.5 mmol) after isolation by flash chromatography (3% ethyl acetate in hexanes). Recrystallization from pentane gave the analytical sample: mp 74–75 °C; ^1H NMR δ 7.28 (m, 5 H), 5.50 (s, 1 H), 3.96 (dd, J = 6.6, 22.7 Hz, 2 H), 3.41 (dt, J = 4.3, 10.4 Hz, 1 H), 1.43 (s, 3 H), 1.30 (s, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), and others; ^{13}C NMR δ 202.4 (C), 133.4 (C), 129.6 (CH), 128.3 (CH), 126.7 (CH), 82.0 (CH), 77.1 (CH), 50.3 (CH), 44.8 (CH_2), 44.1 (C), 41.5 (CH_2), 34.6 (CH_2), 31.4 (CH), 29.3 (CH_3), 24.3 (CH_2), 22.5 (CH_3), 22.2 (CH_3); IR (neat, film) 3030, 2925, 2869, 1730 (s, C=O), 1602, 1496, 1454, 1387, 1371, 1150, 1068, 1010 cm^{-1}; MS m/e (rel abund) 319 (M^+ + 1, 1), 318 (M^+, 2), 199 (100), 137 (91), 95 (45), 91 (56), 81 (76). Anal. Calcd for $C_{19}H_{26}O_2S$: C, 71.66; H, 8.23. Found: C, 71.63; H, 8.11.

(*p*-Chlorophenoxy)methyl Oxathianyl Ketone 1f (R = $CH_2OC_6H_4Cl$-*p*). Using the procedure described above, 310 mg (84%) of pure **1f** was obtained from oxathiane **3** (1.0 mmol) and freshly distilled *p*-(chlorophenoxy)acetyl chloride (1.5 mmol) after isolation by flash chromatography (10% ethyl acetate in hexanes). Recrystallization from diethyl ether–pentane gave the analytical sample: mp 92–93 °C; ^1H NMR δ 7.22 (m, 2 H), 6.82 (m, 2 H), 5.64 (s, 1 H), 5.03 (dd, J = 7.8, 18.4 Hz, 2 H), 3.46 (dt, J = 4.3, 10.4 Hz, 1 H), 1.47 (s, 3 H), 1.31 (s, 3 H), 0.95 (d, J = 6.4 Hz, 3 H), and others; ^{13}C NMR δ 199.8 (C), 129.2 (CH), 115.8 (CH), 81.4 (CH), 76.9 (CH), 69.8 (CH_2), 50.3 (CH), 44.4 (CH), 41.4 (CH_2), 34.5 (CH_2), 31.3 (CH), 29.2 (CH_3), 24.2 (CH_2), 22.4 (CH_3), 22.0 (CH_3); IR (neat, film) 3071, 2926, 2870, 1744 (s, C=O), 1679, 1650, 1589, 1584, 1492, 1454, 1371, 1290, 1230, 1149, 1092, 1070, 1007 cm^{-1}; MS m/e (rel abund) 369 (M^+, 4), 335 (1), 199 (100), 137 (87), 95 (39), 81 (60). Anal. Calcd for $C_{19}H_{25}O_3SCl$: C, 61.86; H, 6.83. Found: C, 61.76; H, 6.79.

***tert*-Butyl Oxathianyl Ketone 1g (R = $C(CH_3)_3$).** Using the procedure described above, 240 mg (86%) of pure **1g** was obtained from oxathiane **3** (1.0 mmol and trimethylacetyl chloride (1.5 mmol) after isolation by flash chromatography (2% ethyl acetate in hexanes), mp 97–98 °C (lit.[4] mp 94.5–96.5 °C). The ^1H NMR spectrum was identical with that reported.[4]

Phenyl Oxathianyl Ketone 1h (R = Ph). Using the procedure described above, 260 mg (87%) of pure **1h** was obtained from oxathiane **3** (1 mmol) and benzoyl chloride (1.5 mmol) after isolation by flash chromatography (5% ethyl acetate in hexanes), mp 92–93 °C (lit.[4] mp 93–94.5 °C). The ^1H NMR spectrum was identical with that reported.[2a,4]

***trans*-Cinnamyl Oxathianyl Ketone 1i (R = CH=CHPh).** Using the procedure described above, 270 mg (82%) of pure **1i** was obtained from oxathiane **3** (1 mmol) and *trans*-cinnamoyl chloride (1.5 mmol) after isolation by flash chromatography (5% ethyl acetate in hexanes). Recrystallization from diethyl ether–pentane gave the analytical sample: mp 133–134 °C; ^1H NMR δ 7.79 (d, J = 16 Hz, 1 H), 7.61 (m, 2 H), 7.17 (d, J = 16 Hz, 1 H), 5.67 (s, 1 H), 3.52 (dt, J = 4.3, 10.4 Hz, 1 H), 1.52 (s, 3 H), 1.32 (s, 3 H), 0.96 (d, J = 6.5 Hz, 3 H), and others; ^{13}C NMR δ 192.7 (C), 144.6 (CH), 134.2 (C), 130.6 (CH), 128.6 (CH), 128.5 (CH), 120.3 (CH), 82.3 (CH), 76.9 (CH), 50.2 (CH), 44.1 (C), 41.5 (CH_2), 34.5 (CH_2), 31.3 (C), 29.3 (CH_3), 24.3 (CH_2), 22.5 (CH_3), 22.1 (CH_3); MS m/e (rel abund) 332 (M + 1, 2), 331 (M^+, 8), 199 (100), 137 (94), 131 (32), 103 (55), 95 (46), 81 (86). Anal. Calcd for $C_{20}H_{26}O_2S$: C, 72.69; H, 7.93. Found: C, 72.60; H, 7.91.

Propenyl Oxathianyl Ketone 1j (R = CH=CHCH$_3$). Using the procedure described above, 250 mg (93%) of pure **1j** was obtained from oxathiane **3** (1 mmol) and freshly distilled crotonyl chloride (1.5 mmol) after isolation by flash chromatography (5% ethyl acetate in hexanes): mp 58–59 °C; ^1H NMR δ 7.11 (m, 1 H), 6.53 (dt, J = 1.6, 15.7 Hz, 1 H), 5.57 (s, 1 H), 3.47 (dt, J = 4.3, 10.3 Hz, 1 H), 1.92 (dd, J = 1.5, 7.0 Hz, 3 H), 1.48 (s, 3 H), 1.30 (s, 3 H), 0.94 (d, J = 6.5 Hz), and others; ^{13}C NMR δ 192.3 (C), 145.3 (CH), 125.8 (CH), 81.8 (CH), 76.8 (CH), 50.1 (CH), 43.9 (C), 41.4 (CH_2), 34.4 (CH_2), 31.2 (CH), 29.2 (CH_3), 24.2 (CH_2), 22.4 (CH_3), 21.9 (CH_3), 18.5 (CH_3). Anal. Calcd for $C_{15}H_{24}O_2S$: C, 67.12; H, 9.01. Found: C, 67.11; H, 9.06.

2-Furyl Oxathianyl Ketone 1k (R = 2-C_4H_3O). Using the procedure described above, 260 mg (90%) of pure **1k** was obtained from oxathiane **3** (1.0 mmol) and freshly distilled 2-furoyl chloride (1.5 mmol) after isolation by flash chromatography (10% ethyl acetate in hexanes), mp 108–109.5 °C. The ^1H and ^{13}C NMR spectra were identical with those reported.[4]

6-Chloro-3-pyridyl Oxathianyl Ketone 1l (R = 3-(6-Cl)-C_5H_3N). Using the procedure described above, 300 mg (87%) of pure **1l** was obtained from oxathiane **3** (1 mmol) and freshly sublimed 6-chloronicotinyl chloride (1.5 mmol) after isolation by flash chromatography (10% ethyl acetate in hexanes). Recrystallization from hexanes gave the analytical sample: mp 110–111 °C; ^1H NMR δ 9.17 (d, J = 2.1 Hz, 1 H), 8.33 (dd, J = 2.4, 8.4 Hz, 1 H), 7.40 (d, J = 8.5 Hz, 1 H), 6.0 (s, 1 H), 3.55 (dt, J = 4.3, 10.5 Hz, 1 H), 1.53 (s, 3 H), 1.31 (s, 3 H), 0.92 (d, J = 6.5, 3 H), and others; ^{13}C NMR δ 191.3 (C), 155.7 (CH), 151.8 (CH), 139.7 (CH), 128.7 (CH), 124.2 (CH), 82.0 (CH), 77.7 (CH), 50.6 (CH), 44.9 (C), 41.5 (CH_2), 34.5 (CH_2), 31.4 (CH), 29.3 (CH_3), 24.3 (CH_2), 22.4 (CH_3), 22.0 (CH_3). IR (KBr): 3040, 2970, 2950, 2910, 2870, 2850, 1690 (s, C=O), 1570, 1465, 1370, 1105, 1060, 1000, 795 cm^{-1}; MS (m/e) 342 (M + 2), 340 (M^+), 306, 242, 199, 137. Anal. Calcd for $C_{17}H_{22}O_2NSCl$: C, 60.08; H, 6.52; N, 4.12. Found: C, 59.90; H, 6.45; N, 4.03.