Tetrahedron Vol. 42, No. 19, pp. 5267 to 5272, 1986
Printed in Great Britain.

0040-4020/86 $5.00+.00
Pergamon Journals Ltd.

METAL-HYDRIDE REDUCTION OF ISOXAZOLINE-3-CARBOXYLATE ESTERS

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(*Received in USA* 22 *May* 1986)

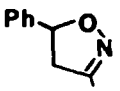
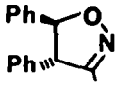
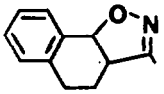
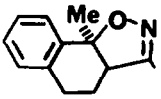
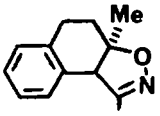
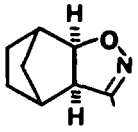
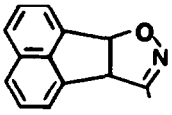
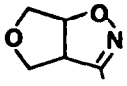
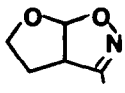
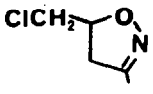
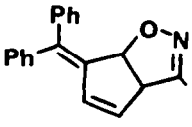
Abstract The reduction of a series of isoxazoline-3-carboxylate esters with sodium borohydride gave 3-(hydroxymethyl)isoxazolines in 34-98% yield. Reduction with DIBAH gave isoxazoline-3-carboxaldehydes in 63 and 85% yields for the two reactions studied. Isoxazoline-3-carboxaldehydes could also be prepared by Swern oxidation of the corresponding 3-(hydroxymethyl)isoxazolines. The hydroxyl group of 3-(hydroxymethyl)isoxazoline **11b** was silylated and the endocyclic double bond was cleaved by ozonolysis to produce a monosilylated triol.

In complementary programs directed towards the synthesis of biologically active derivatives via 1,3-dipolar cycloaddition[1], we have developed a general methodology for the synthesis of 3-(hydroxymethyl)isoxazolines and two alternative ways to prepare isoxazoline-3-carboxaldehydes. 3-(Hydroxymethyl)isoxazolines and isoxazoline 3-carboxaldehydes are potential precursors to various classes of biologically interesting compounds such as aminosugars[2], antibiotics[3], β-hydroxy acids[3,4], and α-methylene lactones[5]. Existing approaches to these 3-α-oxygenated isoxazolines have centered on the cycloaddition of suitably protected nitroethanol and nitroacetaldehyde acetals with dipolarophiles following the Mukaiyama procedure[6].

Our approach to 3-(hydroxymethyl)isoxazolines takes advantage of the ready availability of ethyl isoxazoline-3-carboxylate esters, prepared by 1,3-dipolar cycloaddition reactions of ethoxycarbonylformonitrile oxide. This nitrile oxide can be generated from the methyl nitronic ester of ethyl nitroacetate (in some cases ethyl nitroacetate itself can be used) in the presence of acid catalysts[7]. Alternatively, ethoxycarbonylformonitrile oxide can be generated from ethyl chlorooximinoacetate, either by using base (Huisgen's methodology[8]) or by thermal decomposition[9]. The last method is particularly suitable for cycloadditions involving recalcitrant dipolarophiles[9].

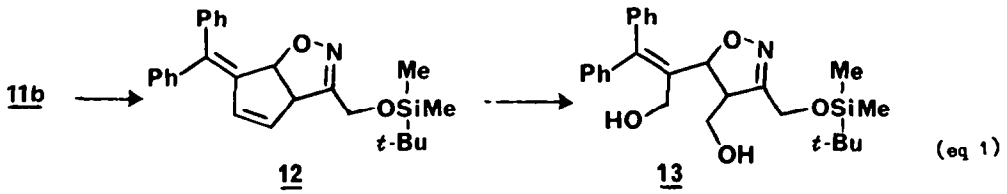
Treatment of isoxazoline-3-carboxylates at room temperature with an excess of sodium borohydride leads to their smooth reduction to the corresponding 3-(hydroxymethyl)isoxazolines in 34-98% yield (Table 1). There are some scattered reports of similar preparations of isoxazolines[7, 10] and isoxazoles[11], but this is the first detailed study of the reaction. The ester functionality, apparently because it is attached to a carbon-nitrogen double bond, is activated compared to simple esters, thus permitting high yields of product under unusually mild conditions.

TABLE 1. REDUCTION OF ISOXAZOLINE-3-CARBOXYLATE ESTERS USING SODIUM BOROHYDRIDE

R	$R-CO_2Et$	$R-CH_2OH$	YIELD	MP
	1a	1b	81%	65-68°C (cyclohexane - EtOAc)
	2a	2b	78%	oil
	3a[a]	3b	86%	100-102°C (Et_2O)
	4a	4b	66%	oil
	5a[a]	5b	78%	oil
	6a	6b	83%	89-90°C (cyclohexane)
	7a	7b	98%	129-31°C (cyclohexane - EtOAc)
	8a	8b	34%	oil
	9a	9b	52%	oil
	10a	10b	66%	oil
	11a[b]	11b	89%	140.5-142°C (CCl_4)

[a] Preparation by 1,3-dipolar cycloaddition gave a small amount of the corresponding regioisomer[9]. [b] The methyl ester was employed.

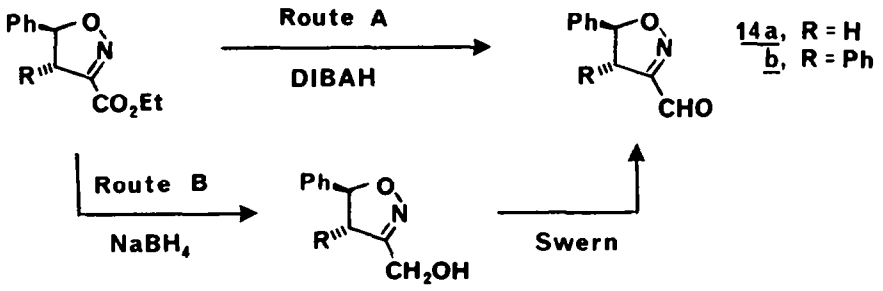
The methyl isoxazoline-3-carboxylate **11a** was prepared[12] by cycloaddition using methyl chlorooximinoacetate and triethylamine for the *in situ* generation of methoxycarbonylformonitrile oxide. Ester **11a** was reduced by the borohydride procedure to the 3-(hydroxymethyl)isoxazoline **11b** in 89% yield. Further transformations of the hydroxyl group and the endocyclic double bond of **11b** were also carried out. Imidazole-catalyzed reaction of **11b** with *t*-butyldimethylsilyl chloride gave the *t*-butyldimethylsilyl ether **12** in 92% yield (eq 1). Cleavage with one equivalent of ozone, followed by sodium borohydride - dimethyl sulfide workup, gave the monosilylated triol **13** in 62% yield.



(eq 1)

We have also investigated two alternative ways to prepare isoxazoline-3-carboxaldehydes, one based on the direct reduction of the corresponding ethyl isoxazoline-3-carboxylates and the other indirectly through Swern oxidation[13] of the alcohols derived from sodium borohydride reduction (Scheme 1). Direct reduction (Route A) was performed using di-*iso*-butylaluminum hydride (DIBAH) at low temperature. This reaction is best carried out with excess hydride reagent (3-5 equivalents) at -78°C in methylene chloride. Under these conditions, the aldehyde **14a** was obtained in 63% yield and aldehyde **14b** was obtained in 85% yield. In preliminary experiments run at -20°C, some overreduction to the alcohol was observed. Even at -78°C a small amount (<5% by NMR and TLC) of alcohol was produced, likely due to the high reactivity of the carbonyl group attached to a carbon-nitrogen double bond.

SCHEME 1.



The second procedure investigated for preparation of isoxazoline-3-carboxaldehydes involved Swern oxidation of the corresponding 3-(hydroxymethyl)isoxazolines (Scheme 1, Route B). Addition of the alcohol **2b** to a DMSO-oxalyl chloride solution at -60°C followed by the addition of base gave the aldehyde **14b** in 82% yield. Similar reaction of alcohol **1b** gave aldehyde **14a** in 80% yield.

In synthesizing isoxazoline-3-carboxaldehydes, it is necessary to choose either the one-step DIBAH reduction or the two-step borohydride reduction - Swern oxidation sequence. The direct reduction is somewhat quicker and gives a slightly higher overall yield. However, the two-step approach requires less stringent control of conditions.

Experimental

General Methods. ^{1}H-NMR spectra were recorded (with Me_4Si as internal standard in $CDCl_3$, unless otherwise noted) on Hitachi-Perkin Elmer R-600FT, JEOL FX-90Q, and Varian HFT-80 instruments. Infrared spectra were obtained using Perkin Elmer 1310, 457, and 137 spectrophotometers. Mass spectra were obtained on Finnegan 4023 GC-MS or A.E.I. spectrometers. Thin-layer chromatography was carried out on Merck and Analtech 0.25 mm and Analtech 1 mm precoated silica gel GF_{254} plates. Column chromatography was carried out on Merck silica gel, 60-200 mesh, unless otherwise noted.

Ethyl Isoxazoline-3-carboxylates 1a-10a. Procedue A. A toluene solution (5mL) of ethyl chlorooximinoacetate (5 mmol) was added dropwise to a refluxing solution of the dipolarophile (5 mmol) in toluene (10 mL). After 18 h at reflux, volatiles were stripped at reduced pressure and the resulting residue was column chromatographed. Compounds **3a**, **4a**, **5a**, and **8a** were prepared in this fashion.

Procedure B[8]. Triethylamine (3 mmol) in diethyl ether (10 mL) was added dropwise over approximately 2 h to a stirred solution of dipolarophile (10 mmol) and ethyl chlorooximinoacetate (2 mmol). The resulting slurry was stirred for 3 h, poured into water, and extracted with several portions of ether. The combined extracts were dried (anhyd. Na_2SO_4) and concentrated at reduced pressure. The resulting residue was column chromatographed: esters **1a**, **2a**[14], **6a**, **7a**, **9a**, and **10a** were prepared in this fashion.

Procedure C. A 0.4 M etheral solution of diazomethane[15] (60 mL, 0.024 mol) was cautiously added to a cold (0-5°C) solution of ethyl nitroacetate (2.11 g, 0.016 mol) in CH_2Cl_2 (10 mL). The resulting solution was partially stripped (final volume was 10 mL; **caution!** *crude concentrated nitronic esters are potential explosives!*). Methylene chloride (30 mL) was added followed by styrene (16.5 g, 0.16 mol) and *p*-toluenesulfonic acid (3.0 g, 0.017 mol). The resulting solution was refluxed for 2 h, cooled, and washed successively with 5% NaOH (50 mL) and water. Drying (anhyd. Na_2SO_4), concentration at reduced pressure, kugelrohr distillation (bp 140-160°C [0.025 Torr], and column chromatography ('Baker Analyzed' silica gel, 60-200 mesh; CH_2Cl_2 elution) gave 2.32 g (66% yield) of pure **1a**.

Methyl Chlorooximinoacetate. The procedure followed was analagous to the preparation of ethyl chlorooximinoacetate[16]. The product was twice recrystallized from CCl_4 giving a 34% yield of white solid: mp 61-62°C [Lit[17] mp 57-60 °C].

Anal. Calcd for $C_3H_4ClNO_3$: C, 26.20; H, 2.93; N, 10.18; Cl, 25.78. Found: C, 26.23; H, 2.97; N, 10.23; Cl, 25.83.

Methyl Isoxazoline-3-Carboxylate 11a. Procedure B[8] used in preparing the analogous ethyl esters was repeated with methyl chlorooximinoacetate and ω,ω-diphenylfulvene. Column chromatography (95:5 CCl_4 - ethyl acetate) on the crude product gave an 85:15 mixture, respectively, (NMR) of **11a** and the regioisomer formed from reverse attack on the fulvene endocyclic double bond. Recrystallization of this mixture from methanol gave **11a** (51% yield) as a solid: mp 160-161°C; IR ($CHCl_3$ 1720 cm^{-1} (C=O); NMR δ 7.3-8.0 (m, 10 H, aryl), 6.41 (dd, 1 H, J = 5.64, 2.17 Hz, H-7), 6.06 (dd, 1 H, J = 5.64, 2.17 Hz, H-6), 5.42 (d, 1 H, J = 7.92 Hz, H-1), 4.50 (dt, 1 H, J = 7.92, 2.17 Hz, H-5), and 3.88 (s, 3 H); MS m/e 331 (M^+).

Reduction of Ethyl Isoxazoline-3-carboxylates. A ten-fold excess of $NaBH_4$ was added portionwise to a solution of the ester (1.0 mmol) in ethanol or CH_2Cl_2 (10 mL). The reaction was stirred at room temperature until disappearance of the starting material (3-4 h). The mixture was then poured into water (15 mL) and extracted with $CHCl_3$ (3 X 20 mL). The combined extracts were dried (anhyd. Na_2SO_4) and concentrated at reduced pressure. The crude alcohols (Table 1) were purified by column chromatography and gave characteristic NMR spectra.

1b: δ 7.4 (m, 5 H, aryl), 5.7 (dd, 1 H, $J_{4,5}$ = 10 Hz, $J_{4',5}$ = 8 Hz, H-5), 4.5 (s, 2 H, CH_2OH), 3.5 (dd, 1 H, $J_{4,4'}$ = 18 Hz, H-4), 3.1 (dd, 1 H, H-4'), 2.3 (s, 1 H, OH).

2b: δ 7.43 (s, 10 H, aryl) 5.52 (d, 1 H, $J_{4,5}$ = 6.8 Hz, H-5), 4.38 (d, 1 H, H-4), 4.0-4.5 (m, 3 H, CH_2OH).

3b: δ 7.3 (m, 4 H, aryl), 5.5 (d, 1 H, $J_{1,5}$ = 9.0 Hz, H-1), 4.5 (s, 2 H, CH_2OH), 3.7 (m, 1 H, H-5), 2.7 (m, 3 H, 2 H-7 and OH), 1.9 (m, 2 H, 2 H-6).

4b: δ 7.0-7.8 (m, 4 H, aryl), 4.45 (s, 2 H, CH_2OH), 3.25 (dd, 1 H, $J_{5,6}$ = 6.0 Hz, $J_{5,6'}$ = 9.0 Hz, H-5), 2.5-2.9 (m, 3 H, 2 H-7 and OH), 1.7-2.2 (m, 2 H, 2 H-6), 1.6 (s, 3 H, Me).

5b: δ 7.25 (m, 4 H, aryl), 4.25 (s, 2 H, CH_2OH), 4.15 (s, 1 H, H-1), 2.0-3.0 (m, 4 H, 2 H-6 and 2 H-7), 1.5 (s, 3 H, Me).

6b: δ 4.55 (d, 1 H, $J_{2,6}$ = 8.0 Hz, H-2), 4.4 (s, 2 H, CH_2OH), 3.2 (d, 1 H, H-6), 2.5 (bs, 3 H, H-1, H-7 and OH), 0.9-1.8 (m, 6 H, 2 H-8, 2 H-9 and 2 H-10).

7b: δ 7.1-7.8 (m, 6 H, aryl), 6.35 (d, 1 H, $J_{1,5}$ = 9.0 Hz, H-1), 5.2 (d, 1 H, H-5), 4.4 (bs, 2 H, CH_2OH), 3.2 (bs, 1 H, OH).

8b: (pyridine-D_5) δ 5.22 (d, 1 H, H-1), 2.7-4.8 (m, 7 H, CH_2OH, H-5, 2 H-6 and 2 H-8).

9b: δ 6.3 (d, 1 H, $J_{1,5}$ = 6.0 Hz, H-1), 4.4 (s, 2 H, CH_2OH), 3.3-4.3 (m, 4 H, H-5, 2 H-7 and OH), 2.2 (m, 2 H, 2 H-6).

10b: δ 4.90 (m, 1 H, H-5), 4.5 (s, 2 H, CH_2OH) 3.60 (d, 2 H, CH_2Cl, J = 5.0 Hz), 3.20 (m, 2 H, 2 H-4).

11b: δ 7.3-8 (m, 10 H, aryl), 6.29 (dd, 1 H, J = 5.20, 2.28 Hz, H-7), 5.95 (dd, 1 H, H-6), 5.20 (d, 1 H, J = 7.49 Hz, H-1), 4.41 (d, 2 H, J = 5.82 Hz, CH_2OH), 4.27 (dt, 1 H, J = 7.49, 2.28 Hz, H-5), 1.86 (t, 1 H, J = 5.82 Hz, OH).

DIBAH Reduction of Ethyl trans-4,5-Dihydro-4,5-diphenylisoxazole-3-carboxylate (2a). DIBAH (1.4 mL of an 0.79 M cyclohexane solution; 1.1 mmol) was added dropwise over 1 min to a cold (-78°C) solution of **2a** (103 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) under N_2. The resulting solution was stirred for 50 min and then water (10 mL) was added, the mixture was allowed to warm and 1% aqueous HCl (3 mL) was added. The organic products were extracted with CH_2Cl_2 and the extracts were washed (water), dried (anhyd. Na_2SO_4), and concentrated to an oil. Preparative TLC (CH_2Cl_2) gave pure (NMR, TLC) aldehyde **14b** (74 mg, 85% yield) as an oil. Kugelrohr distillation of the oil gave the analytical sample: bp 140-145°C (0.025 Torr); IR (neat) 1690 cm^{-1} (C=O); NMR δ 9.91 (s, 1 H, CHO), 7.1-7.5 (m, 10 H, aryl), 5.68 (d, 1 H, J = 6.1 Hz, H-5), and 4.5 (d, 1 H, J = 6.1 Hz, H-4); MS m/e 251 (M^+).

A satisfactory elemental analysis could not be obtained in several attempts for aldehyde **14b**. A sample was converted to the 2,4-dinitrophenylhydrazone: mp 194-95°C.

Anal. Calcd for $C_{22}H_{17}N_5O_5$: C, 61.21; H, 3.97. Found: C, 61.12; H, 4.03.

DIBAH Reduction of Ethyl 4,5-Dihydro-5-phenylisoxazole-3-carboxylate (1a). The reduction of **1a** was carried out analogously to reduction of **2a**. Preparative TLC (CH_2Cl_2) gave pure (NMR, TLC) aldehyde **14a** (63% yield) as an oil. Kugelrohr distillation gave the analytical sample: bp 90-100°C (0.025 Torr); IR (neat) 1690 cm^{-1} (C=O); NMR δ 9.97 (s, 1 H, CHO), 7.2-7.5 (m, 5 H, aryl), 5.81 (dd, 1 H, J = 9, 11.4 Hz, H-5), 3.55 (dd, 1 H, J = 11.4, 17.6 Hz, H-4), and 3.11 (dd, 1 H, J = 9, 17.6 Hz, H-4'); MS m/e 175 (M^+).

Anal. Calcd for $C_8H_9NO_2$: C, 68.57; H, 5.14. Found: C, 68.76; H, 5.36.

Swern Oxidation[13] of trans-4,5-Dihydro-3-(hydroxymethyl)-4,5-diphenylisoxazole (2b). A solution of DMSO (0.1 g, 1.3 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 1 min to a cold (-65°C) solution of oxalyl chloride (0.07 g, 0.6 mmol) in CH_2Cl_2 (2 mL) under N_2. After 10 min, a solution of **2b**[14] (66 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 1 min maintaining the temperature at <-60°C. The resulting solution was stirred for 15 min and Et_3N (0.35 mL) was added. The reaction mixture was then allowed to warm to 0°C and water was added. The layers were separated and the organic phase was washed (water), dried (anhyd. Na_2SO_4), and concentrated at reduced pressure. Preparative TLC (CH_2Cl_2) gave 56 mg (82% yield) of pure (NMR, TLC) **14b**.

Swern Oxidation[13] of 4,5-Dihydro-3-(hydroxymethyl)-5-phenylisoxazole (1b). The preceding procedure was repeated using 51 mg of alcohol **1b**. The crude product was purified by preparative TLC (CH_2Cl_2) to give 41 mg (80% yield) of aldehyde **14a**.

Silylation of Alcohol 11b[12]. A solution containing alcohol **11b** (101 mg; 0.33 mmol), t-butyldimethylsilyl chloride (111 mg; 0.74 mol), and imidazole (118 mg; 1.70 mmol) in DMF (0.3 mL) was heated for 8 h at 40-45°C under Ar. The resulting solution was poured into water containing pH 7.0 buffer solution (5.0 mL acetic acid - sodium acetate buffer concentrate, diluted to 25 mL). Extraction (CH_2Cl_2), washing (water), drying (anhyd. Na_2SO_4), and concentration at reduced pressure gave crude silyl ether **12**. This was purified by preparative TLC (60:40 hexanes - ethyl acetate) to give an oil (128 mg; 92% yield) which crystallized on standing: mp 108-111°C; NMR δ 7.3-8.0 (m, 10 H, aryl), 6.31 (dd, 1 H, J = 5.51, 2.12 Hz, H-7), 6.02 (dd, 1 H, J = 5.51, 2.12 Hz, H-6), 5.20 (d, 1 H, J = 7.42 Hz, H-1), 4.45 (s, 2 H), 4.32 (dt, 1 H, J = 7.42, 2.12 Hz, H-5), 0.90 (s, 9 H, CH_3C), and 0.10 (s, 6 H, Me_2Si); MS m/e 417 (M^+).

Ozonolysis of silyl ether 12[12]. A cloudy solution of **12** (128 mg; 0.31 mmol) in absolute methanol

(25 mL) and CH_2Cl_2 (20 mL) was cooled in a Dry ice bath for 15 min. An O_2 stream containing ca. 3% ozone was carefully standardized iodometrically to deliver 0.0262 mmol / min of O_3. This stream was then passed through the solution for 12 min (0.31 mmol of delivered O_3). The reaction mixture was stirred for 20 min at -78°C and was then allowed to warm to -25°C. After 5 min $NaBH_4$ (0.21 g; 5.52 mmol) was added and stirring at -20 to -25°C was continued for an additional 25 min. Dimethyl sulfide (0.3 mL) was added and the reaction was allowed to warm to 10°C over 5 h. Volatiles were removed under reduced pressure and the residue was taken up in CH_2Cl_2. The resulting solution was washed (water), dried (anhyd. Na_2SO_4), and concentrated to an oil containing one major and five minor products (TLC). Preparative TLC (80:20 hexanes - ethyl acetate) gave the monosilylated triol **13** (86.6 mg; 62% yield) as an off-white solid: mp 113.5-114.5°C; IR ($CHCl_3$) 2.95 (b, OH) cm^{-1}; NMR δ 7.3-8.0 (m, 10 H, aryl), 5.75 (d, 1 H, J = 11.2 Hz, 5-H), 4.80 (dd, 2 H), 4.62 (dd, 2 H), 4.22 (dd, 2 H, J = 3.75 Hz), 3.45 (dt, 1 H, J = 11.2, 3.75 Hz, 4-H), 1.6 (s, 2 H, 2 OH), 0.86 (s, 9 H), and 0.11 (d, 6 H, J = 1 Hz); MS m/e 453 (M^+).

Acknowledgement. Financial support from the Ministero della Pubblica Istruzione (Italy) and IBM Corporation is gratefully acknowledged.

References and Footnotes

1. De Micheli, C.; De Amici, M.; Santagostino Barbone, M. G.; Zonta, F.; Grana, E. Il Farmaco Ed. Sci. **1983**, 38, 817. (b) Wade, P. A.; Pillay, M. K.; Singh, S. M. Tetrahedron Lett. **1982**, 23, 4563. (c) De Micheli, C.; De Amici, M.; Scalfi, M. Il Farmaco Ed. Sci. **1984**, 39, 487. (d) Wade, P. A.; Singh, S. M.; Pillay, M. K. Tetrahedron **1984**, 40, 601.

2. (a) Jäger, V.; Grund, H.; Buss, V. Schwab, W.; Müller, I. Schohe, R.; Franz, R.; Ehler, R. Bull. Soc. Chim. Belg. **1983**, 92, 1039. (b) Jäger, V.; Schohe, R. Tetrahedron **1984**, 40, 2199 and references cited therein. (c) Jäger, V.; Müller, I. Tetrahedron Lett. **1985**, 26, 2997. (d) Wade, P. A.; Price, D. T.; Bereznak, J. F.; unpublished studies.

3. Kozikowski, A. P.; Ghosh, A. K. J. Org. Chem. **1984**, 49, 2762.

4. Curran, D. P.; Scanga, S. A.; Fenk, C. J. J. Org. Chem. **1984**, 49, 3474.

5. Kozikowski, A. P.; Ghosh, A. K. Tetrahedron Lett. **1983**, 24, 2623.

6. Mukaiyama, T.; Hoshino, T. J. Am. Chem. Soc. **1960**, 82, 5339.

7. Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. J. Org. Chem. **1984**, 49, 4595.

8. Christl, M.; Huisgen, R. Chem. Ber. **1973**, 106, 3345.

9. Caldirola, P.; De Amici, M.; De Micheli, C. Heterocycles **1985**, 23, 2479.

10. The isoxazoline-3-carboxylate ester obtained from reaction of ethoxycarbonylformonitrile oxide with excess cyclohexene has been reduced with sodium borohydride: Lee, V.; Woodward, R. B.; unpublished studies performed at Harvard University, 1975-1976 [Personal communication from V. Lee (Lederle Laboratories)]. This is apparently the first example of the transformation of an isoxazoline-3-carboxylate ester to a 3-(hydroxymethyl)isoxazoline.

11. (a) Barco, A.; Benetti, S.; Baraldi, P. G.; Guarneri, M.; Pollini, G. P.; Simoni, D.; J. Chem. Soc., Chem. Commun. **1981**, 599. (b) Baraldi, P. G.; Simoni, D.; Moroder, F.; Manfredini, S.; Mucchi, L.; Dalla Vecchia, F.; Orsolini, P. J. Heterocyclic Chem. **1982**, 19, 557. (c) Baraldi, P. G.; Moroder, F.; Pollini, G. P.; Simoni, D. Barco, A.; Benetti, S. J. Chem. Soc., Chem. Commun. **1982**, 2983. (d) Baraldi, P. G.; Barco, A.; Benetti, D.; Manfredini, S.; Pollini, G. P.; Simoni, D. Tetrahedron Lett. **1984**, 25, 4313. (e) For the related reduction of ethyl thiazolidine-4-carboxylate, see: Habermehl, G. G.; Ecsy, W. Heterocycles **1977**, 7, 1027.

12. This work was performed in the Converse Research Laboratories, Harvard University, 1975-1976.

13. Omura, K.; Swern, D. Tetrahedron **1978**, 34, 1651.

14. Ester **2a** used in the aldehyde studies was prepared directly from ethyl nitroacetate by TSA-catalyzed reaction with stilbene[7].

15. Moore, J. A.; Reed, D. E. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. 5, p 351.

16. Skinner, G. S.; J. Amer. Chem. Soc. **1924**, 46, 738.

17. Kashutina, M. V.; Ioffe, S. L.; Shitkin, V. M.; Cherskaya, N. O.; Korenevskii, V. A.; Tartakovskii, V. A. J. Gen. Chem. SSSR **1973**, 43, 1699.