2 H); IR (CCl_4) 3060 (m), 2950 (m), 1415 (vs) cm^{-1}.

***N*-Methyl-3-phenyl-5-(trimethylsilyl)isoxazolidine (3a)**: NMR ($CDCl_3$) 0.1 (s, 9 H), 1.8–2.9 (m, 2 H), 2.7 (s, 3 H), 3.2–3.9 (m, 2 H), 7.3 (m, 5 H); IR (neat) 3030 (m), 2960 (vs), 2840 (s), 1245 (vs) cm^{-1}.

α-Furyl-*N*-methylnitrone (2b): NMR ($CDCl_3$) 3.6 (s, 3 H), 6.3 (m, 1 H), 7.2 (m, 2 H), 7.5 (m, 1 H); IR (CCl_4) 3020 (w), 2940 (w), 1590 (w), 1410 (vs), 1145 (vs) cm^{-1}.

***N*-Methyl-3-furyl-5-(trimethylsilyl)isoxazolidine (3b)**: NMR ($CDCl_3$) 0.1 (s, 9 H), 1.9–2.6 (m, 2 H), 2.6 (s, 3 H), 3.1–3.8 (m, 2 H), 6.1 (m, 2 H), 7.2 (m, 1 H); IR (CCl_4) 2970 (m), 1255 (m), 1170 (vs) cm^{-1}; mass spectrum, *m/z* (relative intensity) 225 (M^+, 62), 210 (10), 73 (100).

β-Furylacrolein (4b): NMR ($CDCl_3$) 6.46 (dd, J = 1.8, 3.5, 1 H), 6.53 (dd, J = 7.9, 15.8, 1 H), 6.70 (d, J = 3.5, 1 H), 7.17 (d, J = 15.8, 1 H), 7.49 (d, J = 1.4, 1 H), 9.53 (d, J = 7.9, 1 H); IR (CCl_4) 3120 (w), 2805 (s), 2715 (s), 1685 (vs), 1630 (vs) cm^{-1}; mass spectrum, *m/z* (relative intensity) 122 (M^+, 100), 94 (45), 65 (40), 39 (31).

***N*-Methylnitrone 2c**: NMR ($CDCl_3$) 1.77 (s, 3 H), 3.19 (s, 3 H), 4.85 (A of AB q, J = 11.7, 1 H), 4.90 (B of AB q, J = 11.7, 1 H), 4.96 (A of AB q, J = 11.4, 1 H), 5.02 (B of AB q, J = 11.4, 1 H), 5.45 (d, J = 7.4, 1 H), 6.10 (s, 1 H), 6.74 (d, J = 7.4, 1 H), 6.8 (m, 2 H), 7.3 (m, 16 H); IR (CCl_4) 3030 (w), 2995 (m), 2830 (w), 1585 (m), 1490 (s) cm^{-1}; mass spectrum, *m/z* (relative intensity) 509 (M^+, 0.1), 280 (8), 91 (100).

***N*-Methyl-5-(trimethylsilyl)isoxazolidine 3c**: NMR ($CDCl_3$) 0.1 (s, 9 H), 1.8 (s, 3 H), 2.1–2.5 (m, 2 H), 2.3 (s, 3 H), 3.1 (m, 1 H), 3.3 (m, 1 H), 4.3 (m, 1 H), 5.1 (s, 2 H), 5.2 (s, 2 H), 5.9 (s, 1 H), 6.9 (m, 2 H), 7.3 (m, 16 H); IR (CCl_4) 3050 (m), 2970 (s), 2880 (s), 1480 (vs), 1200 (vs) cm^{-1}; mass spectrum, *m/z* (relative intensity), 609 (M^+, 0.1), 536 (2), 280 (14), 91 (100).

α,β-Unsaturated aldehyde 4c: NMR ($CDCl_3$) 1.46 (s, 3 H), 4.99 (dd, J = 1.1, 2.5, 1 H), 5.07 (s, 4 H), 5.74 (s, 1 H), 6.3 (m, 2 H), 6.9 (m, 2 H), 7.4 (m, 16 H), 8.86 (d, J = 7.5, 1 H); IR (CCl_4) 3050 (w), 2880 (w), 2730 (w), 1695 (vs) cm^{-1}; mass spectrum, *m/z* (relative intensity) 506 (M^+, 0.1), 332 (7), 91 (100). Anal. Calcd[11] for $C_{33}H_{30}O_5$: C, 78.22; H, 5.97. Found: C, 78.03; H, 6.12.

α-*n*-Hexyl-*N*-methylnitrone (2d): NMR ($CDCl_3$) 0.8–1.5 (m, 11 H), 2.3–2.7 (m, 2 H), 3.6 (s, 3 H), 6.7 (t, J = 7, 1 H); IR (neat) 3050 (w), 2930 (vs), 1605 (s), 1410 (vs) cm^{-1}; mass spectrum, *m/z* (relative intensity) 144 (M^+ + 1, 25), 86 (50), 73 (100).

***N*-Methyl-3-*n*-hexyl-5-(trimethylsilyl)isoxazolidine (3d)**: NMR ($CDCl_3$) 0.1 (s, 9 H), 0.8–1.0 (m, 3 H), 1.2–1.6 (m, 10 H), 1.8–2.4 (m, 3 H), 2.6 (s, 3 H), 3.1–3.9 (m, 1 H); IR (neat) 2960 (vs), 2860 (s), 1250 (s), 825 (vs), cm^{-1}; mass spectrum, *m/z* (relative intensity) 243 (M^+, 15) 227 (41), 170 (39), 158 (25), 140 (67), 73 (100).

2-Nonenal (4d): NMR ($CDCl_3$) 0.89 (m, 3 H), 1.29–1.57 (m, 8 H), 2.36 (ddt, J = 1.5, 6.8, 5.0, 2 H), 6.12 (ddt, J = 1.5, 7.9, 15.6, 1 H), 6.86 (dt, J = 6.8, 15.6, 1 H), 9.50 (d, J = 7.9, 1 H); IR (neat) 2940 (vs), 2740 (w), 1690 (vs), 890 (vs), 715 (vs) cm^{-1}; mass spectrum, *m/z* (relative intensity) 140 (M^+, 100).

α-Carbethoxy-*N*-benzylnitrone (2e) (E and Z mixture): NMR ($CDCl_3$) 1.3 (t, 3 H), 4.3 (q, 2 H), 5.5 (m, 2 H), 7.1 (s, 1 H), 7.4 (m, 5 H); IR (CCl_4) 3030 (w), 2980 (m), 1745 (s), 1140 (vs) cm^{-1}.

***N*-Benzyl-3-carbethoxy-5-(trimethylsilyl)isoxazolidine (3e)**: NMR ($CDCl_3$) 0.1 (s, 9 H), 1.1 (t, 3 H), 2.0–2.6 (m, 2 H), 3.3–4.2 (m, 6 H), 7.2 (s, 5 H); IR (neat) 3040 (m), 2960 (s), 2840 (m), 1745 (vs), 1185 (vs) cm^{-1}; mass spectrum, *m/z* (relative intensity) 307 (M^+, 15), 234 (22), 91 (100).

***p*-Nitrophenylhydrazone of 4e**: mp 158–162 °C; NMR (Me_2SO-d_6) 1.23 (t, J = 7.1, 3 H), 4.15 (q, J = 7.1, 2 H), 6.35 (d, J = 15.6, 1 H), 7.15 (A of AB q, J = 9.2, 2 H), 7.25 (dd, J = 15.6, 9.7, 1 H), 7.84 (d, J = 9.7, 1 H), 8.14 (B of AB q, J = 9.2, 2 H); IR (CCl_4) 3050 (w), 2940 (m), 1735 (m), 1610 (m), 1340 (vs) cm^{-1}.

Acknowledgment. We acknowledge the generous financial support of the Public Health Service (GM 30743-01). We thank Dr. Robert Minard and Mr. Greg Hancock for help in obtaining mass spectra and Mr. Alan Freyer and Dr. V. Elango for FT-NMR spectra.

(11) Elemental analyses were performed by Micro-Tech Laboratories, Skokie IL.

Registry No. **1a**, 100-52-7; **1b**, 98-01-1; **1c**, 91328-45-9; **1d**, 111-71-7; **1e**, 924-44-7; (*Z*)-**2a**, 7372-59-0; (*Z*)-**2b**, 91328-46-0; **2c**, 91328-47-1; (*Z*)-**2d**, 91328-48-2; (*E*)-**2e**, 81206-60-2; (*Z*)-**2e**, 81206-61-3; *cis*-**3a**, 91328-49-3; *trans*-**3a**, 91328-56-2; *cis*-**3b**, 91328-50-6; *trans*-**3b**, 91328-57-3; **3c**, 91328-51-7; *cis*-**3d**, 91328-52-8; *trans*-**3d**, 91328-58-4; *cis*-**3e**, 91328-53-9; *trans*-**3e**, 91328-59-5; (*E*)-**4a**, 14371-10-9; (*E*)-**4b**, 39511-08-5; **4c**, 91328-54-0; (*E*)-**4d**, 18829-56-6; (*E*)-**4e**, 2960-66-9; (*E*)-**4e** (*p*-nitrophenylhydrazone), 91328-55-1; MeNHOH·HCl, 4229-44-1; CH_2=$CHSiMe_3$, 754-05-2.

Reduction of 4-Cyanoisoxazoles with Lithium Aluminum Hydride. Synthesis of 5-Aminoisoxazoles

Angel Alberola,* Ana María González, Miguel Angel Laguna, and Francisco José Pulido

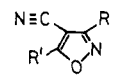
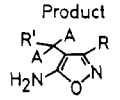
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid, Valladolid, Spain

Received January 18, 1984

In the course of our investigations of the reduction of isoxazole derivatives with complex metal hydrides, 2-, 3-, and 4-isoxazolines have been selectively synthesized in good yields.[1-3] In order to obtain adequate reactivity of the isoxazole ring toward reduction, activation of the nucleus by quaternization of the nitrogen[1] or introduction of electron-accepting groups at C-4[2] is necessary. In particular, 3,5-dimethylisoxazoles with electron-withdrawing groups at C-4 on reaction with sodium borohydride are reduced to 2-isoxazolines regiospecifically.[2] Although the reduction of 4-cyano-3,5-dimethylisoxazole with sodium borohydride leads to the expected 4-cyano-2-isoxazoline,[2] surprisingly, we found that reduction of 4-cyano-3,5-dimethylisoxazole with lithium aluminum hydride leads to 5-amino-4-ethyl-3-methylisoxazole resulting from an unusual rearrangement.

The interest in 5-aminoisoxazoles as intermediates for the synthesis of derivatives with antihistaminic,[4] analgesic,[5] antibactericidal,[6] and insecticidal[7] activity led us to study

Table I. Reduction of 3,5-Disubstituted-4-cyanoisoxazoles 1a-c with Lithium Aluminum Hydride (1 Equiv) at 0 °C in Ether for 6 h

	Metal Complex Hydride	Product 	Yield %
1a, R=R'=CH_3	$LiAlH_4$	2a, R=R'=CH_3, A=H	55
1a, R=R'=CH_3	$LiAlD_4$	2b, R=R'=CH_3, A=D	55
1b, R=Ph, R'=CH_3	$LiAlH_4$	2c, R=Ph, R'=CH_3, A=H	75
1b, R=Ph, R'=CH_3	$LiAlD_4$	2d, R=Ph, R'=CH_3, A=D	75
1c, R=R'=Ph	$LiAlH_4$	2e, R=R'=Ph, A=H	45

(1) Alberola, A.; González, A. M.; Laguna, M. A.; Pulido, F. J. *Synthesis* **1982**, 1067.
(2) Alberola, A.; González, A. M.; Laguna, M. A.; Pulido, F. J. *Synthesis* **1983**, 413.
(3) Alberola, A.; González, A. M.; Laguna, M. A.; Pulido, F. J. *Synthesis*, in press.
(4) Kano, H.; Makisumi, N. Japan Patent 9228, Oct 30, 1957.
(5) Takahashi, T.; Fujimura, H.; Asai, A. *Yakugaku Zasshi* **1962**, *82*, 474.
(6) Pinzauti, S.; Dal Piaz, V.; Berdondini, I.; Lenzi, L. *Boll. Chim. Farm.* **1974**, *113*(1), 26.
(7) Fancher, O.; Llewellyn W. U.S. Patent 4 104 375, Feb 24, 1977.

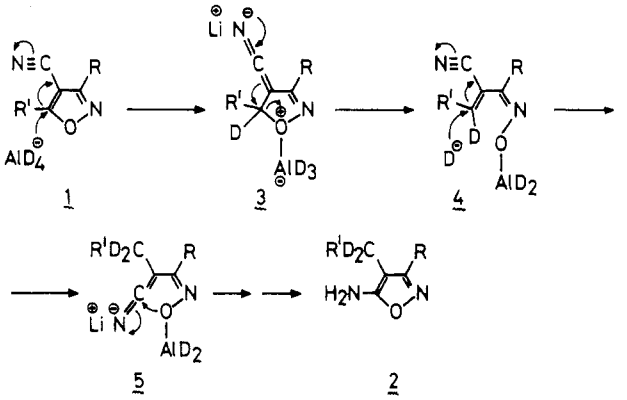
0022-3263/84/1949-3423$01.50/0

Table II. Reduction of 4-Cyanoisoxazoles 1a-c with Lithium Aluminum Hydride

product	mp, °C	mol form[a]	MS (70 eV), m/e (M^+, rel intensity)	IR (Nujol) ν (cm^{-1})	^1H NMR ($CDCl_3$, 60 Hz) δ, J (Hz)
2a[b]	84-85 (hexane-ether)	$C_6H_{10}N_2O$	126 (88)	3400, 3250, 1640	1.05 (t, 3 H, J = 7.1, 4-CH_2CH_3e, 2.05 (s, 3 H, 3-CH_3), 2.25 (q, 2 H, J = 7.1, 4-CH_2CH_3), 5.60 (br s, 2 H, NH_2)
2b	87-88 (hexane-ether)	$C_6H_8D_2N_2O$	128 (71)	3400, 3250, 2200, 2120, 1640	1.05 (s, 3 H, 4-CD_2CH_3e, 2.10 (s, 3 H, 3-CH_3), 4.70 (br s, 2 H, NH_2)
2c	58-59 (benzene)	$C_{11}H_{12}N_2O$	188 (18)	3350, 3200, 1650	1.00 (t, 3 H, J = 7.6, 4-CH_2CH_3), 2.30 (q, 2 H, J = 7.6, 4-CH_2CH_3), 5.20 (br s, 2 H, NH_2), 7.40 (m, 5 H, 3-C_6H_5)
2d	60-61 (benzene)	$C_{11}H_{10}D_2N_2O$	190 (10)	3450, 3200, 2250, 2140, 1650	1.00 (s, 3 H, 4-CD_2CH_3), 5.10 (br s, 2 H, NH_2), 7.50 (m, 5 H, 3-C_6H_5)
2e	88-89 (hexane-benzene)	$C_{16}H_{14}N_2O$	250 (42)	3350, 3200, 1630	3.60 (s, 2 H, 4-$CH_2C_6H_5$), 7.20 (m, 5 H, 4-$CH_2C_6H_5$), 7.50 (m, 5 H, 3-C_6H_5), 7.80 (br s, 2 H, NH_2)

[a] Satisfactory analytical data (C ± 0.19%, H ± 0.17%, N ± 0.18%). [b] ^{13}C NMR ($CDCl_3$) δ 9.07 (CH_3 attached to methylene group), 12.65 (CH_3 attached to C-3), 13.46 (CH_2), 92.60 (C-4), 159.66 (C-3), 163.95 (C-5).

Scheme I



the scope of this process. We report here an apparently general method for the regiospecific synthesis of 5-aminoisoxazoles[8] by reduction of 4-cyanoisoxazoles with lithium aluminum hydride. Furthermore, the mechanism of the reaction has been elucidated by incorporation of deuterium in the resulting 5-aminoisoxazoles when the reduction is carried out with lithium aluminum deuteride.

Result and Discussion

3,5-Disubstituted-4-cyanoisoxazoles **1a-c** react with $LiAlH_4$ or $LiAlD_4$ to give 3,4-disubstituted-5-aminoisoxazoles **2a-e** in 45-75% yields (Table I). Incorporation of deuterium in the methylene group attached at C-4 of **2b,d** clearly shows that the methylene carbon comes from the original C-5 carbon atom of **1a,b**.

From the deuteration experiments the mechanism of the reaction appears to occur by initial attack of hydride at C-5 and formation of the intermediate **3** (Scheme I) which is common for all the reductions of 4-functionalized 3,5-disubstituted isoxazoles with complex metal hydride.[2] The second hydride attack at C-5 may occur with preliminary Lewis acid catalyzed ring cleavage and formation of an α,β-unsaturated nitrile intermediate **4** followed by intramolecular addition of the nitrile salt intermediate **5** which cyclizes to the respective 5-aminoisoxazole.

(8) For references of known methods for synthesis of 5-aminoisoxazoles, see: (a) Yamada, S.; Kowaki, C. *J. Pharm. Soc. Jpn.* **1951**, *71*, 1356. (b) Lopez, L.; Barrans, J. *C. R. Hebd. Seances Akad. Sci., Ser. C.* **1966**, *263*(7), 557. (c) Harsanyi, K.; Takacs, K.; Horvath, K. *Chem. Ber.* **1974**, *107*(8), 2563. (d) Colau, R.; Viel, C. *Bull. Soc. Chim. Fr.* **1980**, 163.

Experimental Section

All reactions were carried out under nitrogen atmosphere. Melting points are uncorrected. 4-Cyanoisoxazoles were prepared by established procedures.[9] ^1H NMR spectra were recorded on a Varian A-60 analytical spectrometer. ^{13}C NMR spectra were determined with a Varian FT-80 instrument. Chemical shifts are reported in part per million relative to Me_4Si as the internal standard by using $CDCl_3$ as solvent. Infrared spectra were recorded for Nujol mulls, using a Pye-Unicam SP-1100 spectrophotometer. Solvents and reagents were purified by conventional methods. Electron ionization mass spectra were obtained on a Hewlett-Packard 5946-A.

5-Amino-4-ethyl-3-methylisoxazole (2a). General Procedure. (4-Cyano-3,5-dimethylisoxazole[9a] (**1a**; 6.1 g, 0.05 mol) in ether (100 mL) is added to a suspension of lithium aluminum hydride (2 g, 0.05 mol) in 50 mL of ether. The mixture is stirred at 0 °C for 6 h and then hydrolyzed with a saturated solution of ammonium chloride. The ethereal layer is separated and dried with magnesium sulfate. Evaporation of the solvent leaves a solid, which is chromatographed on silica gel with dichloromethane; yield 3.46 g (55%) of **2a**; mp 84-85 °C (hexane-ether). Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 56.99; H, 7.94; N, 22.12.

Physical constants and spectral and analytical data for compounds **2a-e** are summarized in Table II.

Registry No. **1a**, 31301-46-9; **1b**, 24400-67-7; **1c**, 54535-49-8; **2a**, 91084-67-2; **2b**, 91084-68-3; **2c**, 91084-69-4; **2d**, 91084-70-7; **2e**, 91084-71-8; $LiAlH_4$, 16853-85-3; $LiAlD_4$, 14128-54-2.

(9) (a) Kochetkov, N. K.; Sokolov, S. D.; Luboshnikova, V. M. *Zh. Obshch. Khim.* **1962**, *32*, 1778. (b) Renzi, G.; Dal Piaz, V.; Pinzauti, S. *Gazz. Chim. Ital.* **1969**, *98*, 753. (c) Quilico, A.; Fusco, R. *Rend. R, Ist. Lomb. Sci. Lett.* **1936**, *69*, 439.

NMR Studies of Geometric Isomers of 3-Dehydro-β-ionone[†]

Agnes T. Nakayama, T. T. Bopp, and R. S. H. Liu*

Department of Chemistry, 2545 The Mall, University of Hawaii, Honolulu, Hawaii 96822

Received February 8, 1984

Recently a considerable amount of effort has been directed toward studies of structural properties of retinal and

[†] Taken from the Senior Honors Thesis of A.T.N., University of Hawaii.

0022-3263/84/1949-3424$01.50/0