# Synthesis of 4-Isoxazolines by Reduction of *N*-Methylisoxazolium Salts with Complex Metal Hydrides

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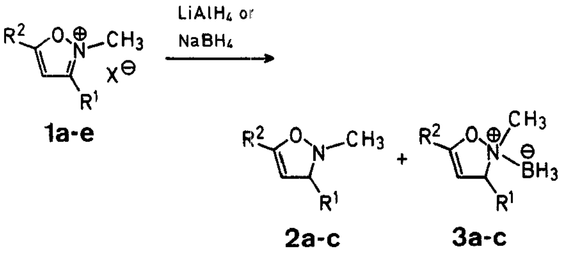
It has been reported that complex metal hydrides do not affect the isoxazole ring and can be successfully used to reduce functional groups in the side chain of isoxazole derivatives[1]. On the contrary, a few examples of reduction of 3- or 5-unsubstituted isoxazolium salts with sodium borohydride indicate the production of isoxazolines and isoxazolidines along with ring cleavage products[2].

We have found that 3,5-disubstituted *N*-alkylisoxazolium salts **1** react with lithium aluminium hydride or sodium borohydride to give 4-isoxazolines **2** as the only products. In some cases, a part of **2** is obtained as its borane complex **3**, which can be converted into the 4-isoxazoline **2** by treatment with triethylamine or ether. The results of all these reactions are summarised in the Table 1.



Formation of borane complexes depends on the involved anion of **1** and the hydride used. The formation of **3a** and **3b** in the reaction of **1a** and **1c** with lithium aluminium hydride must be interpreted on the basis of a fluorine-hydrogen exchange upon the boron atom.

3-Isoxazolines were not isolated. Work in progress indicates that similar reactions of 2,3,5-trimethylisoxazolium salts with unsaturated electron-accepting groups at C-4 lead to *N*-substituted 4- and 3-isoxazolines as major products. Thus, the reduction of 2,3,5-trimethyl-4-cyanoisoxazolium tetrafluoborate with sodium borohydride lead to an almost theoretical yield of 4-cyano-2,3,5-trimethyl-3-isoxazoline and 4-cyano-2,3,5-trimethyl-4-isoxazoline.

**3,5-Diphenyl-2-methyl-4-isoxazoline (2a); Typical Procedure:**

3,5-Diphenyl-2-methylisoxazolium tetrafluoborate[3] (**1a**; 2 g, 6.2 mmol) dissolved in ethanol (20 ml) is added to a suspension of sodium borohydride (0.47 g, 12.4 mmol) in ethanol. The mixture is stirred at 25 °C for 4 h, acidified with a saturated solution of ammonium chloride (30 ml), and then extracted with ether (2 × 25 ml). The organic layer is dried with magnesium sulphate and the solvents removed. The crude product is chromatographed on silica gel with dichloromethane; yield: 0.95 g (65%); m.p. 81 °C (hexane).

| | | | | |
|---|---|---|---|---|
| $C_{16}H_{15}NO$ | calc. | C 81.01 | H 6.33 | N 5.90 |
| (237.3) | found | 81.03 | 6.31 | 5.66 |

**3,5-Diphenyl-2-methyl-4-isoxazoline : Borane Complex (3a); Typical Procedure:**

3,5-Diphenyl-2-methylisoxazolium tetrafluoborate (**1a**; 4 g, 12.4 mmol) in ether (50 ml) is added to a suspension of lithium aluminium hydride (0.94 g, 24.8 mmol) in ether. The mixture is stirred at 25 °C for 4 h and hydrolysed with a saturated solution of ammonium chloride (40 ml). The ethereal layer is separated and dried with magnesium sulphate. Evaporation of the solvent leaves a solid, which is chromatographed on silica gel with dichloromethane. The following products are obtained:

*3,5-Diphenyl-2-methyl-4-isoxazoline : borane complex* (**3a**) from the 1st fraction. Yield: 2.48 g (80%); m.p. 91 °C (from hexane).

| | | | | |
|---|---|---|---|---|
| $C_{16}H_{18}BON$ | calc. | C 76.56 | H 7.18 | N 5.58 |
| (251.1) | found | 76.70 | 7.01 | 5.49 |

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**Table 1.** Reduction of 3,5-Disubstituted Isoxazolium Salts (**1**) with Complex Metal Hydrides

| Substrate No. | $R^1$ | $R^2$ | $X^{\ominus}$ | Hydride[a] | Solvent | Temperature | Time | Product | Yield[b] [%] |
|---|---|---|---|---|---|---|---|---|---|
| **1a** | $C_6H_5$ | $C_6H_5$ | $BF_4^{\ominus}$ | $LiAlH_4$ | ether | 25 °C | 4 h | **2a** | 85[c] |
| **1a** | $C_6H_5$ | $C_6H_5$ | $BF_4^{\ominus}$ | $NaBH_4$ | ethanol | 25 °C | 4 h | **2a** | 65 |
| **1b** | $C_6H_5$ | $C_6H_5$ | $H_3CO—SO_3^{\ominus}$ | $LiAlH_4$ | ether | 25 °C | 4 h | **2a** | 45 |
| **1b** | $C_6H_5$ | $C_6H_5$ | $H_3CO—SO_3^{\ominus}$ | $NaBH_4$ | ethanol | 0 °C | 2 h | **2a** | 75 |
| **1c** | $CH_3$ | $C_6H_5$ | $BF_4^{\ominus}$ | $LiAlH_4$ | ether | 0 °C | 4 h | **2b** | 50[c] |
| **1c** | $CH_3$ | $C_6H_5$ | $BF_4^{\ominus}$ | $NaBH_4$ | ethanol | 0 °C | 4 h | **2b** | 55 |
| **1d** | $CH_3$ | $C_6H_5$ | $H_3CO—SO_3^{\ominus}$ | $LiAlH_4$ | ether | 0 °C | 4 h | **2b** | 45 |
| **1d** | $CH_3$ | $C_6H_5$ | $H_3CO—SO_3^{\ominus}$ | $NaBH_4$ | ethanol | 0 °C | 4 h | **2b** | 50 |
| **1e** | $CH_3$ | $CH_3$ | $J^{\ominus}$ | $LiAlH_4$ | ether | 0 °C | 3 h | **2c** | 25 |
| **1e** | $CH_3$ | $CH_3$ | $J^{\ominus}$ | $NaBH_4$ | ether | 0 °C | 20 h | **2c** | 60[c] |

[a] Molar ratio **1** : hydride = 1 : 2.

[b] Yields refer to chromatographed products. Purity of **2** and **3** higher than 97% (G.L.C. analysis, conditions: 3% Dexil 300 on Chromosorb Q, 4 m × 3 mm, 130 °C).

[c] After treatment with ether. In all these cases mixtures of **2** and **3** are initially obtained: **2a** (5%) + **3a** (80%), **2b** (45%) + **3b** (5%), and **2c** (30%) + **3c** (30%).

**Table 2.** *N*-Methyl-4-isoxazolines **2a-c** and *N*-Methyl-4-isoxazoline : Borane Complexes **3a** and **3c**

| Product | m.p. [°C] or b.p. [°C]/torr | Molecular formula[a] or Lit. b.p. | I.R. (nujol or film $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. ($CDCl_3$, 60 MHz) $\delta$ [ppm] | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | H-3 | H-4 | $R^1$ | $R^2$ | N—$CH_3$ |
| **2a** | 81° | 67-68°[4] | 1645 (C=C) | 4.65 (d, $J$=3 Hz) | 5.10 (d, $J$=3 Hz) | 7.1 (m) | 7.1 (m) | 2.85 (s) |
| **2b** | 148-150°/710 | $C_{11}H_{13}NO$ (175.2) | 1655 (C=C) | 3.75 (dq, $J$=2.5 Hz, 6 Hz) | 5.05 (d, $J$=2.5 Hz) | 1.20 (d, $J$=6 Hz) | 7.2 (m) | 2.70 (s) |
| **2c** | oil[b] | $C_6H_{11}NO$ (113.2) | 1665 (C=C) | 3.55 (dq, $J$=2 Hz, 6 Hz) | 4.30 (d, $J$=2 Hz) | 1.10 (d, $J$=6 Hz) | 1.70 (s) | 2.60 (s) |
| **3a** | 91° | $C_{16}H_{18}BNO$ (251.1) | 1675 (C=C);<br>2410 ($\nu_{B—H}$) | 5.35 (d, $J$=3 Hz) | 5.90 (d, $J$=3 Hz) | 7.35 (m) | 7.35 (m) | 2.65 (s) |
| **3c** | oil[b] | $C_6H_{14}BNO$ (127.0) | 1690 (C=C);<br>2430 ($\nu_{B—H}$) | 4.00 (dq, $J$=2 Hz, 7 Hz) | 4.65 (d, $J$=2 Hz) | 1.40 (d, $J$=7 Hz) | 1.85 (s) | 3.10 (s) |

[a] Satisfactory microanalyses obtained: C ±0.18, H ±0.17, N ±0.19.

[b] Unstable oily compound.

*3,5-Diphenyl-2-methyl-4-isoxazoline* (**2a**) from the 2nd fraction; yield: 0.15 g (5%); m.p. 81 °C (from hexane).

| | | C | H | N |
|---|---|---|---|---|
| $C_{16}H_{15}ON$ | calc. | 81.01 | 6.33 | 5.90 |
| (237.3) | found | 81.03 | 6.31 | 5.66 |

**Conversion of 3a to 2a; Typical Procedure:**

A solution of **3a** (1 g) in ether (70 ml) is allowed to stand at 25 °C for two days and then evaporated. The residue is chromatographed on silica gel with dichloromethane and recrystallised from hexane to give **2a**; yield: 0.91 g (96%).

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