Synthesis of 3- and 4-Isoxazolines by Reduction of 4-Functionalized Isoxazolium Salts with Complex Metal Hydrides

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In previous papers[1,2] we have reported the synthesis of 4-isoxazolines and 2-isoxazolines by reduction of 3,5-disubstituted *N*-alkylisoxazolium salts, and 3,5-dialkylisoxazoles bearing electron-withdrawing groups at C—4, respectively, with lithium aluminium hydride and sodium borohydride.

Table 1. Reduction[a] of 4-Functionalized 3,5-Dimethylisoxazolium Salts **1** with Complex Metal Hydrides

Substrate No.	X	R	$A^{\ominus}$	Complex Metal Hydride	Solvent	Reaction Time [h]	Products and (Yields [%][b])
1a	NO_2	CH_3	$H_3CSO_3^{\ominus}$	$NaBH_4$	C_2H_5OH	5	**4a** (41)[c]
1b	NO_2	C_2H_5	$BF_4^{\ominus}$	$LiAl(OC_4H_9\text{-}t)_3H$	THF	5	**4b** (60)[c]
1c	CN	C_2H_5	$BF_4^{\ominus}$	$NaBH_4$	C_2H_5OH	5	**2c** (25) + **3c** (43)
				$LiAlH_4$	$(C_2H_5)_2O$	3	**3c** (3)
				$LiAl(OC_4H_9\text{-}t)_3H$	THF	5	**2c** (24) + **3c** (43)
1d	$COOC_2H_5$	C_2H_5	$BF_4^{\ominus}$	$NaBH_4$	C_2H_5OH	3	**2d** (40) + **3d** (30)
				$LiAlH_4$	$(C_2H_5)_2O$	2	**2d** (22) + **3d** (24)
				$LiAl(OC_4H_9\text{-}t)_3H$	THF	3	**2d** (23) + **3d** (23)
1e	CO—CH_3	CH_3	$H_3CSO_3^{\ominus}$	$NaBH_4$	C_2H_5OH	4	**2e** (30) + **3e** (45)
				$LiAlH_4$	$(C_2H_5)_2O$	4	**4e** (62)
1f	CO—C_6H_5	CH_3	$ClO_4^{\ominus}$	$NaBH_4$	C_2H_5OH	4	**2f** (23) + **3f** (20)
1f′	CO—C_6H_5	CH_3	$BF_4^{\ominus}$	$LiAlH_4$	$(C_2H_5)_2O$	4	**3f** (7) + **4f** (36)
1g	Cl	C_2H_5	$BF_4^{\ominus}$	$NaBH_4$	C_2H_5OH	2.5	**2g** (45) + **4g** (7)
				$LiAlH_4$	$(C_2H_5)_2O$	1.5	**2g** (23) + **4g** (3)
1h	Br	C_2H_5	$BF_4^{\ominus}$	$NaBH_4$	C_2H_5OH	2.5	**2h** (55)
				$LiAlH_4$	$(C_2H_5)_2O$	1.5	**2h** (26) + **4h** (2)

[a] Reaction at 0°C with a molar ration of **1**: hydride = 1:2.

[b] Yields refer to isolated pure 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] The reductions of **1a** and **1b** with $LiAlH_4$ lead to complex mixtures of products.

Table 2. 4-Functionalized *N*-Alkyl-4-isoxazolines **2**, *N*-Alkyl-3-isoxazolines **3**, and *N*-Alkylisoxazolidines **4**

Product	m.p. [°C] or b.p. [°C]/torr	Molecular Formula[a]	I.R. (Nujol or film) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$/TMS; 60 MHz) δ [ppm] J [Hz]				
				3-CH_3	5-CH_3	3-H	4-H	5-H
2c	oil[b]	$C_8H_{12}N_2O$ (152.2)	1660 (C=C)	1.25 (d, J = 6)	2.05 (s)	3.95 (q, J = 6)	–	–
2d	oil[b]	$C_{10}H_{17}NO_3$ (199.2)	1660 (C=C)	1.35 (d, J = 7)	2.15 (s)	4.10 (q, J = 7)	–	–
2e	oil[b]	$C_8H_{13}NO_2$ (155.2)	1630 (C=C)	1.20 (d, J = 7)	2.20 (s)	3.90 (q, J = 7)	–	–
2f	oil[b]	$C_{13}H_{15}NO_2$ (217.3)	1630 (C=C)	1.20 (d, J = 6)	1.65 (s)	4.10 (q, J = 6)	–	–
2g	oil[b]	$C_7H_{12}ClNO$ (161.6)	1700 (C=C)	1.25 (d, J = 6)	1.85 (s)	3.75 (q, J = 6)	–	
2h	oil[b]	$C_7H_{12}BrNO$ (206.1)	1690 (C=C)	1.25 (d, J = 6)	1.90 (s)	3.80 (q, J = 6)	–	–
3c	oil[b]	$C_8H_{12}N_2O$ (152.2)	1630 (C=C)	1.90 (s)	1.40 (d, J = 6)	–	–	4.90 (q, J = 6)
3d	oil[b]	$C_{10}H_{17}NO_3$ (199.2)	1620 (C=C)	1.95 (s)	1.20 (d, J = 6)	–	–	5.05 (q, J = 6)
3e	oil[b]	$C_8H_{13}NO_2$ (155.2)	1610 (C=C)	2.10 (s)	1.30 (d, J = 6)	–	–	5.25 (q, J = 6)
3f	206–210°/710	$C_{13}H_{15}NO_2$ (217.3)	1610 (C=C)	1.70 (s)	1.30 (d, J = 5)	–	–	5.30 (q, J = 5)
4a	oil[b]	$C_6H_{12}N_2O_3$ (160.2)	–	1.05 (d)	1.30 (d)	3.10 (m)	4.70 (m)	4.45 (m)
4b	oil[b]	$C_7H_{14}N_2O_3$ (174.2)	–	1.05 (d)	1.15 (d)	3.25 (m)	4.55 (m)	4.00 (m)
4e	215–220°/710	$C_8H_{15}NO_2$ (157.2)	–	1.15 (d)	1.25 (d)	2.90 (m)	–[c]	4.60 (m)
4f	oil[b]	$C_{13}H_{17}NO_2$ (219.3)	–	1.10 (d)	1.35 (d)	3.75 (m)	–[d]	4.65 (m)
4g	oil[b]	$C_7H_{14}ClNO$ (163.6)	–	1.20 (d)	1.30 (d)	3.20 (m)	4.55 (m)	4.40 (m)
4h	39–41°	$C_7H_{14}BrNO$ (208.1)	–	1.25 (d)	1.30 (d)	3.15 (m)	4.70 (m)	4.45 (m)

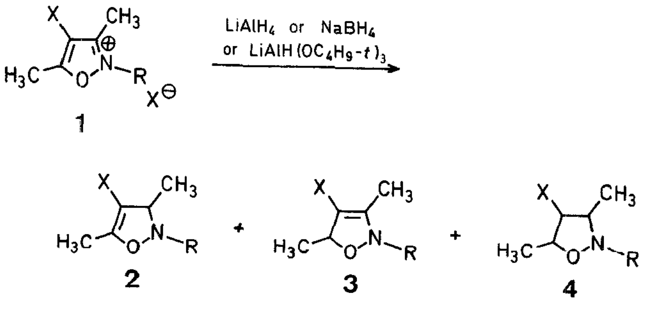
[a] Satisfactory microanalyses obtained: C, ±0.18; H, ±0.17; N, ±0.19.

[b] Unstable oily compound.

[c] =CH—CH_3; δ = 1.65 (m); 5.20 ppm (m).

[d] =CH—C_6H_5; δ = 6.10 (m); 7.10 ppm (s).

We have now found that 2,3,5-trialkylisoxazolium salts (**1**) with electron-withdrawing substituents at C—4 can also be reduced by the same hydrides and by lithium tri-*t*-butoxyaluminium hydride to give 4-functionalized 4- (**2**) and 3-isoxazolines (**3**). Some of these processes also afforded isoxazolidine derivatives **4**. The results obtained in all these reactions are summarised in the Table 1.



4-Cyano-*N*-ethyl-3,5-dimethyl-4-isoxazoline (2c) and 4-Cyano-*N*-ethyl-3,5-dimethyl-3-isoxazoline (3c); Typical Procedure:

4-Cyano-*N*-ethyl-3,5-dimethylisoxazolium tetrafluoroborate[3] (**1c**; 9.5 g, 40 mmol) dissolved in ethanol (50 ml) is added to a suspension of sodium borohydride (3.0 g, 80 mmol) in ethanol (25 ml). The mixture is stirred at 0 °C for 5 h, acidified with a saturated solution of ammonium chloride (50 ml), and then extracted with diethyl ether (3 × 25 ml). The organic layer is dried with magnesium sulfate. Evaporation of the solvents leaves an oil which is chromatographed on silica gel with dichloromethane as eluent. The following compounds are obtained:

4-Cyano-*N*-ethyl-3,5-dimethyl-3-isoxazoline (**3c**) from the 1st fraction; yield: 2.6 g (43 %); oil.

$C_8H_{12}N_2O$	calc.	C 63.13	H 7.95	N 18.41
(152.2)	found	63.23	7.92	18.35

4-Cyano-*N*-ethyl-3,5-dimethyl-4-isoxazoline (**2c**) from the 2nd fraction; yield: 1.52 g (25 %); oil.

$C_8H_{12}N_2O$	calc.	C 63.13	H 7.95	N 18.41
(152.2)	found	63.02	7.91	18.52

The reductions with lithium tri-*t*-butoxyaluminium hydride are carried out in an analogous fashion, but under nitrogen and with tetrahydrofuran as solvent.

4-Bromo-*N*-ethyl-3,5-dimethyl-2-isoxazoline (2h) and 4-Bromo-*N*-ethyl-3,5-dimethylisoxazolidine (4h); Typical Procedure:

4-Bromo-*N*-ethyl-3,5-dimethylisoxazolium tetrafluoroborate[3] (**1h**; 8.2 g, 28 mmol) in diethyl ether (50 ml) is added to a suspension of lithium aluminium hydride (2.12 g, 56 mmol) in the same solvent (25 ml). The mixture is stirred at 0 °C for 1.5 h and hydrolysed with a saturated solution of ammonium chloride (40 ml). The organic layer is separated and dried with magnesium sulfate. Evaporation of the solvent leaves an oil, which is chromatographed on silica gel with dichloromethane as eluent. The following products are obtained:

4-Bromo-*N*-ethyl-3,5-dimethyl-4-isoxazoline (**2h**) from the 1st fraction; yield: 1.5 g (26 %); oil.

$C_7H_{12}BrNO$	calc.	C 40.80	H 5.87	N 6.80
(206.1)	found	40.92	5.84	6.83

4-Bromo-*N*-ethyl-3,5-dimethylisoxazolidine (**4h**) from the 2nd fraction; yield: 0.11 g (2 %); m.p. 39–41 °C (from *n*-hexane).

$C_7H_{14}BrNO$	calc.	C 40.40	H 6.78	N 6.73
(208.1)	found	40.31	6.72	6.86

Received: December 19, 1983

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[1] A. Alberola, A.M. González, M.A. Laguna, F.J. Pulido, *Synthesis* **1982**, 1067.

[2] A. Alberola, A.M. González, M.A. Laguna, F.J. Pulido, *Synthesis* **1983**, 413.

[3] Isoxazolium salts were prepared by conventional procedures: R.B. Woodward, R.A. Olofson, *Tetrahedron Suppl.* **7**, 415 (1966).