Chemistry of Amine–Boranes. Part 5.[1] Reduction of Oximes, *O*-Acyl-oximes, and *O*-Alkyl-oximes with Pyridine–Borane in Acid

By **Masami Kawase** and **Yasuo Kikugawa,*** Faculty of Pharmaceutical Sciences, Josai University, 1–1 Keyaki-dai, Sakadoshi, Saitama 350–02, Japan

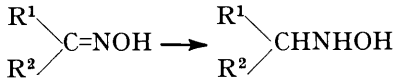
Oximes, *O*-acyl-oximes, and *O*-alkyl-oximes were reduced with pyridine–borane in the presence of acid to the corresponding hydroxylamine derivatives without over-reduction. Unstable *O*-acyl-hydroxylamines were directly synthesized for the first time from the corresponding *O*-acyl-oximes.

We have previously reported [2] that treatment of oximes with pyridine–borane afforded the corresponding *N*-monosubstituted hydroxylamines and that other functional groups present in the oxime molecule were not reduced under these conditions; alternative methods of preparing *N*-monosubstituted hydroxylamines have been reported.[3,4a,b]

We now report the experimental procedure for these reductions, and the reduction of *O*-acyl- and *O*-alkyl-oximes. *O*-Acyl-oximes are more readily reducible than oximes, and diborane reduced [5a,b] them with ease to the corresponding amines without producing *O*-acyl-hydroxylamines, even with conditions under which oximes were reduced to the corresponding hydroxylamines. For this reason, *O*-acyl-hydroxylamines have usually been synthesized through several steps; *e.g.* acylation of *N*-protected hydroxylamines followed by removal of the protecting group.[6]

However, reduction of *O*-acyl-oximes with pyridine–borane provides an attractive one-step synthesis of *O*-acyl-hydroxylamines, and *O*-alkyl-oximes were also reduced to the corresponding *O*-substituted hydroxylamines without over-reduction. As pyridine–borane does not reduce the resulting hydroxylamines, *O*-acyl-hydroxylamines, or *O*-alkyl-hydroxylamines further, this procedure offers a convenient method for the preparation of hydroxylamine derivatives from readily available oxime derivatives.

Reduction of Oximes to Hydroxylamines.—As shown in Table 1, reduction of the aldoximes and ketoximes (1) gave good yields of the corresponding *N*-monosubstituted hydroxylamines (2). Acidic conditions are



(1) (2)

essential for reduction of oximes with pyridine–borane, and reduction was not observed without the presence of an acid. Benzaldoximes carrying an electron-releasing group on the benzene ring were reduced to hydroxylamines, while benzophenone oxime and fluorenone oxime were not reduced at all under the same conditions. Although the exact reason why these oximes cannot be reduced with pyridine–borane is obscure, a similar resistance to reduction was observed with diborane, and these oximes were recovered quantitatively even after prolonged reaction and at a high temperature.[3] However, the corresponding hydroxylamines (4h) and (4i) could be obtained in good yields from the reduction of the *O*-acyl-oximes (3h) and (3i) with pyridine–borane (Table 2).

TABLE 1

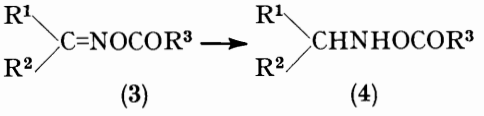
Pyridine–borane reduction of oximes

					Analyses					
					Required (%)			Found (%)		
(2)	R^1	R^2	M.p. (°C)	Yield of (2) (%)	C	H	N	C	H	N
a	Ph	H	57—58.5 [a]	87						
b	Ph	Pr^n	66—67	91	72.7	9.15	8.5	72.7	9.1	8.5
c	$PhCH_2CH_2$	Me	74—75	92	72.7	9.15	8.5	72.5	8.9	8.4
d	Pr^n	Pr^n	112—114 [b]	91						
e	*m*-$NO_2C_6H_4$	H	81—83	91	50.0	4.8	16.7	49.6	4.8	16.4
f	*p*-$MeO_2CC_6H_4$	H	80.5—82	74	59.7	6.1	7.7	59.8	6.0	7.7
g	*p*-NCC_6H_4	H	127—128.5 [c]	85	64.85	5.4	18.9	64.9	5.5	18.8
h	*p*-ClC_6H_4	H	87—88.5	92	53.35	5.1	8.9	53.2	5.1	9.0
i	*p*-$Me_2NOCC_6H_4$	H	168—170 [d]	88	45.4	4.05	16.5	45.2	4.05	16.5
j	Ph	Me	71—72 [e]	87						
k	$Me[CH_2]_6$	H	76—77 [f]	89	66.15	13.2	9.6	66.35	12.9	9.6
l	PhC(OH)H	Ph	129—130.5	89	73.3	6.6	6.1	73.1	6.5	6.1
m	α-Tetralone oxime		137—137.5	93	73.6	8.0	8.6	73.8	7.8	8.7

[a] Lit. m.p. 57° (R. Behrend and K. Leuchs, *Annalen*, 1890, **257**, 214.). [b] As the oxalate (free hydroxylamine, m.p. 49—52°), lit. m.p. 115° (G. Vavon and M. Krajcinovic, *Bull. Soc. chim. France*, 1928, **43**, 231). [c] Reduction in 20% HCl–EtOH. [d] As the picrate. [e] Lit.[4a] m.p. 69—70°. [f] Lit.[3] m.p. 73.5°.

Reduction of O-Acyl-oximes to O-Acyl-hydroxylamines.—While the reduction of *O*-acyl-oximes with diborane was reported [5a] to afford amines in high yields, there are no reports concerning the direct synthesis of *O*-acyl-hydroxylamines from *O*-acyl-oximes. As shown in Table 2, various *O*-acyl-oximes (3) were reduced to

the corresponding *O*-acyl-hydroxylamines (4) with pyridine–borane in good yields; in the case of (3a) and (3f), a small amount of the hydroxylamines (2a) and (2k), respectively, products of hydrolysis of (4a) and (4f), were obtained as by-products. The reduction of (3d) is relatively slow and (3d) was not consumed completely before the pyridine–borane decomposed. Methylene chloride–glacial acetic acid was used as solvent to prevent rapid decomposition of pyridine–borane, and (4d) was obtained in 74% yield. In the reduction of (3h) and (3i), 20% ethanolic hydrogen chloride was used as solvent because of their low solubility in ethanol–10% aqueous hydrochloric acid, and the products, (4h) and (4i), which are difficult to prepare by other methods, were obtained as the hydrolysed form in good yields. *O*-Acyl-hydroxylamines derived from *O*-acyl-aldoximes were less stable than those derived from ketoximes, and n.m.r. measurements indicated that *O*-acetylbenzylhydroxylamine (4a) rearranged partially to *N*-benzylacetohydroxamic acid (25%) after 3 days in deuteriochloroform. The lability of *O*-acyl-hydroxylamines



and their spontaneous O ⟶ N acyl migration have been described,[7] and careful work-up and rapid after-treatment are accordingly necessary to obtain an optimum yield of *O*-acyl-hydroxylamines. In our case, rapid chromatographic purification on Florisil (not silica gel) was carried out to avoid decomposition. On the other hand, *O*-acyl-hydroxylamines derived from ketoximes were stable to rearrangement and no O ⟶ N acyl migration was observed in any of the examples in Table 2.

TABLE 2

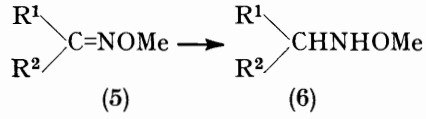
Pyridine–borane reduction of *O*-acyl-oximes

(3)	R¹	R²	R³	Yield of (4) (%) [a]
a	Ph	H	Me	69 [a]
b	–[CH₂]₅–		Me	74
c	Prⁿ	Prⁿ	Me	73
d	Ph	Prⁿ	Me	74 [b]
e	$PhCH_2CH_2$	Me	Me	82
f	$Me[CH_2]_6$	H	Me	76 [c]
g	–[CH₂]₅–		Ph	87 [d]
h	Ph	Ph	Me	95 [f,g]
i	Fluorenone *O*-acetyloxime			77 [f,h]

[a] For identification of (4a—g), see Experimental section. [b] (2a) was also obtained in 13% yield as a by-product. [c] CH_2Cl_2–AcOH was used as solvent. [d] (2k) was also obtained in 10% yield as a by-product. [e] As hydrochloride, m.p. 156—159°; lit. m.p. 156—158° (G. Zinner, *Arch. Pharm.*, 1963, **296**, 57). [f] Isolated as hydroxylamine. [g] Lit. m.p. 76° (W. Kliegel, G. Zinner, and R. Vollrath, *Annalen*, 1970, **736**, 173) (Found: C, 78.4; H, 6.6; N, 7.0. Calc. for $C_{13}H_{13}NO$: C, 78.4; H, 6.6; N, 7.0%). [h] (Found: C, 78.95; H, 5.7; N, 6.8. Calc. for $C_{13}H_{11}NO$: C, 79.2; H, 5.6; N, 7.1%).

The structures of the *O*-acyl-hydroxylamines were assigned from their i.r. and n.m.r. spectra as described in the literature.[7]

Reduction of O-Methyl-Oximes to O-*Methyl-hydroxylamines.*—Sodium cyanoborohydride reduces *O*-alkylbenzaldoximes to the corresponding *O*-alkyl-benzylhydroxylamines in poor to moderate yields under certain conditions (pH = 3) [8] and diborane reduces *O*-alkyl-oximes to the corresponding amines at room temperature.[5a] In our case, reactions were carried out only with the *O*-methyl-oximes (5), because they were



easily prepared by treatment of aldehydes and ketones with methoxyamine hydrochloride, and *O*-methylhydroxylamines (6) were obtained in good yields as shown in Table 3.

TABLE 3

Pyridine–borane reduction of *O*-methyl-oximes

					Analyses					
					Required (%)			Found (%)		
(5)	R¹	R²	M.p.[a]/°C	Yield of (6) (%)	C	H	N	C	H	N
a	$PhCH_2CH_2$	Me	91—93	83	61.25	8.41	6.49	61.25	8.41	6.49
b	*p*-ClC_6H_4	H	157—158 [b]	92						
c	Ph	Ph	175—176	98	67.33	6.46	5.61	67.13	6.35	5.56

[a] Hydrochloride. [b] Lit.[8] m.p. 160°.

EXPERIMENTAL

All m.p.s are uncorrected. I.r. spectra were obtained with a Shimadzu IR-400 spectrophotometer, and n.m.r. spectra (tetramethylsilane as internal standard) with a JNM-C-60HL spectrometer.

Reagents.—The oximes (1a—h, j, k, and m) were prepared in good yield from the corresponding carbonyl compounds with hydroxylamine hydrochloride in 50% ethanol–pyridine at room temperature. Compound (1i) was synthesized from 4-formylbenzoic acid in the usual way. Compound (1l) and cyclohexanone oxime were purchased from Wako Chemical Industries Ltd., Tokyo. The *O*-acetyl-oximes (3a—f, h, and i) were prepared in good yield from the corresponding oximes by the addition of acetic anhydride in diethyl ether under reflux. The *O*-benzoyloxime (3g) was synthesized from benzoyl chloride–pyridine. The *O*-methyl-oximes (5a—c) were prepared in good yield from the corresponding carbonyl compounds with methoxyamine hydrochloride in absolute ethanol–pyridine under reflux.

Physical Data of Starting Compounds.—(1a), b.p. 94° at 5 mmHg; (1c), m.p. 80—84° (from 50% aq. EtOH); (1d), b.p. 111° at 34 mmHg; (1e), m.p. 120.5—122° (50% aq. EtOH); (1f) m.p. 120—121° (benzene); (1g), m.p. 143—145° (EtOH); (1h), m.p. 110—111° (benzene); (1i), m.p.

171—172° (EtOH); (1j), m.p. 60—62° (hexane); (1k), b.p. 108° at 11 mmHg; (1l), m.p. 153—155°; (1m), m.p. 102—103° (hexane); (1n) (benzophenone oxime), m.p. 143—144°; (1o) (fluorenone oxime), m.p. 191—194° (EtOH). (3a), b.p. 123° at 4 mmHg; (3b), b.p. 86—87° at 3 mmHg; (3c), 83—84.5° at 5 mmHg; (3d), b.p. 144—148° at 6 mmHg; (3e), b.p. 148—153° at 6 mmHg; (3f), b.p. 112—113° at 5 mmHg; (3h), m.p. 73° (hexane); (3i), m.p. 76—78° (hexane). (5a), b.p. 88° at 5 mmHg; (5b), m.p. 28—30°; (5c), m.p. 62—63° (hexane). Compounds (1b) and (3g) were purified by silica gel (Merck, Art. 7734) column chromatography using benzene–acetone (6 : 1) as eluant and employed without further purification.

General Procedure for Reduction of Oximes.—A mixture of the oxime (3 mmol) and pyridine–borane (10 mmol) in ethanol (5 ml) was kept below 5°. To this solution, 10% aqueous hydrochloric acid (10 ml) was added dropwise and the mixture was stirred for 10 min at room temperature. The solution was made alkaline with sodium carbonate with cooling, and extracted with benzene or chloroform (25 ml × 3). The combined extracts were dried (anhyd. Na_2SO_4). After evaporation (2a—e, i, k, and l) were purified by column chromatography over Polyamide C-200 (Wako Chemical Industries Ltd., Tokyo) using benzene as eluant and (2f—h, j, and m) were purified by washing with hexane. Compounds (2) were all recrystallized from suitable solvents: (2a—c, h, j, and k) (hexane); (2d) (oxalate) and (2e—g, l, and m) (benzene); (2i) (picrate) (EtOH). For the reduction of (1g), 20% ethanolic hydrogen chloride was used instead of 10% aqueous hydrochloric acid.

Reduction of O-Acyl-oximes.—Reduction of (3a—c *and* e—g). The procedure was the same as just described, with purification by column chromatography over Florisil (Wako Chemical Industries Ltd., Tokyo) using benzene–acetone (6 : 1) as eluant.

Reduction of (3h *and* i). The procedure was the same as just above except that 20% ethanolic hydrogen chloride was used as solvent instead of 10% aqueous hydrochloric acid.

Reduction of (3d). To a mixture of (3d) (3 mmol) and pyridine–borane (10 mmol) in dichloromethane (5 ml), glacial acetic acid (3 ml) was added and the mixture was heated under reflux for 5 h. The solvent was evaporated off *in vacuo* and 10% aqueous hydrochloric acid (10 ml) was added to decompose the excess of pyridine–borane. The solution was made alkaline with sodium carbonate with cooling and extracted with benzene. Purification of the product as just described gave (4d) (74%).

Identification of (4a—g).—A mixture of the *O*-acylhydroxylamine (4a—f) (200 mg), which showed i.r. and n.m.r. spectra consistent with this assignment and 10% aqueous hydrochloric acid (5 ml) was refluxed for 1 h. The solution was made alkaline with 20% aqueous sodium hydroxide with cooling and extracted with benzene. The benzene extract was dried (anhyd. Na_2SO_4) and evaporated and the residue was recrystallized from hexane and identified by mixed m.p. measurements with an authentic sample. The identity of (4g) was also established by spectroscopic comparison with an authentic sample.

TABLE 4

Spectral data of the *O*-acyl-hydroxylamines (4a—g)

(4)	ν_{max} (film)/cm^{-1} CO	NH	^{1}H N.m.r. (δ) in $CDCl_3$
a [a]	1 740	3 245	2.02 (3 H, s, Me), 4.15 (2 H, s, CH_2), 7.41 (5 H, s, ArH)
b	1 735	3 220	0.83—2.20 (10 H, br.m, CH_2 × 5), 2.13 (3 H, s, Me), 2.63—3.23 (1 H, br.m, CH), 7.30—7.66 (1 H, br, NH)
c	1 740	3 250	0.70—1.87 (14 H, br, Pr^n × 2), 2.13 (3 H, s, Me), 2.66—3.20 (1 H, br.m, CH), 6.17—7.73 (1 H, br, NH)
d	1 740	3 220	0.77—2.00 (7 H, br, Pr^n), 1.97 (3 H, s, Me), 3.85—4.22 (1 H, m, CH), 7.40 (5 H, s, ArH), 7.70—7.90 (1 H, d, NH)
e	1 735	3 230	1.15 (3 H, d, CHMe), 1.53—1.97 (2 H, m, CH_2), 2.10 (3 H, s, Me), 2.73 (2 H, t, $PhCH_2CH_2$), 3.12 (1 H, m, C*H*Me)
f	1 740	3 245	0.73—1.11 (3 H, br.t, Me), 1.11—1.97 (14 H, br.m, CH_2 × 7), 2.13 (3 H, s, Me), 2.83—3.26 (2 H, br.t, CH_2NH)
g	1 720	3 230	1.00—2.23 (10 H, br.m, CH_2 × 5), 2.80—3.37 (1 H, br.m, CH), 7.13—7.60 (3 H, m, ArH), 7.83—8.17 (2 H, m, ArH)

[a] Physical data of *N*-benzylacetohydroxamic acid, the O→N acyl migration product of (4a), are as follows: m.p. 125.5° (lit., 127°, P. Grammaticakis, *Compt. rend.*, 1947, **224**, 1066), ν_{max} (Nujol) 1 600 (NCO) and 3 100 cm^{-1} (OH), δ[$(CD_3)_2SO$] 2.08 (3 H, s, Me), 4.74 (2 H, s, CH_2), 7.40 (5 H, s, ArH), and 9.92 (1 H, s, OH).

General Procedure for Reduction of O-Methyl-oximes.—10% aqueous hydrochloric acid was used as solvent for the reduction of (5a), and 20% ethanolic hydrogen chloride for (5b) and c); the procedure was the same as already described. Compounds (6) were all converted into their hydrochlorides and recrystallized from suitable solvents: (6a)-HCl (Et_2O–CH_2Cl_3), (6b)- and (6c)-HCl (Pr^iOH).

We thank Professor Shun-ichi Yamada of this University for encouragement.

[8/238 *Received*, 13*th February*, 1978]

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