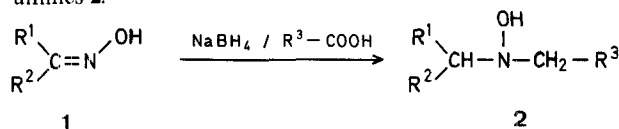


Reactions of Sodium Borohydride in Acidic Media; V. Reduction and Alkylation of Oximes with Carboxylic Acids; A New Synthesis of *N,N*-Dialkylhydroxylamines¹

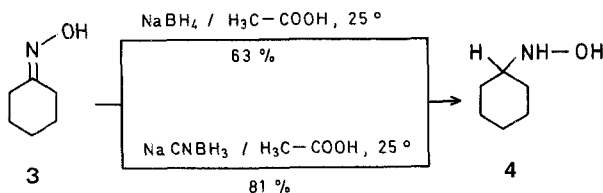
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We wish to report that the action of sodium borohydride on oximes **1** in carboxylic acids leads to *N,N*-dialkylhydroxylamines **2**.



Our earlier work on the reduction of indoles, quinolines, and isoquinolines² and the alkylation of amines^{2,3} and Borch's observation that oximes can be reduced to *N*-alkylhydroxylamines with sodium cyanoborohydride in acidic methanol⁴ suggested to us that sodium borohydride in carboxylic acids would accomplish the reduction/alkylation of oximes **1**, leading to a new and potentially versatile synthesis of *N,N*-dialkylhydroxylamines **2**. We have examined several oximes and carboxylic acids under three different reaction conditions (Methods A–C) and find that the reaction is quite general, although the yields of **2** range from 36–87%. No particular advantage accrues from using one reaction method over another, as each of the three methods is capable of giving good yields of **2**. Of the oximes studied only benzophenone oxime and dibenzyl ketoxime fail to react under these conditions. Most of our work has involved ketoximes but aldoximes appear to react equally well, except for the difficulty noted later.

The reaction presumably involves initial reduction of **1** to the *N*-alkylhydroxylamine followed by alkylation. Indeed, we find that cyclohexanone oxime (**3**) is smoothly reduced to *N*-cyclohexylhydroxylamine (**4**) with sodium borohydride/acetic acid under mild conditions or in higher yield with sodium cyanoborohydride/acetic acid. We have previously shown that these latter conditions do not give significant *N*-alkylation². By comparison, Borch reports a 66% yield of **4** from the reaction of **3**⁴.



The variable yields may in part be due to the relative instability⁵ and/or water solubility of some of the *N,N*-dialkylhydroxylamines **2**. In some cases we have observed by mass spectrometry or have isolated products corresponding to overreduction⁶ and subsequent alkylation, and products resulting from condensation of the initially formed monoalkylhydroxylamine with oxime, followed by reduction to the symmetrical dialkylhydroxylamine. This latter pathway was observed by Borch during his reduction of aldoximes⁴. For example, in the reaction of butanal oxime with sodium borohydride/acetic acid we see in addition to **20** an ion in the mass spectrum of the crude product corresponding to *N,N*-di-*n*-butylhydroxylamine. In one case using Method C this

product was isolated. Similarly, benzaldoxime gives some *N,N*-dibenzylhydroxylamine in addition to **2r**. 2,2-Dimethylpropanoic acid/sodium borohydride gives very poor yields of dialkylhydroxylamines from oximes (not in Table) and in the reaction with benzaldoxime we observe by mass spectrometry *N,N*-dineopentylbenzylamine and *N*-neopentylidibenzylamine, products of overreduction and subsequent alkylation. These side products are often difficult to remove and may be responsible for the impure oxalates that are obtained in some cases, especially with the aldoximes. Further work is necessary to ameliorate the generality of the reaction of oximes with sodium borohydride/carboxylic acids.

In spite of these drawbacks and the limitations inherent in the method, it is excellent for preparing unsymmetrical *N,N*-dialkylhydroxylamines of type **2** from ketoximes, which of course are readily available from ketones, and offers an attractive alternative to the existing general methods⁷: alkylation of *N*-alkylhydroxylamines, oxidation of secondary amines, pyrolysis of tertiary amine oxides, and reduction of nitrones.

Preparation of *N*-Isopropyl-*N*-propylhydroxylamine (**2b**); Method A/Workup A:

To a stirred solution of acetone oxime (0.73 g, 10 mmol) in propanoic acid (20 g) at 50° under nitrogen are added sodium borohydride pellets (Ventron) (2.3 g, 61 mmol) over 5 h. The mixture is heated at 50° for 5 h, allowed to cool, and made basic with 50% aqueous sodium hydroxide. The mixture is extracted with ether. The ether extract is extracted with 1 normal hydrochloric acid. The acid extract is made basic with aqueous sodium hydroxide and extracted with ether. The ether extract is dried with anhydrous potassium carbonate and concentrated in vacuo. The resulting yellow oil (0.81 g) is distilled in vacuo to give *N*-isopropyl-*N*-propylhydroxylamine (**2b**) as a colorless oil; yield: 0.79 g (68%); b.p. 55–56°/10 torr.

I.R. (liquid film): ν_{\max} = 3280; 2995; 1465; 1380; 1360 cm^{-1} .

¹H-N.M.R. (CDCl_3): δ = 1.00 (t, 3H); 1.06 (d, 6H); 1.55 (m, 2H); 2.64 (t, 2H); 2.97 (m, 1H); 7.70 ppm (s, 1H).

The oxalate derivative of **2b** is prepared by adding a solution of **2b** (0.156 g, 1.3 mmol) in ether (5 ml) dropwise to a solution of dry oxalic acid (0.16 g, 1.8 mmol) in ether (10 ml). The resulting precipitate (0.14 g, 52% yield) is recrystallized seven times from absolute ethanol; m.p. 124–124.5°.

$\text{C}_8\text{H}_{17}\text{NO}_5$ calc. C 46.37 H 8.27 N 6.76
(207.2) found 46.39 8.36 6.65

Preparation of *N*-Cyclohexyl-*N*-ethylhydroxylamine (**2i**); Method B/Workup B:

To stirred acetic acid (40 ml) at 30° under nitrogen are added sodium borohydride pellets (1.0 g, 26 mmol). Upon dissolution, cyclohexanone oxime (3.39 g, 30.0 mmol) and additional sodium borohydride pellets (1.0 g) are added simultaneously. The mixture is heated to 40° and additional sodium borohydride pellets (1.0 g) are added (total: 3.0 g, 79 mmol). Heating at 40° is continued for 5 h. The mixture is allowed to cool, made basic with 50% aqueous sodium hydroxide, and extracted with ether. The ether extract is dried, concentrated in vacuo, and distilled to give *N*-cyclohexyl-*N*-ethylhydroxylamine (**2i**) as a colorless oil; yield: 2.19 g (51%); b.p. 65–67°/0.35 torr.

I.R. (liquid film): ν_{\max} = 3280; 2965; 2900; 1455; 1080 cm^{-1} .

¹H-N.M.R. (CDCl_3): δ = 1.15 (t, 3H); 1.6 (m, 10H); 2.6 (m, 1H); 2.75 (q, 2H); 7.47 ppm (s, 1H).

The oxalate is prepared in 68% yield as above and has m.p. 155–156° after five recrystallizations from ethanol.

$\text{C}_{18}\text{H}_{36}\text{N}_2\text{O}_6$ calc. C 57.42 H 9.64 N 7.44
(376.5) found 57.14 9.86 7.16

Preparation of *N*-Benzyl-*N*-*n*-butylhydroxylamine (**2r**); Method C/Workup C:

To a stirred paste of benzaldoxime (1.21 g, 10.0 mmol) and sodium borohydride powder (2.0 g, 53 mmol) at 0° under nitrogen is added butanoic acid (25 ml) dropwise over 2 h. The mixture is then heated at 40° for 4 h, an additional amount of sodium borohydride (0.37 g, 10 mmol) is added and the mixture is heated for 1 h more. Workup as in Workup B gives a yellow oil which is dissolved in ether (2 ml) and added to a solution of oxalic acid (1.50 g, 16.7 mmol) in ether (5 ml) to give the crude oxalate; yield: 1.86 g (69%). The oxalate is dissolved in water, made basic with aqueous sodium hydroxide, and extracted with ether. After the usual workup, the resulting oil is distilled to give *N*-benzyl-*N*-*n*-butylhydroxylamine (**2r**) as a colorless oil; yield: 1.04 g (58%); b.p. 84–85°/0.15 torr.

I.R. (liquid film): ν_{\max} = 3280; 3060; 2985; 2900; 1495; 1450 cm^{-1} .

¹H-N.M.R. (CDCl_3): δ = 0.95 (m, 3H, virtual coupling); 1.4 (m, 4H); 2.60 (t, 2H); 3.63 (s, 2H); 7.22 (s, 5H); 7.80 ppm (s, 1H).

M.S.: m/e = 179.1316 (calc. 179.1310).

Preparation of *N*-Cyclohexylhydroxylamine (**4**) using Sodium Cyanoborohydride/Acetic Acid:

To stirred acetic acid (25 ml) at 25° under nitrogen are added cyclohexanone oxime (**3**; 1.16 g, 10.3 mmol) and sodium cyanoboro-

Table. Reaction of Oximes **1** with Sodium Borohydride in Carboxylic Acids

Product No.	R ¹	R ²	R ³	Method ^a / Workup ^b	Reaction conditions Temp./Time	Yield ^c of 2 [%]	b.p./torr or m.p.	m.p. of Oxalate ^d	Molecular Formula ^e
2a	CH ₃	CH ₃	CH ₃	A/A	50°/24 h	36	45–48°/10	101–102°	C ₇ H ₁₅ NO ₅ (193.2)
2a	CH ₃	CH ₃	CH ₃	B/A	40°/4 h	38			
2b	CH ₃	CH ₃	C ₂ H ₅	A/A	50°/20 h	68	55–56°/10	124–124.5°	C ₈ H ₁₇ NO ₅ (207.2)
2c	CH ₃	CH ₃	<i>i</i> -C ₃ H ₇	A/A	50°/20 h	52	55–61°/10	142–143°	C ₉ H ₁₉ NO ₅ (221.3)
2d	CH ₃	C ₂ H ₅	CH ₃	A/B	45°/20 h	63	65–67°/17	92–93°	C ₈ H ₁₇ NO ₅ (207.2)
2e	CH ₃	C ₂ H ₅	C ₂ H ₅	C/C	40°/5 h	61	66–69°/10	97–98°	C ₇ H ₁₇ NO ^f (131.2)
2f	CH ₃	<i>t</i> -C ₄ H ₉	CH ₃	A/B	50°/6 h	75	70–71°/17	115.5–116°	C ₁₀ H ₂₁ NO ₅ (235.3)
2g	CH ₃	<i>t</i> -C ₄ H ₉	C ₂ H ₅	A/A	50°/30 h	53	68–71°/10	147–147.5°	C ₁₁ H ₂₃ NO ₅ (249.3)
2h	CH ₃	<i>t</i> -C ₄ H ₉	<i>i</i> -C ₃ H ₇	A/A	50°/30 h	47	68–73°/10		C ₁₀ H ₂₃ NO ^g (173.3)

Table. (Continued)

Product No.	R ¹	R ²	R ³	Method ^a / Workup ^b	Reaction conditions Temp./Time	Yield ^c of 2 [%]	b.p./torr or m.p.	m.p. of Oxalate ^d	Molecular Formula ^e
2i	—(CH ₂) ₅ —	—	CH ₃	B/B	40°/5 h	51	65–67°/0.35	155–156°	C ₁₈ H ₃₆ N ₂ O ₆ (376.5)
2i	—(CH ₂) ₅ —	—	CH ₃	A/A	55°/72 h	58			
2j	—(CH ₂) ₅ —	—	C ₂ H ₅	A/A	55°/20 h	87	68–70°/0.25	136–137°	C ₁₁ H ₂₁ NO ₅ (247.3)
2k	CH ₃	C ₆ H ₅	CH ₃	A/C	55°/31 h	41	68–69°/0.2	136–137°	C ₂₂ H ₃₂ N ₂ O ₆ (420.5)
2l	CH ₃	CH ₂ C ₆ H ₅	CH ₃	A/B	55°/20 h	68 ^b	97–105°/0.35	172–173° (Lit. ⁸ 161–162°)	C ₂₄ H ₃₆ N ₂ O ₆ (448.6)
2m	CH ₃	CH ₂ C ₆ H ₅	C ₂ H ₅	C/C	40°/4 h	47 ^b	107–110°/0.3	142–143° (Lit. ⁹ 142–143°)	C ₁₄ H ₂₁ NO ₅ (283.3)
2n	CH ₃	CH ₂ C ₆ H ₅	<i>n</i> -C ₃ H ₇	C/B	40°/4 h	70 ^b	109–116°/0.2	165–166° (Lit. ⁸ 157–159°)	C ₁₅ H ₂₃ NO ₅ (297.4)
2o	H	<i>n</i> -C ₃ H ₇	CH ₃	A/B	5°, 45°/4 h	55	64–68°/11	98–99°	C ₆ H ₁₅ NO ⁱ (117.1)
2p	H	C ₆ H ₅	CH ₃	B/B	40°/5 h	56	75–77°/0.35 (Lit. ¹⁰ 88°/1.1)	111–112°	C ₉ H ₁₃ NO ^j (151.2)
2q	H	C ₆ H ₅	C ₂ H ₅	A/B	25°/72 h	72	77–78°/0.2	120–120.5°	C ₁₂ H ₁₇ NO ₅ (255.3)
2r	H	C ₆ H ₅	<i>n</i> -C ₃ H ₇	C/C	40°/5 h	58	84–85°/0.15	119–121°	C ₁₁ H ₁₇ NO ^k (179.3)
2s	H	C ₆ H ₅	<i>i</i> -C ₃ H ₇	C/B	40°/4 h	65	60–61°	140.5°	C ₁₃ H ₁₉ NO ₅ (269.3)

^a Method A: Sodium borohydride pellets are added to a solution of oxime in the neat carboxylic acid at the specified temperature and the mixture is heated.

Method B: The oxime is added to a mixture of sodium borohydride pellets in the neat carboxylic acid and the mixture is heated.

Method C: A mixture of the oxime and powdered sodium borohydride at 0° is treated with the carboxylic acid and the mixture is heated.

^b Workup A: The reaction mixture is made basic and extracted with ether. The ether extracts are extracted with dilute hydrochloric acid. The acid extracts are basified and extracted with ether. Drying, concentration, and distillation afford the product.

Workup B: The reaction mixture is made basic and extracted with ether. Drying, concentration, and distillation afford the product.

Workup C: As in workup B except that the crude product is treated with oxalic acid in ether. The crude oxalate is dissolved in water, made basic, and extracted with ether. The product is isolated as in the above workup methods.

^c Yields represent distilled or, in one case (**2s**), recrystallized product. Products exhibited satisfactory I.R. and ¹H-N.M.R. spectra. The reactions have not been optimized.

^d Oxalates were recrystallized several times from ethanol, ethanol/ether, or dichloromethane.

^e Unless otherwise noted all oxalates gave satisfactory microanalyses: C ± 0.28%, H ± 0.25%, N ± 0.28%.

^f The oxalate, recrystallized six times, did not analyze correctly. M.S.: *m/e* = 130.1241 (M⁺ – 1, calc. 130.1232).

^g A crystalline oxalate was not obtained. M.S.: *m/e* = 172.1689 (M⁺ – 1, calc. 172.1701).

^h Some oxime is present in the product.

ⁱ The oxalate, recrystallized five times, analyzed slightly outside acceptable limits. M.S.: *m/e* = 116.1077 (M⁺ – 1, calc. 116.1075).

^j The oxalate analyzed as a 1:1 mixture of C₁₁H₁₅NO₅ and C₂₀H₂₈N₂O₆. M.S.: *m/e* = 151.0977 (M⁺, calc. 151.0997).

^k The oxalate, recrystallized four times, did not analyze correctly. M.S.: *m/e* = 179.1316 (M⁺, calc. 179.1310).

hydroxide (pellets). The resulting white solid is collected, washed, and dried to afford *N,N*-di-*n*-butylhydroxylamine as off-white flakes; yield 0.31 g (21%); m.p. 48.5–50.5°; Lit.¹¹ 52–53°.

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hydride (0.93 g, 15 mmol). The mixture is stirred for 3 h and then water is added. The mixture is made basic with sodium hydroxide (pellets) and the resulting white solid is collected. The aqueous filtrate is extracted with ether and the ether extract is dried and concentrated in vacuo to afford a white solid. The combined solids are recrystallized from ether to give *N*-cyclohexylhydroxylamine (**4**) as colorless flakes; yield: 0.96 g (81%); m.p. 138–139°; Lit.⁴ m.p. 138–139°.

A longer reaction time (20 h) using Method C conditions gave *N*-cyclohexyl-*N*-ethylhydroxylamine (**2i**) in 44% yield.

Preparation of *N,N*-Di-*n*-Butylhydroxylamine:

To stirred acetic acid (15 ml) at 15° is added 1 pellet of sodium borohydride. Upon dissolution, butanal oxime (0.88 g, 10 mmol) is added. The mixture is heated to 40–50° over the period of 1 h and a second pellet of sodium borohydride is added (total: 0.47 g, 12 mmol). After 2 h total reaction time the mixture is cooled, diluted with water (50 ml), and made basic with sodium

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