Synthesis of Masked Glyoxal Monoxime and 1-Hydroxylaminoacetaldehyde Derivatives

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Sodium ethoxide-catalyzed cleavage of azo-*N,N'*-bis(2,2-diethoxyethyl)-*N,N'*-dioxide **(2)** to an *E/Z*-mixture (6.5:1) of 1-hydroxyimino-2,2-diethoxyethane **(3a)** is reported. Alkylation of the oxime sodium salt provides mainly the *E*-isomers of the alkyloxyimino-2,2-diethoxyethanes **3b–e**. The same compounds are also prepared by the reaction of hydroxylamine or *O*-alkylhydroxylamines with diethoxyacetaldehyde **(4)**. The oxime and the *O*-alkyloximes were reduced with sodium cyanoborohydride to the corresponding hydroxylamine derivatives **5a–e**.

In connection with the syntheses of 4,5-unsubstituted 1-hydroxyimidazole derivatives we had need for 1-hydroxyiminoacetaldehyde (glyoxal monoxime), alkyloxyiminoacetaldehydes and their corresponding hydroxylamino derivatives in masked form. To our knowledge glyoxal monoxime has never been prepared in pure form, but an *in situ* preparation using glyoxal and acetone oxime has been described.[1]

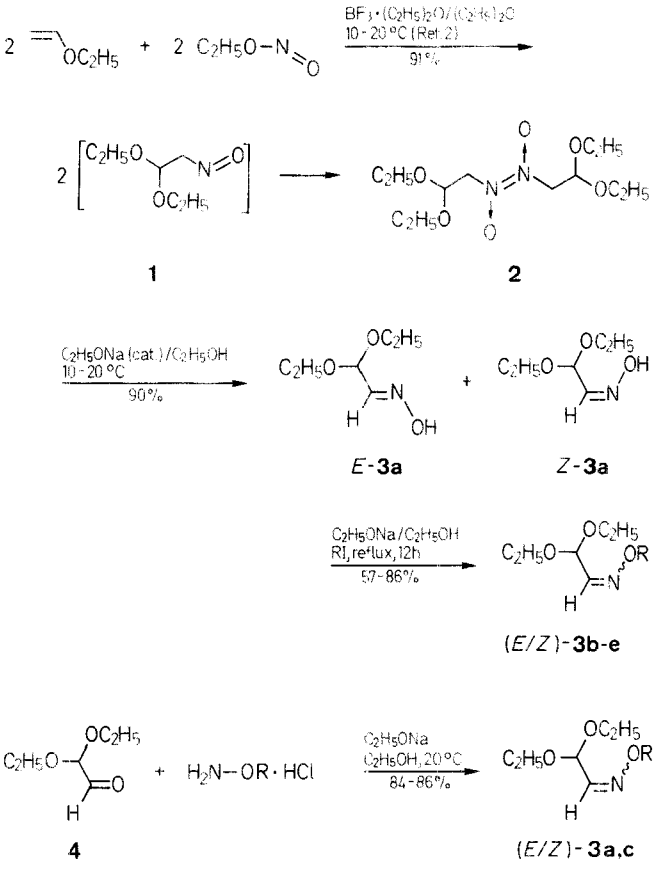
The key compound of this series, 1-hydroxyimino-2,2-diethoxyethane **(3a)**, which represents a masked form of glyoxal monoxime, may alternatively be prepared by the short and straightforward method A (overall yield 80%) or more time consuming by the fourstep method B (overall yield ca. 25%).

Method A: Boron trifluoride catalyzed addition of ethyl nitrite to ethyl vinyl ether yields azo-*N,N'*-bis(2,2-diethoxyethyl)-*N,N'*-dioxide **(2)** in high yield.

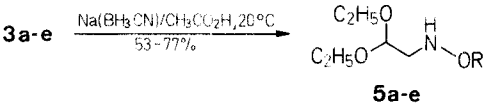
A transient blue coloration during the addition of ethyl vinylether indicates the formation of the monomer **1** prior to its dimerization. According to literature,[2] **1** should be the sole reaction product, but spectroscopic evidence (see experimental part) clearly demonstrates the formation of **2**.

The purification of the dimer **2** by vacuum distillation is unnecessary for further process, and strictly to be avoided due to the danger of explosive decomposition at higher temperatures (< 100°C). The treatment of **2** with catalytic amounts of sodium ethoxide transforms the dimer to an *E/Z*-mixture (6.5:1) of 1-hydroxyimino-2,2-diethoxyethane **(3a)** in high yield. The oxime **3a** now can be purified by vacuum distillation after TLC- and ^{1}H-NMR control of the complete transformation from **2** to **3a**. The alkylation of the sodium salt of the oxime **3a** provides an *E/Z*-mixture (10:1 to almost pure *E*) of the *O*-alkyloximes **3b–e** (Table 1).

Method B: An *E/Z* mixture (~ 5:1) of the oxime **3a** is prepared from diethoxyacetaldehyde **(4)** in the usual way. Diethoxyacetaldehyde **(4)** is obtained from acrolein by known procedures.[3–6] The *O*-alkyloximes, for example **3c**, may also be prepared according to Method B using diethoxyacetaldehyde **(4)** and *O*-alkylhydroxylamine.



The sodium cyanoborohydride reduction of the oxime **3a** and the alkyloximes **3b–e** gives 1-hydroxylamino-2,2-diethoxyethane **(5a)** and the 1-alkyloxyamino-2,2-diethoxyethanes **5b–e** (Table 2).



1-Hydroxyimino-2,2-diethoxyethane (3a) and 1-Alkyloxyimino-2,2-diethoxyethanes 3b–e; General Procedures:

Method A: *Azo-N,N'-bis-(2,2-diethoxyethyl)-N,N'*-dioxide **(2)**: A solution of ethylnitrite (37.5 g, 0.5 mol) and boron trifluoride etherate (0.4 g) in anhydrous ether (80 ml) is placed in a two necked flask surrounded by an ice bath and equipped with a reflux condenser cooled with ice water. With stirring, a solution of ethyl vinylether (37.8 g, 0.52 mol) in anhydrous ether (80 ml) is slowly added, keeping the temperature below 10°C. After additional stirring for 1 h at room temperature, a solution of potassium fluoride (0.8 g) in water (40 ml) is added and the stirring continued for 10 min. The organic layer is separated, washed with water (2 × 20 ml), dried with sodium sulfate and the solvent is evaporated at 30–40°C. The residual yellow oil **2**; yield: 67.1 g (91%) cannot be distilled *in vacuo* without forming a mixture of monomeric **1** and **3a**. At higher temperatures explosive decomposition may occur.

Table 1. Oxime **3a** and *O*-Alkyloximes **3b–e** Prepared

Product	R	Method	Yield (%) ($E:Z$)[a]	b.p. (°C)/mbar	n_D^{20}	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
3a	H	A	90 (6.5 : 1)	63/0.04	1.4338	$C_6H_{13}NO_3$ (147.2)	1.20 (t, 6H, J = 7 Hz, CH_3); 3.59, 3.62 (2qd, 4H, J = 7 Hz, OCH_2); 4.90 (d, 1H, J = 5 Hz, $CH(OC_2H_5)_2$, E); 5.50 (d, 1H, J = 5 Hz, $CH(OC_2H_5)_2$, Z); 6.70 (d, 1H, J = 5 Hz, CH=N, Z); 7.30 (d, 1H, J = 5 Hz, CH=N, E); 9.10 (s, 1H, OH)
		B	86 (5.3 : 1)				
3b	C_2H_5	A	57 (E) (Z-traces)	110/13	1.4205	$C_8H_{17}NO_3$ (175.2)	1.20 (t, 9H, J = 7 Hz, CH_3); 3.59, 3.62 (2qd, 4H, J = 7 Hz, OCH_2); 4.10 (q, 2H, J = 7 Hz, $NOCH_2$); 4.85 (d, 1H, J = 6 Hz, $CH(OC_2H_5)_2$, E); 7.25 (d, 1H, J = 6 Hz, N=CH, E)
3c	n-C_3H_7	A	58 (9 : 1)	130/13	1.4244	$C_9H_{19}NO_3$ (189.3)	1.00 (t, 3H, J = 7 Hz, CH_3); 1.20 (t, 6H, J = 7 Hz, CH_3); 1.65 (q, 2H, J = 7 Hz, CH_2); 3.59, 3.62 (2qd, 4H, J = 7 Hz, OCH_2); 3.95 (t, 2H, $NOCH_2$); 4.85 (d, 1H, J = 6 Hz, $CH(OC_2H_5)_2$, E); 5.45 (d, 1H, J = 6 Hz, $CH(OC_2H_5)_2$, Z); 6.65 (d, 1H, J = 6 Hz, N=CH, Z); 7.25 (d, 1H, J = 6 Hz, N=CH, E)
		B	84 (10 : 1)				
3d	n-C_4H_9	A	58 (E) (Z-traces)	52/0.007	1.4268	$C_{10}H_{21}NO_3$ (203.3)	0.80–1.75 (m, 7H, C_3H_7); 1.20 (t, 6H, J = 7 Hz, CH_3); 3.59, 3.62 (2qd, 4H, J = 7 Hz, O–CH_2–); 4.05 (t, 2H, J = 7 Hz, $NOCH_2$); 4.85 (d, 1H, J = 6 Hz, $CH(OC_2H_5)_2$, E); 7.20 (d, 1H, J = 6 Hz, ON=CH, E)
3e	$C_6H_5CH_2$	A	86 (E) (Z-traces)	130/0.013	1.4959	$C_{13}H_{19}NO_3$ (237.3)	1.20 (t, 6H, J = 7 CH_3); 3.59, 3.62 (2qd, 4H, J = 7 Hz, OCH_2); 4.85 (d, 1H, J = 6 Hz, $CH(OC_2H_5)_2$, E); 5.05 (s, 2H, $ArCH_2$); 7.20 (d, 1H, J = 6 Hz, O–N=CH, E); 7.25 (s, 5H, C_6H_5)

[a] The $E:Z$ relation is estimated by comparing the integrated doublet signals of $CH(OC_2H_5)_2$ and CH=NO as an inner standard.
[b] Satisfactory microanalyses obtained: C ±0.21, H ±0.38, N ±0.21.
[c] Kugelrohr distillation, bath temperature is given.

Table 2. Hydroxylamine Derivatives **5a–e** Prepared

Product	Yield (%)	b.p. (°C)/mbar	Molecular Formula	^{1}H-NMR (CCl_4/TMS) δ (ppm)
5a	53	130/0.07	$C_6H_{15}NO_3$ (149.2)	1.05 (t, 6H, J = 7 Hz, CH_3); 2.66 (d, J = 6 Hz, 2H, NCH_2); 3.40 (q, 4H, J = 7 Hz, OCH_2); 4.51 [t, J = 6 Hz, 1H, $CH(OC_2H_5)_2$]; 7.1 (s, 1H, OH)
5b	68	125/13	$C_8H_{19}NO_3$ (177.2)	1.13 (m, 9H, CH_3); 2.78 (d, J = 6 Hz, 2H, NCH_2); 3.50 (m, 6H, CH_2); 4.55 [t, J = 6 Hz, 1H, $CH(OC_2H_5)_2$]; 5.17 (s, br, 1H, NH)
5c	71	140/13	$C_9H_{21}NO_3$ (191.3)	1.03 (m, 9H, CH_3); 1.45 (m, 2H, CH_2); 2.78 (d, J = 6 Hz, 2H, NCH_2); 3.46 (m, 6H, CH_2); 4.55 [t, J = 6 Hz, 1H, $CH(OC_2H_5)_2$]; 5.28 (s, br, 1H, NH)
5d	71	43/0.05	$C_{10}H_{23}NO_3$ (205.3)	0.8–1.8 (m, 13H, CH_3, CH_2); 2.95 (d, J = 6 Hz, 2H, NCH_2); 3.60 (m, 6H, OCH_2, $NOCH_2$); 4.70 [t, J = 6 Hz, 1H, $CH(OC_2H_5)_2$]; 5.50 (s, 1H, NH)
5e	77	135/0.05	$C_{13}H_{21}NO_3$ (234.3)	1.10 (t, 6H, J = 7 Hz, CH_3); 2.80 (d, J = 6 Hz, 2H, NCH_2); 3.47 (m, 4H, OCH_2); 4.52 [d, J = 6 Hz, 1H, $CH(OC_2H_5)_2$]; 4.57 (s, 2H, $ArCH_2$); 5.53 (s, br, 1H, NH); 7.13 (s, 5H, C_6H_5)

[a] For substituent R, see Table 1.
[b] Satisfactory microanalyses obtained: C ±0.32, H ±0.19, N ±0.06.

TLC: Polygram SIL G/UV sheet, petroleum ether/ethylacetate 1:1 R_f = 0.70, fluorescence extinction at 254 nm.

$C_{12}H_{26}N_2O_6$ (294.3).

IR (KBr): ν = 1215 cm^{-1} [=N(O)-]

^{1}H-NMR (CCl_4): δ = 1.2 (t, 12H, J = 7 Hz, CH_3); 3.59, 3.62 (2qd, 8H, J = 7 Hz, CH_2O); 4.35 (d, 4H, J = 5 Hz, CH_2N); 5.10 ppm (t, 2H, J = 5 Hz, $CH(OC_2H_5)_2$)

MS (80eV): m/e = 249 [M^+-(C_2H_5O·)]

Conversion of **2** *into E,Z-1-Hydroxyimino-2,2-diethoxyethane* (**3a**): Azo-*N,N'*-bis-(2,2-diethoxyethyl)-*N,N'*-dioxide (**2**; 58.9 g, 0.2 mol) is placed in a three necked flask surrounded by an ice bath and equipped with a reflux condenser, dropping funnel and a thermometer. A sodium ethoxide solution prepared from sodium (0.23 g, 10 mmol) and anhydrous ethanol (15 ml) is added with magnetic stirring, maintaining the reaction temperature below 10 °C. The mixture is kept for 4 h at 20–22 °C. A small sample is checked after work up by ^{1}H-NMR and TLC (see below).

The ethanol is evaporated on a rotary evaporator at 40 °C, 5% aqueous acetic acid (20 ml) is added and the oily layer extracted with dichloromethane (200 ml). After washing with water (2 × 10 ml), drying and evaporation of the organic layer the residual yellow-brownish oil (56 g,

95% crude **3a**) is checked again and prior to vacuum distillation (see Table 1) for complete transformation of **2** to **3a**. ^{1}H-NMR should display the complete absence of the doublet at $\delta = 4.35$ and TLC the complete absence of the spot at $R_f = 0.70$, both characteristic for **2** as demonstrated in the preceding experiment. The newly formed **3a** ($R_f = 0.74$, conditions as above) is detectable on TLC only after exposure to an iodine chamber in contrast to **2**.

Alkylation of 1-Hydroxyimino-2,2-diethoxyethane: To a solution of sodium ethoxide in ethanol (prepared from sodium (0.57 g, 25 mmol) and anhydrous ethanol (25 ml), 1-hydroxyimino-2,2-diethoxyethane (3.68 g, 25 mmol) and the appropriate alkyl iodide (25 mmol) is added. [Benzylchloride (25 mmol) and potassium iodide (1.25 mmol) is used to prepare **3e**]. The mixture is gently refluxed for 12 h. After evaporation, the residue is diluted with ether (50 ml) and extracted with 1 normal sodium hydroxide solution (50 ml). The organic layer is washed with water (25 ml) and dried with magnesium sulfate. The solvent is evaporated and the residual oil is distilled in a Kugelrohrapparatus (Table 1).

Method B:

1-Hydroxyimino-2,2-diethoxyethane **3a** and 1-Propyloxyimino-2,2-diethoxyethane **3c**: A solution of hydroxylamine hydrochloride or the appropriate *O*-alkylhydroxylamine hydrochloride (10 mmol) in anhydrous ethanol (15 ml) is added at 10 °C to a solution of sodium ethoxide in ethanol (prepared from sodium (10 mmol) and anhydrous ethanol (15 ml). After filtration of the precipitated sodium chloride, 2,2-diethoxy acetaldehyde[3-6] (**4**; 1.2 g, 9 mmol) is added. This solution is kept at 20 °C for 12 h. After evaporation of the solvent on a rotary evaporator the residue is treated with water (10 ml) and then extracted with dichloromethane (2 × 15 ml); the organic layer is dried with magnesium sulfate and evaporated. The residual oil is distilled in a Kugelrohr apparatus (Table 1).

1-Hydroxylamino-2,2-diethoxyethane 5a and 1-Alkyloxyamino-2,2-diethoxyethanes 5b–e; General Procedure:

To a stirred and cooled solution of the appropriate 1-hydroxy- or 1-alkyloxyimino-2,2-diethoxyethane **3** (12.5 mmol) in a mixture of glacial acetic acid (10 ml) and anhydrous ethanol (10 ml), sodium cyanoborohydride (0.94 g, 15 mmol) is added in small portions maintaining the reaction temperature at 5–7 °C. The mixture is stirred for 12 h at 20 °C. After evaporation on a rotary evaporator at 40 °C the residue is adjusted to pH 8–9 by addition of saturated sodium hydrogencarbonate solution and the aqueous layer is extracted with dichloromethane (3 × 25 ml). The combined organic layer is washed with water (15 ml) and saturated sodium chloride solution (15 ml). After drying with magnesium sulfate the solvent is evaporated and the residual oil is distilled (Table 2).

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(1) Taylor, E.C., Perlman, K.L., Young-Ho Kim, Sword, J.P., Jacobi, P.A. *J. Am. Chem. Soc.* **1973**, *95*, 6413.
(2) Tchekitcheff, S. *US-Patent* 2674626 (1954) Société des Usines Chim. Rhône-Poulenc; *C.A.* **1955**, *49*, 6301.
(3) VanAllan, J.A. *Org. Synth. Coll. Vol. IV* **1963**, 21.
(4) Witzemann, E.J., Evans, L., Hass, H., Schroeder, E.F. *Org. Synth. Coll. Vol II* **1947**, 307.
(5) Fischer, H.O.L., Baer, E. *Helv. Chim. Acta* **1935**, *18*, 516.
(6) Stetter, H., Mohrmann, K.H. *Synthesis* **1981**, 129.
Bestmann, H.J., Ermann, P. *Chem. Ber.* **1983**, *116*, 3264.