A New Convenient Route to Alkyl Hydroximates and their O^N-Alkyl Derivatives (Alkyl *N*-Hydroxy- and *N*-Alkoxycarboximidates)

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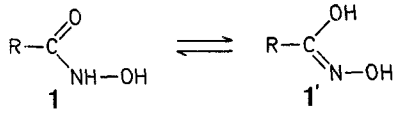
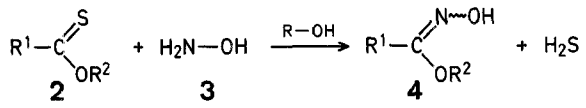
Because of the tautomeric structure of hydroxamic (hydroximic) acids (**1** ⇌ **1'**) and the possibility of triple alkylation at the O- and N-atoms, *O*-monoalkylation and O,O^N-dialkylation products of the types **4** and **6** may only be obtained by rather difficult methods which sometimes are not reliable as regards selectivity[1,2,3].



1 **1'**

The thioacylation of *O*- and *N*-substituted hydroxylamines with *O*-alkyl thiocarboxylates in the presence of sodium alkoxide leads to the formation of the sodium salts of thiohydroxamic acids[4]. We have now found that the reaction of *O*-alkyl thiocarboxylates **(2)** with hydroxylamine **(3)** (freshly generated from hydroxylamine hydrochloride and an equimolecular amount of sodium methoxide in methanol) in ethanol takes a different course (due to the different conditions) to afford alkyl hydroximates **(4)** in moderate to good yields.

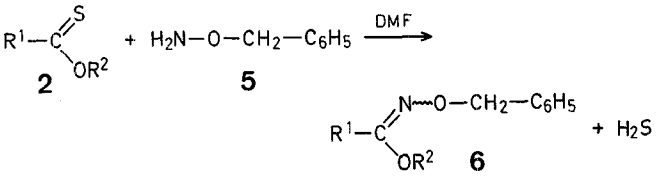


2 **3** **4**

R = CH_3, C_2H_5

The preparation of compounds **4a, b, c** is carried out at room temperature and leads to the exclusive formation of the (*E*)-isomers of **4a, b, c.** Compounds **4e, f** are prepared in boiling ethanol or methanol, respectively, and are obtained as mixtures of the (*E*)- and (*Z*)-isomers which can be separated by preparative layer chromatography (P.L.C.).

The analogous preparation of alkyl O^N-benzylhydroximates (**6**, alkyl *N*-benzyloxycarboximidates) from *O*-alkyl thiocarboxylates **(2)** and *O*-benzylhydroxylamine **(5)** is performed in an aprotic dipolar solvent such as dimethylformamide at temperatures of 25–80 °C.



2 **5** **6**

Compounds **6a, c, d** are exclusively obtained as the (*E*)-isomers whereas the reaction is less stereoselective for the preparation of compounds **6e, f** which are obtained as (*E*/*Z*)-mixtures with the (*E*)-isomer predominating due to steric hindrance by the benzyloxy group.

The *O*-ethyl thiocarboxylates **(2)** were prepared from ethyl carboximidates and hydrogen sulfide[5]. *O*-Benzylhydroxylamine **(5)** was obtained from hydroxylamine hydrochloride via ethyl *N*-hydroxycarbamate and ethyl *N*-benzyloxycarbamate[6].

Ethyl Acetohydroximate (4a): Typical Procedure:
Hydroxylamine hydrochloride (2.30 g, 0.033 mol) is dissolved in hot methanol (20 ml). A solution of sodium methoxide (1.78 g, 0.033 mol) is added with stirring. The precipitated sodium chloride is filtered off and the solution is added to a stirred solution of *O*-ethyl thioacetate (**2a**; 3.12 g, 0.03 mol) in ethanol (5 ml). The stirred mixture is allowed to stand at room temperature for 48 h until evolution of hydrogen sulfide ceases. Sulfur (0.1 g) is filtered off and the solvent is removed in vacuo. The residue is extracted with ether, the extract evaporated, and the residual oil distilled in vacuo; yield: 2.20 g (71%); b.p. 64 °C/14 torr.

2-(Dimethylamino)-ethyl Benzohydroximate (4f):
Hydroxylammonium hydrochloride (765 mg, 11 mmol) is dissolved in hot methanol (10 ml) and a solution of sodium methoxide [595 mg, 11 mmol; from 253 mg (11 mmol) of sodium] in methanol (6 ml) is added. The resultant sodium chloride is filtered off. To this solution of hydroxylamine, sodium (0.23 g, 10 mmol) and *O*-(2-dimethylaminoethyl) thiobenzoate hydrochloride (prepared according to Ref.[7]; 2.45 g, 10 mmol) are added and the mixture is heated to reflux for 24 h. The

Table 1. Alkyl Hydroximates **(4)** and Alkyl O^N-Benzylhydroximates **(6)**

Product	R^1	R^2	Reaction time and temperature [h], [°C]	Yield [%]	Configuration or (*E*/*Z*)-Ratio[a]	b.p./torr or m.p. [°C]	Molecular formula[b] or Lit. Data
4a	CH_3	C_2H_5	48, 25°	71	*E*	b.p. 64°/14	b.p. 62°/12[6]
6a	CH_3	C_2H_5	3, 40°	81	*E*	b.p. 115°/11	$C_{11}H_{15}NO_2$ (193.2)
4b	C_2H_5	C_2H_5	48, 25°	51	*E*	b.p. 77–78°/23	$C_5H_{11}NO_2$ (117.1)
4c	C_6H_5—CH_2—	C_2H_5	48, 25°	78	*E*	b.p. 109°/0.4	$C_{10}H_{13}NO_2$ (179.2)
6c	C_6H_5—CH_2—	C_2H_5	24, 25°	75	*E*	b.p. 139°/0.07	$C_{17}H_{19}NO_2$ (269.3)
6d	C_6H_5—CH_2—	—CH_2—CH_2—$N(CH_3)_2$	48, 25°	50	*E*	[c]	$C_{19}H_{24}N_2O_2$[c] (312.4)
4e	C_6H_5	C_2H_5	24, 78°	79	37/63	(*E*): m.p. 66° (*Z*): m.p. 52°	*E*: m.p. 67°[8] *Z*: m.p. 53°[8]
6e	C_6H_5	C_2H_5	24, 80°	78	61/39	b.p. 140°/0.1	$C_{16}H_{17}NO_2$ (255.3)
4f	C_6H_5	—CH_2—CH_2—$N(CH_3)_2$	24, 65°	68	21/79	[d]	$C_{11}H_{16}N_2O_2$ (208.3)
6f	C_6H_5	—CH_2—CH_2—$N(CH_3)_2$	6, 80°	76	75/25	[e]	$C_{18}H_{22}N_2O_2$[e] (298.4)

[a] The configuration may be assigned on the basis of ^{1}H-N.M.R. data (see Ref.[8]) for products **4e, 4f, 6e,** and **6f**. The structure of compounds **4a, 4b, 4c, 6a, 6c,** and **6d** may be assigned, however, on the basis of the ^{13}C-N.M.R. spectra which show only one isomer (see Table 2).

[b] The microanalyses showed the following maximum deviations from the calculated values: C, ±0.28; H, ±0.24; N, ±0.31. Exceptions: **6a**, C, −0.47; **6e**, C, −0.39.

[c] Compound **6d** was isolated and analyzed as the *N*-methyl iodide; m.p. 125 °C; $C_{20}H_{27}JN_2O_2$ (440.3).

[d] Isolated by P.L.C. on silica gel using acetone/ether (95/5) as eluent.

[e] The (*E*)-isomer was isolated and analyzed as the *N*-methyl iodide; m.p. 138 °C; $C_{19}H_{25}JN_2O_2$ (430.3).

Table 2. Spectral Data of Compounds **4** and **6**

Compound	I.R. (neat)[a] ν [cm^{-1}]	^{1}H-N.M.R. (solvent/TMS$_{int}$)[c] δ [ppm]	^{13}C-N.M.R. (solvent/TMS$_{int}$)[c] δ [ppm]
4a	3300, 1660	(CCl_4): 1.3 (t, H_3C—C); 1.9 (s, CH_2—CH_3); 3.95 (q, CH_2—CH_3); 8.1 (OH)[d]	12.7 (H_3C—C); 14 (CH_2—CH_3); 62 (CH_2—CH_3); 162.9 (C=N)[e]
6a	1645	($CDCl_3$): 1.2 (t, H_3C—C); 2.0 (s, CH_2—CH_3); 3.95 (q, CH_2—CH_3); 4.9 (s, N—O—CH_2); 7.3 (OH)[d]	14 (H_3C—C); 14.6 (CH_2—CH_3); 62.4 (CH_2—CH_3); 75.9 (N—O—CH_2—C_6H_5); 138.2, 128.1, 127.5 (phenyl); 162.6 (C=N)
4b	3300, 1650	($CDCl_3$): 1.1 (t, CH_3); 1.3 (t, CH_3); 2.4 (q, CH_2); 3.95 (q, CH_2); 7.7 (OH)[d]	
4c	3280, 1665[f]	($CDCl_3$): 1.2 (t, CH_3); 3.75 (s, CH_2); 4.0 (q, CH_2); 7.3 (s, 5 H_{arom}); 7.8 (OH)[d]	14.1 (CH_2—CH_3); 33.1 (C_6H_5—CH_2); 62.4 (CH_2—CH_3); 126.4, 128.2, 128.2, 135.5 (phenyl); 163.6 (C=N)
6c	1620	($CDCl_3$): 1.15 (t, H_3C—C); 3.7 (s, CH_2); 4.0 (q, CH_2); 5.0 (s, N—O—CH_2); 7.2 (s, 5 H_{arom}); 7.3 (s, 5 H_{arom})	
6d	1635	($CDCl_3$): 2.2 [s, $N(CH_3)_2$]; 2.5 (t, CH_2—N); 3.7 (s, CH_2); 4.1 (t, CH_2); 5.0 (s, N—O—CH_2); 7.2 (s, 5 H_{arom}); 7.3 (s, 5 H_{arom})	
(*E*)-**4e**	3280, 1660	(CCl_4): 1.35 (t, CH_2—CH_3); 4.1 (q, CH_2—CH_3); 7.3 (m, *m*- and *p*-H_{arom}); 7.7 (m, *o*-H_{arom}); 8.3 (OH)[d]	16.7 (CH_2—CH_3); 65.2 (CH_2—CH_3); 130.3 (phenyl: C-3, C-5); 131.3 (phenyl: C-2, C-6); 131.7 (phenyl: C-1); 132.5 (phenyl: C-4); 162 (C=N)
(*Z*)-**4e**	3300, 1630	(CCl_4): 1.4 (t, CH_2—CH_3); 4.15 (q, CH_2—CH_3); 7.3 (m, *m*- and *p*-H_{arom}); 7.55 (m, *o*-H_{arom}); 8.7 (OH)[d]	17.9 (CH_2—CH_3); 70 (CH_2—CH_3); 129.5 (phenyl: C-3, C-5); 130.7 (phenyl: C-2, C-6); 132.4 (phenyl: C-4); 158.2 (C=N)
(*E*)-**6e**	1620	($CDCl_3$): 1.3 (t, CH_2—CH_3); 4.15 (q, CH_2—CH_3); 5.0 (s, N—O—CH_2); 7.3 (m, *m*- and *p*-H_{arom}); 7.75 (m, *o*-H_{arom})	
(*Z*)-**6e**	1610	($CDCl_3$): 1.3 (t, CH_2—CH_3); 4.3 (q, CH_2—CH_3); 5.1 (s, N—O—CH_2); 7.4 (m, *m*- and *p*-H_{arom}); 7.7 (m, *o*-H_{arom})	
(*E*)-**4f**	1650	(CCl_4): 2.4 [s, $N(CH_3)_2$]; 2.6 (t, CH_2—N); 4.2 (t, CH_2—CH_3); 7.4 (m, *m*- and *p*-H_{arom}); 8.0 (m, *o*-H_{arom}); 7.8 (OH)[d]	
(*Z*)-**4f**	1630	(CCl_4): 2.4 [s, $N(CH_3)_2$]; 2.8 (t, CH_2—N); 4.5 (t, CH_2—CH_3); 7.5 (m, *m*- and *p*-H_{arom}); 7.7 (*o*-H_{arom}); 9.4 (OH)[d]	
(*E*)-**6f**	1630	($CDCl_3$): 2.3 [s, $N(CH_3)_2$]; 2.6 (t, CH_2—N); 4.2 (t, CH_2); 5.0 (s, N—O—CH_2); 7.3 (m, *m*- and *p*-H_{arom}); 7.7 (m, *o*-H_{arom})	
(*Z*)-**6f**	1630	($CDCl_3$): 2.25 [s, $N(CH_3)_2$]; 2.6 (t, CH_2—N); 4.3 (t, CH_2); 5.1 (s, N—O—CH_2); 7.3 (m, *m*- and *p*-H_{arom}); 7.75 (m, *o*-H_{arom})	

[a] Measured on a Perkin-Elmer 257 Infrared Spectrometer.
[b] Recorded on a Varian NMR spectrometer at 60 MHz.
[c] Recorded on a Varian CF 20 spectrometer. The solvents used are the same as for the ^{1}H spectra.
[d] Exchangeable with D_2O.
[e] The (*E*)-configuration is based on comparison with the spectrum of ethyl acetimidate [^{13}C-N.M.R. spectrum ($CDCl_3$/TMS$_{int}$)]: $\delta = 17$ (CH_2—CH_3); 24 (H_3C—C); 56.3 (CH_2—CH_3); 175.1 ppm (C=N). In the (*E*)-isomer, the signal of H_3C—C(NOH)—OC_2H_5 appears at higher field as a result of steric hindrance (caused by interaction with the OH group) whereas the signal of O—CH—CH_3 is deshielded.
[f] In KBr.

solvents are removed in vacuo and the residue is extracted with chloroform/ether (1/1; 15 ml). The sulfur (formed as side product) is filtered off and the solvent is removed in vacuo; yield: 11.42 g (68%) of **4f** as isomer mixture. The isomers (*E*)-**4f** and (*Z*)-**4f** are separated by P.L.C. (silica gel Merck 7747, thickness: 1.5 mm; solvent: acetone/ether 95/5).

Ethyl *O*^{N}-Benzylphenylacetohydroximate (Ethyl *N*-Benzyloxyphenylacetimidate, 6c); Typical Procedure:

O-Ethyl phenyl-thioacetate (1.80 g, 10 mmol) is added to a stirred solution of *O*-benzylhydroxylamine (1.232 g, 10 mmol) in dimethylformamide (7.5 ml). Stirring is continued at 25 °C until evolution of hydrogen sulfide has ceased. The mixture is filtered and product **6c** isolated by distillation in vacuo; yield: 2.02 g (75%); b.p. 138–139 °C/0.07 torr.

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