The Addition of Lithium Salts of *O*-Alkyloximes to Aldehydes: Synthesis of β-Keto *O*-Alkyloximes

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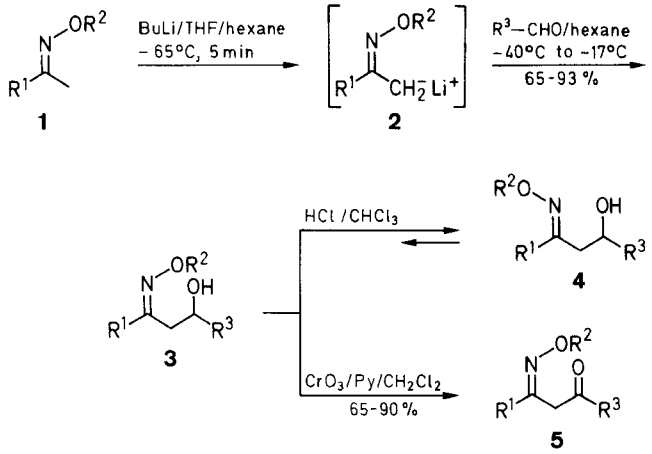
Addition of lithium salts of oxime *O*-ethers to aldehydes affords the thermodynamically unfavored β-hydroxy (*Z*)-*O*-alkyloximes. Oxidation of the hydroxy function with chromium trioxide/pyridine complex gives the β-keto *O*-alkyloximes. Facile alkylation of the 1,3-dicarbonyl analogs is possible via their sodium or lithium salts.

As part of a continuing study on the synthetic utility of the lithium salts of *O*-alkyloximes,[1-5] we have examined the addition of a series of acetoxime derivatives to aldehydes. We now report the formation of the β-hydroxy *O*-alkyloximes, their dehydration and oxidation to the corresponding β-keto *O*-alkyloximes.

Deprotonation of the *O*-alkyloximes **1** with butyllithium in tetrahydrofuran at −65 °C gives the (*Z*)-lithium salts **2**. Reaction with the aldehydes[6] affords the thermodynamically unfavored β-hydroxy (*Z*)-*O*-alkyloximes **3**.[7] The addition products **3** are isolated in good yields after purification by chromatography (Table 1).

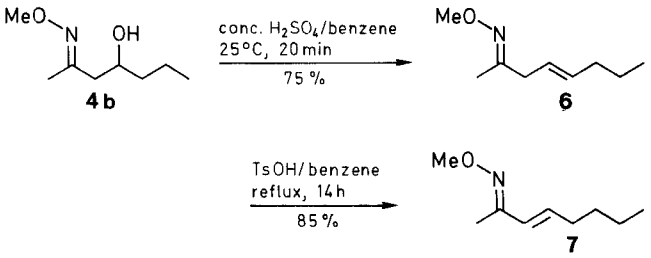
The compounds **3** undergo rapid acid-catalyzed isomerization to give equilibrium mixtures of **3** and the thermodynamically favored β-hydroxy (*E*)-*O*-alkyloximes **4**. We were, however, able to isolate **4a,b** by column chromatography from the equilibrium mixture.



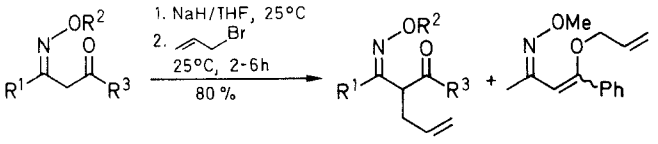
1–5	R^1	R^2	R^3
a	Me	Me	Ph
b	Me	Me	Pr
c	Ph	Me	*t*-Bu
d	Me	$CH_2O(CH_2)_2OMe$	CH_2Ph
e	Ph	Me	Et
f	Me	Me	*i*-Pr
g	Me	$CH_2O(CH_2)_2OMe$	$3\text{-}O_2NC_6H_4$
h	Me	$CH_2O(CH_2)_2OMe$	Ph
i	Me	$CH_2O(CH_2)_2OMe$	Pr
j	Me	Me	$CH{=}CH_2$

The secondary alcohols **3a–i** were oxidized to the corresponding β-keto *O*-alkyloximes **5a–i** with chromium trioxide/pyridine complex[8] in good yield (Table 2).

Elimination of water from the β-hydroxy (*E*)-*O*-alkyloximes **4** could be acheived only under extreme reaction conditions. For example, **4b** was converted to a 7:1 mixture of the corresponding olefins **6** and **7** after reaction with concentrated sulfuric acid at room temperature for 20 min in 75% yield. Compound **6** was isolated in pure form and was isomerized to the more stable **7** in 85% yield.



Reaction of the sodium or lithium salts of **5a–c** with allyl bromide resulted in the exclusive formation of the *C*-alkylation products **8a–c**, respectively.



5, 8	R^1	R^2	R^3
a	Me	Me	Ph
b	Me	Me	Pr
c	Ph	Me	*t*-Bu

However, reaction of the sodium salt of **5a** with allyl methanesulfonate[9] resulted in a mixture of *C*- and *O*-alkylation products, **8a** (54%) and **9** (30%) of the enol ether, respectively.

The geometrical directed generation of α-lithio *O*-alkyl oximes **2** enables the direct synthesis of the thermodynamically unfavored β-hydroxy (*Z*)-*O*-alkyl oximes **3** and subsequently the β-keto (*E*)-*O*-alkyl oximes **5**. These may be synthetically useful for the stereoselective synthesis of β-hydroxy alcohols for example,[7] and serve as synthetic intermediates for further directed carbon–carbon bond formation.

Acetone *O*-Methyloxime (1a); Typical procedure:

In a dried, nitrogen-filled round-bottom flask fitted with stirrer and addition funnel, acetoxime (126 g, 2 mol) and NaH (46 g, 2 mol) are allowed to react in xylene (750 mL) at 0 °C for 1 h. A cold (0 °C) solution of MeBr (186 g, 2 mol) in xylene (750 mL) is then added in small portions at 5 °C in (30 min). The mixture is warmed to r.t. temperature and stirred for 14 h. The reaction flask is then equipped

Table 1. Compounds **3** Prepared

Product	Yield (%)	Molecular Formula[a]	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
3a	82	$C_{11}H_{15}NO_2$ (193.2)	3500–3100, 1640, 1610, 900, 760	1.73 (s, 3H), 2.83 (dd, 1H, J = 13.2, 8.4), 2.61 (dd, 1H, J = 13.2, 4.6), 3.23 (br s, 1H), 3.81 (s, 3H), 4.96 (m, 1H), 7.29 (m, 5H)
3b	73	$C_8H_{17}NO_2$ (159.2)	3400, 1645	0.94 (t, 3H, J = 7), 1.42 (m, 4H), 1.86 (s, 3H), 2.28 (m, 2H), 2.99 (br s, 1H), 3.84 (s, 3H), 3.95 (m, 1H)
3c	98	$C_{14}H_{21}NO_2$ (235.3)	3450, 1640, 1450, 1370, 1050	0.95 (s, 9H), 2.60 (br s, 1H), 2.81 (dd, 1H, J = 13.5, 2.4), 2.99 (dd, 1H, J = 13.5, 10.7), 3.51 (m, 1H), 3.96 (s, 3H), 7.32 (m, 3H), 7.65 (m, 2H)
3d	65	$C_{15}H_{23}NO_4$ (281.4)	3450, 2910, 1635, 1415, 980, 840, 760	1.93 (s, 3H), 2.50 (dd, 1H, J = 13.0, 4.6), 2.62 (dd, 1H, J = 13.3, 9.0), 2.76 (d, 2H, J = 5.3), 3.15 (br s, 1H), 3.32 (s, 3H), 3.53 (t, 2H, J = 5.2), 3.74 (t, 2H, J = 5.1), 4.17 (m, 1H), 5.14 (s, 2H), 7.24 (m, 5H)
3e	83	$C_{12}H_{17}NO_2$ (207.3)	3450, 1640, 1450, 1370, 1060	0.87 (t, 3H, J = 7.4), 1.42 (m, 2H), 2.87 (m, 2H), 3.07 (br s, 1H), 3.77 (m, 1H), 3.90 (s, 3H), 7.27 (m, 3H), 7.63 (m, 2H)
3f	68	$C_8H_{17}NO_2$ (159.2)	3450, 1640, 1470, 1370, 1060	0.93 (d, 3H, J = 6), 0.95 (d, 3H, J = 6), 1.67 (m, 1H), 1.94 (s, 3H), 2.37 (dd, 1H, J = 13.4, 9.9), 2.57 (dd, 1H, J = 13.4, 3.1), 2.85 (br s, 1H), 3.61 (m, 1H), 3.80 (s, 3H)
3g	50	$C_{14}H_{20}N_2O_6$ (312.3)	3500, 2900, 1630, 1400, 960, 830, 740	1.89 (s, 3H), 2.75 (dd, 1H, J = 14, 5), 2.82 (dd, 1H, J = 14, 9), 3.37 (s, 3H), 3.57 (t, 2H, J – 5), 3.79 (t, 2H, J = 5), 4.79 (br s, 1H), 5.18 (s, 2H), 5.25 (m, 1H), 7.53 (m, 1H), 7.72 (m, 1H), 8.13 (m, 1H), 8.27 (s, 1H)
3h	70	$C_{14}H_{21}NO_4$ (267.3)	3400, 2900, 1630, 1420, 1000, 840, 750	1.82 (s, 3H), 2.68 (dd, 1H, J = 13, 4.6), 2.89 (dd, 1H, J = 13, 6.6), 3.28 (br s, 1H), 3.37 (s, 3H), 3.55 (t, 2H, J = 5), 3.77 (t, 2H, J = 4.9), 5.07 (m, 1H), 5.18 (s, 2H), 7.36 (m, 5H)
3i	55	$C_{11}H_{23}NO_4$ (233.3)	3500, 2900, 1640, 1410	0.92 (t, 3H, J = 7.4), 1.38 (m, 2H, J = 7.3), 1.81 (s, 3H), 2.34 (m, 2H), 2.45 (m, 2H), 2.93 (br s, 1H), 3.34 (s, 3H), 3.45 (t, 2H, J = 3.8), 3.58 (t, 2H, J = 3.6), 3.85 (m, 1H), 4.95 (s, 2H)
3j	56	$C_7H_{13}NO_2$ (143.2)	3500–3100, 1650, 990, 925, 920	1.99 (s, 3H), 2.56 (m, 2H), 2.9 (br s, 1H), 3.82 (s, 3H), 4.5 (m, 1H), 5.13 (dd, 1H, J_{cis} = 11), 5.27 (d, 1H, J_{trans} = 17), 5.8–6.0 (m, 1H)

[a] Satisfactory microanalyses obtained: C, H, N ±0.3.

Table 2. Compounds **5a–j** and **8a–c** Prepared

Product	Yield (%)	Molecular Formula[a]	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J (Hz)
5a	67	$C_{11}H_{13}NO_2$ (191.2)	1785, 1600, 990, 885, 750	1.96 (s, 3H), 3.83 (s, 2H), 3.87 (s, 3H), 7.98–8.00 (m, 2H), 7.45–7.47 (m, 3H)
5b	59	$C_8H_{15}NO_2$ (157.2)	1715, 1630	0.92 (t, 3H, J = 7.4), 1.58 (m, 2H, J = 8.8), 1.86 (s, 3H), 2.50 (t, 2H, J = 6), 3.28 (s, 2H), 3.85 (s, 3H)
5c	44	$C_{14}H_{19}NO_2$ (233.3)	1715, 1640, 890, 880, 740	1.14 (s, 9H), 3.84 (s, 2H), 3.86 (s, 3H), 7.24 (m, 3H), 7.47 (m, 2H)
5d	68	$C_{15}H_{21}NO_4$ (279.4)	2900, 1680, 1590, 1310, 970, 740	1.84 (s, 3H), 3.34 (s, 2H), 3.38 (s, 3H), 3.55 (t, 2H, J = 4.7), 3.73 (t, 2H, J = 4.8), 3.76 (s, 2H), 5.18 (s, 2H), 7.24 (m, 5H)
5e	73	$C_{12}H_{15}NO_2$ (205.3)	1715, 1635, 900, 800, 760	0.96 (t, 3H, J = 7.4), 2.45 (q, 2H, J = 7.4), 3.73 (s, 2H), 3.91 (s, 3H), 7.27 (m, 3H), 7.54 (m, 2H)
5f	68	$C_8H_{15}NO_2$ (157.2)	1700, 1630	1.13 (d, 6H, J = 6.5), 1.83 (s, 3H), 2.70 (m, 1H, J = 6.8), 3.35 (s, 2H), 3.86 (s, 3H)
5g	40	$C_{14}H_{18}N_2O_6$ (310.3)	1785, 1645, 1610, 1595, 980, 840, 745	1.95 (s, 3H), 3.39 (s, 3H), 3.58 (t, 2H, J = 4.6), 3.84 (t, 2H, J = 4.7), 5.30 (s, 2H), 5.42 (s, 2H), 7.73 (s, 1H), 8.49 (m, 3H)
5h	90	$C_{14}H_{19}NO_4$ (265.3)	2900, 1675, 1600, 1590, 1320, 980, 830, 740	1.99 (s, 3H), 3.38 (s, 3H), 3.54 (t, 2H, J = 4.8), 3.71 (t, 2H, J = 4.9), 4.05 (s, 2H), 5.19 (s, 2H), 7.52 (m, 3H), 8.00 (m, 2H)
5j	90	$C_{11}H_{21}NO_4$ (231.3)	2900, 1710, 1640, 1400	0.92 (t, 3H, J = 7.5), 1.61 (m, 2H), 1.92 (s, 3H), 2.47 (t, 2H, J = 7.3), 3.32 (s, 2H), 3.40 (s, 3H), 3.57 (t, 2H, J = 4.6), 3.75 (t, 2H, J = 4.9), 5.19 (s, 2H)
8a	72	$C_{14}H_{17}NO_2$ (231.3)	1700, 1650, 1460, 1070	1.75 (s, 3H), 2.60 (m, 2H), 3.85 (s, 3H), 4.41 (t, 1H, J = 7.5), 5.13 (m, 2H), 5.76 (m, 1H), 7.50 (m, 3H), 8.03 (m, 2H)
8b	64	$C_{11}H_{19}NO_2$ (197.3)	1715, 1640, 1470, 1440, 1370, 1060, 920	0.89 (t, 3H, J = 7.4), 1.58 (m, 2H), 1.73 (s, 3H), 2.46 (m, 4H), 3.44 (t, 1H, J = 7.5), 3.88 (s, 3H), 5.05 (m, 2H), 5.66 (m, 1H)
8c	55	$C_{17}H_{23}NO_2$ (273.4)	1710, 1640, 1480, 1470, 1450, 1370, 1330, 1100, 985	1.15 (s, 9H), 2.45 (m, 2H), 3.81 (s, 3H), 4.13 (dd, 1H, J = 8.4, 5.4), 5.01 (m, 2H), 5.72 (m, 1H), 7.37 (m, 5H)

[a] Satisfactory microanalyses obtained: C, H, N ±0.3.

with a distillation head and the crude product (167 g) is collected by distillation; boiling range 55–85 °C. The *O*-methyloxime is further purified by distillation through a 30 cm Vigreux column; yield: 114 g (66%); 72–74 °C/760 Torr (Lit.[10] 72–73/760 Torr).

β-Hydroxy (*Z*)-*O*-Alkyloximes 3; General Procedure:
To a solution of *O*-alkyloxime **1a–c** (1 mmol) in dry THF (20 mL) at −65 °C under N_2 atmosphere, BuLi (1 equiv in THF/hexane, 1:1) is added dropwise over 10 min. After reaction for additional 10 min at −65 °C, aldehyde **2a–j** (1 mmol) in THF (10 mL) is added dropwise. The mixture is stirred for 20 min at −65 °C and allowed to warm up to r.t. during 15 min. Water (30 mL) is added and the product is extracted with Et_2O (2 × 30 mL). The organic solution is dried ($MgSO_4$) and the solvent removed under reduced pressure. The products **3** (Table 1) are purified by column chromatography (silica gel, hexane/EtOAc, 3:1).

Equilibration of 3-Hydroxy-3-phenylbutan-3-one *O*-Methyloxime (3a); Typical Procedure:
A solution of **3a** (193 mg, 1 mmol) in 0.1% HCl/$CHCl_3$ (20 mL) is stirred at 25 °C for 30 min. The solvent is removed under reduced pressure. Purification by column chromatography (silica gel, hexane/EtOAc, 10:1) gives **3a** (yield: 12.3 mg (6%) (Table 1) and **4a**; yield: 144 mg (74%).

4a:

$C_{11}H_{15}NO_2$	calc.	C 68.37	H 7.82	N 7.20
(193.2)	found	68.11	8.00	6.98

IR (film): ν = 3500–3100, 1645, 1610, 910, 760 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.95 (t, 3H, J = 7.1 Hz), 1.80 (s, 3H), 2.18–2.36 (m, 2H), 3.83 (s, 3H), 4.95 (m, 1H), 7.31 (m, 2H).

Similarly, equilibration of **3b** affords **3b**; yield: 22.7 mg (14%) and **4b**; yield: 121 mg (76%).

4b:

$C_8H_{17}NO_2$	calc.	C 60.35	H 10.76	N 8.70
(159.3)	found	60.19	11.00	8.98

IR (film): ν = 3500–3100, 1645 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.95 (t, 3H, J = 7.1 Hz), 1.40 (m, 4H); 1.84 (s, 3H), 2.18–2.36 (m, 2H), 2.99 (br s, 1H), 3.86 (s, 3H), 3.8–4.01 (m, 1H).

4-Octen-2-one *O*-Methyloxime (6):
To a solution of **4b** (500 mg, 3.14 mmol) in dry benzene (30 mL), conc. H_2SO_4 (100 mg) is added at r.t. Azeotropic distillation during 20 min is followed by neutralization with solid $NaHCO_3$. The inorganic solids are removed by filtration and the solvent is evaporated at r.t. under reduced pressure. The product mixture is isolated by Kugelrohr distillation; bp 93–95 °C/55 mbar. Capillary gas chromatographic analysis (fused silica, SE-30, 30 m by 0.25 mm, internal pressure 5 kg/cm^2, FID) reveals a mixture of 4 main components in approximately 14:2:1:1 ratio of the various isomeric olefins. The main component, the *E,E* isomer **6** is isolated by distillation; yield: 370 mg (75%); bp 95 °C/55 mbar.

$C_8H_{15}NO$	calc.	C 68.04	H 10.07	N 9.91
(141.2)	found	68.01	10.08	9.73

IR (film): ν = 1680, 1630 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.95 (t, 3H, J = 7.1 Hz), 1.96 (s, 3H), 2.10–2.36 (m, 4H), 3.88 (s, 3H), 6.04–6.21 (m, 2H).

(*E*)-3-Octen-2-one (*E*)-*O*-Methyloxime (7):
The unsaturated β,γ-unsaturated oxime ether **6** (157 mg, 1 mmol) is refluxed in benzene (20 mL) in the presence of TsOH (5 mg) over 14 h. The reaction is quenched with sat. aq $NaHCO_3$ (10 mL). Drying ($MgSO_4$), concentration and distillation (bp 80 °C/45 mbar) gives the pure α,β-unsaturated *O*-alkyloxime **7** (*E,E* isomer), yield: 133 mg (85%); bp 80 °C/45 mbar.

$C_8H_{15}NO$	calc.	C 68.04	H 10.07	N 9.91
(141.2)	found	68.02	10.09	9.89

IR (film): ν = 1690, 1610 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 0.93 (t, 3H, J = 7.2 Hz), 1.50 (sextet, 2H, J = 7.2 Hz), 1.67 (m, 2H), 1.97 (s, 3H), 3.82 (s, 3H), 6.04–6.19 (m, 1H), 6.76 (d, 1H, J = 18 Hz)

Oxidation of β-Hydroxy *O*-Alkyloximes 3a–j to the β-Keto *O*-Alkyloximes 5a–j; General Procedure:
To a solution of **3a–j** (1 mmol)in dry CH_2Cl_2 at r.t., pyridinium dichromate (1.5 equiv) and powdered 4Å molecular sieves (1 g/mmol substrate) is added. The progress of the reaction is monitored by TLC (silica gel, EtOAc/hexane, 1:4). After completion (2–8 h), the mixture is filtered over Celite, the solvent is removed under reduced pressure and the products **5a–j** (Table 2) are purified by column chromatography[11] (silica gel, EtOAc/hexane, 1:4).

Alkylation of β-Keto *O*-Alkyloximes 5a–c; General Procedure:
To a suspension of NaH (26 mg, 2 mmol) or LiH (14 mg, 2 mmol) in dry THF (30 mL) at r.t., a solution of **5a–c** (2 mmol) in dry THF (10 mL) is added dropwise. Stirring continues until evolution of H_2 ceases. After an additional 15 min at r.t., a solution of allyl bromide (242 mg, 2 mmol) in THF (3 mL) is added dropwise over a period of 5 min. The progress of the reaction is monitored by TLC (silica gel, hexane/EtOAc, 4:1). After 2–6 h, water (10 mL) is added, the organic matter is extracted with Et_2O (2 × 10 mL) and CH_2Cl_2 (2 × 20 mL). The combined organic layers are dried ($MgSO_4$), filtered and the solvents are removed under reduced pressure. The products are purified by chromatography on a silica gel column (100 g) using a mixture of hexane/EtOAc (5:1) as eluent to give **8a–c** (Table 2).

3-Benzyl-5-hexene-2-one *O*-Methyloxime (8a) and 1-(Allyloxy)-1-phenyl-1-buten-3-one *O*-Methyloxime (9):
The reaction is carried out in analogy to the alkylation as above, but with allyl methanesulfonate (2 mmol), **5a** (2 mmol) and NaH (2 mmol) in THF (30 mL) at r.t. for 3 h. The products are isolated by chromatography on a silica gel column (100 g) using hexane/EtOAc (4:1) as eluent for the *C*-alkylation product **8a**; yield: 54%, and hexane/EtOAc (3:1) as eluent for **9**; yield: 30%.

9:

$C_{14}H_{17}NO_2$	calc.	C 72.70	H 7.40	N 6.56
(231.3)	found	72.45	7.15	6.82

^{1}H-NMR (200 MHz, $CDCl_3$/TMS): δ = 1.69 (s, 3H), 3.96 (s, 3H), 5.03 (d, 2H, J = 8.5 Hz), 4.92–5.05 (m, 2H), 5.47–5.56 (m, 2H), 7.40–7.51 (m, 3H), 7.92–7.96 (m, 2H).

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