Alkylation and Aldol Reactions of Aldoxime Anions[1)]

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Received March 18, 1988 (Revised Manuscript Received June 24, 1988)

The reaction of *Z* aldoximes with BuLi to give dianions and the properties of the latter were examined. D-Labelling and silylation confirm previous findings that only the *Z* isomer forms the dianion. *Z*-Hexanal oxime and *Z*-octanal oxime were deprotonated with BuLi, and the anions underwent aldol condensation reactions with several aldehydes and ketones including α,β-unsaturated aldehydes. Attempts to alkylate monoanions of OTHP ethers of aldoximes failed. However, carbanion addition to the C=N bond of some oxime OTHP ethers was observed.

Alkylierung und Aldol-Reaktionen von Aldoxim-Anionen[1)]

Z-Aldoxime liefern mit BuLi Dianionen, deren Eigenschaften untersucht wurden. Isotopenmarkierung (mit D) und Silylierung bestätigen frühere Befunde, daß nur das *Z*-Isomer Anionen bildet. *Z*-Hexanal- und *Z*-Octanal-oxim wurden mit BuLi deprotoniert. Deren Anionen reagieren in Aldol-Kondensations-Reaktionen mit verschiedenen Aldehyden und Ketonen einschließlich α,β-ungesättigten Aldehyden. Versuche, die Monoanionen von *O*-Tetrahydropyranyl-Ethern von Aldoximen zu alkylieren, schlugen fehl. Dagegen wurde bei einigen *O*-Tetrahydropyranyl-Ethern von Oximen eine Addition des Carbanions an die C=N-Bindung beobachtet.

The aldol condensation, one of the oldest reactions in the synthetic repertory, is still a topic of current interest[2)], and the mixed aldol reaction between an aldehyde nucleophile and a ketone electrophile continues to present a challenge. In our studies on intramolecular nitrile olefin cyclizations[3)] we had need of a method to produce α-substituted functionalized aldoximes since the latter can be converted readily into nitrile oxides. Hence, the aldol condensation of aldoxime anions with ketones looked particularly attractive.

Oxime dianions have been used extensively in alkylation of ketoximes[4)], and recently Gaudemar and co-workers[5)] showed that LDA can convert acetaldoxime and propionaldoxime into dianions which undergo aldol condensation with cyclohexanone in variable yields.

It was clear from these studies that only the *Z* (*syn*) aldoxime of the *Z*/*E* mixture reacted to form the dianion which underwent further alkylation. Recently, Gawley et al.[6)] indicated that acetaldoxime, upon prolonged refrigeration, consists mainly of the *syn* isomer and therefore can be α-alkylated in high yield. We report here our studies aimed at extending the scope of the reaction of aldoxime dianions and their applications to cases in which diastereomeric products are formed.

By means of D-labelling and NMR we were able to confirm that no dianion formation occurs from the *E* (*anti*) form of propanal oxime (**1a**). Thus, a 56:44 *E*:*Z* mixture of **1a** treated with up to 5 equivalents of BuLi in hexane at 0°C followed by quenching with D_2O led to quantitative deuteration of the *Z* aldoxime while no D at C-2 of the *E* isomer was detectable by NMR. Changing the solvent to ether or THF/HMPA and the base to LDA or NaH-BuLi had no effect. When propanal oxime (**1a**) was treated with 2 equiv. of LDA followed by trimethylsilyl chloride at −78°C, a mixture of **2**-*Z*, **2**-*E*, **3**-*Z* and silylated diisopropylamine was obtained but no **3**-*E* formed. The preference for formation of a dianion from the *Z* oxime can be attributed to stabilization by intramolecular chelation (see **4**)[5)].

Pure *Z* isomers of hexanal oxime (**1b**) and octanal oxime (**1c**) were obtained by crystallization. Treatment of **1b** with 2 equiv. of BuLi in hexane followed by D_2O led to quantitative deuteration at the α-carbon. Similarly, (*Z*) octanal oxime (**1c**) was converted into its dianion and was quantitatively methylated (MeI, at −40°C) to give (*Z*)-*O*-methyl-2-methyloctanal oxime (**5**).

The dianions of *Z* oximes **1b** and **1c** reacted with aldehydes and ketones to give β-hydroxy aldoximes **6** and **7** in high yields (Table 1). The condensation with ketones is not diastereoselective and leads to 1:1 mixtures of diastereomers. With aldehydes, the diastereoselectivity increases up to a 3:1 ratio. The diastereomeric ratio of the products was determined by integration of the low-field doublet of the oxime protons. With conjugated aldehydes only addition to the carbonyl and no Michael addition was observed.

We then prepared the *O*-tetrahydropyranyl (OTHP) ethers of oximes **1a**, **1b**, and of acetaldoxime in order to examine whether they can be used for regiospecific alkylation. We found that, unlike OTHP derivatives of ketoximes which undergo regiospecific alkylation[7)], the aldoxime ethers **8** when treated with LDA at −78°C and subsequently with methyl iodide or aldehydes led to nitriles. In the reaction of **8c** with LDA and methyl iodide a product identified as **10** was isolated in 60% yield.

Apparently, the α-anion of the initially formed nitrile **9** adds to the C=N bond of unreacted oxime OTHP ether **8c**. The intermediate is then trapped by MeI to form **10**. The structure of **10** (a 4:1 diastereomeric mixture) was assigned on the basis of the ^{1}H- and ^{13}C-NMR and mass spectrum. Characteristic absorption of the *N*-methyl group was found at 2.71 ppm in the proton NMR and at 41.27 ppm in ^{13}C-NMR for the major isomer (2.77 and 43.99 ppm for

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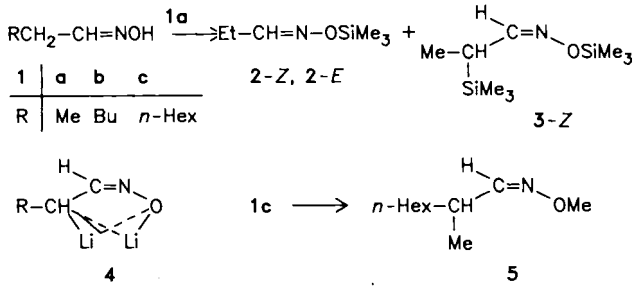


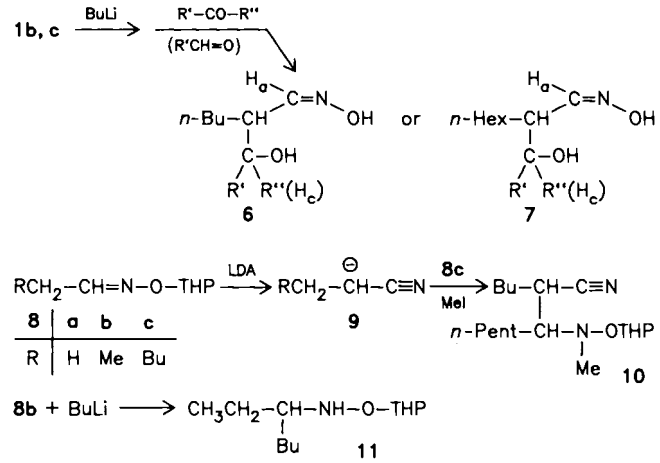
Table 1. Formation of aldol oximes **6** and **7** by reaction of the dianion of the aldoxime **1b** and **1c** with ketones or aldehydes

Product[a]	Electrophile	Yield[b] (%)	Time[c] [h]	Diastereomers[f]
6a	Cyclohexanone	80	15	–
6b	2-Pentanone	99	4	1:1 (oil)
6c	(2-Cyclopentenyl)-acetone	91	15	1:1:1:1 (oil)
6d	5-Hexen-2-one	76	1	1:1 (oil)
6e	Isobutyraldehyde	90[c]	3	1:3 (oil)
6f	Benzaldehyde	82	2	1:2.5[g] (oil)
6g	Cinnamaldehyde	53[d]	15	1:2 (oil)
6h	2-Heptenal	44[d]	15	1:2 (oil)
6i	Crotonaldehyde	32[d]	15	1:2 (oil)
7b	2-Pentanone	99[c]	35	1:1 (oil)
7e	Isobutyraldehyde	90[c]	4	1:3 (oil)

	^{1}H NMR data, δ values[h]					
	OH	H_a	C=C	H_c	H_b	$-[CH_2]_n-$	CH_3
6a	7.7	6.79 (d, 8 Hz)			3.17	1.6–1.3	
6b	8.7	6.67 (2 d, 9 Hz)			3.21	1.7–1.2	1.19, 1.16 (s) 0.92, 0.89 (t)
6c	not obs.	6.65 (4 d, 8 Hz)	5.71 (m)		3.23	1.7–1.2	0.50
6d	not obs.	6.64 (2 d, 8 Hz, 9 Hz)	5.61 (m) 4.97 (m)		3.21	1.6–1.2	0.88
6e	8.8	6.65 (2 d, 8 Hz)		3.37	3.30	1.6–1.2	0.95 (2 d, 7 Hz) 0.89 (m)
6f	7.7	6.60 (2 d, 8 Hz)		4.87	3.56	1.7–1.3	0.85 (t)
6g	8.1	6.63 (2 d)	6.63, 6.22	4.35	3.32	1.6–1.3	0.89 (t)
6h	8.9	6.58 (2 d)	5.66, 5.48	4.12	3.32	1.6–1.3	0.89 (t)
6i	8.0	6.58 (2 d)	6.63, 6.22	4.11	3.33	1.6–1.3	1.71 (d) 0.88 (t)
7b	8.6	6.72 (2 d, 9 Hz)			3.21	1.7–1.3	1.26, 1.23 (s) 0.99, 0.95 (t)
7e	8.8	6.63 (2 d, 8 Hz)		3.36	3.30	1.6–1.2	0.95 (2 d, 7 Hz) 0.89 (t)

[a] As *Z* isomer, except that mixtures of *E* and *Z* oximes are obtained when the reaction is neutralized with 1 N HCl instead of satd. NH_4Cl; all structures were confirmed by NMR and some by mass spectra. – [b] Isolated yields after purification by flash chromatography, except as indicated by[c]; oils. – [c] Yields estimated by ^{1}H-NMR of crude product. – [d] Not optimized. – [e] Reaction time at room temp. – [f] Ratio of diastereomers determined by integration of the H_a signal in $R-CH_a=NOH$. – [g] Diastereomers separated by chromatography. – [h] Multiplicity of signal: multiplet or broad if not stated otherwise (s = singlet, d = doublet, t = triplet, 2 d = two doublets due to diastereomers), assignment according to formula **6**, **7**. Aromatic protons for **6f** and **6g** absorb at 7.33. Isopropyl $CHMe_2$ in **6e** and **7e** absorb at 1.72 as septuplet, J = 7 Hz.

the minor isomer). That nucleophilic addition to the C=N bond of such oxime ethers is possible, was shown by isolation of **11** upon treatment of propanal oxime OTHP ether (**8b**) with BuLi at 0°C. Further studies of these systems aimed at improving diastereoselectivity are under way.



We thank the *Alexander-von-Humboldt-Stiftung* for a Feodor Lynen stipend to F. N. This research was supported by a grant from the *US-Israel Binational Science Foundation*, Jerusalem, Israel.

Experimental

IR-spectra were recorded on a Perkin-Elmer 457 spectrometer, NMR spectra on a 300-MHz Bruker AM-300 spectrometer. GC/MS analysis were performed on a Varian-Finnigan system. All compounds gave satisfactory elemental analyses or spectroscopic data.

All ground glassware utilized in the preparation of organometallic intermediates and subsequent reactions was dried in an oven at 150°C, assembled while hot, and cooled under a stream of argon. Round-bottom flasks were equipped with a gas inlet, and a mercury bubble valve maintained a slight pressure of argon during all manipulations.

n-Butyllithium (1.5 molar in hexane) was purchased from Aldrich and standardized by titration with 2-butanol/xylene[7]. LDA was prepared prior to use as described in ref.[8]. Aldoximes were prepared by adding Na_2CO_3 solution to a suspension of the aldehyde in aqueous $NH_2OH \cdot HCl$[9]. Liquid oximes were extracted with CH_2Cl_2 and distilled. Solid oximes were extracted with petroleum ether and crystallized twice from petroleum ether. The *E*:*Z* ratio was determined by ^{1}H-NMR spectroscopy according to Karabatsos and Tailler[10]. Alkyl halides, aldehydes, and ketones were distilled before used as electrophiles.

THF and ether were distilled from sodium under N_2 using benzophenone as indicator. HMPA was distilled from CaH_2 under reduced pressure and loaded with argon. Chloroform was dried over molecular sieves.

Preparation of Aldoxime Dianions and Reactions with Electrophiles: The preparation of **6b** is representative for the dianion formation. Ketones or aldehydes were dissolved in THF and added dropwise to the stirred dianion solution at 0°C, the mixture was allowed to warm to room temperature and stirring was maintained for 2 to 15 h (see Table 1 for reaction times). The reaction mixture was then hydrolyzed with ice and neutralized with saturated aqueous NH_4Cl. Deuteration experiments were carried out by quenching the dianion solution with D_2O (99.5%) followed by neutralization with aqueous NH_4Cl.

Elemental analyses of representative β-hydroxy oximes:

6a: $C_{12}H_{23}NO_2$ (213.3) Calcd. C 67.57 H 10.87 N 6.57
Found C 67.92 H 11.10 N 6.70

6f: $C_{13}H_{19}NO_2$ (221.3) Calcd. C 70.56 H 8.65 N 6.33
Found C 70.98 H 8.64 N 6.37

Table 2. ^{1}H NMR data of aldoxime OTHP ethers (δ values)[a]

			CH=N	OCH−O	CH_2O	CH_3[b]	CH_3
8a	*E*	46%	7.52 q, 6 Hz	5.19 dd, 11.5 Hz	3.62 m	1.90 d, 6 Hz	–
	Z	54%	6.99 q, 6 Hz	5.26 dd, 10.5 Hz	3.92 m	1.81 d, 6 Hz	–
8b	*E*	61%	7.49 t, 6 Hz	5.20 dd	3.62 m	2.23 m	0.89 m, 3H
	Z	39%	6.77 t, 5.5 Hz	5.20 dd	3.92 m	2.40 m	
8c	*E*	61%	7.50 t, 6 Hz	5.20 dd, 11.5 Hz	3.62 m	2.27 m	1.10 t, 7.5 Hz
	Z	39%	6.75 t, 5.5 Hz	5.25 dd, 10.5 Hz	3.93 m	2.42 m	1.09 t, 8 Hz

[a] Multiplet, unless stated otherwise. – [b] CH_3 or CH_2 next to C=N; CH_2O signals in **8a–c** appear as two multiplets at 3.62 and 3.92; $CH_2CH_2CH_2$ signals in THP appear at 1.50–1.88 as multiplet.

Preparation of (Z)-2-Butyl-3-hydroxyhexanal Oxime (**6b**): (*Z*)-Hexanal oxime (**1b**) (0.70 g, 6.08 mmol, dissolved in ca. 12 ml of THF) was treated dropwise under intensive magnetic stirring with 8.5 ml of *n*-butyllithium solution (1.5 molar) at 0°C. First, a white precipitate of the mono lithium salt formed which dissolved completely upon stirring the mixture at room temperature for 20 to 30 min. The clear and colourless solution of the dianion was recooled to 0°C, and a solution of 0.53 g (6.15 mmol) of 2-pentanone in 5 ml of THF was added dropwise. The mixture was allowed to warm to room temperature and stirred for 4 h, then hydrolyzed with ice, and neutralized with saturated aqueous NH_4Cl. The organic phase was separated, combined with the CH_2Cl_2 extracts of the aqueous phase, washed with brine, dried ($MgSO_4$), and evaporated. Purification by flash chromatography on SiO_2 (20 × 2 cm, eluent 25% ethyl acetate in hexane) gave 1.21 g (99%) of **6b** as a colourless oil (see Table 1 for NMR data).

Preparation of (Z)-O-Methyl-2-methyloctanal Oxime (**5**): (*Z*)-Octanal oxime (**1c**) (0.88 g, 6.15 mmol) was deprotonated with 8.5 ml of *n*-butyllithium solution of (1.5 molar) as described above. The solution of the dianion was cooled to −40°C, and excess methyl iodide (1 ml, ca. 20 mmol, in 2 ml THF) was added dropwise. The mixture was stirred for 1 h during which it warmed to −30°C and was then hydrolyzed with saturated aqueous NH_4Cl. The organic phase was separated, combined with the CH_2Cl_2 extracts of the aqueous phase, washed with brine, dried ($MgSO_4$), and evaporated to give 1.05 g (100%) of **5** as a colourless oil. – ^{1}H NMR ($CDCl_3$): δ = 0.88 (3H, t, *J* = 5 Hz), 1.08 (3H, t, *J* = 7 Hz), 1.20–1.50 (12H, br. m), 3.08 (1H, m), 3.67 (3H, s), 6.50 (H, d, *J* = 7.5 Hz).

Preparation of O-Tetrahydropyranyl Aldoximes: To a solution of 2.36 g (40 mmol) of acetaldoxime and 3.50 g (42 mmol) of dihydropyran in 40 ml of dry $CHCl_3$, ca. 1.0 g of $F_3B{-}OEt_2$ was added dropwise at 0°C. The mixture was stirred at room temperature for 48 h, then washed with aqueous $NaHCO_3$, brine, dried ($MgSO_4$), and evaporated. Kugelrohr distillation gave 4.73 g (79%) of acetaldoxime OTHP ether (**8a**) (boiling range 140–170°C/30 Torr) as a colourless liquid. In a similar way, propanal oxime OTHP ether (**8b**) (83% yield, boiling range 160–170°C/20 Torr) and hexanal oxime OTHP ether (**8c**) (75% yield, boiling range 135–155°C/0.1 Torr) were obtained (see Table 2 for NMR data).

Attempted Methylation of Hexanal Oxime OTHP Ether (**8c**). – *Isolation of* **10**: A solution of 279 mg (1.40 mmol) of hexanal oxime OTHP ether (**8c**) in 2 ml of THF was added dropwise at −78°C to a solution of 1.50 mmol LDA (freshly prepared from 158 mg diisopropyl amine in 1 ml THF and 1 ml of *n*-BuLi). The mixture turned red immediately and was stirred for 1 h between −45 and −30°C. Then excess methyl iodide (0.3 ml ca. 6 mmol) in 1 ml of THF was added at −78°C, the mixture was allowed to warm to 0°C, and was hydrolyzed with saturated aqueous NH_4Cl. After the usual workup, kugelrohr distillation gave 130 mg (60%) of **10** (boiling range 180–200°C/0.1 Torr. – IR (film): 2233 cm^{-1} (C≡N). – ^{1}H NMR ($CDCl_3$): δ = 0.90 (3H, t, *J* = 7 Hz), 0.93 (3H, t, *J* = 7 Hz), 1.20–1.80 (20H, br. m), 2.71 (2.4H, s), 2.75 (1H, br. m), 2.77 (0.6H, s), 3.09 (1H, ddd, *J* = 3, 6, 10 Hz), 3.56 (1H, m), 3.95 (1H, m), 4.78 (0.8H, m), 4.87 (0.2H, m). – ^{13}C NMR (abbreviations: *p* = primary, *s* = secondary, *t* = tertiary, *q* = quaternary); major isomer ($CDCl_3$): δ = 13.58 (*p*), 20.08 (*s*), 21.94 (*s*), 22.30 (*s*), 25.23 (*s*), 27.05 (*s*), 28.36 (*s*), 29.31 (*s*), 29.71 (*s*), 30.97 (*s*), 31.69 (*t*), 31.74 (*s*), 41.27 (*p*), 63.12 (*s*), 67.44 (*t*), 101.42 (*t*), 121.29 (*q*). – MS (EI): *m/z* (rel. intensity): *m/z* = [M + 1] (39), 227 [M + 1 − C_5H_8O] (28), 209 (7), 130 (24), 86 (100), 67 (13).

$C_{18}H_{34}N_2O_2$ (310.5) Calcd. C 69.63 H 11.04
Found C 70.05 H 11.20

Nucleophilic Addition of n-Butyllithium to the C=N Bond of **8b**. – *Isolation of* **11**: To a solution of 220 mg (1.40 mmol) of propanal oxime OTHP ether (**8b**) in 2 ml of THF was added 1 ml of butyllithium (1.5 molar) at 0°C, and the mixture was then stirred for 1 h at room temperature. After hydrolysis, usual workup, and kugelrohr distillation, 106 mg (35%) of the OTHP hydroxylamine **11** (boiling range 150–160°C/20 Torr) was obtained. – ^{1}H NMR ($CDCl_3$): δ = 0.91 (6H, m), 1.20 (14H, br. m), 2.82 (1H, m), 3.56 (1H, m), 3.92 (1H, m), 4.80 (0.8H, m), 4.96 (0.2H, m). – ^{13}C NMR (major isomer; ($CDCl_3$): δ = 9.60 (*p*), 13.78 (*p*), 20.20 (*s*), 22.76 (*s*), 24.68 (*s*), 28.17 (*s*), 29.14 (*s*), 30.68 (*s*), 61.43 (*t*), 62.96 (*s*), 101.69 (*t*); abbreviations see above.

CAS Registry Numbers

(*E*)-**1a**: 22042-15-5 / (*Z*)-**1a**: 22067-09-0 / (*Z*)-**1b**: 5780-43-8 / (*Z*)-**1b** (α-D): 115679-09-9 / (*Z*)-**1c**: 5780-44-9 / (*E*)-**2**: 115679-07-7 / (*Z*)-**2**: 115679-06-6 / (*Z*)-**3**: 115679-08-8 / (*Z*)-**5**: 115679-10-2 / (*Z*)-**6a**: 115679-11-3 / (*Z*)-**6b** (isomer 1): 115679-12-4 / (*Z*)-**6b** (isomer 2): 115679-13-5 / **6c** (isomer 1): 115792-91-1 / **6c** (isomer 2): 115792-92-2 / **6c** (isomer 3): 115792-93-3 / **6c** (isomer 4): 115792-94-4 / (*Z*)-**6d** (isomer 1): 115679-16-8 / (*Z*)-**6d** (isomer 2): 115704-75-1 / (*Z*)-**6e** (isomer 1): 115679-17-9 / (*Z*)-**6e** (isomer 2): 115679-18-0 / (*Z*)-**6f** (isomer 1): 115679-21-5 / (*Z*)-**6f** (isomer 2): 115679-22-6 / (*Z,X*)-**6g** (isomer 1): 115679-23-7 / (*Z,X*)-**6g** (isomer 2): 115679-24-8 / (*Z,X*)-**6h** (isomer 1): 115679-25-9 / (*Z,X*)-**6h** (isomer 2): 115679-26-0 / (*Z,X*)-**6i** (isomer 1): 115679-27-1 / (*Z,X*)-**6i** (isomer 2): 115679-28-2 / (*Z*)-**7b** (isomer 1): 115679-14-6 / (*Z*)-**7b** (isomer 2): 115679-15-7 / (*Z*)-**7e** (isomer 1): 115679-19-1 / (*Z*)-**7e** (isomer 2): 115679-20-4 / (*E*)-**8a**: 115679-29-3 / (*Z*)-**8a**: 115679-33-9 / (*E*)-**8b**: 67401-83-6 / (*Z*)-**8b**: 67401-84-7 / (*E*)-**8c**: 115679-30-6 / (*Z*)-**8c**: 115679-34-0 / **10**: 115679-31-7 / **11**: 115679-32-8 / (*i*-Pr)$_2$NTMS: 17425-88-6 / MeCH=NOH: 107-29-9 / EtCH=NOH: 627-39-4 / $Me(CH_2)_4CH$=NOH: 6033-61-0 / PrAc: 107-87-9 / $Ac(CH_2)_2$-CH=CH_2: 109-49-9 / *i*-PrCHO: 78-84-2 / PhCHO: 100-52-7 /

PhCH=CHCHO: 104-55-2 / BuCH=CHCHO: 2463-63-0 / MeCH=CHCHO: 4170-30-3 / cyclohexanone: 108-94-1 / 2-cyclopentenyl acetone: 105-24-8

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