

Reduction of O-Methyl Oxime Ethers of Conjugated Cyclohexenones with Aluminum Hydride

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Received 27 November 1991

ABSTRACT

The reduction of representative O-methyl oxime ethers 1-4 with aluminum hydride in tetrahydrofuran yielded allylic amines and saturated aziridines as the main products. The stereochemical course of the reduction to aziridines depends on the oxime ether configuration. Thus, E-3, E-4 and Z-3, Z-4 gave 15, 16 and 21, 22, respectively, with high stereoselectivity. Higher reactivity of Z than E isomers was utilized for the preparation of pure E isomers of oxime ethers from E, Z mixtures.

In contrast to the highly selective reduction of conjugated ketones to allylic alcohols by hydride reducing agents [1-3], much lower selectivity has been achieved in a similar transformation of conjugated oximes to allylic amines. Lithium aluminum hydride, most often used for the reduction of these oximes, reacts sluggishly to give mixtures of saturated and unsaturated amines and aziridines [4-9]. Recently, we showed that aluminum hydride reacts with conjugated cyclohexenone oximes faster and more selectively than lithium aluminum hydride, providing allylic amines in higher yields and with less side products [10]. These results prompted us to extend our studies to readily available O-methyl oxime ethers.

RESULTS AND DISCUSSION

In our previous study on the reduction of oximes with aluminum hydride, it was observed that se-

lectivity of the reaction depended on the oxime configuration. Consequently, in this study, pure E and Z isomers of representative O-methyl oxime ethers 1-4 were used. The ethers were obtained by the methylation of oximes (method A) or by the reaction of ketones with methoxyamine (method B). Method A provided products of higher purity and in better yields. Products obtained by method B were contaminated with the unreacted ketone and required further purification. 2-Methyl-2-cyclohexenone gave exclusively the E-2 isomer. Pure E and Z isomers of the other oxime ethers were isolated from E, Z mixtures by preparative gas chromatography (GC). The E isomers were identified by comparison (GC and ^1H and ^{13}C NMR) with authentic samples prepared by the methylation of E isomers of the corresponding oximes. In the ^1H NMR spectra of the oxime ethers 1-4, signals of the methylene group in the α -position to the $\text{C}=\text{NOCH}_3$ group are shifted to lower field for E isomers as compared to Z isomers, whereas signals of the vinyl proton in the α -position to the $\text{C}=\text{NOCH}_3$ group appear at lower field for Z isomers (Table 1).

The reduction of 1-4 with aluminum hydride was carried out in refluxing tetrahydrofuran at the molar ratio 1:1.33. Under these conditions, Z isomers reacted completely in 1 hour, whereas E isomers required longer reaction times (Table 2). The reactivity difference was found to be of advantage for the isolation of pure E isomers from E, Z mixtures by selective reduction of the more reactive isomer. Thus, the reduction of E, Z-4 for 1 hour left the unreacted E isomer which was isolated in 78% yield. The procedure provides a convenient alternative to tedious GC separation when a larger quantity of pure E isomer is required.

The reduction products obtained from 1-4 are

Dedicated to Prof. Herbert C. Brown on the occasion of his eightieth birthday.

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TABLE 1 The ^1H and ^{13}C NMR Spectral Data for E and Z Isomers of 1–4

Compound Number	^1H NMR/ CDCl_3/TMS (ppm)	^{13}C NMR/ CDCl_3/TMS (ppm)
E-1	1.50–1.90 (m, 2H, CH_2), 2.00–2.31 (m, 2H, CH_2), 2.46 (t, $J = 7$ Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3), 6.23 (m, 2H, $\text{CH}=\text{CH}$).	20.98 (t, C-5), 22.81 (t, C-6), 25.16 (t, C-4), 61.55 (q, OCH_3), 124.52 (d, C-2), 135.95 (d, C-3), 155.51 (s, C-1)
Z-1	1.65–2.00 (m, 2H, CH_2), 2.08–2.62 (m, 4H, CH_2), 3.73 (s, 3H, OCH_3), 6.30 (dt, $J = 10$ Hz, $J = 3$ Hz, 1H, $\text{CH}=\text{CH}$), 6.77 (dm, $J = 10$ Hz, 1H, $\text{CH}=\text{CH}$).	22.47 (t, C-5), 26.35 (t, C-4), 28.44 (t, C-6), 61.33 (q, OCH_3), 117.66 (d, C-2), 139.53 (d, C-3), 152.74 (s, C-1).
E-2	1.61 (t, $J = 6$ Hz, 2H, CH_2), 1.78 (d, $J = 1.5$ Hz, 3H, CH_3), 2.06 (m, 2H, CH_2), 2.46 (t, $J = 6$ Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.02 (dt, $J = 6$ Hz, $J = 1$ Hz, 1H, $\text{CH}=\text{C}$).	17.92 (q, CH_3), 21.54 (t, C-5), 23.07 (t, C-6), 25.20 (t, C-4), 61.59 (q, OCH_3), 130.87 (s, C-2), 132.85 (d, C-3), 155.95 (s, C-1).
E-3	1.62 (t, $J = 7$ Hz, 2H, CH_2), 1.81 (d, $J = 1$ Hz, 3H, CH_3), 2.06 (m, 2H, CH_2), 2.46 (t, $J = 6$ Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 5.92 (sextet, $J = 1$ Hz, 1H, $\text{CH}=\text{C}$).	21.20 (t, C-5 or C-6), 22.14 (t, C-5 or C-6), 24.11 (q, CH_3), 30.35 (t, C-4), 61.40 (q, OCH_3), 119.75 (d, C-2), 145.76 (s, C-3), 156.44 (s, C-1).
Z-3	1.85 (s, 3H, CH_3), 1.69–2.38 (m, 6H, CH_2), 3.85 (s, 3H, OCH_3), 6.50 (sextet, $J = 1$ Hz, 1H, $\text{CH}=\text{C}$).	22.55 (t, C-5), 24.30 (q, CH_3), 27.92 (t, C-6), 31.43 (t, C-4), 61.22 (q, OCH_3), 113.66 (d, C-2), 150.02 (s, C-3), 153.64 (s, C-1).
E-4	1.07 (s, 6H, CH_3), 1.70 (d, $J = 1$ Hz, 3H, CH_3), 1.90 (bs, 2H, CH_2), 2.30 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3), 5.90 (sextet, $J = 1$ Hz, 1H, $\text{CH}=\text{C}$).	24.15 (q, CH_3), 26.59 (q, gem CH_3), 30.53 (s, C-5), 35.61 (t, C-6), 44.79 (t, C-4), 61.40 (q, OCH_3), 118.85 (d, C-2), 143.45 (s, C-3), 156.29 (s, C-1).
Z-4	1.70 (s, 6H, CH_3), 1.82 (bs, 3H, CH_3), 1.97 (bs, 2H, CH_2), 2.07 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.51 (m, 1H, $\text{CH}=\text{C}$).	24.30 (q, CH_3), 28.07 (q, gem CH_3), 31.54 (s, C-5), 41.24 (t, C-6), 45.84 (t, C-4), 61.25 (q, OCH_3), 112.80 (d, C-2), 147.82 (s, C-3), 153.53 (s, C-1).

shown in Table 2. They were identified by comparison with authentic samples prepared by other methods. The main products—allylic amines and saturated aziridines—were isolated by preparative GC, and their ^1H or ^{13}C NMR spectra were recorded. Small amounts of side products were identified by GC comparison. The reduction products indicate an influence of the oxime ether configuration on the selectivity of the reaction. Thus, higher yields of allylic amines were obtained from E isomers as compared to Z isomers. The opposite was observed for aziridines, which were formed in higher yields from Z isomers. The reduction to aziridines was highly stereoselective. Stereoisomeric aziridines **15**, **16** and **21**, **22** were obtained from E-3, E-4 and Z-3, Z-4, respectively. The oxime ethers **1**, **3**, and **4** gave 0–6% of perhydroazepines. Only E-2 containing a more highly substituted migrating carbon atom afforded 17% of **13**. Migration of the methylene group located in the α -position to the $\text{C}=\text{NOCH}_3$ group was not observed. Other saturated amines, obtained as side products, were found to be mixtures of isomers.

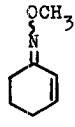



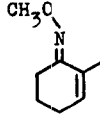






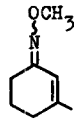








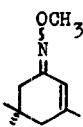








Possible reaction pathways leading to the main products and perhydroazepines are shown in Schemes 1 and 2. Allylic amines are presumably formed via an intermediate common to E and Z isomers, e.g., **28** (Scheme 1). The same intermediate is probably involved in the formation of **19** via a nitrene **29** or via a Beckmann-type rearrangement. Higher yields of aziridines obtained from the

Z isomers and higher reactivity of these isomers compared to the E isomers point to the importance of the oxime ether configuration. It is apparent that, in the case of the Z isomers, the reaction leading to *trans*-aziridines proceeds by an intramolecular hydride transfer after complexation with aluminum hydride. A cyclic transition state **30** accounts for stereoselective formation of **16** (Scheme 2). In the case of the E isomers, only an intermolecular hydride transfer would produce aziridines, e.g., **15**; hence, the reactivity of these isomers is lower compared to the Z isomers. In spite of much longer reaction times of E than Z isomers, the yields of saturated amines obtained from both types of isomers are almost the same, suggesting that allylic amines and aziridines are not easily reduced under the reaction conditions. Indeed, in a separate experiment, **6** was recovered unchanged after refluxing for 1 hour with aluminum hydride in tetrahydrofuran. This observation, however, does not rule out the formation of small amounts of amines **10–12**, **25** and **26** via the corresponding aziridines.

CONCLUSION

The reduction of O-methyl oxime ethers **1–4** with aluminum hydride in tetrahydrofuran is superior to the reduction of their parent oximes with the same reagent or with lithium aluminum hydride. In contrast to the oximes, which were reduced to

TABLE 2 Reduction of O-Methyl Oxime Ethers 1-4 with Aluminum Hydride in Refluxing Tetrahydrofuran at the Molar Ratio 1:1.33

Oxime ether	Time h	% Yield	Products							
			% Composition							
 1 E Z	8	91	 5	 6	 7					
	1	92	58	32	10	30	60	10		
 E-2	11	93	 8	 9	 10	 11	 12	 13		
			50	28	2	1	1	17		
 3 E Z	10	92	 14	 15	 16	 10	 11	 17	 18	 19
	1	93	37	38	2	17 ^a		30 ^a		6
 4 E Z	11	95	 20	 21	 22	 23	 24	 25	 26	 27
	1	94	54	39	0	4	<1	<1	<1	2
		40	0	54	1	1	2	1	1	

^aOverlapping peaks in GC analysis.

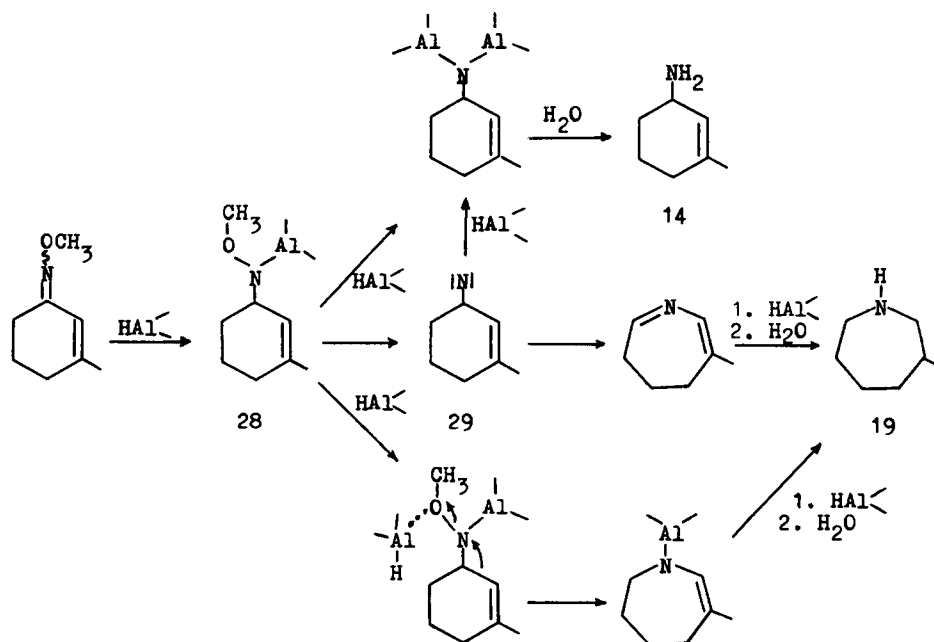
mixtures of several products, O-methyl oxime ethers 1-4 gave two main products—allylic amines and saturated aziridines. The reduction to aziridines is highly stereoselective, depending on the oxime ether configuration.

EXPERIMENTAL

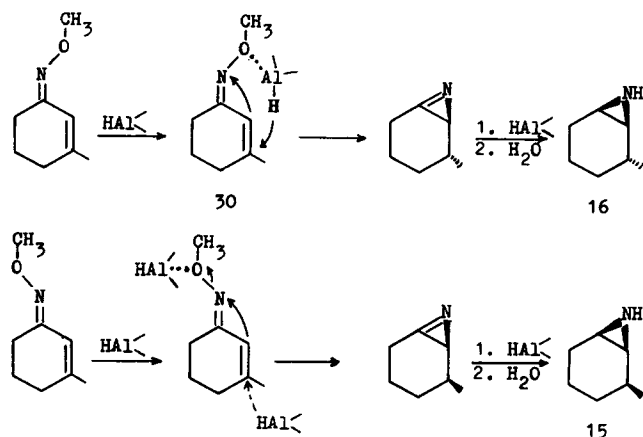
All reductions with aluminum hydride were conducted in an atmosphere of dry argon. The ¹H and ¹³C NMR spectra were recorded on Tesla BS 487C and Tesla 567A spectrometers at 80 and 25.156 MHz, respectively. The GC analyses were performed on a Chrom 4 chromatograph equipped with a glass capillary column, 0.29 mm × 29 m, Carbowax 20 M. Preparative GC separations were carried out on a GCHF 18.3 chromatograph equipped with a 10 mm × 2.5 m column packed with 12% Carbowax 20 M on Chromosorb P AW DMCS.

Materials and Authentic Samples

A mixture of 10 and 11, a mixture of 17 and 18, 3,5,5-trimethyl-2-cyclohexenone, and 7 were commercial samples (Aldrich, Milwaukee, WI). The following compounds were prepared by literature procedures: a solution of aluminum hydride in tetrahydrofuran [11], methoxyamine hydrochloride [12], 2-cyclohexenone [13] and its oxime [14], 3-methyl-2-cyclohexenone [15] and its oxime [16], 2-methyl-2-cyclohexenone oxime [10], 3,5,5-trimethyl-2-cyclohexenone oxime [17], 5 [18], 6 and 9 [19], 8 [10], 11 [20], 12 [21], 13 [5], 14-16 [10], 17 [22], 19 and 20 [10], 21 and 22 [5], 23 and 24 [23], 25 [23], and 27 [10]. A mixture of 25 and 26 (4:5) was prepared by the reduction of 2,4,4-trimethylcyclohexanone oxime [24] with aluminum hydride in tetrahydrofuran. O-Methyl oxime ethers 1-4 were prepared by methylation of the corresponding oxime potassium salts with methyl *p*-toluenesulfon-



SCHEME 1



SCHEME 2

ate in tetrahydrofuran (method A) and by the reaction of the corresponding ketones with methoxyamine hydrochloride in pyridine (method B).

Reduction of *O*-Methyl Oxime Ethers 1–4 with Aluminum Hydride

General Procedure. A solution of aluminum hydride in tetrahydrofuran (15 mL, 13.3 mmol) was added to a solution of *O*-methyl oxime ether (10.0 mmol) in the same solvent (5 mL) at room temperature, and the mixture was refluxed (*Z* isomers

for 1 hour, *E* isomers—see Table 2). After the mixture had been cooled to 0°C, water (2 mL) was added, followed by 7.5 M aqueous sodium hydroxide solution (2 mL, 15 mmol), and the mixture was stirred for 0.5 hour at room temperature. The precipitate which had formed was filtered off and washed with diethyl ether (3 × 20 mL). Organic solutions were combined and dried with anhydrous magnesium sulfate, and the product was isolated by distillation.

Isolation of Pure *E* Isomer from *E*, *Z* Mixtures of 1–4

General Procedure. A solution of aluminum hydride in tetrahydrofuran (75 mL, 66.5 mmol) was added to a solution of *E*, *Z*-4 mixture (81:19, 8.36 g, 50 mmol) in tetrahydrofuran (25 mL) at room temperature, and the mixture was refluxed for 1 hour. Workup, as described earlier, and distillation at 0.02 mm Hg gave fraction 1, 1.20 g, bp 36–44°C, and fraction 2, 5.28 g, 78% yield, bp 52–53°C. The GC analysis showed that fraction 1 was a mixture of amines and aziridines, and fraction 2 was identified as *E*-4 by comparison (GC, ¹H and ¹³C NMR) with an authentic sample.

ACKNOWLEDGMENT

We thank the Polish Academy of Sciences for financial support under Grant CPBP 01.13.

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