ADDITION OF ARYLLITHIUM COMPOUNDS TO OXIME ETHERS

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Abstract: Addition of non-stabilized organolithium reagents to O-alkyl aldoximes in the presence of boron trifluoride etherate gives rise to O-alkyl hydroxylamines. The Z oxime isomer preferentially reacts under these reaction conditions.

Addition reactions of organometallic compounds to oximes or oxime ethers is a potential route to hydroxylamines. Previous reports of this transformation have been mainly limited to the use of stabilized carbanions or to oximes without α -hydrogens. For example, stabilized anions such as ester enolates¹ and allylboronates² have been added to oxime ethers and stabilized penicillin Grignards have been added to *O*-ethylformaldoxime.³

When non-stabilized organometallic reagents are added to oximes with α -hydrogens, deprotonation is often the major reaction. Condensation reactions of oxime enolates with electrophiles is a useful synthetic method.⁴ Addition of phenyl- and alkyllithium reagents to oximes with abstractable hydrogens is reported to provide hydroxylamines in poor yield.⁵ The reaction of nonstabilized Grignards or aryllithium compounds with oximes bearing α -hydrogens in refluxing toluene gave aziridines.⁶

In a recent report,⁷ alkyllithium compounds have been efficiently added to the activated, electrophilic *O*benzyloxime of glycolic acid. As an extention of our previous work,⁸ we now report a procedure for the addition of nonstabilized organometallic reagents to *O*-benzyl aldoximes with α -hydrogens as a method for the synthesis of benzyloxyamines and hydroxylamines.

The O-benzyl aldoximes were prepared by treatment of the corresponding aldehyde with benzyloxyamine hydrochloride in a solution of pyridine and ethanol (1:1) at 90°C for 1 h. Initial attempts to add phenyllithium to O-benzylacetaldehyde oxime (1) were unsuccessful and, consistent with α -hydrogen abstraction, starting oxime was recovered. However, when the reaction was repeated, this time adding one equivalent of boron trifluoride etherate (BF₃-Et₂O) to the phenyllithium prior to the addition of 1, O-benzyl 1-phenylethylhydroxyl amine was obtained in 44% yield (Scheme 1). Unreacted oxime was recovered in 51% yield to provide nearly quantitative mass balance.



The scope of this BF_3 - Et_2O activated addition reaction was investigated with respect to different nucleophiles and oxime ethers. Representative examples are shown in Table I. Additions with aryl, acetylenic and vinyllithium reagents were successful (entries 1-4), while alkyllithiums failed to produce the desired product (entry 5). Allyl Grignard reagents also add to oximes in the presence of BF_3 - Et_2O ; prop-2-enyl magnesium bromide reacted with 1 in good yield (entry 6). The reaction is not restricted to *O*-benzyl oximes, as the *O*-methyl oxime (2) produced the corresponding alkoxyamine in a comparable yield to 1 (entry 7, 8). Only unreacted starting material was recovered from the addition of aryllithium reagents to ketoxime ethers (entry 9). In all the cases studied using stoichiometric amounts of reagents, according to the general procedure, the reaction did not proceed to completion and the remaining mass could be accounted for as recovered starting material.

Several parameters were evaluated in order to optimize the yields in these reactions. The use of higher temperatures, other solvents, and varing amounts of BF₃-Et₂O generally lead to reduced yields. Other Lewis acids were investigated. Only CeCl₃ and Al(CH₃)₃ provided addition products, but yields were not superior to those obtained with BF₃-Et₂O. The yield was improved when an excess of organolithium reagent was employed. When 2 equivalents of 5-methyl-2-thienyllithium was added to 1 in the presence of 2 equivalents BF₃-Et₂O the yield increased from 42% (entry 7) to 63%.

Yields were significantly lower when the oxime ethers contained a large fraction of the *E* geometric isomer. *O*-benzyl isobutyraldehyde oxime **4**, existing as 28% *Z* isomer, produced only a 19% yield of the benzyloxyamine. The unreacted oxime from this reaction (recovered in 69% yield) was found to be exclusively the *E* isomer. When the oxime ether was entirely in the *E* geometry as with **5** no addition products could be detected. These results suggest that the *Z* isomer of the oxime ether reacts preferentially in this addition reaction. Further investigations of this phenomenon were undertaken and are summarized in Table II. The *Z* and *E* isomers of oximes **1** and **6** were separated⁹ and independently reacted with 5-methyl-2thienyllithium in the presence of BF₃-Et₂O. In both cases the *Z* isomer reacted much more efficiently than the *E* oxime. In fact, we were unable to detect the formation of any benzyloxyamine in the reaction of *E* oxime **6b**, while its *Z* counterpart produced the desired adduct in 40% yield. Formation of a small amount of addition product in the reaction of **1b** could be explained by the *E* oxime present in the starting material.¹⁰ The addition of 5-methyl-2-thienyllithium with the cyclic oxime 7¹¹ provided the desired adduct in 61% yield.

We have demonstrated that the addition of organometallic compounds to oxime ethers in the presence of BF_3-Et_2O is a viable route for the preparation of alkoxyamines and the Z oxime isomer preferentially reacts under these reaction conditions. Further investigation is warranted to understand the mechanistic rationale for this observation.

Isomer Composition									
Entry	Lithium Reagent	Oxime	Z:E	Product	Yield				
1	С, n	N ^N OCH₂C4H3 CH3 [™] H 1	47 : 53	HN-OCH ₂ C ₄ H ₅	44% [⊾]				
2	CH _J O	_№ ~ ^{осн} ₂с,н, сн, ¹ н 1	47:53	HN-OCH ₂ C ₆ H ₅	46%°				
3	LI	_N ∿ ^{OCH₂C₄H₃} CH₃ [⊥] н 1	47 : 53 ^{CI}	HN-OCH ₂ C ₆ H ₅	50%⁵				
4	\sim ^{Li}	_N ∿осн₂с₄н₅ сн₃ ^人 н 1	47 : 53	HN-OCH ₂ C ₆ H ₅	32% ^b				
5		_N ∿осн₂с₅н₅ сн₃人 _Н 1	47 : 53		0%				
6	✓ MgBr	N [~] och ₂ c _s h ₅ Ch ₃ H 1	47 : 53	HN- OCH ₂ C ₄ H ₅	59% ^ь				
7	$\int_{r}^{s} \sum_{r}$	_N 、осн ₂ с ₆ н, сн ₃ н 1	47 : 53	HN-OCH ₂ C ₄ H ₅	42% °				
8	\bigwedge_{r}	^{N^{, ОСН,} сн, [↓]н 2}	53 : 47	HN-OCH ₃	41%°				
9	$\int_{r}^{s} \lambda_{r}$	_N , ^{ОСН} ₄С₄Н₅ сн, [↓] сн, 3			0%				
10	$\int_{r}^{s} \lambda_{r_{1}}$	$\bigvee^{N^{OCH_2C_4H_3}} H 4$	28:72	HN-OCH ₂ C ₆ H ₅	19% ^ь				
11	$\sum_{i=1}^{n}$	N ^N OCH ₂ C ₄ H ₅	0 : 100	_	0%				

Table 1. Representative examples for the addition of organolithium compounds to oxime ethers in the presence of BF_3 -Et₂O.

^a Isolated as the HCl salt. ^b Yield determined by NMR analysis. ^cIsolated by column chromatography.

Table 2. Influence of isomer geometry on yield in the reaction of 5-methyl-2-thienyllithium to oxime ethers in the presence of BF_3 - Et_2O .

No	Z-Oxime	Yield ^a	No	E-Oxime	Yield
1a	с,н,сн,о _N сн, ^с н	64%	1b	N∽OCH₅C₅H₅ CH3↓H	7%
6a	C4H3CH2O~N	40%	6b	^N ^{−OCH₂C₄H₄}	0%
7	C ^{o.} N	61%			

* Yield determined by NMR analysis.

General experimental procedure: BF_3 - Et_2O (2 mmol) was rapidly added to a solution of aryllithium (2 mmol) in dry THF (10 mL) at -78°C under a nitrogen atmosphere. This was followed immediately by the addition of a solution of the oxime (2 mmole) in THF (2 mL). The reaction was allowed to stir for 30 min at -78°C, diluted with pH 7 aqueous phosphate buffer solution, and allowed to warm to room temperature. The reaction mixture was extracted with ethyl acetate (3 x 20 mL) and the combined organic extracts were dried with MgSO₄, filtered and concentrated. The desired addition product was purified by column chromatography on silica gel.

References.

- 1. Ikeda, K.; Yoshinaga, Y.; Achiwa, K.; Sekiya, M. Chemistry Lett. 1984, 369.
- 2. Hoffmann, R. W.; Eichler, G.; Endesfelder, A.; Liebigs Ann. Chem. 1983, 2000.
- 3. Pirie, D. K.; Welch, W. M.; Weeks, P. D.; Volkmann, R.A.; Tetrahedron Lett. 1986, 27, 1549.
- 4. (a) Jung, M. E.; Blair, P. A.; Lowe, J. A. Tetrahedron Lett. 1976, 1439; (b) Ensley, H. E.; Lohr, R. Tetrahedron Letters 1978, 1415.
- 5. Richey, H. G., Jr.; McLane, R. C.; Phillips, C. J. Tetrahedron Lett. 1976, 233.
- (a) Kissman, H.M.; Tarbell, D. S.; Williams, J. J. Am. Chem. Soc. 1953, 75, 2959; (b) Chaabouni, R.; Laurent, A. Bull. Soc. Chim. Fr. 1973, 2680.
- 7. Kolasa, T.; Sharma, S.; Miller, M. J. Tetrahedron Lett. 1987, 28, 4973.
- 8. Basha, A.; Brooks, D. W.; J. Chem. Soc., Chem. Comm. 1987, 305.
- 9. The geometric isomers of oxime 1 were separated on silica gel using a prep 500 HPLC, eluting with hexane:CH₂Cl₂:ether (90:5:5). The isomers of 6 were separated *via* routine column chromatography. The identification of the geometric isomers was conducted as previously described: Karabatsos, G. J., Hsi, N. *Tetrahedron*, **1967**, *23*, 1079.
- 10. After separation by chromatography, neat oximes **1a** and **1b** slowly reverted to an equilibrium mixture of 47 : 53 in about 16h.
- 11. Cyclic oxime 7 was prepared as previously described: Norman, R. O. C.; Purchase, R.; Thomas, C.B. J. Chem Soc., Perkin I, 1972, 1701.

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