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Alkylation Studies of Anions from Pyruvate Oxime Ethers and Related Derivatives

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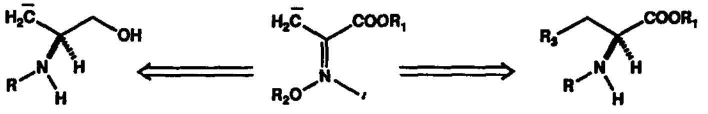
Summary: Studies have demonstrated alkylations of a highly reactive monoanion *via* deprotonation of *tert*-butyl pyruvate oximino ethers. In similar fashion, the oximino THP ethers of α-hydroxyacetone derivatives have exhibited base-dependent regioselective alkylations.

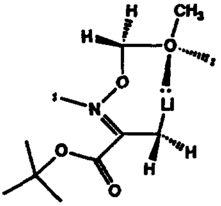
Oxime dianions, monoanions of oxime ethers, and their analogous *N,N*-dialkylhydrazones have proven to be useful and highly reactive agents for advances in enolate alkylation technology.[1,2] It is generally assumed that the deprotonations and alkylations of these systems will display a characteristic regioselectivity for the *Z* (*syn*) geometry.[3] This result is based upon a site-directed deprotonation *via* initial base complexation, and subsequent internal chelation of the proximate cation of the ambident anion. While the former situation is a kinetic result, the latter prescribes conditions of thermodynamic product development. In some cases it is apparent that these thermodynamic considerations are acutely sensitive to changes in substrate, base, solvent and temperature such that generalizations for regiocontrol are inappropriate.[4] Little is known about the effects of additional functionalization of such systems. However, Welch and Seper[5] have recently shown that α-fluoro(*E/Z*)-ketoxime ethers undergo deprotonation and alkylation without effect of fluorination on the observed regioselectivity.

Our interest in the synthesis of alkaloids which display a vicinal amino alcohol moiety has led us to explore C-alkylations of anions of pyruvate oximes 1 and related derivatives as three carbon synthons for the hypothetical carbanion 2. Additionally, these alkylation products could serve as an attractive source of novel amino acid derivatives 3 *via* asymmetric reductions,[6] or other nucleophilic additions[7] to the C=N unit.

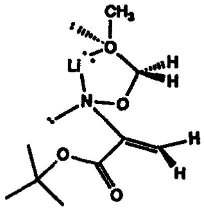


2 1 3

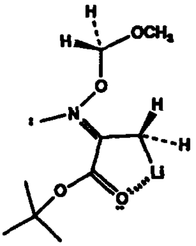
Our initial investigations have utilized the *tert*-butyl esters of pyruvate oximes. These materials were formed exclusively as pure E-oximes thereby facilitating deprotonation of the methyl group, while the *tert*-butyl ester was intended to hinder self-condensations. Furthermore, we hoped that the carbonyl itself might provide an additional coordination site for stabilization of these anions 4abc.[8]



4a



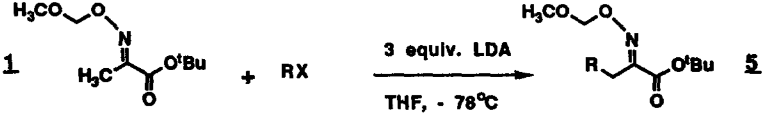
4b

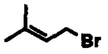
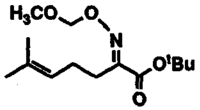
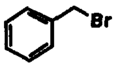
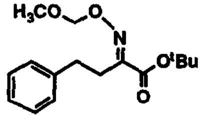
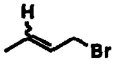
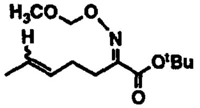
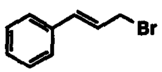
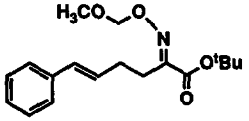
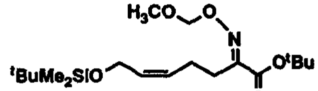
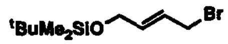
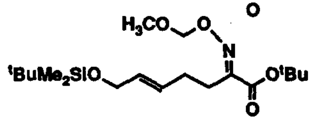
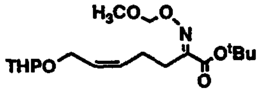
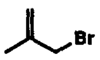
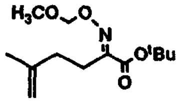


4c

Representative examples within a series of methoxymethyl (MOM) oximino pyruvates 5 are shown in Table I followed by a general procedure. Yields of purified products range from 50 to 77%. Similar results were obtained from the corresponding tetrahydropyranyl (THP) ether of 1 with alkylations using prenyl bromide as the best case (85%). We have found these monoanions to be highly reactive, unstable species which required their generation in the presence of excess alkylating agents. Only allylic and benzylic halides react at sufficiently rapid rates to compete with decomposition pathways.[9] Reactions with primary iodides lead only to recovery of alkylating agent, and attempts with allyl bromide or methyl iodide provide mixtures of mono and dialkylated products. The analogous SAMP/RAMP hydrazones[10] of 1 have exhibited similar reactivity, affording slightly lower yields for the examples of Table I. Attempts to utilize the dianion of the parent *tert*-butyl pyruvate oxime, under a variety of conditions, gave complete decomposition.

TABLE I



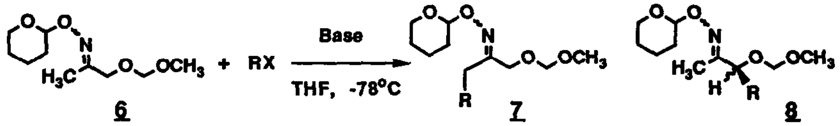
RX	Compound #	Product	% Yield
	5a		77
	5b		66
	5c		52
	5d		54
	5e		67
	5f		52
	5g		65
	5h		51

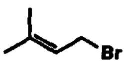
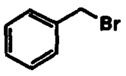
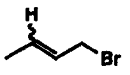
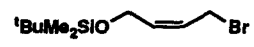
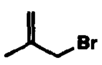
General Procedure for Alkylation of Pyruvate Oxime Ethers: A solution (1.0 M) of the oxime ether 1 in THF was cooled to -78 °C, and bromide R-X (4.0 equiv) was added. Lithium diisopropylamide (0.5 M) in THF (3.0 equiv) was slowly added dropwise at such a rate that a yellow solution was obtained. A rapid addition rate produced an orange solution resulting in lower yields of alkylated material. The mixture was stirred for 15 min after the addition of all base solution, then quenched with saturated aqueous NH_4Cl, and warmed to room temperature. The mixture was diluted with EtOAc, washed with saturated NH_4Cl, and then with saturated aqueous NaCl. The organic phase was dried (Na_2SO_4), filtered, and concentrated to a yellow-orange liquid which was purified by flash chromatography.

The requirement of three equivalents of LDA for our successful reactions was particularly interesting in light of literature accounts of intramolecular chelation and stabilization of such systems. Indeed, two equivalents of LDA led to recovered oxime ether. However, pretreatment of reaction mixtures with two equivalents of anhydrous LiBr followed by introduction of 1.5 equivalents of LDA allowed us to reproduce the yields of Table I. Furthermore, similar results were obtained by replacement of LDA with potassium hexamethyldisilazide (KHMDS; 1.5 equiv) without added LiBr.[11] These experiments imply that our oxime ethers must sequester two equivalents of lithium base in unreactive coordination clusters prior to deprotonation.

When the carbonyl function of oximes 1 was reduced to provide the O-tetrahydropyranyl oxime ethers 6, deprotonation and alkylation demonstrated base-dependent regioselectivity (Table II). The ethers 6 were available as a *E/Z* mixture (5:1 ratio) *via* reaction of acetol with O-THP hydroxylamine, and subsequent protection with MOM-Cl [CH_2Cl_2; *i*-$PrNEt_2$; 0° → 25 °C (66%)].[12]

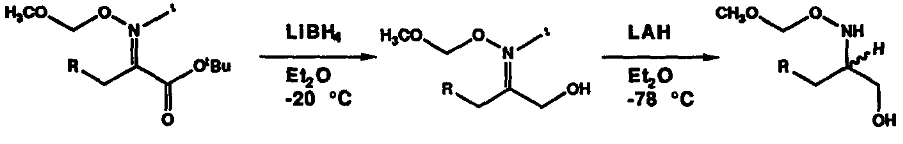
TABLE II



RX	Base	Compound #	% 7	% 8
	KHMDS	7a	61	0
	LDA	8a	0	71
	KHMDS	7b	49	0
	LDA	8b	0	48
	KHMDS	7c	49	0
	LDA	8c	0	46
	KHMDS	7d	50	0
	KHMDS	7e	51	0

Using the experimental conditions previously described, potassium hexamethyldisilazide (1.5 equiv) led exclusively to alkylation of the methyl site yielding 7, whereas lithium diisopropylamide (4 equiv) gave oximes 8 by internal alkylation at the carbon bearing the ether oxygen. As before, these anions were highly reactive, unstable species. The observed regioselectivity was not dependent on the geometry of the starting oxime ether (product *E/Z* ratios are 5:1). Thus, it seems unlikely that chelation of base with the *O*-tetrahydropyranyl moiety has played a significant role in site-directed deprotonations or anion-aggregate stabilization.

Finally, initial efforts have shown that the *tert*-butyl esters of 5 are selectively reduced with lithium borohydride (Et_2O at -20 °C) affording the oximino alcohols 9 (70-75%). Further reduction of the oxime C=N unit was accomplished with lithium aluminum hydride (Et_2O at -78 °C) to produce the N-alkoxyamino alcohols 10 (50-60%).



5 9 10

In conclusion, we have demonstrated conditions for alkylation of anions generated from oxime ethers of *tert*-butyl pyruvate and related acetol derivatives. Contrary to expectations for site-specific, *syn* deprotonations and enhanced stability *via* internal lithium cation coordination, our examples have shown that poorly chelated potassium bases may be the most efficient reagents for these transformations. In such cases, the geometry of the oxime ether may be of little significance for affecting the regiochemical course of the process. Further efforts are under way.

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9. Reactions in which anion formation was followed by addition of alkylating agent (5 min) gave minor amounts (10-15%) of self-condensation material. The polar decomposition products could not be identified. Others have noted extensive decomposition: Spencer, T.; Leong, C. *Tetrahedron Lett.* **1975**, 3889.
10. For a review: Enders, D. "Asymmetric Synthesis," Morrison, J.D. edit.; Academic Press; New York, **1983**, *3*, 243-339.
11. An earlier study had noted the superior quality of potassium bases. Gawley, R.E.; Termine, E.J.; Aube, J. *Tetrahedron Lett.* **1980**, *21*, 3115.
12. The pure *E*-isomer of 6 was also available *via* $LiBH_4$ reduction of the corresponding *O*-THP ether of 1 followed by reaction with MOM-Cl.

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