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REACTIONS OF ORGANOMETALLICS WITH OXIMES. SYNTHESIS OF α-N-HYDROXY AMINO ACIDS

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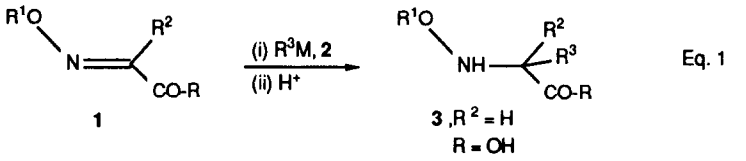
Summary: Reaction of organolithium reagents with glyoxylate and pyruvate derived oximes provides a direct route for the synthesis of unusual α-N-hydroxy amino acids.

The addition of metalated compounds to imines, oximes and hydrazones has become a useful process for syntheses of amines,[1] amino acids,[2,3] β-lactams[4,5] and other compounds of interest. Variations of these reactions have also led to the development of asymmetric syntheses based on chiral imine derivatives.[6,7] Two factors which often diminish the versatility of these reactions are poor electrophilicity of the imine derivative or enolization of substrates with α-hydrogens. In many cases these problems can be overcome by using more activated imines[2-4,8] or less basic reagents.[9] However, with oximes the same problems can be accentuated since oximes are often less electrophilic and less easily activated than the corresponding imines. α-Deprotonation of oximes is also facile[10] and only the use of a considerable excess of organolithium reagents produces addition products.[11] Even addition of allyl-[12] or crotyl-boronates[9], which proceeds smoothly with imines, requires vigorous conditions and has limited applicability with oximes. Despite these limitations, we considered that direct addition of organometallic reagents to oximes derived from α-oxoacids **1** would provide an attractive route to α-N-hydroxy amino acid derivatives **3** (eq 1). A number of these unusual amino acids have been found to play important physiological roles[13], and are of considerable synthetic interest.[14] Herein we describe a direct method for the syntheses of several novel N-hydroxy-α-amino acids (eq 1, Table 1).



1 **3**, $R^2 = H$, $R = OH$ Eq. 1

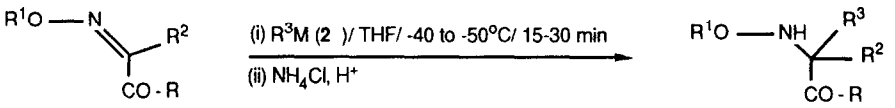
Several considerations were made regarding the types of substituents (R, R_1, R_2) to be incorporated in the initial substrate **1** to promote its conversion to **3**. Studies have shown that electrophilic additions to oximes are facilitated when the oxime oxygen is

protected.[15-18] With this in mind, and in anticipation of eventually preparing the free α-N-hydroxy amino acids, we chose oxygen protecting groups (R_1, Table I) which could be easily removed. The choice of the acyl substituent (R) was most critical, but simple. The group R had to be compatible with strongly nucleophilic reagents **2** and should deactivate the carbonyl toward nucleophilic attack. Both of these criteria were met by using the free carboxylic acid (R = OH) since it would deprotonate under the reaction conditions. By chosing hydrogen for R_2 we anticipated preparing the most common types of α-N-hydroxy amino acids from simple oximes of glyoxylic acid. To illustrate the versatility of the method one example of the reaction with a pyruvate was also included (entry f). Alkyllithiums were the first choice of the organometallic reagent (**2**) because of their potent nucleophilicity and the precedent for reactions of organolithium reagents with other oxime derivatives.[15-18]

As illustrated in Table I, the combination of all of these considerations provides an efficient and direct route for the synthesis of substituted α-N-hydroxy amino acids (**3**). Only a few organometallic reagents were tested in this preliminary study. While magnesium and zinc based reagents were ineffective, all of the alkyl lithium reagents tried were successful. As expected, esters (entries j and k) were incompatible with the process. However, amides were suitable substrates (entries n and p). Reaction of the pyruvate derived substrate also proceeded well to give the desired α,α-disubstituted N-hydroxy amino acid (entry f). Chiral oxime derivatives were also studied. Reaction of an O-phenethyl derivative with n-butyllithium gave a 1:1 mixture of the corresponding diastereomeric amino acids (entry l). Reaction of the same substrate with t-butyllithium (entry m) gave a mixture of the same diastereomers but with 30-40% de based on NMR analysis of the crude reaction mixture. The structures of the two diastereomers have not yet been assigned. Similar modest diastereoselectivity was observed in the reactions of other chiral substrates (entries n, o, and p). Reactions of other organometallic reagents (chiral and non chiral), and chiral oximes are being studied.

In a typical reaction, the oxime (**1**, Table 1, entry a, 0.286 g, 1.6 mmol) was dissolved in dry THF under nitrogen and cooled to -40°C. A solution of nBuLi (2 mL of a 1.6M solution in hexane, 200 mole%) was added and the mixture was stirred at -40°C for 15 min. The reaction was quenched with saturated NH_4Cl, acidified with 1N HCl to pH 2, and extracted with several portions of ethyl actate. The combined organic layers were extracted with a 5% $NaHCO_3$ solution and the organic phase was discarded. The aqueous layer was acidified to pH 2-4 with 1N HCl and extracted with several portions of ethyl acetate. The ethyl acetate extracts were combined, washed with brine, dried over $MgSO_4$, filtered and evaporated to provide 0.29 g (77% yield) of the N-benzyloxy amino acid **3** (entry a). Mp 113-115°C; ^{1}HNMR ($CDCl_3$, 200 MHz) δ 0.79 - 0.92 (m, 3H), 1.22 - 1.45 (m, 4H), 1.83 - 1.99 (m, 2H), 4.12 - 4.24 (t, 1H), 5.10 (s, 2H), 7.35 (s, 5H); mass spectrum, exact mass calcd. for $C_{13}H_{19}NO_3$: 237.137. Found: 237.138.

Table 1



1 **3**

Entry	R	R^1	R^2	R^3M	Mole %, **2**	R^3	% yield[a]
a.	OH	Bzl	H	^{n}BuLi	200	^{n}Bu	77
b.	OH	Bzl	H	^{Sec}BuLi	200	^{Sec}BuLi	63
c.	OH	Bzl	H	^{t}BuLi	200	^{t}Bu	69
d.	OH	Bzl	H	MeLi	200	Me	73
e.	OH	Bzl	H	PhLi	200	Ph	76
f.	OH	Bzl	Me	MeLi	200	Me	67[b]
g.	OH	Bzl	H	H_2C=CHMgBr	200	H_2C=CH-	No Rxn[c]
h.	OH	Bzl	H	Et_2Zn	100	Et	No Rxn[c]
i.	OH	Bzl	H	Et_2Zn	100	Et	No Rxn[d]
j.	OMe	Bzl	H	^{Sec}BuLi	100	^{Sec}Bu	No Product[e]
k.	O^{t}Bu	Bzl	H	^{t}BuLi	100	^{t}Bu	No Product[e]
l.	OH	Ph(Me)CH	H	^{n}BuLi	200	^{n}Bu	70
m.	OH	Ph(Me)CH	H	^{t}BuLi	200	^{t}Bu	69
n.	N(Me)Ph	Bzl	H	^{n}BuLi	200	^{n}Bu	64[b]
o.	OH	THP[f]	H	^{n}BuLi	200	^{n}Bu	65
p.	N(Me)Ph	Bzl	H	^{t}BuLi	200	^{t}Bu	80[g]

[a] The structures of the products were confirmed by IR, ^{1}HNMR, and exact mass calculations. [b] Reaction was not completed in 30 minutes, therefore, yields are based on the starting material consumed. [c] Starting material was recovered with some benzyl alcohol. [d] The reaction was run for 14 h at the room temperature. [e] Other products were obtained. The Alkyl lithium reagent prefered to attack at the ester carbonyl, as expected. [f] Racemic tetrahydropyranyl. [g] The reaction time was increased to 1 h.

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