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Studies on the synthesis of amidoximes from nitroalkanes

Gabriella Sanguineti, Hoang V. Le, Bruce Ganem *

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, NY 14853-1301, United States

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This paper is dedicated to Gilbert Stork, an inspiring teacher and research mentor, on the occasion of his ninetieth birthday

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ABSTRACT

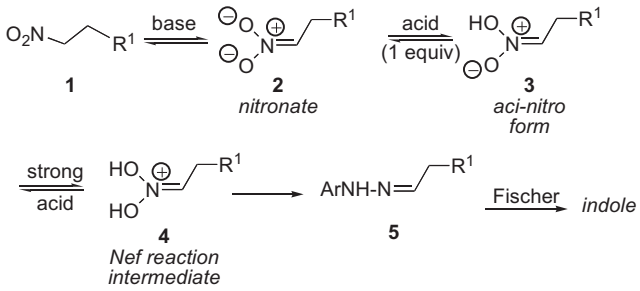
The reaction of primary nitroalkanes with magnesium or lithium amides provides a convenient, one-step synthesis of substituted amidoximes.

1. Introduction

As part of our ongoing effort to expand the repertoire of synthetically useful multicomponent reactions (MCRs), we recently disclosed a new synthesis of substituted indoles from nitroalkanes and arylhydrazines in the presence of base.[1] The success of the method relied on transforming the derived nitronate anion **2** (Scheme 1) either to the monoprotonated aci-nitro species **3** or to the di-protonated iminium species **4**, with subsequent hydrazine addition and N/N interchange to produce arylhydrazone **5**.

This indole synthesis was inspired by two early patents reporting successful nucleophilic additions of thiols to nitronates leading to thiohydroximate esters **9** (Scheme 2).[2] Although no mechanism was proposed in the patents, one likely sequence of transformations is depicted in Scheme 2.[3]

We wondered whether the analogous reaction of nitronates with primary or secondary amines, either alone or in the presence of a thiol or some other catalyst, would afford the corresponding amidoximes **10**. Such amidoximes are of considerable medicinal interest. Besides being involved in the biosynthesis of NO, they display potent pharmacological activity as anticoagulants, platelet inhibitors, antimicrobial agents and matrix metalloprotease inhibitors.[4] We now report our systematic study of this transformation, as well as the scope and generality of organolithium and magnesium-mediated conversion of nitroalkanes into amidoximes **10**.



Scheme 1. Nitro to indole conversion.

2. Results and discussion

Using 1-nitropropane as a model nitroalkane, we successfully prepared the corresponding thiohydroximate ester **9** (R^1=CH_3, R=Ph) using thiophenol according to published conditions ($NaOCH_3$–CH_3OH, reflux).[2] Given that **9** is an oximino analogue of a thioester, we expected it to react smoothly with an amine nucleophile to furnish the corresponding amidoxime **10**. However, the reaction of **9** with aniline (CH_3OH, reflux) was extremely sluggish,

* Corresponding author. Tel.: +1 607 255 7360; e-mail address: bg18@cornell.edu (B. Ganem).

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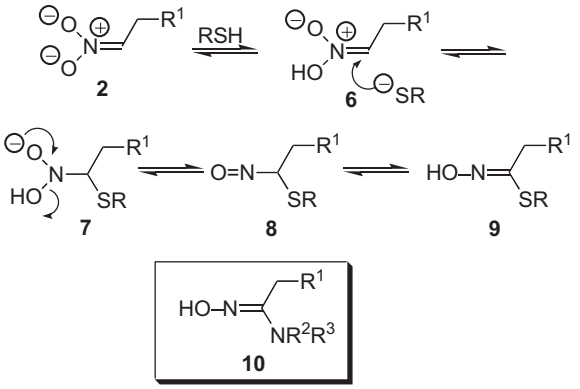

Scheme 2. Proposed mechanism of nitroalkane to thiohydroximate conversion.

and afforded a complex mixture of products. Besides obtaining the hoped-for propionamidoxime **10** (R^1=CH_3, R^2=H, R^3=Ph), we also identified the corresponding *N*,*N*′-diphenylpropionamidine. Both products were formed in low yield. Control experiments established that the amidine was derived from **10**.[5,6]

Taken together, the surprisingly low reactivity of thiohydroximates and the unexpected susceptibility of amidoximes to further nucleophilic addition by amines indicated that the thiohydroximate pathway from nitroalkanes would not likely afford a viable route to amidoximes. We decided to explore instead the direct reaction of 1-nitropropane with nucleophilic amines. After numerous attempts, however, we were unable to identify conditions under which a primary or secondary amine (*n*-butylamine, aniline, pyrrolidine) would react with 1-nitropropane either neat or in a protic (methanol) or aprotic (DMSO) solvent, even at elevated temperatures, to form detectable quantities of the corresponding amidoxime.

We next considered the possibility of boosting the nucleophilicity of the amine component by metallation. A little-cited 1988 Russian report describes the reaction of nitromethane and nitroethane with magnesium *tert*-butylamide (2.5 equiv, prepared using EtMgBr and *tert*-butylamine at rt in THF) to afford the corresponding *N*-*tert*-butylformamidoxime and *N*-*tert*-butylacetamidoxime in 40 and 45% yields, respectively.[7]

In applying the published procedure to various combinations of nitroalkanes and amines we observed that EtMgCl metallated the amine component only sluggishly at rt. Therefore, to ensure complete consumption of the Grignard reagent, the amine was added to EtMgCl in THF at reflux with continued heating until gas evolution ceased prior to adding the nitroalkane.

To ascertain whether the yield of amidoxime could be improved using different metallated amines, we studied the reaction of 1-nitropropane and *n*-butylamine using various metallating agents. The results are shown in Table 1.

As indicated in Table 1, promising results were obtained in this pilot study using lithium amides. We therefore undertook a side-by-side comparison of magnesiated (method A) versus lithiated (method B) amides in the synthesis of amidoximes derived from various primary and secondary amines. Those data are summarized in Table 2.

Table 1
Yields of *N*-(*n*-butyl)propionamidoxime from 1-nitropropane using various metallating agents

Base	% Yield
EtMgCl	28
EtMgCl/cat. CuCl	27
n-BuLi	58
NaH	27

Table 2
Effect of metallating agent on the synthesis of *N*-alkylpropionamidoximes

Amine	Yield w/EtMgCl (%)	Yield w/*n*-BuLi (%)
	Method A	Method B
n-Butylamine	28	59
Cyclohexylamine	32	47
tert-Butylamine	32	19
Pyrrolidine	46	26

Data in Table 2 indicate that, perhaps not surprisingly, the yield of amidoxime was affected by steric factors in the primary amines. More interestingly, however, the data suggest that *n*-butyllithium was the preferred reagent for preparing *N*-(primary alkyl) or *N*-(secondary alkyl) amidoximes. Metallation using Grignard reagents was preferred in making amidoximes from *tert*-butylamine or pyrrolidine.

Having tested the effects of various metallating agents and of amine structure, the amidoxime synthesis was further applied to several different nitroalkanes in order to expand its scope and generality. In so doing, the use of additional amine components, including unsaturated amines and anilines, was also explored. Fig. 1 below depicts the structures of the various new amidoximes that were synthesized from nitromethane, nitroethane and 1-nitropropane. Each structure in the figure also indicates the optimal method of preparation, and the yield obtained.

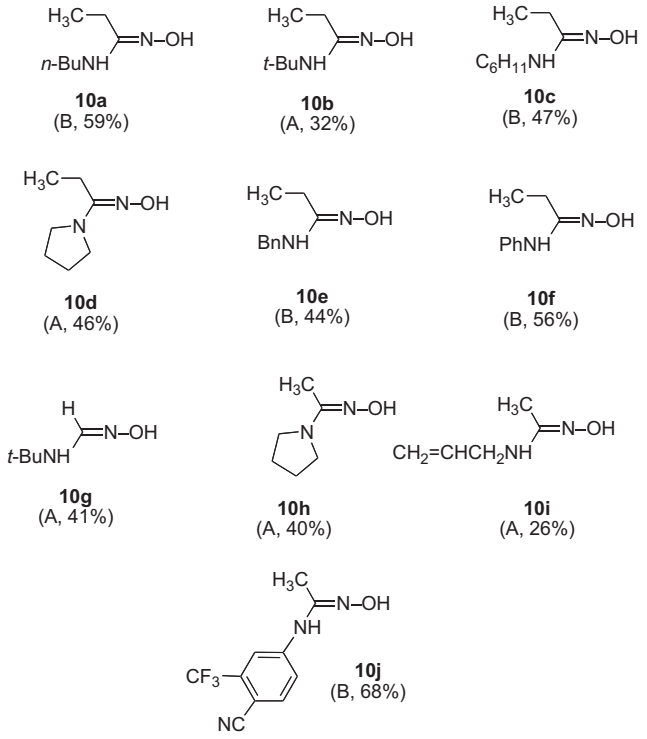

Fig. 1. Examples of amidoximes prepared from nitroalkanes.

Despite the strongly basic conditions involved, the method generally affords amidoximes, although in moderate yields. Attempts to prepare amidoxime **10i** from allylamine were unsuccessful using method B, probably because of polylithiation, which has been reported to be THF-catalyzed.[8] However, by switching to method A, **10i** could be synthesized in low yield.

The amidoxime synthesis seemed to work best using anilines, as indicated by the formation of amidoximes **10f** and **10j**. Besides being notable for its yield (68%), the successful preparation of **10j** establishes that the method tolerates the presence of some reactive (trifluoromethyl, nitrile) functionality in the amine component.