Communications

Synthesis of Alkoxylamines by Alkoxide Amination with 3,3′-Di-*tert*-butyloxaziridine

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Received March 19, 1999

O-Alkyl oximes have become increasingly important in chemical biology and medicinal chemistry research. Chemoselective ligation to provide the oxime linkage is the key step in the synthesis of numerous semisynthetic biopolymers and biomolecules[1−6] and the *O*-alkyl oxime functionality is present in many drugs and drug candidates (Figure 1).[7] The *O*-alkyl oxime functionality is prepared in near-quantitative yields and with almost complete functional group compatibility by the condensation of alkoxylamines with aldehydes and ketones. However, the potential applications of *O*-alkyl oximes are compromised by the narrow range of methods that have been developed to prepare the alkoxylamine precursors. Generally, these methods rely on a specific two-step sequence consisting of (1) nucleophilic attack of an *N*-protected hydroxylamine nucleophile upon an electrophilic carbon and (2) deprotection to provide the alkoxylamine product.[8,9] The direct electrophilic amination of alcohols would provide a more powerful and efficient approach. However, in the only report of the direct electrophilic amination of alcohols, chloroamine was used to aminate simple alkoxides in low yields (30−40%). Moreover, 40-fold excess of the alkoxide was required.[10] Indeed, in a prior report on the reaction of chloroamine with stoichiometric alkoxides, less than 5% yields were observed.[11]

Herein, we report the first high-yielding, single-step procedure for the preparation of alkoxylamines through the direct electrophilic amination of a wide range of alkoxide nucleophiles. Because this reported method relies upon a completely different disconnection than the standard methods, previously inaccessible alkoxylamines can now readily be prepared in high yields. We further report use of this method for the high-yielding, one-pot preparation of *O*-alkyl oximes from alcohols.

In contrast to the amination of alkoxides, there have been numerous reports of electrophilic aminations of the less basic phenoxides to generate phenoxyamines. These methods involve an amine exchange reaction where a phenoxide acceptor attacks an amine donor, XNH_2. Reagents reported for the amination of phenoxides include *O*-(mesitylenesulfonyl)hydroxylamine,[12] hydroxylamine *O*-sulfonic acid,[13] chloroamine,[14−16] and (2,4-dinitrophenoxy)amine.[17] The reactivity of these aminating reagents with phenoxides is due to the electron-deficient nature of the leaving group, which unfortunately also results in competitive deprotonation and rapid decomposition of the reagents upon treatment with electron-releasing phenoxide nucleophiles. Clearly, the amination of the significantly more basic alkoxide nucleophiles is even more problematic.

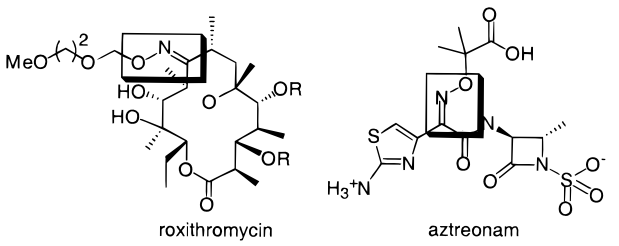

Figure 1. Representative *O*-alkyl oxime drugs.

To eliminate competitive deprotonation and reagent decomposition, we chose to focus on the development of the less acidic oxaziridine-based aminating reagents, since ring strain rather than leaving group electronegativity provides the necessary reactivity. Cyclohexanespiro-3′-oxaziridine, **1**,[18] is the only oxaziridine unsubstituted on nitrogen to have previously been explored as an aminating agent, in particular for the amination of carbon, sulfur, and nitrogen nucleophiles.[19] While the amination of oxygen nucleophiles with **1** has received little attention,[20] oxaziridine **1** is known to decompose to cyclohexanone and nitrogen gas upon treatment with hydroxide.[21]

On the basis of these prior reports, we concluded that oxaziridine **1** is not an acceptable reagent for the amination of alcohols. Not only is oxaziridine **1** unstable and must be used without purification, but the cyclohexanone byproduct can undergo serious competing side reactions, including competitive cyclohexanone deprotonation and rapid condensation with amination products (eq 1). We instead focused on the previously unexplored 3,3′-di-*tert*-butyl oxaziridine, **3**,[22] since we believed that this reagent would not have the inherent limitations of oxaziridine **1**. First, due to increased steric hindrance, we hoped that oxaziridine **3** would be stable and isolable in pure form. Second, the steric hindrance of the 2,2,4,4-tetramethyl-3-pentanone byproduct should significantly retard condensation with the desired alkoxylamine product. Finally, competitive deprotonation of the ketone byproduct would clearly not be possible.

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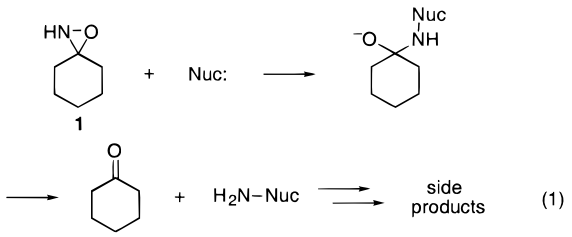
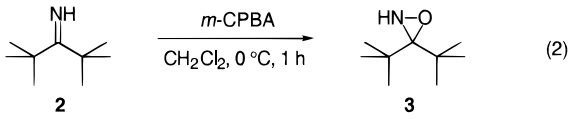
10.1021/jo990490h CCC: $18.00
Published on Web 08/18/1999

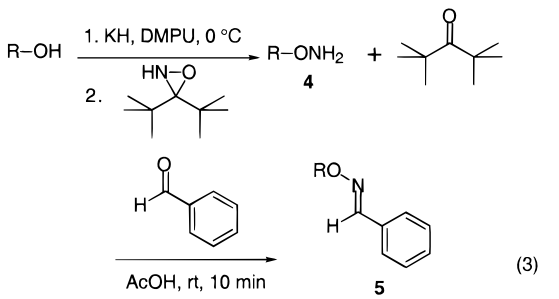


Oxaziridine **3** can be prepared in large quantities in a single step. Oxidation of commercially available 2,2,4,4-tetramethyl-3-pentanone imine **2** with *m*-CPBA provides a 5:1 mixture of **3** and di-*tert*-butyl ketone after bulb-to-bulb distillation (40 °C, 0.5 mmHg) to remove *m*-chlorobenzoic acid (eq 2). Subsequent redistillation (25 °C, 0.5 mmHg) removes the ketone side product, leaving behind analytically pure oxaziridine **3** in 49% yield. Oxaziridine **3** can be stored at room temperature for months without signs of decomposition.



We next investigated a number of different reaction conditions for the amination of alcohols using oxaziridine **3** with large counterion and solvent effects both being observed (Table 1). Attempts to aminate the lithium alkoxide of 3-phenylpropanol in THF/DMPU were not successful (entry 1). The amination of the sodium alkoxide also did not proceed in THF (entry 2). However, with DMPU as solvent, the sodium alkoxide provided a moderate yield (entries 3 and 4), and the potassium alkoxide provided a high yield of the alkoxylamine product (entry 5). Attempts to aminate secondary alcohols with these same conditions were not successful (entry 8). However, by the addition of catalytic amounts of crown ethers, secondary alcohols could also be aminated in high yields (entry 9). On the basis of these studies, the optimal conditions are to perform the amination in DMPU with KH being used to generate the alkoxide and with 0.1 equiv of 18-crown-6 used as an additive (entries 6 and 9).

The utility of oxaziridine **3** was demonstrated by the preparation of a variety of alkoxylamines and the corresponding *O*-alkyl oxime products (eq 3 and Table 2). In all cases, the amination reactions proceeded rapidly and were complete within 2 h. The alkoxylamines **4** were isolated either as the free alkoxylamines upon acid/base extraction or as the corresponding oximes **5** by direct addition of aldehydes or ketones to the amination reaction pot (eq 3). Notably, no condensation between the alkoxylamine product and the generated 2,2,4,4-tetramethyl-3-pentanone was observed, which can be attributed to steric hindrance around the carbonyl center.



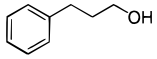
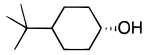
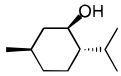
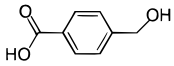
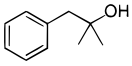
The reported amination chemistry has several important differences from prior nucleophilic substitution methods. In contrast to prior methods, the amination of alcohols utilizing oxaziridine **3** proceeds with retention of stereochemistry as demonstrated by the amination of menthol (entry 3). In addition, oxaziridine **3** is appealing due to its compatibility with certain functional groups, obviating the need for protecting groups and, hence, multiple steps. For example, amination of 4-hydroxymethylbenzoic acid followed by condensation with benzaldehyde provides the desired oxime product in one pot in moderate overall yield (entry 5). While the amination of primary and secondary alkoxides proceeds in moderate to excellent yields (entries 1−5), the amination of tertiary alcohols proceeds in low yields (entry 6), defining the scope of this method.

Table 1. Optimization of Amination Conditions.[a]

entry	base	solvent	additive	ROH	yield (%)
1	LDA	THF/DMPU	none	3-phenylpropanol	NR
2	NaH	THF	none		NR
3	NaH	DMPU	none		40
4	NaH	DMPU	A		46
5	KH	DMPU	none		83
6	KH	DMPU	B		86
7	NaH	DMPU	A	*trans*-4-*tert*-butyl-cyclohexanol	34
8	KH	DMPU	none		NR
9	KH	DMPU	B		70

[a] All deprotonations were performed at room temperature for 1 h followed by addition of alkoxide to a solution of 2 equiv of oxaziridine **3** in DMPU at −40 °C. A: 15-crown-5. B: 18-crown-6.

Table 2. Amination of Alcohols (Eq 3)[a]

entry	R–OH	alkoxylamine **4**/oxime **5** yield (%)[b]
1		86[c]
2		70
3		78[d]
4		51[d]
5		56[d]
6		10

[a] Unless otherwise noted, all reactions were performed with DMPU as solvent and 0.1 equiv of 18-crown-6. [b] Isolated yields of analytically pure material. [c] No 18-crown-6 used. [d] Yield of oxime after condensation with benzaldehyde.

In conclusion, a high-yielding, direct electrophilic amination of primary and secondary alkoxides using 3,3′-di-*tert*-butyl oxaziridine **3** is described**.** Oxaziridine **3** is prepared in a single step from commercially available material. The pure reagent is stable and has been stored for months at room temperature. Finally, using the amination method, the one-pot preparation of oximes from alcohols is demonstrated.

Acknowledgment. The support of the NIH (GM-50353) is gratefully acknowledged.

Supporting Information Available: Supporting Information Available. Detailed experimental procedures and complete characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990490H