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A Convenient Synthesis of 4-Alkyl-5-aminoisoxazoles

Matthew P. Bourbeau* and James T. Rider

Department of Medicinal Chemistry, Amgen Inc., 1 Amgen Center Drive, Thousand Oaks, California 91303

bourbeau@amgen.com

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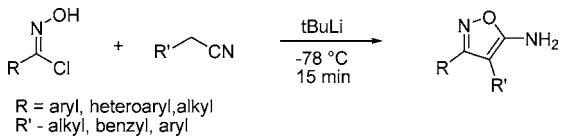
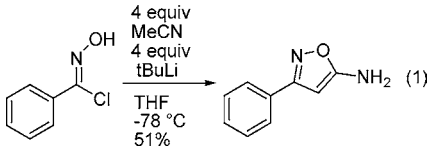
ABSTRACT



A series of 4-alkyl-5-aminoisoxazoles have been synthesized in high yield by nucleophilic addition of lithiated alkyl nitriles to (α)-chlorooximes. The scope and limitations of this reaction were examined by varying the nature of the nitrile and chloride oxime.

Isoxazoles have attracted a great deal of interest as synthetic targets.[1] In particular, the synthesis of 5-aminoisoxazoles has been achieved by a variety of different methods. The most common method for the synthesis of 5-aminoisoxazoles, described by Nishawiki, involves the condensation of esters with nitrile anions, followed by cyclization of the resulting *β*-ketonitrile with hydroxylamine under basic conditions at reflux to afford the desired isoxazole.[2] Additional methods for the synthesis of 5-aminoisoxazoles include the addition of stabilized nitrile anions to (α)-chlorooximes (resulting in 5-aminoisoxazoles with electron withdrawing groups at the C-4 position), condensation of α-bromo ketoximines with cyanide, and rearrangements of 5-alkyl-4-cyanoisoxazoles upon treatment with $LiAlH_4$.[3−5]

During a recent synthetic investigation, we examined the synthesis of 5-aminoisoxazoles with an aryl substituent at the 3 position. We were also interested in incorporating alkyl groups at the C-4 position. Initially, we planned to follow Nishawiki's procedure for the addition of nitriles to esters, followed by cyclization with hydroxylamine.[2] However, there was a specific case that we encountered where the addition of lithiated acetonitrile to an aryl ester did not provide the desired product. To address this problem, we were attracted to the work of Beccalli, who showed that the sodium anions of alkyl nitriles bearing additional electron withdrawing groups α to the nitrile add to (α)-chlorooximes at elevated temperatures, affording the desired isoxazole.[3] To the best of our knowledge there has been no report in the literature regarding the addition of nitrile anions lacking additional electron withdrawing groups to (α)-chlorooximes. We reasoned that (α)-chlorooximes might be sufficiently electrophilic to undergo addition with lithiated nitriles at low temperature. Gratifyingly, we found that when benzaldehyde (α)-chlorooxime[6] was treated with an excess of lithiated acetonitrile, the desired 5-aminoisoxazole was isolated in reasonable yield (eq 1).



Encouraged by this result, we examined this addition with a variety of substituted nitriles (Table 1). The reaction was tolerant of additional alkyl functionality, thus allowing for

(1) Baraldi, P. G.; Barco, A.; Bennetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857−869.
(2) Nishiwaki, T.; Saito, T. *J. Chem. Soc.* (*C*) **1971**, 3021−3026
(3) Beccalli, E. M.; Manfredi, A.; Marchesini, A. *J. Org. Chem.* **1985**, *13*, 2372−2375.
(4) Kong, W. C.; Kim, K.; Park, Y. J. *Heterocycles* **2001**, *55*, 75−89.
(5) Alberola, A.; Gonzalez, A. M.; Laguna, M. A.; Pulido, F. J. *J. Org. Chem.* **1984**, *49*, 3423−3424.
(6) Lam, P. Y. S.; Adams, J. J.; Clark, C. G.; Calhoun, W. J.; Luettgen, J. M.; Knabb, R. M.; Wexler, R. R. *Bioog. Med. Chem. Lett.* **2003**, *13*, 1795−1799.

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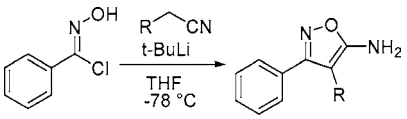
Table 1. The Condensation of Lithiated Nitriles with Benzaldehyde (α)-Chlorooxime[a]



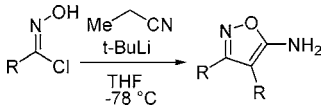
entry	R	yield (%)
1a	H	51
1b	Me	89
1c	*i*-Pr	64
1d	cyclopropyl	78
1e	Ph	86
1f	Bn	91

[a] All reactions unoptimized.

the synthesis of C4-alkylisoxazoles. Increasing the size of the alkyl group from methyl (entry **1b)** to isopropyl (entry **1c**) and cyclopropyl (entry **1d**) showed little effect on the reaction yield. Additionally, 2-phenylacetonitrile (entry **1e**) and 3-phenylpropionitrile (entry **1f**) were also good substrates for this condensation.

Having examined the tolerability of nitrile functionality in the reaction, we next examined the reaction of lithiated propionitrile with a variety of different (α)-chlorooximes (Table 2). Substitution of the phenyl ring of benzaldehyde

Table 2. The Addition of Lithiated Propionitrile to a Variety of (α)-Chlorooximes[a]



entry	R	yield (%)
2a	4-methoxyphenyl	77
2b	4-chlorophenyl	73
2c	3-chlorophenyl	81
2d	2-chlorophenyl	69
2e	cyclohexyl	53
2f	*n*-propyl	74
2g	3-thienyl	34[b]
2h	2-pyridyl	49

[a] All reactions unoptimized. [b] A small amount (<5%) of 3-(2-chlorothien-3-yl)-4-methylisoxazol-5-amine was also isolated.

(α)-chlorooxime had little effect on the yield of the desired transformation (entries **2a**−**d**). Alkyl (α)-chlorooximes were shown to be good substrates for this reaction (entries **2e** and **2f**). 3-Thiophen-3-carbaldeyde (α)-chlorooxime (entry **2g**) gave a somewhat lower yield of the desired product along with a small amount (~5%) of 3-(2-chlorothiophen-3-yl)-4-methylisoxazol-5-amine as a side product.[7] Picolinaldehyde (α)-chlorooxime (entry **2h**) similarly reacted in lower yield.

In considering a mechanistic rational for this process, two potential pathways have been proposed. The first invokes a stepwise process starting with addition of the lithiated nitrile to a nitrile oxide generated by deprotonation of the (α)-chlorooxime, followed by cyclization to form the 5-aminoisoxazole. Alternatively, the reaction may proceed through a concerted pathway, analogous to reactions between (α)-chlorooximes and alkynes.[1]

In summary, the reaction of lithiated nitriles with (α)-chlorooximes has been found to be useful for synthesizing a variety of 5-aminoisoxazoles, particularly ones with alkyl functionality at the 4 position. As (α)-chlorooximes have been shown to also be useful substrates for the synthesis of 5-alkylisoxazoles, this reaction would potentially be useful to chemists seeking to generate libraries of both 5-alkyl- and 5-aminoisoxazoles from the same set of starting materials (Figure 1). Additionally, as both Nishawiki and Becalli's

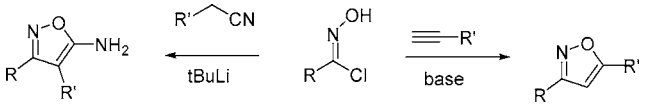


Figure 1. The use of an (α)-chlorooxime as a common intermediate for the synthesis of 5-aminoisoxazoles and 5-alkylisoxazoles.

protocols involve treatment of the substrate with basic conditions at high temperature, this reaction could also be a useful alternative for substrates that would not tolerate such conditions.[2−4] This reaction also avoids a potential regioselectivity issue (5-aminosioxazole formation vs 3-aminoisoxazole formation) that may occur in some cases following Nishiwaki's protocol.[8]

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Supporting Information Available: Experimental details for the preparation of the isoxazoles and ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Presumably, the chloronation occurs during the synthesis of the thienyl (α)-chlorooxime from the corresponding oxime by treatment with *n*-chlorosuccinimide.

(8) Takasem A.; Murabayashi, A.; Sumimoto, S.; Udea, S.; Makisumi, Y. *Heterocycles* **1991**, *32*, 1153−1158.