ORGANIC LETTERS

2009
Vol. 11, No. 5
1159−1162

Synthesis of 3-Aminoisoxazoles via the Addition−Elimination of Amines on 3-Bromoisoxazolines

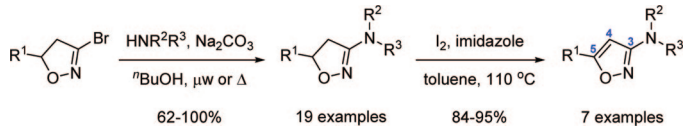
Mélina Girardin,* Pamela G. Alsabeh, Sophie Lauzon, Sarah J. Dolman, Stéphane G. Ouellet, and Greg Hughes

Department of Process Research, Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Highway, Kirkland, Québec, Canada H9H 3L1

melina_girardin@merck.com

Received January 7, 2009

ABSTRACT



A novel two-step procedure for the synthesis of 3-amino-5-substituted-isoxazoles is described. In the presence of a base, readily available 3-bromoisoxazolines react with amines to afford 3-aminoisoxazolines. An oxidation protocol was developed for these heterocycles to provide 3-aminoisoxazoles in consistently high yield.

To rapidly access structurally diverse targets, medicinal chemists require convenient and reliable methodologies, especially in the area of heterocyclic chemistry. Syntheses of 3-alkyl- and 3-aryl-substituted isoxazoles are well-established[1] and include 1,3-dipolar cycloadditions,[2] hydroxylamine condensations,[3] Claisen condensations of ketoxime dianions,[4] and cyclizations of propargylic oximes.[5]

However, there are few reported methodologies for the synthesis of *N*-substituted 3-aminoisoxazoles.[6] A key disconnection for their synthesis would be at the C3-N bond, which would allow for a variety of analogues to be prepared from a single precursor. Despite recent advances in copper- and palladium-catalyzed amination of aryl halides,[7] 3-bromoisoxazoles **3** remain poor substrates for these methodologies and do not provide access to the corresponding 3-aminoisoxazoles **4** (Scheme 1).[8] Thermally mediated aromatic nucleophilic substitution (S_NAr) of 3-chloro-1,2-benzisoxazoles with amines has been reported on a small number of substrates.[9]

(1) (a) Wakefield, B. J. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Shaumann, E., Ed.; Georg Thieme Verlag: Stuttgart, 2001; Vol. 11, pp 229−288. (b) Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925–958.

(2) (a) Hansen, T. V.; Wu, P.; Fokin, V. V. *J. Org. Chem.* **2005**, *70*, 7761–7764. (b) Denmark, S. E.; Kallemeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839–2842. (c) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707–6714. (d) Willy, B.; Rominger, F.; Müller, T. J. J. *Synthesis* **2008**, *2*, 293–303.

(3) (a) Bandiera, T.; Grünanger, P.; Albini, F. M. *J. Heterocycl. Chem.* **1992**, *29*, 1423–1428. (b) Lautens, M.; Roy, A. *Org. Lett.* **2000**, *2*, 555–557.

(4) (a) He, Y.; Lin, N.-H. *Synthesis* **1994**, 989–992. (b) Nitz, T. J.; Volkots, D. L.; Aldous, D. J.; Oglesby, R. C. *J. Org. Chem.* **1994**, *59*, 5828–5832.

(5) (a) Short, K. M.; Ziegler, C. B., Jr. *Tetrahedron Lett.* **1993**, *34*, 75–78. (b) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203–5205.

(6) (a) Moore, J. E.; Spinks, D.; Harrity, J. P. A. *Tetrahedron Lett.* **2004**, 3189–3191. (b) Alberola, A.; Antolin, L. F.; Cuadrado, P.; González, A. M.; Laguna, M. A.; Pulido, F. J. *Synthesis* **1988**, 203–207. (c) Sugai, S.; Sato, K.; Kataoka, K.; Iwasaki, Y.; Tomita, K. *Chem. Pharm. Bull.* **1984**, *32*, 530–537. (d) For a recent review on aminoisoxazoles, see: Kislyi, V. P.; Danilova, E. B.; Semenov, V. V. *Adv. Heterocycl. Chem.* **2007**, *94*, 173–214.

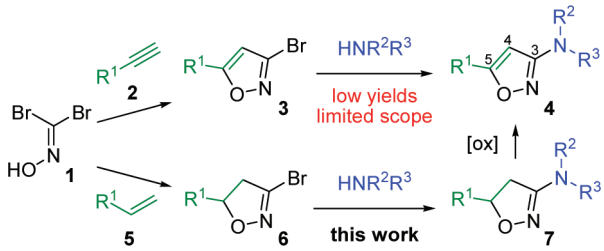
(7) (a) Kienle, M.; Dubbaka, S. R.; Brade, K.; Knochel, P. *Eur. J. Org. Chem.* **2007**, *2007*, 4166–4176. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.

(8) This issue was also noted by others; see ref 6a. For a review of azoles cross-couplings, see: Schnürch, M.; Flasik, R.; Khan, A. F.; Spina, M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, *2006*, 3283–3307.

(9) (a) Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L., Jr. *J. Med. Chem.* **1986**, *29*, 359–369. (b) Urban, F. J.; Breitenbach, R.; Murtiashaw, C. W.; Vanderplas, B. C. *Tetrahedron: Assymetry* **1995**, *6*, 321–324. (c) Böshagen, H. *Chem. Ber.* **1967**, *100*, 3326–3330. (d) For an example with an isoxazolo[4,5-*d*]pyrimidine, see: Wagner, E.; Becan, L. *Pol. J. Chem.* **1995**, *69*, 70–73.

10.1021/ol9000284 CCC: $40.75
Published on Web 02/11/2009

Scheme 1. Synthesis of 3-Aminoisoxazoles



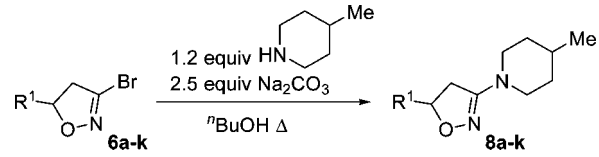
Moore and co-workers obtained modest yields of 3-aminoisoxazoles (5 examples, 30−59% yield) by microwave-assisted S_NAr; however the amine was used as the solvent and a stoichiometric phophazene base was required.[6a] This method is of limited scope and would not be desirable in cases where the amine is a valuable intermediate. Alternatively, 3-aminoisoxazoles have been accessed through a multistep sequence including activation toward S_NAr by quaternization of the nitrogen (2−4 steps depending on the amine, 15−72% yield).[6c]

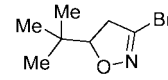
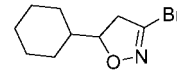
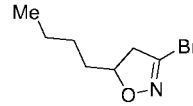
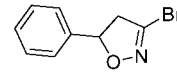
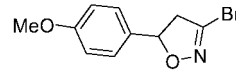
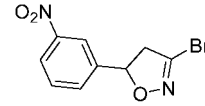
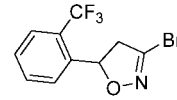
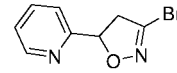
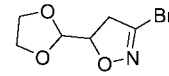
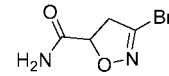
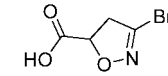
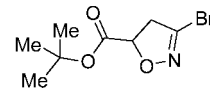
This lack of general methodologies prompted us to evaluate other means of forming the key C3-N bond. We were interested in developing a simple yet robust methodology to access a wide array of 3-amino-5-subtituted isoxazoles **4**. Given the reported poor reactivity of 3-haloisoxazoles, we decided to explore the use of isoxazolines, such as **6**, as surrogates.[10] In this communication, we wish to report the favorable reactivity of 3-bromoisoxazolines toward amines. The 3-aminoisoxazolines **7** obtained in this reaction can then be conveniently oxidized to the desired isoxazoles in high yield.

The known cycloaddition of alkynes and alkenes with dibromoformaldoxime **1**[11] via its nitrile oxide affords 3-bromoisoxazoles **3**[12] and 3-bromoisoxazolines **6**, respectively.[13] The regioselectivities were generally high for alkenes, often affording a single isoxazoline regioisomer.[14]

We began our investigation with 4-methylpiperidine as a model amine and were pleased to observe that when heated

Table 1. Scope of 5-Substituted Substrates



entry	substrate		Δ^a	time (h)	yield (%)[b]
1		**6a**	A	4	78
			B	64	80
2		**6b**	A	1	88
3		**6c**	A	2[c]	85
4		**6d**	A	1.5	92
			B	20	90
5		**6e**	A	1	100
6		**6f**	A	1[c]	72
7		**6g**	A	0.7	94
8		**6h**	C	1.5	92
9		**6i**	B	6	84
10		**6j**	B	1	88
11		**6k**	B	5	71
12		**6l**	D[d]	18	75

[a] Heat source: A = microwave, 200 °C; B = oil bath, 120 °C; C = microwave, 160 °C; D = oil bath, 84 °C. [b] Isolated yield. [c] Unoptimized reaction time. [d] Used ^{t}BuOH instead of ^{n}BuOH.

in the presence of an organic or inorganic base, 3-bromoisoxazolines reacted to generate 3-aminoisoxazolines. While this reaction proceeded in a variety of solvents (PhMe, xylenes, EtOH, ^{n}BuOH, MeCN, THF, DMF), we found that alcoholic solvents provided the cleanest reaction profiles. We selected *n*-butanol because of its high boiling temperature (116−118 °C). Electron-withdrawing substituents in the 5-position allowed for faster reaction rates.[15] For more electron-rich isoxazolines, use of microwave heating at 200 °C in sealed vials dramatically reduced the reaction times. For instance, the reaction time for 5-*tert*-butyl-3-bromoisox-

(10) (a) For an example of the reaction of a 3-bromoisoxazoline with nucleobases, see: Coutouli-Argyropoulou, E.; Pilanidou, P. *Tetrahedron Lett.* **2003**, *44*, 3755–3758. (b) For an example using a phenylsulfonyl leaving group, see: Anderson, W. K.; Raju, N. *Synth. Commun.* **1989**, *19*, 2237–2242.

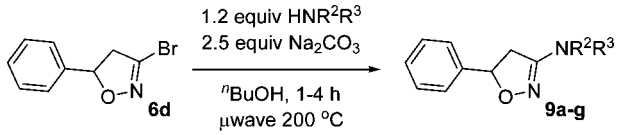
(11) Dibromoformaldoxime is commercially available but is readily prepared; see: (a) Berrier, J. V.; Umarvadia, A. S.; Rohm and Haas Company; Improved synthesis of haloformimine compounds. Eur. Pat. Appl. 979814, Feb 16, 2000. (b) Rohloff, J. C.; Rubinsun, J., III; Gardner, J. O. *Tetrahedron Lett.* **1992**, *33*, 3113–3116.

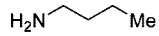
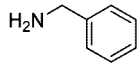
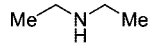
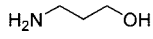
(12) (a) Chiarino, D.; Napoletano, M.; Sala, A. *J. Heterocycl. Chem.* **1987**, *24*, 43–46. (b) De Amici, M.; De Micheli, C.; Carrea, G.; Spezia, S. *J. Org. Chem.* **1989**, *54*, 2646–2650.

(13) (a) For a general discussion of nitrile oxide cycloaddition with alkenes, see: Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocycl. Chem.* **1994**, *60*, 261–327. (b) For specific examples using dibromoformaldoxime, see: Caldirola, P.; Ciancaglione, M.; De Amici, M.; De Micheli, C. *Tetrahedron Lett.* **1986**, *27*, 4647–4650. (c) De Amici, M.; De Micheli, C.; Misani, V. *Tetrahedron* **1990**, *46*, 1975–1986. (d) Kociolek, M. G.; Kalbarczyk, K. P. *Synth. Commun.* **2004**, *34*, 4387–7394. (e) Halling, K.; Thomsen, I.; Torssell, K. B. G. *Liebigs Ann. Chem.* **1989**, *10*, 985–990.

(14) See Supporting Information for the synthesis of the 3-bromoisoxazoline substrates.

Table 2. Scope of Amine Nucleophiles



entry	HNR^2R^3	product	yield (%)[a]
1[b]		**9a**	93
2[b]		**9b**	73
3[b]		**9c**	62
4		**9d**	92
5		**9e**	85
6		**9f**	100
7[b]		**9g**	75

[a] Isolated yield. [b] Used 2.4 equiv HNR^2R^3.

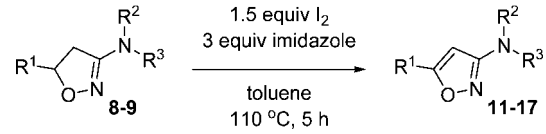
azoline **6a** was shortened from 64 to 4 h using microwave heating (Table 1, entry 1).

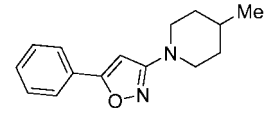
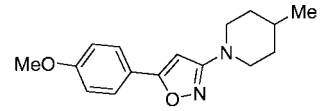
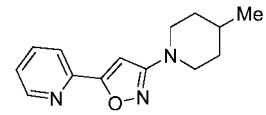
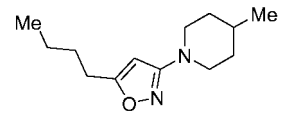
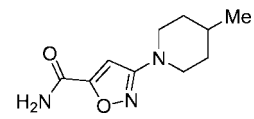
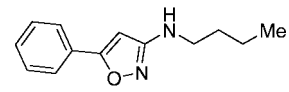
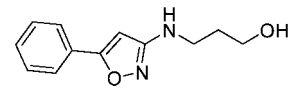
The addition−elimination reaction was demonstrated for a variety of substrates (Table 1). Alkyl-, aryl-, and heteroaryl-substituted bromoisoxazolines (entries 1−8) afforded the desired products in good to excellent yields. 5-Carbonyl or dioxolane substituent increased the 3-bromoisoxazolines reactivity and enabled the reactions to be run at lower temperatures using conventional heating (120 °C, entries 9−11). Care was required with esters to avoid trans-esterification or amidation. Using the bulky *tert*-butyl ester **6l** and performing the reaction in refluxing *tert*-butanol secured a good yield of the desired ester **8l**. The use of a carboxamide **6j** or a carboxylic acid **6k** also circumvented the amidation issue.

We next evaluated the scope of amines suitable for the addition−elimination reaction using 3-bromo-5-phenylisoxazoline **6d** as substrate (Table 2). Primary amines such as *n*-butylamine and benzylamine (entries 1 and 2) afforded the desired 3-aminoisoxazolines **9** in higher yields than the secondary diethylamine (entry 3). As anticipated on the basis of their enhanced nucleophilicity, cyclic secondary amines are superior nucleophiles (entries 4−6). Complete chemoselectivity was observed in the case of 3-aminopropanol (entry 7).[16]

We next turned our attention toward the identification of suitable reaction conditions for the oxidation of the 3-aminoisoxazolines to their corresponding isoxazoles. To the best

Table 3. Substrate Scope for the Oxidation



entry	product		yield (%)[a]
1		**11**	90
2		**12**	84
3		**13**	91
4		**14**	89
5		**15**	89
6		**16**	95
7		**17**	93

[a] Isolated yield.

of our knowledge, there is no literature precedent for this type of transformation. A protocol for MnO_2-mediated oxidation of 3-acetamidoisoxazolines[17] afforded 5-phenylisoxazole **11** in modest yield (<50%); however, a major detraction was the need for superstoichiometric metal (14 equiv). After a number of unsuccessful attempts using literature methodologies suitable for other isoxazolines,[18] we set out to develop new oxidation conditions for our 3-amino-5-substituted-isoxazolines. We were pleased to discover a general oxidation procedure using iodine in the presence of imidazole.[19] The nature of the base played a pivotal role in the outcome of this reaction.[20] To our satisfaction, all of the 3-aminoisoxazolines subjected to the oxidation conditions afforded the desired isoxazoles in high yields (Table 3).

(15) The reaction was performed at 80 °C (DIPEA, EtOH, oil bath) for various substrates and the conversions were determined by HPLC after 18 h. Reaction rates are in the order **6j** > **6f** > **6d** > **6e** ≈ **6c** > **6a**.

(16) This is consistent with the fact that we did not observe the addition−elimination of the solvent *n*-butanol on 3-bromoisoxazolines **6d** when sodium carbonate was used as a base. The 3-butoxyisoxazoline **10** was obtained upon replacement of Na_2CO_3 with K_3PO_4. See Supporting Information.

(17) Manjarrez, N.; Pérez, H. I.; Soria, O.; Luna, H.; Solis, A. *Rev. Soc. Quim. Mex.* **2000**, *44*, 188–193.

(18) (a) For the use of NBS, see: Bianchi, G.; Grünanger, P. *Tetrahedron* 1965, *21*, 817−822. (b) For the use of DDQ, see: Bianchi, G.; De Amici, M. *J. Chem. Res., Synop.* **1979**, 311. (c) For the use of DBH, see: Azarifar, D; Maleki, B.; Mohammadi, K. *Heterocycles* **2007**, *71*, 683–689.

(19) For the use of iodine in DMSO to oxidize 3,5-diarylisoxazolines, see: Deshmukh, A. Y.; Raghuwanshi, P. B.; Doshi, A. G. *Asian J. Chem.* **2002**, *14*, 548–550.

(20) See Supporting Information for the effect of various inorganic and organic bases on the oxidation of **8d** by iodine.

Aromatic, heteroaromatic, and alkyl substituents are equally suitable at the 5 position (entries 1−4). Interestingly, functionalities such as an amide, a secondary amine, and a primary alcohol are well tolerated (entries 5−7).

In summary, 3-bromo-5-substituted-isoxazolines were found to provide a versatile template from which to build a wide variety of 3-aminoisoxazolines and isoxazoles. These substrates can be prepared via a regioselective [3 + 2] cycloaddition and then coupled in high yields with a variety of amines in facile base-promoted addition−elimination reactions. This is in sharp contrast with reported procedures for S_NAr on 3-haloisoxazoles, for which the amine scope is often limited and the yields are modest.[6a−c] Finally, a general iodine-mediated oxidation protocol was developed which enables the conversion of the 3-amino-5-substituted-isoxazolines to the corresponding isoxazoles. In combination, these new methodologies grant reliable and high yielding access to 3-aminoisoxazoles.

Supporting Information Available: Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9000284