ORGANIC LETTERS

2009
Vol. 11, No. 5
1159−1162

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

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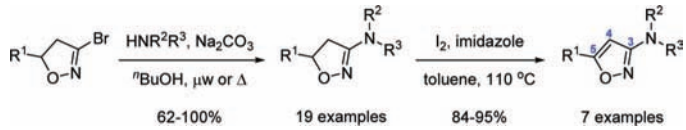
Received January 7, 2009

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

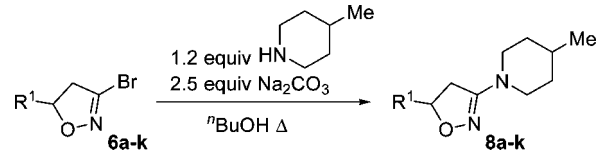
Moore and co-workers obtained modest yields of 3-aminoisoxazoles (5 examples, 30−59% yield) by microwave-assisted S_NAr; however the amine was used as the solvent and a stoichiometric phophazene base was required.[6a] This method is of limited scope and would not be desirable in cases where the amine 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]

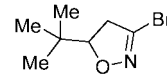
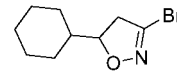
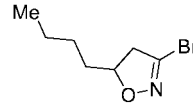
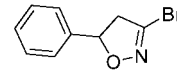
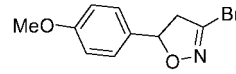
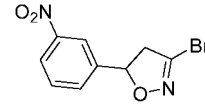
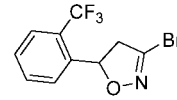
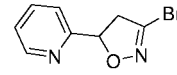
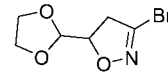
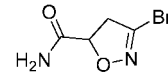
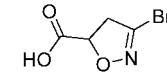
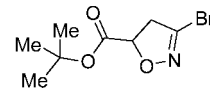
This lack of general methodologies prompted us to evaluate other means of forming the key C3-N bond. We were interested in developing a simple yet robust methodology to access a wide array of 3-amino-5-subtituted isoxazoles **4**. Given the reported poor reactivity of 3-haloisoxazoles, we decided to 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.

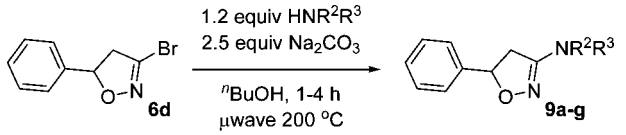
(11) Dibromoformaldoxime is commercially available but is readily prepared; see: (a) Berrier, J. V.; Umarvadia, A. S.; Rohm and Haas Company; Improved synthesis of haloformimine compounds. Eur. Pat. Appl. 979814, Feb 16, 2000. (b) Rohloff, J. C.; Rubinsun, J., III; Gardner, J. O. *Tetrahedron Lett.*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

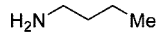
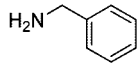
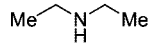
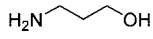
(12) (a) Chiarino, D.; Napoletano, M.; Sala, A. *J. Heterocycl. Chem.* **1987**, *24*, 43–46. (b) De Amici, M.; De Micheli, C.; Carrea, G.; Spezia, S. *J. Org. Chem.* **1989**, *54*, 2646–2650.

(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.

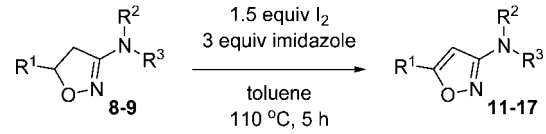
azoline **6a** was shortened from 64 to 4 h using microwave heating (Table 1, entry 1).

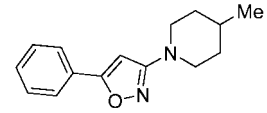
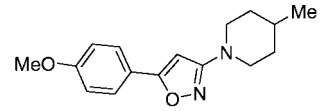
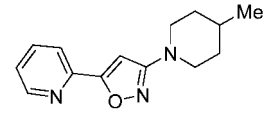
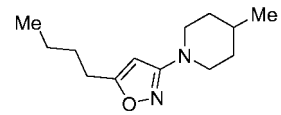
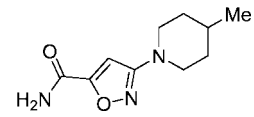
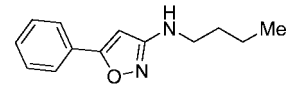
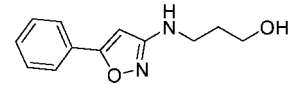
The addition−elimination reaction was demonstrated for a variety of substrates (Table 1). Alkyl-, aryl-, and heteroaryl-substituted bromoisoxazolines (entries 1−8) afforded the desired products in good to excellent yields. 5-Carbonyl or dioxolane substituent increased the 3-bromoisoxazolines reactivity 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