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Directed Lithiation of N-(*tert*-Butoxycarbonyl)aminoisoxazole: Synthesis of 4-Substituted Aminoisoxazoles

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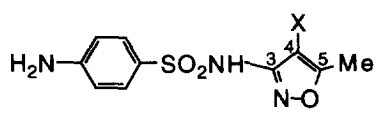
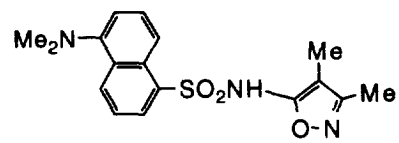
Abstract: Directed lithiation of 3-(Boc-amino)isoxazole **4** and 5-(Boc-amino)isoxazole **9** is described. Dilithioisoxazoles reacted with a variety of electrophiles to give the corresponding 4-substituted isoxazoles.

Aminoisoxazoles are important building blocks of pharmaceuticals including antibacterials and endothelin receptor antagonists. Sulfamethoxazole **1** is a potent antibacterial,[1] and its derivative 4-iodosulfamethoxazole **2** was recently found to be an endothelin antagonist on screening of the Shionogi compound library. Comparison of the antagonistic activities of these two sulfonamidoisoxazoles indicated that a substituent at the 4-position of



Endothelin antagonistic activity $IC_{50}(\mu M)$

1. X = H (sulfamethoxazole) 333
2. X = I 11



3. BMS-182874

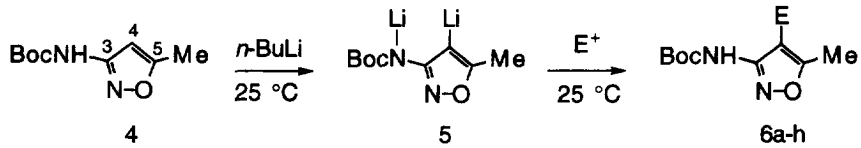
isoxazole plays a crucial role in the activity. While our synthetic study of sulfonamidoisoxazole endothelin antagonists was in progress, Bristol-Myers Squibb independently reported a structurally similar sulfonamide **3**[2] as a potent and orally active endothelin antagonist. In order to discuss the structure-activity relationships of endothelin antagonists of sulfonamidoisoxazoles **2** or **3**, a new and general synthesis of 4-substituted aminoisoxazoles became necessary.

Directed metallation[3] is an established method for functionalization of aryl systems, and a number of useful aryl- or heteroaryllithiums have been generated by ortho-directed lithiation. Indeed, isoxazole metallation[4] has been discussed for those having a variety of structures or directing groups. These studies have shown that the ratio of two metallation modes, one on a side chain and the other on a ring, often depends on the nature of the substituents[5]. Although modification of the 4-position of aminoisoxazoles was essential in the context of our endothelin antagonist research, there was no versatile method for 4-metalloisoxazoles by directed metallation. 4-Metalloisoxazoles were generally prepared by halogen-metal exchange.[6] To generate 4-lithioisoxazoles with an amino side chain, the *tert*-butyl carbamate (Boc) group was chosen as an amino-

protecting group owing to its strong directing effect[7] and its easy deprotection under mild conditions. We decided to explore directed lithiation of 3- and 5-(Boc-amino)isoxazoles as a new route to 4-substituted isoxazole endothelin antagonists.

3-(Boc-amino)-5-methylisoxazole **4**,[8] prepared from commercially available 3-amino-5-methylisoxazole and di-*tert*-butyl dicarbonate, was treated with 2.3 equiv. of *n*-BuLi at –78 °C in THF under a nitrogen atmosphere. The monoanion, which precipitated as a white solid at –78 °C, dissolved when the reaction temperature was raised to –30 °C. The monoanion underwent the further deprotonation around –30~0 °C and

Scheme 1



4 5 6a-h

the resulting dianion **5** precipitated at room temperature to give a white slurry. Addition of a variety of electrophiles at –78 °C gave 4-substituted isoxazoles **6** in good yields (Scheme 1).

The results summarized in Table 1 demonstrate the synthetic utility of the directed metallation for the synthesis of 4-substituted aminoisoxazoles,[9] which is a useful precursor for the sulfonamide endothelin antagonist.

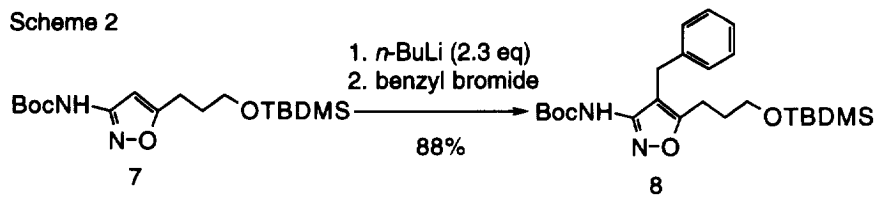
Table 1. Synthesis of 4-Substituted 3-[(*tert*-butoxycarbonyl)amino]-5-methylisoxazoles

electrophile	product	E	yield (%)
CO_2 then CH_2N_2	6a	CO_2Me	81
MeI	6b	Me	92
EtI	6c	Et	92
allyl bromide	6d	allyl	97
TMSCl	6e	TMS	50
DMF	6f	CHO	77
benzyl bromide	6g	benzyl	65
PhSSPh	6h	SPh	67

TMS = trimethylsilyl

To our knowledge, this metallation is the first example of Boc-amino directed lithiation of five-membered nitrogen heterocycles (azoles). Among the metallating reagents examined, *n*-BuLi was the most satisfactory in terms of reagent availability and yield. Metallation by lithium diisopropylamide caused only deprotonation of the 5-methyl group.[10] Some protective groups other than the Boc group were less satisfactory: The benzyloxycarbonyl (Cbz) group gave the alkylation product contaminated with the rearrangement product derived from metallation at the benzylic position.[11] The substituent at the 5-position was not limited to methyl, and a longer alkyl chain bearing the silyloxy group in **7** is well tolerated (Scheme 2). However, 3-(Boc-amino)isoxazole having a hydrogen at the 5-position did not give any alkylated products. Ring cleavage of 5-unsubstituted isoxazoles under strong basic conditions such as metallation is known.[12] The Boc group was

Scheme 2

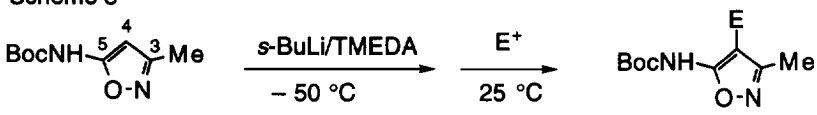


7 8

cleaved by trifluoroacetic acid treatment to give aminoisoxazoles, which gave sulfonamides on treatment with sulfonyl chlorides in pyridine.

In the case of isomeric 5-(Boc-amino)-3-methylisoxazole **9**,[13] *n*-BuLi was not a proper lithiating reagent. Instead, treatment of **9** with 3 equiv. of *s*-BuLi in THF-TMEDA (3 equiv.) gave the dianion intermediate at –50 °C. An electrophile was added at –78 °C and warming to room temperature gave the desired alkylated derivatives **10** in good yields (Scheme 3).

Scheme 3



9 10a,b

	E+	E
10a	CO_2 then CH_2N_2	CO_2Me (80%)
10b	MeI	Me (76%)

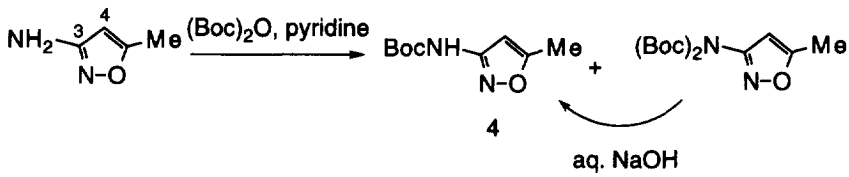
Our Boc-amino directed lithiation method opens the way to a variety of 4-substituted aminoisoxazoles. Synthetic study of endothelin receptor antagonists and investigation of structure-activity relationships are under way.

References and Notes

1. Kano, H; Ogata, K. *Ann. Rep. Shionogi Res. Lab.* **1957**, *7*, 1. See *C.A.* **1957**, *51*, 17889.
2. Stein, P. D.; Hunt, J. T.; Floyd, D. M.; Moreland, S.; Dickinson, K. E. J.; Mitchell, C.; Liu, E. C. -K.; Webb, M. L.; Murugesan, N.; Dickey, J.; McMullen, D.; Zhang, R.; Lee, V. G.; Serafino, R.; Delaney, C.; Schaeffer, T. R.; Kozlowski, M. *J. Med. Chem.* **1994**, *37*, 330.
3. For an extensive review of directed metallation chemistry, see Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
4. For a review of metallation of isoxazoles, see Iddon, B. *Heterocycles* **1994**, *37*, 1263.
5. Alberola, A.; Calvo, L.; Rodríguez, T. R.; Sañudo, C. *J. Heterocyclic Chem.* **1992**, *29*, 445. Micetich, R. G.; Shaw, C. C.; Hall, T. W.; Spevak, P.; Bains, B. K. *Heterocycles* **1985**, *23*, 585. Oster, T. A.; Harris, T. M. *J. Org. Chem.* **1983**, *48*, 4307. Bowden, K.; Crank, G.; Ross, W. J. *J. Chem. Soc. (C).* **1968**, 172. Gainer, J.; Howarth, G. A.; Hoyle, W.; Roberts, S. M.; Suschitzky, H. *J. Chem. Soc. Perkin I*, **1976**, 994.
6. Kalish, R.; Broger, E.; Field, G. F.; Anton, T.; Steppe, T. V.; Sternbach, L. H. *J. Heterocyclic Chem.* **1975**, *12*, 49. Antequera, T.; Ramos, V.; Torroba, T. *Heterocycles* **1986**, *24*, 3203. Alberola, A.; Serrano, A. P.; Rodríguez, M. T. R.; Orozco, C. *Heterocycles* **1989**, *29*, 667.

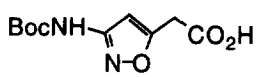
7. For papers on application of Boc-amino directed lithiation of benzene and pyridine, see Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798. Salituro, F. G.; McDonald, I. A. *J. Org. Chem.* **1988**, *53*, 6138. Kelly, T. A.; Patel, U. R. *J. Org. Chem.* **1995**, *60*, 1875.

8. To prepare 3-(Boc-amino)-5-methylisoxazole **4**, 3-amino-5-methylisoxazole was treated with di-*tert*-butyl dicarbonate in pyridine at room temperature yielding a mixture of mono-Boc-isoxazole **4** and di-Boc compound. Subsequent treatment of the mixture with aq. NaOH in MeOH hydrolyzed the di-Boc to give **4** as a sole product. Aqueous work-up and condensation under a reduced pressure gave **4**. The analytically pure sample was obtained as white crystals by recrystallization from EtOAc-hexane (63% yield). **4**: mp. 108-109 °C. IR (KBr): 3420, 2976, 1733, 1622 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.51 (s, 9), 2.37 (s, 3), 6.49 (s, 1), 7.21 (br s, 1). ^{13}C NMR ($CDCl_3$): δ 12.61, 28.17, 81.73, 95.43, 151.81, 158.55, 169.70. Anal. Calcd. for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.40; H, 7.05; N, 14.14.

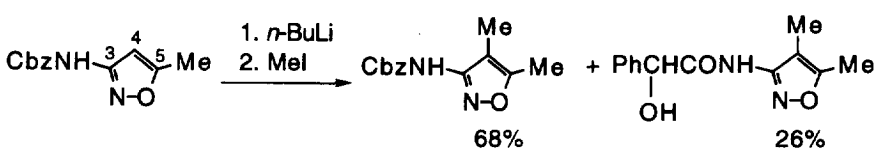


9. Satisfactory ^1H- and ^{13}C-NMR, IR, mass spectra and/or elemental analysis were obtained for all the new compounds.

10. The isoxazolylacetic acid was obtained by the reaction with carbon dioxide.



11. Zhang, P.; Gawley, R. E. *J. Org. Chem.* **1993**, *58*, 3223.
In the alkylation with methyl iodide, the mandelamide was obtained with the desired methylated isoxazole as shown below.



12. Hoppe, I.; Schöllkopf, U. *Liebigs Ann. Chem.* **1979**, 219. Nesi, R.; Ricci, A.; Taddei, M.; Tedeschi, P.; Seconi, G. *J. Organomet. Chem.* **1980**, *195*, 275.
We were unable to isolate and characterize fragments of the isoxazole.

13. 5-(Boc-amino)-3-methylisoxazole **9** was prepared in a similar way to the preparation of **4**.

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