Pergamon

Tetrahedron Letters 39 (1998) 8023–8026

TETRAHEDRON LETTERS

Regioselective Ring Metalation in [2,4]-Bisoxazoles

David R. Williams,* Dawn A. Brooks, and Kevin G. Meyer

Department of Chemistry, Indiana University, Bloomington, Indiana 47405 U.S.A.

Marty Pagel

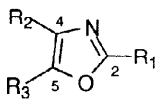
NMR & Molecular Visualization Facility, Department of Chemistry, Indiana University, Bloomington, Indiana 47405 U.S.A.

Received 14 August 1998; accepted 20 August 1998

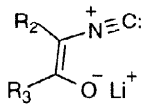
Abstract: The efficient, highly regioselective metalation of a 2,4-disubstituted bisoxazole system is described. The resulting lithio-oxazole is a competent nucleophile in subsequent alkylations.

Recent developments in marine natural product chemistry have heightened interest in the basic chemistry of the oxazole nucleus.[1] Five-membered heterocycles are often utilized in medicinal chemistry for drug development and structure activity studies, providing a polar, hydrogen bond acceptor as a rigid platform for elaboration. Recent advances have focused on methodology for the incorporation of the intact heterocycles[2] as an alternative to classical *de novo* synthesis of these ring systems.[3] Herein, we communicate our results for the directed lithiation of a 2,4-disubstituted bisoxazole and the regioselective incorporation of common electrophiles.[4]

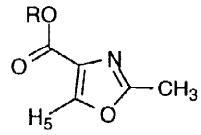
The deprotonation of the oxazole nucleus has been studied in several cases. Reports by Rickborn,[5a] Dondoni,[5b] and Hodges[5c] have demonstrated the removal of hydrogen (pKa ≈ 20) at C-2 of **1**. The 2-lithiooxazole **1a** is in equilibrium with the ring-opened isonitrile **2**,[6] which affords a pathway to oxazoles derived from the Cornforth rearrangement.[7] Facile deprotonation of 2-methyloxazoles **3** has provided a stable carbanion **3a** for synthesis.[8] In contrast, Meyers and Lawson discovered the preferential C-5 deprotonation in 2-methyloxazole-4-carboxylic acid (or ester) (**4**).[9]



1 (R_1=H)
1a (R_1=Li)
3 (R_1=CH_3)
3a (R_1=CH_2Li)



2

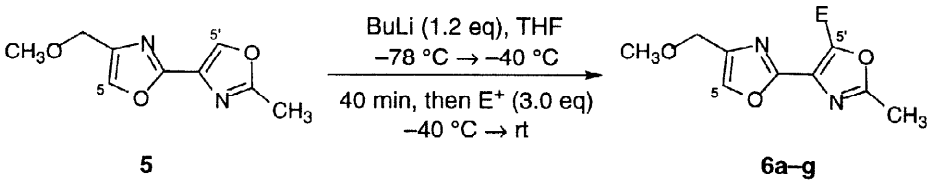


4

Our own metalation studies of 2′-methyl-4-methoxymethyl-[2,4′]bisoxazole (**5**) have revealed an efficient internally directed deprotonation with *n*-BuLi (1.2 eq, –78 °C → –40 °C). This has led to useful yields for the incorporation of various electrophiles at the C-5′ position of the bisoxazole nucleus (Table).[10] The regioselectivity of this process is clearly indicated in the ^{1}H NMR spectrum of the products by the disappearance of the characteristic downfield oxazole hydrogen (δ 8.13 ppm, C-5′ vs δ 7.63 ppm, C-5). Products resulting from deprotonation at the 2′-α methyl substitutent of **5** are not observed. Although we have not attempted to optimize these reactions, alkylation with prenylbromide (entry 5) is difficult, and leads to the recovery of starting

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01792-4

Table: Regioselective Alkylations of Bisoxazole 5.

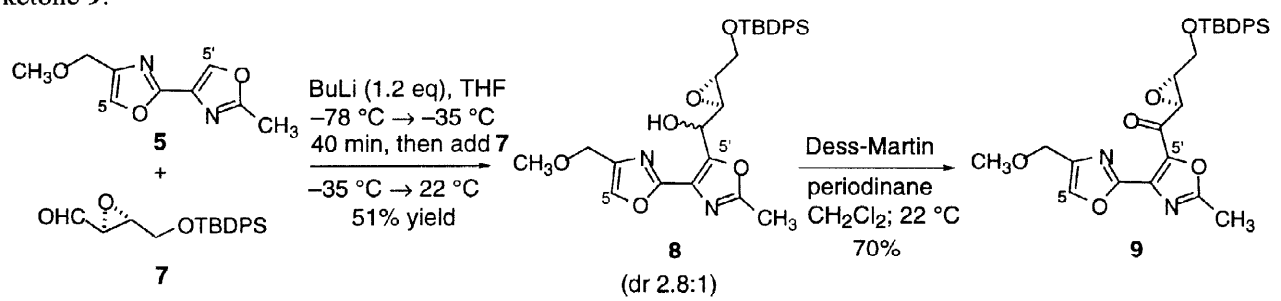


5 **6a–g**

	Electrophile (E^+)	Product	Yield
1	D_2O	**a**	>95%
2	MeI	**b**	63%
3	TMSCl	**c**	83%
4	NCS	**d**	50%
5	prenyl bromide	**e**	35%[a]
6	PhCHO	**f**	85%
7	$(CH_3)_2CCHCHO$	**g**	84%

[a] Isolated yield: 50% starting **5** recovered

5 (50%). This may suggest hydrogen transfer via competing allylic deprotonation in the product **6e**. Aldehydes are excellent substrates (entries 6 and 7) and silylation is efficient. Reaction of the carbanion with trimethylstannylchloride also led to clean formation of the expected product (by TLC). However, substantial protodestannylation occurred during buffered silica gel chromatography. Diastereomeric alcohols **8** were prepared as a 2.8:1 mixture via condensation with optically active epoxyaldehyde **7**, demonstrating a modest preference for Felkin-Anh addition (35% of **5** was recovered). Dess-Martin oxidation[11] of **8** afforded the novel ketone **9**.[12]



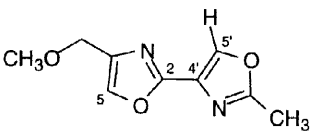
5 + **7** → **8** (dr 2.8:1) → **9**

The highly regioselective metalation of **5** may initially be due to heteroatom-complexation with *n*-butyllithium. The resulting C-5′ lithio-oxazole is stabilized by internal coordination with the Lewis basic nitrogen. The powerful directing effect of oxazolines toward regioselective aromatic metalation is well-precedented by Meyers[13] and Gschwend.[14] Sammakia and Latham have reported that the nitrogen of an oxazoline ring can direct the metalation of conformationally constrained, chiral ferrocenyloxazolines.[15] In addition, Zoltewicz recently reported that the 2-pyridyl group of 2,2′-bipyridine or 2,4′-bipyridine directs lithiation to the ortho position of the adjacent ring.[16]

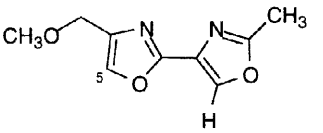
Our semiempirical calculations of **5** using the AM1 and PM3 Hamiltonians[17] have indicated that conformer **I** (Figure 1), which places the C5′-H and the nitrogen in proximity, is slightly more stable than conformer **II**.[18] Computations of four possible lithiated species **A**–**D**, using the EF (eigenvector following)

routine for finding the energy minimum, have illustrated that structure **A** with nitrogen stabilization of the 5′-lithio-oxazole is of considerably lower energy than alternative structure **B**. Compounds **C** and **D**, in which deprotonation occurs at the 5- and 2′-α positions, respectively, are less energetically favorable. From these calculations, it can be concluded that deprotonation leads to the thermodynamically preferred structure **A**.[19]

Figure 1

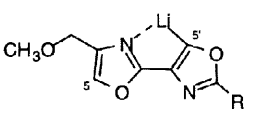


5-I

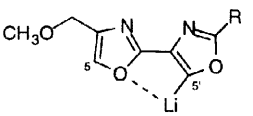


5-II

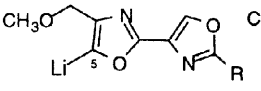
AM1 Hamiltonian 0.0 kJ/mol — 3.2 kJ/mol (0.8 kcal/mol)
PM3 Hamiltonian 0.0 kJ/mol — 7.0 kJ/mol (1.7 kcal/mol)



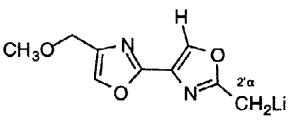
A



B



C



D

PM3 Hamiltonian

EF Routine:	0 kJ	60.3 kJ (14.4 kcal)	72.6 kJ (17.4 kcal)	63.6 kJ (15.2 kcal)

In conclusion, the 2,4-disubstituted bisoxazole system undergoes efficient, highly regioselective metalation and the resulting lithio-oxazole is a competent nucleophile in subsequent alkylation processes. Application of these observations for functionalization and elaboration of substituted bisoxazole systems is anticipated to have general utility in natural product synthesis and medicinal chemistry.

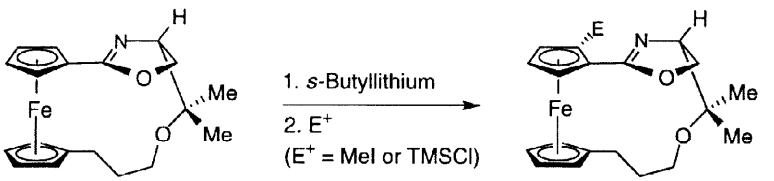
Acknowledgements: Generous financial support for this research was provided by an award sponsored by the National Institutes of Health (GM-41560) and Abbott Laboratories (fellowship for D.A.B.). The support of a Merck Faculty Development Award is gratefully acknowledged.

Note Added In Proof: After submission of this work, a related study has appeared: Liu, P.; Panek, J.S. *Tetrahedron Lett.* **1998**, *39*, 6147.

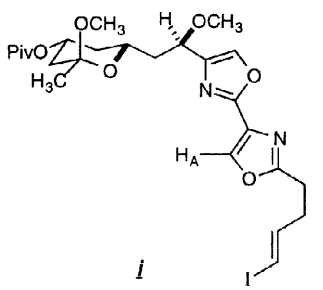
References:

1. For a recent publication in the series see: (a) Faulkner, D.J. *Nat. Prod. Rep.* **1997**, *14*, 259. (b) Lewis, J.R. *Nat. Prod. Rep.* **1996**, *13*, 435.
2. (a) For oxazoles: Shafer, C.M.; Molinski, T.F. *J. Org. Chem.* **1998**, *63*, 551 and references therein. Zhao, Z.; Scarlato, G.R.; Armstrong, R.W. *Tetrahedron Lett.* **1991**, *32*, 1609. (b) For thiazoles: Williams, D.R.; Brooks, D.A.; Moore, J.L.; Stewart, A.O. *Tetrahedron Lett.* **1996**, *37*, 983. (c) For imidazoles: Phillips, J.G.; Fadnis, L.; Williams, D.R. *Tetrahedron Lett.* **1997**, *38*, 7835.
3. (a) Turchi, I.J. In *Heterocyclic Compounds*; Turchi, I.J., Ed.; J. Wiley: New York, 1986; Vol 45. (b) Hartner, F.W. Oxazoles. In *Comprehensive Heterocyclic Chemistry II*; Katritzsky, A.R.; Rees, C.W.; Scriven, E.F.V., Eds.; Pergamon Press: Oxford, 1996; Vol. 6, pp 262-318 and references therein.
4. These results have been described as a part of our studies for the total synthesis of hennoxazole A. Brooks, D.A.; Williams, D.R. American Chemical Society 214th National Meeting; Las Vegas, NV; Sept. 10, 1997; Abstr. 280.
5. (a) Whitney, S.E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1987**, *52*, 3413. (c) Hodges, J.C.; Patt, W.C.; Connolly, C.J. *J. Org. Chem.* **1991**, *56*, 449.

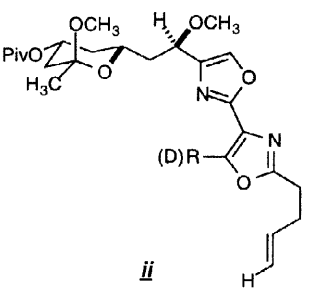
6. For recent advances: Vedejs, E.; Monahan, S.D. *J. Org. Chem.* **1996**, *61*, 5192. Crowe, E.; Horsner, F.; Hughes, M.J. *Tetrahedron* **1995**, *51*, 8889. Harn, N.K.; Gramer, C.J.; Anderson, B.A. *Tetrahedron Lett.* **1995**, *36*, 9453.
7. Williams, D.R.; McClymont, E.L. *Tetrahedron Lett.* **1993**, *34*, 7705.
8. (a) Gangloff, A.R.; Akermark, B.; Helquist, P. *J. Org. Chem.* **1992**, *57*, 4797 and references therein. (b) Lipshutz, B.H.; Hungate, R.W. *J. Org. Chem.* **1981**, *46*, 1410.
9. Meyers, A.I.; Lawson, J.P. *Tetrahedron Lett.* **1981**, *22*, 3163.
10. For all entries, isolated yields are reported for purified (>97%) products following silica gel chromatography. For a representative procedure (E = PhCHO): *n*-BuLi (62 μL of a 2.5 M solution in hexanes) was added to a –78 °C solution of bisoxazole **5** (25 mg, 0.13 mmol) in THF (1 mL). The resulting orange solution was warmed to –40 °C, and after 90 min, freshly distilled benzaldehyde (41 mg, 0.39 mmol, 40 mL) was added. The solution was allowed to warm to ambient temperature. The mixture was concentrated and directly purified by column chromatography (15 g SiO_2, 70% EtOAc/hexanes) to afford alcohol **6f** (33 mg, 85%) as a viscous oil.
11. Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155.
12. Compound **9**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (s, 1H), 7.68 (m, 4H), 7.39 (m, 6H), 4.62 (d, *J* = 1.7 Hz, 1H), 4.31 (d, *J* = 0.7 Hz, 2H), 4.08 (dd, *J* = 2.4, 12.2 Hz, 1H), 3.83 (dd, *J* = 4.4, 12.2 Hz, 1H), 3.47 (ddd, *J* = 2.2, 2.2, 4.3 Hz, 1H), 3.30 (s, 3H), 2.62 (s, 3H), 1.02 (s, 9H).
13. (a) Meyers, A.I.; Mihelich, E.D. *J. Org. Chem.* **1975**, *40*, 3159. (b) Directed metalation of pyridines by oxazolines has also been studied: Meyers, A.I.; Gabel, R.A. *Tetrahedron Lett.* **1978**, 227.
14. Gschwend, H.W.; Hamdan, A. *J. Org. Chem.* **1975**, *40*, 2008.
15. Sammakia, T.; Latham, H.A. *J. Org. Chem.* **1995**, *60*, 6002.



16. Zoltewicz, J.A.; Dill, C.D. *Tetrahedron* **1996**, *52*, 14469.
17. QCPE Program 455, MOPAC Version 93. The authors thank Dr. Marty Pagel for performing these computations.
18. These results correlate well with semiempirical calculations of a model tris-oxazole system of halichondramide: James, D.M.; Wintner, E.; Faulkner, D.J.; Siegel, J.S. *Heterocycles* **1993**, *35*, 675.
19. Facile deprotonation of H_A (at C-5') can impose undesirable consequences for base-induced reactions. For example, attempted metalation of the vinylic iodide ***i*** led to substantial proton transfer providing alkylation (deuterium incorporation) to yield mixtures containing side product ***ii***.



i



ii