JOC *Note*

A Convenient Oxazole C-2 Protecting Group: The Synthesis of 4- and 5-Substituted Oxazoles via Metalation of 2-Triisopropylsilyloxazoles

Ross A. Miller,* Randi M. Smith,[1] and
Benjamin Marcune

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

ross_miller@merck.com

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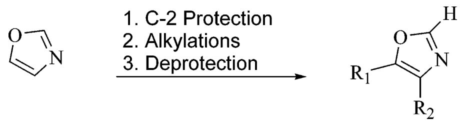


Metalation of oxazoles at the 4 and 5 position was achieved after regioselective C-2 silyl protection. Removal of the protecting group was then accomplished under mild conditions allowing for a straightforward preparation of C-5 monosubstituted and C-4,5 disubstituted oxazoles. The first practical C-2 protecting group of oxazoles has been demonstrated.

Transformation of unsubstituted heterocycles to substituted heterocycles utilizing metalation is a direct way to regioselectively prepare substituted aromatic or heterocyclic compounds. The hallmark of this strategy to prepare polysubstituted compounds is its simplicity, generality, and versatility.[2] However, successful application of this strategy to more complex substrates often depends on the proper protection of an undesired substitution site. Protection of undesired reactive sites with silicon is common practice to avoid chemoselectivity problems.[3] Oxazoles, whose most acidic site is the C-2 position, present a unique challenge for metalation protecting group strategies due to the unusual behavior of the C-2 lithio anion.[4] The C-2 lithio intermediate **2a** is not observed by NMR, only the ring-opened compound **2b**.[5]

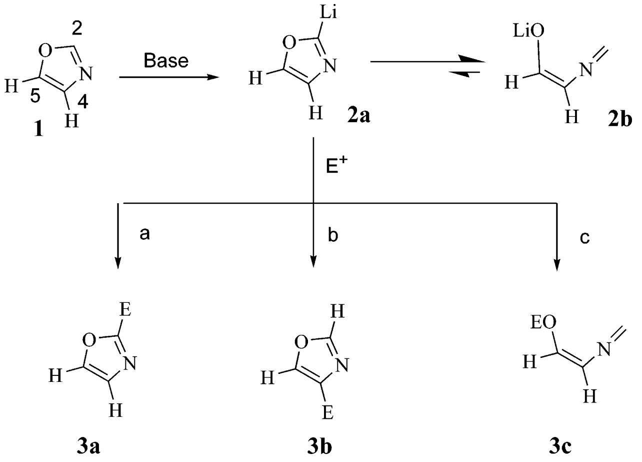
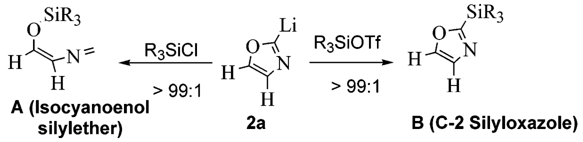


FIGURE 1. Reactivity of C-2 Lithioxazoles.

Nonselective reaction with electrophiles gives mixtures of products (**3a**, **3b**, and **3c**) due to the formation of an isocyanoenolate **2b** (Figure 1).[6] The distribution of products is highly dependent on the electrophile, the nature of the counterion, solvent, etc.[7] Simple, direct C-2 silylation with silyl chlorides has proven irreproducible and unusable in synthesis.[8] To protect the C-2 position of oxazoles, multistep strategies that allowed for C-5 metalation of oxazoles which did not start from the C-2 H oxazoles have been developed, but integration of the methodology into multistep syntheses is awkward.[9] However, recently we found a dramatic difference in the reactivity of C-2 metalated oxazoles between silyl triflates and silyl chlorides that has allowed for selective and general C-2 silylation (eq 1).[10] Herein we report the extension of our direct C-2 silyl oxazoles synthesis and its utility as a useful protecting group for C-2 H oxazoles that allow for simple metalation methodology to prepare 4 and 5 substituted oxazoles.



(1)

As previously reported, C-2 silylation of oxazole **1** was accomplished by treatment with *n*-BuLi followed by quenching with silyltriflates yielding >99:1 C-silylated oxazole **B** versus O-silylated oxazole **A**. C-2 silyloxazoles were prepared in a general manner by treatment with a base such as *n*-BuLi or *i*-PrMgCl in THF at low temperature followed by a silyl triflate. Both the TMS and TBS

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[1] Merck Research Laboratories 2003 UNCF Summer Intern.

[2] For a recent reviews see: Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376 and references therein.

[3] Green, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.

[4] The pK_a of the C-2 H has been estimated to be ~20. For a general review of oxazoles see: (a) Turchi, I. J., Ed. *Heterocyclic Compounds*; J. Wiley and Sons: New York, 1986. (b) Palmer, D. , Ed. *Heterocyclic Compounds*; J. Wiley and Sons: New York, 2003, 2004; Vol. 60, Parts A and B.

[5] Crowe, E.; Hassner, F.; Hughes, M. J. *Tetrahedron* **1995**, *32*, 8889.

[6] (a) Schroder, R.; Schollkopf, U.; Blume, E.; Hoppe, I. *Liebigs Ann. Chem.* **1975**, 533. (b) Reference 5. (c) Hilf, C.; Bosold, F.; Harms, K.; Marsch, M.; Boche, G. *Chem. Ber./Recl.* **1997**, *130*, 1213. (d) Hodges, J. C.; Pratt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449.

[7] (a)Vedejs, E.; Monahan, S. D. *J. Org. Chem.* **1996**, *61*, 5192. (b) Hodges, J. C.; Pratt, W. C.; Connolly, C. J. *J. Org. Chem* **1991**, *56*, 449. (c) Ikemoto, N.; Miller, R. A.; Fleitz, F.; Liu, J.; Petrillo, D.; Leone, J.; Laquidara, J.; Marcune, B.; Karady, S.; Armstrong, J. D.; Volante, R. P. *Tetrahedron Lett.* **2005**, *46*, 1867.

[8] Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058. This paper reports they were unable to prepare 2-(trimethylsilyl)-4-phenyloxazole via the reported literature methodology of O−Si to C−Si isomerization. See refs 4a and 4b in that paper.

[9] Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1998**, *63*, 551.

[10] Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, *43*, 935.

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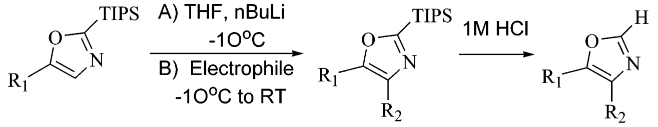
TABLE 1. Lithiation and Reaction of TIPS Protected Oxazoles



4a R$_1$ = H
4b R$_1$= Ph

5a-l

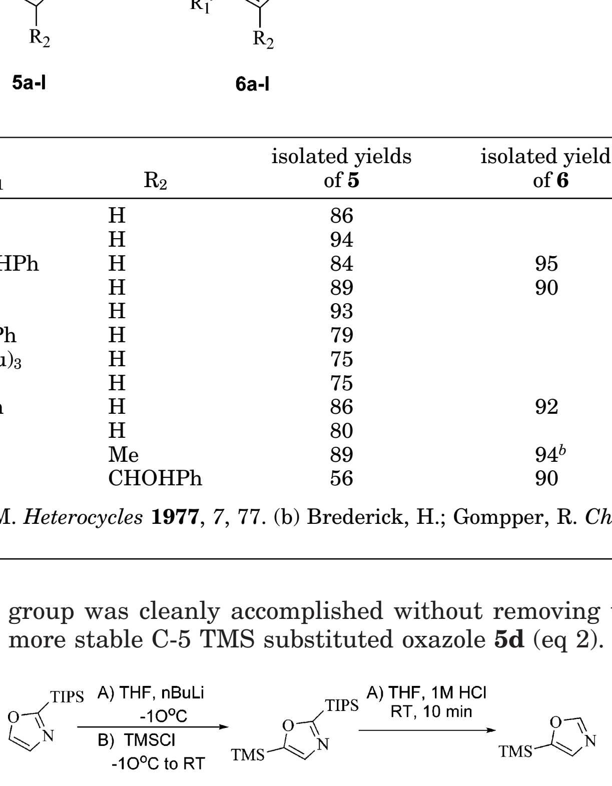
6a-l

entry	R$_1$	electrophile	product	R$_1$	R$_2$	isolated yields of **5**	isolated yields of **6**
1	H	MeI	**5a**	Me	H	86	
2	H	EtI	**5b**	Et	H	94	
3	H	benzaldehyde	**5c**	CHOHPh	H	84	95
4	H	TMSCl	**5d**	TMS	H	89	90
5	H	TBSCl	**5e**	TBS	H	93	
6	H	benzylbromide	**5f**	CH2Ph	H	79	
7	H	tributyltinchloride	**5g**	Sn(Bu)$_3$	H	75	
8	H	allyl bromide[a]	**5h**	allyl	H	75	
9	H	benzonitrile	**5i**	COPh	H	86	92
10	H	DMF	**5j**	CHO	H	80	
11	Ph	MeI	**5k**	Ph	Me	89	94[b]
12	Ph	benzaldehyde	**5*l***	Ph	CHOHPh	56	90

[a] 13% starting material remained. [b] (a) Possel, O.; van Leusen, A. M. *Heterocycles* **1977**, *7*, 77. (b) Brederick, H.; Gompper, R. *Chem. Ber.* **1954**, *87*, 700.

oxazoles showed partial or complete instability to aqueous workup and column chromatography; however, the TIPS (triisopropylsilyl) derivative was observed to be a stable and practical protecting group throughout nonacidic aqueous workups and purification.[11,12] TIPS oxazole **4a** was metalated quantitatively and rapidly with 1.1 equiv of *n*-BuLi at −10 °C as evidenced by >95% deuterium incorporation post quenching with D$_2$O after 5 min age time. Additionally, reaction of this C-5 lithio anion with a variety of electrophiles was examined and the results are shown in Table 1. No instability of the anion was observed under the conditions of the metalation. Aryllithium reagents can vary in the efficiency with which they couple with electrophiles.[2] In this case, a variety of electrophiles reacted in high yield with the C-5 lithiated oxazole, including alkyl halides, allyl and benzyl halides, stannyl chloride, aldehydes, and nitriles. Isolation of the products was simplified over the corresponding C-2 hydrogen oxazoles, due to significantly lower volatility and water solubility. The products were purified on silica gel without any observation of desilylation. Removal of the TIPS protecting group was then carried out easily with acidic conditions to regenerate the C-2 H oxazole, using dilute aqueous acid. Alternatively, the initial reaction mixture could be quenched with acid and the C-2 H compound directly isolated. In the case of stannyl compound **5g**, competitive C-5 destannylation was observed. Due to the volatility of the products, **6a**, **6b**, and **6j** were not desilyated.

Entries 11 and 12 demonstrate applications of this protecting group strategy to prepare disubstituted oxazoles. Interestingly, selective removal of the C-2 TIPS group was cleanly accomplished without removing the more stable C-5 TMS substituted oxazole **5d** (eq 2).



5d

6d

(2)

In conclusion, efficient and direct C-2 protection of oxazoles with silicon has allowed for systematic functionalization of oxazoles. The 4- and 5-lithio anions were reactive in high yield with a variety of electrophiles. Facile deprotection allowed for regeneration of the C-2 unsubstituted oxazoles. This methodology represents the first general protecting group for the C-2 position of oxazoles. Application of this protecting group strategy should find use in a wide variety of synthetic applications involving oxazoles.

Experimental Section

Phenyl[2-[tris(1-methylethyl)silyl]-1,3-oxazol-5-yl]methanol (5c). In a round-bottom flask was charged dry TIPS oxazole **4a** (2.86 gm, 12.7 mmol) and dry THF (42 mL). The solution was cooled to ca. −30 °C and then ^{n}BuLi was slowly added, maintaining the internal temperature less than −20 °C. After a 15 min age, benzaldehyde was added and the reaction mixture was warmed to room temperature over 30 min. The reaction mixture was quenched with water (15 mL) and isopropyl acetate (IPAC) (30 mL) and the layers cut. The organic layer was concentrated and the resulting oil purified by chromatography, using silica gel and 30% IPAC/heptane as eluent. A white solid (3.2 g) was obtained upon evaporation. ^{1}H NMR (399.87 MHz, CDCl$_3$) δ 7.42 (m, 5H), 6.93 (s, 1H), 5.93 (s, 1H), 1.39 (septet, J = 7.5, 3H), 1.24 (d, J = 0.9, 18H). ^{13}C NMR (100.56 MHz, CDCl$_3$) δ 169.0, 154.9, 140.3, 128.6, 128.4, 126.6, 124.1, 68.8, 18.4, 11.0. Theoretical elemental analysis: C 68.83, H 8.82, N 4.22. Found: C 68.92, H 8.91, N 4.22. LRMS calcd 331.2; found M + H 332.5.

1,3-Oxazol-5-yl(phenyl)methanol (6c). Compound **5c** (1 g) was dissolved in 10 mL of THF at room temperature. Addition of 1 mL of 1 M HCl was carried out, followed by a 15 min age.

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(11) TIPSOTf contained 5−10% of *n*-propyldiisopropylsilyl triflate, which complicated the NMR spectrum but not the subsequent chemistry. A similar observation about the purity of TIPSOTF was previously made: Barden, D. J.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **2001**, 2366.

(12) For a thorough review of the triisopropylsilyl group, see: Rucker, C. *Chem. Rev.* **2005**, *95,* 1009.

The reaction mixture was diluted with 10 mL of IPAC and 5 mL of water and the layers cut. The organic layer was concentrated and purified by chromatography, using silica gel and 40% IPAC/heptane as eluent to obtain **6c**. If desired, compound **6c** could be obtained directly without isolation of **5c** by quenching the reaction with 1 N HCl instead of water. ^{1}H NMR (399.87 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.4 (m, 5H), 6.77 (s, 1H), 5.84 (s, 1H), 3.70 (br s, 1H). ^{13}C NMR (100.55 MHz, $CDCl_3$) δ 153.7, 151.2, 139.9, 128.7, 128.6, 126.6, 123.6, 68.3. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.62; H, 5.09, N, 7.91. Exact mass calcd 175.1; found M + H 176.1.

Supporting Information Available: Full characterization of compounds **5a**–***l***, **6c**, **6d**, **6i**, **6k**, and **6*l***. This material is available free of charge via the Internet at http://pubs.acs.org.

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