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General Methodology for the Preparation of 2,5-Disubstituted-1,3-oxazoles

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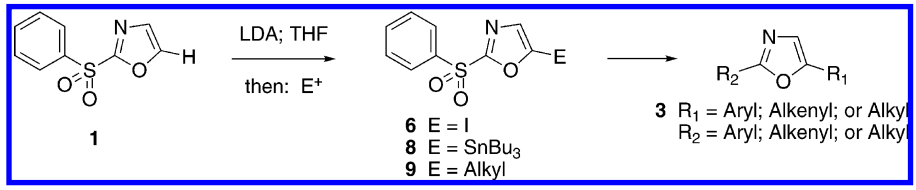
ABSTRACT



Deprotonation of 2-(phenylsulfonyl)-1,3-oxazole (1) readily provides a useful C-5 carbanion that is reactive with a variety of electrophiles. Aldehydes and ketones are useful substrates, and the formation of 5-iodo- and 5-tri-*n*-butylstannyl oxazoles affords access to cross-coupling reactions. Subsequent nucleophilic displacement of the 2-phenylsulfonyl group provides a general route for the synthesis of 2,5-disubstituted-1,3-oxazoles.

Oxazoles represent an important class of five-membered heterocycles.[1] Continuing interest in the chemistry of 1,3-oxazoles has been undoubtedly stimulated by the incorporation of this ring system in a variety of biologically significant secondary metabolites, such as hennoxazole A,[2] telomestatin,[3] phorboxazoles A and B,[4] the ulapualides,[5] diazonamides A and B,[6] and rhizopodin.[7] Depsipeptides often contain 1,3-oxazoles as a result of oxidative cyclodehydrations of serine or threonine residues resulting in 2,4-disubstitution of the heterocycle.[8] Additional examples of naturally occurring 1,3-oxazoles feature 2,5-disubstitution and 5-monosubstitution, and these substances may also exhibit significant biological activity.[9]

The proliferation of interesting structures within this family has inspired the development of methods to address the synthesis of specific substitution patterns. Williams and Wipf have devised oxidative cyclodehydration strategies to provide a general route for the de novo preparation of 2,4-disubstituted oxazoles.[10] Several laboratories have recently described cross-coupling reactions for alkenylation and arylation at C-2 of the oxazole nucleus,[11] as well as studies of Stille reactions of 2-phenyl-1,3-oxazoles leading to C-4 and C-5 substitu-

(1) Taylor, E. C.; Wipf. P. *Oxazoles: Synthesis, Reactions, and Spectroscopy*; John Wiley & Sons: Hoboken, 2003.

(2) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173–3174.

(3) Shin-ya, K.; Wierzba, K.; Matsuo, K.; Ohtani, T.; Yamada, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1262–1263.

(4) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126–8131.

(5) (a) Rosener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846–847. (b) Dalisay, D. S.; Rogers, E. W.; Edison, A. S.; Molinski, T. F. *J. Nat. Prod.* **2009**, *72*, 732–738.

(6) For structure revision of diazonamide A, see: Li, J.; Burgett, A. W. G.; Esser, L.; Amezcua, C.; Harran, P. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4770–4773.

(7) Hagelueken, G.; Albrecht, S. C.; Steinmetz, H.; Jansen, R.; Heinz, D. W.; Kalesse, M.; Schubert, W.-D. *Angew. Chem., Int. Ed.* **2008**, *48*, 595–598.

(8) For examples, see: (a) Kanoh, K.; Matsuo, Y.; Adachi, K.; Imagawa, H.; Nishizawa, M.; Shizuri, Y. *J. Antibiot.* **2005**, *58*, 289–292. (b) Perez, L. J.; Faulkner, D. J. *J. Nat. Prod.* **2003**, *66*, 247–250. (c) Kohno, J.; Kameda, N.; Nisho, M.; Kinumaki, A.; Komatsubara, S. *J. Antibiot.* **1996**, *49*, 1063–1065.

(9) (a) Giddens, A. C.; Boshoff, H. I. M.; Franzblau, S. G.; Barry, C. E., III; Copp, B. R. *Tetrahedron Lett.* **2005**, *46*, 7355–7357. (b) Fresneda, P. M.; Castañeda, M.; Blug, M.; Molina, P. *Synlett* **2007**, 324–326. (c) Shiomi, K.; Arai, N.; Shinose, M.; Takahashi, Y.; Yoshida, H.; Iwabuchi, J.; Tanaka, Y.; Omura, S. *J. Antibiot.* **1995**, *48*, 714–719.

(10) (a) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168. (b) For initial application of this methodology in the synthesis of hennoxazole A, see: Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 1303–1305.

(11) (a) Besselièvre, F.; Piguel, S.; Mahuteau-Betzer, F.; Grierson, D. S. *Org. Lett.* **2008**, *10*, 4029–4032. (b) Flegeau, E. F.; Popkin, M. E.; Greaney, M. F. *Org. Lett.* **2008**, *10*, 2717–2720. (c) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905–2907. (d) Smith, A. B., III; Minbiole, K. P.; Freeze, S. *Synlett* **2001**, 1739–1742.

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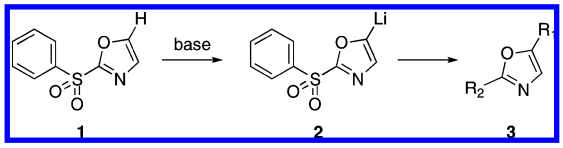
tion.[12] Direct metalations via deprotonations of the 1,3-oxazole ring have been studied in some cases.[13] Removal of the C-2 hydrogen leads to an equilibrium of the ring-closed carbanion and the isomeric ring-opened isonitrile, and acylation reactions produce 4,5-disubstituted oxazoles derived from the Cornforth rearrangement.[14] Examples of ring metalations via complex-induced proximity effects[15] (CIPE) have been recorded in [2,4]bisoxazoles[16] and for 2-methyloxazole-4-carboxylic acid.[17] Very recently, Stambuli and co-workers have described the selective C-5 deprotonation of 2-methylthio-1,3-oxazole with *tert*-butyllithium leading to the production of 2,5-disubstituted oxazoles.[18] These studies advance the earlier precedents of Shafer and Molinski and reports of the regioselective copper-mediated allylation of 2-(*n*-butylthio)-1,3-oxazole.[19] In this letter, we disclose a compilation of our findings for the site-selective deprotonation and the synthetic utility of 2-(phenylsulfonyl)-1,3-oxazole in processes of alkylation, alkenylation, and arylation to afford a general pathway for the synthesis of 2,5-disubstituted oxazoles.

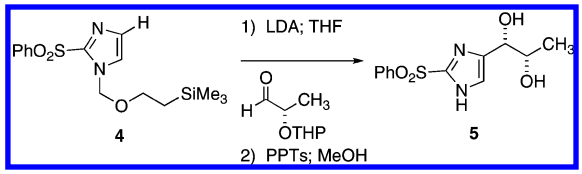
Direct incorporation of five-membered heterocycles into complex molecules is an important and fundamental strategy in medicinal chemsitry. Thus, we have explored the kinetic deprotonation of 2-(phenylsulfonyl)-1,3-oxazole (**1**) and the utility of carbanion **2**. Reactions of **2** with a variety of electrophiles and the subsequent replacement of the 2-phenylsulfonyl group provide a general route for the preparation of 2,5-disubstituted oxazoles **3** (Scheme 1). Our studies are

Scheme 1. Site-Selective Substitutions of 1,3-Oxazole



precedented by the selective (C-4) deprotonation of 1-[2′-(trimethylsilyl)ethoxymethyl]-2-(phenylsulfonyl)imidazole (**4**) and reactions with common electrophiles followed by mild removal of SEM as illustrated in the preparation of **5** (Scheme 2).[20] Reductive desulfonylation with 2% Na(Hg)

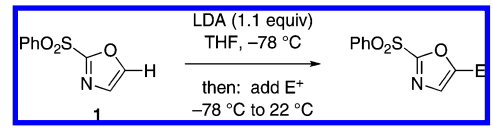
Scheme 2. Selective C-4 Deprotonation of Imidaxzole **4**



in methanol leads to the introduction of the intact imidazole nucleus.

(12) Hämmerle, J.; Spina, M.; Schnürch, M.; Mihovilovic, M. D.; Stanetty, P. *Synthesis* **2008**, 3099–3107.

Table 1. Reactions of 2-(Phenylsulfonyl)-1,3-oxazole **1**



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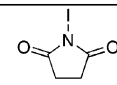
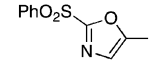
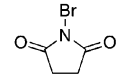
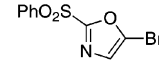
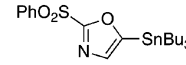
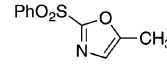
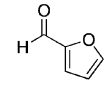
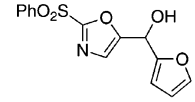
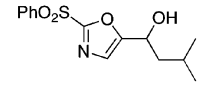
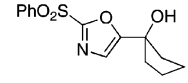
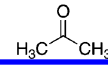
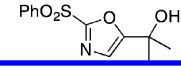
1			**6**	87
2			**7**	81
3	n-Bu_3SnCl		**8**	86
4	CH_3I		**9**	91
5			**10**	72
6			**11**	75
7			**12**	87
8			**13**	81

[a] Reaction conditions: a THF solution of sulfone **1** (1.0 equiv; 2.0 mmol) was added into a solution of LDA (1.1 equiv) in THF at −78 °C. After stirring under N_2 for 1 h, electrophile in THF solution was added with subsequent warming to 22 °C. [b] Products were purified by flash silica gel chromatography. [c] Yields are reported for isolated and purified product.

The preparation of **1** began with the C-2 deprotonation of oxazole using *n*-butyllithium at −78 °C (THF). Diphenyldisulfide was introduced, and reactions were allowed to stir at room temperature (24 h) to give 2-phenylthio-1,3-oxazole (91%) for oxidation with ammonium molybdate tetrahydrate (2.2 equiv) in ethanol containing 30% aqueous H_2O_2 at 22 °C (98% yield).

The selective deprotonation of 2-(phenylsulfonyl)-1,3-oxazole (**1**) with LDA (1.1 equiv) in THF at −78 °C afforded a well-behaved C-5 carbanion **2** that reacted efficiently with a number of electrophiles (Table 1). Under these reaction conditions, alkylation of **2** with allyl bromide proceeded poorly. This problem was overcome by transmetalation of **2** to give the corresponding organozinc species for a Negishi cross-coupling to yield the desired alkylation product **14** (90%) (Scheme 3).

Scheme 3. Negishi Coupling for C-5 Allylation of **1**

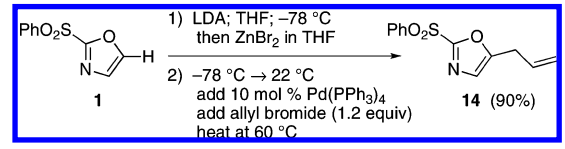
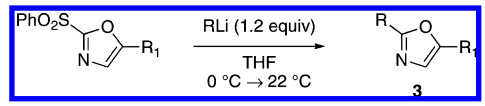
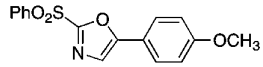
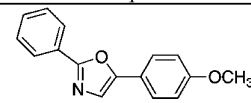
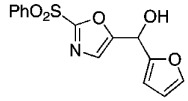
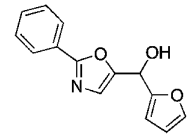
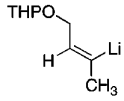
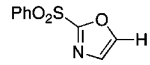
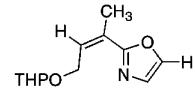
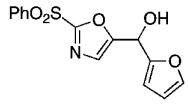
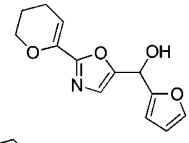
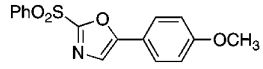
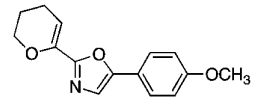
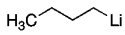
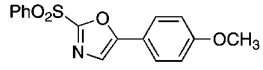
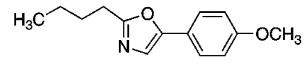
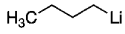
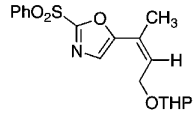
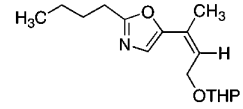
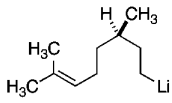
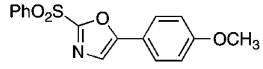
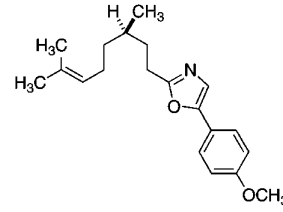
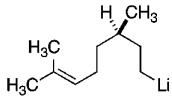
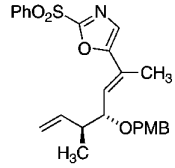
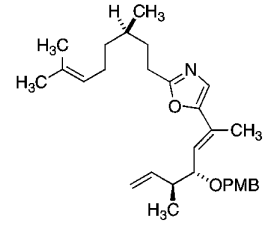
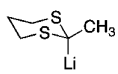
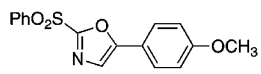
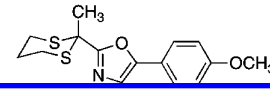


Table 2. Preparation of 2,5-Disubstituted-1,3-oxazoles **3** via Displacement of the 2-Phenylsulfonyl Substituent



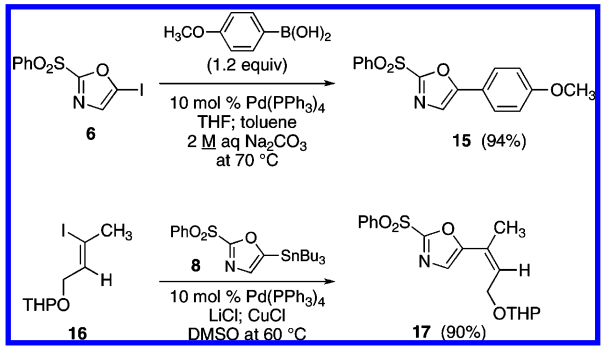
entry	lithium reagent	sulfone		oxazole product[a,b]		yield[c] (%)
1			**15**		**19**	90
2			**10**		**20**	85
3			**1**		**21**	78
4			**10**		**22**	71
5			**15**		**23**	83
6			**15**		**24**	69
7			**17**		**25**	76
8			**15**		**26**	79
9			**18**[d]		**27**	81
10			**15**		**28**	82

[a] Reaction conditions: lithium reagents (1.2 or 2.2 equiv in entries 2 and 4) were added under N_2 to a THF solution of sulfones (0.053 mmol) at 0 °C. Reactions were generally complete within 5 min and warmed to 22 °C prior to addition of aq NH_4Cl. [b] Products were purified by flash silica gel chromatography. [c] All yields are reported for isolated and purified products. [d] Compound **18** was prepared via the Stille cross-coupling reaction as described for **17**.

The efficient production of the iodide **6** (Table 1, entry 1) facilitates studies of Suzuki cross-coupling reactions toward the preparation of 2,5-disubstituted oxazoles. For example, the arylation reaction of **6** with commercially available 4-methoxyphenyl boronic acid using 10 mol % $Pd(PPh_3)_4$ at 70 °C gave **15** in 94% isolated yield. Similarly, our expectations that the 5-stannyl derivative **8** (Table 1, entry 3) would be useful for Stille processes have been confirmed

by the effective cross-coupling with (*Z*)-iodide **16**[21] using 10 mol % $Pd(PPh_3)_4$ in the presence of LiCl (6 equiv) and CuCl (5 equiv) in DMSO at 60 °C to yield oxazole **17** (90% yield) (Scheme 4).

Scheme 4. Stille Cross-Coupling Reactions



With the successful introduction of selective substitution at the C-5 position of **1**, our subsequent studies focused on opportunities for the replacement of the 2-phenylsulfonyl group as a general scheme for the synthesis of 2,5-disubstituted-1,3-oxazoles. In this regard, we have found that organolithium species react via an addition−elimination pathway leading to the effective nucleophilic displacement of the C-2 sulfonyl group. Examples are compiled in Table 2. To our knowledge, this preparation of 1,3-oxazoles describes the first report for replacement of C-2 sulfonyl functionality utilizing aryl, alkenyl, and alkyllithium reagents. Small-scale reactions (0.1−0.05 millimolar scale) demonstrate complete consumption of starting 2-phenylsulfonyl oxazoles upon slow introduction of the organolithium species (1.2 equiv) and warming from 0 °C to room temperature over 5−10 min. We have briefly examined reactions of our 2-phenylsulfonyl oxazoles with the analogous cuprates and have observed an expected lack of reactivity at low temperatures whereas warming to 22 °C led to uncharacterized products that do not contain the 1,3-oxazole nucleus. Similar results were observed in our limited attempts to use allylmagnesium chloride. Overall, the replacement of the 2-sulfonyl substituent upon treatment with reactive organolithium reagents appears to be a general process that may be utilized for the introduction of additional functionalization as evident by reactions with acyl carbanion equivalents affording oxazoles **22**, **23**, and **28** (Table 3, entries 4, 5, and 10).

In summary, an efficient preparation of 2-(phenylsulfonyl)-1,3-oxazole facilitates a convenient, site-selective deprotonation to produce a reactive carbanion for halogenation, stannylation, and alkylation reactions. Negishi, Suzuki, and Stille cross-coupling processes are demonstrated to afford high-yielding arylations and alkenylations leading to the preparation of a variety of 2,5-disubstituted oxazoles. The replacement of the 2-phenylsulfonyl substituent upon reaction with aryl, alkenyl, and akyllithium reagents provides a versatile pathway for the synthesis of a wide variety of complex 2,5-disubstituted oxazoles.

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Supporting Information Available: Experimental procedures and characterization data, including proton and carbon NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For leading references, see: (a) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011–1014. (b) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1991**, *56*, 3058–3063.

(14) Williams, D. R.; McClymont, E. L. *Tetrahedron Lett.* **1993**, *34*, 7705–7708.

(15) Whisler, M. C.; MacNeil, S.; Sneickus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225.

(16) Williams, D. R.; Brooks, D. A.; Meyer, K. G. *Tetrahedron Lett.* **1998**, *39*, 8023–8026.

(17) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1981**, *22*, 3163–3166.

(18) Lee, K.; Counceller, C. M.; Stambuli, J. P. *Org. Lett.* **2009**, *11*, 1457–1459.

(19) (a) Shafer, C. M.; Molinski, T. F. *J. Org. Chem.* **1998**, *65*, 551–555. (b) Marino, J. P.; Nguyn, H. N. *Tetrahedron Lett.* **2003**, *44*, 7395–7398.

(20) Phillips, J. G.; Fadnis, L.; Williams, D. R. *Tetrahedron Lett.* **1997**, *38*, 7835–7838.

(21) Denmark, S. E.; Pan, W. *J. Organomet. Chem.* **2002**, *653*, 98–104.