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Synthesis of 2,4- and 2,5-Disubstituted Oxazoles *via* Metal-Catalyzed Cross-Coupling Reactions

Carla M. Counceller,[a] Chad C. Eichman,[a] Nicolas Proust,[a] and James P. Stambuli[a,*]

[a] Department of Chemistry, The Ohio State University, Evans Laboratories, Columbus, Ohio 43210, USA
Fax: (+1)-614-292-1685; phone: (+1)-614-688-8082; e-mail: stambuli@chemistry.ohio-state.edu

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Abstract: The rapid synthesis of 2,4- and 2,5-disubstituted oxazoles *via* metal-catalyzed cross-coupling reactions is reported. The 4- or 5-position of the corresponding 4- or 5-halogenated 2-butylthiooxazoles was successfully functionalized *via* Suzuki–Miyaura, Sonogashira and Stille cross-coupling reactions. The 2-position of the 2-butylthiooxazoles obtained was further coupled to various organozinc reagents through palladium- or nickel-mediated cross-coupling reactions.

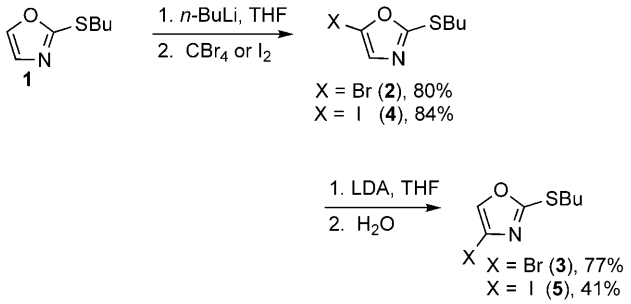
Keywords: cross-coupling; homogeneous catalysis; nickel; nitrogen heterocycles; palladium

Oxazoles are an important class of nitrogen heterocycle that exhibit diverse biological activities.[1] A large number of oxazole-containing natural products that exhibit anticancer, antifungal, or antibacterial properties have been isolated and many of these compounds have been synthesized.[2] Because of the sheer number of biologically relevant oxazole natural products and pharmaceuticals that have emerged in the last twenty years, this class of compound has begun to approach the forefront of important nitrogen heterocycles.[3]

Current methods to produce 1,3-oxazoles include cyclodehydrations,[4] oxidations of oxazolines,[5] direct metallation of the parent oxazole,[6] and, most recently, metal-catalyzed cross-coupling reactions.[7] The most common methods used to prepare oxazoles are cyclodehydration reactions. However, this method does not allow the preparation of all oxazole substitution patterns in high yields, nor does it allow direct functionalization at oxazole. Metal-catalyzed cross-coupling reactions have emerged as a useful approach to functionalize oxazoles. Earlier this year, a group at Merck reported that the selective coupling at either the 2- or the 4-position of 2,4-diiodooxazole can be controlled by the ancillary ligand.[8] One drawback to metal-catalyzed cross-coupling reactions of oxazoles is that many methods require the use of the parent oxazole compound to prepare the requisite starting materials.

Oxazole is commercially available, but expensive, and its laboratory preparation is tedious and low-yielding.[9] Although there have been a number of important contributions to cross-coupling reactions of oxazoles, most of these reactions employ the parent oxazole compound. To avoid the use of oxazole, we developed a cross-coupling reaction that produces substituted oxazoles by coupling 2-alkylthiooxazoles with organozinc reagents in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$.[10] Importantly, the 2-alkylthiooxazole starting material can be prepared on a large scale by reacting the diethyl acetal of glycolaldehyde with potassium thiocyanate, followed by alkylation of the resulting thiol.[11] These coupling reactions provided a variety of alkyl-, alkynyl-, aryl-, and heteroaryloxazoles solely substituted at the 2-position. Although we reported a few examples of 2,5-disubstituted oxazoles starting from the corresponding 2,5-dimethylthiooxazole, there were no examples of 2,4-disubstituted oxazoles.

2,4-Disubstituted oxazoles are prevalent in nature and 2,5-disubstituted oxazoles are important in the pharmaceutical industry. To expand on the use of thiooxazoles as partners in metal-catalyzed cross-coupling reactions of oxazoles and to demonstrate the versatility of the alkylthiooxazolyl group, we set out to prepare 2,4- and 2,5-disubstituted oxazoles. In order to access 2,4-disubstituted oxazoles using our coupling chemistry, a large quantity of 2,4-dialkylthiooxazole was needed. However, the traditional synthetic approach to 2,4-dialkylthiooxazole requires many steps, mostly because the oxazole hydrogen at C-5 is more acidic than the hydrogen at C-4, which disallows selective deprotonation of the oxazole at C-

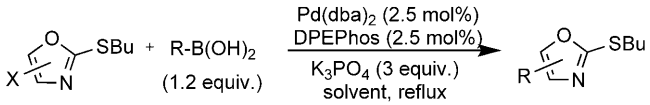


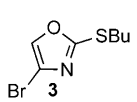
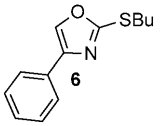
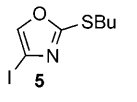
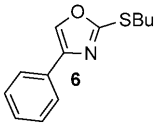
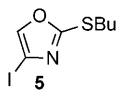
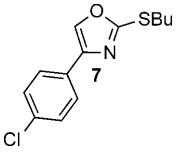
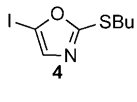
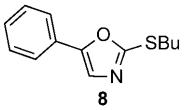
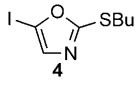
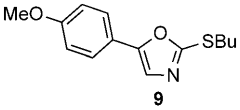
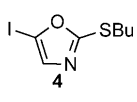
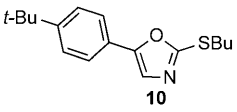
Scheme 1. Synthesis of 2-butylthio-5-bromooxazole (**2**), 2-butylthio-5-iodooxazole (**4**), 2-butylthio-4-bromooxazole (**3**) and 2-butylthio-4-iodooxazole (**5**).

4. Because of this type of chemical scenario, we decided to perform the halogen dance rearrangement of 2-butylthio-5-bromooxazole.[12]

2-Butylthiooxazole (**1**) was deprotonated at the 5-position with *n*-BuLi and quenched with CBr_4 to provide the corresponding 2-butythio-5-bromooxazole (**2**) (Scheme 1). The 5-bromooxazole (**2**) was reacted with LDA to provide 2-butylthio-4-bromooxazole (**3**) in 77% yield. However, the reactivity of 2-butylthio-4-bromooxazole was sluggish (*vide infra*) and preparation of the corresponding iodide was undertaken by replacing CBr_4 above with I_2. To the best of our knowledge, this is the first report of the halogen dance of an iodooxazole. The yield of 2-butylthio-4-iodooxazole (**5**) was lower than that of the corresponding bromide (41%, along with 39% of thiooxazole **1**). This dramatic difference in yield between bromooxazole **3** and iodooxazole **5** is currently the subject of a more detailed investigation. With the desired oxazoles in hand, we examined Suzuki–Miyaura, Sonogashira, and Stille coupling reactions of these compounds. The use of 2-butylthio-4-bromooxazole (**3**) provided good yields in some cases, but the more reactive 2-butylthio-4-iodooxazole (**5**) consistently gave superior results. For example, the reaction of 2-butylthio-4-bromooxazole (**3**) and 2-butylthio-4-iodooxazole (**5**) with phenylboronic acid in the presence of 2.5 mol% of $Pd(dba)_2$/DPEphos in dioxane:water provided 68% and 92% yields, respectively (Table 1, entries 1 and 2). This disparity in yield may be caused by the faster rate of the oxidative addition of aryl iodides over aryl bromides in the presence of palladium.[13] We also observed that the C-4 iodooxazole is less reactive than the corresponding C-5 iodooxazole, and the former reactions were conducted at higher temperatures in a more polar solvent. Various arylboronic acids provide the corresponding 2,4- or 2,5-disubstituted products regardless of substitution at the aryl group. Most importantly, the butylthio group remained untouched, which allowed an additional coupling without needing to employ blocking groups.

Table 1. Suzuki–Miyaura reactions of disubstituted oxazoles.[a]



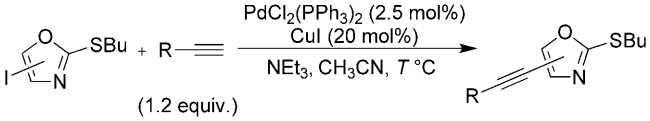
Entry	Substrate	Product	Yield [%]
1[b]			68
2[b]			92
3[b]			86
4[c]			83
5[c]			72
6[c]			82

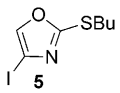
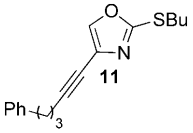
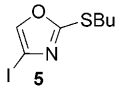
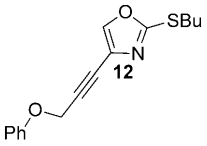
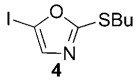
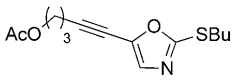
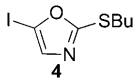
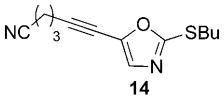
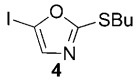
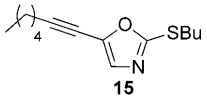
[a] Refer to the Supporting Information for complete experimental details. The reported yields are an average of two reactions (one mmol scale).
[b] Reaction conducted in dioxane:water (1:1).
[c] Reaction conducted in THF.

The cross-coupling methodology was also extended to the Sonogashira reaction (Table 2). The 4- and 5-iodooxazoles were combined with a variety of alkynes, catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI, in NEt_3 and acetonitrile to produce the corresponding substituted oxazoles in good yields. Once again, the C-4 iodooxazole required 60 °C, while reactions of the C-5 iodooxazole proceeded at ambient temperature, except for the outlying nitrile example in entry 4. Again, the butylthio group did not appear to be affected under these conditions.

However, the cause of the mass balance in these reactions is not clear as we did not detect any appreciable amounts of side-products. We have shown in Table 1 that the butylthio group is stable to palladium, and Marino has previously shown that the methylthio group is stable to copper.[14] Moreover, submission of the butylthio product to the reaction conditions did not cause noticeable decomposition.

Table 2. Sonogashira reactions of disubstituted oxazoles.[a]



Entry	Substrate	Product	Yield [%]
1[b]			81
2[b]			75
3[c]			63
4[b]			66
5[c]			77

[a] See Supporting Information for complete experimental details. The reported yields are an average of two reactions (one mmol scale).
[b] Reaction conducted at 60 °C.
[c] Reaction conducted at 23 °C.

One application of this methodology will be as a key step in the synthesis of the natural product leiodelide A (Figure 1).[15]

Leiodelide A contains a macrocyclic ring containing a 2,4-disubstituted oxazole. More specifically, an alkyl chain is at the C-2 position of the oxazole, while a trisubstituted olefin occupies the C-4 position. Since we have previously coupled an alkyl group to the C-2 position of oxazole, we investigated the more challenging coupling of the trisubstituted olefin to the C-4 position. After some experimentation, the Stille cross-coupling reaction (Table 3) provided the best results to install the olefin.[16] Using 5 mol% $PdCl_2(MeCN)_2$ as catalyst with excess LiCl in DMF at elevated temperatures, the C-4 and C-5 vinyloxazoles were produced in good yields. The remaining butylthio group at the C-2 position can now be coupled with the corresponding organozinc product to set the substitution pattern seen in leiodelide A.

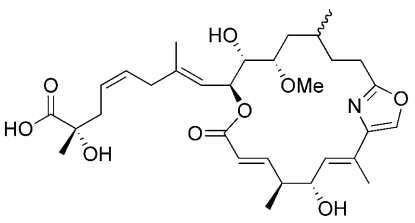
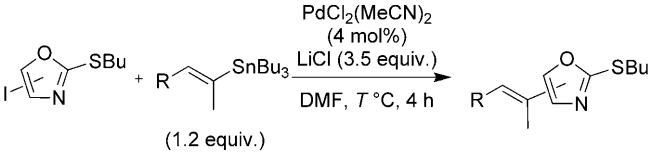
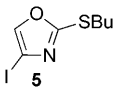
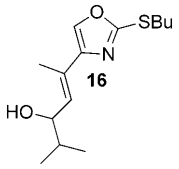
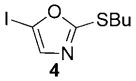
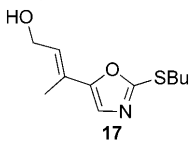


Figure 1. Leiodelide A.

Table 3. Stille reactions of disubstituted oxazoles.[a]



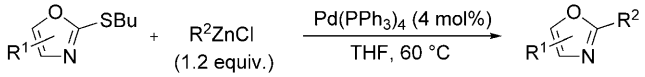
Entry	Substrate	Product	Yield [%]
1[b]			62
2[c]			77

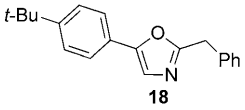
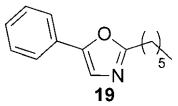
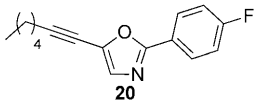
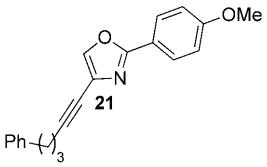
[a] Refer to the Supporting Information for complete experimental details. The reported yields are an average of two reactions (one mmol scale).
[b] Reaction conducted at 90 °C.
[c] Reaction conducted at 60 °C.

After successfully completing the Suzuki–Miyaura, Songashira, and Stille coupling reactions, several of these products were coupled at the 2-butylthio group with a variety of organozinc reagents, using conditions we described previously (Table 4). The reactions produced the desired 2,4- or 2,5-oxazole products in good to high yields. More importantly, these reactions demonstrate the modularity of employing 2-butylthio-4-halooxazoles to prepare 2,4- and 2,5-disubstituted oxazoles.

The use of zinc bromide in Table 4, entry 2 deserves comment. In our previous work, the coupling of oxazoles with alkylzinc reagents required 2.5 equivalents of alkylzinc reagent and provided low yields of the 2-alkyloxazole product (~60%). During the course of this research, we began a careful investigation to account for the lower yields. The protonated organozinc reagent was identified as a major side-product of the reaction. In order to investigate the origin of the proton that was quenching the organozinc reagent, 2-methylthiooxazole was deuterated at the C-5 position (**22**) and at the alkylthio position at C-2 (SCD_3, **23**) as these two hydrogens are the most acidic in the substrate. Submitting the monodeuterated oxazole (**22**) to the standard reactions conditions did not provide an appreciable amount of deuterated propylbenzene (Scheme 2). However, reacting the deuterated thiooxazole (**23**) under the same conditions showed the pro-

Table 4. Alkylthiooxazole couplings with organozinc reagents.[a]



Entry	R^2	Product	Yield [%]
1[b]	$BnCH_2$-	 **18**	85
2[c]	hexyl-	 **19**	78
3	*p*-F-C_6H_4	 **20**	88
4	*p*-MeO-C_6H_4	 **21**	90

[a] Refer to the Supporting Information for complete experimental details. The reported yields are an average of two reactions (one mmol scale).
[b] $NiCl_2(PPh_3)_2$ was used as catalyst.
[c] 1 equivalent of $ZnBr_2$ was used as an additive.

duction of deuterated propylbenzene. We hypothesized that zinc was coordinating to the oxazole nitrogen, which assisted the deprotonation of the methylthio group and ultimately, the protonation of the organozinc reagent. Therefore, the addition of zinc bromide should compete with the organozinc reagent from the oxazole nitrogen and thus, the organozinc reagent would not get protonated. Although we have no direct evidence for this coordination event, the addition of 1 equivalent of $ZnBr_2$ allowed a lesser amount of organozinc reagent (1.5 equiv.) and provided a higher yield of product (76–84%, Scheme 2 *vs.* 56%[10]).

In summary, the metal-catalyzed cross-coupling reactions of 2-butylthio-4-iodooxazole and 2-butylthio-5-iodooxazole produced the corresponding cross-coupling products in good to high yields for the Suzuki–Miyaura, Sonogashira, and Stille coupling reactions. This work demonstrates that 2,4- and 2,5-disubstituted oxazoles can be prepared in a modular fashion without the necessity to use protecting groups. Moreover, this research, along with our previously reported oxazole chemistry, allows rapid access to the synthesis of mono- and disubstituted oxazoles. Finally, the inclusion of $ZnBr_2$ improves the reaction yield and lowers the amount of the stoichiometric organozinc reagent required in coupling reactions of oxazoles.

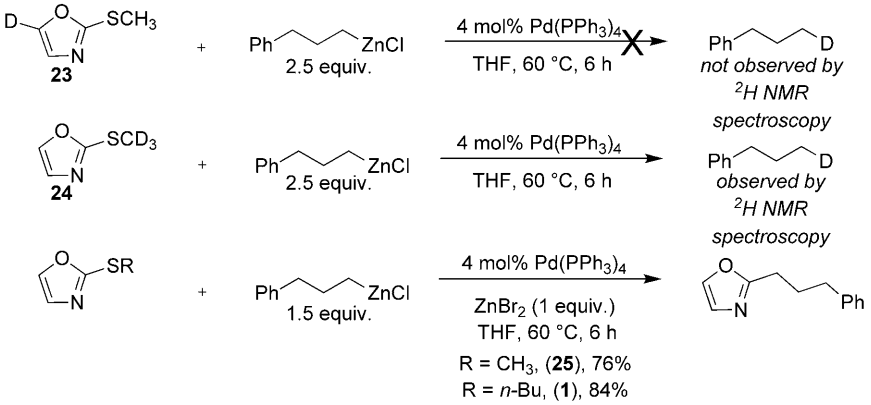
Experimental Section

General Procedure for the Cross-Coupling Reactions of Oxazoles

To a round-bottom flask equipped with a stir bar and a reflux condenser, $Pd(dba)_2$ (2.5 mol%), DPEPhos (2.5 mol%), the boronic acid (1.2 mmol), and K_3PO_4 (3 mmol) were added. The flask was then evacuated and flushed with nitrogen. The oxazole (1 mmol) was then added to the flask followed by THF (5 mL) or a 1:1 (v/v) of dioxane (2.5 mL) and water (2.5 mL). The reaction mixture was heated to reflux for 12 h. After this time, water was added and the reaction was extracted with Et_2O (3×20 mL), dried over $MgSO_4$, and concentrated under vacuum. The remaining crude residue was purified *via* flash chromatography.

Supporting Information

Supporting information for this article including the synthesis of all starting materials, reaction procedures, compound characterization and NMR spectra is available.



Scheme 2. ^2H NMR spectroscopic study of alkylzinc coupling reactions.

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