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Synthesis of 2,5-diaryloxazoles through van Leusen reaction and copper-mediated direct arylation

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ABSTRACT

The direct arylation of 5-aryloxazoles, prepared by the van Leusen reaction, with various aryl iodides is effectively promoted by a system of CuI combined with PPh_3 and Na_2CO_3 as a ligand and a base, respectively, in DMF to produce the corresponding 2,5-diaryloxazoles in good yields.

The oxazole nucleus is found in a large number of biologically active natural and unnatural compounds, and the synthesis of its derivatives is of considerable importance in organic synthesis.[1] Aryalted oxazoles are of interest not only due to their biological properties, but also due to their importance as organic materials such as scintillant compounds and fluorescent dyes.[1,2] For the synthesis of arylated oxazoles having a variety of aryl functions, transition-metal-catalyzed aryl–aryl cross-coupling with aryl halides and arylmetal reagents is one of the most reliable methods,[3] and the reaction has been often employed.

Meanwhile, recent advances in the metal-mediated direct C–H arylation of heteroarenes may also allow an efficient access to aryloxazoles.[4–7] The direct reaction of oxazoles with aryl halides is usually carried out by using a palladium catalyst, and often by adding a copper[6,7c,e] or silver[7d,f] promoter. The arylation of oxazoles via C–H bond cleavage with aryl iodides may also be performed with inexpensive copper alone, and it takes place selectively at the less electron-rich C-2 position.[6,8–11] Recently, Do and Dougulis reported an effective copper-based catalytic system for the reaction with a strong base such as *t*-BuOLi or *t*-BuOK, while an excess amount of aryl iodide is required for a high-yield coupling.[8] The catalytic method was extended to the C-2 vinylation with β-styryl bromides by Piguel and co-workers.[9] We also found that the use of a tractable and mild base such as Na_2CO_3 or K_3PO_4 makes various functional groups tolerable in the copper-promoted arylation of benzazoles including benzoxazole with an almost stoichiometric amount of aryl iodides.[10] Subsequently, as 2,5-diaryloxazoles are of considerable interest biologically and physically,[1,2] we have undertaken their synthesis with our method in combination with the van Leusen reaction[12] that allows a ready access to 5-aryloxazoles using commercially available TosMIC (*p*-toluenesulfonylmethyl isocyanide) and the corresponding aromatic aldehydes, and this has appeared to work effectively. The results as well as optical properties of some π-extended products having a phenylethynyl moiety are described herein. It should be cited that the palladium-catalyzed arylation reactions of 5-aryloxazoles with aryl bromides using CuI as a promoter and those with aryl iodides in the presence of Ag_2CO_3 have been recently described by Piguel[7e] and Greaney,[7d] respectively.

In an initial experiment, 5-phenyloxazole (**1a**) (0.5 mmol), which was prepared by the van Leusen reaction,[12] was treated with iodobenzene (**2a**) (0.6 mmol) under conditions similar to those employed for the copper-promoted arylation of benzazoles without employing palladium.[10] Gratifyingly, when using CuI (0.5 mmol), PPh_3 (0.1 mmol), and Na_2CO_3 (1 mmol) in DMF as the promoting system, the reaction proceeded efficiently to afford 2,5-diphenyloxazole (**3a**) in 83% isolated yield (entry 1 in Table 1). With this result in hand, various 5-aryloxazoles were reacted with aryl iodides as follows.

First, the synthesis of balsoxin (**3b**) was performed.[7e,f] The diaryloxazole is known as a natural product isolated from *Amyris* species of plant.[13a] A related natural 2,5-diaryloxazole having a

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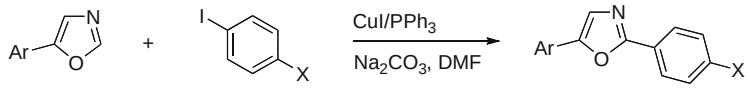
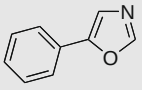
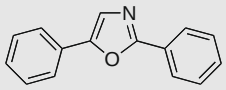
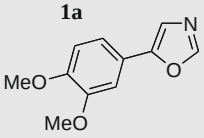
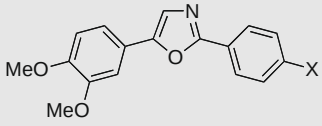
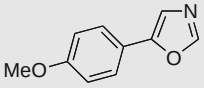
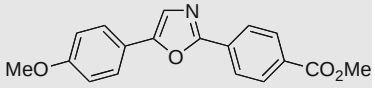
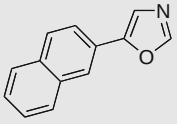
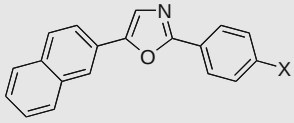
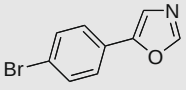
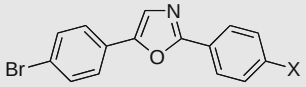
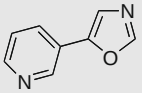
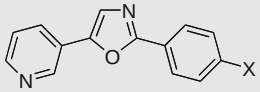
Table 1
Reaction of 5-aryloxazoles (**1**) with aryl iodides (**2**)[a]



1 **2** **3**

Entry	**1**	**2**: X	**3**, % Yield[b]
1	 **1a**	**2a**: X = H	 **3a**, 83
	 **1b**		
2		**2a**: X = H	**3b**: X = H, 94
3		**2b**: X = OMe	**3c**: X = OMe, 91
4		**2c**: X = CO_2Me	**3d**: X = CO_2Me, 85
5		**2d**: X = CN	**3e**: X = CN, 87
6		**2e**: X = Br	**3f**: X = Br, 77
7	 **1c**	**2c**: X = CO_2Me	 **3g**, 86
	 **1d**		
8		**2a**: X = H	**3h**: X = H, 93
9		**2b**: X = OMe	**3i**: X = OMe, 59
10		**2d**: X = CN	**3j**: X = CN, 84
11		**2f**: X = CF_3	**3k**: X = CF_3, 74
12[c]	 **1e**	**2a**: X = H	 **3l**: X = H, 64
13[c]		**2c**: X = CO_2Me	**3m**: **X** = CO_2Me, 70
14	 **1f**	**2a**: X = H	 **3n**: **X** = H, 91
15		**2c**: X = CO_2Me	**3o**: X = CO_2Me, 55

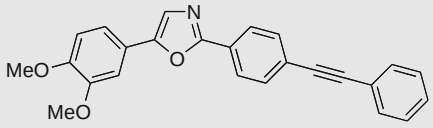
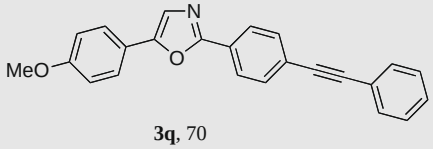
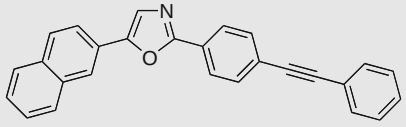
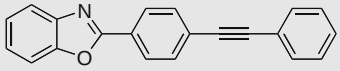
[a] Reaction conditions: [**1**]:[**2**]:[CuI]:[PPh_3]:[Na_2CO_3] = 0.5:0.6:0.5:0.1:1.0 (in mmol), in DMF (1 mL) under N_2 at 160 °C for 2 h.

[b] Isolated yield.

[c] CuBr was used in place of CuI.

pyridyl group from the species, texalin,[13b] and its analogs have been reported to show antimycobacterial activity.[14a,b] Some synthetic balsoxin analogs having a sulfonamide group were also claimed as MMP inhibitors.[14c] Treatment of 5-(3,4-dimethoxyphenyl)oxazole (**1b**) with **2a** under the standard conditions afforded the expected product, balsoxin (**3b**), in 94% yield (entry 2). Then, the reactions of **1b** with various iodobenzenes having an electron-donating or withdrawing substituent **2b–e** effectively proceeded to give the corresponding products **3c–f** in good yields. Thus, methoxy, methoxycarbonyl, cyano, and bromo functions were tolerable under the reaction conditions (entries 3–6). 5-(4-Methoxyphenyl) (**1c**), 5-(2-naphthyl) (**1d**), 5-(4-bromophenyl) (**1e**), and 5-(3-pyridyl)oxazoles (**1f**) were also suitable substrates for the direct arylation (entries 7–15). It should be noted that in

Table 2
Reaction of 5-aryloxazoles **1b–d** and benzoxazole **1g** with 1-iodo-4-(2-phenylethynyl)benzene (**2g**)[a] and optical properties of products **3p–s**

Entry	1	3, % Yield[b]	λ_{abs}[c]	log ε	λ_{em}[d]	Φ_f[e]
1	**1b**	 **3p**, 85	352	4.66	442	0.93
2	**1c**	 **3q**, 70	347	4.67	429	0.93
3	**1d**	 **3r**, 66	355	4.72	418	0.97
4	**1g**	 **3s**, 90	333	4.81	380	0.90

[a] Reaction conditions: [**1**]:[**2g**]:[CuI]:[PPh_3]:[Na_2CO_3] = 0.5:0.6:0.5:0.1:1.0 (in mmol), in DMF (1 mL) under N_2 for 4 h.
[b] Isolated yield.
[c] Absorption maximum in CH_2Cl_2.
[d] Fluorescence maximum in CH_2Cl_2 (5.0×10^{-6} M) exited at 350 nm for **3p–r** and 325 nm for **3s**.
[e] Absolute quantum yield determined by an integrating sphere system.

the reactions of **1e** (entries 12 and 13), CuBr was used in place of CuI, as the bromo function was partly replaced by iodo one when using CuI.[15]

On the other hand, we are interested in the synthesis and physical properties of 4-(phenylethynyl)phenyl-substituted heteroarenes as triple-bond containing π-conjugated organic materials.[16] We also developed a facile method, utilizing a double elimination strategy, for preparing 4-(phenylethynyl)phenyl halides, which are useful building blocks for constructing the π-conjugated systems.[17] Meanwhile, a literature search indicates that 2-[4-(phenylethynyl)phenyl]-substituted 5-phenyloxazole[18a,b] and benzoxazole[18c–e] may act as efficient violet to blue fluorophores.

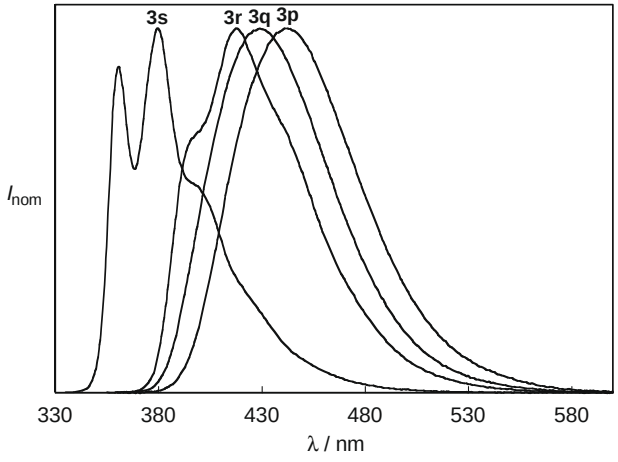


Figure 1. Normalized fluorescence spectra of compounds **3p–s**.

Consequently, we examined the reactions of 5-aryloxazoles **1b–d** as well as benzoxazole (**1g**) with 1-iodo-4-(2-phenylethynyl)benzene (**2g**) prepared by our method. The results as well as optical properties of the products are summarized in Table 2, and the fluorescence spectra are shown in Figure 1. As is seen, the triple bond in **2g** was tolerable, and the reaction took place effectively to afford the π-conjugated compounds **3p–s** in good yields. They were found to show strong fluorescence in a range of λ_{em} 380–442 nm with high absolute quantum yields more than 0.90. The di- and mono-methoxy substitutions in compounds **3p** and **3q** appear to induce the larger red shifts than the π-extension by the naphthalene ring of **3r**. While compound **3s** shows two accompanied shoulder peaks, they are not clear or do not appear in the case of compounds **3p–r**.

In summary, we have demonstrated that the combination of readily available and tractable reagents CuI/PPh_3/Na_2CO_3 can act as an effective promoter system for the direct arylation of 5-aryloxazoles with aryl iodides.[19] It has also been utilized for the synthesis of a natural product, balsoxin and its analogs and of π-extended compounds having a phenylethynyl moiety that exhibits strong fluorescence.[20]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.039.

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19. The copper-mediated arylation reaction of 1,3-azoles may be considered to proceed via the initial cupration of C-2 with the aid of a base.[8b,10] In the case using a mild base, pre-coordination of the copper promoter to the azole nitrogen would be required to abstract the C-2 hydrogen.[6]
20. *Typical procedure [reaction of 5-(3,4-dimethoxyphenyl)oxazole* (**1b**) *with iodobenzene* (**2a**) *or 1-iodo-4-(2-phenylethynyl)benzene* (**2 g**)*, entry 2 in* Table 1 *and entry 1 in* Table 2*]*: In a 20 mL two-necked flask, **1b** (103 mg, 0.5 mmol), **2a** (123 mg, 0.6 mmol) or **2 g** (182 mg, 06 mmol), CuI (95 mg, 0.5 mmol), PPh_3 (26.2 mg, 0.1 mmol), Na_2CO_3 (106 mg, 1 mmol), 1-methylnaphthalene (ca. 50 mg, internal standard), and DMF (1 mL) were added. The resulting mixture was stirred under N_2 (with balloon) for 2 h at 160 °C (bath temperature). After cooling, the mixture was poured into water containing ethylenediamine (ca. 1 mL), extracted with dichloromethane, and dried over sodium sulfate. Product **3b** (132 mg, 94%) was isolated by column chromatography on silica gel using hexane–ethyl acetate (80:20, v/v). The spectroscopic data of **3b** were in agreement with those reported previously.[7e] In the case using **2 g**, after evaporation of the solvent, product **3p** (168 mg, 88%) was obtained by recrystallization from toluene–hexane: mp 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 3.98 (s, 3H), 6.93 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 1.8 Hz, 1H), 7.30 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.35–7.38 (m, 4H), 7.54–7.57 (m, 2H), 7.63 (d, J = 8.1 Hz, 2H), 8.07 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.91, 57.99, 90.93, 93.50, 109.50, 113.49, 119.31, 122.84, 124.45, 124.87, 126.92, 127.91, 128.86, 130.30, 130.44, 133.57, 133.88, 151.32, 151.54, 153.51, 162.00; HRMS (EI) calculated for $C_{25}H_{19}NO_3$ $[M]^+$: 381.1365. Found: 381.1356.