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Ligandless Microwave-Assisted Pd/Cu-Catalyzed Direct Arylation of Oxazoles

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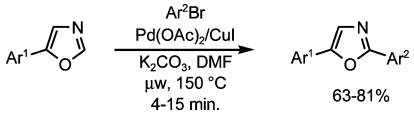

An efficient microwave-assisted palladium/copper co-mediated direct arylation of oxazoles with aryl bromides under ligandless conditions has been developed. The method is functional group tolerant and provides rapid access to medicinally relevant compounds in good yields. Coupled to the van Leusen oxazole ring synthesis, this methodology is illustrated by an expedient two-step synthesis of the four 2,5-diaryloxazole alkaloids texamine, texaline, balsoxin, and *O*-Me-halfordinol from commercially available starting materials.

A functionalized oxazole motif is found in a wide variety of natural products, biologically active compounds, and optical materials such as scintillant molecules and fluorescent dyes. Many strategies for the synthesis of such molecules have emerged, involving the construction of the oxazole ring by nontrivial multistep reaction sequences.[1] As part of an ongoing medicinal chemistry program, we needed a flexible route that would give high yielding and rapid access to different 2,5-diaryloxazoles. A method involving a direct intermolecular arylation at position 2 of a readily available 5-aryloxazole scaffold was identified as an attractive and more operationally simple alternative to traditional cross-coupling methods.[2] Over the past decade, direct arylation of heteroaromatics including pyrroles, indoles, furans, thiophenes, azoles, pyridines, and purines has been intensively studied as an effective and straightforward method for creating aryl−heteroaryl linkages.[3] Typically, this involves the reaction of the heterocycle with reactive aryl iodides and, to a lesser extent, aryl bromides in the presence of a metal catalyst (palladium, rhodium, and/or copper), an inorganic base, and a phosphine ligand in polar solvents such as DMF at elevated temperatures and prolonged reaction times. Importantly, however, this reaction has also been found to proceed under ligandless and even base-free conditions.[4] Furthermore, Bergman and Ellman reported that rhodium catalyzed arylation of azoles with aryl bromides under microwave irradiation requires significantly shorter reaction times.[5] Very recently, Daugulis and co-workers described the use of aryl chlorides in the direct arylation of electron-rich heterocycles.[6] Among the oxazole-type compounds, benzoxazoles and 2-phenyloxazoles are the most frequently encountered substrates.[7] Direct arylations at the 2 position of 4/5-mono- or disubstituted oxazoles with aryl halides are much less well documented. Hoarau et al. have described a regioselective palladium-catalyzed C-2 arylation of ethyl 4-oxazolecarboxylate with iodobenzene, while Li et al. have reported the C-2 arylation of methyl 4-aryl-5-oxazolecarboxylate with aryl iodides under classical conditions in the presence of copper(I) iodide.[8,9] In this context, a study of the direct metal-catalyzed arylation of 5-substituted oxazoles with aryl bromides, being both cheaper and more widely available than the corresponding iodides, was undertaken.

Herein, we report a rapid, efficient, and functional group tolerant method for the intermolecular C-2 direct arylation of 5-aryloxazoles by aryl bromides under ligandless microwave conditions. This methodology gives access to a wide variety of 2,5-diaryloxazole derivatives and this is illustrated by the preparation of four known 2,5-diaryloxazole alkaloids from commercially available starting materials.

As a test reaction, the coupling of 5-phenyloxazole **1a** with bromobenzene was initially studied. Compound **1a** was readily prepared in one step in 85% yield by the van Leusen reaction of benzaldehyde with *p*-toluenesulfonylmethylisocyanide (TosMIC) and K_2CO_3 in refluxing MeOH.[10] Then, inspired by the pioneering work of Miura et al. on heteroarene direct arylations,[11] the key coupling was carried out in the presence of $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), CuI (1 equiv), and Cs_2CO_3 (2 equiv) in DMF at 150 °C. The target 2,5-diphenyloxazole **2a** was cleanly obtained in good yield (79%) after 2 h. In control reactions where the copper additive or $Pd(OAc)_2$ were left out, only trace amounts of **2a** were formed, even after prolonged heating (24 h). However, under ligand-free conditions,

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(1) Palmer, D. C.; Venkatraman, S. In *Oxazoles: Synthesis, Reactions and Spectroscopy, Part A*; J. Wiley & Sons: Hoboken, NJ, 2004.
(2) Zificsak, C. A.; Hlasta, D. J. *Tetrahedron* **2004**, *60*, 8991.
(3) For recent reviews of heteroarenes and arenes direct arylation, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichim. Acta* **2007**, *40*, 35.
(4) (a) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543.
(5) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589.
(6) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449.
(7) For very recent examples, see: (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404 and references cited therein. (b) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996 and references cited therein. (c) For a mechanistic discussion, see: Sanchez, R. S.; Zhuravlev, A. *J. Am. Chem. Soc.* **2007**, *129*, 5824.
(8) Hoarau, C.; Du Fou de Kerdaniel, A.; Bracq, N.; Grandclaudon, P.; Couture, A.; Marsais, F. *Tetrahedron Lett.* **2005**, *46*, 8573.
(9) Li, X.; Murray, W. V.; Macielag, M. J.; Guan, Q. U.S. Patent 113522 A1, 2005.
(10) Van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *23*, 2369.
(11) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

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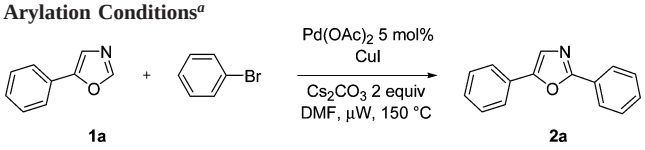
TABLE 1. Optimization of the Microwave-Assisted Pd/Cu Direct Arylation Conditions[a]



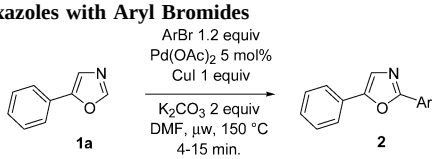
entry	CuI (equiv)	reaction time (min)	yield[b] (%)
1	0.5	15	53
2	0.5	60	57
3	1	30	70
4	2	30	72
5	1	30	72[c]
6	1	15	81[c]
7	1	15	11[c,d]

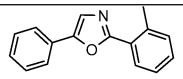
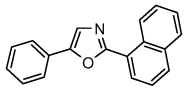
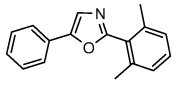
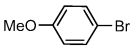
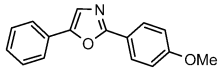
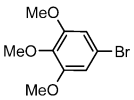
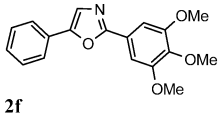
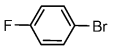
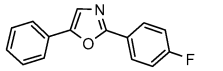
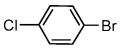
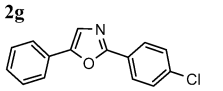
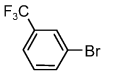
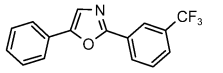
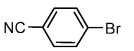
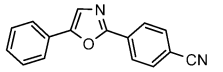
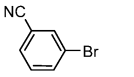
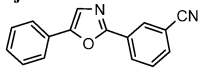
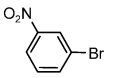
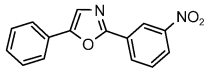
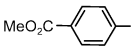
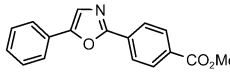
[a] All reactions were performed at 0.4−0.5 M of 5-phenyloxazole **1a** (1 equiv) and bromobenzene (1.2 equiv) in DMF heated at 150 °C in a microwave reactor. [b] Isolated yields. [c] K_2CO_3 was used as base. [d] Thermal heating, 150 °C.

such as those reported by Bellina and co-workers,[4] compound **2a** was isolated in a comparable yield (80%).

Having determined optimal conditions[12] for the formation of **2a** using classical heating, attention was turned toward the possible use of microwave irradiation in order to reduce the reaction time. Organic reactions assisted by microwave irradiation have attracted considerable attention in recent years for the efficient, accelerated synthesis of a variety of organic compounds.[13] Direct arylations are ideal candidates for microwave-assisted synthesis as they typically require extended reaction times at high temperatures.[14] To date, only one example of microwave-assisted direct arylation of benzoxazole has been reported using a rhodium catalyst.[5] We were delighted to find that direct arylation of **1a** under microwave irradiation drastically reduced the reaction time from hours to just a few minutes (Table 1). Thus, when 5-phenyloxazole **1a** was heated for 30 min at 150 °C in a microwave reactor with 1.2 equiv of bromobenzene, 1 equiv of CuI, 5 mol % of $Pd(OAc)_2$, and 2 equiv of Cs_2CO_3 in DMF, product **2a** was isolated in 70% yield (Table 1, entry 3). Interestingly, lower yields of **2a** were obtained using smaller amounts (0.5 equiv) of the CuI additive (entries 1 and 2), and the yield remained unchanged when up to 2 equiv was employed (entry 4). In addition, replacing Cs_2CO_3 by the less expensive K_2CO_3 had no deleterious effect on the reaction (entry 5). Screening with respect to the solvent and temperature showed that the reaction proceed best in DMF at 150 °C with no reaction in DMF at 110 °C. Moreover, commercial grade DMF can be used without particular precaution. Finally, reducing the reaction time from 30 to 15 min led to a significant improvement in yield, from 72 to 81% (entries 5−6). Control reactions at 10 and 5 min provided incomplete conversion and gave **2a** in 64% and 50% isolated yields, respectively. Therefore, 15 min was found to be the optimal reaction time.[15] For comparison, for the same reaction carried out for 15 min using traditional oil bath heating, 2,5-diphenyloxazole **2a** was obtained in only 11% yield (entry 7).

TABLE 2. Scope of Microwave-Assisted Direct Arylation of 5-Phenyloxazoles with Aryl Bromides



Entry	Aryl bromide	Product	Yield (%)[a]
1		 **2b**	72
2		 **2c**	75
3		 **2d**	74[b]
4		 **2e**	72
5		 **2f**	65
6		 **2g**	74
7		 **2h**	69
8		 **2i**	76
9		 **2j**	71[c]
10		 **2k**	74[c]
11		 **2l**	71[c]
12		 **2m**	63[d]

[a] Isolated yields. [b] 30 min of heating. [c] 4 min of heating. [d] 8 min of heating.

These conditions were then used to investigate the scope of the direct arylation with various aryl bromides (Table 2). Both electron-rich (entries 1−5) and electron-deficient (entries 6−12) aryl bromides reacted with phenyloxazole **1a** in good yields, with substitution being tolerated at each of the ortho, meta, and para positions. Importantly, these conditions proved compatible with the presence of important functional groups such as an ester, a cyano group and halides on the aromatic bromide, which may be subject to further synthetic transformations. Sterically hindered aryl bromides were also reactive (entries 1−3), pro-

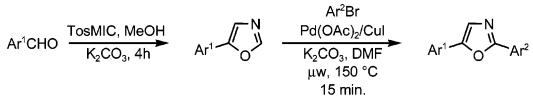
(12) Optimal conditions: 5-phenyloxazole (1 equiv), bromobenzene (1.2 equiv), $Pd(OAc)_2$ (5 mol%), and CuI (1 equiv) as the co-catalysts, Cs_2CO_3 (2 equiv) as the base without ligand in DMF at 150 °C.

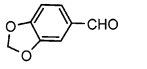
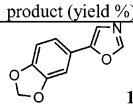
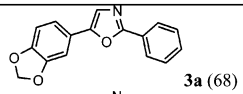
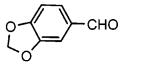
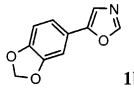
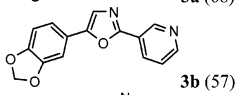
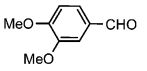
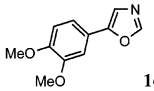
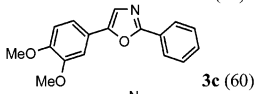
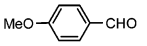
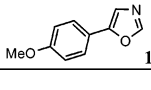
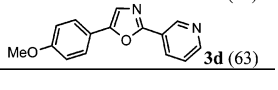
(13) Kappe, O. C.; Stadler, A.; Mannhold, R. In *Microwaves in organic and medicinal chemistry*; Wiley-VCH: Weinheim, Germany, 2006.

(14) During the preparation of this manuscript, a microwave-assisted Pd-catalyzed direct arylation of triazoles was published: Iwasaki, M.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2007**, *2*, 1430.

(15) No product instability was observed under the reaction conditions. In fact, exposing product **2a** to the reaction conditions for 30 min led to full recovery.

TABLE 3. van Leusen/direct Arylation Sequence



Entry	Ar^1CHO	Van Leusen product (yield %)	Ar^2Br	Product (yield %)
1		 **1b** (91)		 **3a** (68)
2		 **1b** (91)		 **3b** (57)
3		 **1c** (87)		 **3c** (60)
4		 **1d** (86)		 **3d** (63)

viding the expected products in good yields. Only in the case where an electron-poor coupling partner is employed, shorter reaction times gave better yields (entries 9−12). For instance, compound **2j** was obtained in 71% yield after only 4 min, whereas heating for 15 min resulted in a reduced yield of 48%.[16]

This methodology, combined with the van Leusen reaction to obtain the requisite 5-substituted oxazole starting materials, was subsequently applied to the synthesis of the four natural 2,5-diaryloxazole alkaloids texamine **3a**, texaline **3b**, balsoxin **3c**, and *O*-Me-halfordinol **3d** (Table 3). Texamine **3a** has been isolated from the roots of the plant *Amyris texana*,[17] and a five-step synthesis has been reported with an overall yield of 36%.[18] Balsoxin **3c**, isolated from the plant *A. plumieri*, has also been synthesized by a seven-step sequence in 10% overall yield.[19,20] In the first step, veratraldehyde, piperonal, and *p*-anisaldehyde were thus converted with TosMIC into their respective oxazoles **1b**−**d** in high yields.[21] Directed C-2 arylation under our optimized conditions with bromobenzene or 3-bromopyridine then gave the target 2,5-diaryloxazoles **3a**−**d** with an average overall yield of 53% (Table 3). Importantly, although the electronic effects of the oxazole substrate had been modified, the direct arylation was still found to be efficient, albeit in lower yield.

In conclusion, a microwave-enhanced and ligandless direct arylation of 5-aryloxazoles with various aryl bromides has been developed to generate 2,5-diaryloxazoles. The high functional group tolerance and the speed of the reaction render this method suitable for the combinatorial synthesis of a variety of 2,5-diarylazoles. Studies on further applications of this direct arylation protocol with aryl chlorides and other heterocycles are in progress in our laboratory.

Experimental Section

General Procedure for the Preparation of 5-Aryloxazole from Aromatic Aldehydes As Illustrated by the Synthesis of 5-Phenyloxazole (1a). A solution of benzaldehyde (3.0 g, 28.3 mmol) and *p*-toluenesulfonylmethyl isocyanide (6.1 g, 31.1 mmol) in MeOH (150 mL) was treated with potassium carbonate (7.8 g, 56.6 mmol) and heated to reflux for 4 h. After being cooled to room temperature, the solvent was removed under reduced pressure and the crude product was triturated with water at 0 °C. A white precipitate appeared and was collected by filtration and dried under vacuum. The solid was crystallized in petroleum ether to give 3.5 g (85%) of white crystals: mp <40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.40 (m, 2H), 7.44 (t, J = 7.7 Hz, 2H), 7.66 (d, J = 7.2 Hz, 2H), 7.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.4, 124.3, 127.7, 128.6, 128.8, 150.4, 151.5; MS (electrospray) *m*/*z* 146.1 (100) $[M + H]^+$. Spectral data were in agreement with those previously reported.[22]

General Procedure for Microwave-Assisted Pd/Cu-Catalyzed Direct Arylation of 5-Aryloxazoles with Aryl Bromides As Illustrated by the Synthesis of 2,5-Diphenyloxazole (2a). A tube was charged with 5-phenyloxazole (100.0 mg, 0.69 mmol), bromobenzene (130.3 mg, 0.83 mmol), potassium carbonate (190.4 mg, 1.36 mmol), $Pd(OAc)_2$ (7.7 mg, 0.03 mmol), and CuI (131.4 mg, 0.69 mmol). The tube was flushed with argon, and DMF (1.5 mL) was added. The tube was sealed with a rubber cap and heated to 150 °C for 15 min under microwave irradiation (200 W) using air cooling. The reaction mixture was filtered through Celite, the Celite washed with CH_2Cl_2, and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with cyclohexane/EtOAc (90/10) to afford the title compound **2a** (123 mg, 81%) as white crystals: mp 72−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (t, J = 7.2 Hz, 1H), 7.40−7.55 (m, 6H), 7.73 (d, J = 7.7 Hz, 2H), 8.10−8.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 123.4, 124.1, 126.2, 127.4, 127.9, 128.4, 128.8, 128.9, 130.3, 151.2, 161.1; MS (electrospray) *m*/*z* 222.2 (100) $[M + H]^+$, 223.1 (17) $[M + H]^+$, 244.1 (25) $[M + Na]^+$. Spectral data were in agreement with those previously reported.[23]

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Supporting Information Available: General experimental procedures and spectral data for compounds **1a**−**d**, **2a**−**m**, and **3a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Compounds **2k**, **2l**, and **2m** were obtained in, respectively, 57%, 55%, and 52% yields after 15 min heating.

(17) Dominguez, X. A.; de la Fuente, G.; Gonzalez, A. G.; Reina, M.; Timon, I. *Heterocycles* **1988**, *27*, 35.

(18) Ciddens, A. C.; Boshoff, H. I. M.; Franzblau, S. G.; Barry, C. E.; Copp, B. R. *Tetrahedron Lett.* **2005**, *46*, 7355.

(19) Burke, B.; Parkins, H.; Talbot, A. M. *Heterocycles* **1979**, *12*, 349.

(20) Hodgetts, K. J; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905.

(21) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1980**, *45*, 2548.

(22) Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5633.

(23) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897.