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Direct Arylation of Oxazoles at C2. A Concise Approach to Consecutively Linked Oxazoles

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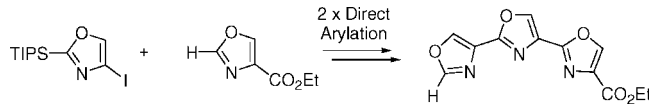
ABSTRACT



The synthesis of bis- and trisoxazoles via direct arylation is discussed. A variety of aryl groups can be installed at the 2-position of 5-aryl and 5-carboxy-substituted oxazoles under mild conditions using palladium catalysis on water. The direct arylation method can be extended to the synthesis of bis- and trisoxazoles if 2-triisopropylsilyl-4-iodooxazole is used as the electrophile in the arylation.

Consecutive C2−C4′ linked oxazole sequences are found in a variety of structurally complex, biologically active natural products.[1] Examples include the bisoxazole hennoxazole A[2] (antiherpes simplex virus activity), the antifungal trisoxazole ulapualide A,[3] and the potent telomerase inhibitor telomestatin, containing seven linked oxazoles and a thiazoline[4] (Figure 1). The C2−C4′ linkage pattern found in polyoxazole sequences is a result of their biosynthetic assembly from serine residues.[5] Consequently, the biomimetic cyclocondensation of peptide precursors is a popular approach to the polyoxazole motif in natural product synthesis, although numerous other methods exist.[6,7]

We have recently described a Suzuki−Miyaura cross-coupling route to the synthesis of bis- and trisoxazole structures.[8,9] While the approach was successful for several phenylated trisoxazoles, it was constrained in terms of substrate scope by the requirement for a stoichiometric organometallic as the nucleophilic coupling partner, a particularly problematic issue given the instability and preparation difficulties associated with certain azolyl organometallics (e.g., oxazoly-2-boronic acids).[10] A more advanced approach would be to employ transition-metal-

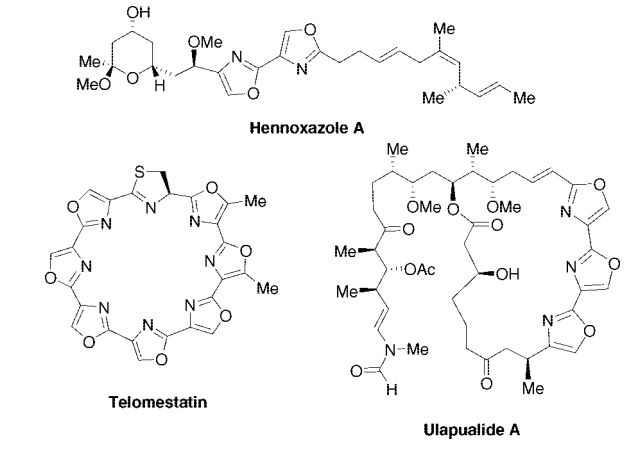


Figure 1. Oxazole containing natural products.

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(1) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995–12042.
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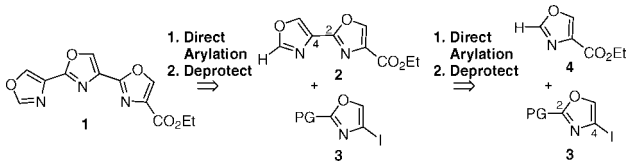
catalyzed direct arylation for oxazole−oxazole coupling, whereby the stoichiometric organometallic is dispensed with and the heteroaryl is arylated at the position of a C−H bond.[11]

The idea is shown in Scheme 1 for synthesis of the trisoxazole unit from ulapualide A: starting from the known[12] oxazole **4** containing an electron-withdrawing carboxylate at the 4-position and the protected 4-iodooxazole **3**, the target heterocycle **1** could be assembled using just two reactions, direct arylation, and deprotection, each repeated once. The route would thus be extremely quick, iterative, and offer the potential for convergency.

Scheme 1. Proposed Strategy for the Synthesis of Trisoxazoles via Direct Arylation (PG = Protecting Group)



The chemistry proposed in Scheme 1 presents a number of challenges to direct arylation chemistry. Oxazole−oxazole arylation has not been reported and will require the development of a C2 selective reaction using the novel bifunctionalized oxazole **3**. Compound **3** has C2 protected with a group that must be stable to the arylation conditions and can be easily cleaved to produce bisoxazole **2** for the second arylation. More importantly, the coupling of two electron-rich heteroaromatics via direct arylation poses a greater synthetic challenge than is usually encountered because the products formed contain *reactive* C−H bonds that may compete with the starting material to undergo further arylation, producing mixtures of products. For the system at hand, the electron-rich oxazole C5 position is of particular concern, as it may compete with C2 for arylation.

We began by examining the direct arylation of the oxazole 2-position using simple aryl iodides. We have recently developed a mild and general palladium-catalyzed method for the arylation of C2-substituted thiazoles at the electron-rich C5 position.[13] We were interested in being able to apply this method to the C2 position of oxazoles with the aim of building up more complexity toward the synthesis of C2−C4′ linked bis- and trisoxazoles of the type found in natural products. The arylation of oxazoles at C2 is a relatively unexplored area in the literature.[14] Recent work from Piguel describes microwave-accelerated arylation of the oxazole C2 position using palladium catalysis in the presence of a stoichiometric amount of copper.[15] Hoarau has reported a careful study on the regioselective C2 phenylation of ethyl 4-oxazolecarboxylate with iodobenzene.[16] Mechanistic studies from Zhuravlev on the C2 arylation of the related benzoxazole system have implicated an anionic cross-coupling mechanism involving deprotonation at C2 as being operative,[17] in contrast to the S_EAr mechanism usually invoked for direct arylation of π-excessive heterocycles.

We began by applying our on water arylation conditions to the synthesis of 2,5-disubstituted oxazoles via C2 direct arylation of 5-substituted oxazoles **5** with a range of aryl iodides **6** (Table 1, entries 1−12). Using a reaction system of $PdCl_2(dppf)/PPh_3$ and silver carbonate on water at 60 °C, we were pleased to observe good reactivity for a range of aryl iodides, affording good to excellent yields of the 2,5-diarylated products. The reaction was effective for both electron-rich (entries 2, 5, 9−11) and poor (entries 3, 7, 8, and 12) aryl iodides, producing clean transformations in each case. We were pleased to observe that 3-iodothiophene was a productive coupling partner, producing arylated oxazole **7d** in a good 66% yield despite the presence of several reactive C−H bonds in its structure. The electron-poor oxazole **5d** was effective in the reaction, giving a good 67% yield of product **7k** when combined with 4-iodotoluene and an acceptable 48% yield of product if coupled with 4-iodobenzonitrile (entries 11 and 12).

We then turned our attention to the synthesis of a protected oxazolyl-4-iodide (**3** in Scheme 1) that would function as an electrophile in our proposed polyoxazole direct arylation route. Oxazoles corresponding to **3** have not been previously described in the literature. Iodination at the oxazole 4-position has been reported by Vedejs, who demonstrated that 5-substituted oxazoles undergo selective 4-iodination when lithiated in the presence of DMPU and iodine.[9c] We were intrigued to see if we could access 4-iodooxazole **10** directly

(6) Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907–1922.

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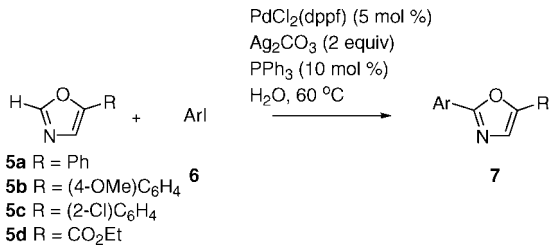
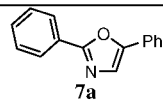
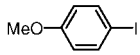
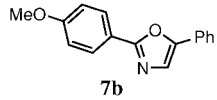
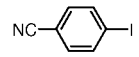
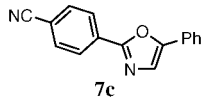
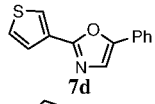
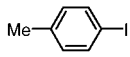
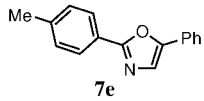
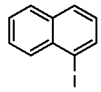
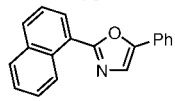
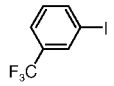
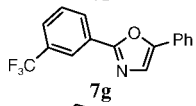
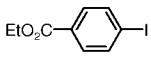
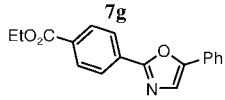
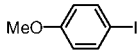
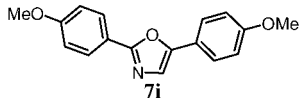
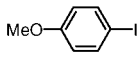
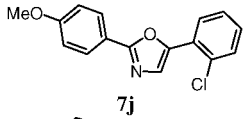
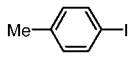
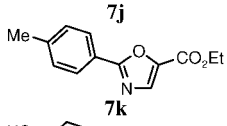
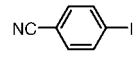
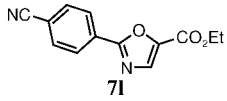
(17) Sánchez, R. S.; Zhuravlev, F. A. *J. Am. Chem. Soc.* **2007**, *129*, 5824–5825.

Table 1. C2 Direct Arylation of 5-Substituted Oxazoles with Aryliodides[a]

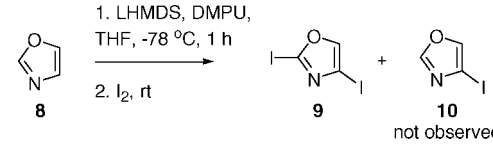


entry	Ar-X	product	yield (%)[a]
1		 **7a**	77
2		 **7b**	89
3		 **7c**	82
4		 **7d**	66
5		 **7e**	87
6		 **7f**	73
7		 **7g**	62
8		 **7h**	80
9		 **7i**	84
10		 **7j**	89
11		 **7k**	67
12		 **7l**	48

[a] Conditions: oxazole (1 equiv) and aryl iodide (1.2 equiv). [b] Isolated yield after SiO_2 column chromatography.

from the unsubstituted parent 1,3-oxazole **8** using the same reaction conditions. The resulting 4-iodooxazole could then be further functionalized at the C2 position (Table 2).

Table 2. 2,4-Diiodination of 1,3-Oxazole[a]

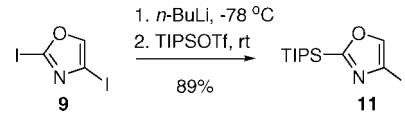


entry	reaction time[b]	yield of **9** (%)[c]
1	5 min	traces[d]
2	30 min	24
3	24 h	38
4	7 days	64
5	14 days	77

[a] Conditions: 2 equiv of LHMDS and 2 equiv of I_2. [b] Reaction time after addition of I_2. [c] Isolated yields after silica gel column chromatography. [d] 1 equiv of LHMDS and 1 equiv of I_2 were used.

A first experiment was carried out following the original conditions, and surprisingly, none of the expected 4-iodooxazole **10** was observed. Instead, small amounts of 2,4-diiodooxazole **9** could be isolated as the only product along with unreacted **8** (entry 1). The yield of **9** could be improved to 77% using prolonged reaction times and 2 equiv of both LHMDS and I_2 (Table 2, entries 2−5).[18] 2,4-Diiodooxazole **9** was isolated as a stable crystalline solid which could be stored at room temperature without noticeable decomposition for several weeks. The requisite protecting group was successfully installed at C2 via selective lithiation and quenching with TIPS-OTf,[19] producing the 2-triisopropylsilyl-4-iodooxazole **11** in an excellent 89% yield (Scheme 2).

Scheme 2. Synthesis of Key Building Block **11**

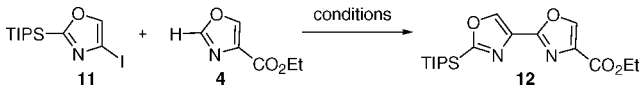


With iodide **11** in hand, we were ready to perform the first oxazole−oxazole arylation. Using 4-oxazolecarboxylate, **4**, as the coupling partner, we anticipated that the C4 electron-withdrawing group would retard any S_EAr arylation at C5, while promoting a deprotonation mechanism at C2. Hoarau and co-workers have demonstrated that C2 over C5 regioselectivity is possible in the phenylation of **4** using bulky ligands.[16] A wide range of conditions was examined for the direct arylation of **4** with iodide **11** (Table 3). Disappointingly, our previously successful C2 direct arylation conditions on water proved to be ineffective for iodide **11**, giving only traces of the desired bisoxazole with a slow reaction rate

(18) This increase in yields after a prolonged reaction time has been observed in a similar context. See ref 7f.

(19) Miller, R. A.; Smith, R. M.; Karady, S.; Reamer, R. A. *Tetrahedron Lett.* **2002**, 935–938.

Table 3. Direct Arylation of **4** with **11**: Optimization Data[a]



entry	catalyst	ligand	solvent	yield of **12** (%)[b]
1[c]	$PdCl_2$(dppf)	PPh_3	water	traces
2[d]	CuI	none	dmf	0
3	$Pd(OAc)_2$	P(*o*-Tol)$_3$	toluene	38
4	$Pd(OAc)_2$	P(*o*-Tol)$_3$	dmf	0
5	$Pd(OAc)_2$	IMes	toluene	complex mixture
6	$Pd(OAc)_2$	X-PHOS	toluene	complex mixture
7	PEPPSI-IPr	none	toluene	51
8	PEPPSI-IPr	none	1,4-dioxane	60
9	PEPPSI-IPr	none	DMF	40
10	HBP	none	toluene	81

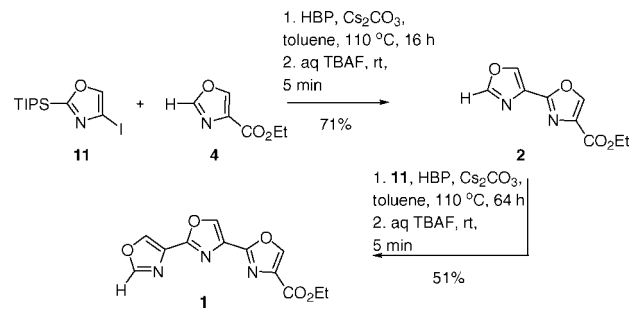
[a] HBP = Hermann−Beller palladacycle. Conditions: 1 equiv of **11** and 1.2 equiv of **4**, 5 mol % of catalyst and 10 mol % of ligand, 1 mL of solvent, 2 equiv of Cs_2CO_3, and 110 °C in a sealed tube. [b] Isolated yield after silica/gel column chromatography. [c] Ag_2CO_3 (2 equiv) at 60 °C. [d] CuI (10 mol %) at 140 °C.

being observed (entry 1). The copper-catalyzed arylation conditions recently described by Daugulis[14b] were likewise unsuccessful with complete degradation of **11** being observed after 30 min at 140 °C (entry 2). The first successful coupling was observed using Pd(OAc)/P(*o*-Tol)$_3$ in toluene, which gave bisoxazole **12** in a modest 38% yield (entry 3). Switching to the more polar DMF, a common direct arylation solvent, under the same system completely degraded **11** after 30 min at 110 °C (entry 4). The use of very bulky/electron-rich Imes or XPhos ligands only led to inseparable complex mixtures (entries 5 and 6).

A substantially better catalyst for the arylation proved to be the N-heterocyclic carbene-based palladium complex PEPPSI-IPr,[20] which gave moderate to good yields in toluene, 1,4-dioxane, and DMF (entries 7, 8, and 9). Finally, to our delight, we found that the Herrmann−Beller palladacycle[21] in toluene gave a very good 81% yield of the bisoxazole (entry 10).

Deprotection of **12** was slow and low yielding under acidic conditions[22] but successful upon brief exposure to aqueous TBAF solution at room temperature, giving the bisoxazole **2** in 71% yield over the two steps (Scheme 3). With an

Scheme 3. Synthesis of the Trisoxazole Moiety Found in Ulapualide A



efficient route to bisoxazole **2** established, synthesis of trisoxazole **1** was attempted. We were pleased to find that a second direct arylation using the same catalyst system was successful, affording the protected trisoxazole in 57% yield. Facile deprotection with aqueous TBAF gave trisoxazole **1** in 51% yield over the two steps, representing an overall six-step preparation from commercially available 1,3-oxazole in 25% overall yield.

This is the quickest synthesis of trisoxazoles reported to date,[6] although the research groups of Vedejs[7f] (eight steps, 39%) and Panek[23] (13 steps, 26%) have described higher yielding routes. The modularity and speed of the direct arylation approach offers significant benefits and should compliment existing methods for polyazole synthesis.

In conclusion, we have developed arylation methods for the C2 position of oxazoles and applied them to the synthesis of bis- and trisoxazoles. Using commercially available 1,3-oxazole as a starting point, the trisoxazole structure found in the ulapualide family of natural products has been prepared in six steps.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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