Multicomponent Reactions

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Four-Component Synthesis of Fully Substituted 1,2,4-Triazoles**

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The generation of α-aza-biaryl linkages continues to challenge synthetic chemists and is the focus of much research effort. Classic transition-metal-catalyzed C–C cross-coupling remains the most prevalent route for biaryl synthesis; however, issues with the unavailability and instability of organometallic reactants for α-heteroatom biaryl coupling still limit the success of this approach. Importantly, recent improvements have been made in the mild generation,[1] increased benchtop stability,[2] controlled release,[3] and mild coupling[4] of these previously unreliable reaction partners. Direct C–H arylation avoids the preparation of stoichiometric organometallic reagents altogether and has proven to be a powerful method for the synthesis of biaryls.[5] However, limitations still exist and reaction optimization for specific coupling partners is commonplace. As many azole and azine heterocycles can be generated by the cyclodehydration of appropriate carbonyl precursors, an alternative approach to α-aza-biaryl coupling stems from the transition-metal-catalyzed carbonylative coupling of acyclic reagents that can undergo in situ cyclodehydration (Figure 1). Importantly, a

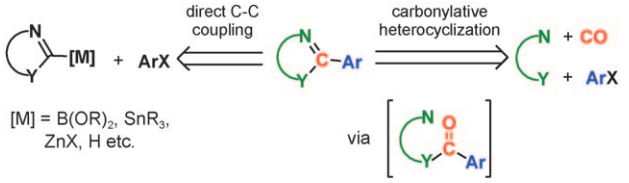

Figure 1. α-Heteroatom biaryl generation of α-heteroatom biaryls.

multicomponent carbonylative heterocyclization can provide access to difficult α-heteroatom biaryl linkages without requiring the synthesis of any organometallic intermediates.[6]

In the course of a drug-discovery program, we required access to several 5-aryl-1,2,4-triazoles **A** from a common aryl iodide (Figure 2). This class of compounds has been prepared previously utilizing zinc and stannyl triazoles in Negishi and Stille C–C coupling reactions,[7] but this approach requires the multistep syntheses of differentially substituted triazoles and

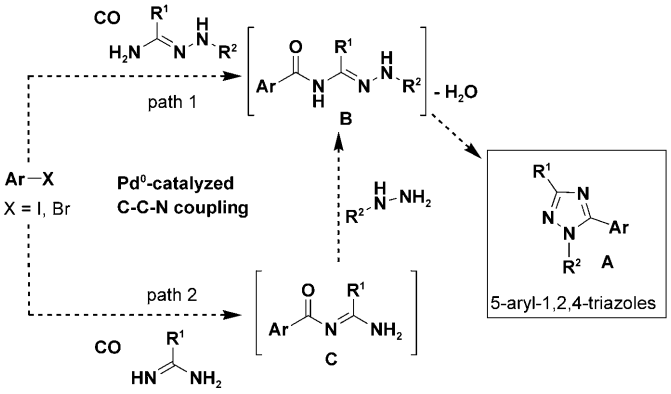

Figure 2. Multicomponent route to 5-aryl-1,2,4-triazoles.

careful handling of the above-mentioned sensitive metalloazole intermediates.[8] Review of the literature revealed few examples of intermolecular C–H arylation of 1,2,4-triazoles.[9] We thus sought an approach to synthesize triazoles **A** through **B**, a key intermediate in the Einhorn–Brunner stepwise synthesis of triazoles (Figure 2).[10] We believed a palladium-catalyzed C-C-N coupling protocol could provide intermediates **B** by carbonylative addition of either amidrazones (path 1) or amidines (path 2) to aryl halides. Herein we describe the multicomponent synthesis of functionally diverse 5-aryl- and –heteroaryl-1,2,4-triazoles by carbonylative heterocyclization.

Perhaps the most direct way to the Einhorn–Brunner intermediate **B** is through carbonylative addition of an amidrazone (path 1). Armed with the recent successes from the Buchwald lab in the carbonylative amination of various aryl halides under atmospheric CO pressures,[11] we believed similar conditions would be appropriate for this carbonylative process. To our delight, use of $Pd(OAc)_2$/Xantphos (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) with triethylamine in DMF under atmospheric CO led to the direct conversion of *p*-iodoanisole to triazole **1a** (56% yield, Scheme 1). Similarly 3-iodopyridine was coupled to carbon monoxide and a difluorophenyl-substituted amidrazone in this three-component process to give 1,3,5-substituted 1,2,4-triazole **1c** in 50% yield.[12]

Albeit direct, the above three-component strategy for the synthesis of trisubstituted triazoles required the use of preformed amidrazones. Few amidrazones are commercially available and, in our hands, their preparation was cumbersome. We therefore sought to access intermediate **B** (Figure 1) by the carbonylative coupling of readily available amidines to aryl halides followed by in situ reaction with monosubstituted hydrazines (path 2, via acyl amidine **C**). This modular four-component approach would promote rapid

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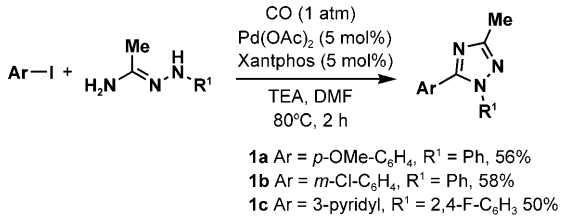


Scheme 1. Carbonylative addition of amidrazones to aryl iodides for direct access to fully substituted 1,2,4-triazoles.

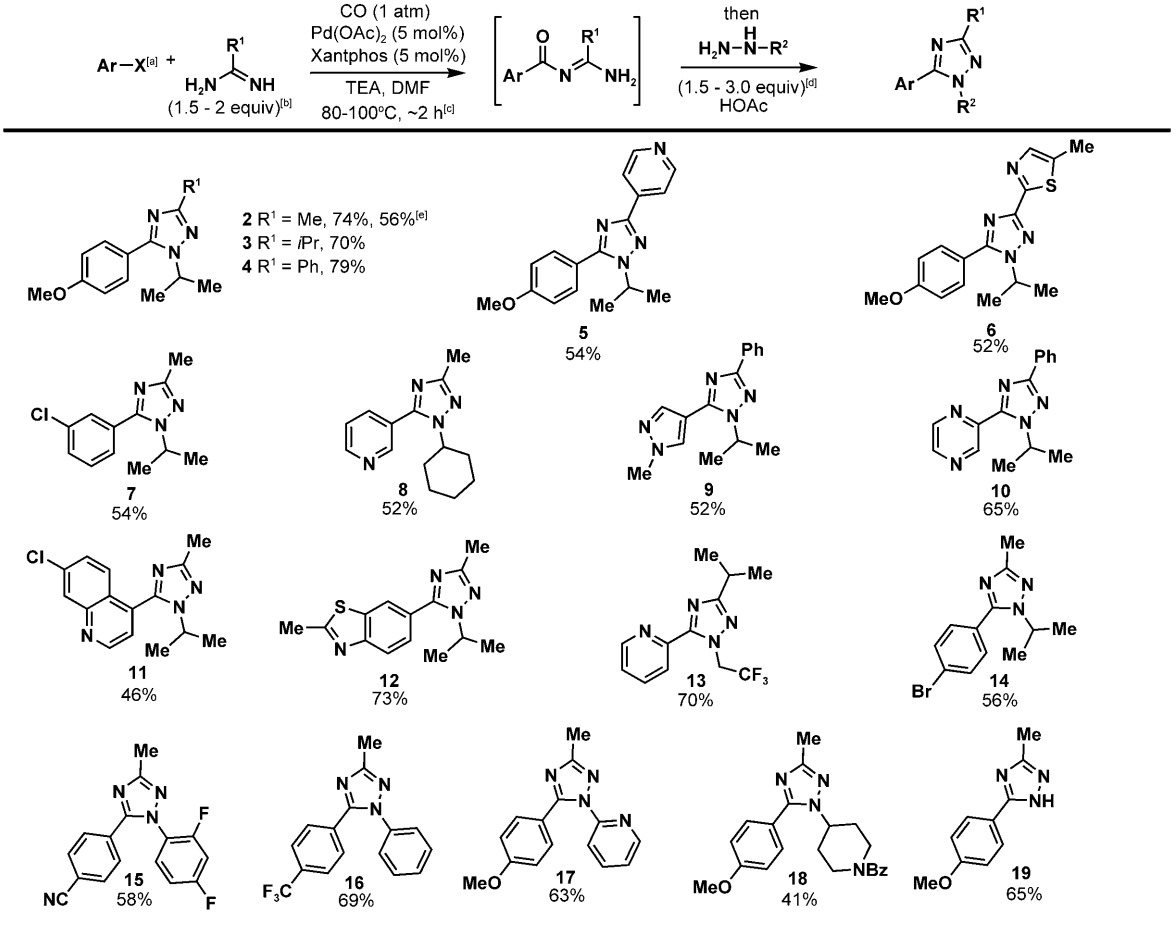
access to diverse valuable trisubstituted triazoles, without required presynthesis.[13]

Application of a one-pot protocol was indeed successful. Thus, carbonylative coupling with acetamidine[14] followed by addition of isopropylhydrazine and acetic acid to the crude reaction mixture gave **2** in 74% overall yield (Scheme 2). Further investigation revealed that this method has wide substrate scope. A variety of commercially available alkyl, aryl, and heteroaryl amidines were successful in this four-component process (e.g. products **3**–**5**).[15] For aryl substrates, electron-withdrawing or -donating substitutents are well-tolerated (e.g. compare products **2**, **7**, and **15**).

This linchpin protocol was also successful for the coupling of both aryl and heteroaryl reagents including pyrazolyl, quinolyl, pyridyl, pyrazyl, and benzothiazyl iodides (products **9**, **11** and **13**, **10**, and **12** respectively). Especially notable among these is the smooth coupling/cyclization of 2-iodopyrazine and 2-iodopyridine (products **10** and **13**). These couplings generate biaryl linkages with three α-heteroatoms in 65% and 70% yield, respectively. Importantly, triazole formation was completely regioselective in all cases.[16] The hydrazino component is easily varied as alkyl, aryl, and heteroaryl hydrazines cyclize efficiently under the reaction conditions (products **13** and **15**–**18**).[17] Aqueous hydrazine can also be used to access 5-aryl-1*H* triazoles as in **19**.

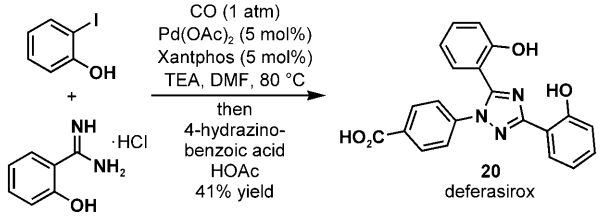
Aryl bromides are also effective reactants in this one-pot, four-component process. For example, compound **2** is generated in 74% and 56% yield from the corresponding aryl iodide and aryl bromide, respectively. When *p*-iodobromobenzene is used and the number of amidine equivalents is controlled, selective monocarbonylative addition is observed (product **14**, 56% yield), and an important synthetic handle remains intact for further functionalization .

Substituted triazoles are present in many important pharmaceutically active molecules. Although many of the compounds in Scheme 2 already display druglike attributes,



Scheme 2. Modular synthesis of substituted triazoles. [a] The aryl iodide was used unless otherwise noted. [b] Amidines were typically added as HCl or HOAc salts. [c] See the Supporting Information for reaction details of each example. [d] Hydrazines were typically added as HCl salts. [e] Aryl bromide was used. Yields are of analytically pure isolated material from reactions run on a 0.6–2.0 mmol scale.

we wanted to demonstrate the utility of this method through the synthesis of a pharmaceutically relevant molecule in a one-pot fashion. Deferasirox (**20**) is an active pharmaceutical ingredient in Exjade, an important metal-chelating treatment for patients with chronic iron overload.[18] A testament to the robust functional group tolerability of this methodology, carbonylative coupling of 2-hydroxybenzamidine with 2-iodophenol preceded addition/cyclization with 4-hydrazinobenzoic acid to provide **20** in 41 % yield after purification by reverse-phase HPLC (Scheme 3).



Scheme 3. One-pot synthesis of deferasirox.

In conclusion, we have developed a palladium-catalyzed multicomponent synthesis of trisubstituted triazoles. This approach features a wide scope, mild reaction temperatures, and low carbon monoxide pressures. Total yields range from 41 % to 79 %, or 80–94 % per bond for the four bonds created. The utility of this process is underscored by the synthesis of druglike and/or pharmaceutically relevant molecules from commercially available materials.[19] As such, this method compares favorably with direct C–H arylation technology. Further application of this strategy is underway and will be disclosed in due course.

Experimental Section

CAUTION: Carbon monoxide should be handled with extreme care. These experiments were run in a well-ventilated hood.

Representative procedure for the synthesis of **1a** (Scheme 1): A 25 mL round-bottom flask with an attached septum was flushed with nitrogen and charged with 3-iodoanisole (165 mg, 0.71 mmol) and *N*′-phenylacetimidohydrazide hydrochloride (197 mg, 1.06 mmol). Anhydrous DMF (5 mL) and triethylamine (0.40 mL) were added under nitrogen purge. $Pd(OAc)_2$ (8 mg, 5 mol %) and Xantphos (20 mg, 5 mol %) were added. The flask was purged with carbon monoxide for 2 min. The reaction mixture was heated under a CO atmosphere (balloon) for 1.5 h at 80 °C. The balloon was removed and the reaction mixture was cooled to room temperature. The mixture was diluted with ethyl acetate (50 mL)and washed with 5 % NaOH (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography (5–45 % EtOAc in hexanes) to give **1a** as a colorless solid (105 mg, 56 % yield). ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta =$ 7.51–7.44 (m, 3H), 7.35 (m, 4H), 6.96–6.90 (m, 2H), 3.76 (s, 3H), 2.35 ppm (s, 3H). ^{13}C NMR (126 MHz, [D_6]DMSO): $\delta = 160.25$, 159.44, 153.40, 138.06, 129.85, 129.35, 128.72, 125.49, 119.90, 113.93, 55.17, 13.45 ppm. HRMS calcd for $C_{16}H_{16}N_3O$ [M+H$^+$] 266.1295, found 266.131.

Representative procedure for the synthesis of **3** (Scheme 2): A 25 mL round-bottom flask with an attached septum was flushed with nitrogen and charged with 4-iodoanisole (250 mg, 1.07 mmol) and isopropylcarbamidine hydrochloride (196 mg, 1.6 mmol). Anhydrous DMF (8 mL) and triethylamine (1 mL) were added under nitrogen purge. $Pd(OAc)_2$ (12 mg, 5 mol %) and Xantphos (31 mg, 5 mol %) were added. The flask was purged with carbon monoxide for 2 min. The reaction mixture was heated under a CO atmosphere (balloon) for 2 h at 80 °C. The balloon was removed and the reaction mixture was cooled to room temperature. Isopropylhydrazine hydrochloride (354 mg, 3.20 mmol) and acetic acid (4 mL) were added. The reaction mixture was heated at 80 °C for 1 h. After cooling to room temperature, the mixture was diluted with 75 mL of ethyl acetate and washed with 5 % NaOH (2×, 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified by flash column chromatography (10–50 % EtOAc in hexanes) to give **3** as a colorless solid (194 mg, 70 % yield). ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 7.53$ (m, 2H), 7.09 (m, 2H), 4.56 (hept, $J = 6.6$ Hz, 1H), 3.83 (s,3H), 2.96 (hept, $J = 6.9$ Hz, 1H), 1.39 (d, $J = 6.6$ Hz, 6H), 1.26 ppm (d, $J = 6.9$ Hz, 6H). ^{13}C NMR (126 MHz, [D_6]DMSO): $\delta = 166.94$, 160.16, 152.94, 130.06, 120.70, 114.17, 55.24, 49.62, 27.61, 22.42, 21.62 ppm. HRMS calcd for $C_{15}H_{22}N_3O$ [M+H$^+$] 260.1764, found 260.1614.

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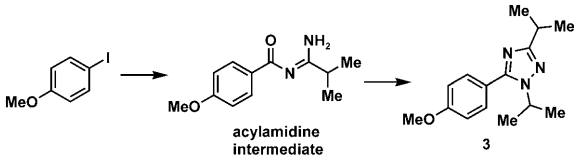
[12] Please see the Supporting Information section for experimental details. All triazole products have consistent ^{1}H NMR, ^{13}C NMR, and HRMS data.

[13] A typical synthesis of a 5-aryl-1,2,4-triazole from an aryl halide involves conversion of the aryl halide to a primary benzamide followed by formation of an acylamidine by heating with a dimethylamide dialkyl acetal (i.e. dimethylacetamide dimethyl acetal) and addition/cyclization of a monosubstituted hydrazine.

[14] To the best of our knowledge, this is the first report of a carbonylative coupling of an amidine to an aryl halide.

[15] Unsuccessful partners included formamidine and trifluroroacetamidines, resulting in transformation to 4-methoxybenzamide presumably through the facile hydrolysis of the unhindered and highly elecrophilic intermediates. No appreciable products were formed in an attempted reaction of 2-iodo-1-methylimidazole and 2-bromopyrimidine with acetamidine. Inorganic bases such as Na_2CO_3 and K_3PO_4 were also competent in the creation of **3**, although the cleanest conversion was observed using NEt_3. Compound **3** was also synthesized in a stepwise fashion. The acylamidine intermediate shown was isolated in 66% yield by reverse-phase HPLC to support its intermediacy in the triazole synthesis (see the Supporting Information for details).



[16] No regioisomers were observed by LCMS analysis of the crude reaction mixtures. Regiochemistry was determined by 2D NOESY for compounds **4**, **10**, **11**, and **13** as well as by HMBC correlation for **10** and **13**. The remaining compounds were assigned by analogy.

[17] The cyclization stage is typically run at $\approx$80 °C to ensure complete conversion of the acylamidine intermediate, although the reaction is often complete at room temperature.

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[19] Notably, all aryl halides, amidines, and hydrazines used are commercially available.

