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Decarboxylative Cross-Coupling of Azoyl Carboxylic Acids with Aryl Halides

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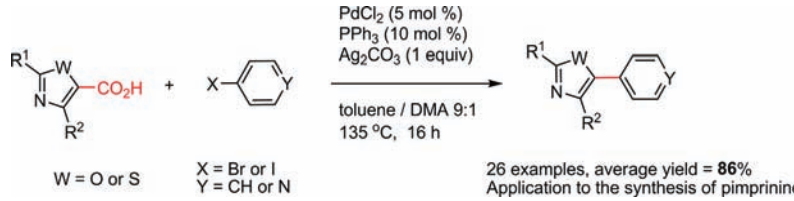
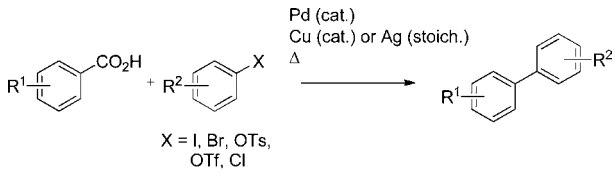
ABSTRACT



Decarboxylative cross-coupling of thiazole and oxazole-5-carboxylic acids with aryl halides is reported. Under a bimetallic system of catalytic palladium and a stoichiometric silver carbonate, a variety of (hetero)arylated azoles can be prepared in excellent yield.

The decarboxylative cross-coupling of aryl carboxylic acids with aryl halides is a recently established method for biaryl synthesis.[1] Carboxylic acids represent a powerful alternative to the conventional organometallic building blocks used as nucleophiles in sp^2 C−C bond formation, conferring advantages of cost, availability, and ease of use. The transformation typically employs bimetallic catalysis—a conventional palladium cycle to activate the electrophile plus a second copper or silver-mediated process to effect decarboxylation (Scheme 1).

Scheme 1. The Decarboxylative Cross-Coupling Reaction



The canonical substrate for a decarboxylative coupling is a σ electron poor benzoic acid, with much of the groundbreaking work being carried out with *o*-nitrobenzoic acid.[2] Recent work has concentrated on expanding this substrate scope, but significant challenges remain in establishing this exciting transformation as a general method for biaryl synthesis.[3] Heterocyclic acids, in particular, remain underexploited in this method.

Pioneering work from Forgione and Bilodeau established the viability of decarboxylative coupling for pyrrole and furan substrates,[4] and work from our own laboratory has demonstrated decarboxylative coupling of azoyl acids with C−H components.[5] Outside of these contributions there have been no focused efforts on heteroaryl carboxylic acid coupling. Given the stability and tremendous accessibility of heteroaryl carboxylic acids relative to heteroaryl organometallics, the reaction has great potential for the synthesis of multiheteroaryl compounds integral to medicinal chemistry. We wish to report our efforts in this area using decarboxylative coupling to prepare arylated thiazoles and oxazoles, compounds of fundamental importance in medicinal, agro, and natural products chemistry.[6]

(1) (a) Bonesi, S. M.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 10022–10025. (b) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100–3120. (c) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 1373–1375.

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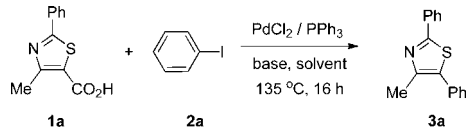
We began by examining the cross-coupling of iodobenzene with 4-methyl-2-phenylthiazole-5-carboxylic acid **1a** as a test reaction (Table 1). Using a simple catalyst system of $PdCl_2$ and PPh_3, we were surprised to observe no cross-coupling at all in the presence of stoichiometric $CuCO_3$ (entry 1), a reagent we have used previously for decarboxylation.[5] By contrast, stoichiometric Ag_2CO_3 proved very effective, affording the phenylated thiazole **3a** in 74% yield in DMA, and 81% yield with toluene/DMA (10:1) (entries 2 and 3). A further jump in yield could be attained by varying the stoichiometry such that the aryl iodide was the limiting reagent (entry 4), affording an excellent 96% yield of **3a**. This stoichiometry is a common feature of decarboxylative cross-coupling with aryl halides;[3] the acid component can undergo proto-decarboxylation to varying degrees and is often used in small excess. The phosphine ligands were not essential for coupling, with ligand free conditions affording **3a** in high yield (entry 5). Triphenylphosphine did generally improve efficiencies, however, so was maintained in the optimized procedure. We could reduce the stoichiometry of Ag_2CO_3 and still observe successful coupling (entry 6), although yields dropped roughly in line with the amount of Ag^+ present in the reaction. Control experiments in the absence of either Pd or silver were negative for arylated product **3a**.

Table 1. Reaction Optimization[a]



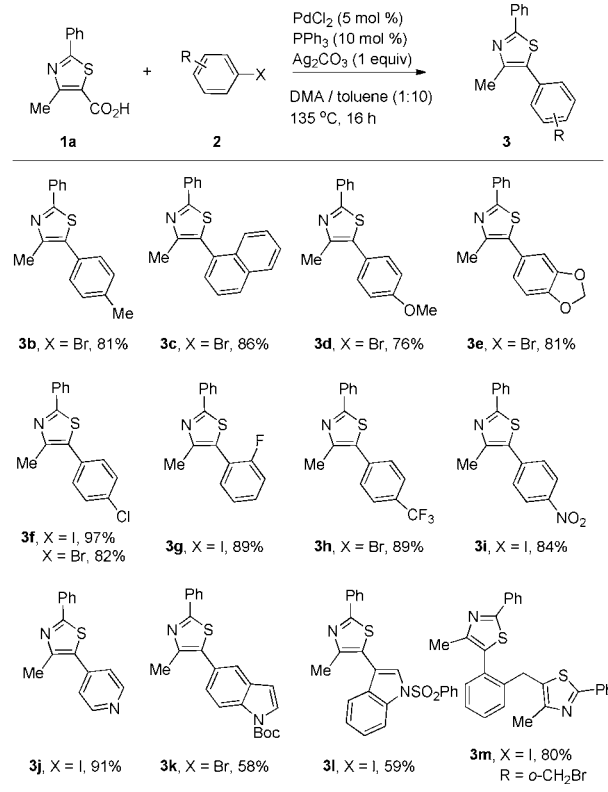
1a **2a** **3a**

entry	base	solvent	yield (%)[b]
1	$CuCO_3$ (1 equiv)	toluene	0
2	Ag_2CO_3 (1 equiv)	DMA	74
3[c]	Ag_2CO_3 (1 equiv)	DMA/toluene (1:10)	81
4[d]	Ag_2CO_3 (1 equiv)	DMA/toluene (1:10)	96
5[d,e]	Ag_2CO_3 (1 equiv)	DMA/toluene (1:10)	81
6[d]	Ag_2CO_3 (0.3 equiv)	DMA/toluene (1:10)	57

[a] Conditions: thiazole **1a** (1 equiv), iodobenzene **2a** (2 equiv), $PdCl_2$ (5 mol %), triphenylphosphine (10 mol %) plus base and solvent as shown in the table. Reactions were carried out on a 0.3 mmol scale and heated to 135 °C for 16 h in a sealed tube under air. [b] Isolated yield. [c] Reaction was conducted with Dean−Stark apparatus under N_2 atmopshere. [d] Thiazole **1a** (1.5 equiv), iodobenzene **2a** (1 equiv). [e] No triphenylphosphine.

With this optimized procedure in hand we applied it to a range of aryl halides (Scheme 2). Yields were generally excellent for a variety of simple aryl bromides and iodides. Electron-rich (**3b**−**e**) and electron-poor (**3f**−**i**) halides were equally successful in the reaction. Halogenated functionality was tolerated (**3f** and **3g**), with **3g** displaying an *o*-fluoro group. We were pleased to find the reaction was effective for heteroaryl halides. 4-Iodopyridine was coupled in excellent yield (**3j**), along with 5- and 3-halo indoles in somewhat reduced yields (**3k** and **3*l***). Synthesis of products **3j**−***l*** in one step illustrates the power of disconnecting through the biaryl bond for multiheteroaromatic compounds. Classic approaches would require longer sequences whereby the heteroaromatic is formed through condensation of acyclic precursors. Finally, we performed a double coupling using *o*-bromomethyliodobenzene, isolating the novel sp^2 and sp^3 coupled product **3m** in 80% yield.

Scheme 2. Decarboxylative Cross-Coupling of Thiazole **1a** with Aryl Halides



(3) Recent examples: (a) Li, M.; Ge, H. *Org. Lett.* **2010**, *12*, 3464–3467. (b) Xie, K.; Yang, Z.; Zhou, X.; Li, X.; Wang, S.; Tan, Z.; An, X.; Guo, C.-C. *Org. Lett.* **2010**, *12*, 1564–1567. (c) Zhou, J.; Hu, P.; Zhang, M.; Huang, S.; Wang, M.; Su, W. *Chem.—Eur. J.* **2010**, *16*, 5876–5881. (d) Arroyave, F. A.; Reynolds, J. R. *Org. Lett.* **2010**, *12*, 1328–1331. (e) Goossen, L. J.; Rodriguez, N.; Lange, P. P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111–1114. (f) Shang, R.; Xu, Q.; Jiang, Y.-Y.; Wang, Y.; Liu, L. *Org. Lett.* **2010**, *12*, 1000–1003. (g) Sun, Z.-M.; Zhang, J.; Zhao, P. *Org. Lett.* **2010**, *12*, 992–995. (h) Kim, H.; Lee, P. H. *Adv. Synth. Catal.* **2009**, *351*, 2827–2832. (i) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 9350–9354. (j) Goossen, L. J.; Zimmermann, B.; Linder, C.; Rodriguez, N.; Lange, P. P.; Hartung, J. *Adv. Synth. Catal.* **2009**, *351*, 2667–2674. (k) Cornella, J.; Lu, P.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5506–5509. (l) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674–3677. (m) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195.

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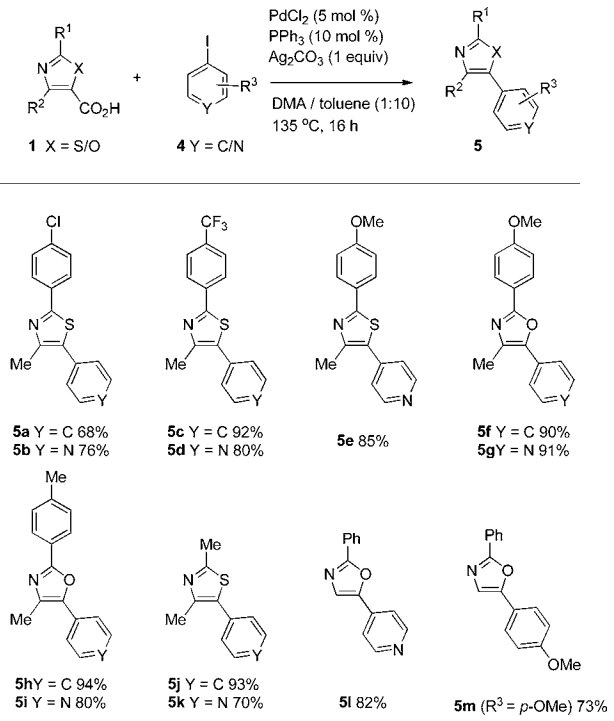
(6) Riego, E.; Hernández, D.; Albericio, F.; Álvarez, M. *Synthesis* **2005**, 1907–1922.

subjected them to the coupling protocol with 4-iodopyridine and benzene derivatives (Scheme 3). A variety of para-

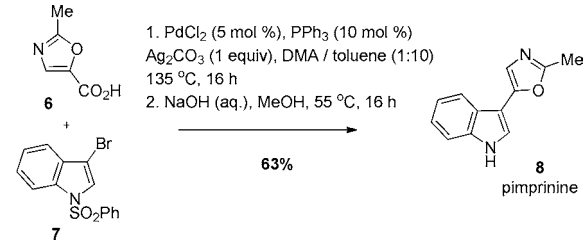
Scheme 3. Decarboxylative Cross-Coupling of Thiazole **1a** with Aryl Halides



substituted aryl substituents in the 2-position all gave excellent yields for thiazoles (**5a**−**e**) and oxazoles (**5f**−**i**). In each case the heterocyclic iodide was equally as effective as the phenyl iodide. The 2-methyl thiazole was a good substrate, producing the 2,4-dialkyl-5-aryl thiazoles **5j** and **5k** in high yield. Importantly, we found that 4-unsubstituted oxazoles were productive in the reaction, affording the 2,5-disubstituted products **5*l*** and **5m**, again in good yield. In contrast, azole-4-carboxylic acids were not good substrates for the cross-coupling under these reaction conditions.

The success of decarboxylative coupling with azoles having a vacant 4-position prompted us to conclude our studies with a short synthesis of the alkaloid pimprinine. Originally isolated in 1960 from *Streptomyces pimprina*,[7] pimprinine was characterized as the oxazolylindole **8**, and is part of a wider class of 5-(3-indolyl)oxazole alkaloids that have been subsequently discovered (Scheme 4).[8]

Scheme 4. Synthesis of Pimprinine



Pimprinine displays a range of biological activities such as monoamine oxidase inhibition, antiplatelet aggregation, and anticonvulsant activity,[9] and has been the subject of several syntheses that use 3-acyl indole derivatives as starting materials.[10] The decarboxylative cross-coupling offers a more modular approach: Starting from 2-methyloxazole-5-carboxylic acid **6**, available through simple hydrolysis of the known ethyl ester,[11] coupling with the commercially available indole **7** under our standard conditions proceeded in 63% yield. Basic hydrolysis removed the tosyl group quantitatively, producing the natural product in a short and efficient sequence.

In conclusion, we have developed a decarboxylative cross-coupling method for the (het)arylation of thiazoles and oxazoles. The reaction employs a very simple catalyst system and delivers excellent yields of a wide variety of bromide and iodide coupling partners.

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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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