ORGANIC LETTERS

2010
Vol. 12, No. 2
224−226

Direct Arylations of 2*H*-Indazoles On Water

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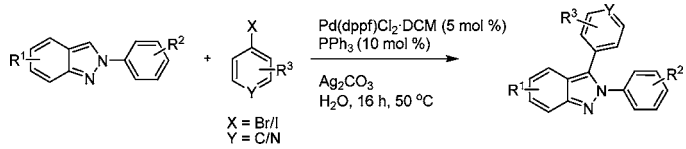
Received November 2, 2009

ABSTRACT



The efficient palladium-catalyzed synthesis of a range of substituted 2*H*-Indazoles via C−H arylation is reported. Reactions are performed on water and provide a direct and mild route toward 2,3-diaryl indazoles of widespread biological significance.

Direct arylation is a powerful approach to the synthesis of functionalized arenes that offers an alternative to conventional cross-coupling methods.[1,2] The direct manipulation of C−H bonds in catalytic C−C or C−X bond formation avoids the preparation and use of stoichiometric organometallics, conferring the strategic benefit of streamlined, operationally simple synthesis with reduced byproduct formation.

A feature of current direct arylation methodology is the high reaction temperatures required to effect C−C bond formation, with relatively few systems being reported to date that proceed below 100 °C.[3] The development of new systems that function at milder temperatures will significantly enhance the scope and functional group tolerance of direct arylation as a general method of sp^2 C−C bond formation. We are addressing this issue through the development of direct arylation chemistry that works on water.[4] We have found that on water conditions, where substrate and catalyst system form a heterogeneous mixture in pure water, can be extremely effective for high yielding direct arylations under mild conditions.[5] We now wish to report our results on the application of on water arylation to the indazole substrate.

Although rare in nature, the indazole heterocycle has vast application in medicinal chemistry, particularly in the field of kinase inhibition.[6] Direct arylation at the C3 position would significantly simplify synthetic routes to this important class of heteroarene. Catalytic direct arylation of indazoles has received little attention, a single elegant study from Lautens on the synthesis of annulated 2*H*-indazoles via intramolecular direct arylation being the only extant report in the literature.[7]

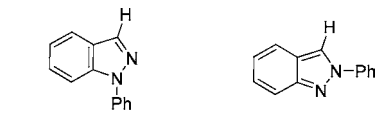


Figure 1. 1*H*- and 2*H*-indazoles.

We began by examining the regioisomeric 1- and 2-phenylindazoles as substrates (Figure 1). The C3 position is known to be markedly less reactive toward substitution in the 1*H*-series, and this was manifested in our direct arylation studies, with **1** undergoing no arylation on water under the mild conditions we were looking to develop. 2-Phenylindazole,[8] by contrast, proved an excellent substrate, undergoing clean on water

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(1) Recent reviews: (a) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2464. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074–1086. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115.

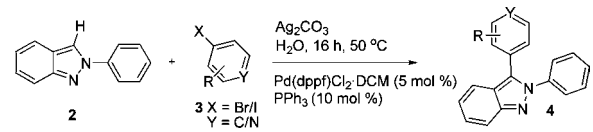
10.1021/ol902537d
Published on Web 12/16/2009

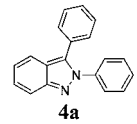
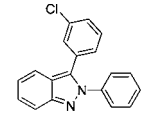
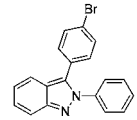
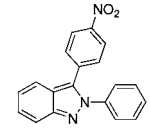
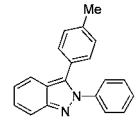
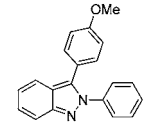
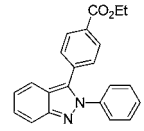
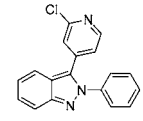
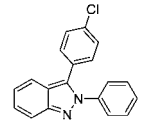
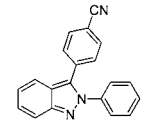
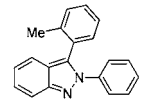
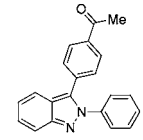
arylation with a variety of aryl halides at just 50 °C on water. A catalyst system of Pd(dppf)Cl_2/PPh_3 or Pd(dppb)Cl_2/PPh_3 in the presence of an equivalent of Ag_2CO_3 produced good to excellent yields of 2,3-diarylindazoles on water. The reaction was generally effective for both aryl iodides and bromides, an advance over our previous on water studies of azole heterocycles which were restricted to aryl iodides (Table 1).

Functional group tolerance was good, with halo (entries 2, 5, and 7), electron withdrawing (entries 4, 8, 11, and 12), and electron donating (entries 3, 6, and 9) groups being tolerated at both para and meta positions. A single ortho-functionalized aryl iodide was productive, but in a diminished 49% yield (entry 6). Heterocyclic 2-chloro-4-iodopyridine produced functionalized indazole **4j** in 95% yield, featuring the highly versatile 2-chloropyridine functionality for further manipulation (entry 10).

In practical terms the reactions were very simple to run and purify—a feature of on water chemistry. The catalyst system and substrates were premixed prior to the addition of water, with good mixing being crucial for successful arylation. While this was easily achieved for solid reactants (entries 2, 3, 4, and 8−10), care needed to be taken for reactions involving liquid aryl halides to prevent the reagent from adhering to the walls of the flask and not being effectively incorporated into the heterogeneous reaction mixture.

Table 1. Palladium-Catalyzed Direct Arylation of 2-Phenylindazole[c]



entry	product	yield (%)	entry	product	yield (%)
1	 **4a**	76 (From ArI) 71 (From ArBr)	7	 **4g**	96 (ArBr)
2	 **4b**	80[a] (ArI)	8	 **4h**	86 (ArBr)
3	 **4c**	91 (ArI) 70 (ArBr)	9	 **4i**	87 (ArI)
4	 **4d**	77 (ArI) 74 (ArBr)	10	 **4j**	95 (ArI)
5	 **4e**	90 (ArI) 69 (ArBr)	11	 **4k**	85 (ArI)
6	 **4f**	49[b] (ArI)	12	 **4l**	81 (ArI)

[a] X-ray structure of product. [b] Reaction run at 60 °C. [c] Conditions: Ag_2CO_3 (1 equiv), PPh_3 (10 mol %), Pd(dppf)Cl_2•DCM (5 mol %). Aryl iodide (1.1 equiv), 2-phenylindazole (1 equiv), water, 50 °C, 16 h. Isolated yields after SiO_2 chromatography.

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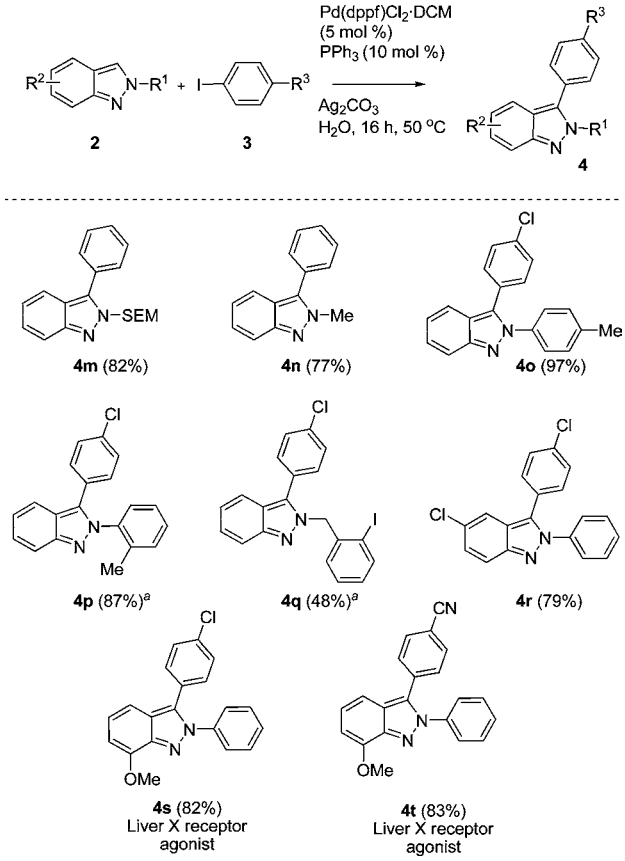
To fully establish the scope of the arylation we prepared a series of N2 substituted indazoles and subjected them to on water arylation (Table 2).

Table 2. Direct Arylation of Various 2*H*-Substituted Indazoles[b]



[a] Reaction run at 60 °C. [b] Conditions: Ag_2CO_3 (1 equiv), PPh_3 (10 mol %), $Pd(dppf)Cl_2$·DCM (5 mol %). Aryl iodide (1.1 equiv), 2-phenylindazole (1 equiv), water, 50 °C, 16 h. Isolated yields after SiO_2 chromatography.

The SEM protecting group proved stable to the arylation conditions, with the versatile 2-SEM protected indazole **4m** being formed in high yield. Alkyl-substituted indazoles were good substrates, as were 2-*p*- and *o*-tolylindazoles **4o** and **4p**. The 2-iodobenzylindazole starting material was prepared to examine the possibility of intramolecular cyclopentannulation via direct arylation. This intramolecular reaction proved ineffective under the conditions—when 4-chloroiodobenzene was added in a competition experiment the intermolecular arylation product was isolated in moderate yield. Functional handles could be incorporated into the indazole ring with the 5-chloro- and 7-methoxyindazole compounds being excellent substrates. Indazoles **4s** and **4t** previously have been prepared in 5 steps as inhibitors of liver X receptor-mediated cardiovascular disease.[9]

The combination of a silver salt and on water conditions was essential for successful arylation. Replacing Ag_2CO_3 with common inorganic bases such as alkali metal carbonates proved completely ineffective with water as solvent. Correspondingly, using acetonitrile in place of water under our reaction conditions gave poor yields of arylated indazoles (12% yield of **4o**, with 80% of starting indazole recovered). Sequestration of halide from the palladium catalytic cycle by Ag^+ appears pivotal to achieving arylation at 50 °C on water.

In summary, we have reported the first study of intermolecular direct arylation of indazoles. Using on water reaction conditions, a simple and efficient protocol has been developed that produces diverse C3-arylated indazoles under notably mild conditions.

Acknowledgment. We thank Novartis, The EU (Marie Curie scholarship for S.O.), and the EPSRC (Leadership Fellowship to M.F.G.) for funding. We also thank the EPSRC mass spectrometry service at the University of Swansea and Dr. Fraser White (School of Chemistry, University of Edinburgh) for assistance with X-ray crystallography. Mr. Didier Pintori (School of Chemistry, University of Edinburgh) is thanked for additional experiments.

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.

OL902537D

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