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A Practical Mild, One-Pot, Regiospecific Synthesis of 2,3-Disubstituted Indoles via Consecutive Sonogashira and Cacchi Reactions

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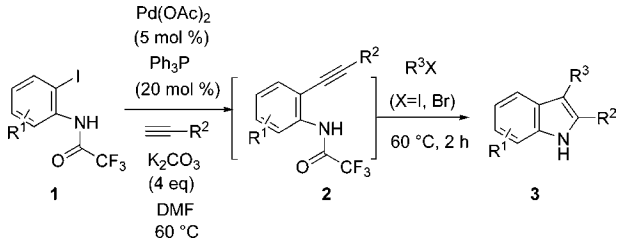
ABSTRACT

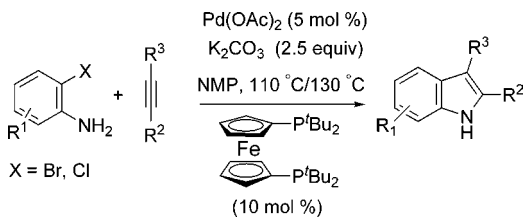


A practical one-pot, regiospecific three-component process for the synthesis of 2,3-disubstituted indoles was developed via consecutive Pd-catalyzed Sonogashira coupling, amidopalladation, and reductive elimination.

The indole nucleus is a prominent structural motif found in numerous natural products and synthetic compounds with vital medicinal value.[1] The assembly of functionalized indoles has captured the attention of synthetic chemists for decades. Despite the fact that many methodologies have been developed,[2] regioselective formation of indoles with substitutions at C2, C3, and at positions other than C5 remains challenging by classical methods, such as the Fischer indolization.[3]

Driven by the need to develop general and economical processes for the synthesis of indoles with multiple functionalities, we have recently developed a novel Pd-catalyzed regioselective indolization of 2-bromo- or 2-chloroanilines with internal alkynes,[4] based on Larock's original protocol (Scheme 1).[5] Although this is an efficient process, one of the common problems is the removal of the minor regioisomer by nonchromatographic techniques. These consider-

Scheme 1



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(1) For a recent review of indole-containing natural products, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155. (b) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175.

(2) For reviews on indole syntheses, see: (a) *Indoles*; Sundberg, R. J., Ed.; Academic: London, UK, 1996. (b) Sundberg, R. J. Pyrroles and their Benzo Derivatives: Synthesis and Applications. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, UK, 1984; Vol. 4, pp 313−376. (c) For a recent review on Fischer indole synthesis, see: Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.

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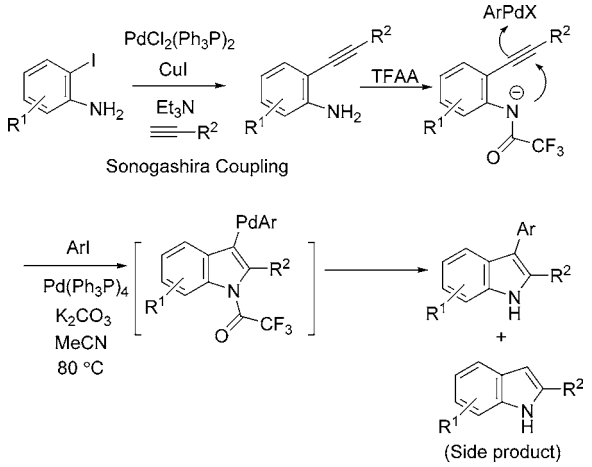
Scheme 2



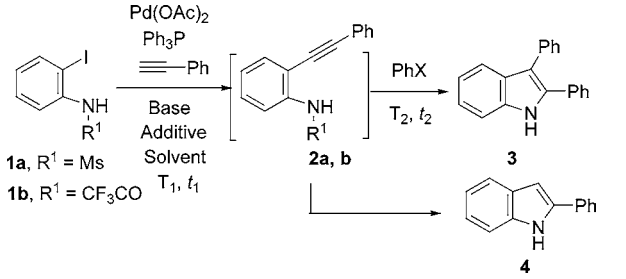
ations led us to investigate the Cacchi reaction (Scheme 2).[6] This sequential process involves (a) the formation of the *o*-alkynylaniline by Sonogashira coupling,[7] (b) acylation with trifluoroacetic anhydride, and (c) cyclization to form the pyrrole ring by aminopalladation and reductive elimination. The major advantage of this method is that the regioselectivity follows from the sequence of events and is unambiguous. The process conditions for each step should be mild, which is desirable in view of the thermal lability of many indole compounds. The drawbacks include the extensive use of costly palladium catalyst, as well as the multistep nature of the operation, which makes this sequence less succinct than the Larock approach. It would help immensely if the Sonogashira/protection/Cacchi domino protocol could be done without isolating the intermediates. Herein we report a practical one-pot process for the preparation of 2,3-disubstituted indoles based on Cacchi's protocol.

Mechanistically, it is possible but not trivial to conduct the Sonogashira coupling and the aminopalladation under the same conditions. To achieve the successful execution of this catalytic process in one pot, it is essential to start with *N*-protected aniline to allow the subsequent cyclization in situ.[6a] However, one must be able to avoid the ready cyclization of *o*-alkynylanilines to 2-substituted indoles, a reaction that is likely to be competitive especially before the RPdX species has been added. Therefore, one prerequisite is to identify proper reaction conditions that would prevent the occurrence of the non-Pd(II) catalyzed nucleophilic cyclization during, or immediately thereafter, the Sonogashira coupling stage. Given that CuI could catalyze this cyclization,[8] we chose to screen conditions without CuI.[9]

Although several copper-free Sonogashira coupling protocols have been reported recently,[10] the reaction rate without copper as additive is usually slower.

We started our investigation of the three-component reaction using 2-iodo-*N*-methanesulfonyl or trifluoroacetylanilide (**1a**,**b**), phenylacetylene, followed, later, by bromobenzene (Scheme 3). Several important parameters were

Scheme 3



examined, including the base, solvent, temperature, and ligand. The results are summarized in Table 1.

The effects of base and solvent were first evaluated. With use of KOAc or K_2CO_3 in DMF, the Sonogashira coupling of **1a** and phenylacetylene was complete at 50 °C in 1 h. However, conversion of **2a** into **3** did not occur at the same temperature after prolonged times (Table 1, entries 1 and 3). In contrast, in the presence of *n*-Bu_4NOAc, conversion of **2a** into **3** proceeded at 50 °C, giving **3** and **4** in the ratio of 68/32 (Table 1, entry 2). Using a combination of tetramethylguanidine (TMG) and *n*-Bu_4NOAc as bases, **2** was converted into **3** within 1 h at 100 °C, but the ratio of **3** vs **4** decreased (Table 1, entry 4). Similarly, with *n*-Bu_4NOAc as base, the Sonogashira coupling of **1b** with phenylacetylene was complete in 19 h at ambient temperature, while the conversion of **2b** into **3** took 7 h at 60 °C, affording **3** and **4** in a 70:30 ratio (Table 1, entry 5). Interestingly, it was found that by using a combination of *n*-Bu_4NOAc and

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(9) Reaction with 5 mol % CuI, $Pd(Ph_3P)_2Cl_2$, and TMG as base in DMF gave the 2-monosubstituted indole as the major product. Extensive dimerization of the alkyne was observed by using 5 mol % CuI, $Pd(Ph_3P)_2Cl_2$, and K_2CO_3 as base in DMF.

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Table 1. Synthesis of 2,3-Disustituted Indoles via the One-Pot, Three-Component Reaction of **1a**,**b**, Phenylacetylene, and Bromobenzene[a]

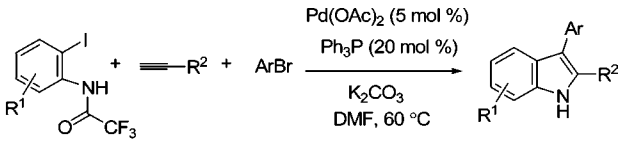
entry	substr.	ligand	base	solvent	T_1/t_1; T_2/t_2 (°C/h)	**2**/**3**/**4**[b]
1	**1a**	Ph_3P	KOAc (3 equiv)	DMF	50/1; 50/17	90/0/10
2	**1a**	Ph_3P	$^nBu_4NOAc$ (3 equiv)	DMF	50/1; 50/17	0/68/32
3	**1a**	Ph_3P	K_2CO_3 (3 equiv)	DMF	50/1; 50/17	56/0/44
4	**1a**	Ph_3P	TMG (2 equiv) + $^nBu_4NOAc$ (1.5 equiv)	DMF	50/1; 100/1	0/58/42
5	**1b**	Ph_3P	$^nBu_4NOAc$ (4 equiv)	DMF	22/19 60/7	0/70/30
6	**1b**	Ph_3P	$^nBu_4NOAc$ (3 equiv) + K_2CO_3 (3 equiv)	ACN	60/2; 60/19	0/94/6
7	**1b**	Ph_3P	K_2CO_3 (3 equiv)	ACN	50/18 ($t_1 + t_2$)	trace
8	**1b**	Ph_3P	K_2CO_3 (4 equiv)	DMF	60/4.5 ($t_1 + t_2$)	0/98/2 (86)[c]
9	**1b**	Ph_3P	K_2CO_3 (4 equiv)	DMF–H_2O (20/1)	60/0.5 ($t_1 + t_2$)	0/97/3 (93)[c]
10[d]	**1b**	Ph_3P	K_2CO_3 (4 equiv)	DMF	60/0.5 ($t_1 + t_2$)	0/98/2 (91)[c]
11[d]	**1b**	(2-furyl)$_3$P	K_2CO_3 (4 equiv)	DMF	60/7 ($t_1 + t_2$)	0/86/14
12[d]	**1b**	(p-F-Ph)$_3$P	K_2CO_3 (4 equiv)	DMF	60/3.3 ($t_1 + t_2$)	complex
13[d]	**1b**	(p-Tol)$_3$P	K_2CO_3 (4 equiv)	DMF	60/0.5 ($t_1 + t_2$)	0/97/3 (89)[c]
14[d]	**1b**	(p-Me-OPh)$_3$P	K_2CO_3 (4 equiv)	DMF	60/23 ($t_1 + t_2$)	0/100/0 (86)[c]

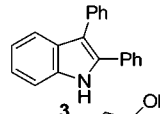
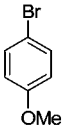
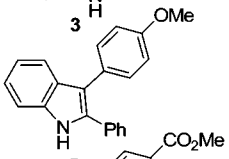
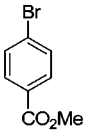
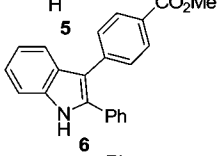
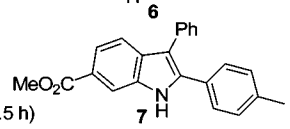
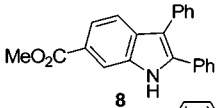
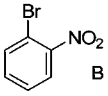
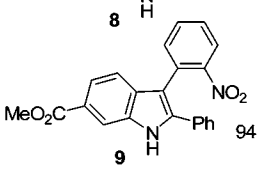
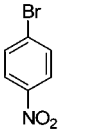
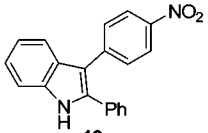
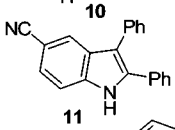
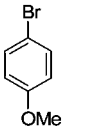
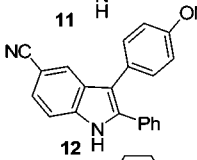
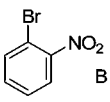
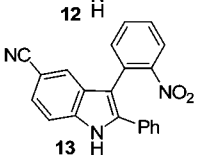
[a] All the reactions were run by mixing 5 mol % $Pd(OAc)_2$, 20 mol % phosphines, 1.2 equiv of the alkyne, and 1.0 equiv of **1a**,**b** in DMF or ACN (c = 0.2 M). 1.2 equiv of bromobenzene was added once the iodoanilide was consumed completely. [b] Measured by HPLC at a wavelength of 248 μm. [c] Solution yields (measured by HPLC). [d] The reaction was performed under the same conditions except that bromobenzene was added at the beginning.

K_2CO_3 as bases in acetonitrile, the conversion of **1b** into **2b**, and **2b** into **3** at 60 °C was completed in 2 and 19 h, respectively. In this case, **3** and **4** was obtained in the ratio of 94:6 (Table 1, entry 6). With K_2CO_3 as the only base in acetonitrile, **2b** was not formed, probably due to the poor solubility of K_2CO_3 in this solvent (Table 1, entry 7). Indeed, replacing acetonitrile with DMF, the reaction proceeded smoothly at 60 °C. Formation of **2b** was complete in 1.5 h while the conversion of **2b** into **3** took 3 h, providing **3** and **4** in ratio of 98:2 (Table 1, entry 8). The advantage of using the trifluoroacetyl as the protecting group is the ready hydrolysis of the product in situ. Addition of small amounts of H_2O, ranging between 1 and 6 equiv, does not affect the reaction rate or the product ratio (Table 1, entry 9) and effects the desired hydrolysis.

On the basis of these initial results, it was concluded that the optimal conditions for this one-pot process include the following: (a) use of trifluoroacetyl as the protecting group of the nitrogen, (b) use of K_2CO_3 as base and DMF as solvent, and (c) reaction temperature of 60 °C. Alternatively, the process can be performed in acetonitrile by using the combination of n-Bu_4NOAc and K_2CO_3 as bases.

Table 2. Synthesis of 2,3-Disustituted Indoles via the One-Pot, Three-Component Sonogashira–Cacchi Domino Reaction[a]



entry	starting materials: alkynes	starting materials: ArBr	Conditions (Time)	product	yield (%)[b]
1	Ph	PhBr	A (0.5 h)	 **3**	91
			B (4.5 h)		86
2	Ph		A (1 h)	 **5**	60
3	Ph		B (2.5 h)	 **6**	85
4	*p*-Tol	PhBr	A (3.5 h)	 **7**	82
5	Ph	PhBr	A (5 h)	 **8**	86
6	Ph		B (3.8 h)	 **9**	94
7	Ph		B (8 h)	 **10**	98
8	Ph	PhBr	A (12.5 h)	 **11**	91
9	Ph		A (1.5 h)	 **12**	78
10	Ph		B (12.5 h)	 **13**	80

[a] Method A: The reactions were run by mixing 5 mol % $Pd(OAc)_2$, 20 mol % Ph_3P, 1.2 equiv of the alkyne, 1.2 equiv of the aryl bromide, and 1.0 equiv of the anilide in DMF (c = 0.2 M) at 60 °C. Method B: The reactions were run by adding 1.2 equiv of arylbromide after the iodoanilide was consumed completely. [b] Solution assays (HPLC).

To further simplify the procedure, bromobenzene was added from the beginning, in a one-pot reaction, thus eliminating the need to monitor the progress of the Sonogashira coupling before proceeding to the next step. Surpris-

ingly, the overall reaction rate is significantly enhanced (Table 1, entry 10) and Sonogashira reaction of the bromobenzene is not a problem. The mechanism for this accelerating effect is not yet understood. Several other ligands were briefly evaluated for comparison (Table 1, entries 11−14). Electron-deficient ligands appear to slow the formation of the desired product, mainly due to inefficient Cacchi cyclization. The reaction can be extended to a variety of aryl halides. In the coupling with aryl bromides containing electron-withdrawing fuctionalities, the sequential procedure was applied, to avoid competing oxidative addition of the latter. To evaluate the scope of this one-pot process, a variety of indoles were synthesized. The results are summarized in Table 2. In all cases examined, excellent yields were obtained. The reaction times described in the table reflect closely the reaction rate in each case since all the reactions were carefully monitored.

Substitutions on all three components have an effect on the reaction rate. The one-pot coupling of the 2-iodoanilide **1b** with phenylacetylene and 4-bromoanisole is complete within 1 h to give **5** in 60% solution yield, while the same reaction with methyl (4-bromo)benzoate is complete in 2.5 h, affording **6** in 85% yield (entries 2 and 3, Table 2). With *p*-tolylacetylene, the Sonogashira coupling was very sluggish under the same conditions and resulted in the formation of unidentified side products. In this case, by using Cs_2CO_3 as base in place of K_2CO_3, the reaction proceeded cleanly in 3.5 h, and in 83% yield (entry 4, Table 2). With an electron-withdrawing group at the para position of the iodide, the Sonogashira coupling, as well as the whole reaction, took longer (entries 5 and 6, Table 2).

In addition, when a nitrile group was present at the para position of the amide, the cyclization became extremely sluggish due to the decreased nucleophilicity of the nitrogen toward Pd(II) (entries 8−10, Table 2).

In summary, we have developed a practical and economical one-pot process for synthesis of 2,3-disubstituted indoles based on Cacchi's original protocol. This Pd-catalyzed domino indolization procedure allows rapid access to a variety of 2,3-disubstituted indoles regiospecifically under fairly mild conditions.

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

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