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2-Aryl and 2-Heteroaryl Indoles from 1-Alkynes and *o*-Iodotrifluoroacetanilide through a Domino Copper-Catalyzed Coupling–Cyclization Process†

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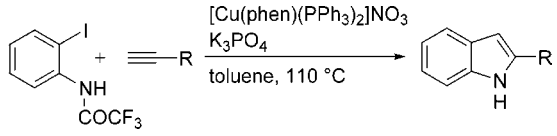
ABSTRACT



A general method for the synthesis of 2-aryl and 2-heteroaryl indoles from aryl iodides and 1-alkynes through a domino copper-catalyzed process is reported. The best results have been obtained with $[Cu(phen)(PPh_3)_2]NO_3$ in the presence of K_3PO_4 in toluene or dioxane at 110 °C. 2-Aryl and 2-heteroaryl indoles can also be isolated in good yields by using catalysts derived from CuI and PPh_3 in dioxane at 110 °C.

The indole nucleus is present in a number of bioactive molecules,[1] and this, undoubtedly, plays a key role in the continued search for the development of new, efficient, and selective protocols for its construction. Classical methods include (to name a few) the Fischer indole synthesis, the Batcho−Limgruber synthesis from *o*-nitrotoluenes and dimethylformamide acetals, the Gassman synthesis from *N*-haloanilines, the reductive cyclization of *o*-nitrobenzyl ketones, and the Madelung cyclization of *N*-acyl-*o*-toluidines.[2] More recently, transition-metal-based reactions, particularly palladium-catalyzed protocols[3] (some of them developed in our laboratories),[3o] have been widely employed providing increased functional group tolerance and improved yields. Surprisingly, little attention has been paid to copper-based protocols. A copper-assisted synthesis has been described in which indoles are prepared upon treatment of *o*-(trimethylsilylethynyl)anilines with 2 equiv of CuI.[4] Formation of indole in moderate yield was observed in the reaction of *o*-ethynyltrifluoroacetanilide with 3.2 equiv of

† Dedicated to Professor Luciano Caglioti on the occasion of his 70th birthday.

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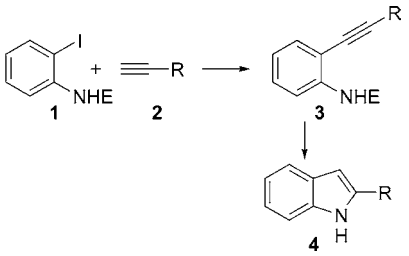
$Cu(OAc)_2$.[5] *N*-Methanesulfonyl and *N*-ethoxycarbonyl derivatives of *o*-alkynylanilines were converted into the corresponding protected indoles through a copper-catalyzed cyclization in the presence of $Cu(OAc)_2$ and $Cu(OTf)_2$.[6] An example of cyclization of *o*-alkynylaniline to prepare a free N−H indole was described, but the target compound was obtained in good yield only in the presence of the moisture-sensitive $Cu(OTf)_2$.[6]

Because of the economic attractiveness of copper-based methods (and hence of their potential in large-scale reactions) and stimulated by the growing interest in copper-catalyzed procedures,[7] we became interested in the development of a copper-catalyzed synthesis of indoles. In particular, we focused our attention on the preparation of 2-substituted free N−H indoles from aryl iodides containing an ortho nitrogen nucleophile and 1-alkynes through an integrated process involving two basic steps: coupling of *o*-iodoaniline (or a suitable derivative) with 1-alkynes followed by a cyclization step (Scheme 1).

Scheme 1

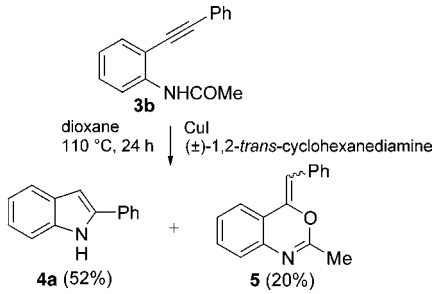


Here, we report the results of this study.

Since it is known that aryl iodides and 1-alkynes can readily give coupling products through copper-catalyzed reactions,[7a,b] preliminary studies explored the feasibility of the copper-catalyzed cyclization of *o*-(phenylethynyl)aniline **3a** (R = Ph, E = H). Treatment of 1 equiv of **3a** [prepared from **1a** (E = H) and phenylacetylene via Sonogashira coupling][8] with 5% of CuI, 2 equiv of K_3PO_4 in dioxane at 110 °C for 24 h gave only trace amounts, if any, of the desired 2-phenylindole **4a**. The addition of a chelating ligand for copper such as (±)-1,2-*trans*-cyclohexanediamine (CHDA), which has been reported by Buchwald and co-workers[7l] to provide more active catalysts, led to the isolation of **4a** in 50% yield (24 h; **3a** was recovered in 45% yield).

Surmising that a more acidic N−H bond might favor the cyclization reaction generating, under basic conditions, a stronger anionic nitrogen nucleophile (or that the nucleophilic attack of nitrogen could be assisted by proton removal in the transition state leading to the cyclization adduct), we attempted the use of the acetamido derivative **3b** (R = Ph; E = COMe). However, despite a higher conversion, essentially the same yield of **4a** (52%) was attained. In fact, its formation was paralleled by the formation of a 20% yield of the alkylidenebenzoxazine **5** (its stereochemistry was not established) derived from a competing *O*-cyclization process (Scheme 2).

Scheme 2



Only upon going to the trifluoroacetamido derivative **3c** (R = Ph, E = $COCF_3$)[9] did the reaction afford **4a** in high yield (83%) after 1.5 h. No evidence of the *O*-cyclization byproduct was attained in this case.

To check the role of copper in this cyclization reaction, **3c** was reacted under the above conditions omitting CuI and the ligand. The indole product was isolated in 13% yield after 1.5 h (**3c** was recovered in 57% yield) and only a moderate increase in the yield was obtained by prolonging the reaction time to 24 h (**4a** was isolated in 30% yield and **3c** was recovered in 42% yield), thus emphasizing the remarkable role of copper in the cyclization step.

Other *o*-alkynyltrifluoroacetanilides, containing a variety of aryl and alkyl substituents, were then converted into the corresponding indole products in good to high yields (Table 1) in the presence of CuI, (±)-1,2-*trans*-cyclohexanediamine,

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Table 1. Copper-Catalyzed Cyclization of *o*-Alkynyltrifluoroacetanilides **3** to 2-Substituted Indoles **4**[a]

entry	*o*-alkynyltrifluoroacetanilide **3**, R	ligand	yield (%) of **4**[b]
1	Ph	CHDA[c]	83
2	Ph	PPh_3	82[d]
3	$CH_2NHCOEt$	CHDA[c]	49
4	*p*-NO_2-C_6H_4	CHDA[c]	60
5	*o*-Br-C_6H_4	CHDA[c]	88
6	*n*-C_5H_{11}	CHDA[c]	84

[a] Unless otherwise stated, reactions were carried out on a 0.5 mmol scale in 2 mL of dioxane by using 1 equiv of *o*-alkynyltrifluoroacetanilide **3**, 5 mol % of CuI, 10 mol % of (±)-1,2-*trans*-cyclohexanediamine, and 2 equiv of K_3PO_4 at 110 °C for 1.5 h. [b] Yields are given for isolated products. [c] CHDA= (±)-1,2-*trans*-cyclohexanediamine. [d] In the presence of 10 mol % of PPh_3.

and K_3PO_4. The use of PPh_3 as the ligand proved equally effective (Table 1, entry 2).

With an efficient protocol for the copper-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides to free N−H indoles in hand, we next set out to develop appropriate conditions to allow for their preparation from *o*-iodotrifluoroacetanilide **1b** (E = $COCF_3$) and 1-alkynes in a single operative step.

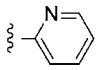
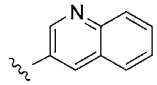
In our first attempt, **1b** was reacted with phenylacetylene in the presence of CuI, (±)-1,2-*trans*-cyclohexanediamine, and K_3PO_4 in dioxane at 110 °C for 24 h. However, 2-phenyl indole was isolated in only 30% yield. The use of PPh_3 as the ligand provided a slightly better result (34% yield). Therefore, we decided to examine some additional variables. It was then observed that high yields of 2-phenyl indole could be obtained by using 15 mol % of CuI in the presence of 30% PPh_3 in dioxane (2-phenyl indole was isolated in 88% yield). Replacement of dioxane by more polar solvents such as DMSO or DMA was found to be detrimental (43 and 31% yields, respectively) while a good yield (71%) was obtained in toluene.

We extended our optimization studies to other copper catalysts. In particular, we explored the use of some of the catalysts recently developed by Venkataraman and coworkers[7c] and found that high yields could be obtained with 10 mol % of $[Cu(phen](PPh_3)_2]NO_3$ and K_3PO_4 in toluene or dioxane at 110 °C (78 and 75% yields, respectively). The use of Cs_2CO_3 as the base produced lower yields (49% in toluene; 41% in dioxane).

After observing that $[Cu(phen)(PPh_3)_2]NO_3$ is superior to the CuI/(±)-1,2-*trans*-cyclohexanediamine catalyst system in the domino process with *o*-iodotrifluoroacetanilide **1b**, we went back and examined its utilization in the cyclization of *o*-(phenylethynyl)aniline **3a**. In case of success, the development of a domino process using *o*-iodoaniline would be feasible. Notably, it afforded **4a** in only 30% yield (**3a** was recovered in 45% yield; toluene, 100 °C, 24 h—with CuI/(±)-1,2-*trans*-cyclohexanediamine **4a** was isolated in 50% yield).

Therefore, **1b** was selected as the building block and the procedure based on the use of $[Cu(phen](PPh_3)_2]NO_3$ (procedure A) was largely employed when the process was extended to include other 1-alkynes, though the use of readily available CuI and PPh_3 (procedure B) was also explored. Our preparative results are summarized in Table 2.

Table 2. Copper-Catalyzed Synthesis of 2-Substituted Indoles from *o*-Iodotrifluoroacetanilide **1b** and 1-Alkynes **2**[a]

entry	1-alkyne **2** R	proc.	solvent	time (h)	**4** (%)[c]	**3** (%)[c]
1	Ph	A	toluene	12	78	-
2	Ph	A	dioxane	24	75	21
3	*p*-MeCO-C_6H_4	A	toluene	20	96	-
4	*p*-MeCO-C_6H_4	B	dioxane	24	73	25
5	*p*-Cl-C_6H_4	A	toluene	6	80	-
6	*p*-Cl-C_6H_4	B	dioxane	24	66	31
7	*p*-MeCONH-C_6H_4	A	toluene	5	71	-
8	*p*-MeCONH-C_6H_4	B	dioxane	24	60	32
9	*p*-MeO-C_6H_4	A	toluene	6	81	-
10	*p*-MeO-C_6H_4	B	dioxane	24	78	10
11	*m*-MeO-C_6H_4	A	toluene	6	92	-
12	*o*-MeO-C_6H_4	A	toluene	2	62	-
13	3,5-Me_2-C_6H_3	A	toluene	3	68	-
14	*p*-MeOOC-C_6H_4	A	toluene	3	93	-
15	*p*-MeOOC-C_6H_4	B	dioxane	24	85	12
16	*p*-OHC-C_6H_4	A	toluene	8	57	-
17	*p*-NO_2-C_6H_4	A	toluene	5	62	-
18	*n*-Bu	A	toluene	16	11	10[d]
19		A	toluene	6	65	-
20		A	toluene	20	89	-

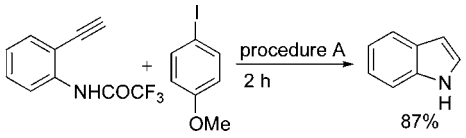
[a] Reactions were carried out on a 0.5 mmol scale in 2 mL of solvent at 110 °C. [b] Procedure A: 1 equiv of *o*-iodotrifluoroacetanilide **1b**, 1 equiv of 1-alkyne **2**, 10 mol % of $[Cu(phen](PPh_3)_2]NO_3$, 2 equiv of K_3PO_4. Procedure B: 1 equiv of *o*-iodotrifluoroacetanilide **1b**, 1 equiv of 1-alkyne **2**, 15 mol % of CuI, 30 mol % of PPh_3, 2 equiv of K_3PO_4. [c] Yields are given for isolated products. [d] **1b** was recovered in 13% yield.

Under these conditions, the reaction proceeds very smoothly and appears to tolerate a wide range of functionalized 1-alkynes, including those containing ether, amide, aldehyde, ester, nitro, and heterocyclic groups. Only 1-hexyne, among the alkynes that we have investigated, produced the desired indole product in low yield (Table 2, entry 18). As the cyclization of the corresponding preformed coupling derivative affords 2-butyl indole in high yield (Table 1, entry 6), it seems that in this case the efficiency of the domino process

is primarily limited by a sluggish coupling step. No attempts have been made to optimize the copper-catalyzed reaction of 1-hexyne with **1b**.

When *o*-ethynyltrifluoroacetanilide was reacted with *p*-iodoanisole (procedure A) to evaluate the feasibility of a method in which 2-substituted indoles could be prepared from the same acetylenic building block and various aryl and vinyl halides or triflates,[10] the cyclization of *o*-ethynyltrifluoroacetanilide to indole (isolated in 87% yield) was found to be faster than its coupling with *p*-iodoanisole and no 2-substituted indole was formed (Scheme 3).

Scheme 3



As for the mechanism, the coupling step should proceed according to the proposal of Miura and co-workers for the CuI-catalyzed reaction of 1-alkynes with aryl and vinyl iodides.[8] The cyclization reaction most probably involves the intramolecular nucleophilic attack of the nitrogen nucleophile across the carbon−carbon triple bond activated by the formation of an η^2-alkyne-copper complex.[11] The trifluoroacetyl group plays an important role in favoring the cyclization step but, unlike the acetyl group, does not afford *O*-cyclization products (at least with the examples that we have investigated). It is also readily removed from indole derivatives under reaction conditions and/or during workup so that the procedure affords free N−H indoles avoiding cumbersome deprotecting protocols.

In conclusion, we have established that $[Cu(phen)(PPh_3)_2]NO_3$ and CuI/PPh_3 serve as efficient catalysts for the preparation of 2-aryl and 2-heteroaryl indoles from *o*-iodotrifluoroacetanilide and 1-alkynes. Our method compares very favorably to the known palladium- and copper-based processes for the preparation of this class of compounds.

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Supporting Information Available: A complete description of experimental details, table with data for optimizing conditions for the preparation of 2-phenyl indole from *o*-iodotrifluoroacetanilide **1b** and phenylacetylene, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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