Palladium-Catalyzed Synthesis of Free-NH Indole 2-Acetamides and Derivatives from Ethyl 3-(*o*-Trifluoroacetamidoaryl)-1-propargylic Carbonates

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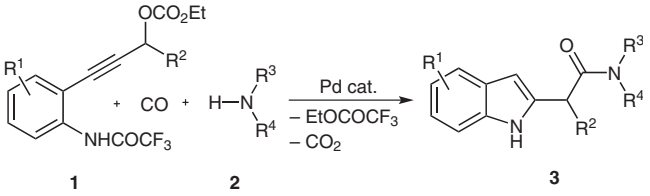
Abstract: The reaction of ethyl 3-(*o*-trifluoroacetamidoaryl)-1-propargylic carbonates with primary or secondary amines in the presence of $Pd_2(dba)_3$, dppf, and carbon monoxide in THF at 80 °C provides ready access to free-NH indole 2-acetamides. The reaction can be applied to the synthesis of free-NH indole 2-acetic acid methyl esters.

Key words: palladium, carbonylation, indoles, alkynes, propargylic esters

The indole moiety is prevalent in a vast array of biologically active natural and unnatural compounds. Consequently, the development of efficient methods to construct functionalized indole scaffolds is a subject of great interest in drug discovery. Utilization of palladium catalysis has provided remarkable advances in this area, greatly expanding the generality of the approaches to this class of compounds both via functionalization of preformed indole rings and via cyclization of suitable precursors.[1] In this context, we became interested in the development of a new, straightforward palladium-catalyzed approach to the synthesis of indole 2-acetamides. These indole derivatives exhibit valuable biological activities[2] and are useful synthetic intermediates.[3] However, the number of syntheses available for their preparation is quite limited. Traditional methods rely on the reaction of indole 2-acetic acid derivatives with amines,[3a,4] or on the reaction of anions of 2-alkylindoles with alkylisocyanates.[5] In both cases, access to the indole 2-acetamides depends on the availability of preformed indole precursors. Their direct preparation from acyclic compounds has not been described.

Recently, we reported on the palladium-catalyzed synthesis of 2-substituted indoles employing ethyl 3-(*o*-trifluoroacetamidoaryl)-1-propargylic carbonates.[6] This reaction is based on an intramolecular N-cyclization leading to π-allylic palladium complexes that are converted into the final products through nucleophilic attack. Therefore, we decided to examine the use of our indole synthesis for the direct construction of the indole 2-acetamido structural motif.

Herein, we report that subjecting ethyl 3-(*o*-trifluoroacetamidoaryl)-1-propargylic carbonates **1** to carbon monoxide, in the presence of a palladium catalyst and either primary or secondary amines, provides ready access to free-NH indole 2-acetamides **3** (Scheme 1).



1 2 3

Scheme 1

Compounds **1** were usually prepared by a two-step process from *o*-(iodo)trifluoroacetanilides via Sonogashira cross-coupling with propargylic alcohols, followed by an esterification step.[7]

We started our study by examining the conversion of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate (**1a)** into the indole 2-acetamide **3a**. Our optimization work using $Pd_2(dba)_3$ in THF at 80 °C, varying the CO pressure, ligands, and the concentration of the reagents, is summarized in Table 1.

When the reaction was carried out in the presence of 1,1′-bis(diphenylphoshino)ferrocene (dppf) in 5 mL of THF under 1 atm of CO, the 2-aminomethylindole **4a** was isolated in 90% yield and no amide derivative **3a** was formed (Table 1, entry 1). Increasing the CO pressure to 20 atm led to the isolation of **3a** in 64% yield, although **4a** was still obtained in significant yield (Table 1, entry 2). Under 40 atm of CO, the formation of **4a** was completely suppressed. Nevertheless, essentially the same yield of **3a** was obtained (Table 1, entry 4). Pleasingly, performing the reaction under 40 atm of CO in 10 mL of THF allowed for the isolation of **3a** in 83% yield (Table 1, entry 5). We also examined other bidentate phosphine ligands, but dppf proved to be superior to all of them, at least with our model system. No indole product was formed with bis(diphenylphosphino)methane (dppm; Table 1, entry 6), while **3a** was isolated in 56% yield employing 1,3-bis(diphenylphosphino)propane (dppp; Table 1, entry 7). The yield increased to 61% using 1,4-bis(diphenylphosphino)butane (dppb; Table 1, entry 8), still lower however than the yield obtained with dppf.

The synthetic scope of the reaction was the explored using $Pd_2(dba)_3$, dppf, and 40 atm of CO in 10 mL of THF at 80 °C.[8] Nevertheless, other substrates gave similar or better results in the presence of dppb (*vide infra*). Therefore,

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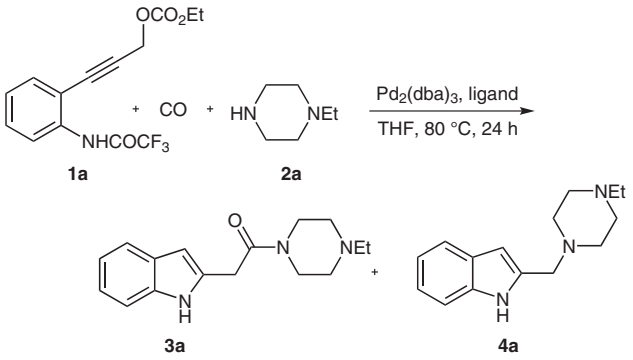
Table 1 Optimization of Reaction Conditions[a]



Entry	Ligand	CO (atm)	THF (mL)	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	dppf	1	5	–	90
2	dppf	20	5	64	22
3	dppf	20	10	61	9
4	dppf	40	5	63	–
5	dppf	40	10	83	–
6	dppm	40	10	–	–[c]
7	dppp	40	10	56	–
8	dppb	40	10	61	–

[a] Reagents and conditions: **1a** (0.3 mmol), **2a** (3 equiv), $Pd_2(dba)_3$ (0.025 equiv), ligand (0.05 equiv), 80 °C, 24 h.
[b] Yield of isolated product.
[c] **1a** was recovered in 77% yield.

it seems advisable that the efficiency of the ligands be evaluated each time.

As shown by the results listed in Table 2, a variety of ethyl 3-(*o*-trifluoroacetamidoaryl)-1-propargylic carbonates and primary or secondary amines were successfully converted into the corresponding indole 2-acetamides. Substitution on the aryl fragment and/or the propargylic carbon was tolerated. Limitations, however, appear to arise with some primary amines. While the bulky *tert*-butylamine and cyclohexylamine gave indoles **3e** and **3f** in good yields (Table 2, entries 5 and 6), treatment of **1a** with aniline and benzylamine met with failure. Indole products were formed only in trace amounts, if any. Deacylated propargylic esters **5** and urea[9] derivatives **6** were among the main products characterized (Figure 1). Apparently, using more hindered primary amines had a beneficial effect on the reaction outcome by limiting these side reactions.

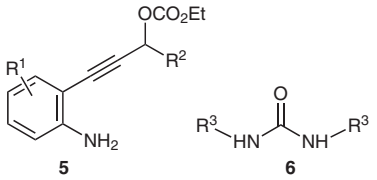


Figure 1

The isolation of **5** without any evidence of indole formation is an indirect proof of the crucial role of the trifluoroacetamido group in this chemistry.[6] Most probably, the nucleophilicity of the free amino group is too low to perform the intramolecular attack on the allenylic/propergylic palladium complex that is required to construct the indole ring (*vide infra*). The acidity of the nitrogen–hydrogen bond might favor the formation of a stronger, anionic nucleophile. Furthermore, the trifluoroacetamido group is readily removed from the indole derivatives under the reaction conditions and/or during work-up, so that the procedure affords free-NH indoles, avoiding cumbersome deprotecting protocols.

We next briefly investigated an extension of this protocol to the preparation of indole 2-acetic acid methyl esters **7**.[10] **7a** and **7b** were isolated in good yields using a large excess of methanol. Reactions (on a 0.3 mmol scale) were carried out under the conditions shown in Scheme 2 (adding 1 mL of MeOH to 10 mL of THF). However, when the preparation of **7c** was attempted, the desired indole derivative was isolated only in 11% yield under these conditions – the main product being the ether **8c** (43% yield; Figure 2). Limiting the excess of methanol to 20 equivalents led to the isolation of **7c** in 46% yield.

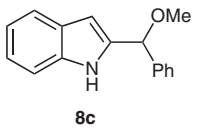
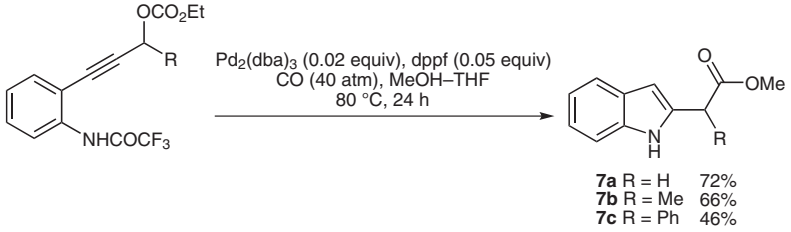


Figure 2



Scheme 2

Table 2 Synthesis of Indole 2-Acetamides **3**[a]

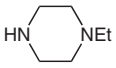
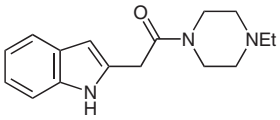
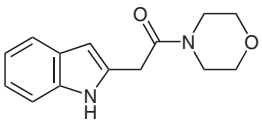
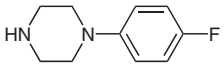
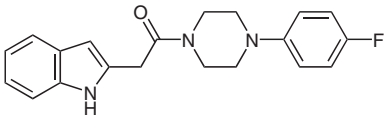
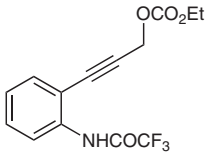
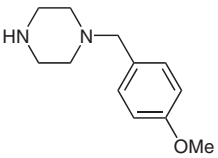
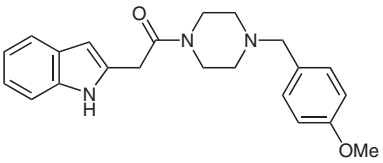
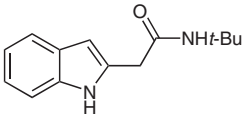
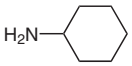
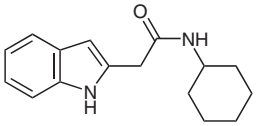
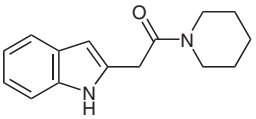
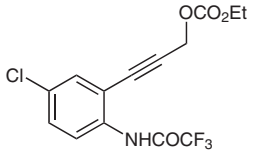
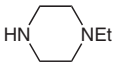
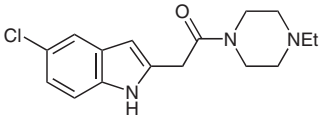
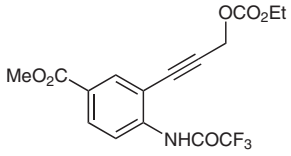
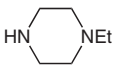
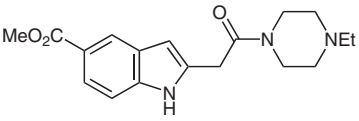
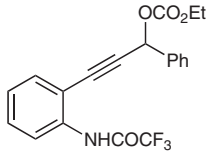
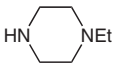
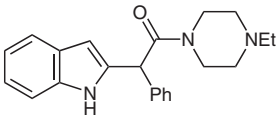
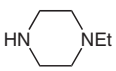
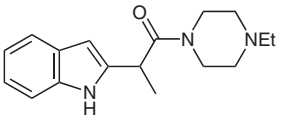
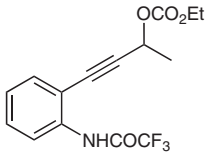
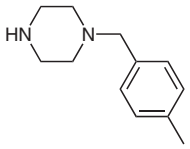
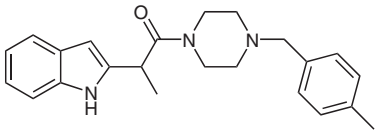
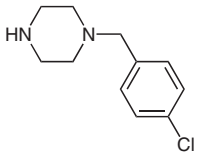
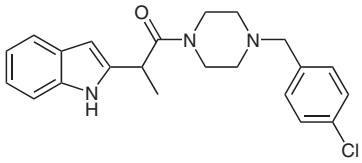
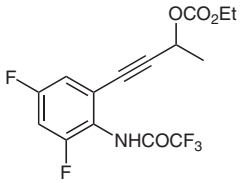
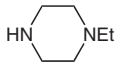
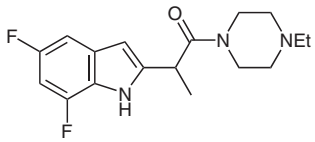
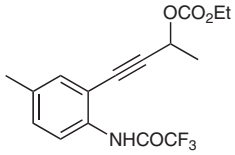
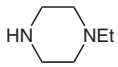
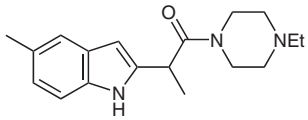
Entry	Propargyl carbonate **1**	Amine **2**	Product **3**		Yield of **3** (%)[b]
1				**3a**	83
2				**3b**	68
3				**3c**	75
4	 **1a**			**3d**	80
5		NH_2t-Bu		**3e**	75
6				**3f**	68
7				**3g**	73
8	 **1b**			**3h**	62
9	 **1c**			**3i**	75
10	 **1d**			**3j**	50
11				**3j**	72[c]
12				**3k**	19
13				**3k**	81[c]

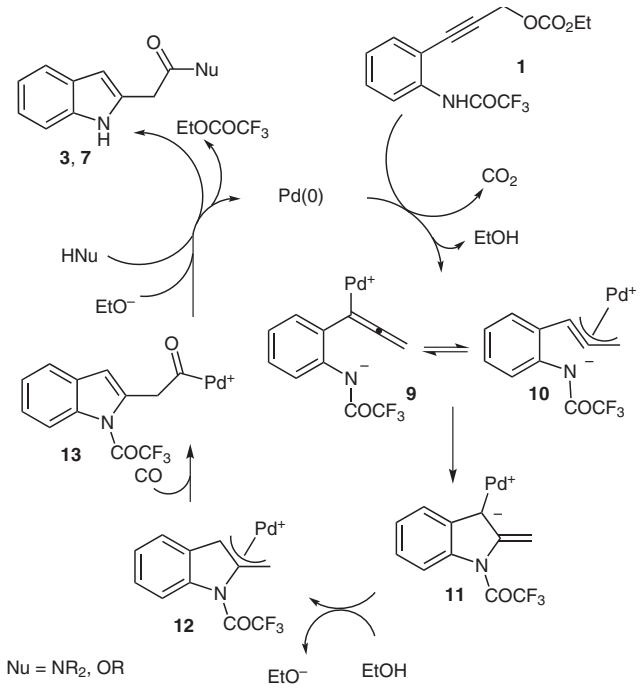
Table 2 Synthesis of Indole 2-Acetamides **3**[a] (continued)

Entry	Propargyl carbonate **1**	Amine **2**	Product **3**		Yield of **3** (%)[b]
14	 **1e**			**3l**	81[c]
15				**3m**	74[c]
16	 **1f**			**3n**	54[c]
17	 **1g**			**3o**	92[c]

[a] Reagents and conditions: **1** (0.3 mmol), THF (10 mL), 80 °C, CO (40 atm), **2** (3 equiv), $Pd_2(dba)_3$ (0.025 equiv), dppf (0.05 equiv), 24 h.
[b] Yield of isolated product.
[c] With dppb.

A plausible rationale for this indole synthesis considers the following basic steps (Scheme 3): (a) initial reaction of the palladium complex with **1** to give the σ-allenyl–palladium complex **9** that would be in equilibrium with the π-propargylic palladium intermediate **10**; (b) intramolecular nucleophilic attack of the nitrogen on the central carbon of the allenylic/propargylic palladium complex; (c) protonation of the resultant carbene **11**; (d) reaction of the π-allylic–palladium complex **12** with carbon monoxide (capture of **12** by nitrogen or oxygen nucleophiles leads to the formation of **4** and **8**); (e) intermolecular nucleophilic attack of the nucleophile on the resultant carbonyl-containing intermediate **13** to afford the indole product and regenerate the active palladium catalyst.

In summary, we have reported a new synthesis of indole 2-acetamides that can be a valid alternative to known procedures based on the functionalization of preformed indole precursors. The reaction was found to be applicable to the preparation of indole 2-acetic acid methyl esters.



Scheme 3

Acknowledgements

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References and Notes

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(7) Compounds **1b**, **1c** and **1f** were prepared via Sonogashira cross-coupling of *o*-iodoanilines with the THP derivative of propargyl alcohol. The cross-coupling products were treated with $(CF_3CO)_2O$. The resultant trifluoroacetamido derivatives were deprotected and subjected to ethyl chlorocarbonate to give the title propargylic esters.

(8) **Typical Procedure for the Preparation of Free-NH Indole 2-Acetamides (3):** A stainless steel reaction vessel was charged with **1a** (94.5 mg, 0.3 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), dppf (8.3 mg, 0.015 mmol), **2d** (185.7 mg, 0.9 mmol), and anhydrous THF (10 mL). The reactor was pressured to 40 atm with CO, warmed to 80 °C, and stirred for 24 h. After cooling and eliminating CO, the volatile materials were evaporated at reduced pressure and the residue was purified by chromatography on neutral aluminum oxide (Brockmann 1; *n*-hexane–EtOAc, 90:10→70:30) to afford **3d** (87 mg, 80% yield); viscous oil; IR (KBr): 3296, 3064, 2989, 2929, 2852, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.36 (br s, 1 H), 7.59–7.58 (m, 1 H), 7.36–7.34 (m, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 7.18–7.12 (m, 2 H), 6.90 (d, *J* = 8.5 Hz, 2 H), 6.31 (s, 1 H), 3.90 (s, 2 H), 3.84 (s, 3 H), 3.69–3.68 (m, 2 H), 3.58–3.56 (m, 2 H), 3.44 (s, 2 H), 2.43–2.40 (m, 2 H), 2.37–2.35 (m, 2 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 168.4, 159.0, 136.5, 132.0, 130.4, 129.6, 128.4, 121.6, 120.0, 119.7, 113.8, 111.1, 101.0, 62.1, 55.3, 52.9, 52.5, 46.4, 42.1, 33.3; MS: *m*/*z* (%) = 121 (100) $[M - C_{14}H_{16}N_3O]^+$, 85 (50), 78 (44), 56 (52); Anal. Calcd. for $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; Found: C, 72.63; H, 6.91.

(9) For some recent selected references on the formation of urea derivatives via palladium-catalyzed reactions of amines with carbon monoxide, see: (a) Gabriele, B.; Salerno, G.; Mancuso, R.; Costa, M. *J. Org. Chem.* **2004**, *69*, 4741. (b) Nishiyama, Y.; Kawamatsu, H.; Sonoda, N. *J. Org. Chem.* **2005**, *70*, 2551.

(10) **Typical Procedure for the Preparation of Free-NH Indole 2-Acetic Acid Methyl Esters (7):** A stainless steel reaction vessel was charged with **1e** (99 mg, 0.3 mmol), $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), dppf (8.3 mg, 0.015 mmol), anhydrous THF (10 mL), and MeOH (1 mL). The reactor was pressured to 40 atm with CO, warmed to 80 °C, and stirred for 24 h. After cooling and eliminating CO, the volatile materials were evaporated at reduced pressure and the residue was purified by chromatography on silica gel (*n*-hexane–EtOAc, 80:20) to afford of **7b** (40.2 mg, 66% yield); mp 90–93 °C; IR (KBr): 3356, 2952, 1714, 1458, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (br s, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 8.0 Hz, 1 H), 7.12 (t, *J* = 7.9 Hz, 1 H), 6.41 (s, 1 H), 4.00 (q, *J* = 7.1 Hz, 1 H), 3.77 (s, 3 H), 1.66 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 174.1, 136.7, 136.2, 128.2, 121.9, 120.3, 119.9, 110.9, 100.3, 52.5, 39.2, 17.5; Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; Found: C, 70.83; H, 6.47.