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# 2-Alkylindoles via palladium-catalyzed reductive cyclization of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates

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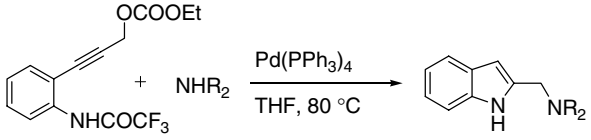
**Abstract**—The reaction of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates with formate anions in the presence of $Pd(PPh_3)_4$ affords 2-alkylindoles in good to excellent yields.


The substituted indole nucleus is an ubiquitous motif in a vast array of biologically active natural and unnatural compounds. In view of this, the construction of this structural unit through cyclization of suitable benzenoid precursors has attracted the interest of many research groups and palladium catalysis has provided an almost unique tool to develop a wide range of synthetic strategies.[1] Based on our continuing interest in indole chemistry,[2] we recently developed a new straightforward approach to the construction of the indole ring system whereby 2-aminomethylindoles can be prepared through the palladium-catalyzed reaction of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate with amines, generating two C–N bonds in a single operative step[3] (Scheme 1).

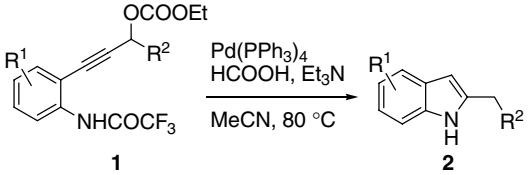
We now report that subjecting ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates **1** to formate anions as a reducing agents in the presence of a palladium catalyst provides a ready access to NH free 3-unsubstituted 2-alkylindoles **2**, including 2-benzylindoles (Scheme 2). Despite the interest for 3-unsubstituted 2-alkylindoles as synthetic intermediates,[4] the number of available routes to this class of compounds is quite limited[5] and the development of new straightforward procedures is desirable.




**Scheme 1.**

The starting ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates **1** were prepared, usually in good to high overall yields, from the corresponding *o*-iodotrifluoroacetanilide through Sonogashira cross-coupling with propargylic alcohols (obtained, in turn, via reaction of aldehydes with commercially available ethynylmagnesium chloride) followed by the reaction of the resultant coupling product with ethyl chloroformate.[6]

Initial cyclization attempts were directed toward finding a general set of reaction conditions that could be applied to a wide range of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates. Compound **1a** ($R^1 = R^2 = H$) was selected as the model system and the following reaction variables were examined: the source of Pd(0) species, the nature of the ligands, the source of




**Scheme 2.**

*Keywords*: Alkylindoles; Cyclization; Palladium; Alkynes; Propargyl esters.
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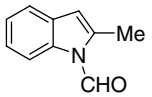
**Table 1.** Palladium precatalysts, formate anions, solvents, and temperature in the cyclization of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate **1a** to 2-methylindole **2a**[a]

| Entry | Palladium precatalyst | Reducing agent | Base | Solvent | *t* (h) | **2a** yield[b] (%) | **3a** yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2/PPh_3$[c] | HCOOK | — | DMF | 4 | 24 | — |
| 2 | $Pd(OAc)_2/PPh_3$[d] | HCOOH | $Et_3N$ | DMF | 4 | 38 | 7 |
| 3 | $Pd(OAc)_2/PPh_3$[d] | HCOOH | $Et_3N$ | THF | 3 | 48 | 5 |
| 4 | $Pd(PPh_3)_4$ | HCOOH | $Et_3N$ | THF | 1.5 | 62 | 12 |
| 5 | $Pd(PPh_3)_4$ | HCOOH | $Et_3N$ | Dioxane | 1 | 56 | 10 |
| 6 | $Pd(PPh_3)_4$ | HCOOH | $Et_3N$ | Toluene | 3 | 48 | 19 |
| 7 | $Pd(PPh_3)_4$ | HCOOH | $Et_3N$ | Dioxane[e] | 1 | 69 | 8 |
| 8 | $Pd(PPh_3)_4$ | HCOOH | $Et_3N$ | MeCN | 1 | 91 | 5 |
| 9 | $Pd_2(dba)_3$/dppe | HCOOH | $Et_3N$ | MeCN | 1 | 84 | — |

[a] Reactions were conducted under argon at 80 °C on a 0.317 mmol scale using 1 equiv of **1a**, 2 equiv of HCOOH, 3 equiv of $Et_3N$ in 2 mL of solvent.
[b] Yields are given for isolated products.
[c] $Pd(OAc)_2$–$PPh_3$ = 1:4.
[d] $Pd(OAc)_2$–$PPh_3$ = 1:2.
[e] In the presence of 1 equiv of $H_2O$.

formate anions, solvents, and temperature. Some of the results of our screening study are summarized in Table 1.

Utilization of HCOOH in the presence of $Et_3N$ proved to be superior to HCOOK (compare entry 1 with entry 2) and $Pd(PPh_3)_4$ gave better results than $Pd(OAc)_2(PPh_3)_2$ (compare entry 3 with entry 4). Under a variety of conditions the main byproduct was *N*-formylindole **3a** which in some cases was isolated in significant yields (entries 4–6).



**3a**

The best result in terms of yield and reaction time was obtained using $Pd(PPh_3)_4$, HCOOH, and $Et_3N$ in MeCN (entry 8). In the presence of dppe-reported to be the best ligand for the palladium-catalyzed reaction of propargyl halides[7] and carbonates[8] with soft nucleophiles and to give more stable π-propargylpalladium

**Table 2.** Palladium-catalyzed reductive cyclization of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates **1** to 2-alkylindoles **2**[a]

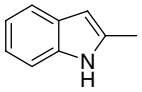
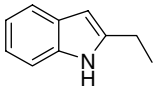
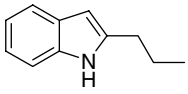
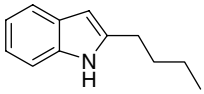
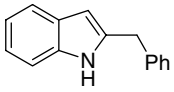
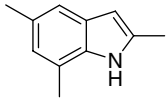
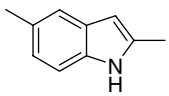
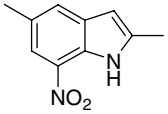
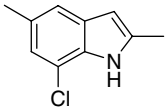
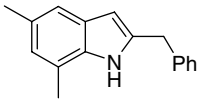
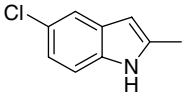
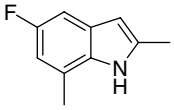
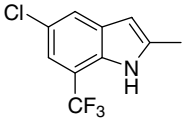
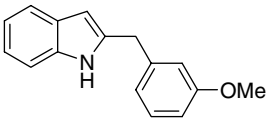
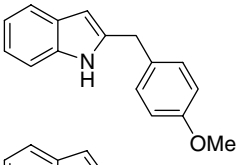
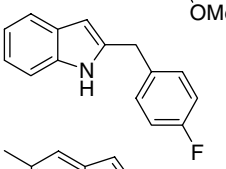
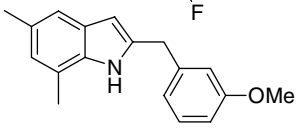
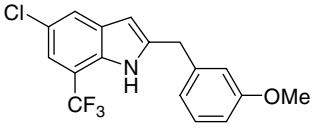
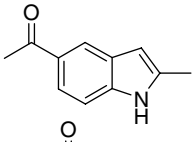
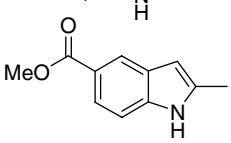
| Entry | **1** | | | *t* (h) | 2-Alkylindole **2** | | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | | | | |
| 1 | H | H | **1a** | 1 |  | **2a** | 91 |
| 2 | H | Me | **1b** | 1 |  | **2b** | 70 |
| 3[b] | H | Et | **1c** | 2 |  | **2c** | 70 |
| 4 | H | *n*-Pr | **1d** | 1 |  | **2d** | 67 |
| 5 | H | Ph | **1e** | 3 |  | **2e** | 75 |
| 6 | 4,6-$Me_2$ | H | **1f** | 1 |  | **2f** | 99 |
| 7 | 4-Me | H | **1g** | 0.5 |  | **2g** | 80 |

**Table 2** (*continued*)

| Entry | 1 | | | *t* (h) | 2-Alkylindole **2** | | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | | | | | |
| 8 | 4-Me, 6-$NO_2$ | H | **1h** | 2 |  | **2h** | 78 |
| 9 | 4-Me, 6-Cl | H | **1i** | 2 |  | **2i** | 51 |
| 10 | 4,6-$Me_2$ | Ph | **1j** | 1 |  | **2j** | 50 |
| 11 | 4-Cl | H | **1k** | 0.5 |  | **2k** | 60 |
| 12 | 4-F, 6-Me | H | **1l** | 1 |  | **2l** | 65 |
| 13 | 4-Cl, 6-$CF_3$ | H | **1m** | 1 |  | **2m** | 86 |
| 14 | H | 3-MeO–$C_6H_4$ | **1n** | 1 |  | **2n** | 75 |
| 15 | H | 4-MeO–$C_6H_4$ | **1o** | 24 |  | **2o** | —[c] |
| 16 | H | 4-F–$C_6H_4$ | **1p** | 1 |  | **2p** | 85 |
| 17 | 4,6-$Me_2$ | 3-MeO–$C_6H_4$ | **1q** | 2 |  | **2q** | 72 |
| 18 | 4-Cl,6-$CF_3$ | 3-MeO–$C_6H_4$ | **1r** | 0.5 |  | **2r** | 85 |
| 19 | 4-MeCO | H | **1s** | 0.66 |  | **2s** | 73 |
| 20 | 4-MeOCO | H | **1t** | 1 |  | **2t** | 70 |

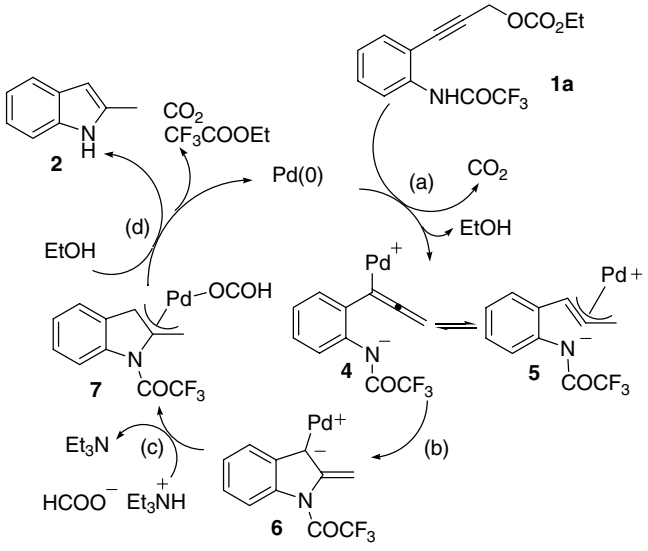
[a] Reactions were conducted under argon at 80 °C on a 0.2–0.3 mmol scale using 1 equiv of **1**, 2 equiv of HCOOH, 3 equiv of $Et_3N$ in 2 mL of MeCN.
[b] Yields are given for isolated products.
[c] The starting material was recovered in 11% yield and the reduction product **4o** was isolated in 38% yield.

complexes,[9] likely intermediates in this type of chemistry (vide infra)—the reaction gave a slightly lower yield (entry 9). Consequently, $Pd(PPh_3)_4$, HCOOH, and $Et_3N$ in MeCN were used when this cyclization to indoles was extended to other ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates[10] (Table 2).

2-Alkylindoles **2** were isolated in good to high yields with a wide range of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonates. The only exception among the substrates that we have investigated is propargyl derivative **1o** (Table 2, entry 15). In this case, no evidence of the desired indole product was attained. The reason of this behavior was not further investigated.

As to the mechanism of this cyclization to indoles, we believe that the reaction proceeds through the basic steps shown in Scheme 3 for **1a**: (a) formation of σ-allenylpalladium complex **4**, in equilibrium with π-propargylpalladium intermediate **5**,[11] via an $S_N2'$reaction of the palladium complex with **1a**, which releases $CO_2$ and the ethoxide anion (this anion formally deprotonates the NH group), (b) intramolecular nucleophilic attack of the nitrogen at the central carbon of the allenyl/propargylpalladium complex,[9,12,13] (c) conversion of the resultant carbene **6** into π-allylpalladium complex **7**, (d) formation of **2** by concerted decarboxylation and hydride transfer to one of the allylic termini of π-allylpalladium complex **8**.[14]

To sum up, we have developed a useful new approach to 2-alkylindoles, usually isolated in good to high yields. The procedure is simple and straightforward, and provides a valuable alternative to the preparation of this class of compounds through the Pd(II)-catalyzed cyclization of *o*-alkynylanilides.[5a] *o*-Alkynylanilides are prepared from *o*-haloanilides and terminal alkynes, and the latter are not always readily available. The required alkyne component for the present cyclization can be readily prepared from ethynylmagnesium chloride and aldehydes.




**Scheme 3.**

## Acknowledgments

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6. *Typical procedure for the preparation of* (**1**). *Sonogashira cross-coupling: o*-Iodotrifluoroacetanilide (1.50 g, 4.76 mmol), $PdCl_2(PPh_3)_2$ (0.067 g, 0.09 mmol) and CuI (0.018 g, 0.09 mmol) were dissolved in 1.5 mL of DMF, 6.0 mL of $Et(i\text{-}Pr)_2N$ and 3.0 mL of $(i\text{-}Pr)_2NH$. The mixture was stirred under argon for 30 min. Then, a solution of 1-(3-methoxyphenyl)-2-propyn-1-ol (0.925 g, 5.71 mmol) in 3.0 mL of $(i\text{-}Pr)_2NH$ was added dropwise in 5 min. The resulting reaction mixture was stirred at room temperature for 12 h. After this time the reaction mixture was diluted with $Et_2O$, washed twice with a saturated $NH_4Cl$ solution, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by chromatography ($SiO_2$, 140 g; *n*-hexane/AcOEt 70/30 v/v) to give 1.492 g (90% yield) of 1-(3-methoxyphenyl)-3-(2-trifluoroacetamido)-2-propyn-1-ol. *Acylation of the cross coupling product*: 1-(3-methoxyphenyl)-3-(2-trifluoroacetamido)-2-propyn-1-ol (1.00 g, 2.86 mmol) and 4-dimethylaminopyridine (0.524 g, 4.3 mmol) were dissolved in 5.0 mL of $CH_2Cl_2$ and stirred at −20 °C for 10 min. Then, a solution of ClCOOEt (0.367 g, 3.4 mmol) in 1.0 mL of $CH_2Cl_2$ was added at the same temperature dropwise in 5 min. The resulting reaction mixture was stirred at −20 °C for 3 h. After this time, the reaction mixture was diluted with AcOEt, washed twice with a HCl 2 N solution

and once with a saturated NaCl solution, dried over $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by preparative chromatography ($SiO_2$, 140 g; *n*-hexane/AcOEt 85/15 v/v) to give 1.107 g (92% yield) of **1n**; mp: 66–68 °C; IR (KBr): 3319, 2987, 1748, 1713, 1379 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.70 (br s, 1H), 8.35 (d, $J = 8.2$ Hz, 1H), 7.51 (dd, $J_1 = 9.1$ Hz, $J_2 = 1.4$ Hz, 1H), 7.43 (t, $J = 8.2$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz 1H), 7.25–7.10 (m, 3H), 6.95 (dd, $J_1 = 8.2$ Hz, $J_2 = 1.8$ Hz, 1H), 6.49 (s, 1H) 4.27 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 160.1, 154.7 (q, $J = 37.6$ Hz), 154.2, 137.2, 136.9, 132.3, 130.6, 130.1, 125.5, 119.9, 119.7, 117.1 (q, $J = 288.8$ Hz), 115.1, 113.1, 112.2, 93.9, 81.8, 69.5, 64.8, 55.4, 14.2; $^{19}F$ NMR ($CDCl_3$) $\delta$ −74.3; Anal. Calcd for $C_{21}H_{18}F_3NO_5$: C,59.86; H, 4.31; N, 3.32. Found: C, 59.80; H, 4.31; N, 3.31. MS *m*/*z* (relative intensity) 377 ($M^+$−15, 10%), 332 (78%), 280 (100%).

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10. *Typical procedure for the cyclization of* (**1**) to (**2**): A Carousel Tube Reaction (Radley Discovery), equipped with a magnetic stirrer, was charged with MeCN (2.0 mL), **1a** (0.100 g, 0.317 mmol), $Pd(PPh_3)_4$ (0.018 g, 0.016 mmol), $Et_3N$ (0.096 g, 0.951 mmol), and HCOOH (0.029 g, 0.634 mmol) under argon. The mixture was stirred at 80 °C for 1 h. After cooling, the reaction mixture was concentrated under reduced pressure and the crude was purified by chromatography ($SiO_2$, 35 g; *n*-hexane/AcOEt 92/8 v/v) to give 0.038 g of **2a** (91% yield): mp: 57–59 °C; lit. mp (Aldrich catalogue) 57–59 °C, ; IR (KBr): 3404, 2935, 2816, 1454; $^1H$ NMR ($CDCl_3$) $\delta$ 7.76 (br s, 1H), 7.59 (d, $J = 7.5$ Hz, 1H), 7.30 (d, $J = 7.6$ Hz, 1H), 7.25–7.10 (m, 2H), 6.29 (s, 1H), 2.46 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 136.1, 135.1, 129.1, 120.9, 119.6, 110.3, 100.4, 13.7; Anal. Calcd for $C_9H_9N$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.50; H, 6.91; N, 10.70. MS *m*/*z* (relative intensity) 131 ($M^+$, 94%), 130 (100%), 77 (20%).
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