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Palladium-Catalyzed Synthesis of 2-(Aminomethyl)indoles from Ethyl 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate

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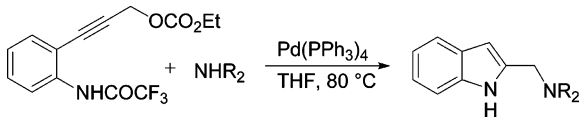
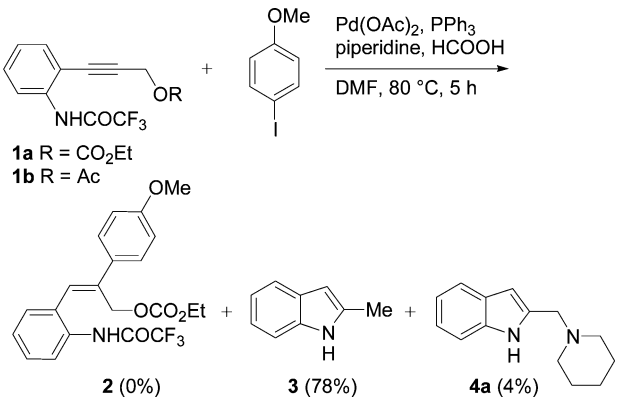
ABSTRACT



The palladium-catalyzed reaction of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate with piperazines in the presence of $Pd(PPh_3)_4$ in THF at 80 °C affords 2-(piperazin-1-ylmethyl)indoles in excellent yields. Good to excellent yields are also obtained with other secondary amines.

Our palladium-catalyzed hydroarylation/cyclization of alkynes bearing nucleophilic and electrophilic centers close to the carbon−carbon triple bond was proved to be a useful tool for the construction of heterocyclic rings.[1] Using this procedure, we prepared butenolides,[2] quinolines,[3] chromenes,[4] coumarins, and chromanols.[5] During our continuing studies on this research area, we had the occasion to examine the reaction of ethyl 3-(*o*-trifluoroacetamidophenyl)-1-propargyl carbonate **1a** with *p*-iodoanisole under the hydroarylation conditions shown in Scheme 1. 2-Methyl indole **3** was isolated in 78% yield, and 2-(piperidin-1-ylmethyl)indole **4** in was isolated in 4% yield; none of the hydroarylation product **2** was observed.

Scheme 1



Though we did not obtain the desired product, the reaction provided us with some data which attracted our attention. Indeed, this is an example of a new palladium-catalyzed cyclization of an acyclic alkyne to free N−H functionalized

(1) Cacchi, S.; Fabrizi, G. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol 1, 1335.

(2) (a) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481. (b) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinellli, F.; Pietroni, B. *Tetrahedron Lett.* **1989**, *30*, 3465. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Eur. J. Org. Chem.* **1999**, 3305.

(3) (a) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Tetrahedron* **1996**, *52*, 10225. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Moreno-Mañas, M.; Vallribera, A. *Tetrahedron Lett.* **2002**, *43*, 5537.

(4) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Eur. J. Org. Chem.* **2000**, 4099. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *J. Mol. Catal. A* **2004**, *214*, 57. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Verdecchia, M. *Synlett*, in press.

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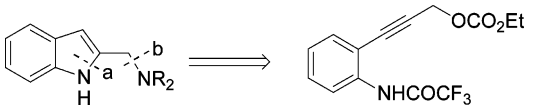
indoles. In particular, of great interest to us was the formation of **4a** (albeit in very poor yield), in which two carbon−nitrogen bonds are formed in a single operative step. The conversion of this side reaction into a synthetically useful process would add to known procedures based on the cyclization of *o*-alkynylanilines and *o*-alkynylanilides[6] a new useful approach for the assembly of the functionalized pyrrole nucleus incorporated into the indole system (Scheme 2) and

Scheme 2. Retrosynthetic Representation of the Palladium-Catalyzed Assembly of the Pyrrole Nucleus from Ethyl 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate **1a**

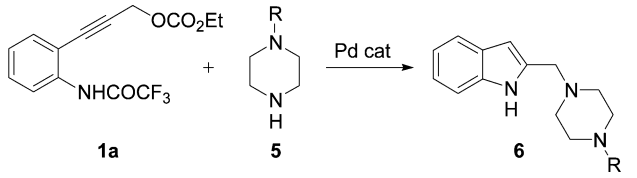


open a straightforward route to an important class of indole derivatives. Indeed, the 2-(aminomethyl)indole motif is a key structural feature present in several biologically active compounds.[7] In particular, 2-(piperazin-1-ylmethyl)indoles, containing two privileged substructures (the indole and piperazine nuclei),[8] exhibit important biological activities and have attracted considerable attention in organic, medical, and pharmaceutical chemistry.[9]

Therefore, the development of a protocol for the preparation of 2-(piperazin-1-ylmethyl)indoles **6** from **1a** and piperazines **5** (Scheme 3) was initially explored when we started this research project.

Compound **1a** was prepared through a four-step process from *o*-iodoaniline via Sonogashira cross-coupling with the tetrahydropyranyl derivative of propargyl alcohol followed by trifluoroacetylation, deprotection, and esterification steps in 80% overall isolated yield, omitting isolation and characterization of reaction intermediates.

Scheme 3



Part of our optimization work using different catalyst systems and solvents is summarized in Table 1. *p*-Iodoanisole

Table 1. Examination of the Reaction of Ethyl 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate **1a** with *N*-Ethylpiperazine **5a**[a]

entry	catalyst system	solvent	time (h)	yield % of **6a**[b]
1	$Pd(OAc)_2$, PPh_3	THF	6	52
2	$Pd_2(dba)_3$, PPh_3	THF	6	58
3	$Pd(PPh_3)_4$	MeCN	6	57[c]
4	$Pd(PPh_3)_4$	DMF	6	54[c]
5	$Pd(PPh_3)_4$	THF	1.5	91
6	$Pd_2(dba)_3$, dppf	THF	6	85
7	$Pd_2(dba)_3$, dppe	THF	24	50
8	$PdCl_2$(2-furyl)$_2$	THF	24	33

[a] Unless otherwise stated, reactions were carried out on a 0.159 mmol scale in 1 mL of solvent under argon at 80 °C by using 1 equiv of **1a**, 3 equiv of **5a**, 0.05 equiv of [Pd], 0.1 equiv of PPh_3, or 0.05 equiv of bidentate phosphine ligand. [b] Yields are given for isolated products. [c] With 0.05 equiv of $Pd(PPh_3)_4$.

(which did not enter the catalytic cycle affording isolated products) and formic acid (very likely involved in the formation of **3**) were omitted. Moderate yields were obtained under a variety of reaction conditions (Table 1, entries 1−4). The best result in terms of yield and reaction time was obtained in the presence of $Pd(PPh_3)_4$ in THF (Table 1, entry 5). Longer reaction times and lower yields were observed with $Pd_2(dba)_3$ and bidentate ligands such as dppf and dppe (Table 1, entries 6 and 7). A longer reaction time and lower yield were also observed using the less reactive propargyl acetate[10] **1b** as the starting alkyne (50% yield; $Pd(PPh_3)_4$, THF, 80 °C, 24 h). A slight increase of the yield (67%) was observed with **1b** at 100 °C after 9 h, but the yield was still significantly lower than that with **1a**.

The best conditions found for **1a** [$Pd(PPh_3)_4$, THF, 80 °C] proved to be very efficient for a number of related cyclizations to 2-(piperazin-1-ylmethyl)indoles as indicated in Table 2. Only with **5j** (Table 2, entry 10), the desired indole product was isolated in moderate yield, very likely because of the low nucleophilicity of the nitrogen derivative due to steric effects.

Then, the extension of the reaction to other secondary amines and even to primary amines was briefly investigated

(6) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873.

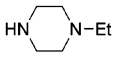
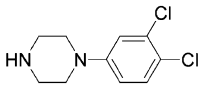
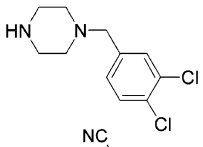
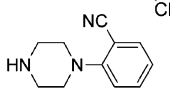
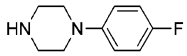
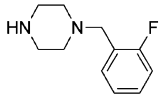
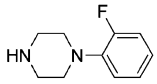
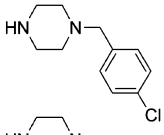
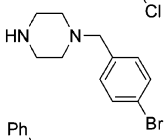
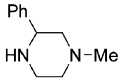
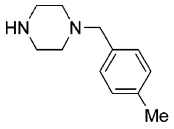
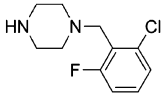
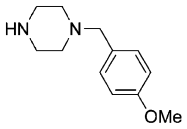
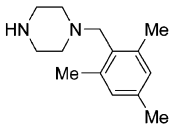
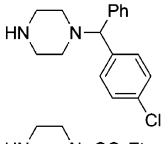
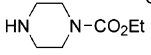
(7) See, for example: (a) Morón, J. A.; Campillo, M.; Perez, V.; Unzeta, M.; Pardo, L. *J. Med. Chem.* **2000**, *43*, 1684. See also: (b) Spadoni, G.; Balsamini, C.; Diamantini, G.; Tontini, A.; Tarzia, G.; Mor, M.; Rivara, S.; Plazzi, P. V.; Nonno, R.; Lucini, V.; Pannacci, M.; Fraschini, F.; Stankov, B. M. *J. Med. Chem.* **2001**, *44*, 2900. (c) Spadoni, G.; Balsamini, C.; Bedini, A.; Diamantini, G.; Di Giacomo, B.; Tontini, A.; Tarzia, G.; Mor, M.; Plazzi, P. V.; Rivara, S.; Nonno, R.; Pannacci, M.; Lucini, V.; Fraschini, F.; Stankov, B. M. *J. Med. Chem.* **1998**, *41*, 3624.

(8) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(9) For some recent references, see: (a) Hübner, H.; Gmeiner, P.; Kraxner, J. *J. Med. Chem.* **2000**, *43*, 4563. (b) Clifford, J. J.; Waddington, J. L. *Neuropsychopharmacol.* **2000**, *22*, 538. Ortner, B.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1283. (c) Moll, A.; Hübner, H.; Gmeiner, P.; Troschutz, R. *Bioorg. Med. Chem.* **2002**, *10*, 1671. (d) Brioni, J. D.; Kolasa, T.; Hsieh, G. C.; Donnelly-Roberts, D. L. WO 2002041894, 2002; *Chem. Abstr.* **2002**, *136*, 395987. (e) Fliri, A. F. J.; Sanner, M. A.; Seymour, P. A.; Zorn, S. H. Eur. Patent 1177792, 2002; *Chem. Abstr.* **2002**, *136*, 145264. (f) Fliri, A. F. J.; Majchrzak, M. J.; Seymour, P. A.; Zorn, S. H.; Rollema, H. U.S. Patent 842,569, 2003; *Chem. Abstr.* **2003**, *138*, 401610. (g) Cowart, M.; Latshaw, S. P.; Bhatia, P.; Daanen, J. F.; Rohde, J.; Nelson, S. L.; Patel, M.; Kolasa, T.; Nakane, M.; Uchic, M. E.; Miller, L. N.; Terranova, M. A.; Chang, R.; Donnelly-Roberts, D. L.; Namovic, M. T.; Hollingsworth, P. R.; Martino, B. R.; Lynch, J. J., III.; Sullivan, J. P.; Hsieh, G. C.; Moreland, R. B.; Brioni, J. D. S.; Andrew, O. *J. Med. Chem.* **2004**, *47*, 3853. (h) Stewart, A. O.; Cowart, M. D.; Moreland, R. B.; Latshaw, S. P.; Matulenko, M. A.; Bhatia, P. A.; Wang, X.; Daanen, J. F.; Nelson, S. L.; Terranova, M. A.; Namovic, M. T.; Donnelly-Roberts, D. L.; Miller, L. N.; Nakane, M.; Sullivan, J. P.; Brioni, J. D. *J. Med. Chem.* **2004**, *47*, 2348.

(10) For a review on the palladium-catalyzed reactions of propargyl esters, see: (a) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589.

Table 2. Palladium-Catalyzed Synthesis of 2-(Piperazin-1-ylmethyl)indoles **6** from Ethyl 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate **1a** and Piperazines **5**[a]

entry	piperazine **5**		time (h)	yield % of **6**[b]
1		**5a**	1.5	**6a** 91
2		**5b**	2	**6b** 96
3		**5c**	24	**6c** 80
4		**5d**	3	**6d** 98
5		**5e**	6	**6e** 96
6		**5f**	6	**6f** 98
7		**5g**	2.5	**6g** 97
8		**5h**	3	**6h** 92
9		**5i**	3	**6i** 94
10		**5j**	6	**6j** 58
11		**5k**	4	**6k** 85
12		**5l**	12	**6l** 78
13		**5m**	4	**6m** 81
14		**5n**	4	**6n** 80
15		**5o**	8	**6o** 92
16		**5p**	20	**6p** 88

[a] Reactions were carried out on a 0.159 mmol scale in 1 mL of THF under argon at 80 °C by using 1 equiv of **1a**, 3 equiv of **5**, and 0.05 equiv of $Pd(PPh_3)_4$. [b] Yields are given for isolated products.

(Table 3). Yields are usually good to high with secondary amines (Table 3, entries 1−3). The moderate yield obtained

Table 3. Palladium-Catalyzed Reaction of Ethyl 3-(*o*-Trifluoroacetamidophenyl)-1-propargyl Carbonate **1a** with Secondary Amines[a]

entry	amine	time (h)	yield % of **4**[b]
1		1	**4a** 94[c]
2		1	**4b** 98
3	Et_2NH	2	**4c** 60[d]
4	$(i\text{-}Pr)_2NH$	4	**4d** 45

[a] Unless otherwise stated, reactions were carried out on a 0.159 mmol scale in 1 mL of THF under argon at 80 °C by using 1 equiv of **1a**, 3 equiv of secondary amine, and 0.05 equiv of $Pd(PPh_3)_4$. [b] Yields are given for isolated products. [c] The indole product **4a** was isolated in 84% yield in the presence of 0.0125 equiv of $Pd_2(dba)_3$ and 0.05 equiv of PPh_3 after 6 h and in 73% yield with 0.025 equiv of $Pd_2(dba)_3$, omitting PPh_3, after 24 h. [d] With 5 equiv of amine.

with diisopropylamine (Table 3, entry 4) was attributed again to the involvement of steric effects. With primary amines, the efficiency of the reaction is flawed by the occurrence of side reactions. For example, with benzylamine and butylamine, complex reaction mixtures were obtained that we have not thoroughly investigated.

Although the precise mechanism for this indole synthesis is not clear, a possible rationale considers the following basic steps: (a) initial formation of the σ-allenylpalladium complex **7** (via a S_N2' reaction of the palladium complex with **1a**) which would be in equilibrium with the π-propargylpalladium intermediate **8**,[11] (b) intramolecular nucleophilic attack of the nitrogen at the central carbon of the allenyl/propargylpalladium complex,[10,12,13] (c) protonation of the resultant carbene **9** to give the π-allylpalladium complex **10**, (d) regioselective intermolecular nucleophilic attack of the nitrogen nucleophile at the less hindered allylic terminus of **10** (Scheme 4).

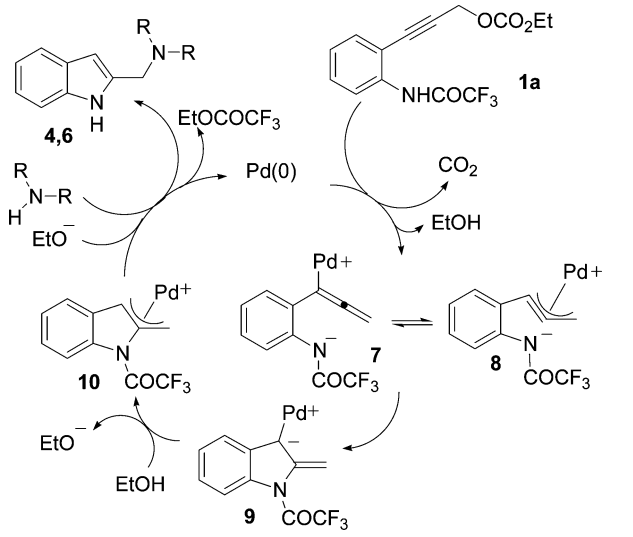
As observed in our previous studies on the aminopalladation-reductive elimination route to indoles,[14] the acidity of the nitrogen−hydrogen bond was found to play a crucial role. When ethyl 3-(*o*-acetamidophenyl)-1-propargyl carbonate **11**, containing a less acidic nitrogen−hydrogen bond, was subjected to 4-ethylpiperazine under our standard

(11) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938.

(12) Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164.

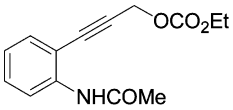
(13) For some examples of reactions involving a nucleophilic attack at the central sp carbon of a σ-propargylpalladium complex to give a π-allylpalladium complex which is further attacked by a second nucleophile, see: (a) Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Synlett* **1996**, 553. (b) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (c) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527. (d) Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874. (e) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, *61*, 4381.

Scheme 4



conditions, a complex reaction mixture was obtained and the indole product was formed only in trace amounts, if any.

Interestingly, the present indole synthesis gives excellent results using a monodentate phosphine ligand, though it has been reported that π-propargylpalladium complexes are formed in a more stable manner in the presence of bidentate



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ligands[15] and that the best ligands for the palladium-catalyzed reaction of propargyl halides[16] and carbonates[10] with soft nucleophiles are the bidentate ligands.

In conclusion, we have developed a straightforward, very useful new approach to 2-(aminomethyl)indoles, including the important class of 2-(piperazin-1-ylmethyl)indoles. The procedure is simple. The reaction proceeds under mild conditions, and indole products are formed in good to excellent yields. Further investigations, directed toward the utilization of this strategy to the assembly of other functionalized indole products, are currently in progress.

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Supporting Information Available: A complete description of experimental details and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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