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A Versatile Approach to 2,3-Disubstituted Indoles through the Palladium-Catalysed Cyclization of *o*-Alkynyltrifluoroacetanilides with Vinyl Triflates and Aryl Halides.

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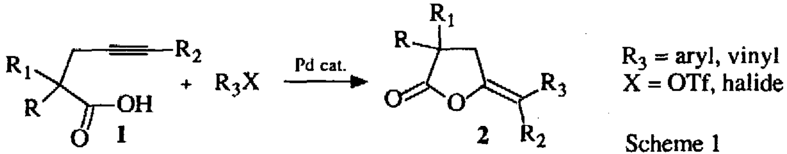
Abstract: *The palladium-catalysed cyclization of o-alkynyltrifluoroacetanilides with vinyl triflates and aryl halides produces 2,3-disubstituted indoles in good to high yield.*

The presence of the indole nucleus in a wide variety of biologically active compounds has led to the development of numerous approaches to its synthesis and many of them rely on palladium-catalysed reactions.[1] Palladium has been mainly employed to allow the intramolecular cyclization of intermediates containing all of the components of the target indole[1,2] or to build up the indole derivative from two separate building blocks.[3]

Recently, we reported that pentynoic acids **1** react with vinyl/aryl triflates and halides to give regio- and stereoselectively substituted γ-alkylidene-γ-butyrolactones **2** through a palladium-catalysed cyclization reaction[4] (Scheme 1).

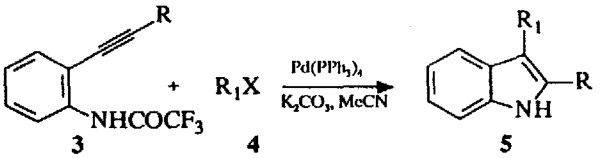


Scheme 1

Since the reaction appeared expecially promising for the preparation of heterocyclic compounds, we decided to examine a possible extension of this cyclization methodology to the synthesis of indole derivatives.

We now report a new and versatile two-component approach to the synthesis of 2,3-disubstituted indoles **5** based on the palladium-catalysed heteroannulation of *o*-alkynyltrifluoroacetanilides **3** in the presence of vinyl triflates and aryl halides (Scheme 2). Our results are summarised in Table.

Best results were obtained using K_2CO_3 as the base. In the presence of Et_3N, yields were sensibly lower (compare entry a with note e and entry b with note f). As far as the aniline moiety is concerned, no indole derivatives were obtained using aniline intermediates containing a free amino group or an acetamido group. For example, reacting *o*-phenylethynylaniline with *p*-chlorophenyl iodide and cyclooct-1-en-1-yl triflate, the starting



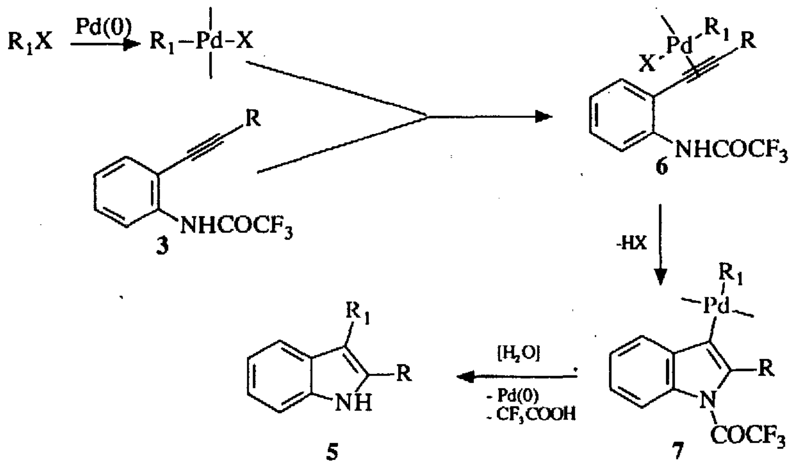
R_1X = aryl halide: 80 °C
R_1X = vinyl triflate: room temperature

Scheme 2

alkyne was recovered in 88% and 79% yield, respectively. When the reaction was carried out with *o*-phenylethynylacetanilide the starting alkyne was recovered in 98% and 97% yield, respectively. The dramatic change observed in the reactivity of the aniline moiety in the presence of an electron-withdrawing group as strong as CF_3CO- supports the notion that the acidity of the nitrogen-hydrogen bond is an important feature of this heteroannulation.

A typical procedure is as follows: to a solution of *o*-hexynyltrifuoroacetanilide (0.159 g, 0.59 mmol) in MeCN (2.5 ml) were added 3,3,5,5-tetramethyl-cyclohex-1-en-1-yl triflate ((0.169 g, 0.59 mmol), K_2CO_3 (0.408 g, 2.95 mmol), and $Pd(PPh_3)_4$ (0.034 g, 0.03 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 1.5 h. Then, the mixture was diluted with diethyl ether and 0.1 N HCl was added. The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated under vacuum. The residue was purified by chromatography on silica gel eluting with a *n*-hexane/EtOAc 97/3 mixture to give **5b** (0.136 g, 74% yield): mp = oil; IR (liquid film) 3360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 - 1.75 (m, 21 H), 2.13 (d, J = 1.6 Hz, 2 H), 2.76 (t, J = 7.5 Hz, 2 H), 5.45 (t, J = 1.6 Hz, 1 H), 7.00 - 7.55 (m, 4 H), 7.77 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.6, 26.2, 30.0, 31.2, 31.8, 32.2, 33.1, 43.8, 49.9, 110.3, 118.6, 119.21, 119.26, 121.0, 127.6, 128.0, 135.1, 135.2, 135.8. MS *m/e* (relative intensity) 309 (M^+, 33), 294 (100).

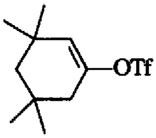
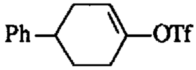
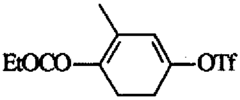
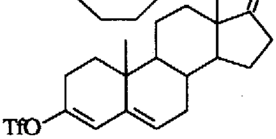
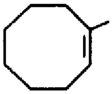
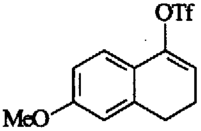
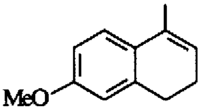
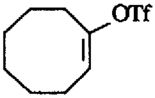
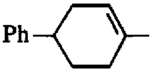
Presumably, the reaction proceeds via the oxidative addition of Pd(0) to vinyl triflates and aryl halides, the formation of the π-palladium complex **6**, the intramolecular *trans*-addition of the nitrogen across the coordinated carbon-carbon triple bond, and subsequent reductive elimination of Pd(0) species from the resulting σ-vinylpalladium intermediate **7** which regenerates the catalyst and releases the indole derivative **5** (Scheme 3).



Scheme 3

The starting *o*-alkynyltrifluoroacetanilides **3** can be easily prepared from *o*-iodotrifluoroacetanilide **8** (Scheme 4, A) or from *o*-ethynyltrifluoroacetanilide **10**[5] (Scheme 4, B) (see Table).

Table. Palladium-Catalysed Cyclization of *o*-Alkynyltrifluoroacetanilides **3** to 2,3-Disubstituted Indoles **5**.[a]

Entry	*o*-Alkynyltrifluoroacetanilide **3** R	(procedure; yield %)[b]	Aryl halide and vinyl triflate **4** R^1-X	Reaction time (h)	2,3-Disubstituted Indole **5** yield %[b]
a	^{n}Bu-	(A; 81)[c]	4-MeO-C_6H_4-I	2	82[d,e]
b	"	" "		1.5	74[f]
c	"	" "		35	81
d	Ph-	(A; 73)[c]		22	90
e	"	" "	4-Cl-C_6H_4-I	7	80[d]
f	"	" "		4	74
g	"	" "		1	50[g]
h		(B; 92)[h]		48	89
i		(B; 72)[h,i]		4	70
l		(B; 64)[h]	4-MeOCO-C_6H_4-I	2	68[d]

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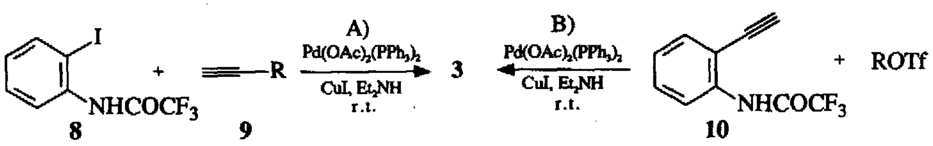
[a] Carried out at room temperature in MeCN using the following molar ratios: **3**: **4**: $Pd(PPh_3)_4$: K_2CO_3 = 1: 1: 0.05: 5 [b] Yields are for pure, isolated products. All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures. [c] Carried out on a 5 mmol scale, at room temperature, in DMF (3 ml) and in the presence of Et_2NH (2.5 ml) by using the following molar ratios: **8**: **9**: $Pd(OAc)_2(PPh_3)_4$: CuI = 1: 1.2: 0.01: 0.02 (Scheme 4, A). [d] At 80 °C. [e] In the presence of Et_3N (5 equiv; 1.5 h) instead of K_2CO_3, **5a** was isolated in 10% yield and the starting alkyne was recovered in 28% yield. [f] In the presence of Et_3N (5 equiv; 1.5 h) instead of K_2CO_3, **5b** was isolated in 39% yield and the starting alkyne was recovered in 11% yield. [g] At 50 °C. [h] Carried out on a 0.5 - 1.5 mmol scale, at room temperature, in DMF (0.5 - 2.5 ml) in the presence of Et_2NH (2 - 5 ml) by using the following molar ratios: **10**: ROTf: $Pd(PPh_3)_4$: CuI = 1: 1: 0.01: 0.02 (Scheme 4, B). [i] $Pd(PPh_3)_4$: CuI = 0.03: 0.06.



Scheme 4

Because of the simple experimental procedure, mild conditions, easy availability of the starting materials, and ability to incorporate a variety of functional groups, the present method represents a valuable tool for the synthesis of 2,3-disubstituted indoles. It is worth noting that the here reported protocol allows a versatile access to vinyl indoles, useful intermediates for the preparation of annelated derivatives.[6] Currently we are examining the extension of this heteroannulation procedure to the synthesis of other heterocyclic systems.

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2. For additional reports on the palladium-catalysed cyclization to indoles, see: *o*-vinyl-anilides: Krolski, M. E., Renaldo, A. F., Rudisill, D. E., Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170-1176; *o*-allyl-anilides: Tremont, S., J., Rahman, H., U. *J. Am. Chem. Soc.* **1984**, *106*, 5759-5760; N-vinyl-*o*-haloanilines: Sakamoto, T., Nagano, T., Kondo, Y., Yamanaka, H. *Synthesis*, **1990**, 215-218; N-allyl-*o*-haloanilines: Larock, R. C., Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291-5294; *o*-(alk-1-yn-1-yl)anilines and anilides: Arcadi, A., Cacchi, S., Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581-2584; Rudisill, D. E., Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856-5866.
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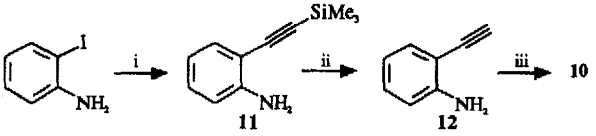
5. Compound **10** was obtained from 2-iodoaniline in 70% overall isolated yield through the following three step sequence, without purification of the intermediates **11** and **12**.



i) trimethylsilylacetylene (1.5 equiv), $Pd(PPh_3)_4$ (0.005 equiv), CuI (0.01equiv), Et_2NH (15 ml), DMF (2 ml), r.t., overnight; ii) KF (3.7 equiv), MeOH (70 ml), 40 °C, 5 h; iii) 2,6-di-*tert*-butyl-4-methylpyridine (1.1 equiv), $(CF_3CO)_2O$ (1.3 equiv), anhydrous CH_2Cl_2 (15 ml), r.t., 3 h. The reaction was carried out on a 14 mmole scale.

6. See for example: Kuehne, M. E., Bornmann, W. G. *J. Org. Chem.* **1989**, *54*, 3407-3420; Kuehne, M. E., Podhorez, D. E., Mulamba, T. Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347-353; Eberle, M. K., Shapiro, M. J., Stucki, R. *J. Org. Chem.* **1987**, *52*, 4661-4665.

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