HETEROCYCLES, Vol. 64, 2004, pp. 475 - 482
Received, 20th July, 2004, Accepted, 1st November, 2004, Published online, 2nd November, 2004

2-(*o*-AMINOARYL)INDOLE DERIVATIVES *VIA* THE COUPLING-CYCLIZATION OF *o*-ALKYNYLANILINES WITH *o*-HALOTRIFLUOROACETANILIDES IN THE PRESENCE OF A PALLADIUM CATALYST

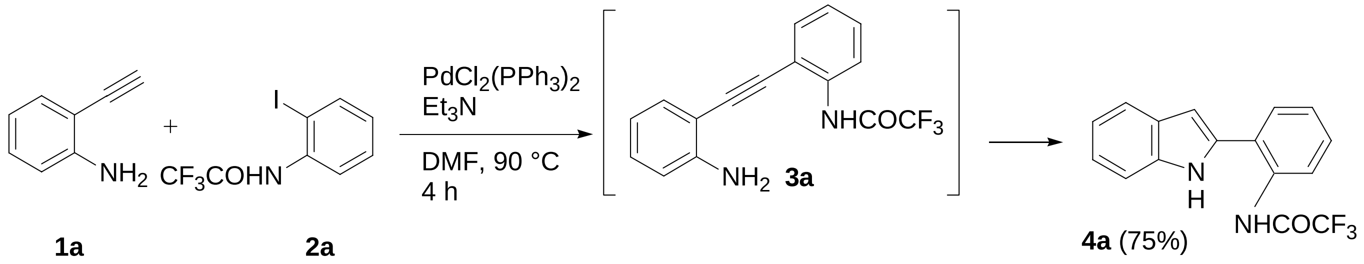
Antonio Arcadi,[a] Sandro Cacchi,[b*] Giancarlo Fabrizi,[b] Fabio Marinelli,[a] and Luca M. Parisi[b]

[a] Department of Chemistry, Chemical Engineering, and Materials, University of L'Aquila, Via Vetoio, Coppito Due, I-67100 L'Aquila, Italy

[b] Department of Studies of Chemistry and Technology of Biologically Active Substances, University "La Sapienza", P. le A. Moro 5, 00185 Rome, Italy

Abstract – The reaction of *o*-ethynylanilines with *o*-halotrifluoroacetanilides in the presence of $PdCl_2(PPh_3)_2$ and Et_3N in DMF at 90 °C affords 2-(*o*-trifluoroacetamidoaryl)indoles. The presence of the free amino group was found to play a crucial role in favoring the cyclization step.

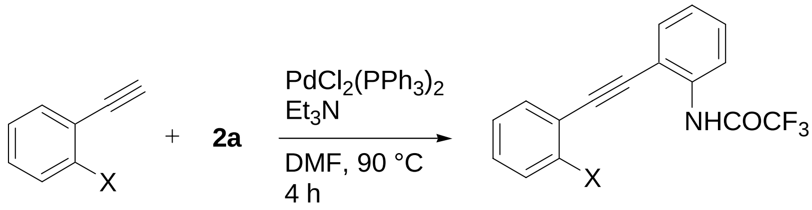
During our continuing studies on the use of palladium catalysis in the construction of the substituted pyrrole nucleus incorporated into indole systems,[1] we have observed that 2-(*o*-trifluoroacetamidoaryl)indoles could be directly obtained from *o*-ethynylaniline **(1a)** and *o*-halotrifluoroacetanilides under palladium-catalyzed cross-coupling conditions, in the presence of Et_3N and omitting copper co-catalysts. For example, the indole product **(4a)** was isolated in 75% yield when **(1a)** was treated with *o*-iodotrifluoacetanilide **(2a)** under the conditions shown in Scheme 1.



Scheme 1

This paper is dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

The reaction most probably involves the intermediacy of the coupling product **(3a)**[2] and its cyclization through the intramolecular addition of a nitrogen nucleophile to the carbon-carbon triple bond. Notably, when phenylacetylene **(1b)** or *o*-ethynylanisole **(1c)** was treated with **2a** under the same conditions, coupling product **(3b)** or **(3c)** was isolated in 85% and 82% yields, respectively, and no evidence of indole derivatives was attained (Scheme 2).



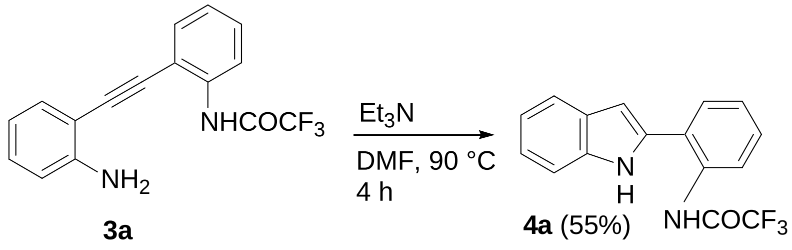
1b (X = H)
1c (X = OMe)

X = H, **3b** (85%)
X = OMe **3c** (82%)

Scheme 2

Intrigued by the different behavior of **1a** compared to **1b**-**c** as well as by the role of 2-(*o*-aminoaryl)indoles as useful reaction intermediates[3] and by the interesting biological activities exhibited by some of them,[4] we decided to investigate further the reaction. Herein we report the preliminary results of this study.

Initial attempts focused on establishing whether the cyclization involves palladium catalysis or a base-promoted process. To clear this point up, compound **(3a)**, prepared through the Sonogashira coupling[5] of **1a** with **2a**[6] at room temperature, was treated with Et_3N under the conditions shown in Scheme 3. The corresponding indole product was isolated in 55% yield (the starting alkyne was recovered in 5% yield).



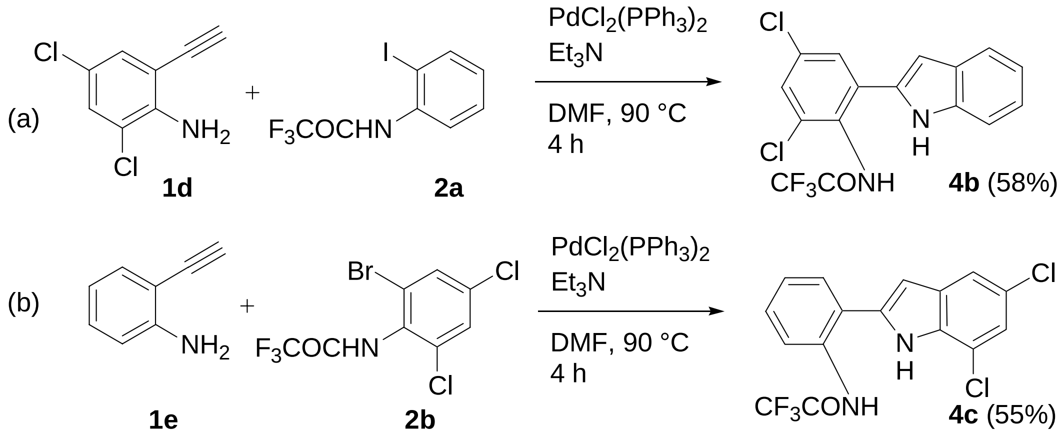
3a

4a (55%)

Scheme 3

Though the possible involvement of a parallel palladium-catalyzed cyclization to indoles cannot be ruled out when indoles are prepared through a domino process from *o*-ethynylanilines and *o*-halotrifluoroacetanilides, this result supports the notion that a base-catalyzed cyclization using a weak base such as Et_3N can take place. This appears to be in sharp contrast with the reported inability of Et_3N to promote the cyclization of *o*-alkynylanilides.[7] In effect, strong oxygen bases[8] or *n*-Bu_4NF[9] have been usually employed for the cyclization of *o*-alkynylanilides to indoles. Recently, the use of strong cesium and potassium bases has been described for the cyclization of *o*-alkynylanilines to indoles.[10] To the best of our knowledge, the only coupling/cyclization of *o*-iodoaniline and *o*-trifluoroacetanilide with terminal alkynes which has been described to give indoles using Et_3N as the base [in the presence of $Pd(OAc)_2$ and triphenylphosphinetrisulfonate sodium salt in MeCN and H_2O] involves a different reaction mechanism, based on the cyclization of an organopalladate intermediate.[11]

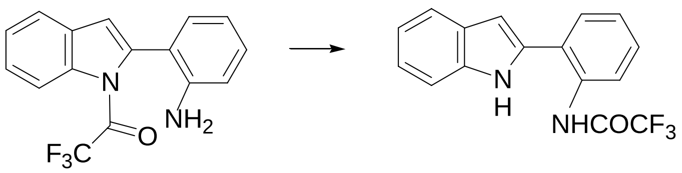
We next turned our attention to the interesting question of establishing the source of the pyrrolic nitrogen. On the basis of the indole product (containing a trifluoroacetamido group on the 2-aryl substituent), the free amino group would appear a reasonable candidate for generating the pyrrole nucleus through nucleophilic attack to the carbon-carbon triple bond. In order to probe the origin of the pyrrolic nitrogen, the following experiments were performed. *o*-Ethynylaniline **(1d)** and *o*-iodotrifluoroacetanilide (**2a**) were treated with $PdCl_2(PPh_3)_2$ and Et_3N in DMF at 90 °C for 4 h. Under these conditions, **4b** was isolated as the only indole product in 58% yield (Scheme 4). In a similar fashion, **1a** was reacted with **2b** to give **4c** in 55% yield (Scheme 4). The structure of **4b** and **4c** has been assigned by NOE experiments.



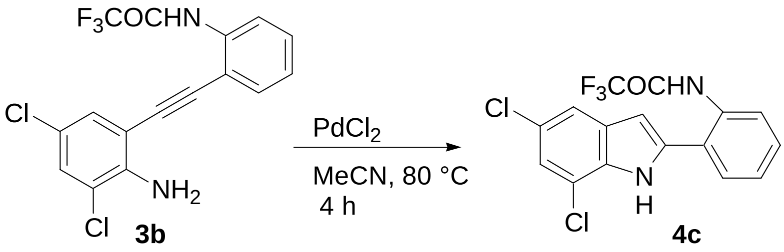
Scheme 4

Taken together, these two experiments indicate that the pyrrolic nitrogen is originated from the trifluoroacetamido group. Most probably, the acidic N-H bond favors the cyclization reaction by generating, under basic conditions, a stronger anionic nitrogen nucleophile (or by proton removal in the transition state leading to the cyclization adduct). The presence of the trifluoroacetamido group on the 2-aryl substituent of the indole product can be accounted for by assuming that a transamidation reaction occurs after formation of the pyrrole ring[12] (Scheme 5).

Interestingly, subjecting the alkyne **(3b)** - prepared independently through Sonogashira coupling of **1d** and **2a** - to 5 mol% of $PdCl_2$ in MeCN at 80 °C for 4 h[13] produced the indole derivative **(4c)** in 80 % yield, thus showing that in the absence of base and with the electrophilic catalysis of $PdCl_2$ the cyclization to indoles involves the free amino group (Scheme 6).



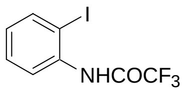
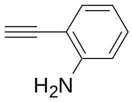
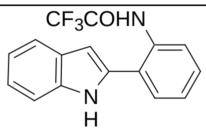
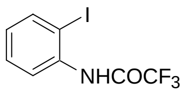
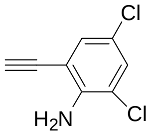
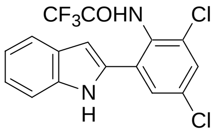
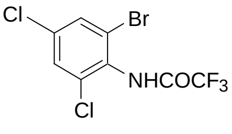
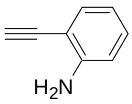
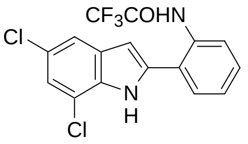
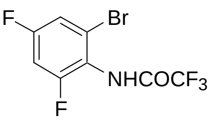
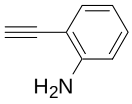
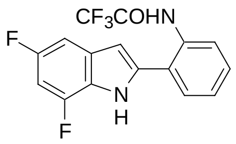
Scheme 5



Scheme 6

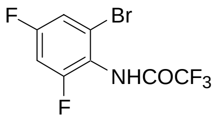
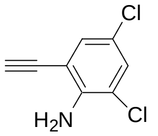
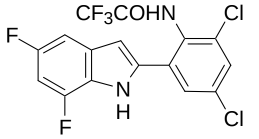
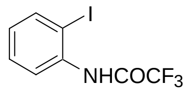
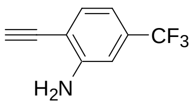
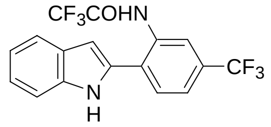
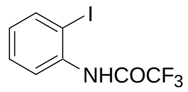
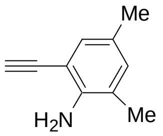
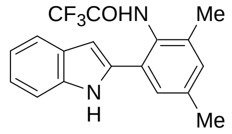
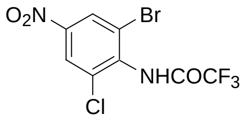
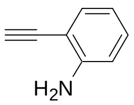
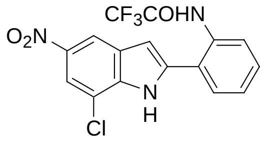
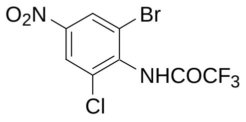
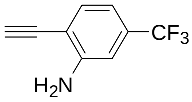
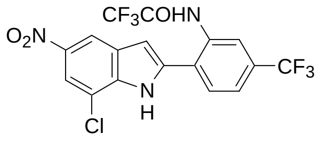
As to the pivotal role of the free amino group in favoring the cyclization step, the reason of its beneficial effect is not yet well understood. A possible working hypothesis considers its ability to stabilize the anion derived from the intramolecular nucleophilic attack of the nitrogen on the carbon-carbon triple bond by hydrogen bonding. Irrespective of the precise role of the amino group, however, it is now possible to synthesize 2-(*o*-aminoaryl)indole derivatives under mild conditions using a weak base. The reaction was extended to other *o*-ethynylanilines and *o*-halotrifluoroacetanilides. Our preparative results are summarized in Table1.

Table 1. Synthesis of 2-(*o*-trifluoroacetamidoaryl)indoles **(4)** from *o*-alkynylanilines **(1)** and *o*-halotrifluoroacetalilides **(2)** .[a]

entry	aryl halide **(2)**		1-alkyne **(1)**		t(h)	indole **(4)** yield %[b]		
1		**2a**		**1a**	4		**4a**	75
2		**2a**		**1d**	4		**4b**	58
3		**2b**		**1a**	4		**4c**	55
4		**2c**		**1a**	4		**4d**	58

(continued)

Table 1. (continued)

entry	aryl halide (2)	1-alkyne (1)	t(h)	indole (4)	yield %[b]
5	 **2c**	 **1d**	4	 **4e**	54
6	 **2a**	 **1e**	8	 **4f**	56
7	 **2a**	 **1f**	4.5	 **4g**	58
8	 **2d**	 **1a**	4	 **4h**	59
9	 **2d**	 **1e**	8	 **4i**	45

[a] Reactions were carried out on a 1.3-2 mmol scale in 2 mL of DMF at 90 °C using 1,3 equiv of **1**, 1 equiv of **2**, 0.03 equiv of $PdCl_2(PPh_3)_2$, and 4 equiv of Et_3N. [b] Yields are given for isolated products.

In conclusion, taking advantage of the effect of the free amino group on the cyclization step, we have developed a simple approach to the synthesis of the important class of 2-(*o*-aminoaryl)indole derivatives from readily available *o*-ethynylanilines and *o*-halotrifluoroacetanilides. Because of the weak base required for the domino coupling-cyclization process, extension to the preparation of indoles containing a variety of important functional groups can be anticipated. Though the yields are moderate, they refer to two consecutive steps and, in addition, no attempts have been made to optimize reaction conditions. It is therefore conceivable that higher yields for a particular case of interest can be obtained

ACKNOWLEDGEMENTS

We are grateful to MIUR for support of this work.

EXPERIMENTAL

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. *o*-Ethynylanilines (**1**) were prepared according to literature.[6] *o*-Halotrifluoroacetanilides (**2**) were prepared *via* reaction of commercially available *o*-haloanilines with trifluoracetic anhydride. All of the other reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification.

Reaction products were purified on axially compressed columns, packed with SiO_2 25-40 μm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/AcOEt mixtures. ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100.6 MHz) were recorded with a Bruker Avance 400 spectrometer using TMS as shift reference. EI (70 EV) mass spectra were recorded with a Varian Saturn 2100T GC/MS apparatus. IR spectra were recorded with a Jasco FT/IR 430 spectrometer. MS spectra were recorded with

Typical procedure for the preparation of 2-(o-trifluoroacetamidoaryl)indoles (4). To a solution of **1a** (0.085 g, 0.73 mmol) in DMF (1.5 mL) **2d** (0.327 g, 0.94 mmol), Et_3N (0.403 mL, 2.90 mmol), and $PdCl_2(PPh_3)_2$ (0.015 g, 0.021 mmol) were added. The mixture was stirred under nitrogen at 90 °C for 4 h. After cooling, the reaction mixture was extracted with 0.5 M NH_4Cl (50 mL) and EtOAc (3 x 40 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatographic on silica gel (n-hexane-EtOAc 85:15 v/v) to give 0.164 g of **4h** (59%): mp 201-203 °C. IR (KBr): 3300, 1730 cm^{-1}; ^{1}H NMR (Me_2CO-d_6) δ = 11.49 (br s, 1H); 10.07 (br s, 1H); 8.50 (d, J = 2.0 Hz, 1H); 8.05 (d, J = 2.0 Hz. 1H); 7,88-7.83 (m, 1H); 7,73-7.69 (m, 1H); 7.55-7.37 (m, 2H); 6.98 (s, 1H, *H-3*). ^{13}C NMR (Me_2CO-d_6) δ = 156.1 (q, J = 37 Hz, *COCF₃*), 142.4, 139.6, 137.6, 133.2, 131.0, 130.1, 129.4, 127.7, 126.8, 126.0, 117.2, 117.0, 116.5, 106.0 (*C-3*). EI-MS *m/z* (%): 385 (M$^+$+2, 34), 383 (M$^+$, 100), 314 (57), 268 (52).

4a: mp 115-117 °C; IR (KBr): 3410, 3320, 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 8.92 (br s, 1H); 8.42 (br s, 1H); 8.38 (dd, J_1 = 8.1 Hz, J_2 = 1.3 Hz, 1H); 7.71-7.66 (m, 1H); 7.53-7.15 (m, 6H); 6.66 (dd, J_1 = 2.1 Hz, J_2 = 0.8 Hz, 1H, *H-3*); ^{13}C NMR ($CDCl_3$): δ = 154.8 (q, J = 37 Hz, *COCF₃*), 136.8, 132.7, 132.5, 129.3, 129.1, 128.7, 126.3, 123.9, 123.3, 121.4, 121.0, 120.8, 111.2, 102.8 (*C-3*); EI-MS *m/z* (%): 304 (M$^+$, 57), 235 (73), 234 (100).

4b: mp 201-203 °C; IR (KBr): 3370, 3320, 1730 cm^{-1}; ^{1}H NMR (Me_2CO-d_6): δ = 10.60 (br s, 1H), 10.34 (br s, 1H), 7.78-7.76 (m, 1H), 7.66-7.58 (m, 2H), 7.49-7.43 (m. 1H), 7.22-7.02 (m, 2H), 6.84 (dd, J_1 = 2.2 Hz, J_2 = 0.8 Hz, 1H, *H-3*); ^{13}C NMR (Me_2CO-d_6): δ = 156.7 (q, J = 38 Hz, *COCF₃*), 138.2, 136.1, 135.8, 135.4, 132.8, 129.5, 129.1, 128.6, 123.8, 121.6, 120.9, 112.3, 104.5 (*C-3*); EI-MS *m/z* (%): 376 (M$^+$ + 4, 11), 374 (M$^+$ + 2, 61), 372 (M$^+$, 89), 305 (75), 303 (100).

4c: mp 143-145 °C; IR (KBr): 3400, 3380, 1720 cm^{-1}; ^{1}H NMR (Me_2CO-d_6): δ = 11.02 (br s, 1H), 10.05 (br s, 1H), 7.92 (dd, J_1 = 7.8 Hz, J_2 = 0.8 Hz, 1H), 7.74-7.69 (m, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.50-7.41 (m, 2H), 7.26 (d, J = 1.8 Hz, 1H), 6.79 (d, J = 2.0 Hz, 1H, *H-3*); ^{13}C NMR (Me_2CO-d_6): δ = 155.6 (q, J = 37 Hz, *COCF₃*), 137.7, 133.2, 133.0, 131.2, 130.7, 129.3, 127.3, 127.0, 125.6, 125.2, 121.4, 118.9, 117.2, 103.4; EI-MS *m/z* (%): 376 (M$^+$ + 4, 13), 374 (M$^+$ + 2, 64), 372 (M$^+$, 100), 303 (92).

4d: mp 138-140 °C; IR (KBr): 3460, 3280, 1710 cm^{-1}; ^{1}H NMR (Me$_2$SO-d$_6$) δ = 11.95 (br s, 1H), 11.11 (br s, 1H) 7.79-7-73 (m, 1H), 7.57-7.45 (m, 3H), 7.23 (dd, J_1 = 9.4 Hz, J_2 = 2.0 Hz, 1H), 6.99 (7d, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H), 6.69 (m, 1H, $\underline{H}$-*3*); ^{13}C NMR (Me$_2$SO-d$_6$): δ = 155.9 (dd, J_1 = 234.1 Hz, J_2 = 10.0 Hz, $\underline{C}$-*F*), 155.4 (q, J = 36.6 Hz, $\underline{C}OCF_3$), 148.1 (dd, J_1 = 246.6 Hz, J_2 = 14.6 Hz, $\underline{C}$-*F*),137.5, 132.1, 130.8 (dd, J_1 = 12.0 Hz, J_2 = 7.1 Hz), 130.0, 128.8 (*C-H*, double intensity peak), 128.5, 127.8, 121.3 (d, J = 13.1 Hz), 116.0 (q, J = 289.1 Hz, $CO\underline{C}F_3$), 102.5 (dd, J_1 = 5.4 Hz, J_2 = 1.1 Hz), 100.8 (dd, J_1 = 23.2 Hz, J_2 = 3.9 Hz), 96.6 (dd, J_1 = 30.4 Hz, J_2 = 20.9 Hz). EI-MS *m/z* (%): 340 (M$^+$, 100), 271 (85).

4e: mp 202-203 °C; IR (KBr): 3450, 3270, 1710 cm^{-1}; ^{1}H NMR (Me$_2$SO-d$_6$) δ = 12.11 (br s, 1H), 11.56 (br s, 1H), 7.91 (dd, J_1 = 2.4 Hz, J_2 = 0.5 Hz, 1H), 7.89 (dd, J_1 = 2.4 Hz, J_2 = 0.5 Hz, 1H), 7.27 (dd, J_1 = 9.3 Hz, J_2 = 2.0 Hz, 1H), 7.06 (td, J_1 = 10.5 Hz, J_2 = 2.0 Hz, 1H), 6.78 (t, J = 2.6 Hz , 1H, $\underline{H}$-*3*); ^{13}C NMR (Me$_2$SO-d$_6$): δ = 156.1 (dd, J_1 = 234.9 Hz, J_2 = 10.0 Hz, $\underline{C}$-*F*), 155.4 (q, J = 37.2 Hz, $\underline{C}OCF_3$), 148.2 (dd, J_1 = 247.1 Hz, J_2 = 14.7 Hz, $\underline{C}$-*F*), 134.7, 134.2, 133.8, 133.5, 130.3 (dd, J_1 = 12.0 Hz, J_2 = 7.0 Hz), 128.8, 128.5, 128.4, 121.6 (d, J = 13.2 Hz), 115.8 (q, J = 285.5 Hz, $CO\underline{C}F_3$), 103.7 (d, J = 2.9), 101.3 (dd, J_1 = 23.4 Hz, J_2 = 4.0 Hz), 97.6 (dd, J_1 = 30.6 Hz, J_2 = 20.6 Hz). EI-MS *m/z* (%):412 (M$^+$ + 4, 7), 410 (M$^+$ + 2, 39), 408 (M$^+$, 56), 341 (100).

4f: mp 123-125 °C; IR (KBr): 3380, 1730 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ = 9.10 (br s, 1H), 8.79 (br s, 1H), 8.73 (s, 1H), 7.73-7-59 (m, 3H), 7.48 (dd, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 7.36-7.21 (m, 2H), 6.76 (dd, J^1 = 2.1 Hz, J_2 = 0.7 Hz, 1H, $\underline{H}$-*3*); ^{13}C NMR (CDCl$_3$): δ = 156.2 (q, J = 37.0 Hz, $\underline{C}OCF_3$), 137.2, 133.1, 131.1, 129.6, 128.6, 124.0, 122.7 (q, J = 3.6 Hz), 121.3, 121.2, 118.4 (q, J = 3.9 Hz), 111.4, 103.8 ($\underline{C}$-*3*); EI-MS *m/z* (%): 372 (M$^+$, 97), 303 (100).

4g: mp 183-185 °C; IR (KBr): 3360, 3320, 1720 cm^{-1}; ^{1}H NMR (Me$_2$CO-d$_6$): δ = 10.42 (br s, 1H), 10.01 (br s, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.45-7.39 (m, 2H), 7.16-6.99 (m, 3H), 6.64 (d, J = 1.9 Hz, 1H, $\underline{H}$-*3*), ^{13}C NMR (Me$_2$CO-d$_6$): δ = 156.6 (q, J = 37.0 Hz, $\underline{C}OCF_3$), 138.6, 137.3, 137.1, 135.2, 131.8, 131.3, 129.3, 128.3, 122.3, 120.7, 120.0, 111.6, 102.5 ($\underline{C}$-*3*), 21.0, 18.1; EI-MS *m/z* (%): 332 (M$^+$, 33), 263 (100).

4i: mp 200-202 °C; IR (KBr): 3300, 1740 cm^{-1}; ^{1}H NMR (Me$_2$CO-d$_6$): δ = 11.6 (br s, 1H), 10.2 (br s, 1H), 8.57 (d, J = 2.0 Hz, 1H), 8.27 (s, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.74-7.69 (m, 1H), 7.12 (d, J = 2.1Hz, 1H, $\underline{H}$-*3*); ^{13}C NMR (Me$_2$CO-d$_6$): δ = 156.4 (q, J = 37 Hz, $\underline{C}OCF_3$), 142.6, 137.8, 134.0, 131.9, 129.2, 127.2, 124.8, 123.9 (q, J = 3.6 Hz), 122.5 (q, J = 3.9 Hz), 117.5, 116.8, 107.0 ($\underline{C}$-*3*); EI-MS *m/z* (%): 453 (M$^+$ + 2, 35), 451 (M$^+$, 100), 382 (52), 336 (65).

REFERENCES

1. G. Battistuzzi, S. Cacchi, and G. Fabrizi, *Eur. J. Org. Chem.*, 2002, 2671.
2. For pioneering works on the palladium-catalyzed coupling of terminal alkynes with aryl halides in

the absence of copper salts, see: (a) L. Cassar, *J. Organomet. Chem.*, 1975, **93**, 253; (b) H. A. Dieck and F. R. Heck, *J. Organomet. Chem.*, 1975, **93**, 259.

3. (a) O. Baudoin, M. Cesario, D. Guénard, and F. Guéritte, *J. Org. Chem.*, 2002, **67**, 1199; (b) P. Barraja, P. Diana, A. Lauria, A. Passannanti, A. M. Almerico, C. Minnei, S. Longu, D. Congiu, C. Musiu, and P. La Colla, *Bioorgan. Med. Chem.*, 1999, **7**, 1591; (c) G. Cirrincione, A. M. Almerico, P. Barraja, P. Diana, A. Lauria, A. Passannanti, C. Musiu, A. Pani, P. Murtas, C. Minnei, M. E. Marongiu, and P. La Colla, *J. Med. Chem.*, 1999, **42**, 2561; (d) A. D. Billimoria and M. P. Cava, *J. Org. Chem.*, 1994, **59**, 6777.
4. (a) W. Wrasidlo, J. Doukas, I. Royston, G. Noronha, J. D. Hood, E. Dneprovskaia, X. Gong, U. Splittgerber, and Zhao, WO 2004030635, 2004 (*Chem. Abstr.*, 2004, **140**, 321386); (b) J. J. Tegeler, E. M. Gardenhire, and G. C. Helsley, EP 406734, 1991 (*Chem. Abstr.*, 1991, **115**, 49397).
5. K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.
6. Compound (**1a**) and the other *o*-ethynylanilines were prepared as according to literature: A. Arcadi, S. Cacchi, and F. Marinelli, *Tetrahedron Lett.*, 1989, **30**, 2581.
7. (a) F. C. Fagnola, I. Candiani, G. Visentin, W. Cabri, F. Zarini, N. Monelli, and A. Tedeschi, *Tetrahedron Lett.*, 1997, **38**, 2307; (b) T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano, and H. Yamanaka, *Chem. Pharm. Bull.*, 1988, **36**, 1305.
8. (a) N. Suzuki, S. Yasaki, A. Yasuhara, and T. Sakamoto, *Chem. Pharm. Bull.*, 2003, **51**, 1170; (b) W.-M Dai, L.-P. Sun, and D.-S. Guo, *Tetrahedron Lett.*, 2002, **42**, 7699; (c) W.-M. Dai, D.-S Guo, and L.-P. Sun, *Tetrahedron Lett.*, 2001, **42**, 5275; (d) Y. Kondo, S. Kojima, and T. Sakamoto, *J. Org. Chem.*, 1997**, 62**, 6507; (e) Y. Kondo, S. Kojima, and T. Sakamoto, *Heterocycles,* 1996, **43**, 2741; (f) K. Shin and K.Ogasawara, *Synlett*, 1996, 922; (g) K. Shin and K. Ogasawara, *Synlett*, 1995, 859; (h) K. Shin and K. Ogasawara, *Chem. Lett.*, 1995, 289.
9. A. Yasuhara, Y. Kanamori, M. Kaneko, A. Numata, Y. Kondo, and T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1999, 529.
10. (a) C. Koradin, W. Dohle, A. L. Rodriguez, B. Schmid, and P. Knochel, *Tetrahedron*, 2003, **59**, 1571; (b) A. L. Rodriguez, C. Koradin, W. Dohle, and P. Knochel, *Angew. Chem., Int. Ed.*, 2000, **39**, 2488; (c) ref. 7b.
11. C. Amatore, E. Blart, J. P. Genêt, A. Jutand, S. Lemaire-Audoire, and M. Savignac, *J. Org. Chem.*, 1995, **60**, 6829.
12. S. Cacchi, G. Fabrizi, P. Pace, and F. Marinelli, *Synlett,* 1999, 620.
13. E. C. Taylor, A. H. Katz, H. Salgado-Zamora, and A. McKillop, *Tetrahedron Lett.*, 1985, **26**, 5963.