Indole[1,2-*c*]quinazolines by Palladium-Catalyzed Cyclization of Bis(*o*-trifluoroacetamidophenyl) acetylene with Aryl and Vinyl Halides or Triflates

Antonio Arcadi,[a] Sandro Cacchi,*[b] Alberto Cassetta,[c] Giancarlo Fabrizi,[b] Luca M. Parisi[b]

[a] Dipartimento di Chimica, Ing. Chimica e Materiali, Via Vetoio, 67100 L'Aquila, Italy

[b] Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy
Fax +39(6)49912780; E-mail: sandro.cacchi@uniroma1.it

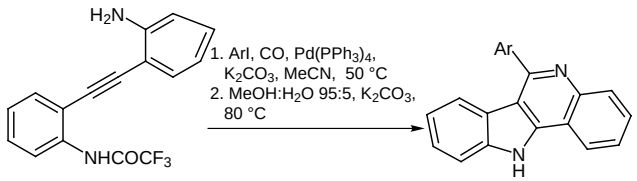
[c] Institute of Structural Chemistry - CNR Trieste, XRD1 beamline - Elettra Trieste

Received 22 June 2001

Abstract: 6-Trifluoromethyl-12-aryl(vinyl)indolo[1,2-*c*]quinazolines are prepared in high yield through the palladium-catalyzed reaction of readily available bis(*o*-trifluoroacetamidophenyl)acetylene with aryl or vinyl halides and triflates, followed by cyclization of the resultant derivatives. The reaction, which tolerates a variety of important functional groups, probably involves the formation of a 3-aryl-2-(*o*-trifluoroacetamidophenyl)indole intermediate, followed by its cyclization to the indolequinazoline product. Formation of the indoloquinazoline nucleus has been unambiguously determined via X-ray analysis.

Key words: indoloquinazolines, cyclization, palladium, catalysis, alkynes

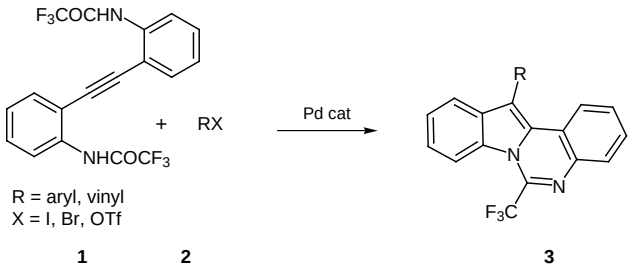
Our reaction of *o*-alkynyltrifluoroacetanilides with aryl and vinyl halides or triflates has been proved to be a versatile tool for the construction of functionalized indole rings from terminal and internal alkynes. By employing this methodology, a variety of 2-unsubstituted 3-arylindoles,[1] 2,3-disubstituted indoles[2] and 2-substituted 3-allylindoles[3] have been prepared. When the reaction is carried out under an atmosphere of carbon monoxide, 2-substituted 3-acylindoles can be obtained in good yields.[4] Adaptation of the methodology to a solid-supported synthesis[5] and applications to the synthesis of biologically active molecules[4,6] have also been reported. More recently, the methodology has been extended to develop a new route to indolo[3,2-*c*]quinolines[7] through a one-pot process involving the reaction of *o*-(*o*-aminophenyl)trifluoroacetanilide with aryl iodides, in the presence of carbon monoxide, followed by the cyclization of the resultant 3-acylindole derivative (Scheme 1).



Scheme 1

We report that reaction of bis(*o*-trifluoroacetamidophenyl)acetylene **1** with aryl or vinyl halides and triflates **2**, in the presence of a palladium catalyst, provides a straightforward approach to functionalized indolo[1,2-*c*]quinazolines **3** (Scheme 2).[8,9]

The starting alkyne required for our approach was readily prepared through palladium-catalyzed coupling of *o*-trifluoroacetamidophenyl iodide with *o*-ethynylaniline,[7] followed by reaction of the resultant coupling product with trifluoroacetic anhydride.[10]



Scheme 2

The palladium-catalyzed reaction of **1** with *p*-iodoanisole was chosen as the model system when we started our investigation of this cyclization chemistry. $Pd(PPh_3)_4$ and K_2CO_3, successfully employed in our previous synthesis of indolo[3,2-*c*]quinolines,[7] were selected as the precatalyst species and the base, respectively. The reaction proved to be strongly influenced by the nature of the solvent, as shown by the results summarized in Table 1.

The highest yield and reaction rate were obtained in DMSO. Consequently, the following reaction conditions were usually employed when the reaction was extended to include other aryl and vinyl halides or triflates: $Pd(PPh_3)_4$, K_2CO_3, DMSO, 50 °C.[11] Our preparative results are summarized in Table 2.

The reaction gives good results with neutral, electron-rich and electron-poor aryl halides as well as with various vinyl bromides and triflates. *p*-Bromoacetophenone requires a higher reaction temperature (Table 2, entry 8). Steric hindrance close to the oxidative addition site appears to hamper the reaction to some extent (Table 2, compare entry 6 with entry 7).

As to the mechanism, the reaction might proceed via the aminopalladation-reductive elimination domino pathway

Synlett 2001, No. 10, 28 09 2001. Article Identifier:
1437-210X,E;2001,0,10,1605,1607,ftx,en;G12901st.pdf.

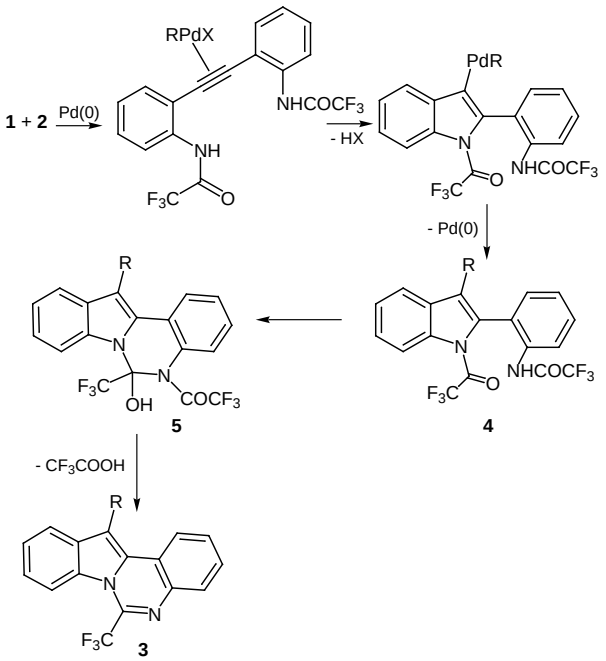
ISSN 0936-5214

Table 1 Solvent Effect in the Palladium-Catalyzed Reaction of Bis(*o*-trifluoroacetamidophenyl)acetylene **1** with *p*-Iodoanisole.[a]

Entry	Solvent	Time [h]	Yield [%] of **3a**[b]
1	THF	24[c]	60
2	Dioxane	24[c]	27
3	MeCN	24[c]	56
4	DMF	24[c]	40
5	DMA	24[c]	40
6	DMSO	1.5[d]	92

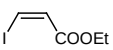
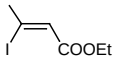
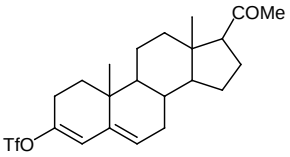
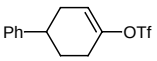
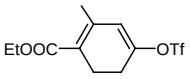
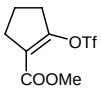
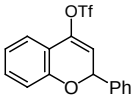
[a] Reactions were conducted at 7.5×10^{-2} M starting substrate in anhyd solvents (5 mL) at 50 °C using the following molar ratios: **1**:*p*-iodoanisole:$Pd(PPh_3)_4$:K_2CO_3 = 1:1:0.05:5.
[b] Yields refer to single runs and are given for isolated products.
[c] After this time, TLC indicated that the starting alkyne was still present into the reaction mixture.
[d] After this time, TLC indicated completion of the reaction.

(as other reactions of this type),[1–7] followed by cyclization of the resultant 3-arylindole derivative **4** to give the tetracyclic derivative **5** that subsequently affords the indoloquinazoline product via elimination of trifluoroacetic acid. Formation of **4** through the alternative reaction pathway involving (1) carbopalladation of the carbon-carbon triple bond, (2) isomerization of the resultant *cis* σ-vinylpalladium adduct to the *trans* σ-vinylpalladium adduct,[15] (3) formation of a six-membered ring nitrogen-containing palladacycle intermediate via nucleophilic attack of nitrogen to palladium, and (4) subsequent regeneration of the palladium(0) catalyst through reductive elimination cannot be *a priori* ruled out (Scheme 3).



Scheme 3

Table 2 Preparation of Indolo[1,2-*c*]quinazolines **3** from Bis(*o*-trifluoroacetamido phenyl)acetylene **1** and Aryl or Vinyl Halides and Triflates **2**.[a]

Entry	Aryl or vinyl halide and triflate **2**	Time [h]	Yield [%] of **3**[b]	
1	*p*-MeO-C_6H_4-I	1.5	92	**a**
2	*p*-MeCO-C_6H_4-I	2	97	**b**
3	*p*-MeCOO-C_6H_4-I	2	86	**c**
4	*p*-F-C_6H_4-I	2	74	**d**
5	PhI	4	72	**e**
6	*p*-Me-C_6H_4-I	4	69	**f**
7	*o*-Me-C_6H_4-I	4	22	**g**
8	*p*-MeCO-C_6H_4-Br	5	90[c]	**h**
9	PhCH = CHBr[d]	2	90	**i**
10		2	75	**j**
11		4	68	**k**
12		2	87	**l**
13		2	85	**m**
14		2	86	**n**
15		1	95	**o**
16		1	91	**p**

[a] Unless otherwise stated, reactions were conducted at 7.5×10^{-2} M in starting substrate in anhyd DMSO (5 mL) at 50 °C using the following molar ratios: **1**:**2**:$Pd(PPh_3)_4$:K_2CO_3 = 1:1:0.05:5.
[b] Yields refer to single runs and are given for isolated products**.** All new products had satisfactory elemental analysis and their spectra were consistent with the postulated structures.
[c] At 100 °C.
[d] Employed as a commercially available *E/Z* mixture. However, only the indolo[1,2-*c*]quinazoline derivative containing the *E* styryl fragment was isolated.

To sum up, we have demonstrated that the palladium-catalyzed reaction of readily available bis(*o*-trifluoroacetamidophenyl)acetylene with aryl or vinyl halides and triflates provides a straightforward new route to the construction of the indolo[1,2-*c*]quinazoline skeleton. The methodology can tolerate many important functional groups and should allow for easy access to a wide variety of substituted derivatives of this class of compounds.

Acknowledgment

Work carried out in the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome. Financial support of this research by the University „La Sapienza", Rome, and by the Consiglio Nazionale delle Ricerche (CNR) is also gratefully acknowledged.

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(10) Bis(*o*-trifluoroacetamidophenyl)acetylene **1** was prepared as follows: to a solution of *o*-(*o*-aminophenylethynyl)trifluoroacetanilide[7] (1.0 g, 3.29 mmol) in THF (10 mL) trifluoroacetic anhydride (0.929 mL, 6.58 mmol) was added dropwise at 0 °C. The solution was stirred at room temperature for 2 h. Then, *n*-hexane (50 mL) was added and the resulting suspension was filtered to give **1** in quantitative yield: mp: 262-263 °C; IR (KBr) 3329, 1710 cm^{-1}; ^{1}NMR (DMSO-d_6): δ = 10.60 (bs, 2 H), 7.71-7.42 (m, 8 H); ^{13}C NMR (DMSO-d_6): δ = 155.1 (q, *J* = 37.0 Hz), 135.7, 132.2, 129.8, 127.6, 126.7, 119.4, 116.0 (q, *J* = 288.5 Hz), 90.4; MS *m/z* (relative intensity) 400 (M^+, 66), 331(11), 286 (50), 234 (100). Anal. Calcd for $C_{18}H_{10}N_2F_6O_2$: C, 54.01; N, 7.00 H, 2.52. Found: C, 54.09; N, 7.02; H, 2.51.
(11) A typical procedure is as follows (Table 2, entry 3): to a solution of bis(*o*-trifluoroacetamidophenyl)acetylene **1** (0.150 g, 0.375 mmol), 4-carbethoxyphenyl iodide (0.075 mL, 0.450 mmol) and K_2CO_3 (0.256 g, 1.875 mmol) in DMSO (5 mL) under argon, $Pd(PPh_3)_4$ (0.022 g, 0.019 mmol) was added. The mixture was stirred at 50 °C for 2 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated under vacuum. The residue was chromatographed on silica gel eluting with *n*-hexane/ethyl acetate (95/5 v/v) to afford 0.140 g (86%) of 4-(6-trifluoromethylindolo[1,2-*c*]quinazolin-12-yl)-benzoic acid ethyl ester **3c**: mp 149-150 °C; IR (KBr) 2982, 1710 cm^{-1}; ^{1}H NMR δ = 8.26 (d, *J* = 8.1 Hz, 2 H), 8.19 (bs, 1 H), 7.84 (d, *J* = 8.1 Hz, 2 H), 7.71-7.35 (m, 7 H), 7.25 (t, *J* = 6.8 Hz, 1 H),), 4.47 (q, *J* = 6.8 Hz, 2 H),), 1.46 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ = 166.5, 139.1, 137.1, 130.9, 130.5, 130.4, 130.3, 129.9, 129.3, 129.1, 129.0, 124.6, 124.1, 123.6, 121.9, 119.4, 119.1 (q, *J* = 275.2 Hz), 114.5 (q, *J* = 7.7 Hz), 113.9, 61.3, 14.5; MS *m/z* (relative intensity) 434 (M^+, 85), 389(100). Anal. Calcd for $C_{25}H_{17}N_2F_3O_2$: C, 69.12; N, 6.45 H, 3.94. Found: C, 69.20; N, 6.48 H, 3.92.
The structure of **3c** was unambiguously confirmed by X-ray analysis. Crystallographic Structure Solution: crystals of **3c** were obtained by slow evaporation of a chloroform solution. Room temperature crystallographic data were collected, by means of a MarResearch 345 Imaging Plate, at the XRD1 synchrotron beamline at Elettra. Wavelength was set to 0.75 Å by means of a double crystal Si (1×1×1)monochromator. Two different data collection were carried out in order to collect good high resolution data and to avoid saturation of the intense low resolution reflections. A grand total of 720 degrees of oscillation were acquired. Raw data were indexed, integrated and then scaled together by using HKL package.[12] The crystal system was found monoclinic with a unit cell: a = 18.130(4), b = 4.7260(10), c = 24.668(6), β = 103.13(2), after the inspection of systematic absences the space group was found P 21/a. Data were merged together giving 4734 unique reflections, the Rmerge was 0.031. The structure solution was solved by direct methods, using the SIR92 program.[13] All the non H atoms of the molecule were clearly identified. Refinement of the structure, based on F^2, was then carried out by using SHELX97[14] refinement program. The final anisotropic refinement cycle (289 parameters)gave R1 = 0.0483 [for I > 2σ(I)] and *w*R2 = 0.1469.
X-ray data were deposited at the Cambridge Crystallographic Data Centre, deposition number: CCDC 167173.
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