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12-Acylindolo[1,2-*c*]quinazolines by Palladium-Catalyzed Cyclocarbonylation of *o*-Alkynyltrifluoroacetanilides

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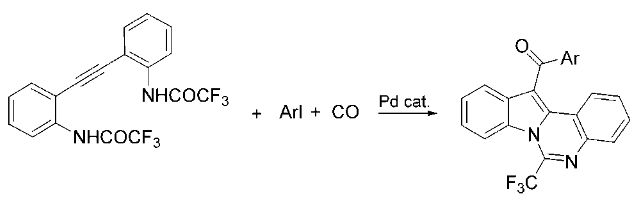
ABSTRACT

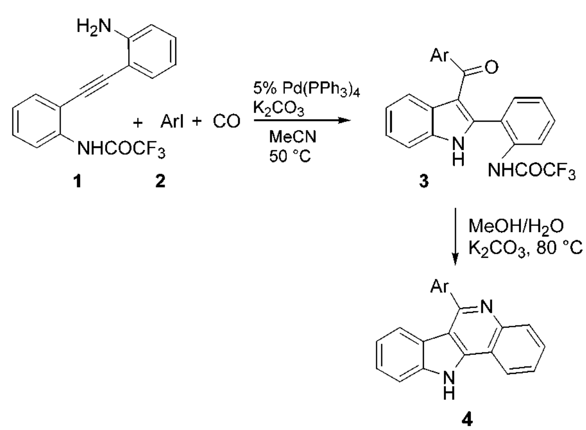


6-Trifluoromethyl-12-acylindolo[1,2-*c*]quinazolines are prepared in high yield through the palladium-catalyzed reaction of bis(*o*-trifluoroacetamidophenyl)acetylene with aryl or vinyl halides and triflates. The reaction, which tolerates a variety of important functional groups, probably involves the formation of a 3-acyl-2-(*o*-trifluoroacetamidophenyl)indole intermediate, followed by its cyclization to the indoloquinazoline product.

We have recently reported that *o*-(*o*-aminophenylethynyl)-trifluoroacetanilide **1** reacts with aryl iodides in the presence of carbon monoxide to give 2-(*o*-trifluoroacetamidophenyl)-3-acylindole **3** derivatives that, in turn, cyclize to indolo-[3,2-*c*]quinolines **4**[1] (Scheme 1). During this study, formation of 6-trifluoromethyl-12-acylindolo[1,2-*c*]quinazolines[2,3] as byproducts was observed in some cases. For example, the reaction of **1** with *m*-trifluoromethylphenyl iodide under our standard conditions [$Pd(PPh_3)_4$, K_2CO_3, MeCN, 50 °C] afforded the expected 3-acylindole derivative **3a** in 66% yield along with a 17% yield of the indoloquinazoline product **5a** (Scheme 2).

The presence of the indolo[1,2-*c*]quinazoline skeleton in natural substances such as Hinckdentine A,[4] an unusual marine alkaloid that has been isolated from the bryozoan

Scheme 1



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(3) For a review on indolo[1, 2-*c*]quinazolines, see: Billimoria, A. D.; Cava, M. P. *Heterocycles* **1996**, *42*, 453−473.

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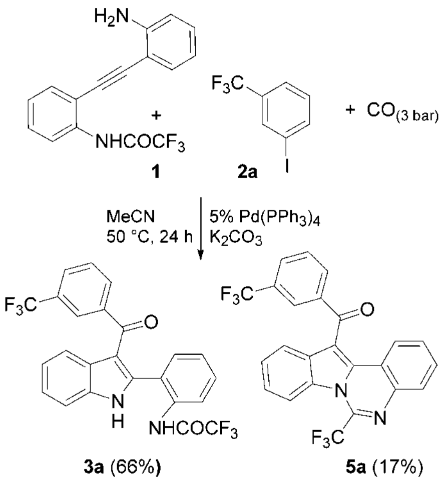
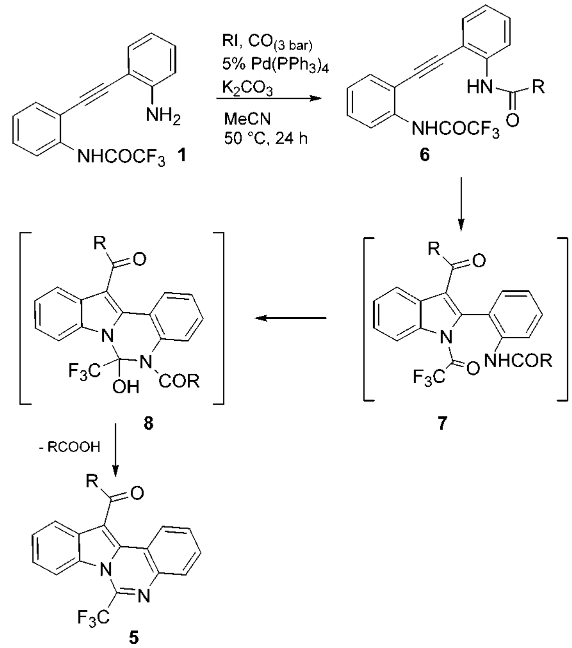
Scheme 2



Scheme 3



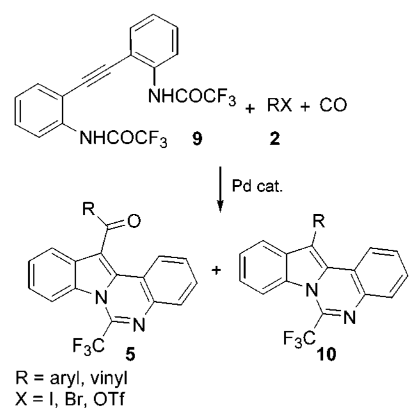
Hincksinoflustra denticulata, as well as the biological activity exhibited by certain derivatives of indolo[1,2-*c*]quinazoline,[5,6] prompted us to investigate further the cyclization of **1** to indolo[1,2-*c*]quinazoline products and, possibly, the synthetic scope of the reaction.

Our initial studies focused on understanding the mechanism of formation of the indoloquinazoline skeleton and showed that **5a**, under reaction conditions, is not generated from **3a** through the nucleophilic attack of the indole nitrogen to the carbonyl of the ortho trifluoroacetamido group. We therefore reasoned that formation of the indoloquinazoline skeleton would involve the following key steps: (1) conversion of the free amino group of **1** into the amide derivative **6** via acylation with an acylpalladium complex formed in situ, (2) aminopalladation−reductive elimination domino reaction to afford the 3-acylindole derivative **7**,[1,7,8] (3) formation of the tetracyclic intermediate **8** via intramolecular nucleophilic attack of the ortho nitrogen to the carbonyl of the trifluoroacetyl group, and (4) subsequent elimination of a carboxylic acid (Scheme 3).

On the basis of this assumption, we prepared the amide **6a** (R = *m*-CF_3−C_6H_4−; the possible intermediate in the formation of **5a** from **1** and **2a**) and subjected it to *m*-trifluoromethylphenyl iodide in the presence of $Pd(PPh_3)_4$, carbon monoxide (3 bar), and anhydrous K_2CO_3 in anhydrous MeCN at 50 °C for 24 h. We were pleased to find that the indoloquinazoline product **5a** was obtained in 70% yield. Employment of anhydrous MeCN and K_2CO_3 was suggested by the observation that early hydrolysis of the trifluoroacetamido group could otherwise take place, thus preventing cyclization. The acidity of the −NHCOR group in compound **6** was also found to play an important role in the formation of the indoloquinazoline skeleton. Indeed, the reaction of **6b** (R = CH_3−) with *m*-trifluoromethylphenyl iodide, under the same reaction conditions, afforded **5a** in only 44% yield.

Consequently, we decided to employ the readily available[9] bis(*o*-trifluoroacetamidophenyl)acetylene **9** (Scheme 4) as the building block for such a transformation.

Scheme 4



The development of an optimum set of reaction conditions was briefly investigated. Solvents, the pressure of carbon

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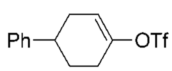
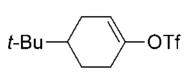
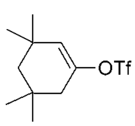
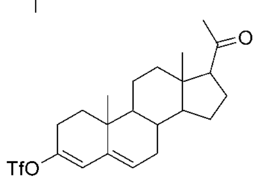
Table 1. Palladium-Catalyzed Synthesis of 6-Trifluoromethyl-12-acylindolo[1,2-*c*]quinazolines **5** from Bis(*o*-trifluoroacetamidophenyl)acetylene **9**, Organic Halides or Triflates **2**, and Carbon Monoxide[a]

entry	RX **2**		yield % of **5**[b,c]
1	*m*-CF_3-C_6H_4-I	**a**	89 (9)
2	3,5-$(CF_3)_2$-C_6H_3-I	**b**	38 (30)[d]
3	*p*-Cl-C_6H_4-I	**c**	60 (5)
4	*p*-F-C_6H_4-I	**d**	92 (6)
5	*o*-F-C_6H_4-I	**e**	82 (14)
6	*p*-EtOOC-C_6H_4-I	**f**	87 (6)
7	*p*-MeOC-C_6H_4-I	**g**	68
8	*p*-NO_2-C_6H_4-I	**h**	34 (23)
9	PhI		85
10	*p*-Me-C_6H_4-I	**i**	90
11	*o*-Me-C_6H_4-I	**l**	93 (5)
12	*p*-MeO-C_6H_4-I	**m**	88
13	PhCH=CH-Br	**n**	78[e]
14		**o**	60 (15)
15		**o**	75 (2)[f]
16		**o**	98[g]
17		**p**	68[g]
18		**q**	90[g]
19		**r**	80(5)[g]

[a] Unless otherwise stated, reactions were conducted at 1.25×10^{-2} M concentrations of starting substrates in anhydrous MeCN (2 mL) at 50 °C under 5 bar of carbon monoxide, for 24 h, using the following molar ratio: **9**:**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 analyses, and their spectra were consistent with the postulated structures. [c] Numbers in parentheses represent the yields of side products **10**. [d] Under 10 bar of carbon monoxide, **5b** and **10b** were isolated in 24 and 54% yields, respectively. [e] Employed as a commercially available *E/Z* mixture. However, only the 12-acylindolo[1,2-*c*]quinazoline derivative containing the (*E*)-styryl fragment was isolated. [f] In the presence of 1.1 equiv of *n*-Bu_4NBr. [g] In the presence of 1.1 equiv of *n*-Bu_4NI.

monoxide, and the nature of the organic halide or triflate were found to influence the reaction outcome, particularly the selectivity between the 12-acylindoloquinazoline product **5** and the 12-arylindoloquinazoline product **10**. For example, the reaction of **9** with *p*-iodoanisole under a balloon of carbon monoxide [$Pd(PPh_3)_4$, K_2CO_3, 50 °C, 24 h] gave the expected **5m** in 88% yield in MeCN, while in DMSO, the 12-aryl-derivative **10m**, not incorporating a molecule of carbon monoxide, was isolated in 78% yield. With aryl iodides bearing electron-withdrawing substituents, a higher pressure of carbon monoxide was found necessary to increase the ratio of **5** to **10**. However, the use of an excessive pressure of carbon monoxide gave lower yields of **5**. In practice, it appears that an optimum pressure of carbon monoxide has to be used to get the best results. For example, when the reaction was carried out in MeCN under a balloon of carbon monoxide with a moderate electron-poor aryl iodide such as *m*-trifluoromethylphenyl iodide, **5a** was isolated in 69% yield along with a 21% yield of **10a**. Raising the pressure of carbon monoxide up to 5 bar led to the isolation of **5a** in 89% yield (**10a** was obtained in 9% yield). A further increase in the pressure of carbon monoxide (10 bar), however, produced **5a** in lower yield (70%), though **10a** was isolated in only 4% yield.

In summary, the best standard reaction conditions thus far developed employ 1 equiv of **9** (0.25 mmol), 1 equiv of the organic halide or triflate **2**, 0.05 equiv of $Pd(PPh_3)_4$, and 5 equiv of anhydrous K_2CO_3 in anhydrous MeCN (2 mL) at 50 °C under 5 bar of carbon monoxide.

Under these conditions, a high **5** to **10** selectivity was usually observed and a variety of aryl iodides afforded the desired indoloquinazoline derivatives in good to high yields (Table). Among the aryl iodides investigated, only with 3,5-di(trifluoromethyl)phenyl iodide and *p*-nitrophenyl iodide were the two indoloquinazoline products isolated in almost equimolar amounts (entries 2 and 8). The presence of ortho substituents in the aryl iodide does not seem to hamper the reaction (cf. entry 10 with entry 11).

With vinylic triflates, the addition of *n*-Bu_4NBr or *n*-Bu_4-NI was found to show a remarkably beneficial effect on the ratio of **5** to **10**. The best results were observed in the presence of *n*-Bu_4NI (cf. entry 14 with entries 15 and 16).

In conclusion, this palladium-catalyzed reaction provides a straightforward route to 12-acylindolo[1,2-*c*]quinazolines from readily available bis(*o*-trifluoroacetamidophenyl)acetylene and a variety of aryl iodides and vinyl triflates. The methodology can tolerate many important functional groups and should allow for easy access to substituted derivatives of this class of compounds.

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Supporting Information Available: Preparation of bis-(*o*-trifluoroacetamidophenyl)acetylene **9**, a typical experimental procedure for the preparation of 12-acylindolo[1,2-*c*]quinazolines **5**, and characterization data for all the compounds listed in Table. This material is available free of charge via the Internet at http://pubs.acs.org.

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