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2,3-Disubstituted pyrrolo[2,3-*b*]quinoxalines via aminopalladation–reductive elimination

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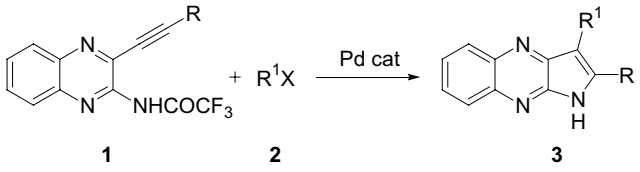
Abstract—2,3-Disubstituted pyrrolo[2,3-*b*]quinoxalines have been prepared in good to high yield through the reaction of 2-alkynyl-3-trifluoroacetamidoquinoxalines with aryl and vinyl halides or triflates in the presence of $Pd(PPh_3)_4$ and K_2CO_3 in MeCN at 100 °C.

The quinoxaline nucleus is present in many pharmaceutical agents exhibiting a broad spectrum of biological activities such as antiviral,[1] antiglucoma,[2] and anticancer[3] activity. Recently, novel pyrrolo[1,2-*a*]quinoxalines have been proved to be potent and selective 5-HT_3 receptor ligands.[4] Because of this, a variety of conventional methods have been developed for the preparation of quinoxaline derivatives.[5] A solid-phase synthesis of quinoxalines has also been described.[6] Rather surprisingly, palladium catalysis, despite its remarkable versatility and efficiency in the synthesis of heterocyclic compounds,[7] has very rarely been mentioned in this area. To the best of our knowledge, Suzuki[8] and Stille[8,9] cross-coupling reactions have been applied to the synthesis of quinoxaline derivatives from haloquinoxalines and an intramolecular Heck reaction[10] on aminoquinoxaline scaffolds has been used in the synthesis of 3-substituted pyrrolo[2,3-*b*]quinoxalines.

As far as pyrrolo[2,3-*b*]quinoxalines are concerned, our aminopalladation–reductive elimination procedure[11] appeared particularly suited for the construction of the functionalized pyrrole ring incorporated into the pyrroloquinoxaline system. Therefore, as part of a program devoted to the development of new synthetic procedures to drug-like products starting from the quinoxaline skeleton, we decided to explore the extension of this chemistry to the synthesis of pyrrolo[2,3-*b*]quinoxaline derivatives.

Here we illustrate a direct entry to 2,3-disubstituted pyrrolo[2,3-*b*]quinoxalines **3** through the reaction of 2-alkynyl-3-trifluoroacetamidoquinoxalines **1** with aryl and vinyl halides or triflates **2** (Scheme 1).

The starting alkynes **1** were prepared from commercially available phenylenediamine as shown in Scheme 2. Treatment of phenylenediamine with diethyl oxalate afforded 1,4-dihydroquinoxaline-2,3-dione.[12] Treatment of 1,4-dihydroquinoxaline-2,3-dione with PBr_5 gave 2,3-dibromoquinoxaline,[13] which was converted into **4**[14] (the procedure described in literature[15] was slightly



1 **2** **3**

R = Ph, **1a**
R = $CH_3(CH_2)_4$-, **1b**
R = *p*-MeO-C_6H_4-, **1c**
R = *m*-MeO-C_6H_4-, **1d**

Scheme 1.

Keywords: Quinoxalines; Alkynes; Palladium; Cyclization; Aminopalladation–reductive elimination.

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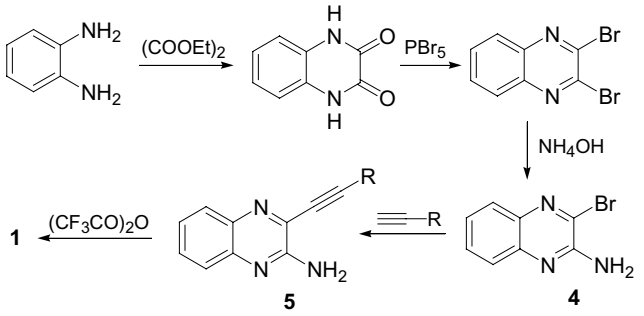


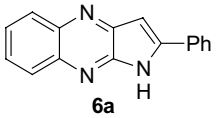
Scheme 2.

modified). The reaction of **4** with 1-alkynes in the presence of $PdCl_2(PPh_3)_2$, CuI, and Et_2NH in DMF at 40 °C[16] afforded the corresponding coupling derivative **5** (R = Ph, **5a**, 85% yield; R = $CH_3(CH_2)_4$–, **5b**, 65%; R = *p*-MeO–C_6H_4–, **5c**, 92%; R = *m*-MeO–C_6H_4–, **5d**, 96%). Treatment of **5** with 2 equiv of trifluoroacetic anhydride and 1 equiv of triethylamine in THF at room temperature furnished the trifluoroacetamido products **1a–d** in almost quantitative yield (compounds **1** were used without further purification during the present study).

The trifluoroacetamido group was used because it was found by us to be the nitrogen derivative of choice for favoring palladium-catalyzed cyclizations[11] of *o*-alkynylaniline derivatives involving η^2-alkyne organopalladium intermediates. In addition, it allows for the formation of free N–H pyrrole nuclei (the amide bond is broken during the reaction or/and the workup), avoiding troublesome and time-consuming deprotecting steps.

The influence of temperature, bases, and solvents on the reaction of **1** with **2** was briefly investigated using **1a** (R = Ph) and *p*-iodoanisole as the model system in the presence of $Pd(PPh_3)_4$. The results of this study are shown in Table 1.

The best results in terms of yields and **1a** to **6a** ratio were obtained in MeCN, at 100 °C using Cs_2CO_3 (Table 1, entry 3) or K_2CO_3 (Table 1, entry 4) as the bases. Compound **6a** is most probably generated through a base-catalyzed cyclization of **1a**. Accordingly, **6a** was isolated in 21% yield when **1a** was reacted under the conditions described in Table 1, entry 4, omitting *p*-iodoanisole and the palladium catalyst. The starting material was recovered in 13% yield and the amino product **5a**, derived from the hydrolysis of **1a**, was isolated in 59% yield. The hypothesis that **6a** may be formed through the base-catalyzed cyclization of **5a** was ruled out on the basis of the fact that **5a** was recovered essentially unchanged after treatment with K_2CO_3 in MeCN at 100 °C for 2 h (no evidence of **6a** was obtained). To check the role of the trifluoroacetamido group in the cyclization step, **5a** was reacted with *p*-iodoanisole under the conditions described in Table 1, entry 4. No 2,3-disubstituted pyrroloquinoxaline product was observed and the starting material was recovered in 82% yield thus emphasizing the role of the trifluoroacetamido group in the cyclization step.



6a

The best conditions developed so far [1 equiv of **1a**, 1.5 equiv of aryl halide, 3 equiv of K_2CO_3, 5 mol% of $Pd(PPh_3)_4$ in MeCN at 100 °C] have been used when the process was extended to include other aryl and vinyl halides or triflates.[17] K_2CO_3 was usually employed instead of Cs_2CO_3 because of its lower cost.

As shown in Table 2, the nature of the aryl halide plays a key role in controlling the reaction outcome, the best results being obtained in the presence of electron-donating or slightly electron-withdrawing substituents. With aryl halides containing strongly electron-withdrawing groups, byproducts **6** are isolated in significant yields and, in some cases (Table 2, entry 10), as the main reaction products.

As to the mechanism of the cyclization reaction, we believe that the reaction proceeds through the basic steps of the aminopalladation–reductive elimination reaction:[11] (a) formation of an η^2-alkyne–σ-organopalladium complex via the reaction of **1** with an organopalladium intermediate generated *in situ* through the oxidative addition of the organic halide or triflate to Pd(0), (b) intramolecular nucleophilic attack of the nitrogen nucleophile across the carbon–carbon triple bond, (c) reductive elimination of the resultant σ-pyrrolyl-σ-organopalladium intermediate that furnishes the desired product **3** and regenerates the active palladium catalyst. Very likely, the beneficial effect of the trifluoroacetyl group on the cyclization step is due to its ability to favor the formation of a stronger anionic nitrogen

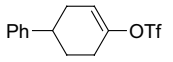
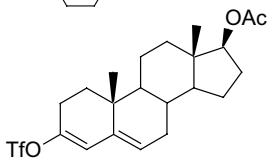
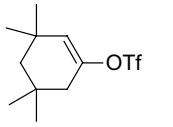
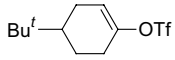
Table 1. Solvent, base, and temperature in the synthesis of **3a** from **1a**[a]

Entry	*T* (°C)	*t* (h)	Solvent	Base	Yield (%)[b] of **3a**	Yield (%)[b] of **6a**
1	80	2	MeCN	K_2CO_3	67	10
2	80	8	DMSO	K_2CO_3	—	—
3	100	2	MeCN	Cs_2CO_3	70	4
4	100	2	MeCN	K_2CO_3	70	4

[a] Reactions were carried out on a 0.293 mmol scale in 3 mL of solvent using 1 equiv of **1a**, 1.5 equiv of *p*-iodoanisole, 3 equiv of base, and 5 mol% of $Pd(PPh_3)_4$.

[b] Yields are given for isolated products.

Table 2. Palladium-catalysed synthesis of 2,3-disubstituted pyrrolo[2,3-*b*]quinoxalines **3** from 2-alkynyl-3-trifluoroacetanilides **1** and aryl/vinyl halides or triflates **2**[a]

Entry	**2**	**1**	*t* (h)	**3** Yield (%)[b]	**6** Yield (%)[b]
1	*p*-MeO–C_6H_4–I	**1a**	2	70 **3a**	4 **6a**
2	*p*-MeO–C_6H_4–Br[c]	**1a**	8	66 **3a**	traces
3	*p*-MeO–C_6H_4–I	**1b**	4	45 **3b**	18 **6b**
4	*m*-CF_3–C_6H_4–I	**1a**	4	75 **3c**	5 **6a**
5	*m*-CF_3–C_6H_4–I	**1c**	2	70 **3d**	20 **6c**
6	*p*-F–C_6H_4–I	**1c**	2	75 **3e**	25 **6c**
7	3,5-$(CF_3)_2$–C_6H_3–I	**1d**	15	70 **3f**	27 **6d**
8	3,5-$(Me)_2$–C_6H_3–I	**1d**	15	82 **3g**	10 **6d**
9	2-NO_2–4-Me–C_6H_3–I	**1d**	15	70 **3h**	14 **6d**
10	*p*-PhCO–C_6H_4–OTf[c]	**1a**	3	30[d] **3i**	40 **6a**
11	*p*-NO_2–C_6H_4–I	**1a**	3	40 **3j**	30 **6a**
12	*p*-NO_2–C_6H_4–OTf[c]	**1a**	3	48[d] **3j**	25 **6a**
13		**1a**	0.3	80[d] **3k**	10 **6a**
14		**1a**	0.5	83[d] **3l**	—
15		**1a**	0.5	95[d] **3m**	—
16		**1a**	0.5	73[d] **3n**	—

[a] Unless otherwise stated, reactions were carried out on a 0.293 mmol scale in 3 mL of MeCN at 100 °C by using 1 equiv of **1a**, 1.5 equiv of aryl halide, 3 equiv of base, and 5 mol% of $Pd(PPh_3)_4$.
[b] Yields are given for isolated products.
[c] 120 °C.
[d] Carried out by using 1.1 equiv of organic triflate.

nucleophile or to promote the intramolecular nucleophilic attack by proton removal in the transition state leading to the cyclization adduct.

In conclusion, the chemistry outlined here provides a simple, straightforward method for the synthesis of functionalized pyrrolo[2,3-*b*]quinoxalines via the palladium-catalyzed reaction of readily available 2-alkynyl-3-trifluoroacetamidoquinoxalines with a variety of aryl and vinyl halides or triflates. Although moderate yields are obtained with strongly electron-poor aryl halides or triflates, the process holds considerable promise for the synthesis of pyrroloquinoxalines containing a highly functionalized pyrrole ring.

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References and notes

1. Harmenberg, J.; Akesson-Johansson, A.; Gräslund, A.; Malmfors, T.; Bergman, J.; Wahren, B.; Akerfeldt, S.; Lundblad, L.; Cox, S. *Antiviral Res.* **1991**, *15*, 193.
2. David, R. *Exp. Opin. Invest. Drug* **1998**, *7*, 1063.
3. Naylor, M. A.; Stephen, M. A.; Nolan, J.; Sutton, B.; Tochcer, J. H.; Fielden, E. M.; Adams, G. E.; Strafford, I. J. *Anticancer Drug Res.* **1993**, *8*, 439.
4. (a) Campiani, G.; Cappelli, A.; Nacci, V.; Anzini, M.; Vomero, S.; Hamon, M.; Cagnotto, A.; Fracasso, C.; Uboldi, C.; Caccia, S.; Consolo, S.; Mennini, T. *J. Med. Chem.* **1997**, *40*, 3670; (b) Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Dalla Valle, F.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362.
5. See, for example: (a) Kreher, R.; Use, G. *Tetrahedron Lett.* **1978**, 4671; (b) Ames, D. E.; Mitchell, J. C.; Takundwa, C. C. *J. Chem. Res.* **1985**, 144; (c) Sugita, M.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1992**, *29*, 771; (d) Zhang, X.-c.; Huang, W.-y. *Tetrahedron* **1998**, *54*, 12465; (e) Kobayashi, K.; Matoba, T.; Irisawa, S.; Matsumoto, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1998**, 551; (f) Kobayashi, K.; Matsumoto, T.; Irisawa, S.; Yoneda, K.; Morikawa, O.; Konishi, H. *Heterocycles* **2001**, *55*, 973, Refs. 4a,b.
6. Wu, Z.; Ede, N. J. *Tetrahedron Lett.* **2001**, *42*, 8115.

7. Li, J. J.; Gribble, G. W. In *Palladium in Heterocyclic Chemistry. A Guide for Synthetic Chemists*; Baldwin, J. E., Williams, R. M., Eds.; Pergamon: Amsterdam, 2000.
8. Li, J. J.; Yue, W. S. *Tetrahedron Lett.* **1999**, *40*, 4507.
9. Dinsmore, A.; Garner, C. D.; Joule, J. A. *Tetrahedron* **1998**, *54*, 3291.
10. Li, J. J. *J. Org. Chem.* **1999**, *64*, 8425.
11. For a review, see: Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.
12. Sarges, R.; Howard, H. R.; Browne, R. G.; Lebel, L. A.; Seymour, K.; Koe, B. K. *J. Med. Chem.* **1990**, *33*, 2240.
13. Usherwood, E. H.; Whiteley, M. A. *J. Chem. Soc.* **1923**, 1069.
14. Synthesis of 2-amino-3-bromoquinoxaline **4**: To a solution of 2,3-dibromoquinoxaline (2.00 g, 6.92 mmol) in DMSO/MeCN (8 mL/12 mL), NH_4OH (1.8 mL, 13.84 mmol, solution 30%) and K_2CO_3 (0.96 g, 6.92 mmol) were added. The solution was stirred at 50 °C for 120 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 130 g; *n*-hexane/EtOAc 75/25 v/v) to give 1.29 g of **5** (83% yield): mp 163–164 °C; IR (KBr): 3290, 3137; ^{1}H NMR ($CDCl_3$) δ 7.86 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.0$ Hz, 1H), 7.72–7.55 (m, 2H), 7.49–7.40 (m, 1H), 5.55 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 149.8, 141.0, 138.2, 130.6, 130.3, 128.5, 125.9, 125.7. Anal. Calcd for $C_8H_6BrN_3$: C, 42.88; H, 2.70; N, 18.75. Found: C, 42.74; H, 2.67; N, 18.88.
15. (a) Tanaka, K.; Takahashi, H.; Takimoto, K.; Sugita, M.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1992**, *29*, 771; (b) Iwata, S.; Sakajyo, M.; Tanaka, K. *J. Heterocycl. Chem.* **1994**, *31*, 1433.
16. (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-WCH: Weinheim, 1998; p 203; (b) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. 1, p 493.
17. Typical procedure for the synthesis of pyrrolo[2,3-*b*]quinoxalines **3**: To a solution of **1d** (0.100 g, 0.29 mmol) in MeCN (3 mL), 5-iodo-*m*-xylene (0.047 mL, 0.44 mmol), $Pd(PPh_3)_4$ (0.017 g, 0.015 mmol) and K_2CO_3 (0.202 g, 1.47 mmol) were added. The solution was stirred at 100 °C for 15 h. After cooling the reaction mixture was suspended on silica gel and the solvent evaporated. The residue was purified by chromatography (silica gel, 40 g; $CHCl_3/CH_2Cl_2$/MeOH 1/1/0.1 v/v/v) to give 0.091 g of **3g** (82% yield): mp 243–245 °C; IR(KBr): 3345, 3004, 1466, 1297 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.45 (s, 1H), 8.08 (dt, $J_1 = 9.3$ Hz, $J_2 = 1.1$ Hz, 2H), 7.72–7.65 (m, 2H), 7.35 (t, $J = 7.9$ Hz, 1H), 7.26 (t, $J = 1.7$ Hz, 1H), 7.21 (d, $J = 7.9$ Hz, 1H), 7.15 (s, 2H), 7.03–7.01 (m, 2H), 3.71 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 159.7, 145.2, 143.0, 140.9, 139.7, 137.8, 133.2, 132.7, 130.3, 129.4, 129.0, 128.7, 128.4, 128.0, 126.9, 121.6, 116.1, 114.4, 112.0, 55.6, 21.6. Anal. Calcd for $C_{25}H_{21}N_3O$: C, 79.13; H, 5.58; N, 11.07. Found: C, 78.80; H, 5.56; N, 11.03.