Tetrahedron Letters 51 (2010) 2409–2412

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

One-pot synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines via palladium-catalyzed heteroannulation in water

Ali Keivanloo *, Mohammad Bakherad, Amin Rahimi, Sayed Ali Naghi Taheri

School of Chemistry, Shahrood University of Technology, Shahrood, Iran

ARTICLE INFO

Article history:
Received 14 January 2010
Revised 10 February 2010
Accepted 19 February 2010
Available online 24 February 2010

Keywords:
Palladium
Pyrroloquinoxaline
Alkyne
Sonogashira reaction

ABSTRACT

The reaction of *N*-alkyl-3-chloroquinoxaline-2-amines with 1-alkynes, catalyzed by Pd–Cu, in the presence of sodium lauryl sulfate as the surfactant in water, leads to the one-pot formation of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines in good-to-high yields.

1. Introduction

Quinoxaline and its derivatives show a broad spectrum of biological activity including antitumor,[1] antiviral,[2] antituberculosis,[3] and anti-inflammatory,[4,5] and hence are an important class of nitrogen-containing heterocycles, and useful intermediates in organic synthesis.[6,7] Furthermore, pyrrolo[1,2-*a*]quinoxalines have been shown to be potent and selective 5-HT3 receptor ligands.[8] As a result, a number of synthetic strategies have been developed for the preparation of substituted quinoxalines.[9]

The Sonogashira reaction catalyzed by palladium and copper is a powerful and straightforward method for the construction of arylated internal alkyne compounds.[10] These are important intermediates in organic synthesis and for the preparation of natural products,[11] biologically active molecules,[12] molecular electronics,[13] and polymers.[14]

Typical Sonogashira reactions are generally performed in the presence of large amounts of palladium, and copper(I) iodide as a co-catalyst in organic solvents, which can be expensive and are detrimental to the environment. This protocol has been improved by several modifications, such as carrying out the reaction in aqueous medium, in an ionic liquid or under microwave irradiation,[15] along with the use of promoters (Zn, Mg, and Sn) or effective ligands.[16]

The use of water or aqueous solutions represents a technique to overcome the economical and the environmental problems caused by the use of organic solvents for metal-catalyzed reactions.[17] Several examples of Pd-catalyzed Sonogashira reactions in aqueous medium have been reported.[18]

In continuation of our recent studies[19] on the Pd-catalyzed reaction of acetylenes leading to heterocyclic compounds of biological significance, we became interested in developing a synthetic route to 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines in water.

In this Letter, a direct and convenient approach to the synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines in water is presented. In order to introduce two substituents on the pyrrolo[2,3-*b*]quinoxaline-fused system, our retrosynthetic analysis implicated the use of 1-alkynes and *N*-alkyl-3-chloroquinoxaline-2-amines as the starting materials. Palladium-catalyzed cross-coupling cyclization is the key step in this synthesis (Scheme 1).

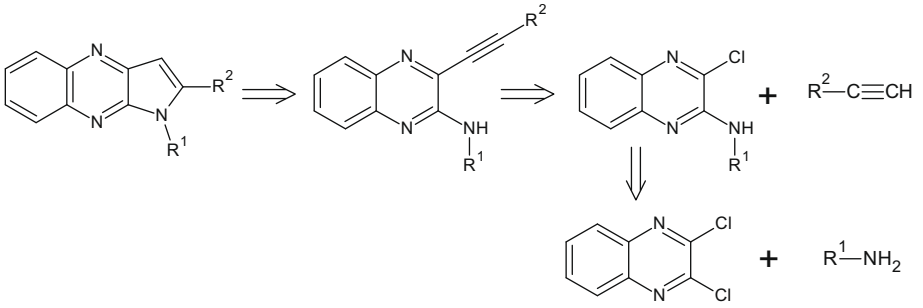
The starting materials **2a–d** were prepared from 2,3-dichloroquinoxaline **1** and primary alkyl amines in ethanol at reflux (Scheme 2).[20]

1,2-Disubstituted pyrrolo[2,3-*b*]quinoxalines **4a–f** were synthesized by the reaction of *N*-alkyl-3-chloroquinoxaline-2-amines **2a–d** with alkynes **3a–c** in the presence of palladium chloride, triphenylphosphine, copper(I) iodide, sodium lauryl sulfate, and potassium carbonate at 70 °C in water under an argon atmosphere (Scheme 3). The results are shown in Table 1.

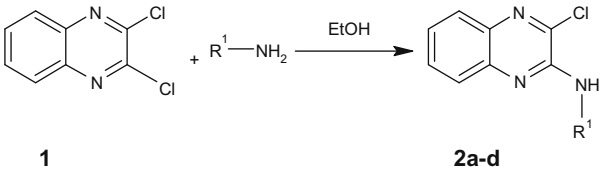
Although $PdCl_2/PPh_3$ was the catalyst of choice, the addition of copper(I) iodide was essential as the co-catalyst. The reactions carried out with $PdCl_2$ alone led to poor yields of mixtures of products. Potassium carbonate was found to be a suitable base for the reaction giving cleaner products and better yields. The choice of surfactant was also critical for the success of the reaction as, without surfactant, the yields were lower than 10%.

* Corresponding author. Fax: +98 2733395441.
E-mail addresses: akeivanloo@yahoo.com, keivanloo@shahroodut.ac.ir (A. Keivanloo).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.02.123



Scheme 1. Reterosynthetic analysis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines.



R^1 = Me, Bn,*i*-Bu, *n*-Pr

Scheme 2. Nucleophilic substitution of 2,3-dichloroquinoxaline with aliphatic amines.

The ^{1}H NMR spectrum of **4a** exhibited an aromatic proton at δ 6.97, which was the characteristic of a fused pyrrole ring. The other nine aromatic protons appeared at 7.55–8.18 ppm. In the aliphatic region, the singlet at δ 3.94 was due to the *N*-methyl group. The mass spectrum displayed the molecular ion peak at *m*/*z* 259.

The following steps can be postulated for the mechanism for the formation of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines (Scheme 4): (i) oxidative addition of Pd(0) to the C–Cl bond; (ii) transmetallation with the Cu salt of the alkyne to generate the alkynyl palladium complex; (iii) reductive elimination results in the extrusion of Pd(0) to yield the substituted alkyne, and (iv) finally nucleophilic attack of the nitrogen on the triple bond activated by Cu(I) leads to intermolecular cyclization and formation of products **4a–f**.

In conclusion, we have developed a palladium-catalyzed, one-pot reaction for the synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines from readily available starting materials in good-to-high yields.

2. General procedure for the preparation of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines

A mixture of *N*-alkyl-3-chloroquinoxaline-2-amine **1** (0.775 mmol), $PdCl_2$ (0.0387 mmol, 5 mol %), CuI (0.0775 mmol, 10 mol %), PPh_3 (0.0775 mmol, 10 mol %), sodium lauryl sulfate (0.0543 mmol, 7 mol %), and K_2CO_3 (2.322 mmol) in H_2O (5 mL) under an argon atmosphere was treated with 1-alkyne **3** (1.55 mmol) slowly, and the reaction mixture was stirred at 70 °C for 20 h. After completion of the reaction, the mixture was filtered, and the remaining solid was washed with H_2O and dried. The crude product was purified by column chromatography using $CHCl_3$–CH_3OH (98:2) as eluent.

2.1. 1-Methyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (4a)

Mp 143–145 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.94 (s, 3H, CH_3), 6.97 (s, 1H, CH, pyrrole), 7.55 (m, 3H, 3CH), 7.67 (m, 2H, 2CH), 7.74 (m, 2H, 2CH), 8.10 (dd, *J* = 6.5, 3.5 Hz, 1H, CH), 8.18 (dd, *J* = 6.5, 3.4 Hz, 1H, CH); IR (KBr): 3095, 2950, 1540, 1480, 1438, 695, 740 cm^{-1}; MS (EI) *m*/*z* 259 (M^+); Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.59; H, 5.11; N, 16.33.

2.2. 1-Benzyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (4b)

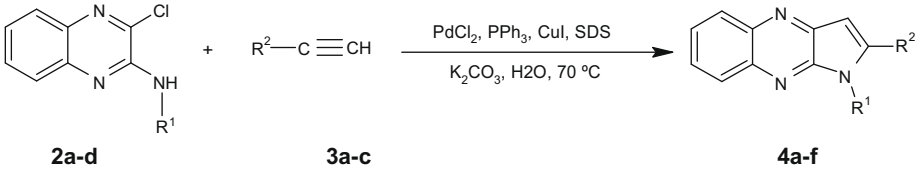
Mp 172–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 5.70 (s, 2H, CH_2), 6.92 (d, *J* = 6.8 Hz, 2H, 2CH), 7.03 (s, 1H, CH, pyrrole), 7.17–7.22 (m, 3H, 3CH), 7.53–7.54 (m, 3H, 3CH), 7.65–7.67 (m, 2H, 2CH), 7.73–7.75 (m, 2H, 2CH), 8.09 (dd, *J* = 6.5, 3.5 Hz, 1H, CH), 8.17 (dd, *J* = 6.5, 3.4 Hz, 1H, CH); IR (KBr): 3098, 1540, 1480, 1405, 740, 725 cm^{-1}; MS (EI) *m*/*z* 335 (M^+); Anal. Calcd for $C_{23}H_{17}N_3$: C, 82.36; H, 5.11; N, 12.53. Found: C, 82.42; H, 5.05; N, 12.58.

2.3. 1-(2-Methylpropyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (4c)

Wax; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.52 (d, *J* = 7.6 Hz, 6H, $2CH_3$), 1.87 (m, 1H, CH), 4.37 (d, *J* = 7.8 Hz, 2H, CH_2), 6.90 (s, 1H, CH, pyrrole), 7.48 (m, 3H, 3CH), 7.61 (m, 2H, 2CH), 7.69 (m, 2H, 2CH), 8.11 (dd, *J* = 6.5, 3.5 Hz, 1H, CH), 8.17 (dd, *J* = 6.5, 3.4 Hz, 1H, CH); IR (CCl_4): 3096, 2950, 1540, 1480,1374, cm^{-1}; MS (EI) *m*/*z* 301 (M^+); Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.53; H, 6.42; N, 14.07.

2.4. 1-Propyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (4d)

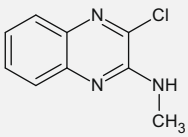
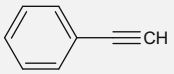
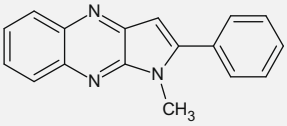
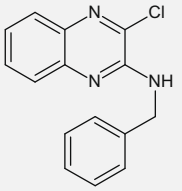
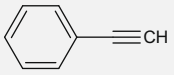
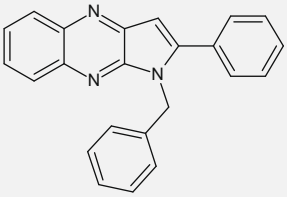
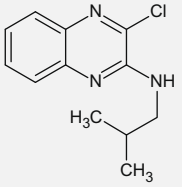
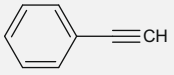
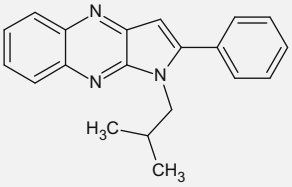
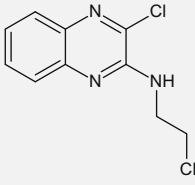
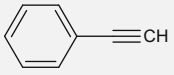
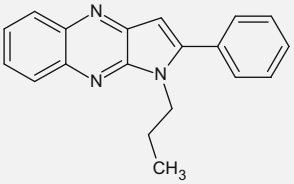
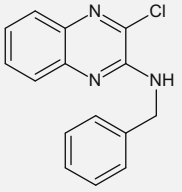
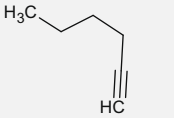
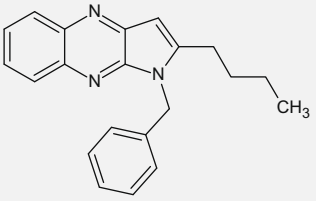
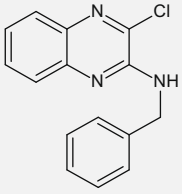
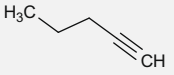
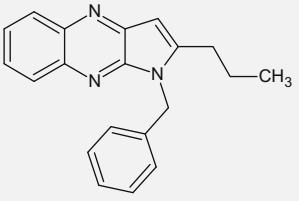
Wax; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.71 (t, *J* = 7.5 Hz, 3H, CH_3), 1.62 (m, 2H, CH_2), 4.39 (t, *J* = 7.7 Hz, 2H, CH_2), 6.88 (s, 1H,

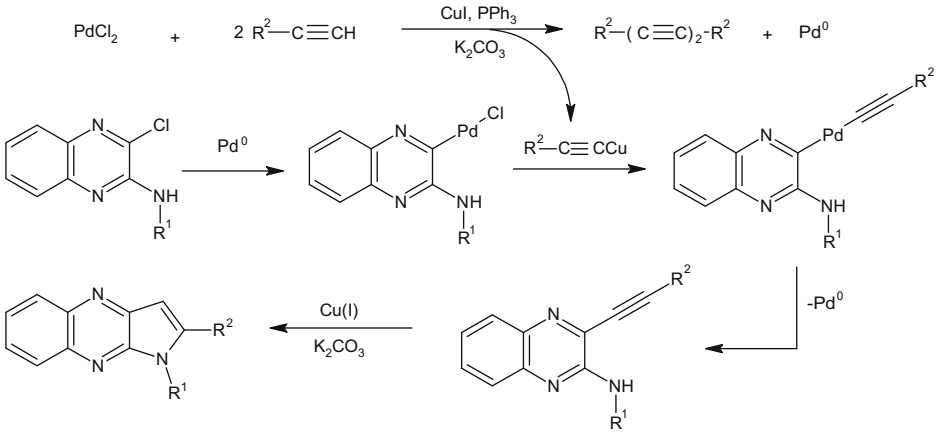


R^1 = Me, Bn,*i*-Bu, *n*-Pr
R^2 = Ph, *n*-C_4H_9, *n*-C_3H_7

Scheme 3. Sonogashira coupling of *N*-alkyl-3-chloroquinoxaline-2-amines **2a–d** with 1-alkynes **3a–c**.

Table 1
Synthesis of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines

Entry	Amine **2**	Alkyne **3**	Product		Yield (%)
1				**4a**	92
2				**4b**	87
3				**4c**	75
4				**4d**	70
5				**4e**	83
6				**4f**	78



Scheme 4. Proposed mechanism for the formation of 1,2-disubstituted pyrrolo[2,3-*b*]quinoxalines **4a–f**.

CH, pyrrole), 7.44 (m, 3H, 3CH), 7.56 (m, 2H, 2CH), 7.63 (m, 2H, 2CH), 8.01 (dd, J = 6.4, 3.4 Hz, 1H, CH), 8.09 (dd, J = 6.4, 3.2 Hz, 1H, CH); IR (CCl_4): 3098, 2930, 1545, 1480, 1428, 1120 cm^{-1}; MS (EI) m/z 287 (M^+); Anal. Calcd for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96; N, 14.62. Found: C, 79.59; H, 5.79; N, 14.80.

2.5. 1-Benzyl-2-butyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (4e)

Wax; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.86 (t, J = 7.8 Hz, 3H, CH_3), 1.41 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.81 (t, J = 7.6 Hz, 2H, CH_2), 5.72 (s, 2H, CH_2), 6.73 (s, 1H, CH, pyrrole), 7.12 (d, J = 6.8, 2H, 2CH), 7.22–7.27 (m, 3H, 3CH), 7.58–7.63 (m, 2H, 2CH), 8.05 (dd, J = 6.4, 3.4 Hz, 1H, CH), 8.12 (dd, J = 6.4, 3.5 Hz, 1H, CH); IR (CCl_4): 3060, 2920, 1543, 1418, cm^{-1}; MS (EI) m/z 315 (M^+); Anal. Calcd for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.76; H, 6.88; N, 13.25.

2.6. 1-Benzyl-2-propyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (4f)

Wax; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.95 (t, J = 7.7, 3H, CH_3), 1.60 (m, 2H, CH_2), 2.73 (t, J = 7.2, 2H, CH_2), 5.74 (s, 2H, CH_2), 6.75 (s, 1H, CH, pyrrole), 7.10 (d, J = 6.7, 2H, 2CH), 7.20–7.25 (m, 3H, 3CH), 7.56–7.61 (m, 2H, 2CH), 8.07 (dd, J = 6.4, 3.5 Hz, 1H, CH), 8.13 (dd, J = 6.5, 3.4 Hz, 1H, CH); IR (CCl_4): 3073, 2925, 1548, 1420, cm^{-1}; MS (EI) m/z 301 (M^+); Anal. Calcd for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.89; H, 6.27; N, 13.76.

Acknowledgment

The authors would like to thank the Research Council of Shahrood University of Technology for the financial support of this work.

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20. *General procedure for the preparation of N-alkyl-3-chloroquinoxaline-2-amines*: a mixture of 2,3-dichloroquinoxaline (0.01 mmol) and primary alkyl amine (0.02 mmol) in EtOH (5 mL) was heated under reflux for 4 h. The solvent was then removed under reduced pressure, and the resulting solid was washed with H_2O and dried. The product so obtained was pure enough to be used in the next step without any further purification.
3-Chloro-N-methylquinoxalin-2-amine (**2a**): yield, 95%; mp 89–90 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.07 (d, J = 5.3 Hz, 3H, CH_3), 7.51–8.13 (m, 5H, ArH, NH), IR (KBr): 3410 (NH), 1580, 1080, 750 cm^{-1}; Anal. Calcd for $C_9H_8N_3Cl$: C, 55.83; H, 4.16; N, 21.70. Found: C, 55.68; H, 4.31; N, 21.88.
N-Benzyl-3-chloroquinoxalin-2-amine (**2b**): yield, 92%; mp 69–71 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 4.75 (d, J = 6.1 Hz, 2H, CH_2), 7.12–8.23 (m, 10H, ArH, NH); IR (KBr): 3400 (NH), 1550, 1500, 1065 cm^{-1}; Anal. Calcd for $C_{15}H_{12}N_3Cl$: C, 66.79; H, 4.48; N, 15.58. Found: C, 66.61; H, 4.61; N, 15.66.
3-Chloro-N-(2-methylpropyl)quinoxalin-2-amine (**2c**): yield, 86%; mp 40–41 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.95 (d, J = 6.6 Hz, 6H, $2CH_3$), 2.14 (m, 1H, CH), 3.23 (d, J = 5.9 Hz, 2H, CH_2), 7.13–8.12 (m, 5H, ArH, NH), IR (KBr): 3400 (NH), 2800, 1540, 1520, 1080 cm^{-1}; Anal. Calcd for $C_{12}H_{14}N_3Cl$: C, 61.15; H, 5.99; N, 17.83. Found: C, 60.98; H, 5.88; N, 18.01.
N-Propyl-3-chloroquinoxalin-2-amine (**2d**): yield, 80%; mp 43–45 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.04 (t, J = 7.2 Hz, 3H, CH_3), 1.75 (m, 2H, CH_2), 3.56 (t, J = 6.6 Hz, 2H, CH_2), 7.11–7.84 (m, 5H, ArH, NH); IR (KBr): 3390 (NH), 2900, 1555, 1525, 1080 cm^{-1}; Anal. Calcd for $C_{11}H_{12}N_3Cl$: C, 59.60; H, 5.46; N, 18.95. Found: C, 59.80; H, 5.41; N, 18.87.