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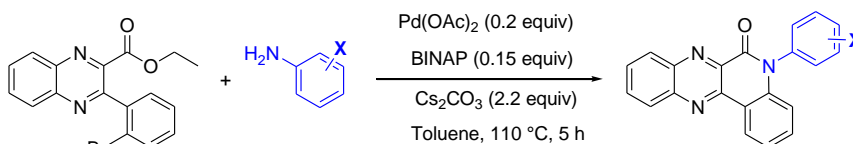
# Rapid and Convenient Synthesis of Original 5-(substituted)quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones under Eco-Friendly Conditions

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**Abstract**We report herein the synthesis of 5-(substituted)quinolino[3,4-*b*]quinoxalin-6(5*H*)-one derivatives from ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate under one-pot Buchwald-Hartwig coupling/lactamization reaction.

**Quinoline, Aromatic anilines, Buchwald-Hartwig reaction**

**Key words** quinoxaline, aromatic anilines, Buchwald-Hartwig reaction, lactamization reaction

## Introduction

Quinoxalines are common structural motifs in many natural and synthetic compounds with interesting biological activities. Many quinoxaline derivatives show a wide range of biological activities, making them potential antitumor,<sup>1</sup> antibiotic,<sup>2</sup> antiviral,<sup>3</sup> anti-HIV<sup>4</sup> and anti-inflammatory agents<sup>5</sup>. The list of their uses in medicinal chemistry is long.<sup>6</sup> The olaquinox (OLA), 2-[(2-hydroxyethyl)carbamoyl]-3-methylquinoxaline 1,4-dioxide, presents strong antimicrobial activities and is used in subtherapeutics (animal feed) to promote animal growth.<sup>7</sup> Quinacillin is significantly active (0.15–0.62 µg/mL, 0.32–1.35 µM) against *Staphylococcus aureus*.<sup>8</sup>

The phenanthridin group is present in many bioactive natural and pharmaceutical products.<sup>9</sup> They show particularly interesting biological activity as anticancer agents.<sup>10</sup> In order to synthesize structures with high biological activity potential, we combined the quinoxaline moiety with the phenanthridin moiety. Furthermore, to the best of our knowledge, few syntheses of quinolino[3,4-*b*]quinoxalin-6(5*H*)-one derivatives have been reported<sup>11</sup> and none used coupling reactions.

Palladium-catalyzed coupling reactions have been extensively used in medicinal chemistry. The synthesis process is not expensive and possesses a wide compatibility with many functional groups. This approach is an effective way of functionalizing the quinoxaline derivatives as Suzuki-Miyaura,<sup>12</sup> Sonogashira<sup>13</sup> or Buchwald-Hartwig<sup>14</sup> reactions, and the 2-bromophenylboronic acid (**2**) proved promising as a substrate for coupling/lactamization reaction.<sup>15</sup>

As part of our research program to develop new bioactive compounds,<sup>16</sup> we report herein the first one-pot Buchwald-Hartwig coupling/lactamization reaction in a quinoxaline series for the synthesis of 5-(substituted)quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones.

The starting product, for one-pot coupling/lactamization reaction, ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate **3**, was synthesized by Suzuki-Miyaura reaction between ethyl 3-chloroquinoxaline-2-carboxylate (**1**) and 2-bromophenylboronic acid (**2**) using 0.02 equiv of Pd(PPh<sub>3</sub>)<sub>4</sub> as a palladium source and 5 equiv of Na<sub>2</sub>CO<sub>3</sub> as a base in acetonitrile–water mixture (3/1) at 100 °C for 5 h (Scheme 1). The key product **3** was obtained in good yields (73%).<sup>17</sup>

## Scheme 1 Preparation of ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate (**3**)

Our initial strategy consisted in the introduction of the amide group from ester, first replacing the ethoxy group, which was followed by an intramolecular Buchwald-Hartwig reaction/cyclization. The amidation reaction was tested with starting product **3** and aniline in presence of *t*-BuOK at room temperature in toluene for 30 min. The formation of intermediate 3-(2-bromophenyl)-*N*-phenylquinoxaline-2-carboxamide was confirmed by TLC and LCMS. Then, we applied the coupling reaction conditions with different catalysts (Pd(OAc)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>), in presence of bases (K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, *t*-BuOK) at 110 °C. The best yield (44%) of 5-phenylquinolino[3,4-*b*]quinoxalin-6(5*H*)-one (**5a**) was obtained with palladium acetate, BINAP as supporting ligand and Cs<sub>2</sub>CO<sub>3</sub> at 110 °C for 12 h.

In view of these last poor yields, a simpler strategy was developed, only involving coupling reaction conditions with ethyl 3-

(2-bromophenyl)quinoxaline-2-carboxylate (**3**). Preliminary tests were conducted with ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate (**3**) and aniline with different catalysts [Pd(OAc)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub>], in the presence of base (K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, *t*-BuOK) at 110°C in toluene (Table 1).

A better yield was obtained with palladium acetate as catalyst and BINAP as ligand in presence of Cs<sub>2</sub>CO<sub>3</sub> in toluene at 110°C for 5h (97% yield).

**Scheme 2** Reaction of ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate (**3**) and aniline (**4a**)

**Table 1** Optimization reaction between ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate and aniline<sup>a</sup>

Entry	Catalyst <sup>a</sup>	Ligand <sup>a</sup>	Base <sup>a</sup>	Time (h)	Yield <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub>	BINAP	K <sub>2</sub> CO <sub>3</sub>	15	78
2	Pd(OAc) <sub>2</sub>	BINAP	<i>t</i> -BuOK	15	Complex mixture
3	Pd(OAc) <sub>2</sub>	BINAP	Cs <sub>2</sub> CO <sub>3</sub>	5	97
4	Pd(PPh <sub>3</sub> ) <sub>4</sub>	-	K <sub>2</sub> CO <sub>3</sub>	10	Starting material

<sup>a</sup> All reactions are performed using 1.5 equiv of aniline, 20 mol% of Pd, 15 mol% of ligand, and 2.2 equiv of base. <sup>b</sup> All yields refer to chromatographically pure products based on substrate **3**.

Aromatic amine	Product <sup>a</sup>	Yield <sup>b</sup> (%)
Aniline	<b>5a</b>	97
2-Chloroaniline	<b>5b</b>	63
3-Chloroaniline	<b>5c</b>	80
3-Fluoroaniline	<b>5d</b>	72
3-(Trifluoromethyl)aniline	<b>5e</b>	65
3-Aminobenzonitrile	<b>5f</b>	82
4-Chloroaniline	<b>5g</b>	82
4-Fluoroaniline	<b>5h</b>	88
4-Methoxyaniline	<b>5i</b>	17 (50) <sup>c</sup>
3,4-Chloroaniline	<b>5j</b>	50 (60) <sup>c</sup>
2,3-Chloroaniline	<b>5k</b>	76
<i>p</i> -Toluidine	<b>5l</b>	90

**Scheme 3** Synthesis of 5-(substituted)quinolino[3,4-*b*]quinoxalin-6(5*H*)-ones **5a–l**

**Table 2** Generalization of one-pot coupling/lactamization reactions

<sup>a</sup> All the reactions are performed using 1.5 equiv of aniline, 20 mol% of Pd(OAc)<sub>2</sub>, 15 mol% of BINAP, 2.2 equiv of Cs<sub>2</sub>CO<sub>3</sub> in toluene for 5h in 110°C. <sup>b</sup> All yields refer to chromatographically isolated pure products based

on substrate **3**.

<sup>c</sup> The reactions are performed using 20 mol% of Pd(OAc)<sub>2</sub>, 15 mol% of BINAP, 3 equiv of K<sub>2</sub>CO<sub>3</sub> in toluene for 24h in 110°C

After optimization of the conditions (Table 1, entry 3) we generalized the coupling/lactamization reaction with different aniline derivatives and the corresponding 5-(substituted)quinolino[3,4-*b*]quinoxalin-6(5*H*)-one derivatives were obtained in good yields (50–97% Scheme 3, Table 2). Very good yields were obtained with no substituted aniline (**5a** 97%) and *p*-toluidine (**5l** 90%). Good yields were obtained with anilines substituted by halogen atom in *ortho*, *meta* or *para* position (63–88%). A yield of 82% was obtained with anilines substituted by CN or 65% yield with CF<sub>3</sub> group in *meta* position. With dichlorinated anilines, moderate to good yields (**5j** 60% and **5k** 76%) were obtained. No reaction was observed with anilines substituted by nitro or cyano group in *para* position. Finally, a low yield was obtained with 4-methoxyaniline (**5i** 17% with Cs<sub>2</sub>CO<sub>3</sub> for 5h and 50% with K<sub>2</sub>CO<sub>3</sub> for 24h).

In conclusion, we developed a very efficient one-pot reaction combining Buchwald-Hartwig and lactamization reactions for the synthesis of quinolino[3,4-*b*]quinoxalin-6(5*H*)-one derivatives. Starting material ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate (**3**) was prepared by Suzuki–Miyaura reaction from ethyl 3-chloroquinoxaline-2-carboxylate and 2-bromophenylboronic acid. The pharmacological evaluation of these highly potential bioactive compounds is under active investigation.

### Acknowledgment

This work was supported by the Centre National de la Recherche Scientifique, Aix-Marseille. We express our thanks to V. Remusat for recording <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra and T. Schembri for recording mass spectra.

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- (17) Ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate (3)  
To a mixture of ethyl 3-chloroquinoxaline-2-carboxylate (1g, 4.22mmol) and 2-bromophenylboronic acid (0.93 g, 4.64mmol) in acetonitrile (30 mL), was added Pd(PPh<sub>3</sub>)<sub>4</sub> (0.097 g, 0.084mmol) and 2M aqueous sodium carbonate solution (10 mL). The resulting mixture was stirred at 100°C for 5h. After cooling the mixture was diluted with dichloromethane and washed 3 times with water and dried over MgSO<sub>4</sub>. After evaporation, the crude product was purified by silica gel chromatography with CH<sub>2</sub>Cl<sub>2</sub> as eluant furnished the product **3** as yellow solid; yield: 1.1 g (73%); mp 100°C; <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ = 1.19 (t, J = 7.1 Hz, 3H, CH<sub>3</sub>), 4.33 (q, J = 7.1 Hz, 2H, CH<sub>2</sub>), 7.33-7.40 (m, 1H, H<sub>Ar</sub>), 7.45-7.85 (m, 2H, H<sub>Ar</sub>), 7.67 (d, J = 8.0 Hz, 1H, H<sub>Ar</sub>), 7.89-7.93 (m, 2H, H<sub>Ar</sub>), 8.19-8.23 (m, 1H, H<sub>Ar</sub>), 8.31-8.35 (m, 1H, H<sub>Ar</sub>). <sup>13</sup>C NMR (62.5MHz, CDCl<sub>3</sub>) δ = 13.7, 62.3, 122.1, 127.6, 129.3, 130.0, 130.3, 130.5, 131.0, 132.1, 132.3, 139.8, 140.4, 142.0, 144.4, 153.2, 164.7. Anal. Calcd for C<sub>17</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 57.16; H, 3.67; N, 7.84. Found: C, 57.61; H, 3.61. N, 7.86.
- (18) General procedure of one-pot Buchwald-Hartwig/lactamization reactions (**5a-1**)  
A mixture of ethyl 3-(2-bromophenyl)quinoxaline-2-carboxylate (**3**) (50 mg, 0.14mmol), aniline (0.21mmol, 1.5equiv) in toluene (3mL), Cs<sub>2</sub>CO<sub>3</sub> (100mg, 0.3mmol), Pd(OAc)<sub>2</sub> (6.2 mg, 0.028mmol), BINAP (14 mg, 0.021mmol) was added to a 4mL sealed vial. The resulting mixture was stirred at 110°C for 5h. After cooling the mixture was diluted with dichloromethane, washed with H<sub>2</sub>O (3x40 mL) and dried over MgSO<sub>4</sub>. After evaporation, the crude product was purified by silica gel chromatography (CH<sub>2</sub>Cl<sub>2</sub>/ diethylether: 97/3).  
5-phenylquinolino[3,4-b]quinoxalin-6(5H)-one (**5a**) yellow solid; mp 240°C; <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ = 6.73 (d, J = 7.9 Hz, 1H, H<sub>Ar</sub>); 7.38-7.46 (m, 4H, H<sub>Ar</sub>); 7.59-7.70 (m, 3H, H<sub>Ar</sub>); 7.87-8.01 (m, 2H, H<sub>Ar</sub>); 8.33 (d, J = 8.4 Hz, 1H, H<sub>Ar</sub>); 8.48 (d, J = 8.5 Hz, 1H, H<sub>Ar</sub>); 9.05-9.08 (m, 1H, H<sub>Ar</sub>). <sup>13</sup>C NMR (62.5MHz, CDCl<sub>3</sub>) δ = 116.9, 119.6, 123.5, 125.8, 129.0, 129.2, 130.4, 130.4, 130.7, 131.0, 131.9, 132.9, 137.6, 140.5, 143.1, 144.5, 145.7, 160.3. Anal. Calcd for C<sub>21</sub>H<sub>13</sub>N<sub>3</sub>O: C, 78.00; H, 4.05; N, 13.00. Found: C, 78.12; H, 4.00. N, 12.91.

