Palladium- and Copper-Catalyzed Highly Selective Mono-Coupling Between 2,6-Diiodoanisoles and Terminal Alkynes in the Production of Alkynylated Anisoles as Potential Precursors of Benzo[b]furans

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A reação de acoplamento entre 2,6-diiodoanisóis e alcinos terminais usando Pd(PPh₃)₂Cl₂ e CuI como catalisadores e diisopropilamina como base em tolueno a temperatura ambiente por 12 h produziu seletivamente 2-iodoanisóis aquinilados, em rendimentos de bons a excelentes (52-95%), os quais são blocos de construção úteis com potencial aplicação na síntese de benzo[b]furans.

The coupling reaction between 2,6-diiodoanisoles and terminal alkynes using Pd(PPh₃)₂Cl₂ and CuI as catalysts and diisopropylamine as base in toluene at room temperature for 12 h produced selectively alkynylated 2-iodoanisoles, in good to excellent yields (52-95%), which are useful building blocks with potential application in the synthesis of functionalized benzo[b]furans.

Keywords: Sonogashira reaction, selective mono-coupling, alkynylated anisoles, diiodinated benzo[b]furans, palladium and copper catalysis

Introduction

Palladium-catalyzed cross-coupling reactions can be considered powerful transformations for the construction of carbon-carbon and carbon-heteroatom bonds, including, for example, Sonogashira, Stille, Suzuki and Buchwald-Hartwig reactions. The mentioned transformations have been often employed in total syntheses of complex molecules, in the preparation of functional materials and for the production of polymers of importance in materials science. Furthermore, palladium-catalyzed reactions are in agreement with some principles of green chemistry. In this sense, a significant number of high-quality articles involving palladium-catalyzed cross-coupling reactions have been reported in the literature. However, a critical evaluation of this active area of the organic chemistry indicates that methodologies for site-selective couplings, involving selective mono-couplings, are still required in organic synthesis, constituting a vast field for investigation. Nevertheless, significant advances for palladium-catalyzed selective couplings between organic halides and organometallic reagents have been reported in the literature. Among them, we can mention advances achieved for selective Sonogashira mono-couplings. Despite the advances mentioned, to the best of our knowledge, there is no methodology employing palladium as a catalyst for the selective mono-coupling between 2,6-diiodoanisoles and terminal alkynes, in order to produce alkynylated 2-iodoanisoles, which are useful intermediates in organic synthesis. Accordingly, aiming to enrich the literature, we wish to present in this manuscript results which conducted to the development of a selective mono-coupling between 2,6-diiodoanisoles (1) and terminal alkynes (2) using palladium and copper as catalysts in the presence of a nitrogen-containing base, in order to produce exclusively alkynylated 2-iodoanisoles (3) in good to excellent yields, which are useful building blocks with potential application in the synthesis of functionalized benzo[b]furans, that compose a class of aromatic heterocyclic compounds with an extensive number of pronounced biological activities, comprising, for

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example, anticancer, antiviral and anti-inflammatory activities.

**Results and Discussion**

Initially, the reaction between 2,6-diiodoanisole (1a) and 2 equiv. of phenylacetylene (2a) using 10 mol% of Pd(PPh$_3$)$_2$Cl$_2$ and 10 mol% of CuI in the presence of 2 equiv. of triethylamine (Et$_3$N) as base and MeCN as solvent at 50 °C for 24 h gave 1-iodo-2-methoxy-3-(phenylethynyl) benzene (3a) in a 41% yield (Table 1, entry 1). In an attempt to produce compound 3a in a higher yield, we allowed 2,6-diiodoanisole (1a) to react with 1.5 equiv. of phenylacetylene (2a) using 5 mol% of Pd(OAc)$_2$, 10 mol% of triphenylphosphine (PPh$_3$) and 5 mol% of CuI in the presence of 2 equiv. of Et$_3$N as base and MeCN as solvent at 50 °C for 24 h and obtained the alkynylated 2-iodoanisole 3a in a moderate yield of 43% (entry 2). Thereafter, we carried out the reaction employing 2,6-diiodoanisole (1a), 1.5 equiv. of compound 2a, 10 mol% of Pd(PPh$_3$)$_2$Cl$_2$, 10 mol% of CuI and 2 equiv. of Et$_3$N in tetrahydrofuran (THF) at 60 °C. After 24 h, compound 3a was obtained in only 37% yield (entry 3). Ultimately, by the reaction between 2,6-diiodoanisole (1a) and 2 equiv. of phenylacetylene (2a) using 5 mol% of Pd(PPh$_3$)$_2$Cl$_2$ and 15 mol% of CuI in the presence of 1 equiv. of diisopropylamine (DIPA) as base and toluene as solvent at room temperature for 12 h, we produced 1-iodo-2-methoxy-3-(phenylethynyl) benzene (3a) in a 68% yield (entry 4). We did not observe the formation of the di-alkynylated product. However, we observed by GC/MS the formation of the alkynyl-alkyne homo-coupling as a byproduct.

Afterwards, we focused on the optimization of the conditions for the reaction shown in entry 4 of Table 1, performing variations in the stoichiometry of reagents, temperature and time of reaction, envisioning the production of 1-iodo-2-methoxy-3-(phenylethynyl)benzene (3a) in a higher yield. Thus, as can be seen in Table 2, the best result was achieved when we carried out the reaction between 2,6-diiodoanisole (1a) and 2 equiv. of phenylacetylene (2a) in the presence of 5 mol% of Pd(PPh$_3$)$_2$Cl$_2$ and 15 mol% of CuI using 2 equiv. of DIPA as base and toluene as solvent at room temperature for 12 h, producing the alkynylated 2-iodoanisole 3a in a very good yield of 82% (Table 2, entry 4). In this case, we did not observe the formation of the di-alkynylated product. However, we observed by GC/MS the formation of the alkynyl-alkyne homo-coupling as a byproduct.

Employing the optimal conditions shown in Table 2, entry 4, we examined the scope of the selective mono-coupling reaction using for some entries 2,6-diiodoanisoles containing electron-withdrawing and electron-donating groups (1b-c) and functionalized terminal alkynes (2c-f) (Table 3). The coupling between 2,6-diiodoanisole (1a) and 2 equiv. of 1-hexyne (2b) in the presence of 5 mol% of Pd(PPh$_3$)$_2$Cl$_2$ and 15 mol% of CuI using 2 equiv. of DIPA as base and toluene as solvent at room temperature for 12 h gave exclusively the compound 3b in an 82% yield (entry 2). By using 4-choro-2,6-diiodoanisole (1b), which contains an electron-withdrawing group, reactions with the alkynes 2a and 2b led to the alkynylated 2-iodoanisoles 3c and 3d, respectively, in excellent yields (≥ 93%) (entries 3 and 4). For entries 3 and 4 we observed by GC/MS the formation of di-alkynylated products in trace amounts. On the other hand, employing 4-methyl-2,6-diiodoanisole (1c), which contains an electron-donating group, reactions with the alkynes 2a and 2b were relatively

Table 1. Preparation of compound 3a

<table>
<thead>
<tr>
<th>entry</th>
<th>Palladium catalyst (mol%)</th>
<th>CuI / mol%</th>
<th>Terminal alkyne 2a / equiv.</th>
<th>Base (equiv.)</th>
<th>Solvent</th>
<th>Temperature / °C</th>
<th>time / h</th>
<th>Isolated yield / %</th>
</tr>
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<tr>
<td>1</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$ (10)</td>
<td>10</td>
<td>2</td>
<td>Et$_3$N (2)</td>
<td>MeCN</td>
<td>50</td>
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<td>41</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$ (5) plus PPh$_3$ (10)</td>
<td>5</td>
<td>1.5</td>
<td>Et$_3$N (2)</td>
<td>MeCN</td>
<td>50</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$ (10)</td>
<td>10</td>
<td>1.5</td>
<td>Et$_3$N (2)</td>
<td>THF</td>
<td>60</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh$_3$)$_2$Cl$_2$ (5)</td>
<td>15</td>
<td>2</td>
<td>DIPA (1)</td>
<td>PhCH$_3$</td>
<td>r.t.</td>
<td>12</td>
<td>68</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 mmol of compound 1a, the indicated amount of palladium catalyst, the indicated amount of CuI, the presented amount of 2a, the presented amount of base and 5 mL of solvent were stirred at the shown temperature for the time presented under nitrogen atmosphere. r.t.: room temperature.*
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Table 2. Optimization of conditions for the preparation of compound 3a

<table>
<thead>
<tr>
<th>entry</th>
<th>2a / equiv.</th>
<th>DIPA / equiv.</th>
<th>Temperature / °C</th>
<th>time / h</th>
<th>Isolated yield / %</th>
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</thead>
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<tr>
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<tr>
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<td>2</td>
<td>1</td>
<td>r.t.</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>2</td>
<td>r.t.</td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2</td>
<td>50</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>2</td>
<td>r.t.</td>
<td>24</td>
<td>81</td>
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</table>

*a* Reaction conditions: 1 mmol of compound 1a, 5 mol% of Pd(PPh₃)₂Cl₂, 15 mol% of CuI, the indicated amount of 2a, the indicated amount of DIPA and 5 mL of toluene were stirred at the shown temperature for the presented time under nitrogen atmosphere. r.t.: room temperature.

The highly selective formation of alkynylated 2-iodoanisoles 3e and 3f, respectively, in yields around 70% (entries 5 and 6). For entries 5 and 6 we did not observe the formation of di-alkynylated products. In addition, transformations carried out with functionalized terminal alkynes 2c-f produced the mono-coupling products 3g-k in good yields (52-85%) (entries 7-11). Allowing the reaction between 1-iodo-2-methoxy-3-(phenylethynyl)benzene (3a) and 2 equiv. of 1-hexyne (2b) in the presence of 5 mol% of Pd(PPh₃)₂Cl₂ and 15 mol% of CuI using 2 equiv. of DIPA as base and toluene as solvent at room temperature for 12 h, we obtained the unsymmetrical dialkyne 3l in a good yield of 78% (entry 12). It is noteworthy that when we carried out the coupling reaction between 1,4-diiodobenzene and phenylacetylene (2a), employing the optimal conditions shown in Table 2, entry 4, by the addition of DIPA all at once, we observed the prompt formation of a viscous mixture and the exclusive production of the di-coupled product after 12 h, according to GC/MS analysis. Performing the same transformation, however, by the addition of DIPA in portions, we did not notice the formation of a viscous mixture and we observed the production of the mono-coupled product along with the di-coupled product in a ratio of 1 to 1.25 after 12 h, according to GC/MS analysis.

The structures of the compounds 3a-l and 4 have been assigned on the basis of a variety of spectroscopic techniques, namely, according to their mass spectra (MS), infrared (IR), ¹H and ¹³C nuclear magnetic resonance (NMR) spectra. All compounds (3a-l and 4) provided high-resolution mass spectra (HRMS) that are in agreement with the proposed structures.

**Conclusions**

In summary, we developed a highly selective reaction for the mono-coupling between 2,6-diiodoanisoles (1) and terminal alkynes (2) using Pd(PPh₃)₂Cl₂ and CuI as catalysts and DIPA as base, in order to produce alkynylated 2-iodoanisoles (3) in good to excellent yields (52-95%). Employing the same reaction conditions, the coupling
Table 3. Coupling between iodoanisoles (1 or 3a) and terminal alkynes (2) in the preparation of alkynylated anisoles (3) using Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and CuI as catalysts and diisopropylamine as base in toluene at room temperature.

<table>
<thead>
<tr>
<th>entry</th>
<th>Iodoanisole (1 or 3a)</th>
<th>Terminal alkyne (2)</th>
<th>Alkynylated anisole (3)</th>
<th>Isolated yield / %</th>
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<td><img src="image2" alt="2a" /></td>
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</table>
between alkynylated 2-iodoanisole 3a and 1-hexyne (2b) led to the formation of the unsymmetrical dialkyne 3l in a good yield of 78%. Besides, 1-iodo-2-methoxy-3-(phenylethynyl)benzene (3a) has found application in the preparation of the diiodinated benzo[b]furan 4 in a moderate yield of 44%.

**Experimental**

**General methods**

1H and 13C NMR spectra were recorded on spectrometers operating at 300 or 200 MHz and 75 or 50 MHz, respectively. 1H NMR spectra were taken in CDCl3 and the chemical shifts of the signals are given in ppm with respect to tetramethylsilane (TMS) used as an internal standard. 13C NMR spectra were taken in CDCl3 and the chemical shifts of the signals are given in ppm with respect to the central peak of the deuterated solvent adjusted to 77.00 ppm and used as a reference. Infrared spectra were obtained using attenuated total reflectance (ATR) or KBr pellets in the 4000-400 cm⁻¹ region. Mass spectra were registered on a mass spectrometer connected to a gas chromatograph using electron impact ionization at 70 eV. High-resolution mass spectra were performed on a time-of-flight mass spectrometer. All melting point values are uncorrected. Column chromatography separations were carried out using 70-230 mesh silica gel. Catalysts, reagents and solvents were used as obtained commercially. 2,6-Diiodoanisoles (1a-c) were prepared according to literature procedures. 20

General procedure for preparation of mono-coupling products (3a-k) and unsymmetrical dialkyne 3l

To a solution of the appropriate 2,6-diiodoanisole (1a-c) or compound 3a (1 mmol), Pd(PPh3)2Cl2 (0.0351 g, 0.05 mmol) and CuI (0.0285, 0.15 mmol) in toluene (5 mL) under nitrogen atmosphere were added the appropriate terminal alkyne (2a-f) (2 mmol) and diisopropylamine (0.2020 g, 2 mmol). After that, the mixture was stirred at room temperature for 12 h. Then, brine (20 mL) was added to the reaction, which was extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over MgSO4. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane as eluent, unless
otherwise indicated, affording mono-coupling products (3a-k) and the unsymmetrical dialkyn benzene 3l.

Procedure for preparation of benzo[b]furan 4

To a vial (20 mL) were added 2-iodo-2-methoxy-3-(phenylethynyl)benzene (3a) (0.0835 g, 0.25 mmol) and a solution of iodine (0.1270 g, 0.5 mmol) in CHCl3 (5 mL). The vial was sealed using a cap, and the mixture was stirred at 40°C for 12 h. Afterwards, a saturated solution of sodium thiosulfate (10 mL) was added to the reaction, which was extracted with ethyl acetate (3 × 10 mL). The organic phase was dried over MgSO4. After filtration, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane as eluent, affording 3,7-diiodo-2-phenylbenzo[b]furan (4).

Characterization data for compounds 3a-l and 4

1-Iodo-2-methoxy-3-(phenylethynyl) benzene (3a): Rf = 0.33 (obtained after three runs in hexane); yield 0.2739 g (82%); yellowish oil; 1H NMR (200 MHz, CDCl3) δ 7.75 (dd, 1H, J 7.9, 1.6 Hz), 7.57-7.52 (m, 2H), 7.74 (dd, 1H, J 7.7, 1.6 Hz), 7.39-7.34 (m, 3H), 6.82 (t, 1H, J 7.8 Hz), 4.03 (s, 3H); 13C NMR (50 MHz, CDCl3) δ 160.3, 139.4, 133.7, 131.5, 128.6, 128.4, 125.4, 122.9, 117.6, 94.5, 91.8, 85.0, 61.0; IR (ATR) νmax/cm⁻¹ 1653, 1238, 1026, 522; LRMS m/z (%) 334 (100.0), 257 (5.1), 178 (6.4), 164 (2.8); HRMS [M + Na]+ found: 356.9746, calcd.: 356.9752.

5-Chloro-1-(hex-1-ynyl)-3-iodo-2-methoxybenzene (3d): Rf = 0.51 (obtained after three runs in hexane); yield 0.3236 g (93%); yellowish oil; 1H NMR (200 MHz, CDCl3) δ 7.65 (d, 1H, J 2.5 Hz), 7.32 (d, 1H, J 2.5 Hz), 3.91 (s, 3H), 2.44 (t, 2H, J 6.8 Hz), 1.61-1.46 (m, 4H), 0.95 (t, 3H, J 7.2 Hz); 13C NMR (50 MHz, CDCl3) δ 159.2, 137.7, 133.3, 129.3, 119.1, 97.3, 91.8, 75.1, 60.8, 30.5, 22.0, 19.3, 13.6; IR (ATR) νmax/cm⁻¹ 2228, 1232, 1099, 723, 509; LRMS m/z (%) 349 (100.0), 291 (10.9), 178 (6.6); HRMS [M + Na]+ found: 370.9673, calcd.: 370.9676.

1-Iodo-2-methoxy-5-methyl-3-(phenylethynyl)benzene (3e): Rf = 0.47 (obtained after three runs in hexane); yield 0.2436 g (70%); orange oil; 1H NMR (200 MHz, CDCl3) δ 7.56-7.48 (m, 3H), 7.36-7.31 (m, 3H), 7.26 (d, 1H, J 2.1 Hz), 3.97 (s, 3H), 2.23 (s, 3H); 13C NMR (50 MHz, CDCl3) δ 158.1, 139.8, 135.1, 134.0, 131.4, 128.4, 128.3, 122.9, 116.8, 94.0, 91.5, 85.1, 60.9, 20.0; IR (ATR) νmax/cm⁻¹ 1003, 1242, 756; LRMS m/z (%) 348 (100.0), 347 (26.2), 178 (7.5); HRMS [M + H]+ found: 349.0072, calcd.: 349.0089.

5-Chloro-1-(hex-1-ynyl)-3-iodo-2-methoxy-5-methylbenzene (3f): Rf = 0.31 (obtained after three runs in hexane); yield 0.2231 g (68%); yellowish oil; 1H NMR (200 MHz, CDCl3) δ 7.49 (dd, 1H, J 2.2, 0.6 Hz), 7.14 (dd, 1H, J 2.0, 0.6 Hz), 3.89 (s, 3H), 2.45 (t, 2H, J 6.8 Hz), 2.21 (s, 3H), 1.61-1.46 (m, 4H), 0.95 (t, 3H, J 7.1 Hz); 13C NMR (50 MHz, CDCl3) δ 158.1, 139.0, 135.0, 134.2, 117.7, 95.4, 91.3, 60.6, 30.6, 29.6, 21.9, 19.9, 19.2, 13.6; IR (ATR) νmax/cm⁻¹ 2230, 1240, 1005, 725, 581; LRMS m/z (%) 328 (100.0), 313 (13.5), 271 (16.8), 171 (9.5); HRMS [M + Na]+ found: 351.0210; calcd.: 351.0222.
3g

1-iodo-2-methoxy-3-(3-methylbut-3-en-1-ynyl)benzene (3g): \( R_f = 0.58 \) (obtained after three runs in hexane); yield 0.1937 g (65%); colorless oil; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta \) 7.72 (dd, 1H, \( J = 7.9, 1.6 \) Hz), 7.38 (dd, 1H, \( J = 7.7, 1.6 \) Hz), 6.78 (t, 1H, \( J = 7.8 \) Hz), 5.43-5.41 (m, 1H), 5.35-5.32 (m, 1H), 3.97 (s, 3H), 2.00 (dd, 3H, \( J = 1.5, 1.1 \) Hz); \(^1\)C NMR (50 MHz, CDCl\(_3\)) \( \delta \) 160.2, 139.3, 133.6, 126.6, 125.3, 122.4, 117.5, 95.7, 91.7, 83.9, 60.8, 23.2; IR (ATR) \( \nu_{\text{max}}/\text{cm}^{-1} \) 2936, 1238, 1032, 1003, 779; LRMS \( m/z \) (%) 2949 (43.3), 2227 (19.3), 192 (13.6); HRMS [M+Na\(^+\)] found: 320.9723, calcd.: 320.9752.

3h

3-(3-iodo-2-methoxyphenyl)-N,N-dimethylprop-2-yn-1-amine (3h): The eluents used were ethyl acetate and then methanol. \( R_f = 0.62 \) (ethyl acetate and then methanol); yield 0.1953 g (62%); brownish solid; m.p. 49-50 \(^\circ\)C; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta \) 7.73 (dd, 1H, \( J = 7.9, 1.6 \) Hz), 7.40 (dd, 1H, \( J = 7.7, 1.6 \) Hz), 6.78 (t, 1H, \( J = 7.8 \) Hz), 3.95 (s, 3H), 3.56 (s, 2H), 2.40 (s, 6H); \(^1\)C NMR (50 MHz, CDCl\(_3\)) \( \delta \) 160.3, 138.6, 133.9, 125.3, 117.5, 91.7, 89.6, 81.0, 60.9, 48.5, 44.0; IR (KBr) \( \nu_{\text{max}}/\text{cm}^{-1} \) 2934, 2210, 1241, 777; LRMS \( m/z \) (%) 341 (25.1), 300 (10.1), 284 (15.7), 270 (100.0), 157 (8.4); HRMS [M+H\(^+\)] found: 316.0196, calcd.: 316.0198.

3i

1-(4-Iodo-3-cyclopentylprop-1-ynyl)benzene (3i): \( R_f = 0.41 \) (obtained after three runs in hexane); yield 0.2652 g (78%); yellowish oil; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta \) 7.68 (dd, 1H, \( J = 7.9, 1.6 \) Hz), 7.34 (dd, 1H, \( J = 7.7, 1.6 \) Hz), 6.75 (t, 1H, \( J = 7.8 \) Hz), 3.94 (s, 3H), 3.56 (s, 2H), 2.47 (d, 2H, \( J = 6.7 \) Hz), 2.16 (septet, 1H, \( J = 7.3 \) Hz), 1.88-1.79 (m, 2H), 1.68-1.57 (m, 4H), 1.41-1.30 (m, 2H); \(^1\)C NMR (50 MHz, CDCl\(_3\)) \( \delta \) 160.3, 138.6, 133.9, 125.3, 118.5, 95.5, 91.7, 60.7, 39.0, 32.0, 29.7, 25.4, 25.3; IR (ATR) \( \nu_{\text{max}}/\text{cm}^{-1} \) 2949, 2227, 1238, 1003, 776; LRMS \( m/z \) (%) 340 (24.8), 325 (43.3), 297 (19.4), 257 (100.0), 146 (98.6); HRMS [M+Na\(^+\)] found: 363.0217, calcd.: 363.0222.

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1,3-Diiodo-2-phenyl[benzo[b]furan (4): \( R_f = 0.54 \) (hexane); yield 0.0490 g (44%); off-white solid; m.p. 110-112 \(^\circ\)C; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \( \delta \) 8.23-8.17 (m, 2H), 7.70 (dd, 1H, \( J = 7.7, 1.1 \) Hz), 7.55-7.43 (m, 3H), 7.39 (dd, 1H, \( J = 7.8, 1.1 \) Hz), 7.06 (t, 1H, \( J = 7.7 \) Hz); \(^1\)C NMR (50 MHz, CDCl\(_3\)) \( \delta \) 153.9, 153.4, 134.4, 132.4, 129.5, 129.4, 128.5, 127.5, 125.0, 121.9, 75.6, 62.4; IR (KBr) \( \nu_{\text{max}}/\text{cm}^{-1} \) 3057, 2955, 2932, 1524, 1412, 1326, 1236, 1005, 754; LRMS \( m/z \) (%) 288 (100.0), 273 (14.1), 245 (30.2), 231 (27.3), 207 (20.3), 152 (9.1), 77 (7.4); HRMS [M+NH\(^+\)] found: 306.1849, calcd.: 306.1858.
Supplementary Information

Supplementary information (copies of 1H and 13C NMR spectra) is available free of charge at http://jbcs.sbq.org.br as a PDF file.

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