Synthesis of Isoquinoline Alkaloids via Oxidative Amidation–Bischler–Napieralski Reaction

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Abstract: A straightforward synthesis of α-keto amides by coupling primary amines witharyl dibromoethanones under oxidative amidation conditions has been developed. The α-keto amides were then subjected to heterocyclodehydration reaction under Bischler–Napieralski conditions followed by aromatization with DBU provided 1-benzoyl isoquinolines in a two-stage process. Utilizing this methodology, isoquinoline alkaloids such as thalmicrinone, papavaraldine, and pulcheotine A were synthesized in excellent yields.

Key words: oxidative amidation, Bischler–Napieralski cyclization, aromatization, isoquinoline alkaloids, thalmicrinone, papavaraldine, pulcheotine A

The synthesis of isoquinoline alkaloids and their congeners has received considerable attention because of their widespread presence in numerous biologically active natural products and pharmaceuticals. Broadly there are two types of isoquinoline alkaloids exist in nature, 1-benzoylisooquinoline as well as 1-benzylisooquinoline alkaloids. Isoquinoline alkaloids exhibits antimicrobial, antimalarial, antitumor, anti-HIV activities, and also have antioxidant capacity. They also have shown affinity for dopamine receptors from striatal membranes. Isoquinolines also act as antitumor agents as inhibitors of the mitochondrial electron-transport chains.

Numerous strategies have been reported in the literature for the synthesis of 1-benzoylisooquinoline alkaloids. These synthetic protocols involve three stages, 1) construction of 1-benzyl dihydroisooquinoline framework from open-chain precursor, 2) oxidation of 1-benzyl dihydroisooquinoline to the corresponding 1-benzoyl dihydroisooquinoline, and 3) the aromatization of 1-benzoyl dihydroisooquinoline to isoquinoline. The most prominent approach for the synthesis of 1-benzyl dihydroisooquinoline is via the intramolecular cyclodehydration of N-phenethyl-2-phenylacetamide under Bischler–Napieralski reaction conditions. The conversion of 1-benzyl dihydroisooquinoline to 1-benzoyl dihydroisooquinoline is reported with several oxidizing agents. Whereas aromatization is carried out with oxidants such as chromium trioxide, manganese dioxide, and also with sulfur. Some reports are also known in literature for direct conversion of 1-benzyl dihydroisooquinoline to the corresponding 1-benzoyl isoquinoline. Most of these oxidants are either toxic or hazardous metal materials, which create environmental problems during their disposal. The apparent difficulty in the synthesis of appropriately substituted alkoxy phenyl acetic acid coupled with the toxic nature of oxidants makes this three-stage synthesis of isoquinolines less attractive.

In the context of our ongoing research project on the total synthesis of biologically active natural products and its derivatives, we wish to develop an efficient and general strategy for the synthesis of 1-benzoyl isoquinolines via oxidative amidation–Bischler–Napieralski reaction. 3,4-Dihydropapaveraldine (1), Figure 1, papaveraldine (xanthaline) (2), thalmicrinone (3), and pulcheotide A (4) were chosen as the target isoquinoline alkaloids because of their unique structural features and important biological activities.

Recently we have disclosed a straightforward synthesis of α-keto amides by coupling secondary amines with aryl and heteroaryl dibromoethanones under aerial oxidation conditions. With anticipation that the oxidative amidation methodology could be used as key step in isoquinoline synthesis, we have designed an efficient synthetic route for the isoquinoline synthesis as shown in the retrosynthetic scheme (Scheme 1). 1-Benzoylisooquinoline (5a) could efficiently be synthesized from the corresponding 1-benzoyl-3,4-dihydroisooquinoline (6a) by aromatiza-
tion. The cyclodehydration of α-keto amide 7a under Bischler–Napieralski conditions would construct 1-benzoyl-3,4-dihydroisoquinoline (6a) in good yields. The 2-oxo-N-phenethyl-2-phenylacetamide (7a) required for isoquinoline synthesis in turn could be prepared by coupling of 2,2-dibromo-1-phenylethanone 8a with 2-phenyl ethylamine (9a) under oxidative amidation reaction conditions (Scheme 1).

![Scheme 1](image)

**Scheme 1**

We initiated our investigation on the synthesis of 2-oxo-N-phenethyl-2-phenylacetamide (7a) by coupling of 2,2-dibromo-1-phenylethanone (8a) with 2-phenyl ethylamine (9a) under our earlier reported aerial oxidative amidation reaction conditions.13 However, oxidative amidation under these reaction conditions yielded N-phenethylbenzamide (14) as the major product instead of the required keto amide 7a. We speculated that less reactivity of the dibromomethylene unit in 2,2-dibromoethanone 8a in comparison to the carbonyl carbon and the absence of a strong oxidizing agent could be the probably cause for low yield formation of the required α-keto amide 7a in this oxidative amidation reaction. Different types of reaction conditions were then screened, and finally, alternate oxidative amidation reaction conditions have been developed which resulted in the required α-keto amide, 2-oxo-N-phenethyl-2-phenylacetamide (7a) in 50% yield (Scheme 2).

![Scheme 2](image)

**Scheme 2** *Reagents and conditions:* THF, O2, Et3N, 70 °C, 48 h; (b) NaI, K3PO4, sulfolane, t-BuOOH, 30 °C, 5–8 h.

In a prototype experiment, a mixture of 2,2-dibromo-1-phenylethanone (8a, 6.0 g, 21.6 mmol) and sodium iodide (6.48 g, 43.2 mmol) in sulfolane (30.0 mL) at 20–25 °C was stirred for 40–50 minutes. Powdered tripotassium phosphate (11.46 g, 54 mmol) and 2-phenyl ethylamine (9a, 3.15 g, 25.8 mol) were then added into the reaction mixture under a nitrogen atmosphere and was stirred for about two hours at room temperature (30–35 °C). tert-Butyl hydroperoxide solution (5.5 M in decane, 4.89 mL, 27 mmol) was then added into the reaction mixture over a period of five minutes, and the reaction mixture was stirred for another 4–6 hours at room temperature. After completion of the reaction (TLC) and usual organic extractive workup followed by column chromatographic purification, the expected 2-oxo-N-phenethyl-2-phenylacetamide (7a) was isolated in 50% yield (2.76 g). The isolated product was then well characterized by 1H NMR spectroscopy, mass spectrometry, and by other spectral and analytical methods.

A tentative mechanism for the oxidative amidation reaction is proposed in Scheme 3. The reaction sequence begins with the displacement of bromine in 2,2-dibromoethanone 8a by 2-phenyl ethylamine (9a). The nucleophilic displacement of halogen in 8a by amine 9a is accelerated by the presence of potassium iodide, probably due to halogen-exchange reaction. Thus the reaction of 8a with phenyl ethylamine (9a) leads to the formation of 2-halo-(phenethylamino)-1-phenylethanone 10. Further elimination of hydrogen halide from 10 generates the imine (Schiff base) 11.14 The Schiff base 11 under in situ oxidation with tert-butyl hydroperoxide can result in the unstable oxaziridine 12. The ring opening of oxaziridine 12 in the presence of a base yields 13 which after ketominal tautomerism provides the expected α-keto amide 7a.15 Nucleophilic displacement of the dibromomethylene unit by an amine in 8a produced benzamide 14 in up to 20% yield. The formation of benzamide 14 in the reaction though was able to control below 20%, it was not possible to avoid its formation during this oxidative amidation process. The substrate scope of the oxidative amidation reaction of substituted aryl dibromoethanones16 8a–c with various primary amines 9a–e was then explored. As can be seen,
a series of substrates could be converted into the corresponding α-keto amide 7a–g under the optimized condition in less than eight hours (Table 1, entries 1–7). Under these oxidative amidation reaction conditions, the α-keto amides 7a–g were isolated in almost consistent yield.

Table 1  Synthesis of Keto Amides 7a–g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dibromoethanone</th>
<th>Amine</th>
<th>Keto amide</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
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<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>9a</td>
<td>7a</td>
<td>50</td>
<td>liquid</td>
</tr>
<tr>
<td>2</td>
<td>8a</td>
<td>9b</td>
<td>7b</td>
<td>48</td>
<td>liquid</td>
</tr>
<tr>
<td>3</td>
<td>8b</td>
<td>9c</td>
<td>7c</td>
<td>51</td>
<td>86–88</td>
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<tr>
<td>4</td>
<td>8b</td>
<td>9d</td>
<td>7d</td>
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<tr>
<td>5</td>
<td>8b</td>
<td>9e</td>
<td>7e</td>
<td>50</td>
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<tr>
<td>6</td>
<td>8c</td>
<td>9b</td>
<td>7f</td>
<td>48</td>
<td>96–98</td>
</tr>
<tr>
<td>7</td>
<td>8c</td>
<td>9b</td>
<td>7g</td>
<td>53</td>
<td></td>
</tr>
</tbody>
</table>

* The yields based on the isolated 99% analytically pure compounds and not on the reaction conversion or on the crude weight.
yields (48–53%). In all these reactions, the corresponding benzamide impurities were isolated in 15–20% yields.

Having demonstrated that α-keto amide could be synthesized by the reaction of various primary amines 9a–e with aryl dibromoethanones 8a–c, we decided to exploit the α-keto amide for the synthesis of 1-benzoyl dihydroisoquinolines 6a–f by carrying out the cyclodehydration reaction under Bischler–Napieralski conditions (Scheme 4). Thus, 2-oxo-N-phenethyl-2-phenylacetamide (7a) was subjected for the cyclodehydration reaction with freshly distilled phosphorous oxychloride (ten volumes) over a period of 12–14 hours at 80 °C. After workup and column chromatographic purification, 1-benzoyl dihydroisoquinolines 6a and 14 were isolated in 70% yield as an isomeric mixture (Scheme 4).

All the α-keto amides 7a–g thus synthesized were then subjected to the Bischler–Napieralski cyclodehydration reaction (Table 2) and highly substituted 1-benzoyl dihydroisoquinolines 6a–f were obtained in very high yields. In this alkoxy-substituted dihydroisoquinoline synthesis, no isomerization of double bonds was observed, and the reaction has been completed in almost 12 hours at 80–85 °C using ten volumes of phosphorous oxychloride.18 The 3,4-dihydropapaveraldine (1), the dihydro derivative of papaveraldine (2) was synthesized in 85% yield under these reaction conditions and was characterized by spectral and analytical methods. The isolated yields of substituted 1-benzoyl dihydroisoquinolines 6b–f19 under the

![Scheme 4](image)

Table 2 Synthesis of Isoquinolines via Oxidative Amidation Approach

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Keto amides</th>
<th>Dihydroisoquinoline</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>Isoquinoline</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7a</td>
<td>6a</td>
<td>76</td>
<td>low melting solid</td>
<td>5a</td>
<td>80</td>
<td>75–77</td>
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</table>

The aromatization of 1-benzoyl-3,4-dihydroisoquinoline (6a), synthesized via oxidative amidation Bischler–Napieralski approach, was then carried out. Initially, aromatization of 1-benzoyl dihydroisoquinoline (6a) reaction was performed with dichlorodicyanoquinone (DDQ); however, the required transformation did not proceed very smoothly, and the aromatized product was isolated in poor yield. When the aromatization of 1-benzoyl-3,4-dihydroisoquinoline (6a) was attempted via a regioselective base-catalyzed air oxidation using 1,8-diazabicycloundec-7-ene (DBU), 1-benzoyl isoquinoline (5a) was isolated in excellent yield (80%, Scheme 5).20

![Scheme 5](image)
Aromatization of other 1-benzoyl dihydroisoquinolines 6b–f and 1 were then carried out under DBU-assisted aromatization conditions. The alkaloids, papaveraldine (2), thalmicrinone (3), as well as pulcheotine A (4) were synthesized in 79%, 80%, and 80% yields, respectively, by the aromatization reaction of its corresponding dihydroisoquinoline derivatives 1, 6d, and 6c (Table 2). The spectral and analytical data of all synthetic alkaloids were found to be in conformity with the reported literature values.22 Other substituted 1-benzoyl isoquinolines such as 5a–d were also synthesized in very high yields in similar ways.

In summary, we have successfully developed a simple but highly useful and practical method for the synthesis of isoquinoline alkaloids via oxidative amidation–Bischler–Napieralski approach. The oxidative amidation–Bischler–Napieralski reaction developed for the synthesis of 1-benzoyl isoquinolines provides a direct access to the 1-benzoyl dihydroisoquinolines from open-chain precursors other than reported by Wasserman and coworkers.23 The modified aromatization conditions resulted in highly substituted 1-benzoyl isoquinoline in good yields from the corresponding dihydroisoquinoline derivatives. The scope and limitation of this unique oxidative amidation–Bischler–Napieralski approach for the synthesis of several other isoquinoline and carboline alkaloids are in progress and will be reported in due course.
Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes


phenyl)-2-oxoacetamide (7c)

Yellow solid; yield 2.64 g (51.0%); mp 86–88 °C. IR (KBr): 517, 620, 722, 803, 849, 1038, 1171, 1265, 1296, 1357, 1527, 1598, 1638, 1829, 2937, 3367 cm⁻¹. ¹H NMR (400 MHz, CDCl₃), δ = 2.82 (t, 2 H, J = 6.8 Hz), 3.60 (q, 2 H, J = 6.8 Hz), 3.88 (s, 3 H), 5.93 (s, 2 H), 6.66–6.76 (m, 3 H), 6.92–6.95 (m, 2 H), 7.2 (br, NH), 8.37–8.40 (m, 2 H). ¹³C NMR (200 MHz, CDCl₃), δ = 35.1, 40.6, 55.4, 100.8, 108.3, 108.9, 113.7, 121.6, 126.2, 130.2, 133.8, 146.7, 148.2, 162.2, 164.6, 185.6. MS: m/z (%) = 328.2 [M + 1].

2-(4-Methoxyphenyl)-2-oxo-N-(2,3,4-trimethoxyphenyl)acetamide (7d)

Yellow oil; yield 2.85 g (53.0%). IR (neat): 669, 850, 1169, 1215, 1420, 1598, 1660, 2400, 3019 cm⁻¹. ¹H NMR (400 MHz, CDCl₃), δ = 2.84 (t, 2 H, J = 6.8 Hz), 3.57 (q, 2 H, J = 6.8 Hz), 3.84 (s, 3 H), 3.85 (s, 3 H), 3.88 (s, 3 H), 3.97 (s, 3 H), 6.61 (d, 1 H, J = 8.4 Hz), 6.85 (d, 1 H, J = 8.4 Hz), 6.92 (d, 2 H, J = 8.4 Hz), 7.35 (br, NH), 8.35–8.38 (m, 2 H). ¹³C NMR (200 MHz, CDCl₃), δ = 29.5, 40.2, 55.4, 55.9, 60.6, 60.8, 107.3, 113.7, 124.3, 126.4, 133.7, 142.2, 151.9, 152.7, 162.4, 164.5, 185.8. MS: m/z (%) = 374.2 [M + 1].

(75)-8-Dihydro-1,3]dioxolol[4,5-g]isoquinolin-5-yl)4-methoxyphenyl)methanone (1)

Cream color solid; yield 1.23 g (86.0%); mp 155–156 °C. IR (KBr): 525, 740, 786, 866, 1134, 1174, 1361, 1417, 1595, 1617, 2640, 2907 cm⁻¹. ¹H NMR (400 MHz, CDCl₃), δ = 2.81 (t, 2 H, J = 7.6 Hz), 3.76 (s, 3 H), 3.88 (s, 3 H), 3.97 (s, 3 H), 6.75 (s, 1 H), 6.78–6.93 (m, 3 H), 7.20 (br, NH), 7.86 (d, 1 H, J = 2.0 Hz), 8.23 (dd, 1 H, J = 8.8, 2.0 Hz). ¹³C NMR (200 MHz, CDCl₃), δ = 34.9, 40.5, 55.8, 55.9, 56.0, 110.0, 111.3, 118.8, 126.4, 153.2, 154.6, 162.2, 185.4. MS: m/z (%) = 404.2 [M + 1].

N-[3,4-Dimethoxyphenyl]-2-(3,4-dihydroisoquinolin-1-yl)methanone (7f)

Yellow solid; yield 2.93 g (53.0%); mp 78–79 °C. IR (KBr): 657, 766, 868, 1029, 1141, 1267, 1421, 1514, 1591, 1648, 2525, 2836, 2935, 3311 cm⁻¹. ¹H NMR (400 MHz, CDCl₃), δ = 2.85 (br, 2 H), 3.60 (br, 2 H), 3.83 (s, 3 H), 3.85 (s, 6 H), 3.94 (s, 3 H), 3.97 (s, 3 H), 6.45 (s, 2 H), 6.91 (d, 1 H, J = 8.4 Hz), 7.20 (br, NH), 7.86 (s, 1 H), 8.20 (d, 1 H, J = 7.6 Hz). ¹³C NMR (200 MHz, CDCl₃), δ = 35.8, 40.4, 55.9, 56.0, 60.7, 105.5, 110.1, 112.5, 126.2, 127.2, 133.9, 136.6, 148.7, 153.2, 154.5, 162.2, 185.4. MS: m/z (%) = 362.2 [M + 1].

(75)-8-Dihydro-1,3][dioxolol[4,5-g]isoquinolin-5-yl)4-methoxyphenyl)methanone (6c)

Pale yellow solid; yield 1.36 g (88.0%); mp 143–145 °C. IR (KBr): 634, 724, 881, 983, 1018, 1133, 1264, 1316, 1417, 1595, 1617, 2640, 2907 cm⁻¹. ¹H NMR (400 MHz, CDCl₃), δ = 2.81 (t, 2 H, J = 7.6 Hz), 3.76 (s, 3 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 6.70 (s, 1 H), 6.95 (d, 1 H, J = 8.8 Hz), 8.01–0.82 (m, 2 H). ¹³C NMR (200 MHz, CDCl₃), δ = 18.7, 47.0, 55.5, 56.1, 60.9, 61.0, 106.4, 113.8, 123.8, 128.4, 132.0, 145.8, 150.1, 151.9, 164.2, 192.4. MS: m/z (%) = 356.2 [M + 1].

(4-Methoxyphenyl)6,7,8-trimethoxy-3,4-dihydroisoquinolin-1-yl)methanone (6d)

Cream color solid; yield 1.23 g (86.0%); mp 165–167 °C. IR (KBr): 609, 724, 801, 983, 1107, 1132, 1264, 1361, 1405, 1595, 1668, 2840, 2937 cm⁻¹. ¹H NMR (400 MHz, CDCl₃), δ = 2.74 (t, 2 H, J = 7.6 Hz), 3.58 (s, 3 H), 3.77 (s, 3 H), 3.84 (br, 2 H), 3.91 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 6.55 (s, 1 H), 6.88 (d, 1 H, J = 8.4 Hz), 7.54 (dd, 1 H, J = 8.2 Hz), 7.66 (d, 1 H, J = 1.6 Hz). ¹³C NMR (200 MHz, CDCl₃), δ = 25.9, 46.8, 55.9, 56.0, 60.2, 60.5, 106.2, 109.9, 110.8, 115.2, 125.5, 128.3, 134.7, 140.1, 148.9, 150.8, 153.3, 156.4, 163.7, 192.4. MS: m/z (%) = 386.2 [M + 1].
7.67 (d, 1 H, J = 1.6 Hz). 13C NMR (200 MHz, CDCl3): δ = 25.3, 47.1, 55.9, 56.0, 109.6, 109.9, 110.4, 111.2, 119.4, 126.4, 128.5, 130.9, 147.5, 149.0, 150.1, 154.0, 164.5, 192.6. MS: m/z (%) = 356.2 [M + 1].

(20) 1-Benzoyl Isoquinoline (5a)

To a stirred solution of 1-benzoyl dihydroisoquinoline (6a, 14.1 g, 48.9 mmol) in CHCl3 (12 mL) was added DBU (2.2 mL, 14.6 mmol), and the mixture was stirred at 25 °C for 12 h. The mixture was concentrated in vacuo, and the obtained residue was purified by column chromatography (silica gel, PE–EtOAc = 7:3) to give 5a as a light yellow color solid (0.91 g, 80%).


(22) (6,7-Dimethoxyisoquinolin-1-yl)(phenyl)methanone (5b)

Light brown color solid; yield 0.72 g (80.0%); mp 146–148 °C. IR (KBr): 647, 740, 832, 934, 1030, 1053, 1127, 1257, 1479, 1601, 2944, 3735 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.06 (s, 3 H), 3.93 (s, 3 H), 4.02 (s, 3 H), 4.07 (s, 3 H), 6.95 (d, 1 H, J = 8.8 Hz), 7.36 (s, 1 H), 7.93–7.99 (m, 2 H), 8.48 (d, 1 H, J = 5.2 Hz). 13C NMR (400 MHz, CDCl3): δ = 55.4, 56.0, 61.1, 61.5, 100.3, 113.6, 116.4, 123.7, 129.1, 129.7, 133.2, 139.5, 141.1, 146.6, 154.0, 154.4, 163.9, 193.7. MS: m/z (%) = 354.2 [M + 1].

(4-Methoxyphenyl)(6,7,8-trimethoxyisoquinolin-1-yl)methanone (5c)

Light brown color solid; yield 0.58 g (82.0%); mp 216–218 °C. IR (KBr): 635, 722, 756, 991, 1018, 1116, 1271, 1348, 1420, 1584, 1667, 2837, 2936, 3078 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.51 (s, 3 H), 3.78 (s, 3 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 3.99 (s, 3 H), 6.95 (q, 2 H, J = 8.4 Hz), 7.34 (s, 1 H), 7.40 (s, 1 H), 7.79 (d, 1 H, J = 5.6 Hz) 8.40 (d, 1 H, J = 5.6 Hz). 13C NMR (400 MHz, CDCl3): δ = 55.5, 55.7, 56.2, 60.3, 60.6, 101.8, 109.8, 110.7, 116.7, 119.5, 125.0, 129.1, 134.1, 141.3, 147.2, 148.8, 153.1, 154.8, 157.0, 192.6. MS: m/z (%) = 384.2 [M + 1].

(6,7-Dimethoxyisoquinolin-1-yl)(3,4-dimethoxyphenyl)methanone (4)

Off white color solid; yield 0.71 g (80.0%); mp 156–158 °C. IR (KBr): 518, 605, 843, 950, 1263, 1463, 1596, 1652, 1920, 2913 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.87 (s, 3 H), 6.09 (s, 2 H), 6.92–6.96 (m, 2 H), 7.14 (s, 1 H), 7.48 (s, 1 H), 7.60 (d, 1 H, J = 5.6 Hz), 7.92–7.95 (m, 2 H), 8.43 (d, 1 H, J = 5.2 Hz). 13C NMR (200 MHz, CDCl3); δ = 55.5, 101.7, 102.2, 102.6, 113.6, 121.7, 123.8, 129.5, 133.1, 135.4, 140.3, 149.2, 151.0, 154.7, 163.9, 193.5. MS: m/z (%) = 308.1 [M + 1].

(4-Methoxyphenyl)(5,6,7-trimethoxyisoquinolin-1-yl)methanone (3)

Cream color solid; yield 0.72 g (80.0%); mp 146–148 °C. IR (KBr): 647, 740, 832, 934, 1030, 1053, 1127, 1257, 1479, 1601, 2944, 3735 cm–1. 1H NMR (400 MHz, CDCl3): δ = 3.88 (s, 3 H), 3.93 (s, 3 H), 4.02 (s, 3 H), 4.07 (s, 3 H), 6.95 (d, 1 H, J = 8.8 Hz), 7.36 (s, 1 H), 7.93–7.99 (m, 2 H), 8.48 (d, 1 H, J = 5.2 Hz). 13C NMR (400 MHz, CDCl3): δ = 55.4, 56.0, 61.1, 61.5, 100.3, 113.6, 116.4, 123.7, 129.1, 129.7, 133.2, 139.5, 141.1, 146.6, 154.0, 154.4, 163.9, 193.7. MS: m/z (%) = 354.2 [M + 1].