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Chemoselective Suzuki–Miyaura reactions of 4-trifluoromethylsulfonyloxy-6-bromocoumarin

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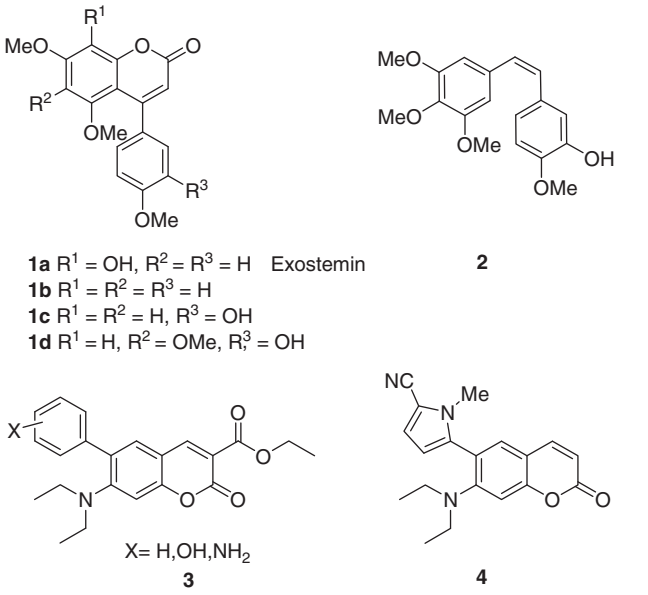
ABSTRACT

Suzuki–Miyaura reactions of 4-trifluoromethylsulfonyloxy-6-bromocoumarin provide a convenient access to arylated coumarins. The reactions proceed with excellent chemoselectivity in favour of position 4.

Coumarin (2*H*-1-benzopyran-2-one) represents a privileged oxygen heterocycle which is widely distributed throughout the plant kingdom.[1] Among naturally occurring coumarins, 4-arylcoumarins (neoflavones) constitute a subgroup of flavonoids found in plants of the families *Guttiferae*, *Passifloraceae*, *Leguminosae* and *Rubiaceae* (**1a**) (Scheme 1).[2–4] Since natural and synthetic neoflavones exhibit a broad range of pharmacological activities[5], much effort has been devoted to their synthesis[6] and isolation.[7] 4-Arylcoumarins have been reported to show anti-HIV,[8] anti-HCV (hepatitis C virus),[9] antimalarial,[10] antibacterial,[11] and cytotoxic activity. Examples include both natural products (e.g., **1b**)[12] and synthetic molecules (e.g., **1c,d**).[13] 4-Arylcoumarin analogues of the stilbene combretastatin A-4 (**2**) have been reported to exhibit potent cytotoxic activity against human leukemia CEM cell lines. Recently, 6-arylcoumarins received considerable attention, because of their pharmacological and photophysical properties. Some derivatives have been used as fluorescent sensors (e.g., **3**)[14] and others exhibit potent progesterone antagonist activity (e.g., **4**).[15]

Classically, 4-arylcoumarins have been prepared from phenols by condensation with carbonyl compounds (Pechmann or Perkin reactions)[16] or by Kostanecki acylation of 2-hydroxybenzophenones with acid anhydrides or chlorides followed by base-induced ring-closure.[17] In addition, 4-arylcoumarins are available by Wittig olefination of 2-hydroxybenzophenone with ethyl (triphenylphosphoranylidene)acetate[18] or by cyclization of phenyl 3-arylpropionates in the presence of HSO_3F or $AlBr_3$.[19] 4-Arylcoumarins have



1a R^1 = OH, R^2 = R^3 = H Exostemin
1b R^1 = R^2 = R^3 = H
1c R^1 = R^2 = H, R^3 = OH
1d R^1 = H, R^2 = OMe, R^3 = OH

2

3

4

Scheme 1. Pharmacologically relevant arylated coumarins **1**, **3**, and **4** and stilbene combretastatin A-4 (**2**).

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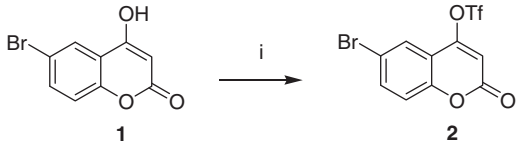
been synthesized by palladium, nickel or rhodium catalyzed reactions of 4-tosyloxy-, 4-trifluormethanesulfonyloxy-, and 4-(diethylphosphonyloxy)coumarins or of 4-(coumarinyl)zinc bromide.[20–25] Other methods have been also reported to introduce aryl groups at position 4 of coumarins. This includes a domino Heck-cyclization process between cinnamates with aryl halides[26] or the Cu-catalyzed hydroarylation of phenylpropiolates with arylboronic acids.[27]

The synthesis of 6-arylated coumarins has only been scarcely reported. Examples include classic transformations[28–30] and palladium-catalyzed cross coupling reactions.[14,31,32] Herein, we report a new and convenient synthesis of arylated coumarins (neoflavones) by what are, to the best of our knowledge, the first Suzuki–Miyaura reactions of 4-trifluoromethylsulfonyloxy-6-bromocoumarin. The reactions proceed with excellent chemoselectivity in favour of position 4.

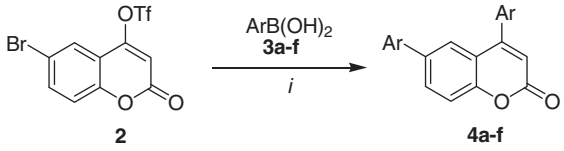
The reaction of 4-hydroxy-6-bromocoumarin (**1**) with triflic anhydride afforded the triflate **2** (Scheme 2).[33]

The Suzuki–Miyaura reaction of 4-trifluoromethyl-sulfonyloxy-6-bromocoumarin (**2**) with arylboronic acids **3a–f** (2.2 equiv) afforded the 4,6-diarylcoumarins **4a–f** in 60–88% yield (Scheme 3, Table 1).[34,35] Both electron rich and poor arylboronic acids could be successfully employed.

The Suzuki–Miyaura reaction of **2** with one equivalent of arylboronic acids afforded the 4-aryl-6-bromocoumarins **5a–g** in 60–88% yield (Scheme 4, Table 2).[36,37] The reaction proceeds by



Scheme 2. Synthesis of **2** Reagents and Conditions: (i), **1** (1.0 equiv), Tf_2O (1.3 equiv), Et_3N (2.0 equiv), CH_2Cl_2, −15 °C, 2 h.

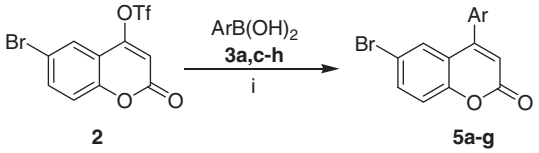


Scheme 3. Synthesis of **4a–f**. Reagents and Conditions: (i), **2** (1.0 equiv), $ArB(OH)_2$ (2.2 equiv), $Pd(PPh_3)_4$ (6 mol %), K_3PO_4 (3.0 equiv), dioxane, 90 °C, 10 h.

Table 1
Synthesis of 4,6-diarylcoumarins **4a–f**

3,4	Ar	% (**4**)[a]
a	4-(MeO)C_6H_4	86
b	4-EtC_6H_4	88
c	4-*t*BuC_6H_4	60
d	3,5-$Me_2C_6H_3$	75
e	4-ClC_6H_4	82
f	4-FC_6H_4	71

[a] Yields of isolated compounds.



Scheme 4. Synthesis of **5a–g**. Reagents and Conditions: (i) **2** (1.0 equiv), $ArB(OH)_2$ (1.1 equiv), $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), toluene/dioxane (9:1), 65 °C, 5 h.

Table 2
Synthesis of **5a–g**

3	5	Ar	% (**5**)[a]
a	**a**	4-(MeO)C_6H_4	87
c	**b**	4-*t*BuC_6H_4	95
d	**c**	3,5-$Me_2C_6H_3$	81
e	**d**	4-ClC_6H_4	77
f	**e**	4-FC_6H_4	70
g	**f**	2-(MeO)C_6H_4	79
h	**g**	3-ClC_6H_4	83

[a] Yields of isolated compounds.

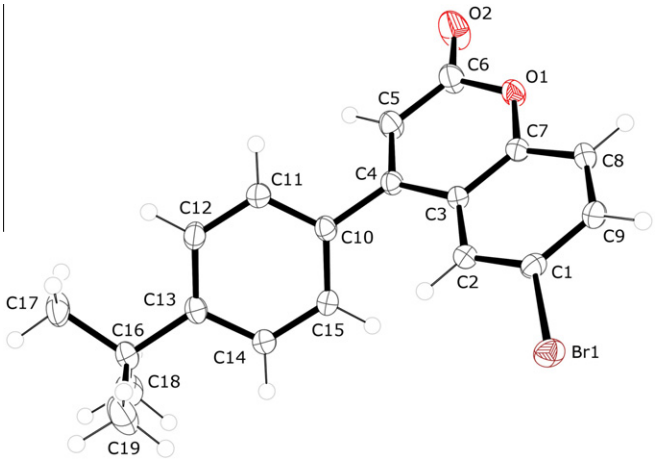


Figure 1. Crystal structure of compound **5b**.

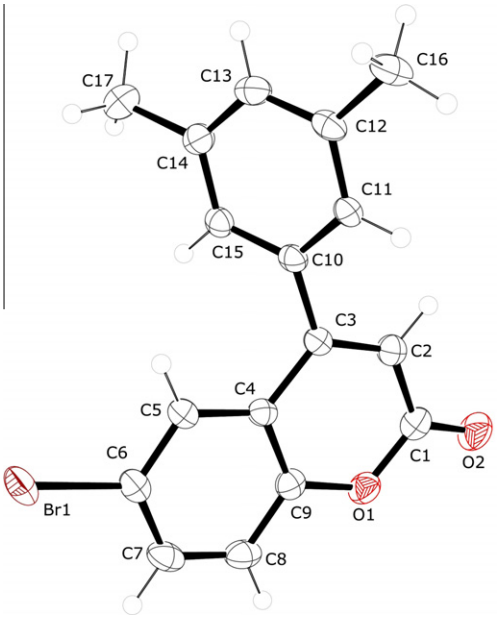
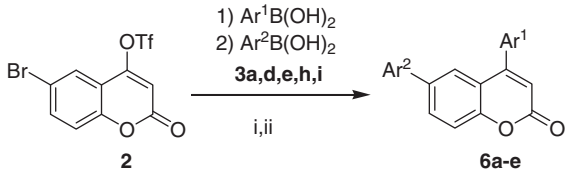


Figure 2. Crystal structure of compound **5c**.

chemoselective attack onto the triflate group, despite the fact that it is known that usually bromides are more reactive than triflates in the Suzuki reaction, due to the formation of a stable boron-bromide bond. The selectivity can be explained by the highly electron deficient character of position 4 of the coumarin moiety. During the optimization, it proved to be important to carry out the reaction at lower temperature (65 °C) as compared to the synthesis of the diarylated coumarins. In addition, the employment of a solvent mixture of toluene and dioxane (instead of pure dioxane) proved to be advantageous. Again, both electron rich and poor arylboronic acids gave very good yields. The structures of **5b** and **5c** were independently confirmed by X-ray crystal structure analyses (Figs. 1 and 2).[38]

The one-pot reaction of **2** with two different arylboronic acids (sequential addition) afforded the diarylated coumarins **6a–e** in 60–88% yield (Scheme 5, Table 3).[39,40] The reaction proceeds by chemoselective attack onto the triflate group. Both electron rich and poor arylboronic acids could be successfully employed in the first or in the second step of the one-pot reaction. During the optimization it again proved to be important to carry out the first step at 65 instead of 90 °C. A fresh portion of the catalyst had to be added in the second step in order to obtain good yields. The structure of **6b** was independently confirmed by X-ray crystal structure analysis (Fig. 3).[38]



Scheme 5. Synthesis of **6a–e**. Reagents and Conditions: (i), **2** (1.0 equiv), $Ar^1B(OH)_2$ (1.0 equiv), $Pd(PPh_3)_4$ (3 mol %), K_3PO_4 (1.5 equiv), dioxane/toluene (9:1), 65 °C, 8 h; (ii), $Ar^2B(OH)_2$ (1.3 equiv.), K_3PO_4 (1.5 equiv), $Pd(PPh_3)_4$ (6 mol %), dioxane, 90 °C, 14 h.

Table 3
Synthesis of **6a–e**

3	6	Ar^1	Ar^2	% (**6**)[a]
a,**e**	**a**	4-(MeO)C_6H_4	4-ClC_6H_4	78
a,**h**	**b**	4-(MeO)C_6H_4	3-ClC_6H_4	81
d,**a**	**c**	3,5-$Me_2C_6H_3$	4-(MeO)C_6H_4	70
e,**a**	**d**	4-ClC_6H_4	4-(MeO)C_6H_4	63
e,**i**	**e**	4-ClC_6H_4	3-FC_6H_4	85

[a] Yields of isolated compounds.

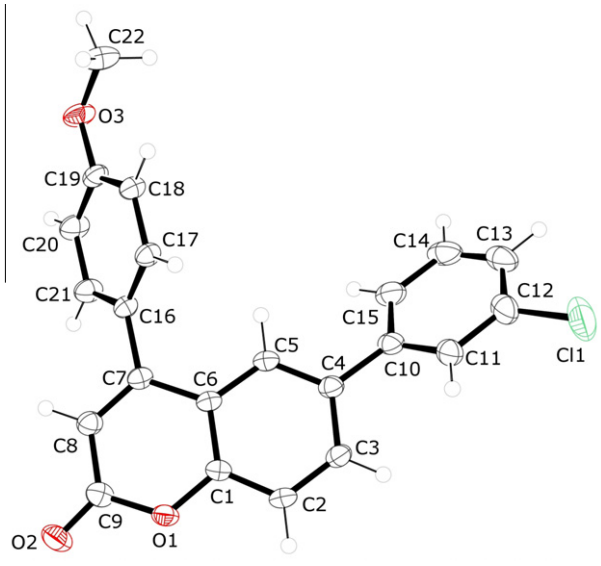


Figure 3. Crystal structure of **6b**.

In conclusion, we have reported the first Suzuki–Miyaura reactions of 4-trifluoromethylsulfonyloxy-6-bromo-coumarin. These reactions provide a convenient access to arylated coumarins. The reactions proceed with excellent chemoselectivity in favour of position 4.

Acknowledgments

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33. *Synthesis of 6-bromo-2-oxo-2H-chromen-4-yl trifluoromethanesulfonate (2).* Tf_2O (0.41 mL, 2.43 mmol) was added at −15 °C to a solution of 1 (0.45 g, 1.87 mmol) and triethylamine (0.5 mL, 3.74 mmol) in CH_2Cl_2 (15 mL) and the reaction mixture was stirred at the same temperature under argon atmosphere for 2 h. To the reaction mixture was added toluene (10 mL) and the solution was concentrated in vacuo. The residue was chromatographed (EtOAc/Heptanes: 9/300) without aqueous work up to yield 2 as a white solid (0.42 g, 60%), mp 110–112 °C. ^{1}H NMR (300 MHz, CDCl3): δ = 6.47 (s, 1H, C═CH), 7.25 (d, 1H, *J* = 8.9 Hz, ArH), 7.69–7.73 (m, 2H, ArH). ^{19}F NMR (282.4 MHz, $CDCl_3$): δ = −72.5. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 105.5 (CH), 114.4, 117.1 (C), 118.1 (CH), 118.3 (q, $J_{C,F}$ = 320.6 Hz, CF_3), 124.0, 136.0 (CH), 151.2, 154.8, (C), 157.8 (CO). IR (KBr): ν = 3119, 3087, 3054, 2918, (w), 1727 (s), 1628, 1599, 1562, 1473 (m), 1436, 1418, 1349 (s), 1307, 1266 (w), 1250 (m), 1213, 1184 (s), 1170 (m), 1041 (s), 937 (w), 876, 852, 825, 826, 808, 788, 759 (m), 741, 712, 696, 653, 633 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 374 ([M, ^{81}Br]$^+$, 100), 372 ([M, ^{79}Br]$^+$, 97), 282 (29), 280 (29), 213 (51), 211 (53). HRMS (EI, 70 eV): calcd for $C_{10}H_4BrF_3O_5S$ [M, ^{79}Br]$^+$: 371.89094; found 371.89097, calcd for $C_{10}H_4BrF_3O_5S$ ([M, ^{81}Br]$^+$: 373.88890; found 373.88890.
34. *General procedure A for the synthesis of **4a–f**:* A 1,4-dioxane solution (2 mL) of **2** (0.13 mmol), arylboronic acid (2.2 equiv), K_3PO_4 (3.0 equiv) and $Pd(PPh_3)_4$ (6 mol %) was heated at 90 °C for 10 h under argon atmosphere. After cooling to 20 °C, H_2O was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/Heptanes: 6/300).
35. *4,6-Bis(4-ethylphenyl)-2H-chromen-2-one (**4b**). Starting with **2*** (50 mg, 0.134 mmol), arylboronic acid (44 mg, 0.29 mmol), K_3PO_4 (85 mg, 0.4 mmol) and $Pd(PPh_3)_4$ (9 mg, 6 mol %), **6b** was prepared as a yellow highly viscous oil (42 mg, 88%): Reaction temperature: 90 °C for 10 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, 3H, *J* = 7.6 Hz, CH_3), 1.24 (t, 3H, *J* = 7.6 Hz, CH_3), 2.60 (q, 2H, *J* = 7.6 Hz, CH_2), 2.67 (q, 2H, *J* = 7.6 Hz, CH_2), 6.32 (s, 1H, C═CH), 7.16–7.19 (m, 2H, ArH), 7.27–7.35 (m, 6H, ArH), 7.38 (d, 1H, *J* = 8.5 Hz, ArH), 7.63 (d, 1H, *J* = 2.1 Hz, ArH), 7.66 (dd, 1H, *J* = 2.1, 8.5 Hz, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.3, 15.6 (CH_3), 28.5, 28.7 (CH_2), 115.2, 117.6 (CH), 119.2 (C), 125.1, 127.1, 128.2, 128.4, 128.5, 130.7 (CH), 132.7, 137.1, 137.5, 143.9, 146.2, 153.5, 155.8 (C), 160.9 (CO). IR (KBr): ν = 3024, 2962, 2928, 2871 (w), 1721 (s), 1613, 1569, 1558, 1509, 1481 (m), 1454 (w), 1428, 1413 (m), 1400 (w), 1360, 1266, 1257, 1177 (m), 1141 (w), 1121 (m), 1060, 1050, 1018, 953 (w), 929 (m), 901, 869 (w), 818 (s), 773, 759, 736, 710, 683, 634, 614, 600, 539, 537 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 354 ([M]$^+$, 100), 339 (33), 325 (13), 311 (24), 296 (10), 252 (07). HRMS (EI, 70 eV): calcd for $C_{25}H_{22}O_2$ [M]$^+$: 354.16143; found 354.16181.
36. *General procedure B for the synthesis of **5a–g**.* A toluene/1,4-dioxane solution (9:1, 2 mL) of **2** (0.13 mmol), arylboronic acid (1.1 equiv), K_3PO_4 (1.5 equiv) and $Pd(PPh_3)_4$ (3 mol %) was heated at 65 °C for 5 h under argon atmosphere. After cooling to 20 °C, CH_2Cl_2 (20 mL) was added and the mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc/Heptanes: 3:300).
37. *6-Bromo-4-(4-(tert-butyl) phenyl)-2H-chromen-2-one (**5b**).* Starting with **2** (50 mg, 0.134 mmol), **5b** was prepared as a white solid (45 mg, 95%), mp 162 °C. Reaction temperature: 65 °C for 5 h. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 9H, $3CH_3$), 6.31 (s, 1H, C═CH), 7.21 (d, 1H, *J* = 8.7 Hz, ArH), 7.30 (d, 2H, *J* = 8.4 Hz, ArH), 7.48 (d, 2H, *J* = 8.5 Hz, ArH), 7.55 (dd, 1H, *J* = 2.3, 8.7 Hz, ArH), 7.59 (d, 1H, *J* = 2.3 Hz, ArH). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 31.2 ($3CH_3$), 34.9 (C), 115.8 (CH), 116.9 (C), 119.0 (CH), 120.7 (C), 126.1, 128.1, 129.4 (CH), 131.5 (C), 134.6 (CH), 153.1, 153.4, 154.5 (C), 160.1 (CO). IR (KBr): ν = 3117, 3084, 3068, 3055, 2961, 2901, 2866, 1926 (w), 1721 (s), 1612, 1593, 1551, 1510 (m), 1501 (w), 1467, 1462, 1406 (m), 1305 (w), 1259 (m), 1246, 1199 (s), 1174, 1130, 1104, 1071, 1020, 952, 944 (w) 931 (s), 888, 870, 847 (m), 832, 826 (s), 799, 757, 746, 734, 710, 666, 659, 626 (w), 603 (s), 563, 545, 530 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 358 ([M, ^{81}Br]$^+$, 37), 356 ([M, ^{79}Br]$^+$, 37), 343 (98), 341 (99), 315 (15), 313 (14), 281 (10), 253 (09), 234 (13), 208 (21), 207 (100), 191 (17), 189 (17). HRMS (ESI-TOF/MS): calcd for $C_{19}H_{18}BrO_2$ [M+H, ^{79}Br]$^+$: 357.04847; found 357.04926, calcd for $C_{19}H_{18}BrO_2$ [M+H, ^{81}Br]$^+$: 359.04663; found 359.04746.
38. CCDC 875642–875644 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk.
39. *General procedure C for one-pot unsymmetrical 4,6-diarylcoumarins **6a–e**.* A toluene/1,4-dioxane solution (9:1: 2 mL) of 6-bromo-2-oxo-2H-chromen-4-yl trifluoromethanesulfonate **2** (0.134 mmol), $Ar^1B(OH)_2$ (1.0 equiv), K_3PO_4 (1.5 equiv) and $Pd(PPh_3)_4$ (3 mol %) was heated at 65 °C for 8 h under argon atmosphere. After cooling to 20 °C, $Ar^2B(OH)_2$ (1.3 equiv), $Pd(PPh_3)_4$ (6 mol %), dioxane (1 mL) were added and reaction mixture was heated at 90 °C for further 14 h. Reaction mixture was cooled again to 20 °C, H_2O was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), organic layers were dried (Na_2SO_4), filtered and then concentrated in vacuo. The residue was purified by column chromatography (EtOAc/Heptanes: 6:300).
40. *6-(4-Chlorophenyl)-4-(4-methoxyphenyl)-2H-chromen-2-one (**6a**)* Starting with **2** (50 mg, 0.13 mmol), 4-methoxyphenylboronic acid as $Ar^1B(OH)_2$ (20 mg, 0.13 mmol), K_3PO_4 (43 mg, 0.2 mmol), $Pd(PPh_3)_4$ (4.5 mg, 3 mol %) and 4-chlorophenylboronic acid as $Ar^2B(OH)_2$ (27 mg, 0.17 mmol), **6b** was prepared according to *general procedure C* as an off-white solid (38 mg, 78%), mp 154–156 °C. Conditions: 65 °C for 8 h (first step) and 90 °C for 14 h (second step). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OCH_3), 6.31 (s, 1H, C═CH), 6.98 (d, 2H, *J* = 8.8 Hz, ArH), 7.30–7.33 (m, 4H, ArH), 7.35–7.42 (m, 3H, ArH), 7.61–7.66 (m, 2H, ArH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 55.5 (OCH_3), 114.5, 115.1, 117.9 (CH), 119.5 (C), 125.2 (CH), 127.3 (C), 128.3, 129.1, 129.9, 130.5 (CH), 133.8, 136.2, 138.2, 153.8, 155.2, 160.7 (C), 161.0 (CO). IR (KBr): ν = 3116, 3096, 2964, 2928, 2897, 2834, 1947, 1887, 1855 (w), 1730 (s), 1605 (m), 1573, 1564, 1557 (w), 1512, 1477, 1460, 1424 (m), 1389 (w), 1358, 1305, 1290 (m), 1259, 1247, 1181, 1173 (s), 1140, 1123, 1114, 1091 (w), 1031, 1008 (m), 974, 948 (w), 925, 893 (m), 840 (s), 824, 815 (w), 800 (s), 781, 758, 736, 729, 706, 674, 649, 636, 626 (w), 603, 584 (m), 567 (w), 547 (m). cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 364 ([M, ^{37}Cl]$^+$, 40), 362 ([M, ^{35}Cl]$^+$, 100), 336 (16), 334 (50), 321 (12), 319 (28), 228 (15), 226 (24). HRMS (EI, 70 eV): calcd for $C_{22}H_{15}ClO_3$ [M, ^{35}Cl]$^+$: 362.07042; found 362.07013, calcd for $C_{22}H_{15}ClO_3$ [M, ^{37}Cl]$^+$: 364.06747; found 364.06794.