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PALLADIUM-CATALYZED INTRAMOLECULAR HYDROARYLATION OF 6-BENZOFURANYL ALKYNOATES

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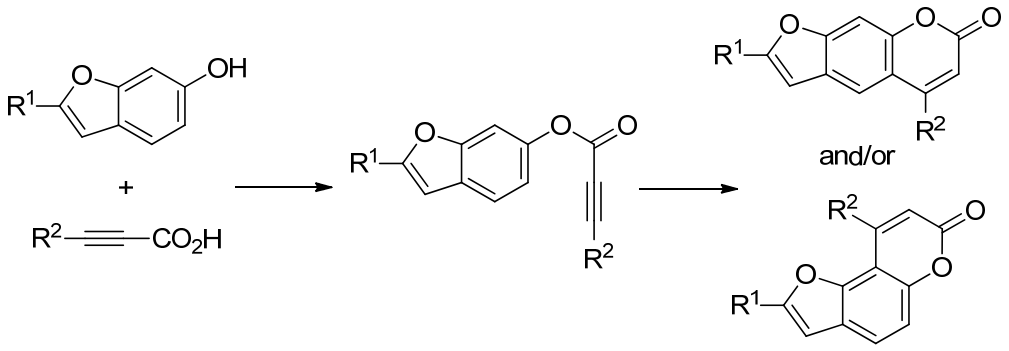
Abstract – Intramolecular hydroarylation of 6-benzofuranyl alkynoates efficiently proceeded using $Pd(OAc)_2$ as catalyst in TFA and CH_2Cl_2 at room temperature. This intramolecular hydroarylation gave a mixture of regioisomers of furocoumarins, i.e., psoralens and allopsorallens.

Furocoumarins are an important class of tricyclic aromatic compounds composing of a fused structure of coumarin and furan nuclei. They have long attracted much attention because of their biological and industrial applications. Furocoumarin derivatives are naturally occurring or synthetic compounds and are known to possess a high photobiological activity, as discussed in many reviews.[1]

For the reasons mentioned above, many synthetic methods for furocoumarins have been extensively developed so far.[1a,1b,1g,2] There are two main approaches to construct the furocoumarin skeleton, namely, furan-ring construction and pyrone-ring construction. Among these methods, the methodology fusing a furan ring on a coumarin nucleus has been traditionally and widely applied for the synthesis of furocoumarins.[1a,1b] On the other hand, hydroxybenzofuran derivatives have been used for the furocoumarin synthesis via the pyrone-ring construction as starting materials, and the synthetic method involves the Perkin condensation,[3] the Pechmann reaction,[4] the Wittig reaction,[2d,5] and related reactions.[6]

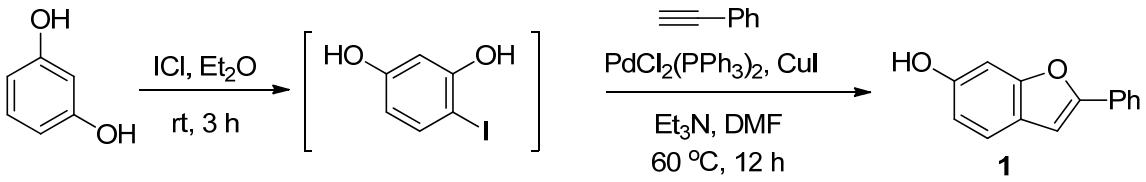
Intramolecular hydroarylation of alkynes is an efficient and promising method for synthesizing carbocyclic and heterocyclic aromatic compounds.[7] Recently several coumarin derivatives have been prepared by transition metal-catalyzed hydroarylation reactions.[8] However, to the best of our knowledge, there is only one report on synthesis of furocoumarins by the intramolecular hydroarylation methodology.[9] In this paper, we want to report another palladium-catalyzed intramolecular hydroarylation yielding furocoumarin derivatives, as shown in Scheme 1.

Dedicated with respect to Dr. Ei-ichi Negishi on the occasion of his 77th birthday.



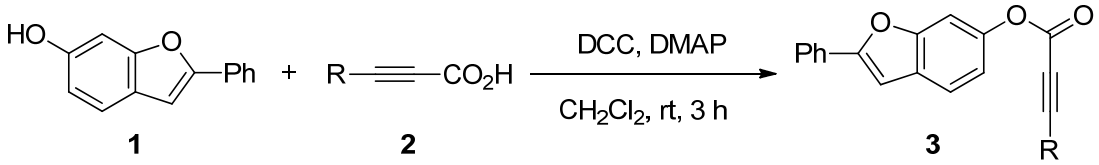
Scheme 1

First, 6-hydroxybenzofurans were prepared by the Sonogashira-Hagihara coupling of 4-iodoresorcinol with phenylacetylene as shown in Scheme 2. Iodination of resorcinol with ICl was examined according to the literature method.[10] The reaction of resorcinol with ICl at room temperature for 3 h gave 4-iodoresorcinol. The ^{1}H NNR spectrum of the product showed the presence of 4-iodoresorcinol in a high yield but purification by column chromatography on silica gel resulted in a large loss of the product due to the contamination with unreacted resorcinol and diiodoresorcinol. Then, we decided to use the crude 4-iodoresorcinol for the Sonogashira-Hagihara coupling reaction. The coupling reaction of the crude 4-iodoresorcinol with phenylacetylene was conducted in the presence of $PdCl_2(PPh_3)_2$ and CuI in triethylamine and DMF at 60 °C for 12 h. After separation by column chromatography on silica gel, 6-hydroxy-2-phenylbenzofuran (**1**) was obtained in 45% yield based on the starting resorcinol.



Scheme 2

Next, to prepare benzofuranyl alkynoates, the condensation of 6-hydroxy-2-phenylbenzofuran (**1**) and alkynoic acids (**2**) was conducted using DCC and DMAP in CH_2Cl_2 at room temperature (Scheme 3). The results are given in Table 1. 6-Benzofuranyl alkynoates (**3**) was obtained in good to high yields.



Scheme 3

Table 1. Preparation of 6-benzofuranyl alkynoates (**3**)[a]

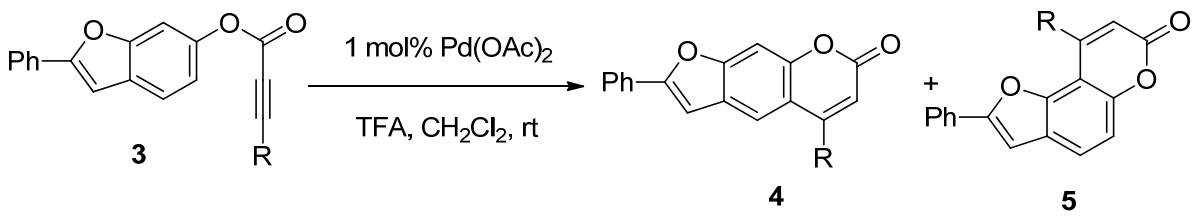
Entry	Alkynoic acid **2**	Product **3**	Yield (%)[b]
1	**2a** (R = Ph)	**3a**	89
2	**2b** (R = *n*-C_5H_{11})	**3b**	89
3	**2c** (R = Me)	**3c**	93
4	**2d** (R = H)	**3d**	68

[a] Conditions: **1** (2 mmol), **2** (2 mmol), DCC (2 mmol), DMAP (0.2 mmol), CH_2Cl_2 (2 mL), rt, 3 h.
[b] Isolated yield.

Intramolecular hydroarylation was performed using $Pd(OAc)_2$ catalyst in a mixed solvent of TFA and CH_2Cl_2. The outline was shown in Scheme 4. The results are given in Table 2. When 6-benzofuranyl phenylpropynoate (**3a**) was allowed to react with 1 mol% $Pd(OAc)_2$ at room temperature for 1 h, the desired furocoumarin derivatives were obtained in 90% yield (Entry 1). However, ^{1}H NMR spectrum of the product showed that it was a 23:77 regioisomeric mixture of furocoumarins **4a** and **5a**. The ratio was determined by the integral of the characteristic vinylic proton at the 3 position. The elemental analysis of the regioisomeric mixture was consistent with the proposed furocoumarins. In addition, the major isomer was obtained by repeated column chromatography and recrystallization and assigned to **5a** based on a characteristic AB pattern of the aromatic protons: δ 7.34 (d, J = 8.6 Hz) and 7.73 (d, J = 8.6 Hz).

Under the similar conditions the reaction of 6-benzofuranyl octynoate (**3b**) gave furocoumarin derivatives **4b** and **5b** by the ratio of ca. 40:60 in 68-88% yields (Entries 2 and 3). 6-Benzofuranyl butynoate (**3c**) also showed a similar behavior to **3b**, giving furocoumarins **4c** and **5c** in 56-58% yields. 6-Benzofuranyl propynoate (**3d**) afforded a mixture of furocoumarins **4d** and **5d** by the ratio of 50:50 in 27% yield due to the side-reactions. Then, to suppress the side-reactions, the reaction of **3d** was conducted with an increased amount of solvent. Although the use of large amount of solvent improved the yield of **4d** and **5d**, the best result was 47% (Entries 7-9).

The intramolecular hydroarylation of 6-benzofuranyl alkynoates (**3**) has two processes. The cyclization at the 5 position of the benzofuran ring gives furocoumarins **4** (psoralens), while the cyclization at the 7 position affords **5** (allopsoralens).



Scheme 4

Table 2. Intramolecular hydroarylation of **3** with $Pd(OAc)_2$ catalyst[a]

Entry	R	CH_2Cl_2 /mL	TFA /mL	Time /h	Product	Yield /%[b]	Ratio[c] **4** : **5**
1	Ph	0.5	0.5	1	**4a** and **5a**	90	23:77
2	C_5H_{11}	0.5	0.5	1	**4b** and **5b**	68	38:62
3	C_5H_{11}	0.75	0.25	1	**4b** and **5b**	88	41:59
4	CH_3	0.5	0.5	1	**4c** and **5c**	56	33:67
5	CH_3	0.75	0.25	1	**4c** and **5c**	58	41:59
6	H	0.5	0.5	1	**4d** and **5d**	27	50:50
7	H	12	4	24	**4d** and **5d**	44	45:55
8	H	30	10	24	**4d** and **5d**	47	49:51
9[d]	H	45	15	24	**4d** and **5d**	42	48:52

[a] Conditions: **3** (1 mmol), $Pd(OAc)_2$ (0.01 mmol), TFA, CH_2Cl_2, rt.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] At 50 °C.

As discussed in the previous paper,[9] it is considered that the intramolecular hydroarylation of 6-benzofuranyl alkynoates also proceeds as follows. First, TFA undergoes ligand exchange of $Pd(OAc)_2$ with acetate ion to generate a more reactive $Pd(OCOCF_3)_2$. Thus, the resulting reactive palladium species coordinates with the triple bond to induce intramolecular electrophilic aromatic substitution leading to a furanocoumaryl palladium complex. This intramolecular cyclization occurs both at the 5 and 7 positions of the benzofuran ring. The resulting furanocoumaryl palladium complexes undergo protonation with TFA to give furocoumarins and the palladium species is regenerated.

In conclusion, we have demonstrated an efficient palladium-catalyzed intramolecular hydroarylation of 6-benzofuranyl alkynoates, which gives a mixture of regioisomers of furocoumarins, i.e., psoralens and allopsorallens.

EXPERIMENTAL

All solvents and starting materials were used during the research work as received without further purification unless otherwise indicated. ^1H and ^{13}C NMR were recorded on a JEOL JNMR-AL 300 FT-NMR spectrometer (TMS as an internal standard). Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. Elemental analysis was performed by the Service Center of the Elemental Analysis of Organic Compounds, Faculty of Science, Kyushu University, Fukuoka, Japan. High resolution mass spectra were measured by the Analytical Center, Institute for Materials Chemistry and Engineering, Kyushu University. Column chromatographic separation was carried out using Silica Gel 60, spherical (Kanto Chemical Co.).

Preparation of 4-Iodoresorcinol. A solution of ICl (1 mmol) in ether (40 mL) was added to resorcinol (1 mmol) and the mixture was stirred at room temperature for 3 h. The reaction mixture was quenched with aqueous sodium sulfite and extracted with Et_2O. The ethereal solution was washed with water, then with brine, and dried over anhydrous sodium sulfate. The crude 4-iodoresorcinol was used for the Sonogashira-Hagihara coupling reaction without further purification.

4-Iodoresorcinol:[10] a colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53 (s, 1H, OH), 5.77 (s, 1H, OH), 6.25 (dd, *J* = 2.3, 8.6, 1H, aryl), 6.52 (d, *J* = 2.3 Hz, 1H, aryl), 7.43 (d, *J* = 8.6 Hz, 1H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.51, 102.72, 110.55, 138.46, 155.50, 157.36.

Preparation of 6-Hydroxy-2-phenylbenzofuran (1). To the crude 4-iodoresorcinol (ca 1 mmol) prepared above, were added successively phenylacetylene (2 mmol), $PdCl_2(PPh_3)_2$ (0.035 mmol), CuI (0.0525 mmol), Et_3N (2 mL), and DMF(2.5 mL). The mixture was stirred at 60 °C for 12 h under argon atmosphere. The reaction mixture was acidified with diluted HCl and extracted with Et_2O. The ethereal extract was washed with water, then with brine, and dried with anhydrous sodium sulfate. After concentration in vacuo, the product was separated by column chromatography on silica gel using CH_2Cl_2/hexane as eluent.

6-Hydroxy-2-phenyl-benzofuran (1):[11] white solids; mp 177−179 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 6.86 (dd, *J* = 2.4, 8.3 Hz, 1H, aryl), 7.06−7.13 (m, 2H, aryl), 7.29−7.46 (m, 4H, aryl), 7.83−7.86 (m, 2H, aryl), 8.54 (s, 1H, OH); ^{13}C NMR (75 MHz, acetone-d_6) δ 98.50, 102.36, 113.32, 122.06, 122.61, 125.01, 128.79, 129.63, 131.60, 155.30, 156.74, 156.91.

General Procedure for Preparation of 2-Phenylbenzofuran-6-yl Alkynoates (3). A mixture of 6-hydroxy-2-phenylbenzofuran (**1**) (2 mmol), alkynoic acid (**2**) (2 mmol), and 4-(dimethylamino)pyridine (DMAP) (0.2 mmol) was stirred at 0 °C for 5 min using an ice/water bath and then *N*,*N*-dicyclohexylcarbodiimide (DCC) (2 mmol) was added. The mixture was stirred at 0 °C for 5 min and then at room temperature for 3 h. After filtration of the resulting solids, the mother liquor was treated with diluted HCl and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo, the product was separated by column chromatography on silica gel using CH_2Cl_2/hexane as eluent.

2-Phenylbenzofuran-6-yl Phenylpropynoate (3a): white solids; mp 140−142 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H, aryl), 7.08 (dd, *J* = 1.8, 8.4 Hz, 1H, aryl), 7.33−7.51 (m, 7H, aryl), 7.57 (d, *J* = 8.4 Hz, 1H, aryl), 7.62−7.65 (m, 2H, aryl), 7.83−7.86 (m, 2H, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.26, 88.85, 101.01, 105.06, 116.90, 119.24, 120.94, 124.89, 127.59, 128.66, 128.75, 128.81, 130.09, 131.04, 133.19, 147.22, 152.60, 154.55, 157.27. HRMS Calcd for $C_{23}H_{14}O_3$: M, 338.0943. Found: *m/z* 338.0942.

2-Phenylbenzofuran-6-yl 2-octynoate (3b): white solids; mp 94−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ

0.92 (t, J = 7.2 Hz, 3H, CH_3), 1.31−1.46 (m, 4H, CH_2), 1.56−1.66 (m, 2H, CH_2), 2.41 (t, J = 7.2 Hz, 2H, CH_2), 7.00 (s, 1H, aryl), 7.02 (dd, J = 2.1, 8.4 Hz, 1H, aryl), 7.33−7.38 (m, 2H, aryl), 7.42−7.45 (m, 2H, aryl), 7.54 (d, J = 8.4 Hz, 1H, aryl), 7.82−7,85 (m, 2H, aryl); ^{13}C NMR (75 MHz,$CDCl_3$) δ 13.84, 18.81, 22.09, 27.13, 30.97, 72.71, 92.64, 101.00, 105.06, 116.92, 120.87, 124.88, 127.47, 128.72, 128.80, 130.13, 147.26, 152.34, 154.55, 157.18. Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.47; H, 6.04.

2-Phenylbenzofuran-6-yl 2-butynoate (3c): white solids; mp 113-118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H, CH_3), 7.00−7.04 (m, 2H, aryl), 7.34−7.47 (m, 4H, aryl), 7.54 (d, J = 8.4 Hz, 1H, aryl), 7.82−7.85 (m, 2H, aryl); ^{13}C NMR (75 MHz,$CDCl_3$) δ 3.72, 72.06, 88.19, 100.92, 104.87, 116.75, 120.78, 124.74, 127.37, 128.59, 128.67, 129.98, 147.15, 152.02, 154.43, 157.08. Anal. Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.25; H, 4.33.

2-Phenylbenzofuran-6-yl propynoate (3d): white solids; mp 218-220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 1H, CH), 7.00−7.05 (m, 2H, aryl), 7.33−7.47 (m, 4H, aryl), 7.55 (d, J = 8.4 Hz, 1H, aryl), 7.82−7.85 (m, 2H, aryl); ^{13}C NMR (75 MHz,$CDCl_3$) δ 74.30, 76.90, 77.20, 100.98, 104.90, 116.64, 120.97, 124.93, 127.75, 128.82, 130.07, 146.91, 151.18, 154.51, 157.43. HRMS Calcd for $C_{17}H_{10}O_3$: M, 262.0630. Found: *m/z* 262.0632.

General Procedure for Intramolecular Hydroarylation of 3. A solution of benzofuran-6-yl alkynoate **3** (1 mmol) and $Pd(OAc)_2$ (0.01 mmol) in CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) was stirred at room temperature for 30 min. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and dried over anhydrous sodium sulfate. After concentration in vacuo, the product was separated by column chromatography on silica gel using CH_2Cl_2/hexane as eluent.

A Mixture of 2,5-Diphenyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one (4a) and 2,9-Diphenyl-7*H*-furo[2,3-*f*][1]benzopyran-7-one (5a): white solids; mp 137−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32 (s, vinyl, **4a**), 6.38 (s, vinyl, **5a**), 6.95 (s, aryl), 7.27−7.60 (m, aryl), 7.69 (d, J = 8.1 Hz, aryl), 7.81 (d, J = 7.2 Hz, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.70, 100.39, 100.64, 105.90, 113.05, 113.26, 115.65, 115.81, 118.59, 124.00, 124.33, 124.87, 126.01, 126.38, 128.03, 128.14, 128.38, 128.52, 128.56, 128.79, 128.97, 129.10, 129.33, 129.37, 129.52, 135.73, 137.13, 149.33, 151.88, 152.12, 153.29, 156.06, 156.18, 156.50, 157.91, 160.40, 160.88. One carbon is overlapped. Anal. Calcd for $C_{23}H_{14}O_3$: C, 81.64; H, 4.17. Found: C, 81.64; H, 4.18. **5a:** mp 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (s, 1H, vinyl), 6.98 (s, 1H, aryl), 7.25−7.32 (m, 5H, aryl), 7.34 (d, J = 8.6 Hz, 1H, aryl), 7.53−7.64 (m, 5H, aryl), 7.73 (d, J = 8.6 Hz, 1H, aryl).

A Mixture of 5-Pentyl-2-phenyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one (4b) and 9-Pentyl-2-phenyl-7*H*-furo[2,3-*f*][1]benzopyran-7-one (5b): white solids; mp 115−128 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ

0.92−1.01 (m, CH_3), 1.41−1.55 (m, CH_2), 1.69−1.77 (m, CH_2), 2.77 (t, J = 7.4 Hz, CH_2, **4b**), 3.14 (t, J = 7.4 Hz, CH_2, **5b**), 6.20 (s, vinyl, **4b**), 6.26 (s, vinyl, **5b**), 6.99 (s, aryl), 7.00 (s, aryl), 7.20 (d, J = 8.4Hz, aryl), 7.35−7.81 (m, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.85, 13.93, 22.36, 22.47, 27.72, 28.19, 31.56, 31.74, 32.02, 34.88, 99.61, 100.60, 101.08, 106.75, 111.98, 113.21, 113.79, 115.57, 115.91, 123.43, 124.48, 124.88, 125.69, 126.31, 128.49, 128.81, 128.88, 129.06, 129.47, 129.68, 149.76, 151.79, 152.03, 155.30, 156.03, 156.47, 156.65, 157.85, 160.73, 161.15. Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.55; H, 5.97.

A Mixture of 5-Methyl-2-phenyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one (4c) and 9-Methyl-2-phenyl-7*H*-furo[2,3-*f*][1]benzopyran-7-one (5c): white solids; mp 174−188 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ 2.44 (s, CH_3, **4c**), 2.78 (s, CH_3, **5c**), 6.20 (s, vinyl, **4c**), 6.23 (s, vinyl, **5c**), 6.97 (s, aryl), 7.17 (d, J = 8.4 Hz, aryl), 7.36−7.79 (m, aryl); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.81, 21.63, 99.06, 100.32, 100.70, 106.75, 112.69, 113.02, 114.50, 115.67, 116.31, 123.25, 124.23, 124.61, 125.35, 126.08, 128.64, 128.67, 128.72, 128.93, 129.15, 129.30, 149.86, 150.94, 151.24, 151.38, 152.39, 155.81, 156.45, 157.58, 160.31, 160.70. Anal. Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38. Found: C, 78.08; H, 4.35.

A Mixture of 2-Phenyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one (4d) and 2-Phenyl-7*H*-furo[2,3-*f*][1]benzopyran-7-one (5d): yellow solids; mp 242-261 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.36 (d, J = 9.6 Hz, vinyl, **4d**), 6.51 (d, J = 9.6 Hz, vinyl, **5d**), 7.00 (s, aryl), 7.03 (s, aryl), 7.20−7.25 (m, aryl), 7.38−7.46 (m, aryl), 7.60−7.67 (m, aryl), 7.74−7.84 (m, aryl and vinyl), 8.24 (d, J = 9.6 Hz, vinyl, **5d**); ^{13}C NMR (75 MHz, $CDCl_3$) δ 99.61, 100.46, 101.41, 105.45, 112.51, 114.49, 115.52, 116.29, 119.20, 123.75, 124.41, 124.74, 125.00, 125.03, 126.70, 128.68, 128.91, 128.93, 129.21, 129.48, 129.74, 136.84, 144.01, 149.79, 151.88, 152.04, 156.39, 157.13, 158.08, 160.67. HRMS Calcd for $C_{17}H_{10}O_3$: M, 262.0630. Found: *m/z* 262.0634.

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