An Efficient and Versatile Synthesis of Isoflavones from 2-Methoxybenzoic Acids

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Isoflavones (3-aryl-4*H*-1-benzopyran-4-ones) are found naturally in soybeans and many plants of the Leguminosae family.[1] They have attracted much attention due to their biological activities, such as their anti-cancer,[2] anti-inflammatory,[3] and antifungal properties.[4] Isoflavones intake through foods is important to human health, because they potentially regulate fatty acid metabolism[5] and methoxy-substituted isoflavones in particular increase cell permeability.[2b]

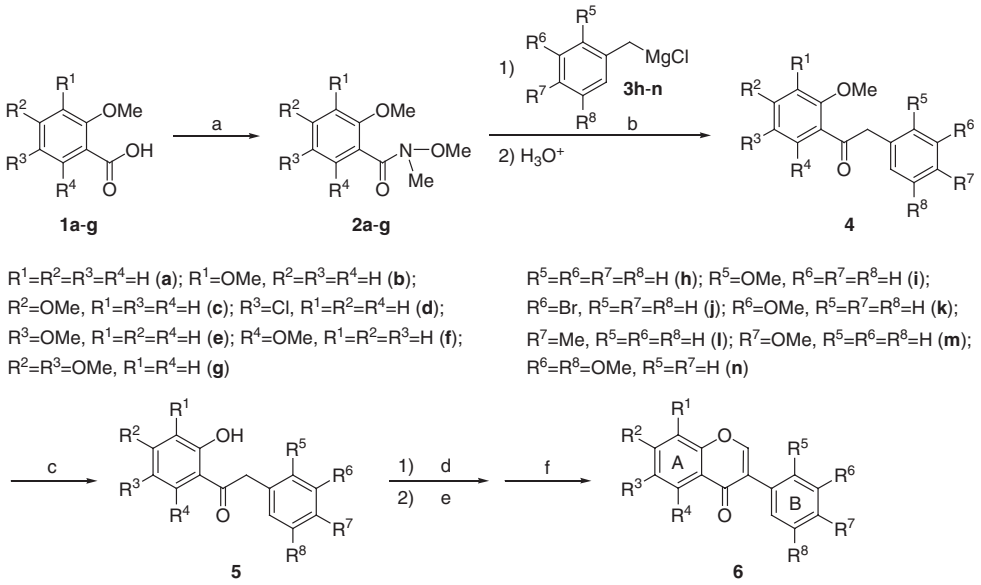
Isoflavones have been generally synthesized *via* 2-hydroxydeoxybenzoin or 2′-hydroxychalcone intermediates.[6] The 2-hydroxydeoxybenzoins were prepared by the electrophilic substitution of phenols with phenylacetic acids[7] and benzyl cyanides[8] in the presence of $BF_3{\cdot}Et_2O$ and $ZnCl_2$/HCl, respectively, using heating. The methylene group of the resulting 2-hydroxydeoxybenzoins were formylated with *N*-formyl imidazole,[9] acetic formic anhydride,[10] DMF dimethyl acetal,[11] PCl_5[7a] or CH_3SO_2Cl[7b,c,8] in DMF. These intermediates were followed by ring closure to provide the corresponding isoflavanones, which were then converted into isoflavones under acidic heating conditions. The treatment of 2′-hydroxychalcones, prepared by the condensation of 2′-hydroxyacetophenones and benzaldehydes using KOH, with thallium(III) nitrate[12] or phenyliodine diacetate[13] in trimethyl orthoformate provided the corresponding dimethyl acetals. The dimethyl acetals underwent 1,2-aryl shift and subsequent elimination of CH_3OH to provide isoflavones.

Isoflavones have also been synthesized by the coupling of 3-iodochromones with arylboronic acids. The condensation of 2′-hydroxyacetophenones with DMF dimethyl acetal formed 3-(dimethylamino)-2′-hydroxyphenylpropenones, which were cyclized using iodine to form 3-iodochromones. This process was followed by Suzuki coupling with arylboronic acids or aryl boronates to obtain isoflavones.[14] 3-Iodochromones were also coupled with triarylbismuths under catalytic palladium to form isoflavones.[15] Furthermore, the metalation of chromones with 2,2,6,6-tetramethyl piperidyl zinc chloride led to the C_3-zincated intermediates, which were coupled with *p*-iodoanisole under palladium catalyst to form isoflavones.[16] Alternatively, the oxidation of isoflavanones, which were prepared from the gold(I)-catalyzed annulation of salicylaldehydes and arylacetylenes at 150°C, with *o*-iodoxybenzoic acid formed isoflavones in moderate yields.[17]

Although several methods have been developed for the synthesis of isoflavones, some have disadvantages, including multiple steps, vigorous conditions, low yields, and tedious separations. Furthermore, the synthesis of 2-hydroxydeoxybenzoins by electrophilic substitution was effective only for the symmetrical phenol derivatives. In this study, we developed an efficient and versatile method for the synthesis of isoflavones from 2-methoxybenzoic acids under mild conditions.

N-Methoxy-*N*-methyl 2-methoxybenzamides (**2a**–**2e**, **2g**) were readily prepared by treating 2-methoxybenzoic acids (**1a**–**1e**, **1g**) with *N*-methoxy-*N*-methylcarbamoyl chloride and triethylamine (Scheme 1). The addition of 0.05 equiv of 4-(dimethylamino)pyridine (4-DMAP) accelerated the rate of conversion of carboxylic-carbamic anhydride intermediates to **2a**–**2e** and **2g** in acetonitrile. The reaction was completed within 2 h at room temperature and **2a**–**2e**/**2g** were obtained in 79–91% yields after the usual basic work-up (**2a**: 84%, **2b**: 83%, **2c**: 91%, **2d**: 79%, **2e**: 83%, **2g**: 85%).

The synthesis of 1-(2-methoxyphenyl)-2-phenylethanones (**4**) was carried out by the acyl substitution of **2** with benzylmagnesium chlorides (**3h**–**3n**) in THF. The reaction proceeded smoothly for 0.5 h at 0°C, regardless of the kind of electron-withdrawing and electron-donating substituents in both phenyl rings, and **4** was obtained in 78–93% yields after the usual acidic work-up (**4ah**: 81%, **4ai**: 93%, **4bj**: 83%, **4bk**: 82%, **4cl**: 92%, **4cm**: 91%, **4dm**: 80%, **4dn**: 78%, **4ej**: 83%, **4gh**: 88%). However, an attempt to prepare 1-(2,6-dimethoxyphenyl)-2-phenylethanone (**4fh**) by the reaction of *N*-methoxy-*N*-methyl 2,6-dimethoxybenzamide (**2f**) and benzylmagnesium chloride was not successful, probably due to the steric effects of the two 2,6-dimethoxy groups. **2f** was prepared by the acyl substitution of 2,6-dimethoxybenzoyl chloride with *N,O*-dimethylhydroxylamine hydrochlide in the presence of 2 equiv of triethylamine in 91% yield. Therefore, **4fh** was prepared by the acyl substitution of 2,6-dimethoxybenzoyl chloride with benzylmagnesium chloride pretreated with copper(I) cyanide, in THF for 1 h between 0°C and room temperature in 78% yield.



Scheme 1. Reagents and conditions: (a) ClCONMe(OMe), Et_3N, 0.05 equiv 4-DMAP, CH_3CN, rt, 2 h; (b) THF, 0°C, 0.5 h, CuCN for **4fh**; (c) 1 equiv BBr_3, CH_2Cl_2, approximately −20°C–rt, 1 h; (d) approximately 3–5 equiv $BF_3{\cdot}Et_2O$, THF, approximately 0°C–rt, 0.5 h; (e) 2 equiv DMF-$POCl_3$, THF, rt, approximately 2–6 h; (f) 0.1 N HCl, rt, 1 h.

Selective demethylation of the 2-methoxy group in **4** was successfully accomplished using boron tribromide. The addition of 1 equiv of boron tribromide to a solution of **4** in methylene chloride at −20°C seemed to produce 6-membered chelates between the oxygen atoms of the 2-methoxy/carbonyl group and boron atom. Subsequent displacement of the methyl group by the attack of the bromide anion produced the corresponding alkoxy borates, which were hydrolyzed with H_2O to produce **5** in 67–93% yields (**5ah**: 87%, **5ai**: 91%, **5bj**: 90%, **5bk**: 89%, **5cl**: 77%, **5cm**: 74%, **5dm**: 67%, **5dn**: 70%, **5ej**: 81%, **5fh**: 93%, **5gh**: 85%). In particular, only one methoxy group of **4fh** was selectively demethylated with 1 equiv of boron tribromide at −20°C to produce 1-(2-hydroxy-6-methoxyphenyl)-2-phenylethanone (**5fh**) in 93% yield.

The synthesis of isoflavones (**6**) from **5** was based on the formylation of the methylene group of **5** using DMF-$POCl_3$. Previously, the reaction of the DMF-$POCl_3$ complex on benzyl 2-hydroxyphenyl ketones led to isoflavones, for which DMF was used as the reagent and solvent for 18 h at gentle reflux.[18] However, few examples have been reported and thus the scope of the reaction was not fully investigated. Furthermore, 6-methoxy-substituted 2-hydroxyphenyl benzyl ketone failed to produce 5-methoxy-substituted isoflavone by treatment with DMF-$POCl_3$ under various conditions. Our methods circumvented these disadvantages using $BF_3{\cdot}Et_2O$ as Lewis acid and THF as the solvent under mild conditions.

The treatment of DMF with $POCl_3$ in THF for 0.5 h between 0°C and room temperature produced a pale pink colored solution. The resulting *N,N*-dimethyl(chloromethylene)ammonium salt was added to the solution of **5** pretreated with $BF_3{\cdot}Et_2O$ in THF for 0.5 h between 0°C and room temperature. The reaction proceeded smoothly with the substitution on *N,N*-dimethyl(chloromethylene)-ammonium salt by boron enolate of **5** and subsequent ring closure. After stirring for 2–6 h at room temperature, the resulting tan solution was treated with 0.1 N HCl solution and further stirring for 1 h led to the elimination of the dimethylamino group to produce isoflavones (**6**) in 78–94% yields after the usual acidic work-up. Thus, the synthesis of **6** from **5** was carried out successfully in the one pot operation of substitution, cyclization, and elimination. The use of $POCl_3$ for the formylation of **5** has solubility advantage over those of $SOCl_2$ and $(COCl)_2$, for which the corresponding *N,N*-dimethyl(chloromethylene)ammonium salt was not soluble in THF.

As shown in Table 1, various isoflavones were synthesized from 2-methoxybenzoic acids in overall high yields. The acyl substitution of **2** with **3** proceeded regardless of the position of the methoxy or halo (bromo, chloro) groups in **2** and **3**. In addition, the selective demethylation of 2-methoxy group in **4** was not affected by these groups with 1 equiv of boron tribromide. The ring closure of **5** based on the formylation using DMF-$POCl_3$ proceeded well with both the electron-donating groups (**6bj**, **6bk**, **6cl**, **6cm**, **6ej**, **6gh**) and the electron-withdrawing groups (**6dm**, **6dn**) of the A-ring. The ring closure also proceeded with both the electron-donating groups (**6ai**, **6bk**, **6cl**, **6cm**, **6dm**, **6dn**) and the electron-withdrawing groups (**6bj**, **6ej**) of the B-ring under the same conditions. In particular, the reaction of **4fh** pretreated with $BF_3{\cdot}Et_2O$ using DMF-$POCl_3$ proceeded smoothly for 3 h at room temperature to produce 5-methoxyisoflavone (**6fh**) regardless of the steric hindrance of the *o*-methoxy group in **5fh** in 85% yield.

Table 1. Synthesis of isoflavones **6** from **5**.

Entry **6**	Chemical name	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Isolated yields, %[a]
ah	Isoflavone	H	H	H	H	H	H	H	H	80 (47)
ai	2′-Methoxyisoflavone	H	H	H	H	OMe	H	H	H	84 (60)
bj	3′-Bromo-8-methoxyisoflavone	OMe	H	H	H	H	Br	H	H	81 (50)
bk	3′,8-Dimethoxyisoflavone	OMe	H	H	H	H	OMe	H	H	85 (51)
cl	7-Methoxy-4′-methylisoflavone	H	OMe	H	H	H	H	Me	H	82 (53)
cm	4′,7-Dimethoxyisoflavone	H	OMe	H	H	H	H	OMe	H	81 (50)
dm	6-Chloro-4′-methoxyisoflavone	H	H	Cl	H	H	H	OMe	H	81 (34)
dn	6-Chloro-3′,5′-dimethoxyisoflavone	H	H	Cl	H	H	OMe	H	OMe	83 (36)
ej	3′-Bromo-6-methoxyisoflavone	H	H	OMe	H	H	Br	H	H	78 (44)
fh	5-Methoxyisoflavone	H	H	H	OMe	H	H	H	H	85 (62)[b]
gh	6,7-Dimethoxyisoflavone	H	OMe	OMe	H	H	H	H	H	94 (60)

[a] The numbers in parentheses indicate the overall yields from 2-methoxybenzoic acids **1**.
[b] The number in parenthesis indicates the overall yields from 2,6-dimethoxybenzoyl chloride.

Experimental

Preparation of *N*-methoxy-*N*-methyl 2-methoxybenzamide (2). 2-Methoxybenzoic acid (**1a**, 761 mg, 5.0 mmol), triethylamine (725 μL, 5.2 mmol), and 4-DMAP (61 mg, 0.5 mmol) was added to a solution of *N*-methoxy-*N*-methyl carbamoyl chloride (619 mg, 5.0 mmol) in acetonitrile at room temperature and stirred for 1.5 h. After evaporation of acetonitrile, the mixture was poured into saturated $NaHCO_3$ solution (40 mL) and extracted with methylene chloride (3 × 25 mL). The condensed residue was purified with short pathway silica gel column chromatography using 50% EtOAc/*n*-hexane to give **2a** (820 mg, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.39 (m, 1H), 7.24–7.28 (m, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 6.4 Hz, 1H), 3.85 (s, 3H), 3.49 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 155.8, 130.6, 127.7, 125.3, 120.5, 111.2, 61.0, 55.7 (overlapped); FT-IR (film) 1640 (C═O) cm^{-1}; MS *m/z* (%) 195 (M^+, 2), 135 (100).

Preparation of 1-(2-methoxyphenyl)-2-(2-methoxyphenyl)ethanone (4ai). 2-Methoxybenzylmagnesium chloride (**3i**, 0.25 M in THF, 16 mL, 4.0 mmol) was added to a solution of **2a** (742 mg, 3.8 mmol) in THF (6 mL) at 0°C. The mixture was stirred for 0.5 h between 0°C and room temperature and then quenched with a 0.1 N HCl solution (5 mL). After the evaporation of THF, the mixture was poured into a 0.1 N HCl solution (40 mL) and extracted with methylene chloride (3 × 20 mL). The condensed residue was purified with silica gel column chromatography using 20% EtOAc/*n*-hexane to give **4ai** (906 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.42–7.48 (m, 1H), 7.22–7.30 (m, 1H), 7.18 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.02 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.91–6.99 (m, 2H), 6.86 (d, *J* = 8.2 Hz, 1H), 4.28 (s, 2H), 3.92 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 158.3, 157.6, 132.9, 131.2, 130.3, 128.9, 128.1, 124.7, 120.5, 120.4, 111.4, 110.4, 55.5, 55.3, 45.4; FT-IR (film) 1675 (C═O) cm^{-1}; MS *m/z* (%) 256 (M^+, 20), 135 (100).

Preparation of 1-(2-hydroxyphenyl)-2-(2-methoxyphenyl)ethanone (5ai). Boron tribromide (1.0 M in CH_2Cl_2, 3.2 mL, 3.2 mmol) was slowly added to a solution of **4ai** (820 mg, 3.2 mmol) in methylene chloride (12 mL) at −20°C. The mixture was stirred for 1 h between −20°C and room temperature and then quenched with H_2O (2 mL). The mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with methylene chloride (3 × 20 mL). The condensed residue was purified with silica gel column chromatography using 20% EtOAc/*n*-hexane to give **5ai** (706 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.24 (s, 1H), 7.93 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.43–7.49 (m, 1H), 7.25–7.32 (m, 1H), 7.18 (dd, *J* = 7.4, 1.6 Hz, 1H), 6.94–7.00 (m, 2H), 6.87–6.93 (m, 2H), 4.31 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 162.6, 157.2, 136.2, 131.0, 130.3, 128.7, 123.0, 120.7, 119.4, 118.8, 118.5, 110.7, 55.4, 39.6; FT-IR (film) 3436 (OH), 1642 (C═O) cm^{-1}; MS *m/z* (%) 242 (M^+, 26), 241 (100).

Preparation of 2′-methoxyisoflavone (6ai). $BF_3{\cdot}Et_2O$ (1.2 mL, 9.7 mmol) was added to a solution of **5ai** (582 mg, 2.4 mmol) in THF (6 mL) at 0°C and stirred for 0.5 h between 0°C and room temperature. Phosphorus(V) oxychloride (447 μL, 4.8 mmol) was added to another flask containing DMF (351 mg, 4.8 mmol) in THF (6 mL) at 0°C and stirred for 0.5 h between 0°C and room temperature. The resulting pale pink colored solution containing *N,N*-dimethyl (chloromethylene)ammonium salt was added to the above reaction mixture at room temperature. After being stirred for 6 h, 0.1 N HCl solution (25 mL) was added to the mixture and was stirred further for 1 h. The solvent was removed *in vacuo*, then the mixture was poured into a 0.1 N HCl solution (25 mL), and extracted with methylene chloride (3 × 20 mL). The condensed residue was purified by recrystallization in 10% EtOAc/*n*-hexane twice to give **6ai** (509 mg, 84%). Mp 184–186°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.00 (s, 1H), 7.65–7.71 (m, 1H), 7.48 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.31–7.45 (m, 3H), 7.03 (dd, *J* = 7.4, 1.0 Hz, 1H), 6.97–7.01 (m, 1H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 157.5,

156.3, 154.2, 133.3, 131.7, 129.7, 126.3, 125.0, 124.6, 122.7, 120.9, 120.5, 118.0, 111.3, 55.7; FT-IR (KBr) 1647 (C═O) cm^{-1}; MS *m/z* (%) 252 (M^+, 100).

6ah, 6cm, 6dm, 6gh. Known compounds.[2b,7a,15]

3′-Bromo-8-methoxyisoflavone (6bj). Mp 174–176°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.87 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.75 (t, *J* = 1.7 Hz, 1H), 7.50–7.55 (m, 2H), 7.28–7.40 (m, 2H), 7.21 (dd, *J* = 8.0, 1.4 Hz, 1H), 4.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 153.0, 148.7, 146.6, 133.8, 131.8, 131.3, 130.0, 127.6, 125.5, 125.2, 124.2, 122.5, 117.2, 114.4, 56.5; FT-IR (KBr) (C═O) 1646 cm^{-1}; MS *m/z* (%) 332 (M^++2, 98), 330 (M^+, 100).

3′,8-Dimethoxyisoflavone (6bk). Mp 145–146°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.87 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.32–7.38 (m, 2H), 7.16–7.21 (m, 2H), 7.12 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 8.3, 2.6 Hz, 1H), 4.02 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 159.6, 152.8, 148.7, 146.6, 133.1, 129.5, 125.6, 125.3, 124.9, 121.2, 117.3, 114.6, 114.2, 114.1, 56.4, 55.3; FT-IR (KBr) 1645 (C═O) cm^{-1}; MS *m/z* (%) 282 (M^+, 100).

7-Methoxy-4′-methylisoflavone (6cl). Mp 142–143°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.9 Hz, 1H), 7.91 (s, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.98 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.84 (d, *J* = 2.3 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 164.0, 158.0, 152.3, 137.9, 129.1, 129.0, 128.8, 127.8, 125.2, 118.5, 114.4, 100.2, 55.8, 21.2; FT-IR (KBr) 1626 (C═O) cm^{-1}; MS *m/z* (%) 266 (M^+, 100).

6-Chloro-3′,5′-dimethoxyisoflavone (6dn). Mp 160–161°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (d, *J* = 2.6 Hz, 1H), 8.03 (s, 1H), 7.62 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.44 (d, *J* = 8.9 Hz, 1H), 6.70 (d, *J* = 2.1 Hz, 2H), 6.50 (t, *J* = 2.1 Hz, 1H), 3.82 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 160.8, 154.4, 153.3, 133.8, 133.3, 131.3, 125.8, 125.5, 125.4, 119.8, 107.1, 100.7, 55.4; FT-IR (KBr) 1650 (C═O) cm^{-1}; MS *m/z* (%) 318 (M^++2, 30), 316 (M^+, 100).

3′-Bromo-6-methoxyisoflavone (6ej). Mp 134–136°C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.74 (t, *J* = 1.7 Hz, 1H), 7.65 (d, *J* = 3.1 Hz, 1H), 7.49–7.54 (m, 2H), 7.43 (d, *J* = 9.1 Hz, 1H), 7.29–7.34 (m, 1H), 7.27 (dd, *J* = 4.7, 1.6 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 157.2, 153.1, 151.0, 134.1, 131.8, 131.1, 129.9, 127.6, 125.1, 123.9, 123.3, 122.5, 119.5, 105.5, 55.9; FT-IR (KBr) (C═O) 1638 cm^{-1}; MS *m/z* (%) 332 (M^++2, 96), 330 (M^+, 100).

5-Methoxyisoflavone (6fh). Mp 89–90°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.49–7.56 (m, 3H), 7.33–7.42 (m, 3H), 7.00 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 160.4, 158.3, 151.0, 133.6, 132.0, 129.2, 128.2, 128.0, 126.5, 115.3, 110.0, 106.5, 56.4; FT-IR (KBr) (C═O) 1645 cm^{-1}; MS *m/z* (%) 252 (M^+, 100).

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