A New Synthetic Route to Isoquinolin-1(2*H*)-one Derivatives from 3-Hydroxyphthalides

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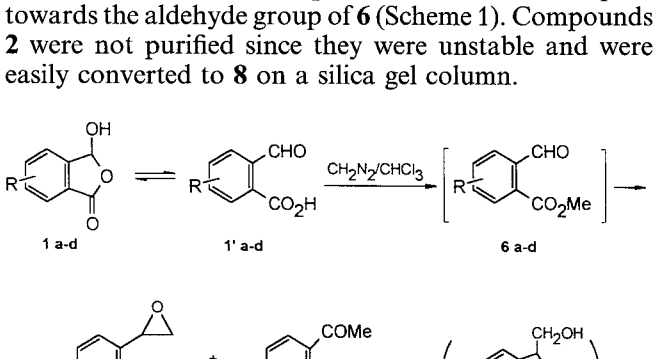
A new synthetic route for the conversion of substituted 3-hydroxyphthalides into the corresponding isoquinolin-1(2*H*)-one was established. This method can be applied to the preparation of isoquinolin-1(2*H*)-ones with electron-withdrawing groups that are relatively difficult to synthesize by conventional procedures.

It was well known that many of naturally occurring or synthetic isoquinolone derivatives show various biological activities. We are interested in a variety of substituted isoquinolin-1(2*H*)-one derivatives **5** on account of our recent studies of the structure–activity relationship in platelet antiaggregation. The studies indicated that one of these isoquinolone derivatives **5d** should have antiaggregating activity. However, the synthesis of **5d** could not be accomplished by classical methods. This could be due to the following reasons. Classical methods for the preparation of isoquinoline derivatives involve ring closure between a nucleophilic carbon on a benzene ring and an electrophilic site on a side chain of the benzene ring. Therefore, when a ring is electron-deficient due to electron-withdrawing groups or if bulky substitutents are located near the functional position on the ring, such as **5d**, this cyclization is difficult. We have now investigated a general synthetic route to isoquinolin-1(2*H*)-ones unaffected by substituents on the benzene ring and report here our newly established procedure.

Dodsworth et al.[1] have shown that lithium salts of phthalides react with aromatic Schiff bases to form a mixture of *cis*- and *trans*-2,3-diaryl-4-hydroxy-3,4-dihydro-isoquinol-1(2*H*)-ones via lithium salts of 3-arylaminomethylphthalides. Unfortunately this method is limited to the preparation of 2,3-diaryldihydroisoquinolones. It was also found that 3-aminomethylphthalide obtained by the reduction of 3-nitromethylphthalide could be converted to 4-hydroxy-3,4-dihydroisoquinol-1(2*H*)-one with ammonia in methanol.[2] This procedure was inapplicable to the synthesis of *N*-substituted isoquinolones. However, these two reports suggested that both 3-aromatic and aliphatic aminomethylphthalides could be converted to 4-hydroxy-3,4-dihydroisoquinolones under basic conditions. On the other hand, 3-hydroxy-4-nitrophthalide, which was considered to be present as an equilibrium mixture with 2-formyl-3-nitrobenzoic acid, reacts with two moles of diazomethane, producing 2-methoxycarbonyl-6-nitrostyrene oxide.[3] We considered that the styrene oxides **2** derived from 3-hydroxyphthalides **1** could be converted to *N*-substituted-3,4-dihydroisoquinolones **4** with various added amines. If the reaction proceeds to form 3-aminomethylphthalide **3** instead of **4**, **3** should be transformed to **4** under the basic conditions mentioned above. The dehydration of **4** is presumed to lead to the corresponding isoquinolone derivatives **5** using the conventional method.

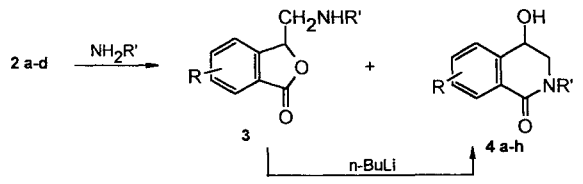
The starting phthalide derivatives **1a–d** were prepared according to the procedures described before.[4,5] The reaction of **1** with diazomethane (> 2 equivs) gave **2** along with **7**. The intermediate **6** was always immediately formed with one mole of diazomethane. However, the reaction of **6** to **2** and **7** with another mole of diazomethane proceeded relatively slowly, which was a rate limiting step that varied according to substituent and solvent. A compound with an electron-withdrawing group as a substituent and the reaction in chloroform as a solvent proceeded faster than those with no substituent and diethyl ether. Also, the formation of **7** decreased by introducing an electron-withdrawing substituent. The degree of decrease was more marked when the substituent was introduced at ortho position rather than at para towards the aldehyde group of **6** (Scheme 1). Compounds **2** were not purified since they were unstable and were easily converted to **8** on a silica gel column.



1	R	conditions	yield (%) 2	yield (%) 7
a	H	r.t. 12 h.	38.0	51.0
b	6-NO_2	r.t. 1 h.	50.0	18.3
c	4-NO_2	r.t. 1 h.	92.4	0.0
d	5,7-$(Me)_2$-6-CO_2Et	r.t. 1 h.	53.0	18.0

Scheme 1

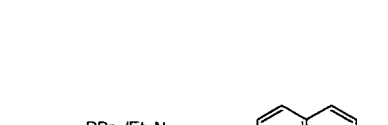
The synthesis of 4-hydroxy-3,4-dihydroisoquinol-1(2*H*)-one derivatives **4** from **2** was achieved using ammonia and methylamine in methanol at room temperature or in a sealed tube at 80 °C. Only for **4f** was the addition of Lewis acid required to activate the reaction. When **2a** was treated with methylamine at room temperature, 3-(*N*-methylamino)methylphthalide **(3e)** was formed in 12 hours. The ratio of **3e** to **4e** reached about 1:1 by 42 hours. Trisubstituted derivatives, **4d** and **4h** were prepared by the conversion of corresponding 3-aminomethylphthalide derivatives **3** with butyllithium (Scheme 2). Finally, the dehydration of **4** using phosphorus tribromide, afforded the required isoquinolones **5** in moderate yields (Scheme 3).



2	R	R'	conditions			4	yield (%)
			solvent	temp. °C	time(h)		
a	H	H	MeOH	r.t.	68	a	58.7
	H	Me	MeOH	sealed tube/80	14	e	73.8
b	5-NO_2	H	MeOH	r.t.	120	b	59.1
		Me	THF/Ti(i-PrO)$_4$	r.t.	25	f	50.1
c	3-NO_2	H	MeOH	sealed tube/80	13	c	63.8
		Me	MeOH	sealed tube/80	12	g	32.8
d	4,6-$(Me)_2$-5-CO_2Et	H	MeOH	r.t.	48	d	62.4*
		Me	MeOH	r.t.	48	h	49.3*

* yield was calculated after treatment with a n-BuLi (see experimental part).

Scheme 2



4	R	R'	conditions		5	yield (%)
			solvent	reflux time (h)		
a	H	H	benzene	1		82.2
b	7-NO_2	H	benzene	3		59.5
c	5-NO_2	H	$(CH_2)_2Cl_2$	1		33.6
d	6,8-$(Me)_2$-7-CO_2Et	H	$(CH_2)_2Cl_2$	1		63.8
e	H	Me	benzene	1		83.2
f	7-NO_2	Me	$(CH_2)_2Cl_2$	1		42.5
g	5-NO_2	Me	$(CH_2)_2Cl_2$	2		39.8
h	6,8-$(Me)_2$-7-CO_2Et	Me	$(CH_2)_2Cl_2$	1		51.3

Scheme 3

In conclusion, we found a new convenient route to synthesize isoquinolin-1(2*H*)-one derivatives from 3-hydroxyphthalides. This method can be used to synthesize isoquinolones or *N*-alkylisoquinolones with many kinds of substituents.

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi Model 285 spectrometer. ^1H NMR spectra were recorded on a Hitachi R-600 FT-NMR spectrometer. Mass spectra (MS) were determined on a JEOL JMS-D300 mass spectrometer. Column chromatography was carried out on Merck silica gel (35–70 mesh), unless otherwise stated. Satisfactory microanalyses were obtained for all new compounds: C ± 0.19, H ± 0.09, N ± 0.15.

2-Methoxycarbonylstyrene Oxide (2a); Typical Procedure:
An ethereal solution of CH_2N_2 (> 2 equivs) was added dropwise to a solution of *o*-phthalaldehydic acid (3-hydroxyphthalide) **1a**; (3.0 g, 20 mmol) in $CHCl_3$ (20 mL) at 0 °C. The solution was stirred overnight at r.t. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (Merck silica gel 100). At first, the oily epoxide **2a** was eluted with Et_2O/hexane (1:9), then methyl *o*-acetylbenzoate **(7a)** was obtained using Et_2O/hexane (3:7) as eluent.

2a; yield: 1.36 g (38%).

MS: m/z = 178 (M^+), 163 ($M^+ - 15$), 160 ($M^+ - 18$), 150, 148.

IR ($CHCl_3$): ν = 3010, 1720 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.60 (1 H, dd, J = 6.0, 3.0 Hz), 3.22 (1 H, dd, J = 6.0, 5.0 Hz), 3.93 (3 H, s), 4.59 (1 H, dd, J = 5.0, 3.0 Hz), 7.35–7.58 (3 H, m), 7.92–8.07 (1 H, m).

7a; yield: 1.82 g (51%); bp 111 °C/2 Torr.

MS: m/z = 178 (M^+), 163 ($M^+ - 15$, base ion peak), 147, 133.

IR ($CHCl_3$) ν = 2990, 2940, 1715, 1700 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.53 (3 H, s), 3.89 (3 H, s), 7.53 (3 H, m), 7.78 (1 H, m).

Compounds **2b–2d** were prepared in a similar manner as described above.

2b; mp 73–75 °C (Et_2O).

MS: m/z = 223 (M^+), 208 ($M^+ - 15$), 195 ($M^+ - 28$), 193, 191, 178 ($M^+ - 45$, base ion peak).

IR (KBr): ν = 1720, 1520, 1350 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.63 (1 H, dd, J = 6.0, 3.0 Hz), 3.31 (1 H, dd, J = 6.0, 5.0 Hz), 4.00 (3 H, s), 4.67 (1 H, dd, J = 5.0, 3.0 Hz), 7.69 (1 H, d, J = 8.0 Hz), 8.37 (1 H, dd, J = 8.0, 2.0 Hz), 8.84 (1 H, d, J = 2.0 Hz).

2c; mp 60–63 °C (Et_2O/hexane).

MS: m/z = 223 (M^+), 208 ($M^+ - 15$), 192 ($M^+ - 31$), 178, 161 ($M^+ - 62$, base ion peak).

IR (KBr): ν = 1730, 1530, 1370, 1270 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.53 (1 H, dd, J = 5.0, 3.0 Hz), 3.16 (1 H, t, J = 5.0 Hz), 3.98 (3 H, s), 4.51 (1 H, dd, J = 5.0, 3.0 Hz), 7.38–8.11 (3 H, m).

2d

MS: m/z = 278 (M^+), 264 ($M^+ - 14$), 263 ($M^+ - 15$), 262 ($M^+ - 16$), 248 ($M^+ - 30$), 233 ($M^+ - 45$, base ion peak).

IR ($CHCl_3$): ν = 3020, 1730, 1245 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.38 (3 H, s), 2.31 (6 H, s), 2.63 (1 H, dd, J = 6.0, 3.0 Hz), 3.08 (1 H, dd, J = 6.0, 5.0 Hz), 3.10 (3 H, s), 4.40 (2 H, q, J = 7.0 Hz), 4.50 (1 H, dd, J = 5.0, 3.0 Hz), 7.03 (1 H, s).

4-Hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (4a); Typical Procedure:
A saturated methanolic ammonia solution was added to **2a** (350 mg, 1.96 mmol) and stirred for 68 h at r.t. After evaporation of the solvent, the residue was recrystallized from acetone to give **4a** (188.2 mg, 58.7%); mp 159–162 °C.

MS: m/z = 163 (M^+), 145 ($M^+ - 18$, base ion peak), 134 ($M^+ - 29$), 118, 105.

IR (KBr) ν = 3400, 3050, 1660 cm^{-1}.

^1H NMR (d_6-DMSO): δ = 3.29–3.43 (2 H, m), 4.78 (1 H, br s), 5.56 (1 H, d, J = 5.0 Hz), exchangeable with D_2O), 7.28–7.89 (5 H, m, after the addition of D_2O, 4 H).

The following compounds were prepared by the same procedure under the conditions shown in Scheme 2.

4b; mp 229–231 °C (MeOH).

MS: m/z = 208 (M^+), 179 ($M^+ - 29$), 150 ($M^+ - 58$, base ion peak), 132, 105, 77.

IR (KBr): ν = 3420, 3200, 3080, 1670, 1510, 1350 cm^{-1}.

^1H NMR (d_6-DMSO): δ = 3.35–3.50 (2 H, m), 4.74–5.07 (1 H, m), 6.00 (1 H, d, J = 5.0 Hz, exchangeable with D_2O), 7.79 (1 H, d, J = 8.0 Hz), 8.23 (1 H, br s, exchangeable with D_2O), 8.31–8.54 (3 H, m).

4c; mp 199–201 °C (MeOH).

MS: $m/z = 208$ (M^+), 190 ($M^+ - 18$), 162 ($M^+ - 46$), 161 ($M^+ - 47$, base ion peak).

IR (KBr): ν = 3380, 3210, 1690, 1530, 1340 cm^{-1}.

^1H NMR (d_6-DMSO): δ = 3.28 (1 H, s, exchangeable with D_2O), 3.39–3.51 (2 H, m), 5.06–5.26 (1 H, m), 5.69 (1 H, br s, exchangeable with D_2O), 7.54–8.31 (3 H, m).

4e; mp 124–126 °C (MeOH/Et_2O).

MS: $m/z = 177$ (M^+), 134 ($M^+ - 43$), 105, 77, 44 ($M^+ - 133$, base ion peak).

IR (KBr): ν = 3325, 1630 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.98 (3 H, s), 3.59 (1 H, d, J = 4.0 Hz), 3.68 (1 H, d, J = 4.0 Hz), 4.26 (1 H, d, J = 8.0 Hz, exchangeable with D_2O), 4.73 (1 H, m), 7.15–7.50 (3 H, m), 7.70–8.00 (1 H, m).

4f; mp 192.5–194.5 °C (MeOH).

MS: $m/z = 222$ (M^+), 204 ($M^+ - 18$, base ion peak), 158 ($M^+ - 64$).

IR (KBr): ν = 3240, 1640, 1500, 1320 cm^{-1}.

^1H NMR (d_6-DMSO): δ = 3.08 (3 H, s), 3.50–3.66 (2 H, m), 4.92 (1 H, br s), 6.02 (1 H, d, J = 6.0 Hz, exchangeable with D_2O), 7.75 (1 H, d, J = 8.0 Hz), 8.38 (1 H, dd, J = 8.0, 2.0 Hz), 8.56 (1 H, d, J = 5.0 Hz).

4g; mp 116–118 °C ($CHCl_3$).

MS: $m/z = 222$ (M^+), 204 ($M^+ - 18$, base ion peak), 162 ($M^+ - 60$), 161 ($M^+ - 61$).

IR (KBr): ν = 3340, 1640, 1530, 1350 cm^{-1}.

^1H NMR(d_6-DMSO): δ = 3.08 (3 H, s), 3.58–3.74 (2 H, m), 5.27 (1 H, br s), 5.77 (1 H, d, J = 6.0 Hz, exchangeable with D_2O), 7.68 (1 H, t, J = 7.0 Hz), 8.12 (1 H, dd, J = 7.0, 2.0 Hz), 8.25 (1 H, dd, J = 7.0, 2.0 Hz).

7-Ethoxycarbonyl-3,4-dihydro-4-hydroxy-6,8-dimethylisoquinolin-1(2*H*)-one (4d):

Compound **2d** (322.7 mg, 1.16 mmol) was dissolved in absolute MeOH (20 mL). The solution was saturated with NH_3 at 0 °C and stirred for 48 h at r.t. The solvent was removed and the residue was chromatographed on silica gel with 1% MeOH/$CHCl_3$. The first eluted fraction was recrystallized from Et_2O/hexane to give **3d** (210.3 mg, 69%); mp 60–63 °C.

MS: $m/z = 263$ (M^+), 234 ($M^+ - 29$, base ion peak), 218 ($M^+ - 45$), 205 ($M^+ - 58$), 189.

IR ($CHCl_3$): ν = 3025, 2970, 1760, 1730, 1615, 1265, 1180 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.41 (4 H, br t, after the addition of D_2O, 3 H, t, J = 7.0 Hz), 2.42 (3 H, s), 2.65 (3 H, s), 3.00–3.40 (2 H, m), 4.43 (2 H, J = 7.0 Hz), 5.25–5.50 [1 H, m, after the addition of D_2O, shifted to 5.35 (1 H, br s)], 7.12 (1 H, s). The second eluted fraction was **4d** (34.9 mg, 11.4%); mp 113–115 °C (Et_2O/hexane).

MS: $m/z = 263$ (M^+), 245 ($M^+ - 18$), 234 ($M^+ - 29$, base ion peak), 218 ($M^+ - 45$).

^1H NMR ($CDCl_3$): δ = 1.38 (3 H, t, J = 7.0 Hz), 2.30 (3 H, s), 2.50 (3 H, s), 3.30–3.60 [2 H, m, after the addition of D_2O, shifted to 3.41 (2 H, br d, J = 4.0 Hz)], 4.40 (2 H, q, J = 7.0 Hz), 4.50–4.70 (1 H, m), 7.14 (1 H, s).

Preparation of 4d via the Conversion of the 3-Aminomethylphthalide Derivative 3d:

A solution of **2d** (286.5 mg, 1.03 mmol) in absolute MeOH (25 mL) was saturated with NH_3. After stirring at r.t. overnight, the solvent was removed and dried under reduced pressure. Under Ar, an hexane solution of BuLi (1.6 mmol) was added dropwise to the residue in THF (5 mL) below −50 °C. The mixture was stirred for 30 min at −50 °C, then overnight at r.t. under Ar. Ice-cold water was added to the reaction mixture, and the mixture was acidified to pH 3 or 4 with 10% HCl, then extracted with $CHCl_3$. The combined extracts were washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on a column of silica gel with $CHCl_3$ to give **3d** (23.7 mg, 8.7%), and **4d** (126.6 mg, 46.7%).

Compounds **3h** and **4h** were also prepared in the same manner using $MeNH_2$ instead of NH_3.

3h

MS: $m/z = 277$ (M^+), 259 ($M^+ - 18$), 246 ($M^+ - 31$), 232 ($M^+ - 45$), 189 (base ion peak).

^1H NMR ($CDCl_3$): δ = 1.41 (3 H, t, J = 7.0 Hz), 1.98 (1 H, s, exchangeable with D_2O), 2.42 (3 H, s), 2.50 (3 H, s), 2.80–3.20 (2 H, m), 4.44 (2 H, q, J = 7.0 Hz), 5.30–5.60 (1 H, m), 7.13 (1 H, s).

4h

MS: $m/z = 277$ (M^+), 259 ($M^+ - 18$), 230 ($M^+ - 47$, base ion peak), 214 ($M^+ - 63$).

^1H NMR ($CDCl_3$): δ = 1.39 (3 H, t, J = 7.0 Hz), 2.29 (3 H, s), 2.57 (3 H, s), 3.02 (3 H, s), 3.40–3.80 [3 H, m, after the addition of D_2O, shifted to 3.40–3.65 (2 H, m)], 4.41 (2 H, q, J = 7.0 Hz), 4.50–4.80 (1 H, m), 7.11 (1 H, s).

Isoquinolin-1(2*H*)-one (5a); Typical Procedure:

To a solution of **4a** (120 mg, 0.735 mmol) in anhydr. benzene (20 mL) was added PBr_3 (238 mg, 0.88 mmol) and TEA (89 mg, 0.88 mmol). After refluxing for 1 h, excess PBr_3 was decomposed with a small amount of H_2O and the solvent was evaporated. The residue was extracted with $CHCl_3$ and H_2O. The organic layer was washed with 5% $NaHCO_3$, dried ($MgSO_4$) and concentrated. The product was recrystallized from MeOH to give **5a** (87.7 mg, 82.2%). All analytical data and mp agreed with those of the authentic sample obtained commercially (Aldrich, mp 210–212 °C).

The following compounds were prepared by the same procedure under the conditions shown in Scheme 3.

5b; mp 265–267 °C (MeOH).

MS: $m/z = 190$ (M^+, base ion peak), 160 ($M^+ - 30$), 144 ($M^+ - 46$), 132 ($M^+ - 58$), 116, 89.

IR (KBr): ν = 3525, 1670, 1510, 1340 cm^{-1}.

^1H NMR (d_6-DMSO): δ = 6.71 (1 H, d, J = 7.0 Hz), 7.43 (1 H, br s, after the addition of D_2O, d, J = 7.0 Hz), 7.89 (1 H, d, J = 9.0 Hz), 8.44 (1 H, dd, J = 9.0, 2.0 Hz), 8.91 (1 H, d, J = 2.0 Hz), 11.74 (1 H, br s, exchangeable with D_2O).

5c; mp 234–236 °C (MeOH).

MS: $m/z = 190$ (M^+, base ion peak), 161 ($M^+ - 29$), 144 ($M^+ - 46$), 117, 89.

IR (KBr): ν = 3500, 1680, 1520, 1320 cm^{-1}.

^1H NMR (d_6-DMSO) δ = 6.97 (1 H, d, J = 7.0 Hz), 7.46 (1 H, br s, after the addition of D_2O, d, J = 7.0 Hz), 7.63 (1 H, t, J = 8.0 Hz), 8.30 (1 H, dd, J = 8.0, 2.0 Hz), 8.57 (1 H, dd, J = 8.0 Hz, 2.0 Hz), 11.68 (1 H, br s, exchangeable with D_2O).

5d; mp 158–160 °C (MeOH).

MS: $m/z = 245$ (M^+), 230 ($M^+ - 15$), 216 ($M^+ - 29$, base ion peak), 200 ($M^+ - 45$).

IR (KBr): ν = 3410, 1730, 1650, 1270 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.42 (3 H, t, J = 7.0 Hz), 2.39 (3 H, s), 2.89 (3 H, s), 4.45 (2 H, q, J = 7.0 Hz), 6.37 (1 H, d, J = 7.0 Hz), 7.08 (1 H, d, J = 7.0 Hz), 7.20 (1 H, s), 10.23 (1 H, br s, exchangeable with D_2O).

5e; mp 31–33 °C (hexane).

MS: $m/z = 159$ (M^+), 130 ($M^+ - 29$), 118 ($M^+ - 41$), 116 ($M^+ - 43$).

IR ($CHCl_3$): ν = 1650, 1630 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.60 (3 H, s), 6.46 (1 H, d, J = 7.0 Hz), 7.06 (1 H, d, J = 7.0 Hz), 7.38–7.68 (3 H, m), 8.37–8.54 (1 H, m).

5f; mp 217–219 °C (MeOH).

MS m/z: 204 (M^+, base ion peak), 174 ($M^+ - 30$), 158 ($M^+ - 46$), 130 ($M^+ - 74$).

IR (KBr): ν = 1650, 1500, 1330 cm^{-1}.

^1H NMR (d_6-DMSO): δ = 3.56 (3 H, s), 6.74 (1 H, d, J = 7.0 Hz), 7.73 (1 H, d, J = 7.0 Hz), 7.87 (1 H, d, J = 9.0 Hz), 8.40 (1 H, dd, J = 9.0, 2.0 Hz), 8.91 (1 H, d, J = 2.0 Hz).

5g; mp 104–106 °C ($MeOH/Et_2O$).

MS: $m/z = 204$ (M^+, base ion peak), 161 ($M^+ - 43$), 146 ($M^+ - 58$), 130 ($M^+ - 74$), 117 ($M^+ - 87$).

IR (KBr): $\nu = 1650, 1520, 1340\ cm^{-1}$.

^1H NMR (d_6-DMSO): $\delta = 3.55$ (3 H, s), 7.01 (1 H, d, $J = 8.0$ Hz), 7.65 (1 H, t, $J = 8.0$ Hz), 7.72 (1 H, d, $J = 8.0$ Hz), 8.46 (1 H, dd, $J = 8.0, 1.5$ Hz), 8.59 (1 H, dd, $J = 8.0, 1.5$ Hz).

5h

MS: $m/z = 259$ (M^+), 230 ($M^+ - 29$, base ion peak), 214 ($M^+ - 45$).

IR ($CHCl_3$): $\nu = 1725, 1686, 1653, 1270\ cm^{-1}$.

^1H NMR ($CDCl_3$): $\delta = 1.40$ (3 H, t, $J = 7.0$ Hz), 2.36 (3 H, s), 2.87 (3 H, s), 3.50 (3 H, s), 4.43 (2 H, q, $J = 7.0$ Hz), 6.28 (1 H, d, $J = 7.0$ Hz), 7.04 (1 H, d, $J = 7.0$ Hz), 7.11 (1 H, s).

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