The Synthesis, Structural Characterization and Photochemistry of Some 3-Phenylindenones

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Abstract: The synthesis of 3-phenylindenone (**1a**), 6-methoxy-3-phenylindenone (**1b**), 2-bromo-6-methoxy-3-phenylindenone (**1c**) and 2-ethoxycarbonyl-6-methoxy-3-phenylindenone (**1d**) is described using two methods – synthesis via indanone precursors and synthesis via propanedione precursors. Crystal structures of 2-bromo-6-methoxy-3-phenylindanone, the synthetic precursor to **1b** and 2-bromo-6-methoxy-3-phenylindenone were obtained. Preliminary photochemical studies showed that **1b** dimerizes readily, but no transient species were detectable using ns-flash photolysis.

Key words: enone, [2+2] cycloaddition, Friedel–Crafts ring closure, photochemistry

The chemistry of 3-phenylindenone derivatives is of interest, not only in their own right as analogues of the much-studied cyclopentenones, but as synthetic precursors to more elaborate ring structures. Thus 6-methoxyindenone systems should be useful intermediates on routes to furanoindenones. These are planar aromatic molecules and like psoralen, the well-known phototherapeutic drug, they should intercalate into DNA, undergo photo-induced [2+2] cycloaddition to its nucleobases and hence promote cross-linking of the two strands of DNA.[2]

There also continues to be great interest in the photophysics and photochemistry of 3-cycloalkenones. Our particular interest has been with 3-arylcyclopentenones and cyclohexenones which undergo [2+2] cycloaddition with alkenes to provide a useful route to cyclobutane adducts.[3] In addition we have observed that the 3-aryl substituents significantly prolong the excited state triplet lifetimes, thus allowing their excited states to be characterized readily by laser flash photolysis methods. Studies on 3-phenylindenone derivatives will therefore allow us to study the effect of an additional fused ring on the photochemistry and photophysics of the 3-phenylcyclopentenone system.

We describe here the synthesis of 3-phenylindenone (**1a**), 6-methoxy-3-phenylindenone (**1b**), 2-bromo-6-methoxy-3-phenylindenone (**1c**) and 2-ethoxycarbonyl-6-methoxy-3-phenylindenone (**1d**) (Figure 1). In the case of **1a–c**, the enones were synthesized from the corresponding indanones. For **1d**, the compound was synthesized via a propanedione precursor.

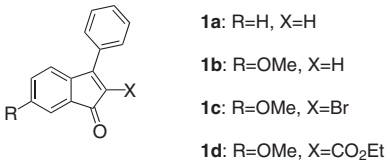
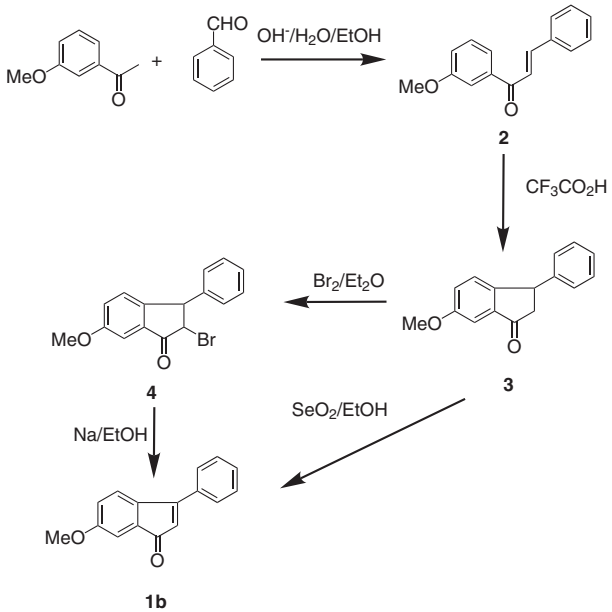


Figure 1 Indenones **1a–d**

Scheme 1 shows the synthetic route taken for 6-methoxy-3-phenylindenone (**1b**). Murphy et al.[4] and Gaviña et al.[5] have previously described the synthesis of 6-methoxy-3-phenylindanone (**3**) using BF_3[4] or $AlCl_3$ from the corresponding chalcone **2**.[5] We found that the use of trifluoroacetic acid gave good yields (88%) of purer material with shorter reaction times under milder conditions. As both Murphy and Gaviña reported, the 6-methoxy isomer **3** is the predominant product (88%), with some 4-isomer detected by NMR spectroscopy (<3%). Separation of the two components required careful column chromatography (CH_2Cl_2, silica gel) although the two components were easily separated at the next stage in the reaction sequence (see below).

Reaction of 6-methoxy-3-phenylindanone (**3**) with bromine in diethyl ether gave 2-bromo-6-methoxy-3-phenylindanone (**4**), the site of bromination at the 2-position



Scheme 1 Synthesis of 6-methoxy-3-phenylindenone (**1b**)

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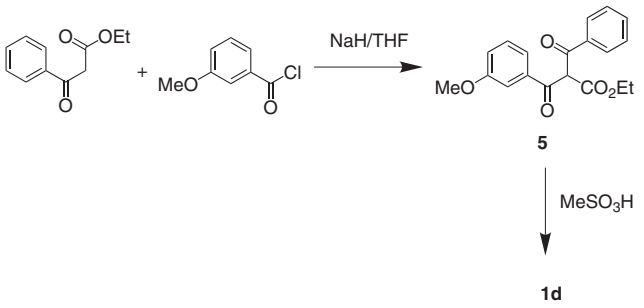
being confirmed by a C–H COSY NMR experiment. Dehydrobromination of **4** was effected with sodium ethoxide in ethanol giving 6-methoxy-3-phenylindenone (**1b**) (13.5% overall). This compound was also prepared by direct oxidation of 6-methoxy-3-phenylindanone (**3**) with selenium dioxide in ethanol. Although reaction times were longer, the yield was higher (28%) and in addition, only reactant and product were present in the crude mixture. The former could therefore be separated by chromatography and recycled. This method was also used to oxidize the parent compound 3-phenylindanone to give 3-phenylindenone (**1a**). However, it required longer reaction times (7 days) than the bromination-dehydrobromination method described above and yields were modest (20%).

Interestingly, bromination of 6-methoxy-3-phenylindanone (**3**) in scrupulously dried diethyl ether led to the formation of 2,2-dibromo-6-methoxy-3-phenylindanone. Dehydrobromination of this compound led to the formation of 2-bromo-6-methoxy-3-phenylindenone (**1c**).

The ethoxycarbonyl indenone **1d** was synthesized by a different route. Anstead et al.[6] describe the synthesis of 2,3-substituted indenones via a propanedione precursor. In a modified version of this, condensation of *m*-anisoyl chloride and ethyl benzoylacetate gave 2-ethoxycarbonyl-1-(3-methoxyphenyl)-3-phenylpropane-1,3-dione (**5**) which ring-closed easily with methanesulfonic acid to give **1d** (Scheme 2).



Scheme 2 Synthesis of 2-ethoxycarbonyl-6-methoxy-3-phenylindenone (**1d**)

Crystal structures of 2-bromo-6-methoxy-3-phenylindanone (**4**) (Figure 2) and the corresponding indenone **1c** were obtained (Figure 3). (It was found that indenones substituted at the 2- and 3-position recrystallized more easily than those with substituents only in the 3-position). For the bromoindanone, the α–β carbon bond length was 1.531 Å, and the torsion angle between the phenyl group and the indanone was 60° to the plane of the indenone. For the indenone, the α–β carbon bond length was 1.356 Å, and the torsion angle of the phenyl substituent to the indenone ring was 59°. These and other relevant parameters are summarized in Table 1.[7]

Preliminary flash photolysis experiments were carried out with acetonitrile solutions of indenone **1b** (10^{-2} < [**1b**] < 10^{-4} M) ($\lambda_{excitation}$ = 355 nm). Even though the extinction coefficient at this wavelength is low (ca. 300 dm^3 mol^{-1}), it was surprising that no transient species were observed within the time range of our instrumentation (>50 ns), neither was steady state emission observed at room temperature or at 77 K (ethanol, glass).

Table 1 Some Parameters Derived from X-ray crystal structure of 2-Bromo-6-methoxy-3-phenylindanone (**4**) and 2-Bromo-6-methoxy-3-phenylindenone (**1c**)

Parameters	Phenylindanone **4**	Phenylindenone **1c**
Formula	$C_{16}H_{13}BrO_2$	$C_{16}H_{11}BrO_2$
Crystal System	monoclinic	triclinic
$\lvert C_\alpha–C_\beta \rvert$ (Å)	1.531	1.356
Phenyl Torsion angle (°)	60	59
|C–O| (Å)	1.210	1.205

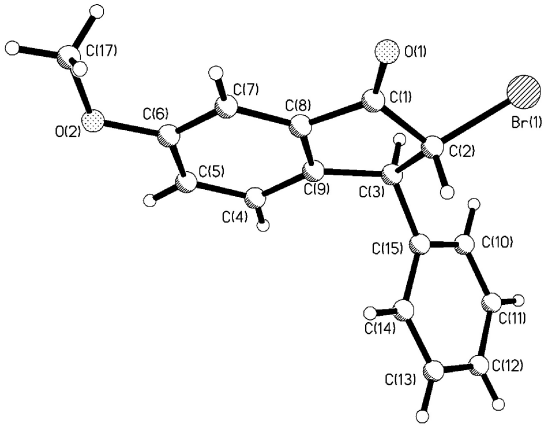


Figure 2 X-ray crystal structure of 2-bromo-6-methoxy-3-phenylindanone (**4**)

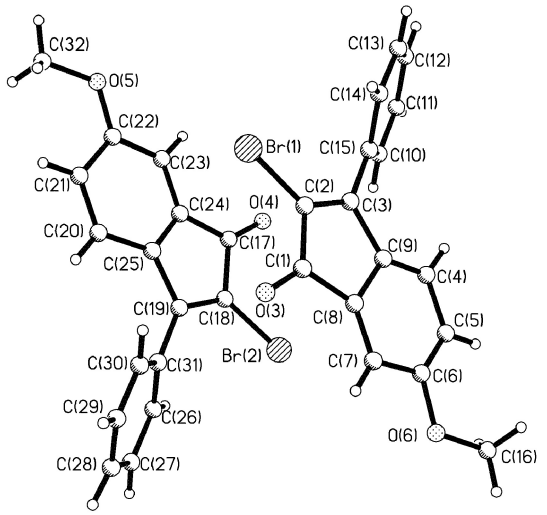
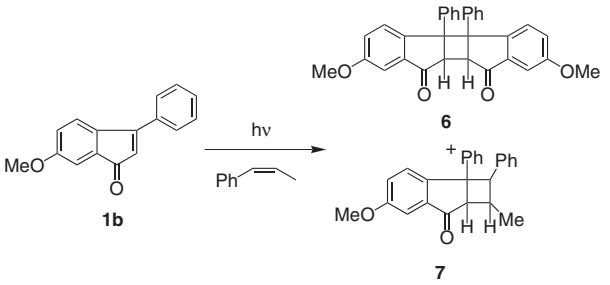


Figure 3 X-ray crystal structure of 2-bromo-6-methoxy-3-phenylindenone (**1c**)

Irradiation of indenone **1b** in deuteroacetonitrile led to efficient dimerization (Scheme 3), as observed by NMR spectroscopy, showing that the compound could indeed undergo self-cycloaddition. Dimerization proceeded efficiently up to 8 minutes after which time the ratio of dimer to monomer peaks remained approximately constant. This indicates the presence of a photostationary state. Moreover when the enone (10 mmol) was irradiated in the presence of (*E*)-methylstyrene (50 mmol), dimerization was the only observed reaction and no enone-alkene adducts were detected by NMR spectroscopy. In addition to dimerization of the enone, *cis-trans* isomerization of the alkene is observed. Given that a glass filter is used in the experiment, this isomerization must be sensitized by the enone-excited state. A similar result was found on increasing the concentration of alkene (100 mmol). The rate of dimer formation was slower than in solutions of enone only, with dimerization proceeding for 12 minutes and 22 minutes for the enone/alkene ratio of 1:5 and 1:10, respectively (Figure 4).



Scheme 3 Irradiation of **1b** in the presence of (*E*)-1-phenylpropene leading to dimerization and adduct formation.

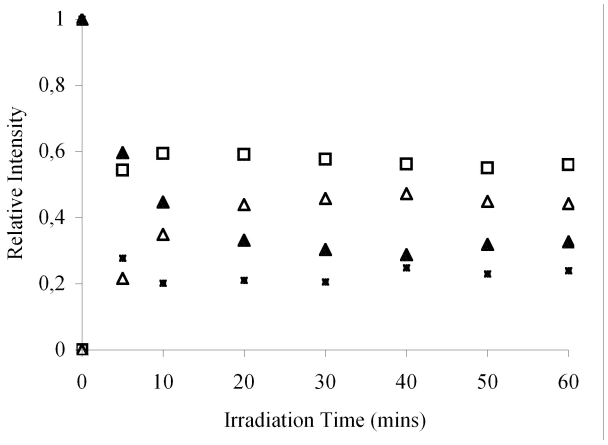


Figure 4 Relative intensities (as measured by integration of methoxy singlets in NMR spectra) of enone monomer (filled shapes) and dimer (hollow shapes) on increasing irradiation time for enone/alkene ratio of 1:5 (squares) and 1:10 (triangles).

The above experiments were repeated in deuterobenzene. Similar results were found, in that the enone dimerization reaction is dominant, although the reaction is not as efficient as in acetonitrile. After 40 minutes irradiation time in acetonitrile, the monomer enone methoxy peak in the NMR spectrum is almost completely depleted, whereas in the case of benzene, the ratio of monomer to dimer at this time was 1:3, and after 90 minutes the ratio was only 1:1 (Scheme 3). The extent of alkene *cis-trans* isomerization is also much lower in the case of benzene.

In benzene there is some evidence for enone-alkene adduct formation. In addition to peaks assigned to the enone dimer, a series of peaks with very low intensity occur in the NMR spectrum on increasing irradiation time. These are the peaks at δ = 1.17 (d), 2.76 (dq), 3.00 (s) and 3.39 (d), which based on previous studies[8] could be assigned to the methyl group, the 7-H, the methoxy methyl and the 6-H respectively. The amount of this product is very small and this must be a tentative assignment.

In conclusion, in this paper we have described the facile synthesis of some 3-phenylindenone systems using two routes. These methods can be used to synthesize a range of 3-phenyl- and 2-substituted-3-phenylindenones. Crystal structures of 2-bromo-6-methoxy-3-phenylindanone (**4**) and 2-bromo-6-methoxy-3-phenylindenone (**1c**) are shown. Initial photochemical studies of 6-methoxy-3-phenylindenone (**1b**) show that this compound dimerizes readily, even in the presence of excess alkene. In addition, in the presence of alkenes, *cis-trans* isomerization of the alkene occurs and given that no transient is observed using ns-flash photolysis, we surmise that the excited state of this enone is very short lived.

All reagents used in synthesis of compounds as described were purchased from Aldrich Chemical Company, and used without further purification. 3′-Methoxychalcone was synthesized according to the method of Murphy et al.[4] Solvents for synthesis and chromatography were distilled prior to use. Et_2O was dried over $CaCl_2$ and distilled from sodium/benzophenone. EtOH was distilled over Mg turnings and I_2. Solvents for spectroscopy were obtained as spectroscopic grade and used as received. Deuterated solvents were used as received (99 + % atom). NMR spectra were recorded on a Bruker DPX 400 (400.13 MHz) instrument. NMR data are recorded in δ values relative to tetramethylsilane. *J* values are given in Hz. Absorption spectra were recorded on a Shimadzu UV-2401 PC spectrometer or a Cary 300 Scan spectrometer. IR spectra were recorded on a Mattson Genesis II FTIR spectrometer. Samples were prepared either as Nujol mulls or applied neat to NaCl windows. ESMS spectra were recorded on a Micromass LCG TOF mass spectrometer. Sample concentrations were made up to be less than 10^{-6} M. TLC analyses were run on Merck silica gel 60 F_{254} pre-coated plates. Flash chromatography was preformed using Merck grade flash silica gel. For photochemical experiments, samples were degassed in an NMR tube by bubbling with continuous stream argon for 30 min. Samples were then irradiated directly by a mercury lamp, using glass and water filter (λ > 330 nm) (500 W) Experiments where samples were degassed by the freeze-pump thaw (3 cycles) gave identical results.

3-Phenylindenone (1a)

3-Phenylindanone (0.5 g, 2.4 mmol) and SeO_2 (0.3 g, 2.7 mmol) in anhyd EtOH (20 mL) were refluxed for 48 h under N_2. The cooled mixture was poured into H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with aq $NaHCO_3$ and H_2O. The organic

phase was dried ($MgSO_4$) and the solvent removed. Purification by column chromatography (CH_2Cl_2, R_f 0.8) gave 100 mg (20%) of product as a red oil.

IR (neat): 1704 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 6.0 (1 H, s, 2-H), 7.3, 7.4 (2 H, dt, *J* = 6.5, 1 Hz, 5-H, 6-H), 7.4, 7.5 (2 H, d, *J* = 6.5 Hz, 4-H, 7-H), 7.6 (5H, s, C_6H_5).

ESMS: *m*/*z* calcd for $C_{15}H_{11}O$: 207.0810; found: 207.0793 (M^+).

6-Methoxy-3-phenylindanone (3)

3′-Methoxychalcone (**2**; 9.2 g, 38.7 mmol) in trifluoroacetic acid (20 mL) was refluxed for 2 days under N_2. Work-up [addition of H_2O, extraction with CH_2Cl_2, and drying ($MgSO_4$)] and evaporation of solvent gave a red-brown oil; yield: 8.1 g (88%). A sample was purified by column chromatography (CH_2Cl_2, R_f 0.4) to give yellow needles; mp 69–71 °C. Partially purified product could also be used in the oxidation step.

IR (Nujol): 1705 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 2.7 (1 H, dd, *J* = 19, 3.5 Hz, 2-H), 3.3 (1 H, dd, *J* = 19, 7 Hz, 2-H), 3.9 (3 H, s, OCH_3), 4.5 (1 H, dd, *J* = 7, 3.5 Hz, 3-H), 7.14 (2 H, dd, *J* = 7, 1.5 Hz, *o*-H_{arom}), 7.18 (2 H, d, *J* = 1.5, 4-H and 7-H overlapping), 7.26 (2 H, m, 5-H, *p*-H_{arom}), 7.3 (2 H, m, *m*-H_{arom}).

ESMS: *m*/*z* calcd for $C_{16}H_{15}O_2$: 239.1072; found: 239.1058

Anal. Calcd for $C_{16}H_{15}O_2$: C, 87.36; H, 4.89. Found: C, 87.16; H, 5.02.

2-Bromo-6-methoxy-3-phenylindanone (4)

Br_2 (1.0 mL) was added dropwise to an ice-cooled solution of 6-methoxy-3-phenylindanone (**3**; 8.1 g, 33.9 mmol) in Et_2O (20 mL) and the mixture was stirred for 20 min. At this time, a precipitate started to fall out of solution. The solution was stirred for a further 10 min and H_2O was added. The solution was allowed to stand overnight and the precipitate that formed was collected by suction filtration. Recrystallization (Et_2O) gave **4**; yield: 6.1 g (55%); mp 83–85 °C.

IR (Nujol): 1713 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.9 (3 H, s, OCH_3), 4.4 (1 H, d, *J* = 6 Hz, 2-H), 4.6 (1 H, d, *J* = 6 Hz, 3-H), 6.8 (1 H, dd, *J* = 8, 2.5 Hz, 5-H), 7.3 (1 H, d, *J* = 2.5 Hz, 7-H), 7.4 (1 H, d, *J* = 8 Hz, 4-H), 7.7 (s, 5 H, C_6H_5).

ESMS: *m*/*z* calcd for $C_{16}H_{13}BrO_2$ (M^+): 316.0102, 318.0142; found: 316.0124, 318.0165.

Anal. Calcd for $C_{16}H_{13}BrO_2$: C, 60.59; H, 4.13. Found: C, 60.23; H, 4.42.

6-Methoxy-3-phenylindenone (1b)

Method A: 2-Bromo-6-methoxy-3-phenylindanone (**4**; 6.1 g, 19.2 mmol) was refluxed with NaOEt [prepared from Na (0.2 g, 8.8 mmol) in EtOH (5 mL)] for 3 h under inert atmosphere. Work-up [washing with brine, and drying ($MgSO_4$)] and column chromatography (CH_2Cl_2, then 3:2 CH_2Cl_2–hexane) gave **1b**; yield: 1.1 g (13.5% overall from **2**).

Method B: 6-Methoxy-3-phenylindanone (0.5 g, 2.1 mmol) and SeO_2 (0.5 g, 2.7 mmol) in anhyd EtOH (20 mL) was refluxed for 48 h under N_2. The mixture was cooled, and added to H_2O. The product was extracted with CH_2Cl_2 and washed with aq $NaHCO_3$ and H_2O. The organic extract was dried ($MgSO_4$) and the solvent removed. Purification by column chromatography (CH_2Cl_2, R_f 0.6) gave 100 mg (28%) of product; mp 81–83 °C.

IR (Nujol): 1700 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.9 (3 H, s, OCH_3), 5.9 (1 H, s, 2-H), 6.8 (1 H, dd, *J* = 8, 2.5 Hz, 5-H), 7.2 (1 H, d, *J* = 2.5 Hz, 7-H), 7.3 (1 H, d, *J* = 8 Hz, 4-H), 7.7 (s, 5 H, C_6H_5).

ESMS: *m*/*z* calcd for $C_{16}H_{13}O_2$: 237.0916 (M^+); found: 237.0922.

Anal. Calcd for $C_{16}H_{13}O_2$: C, 81.34; H, 5.12. Found: C, 81.09; H, 5.22.

2-Ethoxycarbonyl-6-methoxy-3-phenylindenone (1d)

Ethyl benzoylacetate (3.5 mL, 3.89 g, 20.2 mmol) was added to a suspension of NaH (1.1 g, 45.8 mmol) in anhyd THF (20 mL) and the mixture was stirred for 1 h. *m*-Anisoyl chloride (2.8 mL, 3.4 g, 19.9 mmol) was added dropwise over 45 min and the solution turned an intense red color. The solution was carefully poured into cold 5% HCl solution and extracted with CH_2Cl_2. After drying ($MgSO_4$), the solvent was evaporated to give a red oil. This was dissolved in CH_2Cl_2 (30 mL) and the solution cooled in an ice-bath. A solution of $MeSO_3H$ (1 mL, 15.4 mmol) in CH_2Cl_2 (10 mL) was added over 45 min. The ice-bath was removed and the solution stirred for 3 days. The red solution was worked up [washing with aq $NaHCO_3$ and brine, and drying ($MgSO_4$)] and the solvent was evaporated. On addition of a hexane–EtOAc (10:1) mixture, the product precipitated as red crystals; yield: 2.3 g (47%).

^1H NMR ($CDCl_3$): δ = 1.2 (3 H, t, *J* = 7 Hz, CH_3), 4.2 (2 H, q, *J* = 7 Hz, OCH_2), 6.8 (1 H, dd, *J* = 8.5, 2.5 Hz, 5-H), 7.1 (1 H, d, *J* = 8 Hz, 4-H), 7.2 (1 H, d, *J* = 2.5 Hz, 7-H), 7.5 (s, 5 H, C_6H_5).

ESMS: *m*/*z* calcd for $C_{16}H_{15}O_2$: 309.1227 (M^+); found; 309.1218.

Anal. Calcd for $C_{16}H_{15}O_2$: C, 74.01; H, 5.23. Found: C, 73.89; H, 5.40.

2-Bromo-6-methoxy-3-phenylindenone (1c)

Br_2 (1.0 mL) was added dropwise to an ice-cooled solution of 6-methoxy-3-phenylindanone (5 g, 21 mmol) in anhyd Et_2O (20 mL). Almost immediately, a precipitate started to fall out of solution. The solution was stirred for 10 min and H_2O added. The precipitate that formed was collected by suction filtration. This was reacted with NaOEt [prepared from Na (0.2 g, 8.8 mmol) in EtOH (5 mL)] in EtOH (15 mL) for 1 h at r.t. Work-up [washing with brine, and drying ($MgSO_4$)] gave a red oil. Addition of hexane–EtOAc (1:10) prompted precipitation of red crystals of product; yield: 3.4 g (52%); mp 96–98 °C.

IR (Nujol): 1705 cm^{-1} (C=O).

^1H NMR ($CDCl_3$): δ = 3.8 (3 H, s, OCH_3), 6.7 (1 H, dd, *J* = 8, 2 Hz, 5-H), 7.0 (1 H, d, *J* = 8 Hz, 4-H), 7.1 (1 H, d, *J* = 2 Hz, 7-H), 7.4–7.6 (m, 5 H, C_6H_5).

ESMS: *m*/*z* calcd for $C_{16}H_{11}BrO_2$: 313.9904, 315.9945; found: 313.9913, 315.9921 (M^+). Anal. Calcd for $C_{16}H_{11}BrO_2$: C, 60.98; H, 3.52. Found: C, 60.63; H, 3.71.

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