

Direct Synthesis of γ -Substituted Phthalides by Cyclization of Benzyl Radicals Generated from *o*-(Arylmethyl)benzoic Acids*

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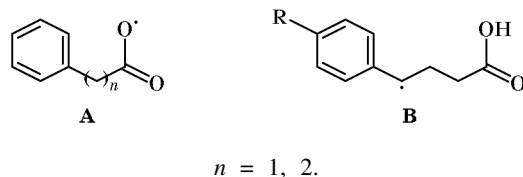
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Abstract—Direct oxidation of *o*-(arylmethyl)benzoic acids with sodium peroxydisulfate–copper(II) chloride in water yields γ -substituted phthalides. The reaction is highly regioselective, and the corresponding γ -butyrolactones are the only products formed through intermediate stable arylmethyl radicals.

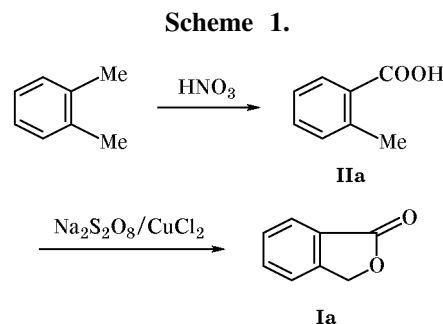
Numerous natural biologically active compounds, as well as some medicines are derivatives of γ -butyrolactones [1–6]. We recently synthesized a series of mono- and disubstituted γ -butyrolactones having aryl and alkyl substituents at the carbon atoms in positions 3, 5 and 3, 4, 5, respectively. These compounds are potential antiglaucoma and antitumor agents [7–10].

In the recent years, chemical reactions occurring in aqueous medium become more important than those performed in organic solvents. From the viewpoint of ecological safety, development of new procedures utilizing less toxic solvents is quite desirable. Among numerous solvents, almost always the best choice is water [11–14]. However, our attempt to use this solvent as a medium for intramolecular cyclization of aryl-substituted acids via carboxy radical **A** to obtain lactones fused to a 5- or 6-membered ring was unsuccessful [15].



The present communication describes the transformation of some 4-substituted aromatic acids in the presence of the oxidizing system $S_2O_8^{2-}-Cu^{2+}$ in water at 85–90°C, which involves intermediate formation of

stable benzyl radical **B** and yields 25–85% of the corresponding butyrolactones. For example, 3*H*-isobenzofuran-1-one (**Ia**) was obtained by direct oxidation of 2-methylbenzoic acid (**IIa**) which was prepared in turn by oxidation of *o*-xylene with nitric acid, following a simple procedure [16] (Scheme 1).

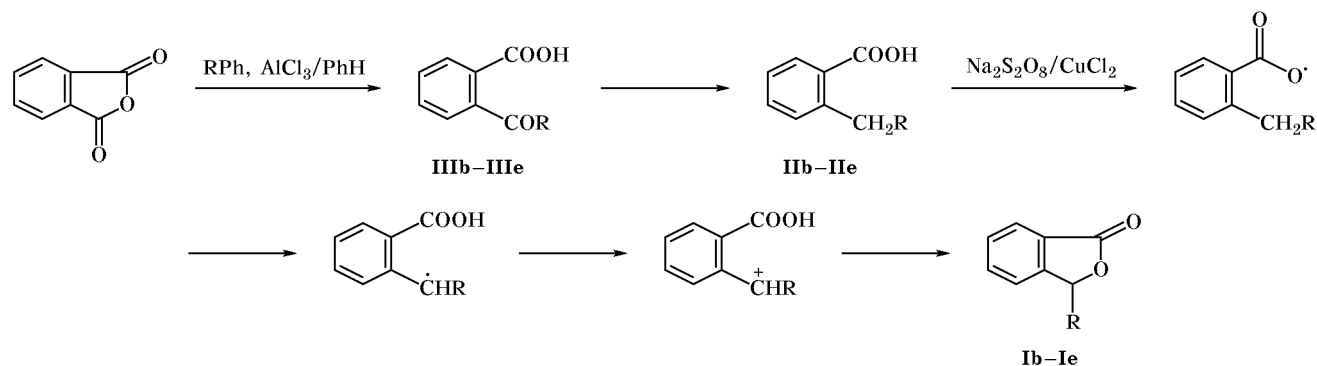


Application of the above procedure to related *o*-(arylmethyl)benzoic acids **IIb–IIe**, which were prepared by reduction of 2-(arylcabonyl)benzoic acids **IIIb–IIIe**, afforded γ -substituted phthalides **Ib–Ie** (Scheme 2). The reaction involves initial formation of carboxyl radicals which are transformed into benzyl radicals via 1,5-hydrogen shift. The latter give rise to unstable cations in the presence of $CuCl_2$, and the subsequent intramolecular cyclization leads to formation of lactones **I**.

While studying the general character of this reaction, we examined the stability of intermediate radical species. As expected, their stability decreased in the following series of R: 4-MeOC₆H₄CH₂ >

* The original article was submitted in English.

Scheme 2.



4-MeC₆H₄CH₂ > 4-PhC₆H₄CH₂. The yields of pure compounds **Ia–Ie**, which were isolated by column or preparative thin-layer chromatography, were 55, 56, 62, 85, and 48%, respectively.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR-470 spectrometer in KBr. The NMR spectra were obtained on Bruker FT (80 MHz) and Bruker Avance (500 MHz) spectrometers using chloroform-*d* as solvent and TMS as internal reference. The mass spectra were run on a Shimadzu MS-QP 1100 EX instrument. The melting points were determined on a Mettler Fp5 device and were not corrected.

3H-Isobenzofuran-1-one (Ia). A mixture of 4.08 g (30 mmol) of compound **Ia**, 27 ml of water, and 5.1 g (30 mmol) of CuCl₂·2H₂O was heated to 85–90°C, and a solution of 8.5 g (30 mmol) of Na₂S₂O₈ in 15 ml of water was added dropwise over a period of 40 min under vigorous stirring. The mixture was then heated for 3 h at the boiling point, cooled, and treated with ether (3×10 ml). The extract was dried over MgSO₄, the solvent was removed, and the residue was subjected to preparative thin-layer chromatography on silica gel using a mixture of ligroin with ethyl acetate (5–10%) as eluent to isolate 2.25 g (55%) of compound **Ia** with mp 73°C [17]. IR spectrum, ν , cm⁻¹: 1755 s, 1055 m. ¹H NMR spectrum, δ , ppm: 5.2 s (2H), 7.5 m (4H). ¹³C NMR spectrum, δ_C , ppm: 70.4, 127.29, 127.3, 129.3, 129.9, 113.0, 142.1, 167.0. Mass spectrum, m/z (I_{rel} , %): 135 (3.5), 134 (37.6), 105 (100), 77 (53.7).

3-(4-Methoxyphenyl)-3H-isobenzofuran-1-one (Id). A solution of 1.2 g (5 mmol) of Na₂S₂O₈ in 10 ml of water was added dropwise over a period of 40 min under vigorous stirring to a mixture of 1.2 g

(5 mmol) of 2-(4-methoxybenzyl)benzoic acid and 0.85 g (5 mmol) of copper(II) chloride dihydrate in 18 ml of water, heated to 85–90°C. The mixture was heated for 3.5 h at the boiling point, cooled, and treated with diethyl ether (3×10 ml). The combined extracts were dried over MgSO₄ and evaporated, and the residue was subjected to chromatography using a mixture of ligroin with ethyl acetate (10–20%) as eluent to obtain 1.01 g (85%) of compound **Id** with mp 114°C. IR spectrum, ν , cm⁻¹: 1750 s, 1070 m. ¹H NMR spectrum, δ , ppm: 7–8.21 m. ¹³C NMR spectrum, δ_C , ppm: 56.5, 83.5, 114.6, 126, 128.5, 129.5, 130.3, 130.5, 133.5, 135.5, 145, 160, 167. Found: M^+ 240.0789. C₁₅H₁₂O₃. Calculated: M 240.0786.

Compounds **Ib**, **Ic**, and **Ie** were synthesized in a similar way.

3-Phenyl-3H-isobenzofuran-1-one (Ib). mp 114°C. IR spectrum, ν , cm⁻¹: 1755 s. ¹H NMR spectrum, δ , ppm: 6.4 s (1H), 7.2–7.9 m (9H). ¹³C NMR spectrum, δ_C , ppm: 83.2, 125.5, 126, 128.1, 128.3, 128.5, 129, 130.3, 133.5, 143, 144.3, 167. Found: M^+ 210.0676. C₁₄H₁₀O₂. Calculated: M 210.0681.

3-(4-Tolyl)-3H-isobenzofuran-1-one (Ic). mp 127°C. IR spectrum, ν , cm⁻¹: 1753 s, 1065 m. ¹H NMR spectrum, δ , ppm: 2.3 s (3H), 6.3 s (1H), 6.9–7.8 m (8H). ¹³C NMR spectrum, δ_C , ppm: 21.1, 83.5, 126, 128.5, 130, 130.3, 130.8, 134, 135.5, 140, 144, 168.5. Found: M^+ 224.0833. C₁₅H₁₂O₂. Calculated: M 224.0837.

3-(1-Naphthyl)-3H-isobenzofuran-1-one (Ie). Yield 85%, mp 134°C. IR spectrum, ν , cm⁻¹: 1760 s, 1065 m. ¹H NMR spectrum, δ , ppm: 7–8.21 m. Mass spectrum, m/z (I_{rel} , %): 260 (73), 259 (10), 213 (13), 215 (40), 155 (20), 127 (17), 104 (38). Found: M^+ 260.0841. C₁₈H₁₂O₂. Calculated: M 260.0837.

2-Methylbenzoic acid (IIa). A mixture of 4 ml (30 mmol) of *o*-xylene, 8 ml of concentrated nitric acid, and 16 ml of water was heated for 55 h at 145–155°C. The progress of the reaction was monitored by TLC. The mixture was cooled to 0°C, and the precipitate was filtered off, washed with 20 ml of water, and dissolved in 10 ml of 10% aqueous NaOH on cooling. Unreacted *o*-xylene was removed by extraction with diethyl ether (3 × 10 ml). The aqueous phase was treated with 0.1 g of charcoal, and the mixture was heated on a steam bath and filtered through a Büchner funnel. The filtrate was neutralized with 2.3 ml of concentrated hydrochloric acid under vigorous stirring, and the precipitate was filtered off, washed with ice water, and dissolved in 3.5 ml of ethanol. The solution was treated with charcoal, heated on a steam bath, and filtered while hot. The filtrate was diluted with 4.8 ml of water at 55–60°C. The mixture was cooled, and the precipitate was filtered off and washed with 2.5 ml of cold 50% ethanol. Yield 2.2 g (55%), mp 100–101°C [17]. IR spectrum, ν , cm^{-1} : 3200 s, 1680 m. ^1H NMR spectrum, δ , ppm: 2.6 s (3H), 7.3 m (3H), 8.1 m (1H), 9.6 s (1H). Mass spectrum, m/z (I_{rel} , %): 137 (5.9), 136 (60), 118 (100), 91 (95.7), 65 (40.4).

2-(Arylmethyl)benzoic acids IIb–IIe (general procedure) [18]. A mixture of 4.3 g (66 mmol) of zinc dust, 0.43 g (1.58 mmol) of mercury(II) chloride, 0.2 ml of concentrated hydrochloric acid, and 5.5 ml of water was stirred at room temperature until it became homogeneous. Water, 2.7 ml, concentrated hydrochloric acid, 0.65 ml, toluene, 3.6 ml, and acid **III**, 10 mmol, were added, and the mixture was heated for 20–40 h at the boiling point, 1.8 ml of concentrated hydrochloric acid being added every 6 h to maintain its concentration constant. The mixture was cooled, and the aqueous phase was separated, diluted with 7.2 ml of water, and extracted with diethyl ether (3 × 15 ml). The extracts were combined with the organic phase, washed with water, dried over MgSO_4 , and evaporated, and the residue was purified by recrystallization.

2-Benzylbenzoic acid (IIb). Reaction time 30 h. Yield 70%, mp 110–112°C [17]. IR spectrum, ν , cm^{-1} : 3200 s, 1695 m. ^1H NMR spectrum, δ , ppm: 4.4 s (2H), 7.2 m (8H), 7.9 d (1H).

2-(4-Methylbenzyl)benzoic acid (IIc). Reaction time 40 h. mp 111–112°C [19]. IR spectrum, ν , cm^{-1} : 3200 s, 1670 m. ^1H NMR spectrum, δ , ppm: 2.4 s (3H), 4.8 s (2H), 7.4 m (7H), 8.3 d (1H).

2-(4-Methoxybenzyl)benzoic acid (IId). Reaction time 40 h. Yield 70%. IR spectrum, ν , cm^{-1} : 3200 s,

1685 m. ^1H NMR spectrum, δ , ppm: 3.7 s (3H), 4.3 s (2H), 7.2 m (7H), 8.1 d (1H).

2-(1-Naphthylmethyl)benzoic acid (IIe). Reaction time 20 h. Yield 60%, mp 137–139°C. IR spectrum, cm^{-1} : 3200 s, 1690 w, 1080 m. ^1H NMR spectrum, δ , ppm: 4.8 s (2H), 6.8–8.2 m (11H).

2-(4-Methoxybenzoyl)benzoic acid (IIIa). A solution of 13.34 g (10 mmol) of powdered anhydrous aluminum chloride in 30 ml of nitrobenzene was added dropwise over a period of 40 min to a solution of 4.4 ml (40 mmol) of anisole and 7.4 g (50 mmol) of phthalic anhydride in 120 ml of nitrobenzene while stirring at room temperature. The mixture was stirred for 5.5 h at room temperature, poured into a mixture of 600 ml of 20% hydrochloric acid and 400 g of ice, and treated with ether (3 × 20 ml + 100 ml). The combined extracts were washed with water (3 × 30 ml) and with a saturated solution of NaHCO_3 (5 × 40 + 100 ml). The alkaline extract was washed with diethyl ether (3 × 20 ml) and acidified with 10% hydrochloric acid. The colorless precipitate was filtered off and dried. Yield 10.8 g (85%), mp 130–132°C. IR spectrum, ν , cm^{-1} : 3200 s, 1685 m. ^1H NMR spectrum, δ , ppm: 3.7 s (3H), 6.7 m (2H), 7.6 m (6H), 9.0 s (1H).

Compounds **IIIb**, **IIIc**, and **IIIe** were synthesized in a similar way.

2-Benzoylbenzoic acid (IIIb). Yield 84%, mp 94°C (monohydrate) [20], mp 128°C [21]. IR spectrum, ν , cm^{-1} : 3200 s, 1670 m. ^1H NMR spectrum, δ , ppm: 7.9 m. Mass spectrum, m/z (I_{rel} , %): 228 (1.6), 227 (8.2), 226 (53.3), 182 (68.6), 149 (82), 105 (100), 77 (85.5), 51 (38.8).

2-(4-Methylbenzoyl)benzoic acid (IIIc). mp 137–138°C [21]. IR spectrum, ν , cm^{-1} : 3200 s, 1690 m. ^1H NMR spectrum, δ , ppm: 2.3 s (3H), 7.5 m (8H). Mass spectrum, m/z (I_{rel} , %): 241 (3.9), 240 (20), 149 (21.2), 119 (100), 91 (32.5), 65 (20).

2-(1-Naphthoyl)benzoic acid (IIIe). Methylene chloride was used as solvent instead of nitrobenzene. mp 173°C [22]. IR spectrum, ν , cm^{-1} : 3200 s, 1680 w, 1650 w. ^1H NMR spectrum, δ , ppm: 7.2–8.2 m (10H), 9.1 m (1H).

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