Direct Synthesis of γ-Substituted Phthalides *Via ortho*-Aryl Benzoic Acid Mediated Benzyl Radical Cyclization

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Direct synthesis of γ-substituted phthalids from related *ortho*-aryl benzoic acids with 48-85% yield are covered. The direct oxidation in the presence of peroxydisulphate-copper (II) chloride in aqueous medium was applied. The reaction is highly regioselective and leads exclusively to γ-butyrolactone, through very stable benzylic radical intermediate.

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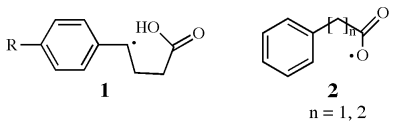
A large number of biologically important natural products and some drugs are derivatives of γ-butyrolactones [1-6]. Recently, we synthesized special mono, and di-substituted γ-butyrolactones with aryl and aliphatic substitution at carbon 3, 5, & 3, 4 and 5 as anti-glaucoma antitumor and essence respectively [7-11].

Currently, we convert several 4-substituted aryl acids to the corresponding butyrolactones by placing them in the presence of an oxidation system such as $S_2O_8^{-2}$-Cu^{2+} in an aqueous solution at 85-90° C. The reaction goes through the stable benzyl radical **1**, and is obtained in mild to high yields (25-85%), (Scheme 1) [12]. Recently, there

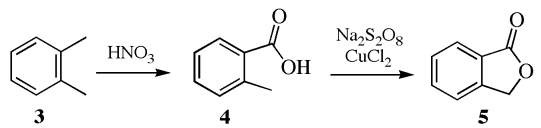
Scheme 1



has been interest in organic reactions that can be carried out in aqueous media rather than organic solvent, due to the ecological advantages of using a less toxic solvent. Among many different kinds of solvents water almost certainly is the best [13-15].

The utilization of this oxidation reagent for the intramolecular reaction of aryl acids *via* carboxylic radical **2** to expected 5- and 6-members fused lactones failed (Scheme 1) [12].

Scheme 2



We now report that a simple, general and efficient approach to the synthesis of Phthalide (3*H*-isobenzofuran-1-one) 5 in aqueous solution at 90 °C from direct oxidation of 2-methyl benzoic acid 4 in the presence of $Na_2S_2O_8$, $CuCl_2$. Acid 4 was prepared from *o*-xylene in the presence of HNO_3 by using simple procedures (Scheme 2) [17].

Application of this method while applied on the related *ortho*-aryl benzoic acids 9 lead to the synthesis of substituted γ-phthalids 13a-13d. The reactions proceed through benzyl radical intermediates 11a-11d and finally the cation intermediates 12a-12d, all of which are aqueous intermediates (Scheme 3). The *ortho*-aryl benzoic acids 9a-9d were prepared from accessible starting materials by applying straightforward procedures. In exploring the scope of this reaction, we examined the stability of a radicals produced after initial cyclization. As expected, the order of stability of the intermediate cyclized radicals is 4-OMe-dibenzyl> 4-Me-dibenzyl> dibenzyl, the yields of isolated lactones were 48-85% (Table1).

Scheme 3

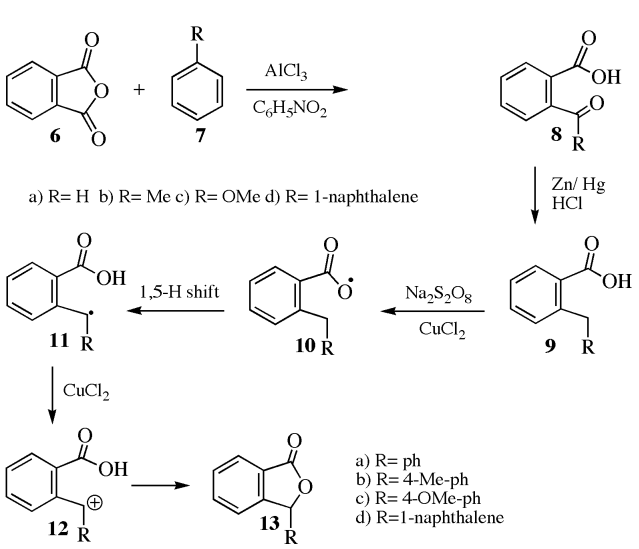


Table 1

Yield of Lactonization from 2-Methyl Benzoic Acids **8a-8d** and *ortho*-Aryl Benzoic Acids **9a-9d**

Entry	**5**	**13a**	**13b**	**13c**	**13d**
Yield %	55	56	62	85	48

The physical property and spectroscopic data for all synthesized compounds are shown in (Table 2).

Table 2

Physical Property of all Synthesized Compounds

Entry	IR cm^{-1}	^1H and ^{13}C NMR δ	Yield %	Mp. °C and MS
4	(KBr): 3200(b), 1680(s) lit. [17]	($CDCl_3$): 2.6 (s, 3H), 7.3(m, 3H), 8.1 (m, 1H), 9.6 (s, 1H)	56	100-101 (lit. 99-101) [17] 137(5.9), 136(60), 118(100%), 91(95.7), 90(80.7), 65(40.4).
5	(KBr): 1755(s), 1055(m)	($CDCl_3$): 5.2 (s, 2H), 7.5 (m, 4H) ($CDCl_3$): 70.4, 127.29, 127.3, 129.3, 129.9, 133.0, 142.1, 167.0	55	73 (lit. 72-74) [18] 135(3.5, 134(37.6), 105(100%), 7(53.7)
8a	(KBr): 3200(b), 1670(s)	($CDCl_3$): 7.9 (m, 9H)	84	8a monohydrate 94 (lit. 94) [18], 8a 128 (lit. 127-128) [19]
9a	(KBr): 3200(b), 1695(s)	($CDCl_3$): 4.4 (s, 2H), 7.2 (m, 8H), 7.9 (d, 1H)	70	110-112 (lit. 110-113) [17]
13a	(KBr): 1775 (s)	($CDCl_3$): 6.4 (s, 1H), 7.2-7.9 (m, 9H)	56	114
8b	(KBr): 3200(b), 1690(s)	($CDCl_3$): 2.3 (s, 3H), 7.5 (m, 8H)	96	137-138 (lit. 138-139) [18]
9b	(KBr): 3200(b), 1670(s)	($CDCl_3$): 2.4 (s, 3H), 4.8 (s, 2H), 7.4 (m, 7H), 8.3 (d, 1H)	-	111-112 (lit.110-113) [20]
13b	(KBr): 1753(s), 1065(m)	($CDCl_3$): 2.3 (s, 3H), 6.3 (s, 1H), 6.9-7.8 (m, 8H)	62	127
8c	(KBr): 3200(b), 1685(s)	($CDCl_3$): 3.7 (s,3H), 6.7 (m, 2H), 7.6 (m, 6H), 9 (s, 1H)	85	130-132
9c	(KBr): 3200(b), 1685(s), 1685(s)	($CDCl_3$):.3.7 (s,3H), 4.3 (2, 2H), 7.2 (m, 7H), 8.1 (d, 1H)	70	-
13c	(KBr): 1070(m), 1750(s)	($CDCl_3$):.3.9 (s, 3H), 6.4 (s, 1H), 7.6 (m, 7H)	85	114
8d	(KBr): 3200(b), 1680(s), 1650(s)	($CDCl_3$): 7.8 (m, 10H), 9.1 (m, 1H)	30	173 (lit. 173)21
9d	(KBr): 3200(b), 1690(s), 1080(m)	($CDCl_3$): 4.8 (s, 2H), 7.8 (m, 11H)	60	137-139
13d	(KBr): 1760(s), 1065(m)	($CDCl_3$): 7.5 (m, 12H)	48	134 , m/e; 260(73), 259(10), 231(13), 215(40), 155(20), 127(17), 104(38)

EXPERIMENTAL

General.

Yields refer to isolated pure center cut from column chromatography or scratched from preparative TLC. Products were characterized by comparison with authentic sample (IR, NMR, GC, TLC, and mp). Melting points are uncorrected and determined by Metller Fp5 melting point apparatus. IR spectra were obtained on a Shimadzu IR-470. All NMR data were recorded in $CDCl_3$ on Brucker 80 MHz FT and Brucker Avance 500-MHz spectrometers. Chemical shifts are reported in parts per million (δ) using TMS as internal reference. Mass spectra were obtained from a GC MS-QP 1100EX Shimadzu instrument.

Synthesis of 2-Methylbenzoic Acid (4).

To a 100 mL round-bottom flask equipped with a reflux condenser was added 4 mL (3.63 g, 30 mmol) *o*-xylene, 8 mL conc. HNO_3 and 16 mL distilled water. The reaction mixture was heated to refluxed in oil bath for 55 h at 145-155 °C. The progress of the reaction was monitored by TLC. After this time the components of the flask were allowed to cool to 0 °C. The solid product was collected by filtration and washed with 20 mL of distilled water. The crude product was dissolved in 10 mL 10% NaOH by heating. The unreacted *o*-xylene was extracted of with 3 X 10 mL of ether. To the aqueous layer 0.1 g active carbon was added and the resulting mixture was heated on the steam bath, and filtered. The filtrate was neutralized with a solution of 2.3 mL conc. HCl stirred vigorously, collected by filtration and washed with cool distilled water. The crude crystals was dissolved in 3.5 mL 96% ethanol followed by addition of active carbon, the resulting mixture was heated on steam bath and filtered hot. To this solution was added 4.8 mL 55-60 °C distilled water. After cooling, filtration and washing of crystals with 2.5 mL cooled 50% ethanol 2.2 g (55%) pure crystal, m.p =100-101 (lit.= 99-101 °C) [17] were obtained. The IR, ^1H, ^{13}C NMR spectra were recorded (Table 2).

Synthesis of 3*H*-Isobenzofuran-1-one (**5**).

To a 250mL round-bottom flask was added 4.08 g (30 mmol) **4**, 27 mL distilled water and 5.1 g (30 mmol) $CuCl_2 \cdot 2H_2O$. The flask was equipped with a reflux condenser and an additional funnel. The solution of 8.5 g (30 mmol) $Na_2S_2O_8$ and 15 mL water was added to the addition funnel. The reaction mixture was allowed to reflux by vigorous stirring while the temperature of solution was adjusted to 85-90 °C. The solution from the additional funnel was added dropwise to a flask during 40 m, and the flask was refluxed for 3 h. After this time, the reaction was stopped. The flask was cooled and extracted with 3 X 10 mL

ether and dried over $MgSO_4$. The solvent was removed and 2.25 g (56%) of **5** mp = 73 °C (lit. 72-74°)[17] was collected as a pure center cut from silica gel plate. The solvent system used was 5-10% EtOAc:ligroin. The IR, ^1H, ^{13}CNMR spectra are recorded (Table2).

Synthesis of 2-(4-Methoxy-benzoyl)-benzoic Acid (**8c**).

A Typical Procedure.

To a two neck round-buttom flask equipped with a reflux condenser and addition funnel was added 4.4 mL (4.32 g, 40 mmol) anisole, 120 mL nitrobenzene (as a solvent) and 7.4 g (50 mmol) phthalic anhydride. To the additional funnel was added a solution of 13.34 g (100 mmol) of powdered anhydrous aluminum chloride and 30 mL nitrobenzene. This solution, at rt, was dropwise added to the flask during 40 m. The contents of the flask were stirred at rt for 5.5 h. After this time the reaction mixture was added to a solution of 600 mL HCl 20% and 400 g ice and mixed throughly, extracted with 3 X 20+100mL ether. This phase was washed with 3 X 30 mL H_2O, and extracted with 5 X 40+100mL saturated $NaHCO_3$. This solution was then washed with 3 X 20 mL ether. The aqueous solution was transfer to a large beaker and acidified with HCl. The white percipitate formed and was collected by filtration through to give 10.8 g (85%) crystals mp = 130-132 °C. The IR and NMR were recorded and are given in (Table 2).

Preparation of 2-(4-Methoy-benzyl)-benzoic Acid (**9c**).

A Typical Procedure.

Zn powder 4.3g (66 mmol), 0.43 g (1.58 mmol) mercury (II) chloride, 0.2 ml conc. HCl and 5.5 ml distilled water, were combined in a 50 ml flask. The mixture was stirred at room temperature for several minutes to produce a homogenous solution. After homogenization was completed, the stirring was stopped and the liquid was decanted as completely as possible. In a flask equipped with reflux condenser, 2.7 ml distilled water, 0.65 ml conc. HCl, 3.6 ml toluene (as solvent) and 2.6 g (10 mmol) 2-(4-methoy-benzyl)-benzoic acid **8c** were combined. The flask was refluxed vigorously for 40 hrs. During this period 1.8 ml conc. HCl was added to the flask at approximately 6 hr intervals during the refluxing period in order to maintain the conc. of HCl. After cooling, the two layers were separated. Water (7.2 mL) was added to the aqueous layer, which was extracted with 3x15 ml ether, the extracted layer was added to toluene, washed with water and dried over $MgSO_4$. The solvent was evaporated to afford 1.7g (70%) of crystal .The IR and NMR spectra are given in Table 2.

Table 3

Reduction Condition for Conversion of 2-Benzoyl-benzoic Acids to 2-Bezyl-benzoic Acids

2-Benzoyl-benzoic Acids	Reagent & Method [23]	Time of Red. hrs	yield %	2-Bezyl-benzoi Acids
8a	amalgamated zinc	30	70	**9a**
8b	amalgamated zinc	40	-	**9b**
8c	amalgamated zinc	40	70	**9c**
8d	amalgamated zinc	20	60	**9d**

Preparation of 3-(4-Methoxy-phenyl)-3*H*-isobenzofuran-1-one (**13c**).

A Typical Procedure.

2-(4-Methoxy-benzyl)-benzoic acid (**9c**) 1.2 g (5 mmol), 18 ml distilled water and 0.85 g (5 mmol) copper (II) chloride•$2H_2O$ were combined in a 100 ml two-neck round bottom-flask. The flask was equipped with a reflux condenser and an additional funnel. A solution of 1.2 g (5 mmol) $Na_2S_2O_8$ and 10 ml water were added to the additional funnel. The reaction mixture was allowed to reflux by vigorous stirring while the temperature of solution was adjusted to 85-90 °C. The solution from the additional funnel was added dropwise to a flask during 40 min. and the flask was refluxed for 3.5 hrs. After this time the reaction was stopped. The flask was cooled and extracted with 3 x 10 ml ether and dried with $MgSO_4$. The solvent was removed and 1.01g (85%) mp=114 °C of **13c** was collected as a pure center cut from preparative chromatography. The solvent system used was 10 to 20% EtOAc:ligroin. The IR, ^1H, ^{13}C NMR spectra and Exact mass (M^+) are given in Table 2.

Synthesis of 2-(Naphthalene-1-carbonyl)-benzoic Acid (**8d**).

A similar procedure as used for **8c** was applied, but instead of nitrobenzene as a solvent dichloromethane was used.

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