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DIRECT SYNTHESIS OF γ-BUTYROLACTONES VIA γ-PHENYL SUBSTITUTED BUTYRIC ACIDS MEDIATED BENZYL RADICAL CYCLIZATION

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ABSTRACT

Synthesis of several γ-butyrolactones with aromatic substitution at carbon 5 from comparative γ-aryl acids with 25–85% yield are covered. The straight oxidation in the presence of peroxydisulphate-copper(II)chloride system in aqueous medium was applied. The reaction is highly regioselective and leads exclusively to γ-butyrolactone, through stable benzylic radical intermediate.

Oxidative addition of carboxylic acids and alkenes was used as a mild methodology for formation of γ-butyrolactones.[1–4] The oxidative systems such as $S_2O_8^{2-}$-Ag^+, $S_2O_8^{2-}$-Ag^+-Cu,[5–7] different oxidants' derivatives of Pb(IV), Co(III), Ag(II), other polyvalent metals,[8–10] and $KMnO_4$[11] can interact with carboxylic acids, resulting usually in their decarboxylation and creation of alkyl radicals. Direct oxidative systems such as oxidative lactonization of carboxylic acids in the presence of

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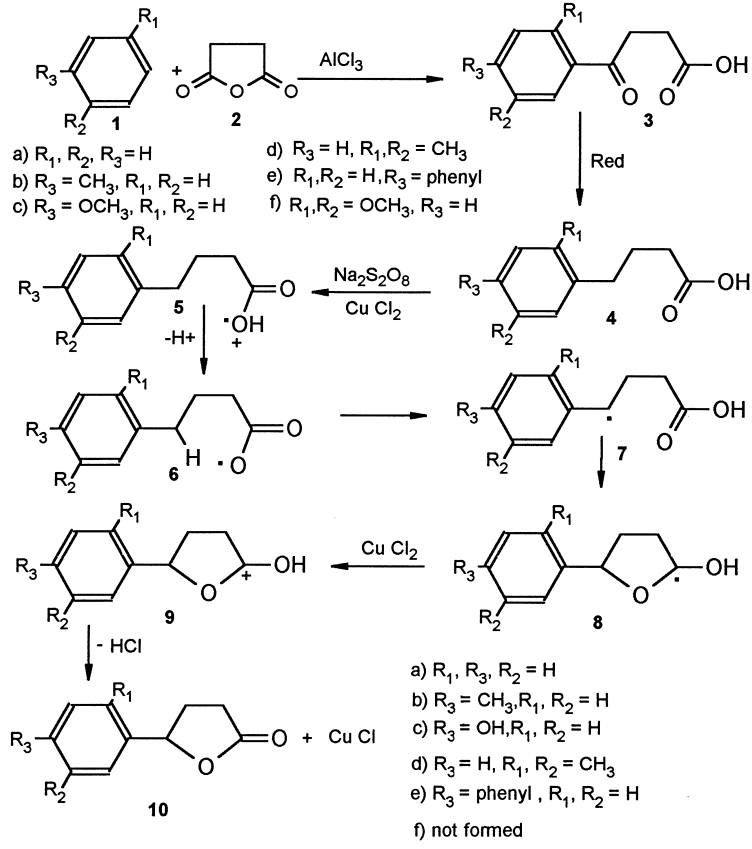
peroxydisulphate-containing systems have been published. However, the yields of conversion are either very low or the reaction is not selective, e.g., 3.3–9.5% and 4–10%, respectively, for mixtures that contain 5- and 6-member ring lactones together with some decarboxyllated compounds.[12] The objectives of this study are to convert 4-substituted aryl acids in the presence of an oxidative system such as $S_2O_8^{2-}$-Cu^{2+} from mild to high yields, and to monitor the conversion to exclusively 5-member lactone ring. Recently, we synthesized several mono, and di-substituted γ-butyrolactones with aryl and aliphatic substitution at carbon 5, 3,5 and 3,4 as an essence,[13] an anti-glaucoma, and an anti-tumor,[14–17] respectively. The direct oxidation system in the presence of peroxydisulphate-copper chloride, and in the aqueous solution at 90°C was applied. The reaction is regioselective and leads mainly to γ-butyrolactone (Scheme 1).



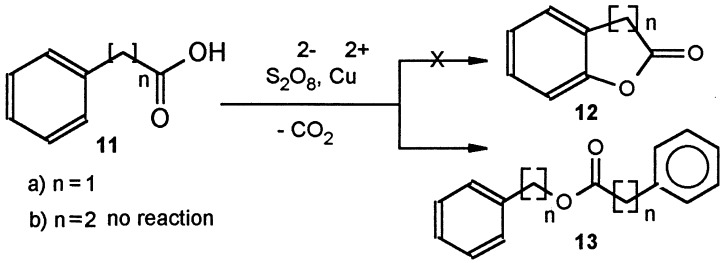
Scheme 1.

Table 1. Yield of Lactonization from 4-Aryl Acids

Lactone	R^1	R^2	R^3	Yield %
10a	H	H	H	41
10b	H	H	Me	51
10c	H	H	OH	84
10d	Me	Me	H	25
10e	H	H	PH	35
10f	OMe	OMe	H	0

Several 4-aryl carboxylic acids for one-pot direct conversion to the corresponding butyrolactones were elected. These acids were prepared from available starting materials by using straightforward procedures. The lactonization was entirely regioselective and only the γ-butyrolactones are isolated with 25–84% yields (Table 1).

Utilization of this oxidation reagent for intramolecular reaction of aryl acids of **11** (Scheme 2) to expected 5- and 6-members fused lactones **12** failed, and, in one case, lead to ester **13a**. Spectroscopic data for all compounds are shown in (Table 2).



Scheme 2.

Formation of lactone **10c** in high yield (Table 1) with hydroxy substitution instead of methoxy group of starting aryl acids **4c** at the para position, implies that the reaction has involved some extent of "through conjugaction"[18] (Scheme 3).

For the same reason, the 4-(2,5-dimethoxy phenyl) butyric acid **4f** was not converted to the corresponding lactone **10f**; instead, that entirely led to the formation of comparable p-benzoquinone, 4-(2,5-cyclohexadiene-1,4-dione) butanoic acid **19**, probably through stable radical **17** and biradical **18** (Scheme 4).

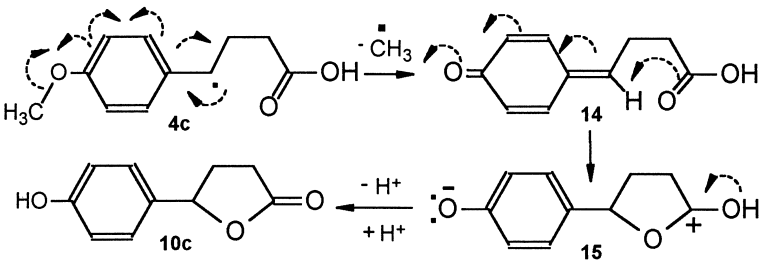
Table 2. Physical Property of All Synthesized Compounds

Entry	IR cm^{-1}	^{1}H & ^{13}C NMR δ	Yield (%)	M.p.°C & MS
3a	(KBr): 3200(b), 1690(b)	($CDCl_3$): 2.4(t) 2H, 3.4(t) 2H, 7.5(m) 3H, 8(m) 2H	90	114–116 (lit. 115)[19]
4a	(KBr): 3200(b), 1700(s)	($CDCl_3$): 2.1(m) 2H, 2.5(t) 2H, 2.7(t) 2H, 7.3(m) 5H, 11.1(s) 1H	89	47–48 (lit. 47–48)[19]
10a	(neat): 1770(s)	($CDCl_3$): 2.5(m) 4H, 5.4(t) 1H, 7.3(s) 5H, 13C ($CDCl_3$): 32, 82, 125, 128, 129, 130, 165	41	Exact mass(M^+): calcd. = 162.0681, found 162.0675
3b	(KBr): 3200(b), 1680(sb)	($CDCl_3$): 2.5(s) 3H, 2.9(t) 2H, 3.3(t) 2H, 7.4(m) 2H, 7.9(m) 2H, 9.9(s) 1H	83	122–125
4b	(KBr): 3200(b), 1690(s)	($CDCl_3$): 1.9(m) 2H, 2.3(s) 3H, 2.4(t) 2H, 2.6(t) 2H, 7.1(s) 4H, 11.3(s) 1H	—	52–55 (lit. 57–48)[20]
10b	(CCl_4): 3005(m), 1780(s)	($CDCl_3$): 2.3(m) 2H, 2.6(t) 3H, 5.5(t) 1H, 7.2(s) 4H 13C($CDCl_3$): 21, 29, 30, 81, 125, 126, 128, 129, 165	51	62–64 Exact mass(M^+):calcd. 176.0837, found 176.0836
3c	(KBr): 3200(b), 1700(s)	($CDCl_3$): 2.7(t) 2H, 3.2(t) 2H, 3.8(s) 3H, 6.9(d) 2H, 7.9(d) 2H	82	144–152 (lit. 148–150)[21]
4c	(KBr): 3200(b), 1700(s)	($CDC1_3$): 1.9(t) 2H, 2.3(m) 2H, 2.6(m) 2H, 3.8(s) 3H, 7.0(m) 4H	71	56–58 (lit. 56–59)[21]
10c	(neat): 3010(m), 1765(s)	($CDCl_3$): 2.5(m) 4H, 5.4(t) 1h, 7.3(m) 4H, 8.7(s) 1H 13C($CDC1_3$): 29, 30, 81, 126, 128, 176	84	Exact mass: (M^+): calcd. 178.0630, found 178.0627
3d	(KBr): 3200(b), 1680(sb)	($CDCl_3$): 2.3(s) 3H, 2.5(s) 3H, 2.7(t) 2H, 3.1(t) 2H, 7.0(s) 2H, 7.6(m) 1H, 11.3(s) 1H	85	100–102
4d	(KBr): 3200(b), 1685(s)	($CDCl_3$): 2(m) 2H, 2.5(s) 6H, 2.8(t) 2H, 5.8(t) 1H, 7.2(m) 3H	82	62–66

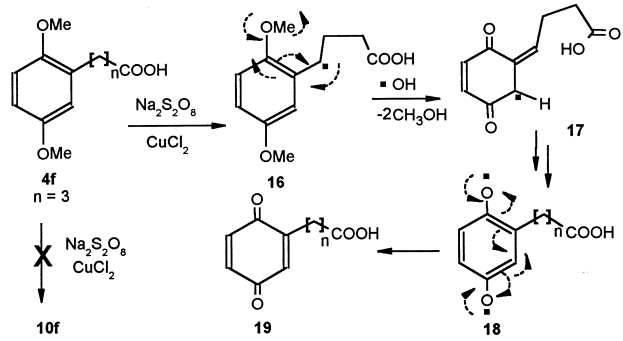
(*continued*)

Table 2. Continued

Entry	IR cm^{-1}	^1H & ^{13}C NMR δ	Yield (%)	M.p.°C & MS
10d	(CCl_4): 3000(m), 1775(s)	($CDCl_3$): 2.5(m) 4H, 5.4(t) 1H, 7.3(s) 5H, 13C ($CDCl_3$): 32, 82, 125, 128, 129, 130, 165	25	Exact mass(M^+): calcd. 190.0994, found 190.0992
3e	(KBr): 3200(b), 1680(sb)	($CDCl_3$): 2.8(t) 2H, 3.3 (t) 2H, 7.5(m) 7H, 8(m) 2H	62	180–182
4e	(KBr): 3200(b), 1680(s)	($CDCl_3$): 1.9(m) 2H, 2.3(s) 3H, 2.4(t) 2H, 2.6(t) 2H, 7.1(s) 4H, 11.3(s) 1H	80	115–118
10e	(CCl_4): 3005(m), 1785(s)	($CDCl_3$): 2.5(m) 4H, 5.5(t) 1H, 7.5(m) 9H	35	Exact mass: (M^+) calcd. 238.0996, found 238.0989
3f	(KBr): 3200(b), 1700(s)	($CDCl_3$) :2.8(t) 2H, 3.4(t) 2H, 3.8(s) 3H, 3.9(s) 3H, 7.0(m) 2H, 7.3(m) 1H, 8.8(s) 1H	88	100–102 (lit. 102)[22]
4f	(KBr): 3200(b), 1700(s)	($CDCl_3$): 1.9(m) 2H, 2.4(t) 2H, 2.6(t) 2H, 3.8(s) 6H, 6.7(s) 2H, 7.2(s) 1H	56	64–68 (lit. 68–69)[22]
19	(CCl_4): 3000(b), 1700(s)	($CDCl_3$): 2(m) 2H, 2.5(t) 2H, 2.8(t) 2H, 6.8(m) 3H, 9(s) 1H	—	Exact mass: (M^+) calcd. 194.0595, found, 194.0592
13a	(neat): 3010(s), 3015(s), 1736(s)	($CDCl_3$): 3.7(s) 2H, 5.11(s) 2H, 7.3(m) 10H	—	Exact mass: (M^+) calcd. 226.0994, found, 226.0989



Scheme 3.



Scheme 4.

EXPERIMENTAL

General

Yields refer to isolated pure center cut from column chromatography or scratched from preparative TLC. Products were characterized by comparison with authentic samples (IR, NMR, GC, TLC, and m.p.). Melting points are uncorrected and determined by Metller Fp5 melting point apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker spectrometer, generally with TMS as internal standard. The IR spectra were recorded with a Shimadzu model 470. The high-resolution mass spectra were obtained from a Fisons Trio-1000 instrument.

Synthesis of 4-Phenyl-4-oxobutanoic Acids 3a: A Typical Procedure

Twenty mL (17.5 g, 0.225 mol) benzene (Na-dried and free of thiophene) and 3.4 g (0.034 mol) succinic anhydride were combined in a 100-mL flask equipped with a reflux condenser connected through a Y-junction to a single efficient gas absorption device. The succinic anhydride dissolved in the benzene, 10 g (0.075 mol) of powdered anhydrous aluminum chloride was added and stirred in the mixture solution. The reaction started immediately; HCl evolved and the mixture became hot. The resulting mixture was then allowed to warm up at room temperature and then again allowed to warm up for 30 m at gentle reflux. The solution was cooled in cold water. Then 15 mL water and 5 mL conc. HCl were added. Excess benzene was removed by steam distillation. The residue was cooled and filtered on a Buchner funnel and washed with 10 mL (1:3) dilute HCl and

1 mL H_2O. The crystals were boiled in Na_2CO_3 (4 g in 25 mL H_2O) for 15 m. The filtrate was cooled and acidified by conc. HCl at 0°C, 5.4 g (90%) crystals m.p. 114°–116°C (lit.,[19] 115°C) was separated. The IR and NMR were recorded and shown in Table 2.

Preparation of 4-Phenyl Butanoic Acids 4a: A Typical Procedure

Zn powder (4.3 g), 0.43 g (1.58 mmol) mercury (II) chloride, 0.2 mL conc. HCl, and 5.5 mL 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 a reflux condenser, 2.7 mL water, 0.65 mL conc. HCl, 3.6 mL toluene(as solvent) and 1.8 g (0.01 mol) 4-phenyl-4-oxobutanoic acid **3a** were combined. The flask was refluxed vigorously for 30 h. During this period, 1.8 mL conc. HCl was added to the flask at approximately 6-h intervals during the refluxing period to maintain the conc. of HCl. After cooling, two layers were seperated water (7.2 mL) was added to the aqueous layer, and was extracted with 3×30 mL ether. The extracted layer was added to toluene, washed with water, and dried over $MgSO_4$. The solvent was evaporated and the residue was distilled 185°C $_{20\,mmHg}$ (1.49 g, 89%), (m.p. 47°–48°C, lit.[20] 47°–48°C). The IR and NMR spectra were recorded (Table 2).

Preparation of 5-Phenyl-γ-butyrolactone 10a: A Typical Procedure

4-Phenyl butanoic acid **4a** (4.92 g, 30 mmol), 27 mL water, and 5.1 g (30 mmol) copper (II) chloride $2H_2O$ were combined in a 250-mL, two-neck, round-bottom flask equipped with a reflux condenser and an additional

Table 3. Red. Condition for Conversion of Keto Acids to 4-Aryl Acids

Keto Acids	Reagent & Method	Time of Red. (h)	Yield (%)	Aryl Acid
3a	amalgamated zinc[16]	30	89	**4a**
3b	amalgamated zinc[16]	45	—	**4b**
3c	amalgamated zinc[16]	40	71	**4c**
3d	amalgamated zinc[16]	42	82	**4d**
3e	amalgamated zinc[16]	40	80	**4e**
3f	NH2-NH2, KOH[17]	7	56	**4f**

funnel. A solution of 8.5 g (30 mmol) $Na_2S_2O_8$ and 15 mL water was 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 m, and the flask was refluxed for 3.5 h. After this time, the reaction was stopped. The flask was cooled and extracted with 3×30 mL ether and dried with $MgSO_4$. The solvent was removed and 2 g (41%) of **10a** was collected as a pure center cut from silica gel column chromatography. The solvent system used was 5–10% EtOAc:ligroin. The IR, ^1H, ^{13}CNMR spectra and Exact mass (M^+) were recorded (Table 2).

Synthesis of 4-(4-Methoxyphenyl)-4-oxobutanoic Acid 3c

Nitrobenzene (60 mL redistilled and dried) as a solvent and 2.5 g (0.025 mol) succinic anhydride were combined in a 250-mL, 2-neck, round-bottom flask equipped with a reflux condenser connected through a y-junction to a single efficient gas absorption device and an additional funnel. Then 6.67 g (0.05 mol) anhydrous $AlCl_3$ powder and 15 mL nitrobenzene (redistilled) from the additional funnel dropwise was added to the solution during 45 m. The resulting mixture was then stirred at room temperature for an additional 6 h. After this time, the reaction mixture was transferred to the solution of 300 mL HCl (20%) and 200 g ice, stirred vigorously, and extracted with 4×30 mL ether. The ether layers were combined and washed with 3×30 mL water, and extracted with 5×30 mL conc. $NaHCO_3$. The aqueous layers were washed with 3×20 mL ether, and acidified with HCl. The white precipitate (3.4 g, 82% yield), m.p. 144°–152°C lit.[21] 148°–150°C. The IR, and NMR are recorded (Table 2)

Synthesis of 4-(4-Methoxy phenyl)butanoic Acid 4c

A similar procedure as used for **4a** was applied, but instead of reflux for 30 h, the solution was refluxed for a 40-h period and 1.8 mL conc. HCl was added to the flask at 8-h intervals.

Preparation of 5-(4-Hydroxy phenyl)-γ-butyrolactone 10c

A similar procedure for **10a** was used. The spectral data were recorded (Table 2).

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