

Utilizing 85% H₂SO₄ in One Pot Synthesis of 5-Mono- and 3,5-Disubstituted γ -Butyrolactones

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One pot synthesis of several 5-monosubstituted dihydro-furan-2-ones such as 5-ethyl-dihydro-furan-2-one (**1a**), 5-propyl-dihydro-furan-2-one (**1b**), 5-pentyl-dihydro-furan-2-one (**1c**) and 5-hexyl-dihydro-furan-2-one (**1d**) (with a strong to mild coconut fragrance) and several disubstituted dihydro-furan-2-ones such as 3-benzyl-5-propyl-dihydro-furan-2-one (**1e**), 3-benzyl-5-*n*-hexyl-furan-2-one (**1f**), 3-butyl-5-*n*-hexyl-furan-2-one (**1g**) and 3-buthyl-5-propyl-furan-2-one (**1h**) in the presence of 85% H₂SO₄ in 40–62% yields is described.

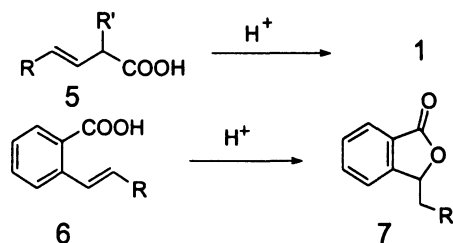
Key Words: Synthesis, 5-Mono- γ -butyrolactone, 3,5-Disubstituted- γ -butyrolactone, Dihydro-furan-2-one, 85% H₂SO₄.

INTRODUCTION

γ -Butyrolactones are important synthetic intermediates found in several natural products and have been synthesized by different methods^{1–4}. In addition, these ubiquitous compounds are valuable key synthetic intermediates⁵. Recently, the direct synthesis of dihydro-furan-2-ones with various aromatic substitutions at carbon five from corresponding aryl acids, mediated benzyl radical cyclization is reported^{6–8}.

The cyclization of alkanolic acids to γ - and δ -butyrolactones is a significant synthetic transformation⁹ most commonly effected by two-step processes involving either halolactonization¹⁰, selenolactonization-oxidation^{10d–f, 11} or sulfenolactonization-oxidation¹² etc.

When a carboxylic acid that contains a double bond in the β - γ or γ - δ chain is treated with a strong acid, the addition occurs internally and the product is a γ and/or δ -butyrolactone¹³. However, this type of conversion is commonly limited to the synthesis of mono-substituted γ -lactones and the yield of conversion is either very low or the reaction is not selective and contains 5- and 6-member ring lactones together with some isomerized α , β -unsaturated carboxylic acid by-product^{10f, 10g}. However, from the viewpoint of intramolecular cyclization, the favourable rigid geometrical structure for *o*-arylenic acid (**6**) is always in approving participation conformation in comparison to flexible molecular structure of enolic acid (**5**)^{14–18} (Scheme-I).

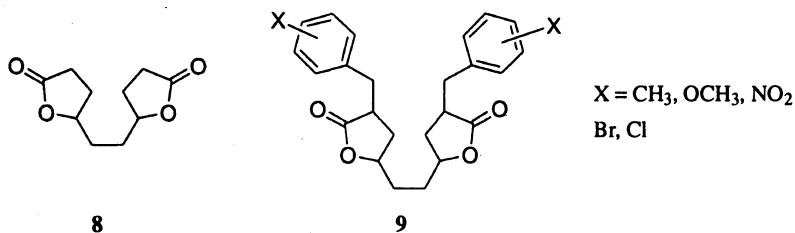


Scheme-I

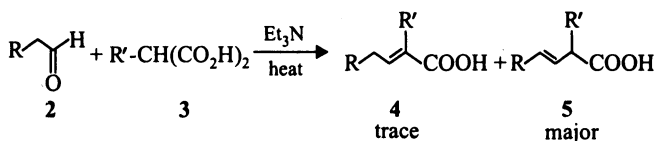
RESULTS AND DISCUSSION

The aim of this study is to convert several pre-made β -enoic acids such as **5**, in one pot and in the presence of bulky base such as triethylamine (TEA) and strong acid, for instance, 85% H_2SO_4 from mild to high yields and to monitor the conversion to exclusively 5-member mono- and 3,5-disubstituted- γ -lactone rings (Schemes I and III).

Although several methods have been reported for the preparation of mono-substituted butyrolactone such as (**1a-d**)^{6, 10f, 10g}, here a very simple and easy one pot procedure on the preparation of 3,5-disubstituted γ -butyrolactones such as (**1e-h**) is reported. With the best of our knowledge, almost no communication on the synthesis of symmetrical bis-lactones such as (**8**) and (**9**) was reported¹⁹ (Scheme-II).



Scheme-II



R) a = Et, b = *n*-pr, c = *n*-Bu, d = *n*-pentyl, e = hexyl

R') a = H, b = benzyl, c = *n*-butyl

a = $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{Et}$

b = $\text{R}_1 = \text{H}$, $\text{R}_2 = n\text{-Pr}$

c = $\text{R}_1 = \text{H}$, $\text{R}_2 = n\text{-Pen}$

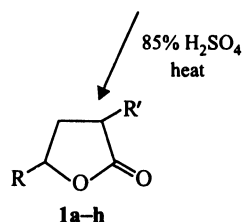
d = $\text{R}_1 = \text{H}$, $\text{R}_2 = n\text{-Hex}$

e = $\text{R}_1 = \text{Bez}$, $\text{R}_2 = n\text{-Pr}$

f = $\text{R}_1 = \text{Bez}$, $\text{R}_2 = n\text{-Hex}$

g = $\text{R}_1 = n\text{-Bu}$, $\text{R}_2 = n\text{-Hex}$

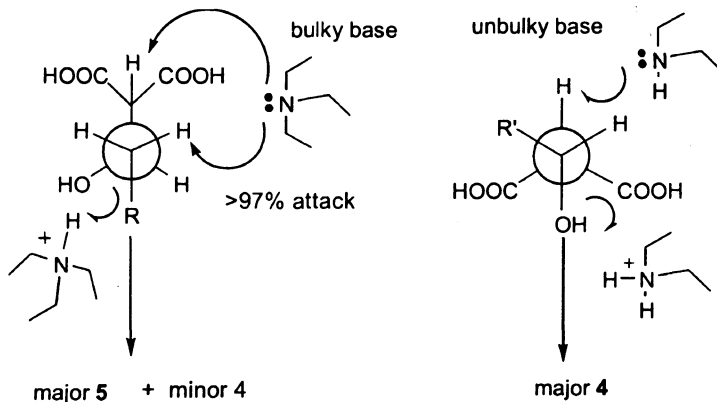
h = $\text{R}_1 = n\text{-Bu}$, $\text{R}_2 = n\text{-Pr}$



Scheme-III

The object of this research is (a) to consider the yield and synthesis of homologous dihydro-furone-2-ones by alternating the size of carbon chain substitution at 5-position of dihydrofuran-2-one ring from precursor (5) in one pot, (b) synthesis of several 3,5-disubstituted dihydro-furan-2-ones utilizing this method. The conclusion based on the yield of mono-substituted dihydro-furan-2-ones (1a-d), clarified that as the number of carbon chains at 5-position decreases, the yield of the products also decreases. Presumably this was due to the unstabilized carbocation or unfavourable entropy of cyclization. The systematic procedure to follow this synthesis is outlined briefly as shown in **Scheme-III**.

Suitable aldehydes were added to the appropriate malonic acid or substituted malonic acids in the presence of a tertiary and bulky base such as TEA and the solution was refluxed on a steam bath. After heating, the β , γ -unsaturated major acid (5) together with a trace of α , β -unsaturated acid (4) was produced (**Scheme-III**). The regioselective formation of unsaturated (5) typically involves anti-elimination: in the transition state the less acidic proton and the leaving group are located in the *anti-relationship*, as compared to the Newman projection (**Scheme-IV**) to the *anti* position. The bulky base such as TEA by E2 mechanism pulls (the less hindered hydrogen) the one which in this case is a less acidic proton away from carbon, simultaneously. Unsaturated acids (4) as a minor product together with (5) as a major product (according to the GC and IR of the crude products 1710 and 1685 for (4) and (5), respectively) without further purification and in the presence of 85% sulfuric acid and in hot steam bath, were utilized for endo style intramolecular lactonization reaction. Separation of these fatty type unsaturated acids (4) and (5) is very difficult. However, acids (4) are prepared as shown in **Scheme-IV** as a trace, *ca.* 1–2%. Economically, many high impact chemicals are relatively expensive, which reflects the small market volume and the difficulties associated with manufacturing and handling such materials. However, high yield preparation of precursors (4) vs. (5) makes these materials more commercially available at a price which enables a flavourist or perfumer to “add value” to their formulation by its use. Physical properties of all synthesized compounds include odour and flavour is shown in Table-1.



Scheme-IV

TABLE-1
 PHYSICAL PROPERTIES OF 5-MONO AND 3,5-DISUBSTITUTED
 DIHYDRO-FURAN-2-ONES

Compd. No.	R ₁	R ₂	IR CM ⁻¹	¹ H NMR δ ppm CDCl ₃	MS exact mass	Yield (%)	Smell
1a	H	Et	Neat: 2950–2850 (vs) 1766 (vs) 1180 (ss)	4.2 (q, 1H), 2.2 (t, 2H), 1.4 (m, 4H), 0.7 (t, 3H)	Exact mass (M ⁺): calcd.: 114.0680, found: 114.0683	40	vs ^a
1b	H	<i>n</i> -Pr	Neat: 2950–2850 (s), 1770 (s), 1180 (s)	4.5 (q, 1H), 2.5 (t, 2H), 1.7 (m, 6H), 1.1 (t, 3H)	Exact mass (M ⁺): calcd.: 128.0837, found: 128.0840	51.25	s ^b
1c	H	<i>n</i> -Pen	Neat: 2950 (s), 1770 (s), 1180 (s)	4.1 (q, 1H), 2.1 (t, 2H), 0.93 (m, 10H), 0.5 (t, 3H)	Exact mass (M ⁺): calcd.: 156.1150, found: 156.1154	58.5	ns ^c
1d	H	<i>n</i> -Hex	Neat: 2950–2850 (vs), 1770 (vs), 1350 (w)	4.1 (q, 1H), 1.9 (m, 2H), 1.1 (m, 12H), 0.47 (t, 3H)	Exact mass (M ⁺): calcd.: 170.1306, found: 170.1309	61.75	ms ^d
1e	benzyl	<i>n</i> -Pr	Neat: 3100–2850 (ss), 1780–1680 (ss, d), 1180 (s)	7.2 (s, 5H), 4.1 (q, 1H), 2–3 (m, 3H), 1.5 (m, 6H), 0.7 (t, 3H) ^e	Exact mass (M ⁺): calcd.: 218.1307, found: 218.1311	—	—
1f	benzyl	<i>n</i> -Hex	Neat: 3100–2850 (ss), 1760–1690 (ss), 1160 (w)	7.1 (s, 5H), 4 (q, 1H), 2–3 (m, 3H), 1.1 (m, 10H), 0.77 (t, 3H)	Exact mass (M ⁺): calcd.: 248.1776, found: 248.1780	45–50	—
1g	<i>n</i> -Bu	<i>n</i> -Hex	CHCl ₃ : 2950–2850 (s), 1770–1720 (ss), 1170 (s)	4.1 (q, 1H), 2.2 (q, 1H), 1.3 (m, 18H), 0.8 (t, 3H)	Exact mass (M ⁺): calcd.: 226.1932, found: 226.1934	51	—

a = very strong, b = strong c = natural smell, d = mild smell.

EXPERIMENTAL

All the starting materials used in this work were commercially available or prepared by standard literature procedures. Yields refer to isolated pure centre 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 Mettler Fp5 melting point apparatus. The ¹H and ¹³C NMR spectra were recorded on a Bruker AC, FT-NMR (80 MHz) in deuteriochloroform (CDCl₃) and CCl₄ with tetramethylsilane (TMS) as internal standard. The IR spectra were recorded with a

Shimadzu model 470. The mass spectra were recorded on a Finnigan Math spectrometer at 70 eV. Thin layer chromatography (TLC) was carried out on Merk-Kieselgel 60H ASTM 35–70.

Typical procedure for synthesis of 5-monosubstituted dihydro-furan-2-one: preparation of (5-pentyl-dihydro-furan-2-one (1c))

In a 125 mL flask malonic acid (5.2 g, 0.05 mol), heptanal (5.7 g, 0.05 mol) and triethylamine (TEA) (1.5 eq, 7.2 g, 0.072 mol) were combined. The resulting mixture was stirred at 80°C on a steam bath for 1 h. During this process CO₂ was evolved. The basic solution was neutralized with cooled HCl (solution of 8 mL 37% HCl and 25 g ice) and extracted with ether. Evaporation of ether led to 3-nonenic acid (major product) (**50**) and 2-nonenic acid (minor product) (**4**). To this mixture 85% conc. H₂SO₄ was added dropwise while thoroughly mixing. The colour of the solution changed to dark brown and mixed and heated on an 80°C steam bath for 1 h. The resulting solution was quenched by adding a solution of sodium carbonate (20 g Na₂CO₃ and 90 mL H₂O). The crude lactone was extracted with ether and dried with MgSO₄, filtered and the solvent was evaporated. The TLC of crude product displayed three spots. The crude material distilled at 130–135°C under 10 torr. The yield of pure 5-pentyl-dihydro-furan-2-one (**1c**) was 58.46%, ¹H NMR(CDCl₃) δ: 3.98 (q, 1H, J = 7.5 Hz), 2.05 (t, 2H, J = 7.5 Hz), 1.8 (t, 2H, J = 7.5 Hz), 1.6–0.7 (m, 8H), 0.5–0.3 (m, 3H); IR (neat): 2950 (s), 1770 (s), 1460 (s), 1350 (w), 1180 (s), 1020 (m), 920 (w), 800 (s), 730 (w), 650 (w) cm⁻¹. Exact mass (M⁺): calcd.: 156.1150; found: 156.1154.

Synthesis of 5-ethyl-dihydro-furan-2-one (1a)

A similar procedure as used for (**1c**) was applied. The crude material distilled at 105°C under 10 torr. The yield of pure (**1a**) was 1.2 g (40%), with a very strong smell of coconut. ¹H NMR (CDCl₃) δ: 4.35 (q, 1H, J = 7.5 Hz), 2.25 (t, 2H, J = 7.5 Hz), 1.95 (t, 2H, J = 7.5 Hz), 1.4–0.9 (m, 4H), 0.7 (t, 3H); IR (neat): 2950–2850 (vs), 1766 (vs), 1460 (s), 1350 (s), 1280 (w), 1180 (s), 970 (s), 900 (s), 850 (m), 650 (m) cm⁻¹. Exact mass (M⁺): calcd.: 114.0680; found: 114.0683.

Synthesis of 5-propyl-dihydro-furan-2-one (1b)

A similar procedure as used for (**1c**) was applied. The crude material distilled at 85–90°C under 10 torr. The yield of pure (**1b**) was 2 g (51.25%), with a strong smell of coconut. ¹H NMR (CDCl₃) δ: 4.5 (q, 1H, J = 7.5 Hz), 2.1 (t, 2H, J = 7.5 Hz), 1.9 (t, 2H, J = 7.5 Hz), 1.7 (m, 4H), 0.9 (t, 3H); IR (neat): 2950–2850 (s), 1770 (s), 1460 (s), 1360 (s), 1180 (s), 980 (m), 920 (m), 800 (w), 740 (w), 650 (w). Exact mass (M⁺): calcd.: 128.0837; found: 128.0840.

Synthesis of 5-hexyl-dihydro-furan-2-one (1d)

A similar procedure as used for (**1c**) was applied. The crude material distilled at 140–145°C under 5 mm Hg. The yield of pure (**1d**) was 3.5 g (61.17%), with a mild smell of coconut. ¹H NMR (CDCl₃) δ: 4.05 (q, 1H, J = 8 Hz), 2.05 (t, 2H, J = 8 Hz), 1.8 (t, 2H, J = 8 Hz), 1.6–0.6 (m, 10H), 0.47 (t, 3H, J = 8 Hz); IR (neat): 2950–2850 (vs), 1770 (vs), 1460 (s), 1350 (w), 650 (w) cm⁻¹. Exact mass (M⁺): calcd.: 170.1306; found: 170.1309.

Synthesis of 3-benzyl-5-*n*-hexyl-dihydro-furan-2-ones (1f)

In a 250 mL round bottom flask 1.94 g (0.01 mol) benzyl malonic acid and 1.41 g (0.014 mol) TEA (triethylamine) were combined and heated to 90°C on a steam bath while added to this dropwise during 30 min from additional funnel 1.44 g (0.01 mol) octanal (**2d**), the solution was refluxed for 2 h. The resulting basic solution was cooled and neutralized with cooled HCl solution (prepared by adding 2 mL HCl on 5 g ice), and extracted with 10 mL ether. The ether layer was washed with 10 mL H₂O, then the solvent was removed. To a resulting 2-benzyl-3-decenoic acid (**5**) (acid (**5**) prepared as a major compound with trace of (**4**) as minor compound) and 2 mL 85% H₂SO₄ was added. The colour of the solution changed to dark brown. The resulting solution was refluxed for 2 h and neutralized with sodium carbonate (prepared from 4 g Na₂CO₃ and 18 mL H₂O) and extracted with 10 mL ether. The ether solution was rinsed with 10 mL H₂O and dried over MgSO₄. The ether was removed. The TLC showed 3 spots. The desired lactone (**1f**) was separated from column chromatography (petroleum ether : EtOAc, 8 : 1 was used); 50% yield. ¹H NMR (CDCl₃) δ: 7.2–7 (m, 5H), 3.9 (q, 1H), 2.1 (t, 2H, J = 7.5 Hz), 2.45 (d, 2H, J = 7.5 Hz), 3–2.5 (m, 1H), 1.6–1.2 (m, 10H), 0.77 (t, 3H); IR (neat): 3100–2850 (s), 1760–1690 (s), 1460 (s), 1367 (m), 1160 (s), 742 (m), 700 (s) cm⁻¹ and ¹³C NMR (CDCl₃) δ: 13.7, 22.5, 25, 26.5, 29, 30, 32, 32.1, 32.5, 35, 36, 38.5, 65, 66, 126, 126.1, 128, 128, 5, 129, 130, 140, 171, 176.5 for the lactone 4 : 1 mixture. The ¹³C NMR as expected shows a relative complex pattern of doubling especially in the upfield region.

Synthesis of 3-Butyl-5-hexyl-dihydro-furan-2-one (1g)

In a 50 mL round bottom flask 1.6 g (0.01 mol) butyl malonic acid and 1.41 g (0.014 mol) TEA (triethylamine) were combined and heated to 90°C on a steam bath while added to this dropwise during 30 min from additional funnel 1.44 g (0.01 mol) octanal (**2d**). The solution was refluxed for 2 h. The resulting basic solution was cooled and neutralized with cooled HCl solution (prepared by adding 1.5 mL HCl on 5 g ice) and extracted with 10 mL ether. The ether layer was washed with 10 mL H₂O and then the solvent was removed. To a resulting 2-butyl-3-decenoic acid (**5**), 2 mL 85% H₂SO₄ was added. The colour of the solution changed to dark brown. The resulting solution was refluxed for 90 min. and neutralized with sodium carbonate (prepared from 4 g Na₂CO₃ and 18 mL H₂O) and extracted with 10 mL ether. The ether solution was rinsed with 10 mL H₂O and dried over MgSO₄. The ether was removed. The TLC showed some impurities. The desired lactone (**1g**) was separated from column chromatography (petroleum ether : EtOAc, 8 : 1 was used); 51% yield. IR (CHCl₃): 2950–2850 (s), 1770–1720 (s), 1460 (s), 1380 (m), 1170 (s), 1100 (w), 720 (w) cm⁻¹; ¹HNMR (CDCl₃) δ: 4 (q, 1H, J = 7.5 Hz), 2.2 (q, 1H J = 7.5 Hz), 1, 9–1.1 (m, 18H), 0.8 (m, 6H). Exact mass (M⁺): calcd.: 226.1932; found: 226.1934.

Synthesis of 3-benzyl-5-propyl-dihydro-furan-2-one (1e)

In a 50 mL round bottom flask 2.43 g (0.011 mol) benzyl malonic acid and 1.8 g (0.0178 mol) TEA (triethylamine) were combined and heated to 90°C on a steam bath while added to this dropwise during 30 min from additional funnel 1.1 g (0.011 mol) valeraldehyde (2c). The solution was refluxed for 2 h. The resulting basic solution was cooled and neutralized with cooled HCl solution (prepared by adding 2 mL HCl on 5 g ice), and extracted with 10 mL ether. The ether layer was washed with 10 mL H₂O and then the solvent was removed. To a resulting 2-benzyl-3-decenoic acid (5), 2 mL 85% H₂SO₄ was added. The colour of the solution changed to dark brown. The resulting solution was refluxed for 2 h and neutralized with sodium carbonate (prepared from 4 g Na₂CO₃ and 18 mL H₂O) and extracted with 10 mL ether. The ether solution was rinsed with 10 mL H₂O and dried over MgSO₄. The ether was removed. The TLC showed 3 spots. The desired lactone (1e) was separated by column chromatography (petroleum ether : EtOAc, 8 : 1 was used); 55% yield. IR (neat): 3100–2850 (s), 1760–1690 (s), 1460 (s), 1367 (m), 1160 (s), 742 (m), 700 (s) cm⁻¹; ¹H NMR (CDCl₃) δ: 7.2–7 (m, 5H), 4.1 (q, 1H, J = 9 Hz), 2.85 (d, 2H, J = 9 Hz), 2.6–2.4 (m, 1H), 2.25 (t, 2H J = 9 Hz), 2–1.1 (m, 4H), 1.1–0.7 (m, 3H). Exact mass (M⁺): calcd.: 218.1307; found: 218.1311.

Synthesis of 3-Butyl-5-propyl-furan-2-one (1h)

In a 50 mL round bottom flask 1.22 g (0.0076 mol) butyl malonic acid and 1.1 g (0.0108 mol) TEA (triethylamine) were combined and heated to 90°C on a steam bath while added to this dropwise during 20 min from additional funnel 0.656 g (0.0071 mol) valeraldehyde (2c); the solution was refluxed for 3 h. The resulting basic solution was cooled and neutralized with cooled HCl solution (prepared by adding 1.5 mL HCl on 5 g ice) and extracted with 10 mL ether. The ether layer was washed with 10 mL H₂O and then the solvent was removed. To a resulting solution 2 mL 85% H₂SO₄ was added. The colour of the solution changed to dark brown. The resulting solution was refluxed for 2 h and neutralized with sodium carbonate (prepared from 4 g Na₂CO₃ and 15 mL H₂O) and extracted with 20 mL ether. The ether solution was rinsed with 10 mL H₂O and dried over MgSO₄. The ether was removed. The TLC shows 2 spots. The desired lactone (1h) was separated by column chromatography (petroleum ether : EtOAc, 8 : 1 was used); 50% yield. IR (CCl₄): 2950–2850 (vs), 1770–1730 (s), 1465 (s), 1370 (m), 1170 (s), 1100 (w), 730 (w); ¹H NMR (CDCl₃) δ: 4.1 (q, 1H, J = 7.5 Hz), 2.2 (q, 1H, J = 7.5 Hz), 2 (m, 2H), 1, 9–1.1 (m, 10 H), 0.8 (m, 6H). Exact mass (M⁺): calcd.: 172.1464; found: 172.1467.

ACKNOWLEDGMENT

The authors would like to thank the Research Council of Guilan University for their financial support.

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