

## Peroxydisulphate-CuCl<sub>2</sub> Utilizing in the Preparation of 3,4-Dihydro-2H-[2,2]-bifuranyl-5-one

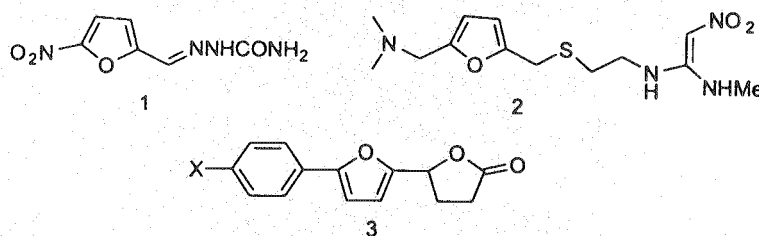
NOSRAT O. MAHMOODI\* and POUPAK DADVAR  
 Department of Chemistry, Organic Research Laboratory  
 University of Guilan, P.O. Box 14, Rasht, Iran  
 E-mail: mahmoodi@guilan.ac.ir

The preformed 4-(furan-2-yl) butyric acid (4) was converted in one pot to the corresponding 5-substituted  $\gamma$ -butyrolactone (8).

**Key Words:** Direct synthesis, Peroxydisulphate-CuCl<sub>2</sub>, 3,4-Dihydro-2H-[2,2]-bifuranyl-5-one.

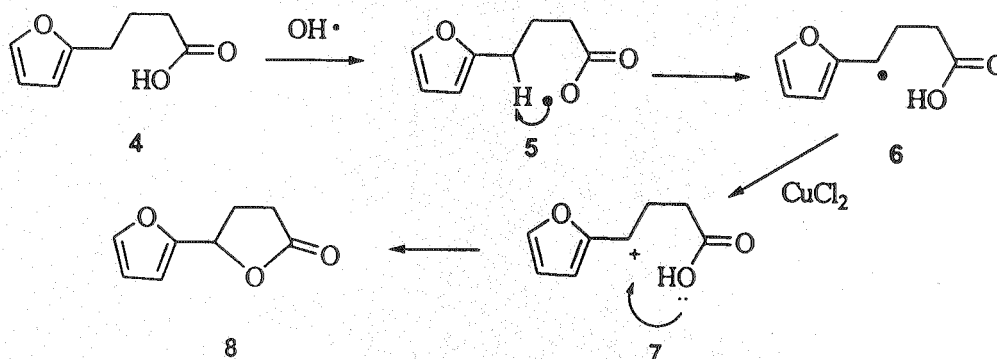
### INTRODUCTION

Furan derivatives are important in medicine, *e.g.*, nitrofurazone (1), a bactericide, ranitidine (2), the most commercially successful medicines used for the treatment of stomach ulcers<sup>1</sup>.



Scheme-1

Furolactones (3) ( $x = \text{Br}, \text{Cl}, \text{F}$ ) act as antiinflammatory agents as evidenced by their ability to inhibit edema induced by the administration of carrageenin<sup>2</sup> (Scheme-1). Recently, a general route for direct conversion of several 4-substituted aryl acids and *o*-alkyl aromatic carboxylic acids was reported<sup>3,4</sup>.

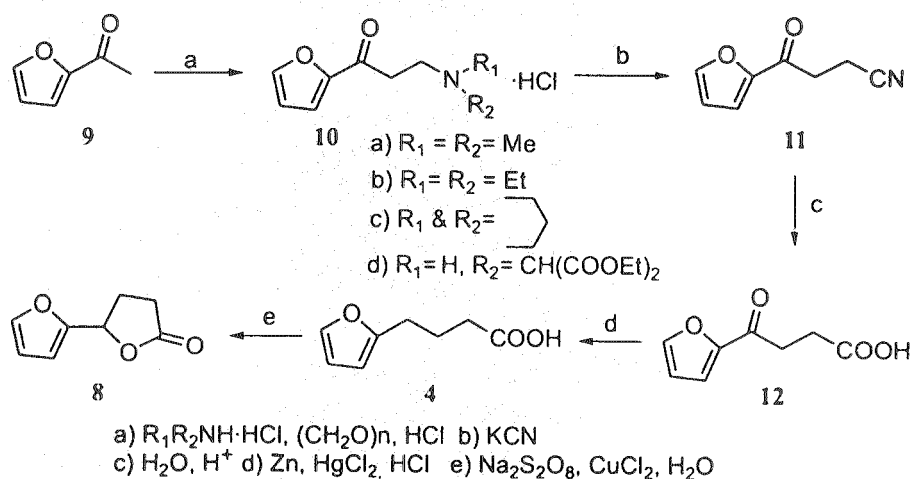


Scheme-2

In contribution to these methods, the preformed 4-furan-2-yl butyric acid (4) successfully leads to the synthesis of 5-substituted  $\gamma$ -butyrolactone (8) (Scheme-2).

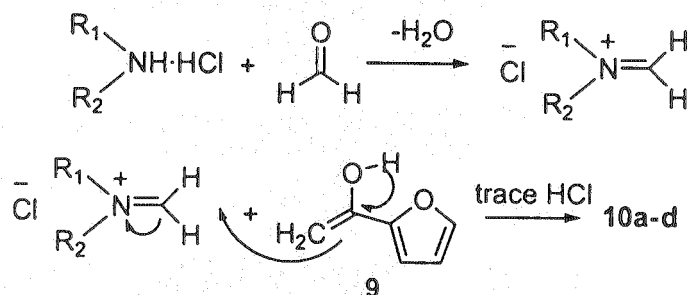
This reaction involves the *in situ* generation of oxy radical (5) followed by 1,5-H-atom transfer for preparation of radical (6) and the consequent oxidation of this radical to cation (7) in the presence of  $\text{CuCl}_2$  accomplished by intramolecular carbocation trapping to achieve the synthesis of (8) (Scheme-2).

The  $\beta$ -(dialkylamin)-1-(furan-2-yl)propan-1-one hydrochlorides (10a-d), obtained by the Mannich reaction, were converted to 4-furan-2-yl-4-oxobutyronitrile (11) by refluxing with aqueous potassium cyanide. The nitrile (11) on hydrolysis yielded 4-furan-2-yl-4-oxo-butyric acid (12). The synthesis of the butyrolactone (8) was completed after Clemmensen reduction of keto acid (12). This acid in the presence of an oxidative system such as  $\text{S}_2\text{O}_8^{2-}\text{-Cu}^{2+}$  led to the formation of corresponding  $\gamma$ -butyrolactone (8) (Scheme-3).



Scheme-3

The mechanism of the synthesis of Mannich salts (10a-d) is outlined in Scheme-4. The yields of (11) were calcd. 70, 60, 55 and 31%, from (10a), (10c), (10b) and (10d), respectively.



Scheme-4

## EXPERIMENTAL

Yields refer to isolated pure centre 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 Mettler FP5 melting point apparatus. IR spectra were obtained on a Shimadzu IR-470. All NMR data were recorded in  $\text{CDCl}_3$  on Bruker Avance 500 MHz spectrometer. Chemical shifts are reported in parts per million ( $\delta$ ) using TMS as internal reference. Elemental analysis was performed at the Research Center of National Oil Co. Solvent reagents and chemical materials were purchased from Merck and Fluka and were used without further purification. The salts of dimethylamine hydrochloride, piperidine hydrochloride, diethylamine hydrochloride were prepared in the laboratory.

#### Preparation of 3-dimethylamino-1-furan-2-yl-propan-1-one hydrochloride acid (10a)

To a 100 mL round bottom flask equipped with a reflux condenser was added 4 g (30 mmol) 1-furan-2-yl-ethanone (**9**), 2.037 g (24 mmol) diethylamino hydrochloride acid, 0.844 g (28 mmol) paraformaldehyde, 60 mL absolute ethanol and 2 drops of conc. HCl. The condenser was connected through a  $\text{CaCl}_2$  tube. The resulting solution was stirred and allowed to reflux for 10 min. After this time one drop HCl and 0.422 g (14 mmol) paraformaldehyde were added. The resulting solution was stirred and allowed to reflux at  $100^\circ\text{C}$  for 4 h. The separated solid was recrystallized from  $\text{H}_2\text{O}$  and washed with dry and cooled acetone. Yield = 5.173 g (70%), m.p. =  $178^\circ\text{C}$ . IR (KBr,  $\text{cm}^{-1}$ ): 3100 (w), tertiary amine stretch, 2800 (w), 2550 (s),  $\text{C}=\text{O}$  1660 (s), 1620 (s), 1480 (m), 1200 (m), 1000 (m).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\text{D}_2\text{O}$ ):  $\delta$ : 2.8 (s, 6H), 3.4 (m, 4H), 6.6 (s, 1H), 7.4 (s, 1H), 7.2 (s, 1H).

#### Preparation of 3-diethylamino-1-furan-2-yl-propan-1-one hydrochloride acid (10b)

A similar procedure as used for (**10a**) was applied, but instead of reflux for 4 h, the solution was refluxed for 6 h. Yield = 2.312 g (55%), m.p. =  $237^\circ\text{C}$ , IR (KBr,  $\text{cm}^{-1}$ ): 3200 (m), 2950 (s), tertiary amine stretch, 2800 (s), 1620 (w),  $\text{C}=\text{O}$  1660 (s), 1460 (m), 1200 (m), 800 (m).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\text{D}_2\text{O}$ ):  $\delta$ : 1.53 (t, 6H  $J = 7.5$  Hz), 3.19 (t, 2H,  $J = 6.5$ ), 3.3 (q, 4H  $J = 6.5$  Hz), 3.47 (t, 2H  $J = 6.5$  Hz), 6.57 (s, 1H), 7.13 (s, 1H), 7.21 (s, 1H).

#### Preparation of 1-furan-2-yl-3-piperidin-1-yl-propan-1-one hydrochloride acid (10c)

A similar procedure as used for (**10a**) was applied, but instead of reflux for 4 h, the solution was refluxed for 5 h. Yield = 2.65 g (60%), m.p. =  $250^\circ\text{C}$ , IR (KBr,  $\text{cm}^{-1}$ ): 3200 (m), tertiary amine stretch, 2800 (s), 2500 (m), 1640 (w),  $\text{C}=\text{O}$  1660 (s), 1460 (m), 1200 (m), 800 (w).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\text{D}_2\text{O}$ ):  $\delta$ : 1.29–1.73 (m, 6H), 3.18–3.43 (m, 8H), 6.6 (s, 1H), 7.22 (s, 1H), 7.43 (s, 1H).

#### Preparation of 2-(3-furan-2-yl-3-oxo-propylamino) malonic acid diethyl ester hydrochloric acid (10d)

A similar procedure as used for (**10a**) was applied, but instead of reflux for 4 h, the solution was refluxed for 6 h. The separated solid was recrystallized from  $\text{H}_2\text{O}$  and washed with dry and cooled acetone. Yield = 1.19 g (31%), m.p. =  $250^\circ\text{C}$ ,

IR (KBr,  $\text{cm}^{-1}$ ):  $\nu(\text{NH})$  3000 (w),  $\nu(\text{C}=\text{O})$  1740 (s), 1660 (m), NH bend 1460 (m), 1200 (m), 1100.  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ,  $\text{D}_2\text{O}$ ):  $\delta$ : 1.4 (t, 6H  $J = 7.5$  Hz), 3.46 (t, 2H  $J = 6.5$  Hz), 3.56 (t, 2H  $J = 6.5$  Hz), 4.12 (q, 4H  $J = 7.5$  Hz), 5.24 (m, 1H), 6.59 (s, 1H), 7.17 (s, 1H), 7.28 (s, 1H).

#### Preparation of 4-furan-2-yl-4-oxo-butyronitrile (11)

To a 100 mL round bottom flask equipped with a reflux condenser was added 2.2 g (10 mmol) 3-dimethylamino-1-furan-2-yl-propan-1-one (10a), 1.4 g (20 mmol) KCN and 60 mL of distilled water. The resulting solution was stirred and allowed to reflux in oil bath for 10 min. The clear orange liquor was cooled and extracted with chloroform ( $4 \times 25$  mL), dried over  $\text{Na}_2\text{S}_2\text{O}_4$ , filtered and evaporated. The remaining oil, recrystallized with hot petroleum ether, gave colourless needle crystals. Again crystallized several times from hot petroleum ether and washed with cooled ether. Yield = 0.95 g (59%), m.p. =  $76^\circ\text{C}$  (lit.  $74\text{--}76^\circ\text{C}$ )<sup>5</sup>. Anal. Found: C, 64.55; H, 4.65; N, 9.45;  $\text{C}_8\text{H}_7\text{O}_2\text{N}$  Calcd.: C, 64.5; H, 4.7; N, 9.4%. IR (KBr,  $\text{cm}^{-1}$ ): 3100 (w), 2200 (m),  $\nu(\text{C}=\text{O})$  1660 (s), 1460 (m), 1200 (m), 1400 (m).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.7 (m, 2H,  $J = 7.5$  Hz), 3.2 (m, 2H,  $J = 7.5$  Hz), 6.6 (s, 1H,  $J = 1.8$  Hz), 7.2 (s, 1H,  $J = 3.3$  Hz), 7.6 (s, 1H,  $J = 1$  Hz).

#### Preparation of 4-furan-2-yl-4-oxo-butyric acid (12)

To a 50 mL round bottom flask equipped with a reflux condenser was added 0.5 g (3 mmol) 4-furan-2-yl-4-oxo-butyronitrile (11) and 20 mL HCl 18%. The resulting solution was stirred and allowed to reflux for 3 h. The reaction mixture was diluted with 20 mL  $\text{H}_2\text{O}$  and few mg charcoal. The pale yellow solution was filtered and evaporated, extracted with ( $4 \times 10$  mL) chloroform and dried over  $\text{Na}_2\text{S}_2\text{O}_4$ . The chloroform layer was heated and diluted with 80 mL petroleum ether, gave almost colourless needle crystals. Yield = 0.507 (90%), m.p. =  $114\text{--}115^\circ\text{C}$  (lit.  $115^\circ\text{C}$ )<sup>5</sup>. Anal. Found: C, 57.20; H, 4.75; Calcd. for  $\text{C}_8\text{H}_8\text{O}_4$ : C, 57.15; H, 4.75%. IR (KBr,  $\text{cm}^{-1}$ ): 3000 (b), 2900 (w), 1690 (s), 1660 (s), 1460 (m), 1200 (m).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ ):  $\delta$ : 2.8 (m, 2H,  $J = 6.7$  Hz), 3.2 (m, 2H,  $J = 6.7$  Hz), 6.5 (dd, 1H,  $J = 1.7$  Hz), 7.2 (d, 1H,  $J = 3.54$  Hz), 7.6 (s, 1H).

#### Preparation of 4-furan-2-yl-butyric acid (4)

4.3 g (66 mmol) Zn powder, 0.43 g (1.58 mmol) mercury(II) chloride, 0.2 mL conc. HCl and 5.5 mL distilled water were mixed 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, 0.3 mL toluene (as solvent) and 1.68 g (10 mmol) 4-furan-2-yl-4-oxo-butyric acid (12) were mixed. The flask was refluxed vigorously for 40 h. During this period 1.8 mL conc. HCl was added to the flask at *ca.* 8 h intervals during the refluxing period in order to maintain the concentration of HCl. After cooling two layers were separated, 7.2 mL water was added to the aqueous layer, and was extracted with ( $3 \times 10$  mL) ether; the extracted layer was added to toluene, washed with water and dried over

MgSO<sub>4</sub>. The solvent was evaporated to afford 1.17 g (76%) crystals. m.p. = 48–50°C. Anal. Calc. for C<sub>8</sub>H<sub>10</sub>O<sub>3</sub>: C, 62.3; H, 6.5%; Found: C, 62.4; H, 6.6. IR (KBr, cm<sup>-1</sup>):  $\nu$ (OH) 3100 (b), 2800 (m),  $\nu$ (C=O) acid 1690 (s),  $\nu$ (C=O) ketone 1660 (m), 1210 (m) <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$ ; 2.6 (q, 2H, J = 7 Hz), 2.7 (t, 2H, J = 7.2 Hz), 3.2 (m, 2H), 6.6 (dd, 1H, J = 1.74, 7.2 Hz), 7.2 (t, 1H, J = 3.3 Hz), 7.6 (d, 1H, J = 1.5 Hz), 8.4 (s, 1H).

#### Preparation of 3,4-dihydro-2H-[2,2]-bifuranyl-5-one (8)

0.45 g (3 mmol) 4-furan-2-yl-butyric acid (4), 13 mL distilled water and 0.51 g (3 mmol) copper(II) chloride were mixed in a 100 mL two-necked round bottom flask. The flask was equipped with a reflux condenser and an additional funnel. Solution of 0.85 g (3 mmol) Na<sub>2</sub>S<sub>2</sub>O<sub>8</sub> and 2 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 additional funnel was added dropwise to a flask during 40 min and the flask was refluxed for 3.5 h. After this time the reaction was stopped. The flask was cooled and extracted with (3  $\times$  3 mL) ether and dried with MgSO<sub>4</sub>. The solvent was removed and 0.24 g (52%) was collected as a pure center cut from preparative chromatography. Anal. Calc. for C<sub>8</sub>H<sub>10</sub>O<sub>3</sub>: C, 63.15; H, 5.26%; Found: C, 63.20; H, 5.20. IR (KBr, cm<sup>-1</sup>): 2900 (w),  $\nu$ (C=O) 1760 (s), 1460 (m), 1100 (m). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$ ; 2.3–2.39 (m, 4H), 5.8 (t, 1H, J = 7.5 Hz), 6.6 (s, 1H), 7.2 (s, 1H), 7.6 (s, 1H).

#### ACKNOWLEDGEMENT

The authors are grateful to the Research Council of Guilan University for financial support given to this study.

#### REFERENCES

1. J.A. Joule and K. Mills, *Heterocyclic Chemistry*, 4th Edn., Blackwell Science Ltd, p. 225 (1995).
2. Jr. Pelosi and S. Stanford, US Patent 4085118, Dec. 17 (1987).
3. N.O. Mahmoodi and M. Jazayri, *Synth. Commun.*, **10**, 1467 (2001).
4. N.O. Mahmoodi and M. Salehpour, *J. Heterocycl. Chem.*, **40**, 875 (2003).
5. E.B. Knott, *J. Chem. Soc.*, 1190 (1947).

(Received: 2 August 2005; Accepted: 3 March 2006)

AJC-4674