

---

---

## FRIEDEL-CRAFTS CYCLIZATION OF SUCCINIC HALF-ESTER DERIVATIVES

**Shar S. Al-Shihry**

Department of Chemistry, College of Education, King Faisal University,  
P.O. Box 1759, Hofuf 31982, Eastern Province, Saudi Arabia.

### **Abstract:**

A number of annelated cyclopentenone derivatives have been prepared, in high yields, starting from fulgenic half ester- acid chlorides. The preparation of a wide range of different types of cyclopentenone derivatives indicated that this reaction seems to be a good general procedure for making compounds of this kind. Irrespective of which half-ester acid chloride was used, the products were cyclopentenone derivatives and never cyclohexenone derivatives were obtained.

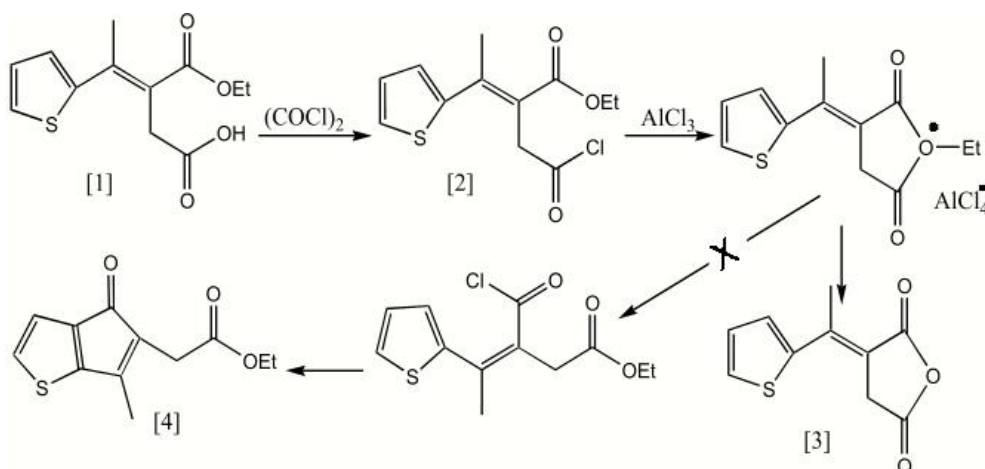
### **Introduction**

A variety of reagents have been used previously for the cyclization of related simple aromatic fulgenic acids, e.g., sulphuric acid<sup>1,2</sup>, hydrogen fluoride<sup>3</sup>, zinc chloride-acetic anhydride<sup>4</sup> aluminum chloride<sup>5</sup>, sodium acetate-acetic acid and acetic anhydride, zinc chloride<sup>6</sup>, and thionyl chloride<sup>7</sup>. The fulgenic half-ester was treated with oxalyl chloride, and indenone derivative was obtained in a low yield<sup>8</sup>. Forbes *et al.*<sup>9</sup> reported that an ester may be converted into the corresponding carboxylic acid in excellent yield by refluxing in benzene in the presence of aluminum chloride. This study describes a method for the synthesis of cyclopentenone derivatives, starting from the fulgenic half-ester and oxalyl chloride in the presence of anhydrous aluminum chloride at room temperature.

### **The cyclization of ethyl 2-thienylethylidenesuccinic half-ester acid chloride [2].**

Ethyl 2-thienylethylidenesuccinic half-ester [1]<sup>10</sup>, prepared via the Stobbe condensation between 2-acetylthiophene and diethyl succinate in the presence of potassium t-butoxide in toluene, was converted into the acid chloride [2] by reaction with oxalyl chloride in dichloromethane. Anhydrous

$\text{AlCl}_3$  was added at room temperature. On work up (E)-2-thienylethylidenesuccinic anhydride [3] was obtained and not the expected cyclopentenone derivative [4] (Scheme 1).



**Scheme 1.**

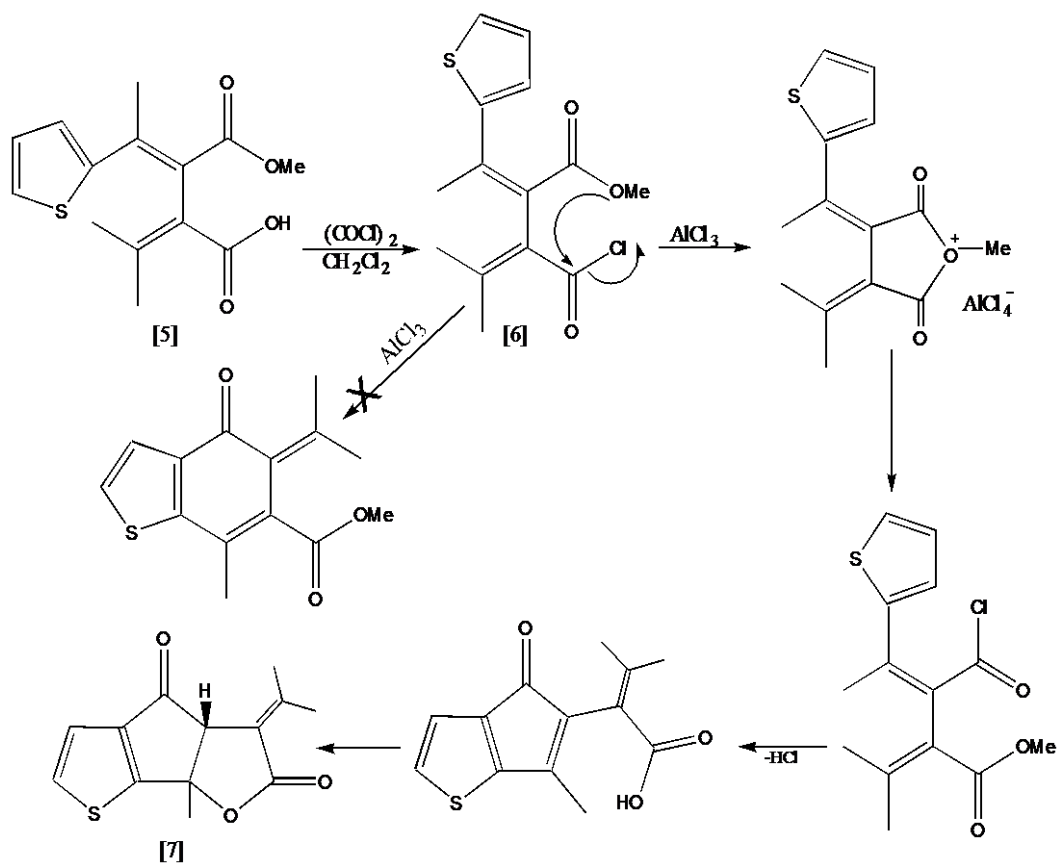
The mass spectrum of the anhydride [3] gave a molecular ion at  $m/z$  208 as the base peak.

The  $^1\text{H}$  nmr spectrum of anhydride [3] indicated the absence of the ethyl group and the presence of the three thienyl protons as two doublets and a multiplet at  $\lambda\delta$  7.68, 7.53 and 7.25 respectively, and that the Friedel Craft cyclization had not taken place. The cyclization gave the anhydride [3].

### **The cyclization of methyl isopropylidene(2-thienylethylidene)succinic half-ester acid chloride [6]**

Methyl isopropylidene(2-thienylethylidene)succinic half-ester [5], obtained *via* the Stobbe condensation of 2-acetylthiophene with dimethyl isopropylidenesuccinate in the presence of potassium *t*-butoxide in toluene, was treated with oxalyl chloride in dichloromethane at room temperature. A vigorous evolution of gas was observed and the solution turned from colourless to yellow. Anhydrous  $\text{AlCl}_3$  was added and the reaction mixture

turned red. On work up, the 5-(1-carboxy-2-isopropylidene)-6-methylthio[b]cyclopentan-4-one-6-lactone [7] was obtained as bright yellow crystals. The mechanism of this reaction can be considered as an intramolecular ester-exchange followed by cyclization. (Scheme 2).



Scheme 2.

The  $^1\text{H}$  nmr spectrum of the lactone [7] exhibits two doublets at  $\delta$  7.51 and 7.13 ( $J = 8\text{Hz}$ ) due to 2-H and 3-H thienyl protons. The 5-H proton is coupled with the two isopropylidene methyl groups. Finally, the structure of the lactone [7] was confirmed by X-ray crystallographic analysis (Figure 1).

### **The cyclization of ethyl isopropylidene(3-thienylethylidene)succinic half-ester acid chloride [9]**

Ethyl isopropylidene(3-thienylethylidene)succinic half-ester [8], prepared via the Stobbe condensation between diethyl isopropylidene succinate and 3-acetylthiophene, was treated with oxalyl chloride and anhydrous  $\text{AlCl}_3$  in dichloromethane. Work up the reaction mixture gave 5-(1-ethoxycarbonyl-2-isopropylidene)4-methylthio[b]cyclopenten-6-one [10] as red crystals (Scheme 3). The cyclohexanone derivative [12] could not be detected. The  $^1\text{H}$  nmr spectrum of product [10] shows the presence of the ethoxy group at  $\delta$  4.18 and clearly shows the loss of one proton of the thienyl group, indicating that the cyclization has taken place. The structure of the cyclopentenone derivative [10] was confirmed by X-ray crystallographic analysis (Figure 2).

5-(1-Carboxy-2-isopropylidene)-4-methylthio[b]cyclopenten-6-one-4-lactone [11] was obtained also from the above reaction. Its  $^1\text{H}$  nmr spectrum shows two doublets at  $\delta$  7.98 and 7.25 ( $J = 8\text{Hz}$ ) respectively, each one integrating for one proton and representing the protons at the 2- and 3-positions of the thienyl group. The triplet at  $\delta$  4.12 integrates for one proton and is assigned to the hydrogen at 5-position.

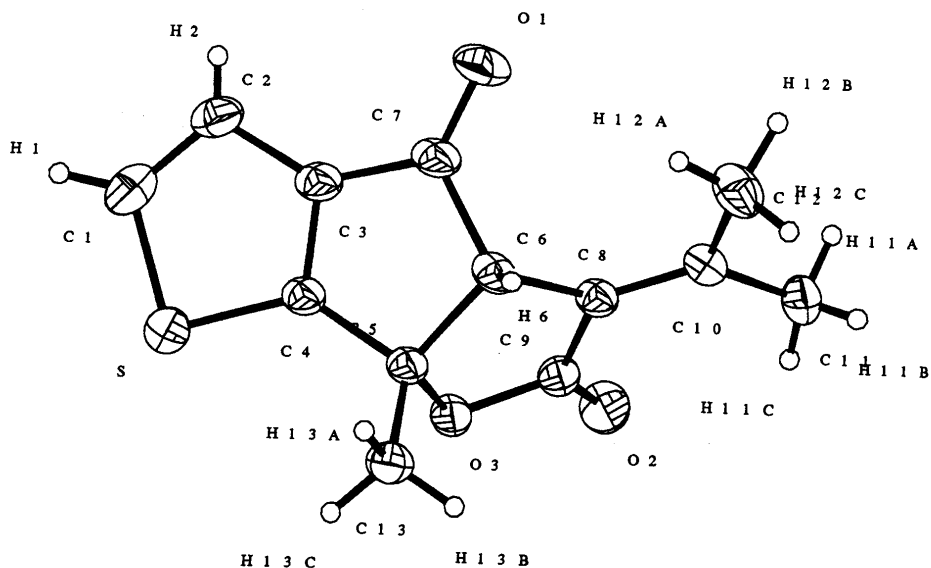
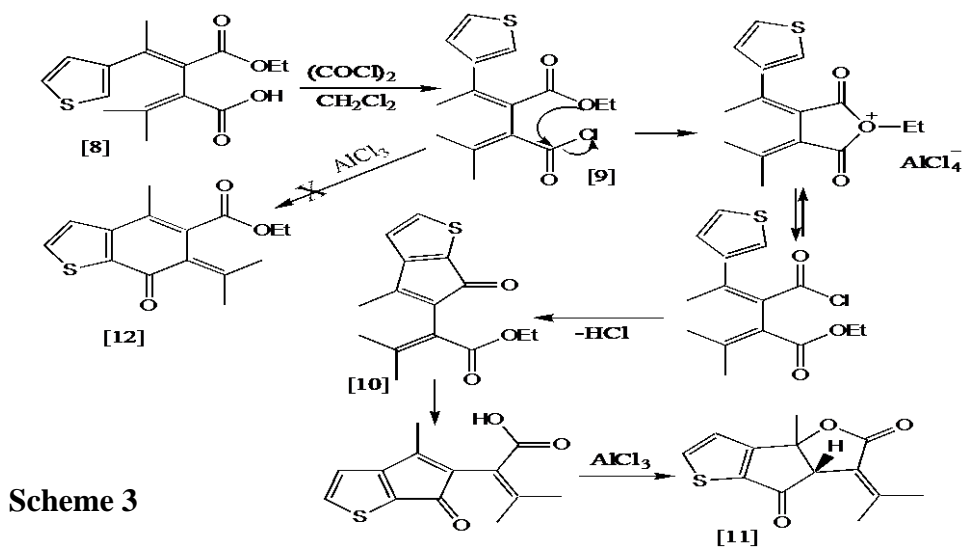
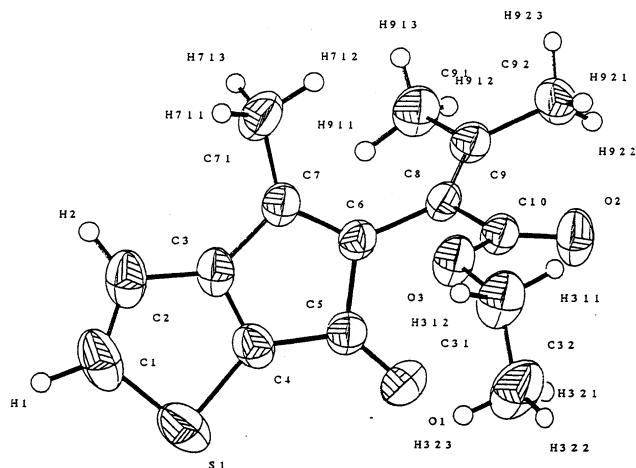


Figure (1) Molecular structure of lactone [7].



Scheme 3



**Figure (2)** Molecular structure of compound [10].

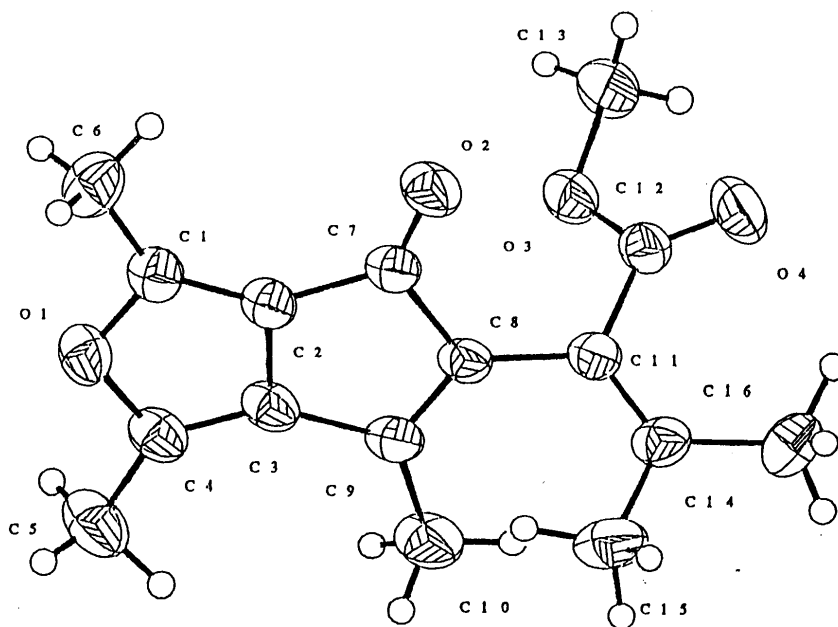
The two doublets at  $\delta$  2.34 and  $\delta$  2.30 (each integrates to three protons) are attributed to the methyl groups protons. A singlet at  $\delta$  1.82, integrating to three protons, is due to the methyl group. The  $^1\text{H}$  nmr spectrum of lactone [11], is similar to the  $^1\text{H}$  nmr spectrum of lactone [7], the structure of which was confirmed by X-ray crystallographic analysis (Figure 1).

**Cyclization of methyl isopropylidene(2,5-dimethyl-3 thienylethylidene) succinic half-ester acid chloride [14b].**

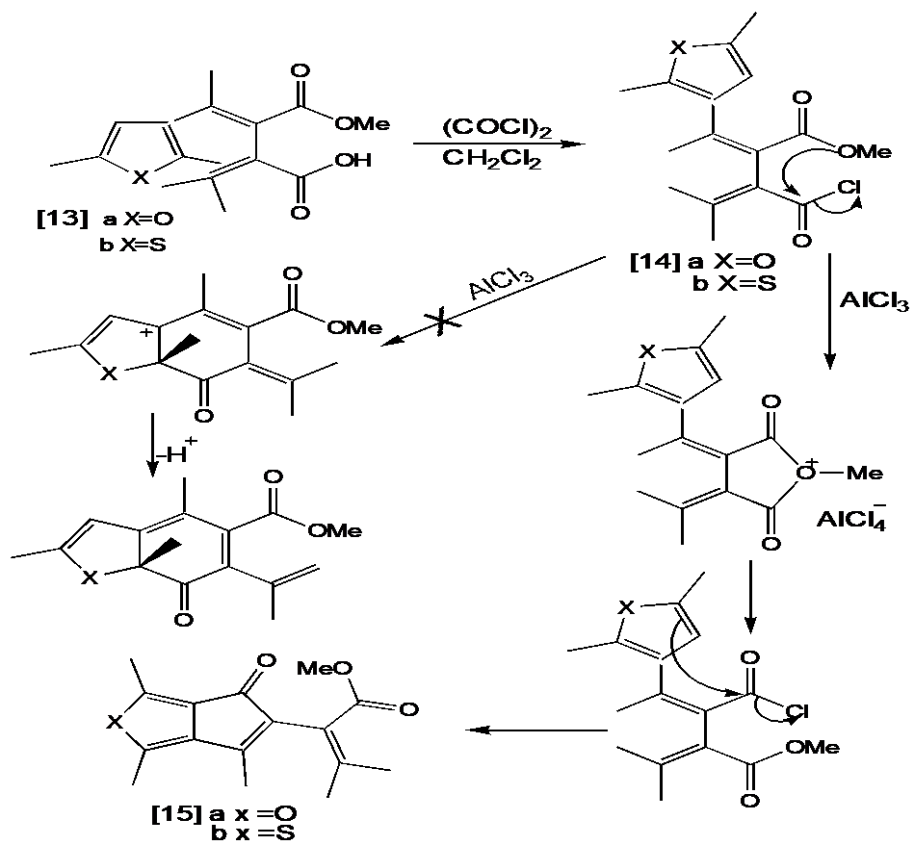
Methyl isopropylidene(2,5-dimethyl-3-thienylethylidene)succinic half-ester [13b], obtained via the Stobbe condensation between dimethyl isopropylidene succinate and 3-acetyl-2,5-dimethylthiophene in the presence of potassium t-butoxide in toluene, was treated with oxalyl chloride to give the corresponding acid chloride [14b]. Anhydrous  $\text{AlCl}_3$  was added. The product from the reaction was purified by column chromatography and crystallized to give the cyclopentenone derivative [15b] as fine yellow crystals from petroleum/ether in 46% yield (Scheme 4). The  $^1\text{H}$  nmr

spectrum of cyclopentenone derivative [15b] was very similar to the spectrum of compound [15a], the structure of which had been established by X-ray crystallographic analysis (Figure 3).

The  $^1\text{H}$  nmr spectrum of the cyclopentenone derivative [15b] indicates that the proton at 4-position of the thiophene group at  $\delta$  6.46 has been replaced, indicating that cyclization had taken place. It exhibits six singlets. The one at  $\delta$  3.66 is attributed to the methoxy group and the other five singlets at  $\delta$  2.48, 2.39, 2.25, 2.04 and 1.76 each integrating to the three protons, represent the five methyl groups. The mass spectrum shows a molecular ion at  $m/z$  209 as the base peak. The combustion analysis was consistent with the proposed structure.



**Figure (3)** Molecular structure of compound [15a].



Scheme 4

### Experimental

High resolution <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance spectra were recorded on a Bruker WM 360 (360MHz) pulsed Fourier transform spectrometer. Chemical shifts are quoted in units relative to tetramethylsilane(δ). Mass spectra (EI) were recorded on Varian Mat. CH5



spectrometer. Ultraviolet spectra were recorded on a Cecil CE6600 spectrophotometer for solutions in toluene.

Melting points were determined on a Reichert hot-stage microscope using a thermometer calibrated against standards of known melting-points. Microanalysis were obtained using a Hewlett Packard model 240B analyzer.

#### **Ethyl 2-thienylethylidenesuccinic half-ester [1]**

A mixture of diethyl succinate (17 g, 0.1mole), 2-acetylthiophene (12.6g, 0.1mole) and potassium *t*-butoxide (13g, 0.12mole) in toluene (150ml) was stirred overnight. After work up, ethyl 2-thienyl ethylidenesuccinic half-ester [1] (19g, 75% yield) was obtained as a brown oil.

#### **Methyl isopropylidene(2-thienylethylidene)succinic half-ester [5]**

A mixture of dimethyl isopropylidenesuccinate (37.2g, 0.2mole), 2-acetylthiophene (26g, 0.2mole) and potassium *t*-butoxide (23.5g, 0.21mole) in tetrahydrofuran (100ml) was stirred for 6 h. After work up, and crystallization from petrol/ether, methyl isopropylidene(2-thienylethylidene)succinic half-ester [5] (53g, 94% yield) was obtained as pale yellow crystals, m. p. 110-111°C, (Found: C, 60.09, H, 6.80, C<sub>14</sub>H<sub>16</sub>O<sub>4</sub> S, requires C, 60, H, 5.71%); <sup>1</sup>H n.m.r.(CDCl<sub>3</sub>): δ 7.32 (1H d, thienyl), 7.26 (1H,d,thienyl), 6.98 (1H, t, thienyl), 3.75 (3H, s, OCH<sub>3</sub>), 2.56, 2.22, 1.75 (9H, s, 3 x CH<sub>3</sub>).

#### **Ethyl isopropylidene(3-thienylethylidene)succinic half-ester [8]**

A mixture of diethyl isopropylidenesuccinate (21.4g, 0.1mole), 3-acetylthiophene (13 g, 0.1mole) and potassium *t*-butoxide (13.5 g, 0.12 mole) in toluene (100 ml) was stirred for 5 h. After work up, the crude product was crystallized from petrol/ether to give ethyl isopropylidene(3-thienyl-ethylidene)succinic half-ester [8] (18g, 61% yield) as pale yellow crystals, m. p. 118-120°C.



**Methyl isopropylidene(2,5-dimethyl-3-furylethylidene)succinic half-ester [13a]**

A mixture of dimethyl isopropylidenesuccinate (18.6g, 0.1mole), 3-acetyl-2,5-dimethylfuran (13.82g, 0.1mole) and potassium *t*-butoxide (13.44g, 0.12mole) in tetrahydrofuran (100ml) was stirred overnight. Work up gave a dark orange oil which was crystallized from petroleum and ether to give methyl isopropylidene (2,5-dimethyl-3-furylethylidene) succinic half-ester [13a] (23g, 79% yield), m. p. 126-128°C, (Found: C, 65.67, H, 6.93; C<sub>16</sub>H<sub>20</sub>O<sub>5</sub>, requires C, 65.75 ; H, 6.85%), <sup>1</sup>H n.m.r.(CDCl<sub>3</sub>): δ 6.89 (1H, s, furyl), 3.62 (3H, s, OMe), 2.26, 2.25, 2.14, 1.80, 1.72 (15H, s, 5 x CH<sub>3</sub>).

**Reaction of methyl isopropylidene(2-thienylethylidene) succinic half-ester [5] with oxalyl chloride in the presence of AlCl<sub>3</sub>**

A mixture of methyl isopropylidene (2-thienylethylidene) succinic half-ester [5] (1g, 3 mmoles) and oxalyl chloride (0.5 g, 4 mmoles) in dichloromethane (4 ml) was stirred for 30 min before AlCl<sub>3</sub> (0.23 g) was added. The reaction mixture was stirred for a further 10 h. Ethanol was added dropwise and solvent was removed. The crude product was extracted with ether, washed with water and dried over magnesium sulphate. The solvent was removed to leave the crude product which was crystallised from petrol and ether to give the lactone [7] ( 0.12 g) in 14% yield, as yellow cubic crystals, m. p. 165-167°C; Found: C, 63.38, H, 4.96; C<sub>13</sub>H<sub>12</sub>O<sub>3</sub>S requires C, 62.90, H, 4.84%; m/z , 248; <sup>1</sup>H nmr δ 7.51 (1H, d, 8Hz, thienyl), 7.13 (1H, d, 8Hz, thienyl), 4.12 (1H, t, -O=C-CH-), 2.34, 2.30 (6H, d, 7Hz, 2 x CH<sub>3</sub>), 1.88 (3H, s, CH<sub>3</sub>). The structure of the lactone [7] was determined by X-ray crystallography.

**Reaction of ethyl (2-thienyl) ethylidene succinate [1] with oxalyl chloride in the presence of AlCl<sub>3</sub>.**

AlCl<sub>3</sub> (0.27 g) was added to mixture of ethyl (2-thienylethylidene)succinate [1] (1 g, 4 mmoles) and oxalyl chloride (0.6 g, 5 mmoles) in dichloromethane (4 ml) and the reaction mixture was stirred 8 h.. Ethanol was added and the solvent was removed. The crude product was extracted with ether, washed with water and ether layer was dried over

magnesium sulphate. Solvent was removed and the product was crystallized from petroleum ether to give the anhydride [3] (.63 g) in 77% yield, as pale yellow crystals, m. p. 168-171°C; m/z = 208 as the base peak;  $^1\text{H}$  nmr,  $\delta$  7.68 (1H, d, 7Hz, thienyl), 7.53 (1H, d, 7H, thienyl), 7.25 (1H, t, 7Hz, thienyl), 3.82 (2H, s, -CH<sub>2</sub>), 2.86 (3H, s, CH<sub>3</sub>).

### **Cyclization of ethyl isopropylidene (3-thienylethylidene) succinic half-ester acid chloride [9]**

Oxalyl chloride (1g, 7 mmoles) was added to ethyl isopropylidene (3-thienylethylidene)- succinic half-ester [8] (2 g, 7 mmoles) in dichloromethane (8 ml). AlCl<sub>3</sub> (0.5 g) was added and the reaction mixture was stirred overnight. Ethanol was added dropwise. The solvent was removed to leave the oily crude product which was extracted into ether, washed with water and dried over magnesium sulphate. Ether was removed and the crude product was crystallised from petrol/ether or ethanol to give two different types of crystals. The cyclopentenone derivative [10] was obtained as red crystals (0.16g, 8%) and the lactone [11] was obtained (0.65g, 37%) as brown crystals from petroleum ether and ether, m. p. 245-247°C. Found: C, 62.97, H, 4.87. C<sub>13</sub>H<sub>12</sub>O<sub>3</sub>S. requires C, 62.90; H, 4.84%; m/z , 248;  $^1\text{H}$  nmr  $\delta$  7.98, 7.25 (2H, d, 7Hz, thienyl), 4.12 (1H, t, ), 2.34, 2.30, 1.82 (9H, d, 7Hz, 3 x CH<sub>3</sub>);  $^{13}\text{C}$  nmr  $\delta$  190.44, 167.66 (2 x s, 2 x C=O); 167.11, 158.10, 152.51 (3 x s, C=C and C-S) 141.75, 122.26 (2 x d, HC=CH); 118.11, 79.77 (2 x s, HC-C-C(Me)=O and HC-C-C(Me)=O); 62.63 (d, O=C-CH); 26.21, 24.29, 21.05 (3 x q, 3 x CH<sub>3</sub>).

Cyclopentenone derivative [10], m. p. 64-66°C, Found: C, 65.25; H, 5.83. C<sub>15</sub>H<sub>16</sub>O<sub>3</sub>S requires C, 65.22; H, 5.80%;  $^1\text{H}$  nmr  $\delta$  7.62, 6.87 (2H, d, Hz, thienyl), 4.18 (2H, q, 8Hz, CH<sub>2</sub>-ester), 2.24, 1.98, 1.82 (9H, s, CH<sub>3</sub>), 1.23 (3H, t, 8Hz, CH<sub>3</sub>-ester). The structure of the cyclopentenone derivative [10] was established by X-ray crystallographic analysis.

**Cyclization of methyl isopropylidene (2,5-dimethyl-3-furylethylidene) succinic half-ester acid chloride [14a]**

A mixture of methyl isopropylidene (2,5-dimethyl-3-furylethylidene) succinic half-ester [13a] (2g, 7 mmoles) and oxalyl chloride (1g, 8 mmoles) in dichloromethane (8 ml) was stirred for 30 min. before  $\text{AlCl}_3$  (0.5 g, 4 mmoles) was added. The reaction mixture was stirred for a further 10 h. Ethanol was added dropwise and solvent was removed and the crude product was extracted with ether, washed with water and dried over magnesium sulphate. The solvent was removed to leave the crude product which was purified by column chromatography, eluted by petrol and ether. The purified product was crystallised from ethanol to give the cyclopentenone derivative [15a] (0.5 g 26% yield) as brown crystals, m. p. 114-115°C; Found: C, 70.19, H, 6.53.  $\text{C}_{16}\text{H}_{18}\text{O}_4$  requires C, 70.07, H, 6.57 %;  $m/z = 274$ ;  $^1\text{H}$  nmr  $\delta$  3.65 (3H, s, O-CH<sub>3</sub>), 2.32, 2.29, 2.24, 2.02, 1.76 (15H, s, 5 x CH<sub>3</sub>). The structure of cyclopentenone derivative [15a] was determined by X-ray crystallography.

**Cyclization of methyl isopropylidene (2,5-dimethyl-3-thienylethylidene) succinic half-ester acid chloride [14b]**

Methyl isopropylidene (2,5-dimethyl-3-thienylethylidene) succinic half-ester [13b] (1g, 3 mmoles) and oxalyl chloride (0.4 g, 3 mmoles) in dichloromethane (4 ml) was stirred for 30 min. before  $\text{AlCl}_3$  (0.2 g, 1.6mmole) was added. The reaction mixture was then stirred for further 10 h. Ethanol was added dropwise and solvent was removed and the crude product was extracted with ether, washed with water and dried over magnesium sulphate. The solvent was removed to leave the crude product which was purified by column chromatography, eluted by petrol and ether. The purified product was crystallised from petrol and ether to give cyclopentenone derivative [15b] (0.4g, 46% yield) as yellow crystals, m. p. 108-109°C; Found: C, 66.22; H, 6.24.  $\text{C}_{16}\text{H}_{18}\text{O}_3\text{S}$ . requires C, 66.21; H, 6.21 %;  $m/z = 290$ ;  $^1\text{H}$  nmr  $\delta$  3.66 (3H, s, O-CH<sub>3</sub>), 2.48, 2.39, 2.25, 2.04, 1.76 (15H, s, 5 x CH<sub>3</sub>).;  $^{13}\text{C}$  nmr  $\delta$  188.7, 167.10 (2 x s, 2 x  $\text{C}=\text{O}$ ); 153.10, 152.70, 141.77, 141.27, 140.86, 134.96, 129.89, 119.60 (8 x s 4 x  $\text{C}=\text{C}$ ); 50.16, 24.85, 22.80, 14.60, 13.60, 13.20 (6 x q, OCH<sub>3</sub>, and 5 x CH<sub>3</sub>).

**Acknowledgment**

The author is grateful to Professor H. G. Heller, Professor M. B. Hursthouse, and Mr. D. Hughes of the University of Wales, Cardiff, for the X-ray analysis.

### References

1. E. B. Knott, *J. Chem. Soc.*, 1945, 189.
2. C. L. Hewett, *J. Chem. Soc.*, 1942, 585.
3. W. S. Johnson and A. Goldman, *J. Amer. Chem. Soc.*, 1944, 66, 1030.
4. W. S. Johnson and A. Goldman, *J. Amer. Chem. Soc.*, 1945, 67,430.
5. C. F. Koelsch and H. J. Richter *J. Org. Chem*, 1938, 3, 465.
6. W. S. Johnson and G. H. Daub, “*Organic reaction*” J. Wiley and Sons. Inc. 1951, **6**, 1,.
7. S. Marchalin and B. Decroix, *Heterocycles*, 1995, 41,689.
8. W. Johncock, Ph.D. thesis University of Wales, 1981.
9. I. T. Forbes, C.N. Johnson, and M. Thompson, *J. Chem. Soc. Perkin Trans 1*.1992, 1, 275.
10. A. P. Glaze, S. A. Harris, H. G. Heller, W. Johncock, S. N. Oliver, P. J. Strydom and J. Whittall, *J. Chem. Soc., Perkin Trans 1*, 1985, 957.

## تخليق فريدل - كرافتس لمشتقات الاسترات الأحادية لحمض السكسينيك

شار بن سعد الشهري  
قسم الكيمياء - كلية التربية  
جامعة الملك فيصل

### المخلص :

تم تحضير عدد من مشتقات البنزينون الحلقي، و بمحصول عال، بداية من مركبات الفولجينييك نصف- استر كلوريدات الحمض في وجود كلوريد الألومنيوم اللامائي.

و يمكن القول بعد تحضير عدد من مشتقات البنزينون الحلقي إمكانية استخدام هذا التفاعل كطريقة عامة لتحضير العديد من هذه المشتقات. و بغض النظر عن نوع نصف الاستر الذي يبدأ به التفاعل فإن الناتج دائماً يكون مشتق بنزينون حلقي ولم يتم الحصول على مشتق الهكسينون الحلقي.