# UNEXPECTED LACTONIZATION ACCOMPANYING ADDITION OF ETHYL ACETOACETATE TO CHALCONES DERIVED FROM 3-ACETYLTHIOPHENE

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Chalcone derivatives containing thiophene ring were prepared by the condensation of 3-acetylthiophene with aromatic aldehydes in excellent yields. The addition of ethyl acetoacetate to chalcone derivatives 3a-3h in the presence of solid NaOH in  $CH_2Cl_2$  resulted in the formation of the mixture of bicyclic lactone derivatives 5a-5h and 6-(ethoxy-carbonyl)cyclohexenone derivatives 6a-6h.

**Keywords**: Chalcone; Ethyl acetoacetate; Cyclization; Lactonization; Cyclohexenones; Lactones; Cycloaddition.

Chalcones and the corresponding heterocyclic analogs are valuable intermediates in organic synthesis<sup>1</sup> and exhibit a multitude of biological activities<sup>2</sup>. From a chemical point of view, an important feature of chalcones is the ability to act as activated unsaturated systems in conjugated addition reactions of carbanions in the presence of basic catalysts<sup>3</sup>. This type reaction may be exploited with the aim to obtain highly functionalized cyclohexene derivatives<sup>4</sup>, but commonly used for the preparation of 3,5-diaryl-6-(ethoxycarbonyl)cyclohexenones via Michael addition of ethyl acetoacetate. The mentioned cyclohexenones are efficient compounds in building spiro compounds<sup>5</sup> or intermediates in the synthesis of fused heterocycles such as benzoselenadiazoles, benzothiadiazoles<sup>6</sup>, benzopyrazoles and benzisoxazoles<sup>7</sup> or carbazole derivatives<sup>8</sup>. The Michael addition of 1,3-dicarbonyl compounds to chalcone, the catalyst plays a key role in directing the reaction to different final products. Weaker base catalysts such as Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, piperidine, quaternary ammonium hydroxide, tertiary amines have higher product selectivity, affording only Michael adduct. When Michael reaction was catalyzed by strong bases such as KF/Al<sub>2</sub>O<sub>3</sub>, NaOH, KOH, etc., **6**-type compounds were formed via further aldol condensation<sup>9,10</sup>.

### **RESULTS AND DISCUSSION**

This paper reports the synthesis of unexpected lactone derivatives **5a–5h** besides 6-ethoxycarbonylcyclohexenones **6a–6h** from the reaction of ethyl acetoacetate with chalcone **3a–3h** in the presence of NaOH at room temperature.

A similar lactones structure and spectral results have been previously obtained by Jung et al.<sup>11,12</sup> from the thermal cycloaddition of ketene dimethyl- or diethyl acetal with 2-oxo-2*H*-pyran-5-carboxylate derivatives.

The chalcone derivatives 3a-3h were synthesized according to our recently published reports<sup>13,14</sup> (Scheme 1). We recently performed the reaction of 3a-3h with ethyl acetoacetate in the presence of *t*-BuOK, and obtained the cyclohexenone derivatives 6a-6h as single products in excellent yield<sup>14</sup>. This study, solid NaOH was used instead of *t*-BuOK for the same reaction. The unexpected lactone derivatives 5a-5h were isolated as well as the cyclohexenone derivatives 6a-6h (Scheme 2, Table I). The compounds 5 and 6 were purificated by column chromatography on silica gel or preparative TLC using *n*-hexane/EtOAc as eluent.



Scheme 1

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TABLE I				
Synthesized	compounds	5a-5h	and	6a–6h

Reagent		Products		
3	5	m.p., yield (%)	6	m.p., yield (%)
H <sub>3</sub> CO	0 H <sub>3</sub> CO 5a	100–101 °C, 59		106–107 °C, 38
3a	o o o o o o o o o o o o o o o o o o o	viscous oil, 52	6b S	116–117 °C, 46
3b S	o fo	154–155 °C, 63		139–140 °C, 35
Br 3c	Br 5c S O O	viscous oil, 55		111–112 °C, 42
	CH <sub>3</sub> 5d 0 0 0 H <sub>3</sub> C 5e	viscous oil, 52	CH <sub>3</sub> CH O O H <sub>3</sub> C O Ge S	147–148 °C, 47
H <sub>3</sub> CO O S	H <sub>3</sub> CO O O O O O O O O O O O O O O O O O O	viscous oil, 46	O O OCH <sub>3</sub> S 6f	99–100 °C, 42
		viscous oil, 51		viscous oil, 45
	CI 5h	viscous oil, 41		145–146 °C, 51

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The structures of cyclohexenones **6a–6h** were determined by the spectral data and comparison with an authentic sample<sup>14,15</sup>. The structures of all new lactones **5a–5h** were corroborated through their IR, <sup>1</sup>H and <sup>13</sup>C NMR spectra and elemental analysis. The IR spectra of these compounds revealed two sharp strong absorption bands around 1682–1662 ( $v_{C=O}$  ketone) and 1739–1724 ( $v_{C=O}$  ester) cm<sup>-1</sup>. These absorption bands confirm the presence of the ester group and the carbonyl group, respectively. In the <sup>1</sup>H NMR spectra of compounds **5a–5h**, absence of the signal of the ethoxy group and lack of any signal in the olefinic region indicate the intramolecular lactonization. An addition to this, in <sup>13</sup>C NMR spectra of **5a–5h** the signal at  $\delta \sim$  74 ppm arising from C–O bond supports the lactone structure.

The formation mechanism of lactone derivatives 5a-5h explained Scheme 2. Michael addition of ethyl acetoacetate to chalcone 3 gives adducts 7 which is converted to carbanionic intermediate 8 by action of base. Intermediate 8 is transformed to 9 via intramolecular cyclization. While the intramolecular transesterification of intermediate 9 gives bicyclic lactone derivatives 5a-5h (Scheme 2a), the loss of H<sub>2</sub>O from the intermediate 9 gives cyclohexenones 6a-6h (Scheme 2b).



Scheme 2

In conclusion, the new bicyclolactones **5a–5h** were isolated besides cyclohexenone derivatives **6a–6h** from the reaction of chalcone derivatives **3a–3h** with ethyl acetoacetate (4) in the presence of solid NaOH in  $CH_2Cl_2$  under mild reaction conditions. We assume that the thiophene ring and the slow reaction in the presence of solid NaOH are essential for the formation of lactone derivatives.

#### EXPERIMENTAL

Melting points were measured on Electrothermal 9100 apparatus. IR spectra (KBr or liquid) were recorded on a Jasco FT/IR-430 spectrometer (v, cm<sup>-1</sup>). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance III instrument (400 MHz). As internal standards served TMS ( $\delta$  0.00) for <sup>1</sup>H NMR and CDCl<sub>3</sub> ( $\delta$  77.0) for <sup>13</sup>C NMR spectroscopy ( $\delta$ , ppm; *J*, Hz). The multiplicities of the signals in the <sup>1</sup>H NMR spectra are abbreviated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad) and combinations thereof. Elemental analyses were obtained from a LECO CHNS 932 elemental analyzer.

#### Synthesis of 5a-5h and 6a-6h. General Procedure

A solution of chalcone derivatives 3a-3h (1 mmol) and ethyl acetoacetate (4) (1 mmol) in  $CH_2Cl_2$  (10 ml) was stirred at room temperature for 3–4 h in the presence of solid NaOH (1 mmol). After the reaction was completed, the reaction mixture was extracted with  $CH_2Cl_2$ . The extract was washed with  $H_2O$ , and dried (Na<sub>2</sub>SO<sub>4</sub>). The solvent was evaporated (45 °C, 2.6 kPa). Crude products were purified by column chromatography on silica gel or preparative TLC (20 × 20 cm plates, 2 mm thickness) using *n*-hexane/EtOAc (9:1) as eluent.

8-(4-Methoxyphenyl)-1-(thiophen-3-yl)-2-oxabicyclo[2.2.2]octane-3,5-dione (5a): White crystals, m.p. 100–101 °C, yield 59%. IR (KBr): 3029 (s), 2919 (m), 1726 (s) ( $v_{C=O}$  ester), 1672 (s) ( $v_{C=O}$  ketone), 1218 (s), 771 (s). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.38–7.37 m, 1 H, 7.29–7.24 m, 1 H, 7.16–7.04 m, 2 H, 6.88–6.84 m, 1 H, 6.72–6.70 m, 2 H, 3.82 d, *J* = 7.6, 1 H, 3.75 s, 3 H, (-OCH<sub>3</sub>), 3.01–2.96 m, 1 H, 2.74–2.66 m, 1 H, 2.58–2.52 m, 1 H, 2.29–2.24 m, 1 H, 2.18–2.12 m, 1 H. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 178.4, 176.9, 157.9, 145.6, 136.5, 128.1, 126.2, 125.2, 120.9, 113.9, 74.3, 55.2, 47.9, 46.2, 41.9, 36.5. For C<sub>18</sub>H<sub>16</sub>O<sub>4</sub>S (328.4) calculated: 65.84% C, 4.91% H, 9.76% S; found: 65.76% C, 4.97% H, 9.79% S.

*8-Phenyl-1-(thiophen-3-yl)-2-oxabicyclo*[*2.2.2*]*octane-3,5-dione* (**5b**): Liquid, yield 52%. IR (KBr): 3033 (s), 2979 (m), 1724 (s) ( $v_{C=O}$  ester), 1668 (s) ( $v_{C=O}$  ketone), 1218 (s), 771 (s). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.38–7.35 m, 1 H, 7.33–7.27 m, 1 H, 7.24 m, 1 H, 7.17–7.13 m, 2 H, 7.08–7.04 m, 1 H, 6.98–6.92 m, 2 H, 2.93–2.83 m, 2 H, 2.61 q, 1 H, *J* = 7.2, 2.49–2.40 m, 2 H, 2.16–2.04 m, 1 H. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 173.6, 173.2, 148.2, 146.4, 128.4, 127.6, 126.7, 126.1, 125.9, 120.8, 74.7, 48.6, 47.7, 41.5, 37.9. For C<sub>17</sub>H<sub>14</sub>O<sub>3</sub>S (298.4) calculated: 68.44% C, 4.73% H, 10.75% S; found: 68.56% C, 4.61% H, 10.78% S.

8-(3-Bromophenyl)-1-(thiophen-3-yl)-2-oxabicyclo[2.2.2]octane-3,5-dione (5c): White crystals, m.p. 154–155 °C, yield 65%. IR (KBr): 3027 (s), 2974 (m), 1726 (s) ( $v_{C=O}$  ester), 1662 (s) ( $v_{C=O}$  ketone), 1220 (s), 773 (s). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.33–7.30 m, 1 H, 7.23–7.19 m, 2 H, 7.10–7.06 m, 1 H, 7.05 s, 1 H, 6.94–6.92 m, 1 H, 6.88–6.87 m, 1 H, 2.91–2.83 m, 2 H, 2.63 q, 1 H, *J* = 7.2, 2.49–2.44 m, 2 H, 2.09–2.02 m, 1 H. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 173.7, 173.5, 149.2, 148.3, 130.6, 130.5, 128.9, 126.7, 126.6, 125.8, 121.7, 120.8, 74.4, 48.3, 47.9, 41.6, 37.8. For C<sub>17</sub>H<sub>13</sub>BrO<sub>3</sub>S (376.0) calculated: 54.12% C, 3.47% H, 8.50% S; found: 54.21% C, 3.39% H, 8.45% S.

1-(*Thiophen-3-yl*)-8-*m*-tolyl-2-oxabicyclo[2.2.2]octane-3,5-dione (5d): Liquid, yield 55%. IR (KBr): 3018 (s), 2915 (m), 1726 (s) ( $v_{C=0}$  ester), 1662 (s) ( $v_{C=0}$  ketone), 1220 (s), 773 (s). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.38–7.36 m, 1 H, 7.24–7.23 m, 1 H, 7.03 t, 1 H, *J* = 7.6, 6.95–6.94 m, 1 H, 6.88–6.86 m, 1 H, 6.74–6.72 m, 1 H, 6.69 s, 1 H, 2.91–2.86 m, 1 H, 2.83–2.78 m, 1 H, 2.62 q, 2 H, *J* = 14.4, 2.49–2.38 m, 1 H, 2.18 s, 3 H (-CH<sub>3</sub>), 2.13–2.06 m, 1 H. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 173.7, 172.1, 148.1, 146.4, 137.3, 128.3, 126.7, 126.7, 125.9, 124.5, 120.9, 120.8, 74.7, 48.6, 47.6, 41.4, 37.7, 21.5. For  $C_{18}H_{16}O_3S$  (312.4) calculated: 69.21% C, 5.16% H, 10.26% S; found: 69.28% C, 5.12% H, 10.35% S.

1-(*Thiophen-3-yl*)-5-*p*-tolyl-2-oxabicyclo[2.2.2]octane-3,8-dione (5e): Liquid, yield 52%. IR (KBr): 3091 (s), 3013 (m), 1739 (s) ( $v_{C=0}$  ester), 1672 (s) ( $v_{C=0}$  ketone), 1592 (s), 1287 (s), 1168 (s), 794 (s). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.39–7.35 m, 1 H, 7.28–7.19 m, 1 H, 7.04 t, 1 H, *J* = 7.5, 6.90–6.89 m, 1 H, 6.84–6.80 m, 1 H, 6.72–6.68 m, 1 H, 6.60 s, 1 H, 2.91–2.86 m, 1 H, 2.83–2.78 m, 1 H, 2.62 q, 2 H, *J* = 14.2, 2.49–2.38 m, 1 H, 2.35 s, 3 H (-CH<sub>3</sub>), 2.24–2.22 m, 1 H. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 183.9, 179.1, 144.2, 143.2, 141.0, 132.1, 131.8, 129.7, 128.5, 127.5, 126.4, 121.7, 75.0, 50.2, 49.6, 43.4, 38.7, 22.8. For C<sub>18</sub>H<sub>16</sub>O<sub>3</sub>S (312.4) calculated: 69.21% C, 5.16% H, 10.26% S; found: 69.33% C, 5.18% H, 10.14% S.

 $5\text{-}(2\text{-}Methoxyphenyl)\text{-}1\text{-}(thiophen-3\text{-}yl)\text{-}2\text{-}oxabicyclo[}2.2.2]\text{octane-}3,8\text{-}dione}$  (5f): liquid, yield 46%. IR (KBr): 3104 (s), 3020 (m), 1730 (s) (v\_{C=0} ester), 1682 (s) (v\_{C=0} ketone), 1652 (s), 1592 (s), 1247 (s), 1027 (s), 752 (s).  $^{1}\text{H}$  NMR (400 MHz, CDCl\_3): 7.38–7.36 m, 1 H, 7.19–7.13 m, 1 H, 6.95–6.89 m, 2 H, 6.82–6.74 m, 1 H, 6.59–6.54 m, 2 H, 3.93 m, 1 H, 3.85 s, 3 H, (-OCH\_3), 3.27–3.02 m, 1 H, 2.84–2.81 m, 1 H, 2.47–2.27 m, 1 H, 2.21–2.20 m, 1 H, 2.08–1.90 m, 1 H.  $^{13}\text{C}$  NMR (100 MHz, CDCl\_3): 179.1, 178.4, 158.8, 143.4, 139.6, 129.2, 126.3, 126.1, 120.7, 111.2, 76.0, 55.6, 50.2, 42.0, 37.2, 31.6. For C $_{18}\text{H}_{16}\text{O}_{4}\text{S}$  (328.4) calculated: 65.84% C, 4.91% H, 9.76% S; found: 65.56% C, 4.82% H, 9.70% S.

 $5\text{-}(2\text{-}Chlorophenyl)\text{-}1\text{-}(thiophen\text{-}3\text{-}yl)\text{-}2\text{-}oxabicyclo[2.2.2]octane\text{-}3,8\text{-}dione}~(5g)\text{:}$ Liquid, yield 51%. IR (KBr): 3100 (s), 3060 (m), 1730 (s) (v\_{C=O} ester), 1672 (s) (v\_{C=O} ketone), 1230 (s), 752 (s). <sup>1</sup>H NMR (400 MHz, CDCl\_3): 7.48–7.41 m, 1 H, 7.24–7.21 m, 2 H, 7.12–7.07 m, 1 H, 7.05 m, 1 H, 6.98–6.94 m, 1 H, 6.90–6.85 m, 1 H, 3.02–2.98 m, 2 H, 2.66 m, 1 H, 2.48- 2.43 m, 2 H, 2.12–1.99 m, 1 H. <sup>13</sup>C NMR (100 MHz, CDCl\_3): 175.8, 173.3, 148.5, 148.3, 130.3, 129.2, 128.2, 126.9, 126.5, 125.4, 120.0, 119.7, 74.6, 53.1, 50.0, 42.8, 34.7. For C<sub>17</sub>H<sub>13</sub>ClO<sub>3</sub>S (332.8) calculated: 61.35% C, 3.94% H, 9.63% S; found: 61.42% C, 3.87% H, 9.72% S.

*5-(4-Chlorophenyl)-1-(thiophen-3-yl)-2-oxabicyclo*[*2.2.2]octane-3,8-dione* (**5h**): Liquid, yield 41%. IR (KBr): 3090 (s), 3010 (m), 1727 (s) ( $v_{C=O}$  ester), 1682 (s) ( $v_{C=O}$  ketone), 1650 (s), 1598 (s), 1247 (s), 1022 (s), 767 (s). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): 7.42–7.38 m, 1 H, 7.28–7.26 m, 1 H, 7.18 m, 1 H, 7.07–7.04 m, 1 H, 6.90–6.88 m, 1 H, 6.82–6.78 m, 1 H, 6.69 m, 1 H, 3.05–2.99 m, 1 H, 2.90–2.88 m, 1 H, 2.50 m, 2 H, 2.38–2.31 m, 1 H, 2.25–2.16 m, 1 H. <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): 177.2, 175.2, 148.3, 144.1, 139.4, 133.2, 130.1, 128.2, 127.6, 127.4, 75.1, 49.8, 45.7, 42.8, 38.7. For C<sub>17</sub>H<sub>13</sub>ClO<sub>3</sub>S (332.8) calculated: 61.35% C, 3.94% H, 9.63% S; found: 61.31% C, 3.87% H, 9.68% S.

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