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

Yakup BUDAK[1,*] and Esra FINDIK[2]

Department of Chemistry, Faculty of Arts and Sciences, Gaziosmanpasa University, 60250 Tokat, Turkey; e-mail: [1] ybudak@gop.edu.tr, [2] esrafndk@gop.edu.tr

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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-(ethoxycarbonyl)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[1] and exhibit a multitude of biological activities[2]. 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[3]. This type reaction may be exploited with the aim to obtain highly functionalized cyclohexene derivatives[4], 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[5] or intermediates in the synthesis of fused heterocycles such as benzoselenadiazoles, benzothiadiazoles[6], benzopyrazoles and benzisoxazoles[7] or carbazole derivatives[8]. 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_2CO_3, K_2CO_3, 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_2O_3,

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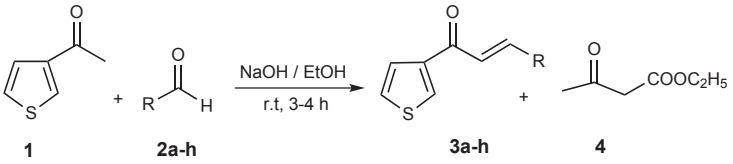
NaOH, KOH, etc., **6**-type compounds were formed via further aldol condensation[9,10].

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.[11,12] from the thermal cycloaddition of ketene dimethyl- or diethyl acetal with 2-oxo-2*H*-pyran-5-carboxylate derivatives.

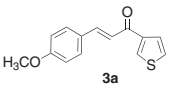
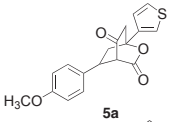
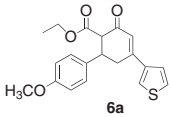
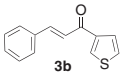
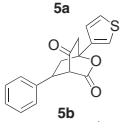
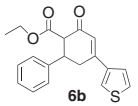
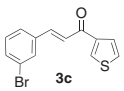
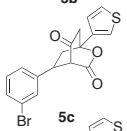
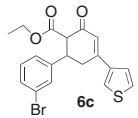
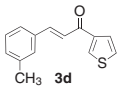
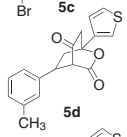
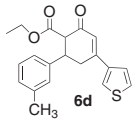
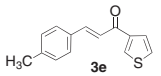
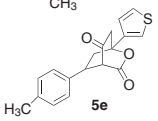
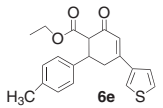
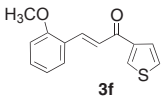
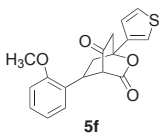
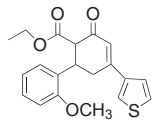
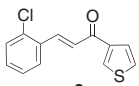
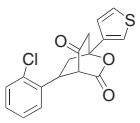
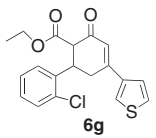
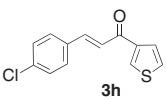
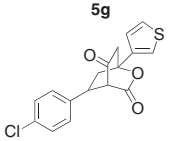
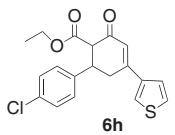
The chalcone derivatives **3a–3h** were synthesized according to our recently published reports[13,14] (Scheme 1). We recently performed the reaction of **3a–3h** with ethyl acetoacetate in the presence of *t*-BuOK, and obtained the cyclohexenone derivatives **6a–6h** as single products in excellent yield[14]. 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.



Compound	R
a	4-CH_3O-C_6H_4
b	C_6H_5
c	3-Br-C_6H_4
d	3-CH_3-C_6H_4
e	4-CH_3-C_6H_4
f	2-CH_3O-C_6H_4
g	2-Cl-C_6H_4
h	4-Cl-C_6H_4

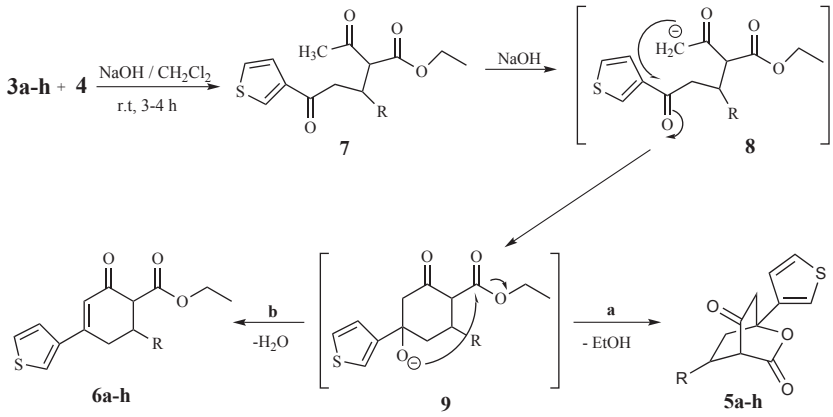
SCHEME 1

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

Reagent	Products			
3	**5**	m.p., yield (%)	**6**	m.p., yield (%)
 **3a**	 **5a**	100–101 °C, 59	 **6a**	106–107 °C, 38
 **3b**	 **5b**	viscous oil, 52	 **6b**	116–117 °C, 46
 **3c**	 **5c**	154–155 °C, 63	 **6c**	139–140 °C, 35
 **3d**	 **5d**	viscous oil, 55	 **6d**	111–112 °C, 42
 **3e**	 **5e**	viscous oil, 52	 **6e**	147–148 °C, 47
 **3f**	 **5f**	viscous oil, 46	 **6f**	99–100 °C, 42
 **3g**	 **5g**	viscous oil, 51	 **6g**	viscous oil, 45
 **3h**	 **5h**	viscous oil, 41	 **6h**	145–146 °C, 51

The structures of cyclohexenones **6a–6h** were determined by the spectral data and comparison with an authentic sample[14,15]. The structures of all new lactones **5a–5h** were corroborated through their IR, ^{1}H and ^{13}C NMR spectra and elemental analysis. The IR spectra of these compounds revealed two sharp strong absorption bands around 1682–1662 ($\nu_{C=O}$ ketone) and 1739–1724 ($\nu_{C=O}$ ester) cm^{-1}. These absorption bands confirm the presence of the ester group and the carbonyl group, respectively. In the ^{1}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 ^{13}C NMR spectra of **5a–5h** the signal at δ ~ 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_2O 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 (ν, cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III instrument (400 MHz). As internal standards served TMS (δ 0.00) for ^1H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR spectroscopy (δ, ppm; *J*, Hz). The multiplicities of the signals in the ^1H 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_2SO_4). 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) ($\nu_{C=O}$ ester), 1672 (s) ($\nu_{C=O}$ ketone), 1218 (s), 771 (s). ^1H NMR (400 MHz, $CDCl_3$): 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_3), 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. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{16}O_4S$ (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) ($\nu_{C=O}$ ester), 1668 (s) ($\nu_{C=O}$ ketone), 1218 (s), 771 (s). ^1H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{14}O_3S$ (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) ($\nu_{C=O}$ ester), 1662 (s) ($\nu_{C=O}$ ketone), 1220 (s), 773 (s). ^1H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{13}BrO_3S$ (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) ($\nu_{C=O}$ ester), 1662 (s) ($\nu_{C=O}$ ketone), 1220 (s), 773 (s). ^1H NMR (400 MHz, $CDCl_3$): 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_3), 2.13–2.06 m, 1 H. ^{13}C NMR (100 MHz, $CDCl_3$): 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) ($\nu_{C=O}$ ester), 1672 (s) ($\nu_{C=O}$ ketone), 1592 (s), 1287 (s), 1168 (s), 794 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 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_3), 2.24–2.22 m, 1 H. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{16}O_3S$ (312.4) calculated: 69.21% C, 5.16% H, 10.26% S; found: 69.33% C, 5.18% H, 10.14% S.

5-(2-Methoxyphenyl)-1-(thiophen-3-yl)-2-oxabicyclo[2.2.2]octane-3,8-dione (**5f**): liquid, yield 46%. IR (KBr): 3104 (s), 3020 (m), 1730 (s) ($\nu_{C=O}$ ester), 1682 (s) ($\nu_{C=O}$ ketone), 1652 (s), 1592 (s), 1247 (s), 1027 (s), 752 (s). ^{1}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}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 $C_{18}H_{16}O_4S$ (328.4) calculated: 65.84% C, 4.91% H, 9.76% S; found: 65.56% C, 4.82% H, 9.70% S.

5-(2-Chlorophenyl)-1-(thiophen-3-yl)-2-oxabicyclo[2.2.2]octane-3,8-dione (**5g**): Liquid, yield 51%. IR (KBr): 3100 (s), 3060 (m), 1730 (s) ($\nu_{C=O}$ ester), 1672 (s) ($\nu_{C=O}$ ketone), 1230 (s), 752 (s). ^{1}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. ^{13}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 $C_{17}H_{13}ClO_3S$ (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) ($\nu_{C=O}$ ester), 1682 (s) ($\nu_{C=O}$ ketone), 1650 (s), 1598 (s), 1247 (s), 1022 (s), 767 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 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. ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{17}H_{13}ClO_3S$ (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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REFERENCES

1. Dhar D. N.: *The Chemistry of Chalcones and Related Compounds*. Wiley–Interscience, New York 1981.
2. Dimmock J. R., Elias D. W., Beazely M. A., Kandepu N. M.: *Curr. Med. Chem.* **1999**, *6*, 1125.
3. Jung M. E.: *Comprehensive Organic Synthesis* (B. M. Trost, I. Fleming and C. H. Heathcock, Eds), Vol. 4. Pergamon Press, Oxford 1991.

4. Tabba H. D., Yousef N. M., Al-Arab M. M.: *Collect. Czech. Chem. Commun.* **1995**, *60*, 594.
5. Padmavathi V., Sharmila K., Reddy A. S., Reddy D. B.: *Ind. J. Chem., Sect. B* **2001**, *40*, 11.
6. Reddy D. B., Reddy A. S., Padmavathi V.: *J. Chem. Res. (S)* **1998**, 784.
7. Padmavathi V., Sharmila K., Balaiah A., Somasekhar A. R., Bhaskar D. R.: *Synth. Commun.* **2001**, *31*, 2119.
8. Padmavathi V., Sharmila K., Padmaja A., Bhaskar D. R.: *Heterocycl. Commun.* **1999**, *5*, 45.
9. Zhang Z., Dong Y. W., Guan W. W., Komatsu K.: *Synlett* **2004**, 61.
10. Rao H. S. P., Jothilingam S.: *J. Chem. Sci.* **2005**, *117*, 323.
11. Jung M., Hagenah J. A.: *Heterocycles* **1987**, *25*, 117.
12. Jung M., Hagenah J. A.: *J. Org. Chem.* **1987**, *52*, 1889.
13. Budak Y., Ceylan M.: *Chin. J. Chem.* **2009**, *27*, 1575.
14. Budak Y., Findik E., Ceylan M.: *S. Afr. J. Chem.* **2010**, *63*, 1.
15. Roman G.: *Acta Chim. Slov.* **2004**, *51*, 537.