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Michael and Ring Expansion Reactions of 6-Carboethoxy-3,5-diaryl-2-cyclohexen-1-ones

E. M. Afsah[a,*], **M. M. Abou-Elzahab**[a], **M. T. Zimaity**[a], and **G. R. Proctor**[b]

[a] Chemistry Department, Faculty of Science, Mansoura University, Mansoura, Egypt

[b] Department of Pure and Applied Chemistry, Strathclyde University, Glasgow G1 1XL, Scotland, U.K.

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When β-keto-ester **1a** was reacted with dimethyl acetylenedicarboxylate ring expansion occurred to give substituted cyclooctadienones. *Michael* reactions of the title compounds **1** with unsaturated ketones gave adducts, some of which underwent further cyclization reactions. A new route to α-tetralone ring system **10** via cyclization of the intermediate *Michael* adduct **9** is described.

(Keywords: Diaryl-2-cyclohexen-1-ones; Ring expansion reactions; Cyclooctadienones; Diaryl-α-tetralone; Synthesis)

Michael- und Ringerweiterungsreaktionen von 6-Carboethoxy-3,5-diaryl-2-cyclohexen-1-onen

Bei der Reaktion von β-Keto-ester **1a** mit Dimethyl-acetylendicarboxylat wurden unter Ringerweiterung substituierte Cyclooctadienone erhalten. Die *Michael*-Reaktion der Titelverbindung **1** mit ungesättigten Ketonen ergab Addukte, von denen einige weitere Cyclisierungsreaktionen eingingen. Es wird ein neuer Weg zum α-Tetralonsystem **10** über die Cyclisierung des intermediären *Michael*-Addukts **9** beschrieben.

Introduction

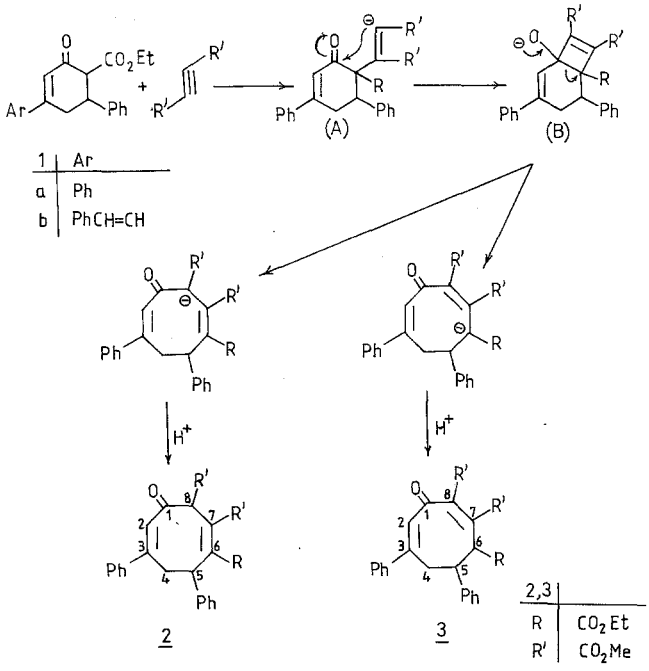
It was reported recently[1–3], that the *Michael* adduct from dimethyl acetylenedicarboxylate and 4-carboethoxy-1-benzoazepin-5-one or 2-carboethoxy-6-methoxytetralone-1 undergoes ring expansion simultaneously to give 1-benzoazoninone and benzocyclooctenone derivatives, respectively. It seemed, therefore, that it would be interesting to investigate the behaviour of the title compounds in such reactions.

Results and Discussion

The reaction of the sodio derivative of β-keto-ester **1a**[4] with dimethyl acetylenedicarboxylate gave a mixture of two compounds, which were identified as dimethyl ethyl 3,5-diphenyl-2,6- (and -2,7-)-cyclooctadiene-6,7,8-tricarboxylates (**2** and **3**). The structure of the two compounds was supported by analytical and spectral studies.

The ^{1}H-NMR spectrum showed that the product contains compound **2** (70%) and **3** (30%). In particular, compound **2** showed a singlet at δ 13 for the proton at C-8, whereas for **3** a proton at C-6 appeared at δ 12.8. The ^{13}C-NMR spectrum supplies further support for both structures, in particular, C-8, C-6, and C-1 of **2** appeared at δ 47.8, 148.7 and 172.6 while those of **3** were at δ 149.3, 40.3 and 172.0, respectively. The mass spectrum gave the molecular ion at *m/e* 462 for the two compounds.

Scheme 1

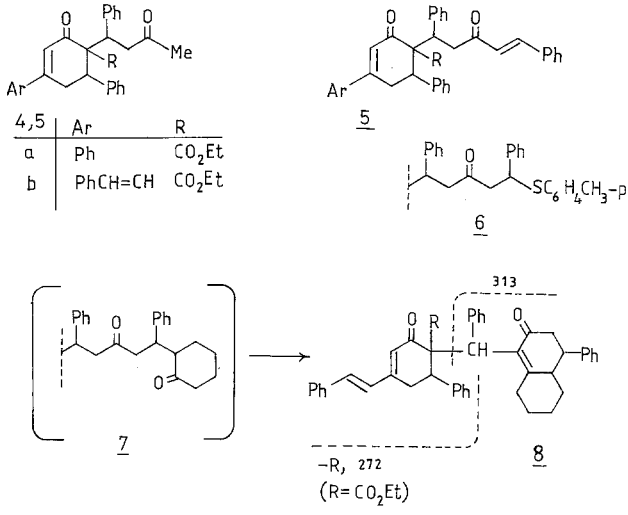


It is believed that the ring expansion of **1a** on treatment with dimethyl acetylenedicarboxylate involves the formation of the intermediate (A), which undergoes 4-exo-trig cyclization[5] to give (B), from which the final products can be obtained via ring expansion (see Scheme 1).

Michael reaction of **1a, b** with benzylideneacetone was performed with the expectation that a tetrahydro-2-oxo-4,5,7-triarylnaphthalene would be formed via intramolecular cyclization of the *Michael* adduct. However, the reaction led to **4a, b** as the only products, and none of the cyclized products were isolated.

On the other hand, the *Michael* reaction of **1a, b** with dibenzylideneacetone afforded **5a, b**. The identification followed from analytical and spectral data which showed that only the mono-adducts **5** were formed. Further support for structure **5** was obtained from reaction of (**5b** with *p*-thiocresol to give the *p*-tolylthioetheryl derivative **6**.

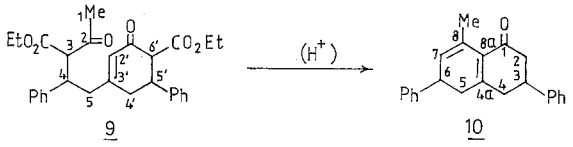
Reaction of **5b** and cyclohexanone gave compound **8** as the final product through intramolecular condensation of the aldol-crotonic type[6,7]. Additional evidence for structure **8** was obtained from its mass spectrum, which showed two fragments *m/e* 313 ($C_{23}H_{21}O$) and 272 ($C_{20}H_{16}O$).



It is interesting in this connection that—although *Michael* reaction between dibenzylideneacetone and ethyl acetoacetate in a molar ratio of (1 : 1) gave compound **1b**—the same reactants in a molar ratio of (1 : 2) led to the formation of 4-phenyl-4-[(6-carboethoxy-5-phenyl-2-cyclohexen-1-one-3-yl)methyl]-3-carboethoxy-2-butanone (**9**), the structure of which was confirmed by its ^{1}H-NMR spectrum and also by its mass spectrum which showed a molecular ion at *m/e* 476 (M^+).

Treatment of compound **9** with an acetic-hydrochloric acid mixture gave 5,6-dihydro-3,6-diphenyl-8-methyl-α-tetralone (**10**). To our

knowledge, this is the first example of formation of the α-tetralone ring system via a *Michael* adduct intermediate. The structure **10** assigned to the product is based on its analytical and spectral data.



9 10

The IR spectrum showed the absence of the ester groups and a band at 1640 cm^{-1} (CO). The ^{1}H-NMR spectrum displays signals at δ 2.8 (CH_3) and 3.0 (cyclic CH_2CO), whereas its ^{13}C-NMR spectrum showed the (CH_3) group at δ 23.5, and six singlet peaks, due to C-1, C-4a, C-8a, C-8 and two aromatic carbon atoms attached at C-3 and C-6. The mass spectrum exhibits a molecular ion peak at *m/e* 314.

Experimental

All melting points (°C) were uncorrected and were taken in a Gallenkamp-electric melting point apparatus. IR spectra were performed on a Unicam SP 2000 Infrared Spectrophotometer using KBr. ^{1}H-NMR spectra were obtained in $CDCl_3$ solution with a Perkin-Elmer R 32 NMR Spectrometer 90 MHz. ^{13}C-NMR was detected on Jeol PFT 100 MHz. Mass spectra were determined on Kratos MS 9 Mass Spectrometer and using a GEC-905 Computer system for data capture and processing. Elementry analyses (C, H) of **2**, **3**, **4a—b**, **5a—b**, **6**, **8**, **9**, and **10** were in good agreement with the proposed structures.

Dimethyl ethyl 3,5-diphenyl-2,6 (and 2,7)-cyclooctadiene-6,7,8-tricarboxylate (**2** *and* **3**)

To sodium hydride (50% dispersion in oil; 0.4 g; 0.02 mol) in dry toluene (30 ml) under nitrogen, compound **1a** (3.2 g; 0.01 mol) was added with stirring over 0.5 h. The white paste so obtained was stirred at room temperature for 1 h, and then cooled to 0–5°. While stirring, dimethyl acetylenedicarboxylate (2.34 g; 0.016 mol) was added during 1 h, keeping the temperature of the reaction mixture below 10°. After 5 h at this temperature the reaction was shown by TLC to be complete. The reaction mixture was cooled before adding acetic acid (6 ml) followed by hydrochloric acid (2 *M*, 10 ml), and the aqueous layer separated and washed with toluene (3 × 10 ml). The organic phase was washed with water (10 ml), dried and evaporated under reduced pressure to give a dark red gum which crystallized from ethanol to afford colourless crystals in 65% yield. M.p. 129°. The ^{1}H-NMR spectrum showed that this product contained compound **2** (70%) and **3** (30%). IR (KBr): 1710 (ester), 1640 (CO) and 1600 cm^{-1} (C=C).

Compound **2**: ^{1}H-NMR ($CDCl_3$): δ 0.9 (t, 3H, $OCH_2\mathbf{CH_3}$), 3.25 (m, 2H, 4-H_2), 3.7 (s, 3H, $CO_2\mathbf{CH_3}$ at C-7), 3.85 (s, 3H, $CO_2\mathbf{CH_3}$ at C-8), 4.0 (q, 2H, $O\mathbf{CH_2}Me$), 4.85 (m, 1H, 5-H), 6.1 (s, 1H, 2-H), 7.6–7.1 (m, 10H, aromatic protons) and 13 (s, 1H, 8-H); ^{13}C-NMR ($CDCl_3$): δ 13.6 ($OCH_2\mathbf{CH_3}$), 38.2 (C-4), 44.2 ($CO_2\mathbf{CH_3}$ at C-8), 47.8 (C-8), 52.3 ($CO_2\mathbf{CH_3}$ at C-7), 60.9 ($O\mathbf{CH_2}Me$), 97.9 (C-2), 100.4 (C-5), 139.1 (aromatic carbon at C-5), 141.9 (aromatic carbon at C-3), 144.4 (C-7), 148.7 (C-6),

150.2 (C-3), 165.8 ($\mathbf{C}O_2Me$ at C-7), 168.2 ($\mathbf{C}O_2Me$ at C-8), 170.3 ($\mathbf{C}O_2Et$) and 172.6 (C-1).

Compound **3**: ^{1}H-NMR ($CDCl_3$): δ 1.1 (t, 3H, $OCH_2C\mathbf{H}_3$), 4.05 (q, 2H, $OC\mathbf{H}_2$), 6.4 (s, 1H, 2-H), 12.8 (s, 1H, 6-H), the remaining signals of **3** are the same as **2**. ^{13}C-NMR ($CDCl_3$): δ 40.3 (C-6), 145.2 (C-7), 149.3 (C-8), 172.0 (C-1), the remaining signals are the same as **2**. MS: *m*/e (%): 463 M^+ (40), 431 (27), 403 (11), 357 (97), and 193 (100).

Ethyl 2-oxo-1-[3-oxo-1-phenylbutanyl]-4,6-diaryl-3-cyclohexene-1-carboxylates (**4a, b**)

To a solution of **1a, b** (0.01 mol) in methanol (30 ml) containing potassium methoxide (0.01 mol), benzylideneacetone (0.01 mol) was added. The reaction mixture was refluxed for 6 h, left to stand overnight, and poured into ice-cold dilute acetic acid (20%). The product that separated was crystallized from ethanol to give **4a—b** in 70–75% yield. M.p. 233° (**4a**), 160° (**4b**).

Ethyl 2-oxo-1-[3-oxo-1,5-diphenyl-4-pentenyl]-4,6-diaryl-3-cyclohexene-1-carboxylates (**5a, b**)

These compounds were synthesized in the same manner as above, from **1a, b** except that dibenzylideneacetone (0.01 mol) was used. Compounds **5a–b** were obtained in 69–76% yield. M.p. 135° (**5a**), 115° (**5b**).

Ethyl 2-oxo-1-[3-oxo-5-(p-tolylthioetheryl)-1,5-diphenylpentyl]-6-phenyl-4-styryl-3-cyclohexene-1-carboxylate (**6**)

A mixture of **5b** (5.8 g; 0.01 mol) and *p*-thiocresol (1.3 g; 0.01 mol) in methanol (40 ml), containing potassium methoxide (0.6 g; 0.01 mol) was refluxed for 6 h. After standing overnight, the product was isolated as described for **4**. Compound **6** was crystallized from ethanol as yellow needles in 76% yield. M.p. 128°.

Ethyl 1-[α-(2,3,4,4a,5,6,7,8-octahydro-2-oxo-4-phenyl-1-naphthyl)benzyl]-2-oxo-6-phenyl-4-styryl-3-cyclohexene-1-carboxylate (**8**)

The same procedure as described for **6** was followed but cyclohexenone (0.98 g; 0.01 mol) was used as a *Michael* donor instead of *p*-thiocresol. Compound **8** crystallized from ethanol as yellow crystals in 80% yield. M.p. 180°. MS: *m*/e (%): 336 (2), 313 (2), 272 (1), 235 (14), 131 (100), 91 (71).

4-Phenyl-4-[(6-carboethoxy-5-phenyl-2-cyclohexen-1-one-3-yl)methyl]-3-carboethoxy-2-butanone (**9**)

Ethyl acetoacetate (30 g; 0.023 mol) was added to a solution of sodium ethoxide (1.36 g; 0.02 mol) in ethanol (30 ml). After stirring the mixture for 1 h, dibenzylideneacetone (2.34 g; 0.01 mol) was added and the resulting solution was refluxed for 3 h, and then left to stand overnight. Acidification with dilute HCl gave yellowish brown semisolid, which was crystallized from ethanol to give colourless crystals of **9** in 50% yield (after 1 week). M.p. 154°. NMR ($CDCl_3$): δ 0.9 (t, 3H, acyclic $OCH_2C\mathbf{H}_3$), 1.07 (t, 3H, cyclic $OCH_2C\mathbf{H}_3$), 1.66 (s, 3H, 1-$\mathbf{H}_3$), 2.55 (broad s, 4H, 4′-$\mathbf{H}_2$ and 5-$\mathbf{H}_2$), 3.25 (m, 1H, 4-H), 3.75 (m, 1H, 5′-H), 3.95 (q, 2H, acyclic $OC\mathbf{H}_2Me$), 3.97 (q, 2H, cyclic $OC\mathbf{H}_2Me$), 4.8 (s, 1H, 2′-H) and 7.1 (s, 10H, aromatic protons); MS: *m*/e (%): 476 M^+ (4.5), 431 (14), 386 (47), 346 (2), 312 (40), 300 (76), 77 (52).

5,6-Dihydro-3,6-diphenyl-8-methyl-α-tetralone (**10**)

A mixture of **9** (6 g; 0.015 mol), acetic acid (120 ml), water (18 ml) and hydrochloric acid (38%, 18 ml) was refluxed for 28 h. The solvent was evaporated under reduced pressure and the product was extracted with toluene. Purification by column chromatography using neutral alumina (toluene-chloroform; 95 : 5) gave colourless crystals which were recrystallized from ethanol to give **10** in 40% yield. M.p. 92°. IR (KBr): 1 640 cm^{-1} (CO); ^{1}H-NMR ($CDCl_3$): δ 2.8 (s, 3H, CH_3), 3.0 (d, 2H, 2-H_2), 3.3 (d, 4H, 4-H_2 and 5-H_2), 3.5 (m, 2H, 3-H and 6-H) and 7.7–7.1 (m, 11 H, 7-H and aromatic protons); ^{13}C-NMR ($CDCl_3$): δ 23.5 (CH_3), 39.0 (C-2), 40.7 (C-4 and C-5), 47.9 (C-3 and C-6), 140.1 (aromatic carbon at C-6), 142.0 (aromatic carbon at C-3), 143.9 (C-8), 145.0 (C-8a), 145.5 (C-4a) and 199.4 (C-1); MS: *m/e* (%): 314 M^+ (1), 312 (66), 208 (100), 131 (14), 91 (19), 77 (18) and 65 (5).

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