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Cyclization of Cycloalkanone Enamines with Fumaric Acid Monoester Chlorides

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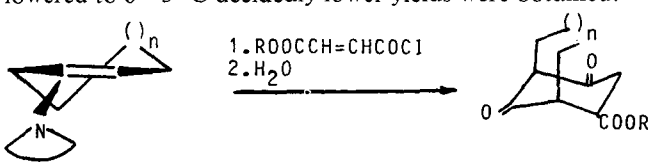
Enamines have found numerous applications in organic synthesis, and their use in carbocyclic ring formation is well precedented [1]. The number of useful syntheses of bicyclic structures and adamantane derivatives which involve cycloalkanone enamine cyclization is steadily growing [2 – 7]. The synthesis of polyfunctionalized bicyclic systems has been effected through reaction of substituted cyclohexanone enamines with electrophilic olefins. Several reagents including α,β-unsaturated acid chlorides have been used in carbocyclization reaction. However, there is a lack of simple attractive methods by which common functional groups could be introduced in the final structure using electrophile reactand. We have found that the reaction of electrophilic fumarate with cyclic ketone enamines leads to bicyclic products. This paper describes a one pot synthesis of substituted bicyclo[3.n.1]alkane-2-carboxylates from cyclohexanone and cyclopentanone enamines with fumaric acid monoalkyl ester chlorides.

Results and Discussion

A slow addition of a benzene solution of fumaric acid monomethyl ester chloride **2a** to a benzene solution of the morpholine enamine of cyclohexanone **1a** at room temperature in nitrogen atmosphere and subsequent hydrolysis gave methyl 4,9-dioxobicyclo[3.3.1]nonane-2-carboxylate **3a** upon workup in yields of up 60 %. The formation of the bicyclic diketo ester **3a** was found to be critically affected by variation in reaction conditions. The yield of the desired bicyclic material was far lower in concentrated reaction mixtures and rapid addition of the acid chloride **2a** solution to a benzene solution of enamine. The cyclization proceeded in low yields in other solvents such as carbon tetrachloride, methylene chloride, ether. The reaction was proved to be extremely sensitive toward the temperature. For example, in boiling benzene or when the temperature of the reaction was lowered to 0 – 5 °C decidedly lower yields were obtained.



1a, n = 1
n = 0

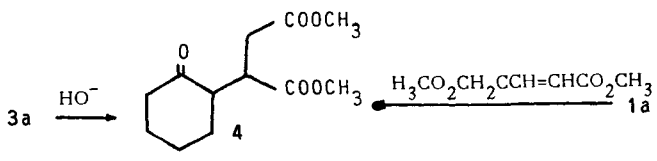
2a, R = CH_3
b, R = C_2H_5

3a, n = 1, R = CH_3
b, n = 1, R = C_2H_5
c, n = 0, R = CH_3

Procedures involving morpholine enamine of cyclopentanone **1b** gave similar results. However, the methyl bicyclo[3.2.1]octane-2-carboxylate **3c** was isolated in but moderate yields (40 – 45 %) owing to the formation of a greater amount of byproducts. The same reaction with the fumaric acid monoethyl chloride **2b** as well as with the enamines bearing other secondary amine moiety gave disappointingly low yields of the bicyclic material. No attempt was made to optimize yields in these cases since the methyl ester **2a** and the morpholine enamines were more easily prepared.

The structures of bicyclic compounds **3a – c** were determined from their spectral properties and analytical data. The assignments of the ^{13}C chemical shifts were based on standard methods, i. e. relative intensities, off-resonance continuous wave decoupling, and a comparison of the signal shift between closely related compounds [8, 9]. The agreement of the chemical shifts of the corresponding carbons is very good between the bicyclo[3.3.1]-nonane framework of **3a, b** and related substituted bicyclononanes and cyclohexanones.

The bicyclic diketo esters **3a – c** were obtained in stereochemically pure forms what evidenced the ^1H and ^{13}C-n.m.r. spectra pattern. However, the stereochemistry of the addition products could not been defined directly from the half width of proton at C-2 signal (12 Hz) as for other 2- and 2,6-substituted bicyclo[3.3.1]nonanes [10]. The molecular models of the title compounds suggest a greater amount of flattening in both cyclohexane rings. Although the stereochemistry of the bicyclic products has not been defined unequivocally, both the steric and stereoelectronic arguments predict the formation of 2-endo isomer. In an attempt to prove chemically the configuration at C-2, diketo ester **3a** was reduced to bicyclo[3.3.1]nonane -2-carboxylic acid. However, the reduction gave a mixture of epimerized acid. Hydrolysis with recyclization might occur more readily from the less hindered side. If the ester group in **3a** occupies a quasi-equatorial site then the weak nucleophile may be able preferrably to approach from exo site. Treatment of diketo ester **3a** with weakly basic solution of potassium carbonate in methanol yielded the oxocyclohexyl diester derivative **4** as the main product.



Evidence for the formation of compound **4** was obtained by direct synthesis of this compound by enamine **1a** alkylation with dimethyl fumarate. The identity of compounds obtained by different pathways and the structural assignment was made on the basis of the I.r. and ^{1}H-n.m.r. data as well as their physical properties.

Experimental

The infrared spectra were obtained on a Specord M80 infrared spectrophotometer. ^{1}H nuclear magnetic resonance (n.m.r.) spectra were determined on a BS 487 C Tesla spectrometer (80 MHz), ^{13}C-n.m.r. spectra were obtained on a BS 587 A Tesla spectrometer (20 MHz). The n.m.r. spectra were recorded as chloroform-d solutions with chemical shifts reported in ppm downfield from internal reference tetramethylsilane. The mass spectra were obtained on a Kratos MS-50 instrument operating in the electrone-impact mode with an ionizing energy of 70 eV.

Thin-layer chromatography was performed by using Silufol aluminium sheets precoated with silica gel, column chromatography was performed by using Lachema silica gel L 40/100 (Czechoslovakia). All reactions were run under a nitrogen atmosphere except hydrolyses. Solvents were dried over and distilled from appropriate reagents. Melting points are uncorrected.

Preparation of fumaric acid monoalkyl ester chlorides **(2a, b)**

A mixture of 0.4 mol maleic acid anhydride and 0.4 mol freshly distilled methanol or ethanol was allowed to stand for 12 h at room temperature. The solution was heated for 0.5 h on a water bath, and then 0.5 mol of thionyl chloride in 40 ml of benzene was added. The resulting mixture was heated at reflux for 18 h. The solvents were distilled at atmospheric pressure, and the residue was distilled at reduced pressure to give **2a, b** in 70 – 75 % yield.

Cyclohexanone und *Cyclopentanone enamines* were prepared by the literature methods [11].

General procedure for reaction of enamines (1a – c) with fumaric acid monoalkyl ester chlorides (2a, b)

To a stirred solution of 60 mmol of freshly distilled N-(1-cycloalkenyl)morpholine in 400 ml of anhydrous benzene was added dropwise 60 mmol of fumaric acid monoalkyl ester chloride solution in 10 ml of benzene maintaining the mixture temperature at 20 °C (5 – 6 h). The resulting reaction mixture was stirred at room temperature with exclusion of moinsture for an additional hour, and then filtered. The crystalline precipitate was washed with dry hexane and dissolved in 200 ml of ice-water. The aqueous solution was allowed to stand over night and extracted with methylene chloride. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated at reduced pressure. The crude bicyclic products were purified by recrystallization from anhydrous solvent.

Methyl 4,9-dioxobicyclo[3.3.1]nonane-2-carboxylate **(3a)**

Colourless crystals, yield 60 %, m.p. 68 – 70° C (from ether). I.r. (Nujol): 1705 cm^{-1} (broad, carbonyl CO), 1760 cm^{-1} (ester CO). ^{1}H-n.m.r.: 1.7 (2H, m), 2.17 (4H, m), 2.65 – 3.0 (4H, m), 3.15 (1H, m, $w_{1/2}$ 12 Hz), 3.6 (3H, s, CH_3). ^{13}C-n.m.r.: 209.5 and 207.3 (carbonyl C), 173.5 (ester C), 63.5 (C-5), 52.6 (C-1), 48.1 (OCH_3), 42.1 (C-2), 40.7 (C-3), 35.7 and 35.5 (C-6 and C-8), 18.8 (C-7).

$C_{11}H_{14}O_4$	Calcd.	C 62.84	H 6.71
	Found	C 62.65	H 6.59

Ethyl 4,9-dioxobicyclo[3.3.1]nonane-2-carboxylate **(3b)**

Colourless crystals, yield 32 %, m.p. 63 – 65° C (from ether-hexane). I.r. (Nujol): 1715 cm^{-1} (carbonyl CO), 1730 cm^{-1} (ester CO). ^{1}H-n.m.r.: 1.1 (3H, t, J = 7 Hz, CH_3), 1.65 (2H, m), 2.1 (4H, m), 2.6 – 3.0 (4H, m), 3.1 (1H, m, $w_{1/2}$ 11 Hz), 4.0 (2H, q, J = 7 Hz, CH_2).

$C_{12}H_{16}O_4$	Calcd.	C 64.27	H 7.19
	Found	C 64.19	H 7.20

Methyl 4,8-dioxobicyclo[3.2.1]octane-2-carboxylate **(3c)**

Colourless crystals, yield 40 %, m.p. 144 – 146° C (ether-ethanol). I.r. (Nujol): 1700 cm^{-1} (carbonyl CO), 1740 (ester CO). ^{1}H-n.m.r.: 1.3 – 3.0 (8H, m), 3.15 (1H, m, $w_{1/2}$ 9 Hz), 3.65 (3H, s, CH_3). MS: m/z = 196 ($M^{\oplus}$, 56 %), 168 (M-CO, 62.5), 154 (M-CH_2CO, 47.5), 137 (M-$COOCH_3$, 61), 136 (M-$HCOOCH_3$, 60), 123 (M-CH_2COOCH_3, 22.5), 122 (35), 114 (50), 113 (60), 110 (40), 109 (61), 108 (52), 95 (22.5), 83 (M-$COCH_2CHCO_2CH_3$, 60), 55 (75).

$C_{10}H_{12}O_4 \cdot C_2H_5OH$	Calcd.	C 59.49	H 7.49
	Found	C 59.49	H 8.00

Reduction of diketo ester **3a**

The mixture of 1.05 g (5 mmol) of diketo ester **3a**, 1.5 g (30 mmol) of hydrazine hydrate in 10 ml of diethylene glycol were stirred at room temperature for several hours. The formed water and excess of hydrazine hydrate were removed at reduced pressure. To the residue 2.8 g (50 mmol) of potassium hydroxide was added, and heated at 200 °C till nitrogen evolved. The reaction mixture was cooled and neutralized with diluted hydrochloric acid. The resulted solution was continuously extracted with ether. Solvent removal and column chromatography (benzene/acetone 9 : 1) gave 0.5 g (60 %) of acid, m.p. 46 °C. MS: m/z = 168 ($M^{\oplus}$, 8 %), 150 (33), 132 (8.5), 108 (53), 96 (18), 81 (100), 73 (24), 67 (44.5).

$C_{10}H_{16}O_2$	Calcd.	C 71.39	H 9.76
	Found	C 71.10	H 9.79

^{13}C-n.m.r. of the prepared methyl ester indicated that it was a mixture of stereoisomers.

Dimethyl (2-oxocyclohexyl)butanedioate **(4)**

Method A: Hydrolysis of diketo ester **3a**. 0.5 g (2 mmol) of diketo ester **3a** in 3 ml of anhydrous methanol and 0.3 g of potassium carbonate were stirred at room temperature for 6 h. The reaction mixture was then filtered, concentrated and chromatographed eluting with benzene/acetone 5 : 1 to yield 0.5 g (90 %) of diester **4**, m.p. 54 – 55 °C. I.r.: 1746 cm^{-1} and 1726 cm^{-1} (ester, CO), 1716 (carbonyl CO). ^{1}H-n.m.r.: 1.5 – 2.0 (6H, m), 2.25 (2H, m, cyclohexanone ring protons adjacent CO), 2.45 (2H, dd, CH_2COO), 2.65 – 2.7 (1H, dt, CHCOO), 2.9 – 3.3 (1H, m). ^{13}C-n.m.r.: 207.9, 172.2, 170.7, 49.8, 40.0, 38.4, 30.8, 28.1, 25.4, 23.1.

Method B: Direct preparation from enamine **1a**. To a stirred solution of 3 g (18 mmol) of enamine **1a** in 7 ml of dry methanol was added 3.3 g (23 mmol) of dimethyl fumarate. The solution was heated at reflux for 3 h, then 2 ml of the buffered acetic acid hydrolysis mixture was added (prepared from 25 ml of acetic acid, 25 ml of water and 12.5 g of sodium acetate). The mixture was heated at reflux for an additional hour, poured into water and extracted three times with ether. The combined etheral extracts were washed with saturated aqueous sodium bicarbonate, water, and brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Column chromatography eluting with benzene/acetone 9 : 1 afforded 2.5 g (57 %) of colorless oil, which crystallized upon standing, m.p. 55 °C. This was identical with material prepared by hydrolysis of **3a**.

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