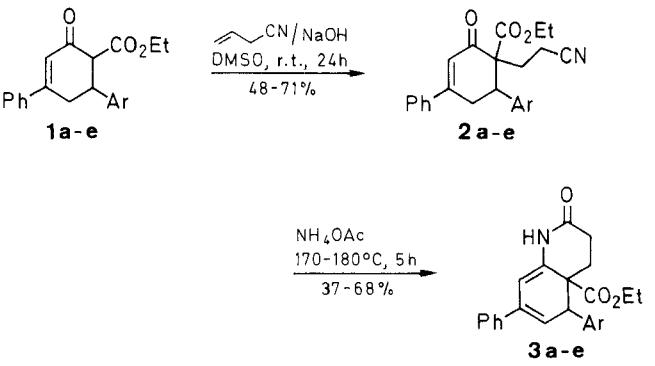
Synthesis of Ethyl 5-Aryl-2-oxo-7-phenyl-1,2,3,4,4a,5-hexahydroquinoline-4a-carboxylates

K. Popandova-Yambolieva
Department of Chemistry, University of Sofia, BG-1126 Sofia, Bulgaria

The addition of ethyl 6-aryl-4-phenyl-2-oxo-3-cyclohexene-1-carboxylates **1a–e** to acrylonitrile in the presence of aqueous sodium hydroxide is studied. The products **2a–e** are transformed to the corresponding 2-oxo-1,2,3,4,4a,5-hexahydroquinolines **3** by heating with ammonium acetate at 180°C.

The condensation of chalcones with ethyl acetoacetate in the presence of bases has been reported[1–4] to proceed smoothly giving ethyl 6-aryl-4-phenyl-2-oxo-3-cyclohexene-1-carboxylates **1**. However, the use of **1** as CH-acidic compounds in organic synthesis has been hardly described. Thus, only the addition reactions of ethyl 2-oxo-4,6-diphenyl-3-cyclohexene-1-carboxylate **(1a)** and ethyl 2-oxo-6-phenyl-4-styryl-3-cyclohexene-1-carboxylate to *trans*-4-phenyl-3-buten-2-one in the presce of sodium methoxide are known.[5]

We report here the reaction of **1** with acrylonitrile and cyclization of the obtained adducts **2** to tetrahydro-2(1*H*)-quinolinones **3** having two aryl groups at C-5 and C-7 and an angular ethoxycarbonyl group (Scheme **A**). The reaction of **1a–e** with acrylonitrile is carried out at room temperature with a catalytic amount of aqueous sodium hydroxide in dimethyl sulfoxide for 24 h. The starting β-keto esters **1a–e** are known compounds.[1–4] Their structure was confirmed by spectral data.[3] It is worth noting that all the β-keto estes **1** are tautomerically and conformationally homogenous, existing in the keto form with equatorial ethoxycarbonyl and aryl groups. No reaction took place in the case of **1f**, which has an aryl group with an *ortho*substituent.

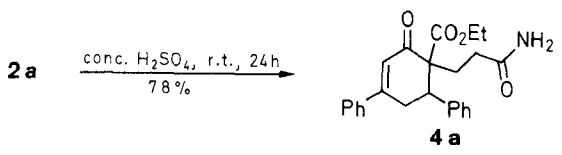


1–3	Ar	1–3	Ar
a	Ph	**d**	4-ClC_6H_4
b	4-$CH_3C_6H_4$	**e**	4-$Me_2NC_6H_4$
c	4-$MeOC_6H_4$	**f**	2-ClC_6H_4

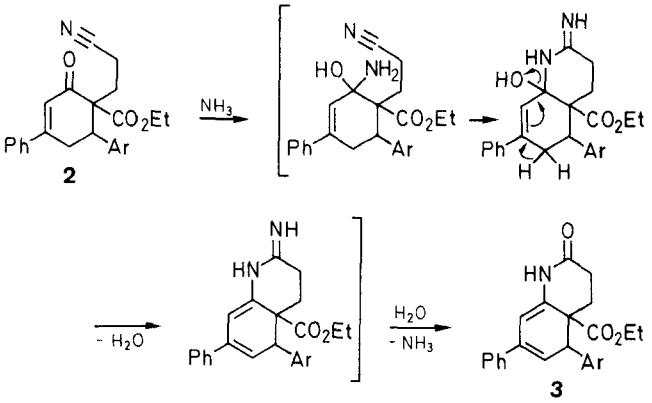
Scheme **A**

Compounds **2a–e** prepared are new compounds, which exist in two diastereoisomeric forms. In all cases we isolated only one of the isomers. However, configuraonal assignments can not be made only on the basis of ^{1}H-NMR spectra. Unfortunately, attempts to extend the reaction to other α,β-unsaturated nitriles (e.g. cinnamonitrile or 2-phenylcinnamonitrile) were not successful; the starting ester **1a** was isolated unchanged.

Attempts remove the ethoxycarbonyl group by heating **2a** with aqueous methanolic sodium hydroxide as described for similar compounds[6] were also unsuccessful, the starting material **2a** was isolated unchanged. Treatment of **2a** with concentrated sulfuric acid at room temperature for 24 hours gave the ester-amide **4a** in 78% yield.



In analogy to our earlier work[7] on the cyclization of 5-oxonitriles, compounds **2** were transformed to **3** by heating with ammonium acetate at 180 °C (without solvent). With the exception of **2c**, where the starting **2c** was isolated unchanged, the corresponding ethyl 5-aryl-2-oxo-7-phenyl-1,2,3,4,4a,5-hexadroquinoline-4a-carboxylates **3** were obtained in good yields. The mechanism of cyclization of **2** to **3** by ammonium acetate was not studied. In the literature[8] ammonium acetate has been used for the cyclization of some δ-keto amides, without commenting on the mechanism of the reaction. It is well known that ammonium acetate releases ammonia on heating. Therefore the pathway given in Scheme **B** can be assumed.



Scheme **B**

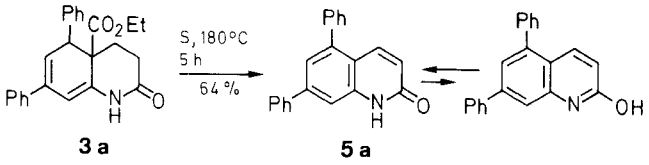
The compounds **3** can be transformed by heating with sulfur to quinoline derivatives. There are instances where sulfur has been used as a dehydrogenating agent.[9] The dealkoxycarbonylation by means of sulfur is also known.[10] We examined the reaction of **3a** with sulfur to

Table. Compounds **2** and **3** Prepared

Compound	Yield (%)	mp (°C)[a]	Molecular Formula[b]	IR ($CHCl_3$) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J (Hz)
2a	68	148–150	$C_{24}H_{23}NO_3$ (373.4)	2240, 1740, 1665, 1620	1.18 (t, 3H, J = 7, CH_3), 1.91–2.75 (m, 4H, CH_2CH_2CN), 2.97 (m, 2H, H-5), 3.49 (s, 1H, H-6), 4.19 (m, 2H, CH_2CH_3), 6.60 (s, 1H, H-3), 7.13–7.90 (m, 10H_{arom})
2b	71	141–142	$C_{25}H_{25}NO_3$ (387.5)	2240, 1740, 1665, 1620	1.24 (t, 3H, J = 7, CH_3), 2.00–2.72 (m, 4H, CH_2CH_2CN), 2.41 (s, 3H, $ArCH_3$), 2.97 (m, 2H, H-5), 3.50 (s, 1H, H-6), 4.22 (m, 2H, CH_2CH_3), 6.66 (s, 1H, H-3), 7.08–7.70 (m, 9H_{arom})
2c	60	138–140	$C_{25}H_{25}NO_4$ (403.5)	2240, 1740, 1665, 1620	1.21 (t, 3H, J = 7, CH_3), 1.75–2.66 (m, 4H, CH_2CH_2CN), 2.72–3.25 (m, 2H, H-5), 3.48 (s, 1H, H-6), 3.85 (s, 3H, MeO), 4.20 (m, 2H, CH_2CH_3), 6.58 (s, 1H, H-3), 6.80–7.70 (m, 9H_{arom})
2d	48	106–107	$C_{24}H_{22}ClNO_3$ (407.5)	2240, 1740, 1665, 1620	1.23 (t, 3H, J = 7, CH_3), 1.63–2.68 (m, 4H, CH_2CH_2CN), 3.05 (m, 2H, H-5), 3.50 (s, 1H, H-6), 4.15 (m, 2H, CH_2CH_3), 6.45 (s, 1H, H-3), 7.08–7.72 (m, 9H_{arom})
2e	66	173–174	$C_{26}H_{28}N_2O_3$ (416.5)	2240, 1740, 1665, 1620	1.22 (t, 3H, J = 7, CH_3), 2.00–2.70 (m, 4H, CH_2CH_2CN), 2.96 (s, 6H, NMe_2), 3.03–3.74 (m, 3H, H-5 + H-6), 4.20 (m, 2H, CH_2CH_3), 6.60 (s, 1H, H-3), 6.75–7.68 (m, 9H_{arom})
3a	40	240–242	$C_{24}H_{23}NO_3$[d] (373.4)	3420, 1725, 1675	1.10 (t, 3H, J = 7, CH_3), 2.38–2.70 (m, 4H), 3.77–4.20 (m, 3H, H-5 + CH_2CH_3), 5.90 (d, 1H, J = 2.5, H-6), 6.00 (s, 1H, H-8), 7.20–7.58 (m, 10H_{arom}), 9.12 (s, 1H, NH)
3b	37	236–237	$C_{25}H_{25}NO_3$ (387.5)	3415, 1735, 1680	1.13 (t, 3H, J = 7, CH_3), 2.30–2.70 (m, 4H), 2.35 (s, 3H, $ArCH_3$), 4.03 (m, 3H, H-5 + CH_2CH_3), 5.90 (d, 1H, J = 2.5, H-6), 5.92 (s, 1H, H-8), 7.07–7.50 (m, 9H_{arom}), 8.66 (s, 1H, NH)
3d	68	225–227	$C_{24}H_{22}ClNO_3$ (407.5)	3410, 1725, 1675	1.08 (t, 3H, J = 7, CH_3), 2.09–2.70 (m, 4H), 3.43 (s, 1H, H-5), 3.90–4.18 (m, 2H, CH_2CH_3), 5.78 (d, 1H, J = 2.5, H-6), 6.10 (s, 1H, H-8), 6.97–7.80 (m, 9H_{arom}), 10.25 (s, 1H, NH)
3e	48	189–191	$C_{26}H_{28}N_2O_3$ (416.5)	3415, 1735, 1680	1.10 (t, 3H, J = 7, CH_3), 2.35–2.70 (m, 4H), 2.98 (s, 6H, NMe_2), 3.40 (s, 1H, H-5), 4.10 (m, 2H, CH_2CH_3), 5.90 (d, 1H, J = 2.5, H-6), 5.96 (s, 1H, H-8), 6.75–7.60 (m, 9H_{arom}), 8.84 (s, 1H, NH)

[a] MeOH/EtOAc (1 : 1).
[b] Satisfactory microanalyses obtained: C ±0.16, H ±0.30, N ±0.23 (exception: **3d**, C + 0.7).
[c] NH signals are exchangeable with D_2O.

give **5a**, which exists predominantly in the quinolinone structure as shown by their IR spectra; ν = 3650 (weak), 3400 (broad) and 1665 cm^{-1} (strong).



3a **5a**

All compounds were characterized by their ^{1}H-NMR and IR spectra as well as by their microanalytical data (Table).

Melting points are determined on a hot stage microscope (Boetius-DDR) and are uncorrected. ^{1}H-NMR spectra were obtained on a TESLA BS 487-C (80 MHz). IR spectra were recorded on a Specord 71 IR spectrophotometer (DDR). The starting δ-keto esters **1a–e** are known compounds.[1–4] For the present investigations **1a–f** (**1f** is not previously reported) are prepared by analogy to Ref. 11.

Ethyl 6-Aryl-2-oxo-4-phenyl-3-cyclohexene-1-carboxylates 1a–f; General Procedure:

To a stirred mixture of ethyl acetoacetate (3.3 g, 25 mmol), K_2CO_3 (3.45 g, 25 mmol), and benzyltriethylammonium chloride (0.12 g, 0.5 mmol) in benzene (10 mL) is added the corresponding chalcone (25 mmol). The mixture is stirred at 40–45 °C for 2 h. In most cases the reaction mixture solidifies after 30–40 min. Then cold water (100 mL) is added, and the precipitate is filtered, washed with water and recrystallized from EtOH/EtOAc (1:1). The melting points of the known compounds **1a–e** are in agreement with reported values.[3,4]

1f; yield: 4.8 g (51 %); mp 123–125 °C.

$C_{21}H_{19}ClO_3$	calc.	C 71.08	H 5.36	
(354.5)	found	71.36	5.09	

IR ($CHCl_3$): ν = 1740 (ester C=O), 1680 (C=O), 1620 cm^{-1} (C=C).

^{1}H-NMR: δ = 1.08 (t, 3 H, J = 7 Hz, CH_3), 2.75–3.12 (m, 2 H, H-5), 3.87–4.63 (m, 4 H, $C\underline{H}_2CH_3$, H-1, 6), 6.63 (s, 1 H, H-3), 7.02–7.70 (m, 9 H_{arom}).

Ethyl 6-Aryl-1-(2-cyanoethyl)-2-oxo-4-phenyl-3-cyclohexene-1-carboxylates 2a–e; General Procedure:

To a solution of **1** (10 mmol) and acrylonitrile (0.53 g, 10 mmol) in DMSO (10 mL) is added 4 % aq. NaOH (1 mL). After 24 h, water (100 mL) is added, and the oily product is taken up in MeOH (20 mL). The products **2a–e** are purified by recrystallization from MeOH/EtOAc (1:1) (Table).

Ethyl 1-(2-Carbamoylethyl)-2-oxo-4,6-diphenyl-3-cyclohexene-1-carboxylate (4a):

A solution of **2a** (1 g, 2.8 mmol) in conc. H_2SO_4 (10 mL) is left at r.t. for 24 h. The mixture is poured on crushed ice (100 g) and the solid product is collected by filtration; yield: 0.80 g (78 %); mp 177–179 °C (MeOH).

$C_{24}H_{25}NO_4$	calc.	C 73.63	H 6.44	N 3.58
(395.5)	found	73.88	6.29	3.52

IR ($CHCl_3$): ν = 3410, 3230 (NH_2), 1735 (ester C=O), 1700 (amide C=O), 1670 (C=O), 1620 cm^{-1} (C=C).

^{1}H-NMR: δ = 1.13 (t, 3 H, J = 7 Hz, $CH_2C\underline{H}_3$), 2.20–2.56 (m, 4 H), 2.90–3.34 (m, 2 H, H-5), 3.55 (m, 1 H, H-6), 4.10 (q, 2 H, J = 7 Hz, $C\underline{H}_2CH_3$), 5.93 (br s, 2 H, NH_2), 6.56 (s, 1 H, H-3), 7.15–7.75 (m, 10 H_{arom}).

Ethyl 5-Aryl-2-oxo-7-phenyl-1,2,3,4,4a,5-hexahydroquinoline-4a-carboxylates 3; General Procedure:

A mixture of **2** 10 mmol) and freshly dried NH_4OAc (1.54 g, 20 mmol) is heated at approximately 180 °C for 5 h. After cooling, water (100 mL) is added, and the solid is filtered and recrystallized from MeOH/EtOAc (1:1).

Ethyl 2-Oxo-5,7-diphenyl-1,2,3,4,4a,5-hexahydroquinoline-4a-carboxylate (3a):

A mixture of **4a** (0.98 g, 2.5 mmol) and freshly dried NH_4OAc (0.40 g, 5 mmol) is heated at approximately 180 °C for 5 h. After cooling, water (100 mL) is added, the solid is filtered, and recrystallized from MeOH/EtOAc (1:1); yield: 0.20 g (21 %); mp 235–237 °C.

5,7-Diphenyl-2-(1*H*)-quinolinone (5):

A mixture of **3a** (0.09 g, 0.025 mmol) and sulfur (0.02 g, 0.05 mmol) is heated on a sand-bath to 175–180 °C until the test for H_2S is negative (about 6 h). After cooling, HOAc (0.5 mL) is added, then EtOH (5 mL) and the yellow precipitate is filtered and recrystallized from EtOAc; yield: 0.045 g (64 %); mp 128–130 °C

$C_{21}H_{15}NO$	calc.	C 84.85	H 5.05	N 4.71
(297.2)	found	84.43	5.29	4.46

IR ($CHCl_3$): ν = 3650 (weak, OH), 3400 (br, strong, OH), 1665 cm^{-1} (strong, C=O).

^{1}H-NMR: δ = 6.65–7.92 (m, 14 H_{arom}), 12.28, 12.54 (2 br s, NH and OH, exchangeable with D_2O).

MS (70 eV): m/z (%) = 297 (M^+, 100), 269 (10).

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