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CONDENSATION OF ETHYL α-ACETYLCINNAMATES WITH THIOUREAS

M. A. ELKASABY

Faculty of Science, Ain Shams University, Cairo, Abbassia, A.R. Egypt

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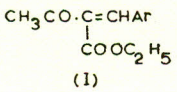
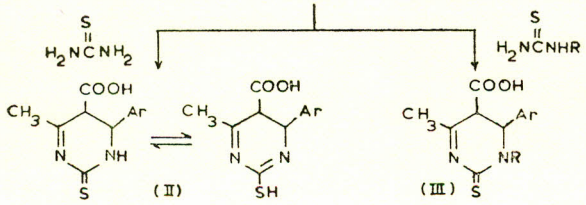
Dihydropyrimidinethiones can be obtained by the reaction of various ethyl α-acetylcinnamates with thioureas or ammonium thiocyanate.

Following previous studies of the condensation of chalcones with thiourea [1,2] it has now been found that ethyl α-acetylcinnamates (I) behave like other α-β-unsturated ketones[3] in condensing with thiourea, phenyl and benzylthiourea yielding 1-phenyl, benzyl or unsubstituted 6-aryl-5,6-dihydro-4-methyl-2-thioxo (1H) pyrimidine-5-carboxylic acids (IIa-d and IIIa-g)



(I)

a, Ar = C_6H_5 ; *b*, Ar = *p*-$MeOC_6H_4$
c, Ar = *p*-$Me_2NC_6H_4$; *d*, Ar = *o*-HO-C_6H_4

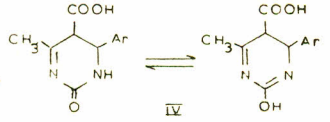


(II) (III)

a, Ar = C_6H_5
b, Ar = *p*-$MeOC_6H_4$
c, Ar = *p*-$Me_2NC_6H_4$
d, Ar = *o*-HO C_6H_4

a, Ar = C_6H_5 ; R=C_6H_5
b, Ar=*p*-$MeOC_6H_4$;R=C_6H_5
c, Ar=*p*-$Me_2NC_6H_4$;R=C_6H_5
d, Ar=*o*-HOC_6H_4;R=C_6H_5
e, Ar=C_6H_5 ; R=$C_6H_5CH_2$
f, Ar=*p*-$MeOC_6H_4$;R=$C_6H_5CH_2$
g, Ar=*p*-$Me_2NC_6H_4$;R = $C_6H_5CH_2$

Similarly, condensation of Ia-d with urea afforded the 6-aryl-5,6-dihydro-4-methyl-2-oxo(1H) pyrimidine-5-carboxylic acids IVa-d.



IV

a, Ar = C_6H_5
b, Ar = *p*-$MeOC_6H_4$
c, Ar = *p*-$Me_2NC_6H_4$
d, Ar = *o*-HOC_6H_4

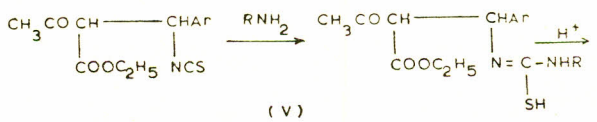
The structures of the mercaptopyrimidines (II and III) were established by their IR absorption. Thus the IR spectrum showed bands assigned to NH, OH (3448 cm^{-1} and 3290 cm^{-1} broad), C=N (1613 cm^{-1}), carboxylic C=O (1725 cm^{-1}), C=S 1280 cm^{-1}) and C—N=S (1471 cm^{-1})[4]. In addition, the IR sepectrum of IVa exhibited bands assigned to NH, OH (3247 cm^{-1} and 3290 cm^{-1} broad), C=N 1608 cm^{-1}), carboxyl C=O (1720 cm^{-1}) and ketonic C=O (1698 cm^{-1}), confirming the given structure.

Since compounds IIIa-g cannot exist in the thiol form and contain no NH groups either one cannot expect to observe SH and NH bands here. Further evidence for structures II and III were furnished by: (i) The *S*-methylated derivative of IIa was obtained readialy by direct methylation with dimethylsulphate in alkaline medium. (ii) The 1-nitroso derivative was isolated by nitrosation of IIa with nitrous acid. (iii) Compound IIa was converted into compound IIIa by known desulphurization procedures for converting mercapto into hydroxypyrimidines. The two products were established identical by the results of elemental analysis, IR spectra, and m.ps. The conversion methods are: (a) Action of hydrogen peroxide on ethanolic solution of IIa, a sulphone intermediate, was believed to be formed but could not be isolated (b) Boiling the *S*-methyl derivative of IIa with hydrochloric acid results in evolution of methylmercaptan (c) Through the oxidising action of bromine in methanol–methylene chloride solution. (iv) Compound IIa was also prepared via the reaction of phosphorus pentasulphide in anhydrous dioxane followed the specific thiation pathway.

Ia-c and ammonium thiocyanate reacted in the presence of sulphuric acid to give 1-aryl-1-isothiocyano-3 butanone-2-carboxylate (V). The IR absorption spectra of V showed bands attributed to isothiocyano (2092 cm^{-1}), ketonic C=O (1686 cm^{-1}) and ester C=O (1735 cm^{-1}) groups [4].

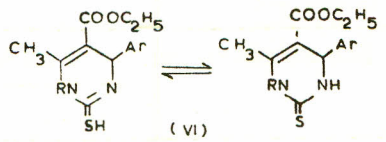
When (V) was shaken with ammoniacal silver nitrate in aqueous ethyl alcohol it gave readily silver sulphide, and on treatment with ammonia or thiourea II was obtained.

Cyclization with primary amines e.g. ethylamine, benzylamine and *p*-toluidine gave 4-aryl-1,4-dihydro-6-methyl-2-pyrimidinethiol-5-carboxylates(VIa-f)



(V)

a, Ar = C_6H_5
b, Ar = *p*-$MeOC_6H_4$



(VI)

a, Ar = C_6H_5; R = C_2H_5
b, Ar = *p*-$MeOC_6H_4$; R = C_2H_5
c, Ar = C_6H_5; R = $C_6H_5CH_2$
d, Ar = *p*-$MeOC_6H_4$; R = $C_6H_5CH_2$
e, Ar = C_6H_5; R = *p*-MeC_6H_4
f, Ar = *p*-$MeOC_6H_4$; R = *p*-MeC_6H_4

The IR spectra of VI showed bands attributed to NH, OH (3320 cm^{-1} and 3190 cm^{-1}) C=N (1610 cm^{-1}), ester C=O (1720 cm^{-1})[4] and C=S (1285 cm^{-1})

EXPERIMENTAL

M. ps. are uncorrected. The IR absorption spectra were determined with a Unicam SP 1200 spectrometer using potassium bromide Wafer technique,

Formation of II and III from I and Thioureas. General Procedure.

Method A. A. mixture of I (0.02 mole), thiourea (1.5 g, 0.02 mole), potassium hydroxide (2 g), ethanol (100 ml) and water (2 ml) was refluxed for 3 hr. The heavy precipitate formed on concentration and cooling was collected, dried and recrystallised from a suitable solvent to give II and III as colourless crystals (cf. Table 1).

Method B. To a solution of sodium metal (0.5 g) in anhydrous ethanol was added I (0.02 mole) and thiourea (1.5 g, 0.02 mole). The mixture was heated on steam bath for 10 hr and worked up as usual (cf. Table 1).

Method C. Thiourea (1.5 g) in ethanol (20 ml) was added enough hydrochloric acid to keep the solution clear, the unsaturated compound (I, 0.02 mole) was added and the mixture heated on the steam-bath for 8 hr. The precipitate formed on cooling was collected and washed with alcoholic hydrochloric acid, then treated with cold sodium hydroxide (50 ml, 5*N*) and the white precipitate formed filtered off, dried and recrystallized to give II and III.

Condensation of I with Urea. Formation of IV.

To urea (2 g) in ethanol (20 ml) was added enough hydrochloric acid to celar the solution I (0.02 mole) was added and the mixture heated on steam-bath for 8 hr. On concentration and cooling the mixture was treated with 5*N* sodium hydroxide (50 ml). The precipitate was collected and recrystallised from a suitable solvent to give IV as colourless crystals (cf. Table 2).

Methylation of IIa

To a mixture of IIa (2 g) and 1*N* sodium hydroxide (50 ml), dimethylsulphate (3 ml) was added and the mixture stirred until the methyl sulphate disappeared. The precipitate formed was collected, recrystallised from ethanol to give the *S*-methyl-derivative as colourless crystals, m.p. 112° (50%). Found : C, 59.66;H, 5.30; N; 10.78;S, 12.30%. $C_{13}H_{14}N_2O_2S$ (262) requires: C, 59.54; H, 5.34; N, 10.68; S, 12.21%).

Action of Nitrous Acid on IIa. Formation of N-*nitroso Derivative of IIa.*

To a solution of IIa (0.01 mole) in acetic acid (20 ml) sodium nitrite (3 g) was added, the mixture was left at room temperature for 2 hr diluted with water and the solid separated was collected (72%). It was recrystallised (from ethanol to give the *N*-nitroso derivative of IIa as colourless crystals, m.p. 248° (60%). Found: C, 52.11;H, 3.94;N, 15.06; S, 11.63%. $C_{12}H_{11}N_3O_3S$(277) requires: C, 51.98 H, 3.97 N, 15.16; S, 11.55%).

Desulphurization of II

(*a*) *With Hydrogen Peroxide.* IIa or b was added in small portions to hydrogen peroxide (30 ml, 8%) and sulphuric acid(5 ml, 10%) at 75-80°. After the reaction was over, the solution was heated to 100° for about ½ hr, to give IVa (50%) and IVb (50%) (identified by m.p. and mixed m.p. determination).

(*b*) *With Chloroacetic Acid.* Digestion of IIa (3 g) with boiling chloroacetic acid (3 g in 25 ml water) and sulphuric acid (5 ml, 10%) for 2hr led to complete desulphurization and formation of IVa and b (identified by m.p. and mixed m.p. determination).

(*c*) *With Bromine in Methanol—Methylene Chloride.* To IIa or b (0.01 mole) dissolved in anhydrous methanol (10 ml) and methylene chloride (50 ml), an equimolar amount of bromine in methylene chloride (25 ml) was added. The mixture was stirred for 2 hr and evaporated to dryness under reduced pressure. The solid was purified by recrystallization from ethanol to give IVa (77%) and IVb (80%).

(d) The *S*-methyl derivative of IIa was boiled with 6*N* HCl and gave IVa.

Fomration of IIa and b. To IVa or b(0.01 mole) dissolved in anhydrous dioxane (20 ml) phosphorus pentasulphide (0.05 mole) was added. The suspension was refluxed for 3 hr and evaporated to dryness. The crude material recrystallised from ethanol identified as IIa (43%) and IVb (47%) respectively by m.p. and mixed m.p. determination.

3-*Isothoicyano Derivative V.* To Ia or b(0.01 mole) was added while stirring concd sulphuric acid (2 ml in 5 ml water) and ammonium thiocyanate (5 g in 10 ml water) and the mixture was stirred for 3 hr. The red mixture was extracted with ether. The ether was evaporated to give solid which was recrystallised from benzene to give Va and b respectively as pale yellow crystals.

Ia afforded Va, m.p. 95°. (Found: C,60.78; H,5.46; N, 5.08,S, 11.66%. $C_{14}H_{15}NO_3$ S(277) requires: C, 60.65; H, 5.42: N, 5.05; S, 11.55%).

Ib afforded Vb, m.p. 113°(66%). (Found: C, 58.40; 5.58; N, 4.58; S, 10.30%. $C_{15}H_{17}NO_4$ S(307) requires: C, 58.63:H, 5.54: N, 4.56: S, 10.42%).

Table 1. Mercaptopyrimidine II and III.

Compound	Solvent of crystn	M.p.°C	Yield %	Fomula and mol.wt.	Analysis %	
					Calcd	Found
IIa	E	179	70	$C_{12}H_{12}N_3O_2S$ (248)	C 58.06 H 4.74 N 11.29 S 12.90	58.46 4.80 11.41 13.10
IIb	B	210	72	$C_{13}H_{14}N_2O_3S$ (278)	C 56.12 H 5.03 N 10.07 S 11.51	56.00 5.07 10.26 11.28
IIc	B–P	236	75	$C_{14}H_{17}N_3O_2S$ (291)	C 57.73 H 5.84 N 14.43 S 10.99	57.85 5.79 14.60 10.80
IId	B–P	245	72	$C_{12}H_{12}N_2O_3S$ (264)	C 54.54 H 4.54 N 10.52 S 12.12	54.66 4.60 10.52 12.22
IIIa	B	192	72	$C_{18}H_{16}N_2O_2S$ (324)	C 66.66 H 4.94 N 8.64 S 9.88	66.44 5.00 8.70 9.79
IIIb	E	223	74	$C_{19}H_{18}N_2O_3S$ (354)	C 64.41 H 5.08 N 7.91 S 9.04	64.62 5.14 8.00 9.14
IIIc	E	248	77	$C_{20}H_{21}N_3O_2S$ (367)	C 65.39 H 5.72 N 11.44 S 8.72	65.60 5.76 11.55 8.62
IIId	B	>250	75	$C_{18}H_{16}N_2O_3S$ (340)	C 63.53 H 4.70 N 8.24 S 9.41	63.39 4.76 8.46 9.32
IIIe	B	202	71	$C_{19}H_{16}N_2O_2S$ (338)	C 67.45 H 5.32 N 8.28 S 9.47	67.68 5.30 8.18 9.59
IIIf	B–P	220	73	$C_{20}H_{20}N_2O_2S$ (368)	C 65.22 H 5.43 N 7.60 S 8.69	65.11 5.50 7.72 8.80
IIIg	E	234	72	$C_{21}H_{23}N_3O_2S$ (381)	C 66.14 H 6.04 N 11.02 S 8.39	66.00 6.09 10.92 8.52

Action of Amines on V. Formation of VI

Alcoholic or aqueous solution of amine (0.02 mole) was added over a period of 15 min, to a vigorously agitated solution of Va or b (0.02 mole) in ethanol and hydrochloric acid (5 ml). The reaction mixture was heated to reflux and after cooling to room temperature the product which separated was washed with water and recrystallised from ethonal to give VIa-f as colourless crystals (cf. Table 3).

Table 2. Pyrimidine carboxylic acids IV.

Compound	Solvent of crystn.	M.p.	Yield %	Formula and mol.wt.	Analysis%	
					Calcd	Found
IVa	E	238	68	$C_{12}H_{12}N_2O_3$ (232)	C 62.07 H 5.17 N 12.07	62.28 5.32 12.18
IVb	E	246	75	$C_{13}H_{14}N_2O_4$ (262)	C 59.54 H 5.34 N 10.69	59.67 5.30 10.82
IVc	A	>250	80	$C_{14}H_{17}N_3O_3$ (275)	C 61.09 H 6.18 N 15.27	61.22 6.15 15.40
IVd	A	>250	70	$C_{12}H_{12}N_2O_4$ (248)	C 58.06 H 4.84 N 11.29	58.18 4.81 11.38

Table 3. Pyrimidinethiols VI.

Compound	M.p.°C	Yield %	Formula and mol.wt.	Analysis%	
				Calcd	Found
VIa	159	70	$C_{16}H_{20}N_2O_2S$ (304)	C 63.16 H 6.58 N 9.21 S 10.53	63.00 6.62 9.30 10.62
VIb	175	72	$C_{17}H_{22}N_2O_3S$ (334)	C 61.07 H 6.59 N 8.38 S 9.58	61.27 6.54 8.30 9.70
VIc	164	73	$C_{21}H_{22}N_2O_2S$ (366)	C 68.85 H 6.01 N 7.65 S 8.74	68.61 6.04 7.59 8.68
VId	157	75	$C_{22}H_{24}N_2O_3S$ (396)	C 66.66 H 6.06 N 7.07 S 8.08	66.80 6.00 7.14 8.16
VIe	134	76	$C_{21}H_{22}N_2O_2S$ (366)	C 68.85 H 6.01 N 7.65 S 8.74	68.58 6.06 7.72 8.68
VIf	168	78	$C_{22}H_{24}N_2O_3S$ (396)	C 66.66 N 6.06 N 7.07 S 8.08	66.42 6.09 7.00 8.18

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