Reactions of β-Keto Thioacid Anilides with Acyl Chloride Aryl-Hydrazones

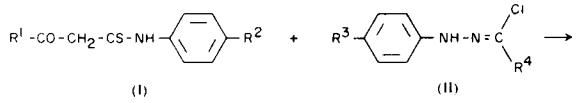
Donato Pocar, Luisa Maria Rossi and Pasqualina Trimarco

Istituto di Chimica Organica, Facoltà di Farmacia, Università di Milano
Viale Abruzzi 42, 20131 Milano, Italy

Received August 5, 1974

Several reactions of the anilides of β-keto thioacids have already been investigated (1). Owing to the presence of several reactive centers, an investigation of the reactions with dipolar reagents was of a certain interest. Previous work in this field confirmed the expected reactivity with aryl azides to obtain 1,5-diaryl-*v*-triazole-4-carboxylic acid anilides (2). Similar reactions with sulfonyl azides have been studied by Regitz (3). In this work we describe the reactions of the anilides of β-keto thioacids with acyl chloride aryl-hydrazones.

By reacting an anilide of the general formula I with an acyl chloride aryl-hydrazone (II), in the presence of a base such as triethylamine or sodium acetate, the corresponding 1,3,4-thiadiazoline derivative (III) was easily obtained, through nucleophilic attack of the thiolate group followed by ring closure and arylamine elimination.

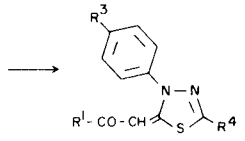


(I)

a: R^1 Ph, R^2 H
b: R^1 4-MePh, R^2 H
c: R^1 Ph, R^2 4-MeO
d: R^1 Me, R^2 H

(II)

a: R^3 H, R^4 Ph
b: R^3 H, R^4 Ac
c: R^3 4-MeO, R^4 Ac
d: R^3 H, R^4 COOEt
e: R^3 Cl, R^4 COOEt
f: R^3 Cl, R^4 COCl
g: R^3 4-MeO, R^4 COOEt



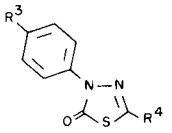
(III)

a: R^1 Ph, R^3 H, R^4 COOEt
b: R^1 Ph, R^3 4-Cl, R^4 COOEt
c: R^1 Me, R^3 4-MeO, R^4 Ac
d: R^1 4-MePh, R^3 4-MeO, R^4 COOEt
e: R^1 4-MePh, R^3 H, R^4 Ph
f: R^1 4-MePh, R^3 H, R^4 COOEt
g: R^1 4-MePh, R^3 4-MeO, R^4 Ac
h: R^1 Ph, R^3 H, R^4 Ac
i: R^1 4-MePh, R^3 H, R^4 Ac

The elimination of the amine moiety was confirmed by the isolation of the same product (IIIh) using IIb and Ic or Ia, respectively as starting material.

The structure of the thiadiazolines III has been also confirmed by the ozonolysis of IIId, which yields 5-carbethoxy-3-(4-methoxyphenyl)-1,3,4-thiadiazolin-2-one (IVa).

An authentical sample of this compound has been independently obtained from IIg by the method of R. Fusco (4) based on the thermal decomposition of the nitroso derivative of the 5-carbethoxy-3-(4-methoxy phenyl)-2-amino thiadiazoline. Compound IVb has been obtained in high yield from IIIg through hydrogen peroxide oxidation in acetic acid.



(IV)

a: R^3 4-MeO, R^4 COOEt
b: R^3 4-MeO, R^4 Ac

A different reaction path was observed when the anilides I react in the presence of strong bases (sodium ethoxyde) with acyl chloride aryl-hydrazones IId, e, g, which all bear a carbethoxy residue. By reacting Ia with IId or IIe the thiazolidinones Va and Vb were obtained respectively in moderate yield as the main products. Such results support a ring closure, followed by elimination of ethanol.

However, Vb was obtained in practically quantitative yield by reaction of the thioanilide Ia with IIf which bears the more reactive chlorocarbonyl group (5). Analogously Vc was obtained from IIf and Id.

The crude reaction material of the reaction between Ia and Id has been separated by column chromatography. Besides Va the following compounds were isolated: i) the sulphide VI, which is probably a by-product derived from a degradation reaction of the starting anilide in the basic medium; ii) a moderate amount of the thiadiazoline IIIa; and iii) a small amount of an unidentified substance having the same analytical data as Va (VII).

Obviously the strength of the basicity of the medium can influence the reaction path.

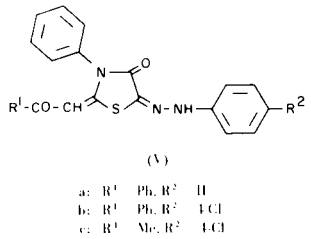
The spectroscopic behaviour of these materials under different conditions could be worth further investigations; for instance thiazolidinone Vc is a yellow compound [λ max (ethanol) 258, 321, 433 mμ, ε max 14,150, 19,550,

Table I

III	Catalyst	Recryst. solvent	Yield %	m.p. °C	Found % C	H	N	Formula	Calcd. % C	H	N	Nmr ($CDCl_3$) δ-CH=
a	AcONa	AcOH	60	175	64.62	4.46	7.65	$C_{19}H_{16}N_2O_3S$	64.77	4.58	7.95	6.74
b	AcONa	EtOH	65	170-171	58.62	4.13	7.52	$C_{19}H_{15}ClN_2O_3S$	58.99	3.90	7.24	6.73
c	TEA AcONa	EtOH	40	125	58.96	4.75	9.74	$C_{14}H_{14}N_2O_3S$	57.93	4.86	9.65	5.88
d	TEA	EtOH AcOH	75	175	63.49	4.95	6.96	$C_{21}H_{20}N_2O_4S$	63.63	5.09	7.07	6.57
e	TEA	EtOH	95	198-199	74.03	4.84	7.57	$C_{23}H_{18}N_2O_2S$	71.49	4.70	7.25	6.71
f	TEA	EtOH	80	156-157	65.10	4.54	7.57	$C_{20}H_{18}N_2O_3S$	65.56	4.95	7.65	6.75
g	TEA AcONa	AcOEt $(CH_2Cl)_2$	65	217	65.16	4.70	7.53	$C_{20}H_{18}N_2O_3S$	65.56	4.95	7.65	6.56
h	TEA	AcOH $(CH_2Cl)_2$	80	262	66.40	4.35	8.68	$C_{18}H_{14}N_2O_2S$	67.07	4.38	8.69	6.67
i	TEA	AcOH	70	235	67.19	4.60	8.22	$C_{19}H_{16}N_2O_2S$	67.85	4.80	8.33	6.64

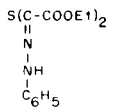
Table II

V	Prep. Method	Recryst. Solvent	Yield %	m.p. °C	Found % C	H	N	Formula	Calcd. % C	H	N	Nmr (DMSO) δ=CH-	δ-NH-
a	a	AcOH EtOH	25	274 dec.	69.15	4.12	10.56	$C_{23}H_{17}N_3O_2S$	69.16	4.29	10.52	6.29	---
b	a	AcOH	30	283 dec.	63.71	3.77	9.90	$C_{23}H_{16}ClN_3O_2S$	63.66	3.71	9.68	6.29	10.65
	b		95										
c	b	AcOH	90	255 dec.	58.05	3.69	11.04	$C_{18}H_{14}ClN_3O_2S$	58.14	3.79	11.30	5.62 2.07 (Me)	10.50



(V)

a: R^1 Ph, R^2 H
b: R^1 Ph, R^2 4-Cl
c: R^1 Me, R^2 4-Cl



(VI)

39,100] which dissolves in ethanolic sodium hydroxide yielding a purple-red anion [λ max (ethanol) 256, 330, 382, 525; ε max 20,550, 18,200, 15,500, 34,350], which is likely the corresponding α-phenylazoenolate.

EXPERIMENTAL

The ^1H nmr spectra were recorded with a Varian A-60 spectrometer operating at 60 MHZ, with TMS as internal standard. The IR spectra were obtained with a Perkin-Elmer Model 237 spectrometer. The uv spectra were recorded with a Beckman DB-GT spectrometer.

1,3,4-Thiadiazolines (IIIa-i).

The thioanilide (10 mmoles) was dissolved or suspended in anhydrous ethanol (25 ml.). To the solution was added 10 mmoles of triethylamine or of fused sodium acetate, followed, after a short time, by the acyl chloride aryl-hydrazone (10 mmoles in 25-30 ml. of ehtanol). The mixture was refluxed for 1-2 hours. Then the solution was cooled and a first crop of product was filtered. The mother liquor was evaporated and a second crop was obtained. If necessary the product was washed with water and recrystallized (Table I).

By reacting IIIg with an excess of hydrazine hydrate the corresponding hydrazone could easily be obtained as gold-yellow crystals (m.p. 215-216°, ethanonitrile); ν max (nujol): 3400, 3290 and 3210 cm^{-1}.

Anal. Calcd. for $C_{20}H_{20}N_4O_2S$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.60; H, 5.02; N, 14.70.

5-Carbethoxy-3-(4-methoxyphenyl)-1,3,4-thiadiazoline-2-one (IVa).

a) Five mmoles of IIId were dissolved in 30 ml. of chloroform and ozonized at −30°. The solution obtained was treated with water and the organic layer was evaporated. By chromatography on a silica column IVa was obtained as white crystals (isopropyl ether); m.p. 71°; ν max: 1730 and 1680 cm^{-1}. The product was identical with the sample obtained in b).

Anal. Calcd. for $C_{12}H_{12}N_2O_4S$: C, 51.43; H, 4.32; N, 9.99. Found: C, 51.25; H, 4.17; N, 10.03.

b) Compound IIg (3 mmoles) was reacted with potassium thiocyanate (4 mmoles) in 50% ethanol (10 ml.). After 1 hour refluxing the reaction mixture was heated with water, extracted with ether and the ethereal fraction was evaporated. The oily residue crystallized slowly, m.p. 76-78°. The crude product was dissolved in acetic acid (5 ml.) and sodium nitrite (0.3 g. in 2 ml. water) was added. The oily product was extracted with toluene, the solution being refluxed for 15 minutes. Compound IVa was obtained by evaporation and recrystallization from isopropyl ether, m.p. 73°, ν max 1730 and 1680 cm^{-1}.

5-Acetyl-3-(4-methoxyphenyl)-1,3,4-thiadiazolin-2-one (IVb).

Compound IIIg (5 mmoles) was dissolved in acetic acid at room temperature and reacted with a slight excess of 36% hydrogen peroxide. After 5 days at room temperature the solution was decolourized and evaporated to dryness. The crude product was recrystallized from isopropyl ether; yield 90%, m.p. 121-122°; ν max: 1685 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}N_2O_3S$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.60; H, 4.03; N, 10.98.

Thiazolidin-4-ones.

a) Compound Va, d:

Ten mmoles of I were dissolved in a solution of 10 mmoles of sodium in 10 ml. of ethanol. Ten mmoles of II in 30-40 ml. of ethanol were then added at room temperature with stirring. The mixture warmed up slightly and became dark red.

After 30 minutes precipitation of sodium chloride began. Four hours later the solvent was evaporated under reduced pressure and the residue was recrystallized. (See Table II).

b) Compound Vb, c:

Five mmoles of IIf were dissolved in 30 ml. of anhydrous ether, then 5 mmoles of I in 25 ml. of ether were added. To this solution 10 mmoles of triethylamine was dropwise added under stirring. A yellow product was immediately formed, filtered out and recrystallized. (See Table II).

c) Compounds IIIa, Va, VI, VII:

Compounds Ia and IId were reacted together as described in a). The crude product was obtained by evaporation of the ethanol solution; water was added and the mixture was extracted with chloroform. After clarifying, the solution was chromatographed on a silica column with chloroform as the eluent. Compounds VI, VII, IIIa and Va were thus separated.

Acknowledgement.

We thank the Italian C.N.R. for financial support.

REFERENCES

(1) D. E. Worral, *J. Am. Chem. Soc.*, **42**, 1055 (1920); S. Hünig, K. Hübner, *Chem. Ber.*, **95**, 937 (1962); D. Pocar, B. Bianchetti and S. Maiorana, *Gazz. Chim. Ital.* **93**, 100 (1963).

(2) D. Pocar, unpublished.

(3) M. Regitz and A. Liedhegener, *Ann. Chem.*, **710**, 118 (1967).

(4) R. Fusco and C. Musante, *Gazz. Chim. Ital.*, **68**, 147 (1938).

(5) This reaction is very similar to the condensation of IIf and diphenyl thiourea (6).

(6) M. O. Lozinskii, S. N. Kukota and P. S. Pel'kis, *Ukr. Khim. Zh.*, **33**, 1096 (1967).