SYNTHESIS OF 2-SUBSTITUTED 3(2H)-ISOTHIAZOLONES FROM 2-SUBSTITUTED 5-AROYL-3(2H)-ISOTHIAZOLONES

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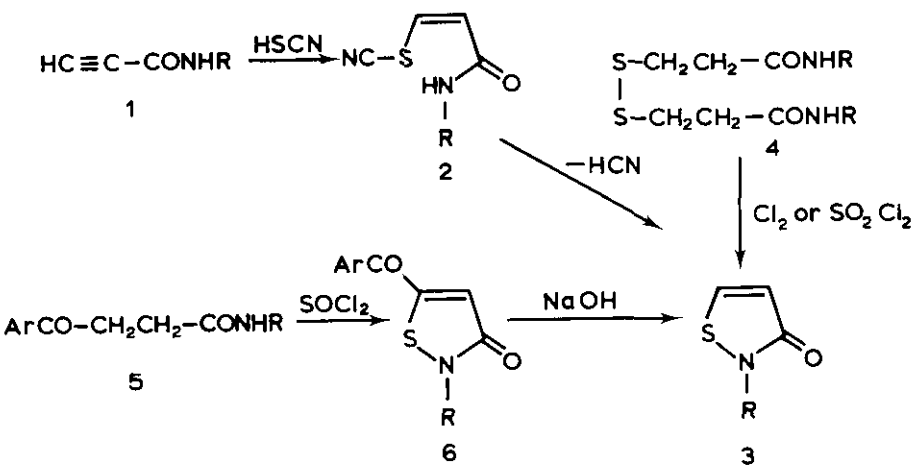
Abstract - 2-Substituted 3(2H)-isothiazolones 3 have been prepared from 2-substituted 5-aroyl-3(2H)-isothiazolones 6, which are readily available from N-substituted 3-aroylpropionamides 5. The nucleophilic displacement on the 5-aroyl group was found to proceed easily and quantitatively when a benzene solution of compound 6 was stirred at room temperature either with a 10% sodium hydroxide solution or with solid sodium hydroxide.

Access to the 3(2H)-isothiazolone ring system was first reported by Crow and Leonard[1] through the sequence 1 to 3 (Scheme 1). 2-Substituted derivatives of this system (3, R=-CH_3 and -CH_2CH_3) were thus obtained via the cyclization of the corresponding cis-3-thiocyanoacrylamides 2. A convenient and general syn-

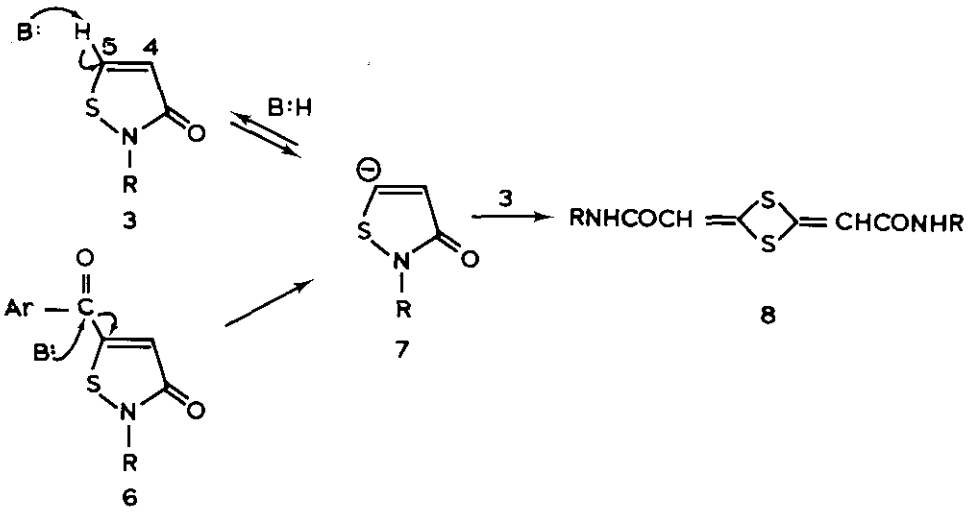
Scheme 1



thesis of a comprehensive series of 2-substituted 3(2H)-isothiazolones 3 was later reported by Lewis, et al.[2] This was achieved by the one-step chlorination-cyclization of readily available 3,3'-dithiopropionamides 4. On the other hand, reaction of γ-keto amides of the general formula 5 with excess thionyl chloride at room temperature results in the formation of 2-substituted 5-aroyl-3(2H)-isothiazolones 6[3,4]. We now report a simple synthesis of 2-substituted 3(2H)-isothiazolones 3 through a nucleophilic displacement on the 5-aroyl group of compounds 6.

N-Substituted 3(2H)-isothiazolones of the general formula 3 have been found[5] to dimerize readily by bases to 2,4-bismethylene-1,3-dithietanes 8 (Scheme 2). The dimerization was shown to proceed through attack of the initially formed 5-anion 7 on the S-N bond of a second isothiazolone molecule 3. Dithietanes of the general formula 8 were also obtained[3] from the N-substituted 5-aroyl-3(2H)-isothiazolones 6 by treatment with bases such as 5N sodium hydroxide, potassium t-butoxide in t-butyl alcohol and sodium ethoxide in ethanol. For instance, reaction of 2-benzyl-5-benzoyl-3(2H)-isothiazolone (6a) with sodium ethoxide in

Scheme 2



6a, Ar =	$-C_6H_5$,	R =	$-CH_2C_6H_5$	3a/8a, R =	$-CH_2C_6H_5$
6b	$-C_6H_5$		$-C_6H_5$	3b	$-C_6H_5$
6c	$-C_6H_5$		$-C_6H_4-Cl-p$	3c	$-C_6H_4-Cl-p$
6d	$-C_6H_4-OCH_3-p$		$-CH_3$	3d/8d	$-CH_3$
6e	$-C_6H_4-NO_2-m$		$-CH_2C_6H_5$		
6f	$-C_6H_2(CH_3)_3-2,4,6$		$-CH_2C_6H_5$		

refluxing ethanol has been found[6] to give the corresponding dithietane 8a in 90% yield. In this case, the 5-anion 7 would result from a nucleophilic displacement on the 5-benzoyl group of compound 6a.

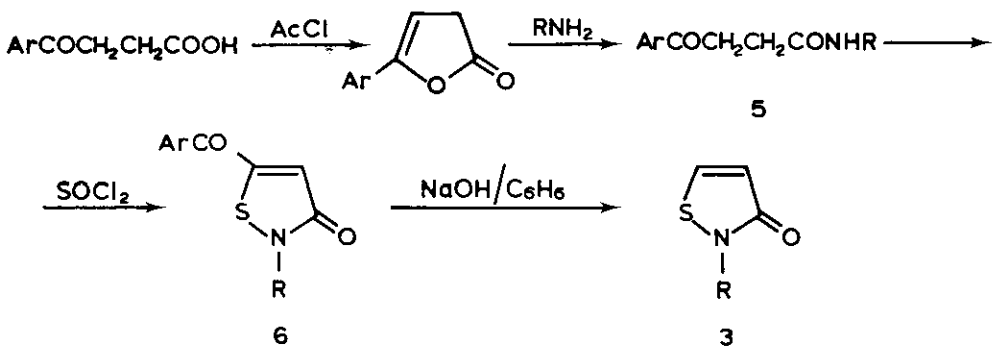
The debenzoylation reaction of compound 6a prior to dimer formation could be observed in sodium hydroxide solution (see Experimental). Thus, stirring compound 6a with a 20% aqueous sodium hydroxide solution for three days at room temperature resulted in complete transformation to the corresponding dithietane 8a, whereas treatment of compound 6a with a 10% sodium hydroxide solution for five days resulted in the isolation of a mixture consisting of the isothiazolone 3a (45%) and the dithietane 8a (55%). Moreover, similar results could be observed when the isothiazolone 3a was treated with a 20% or a 10% sodium hydroxide solution, respectively. The debenzoylation reaction of compound 6a can thus be clearly distinguished from the dimerization reaction of compound 3a, whose rate has been shown[5] to depend linearly on the concentration of the base. Following this observation, the debenzoylation of compound 6a was performed in a two-phase aqueous-organic system, in order to remove the resulting isothiazolone 3a from the basic medium needed for the dimerization reaction. A solution of compound 6a in benzene was thus stirred with a 10% sodium hydroxide solution for two days at room temperature and the isothiazolone 3a was actually isolated quantitatively from the benzene layer. It is then reasonable to assume[7] that the anion 7 is formed by reaction of the benzoylisothiazolone 6a with aqueous hydroxide ion at the interface between the aqueous and organic phases. The anion 7 resulting from the displacement reaction is subsequently protonated and the isothiazolone 3a is finally transferred into the organic phase.

Other 5-benzoylisothiazolones, such as 6b and 6c, could be debenzoylated equally well using the two-phase system and the corresponding isothiazolones, 3b and 3c respectively, were isolated in excellent yields. It should be noted that compound 3a could also be obtained from the m-nitrobenzoylisothiazolone 6e. In this case the transformation was complete in ninety minutes, since the aroyl carbonyl group is now much more reactive. On the other hand, the mesitoylisothiazolone 6f was recovered unchanged from a similar treatment, since the sterically hindered carbonyl of the mesitoyl group is not accessible to nucleophilic attack. However, a similar treatment of the p-methoxybenzoylisothiazolone 6d resulted in the isolation of the corresponding dithietane 8d. Since the cor-

responding N-methylisothiazolone 3d has been reported to be an extremely hygroscopic product[2], its formation was undoubtedly followed by dimerization in the aqueous alkaline phase.

The overall transformation of the aroylisothiazolones 6 to the corresponding isothiazolones 3 was finally found to proceed easily when a solution of 6 in benzene was stirred for just five minutes at room temperature in the presence of solid sodium hydroxide (see Experimental). Under these conditions, even the isothiazolone 3d was obtained from compound 6d in an almost quantitative yield. Consequently, the synthesis of 2-substituted 3(2H)-isothiazolones 3 can be accomplished by the sequence reported in Scheme 3. The nature of the substituent R, an alkyl or a substituted aryl or an aralkyl group, is finally determined from the availability of the open chain N-substituted 3-aroylpropionamides 5, which are easily prepared from 3-aroylpropionic acids.

Scheme 3



EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were obtained with a Perkin Elmer 267 spectrophotometer and were calibrated against the polystyrene 1601 cm^{-1} band; absorption bands, in reciprocal centimeters, are characterized as of strong (s), medium (m) or weak (w) intensity. The ^{1}H-nmr spectra were recorded on a Varian EM-360 60 MHz spectrometer; chemical shifts are given in ppm (δ) downfield from TMS (internal standard) and are accurate to ±0.02 ppm. Elemental analyses were obtained from the microanalytical laboratory of CNRS (France).

2-Substituted 5-aroyl-3(2H)-isothiazolones 6.

The preparation of the aroylisothiazolones 6a-6d by reaction of the corresponding γ-keto amides 5 with thionyl chloride has already been reported.[3]

The mesitoylisothiazolone 6f was prepared starting with 3-mesitoylpropionic acid[6] (cf. Scheme 3).

The same experimental procedure was used for the preparation of the m-nitrobenzoylisothiazolone 6e: A suspension of 7.35 g (35.8 mmol) of 5-(m-nitrobenzoyl)-furan-2(3H)-one, obtained from the reaction of 3-(m-nitrobenzoyl)propionic acid with acetyl chloride[8], in 50 ml of ether was cooled in an ice bath and benzylamine (4 ml, 36.7 mmol) was added portionwise. The mixture was stirred at 0°C for 10 min and then at room temperature for 24 h. The solvent was evaporated under vacuum and the solid residue was crystallized from ethanol to give 7 g (62%) of compound 5 (Ar = $-C_6H_4-NO_2-m$, R = $-CH_2C_6H_5$), mp 151-153°C(dec). Further recrystallizations from ethanol gave an analytically pure product, mp 152-154°C (dec); ir (nujol): sharp bands at 3315 (w), 1698 (s), 1645 (s); nmr (DMSO-d_6): 2.66 and 3.41 (two t, J = 6 Hz, 4H, $-CH_2CH_2-$), 4.33 (d, J = 5.8 Hz, 2H, N-benzyl methylene), 7.35 (s, 5H, phenyl protons), 7.71-8.83 (m, 5H, m-nitrophenyl protons and -NH-). Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.50; H, 5.15; N, 9.00.

A solution of the previous compound (3 g) in thionyl chloride (30 ml) was stirred at room temperature for 6 h and was then concentrated under vacuum. The solid residue was crystallized from ethanol to give 1.95 g (60%) of a yellow crystalline product, mp 108-111°C. Further recrystallizations from ethanol gave an analytically pure sample of compound 6e, mp 113.5-114.5°C; ir (nujol): sharp bands at 1663 (s), 1650 (s), 1615 (m), 1530 (s); nmr ($CDCl_3$): 5.06 (s, 2H, N-benzyl methylene), 6.86 (s, 1H, vinylic proton), 7.48 (s, 5H, phenyl protons), 7.66-8.93 (m, 4H, m-nitrophenyl protons). Anal. Calcd. for $C_{17}H_{12}N_2O_4S$: C, 59.99; H, 3.55; N, 8.23; S, 9.42. Found: C, 60.22; H, 3.44; N, 8.06; S, 9.34.

Reactions of benzoylisothiazolone 6a with aqueous NaOH.

A suspension of 0.3 g of compound 6a in 10 ml of a 20% aqueous sodium hydroxide solution was stirred at room temperature for 3 days. The insoluble material was filtered and washed with water to give 0.18 g (92%) of an almost colorless product, mp > 250°C. This was shown (nmr spectrum in deuteriochloroform) to be identical to the dithietane 8a[5].

A similar reaction of isothiazolone 3a for 6 days resulted also in the isolation of dithietane 8a.

A suspension of 0.5 g of compound 6a in 10 ml of a 10% aqueous sodium hydroxide solution was stirred at room temperature for 5 days. The insoluble material was filtered and shown (nmr spectrum in deuteriochloroform) to be a mixture of the isothiazolone 3a (45%) and the dithietane 8a (55%).

A similar reaction of isothiazolone 3a for 6 days resulted in the isolation of a mixture of the isothiazolone 3a (50%) and the dithietane 8a (50%).

Reaction of aroylisothiazolones 6 with aqueous NaOH/benzene.

General procedure: In a solution of 1 mmole of compound 6 in 20-70 ml of benzene, depending on the solubility of the compound, were added 10 ml (25 mmol) of a 10% aqueous sodium hydroxide solution. The mixture was stirred vigorously at room temperature, usually for 24 to 48 h, and the benzene layer was then separated, washed with water and concentrated under vacuum to give an almost quantitative yield of a solid residue, which was shown (nmr spectrum in deuteriochloroform) to be a pure sample of the corresponding isothiazolone 3[2].

The reaction of the m-nitrobenzoylisothiazolone 6e was complete after stirring the mixture for 90 min at room temperature.

The mesitoylisothiazolone 6f was recovered unchanged after a similar treatment.

The product obtained from the reaction of the p-methoxybenzoylisothiazolone 6d for 24 h at room temperature was shown (nmr spectrum in deuteriochloroform) to be a pure sample of the dithietane 8d[5].

Reaction of aroylisothiazolones 6 with solid NaOH/benzene.

General procedure: In a solution of 1 mmole of compound 6 in 20-70 ml of benzene, depending on the solubility of the compound, were added 0.2 g of powdered solid sodium hydroxide. The mixture was stirred vigorously at room temperature for 5 min, when a fading of the initial yellowish colour of the benzene layer could be observed. The benzene layer was then filtered and concentrated under vacuum to give a solid residue, which was shown (nmr spectrum in deuteriochloroform) to be a pure sample of the corresponding isothiazolone 3[2].

Isothiazolone 3a, obtained from compounds 6a and 6e, was isolated as a solid, mp 76-78°C after recrystallization from benzene/hexane (lit.[2] mp 78-80°C), in 82% yield.

Isothiazolone 3b, obtained from compound 6b, was isolated as a solid, mp 88-89°C

after recrystallization from toluene (lit.[2] mp 91-92°C), in 64% yield. Isothiazolone 3c was obtained from compound 6c as a solid mp 140-142°C after recrystallization from toluene (lit.[2] mp 142-144°C), in 70% yield. Isothiazolone 3d was obtained from compound 6d as an extremely hygroscopic low-melting solid (lit.[2] mp 48-50°C) in 90% yield and was not further purified. The nmr spectra of isothiazolones 3a-3d were identical with those already reported[2].

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