STUDIES ON HETEROCYCLIC CHEMISTRY. PART 22.[1] ACYLATION OF 4-ARYL-3-MERCAPTO-3-ISOTHIAZOLINE-5-THIONES WITH ARYL ISOCYANATE

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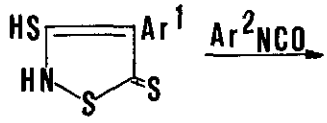
Abstract- The reaction of 4-aryl-3-mercapto-3-isothiazoline-5-thiones with aryl isocyanate result in exclusive formation of an N-acylated product, whose sulfur atom at C-5 undergoes a selective alkylation with diazomethane or alkyl iodide.

Recently we reported[1] that the reaction product of the sodium salt of arylcyanodithioacetic acid with sulfur[2] exists in solution as 4-aryl-3-mercapto-3-isothiazoline-5-thione (1) and it is acylated exclusively at the sulfur atom at C-3 with acid chloride in pyridine or alternatively with acid anhydride. To obtain a further insight into the relative reactivity of nitrogen versus sulfur of (1) towards acylating reagents, the reaction with aryl isocyanate were studied.

When 4-aryl-3-mercapto-3-isothiazoline-5-thiones (1a-c) (2 mmol) and aryl isocyanate (2 mmol) were heated in anhydrous tetrahydrofuran (20 ml), a good yield of the corresponding 1:1 adduct[3] was obtained as the only reaction product. The ir spectrum of the adduct reveals ν(NH), ν(C=O), and ν(C=S) absorptions at 3300, 1675-1695, and 1190-1200 cm^{-1}. The band position of the second falls in the range given for the ν(C=O) band of N-arylthiocarbamates (1662-1699 cm^{-1})[4] or 2-carbamoyl-4-isothiazoline-3-ones (1690-1720 cm^{-1}),[5] thus making difficult the assignment of the site of acylation. Like the starting isothiazolines,[1] the ^1H nmr spectrum of the adduct displays a singlet at δ 3.30 (SH).

The adduct of (1a) with phenyl isocyanate, when heated with dimethyl acetylenedicarboxylate in acetonitrile for 2 h, affords N-(phenylcarbamoyl)-[4,5-bis(methoxycarbonyl)-1,3-dithiol-2-ylidene]phenylethanethioamide (3) [85 %, mp 196-197° (decomp.) (from acetonitrile) (Found: C, 54.48; H, 3.83; N, 5.74; S, 19.77. $C_{22}H_{18}N_2O_5S_3$ requires C, 54.31; H, 3.73; N, 5.76; S, 19.77 %), $\lambda_{max.}$ 310 (log ε

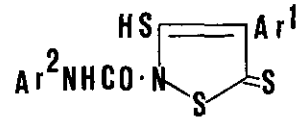


1

a; Ar^1=Ph

b; Ar^1=p-MeC_6H_4

c; Ar^1=p-ClC_6H_4



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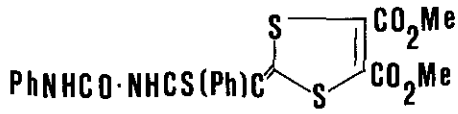
a; Ar^1=Ar^2=Ph

b; Ar^1=Ph, Ar^2=p-ClC_6H_4

c; Ar^1=Ph, Ar^2=α-Naphthyl

d; Ar^1=p-MeC_6H_4, Ar^2=Ph

e; Ar^1=p-ClC_6H_4, Ar^2=Ph



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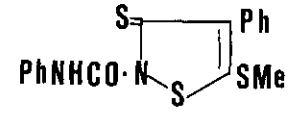

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3.93) and 421 nm (4.36), $\nu_{max.}$ 3300 (NH), 1690 (C=O), and 1215 cm^{-1} (C=S), δ_H ($CDCl_3$) 3.80 (s, 3H), 3.93 (s, 3H), 7.03-7.67 (m, 11H), and 7.93 (s, 1H)]. The ν(C=O) and ν(C=S) bands of (3) falls in the ranges recorded for those of thioacylureas.[6] The compound (3) could be independently prepared in 8 % yield[7] by heating for 24 h dimethyl 2-[phenyl(thiocarbamoyl)methylene]-1,3-dithiole-4,5-dicarboxylate[1] and phenyl isocyanate in benzene *in the presence of cuprous* oxide. Thus, the possibility that the sulfur atom at C-5 had been acylated was ruled out.

The adduct of (1a) with phenyl isocyanate gives an S-methyl derivative upon reaction with diazomethane [80 %, mp 195-197° (decomp.) (from aqueous acetone) (*Found*: C, 57.03; H, 3.90; N, 7.76. $C_{17}H_{14}N_2OS_3$ requires C, 56.96; H, 3.94; N, 7.81 %), $\lambda_{max.}$ 272 (log ε 3.93) and 380 nm (4.17), $\nu_{max.}$ 1705 (C=O), 1210 (C=S), and δ 1310 cm^{-1} (SMe), δ_H($CDCl_3$) 2.60 (s, 3H) and 7.30-7.57 (m, 10H)]. As this compound was unreactive towards dimethyl acetylenedicarboxylate even after heating for 72 h, the structure of 5-methylthio-4-phenyl-2-phenylcarbamoyl-4-isothiazoline-3-thione (4) was assigned. The compound (4) was alternatively prepared in 70 % yield by the treatment of the thallous salt of the adduct (prepared by adding thallous ethoxide into a solution of the adduct in dry tetrahydrofuran) with methyl iodide. Neither of the methods afforded the 3-methylthio derivative.

Thus, it is concluded that acylation of (1) with aryl isocyanate takes place

at nitrogen and the product is formulated as 4-aryl-2-arylcarbamoyl-3-mercapto-3-isothiazoline-5-thiones (2a-e), whose spectroscopic data are given in Table 1. Although we have made no detailed studies on the tautomeric equilibrium of (2), its existence in solution as the 5-thiol-3-thione form will be ruled out because the uv spectrum of (2) differs from that of (4). Our further conclusions derived from the present and earlier[1] observations are that the ralative reactivity of nitrogen versus sulfur of (1) towards acylation highly depends on the nature of an acylation reagent and that the sulfur atom at C-5 appears inert to acylation but it is selectively alkylated.

References and Notes

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3 Uv spectra were run for chloroform solutions and ir spectra as nujol mulls or KBr disks.

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5 S. N. Lewis, G. A. Miller, E. C. Szamborski, and M. Hausman, J. Heterocyclic Chem., 1971, 8, 587.

6 V. I. Cohen, J. Org. Chem., 1974, 20, 3043.

7 Isolation of (3) by means of chromatography (Kiesel gel 60/chloroform) was extremely difficult; the yield may be raised if other adequate separation technique is utilized.

Table 1

Spectroscopic Data of 4-Aryl-2-arylcarbamoyl-3-mercapto-3-isothiazoline-5-thiones (2a-e)

Compd.	Yield (%)	Recrystal. Solvent	Mp (°C) (decomp.)	$\lambda_{max.}$ nm (log ε)	$\nu_{max.}$	δ_H[$(CD_3)_2SO$]
(2a)[a]	96	aq. Me_2CO	203-204	319 (4.20)	3300	3.30 (s, 1H)
				405 (4.09)	1685	7.30 (m, 7H)
					1200	7.60-7.80 (m, 3H)
						9.40 (br s, 1H)
(2b)[b]	72	MeCN	203-204	320 (4.65)	3300	2.05 (s, 3H)
				407 (4.52)	2250	3.37 (s, 1H)
					1695	7.20-7.63 (m, 9H)
					1195	9.40 (br s, 1H)
(2c)[c]	78	MeCN	204-205	317 (4.41)	3350	
				406 (4.39)	2250	
					1695	
					1200	
(2d)[d]	69	$CHCl_3$-Petroleum	190-191	320 (4.25)	3200	2.40 (s, 3H)
				406 (4.17)	1680	3.30 (s, 1H)
					1190	7.46-7.73 (m, 9H)
						9.40 (br s, 1H)
(2e)[e]	68	aq. Me_2CO	188-189	320 (4.42)	3270	2.00 (s, 6H)
				406 (4.36)	1705	3.30 (s, 1H)
					1195	7.13-7.67 (m, 9H)
						9.50 (br s, 1H)

[a] Found: C, 55.90; H, 3.43; N, 8.00. $C_{16}H_{12}N_2OS_3$ requires C, 55.78; H, 3.51; N, 8.13 %. [b] Found: C, 51.54; H, 3.44; N, 10.01; S, 23.17. $C_{16}H_{11}ClN_2OS_3 \cdot CH_3CN$ requires C, 51.47; H, 3.36; N, 10.01; S, 22.91 %. [c] Found: C, 60.80; H, 3.76; N, 8.33; S, 23.27. $C_{20}H_{14}N_2OS_3 \cdot 1/2CH_3CN$ requires C, 60.77; H, 3.76; N, 8.44; S, 23.18 %. [d] Found: C, 54.15; H, 3.67; Cl, 4.63; N, 7.51; S, 25.82. $C_{17}H_{14}N_2OS_3 \cdot 1/6CHCl_3$ requires C, 54.45; H, 3.77; Cl, 4.69; N, 7.41; S, 25.42 %. [e] Found: C, 52.19; H, 3.95; N, 6.40; S, 22.17. $C_{16}H_{11}ClN_2OS_3 \cdot (CH_3)_2CO$ requires C, 52.22; H, 3.92; N, 6.41; S, 22.01 %.

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