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

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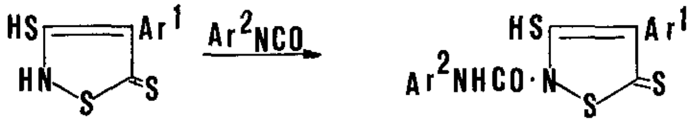
Abstract- The reaction of 4-aryl-3-mercapto-3-isothiazoline-5-thiones with aryl isocyanate result in exclusive formation of an N-acylated product, whose sulfur atom at C-5 undergoes a selective alkylation with diazomethane or alkyl iodide.

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 ^{1}H 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 **2**

a; Ar^1=Ph

b; Ar^1=*p*-MeC$_6$H$_4$

c; Ar^1=*p*-ClC$_6$H$_4$

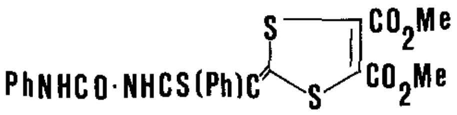
a; Ar^1=Ar^2=Ph

b; Ar^1=Ph, Ar^2=*p*-ClC$_6$H$_4$

c; Ar^1=Ph, Ar^2=α-Naphthyl

d; Ar^1=*p*-MeC$_6$H$_4$, Ar^2=Ph

e; Ar^1=*p*-ClC$_6$H$_4$, Ar^2=Ph



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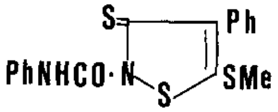

4

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

[1] Part 21, T. Nishiwaki, E. Kawamura, N. Abe, and M. Iori, *J.C.S. Perkin Trans. I*, in the press.

[2] M. Davis, G. Snowling, and R. W. Winch, *J. Chem. Soc. (C)*, 1967, 124.

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

[4] L. J. Bellamy, 'Advances in Infrared Group Frequencies,' Methuen, New Fetter Lane, 1968, p. 181.

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