STUDIES ON ALKYL ISOCYANOACETATES AND RELATED COMPOUNDS. SYNTHESIS OF 6-ARYLTHIO-8-ETHOXYCARBONYL-4-ETHOXYCARBONYL-METHYLAMINOIMIDAZO[5,1-b][1,3,5]THIADIAZINE-2-THIONES

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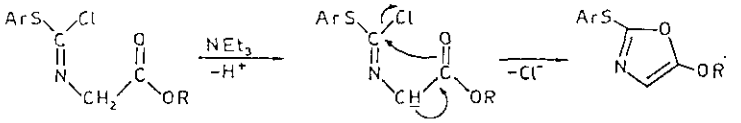
Abstract — *N*-Ethoxycarbonylmethyl-*S*-arylisothiocarbamoylisothiocyanates (**4**) upon treatment with NEt_3 and then with HCl afforded 6-arylthio-8-ethoxycarbonyl-4-ethoxycarbonylmethylamino-imidazo[5,1-b][1,3,5]thiadiazine-2-thiones (**6**).

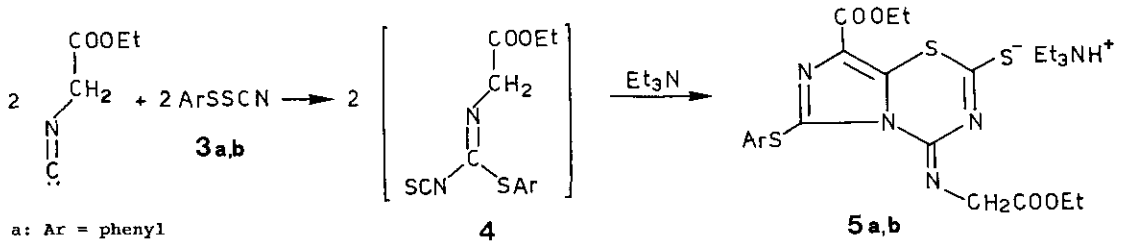
In a previous paper[1] we reported the ring-closure reaction of *N*-alkoxycarbonylmethyl- *S*-arylisothiocarbamoyl chlorides (**1**) to oxazoles **2** with NEt_3.



1 **2**

In continuation of our studies on the reactivity of isonitriles towards compounds containing SCl groups[1-6] and SSCN groups[7] we decided to investigate the behavior of *N*-ethoxycarbonylmethyl- *S*-arylisothiocarbamoyl isothiocyanates (**4**) towards NEt_3 in order to ascertain the changes of reactivity due to the substitution of the

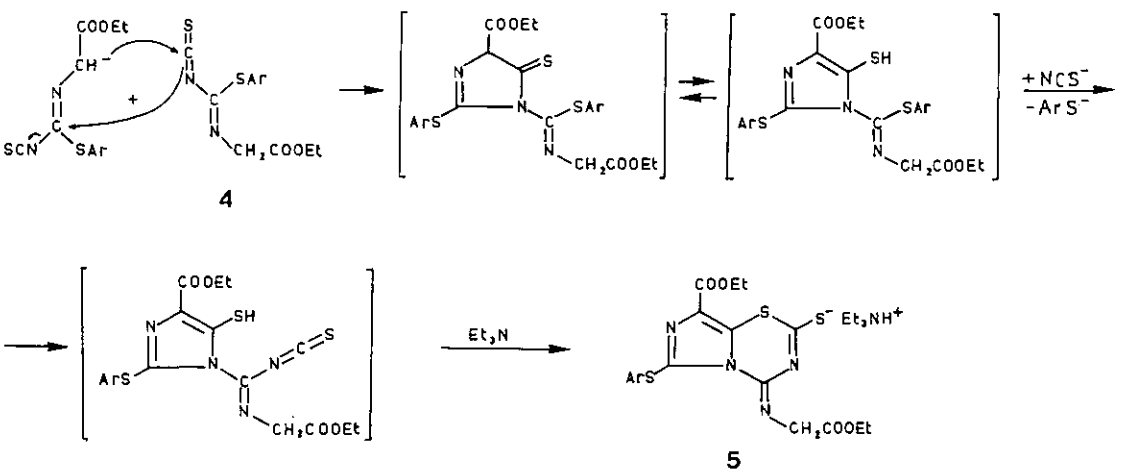
chlorine atom of **1** with a -N=C=S group. Compounds **4** were prepared *in situ* by reacting ethyl isocyanoacetate with arylsulfenyl thiocyanates (**3**) in CH_2Cl_2. Upon treatment of the above solution with NEt_3 an unexpected ring-closure reaction took place which afforded the triethylammonium salts **5**.



a: Ar = phenyl
b: Ar = 4-chlorophenyl

A possible reaction pathway is reported in the scheme.

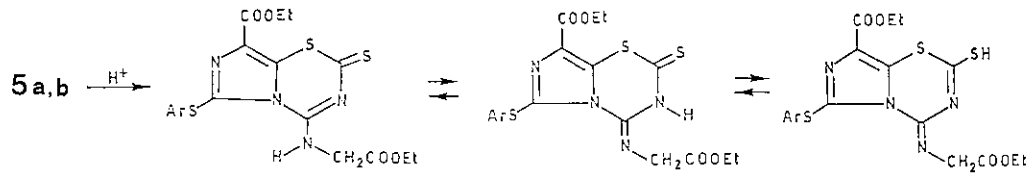
Scheme



Since the analytical and spectral data were insufficient for complete structural determination of **5a,b** we performed an X-ray analysis of 6-(4-chlorophenylthio)-8-ethoxycarbonyl-4-ethoxycarbonylmethylimino-2-mercapto- imidazo[5,1- b][1,3,5]thiadiazine triethylammonium salt (**5b**) (see Figure).

As expected upon treatment of **5** with dilute HCl at room temperature the title compounds **6** were obtained.

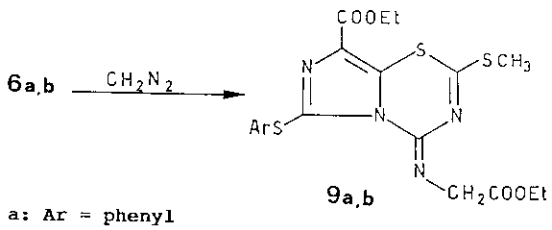
Tautomeric structures **7** and **8** were rejected on the basis of the ^{1}H-nmr data of the products obtained by treating **5** with HCl. In these spectra a signal, due to the exocyclic NH group, appears at about δ 10.45. Furthermore a doublet signal at about δ 4.40 is seen due to the CH_2 group which is coupled with the NH one. Upon treatment with D_2O the signal at about δ 10.45 disappears and a singlet signal due to the CH_2 group appears.



a: Ar = phenyl

b: Ar = 4-chlorophenyl

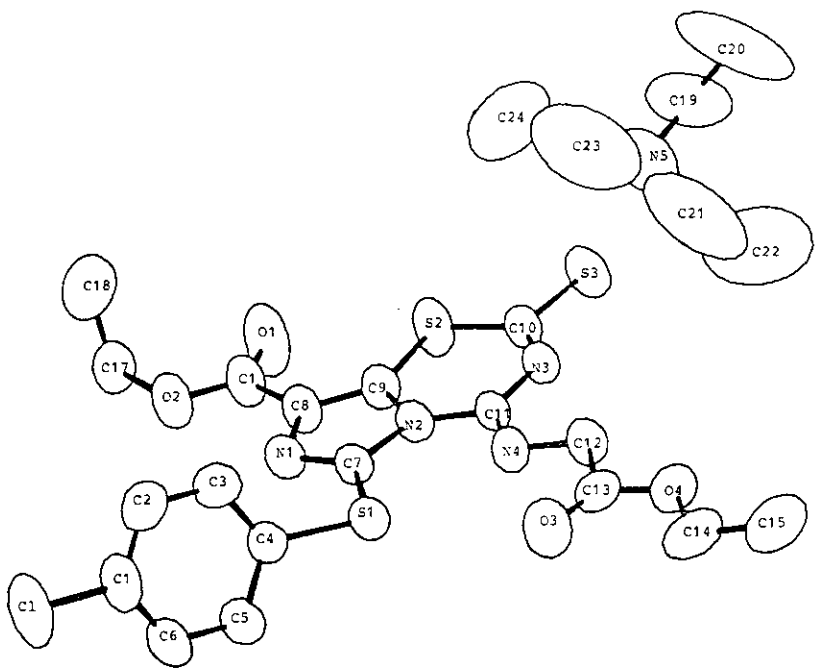
Upon treatment of **6** with CH_2N_2 the SCH_3 derivatives **9** were obtained.



a: Ar = phenyl

b: Ar = 4-chlorophenyl

Figure: Diagram showing the structure of **5b**



EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ^{1}H-nmr spectra were recorded with a Varian VX 300 apparatus, chemical shifts are reported in ppm (δ) from TMS. The ir spectra were recorded with a Perkin-Elmer 881 apparatus for KBr discs.

6-Arylthio-8-ethoxycarbonyl-4-ethoxycarbonylmethylimino-2-mercaptoimidazo[5,1-b][1,3,5]thiadiazine Triethylammonium Salts (5a,b)

General procedure- A solution of arylsulphenyl thiocyanate (**3**)[7] (19 mmol) in CH_2Cl_2 (15 ml) was slowly dropped into a solution of ethyl isocyanoacetate (2.18 g, 19 mmol) in CH_2Cl_2 (15 ml) maintaining the temperature at -50 °C. The resulting solution was allowed to react until the temperature rose to 20 °C and then NEt_3 (3.85 g, 38 mmol) was quickly added. The solvent was partially removed under reduced pressure and then Et_2O (70 ml) was added. The resulting suspension was cooled and filtered to give **5**.

5a: 75% yield, mp 127-128 °C from EtOH; ir: 1755,1685,1660 cm^{-1}; ^{1}H-nmr(DMSO-d_6): 7.52-7.38(m, 5H, aromatic protons), 4.45(s, 2H, CH_2), 4.35-4.13(m, 4H, OCH_2), 3.55(m,1H,NH), 3.43-3.35(m,6H,NCH_2), 1.42-1.05(m, 15H, CH_3). *Anal.* Calcd for $C_{24}H_{33}N_5O_4S_3$: C, 52.25; H, 6.03; N, 12.69. Found: C, 52.42; H, 6.15; N, 12.81.

5b: 77% yield, mp 129-130 °C from EtOH; ir: 1750,1680,1660 cm^{-1}; ^{1}H-nmr(DMSO-d_6): 7.58-7.40(m,4H,aromatic protons), 4.36(s,2H,CH_2), 4.20-4.09(m,4H,OCH_2), 3.27(m,1H,NH), 3.13- 3.05(m,6H,NCH_2), 1.24-1.15(m,15H,CH_3). *Anal.* Calcd for $C_{24}H_{32}N_5O_4ClS_3$: C, 49.18; H, 5.50; N, 11.95. Found: C, 49.09; H, 5.45; N, 11.83.

6-Arylthio-8-ethoxycarbonyl-4-ethoxycarbonylmethylaminoimidazo[5,1-b][1,3,5]thiadiazine-2-thiones (6a,b)

General procedure- A suspension of **5** (10 mmol) in water (75 ml) was stirred for 20 min at room temperature and then acidified with dilute HCl to *p*H 3. Compound **6** was collected in almost quantitative yield by filtration.

6a: 98% yield, mp 133-134 °C from EtOH; ir: 3240,1740,1700,1610 cm^{-1}; ^{1}H- nmr(DMSO-d_6): 10.44(broad,1H,NH), 7.49-7.38(m,5H,aromatic protons), 4.44(d,J = 0.3 Hz,2H,CH_2), 4.31-4.12(m,4H,CH_2), 1.31-1.18(m,6H,CH_3). *Anal.* Calcd for $C_{18}H_{18}N_4O_4S_3$: C, 47.99; H, 4.03; N, 12.44. Found: C, 47.86; H, 3.92; N, 12.26.

6b: 97% yield, mp 165-166 °C from EtOH; ir: 3245,1750,1700,1610 cm^{-1}; ^{1}H- nmr(DMSO-d_6): 10.43(broad,1H,NH), 7.61-7.48(m,4H,aromatic protons), 4.38(d,J = 0.3 Hz,2H,CH_2), 4.27-4.16(m,4H,CH_2), 1.27-1.22(m,6H,CH_3). *Anal.* Calcd for $C_{18}H_{17}N_4O_4ClS_3$: C, 44.58; H, 3.53; N, 11.55. Found: C, 44.61; H, 3.43; N, 11.70.

6-Arylthio-8-ethoxycarbonyl-4-ethoxycarbonylmethylimino-2-methylthioimidazo[5,1-b][1,3,5]thiadiazines (9a,b)

General procedure- A suspension of finely powdered **6** (5 mmol) in EtOH (30 ml) was treated with a large excess of diazomethane in Et_2O. The mixture was allowed to react overnight at room temperature. The resulting solution was evaporated to dryness to give **9** in almost quantitative yield.

9a: 98% yield, mp 133-134 °C from EtOH; ir: 1760,1740,1660 cm^{-1}; ^{1}H- nmr($CDCl_3$): 7.67-7.38(m,5H,aromatic protons), 4.60(s,2H,CH_2), 4.32-4.23(m,4H,CH_2), 2.65(s,3H,SCH_3), 1.35-1.30(m,6H,CH_3). *Anal.* Calcd for $C_{19}H_{20}N_4O_4S_3$: C, 49.12; H, 4.34; N, 12.06. Found: C, 49.25; H, 4.31; N, 12.16.

9b: 98% yield, mp 163-164 °C from EtOH; ir: 1730,1690,1660 cm^{-1}; ^{1}H- nmr($CDCl_3$): 7.57-7.32(m,4H,aromatic protons), 4.57(s,2H,CH_2), 4.31-4.22(m,4H,CH_2), 2.63(s,3H,SCH_3), 1.33-1.28(m,6H,CH_3). *Anal.* Calcd for $C_{19}H_{19}N_4O_4ClS_3$: C, 45.73; H, 3.84; N, 11.23. Found: C, 45.85; H, 3.88; N, 11.35.

X-ray Crystallographic Data

$C_{24}H_{32}N_5O_4ClS_3$, molecular weight = 586.18, crystallizes in the triclinic space group P1 with a = 14.798(2), b = 13.401(2), c = 8.148(1) A; α = 76.0(1)°, β = 79.4(1)°, γ = 70.0(1)°; V = 1464.2 A^3; Z = 2; m = 3.3 cm^{-1}; Dc = 1.32 g cm^{-3}; 7069 independent reflections were read on a Philips PW 1100 four cycle diffractometer, Θ-2Θ scan mode to 2Θ = 56°, using Mo Kα radiation (λ = 0.7107 A). The structure was phased by Multan 80 program and refined by full-matrix least squares with anisotropic thermal parameters for all non hydrogen atoms. Hydrogen atoms were partially located on a DF map and isotropically refined. The final conventional R factor for the 4311 reflections considered observed, $I > 7\sigma(I)$, was 0.0582.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England.

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