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

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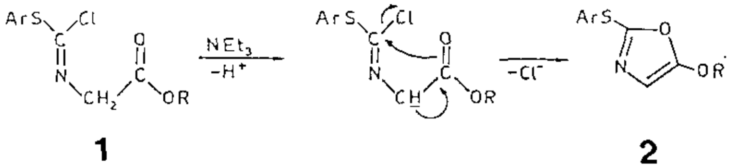
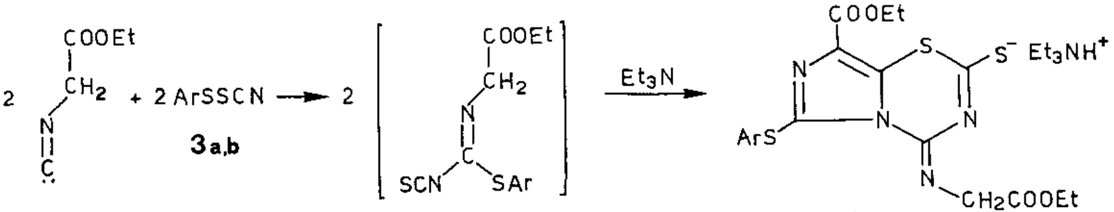
Abstract – *N*-Ethoxycarbonylmethyl-*S*-arylisothiocarbamoylisothiocyanates (**4**) upon treatment with NEt_3 and then with HCl afforded 6-arylthio-8-ethoxycarbonyl-4-ethoxycarbonylmethylamino-imidazo[5,1-b][1,3,5]thiadiazine-2-thiones (**6**).

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**

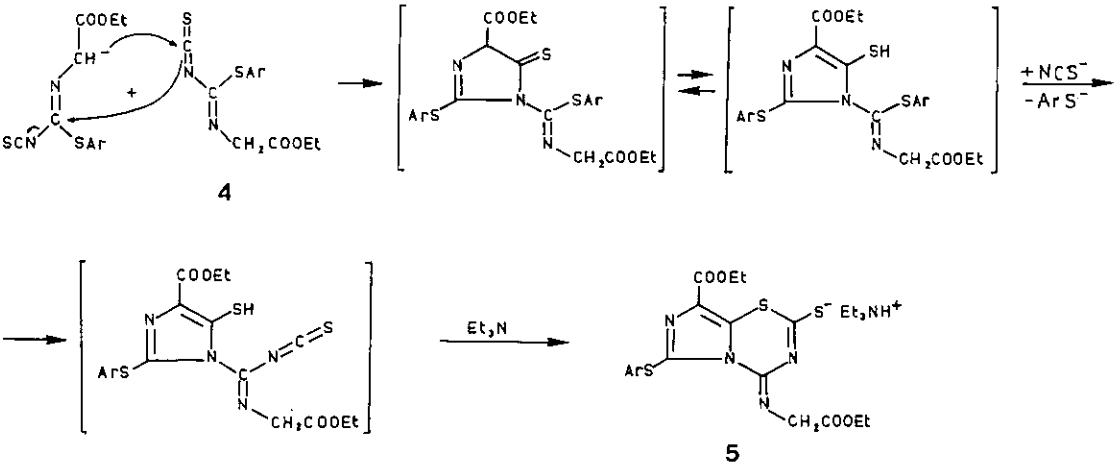
In continuation of our studies on the reactivity of isonitriles towards compounds containing SCl groups[1-6] and SSCN groups[7] we decided to investigate the behavior of *N*-ethoxycarbonylmethyl- *S*-arylisothiocarbamoyl isothiocyanates (**4**) towards NEt_3 in order to ascertain the changes of reactivity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

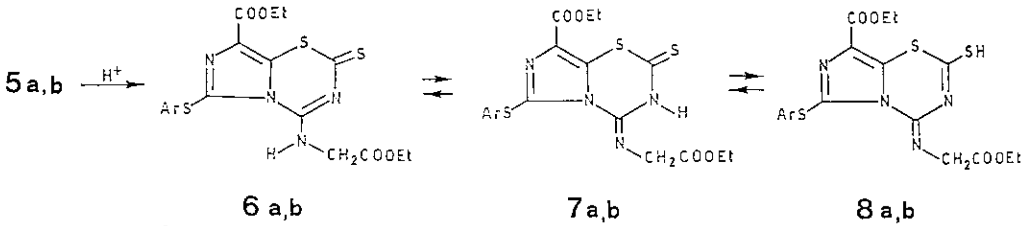
Scheme



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.

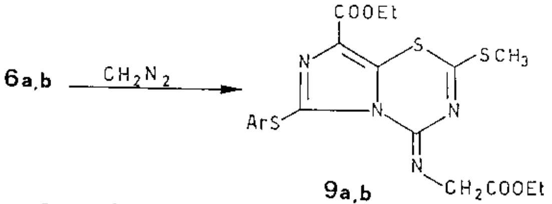
Tautomeric structures **7** and **8** were rejected on the basis of the ^{1}H-nmr data of the products obtained by treating **5** with HCl. In these spectra a signal, due to the exocyclic NH group, appears at about δ 10.45. Furthermore a doublet signal at about δ 4.40 is seen due to the CH_2 group which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

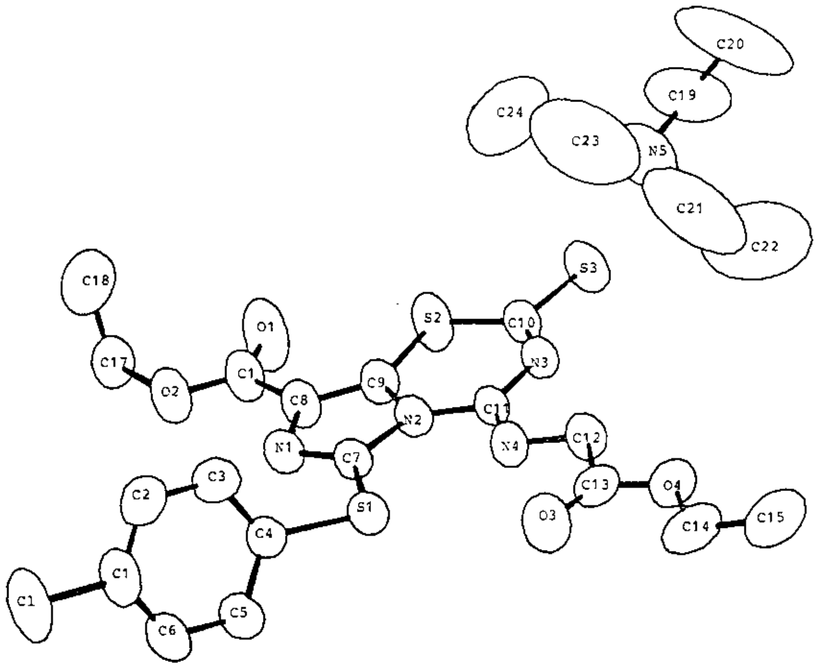
Upon treatment of **6** with CH_2N_2 the SCH_3 derivatives **9** were obtained.



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 ^1H-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.

REFERENCES

1. R. Bossio, S. Marcaccini, and R. Pepino, *Heterocycles*, 1986, **24**, 2003.
2. R. Bossio, S. Marcaccini, and R. Pepino, *Heterocycles*, 1986, **24**, 2411.
3. R. Bossio, S. Marcaccini, and R. Pepino, *Tetrahedron Lett.*, 1986, **27**, 4643.
4. R. Bossio, S. Marcaccini, R. Pepino, T. Torroba, and G. Valle, *Synthesis*, 1987, 1138.
5. R. Bossio, S. Marcaccini, R. Pepino, C. Polo, and G. Valle, *Synthesis*, 1989, 641.
6. R. Bossio, S. Marcaccini, R. Pepino, C. Polo, and T. Torroba, *Heterocycles*, 1989, **29**, 1829.
7. R. Bossio, S. Marcaccini, R. Pepino, C. Polo, T. Torroba, and G. Valle, *Heterocycles*, 1989, **29**, 1843.

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