

SYNTHESIS OF 1-ARYLTHIOCARBONYL-4-ISOPROPYLAMINO-2,5-DIHYDRO-1H-
IMIDAZOLE-2-THIONES, A NOVEL CLASS OF IMIDAZOLE DERIVATIVES

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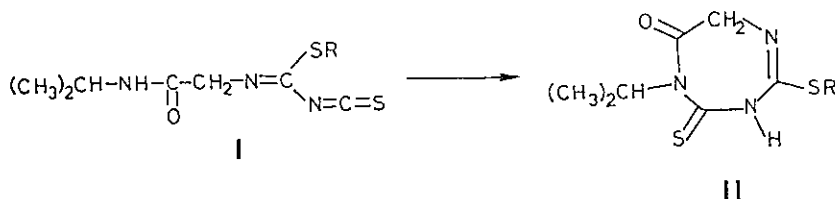
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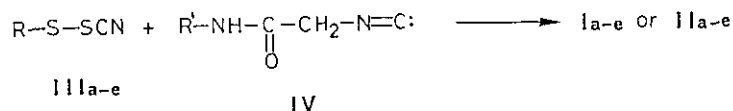
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Abstract — The reaction between *N*-isopropylisocyanacetamide (IV) and arylsulfenyl thiocyanates (IIIa-e) provides a useful route to 1-aryltrithiocarbonyl-4-isopropylamino-2,5-dihydro-1H-imidazole-2-thiones (Va-e), a novel class of imidazole derivatives, whose structure was determined by X-ray analysis.

Continuing our studies on the synthesis of heterocyclic compounds by means of isonitriles and sulfenyl chlorides or related compounds¹⁻⁴, we decided to attempt the synthesis of some triazepine derivatives (II) by cyclizing *S*-aryl-*N*-(isopropylaminocarbonylmethyl)isothiocarbamoyl isothiocyanates (I).



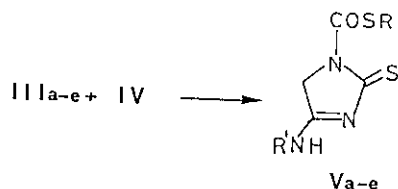
Since sulfenyl thiocyanates readily react with isonitriles to give isothiocarbamoyl isothiocyanates⁵, we reacted arylsulfenyl thiocyanates (III) with *N*-isopropylisocyanacetamide (IV) in order to obtain the desired compounds (I), whose structure appeared to be suitable for an easy cyclization to II.



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|-----------------------|-------------------------------|
| a R = phenyl- | d R = 2-nitrophenyl- |
| b R = 4-methylphenyl- | e R = 4-chloro-2-nitrophenyl- |
| c R = 4-chlorophenyl- | R' = isopropyl- |

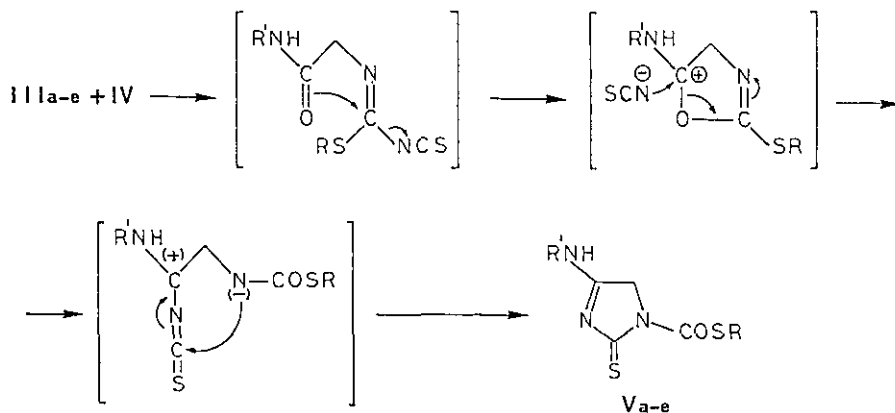
The ^1H -nmr spectra of the reaction products allowed us to eliminate the hypothesis of seven-membered ring structures II since the CH proton of the isopropyl group appears to be coupled with another proton. Upon treatment with D_2O the coupling disappears and this suggests that the isopropyl moiety is linked to a group containing an exchangeable hydrogen. Furthermore the ir spectra of the reaction products allowed us to reject the open structures I since the strong -NCS group absorption is lacking.

Although neither compounds I nor compounds II were obtained, the behaviour of *N*-isopropylisocyanacetamide (IV) toward arylsulfenyl thiocyanates (III) was interesting. In fact the reaction between compounds III and IV afforded the unexpected 1-arylthiocarbonyl-4-isopropylamino-2,5-dihydro-1*H*-imidazole-2-thiones (V) in good yields.



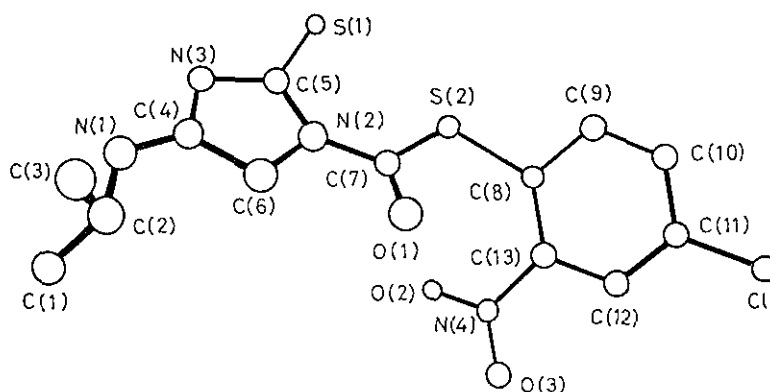
A possible reaction pathway is reported in the scheme.

Scheme



The ir and ^1H -nmr spectra of compounds (V) are closely similar. This agrees with the presence of the same moiety in all of these compounds. Since we considered the analytical and spectral data of compounds (V) as unsuitable for the determination of their structure, we carried out an X-ray analysis of Ve.

Figure: Diagram showing the structure of Ve



The physical and spectral data of compounds V are summarized in the following table.

Table: 1-Arylthiocarbonyl-4-isopropylamino-2,5-dihydro-1H-imidazole-2-thiones V

No.	mp °C ^a Solvent	Yield %	Ir ^b ν (cm ⁻¹)	$^1\text{H-Nmr}$ ^c δ, ppm
Va	223-224 DMF	75	3280 1660	9.35 (d, 1H, NH, $J=0.9$); 4.70 (s, 2H, CH ₂); 4.10 (m, 1H, CH); 1.19 (d, 6H, 2 CH ₃ , $J=0.9$)
Vb	220-221 DMF	70	3280 1645	9.32 (d, 1H, NH, $J=0.9$); 4.70 (s, 2H, CH ₂); 4.10 (m, 1H, CH); 1.19 (d, 6H, 2 CH ₃ , $J=0.9$)
Vc	218-219 DMF/H ₂ O	73	3280 1660	9.45 (d, 1H, NH, $J=0.9$); 4.66 (s, 2H, CH ₂); 4.10 (m, 1H, CH); 1.19 (d, 6H, 2 CH ₃ , $J=0.9$)
Vd	193-194 dioxane	72	3280 1650	9.40 (d, 1H, NH, $J=0.9$); 4.70 (s, 2H, CH ₂); 4.10 (m, 1H, CH); 1.20 (d, 6H, 2 CH ₃ , $J=0.9$)
Ve	159-160 DMF/EtOH	65	3280 1645	9.44 (d, 1H, NH, $J=0.9$); 4.69 (s, 2H, CH ₂); 4.10 (m, 1H, CH); 1.19 (d, 6H, 2 CH ₃ , $J=0.9$)

^a Uncorrected. ^b Measured on a Perkin-Elmer 283 apparatus for KBr discs.

^c Carried out with a Varian VX 300 apparatus for DMSO-d₆ saturated solutions employing TMS as internal reference.

EXPERIMENTAL

Arylsulfenyl thiocyanates IIIa-e

General procedure— The appropriate sulfenyl chloride (16 mmol) was added to a well-stirred suspension of finely powdered and carefully dried ammonium thiocyanate (19.2 mmol) in dry benzene (50 ml). The resulting mixture was stirred at room temperature for 24 h and then filtered. The filtrate was evaporated to dryness under reduced pressure, and the residue used for the successive reaction without further purification, assuming a 100% yield.

N-Isopropylisocyanoacetamide (IV)

This compound (IV) was prepared according to the literature ⁶.

1-Arylthiocarbonyl-4-isopropylamino-2,5-dihydro-1*H*-imidazole-2-thiones Va-e

General procedure— A solution of the appropriate sulfenyl thiocyanate (16 mmol) in CH₂Cl₂ (50 ml) was slowly added to a well-stirred solution of IV (2.02 g, 16 mmol) in CH₂Cl₂ (40 ml) maintaining the temperature at -50 °C. The resulting mixture was stirred, without removing the cooling bath, until the temperature rose to 20 °C, and then evaporated to dryness under reduced pressure. The residue was recrystallized from a suitable solvent to give Va-e.

Microanalytical data:

Va	Calcd for C ₁₃ H ₁₅ N ₃ OS ₂ : C, 53.21; H, 5.15; N, 14.32.
	Found: C, 52.98; H, 5.08; N, 14.16.
Vb	Calcd for C ₁₄ H ₁₇ N ₃ OS ₂ : C, 54.69; H, 5.57; N, 13.67.
	Found: C, 54.71; H, 5.49; N, 13.73.
Vc	Calcd for C ₁₃ H ₁₄ ClN ₃ OS ₂ : C, 47.62; H, 4.30; N, 12.82.
	Found: C, 47.59; H, 4.50; N, 12.90.
Vd	Calcd for C ₁₃ H ₁₄ N ₄ O ₃ S ₂ : C, 46.14; H, 4.17; N, 16.55.
	Found: C, 46.22; H, 4.02; N, 16.70.
Ve	Calcd for C ₁₃ H ₁₃ ClN ₄ O ₃ S ₂ : C, 41.78; H, 3.51; N, 15.02.
	Found: C, 41.73; H, 3.64; N, 14.91.

X-ray Crystallographic Data

C₁₃H₁₃ClN₄O₃S₂, molecular weight = 372.85, crystallizes in the monoclinic system, space group P2₁/_n (N.14) with a = 18.105(2), b = 9.091(1), c = 10.006(1) Å; β = 105.7(2)°; Z = 4; V = 1585.5 Å³; μ = 4.6 cm⁻¹; D_c = 1.413 g cm⁻³, 3902 (3499 unique R = 0.02) reflections were read on a Philips PW1100 four cycle diffractometer θ-2θ

scan mode to $2\theta = 56^\circ$, using Mo K α radiation ($\lambda = 0.7107 \text{ \AA}$). The structure was phased by Multan 80 program and refined by full-matrix least squares with unit weights. The non hydrogen atom thermal parameters were anisotropic, hydrogen atoms were located on a DF map and refined isotropically. The final conventional R factor for the 2348 reflections considered observed, $I \geq 3\sigma(I)$, was 0.0416. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, England.

REFERENCES

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- 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 E.Kühle, *The Chemistry of the Sulfenic Acids*, Georg Thieme Verlag, Stuttgart, 1973, p. 57.
- 6 J.P.Chupp and K.L.Leschinsky, *J.Heterocyclic Chem.*, 1980, 17, 705.

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