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A CONVENIENT SYNTHESIS OF 4-(2-PYRIDYL)IMIDAZOLIDINE-2-THIONES BY THE REARRANGEMENT OF IMIDAZO[1,5-a]PYRIDINE-3-THIONE

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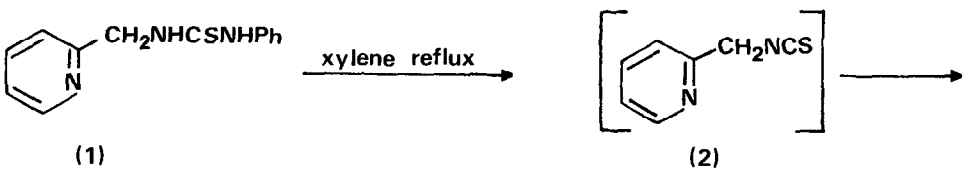
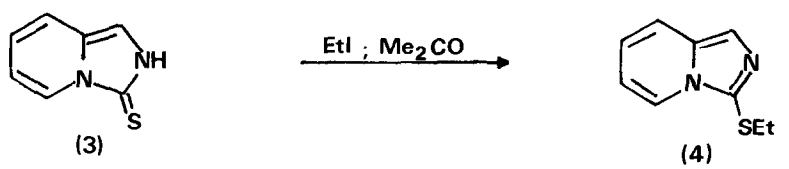
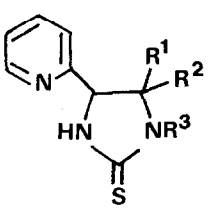
Abstract - Imidazo[1,5-a]pyridine-3(2H)-thione reacts with amines and aldehydes or ketones to give pyridylimidazolidine thiones.

We have recently described the use of the thioether (4) in the synthesis of imidazo[1,5-a] pyridines[1] and other heterocycles[2]. The precursor to the thioether (4) is the imidazopyridine (3) which is prepared by the thermolysis of the thiourea (1) in refluxing xylene[3]. We believe that under these conditions, the thiourea (1) loses aniline to give the isothiocyanate (2)[4-5], which cyclises spontaneously to the imidazopyridine (3). The latter crystallises from the reaction mixture on cooling and is used without further purification.

During the preparation of a large batch of the thioether (4) from the imidazopyridine (3) using acetone as solvent, we isolated a small quantity (200 mg) of the imidazolidine thione (5a). Our crude imidazopyridine (3) is generally contaminated with traces of the







(5)

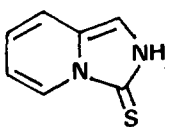
a) $R^1 = R^2 = Me$; $R^3 = Ph$

b) $R^1, R^2 = (CH_2)_5$; $R^3 = Ph$

c) $R^1, R^2 = (CH_2)_5$; $R^3 = CH_2$

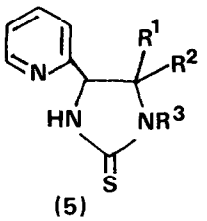
thiourea (1)[6] and as such it was conceivable that the thione (5a) had been formed by cyclodehydration of the thiourea (1) with acetone. This unlikely possibility was ruled out when the thiourea (1) failed to react with acetone under the conditions of the alkylation. However, under more vigorous conditions (180°) cyclohexanone reacted with the thiourea (1) to give a mixture of two imidazolidine thiones (5b) and (5c). The presence of the thione (5c) indicated that the thiourea (1) had undergone disproportionation and hence suggested the intermediacy of the imidazopyridine (3) in the formation of the thiones (5). Indeed the imidazopyridine (3) reacted with aniline and acetone in ethanol at 60° in the presence of a catalytic amount of p-TSA to give the thione (5a) in 93% yield. Further investigation showed that the imidazopyridine (3) reacted in high yield with a variety of primary amines and aldehydes or ketones to give imidazolidinethiones (5)[7], a selection of which is given in the table.

Table



(3)

R^1R^2CO ; R^3NH_2



(5)

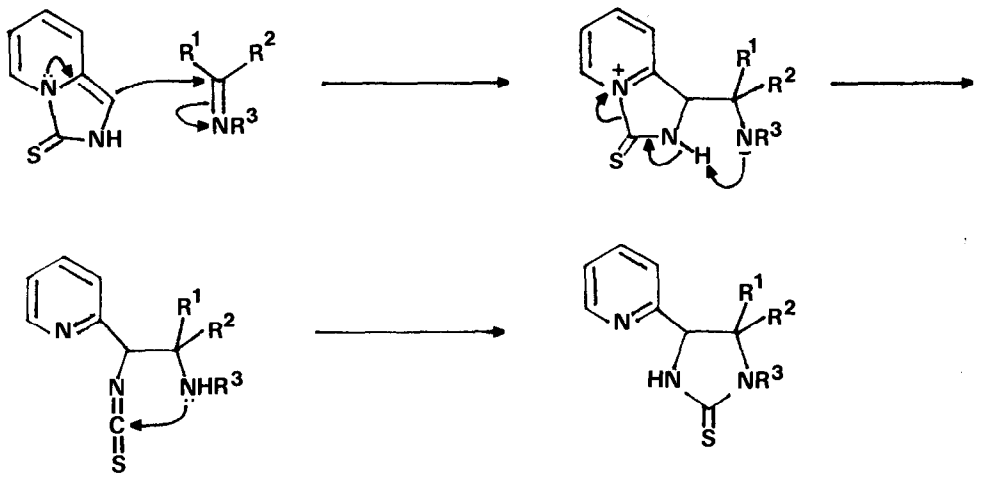
R_1	R_2	R_3	Yield %
H	H	Me	77
H	Ph	Me	95[a]
Me	Me	Me	75
Me	Me	Ph	93
Me	Me	p-$MeOC_6H_4$	70
Me	Me	CH_2Ph	74
-$(CH_2)_5$-		CH_2CH_2OH	93
-$(CH_2)_5$-		$CH_2CH_2NMe_2$	83
Me	Et	Me	91[b]

(a) cis:trans ratio 2 : 1; (b) cis:trans ratio 1 : 1

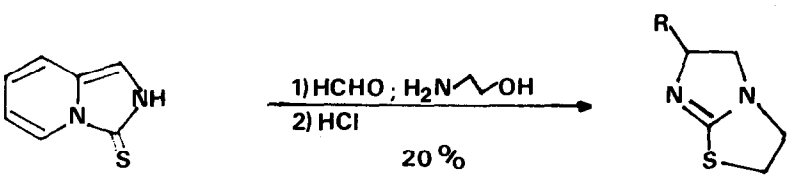
Example: A solution of imidazo[1,5-a]pyridine-3(2H)-thione (10g, 0.066 mol) and p-toluene sulphonic acid (5 mg) in acetone (60 ml) and ethanolic methylamine (33% w/w; 160 ml, 0.132 mol) was stirred at 90°C for 20 min. The mixture was evaporated and the residual yellow solid crystallised from a mixture of ethanol and petroleum ether (bp. 60-80°) to give 4-(2-pyridyl)-1,5,5-trimethylimidazolidine-2-thione as colourless needles (11.1g, 75%) mp. 160-161°. ^{1}H-N.M.R. δ ($CDCl_3$) 0.80(3H,s,C-Me cis to pyridyl), 1.55(3H,s,C-Me), 3.07(3H,s,NMe), 4.77(1H,s,CH), 6.75(1H,broad,NH), 7.25(1H,m,pyridyl 5H), 7.45(1H,broad d, pyridyl 3H), 7.74(1H,dt,J=8Hz,2Hz,pyridyl 4H), 8.60(1H,dd,J=5Hz,2Hz,pyridyl 6H), ν max ($CHBr_3$) 3420,

1495 cm^{-1}(NH). Found: C, 59.6; H, 6.8; N, 18.9; $C_{11}H_{15}N_3S$ requires: C, 59.8; H, 6.8; N, 19.0%

A number of mechanisms for the rearrangement have been considered but since the reaction was found to proceed equally well if the imine was used, we favour the following scheme[8]. This is currently under investigation.



Imidazolidinethiones are useful intermediates for the preparation of a variety of biologically interesting compounds[7,9,10]. One such example that we have prepared utilising our rearrangement is the imidazo[2,1-b]thiazole (6), the 2-pyridyl analogue of Tetramisole (7)[9].



(3)

(6) R = 2-pyridyl

(7) R = Ph

References

1. P. Blatcher and D. Middlemiss, Tetrahedron Letters, 1980, 2195.
2. P. Blatcher et al, Tetrahedron Letters, 1980, 4193.
3. J.E. Kuder, Ph.D. thesis, University of Ohio 1968.
4. See 'Comprehensive Organic Chemistry', Vol. 3, p.464, D.H.R. Barton and W.D. Ollis, Eds., Pergamon, Oxford 1979.

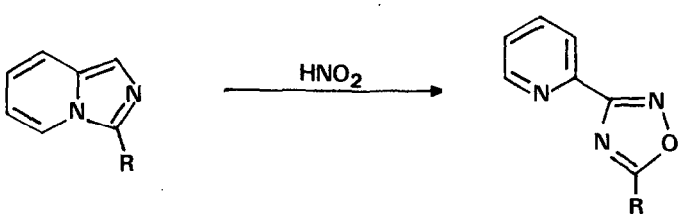
5. The thiourea (8), which cannot eliminate aniline, is recovered unchanged from refluxing xylene, J. Buck and F. Ellis, private communication.

(8)

6. Subsequent examination of the crude imidazopyridine (3) showed that it was also contaminated with traces of aniline.

7. Imidazolidine thiones are generally prepared by the reaction of ethylene diamines with CS_2. For this and other methods see W.L. Matier et al, J.Med.Chem., 1975, 16, 901; G.E. Hardtmann et al., J.Med.Chem., 1975, 18, 447; A.L. Lanis and F. Herr, U S Patent 3,174,975 [Chem.Abstr. 1965, 63, P608d]; F.B. Zienty, J.Amer.Chem.Soc., 1946, 68, 1388.

8. This reaction is related to the rearrangement of imidazo[1,5-a]pyridines in the presence of nitrous acid to give oxadiazoles: see reference 3 and also W.W. Paudler and J.E. Kuder, J.Org.Chem., 1967, 32, 2430; M. Iwao and T. Kuraishi, J.Het.Chem., 1972, 14, 993.



R = H, Me, Ph, OH

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10. A. Kosasayama et al., Chem.Pharm.Bull., 1979, 27, 848.

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