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4,6-Dichloro-5-nitropyrmidine reacts with *S*-methylisothiouronium sulfate to give 1-(4-chloro-5-nitropyrimidin-6-yl)-*S*-methylisothiourea by an unusual nucleophilic attack involving an isothiouronium nitrogen atom.

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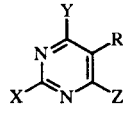
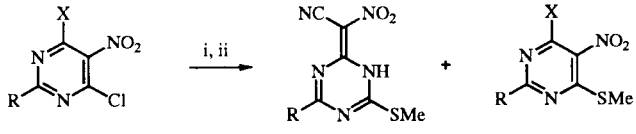
The reaction of chloropyrimidines with thiourea to give the corresponding pyrimidinethione, *via* the intermediate isothiouronium salt, is a well-known reaction [2,3,4]. However, the use of *S*-alkylisothiouronium salts for the introduction of alkylthio groups has been used less frequently, although it has been reported for the synthesis of 4-methyl-6-methylthio-5-nitropyrimidin-2-amine (**1a**) [5], 4,6-bismethyl-thiopyrimidin-2-amine (**1b**) [6], and 2,4,6-trismethylthio-5-nitropyrimidine (**1c**) [7].



	X	Y	R	Z
1a	NH_2	Me	NO_2	MeS
b	NH_2	MeS	H	MeS
c	MeS	MeS	NO_2	MeS

Nemeryuk, *et al.* [8], have reported that the reaction of 4-chloro-5-nitropyrimidines with *S*-methylisothiourea in aqueous alkali has given, not only the methylthiopyrimidine, but also methylthiotriazines (Scheme 1). *S*-Benzylthiourea was reported to react similarly. However, no explanation was offered for this pyrimidine to triazine rearrangement.

Scheme 1



2			**3** Yield %		**4** Yield %		
	R	X	R		R	X	
a	H	Cl	H	>70	H	MeS	6
b	Me	Cl	Me	>70	H	MeS	15
c	H	OMe	H	62	H	MeO	20
d	H	NMe_2	H	0	H	NMe_2	80

Reagents: (i) $MeSC(=NH).H_2SO_4$ (with NH_2), aq NaOH (ii) aq acid

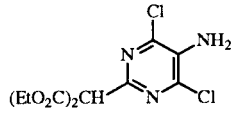
We have carried out reactions of 4,6-dichloro-5-nitropyrimidine with one equivalent of *S*-methylisothiouronium sulfate, in the presence of one equivalent of sodium hydroxide, in hot ethanol for a short time (*ca.* 15 minutes). Removal of the solvent, followed by column chromatography (silica gel, chloroform), has given the recovery of a small quantity of unchanged 4,6-dichloro-5-nitropyrimidine, a quantity of unseparated 4-chloro-6-ethoxy-5-nitropyrimidine and 4-ethoxy-6-methylthio-5-nitropyrimidine, and a further compound (mp 152-154°, from chloroform). The C, H, and N elemental analysis, ^1H nmr spectrum, and mass spectrum of this product indicated that it is the thiourea **6**. The mass spectral fragmentation pattern is rationalized in Scheme 2.

This is an unexpected product since thioureas normally react with reactive halogens at sulfur.

This pyrimidine to triazine rearrangement, **2** to **3**, can be explained by either of the pathways shown in Scheme 3.

The attack of nucleophiles at the 2-position of 4,6-dichloro-5-nitropyrimidine, *e.g.* by the anion from diethyl malonate, with concommitant reduction of the 5-nitro group to give the product **5**, has been observed [9] which might suggest pathway 1 for the rearrangement. The reaction of 5-nitropyrimidine with amidines to give 2-substituted 5-nitropyrimidines, and 5-nitropyridines, has also been observed [10]. This reaction has been proposed to occur *via* an internal attack by the amidine nitrogen on the 4-position which suggests that pathway 2 might be the favored process.

The thiourea **6** which we have isolated is an intermediate in pathway 2, and we propose that this is the route followed in this reaction.



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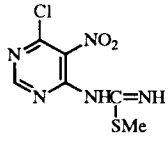

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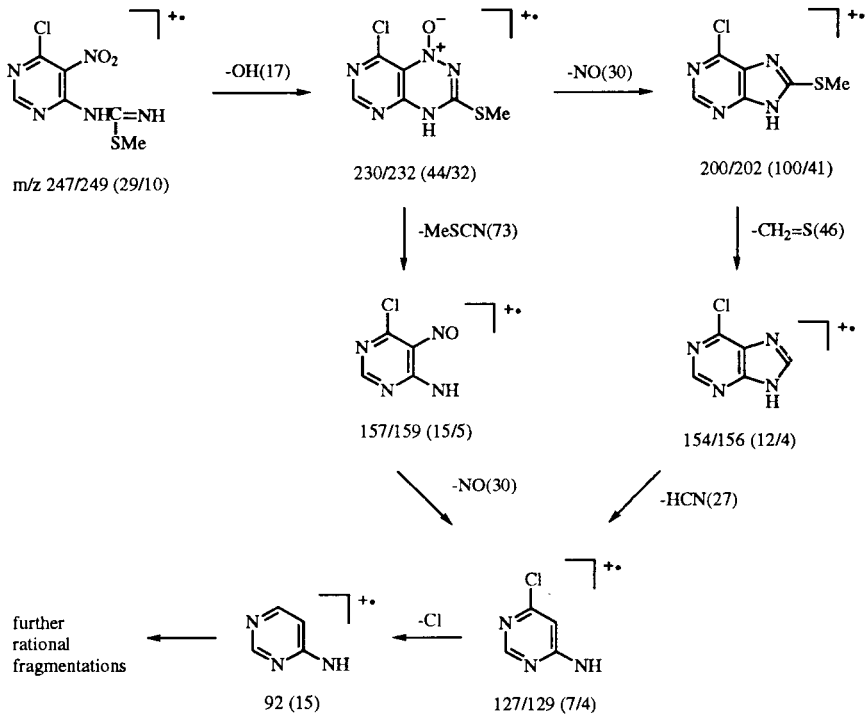
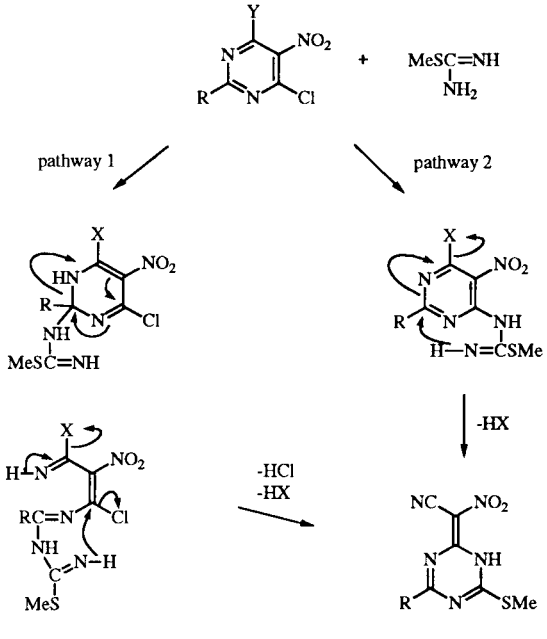
In the case of compounds **2a** and **2b**, in which X = Cl, the loss of chloride ion, and proton, from the intermediate thiourea is relatively favorable. Hence the yield of triazine is high. The higher yield of product **4b** from **2b**, relative to **4a** from **2a**, is probably due to the steric, and electronic, effects of the methyl group which inhibits the

Scheme 2



Scheme 3



formation of **3b** to some extent. The loss of methoxide ion from the thiourea (X = MeO) is less favorable than the loss of chloride, but can still occur so the yield of **3c** is lower than that of **3a** and **3b**. However, loss of dimethylamide anion is not favored, and thus no triazine **3d** is obtained from **1d**.

We have observed previously that the reaction of aryl diazonium ions with 5-alkylpyrimidine-4,6-diones results in a pyrimidine to triazine rearrangement by a somewhat similar transannular reaction but one which involves the loss of hydrogen isocyanate [11].

We hope to carry out further investigations of these reactions at a later date.

EXPERIMENTAL

The nmr spectra were recorded in deuteriochloroform using tetramethylsilane as the internal standard. Elemental analyses were carried out by the Butterworth Laboratories, Teddington, UK. Melting point values are uncorrected.

1-(4-Chloro-5-nitropyrimidin-6-yl)-*S*-methyliosothiourea (**6**).

4,6-Dichloro-5-nitropyrimidine (1.5 g, 7.7 mmoles) was dissolved in absolute ethanol (15 ml) with gentle warming, then *S*-methylisothiouronium sulfate (1.44 g, 7.7 mmoles) in ethanol (10 ml) was added, followed by sodium hydroxide (0.3 g, 7.7 mmoles) in ethanol (5 ml). The mixture was warmed on the waterbath for 15 minutes, then the solvent was removed by distillation under reduced pressure. Extraction of the residue with hexane (2 x 5 ml) gave some recovered pyrimidine starting material (approximately 30 mg). The further residue was dissolved in chloroform and subjected to column chromatography (silica gel using chloroform as eluent). Three fractions were isolated. Fraction 1 was shown (nmr and mass spectrometry) to be a mixture of 4,6-dichloro-5-nitropyrimidine and 4-chloro-6-ethoxy-5-nitropyrimidine. Fraction 2 was shown to a mixture of 4-chloro-6-ethoxy-5-nitropyrimidine and 4-chloro-6-methylthio-5-nitropyrimidine, and the third fraction (approximately 80 mg)

was 1-(4-chloro-5-nitropyrimidin-6-yl)-*S*-methylisothiourea (with a trace of 4-chloro-6-ethoxy-5-nitropyrimidine). Recrystallization from chloroform gave the pure pyrimidinylisothiourea, mp 152-154°; ^{1}H nmr; δ 2.45 (3H, Me), 8.65 (1H, H-2), NH (br, approx. 8.0-9.0); ms: see Scheme 3.

Anal. Calcd. for $C_6H_6ClN_5O_2S$: C, 29.0; H, 2.4; N, 28.26. Found: C, 28.8; H, 2.3; N, 27.6.

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