RECENT DEVELOPMENTS IN THE SYNTHESIS OF HETEROCYCLES FROM ENAMINES AND ISOTHIOCYANATES*

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Dedicated to Professor R.B. Woodward
on the occasion of his sixtieth birthday.

A serendipitous synthesis of multifunctional thiophene derivatives is described. Nitroenamine-isothiocyanate adducts have been used to prepare 3-nitrothiophenes, 4-nitroisothiazoles, 5-nitropyrimidines and 4-nitropyrazoles.

I Introduction

Enamines are versatile starting materials for the synthesis of a wide variety of heterocycles (1). Especially useful intermediates result from the union of enamines and isothiocyanates; these adducts lend themselves to easy synthetic manipulations leading to a plethora of interesting heterocycles (2). In this

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article, we review our own contributions to this field.

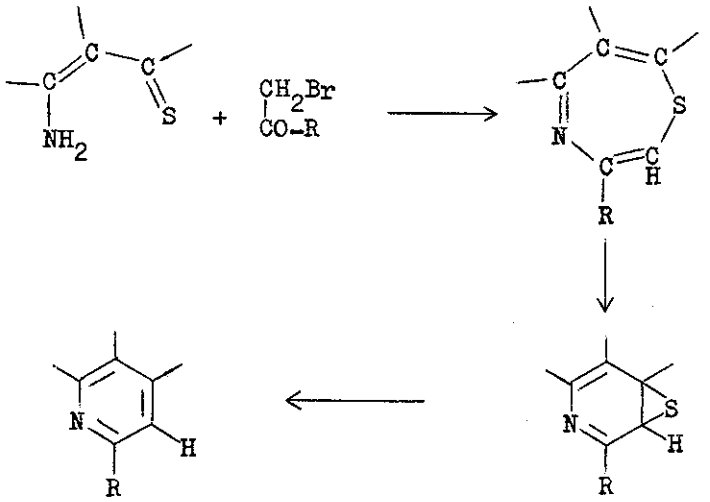
Serendipity was mainly responsible for unmasking a novel synthetic route to thiophenes from such enamine isothiocyanate adducts. Once the reaction was brought to light, however, its scope was explored systematically by varying all the constituents. A logical extrapolation opened the way for the synthesis of similarly substituted thiazoles.

Nitroenamines have been utilised by us for the first time for the construction of nitroheterocycles. In conjunction with isothiocyanates, such nitroenamines have provided access to novel nitrothiophenes, nitroisothiazoles, nitropyrimidines and nitropyrazoles. These synthetic routes are also included in this review.

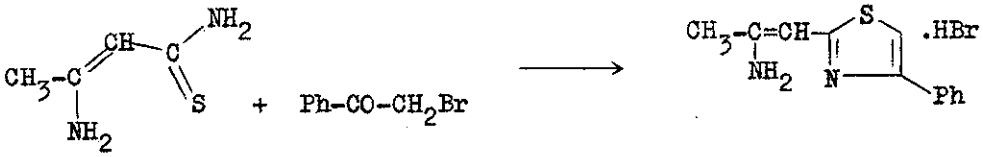
II Synthesis of thiophenes

The reaction of thioamides with α-haloketones to form thiazoles is well-known. To start with, we posed ourselves the question whether a seven-membered ring could be similarly constructed by reaction of a vinylogous thioamide with an α-haloketone. We were also intrigued by the possibility that the resultant 1,4-thiazepine might get converted to a pyridine *via* the episulfide (Scheme 1). Our first attempt to test this idea was not well-conceived. The substrate we chose to react with phenacyl bromide was β-aminothiocrotonamide 1; this compound has a major flaw, in that it possesses a nucleophilic

Scheme 1



centre attached directly to the thiocarbonyl group - a situation capable of leading to the formation of a 5-membered aromatic ring; and this is exactly the course the reaction preferred to take (3).



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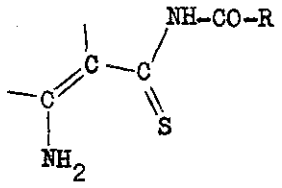
It was obvious that for our purpose, the offending nucleophilic nitrogen attached to the thiocarbonyl had to be either removed or its nucleophilicity nullified. The latter objective could be realised if it were attached to an acyl group as in part structure 2. We preferred to investigate the reactivity of such compounds first, since these are easily prepared by the reaction of enamines with acyl isothiocyanates (2); for example,



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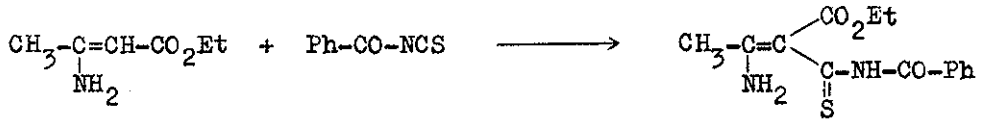
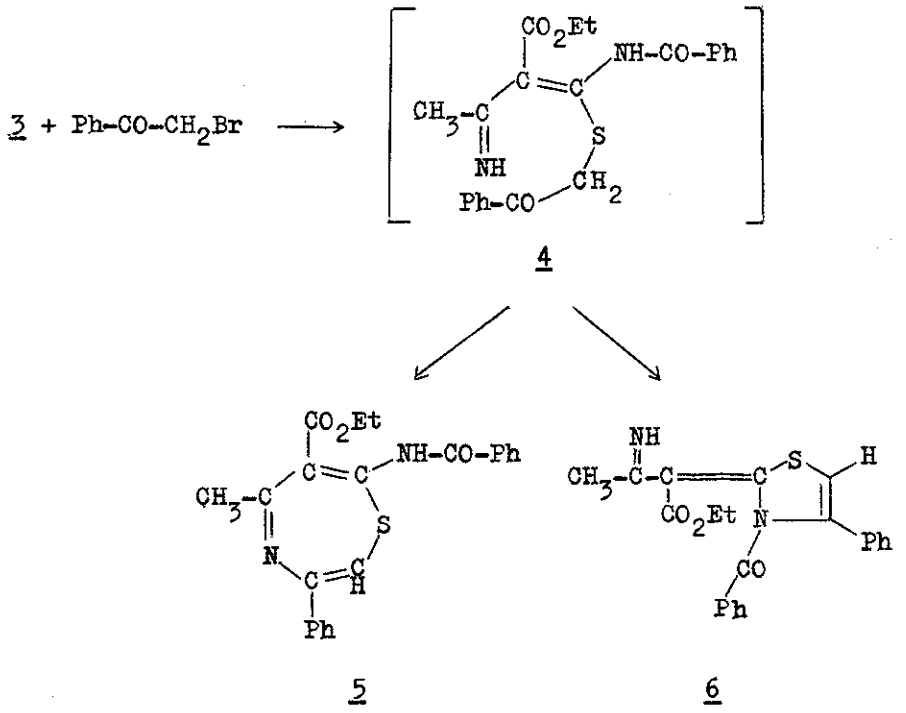


3

β-aminocrotonic ester reacts with benzoyl isothiocyanate to produce the red crystalline adduct 3 in excellent yield.

So, as the second foray into our projected 1,4-thiazepine synthesis, this adduct 3 was reacted with phenacyl bromide in refluxing isopropanol. Reaction was very rapid as indicated by decolourisation and formation of a crystalline product. The expected course of the reaction is shown in Scheme 2. The intermediate S-alkylated product 4 was expected to undergo cyclisation by loss of the elements of water to produce, hopefully, the thiazepine 5, or as a less probable alternative, the thiazoline 6. In either case the molecular formula of the product would be $C_{22}H_{20}N_2O_3S$. However, the product actually obtained (in 55% yield) had the formula $C_{22}H_{19}NO_4S$. There was no singlet corresponding to =CH- in its NMR spectrum; the spectrum showed only bands due to one CH_3, one C_2H_5, two Ph, and one NH (exchangeable with D_2O). It was obvious that the intermediate 4 had lost a molecule of ammonia instead of water; from

Scheme 2

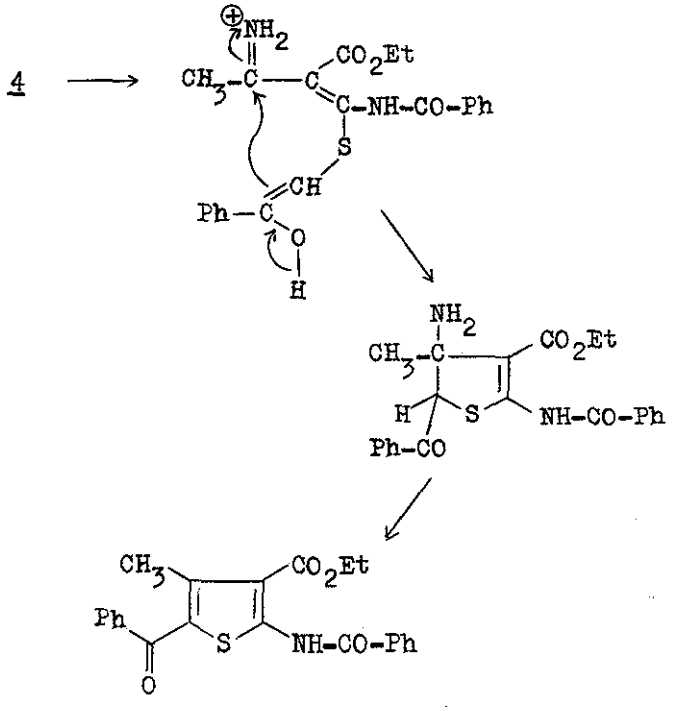


this it was easy to deduce that the product must be the thiophene 7. The postulated course of the reaction is shown in Scheme 3 (4,5).

A particularly interesting sequel to this was the construction of the thieno[2,3-d]pyrimidine ring system by two different routes from enamine acylisothiocyanate adducts (6). In the first, the 2-aminothiophene-3-carboxylic acid obtained from 7 was converted to an oxazinone and thence to the required thieno[2,3-d]-pyrimidine by standard procedures. In the second approach, the process was reversed; a substituted pyrimidine was first formed by base-catalysed cyclisation of the enamine acylisothiocyanate

adduct and this served as the base for the subsequent building of a thiophene ring.

Scheme 3



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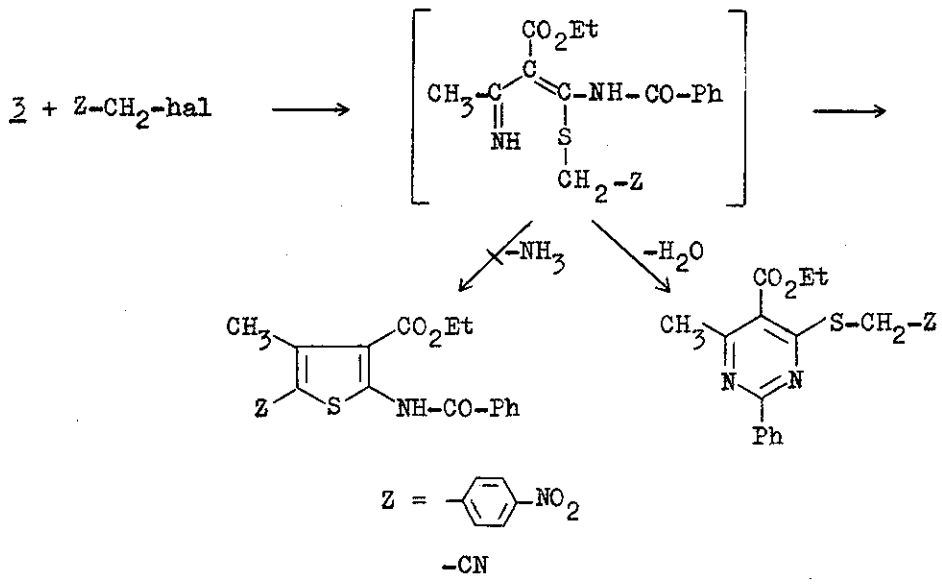
In the cyclisation step in Scheme 3 the carbon atom of the protonated imine group is attacked by an active methylene. In trying to define the scope of the reaction, we reacted the adduct 3 with p-nitrobenzyl bromide and chloroacetonitrile. However, in both the cases, the intermediate S-alkylated compound lost a molecule of water (not ammonia) during cyclisation, leading to products which exhibited two-proton singlet in the NMR spectrum corresponding to $-S-CH_2-$. We had therefore no

doubt about the structure of the products: the imino nitrogen had reacted with the carbonyl of the benzamide to form a pyrimidine ring (Scheme 4) - a reaction for which there is ample precedent in the literature (7).

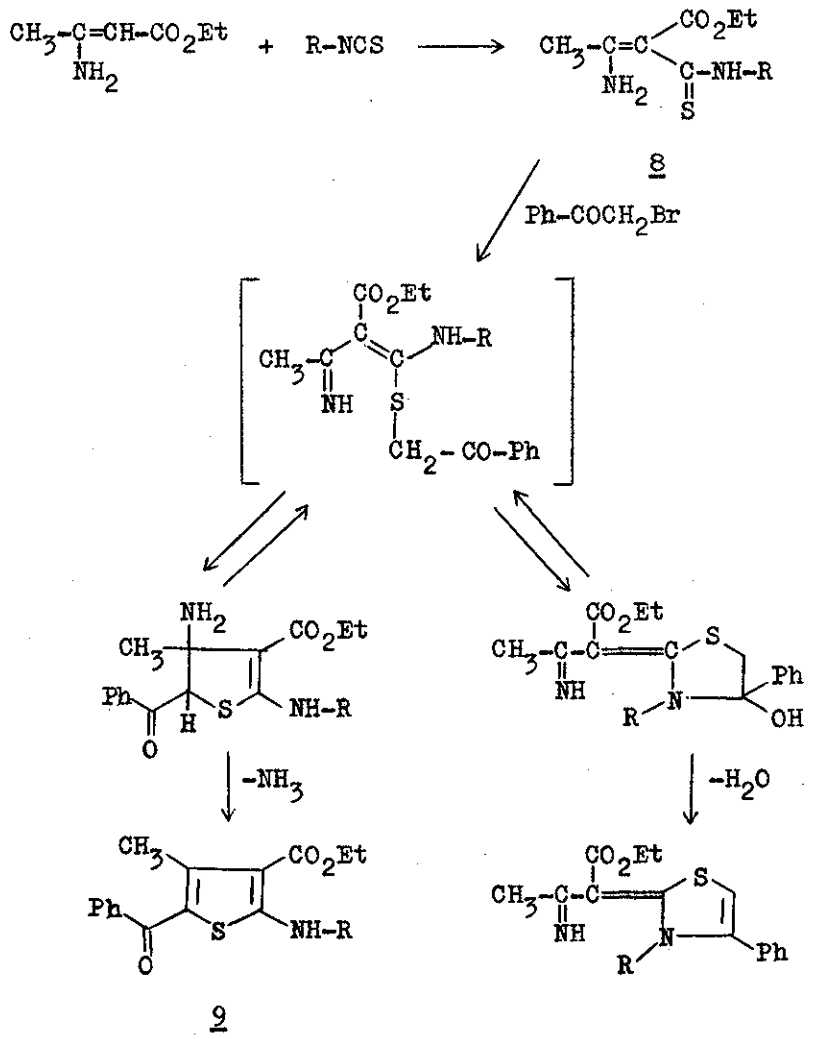
Scheme 4



In an effort to suppress the pyrimidine formation we decided to investigate the reactivity of substrates lacking this carbonyl group, but having in its stead an alkyl or aryl group attached to the nitrogen atom; that is, adducts of enamines with alkyl or aryl isothiocyanates. We were aware that this might only land us in complications arising from the unwanted nucleophilicity of the nitrogen attached to the thiocarbonyl group. However, we argued that thiophene formation might have an edge over thiazoline formation in the reaction with phenacyl bromide, since in the

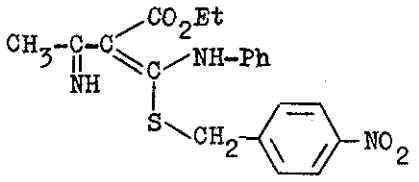
latter event, the product would not be aromatic. We hoped that if the nucleophilic attack on the carbonyl were reversible, the reaction might be pushed towards the thiophene, the driving force being provided by aromatisation (Scheme 5).

Scheme 5



In the event, the thiophene 9 (R=Ph) was formed in 90% yield. Moderate yields of the thiophene were obtained when R was an alkyl group (4,5).

We were now better situated to try out the reaction of other active methylene compounds with the substrate 8. However, p-nitrobenzyl bromide gave only the uncyclised compound 10, and chloroacetonitrile gave no crystalline material. Apparently these two did not possess sufficiently activated methylene groups.



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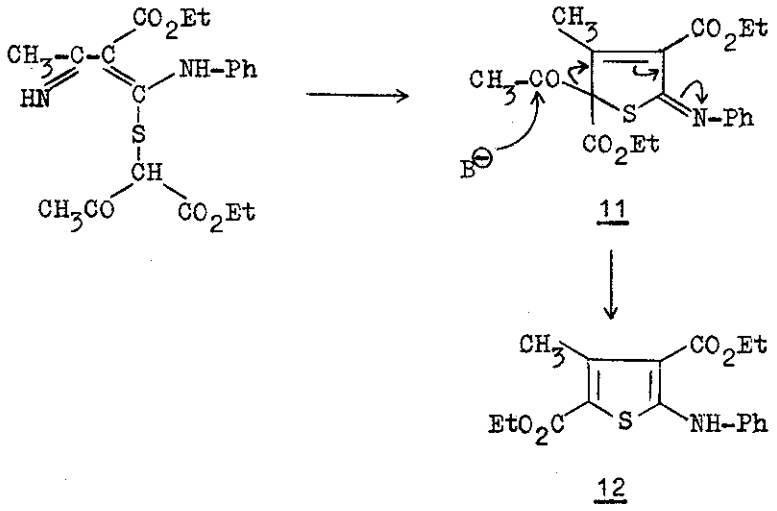
We therefore investigated the reaction of ethyl α-chloroacetoacetate with 8, hoping to obtain an intermediate 11 which could subsequently be induced to lose an acetyl group and aromatise to the thiophene 12 (8) (Scheme 6). It turned out that our expectation was more than justified. The product, obtained in 51% yield after $\frac{1}{2}$ hr (isopropanol) was in fact the fully aromatic thiophene 12 (8) - an outcome reminiscent of the Japp-Klingemann reaction. The enamino ketone - methyl isothiocyanate adduct 13 underwent a similar reaction to produce the thiophene 14 (8).

We have so far discussed changes in the isothiocyanate and active methylene components of the reaction. The third component, viz. the enamine also admits of a wide range of

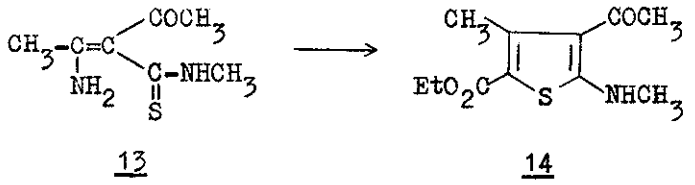
Scheme 6



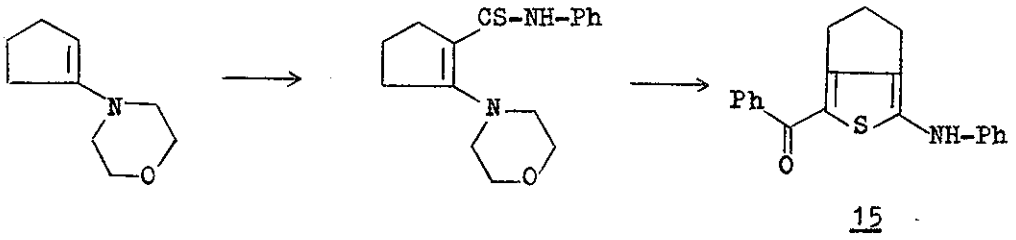
11

12

possible variations. Simple unconjugated enamines have been successfully utilised to produce condensed thiophenes, eg. 15 (8).



13 14



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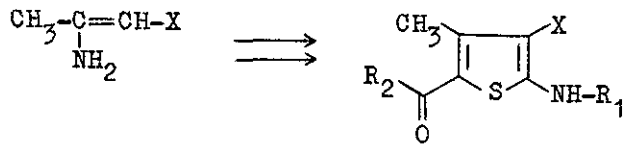
As discussed above, enamines which are conjugated to an ester, ketone or nitrile form good reactive partners, leading to the corresponding 3-substituted thiophenes 16.



16

X = CO_2Et, CO_2tBu, $COCH_3$, CN

Thiophene-3-carboxylic acids (16, X = CO_2H) could be easily prepared from the corresponding t-butyl esters (9).

Our major interest, however, was in the utilization of this synthetic procedure for the preparation of 3-nitrothiophenes. For this, the obligatory starting material would be a nitroenamine of the type 17. However, NMR data, EH calculations, and preliminary experiments on its reactivity indicated that this

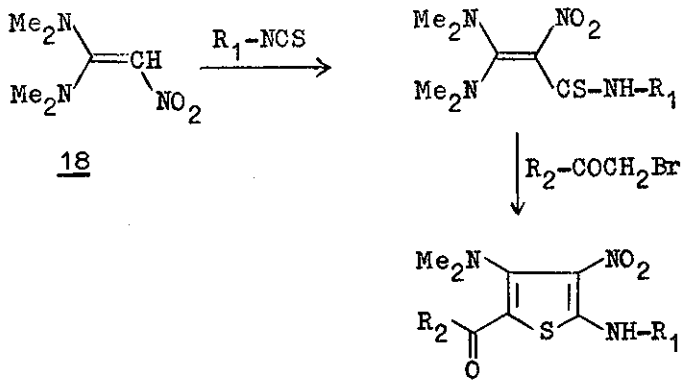
$Me_2N-CH=CH-NO_2$

17

was a very poor enamine, unable to form adducts with alkyl and aryl isothiocyanates (10). Fortunately, a better situation prevailed with nitroketeneaminals of the type 18. Such compounds did react with isothiocyanates. The resulting adducts could be easily converted to 3-nitrothiophenes 19 by treatment with α-haloketones (11,12) (Scheme 7).

Our discussion so far has centred around the various possible modes of cyclisation of the intermediates obtained by S-alkylation of enamine-isothiocyanate adducts. However, it soon became apparent that not all possible pathways had been

Scheme 7



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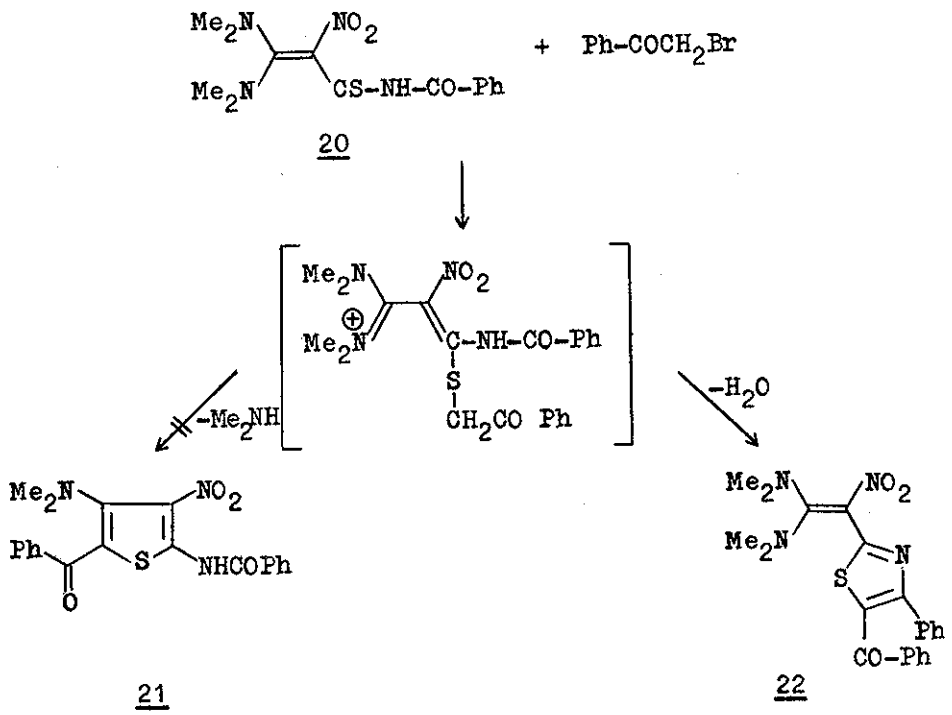
Scheme 8



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21

22

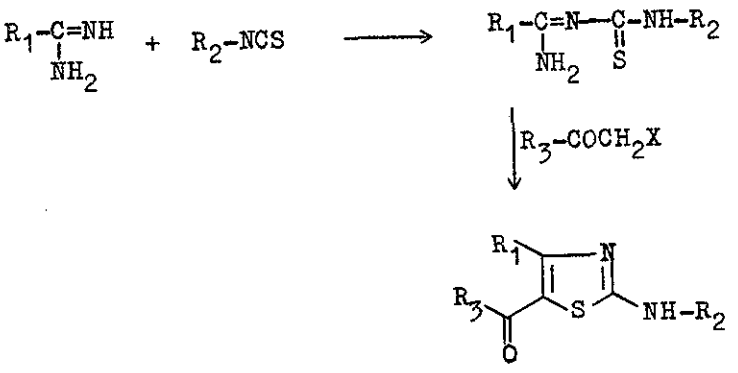
anticipated by us; one more surprise was still in store for us. Condensation of the enamine-benzoyl isothiocyanate adduct 3 with phenacyl bromide had given us the first of the new thiophene derivatives 7. But, in trying to repeat this reaction with the nitroenamine-benzoyl isothiocyanate adduct 20, we obtained a crystalline compound whose analytical values and NMR spectrum quickly proved that it was not the hoped-for thiophene 21, but the thiazole 22. The activated methylene in the intermediate had attacked the carbonyl of the benzamide resulting in loss of a molecule of water (Scheme 8) (12). A new twist had thus been added to the possibilities for ring-closure from such intermediates. Note that this is not a product of the conventional thiazole synthesis in which atoms 4 and 5 are supplied by the phenacyl bromide.

III Synthesis of thiazoles

A totally different type of thiazole synthesis has also been achieved - this time by a planned extension of the thiophene cyclisation. The starting material for this was the adduct of an amidine with isothiocyanate; condensation of this with an α-haloketone gave, as expected, the thiazole 23 (Scheme 9) (13). The reaction undoubtedly proceeds as before through S-alkylation, followed by attack of the activated methylene on the protonated amidine.

Presumably unaware of our prior publication, Ried and Kaiser have recently reported a similar route to thiazoles (14). Their

Scheme 9



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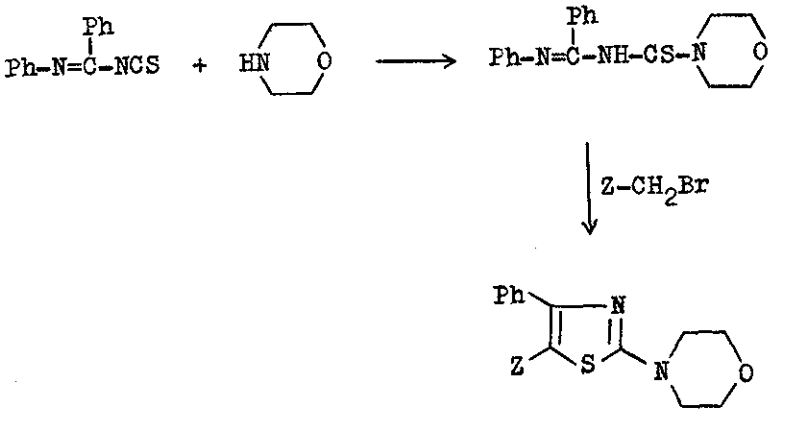
Scheme 10

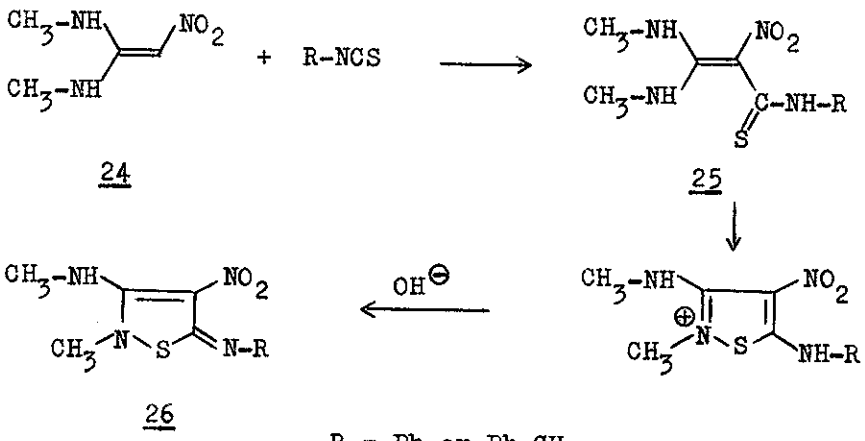


starting materials are derived from imidoyl isothiocyanates and amines (Scheme 10).

IV Synthesis of 4-nitroisothiazoles

Enamine-isothiocyanate adducts have been extensively used by Goerdeler for the synthesis of isothiazoles (2). The cyclisation is effected by an oxidative S-N bond formation. Our interest in this area was mainly to synthesise 4-nitroisothiazoles directly from the adducts of nitro-enamines and isothiocyanates. The nitroketeneaminal 24 reacted with phenyl or benzyl isothiocyanate to produce the adduct 25, which could be oxidised to the isothiazole 26 (Scheme 11) (15). But the scope of this synthesis was severely restricted by the poor nucleophilicity of nitroketene aminals of the type $(R\text{-}NH)_2C{=}CH\text{-}NO_2$. Change-over to a more reactive, unsymmetrical aminal 27, however, wrecked the scheme at the second stage; oxidation led to a benzthiazole 28 rather than to the isothiazoline 29 (Scheme 12). Use of benzyl isothiocyanate in the hope of preventing the benzthiazole formation gave no crystalline product.

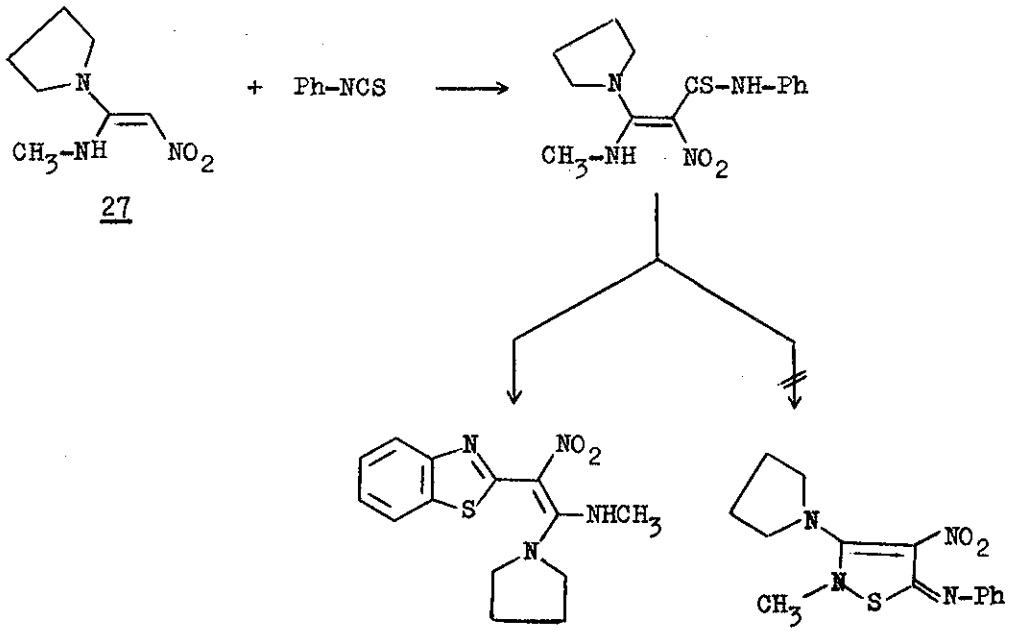
Scheme 11



24 25 26

R = Ph or Ph-CH_2

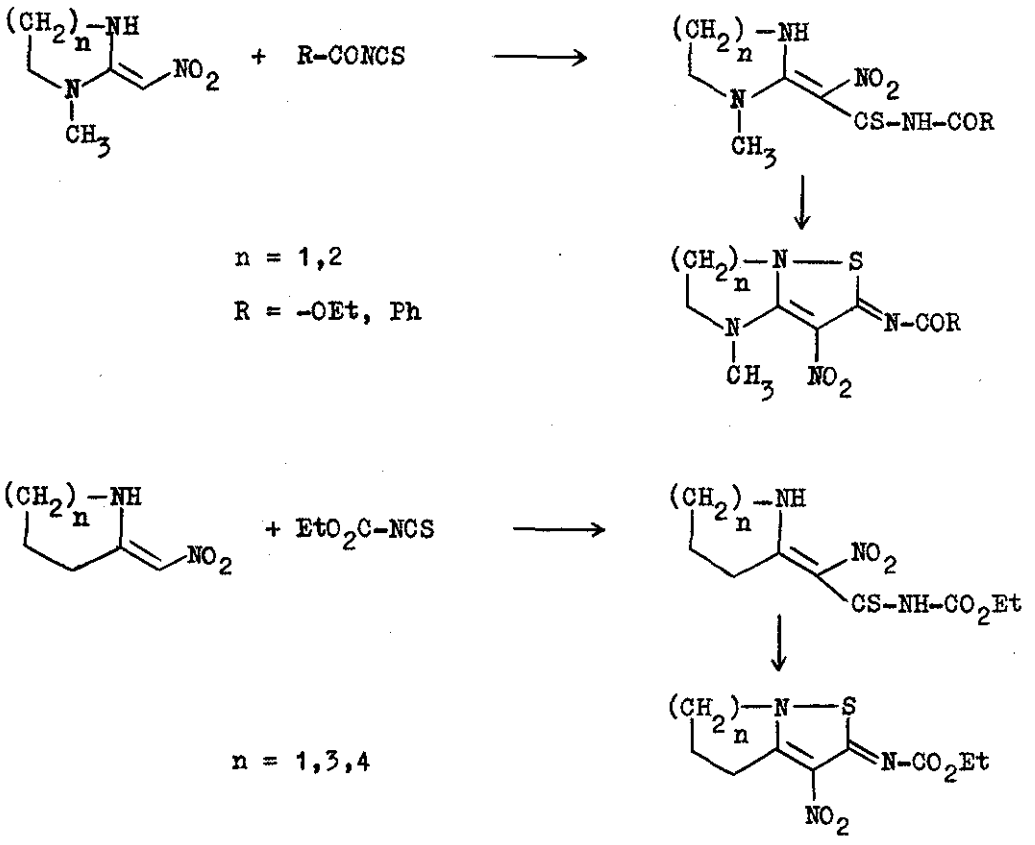
Scheme 12



27 28 29

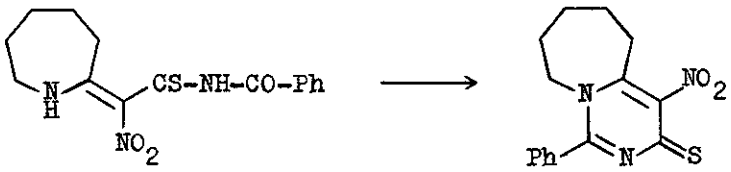
The synthetic scheme could be salvaged to some extent by the use of more reactive isothiocyanates, viz. carbethoxy isothiocyanate or benzoyl isothiocyanate. These acyl isothiocyanates were reactive enough to form adducts not only with nitroketene aminals, but also with nitrovinylamines. Both sets of adducts could be easily oxidised to 4-nitroisothiazole derivatives (Scheme 13) (15, 16).

Scheme 13



V Synthesis of 5-nitropyrimidines

As referred to earlier, the enamine-benzoyl isothiocyanate adduct 3 is known to undergo base-catalysed cyclisation to the corresponding pyrimidine derivative (7). Our aim was to produce nitropyrimidines from the nitroenamine-benzoyl isothiocyanate adducts. We found that such adducts (Scheme 13) dissolved in alkali forming the nitronate salts, and were regenerated on acidification. However, the adduct 30, on crystallisation from acetic acid, cyclised to the pyrimidine 31 (10).

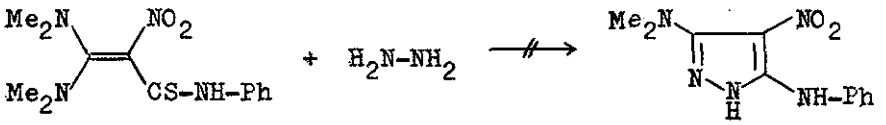


30 31

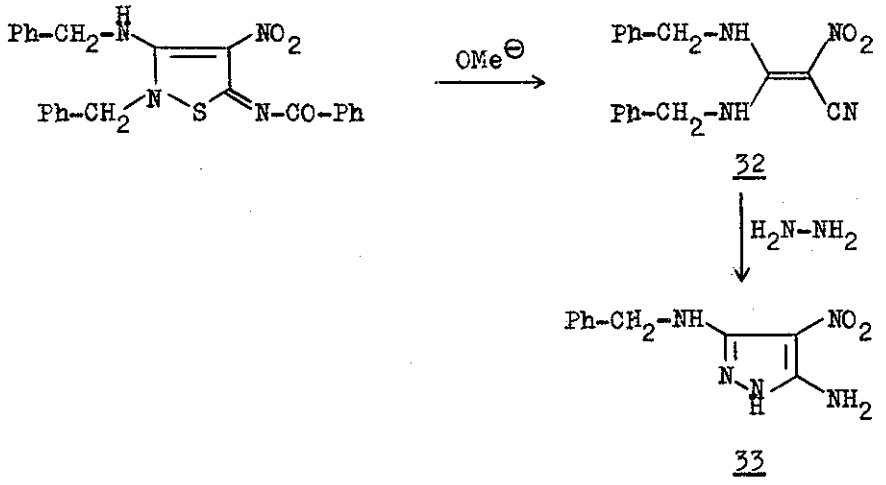
VI Synthesis of 4-nitropyrazoles

Enamine-isothiocyanate adducts are known to react with hydrazine to form pyrazoles (2). However, we were unable to prepare nitropyrazoles from the nitroenamine-isothiocyanate adducts (Scheme 14). Meanwhile we discovered that the 5-benzoyl-imino-4-nitroisothiazolines described before underwent a novel, facile, base-promoted fragmentation to produce 3,3-diamino-2-nitroacrylonitriles (Scheme 15) (16). Such nitroacrylonitriles were ideal starting materials for the synthesis of the required nitropyrazoles. Thus reaction of 32 with hydrazine produced

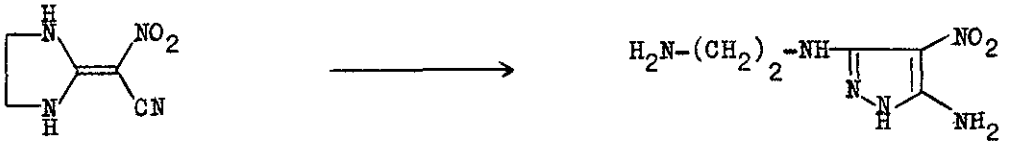
Scheme 14



Scheme 15



the pyrazole 33 in 80% yield (17). Surprisingly, even a cyclic analog 34 could be opened out by hydrazine to the nitropyrazole 35.



34 35

Conclusion

Heterocycles with novel substitution patterns can thus be generated from enamines bearing suitable functional groups and alkyl, aryl or acyl isothiocyanates.

Acknowledgement It is a pleasure to record my indebtedness to Professor T.R. Govindachari and Dr. R.S. Grewal for their interest and encouragement throughout the course of this work. I thank Messrs B.G. Advani and R. Sreenivasan for their very able technical assistance.

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