SYNTHETIC STUDIES ON HETEROCYCLES

ABSTRACT

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SUMMARY

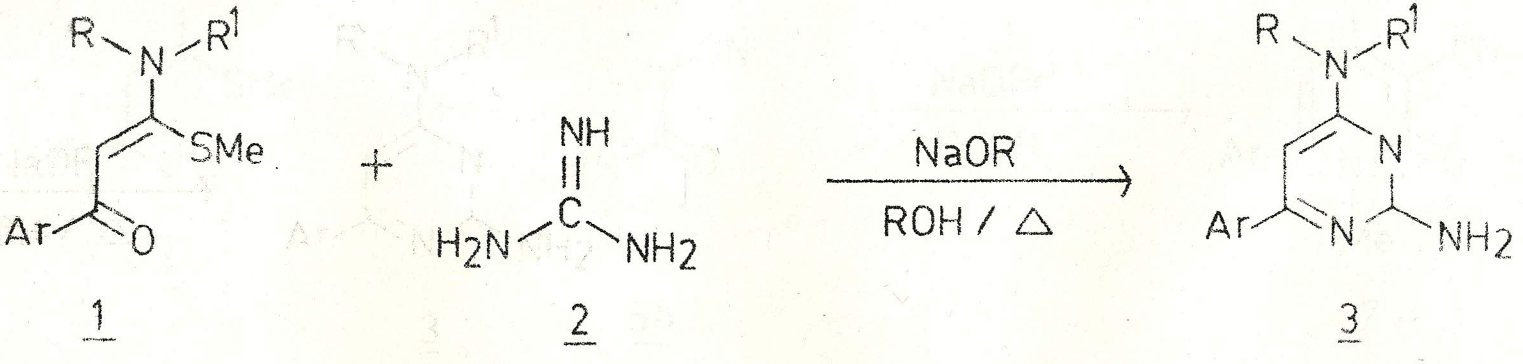
For the synthesis of a variety of heterocyclic systems, more than several methods are found in the literature. Often one finds these methods are not economical for further synthetic elaboration, since they are worked out extensively using all possible structural variants. Therefore, it is desirable if one can device intermediates from easily available starting materials with appropriate electrophilic or nucleophilic centres within the molecule, suitable for ring construction providing a new method for the synthesis of various heterocycles. Such methods can often be used to breed compounds of varied applications, which are otherwise inaccessible by the existing methods.

We have successfully developed, polarized keten dithioacetals as an excellent class of three carbon fragments, which undergo ring closure with various binucleophiles yielding heterocycles of a wide variety.[1] The S,S-acetals are known to undergo facile displacement reaction with amines to give the corresponding S,N- and N,N-acetals, depending upon the reaction conditions. The properties of the S,N- and N,N-acetals are correspondingly altered by substitution of a methylthio group by an amino group. These S,N- and N,N-acetals can be broadly classified into two categories. They can either be called vinylogous amides, if the keto functionality is present in the β-position or vinylamines, if groups like nitro, sulfeno or cyano, other than keto functionality, are present in the β-position. The compounds can be considered as a new class of enamine components which should in principle, behave chemically analogous to the enamines derived from β-ketoesters, linear or cyclic 1,3-diones and amines. Although, the latter class of enamine chemistry is well documented, the new class of S,N- and N,N-acetals have not been fully exploited as important enamine components, either as three carbon fragments in any of the systematic synthetic programmes.

An investigational study on these novel class of compounds has been undertaken in the present work and shown that these S,N- and N,N-acetals are exceptionally more stable, possessing similar reactivities as enamines. For example, in the third chapter, it has been shown for the first time, that the S,N-acetals 1 are good three carbon fragments and undergo condensation with guanidine (2) providing one step synthesis of aminopyrimidines 3 (Scheme 1).[2] It may be noted, that the aminopyrimidines have been variously derived in the literature involving more than one step thus, making the present route a method of choice. The limitations of these methods have been briefly reviewed in the same chapter. A brief review on polarized keten-S,N- and N,N-acetals was considered appropriate and therefore included in the first chapter.

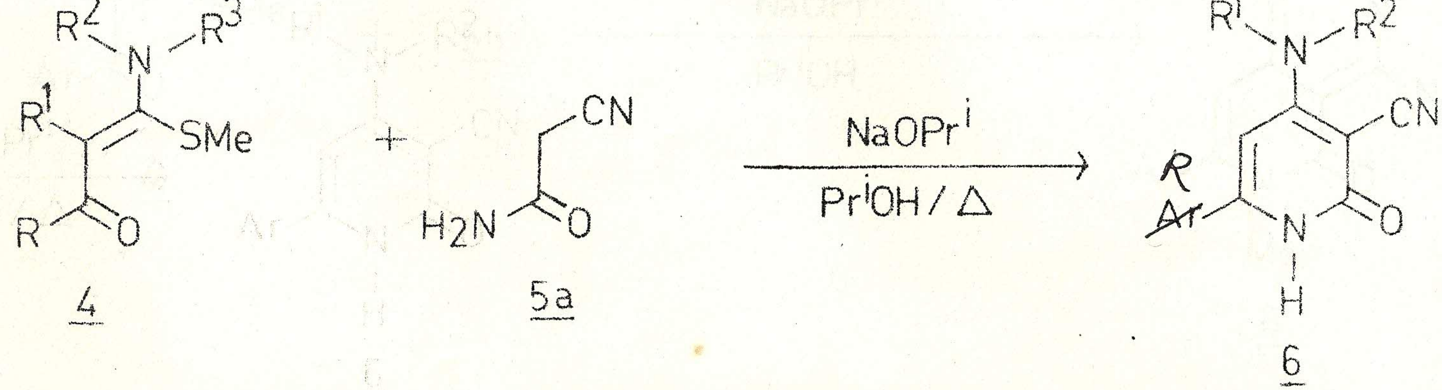
In the fourth chapter, S,N-acetals 4 have been successfully condensed with cyanoacetamide (5a) providing a new general method for the synthesis of 4-amino-3-cyano-6-substituted-2(1H)-pyridones (6) in excellent yields (Scheme 2).[3] The scope of the method has been

Scheme 1



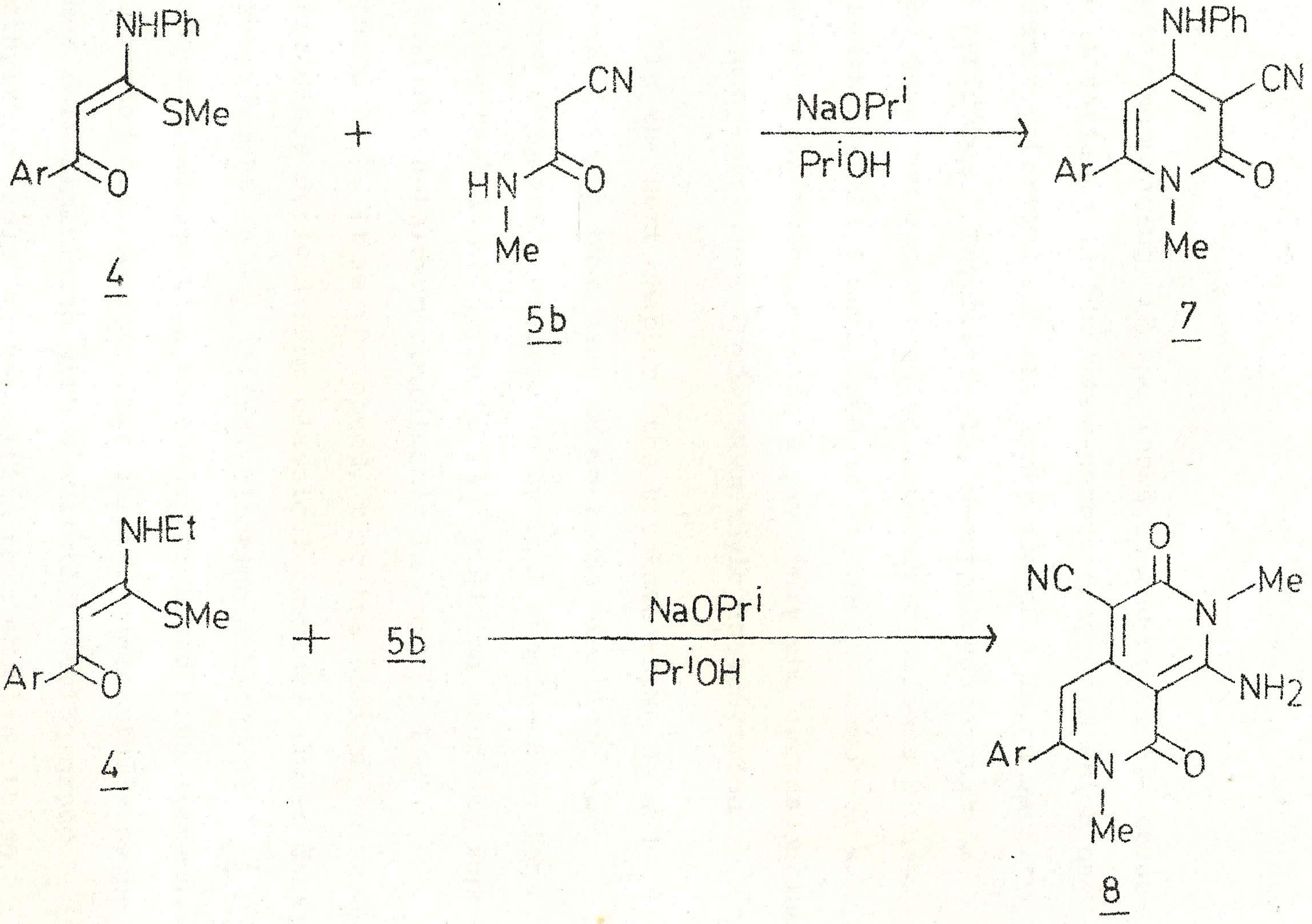
1,3, R=H ; R^1=Et, Ar; R, R^1 = –$(CH_2)_5$– etc.

Scheme 2



4, 6, R, R^1, R^2, R^3=H, alkyl, aryl

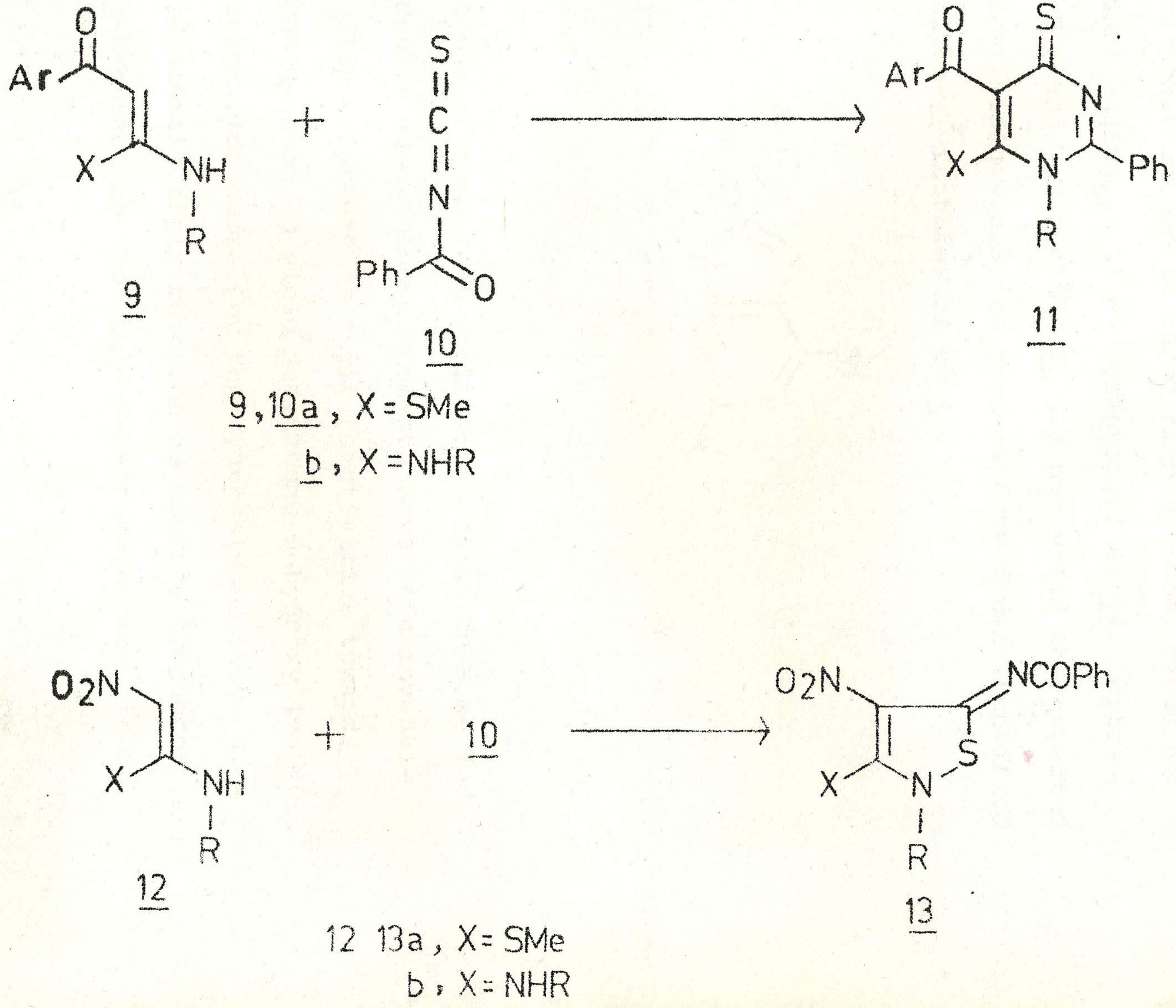
Scheme 2 continued



quite encouraging, if one looks at the choice of structural variants in the three carbon fragments which has further potential for the synthesis of a large variety of pyridones. Interestingly, N-methylcyanoacetamide (5b) gave the corresponding naphthyridindiones 8 when S,N-ethylacetal 4 were used as an enamine components. However, S,N-phenylacetals 4 gave only the corresponding 4-N-phenylpyridones 7 with N-methylcyanoacetamide.

In the next chapter, the ketoketen-S,N- 9a and N,N-acetals 9b have been shown to be excellent two carbon fragments, undergoing typical enamine reactions with benzoyl isothiocyanate (10) yielding usefully functionalised 4-thioxopyrimidines[11] in good yields (Scheme 3).[4] It may be noted, that the similar thioxopyrimidines derived from classical enamines always carry a substituent at 6-position, blocking subsequent structural elaboration to construct fused ring systems. The method described in this chapter successfully overcomes this limitation with a suitable leaving group (methylthio group) at 6-position thus enabling these

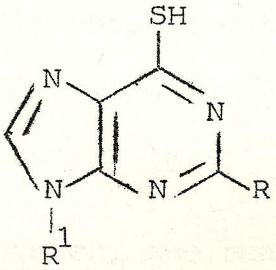
Scheme 3



9, 10a, X = SMe
b, X = NHR

12 13a, X = SMe
b, X = NHR

5,6-functionalized thioxopyrimidines to be used further for the construction of fused ring systems, yielding important analogues of 6-mercaptopurines 14. Nitroketen-S,N and N,N-acetals 12 did not yield the expected thioxopyrimidines and the product formed was identified as 4-nitro-Δ^3-isothiazolines 13.



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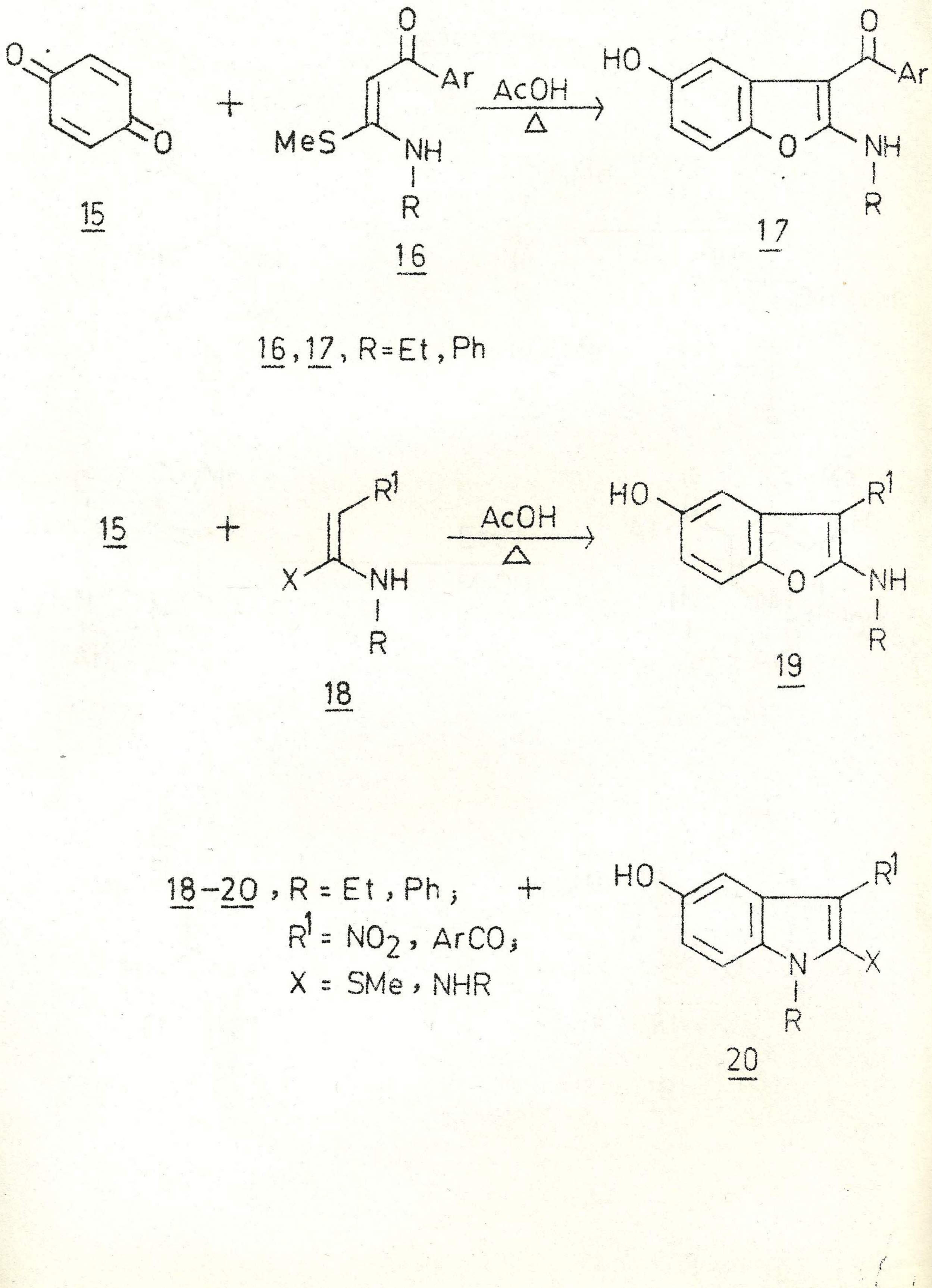
The most important application of keten-S,N- and N,N-acetals as enamine components have been investigated with reference to their reactivities towards 1,4-benzoquinone to yield Nenitzescu 5-hydroxy indoles.[5] Due to the wide scope for the synthesis of these S,N- and N,N-acetals their reaction as enamine components with p-benzoquinone to yield 5-hydroxyindoles, is an important synthetic variation, which widens the scope of 5-hydroxyindole synthesis. These limitations have been briefly described in this chapter. The S,N-acetals 16 derived from acetophenones gave only benzofurans 17 (Scheme 4) and no trace of indoles were detected. Nitroketen-S,N-acetals and N,N-acetals 18 selected for study in this investigation have all been shown to yield 5-hydroxyindoles 20 along with the corresponding benzofurans 19.

In the last chapter, the reaction of S,N- and N,N-acetals with dimethyl acetylenedicarboxylate has been described (Scheme 5). The intermediates 23 formed by the reaction of N,N-acetals 21 with 22 via Michael addition route, undergo subsequent cyclisation in the presence of triethylamine to give 2(1H)-pyridones 24. A few selected systems have been described which gave the corresponding pyridones while the N,N-diethylacetal 25 gave exomethylene-pyrroline 26 instead of the corresponding pyridone. The S,N-acetals 27 undergo reaction with 22 to give 1:1 adducts 30 or 29 either via Michael route or through ring opening of the cyclobutenes 28 respectively.

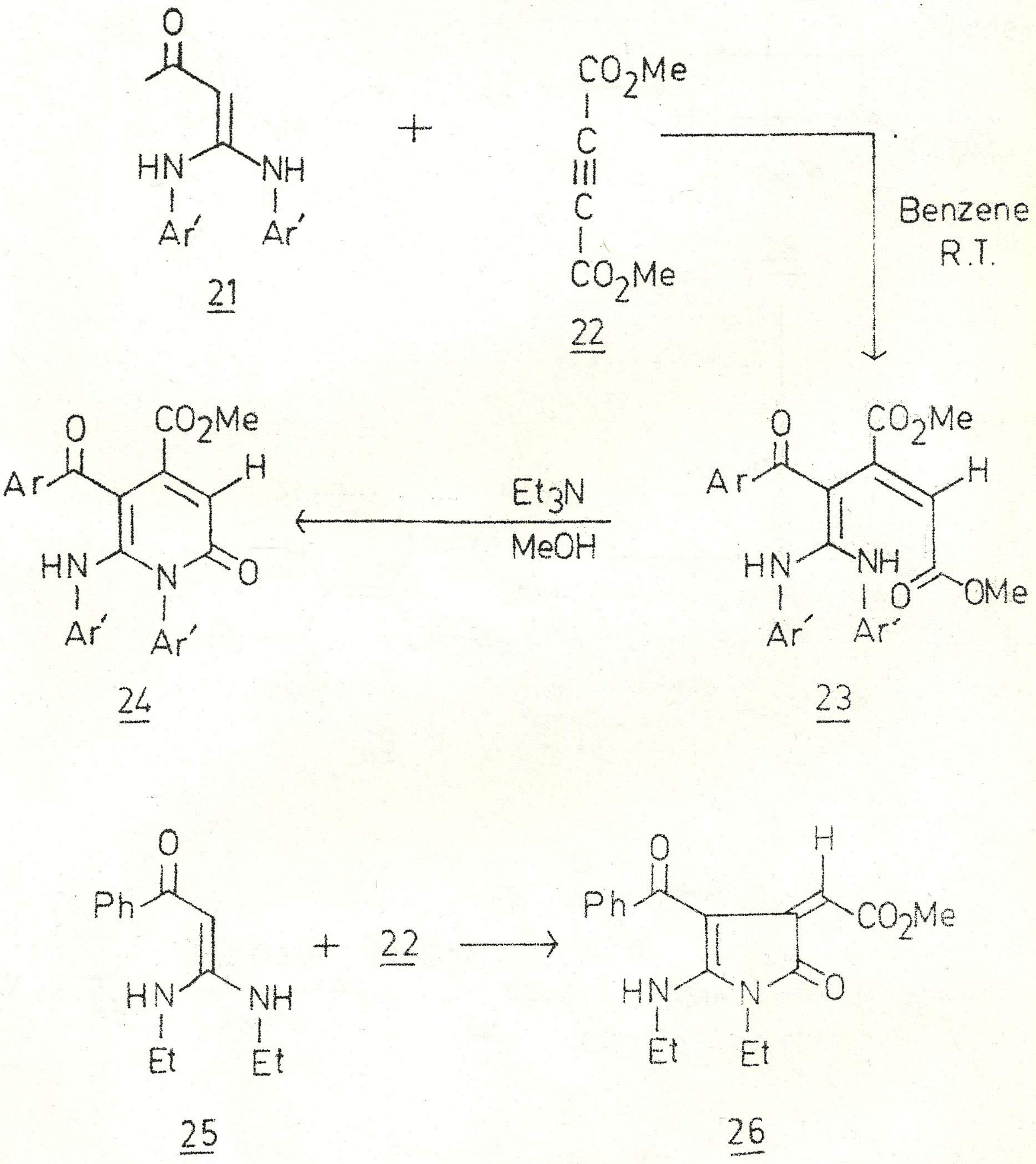
Scheme 4



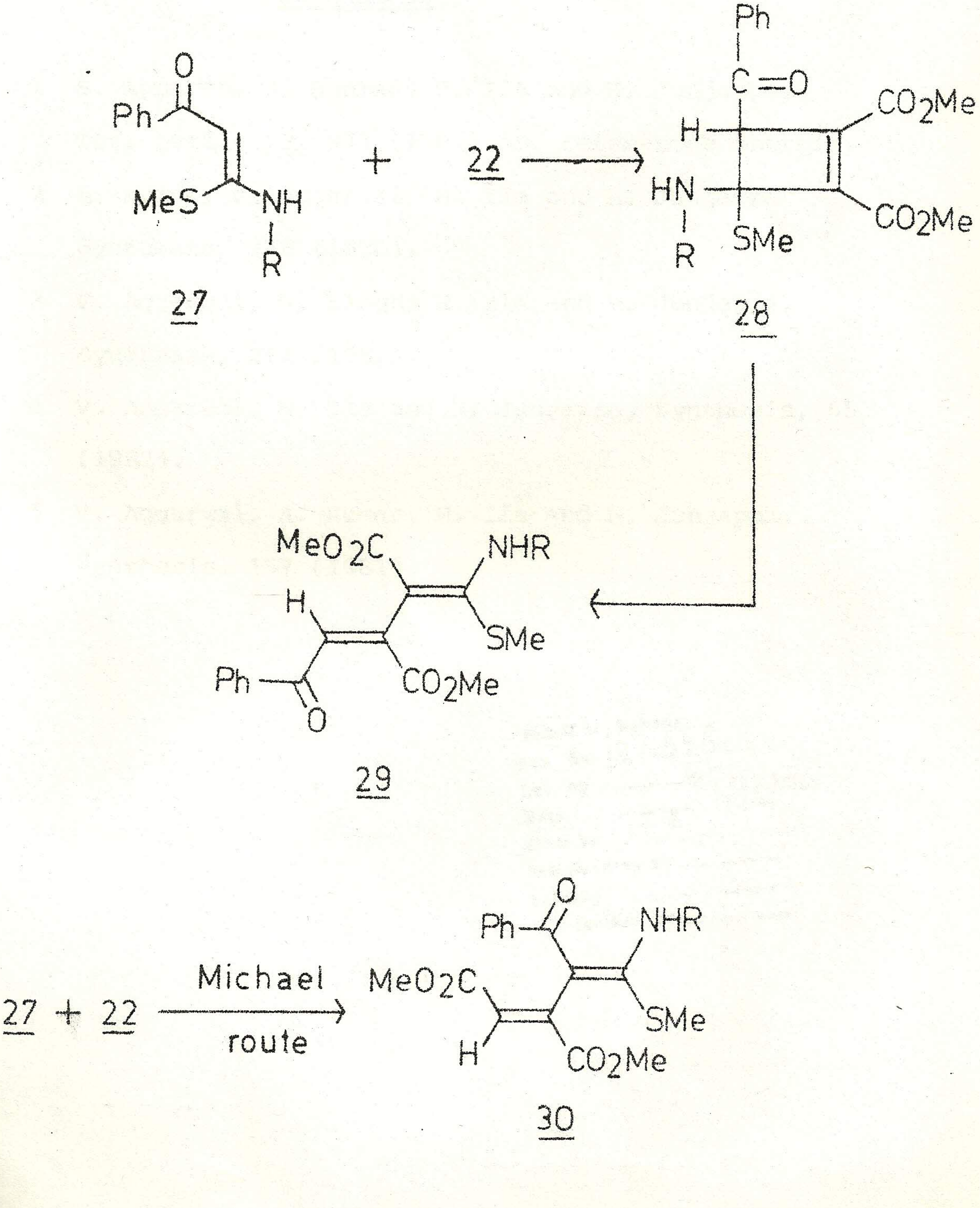
$\underline{16}$, $\underline{17}$, R = Et, Ph

$\underline{18}$–$\underline{20}$, R = Et, Ph;
R^1 = NO_2, ArCO;
X = SMe, NHR

Scheme 5



Scheme 5 continued



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3 V. Aggarwal, G. Singh, H. Ila and H. Junjappa, Synthesis, 214 (1982).

4 V. Aggarwal, H. Ila and H. Junjappa, Synthesis, 65 (1982).

5 V. Aggarwal, A. Kumar, H. Ila and H. Junjappa, Synthesis, 157 (1981).