NOVEL HETEROCYCLIC SYNTHESIS INVOLVING STUDIES RELATED TO 1,3-DIAZABUTADIENES-KETENES CYCLOADDITIONS

ABSTRACT

BY

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DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

A THESIS
SUBMITTED
IN
FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

TO

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SHILLONG-793022
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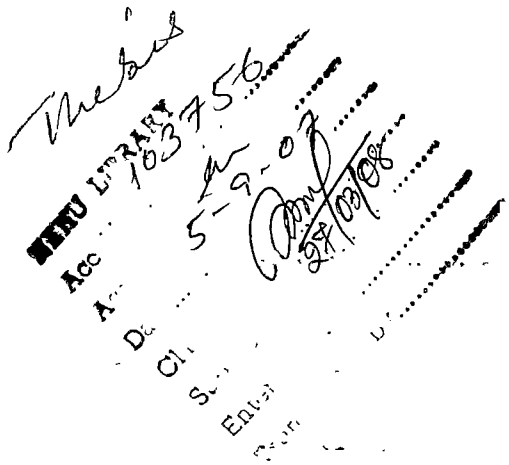
APRIL, 1996



ABSTRACT

CHAPTER-I

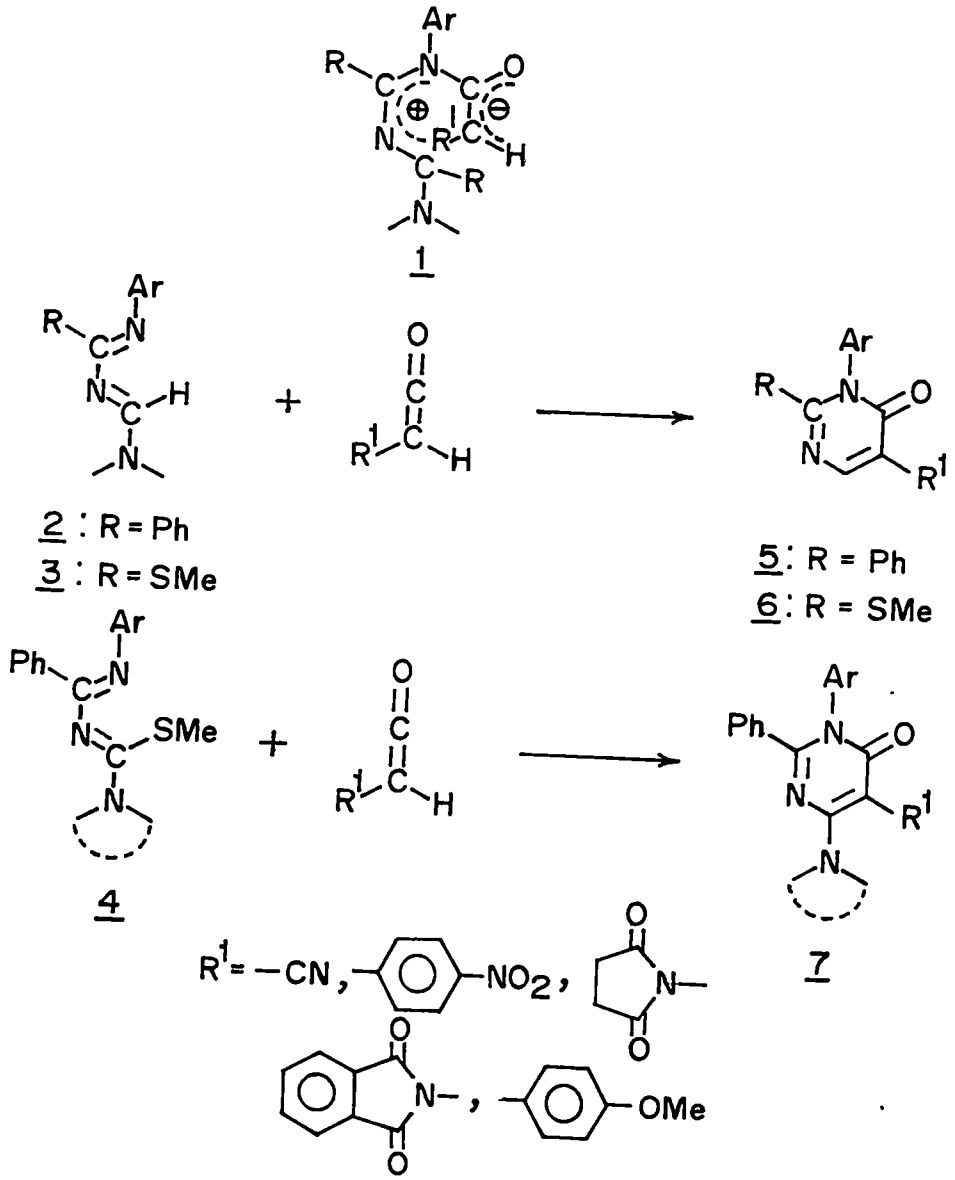
Ketene Chemistry is dominated by [2+2] cycloadditions, which over the years has proved to be an important well documented route to the synthesis of four membered carbocyclic and heterocyclic systems.[1-4] There are numerous reports concerning [2+2] cycloadditions of alkenes with ketenes to yield various cyclobutanone derivatives and of imine-hetene cycloadditions leading to a variety of substituted β-lactam derivatives.[5] A brief review of the cycloadditions of ketenes to alkenes and imines, including monoaza and diazabutadienes, is presented in the first chapter of this thesis.

CHAPTER-II

It has recently been observed that the reactions of polarized 1,3-diaza-1,3-butadienes with monophenyl and monochloroketenes followed [4+2] cycloaddition mode, leading to pyrimidinones as products.[6] The formation of [4+2] cycloadducts in these cases was thought probably due to the higher stability of zwitterionic intermediate (1). In order to examine the influence of the stability of zwitterionic intermediate on the mode of cycloaddition, we have examined in this chapter the reactions with ketenes which can either stabilise the anionic component of such a zwitterion. Thus the reactions of 1,3-diaza-1,3-butadienes (**2-4**) with cyano-, p-nitrophenyl-, succinimido, phthalimido- and phenoxyketenes were investigated and all these reactions were also found to follow [4+2] cycloaddition mode leading to 3-aryl-pyrimidin-4(3*H*)-one derivatives 5,6,7 (Scheme-1). The products were assigned these structures on the basis of analytical and spectral data. From the results above, it may be concluded that the stability of zwitterion/anionic component of zwitterion and to some extent steric factors may not be playing predominant or exclusive role in the observed mode of cycloaddition.

CHAPTER-III

The Chapter III of the thesis describes the reactions of various 1,3-diazabutadienes with bromo-, Iodo-, chloromethyl- and

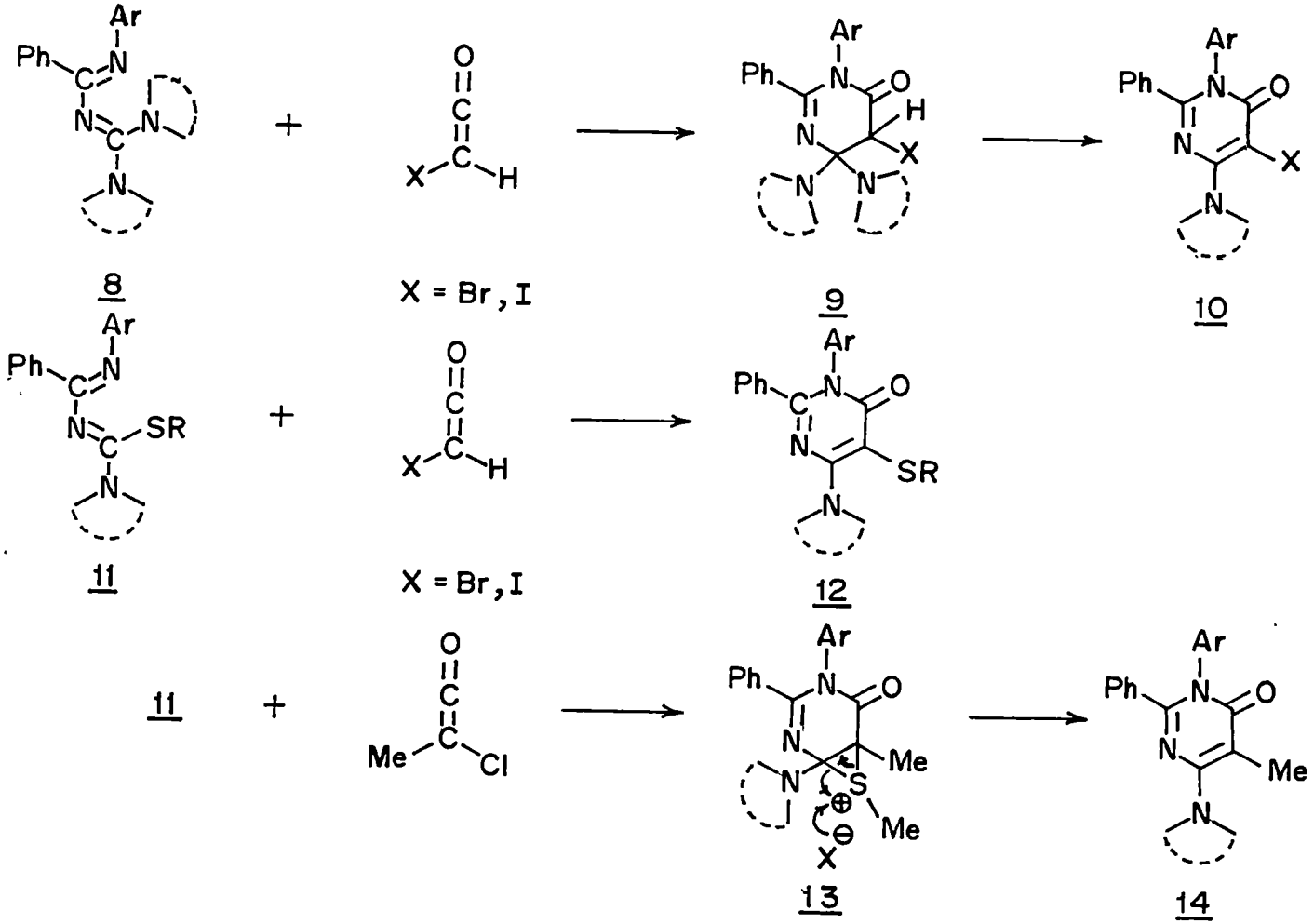


Scheme–1

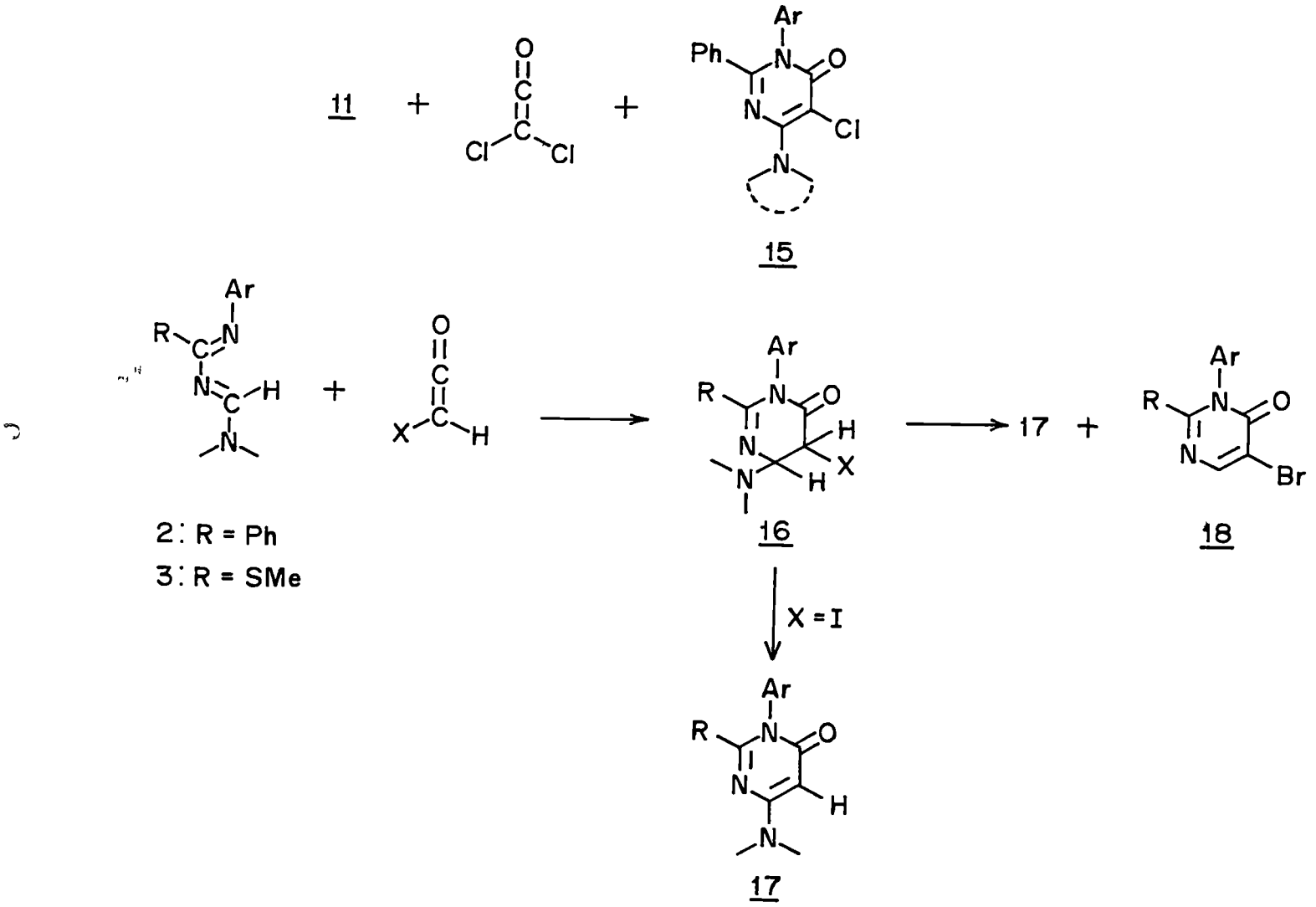
dichloroketene. The reactions of 1-aryl-2-phenyl-4-bis (sec. amino)-1,3-diaza-1,3-butadienes (8) with monobromo- and monoiodoketenes, resulted in good yields of 3-aryl-6-sec. amino-5-bromo/iodo-2-phenyl-pyrimidin-4(3*H*)-one (10), presumably formed *via* the elimination of sec. amines from the initially formed [4+2] cycloadducts 9, as intermediates (Scheme-2).

The reactions of 1-aryl-2-phenyl-4-thioalkyl-4-sec. amino-1,3-diaza-1,butadienes (11) with bromo/iodoketene gave pyrimidones (12) involving [4+2] cycloadditions accompanying 1,2-thioalkyl shift, as observed in case of chloroketene reactions.[7] Various mechanistic possibilities for the formation of rearranged pyrimidinones (12) have been discussed and the mechanism involving episulfonium intermediate has been shown to be most convincing.

The rearrangements accompanying [4+2] cycloadditions have also been shown to occur in reactions of 1,3-diazabutadienes 11 with methylchloro- and dichloroketenes.[7] For example, the reactions of 11 with α-methyl-α-chloroketene resulted in pyrimidinones (14), via epsulfonium intermediates 13. Similarly, the reactions of 11 with dichloroketene gave the pyrimidinones. 15 In reactions of 1,3-diazabutadienes 2 and 3 with iodoketene the initially formed [4+2] cycloadduct intermediate 16, underwent exclusive elimination of hydroiodic acid, in contrast to elimination of dimethylamine in case of chloroketene, to yield pyrimidinones 17 (Scheme-3). In case of bromoketene



Scheme-2



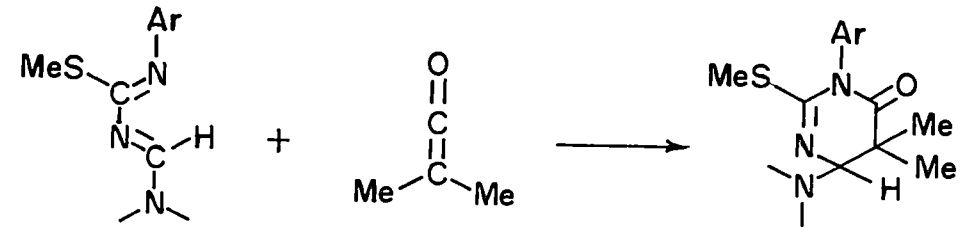
Scheme-3

cycloadditions the intermediate 16 underwent loss, both of dimethylamine and hydrobromic acid to yield pyrimidinones 17 & 18 almost in 1:1 ratio as indicated by the ^{1}H NMR spectrum of the mixture. On the basis of above results a few mechanistic possibilities, in case of 1,3-diazabutadienes-ketenes cycloadditions, were ruled out.

CHAPTER IV

The last chapter of the thesis describes the reactions of various 1,3-diazabutadienes with dimethyl- and diphenylketenes. The structure of the [4+2] cycloadduct reported earlier[8] in case of reaction of 1,3-diazabutadienes 3 with diphenylketene was further confirmed with the help of ^{13}C NMR spectral data. The reactions of 1,3-diazabutadienes 3 with less bulkier dimethylketene, as compared with diphenylketene, also lead to the formation of [4+2] cycloadducts, characterised as previously unknown 5,5-dimethyl-6-dimethylamino-2-thiomethyl-3,4,5,6-tetrahydro-pyrimidin-6-one (19). The observed [4+2] cycloaddition mode in reactions of 1,3-diazabutadienes, having a polar-donating function 2-position, was generalised by carrying out the reactions of 20 and 22 with diphenylketene. Thus, the reactions of 20 and 22 with diphenyl ketene gave pyrimidinones 21 and 23, respectively (Scheme-4).

Further, the reactions of *N*-aryl substituted 1,3-diazabutadienes (24) with diphenylketene did neither yield [2+2] cycloadducts the β-lactams nor [4+2] cycloadducts the



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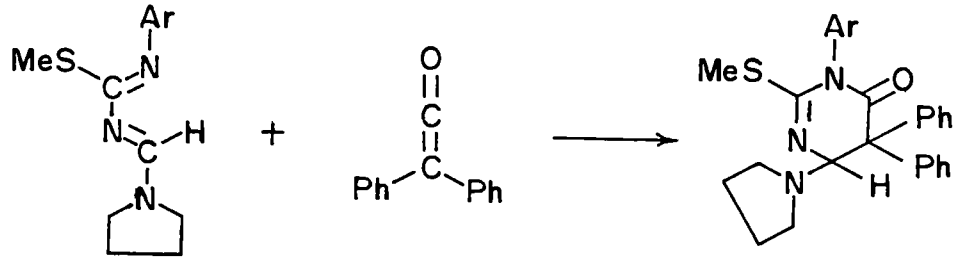

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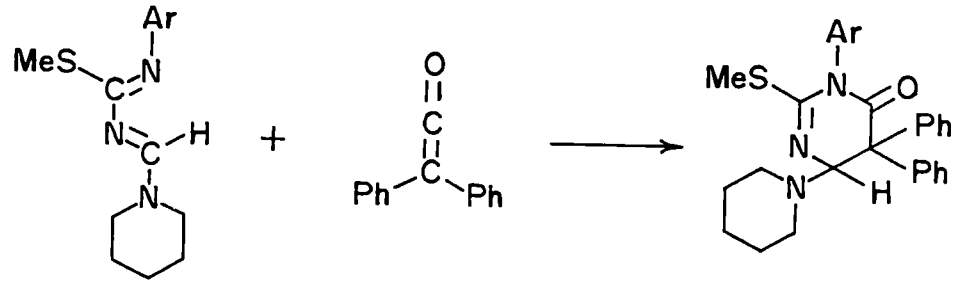


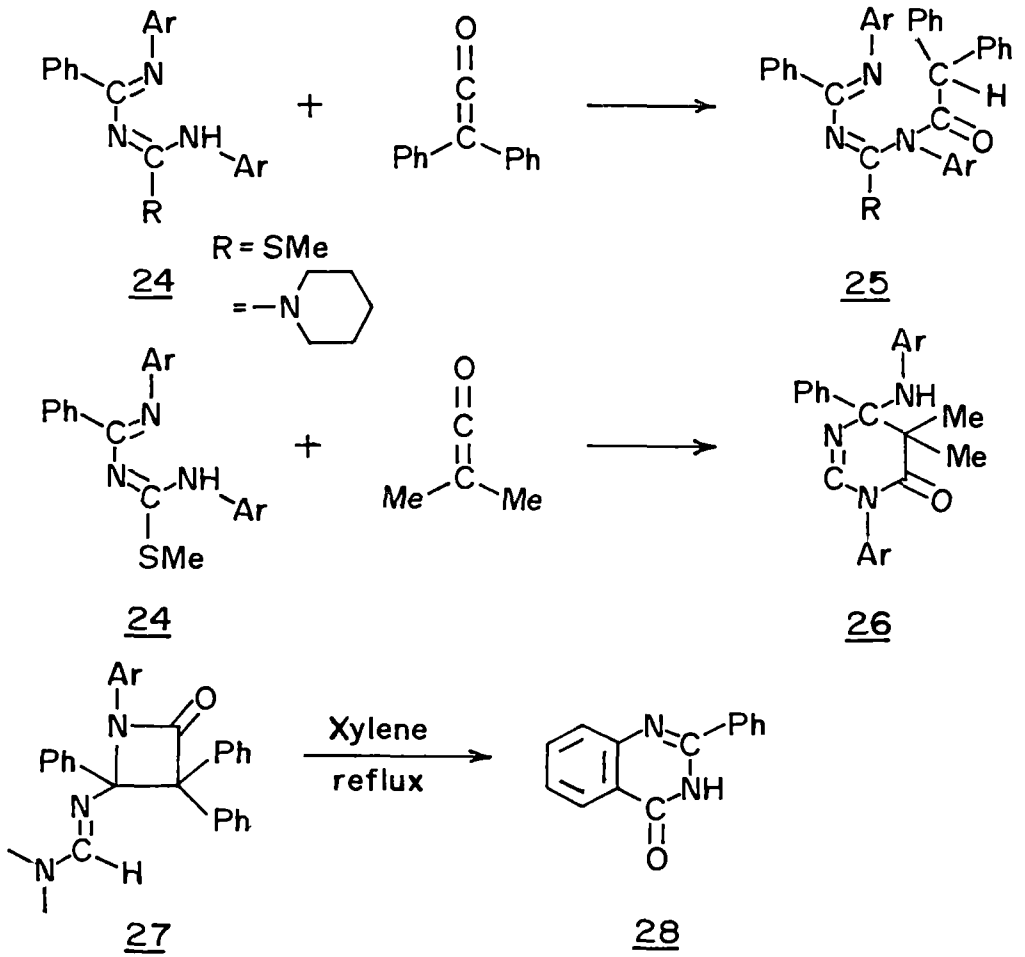
22 23

Scheme-4

pyrimidinones, instead resulted in the formation of N-aryl-N-aryl-amino substituted 1,3-diaza-1,3-butadienes 25 (Scheme-5). However, the reaction of N-diazabutadiene 24 with less bulkier dimethylketene resulted in the formation of [4+2] cycloadduct the pyrimidinone 26.

It has been reported[9] that the formation of β-lactam, [2+2] cycloadduct, in reactions of 1,3-diazabutadienes (2) with diphenylketene is a kinetically governed process. Thus it was thought the thermolysis of β-lactam 27 may yield [4+2] cycloadduct however, such a thermolysis experiment resulted in the formation of 2-phenyl quinazolin-4-one (28).

A number of probable mechanistic pathways leading to the formation of products in reactions of 1,3-diazabutadienes with ketenes have been discussed. Few of the the mechanistic possibilities have been eliminated in order to explain the formation of products formed in these reactions and it could be concluded that (i) steric factors alone perhaps do not influence the mode of cycloaddition in 1,3-diazabutadienes-ketenes cycloadditions (ii) steric and electronic factors together may be responsible in influencing the mode of cycloaddition (iii) Finally, it has been concluded that the most reasonable mechanism which can explain the formation of various products assumes that kinetic control leads to the ring closure of zwitterionic intermediate to initially give β-lactam. Further, the formation of β-lactam is reversible due to the presence of polar donating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R = SMe
=–N
24
25
Me
Me
SMe
26
Xylene
reflux
27
28

Scheme-5

formamidine and/or thiomethyl functions and the reversal to zwitterion allows for the formation of [4+2] adducts and this argument has been reasonably used to rationalise the products formed in reactions of various 1,3-diazabutadienes-ketenes cycloadditions.

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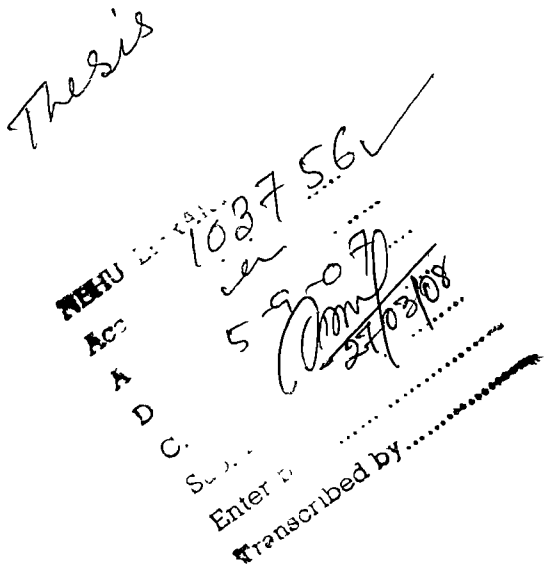
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Professor M.P. Mahajan
Department of Chemistry

CERTIFICATE

This is to certify that the work described in this thesis has been carried out by Ms Sucharita Mukherjee under my supervision. The work described in this thesis is original and has not been submitted for any research degree in this or any other university.

(M.P. Mahajan)
Supervisor

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Shillong
8th April, 1996

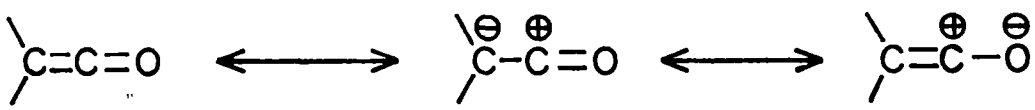
S. Mukherjee.
(Sucharita Mukherjee)

CONTENTS

CHAPTER-I

INTRODUCTION

The pioneering work on ketenes was contributed in the early years of this century by two groups Wilsmore and his co-workers in England and Staudinger and his colleagues at the Technische-Hochschule Korlsruhe in Germany. Staudinger synthesised a variety of substituted ketenes and studied many reactions of this new class of reactive compounds. The broad range of reactivity of ketenes leading to the formation of various carbocyclic and heterocyclic compounds was ascribed to the ambivalent nature of this class of compounds which could be demonstrated by the resonance structures of ketenes shown below



Although various characteristic reactions of ketenes involved in cycloadditions have been well investigated, we shall concentrate here mainly with the cycloadditions across carbon-carbon and carbon-nitrogen double bond and azabutadienes in order to correlate their modes of cycloaddition process, reactivity and mechanistic pathways with our present investigations on the reactions of various ketenes with 1,3-Diaza-1,3-butadienes and related systems.

I. *Cycloaddition Reactions of Ketenes across Carbon-Carbon Double Bond:*

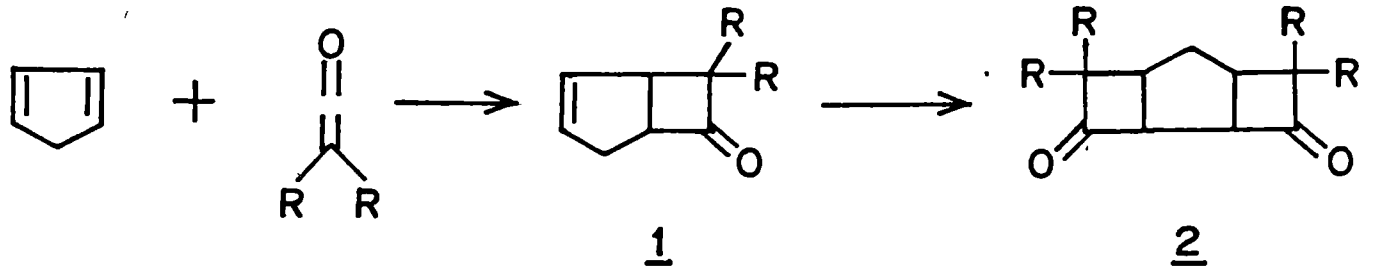
The 1,2-cycloaddition of ketenes to carbon-carbon double bond was first investigated by Staudinger and his co-workers[1-6]. The reaction occurs most readily with activated olefines such as styrenes,[5] cyclopentadiene[6,7], cyclohexadiene[8], cyclooctadienes[9], and indene[9].

The [2+2] cycloadducts obtained from ketene[10-12], dimethylketene[13] and cyclopentadiene were assigned structure **1**, and the cycloadduct **1** ($R=C_6H_5$), upon heating with diphenylketene at 110° for 9 days, afforded the crystalline bisadduct **2**[14]. The 1,2-cycloaddition reaction of dichloroketene, generated in situ, with cyclopentadiene was utilised by Stevns and his co-workers[15] to synthesize tropolone **4**. Thus, reaction of dichloroacetyl chloride with triethylamine and cyclopentadiene afforded the cycloadduct **3** in 75% yield, and hydrolysis of **3** with aqueous potassium acetate gave a 52% yield of tropolone (**4**). Ali and

Roberts have shown that cyclobutanone obtained via [2+2] cycloaddition reaction of ketene[16-18] across carbon-carbon double bond can be converted to -lactones (5), a very important synthetic intermediate. These reactions are outlined in the scheme-1.

Linear conjugated dienes react likewise but rather slowly with ketenes and 1,2-cycloadducts (6) have been obtained from linear dienes and ketene[7], dimethylketene[9,19], butylethylketene[9] and diphenylketene[9]. Because of its slow rate of dimerization, butylethylketene is an especially useful reagent, and the cycloadditions to slowly reacting olefines can be forced by use of elevated temperature. Introduction of a methoxy group at the 1-position of 1,3-butadiene increases the reactivity of the diene. For example, dimethylketene reacts with 1,3-butadienyl methylether at room temperature across the terminal olefin bond to afford the 1,2-cycloadduct[9], when the methoxy group is introduced in the 2-position of the 1,3-butadiene, the reactivity is lowered[9] and with diphenyl- and butylethylketene the 1,4-cycloadducts 8 are obtained exclusively (scheme-2).

The cumulative diene, 2,4-dimethyl-2,3-pentadiene, reacts rapidly at room temperature with dimethyl and diphenylketene to afford the 1,2-cycloadducts 9[9]. Isolated olefines react with ketenes in accordance with the polarization of the double bond, as evidenced by the structure (10) of the 1,2-cycloadducts obtained from styrene and diphenylketene,[20] Staudinger had



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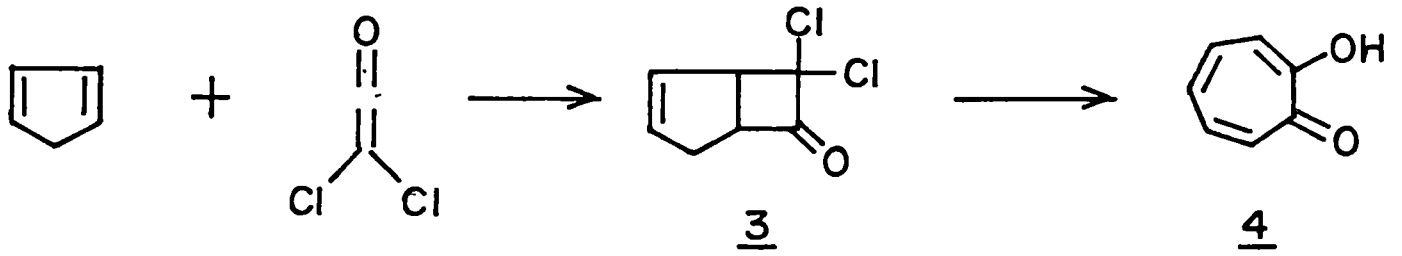

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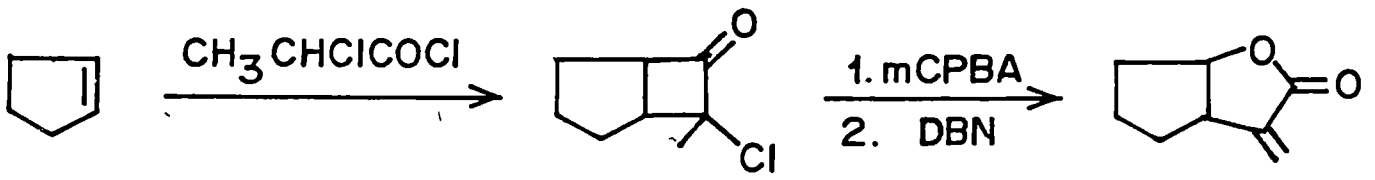

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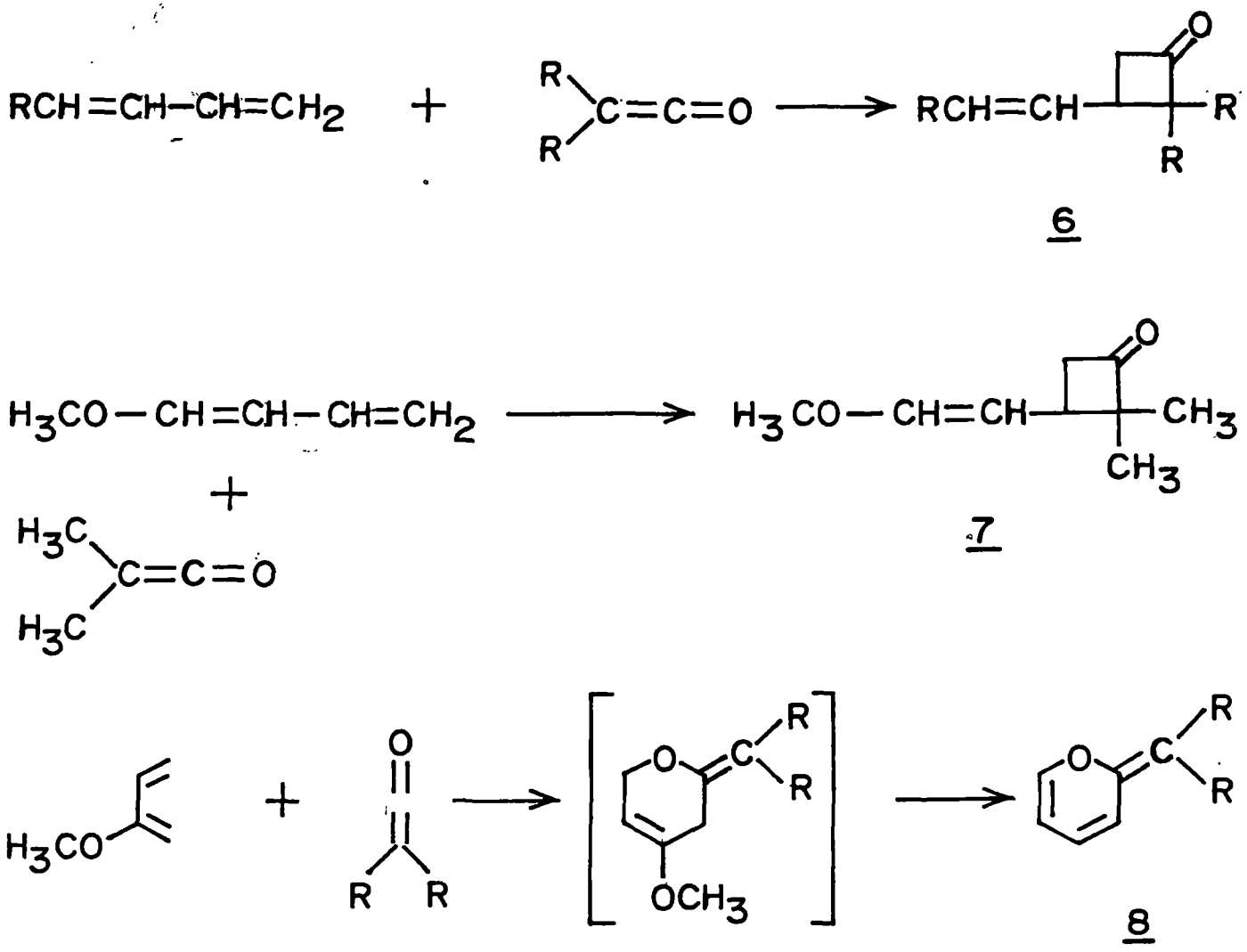
Scheme – 1

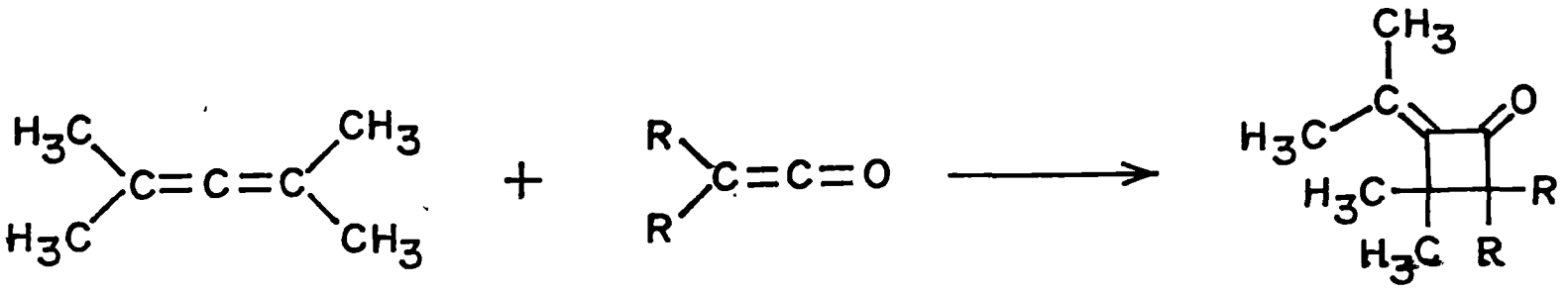


Scheme – 2

erroneously assigned the isomeric cyclic structure to this compound[4]. If diphenylketene is generated from phenylbenzoyldiazomethane in the presence of styrene, both the cyclic adduct 10 and the linear adduct 11 are isolated[21]. These reactions are presented in the Scheme-3. Generation of diphenylketene in the presence of 4-alkoxyl styrenes afforded exclusively the linear adducts, however, cyclopentadiene yielded the cycloadduct[21].

Bis(trifluoromethyl)ketene reacts with propylene at 150° and 800 atm to afford mixtures of cyclolinear adducts[22]. From vinyl benzoate and bis (trifluoromethyl)ketene cycloadducts 12 and 13 are obtained in yields of 34% and 42% respectively[22]. The formation of 12 is the first exception to the general rule that 1,2-cycloaddition of ketenes to olefins occurs across the C=O bond of the ketenes (Scheme-4).

Activated olefines, such as enamines react very rapidly with ketenes to form 1:1 and 1:2 adducts. However, because of the basicity of the nitrogen in enamines often considerable amounts of ketene polymers are produced as by-products[23]. The course of the reaction of enamines with ketenes depends upon the availability of β-hydrogen atoms[23-25]. Enamines lacking β-hydrogen atoms afford the four membered ring cycloadducts with disubstituted ketenes. If ketenes or enamines having β-hydrogen atoms are used, isomerisation to the linear adducts usually occurs. From acetylchloride and 1-morpholinoisobutene in the presence of triethylamine, the cyclobutanone adduct (16) was



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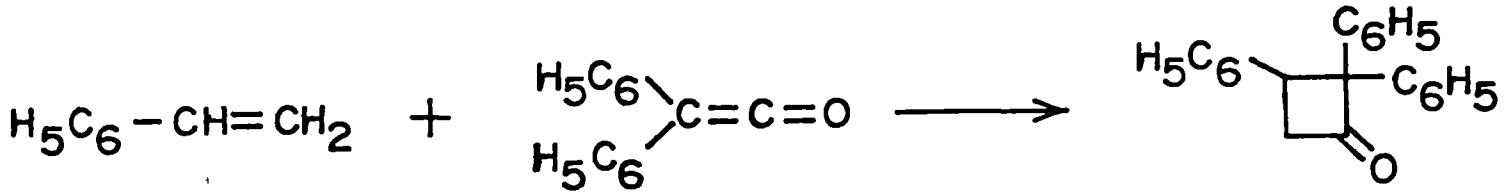

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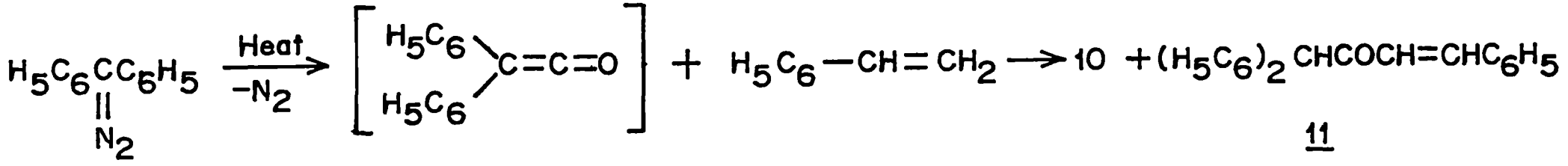

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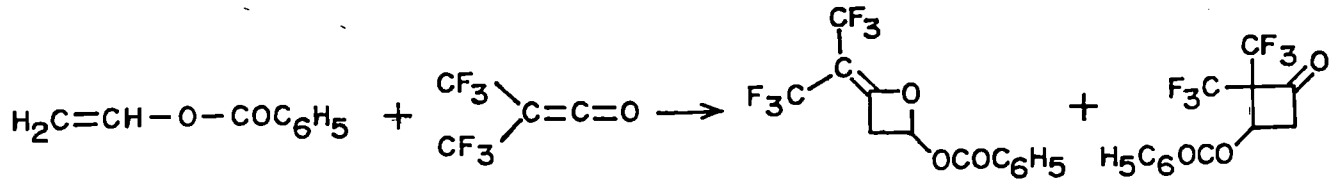
Scheme – 3



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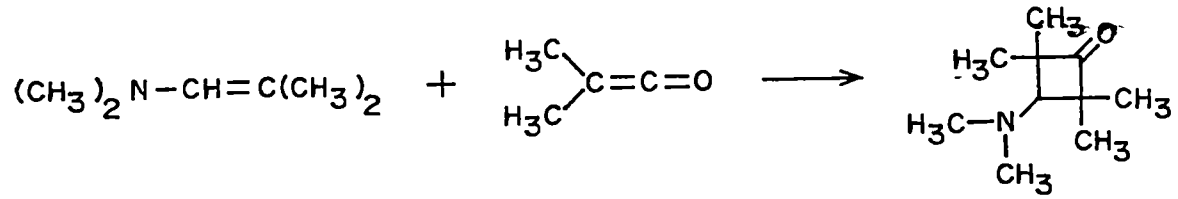

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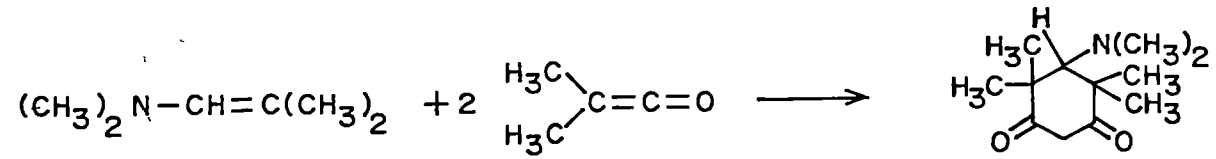

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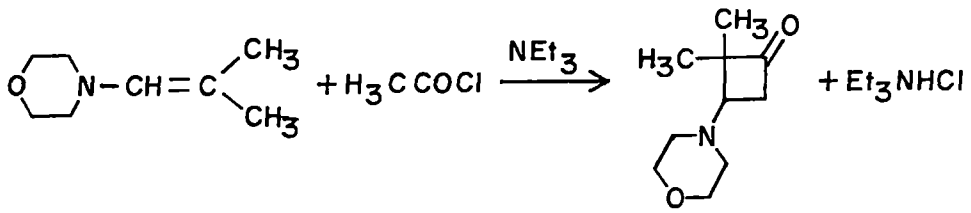


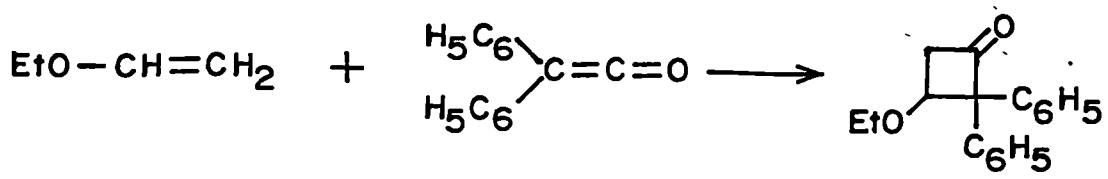
16 17

Scheme-4

obtained in 30% yield and upon attempted vacuum distillation, the rearrangement to the linear adduct (17) occured. These reactions are presented in the Scheme-4 However from 1-pyrrolidino-and 1-pipiridinoisobutene, the linear adducts were obtained exclusively.

Similarly in vinylethers the double bond is sufficiently activated to undergo 1,2-cycloaddition reactions with ketenes. This reaction was already observed by Staudinger and his co-workers.[4,27] The polarity of bonds again determines the course of the reaction, as demonstrated by the isolation of cycloadduct (18) from vinylether and diphenylketene.[4,28] Huisgen[29] demonstrated that the cycloaddition of ketenes onto vinylethers is stereospecific, indicating a concerted one step mechanism. Thus, from *cis* and *trans* propenyl propyl ether (19 and 20) and diphenylketene the cycloadducts (21 and 22) are obtained, the cis-ether reacting 100 times faster than the trans-isomer. Upon heating of 21 and 22 in xylene the same diphenylacetylpropenyl propyl ether (23) is obtained.[29] These reactions are demonstrated in the scheme-5.

Scarpati and Co-workers[30-32] investigated the reaction of ketene acetals with ketenes and the cycloadducts 24 have been obtained from dialkylketene acetals and diphenylketene.[32] However ketene diethylmercaptal reacts with diphenylketene to form the linear 1:1 adduct 25.[33] From dimethylketene and 1-ethyoxyl-N,N-dimethylvinylamine (26) the 1:1 adduct 27 and 2:1



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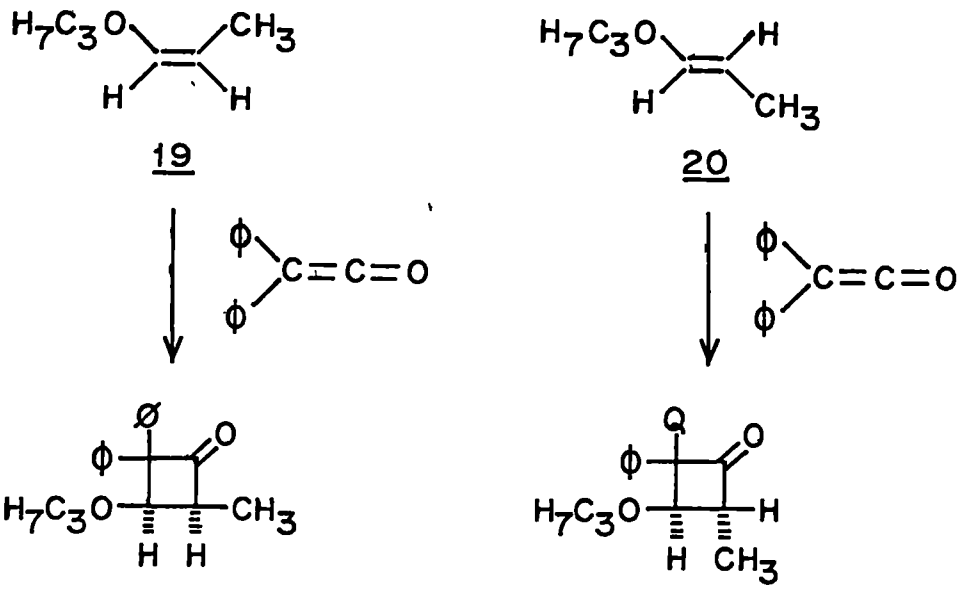


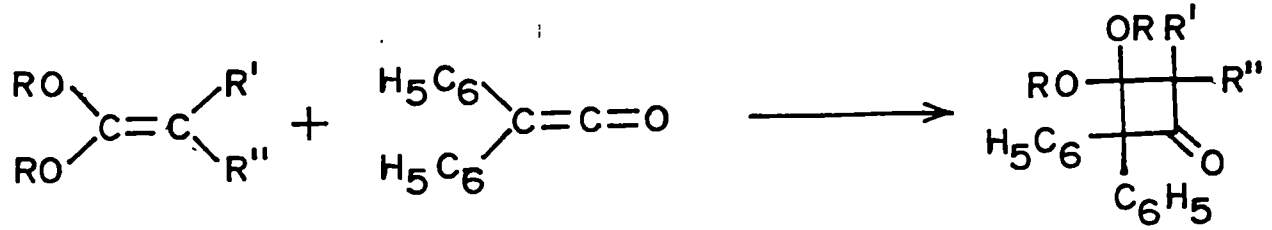
Heat Heat

23

Scheme – 5

adduct 28 were obtained in 36% and 49% yields, respectively[34] (Scheme-6). Intramolecular [2+2] cycloaddition of ketenes to alkenes were reported in the 1960s. Although, numerous isolated examples were reported later on, no attempt was made to develop the reaction in to a general synthetic method. In the early 1980s several groups began a systematic exploration of this reaction and exploitation of it in the synthesis of complex natural products. Snider reviewed these intramolecular cycloaddition reactions of ketenes and those of the related keteniminium salts with alkenes.[35] For example, ketenes 29a and 29b, generated by treatment of the corresponding acid chloride with triethylamine gave cycloadducts 30a and 30b in 65% and 58% yields, respectively. On the other hand, Greuter and Ghosez[36] demonstrated that ketene 29c, generated from the corresponding acid chloride, gave cyclobutanone 30c in only 3% yield and it was further shown that ketene 31 does not give 32.[37] Mori has made use of the intramolecular cycloaddition of ketene 33 in the synthesis of (+) (-) and (-) - grandisol[38]. Ketene 34, generated by treatment of 33 with triethylamine in dichloromethane gave a 3:1 mixture 35a and 35b in 70% yield (Scheme-7). Kulkarni and Snider[39] have also reported that intramolecular [2+2] cycloaddition of the vinylketene 36 (from geranyl chloride) gave 37 which finally converted to the racemic chrysanthenone (38) followed by a double bond shift (Scheme-8).

Intramolecular cycloaddition of ketenes, generated by photolysis or thermolysis of diazoketones, to carbon-carbon



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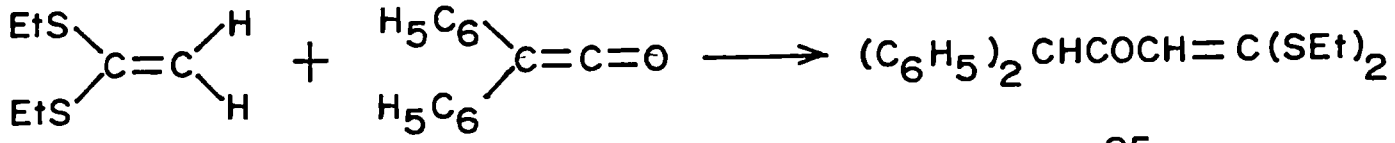

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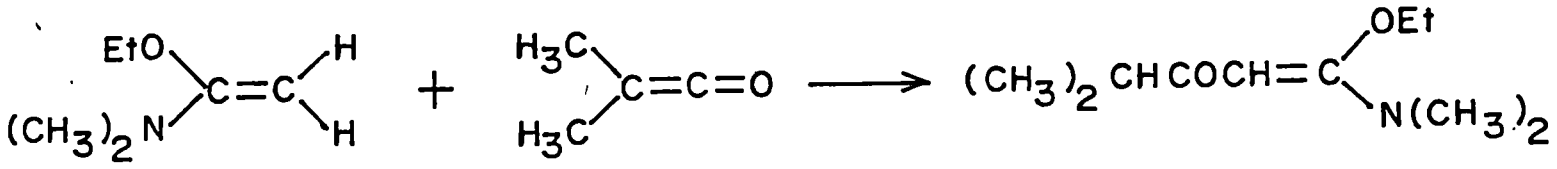

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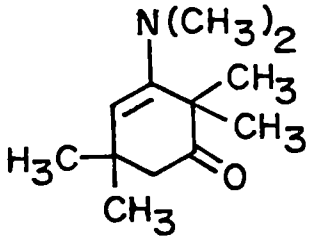
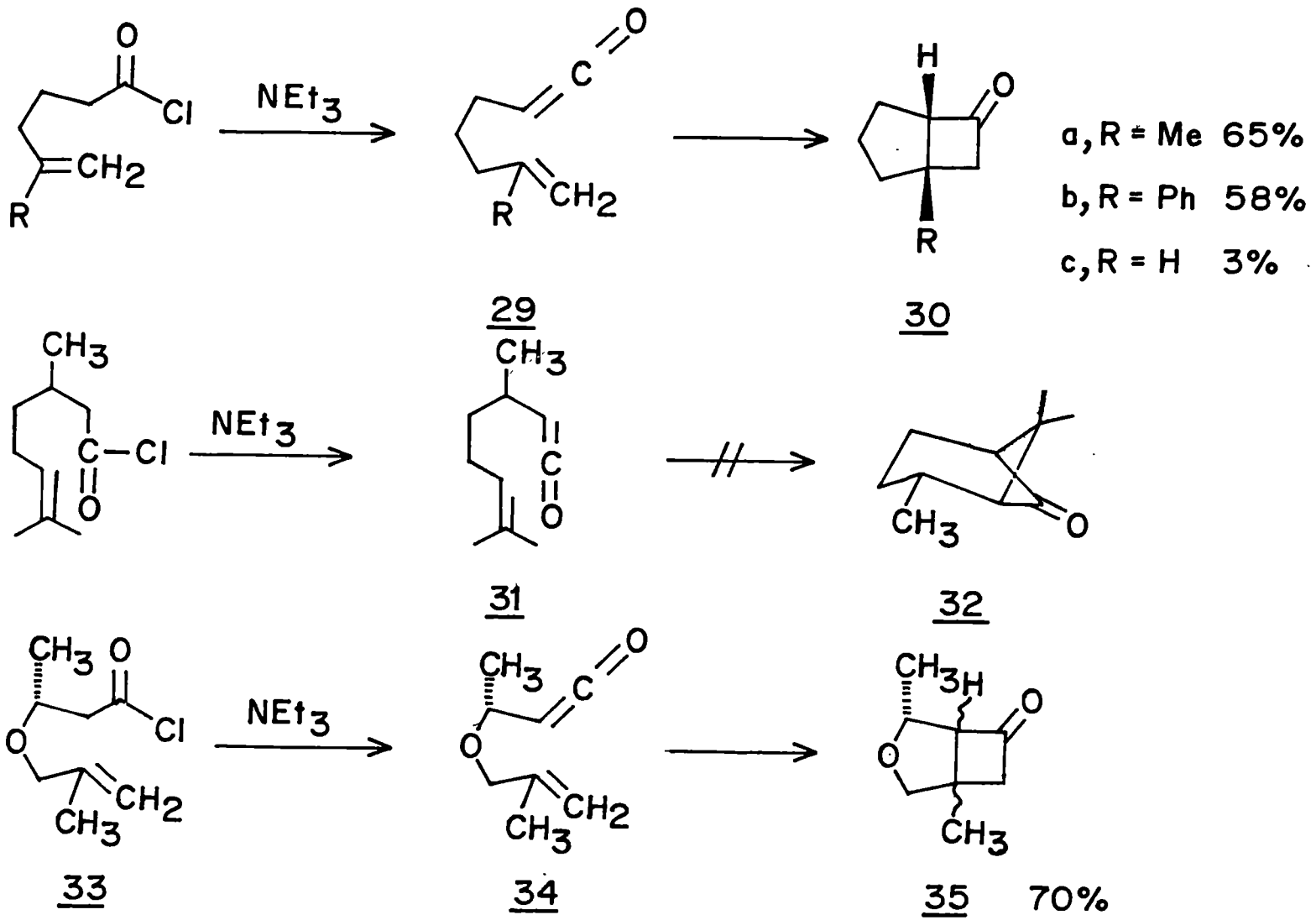


28

Scheme – 6


NEt3
a, R = Me 65%
b, R = Ph 58%
c, R = H 3%
29
30
NEt3
31
32
NEt3
33
34
35 70%
a, β-H, Me
b, α-H, Me

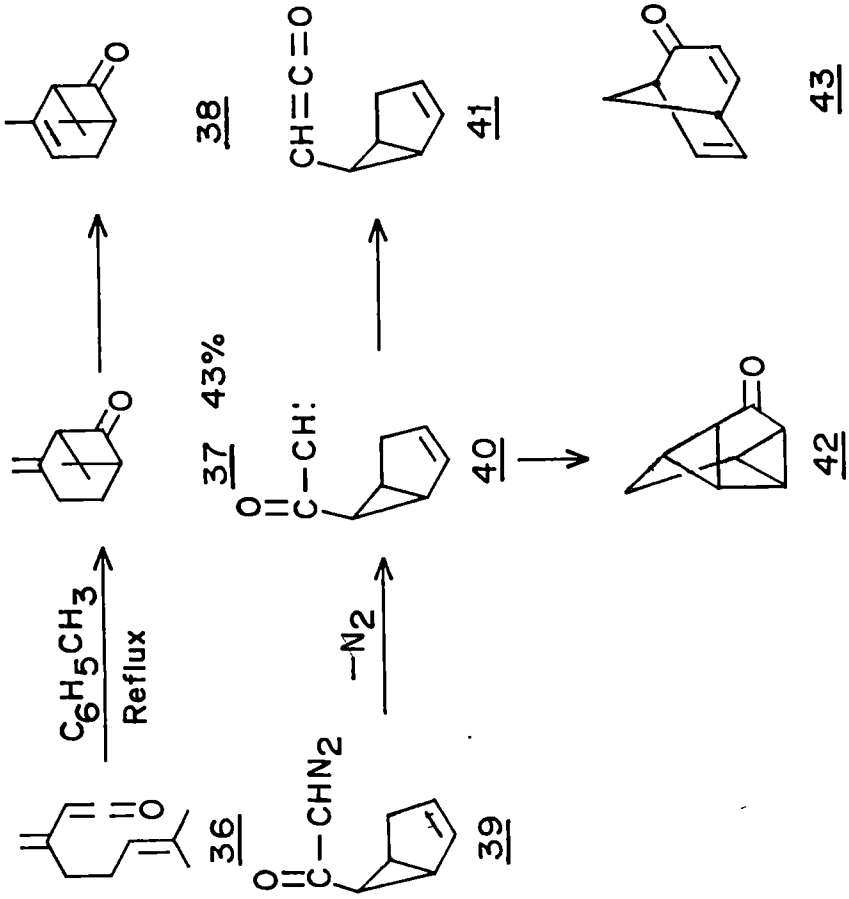
Scheme-7

double bonds has also been reported.[40-41] For example, photolysis of the diazoketone 39 afforded the bicyclic ketone 43, resulting from an intramolecular cycloaddition of the ketene intermediate 41. Tetracyclic ketone 42 was formed as a product by addition of the ketocarbene 40 prior to the Wolff rearrangement.[40] This reaction is outlined in the Scheme-8.

II. *Cycloaddition Reactions of Ketenes across Carbon-Nitrogen Double Bond*

The addition of ketenes to isolated carbon-nitrogen double bond compounds has been investigated by Staudinger and his co-workers and is commonly referred to as Staudinger Reaction. Depending upon the basicity (or perhaps better nucleophilicity) of the nitrogen atom, 1:1 or 2:1 adducts were obtained. The reaction is general and the β-lactams can be isolated in most instances.

The imido thioester (44) reacts with dimethylketene to afford the β-lactam (45).[42] The heterocylic analog of 44, 2-phenyl-β-thiazoline(46) reacts with diphenylketene to form the bicylic β-lactam (47). In the reaction of ethylcarbethoxyketene (48) with benzylidenaniline a labile 1:1 adduct was formed at -10°, which slowly decomposed to the starting materials at room temperature. Sheehan and Corey[44], in their review article on β-lactams, discussed the possibility that the initially formed labile compound may be the 1,4-cycloadduct 49. At elevated temperatures the ketene48 reacts with benzylidenaniline to form



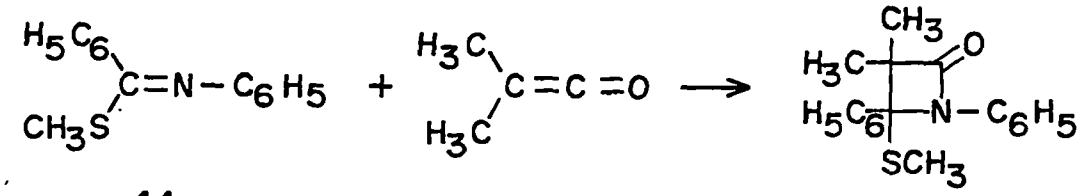
36 37 38 39 40 41 42 43

Scheme-8

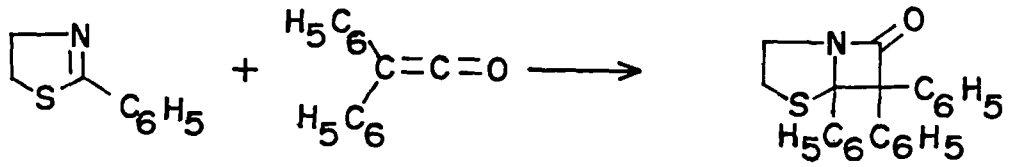
the expected β-lactam (50)[45] (Scheme-9). The 1,2-cyclo adducts upon thermolysis generally undergo ring cleavage in both directions, thereby forming four fragments [3] (Scheme-10). However, the β-lactams obtained from dephenylketene and C-diphenyl-N-P-dimethylminophenylazomethine and C-styryl-N-phenylazomethine, respectively, regenerate the starting materials only.[3] In contrast to the aromatic azomethines, which generally react with ketenes with to form β-lactams, aliphatic azomethines form 2:1 adducts, most likely because of the basicity of the nitrogen atoms. From C-phenyl-N-ethylazomethine and dimethylketene the 2:1 adduct (51) was obtained.[46] Upon treatment with a catalytic amount of sodium methoxide, 51 was converted to the symmetrical 2:1 adduct 52.[46] This reaction is also depicted in Scheme-10.

Cycloaddition across the carbon-nitrogen double bond in amidines can also occur, as evidenced by the reaction products via the formation of (2+2) cycloadduct (53) obtained from phthalylglycyl chloride and amidines (Scheme-11). The reaction of ketenes with isocyanates also proceeds across the carbon-nitrogen double bond. Staudinger and his co-workers[48] reacted diphenylketene with phenylisocyanate at 220° and isolated the 1,2-cycloadduct (54) in 20% yield. The highly reactive sulphonylisocyanate afforded similar 1,2-cycloadducts (55) with ketene itself and the reaction occurs below 0°[49] (Scheme-11).

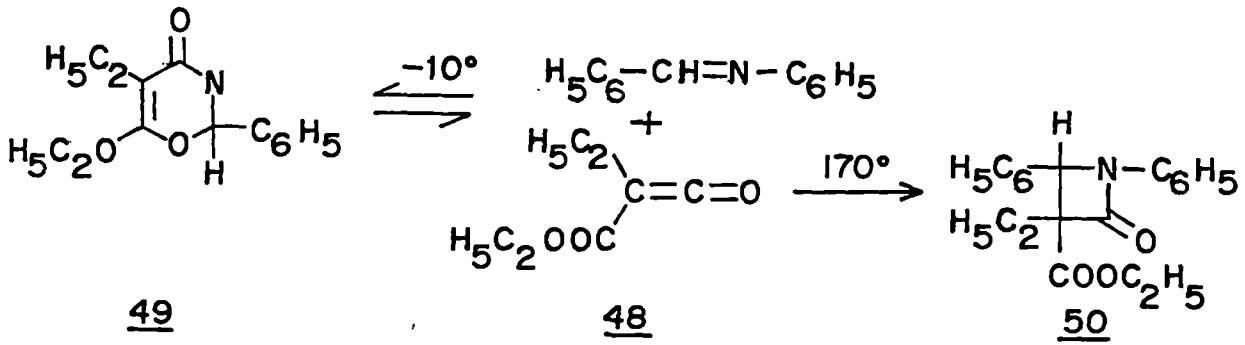
Ziegler and Kleinberg reported that the malonyl chloride



44 45

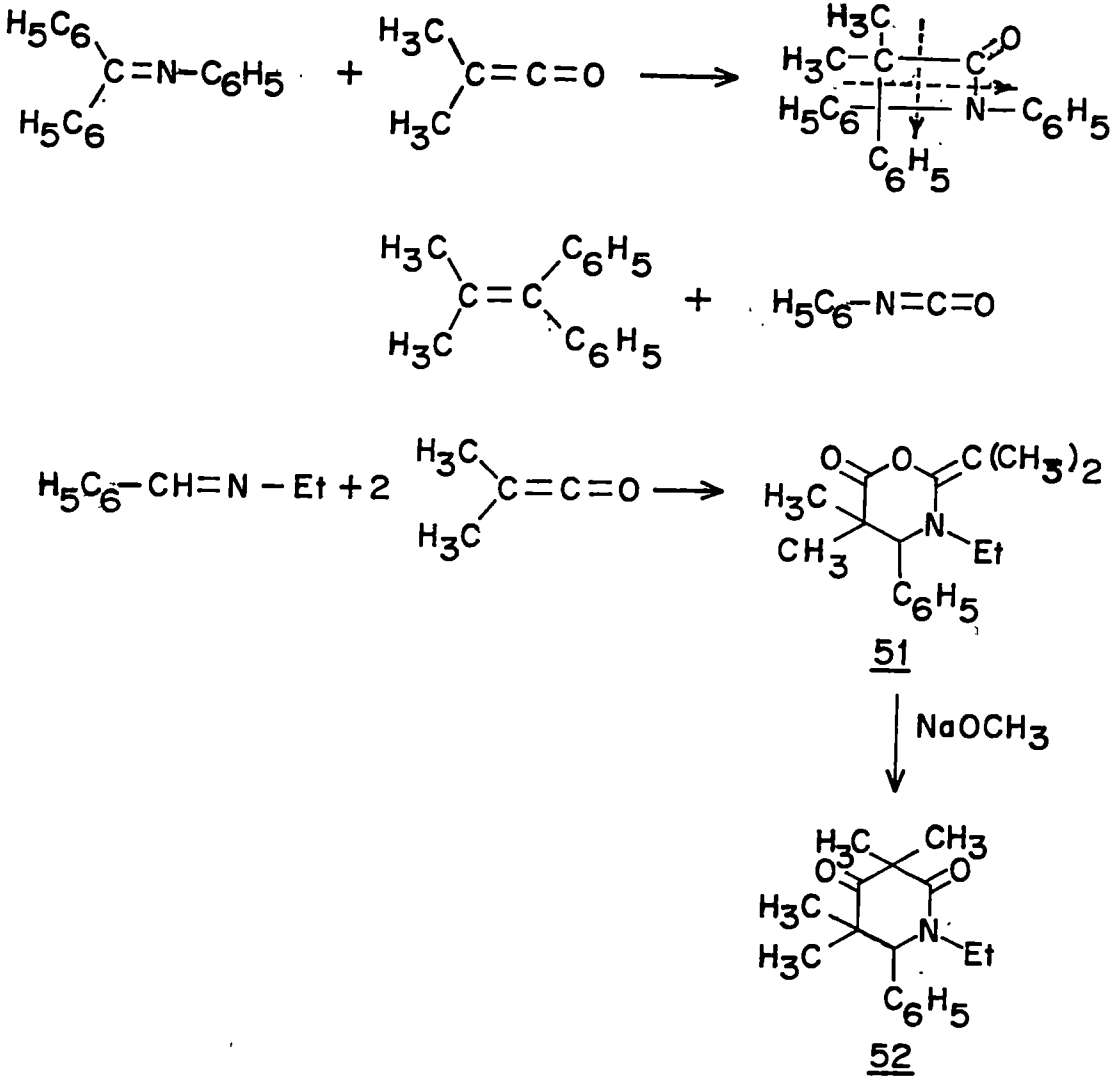


46 47

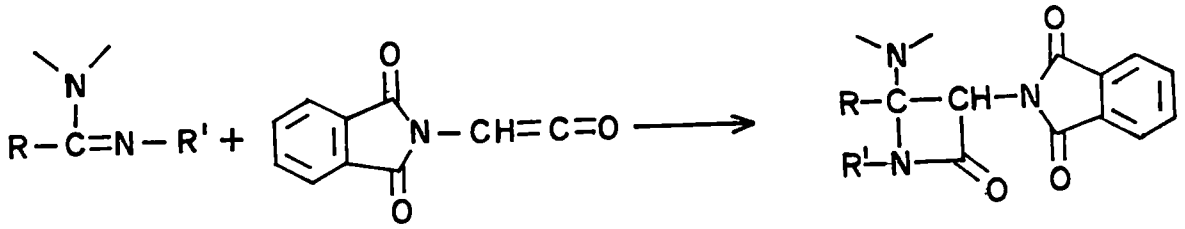


49 48 50

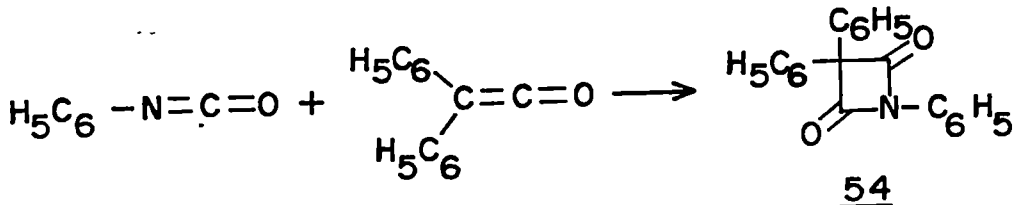
Scheme-9



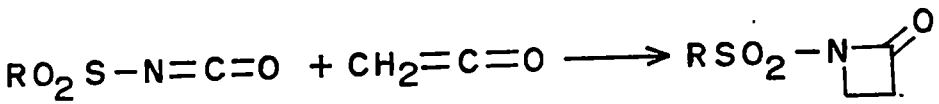
Scheme-10



53



54



55

Scheme-11

derivative (56) reacted with Schiff base in refluxing benzene for 4 hours to give 57 in 47% yield[50] and the authors suggested a non-concerted two step cycloaddition process for this reaction as shown in Scheme 12. Alternatively one could propose an initial dehydrohalogenation to afford ketene 58, which undergoes a concerted cycloaddition to give 57 (Scheme-12).

The substitution requirements with respect to case of formation of the β-lactam from the precursor azomethine and ketene have been reported through the year 1964.[51,52] For example, the relative ease of β-lactam formation from ketenes and benzophenone anil is presented in Fig 1.[51]

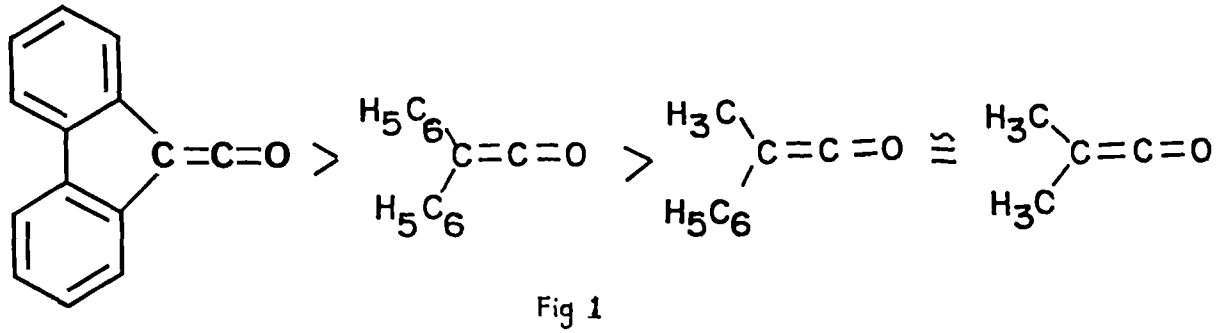
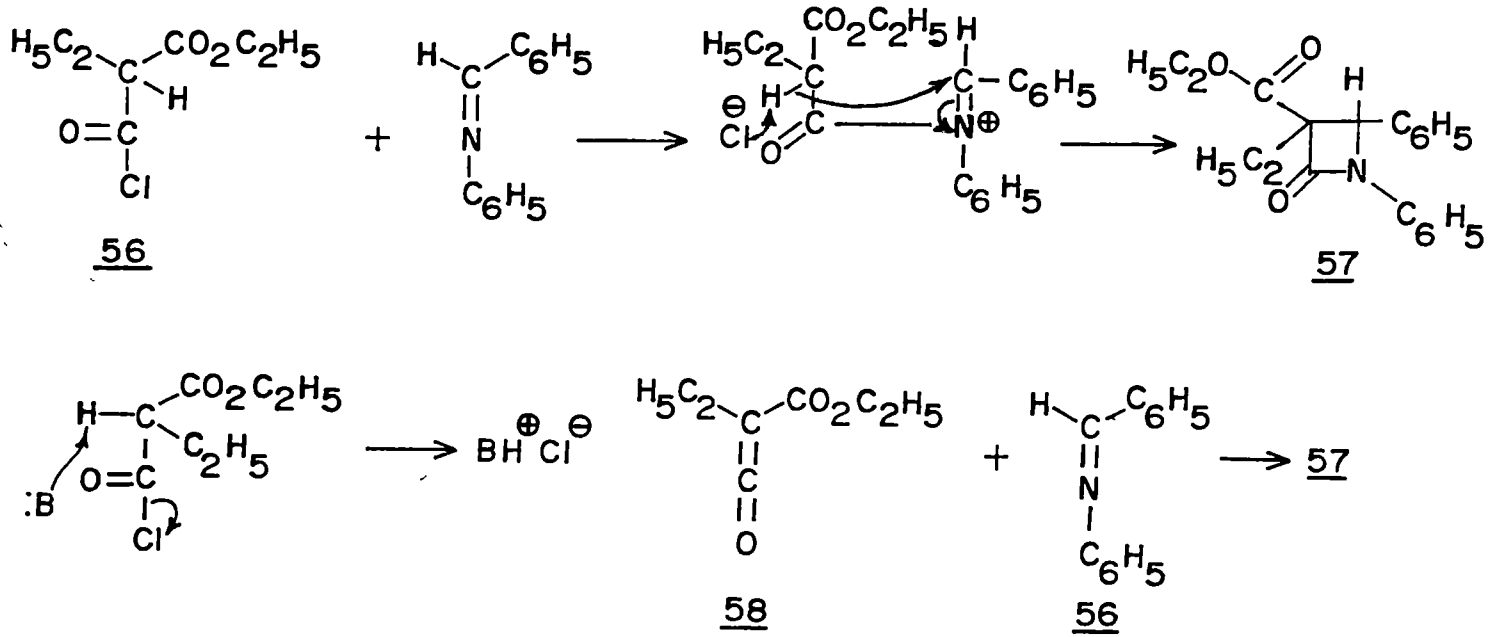


Fig 1

In case of imines having an aromatic group both on nitrogen and carbon, electron donating substituents on *N*-aryl facilitate β-lactam formation and electron withdrawing substituents retard its formation.[52] The reactivity of azomethine substrates substituted with heteroatoms at the carbon atom has also been investigated with respect to [2+2] reactivity with ketenes. Imino chloride 59, phenylhydrazone 60 and oxime ether 61 were found to be unreactive.[51] However, thioimidate 62 reacted with dimethylketene to give 63 in 60% yield.[52,53] In addition, the use of thioimidates in the construction of penicillin β-lactam

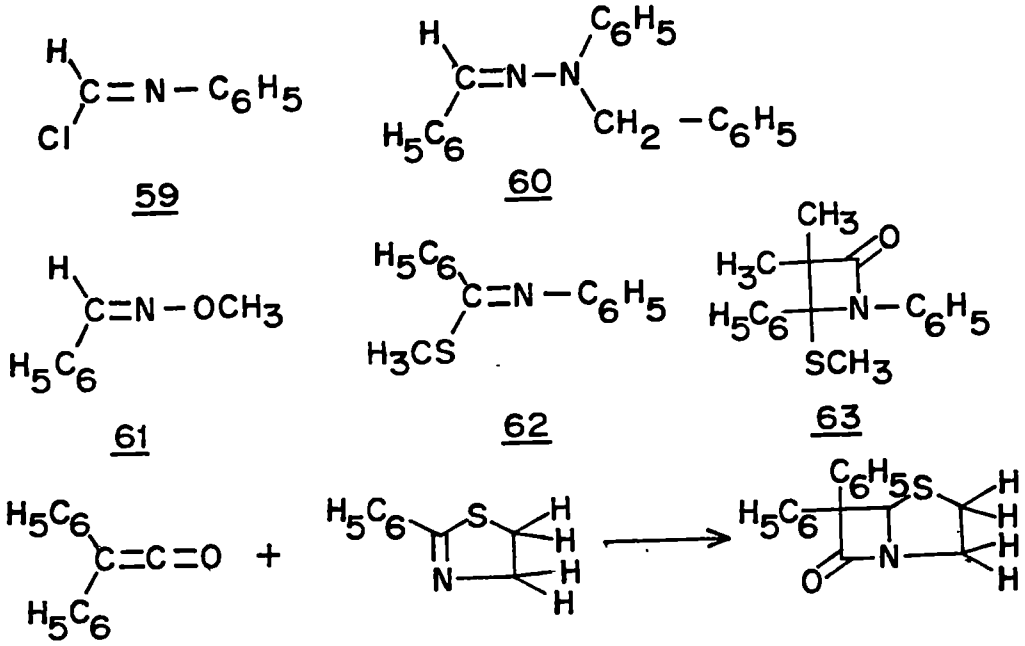


Scheme-12

models was successfully demonstrated in the synthesis of fused β-lactams.[51,54] These reactions are presented in the Scheme-13.

Bose and Kugajevsky extended the utility of azomethine substrates with amendable groups to the [2+2] cycloaddition reaction with the discovery that amidine **64** reacted with diphenylketene to give azetidinone **65** in 45% yield[55] (Scheme-14). The reactivity of halogenated ketenes with azomethine substrates in β-lactam formation was reported independently by two groups of Brady and Hull.[56,57] Fluoroketene **66**, prepared by dehydrohalogenation of fluoroacetyl chloride with triethylamine at -78°C, reacted with N,N-diisopropylcarbodiimide **67**, in refluxing hexane, to give iminoazetidinone **68** in 40% yield.[56] Similarly, the adduct **70**, derived from chloroketene **69** and **67**, was produced in 60% yield.[56] Dichloroketene **71**, prepared in situ by dehydrohalogenation of dichloroacetylchloride with triethylamine reacted with dicyclohexylcarbodiimide **72** to give azetidinone **73** in good yield[57] (Scheme-14). In case of unsymmetric dialkyl carbodiimides, quite interestingly, the less sterically hindered nitrogen becomes the β-lactam nitrogen[58] (e.g. **74**, **75** and **76**) (Scheme-14).

The reactions of haloketenes with Schiff bases were reported independently by Duran and Ghosez[59] and by Bose et. al.[60]. Both these groups discovered that the generation of haloketenes in situ afforded very good yields of the appropriate halogenated β-lactams. For example, the reaction of chloroacetyl chloride **77**

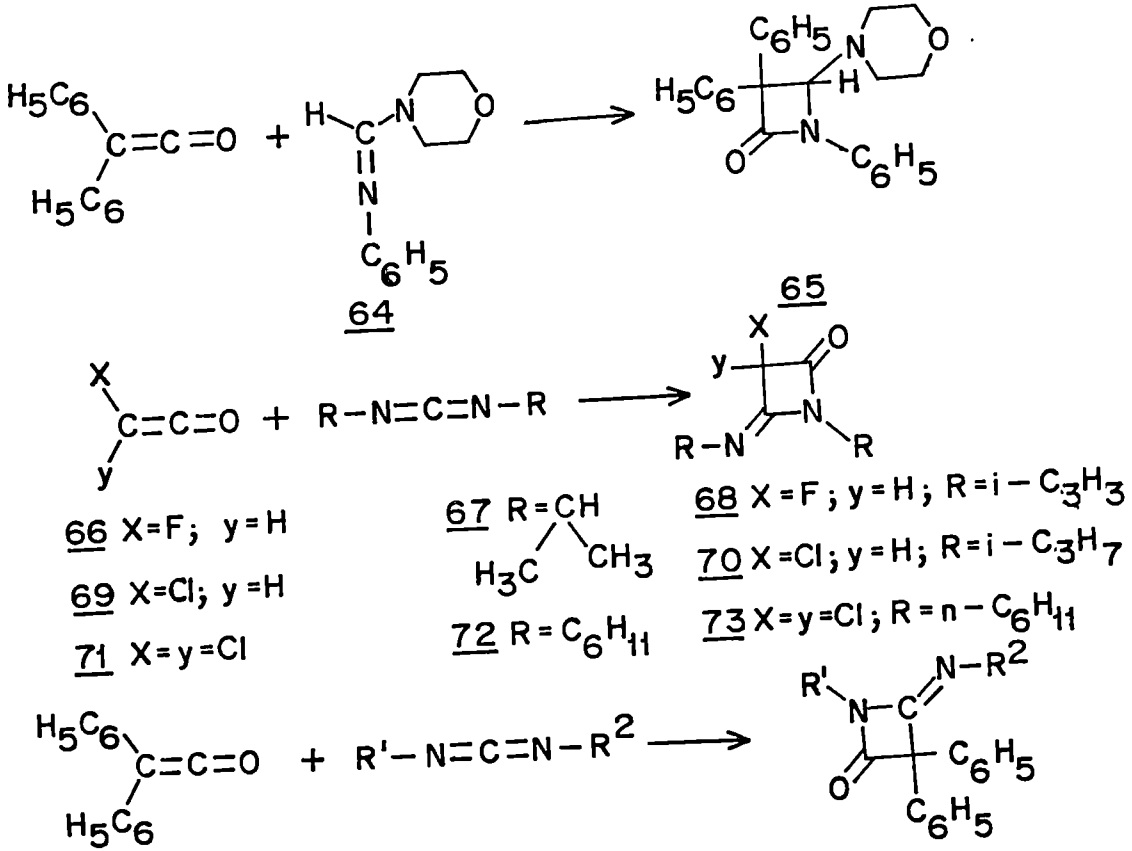


59 60 61 62 63

Scheme-13

in benzene with Schiff base 79 in the presence of triethylamine at room temperature afforded a quantitative yield of 80.[59] Similarly, dichloroacetyl chloride 78 reacted with 79 to give 81 in quantitative yield (Scheme-15).[59] An investigation of the stereochemistry of the cycloaddition reaction of chloroketene with substituted benzalaniline was reported by Nelson.[61] Chloroacetyl chloride was added to a solution of imine and triethylamine at 70-75°C. The reactants and products with respect to cis/trans ratios are illustrated in the Scheme-15. The R^1 group in the ortho position enhanced the formation of cis-isomer 82. In contrast R^1 substituted in the para positions gave only the trans product 83. The author proposed a two-step cycloaddition mechanism in which both steric and electronic effects influence the stereochemistry of the product[61] (Scheme-15).

Moore and co-workers reported in a series of investigations the more elegant constructions of β-lactams utilising "latent functionalized ketenes" such as chlorocyanoketene 86.[62] The requisite precursor β-azido-α-chloro-r-methoxy- crotonolactone (84) was pepared as described in Scheme-16. The lactone 84 on thermolysis was shown to undergo decomposition *via* 85 to yield chlorocyanoketene 86. The reaction of (84) with formimidate 87 produced azetidinone 88 as one diastereomer (with stereochemistry undefined) in 48% yield.[62] The reaction of halocyanoketene derived from butenolide is found to be stereospecific. The orientation of the R^2 substituent and of the chloro and cyano



64

65

66 X=F; y=H

69 X=Cl; y=H

71 X=y=Cl

67 R=CH(CH3)2

72 R=C6H11

68 X=F; y=H; R=i-C3H3

70 X=Cl; y=H; R=i-C3H7

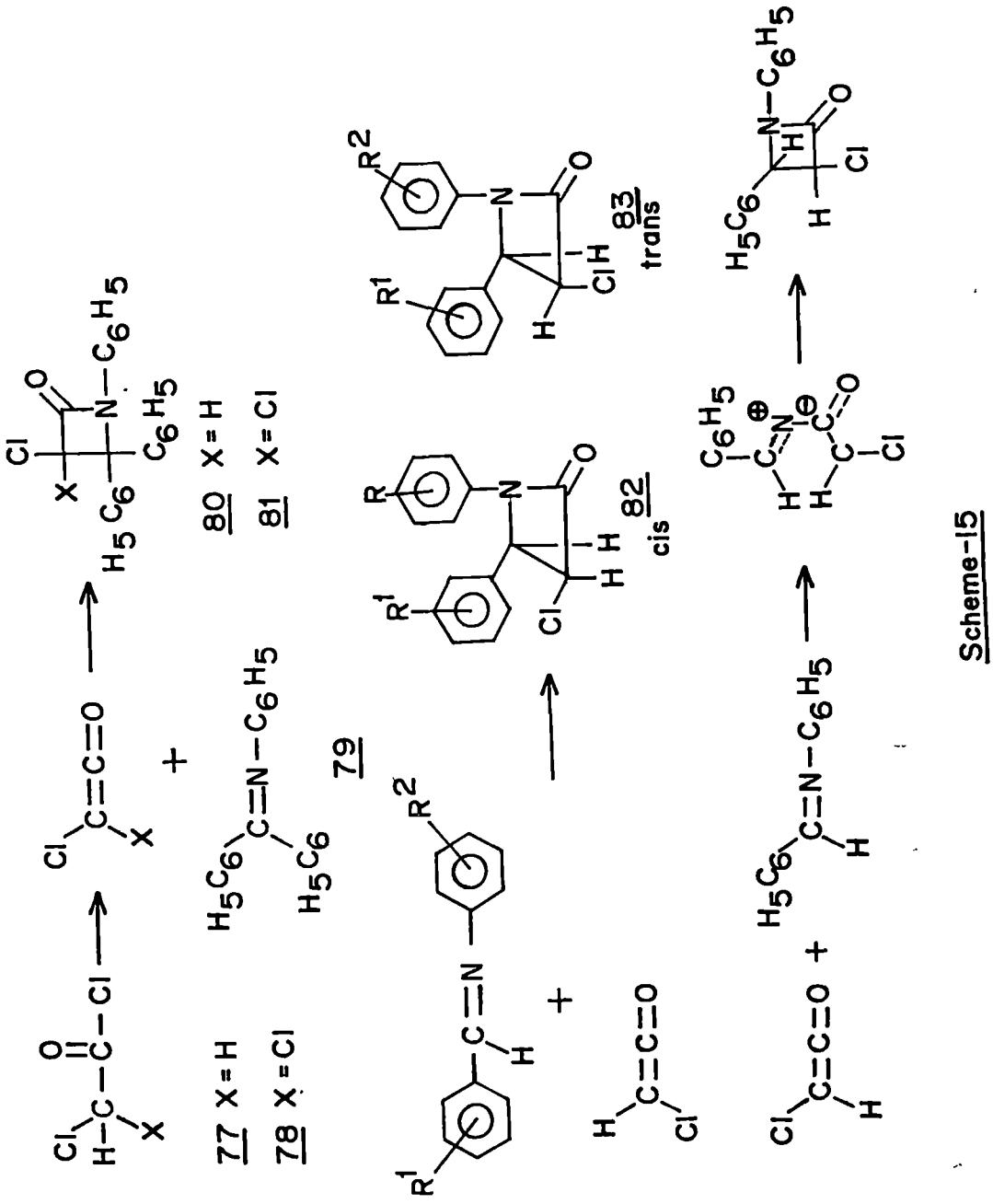
73 X=y=Cl; R=n-C6H11

74 R'=C2H5, R2=(CH3)2CH

75 R'=CH3, R2=(CH3)3C

76 R'=C2H5, R2=(CH3)3C

Scheme-14

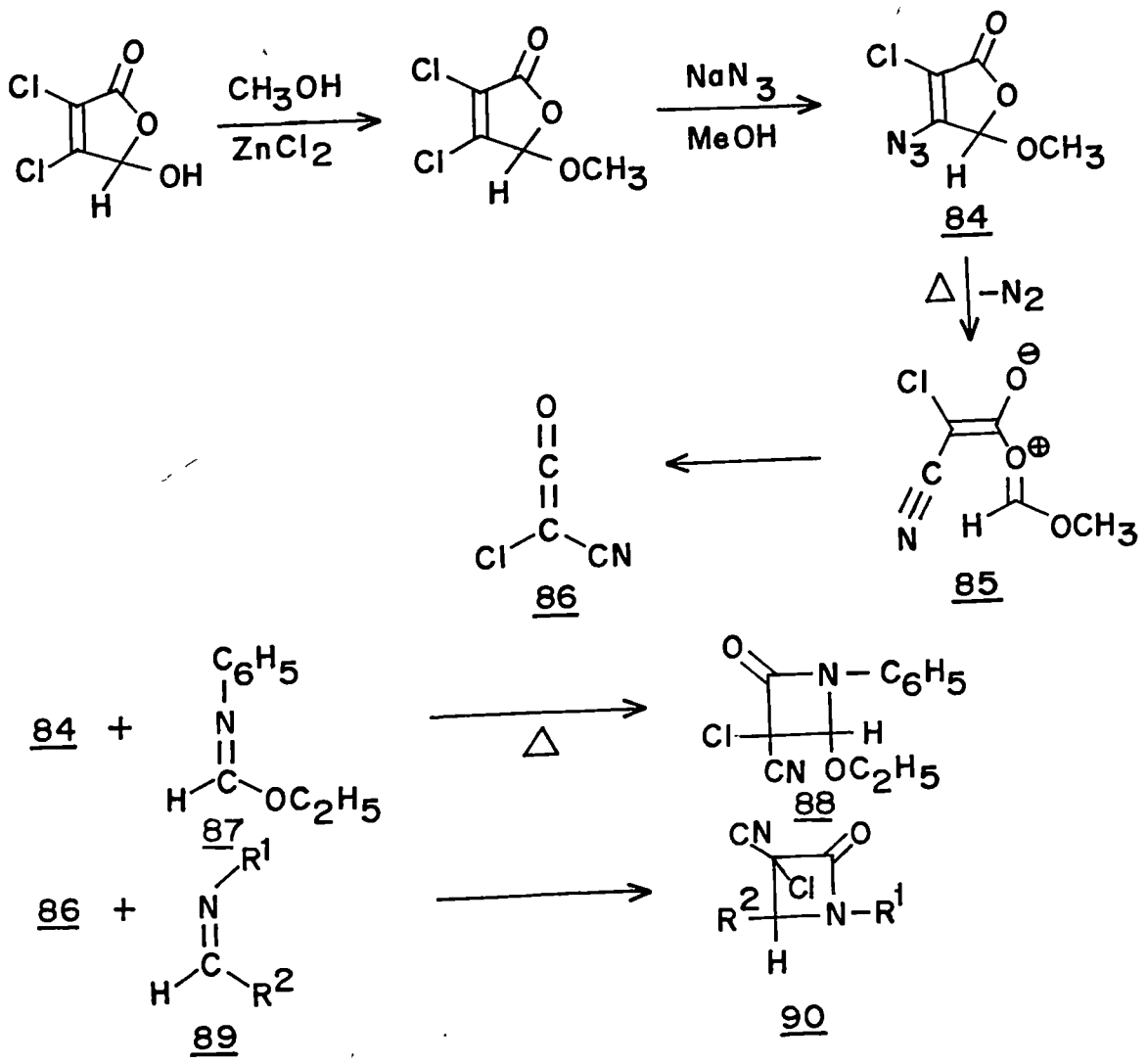


Scheme-15

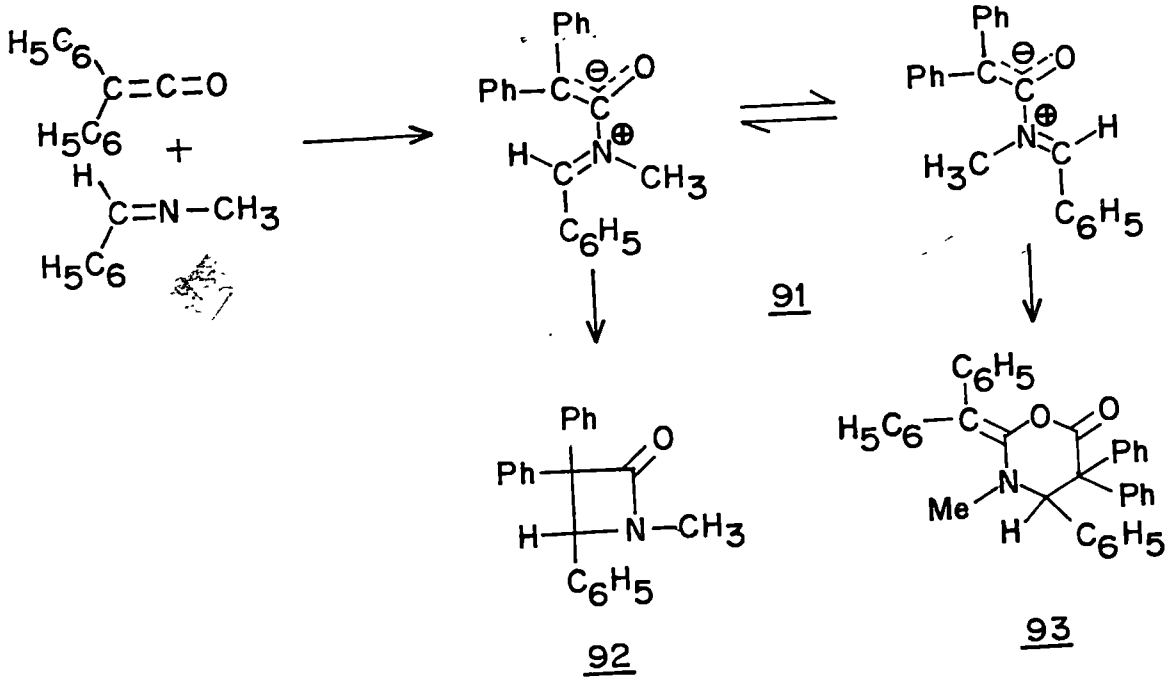
groups is represented in structure 90; this orientation is based on ^{13}C chemical shifts of a variety of compounds derived from chlorocyanoketene 86 and azomethine 89[63] (Scheme 16).

Huisgen et al[64] convincingly demonstrated the stoichiometric dependence of the [2+2] cycloaddition, on the imines and diphenylketene. When diphenylketene was added in acetonitrile) to an excess of 95 (13 equivalents) 82% of β-lactam 92 and 6% of the 2:1 adduct 93 were obtained. In contrast, when 95 was added to 10 equivalents of diphenylketene they observed a striking reversal in product distribution, namely 81% yield of 93 and a 19% yield of 92. In addition, β-lactam 92 did not undergo reaction with diphenylketene at 140°C. These results suggest that zwitterion 91 is a common intermediate with a limited amount of ketene and it closes to the azitidinone, but when there is an excess of ketene, zwitterion 91 is trapped, affording 93. These compounds and a proposed pathway for their formation are illustrated in scheme-17.[64]

Literature survey[65] clearly reveals that despite extensive exploitation of the ketene-imine cycloaddition reactions in the preparation of widely employed β-lactams, the actual mechanism of this reaction is still not clear. According to the experimental results of Moore and co-workers[66], the cycloaddition of ketene to the imine is a two step zwitterionic process rather than a concerted one. This mecanistic proposal is supported by the intermediate 94 by IR in thermal reactions of ketenes 95 with


Cl
O
Cl
OH
H
CH3OH
ZnCl2
OCH3
NaN3
MeOH
N3
84
Δ
-N2
85
86
C
CN
N
C6H5
OC2H5
87
R1
R2
89
88
90

Scheme-16



Scheme-17

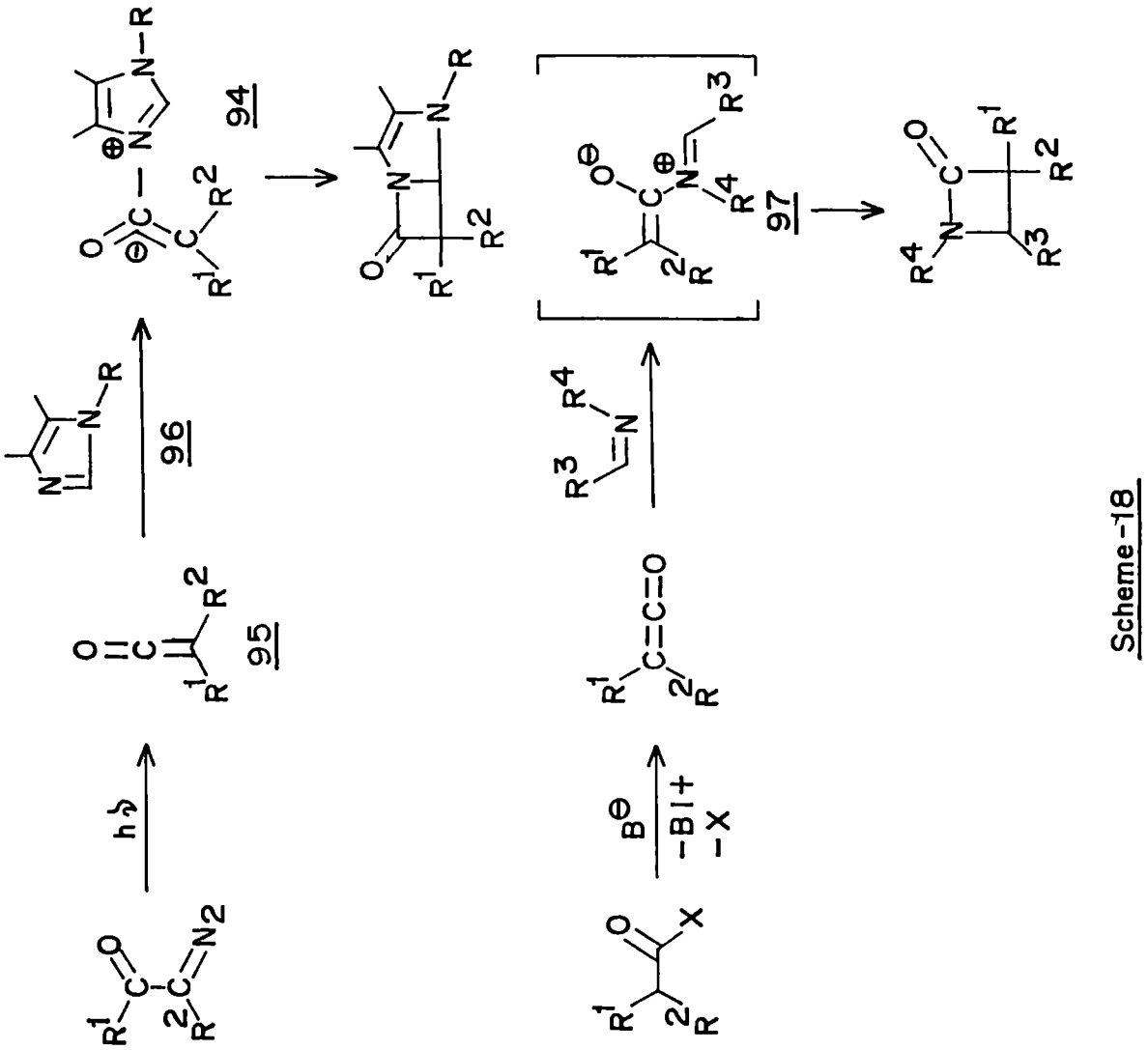
imines 96[67a] and by a detailed kinetic analysis with low temperature FT-IR spectroscopy.[68] The first ab initio study on the mechanism of ketene-imine reaction was reported by T.L. Sordo et.al.[65a] According to their examination of the transition structures 97 a conrotatory electrocyclic ring closure is the rate determining step of a two step mechanism as illustrated in the Scheme-18.

Recently Cossio et.al[65] based on studies performed in their laboratory have also shown that the Staudinger reaction between ketenes and imines takes place via zwitterionic intermediate generated from the nucleophilic attack of the nitrogen lone pair of the imine on the carbonyl group of the ketene.

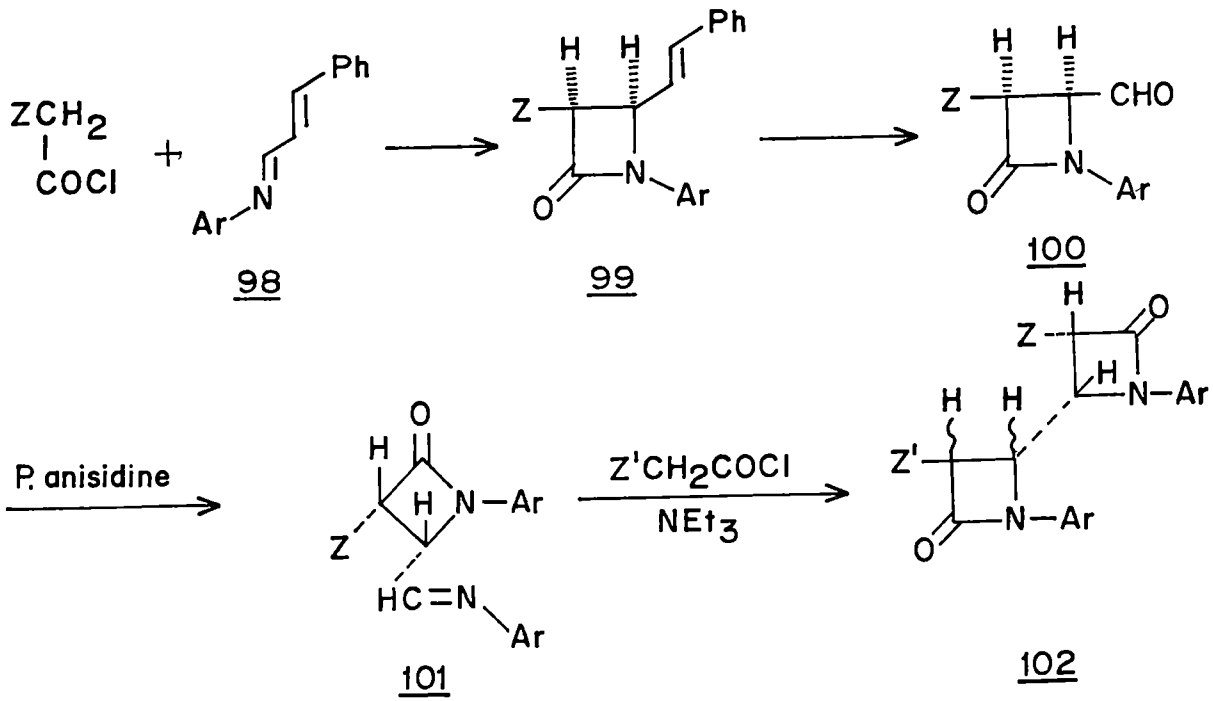
Recently Bose et.al[67(b)] in continuation with their studies on asymmetric synthesis of β-lactams, examined Schiff bases (eg. 101) derived from aldehydes (100) in which the chiral center next to the imino group carried a nitrogen functions. Several β-lactams of type (99), prepared from cinnamaldehyde-derived Schiff bases (98), were ozonized to aldehydes (100) and converted to racemic Schiff bases (101). The reaction of (d1) (101) with acid chloride and triethylamine led to the isolation of a single cis-bis-β-lactam (102) in each investigated case (Scheme 19).

III. *Cycloaddition Reactions of Ketenes with Azadienes*

The literature survey clearly reveals that ketenes add to carbon-carbon double bond and carbon-nitrogen double bond resulting mostly in the preferential formation of [2+2]

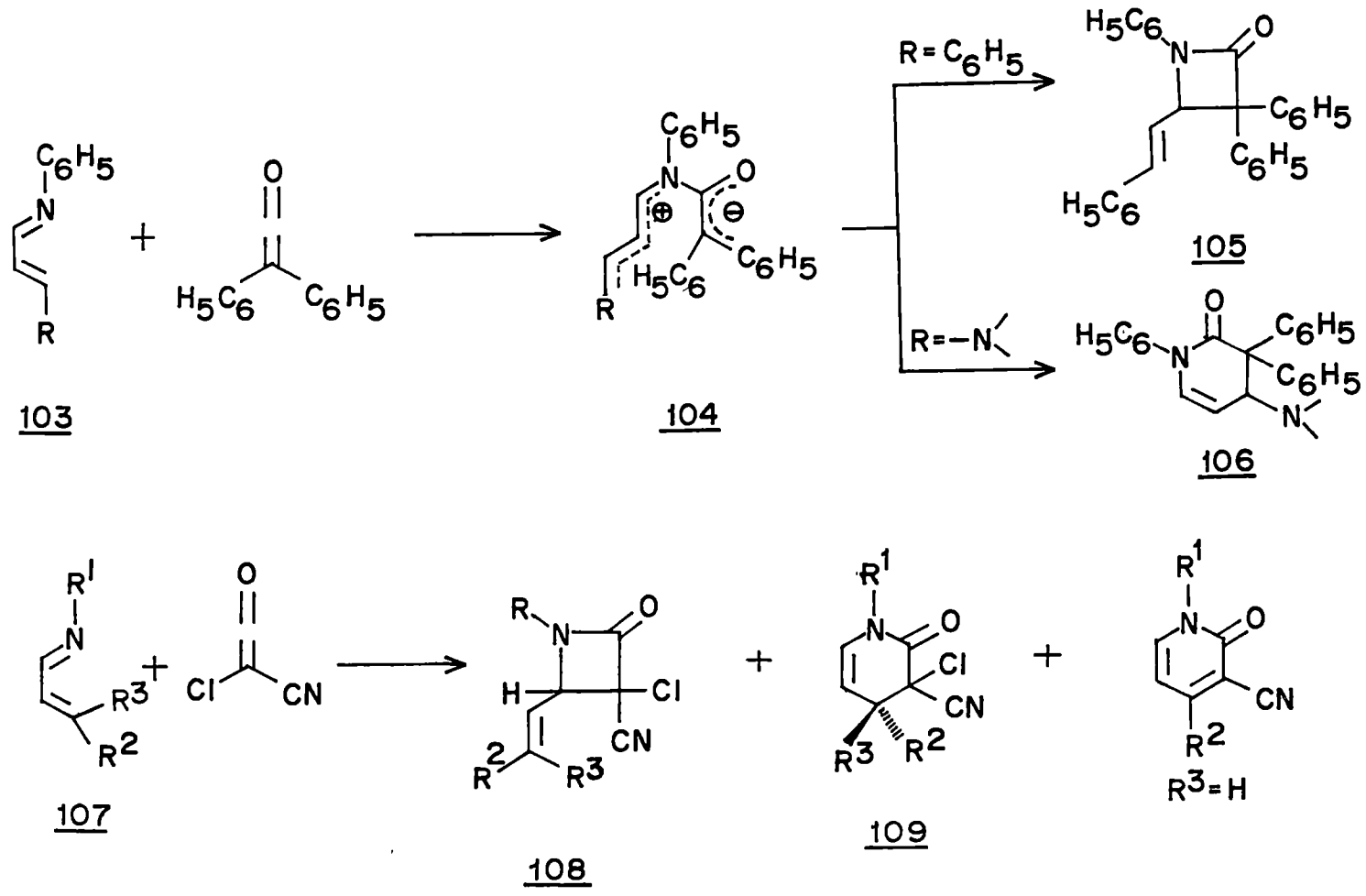


Scheme-18


ZCH2
COCl
+
Ph
N
Ar
98
H
H
Ph
Z
N
Ar
O
99
H
H
Z
CHO
N
Ar
O
100
P. anisidine
O
H
H
N–Ar
Z
HC=N
Ar
101
Z'CH2COCl
NEt3
H
Z
O
H
N–Ar
H
H
Z'
N–Ar
O
102

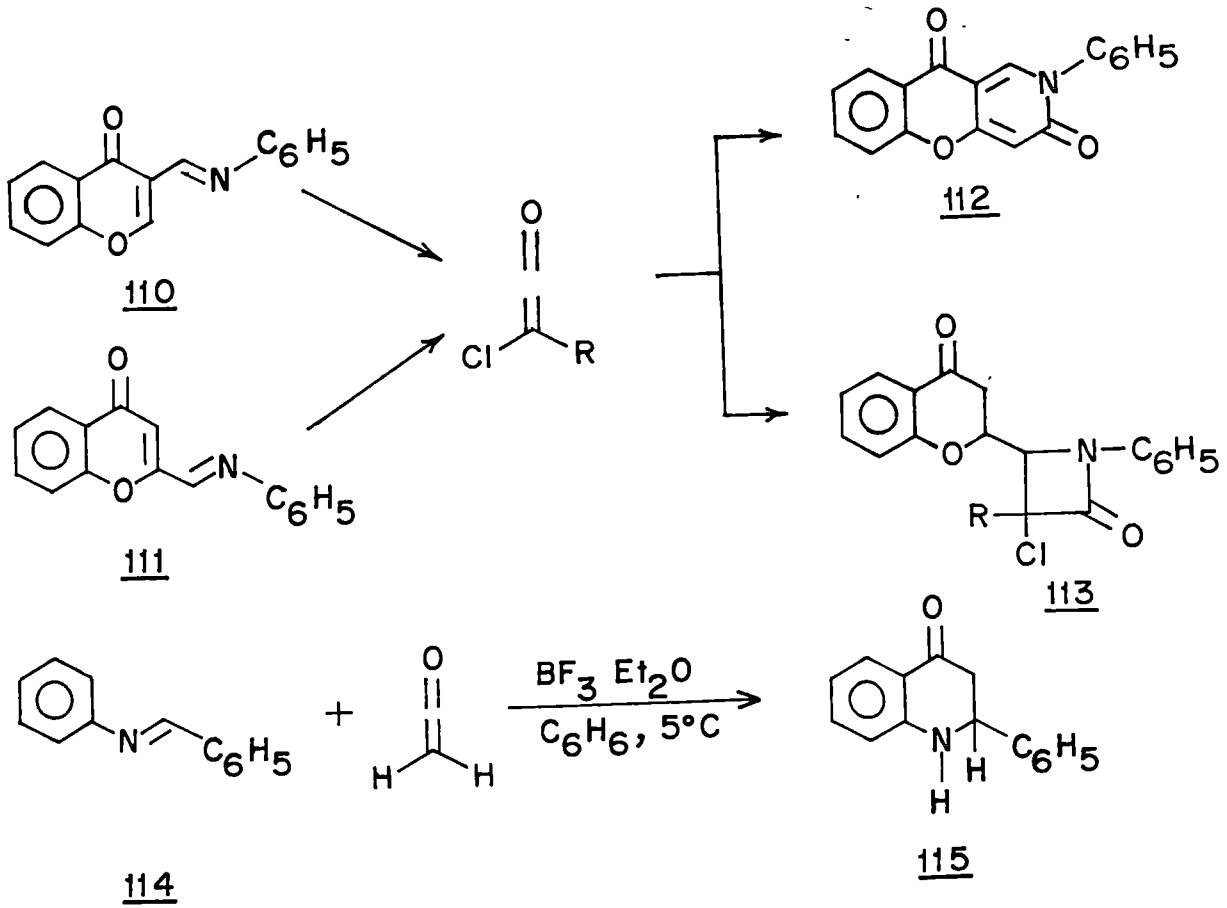
Scheme-19

cycloadducts. The azadienes containing either carbon-carbon double bond and carbon-nitrogen double bond or both carbon-nitrogen double bonds in conjugation have been reported to undergo [2+2] and/or [4+2] cycloaddition with ketenes.[69] Thus, 1-aza-1, 3-butadiene (103) and diphenylketene, gave azetidinone (105) and dihydropyrimidone (106). The formation of (105) and (106) in these reactions has been explained through the intermediary of zwitterion (104). The reaction of chlorocyanoketene with similar 1-aza-1,3-butadiene (107) leading to [2+2] and [4+2] cycloadducts 108 and 109, reestablished the existance of zwitterionic intermediate of type 104 (Scheme-20).[70] Suschitzky et.al[71] reported that the reactions of 3-(aryliminomethyl)chromones (110) and 2-(aryl-iminomethyl)-chromones (111) with chloroketenes followed [4+2] and [2+2] cycloaddition pathway yielding pyridone 112 and β-lactam derivative (113), respectively (Scheme-21). A few more similar reports[72-75] are also available in the literature. The reports regarding the reactions of 2-aza-1,3-butadienes with ketenes are very rare[76,77]. For example, Lewis Acid catalyzed addition of anils (114) to ketene resulted in [4+2] cycloadduct 115.[78] Recently Arrastica et.al[79] reported theoretical and experimental studies on the periselectivity of cycloaddition reactions between activated ketenes and conjugated imines. They have shown that the Staudinger reaction between ketenes(116) and conjugated imines(117) takes place via zwitterionic intermediates and according to this mechanism two different (S-E) and (S-Z)



103 104

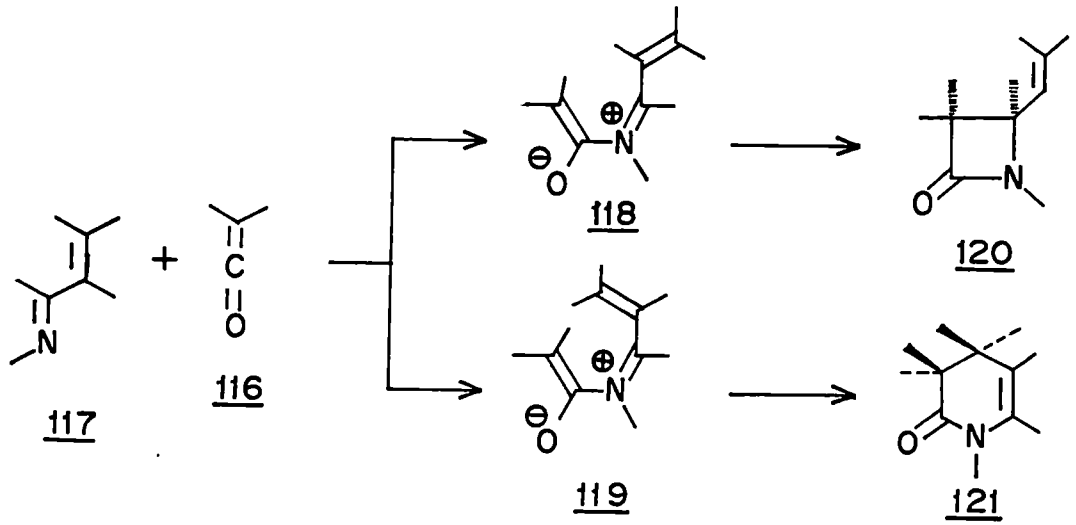
Scheme-20


O
N
C6H5
O
110
O
N
C6H5
O
111
O
Cl
R
O
C6H5
N
O
112
O
N
C6H5
R
Cl
O
113
O
N
C6H5
H
+
O
H
H
BF3 Et2O
C6H6, 5°C
O
N
H
H
C6H5
114
115

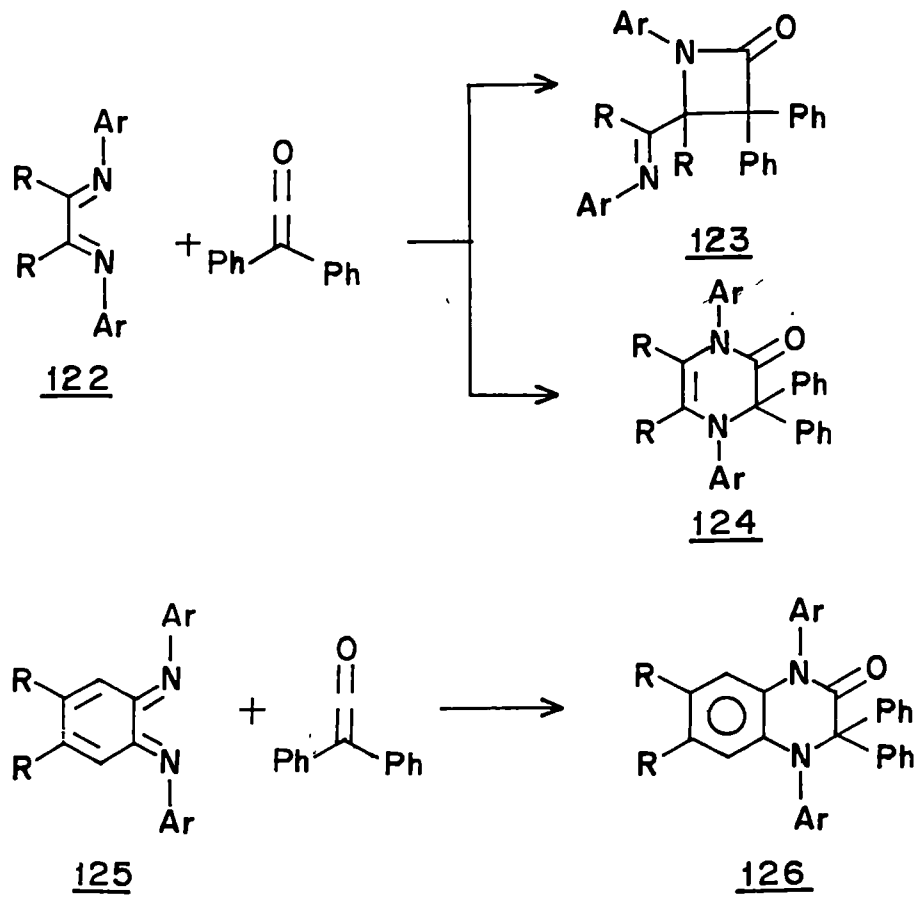
Scheme-21

zwitterions 118 and 119, respectively can be formed (Scheme-22). In principle, the conrotatory electrocyclization of 118 should yield 4-vinyl β-lactam 120, whereas the disrotatory thermal ring closure of the intermediate 119 should lead to the corresponding β-lactam 121. Based on conducted studies it was concluded that the monosubstituted ketenes lead to the preferential formation of β-lactams whereas in case of disubstituted ketenes the energy gap between the transition state saddle points should disappear and could account for preferred [4+2] periselectivity.

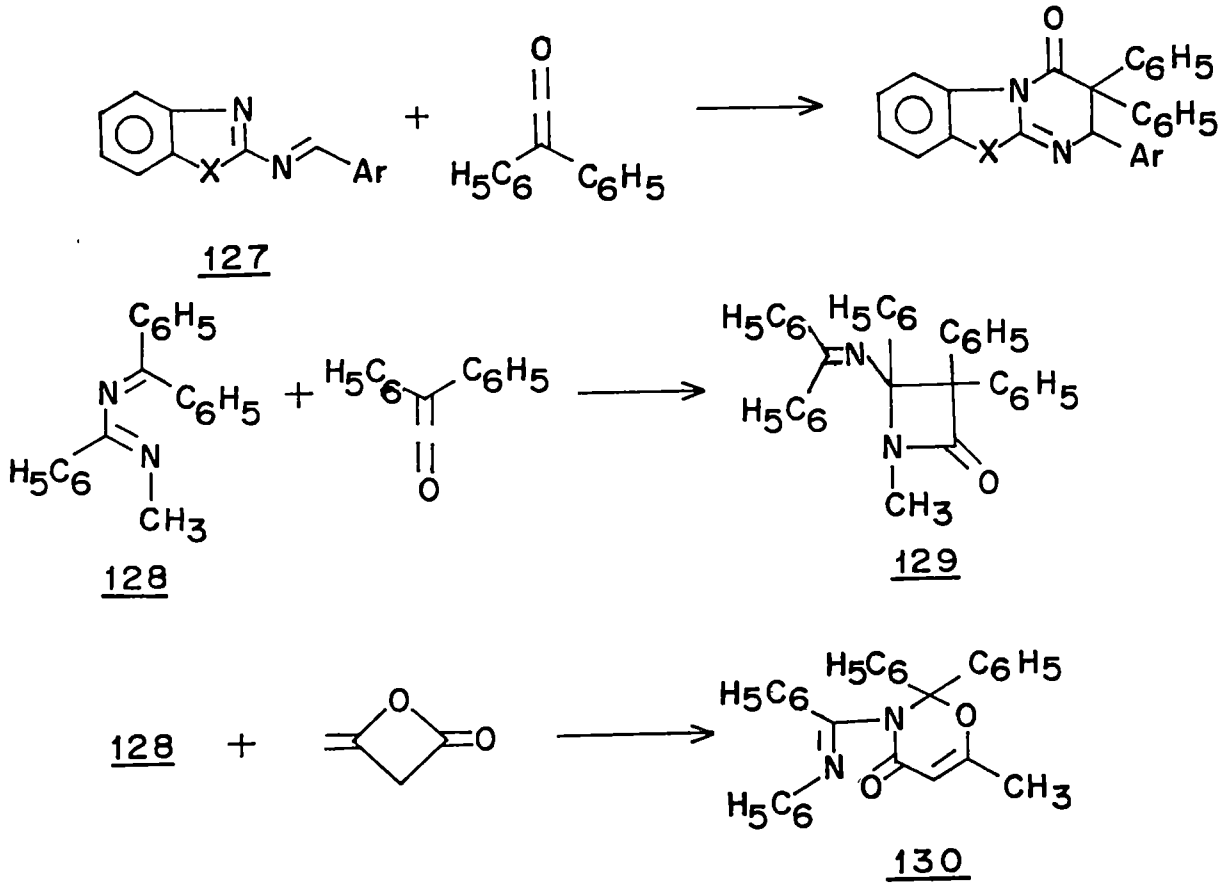
A few cycloaddition reactions of ketenes and 1,4-diaza-1,3-butadienes, have also been reported. For example, the reactions of diphenylketene with α-diimines (122) yielded [2+2] cycloadduct 123, which were initially mistaken to be [4+2] cycloadducts124.[80-82] However, o-benzoquinonediimines (125) were shown to give [4+2] cycloadducts 126 with diphenylketene[83] (Scheme-23). The heterocyclic 1,3-diaza-1,3-butadines 127 are known to undergo facile [4+2] cycloaddition reactions with diphenylketene and diketene.[84,85] In contrast, the simple acyclic 1,3-diaza-1,3-butadienes (128) failed to give a formal cycloadduct with diketene but resulted in oxazinone 130. Also, the reaction of 128 with diphenylketene did not give any [4+2] cycloadduct but underwent [2+2] cycloaddition leading to β-lactam 129[86] (Scheme-24). It was thought that simple acyclic 1,3-diaza-1,3-butadienes having electron donating functions at position 4-are perhaps best bets for [2+2] cycloaddition reactions with



Scheme – 22


Ar
R
N
R
N
Ar
122
O
Ph
Ph
Ar
N
O
R
Ph
N
R
Ph
Ar
123
Ar
R
N
O
Ph
R
N
Ph
Ar
124
Ar
R
N
R
N
Ar
125
O
Ph
Ph
Ar
R
N
O
Ph
R
N
Ph
Ar
126

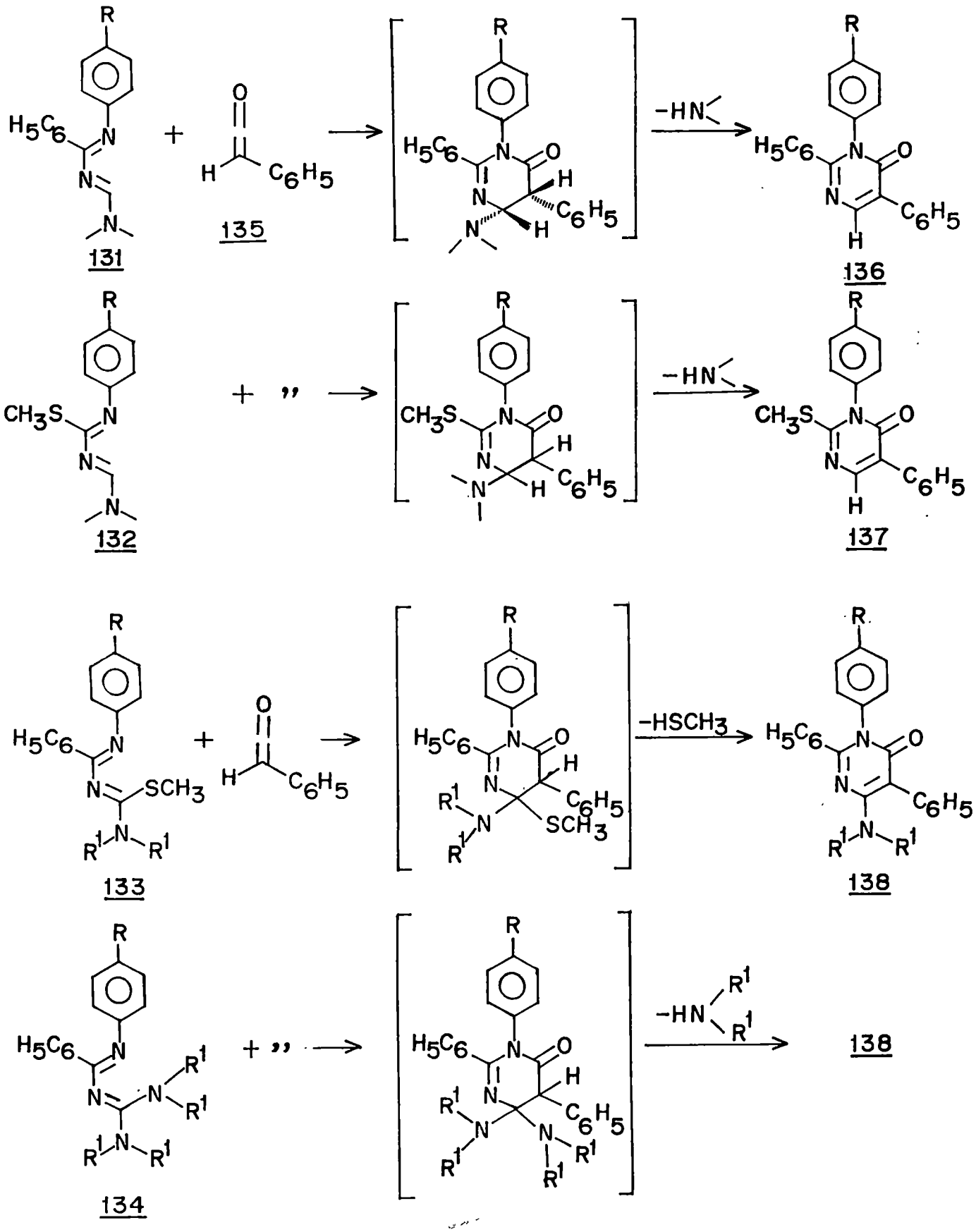
Scheme-23



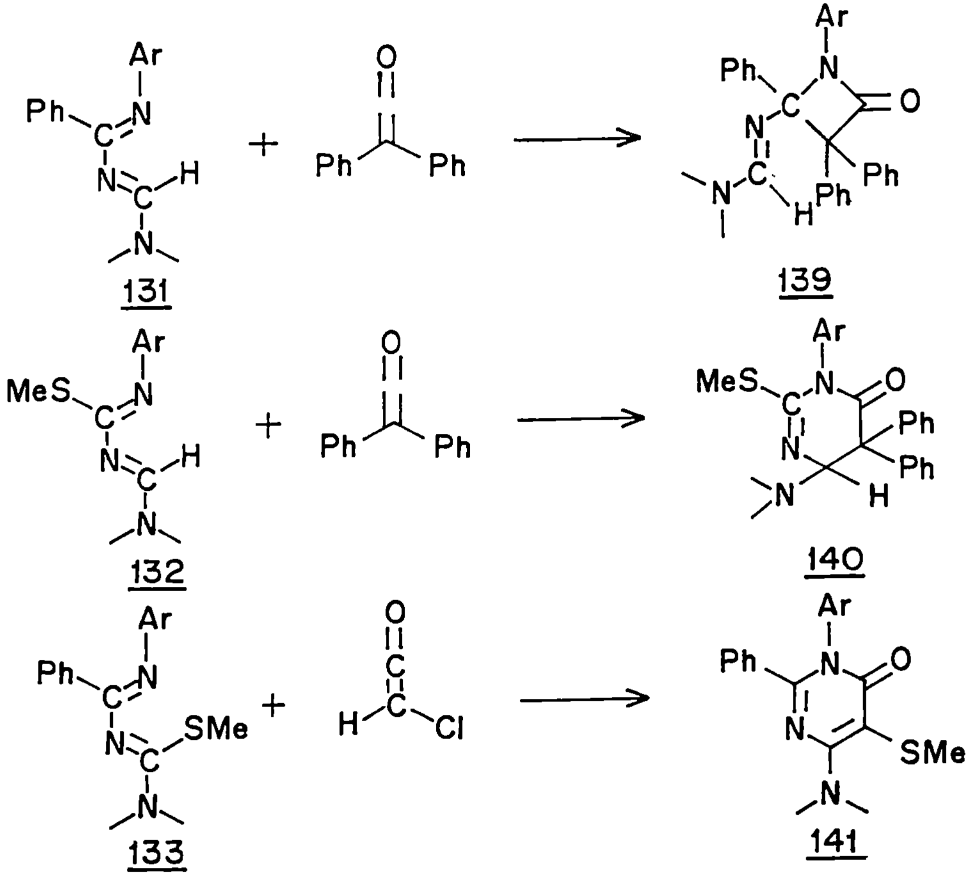
Scheme-24

ketenes. Keeping this in view, recently in our laboratories, the reaction of simple acyclic 1,3-diaza-1,3-butadienes with various ketenes were investigated. The cycloaddition reactions of monophenylketene, generation of which is simple and easy, could not evoke much interest among synthetic organic chemists possibly because of its instability.[87] However, cycloaddition could be realised by its slow generation in presence of reactive substrates. Accordingly the reactions of 1,3-diaza-1,3-butadienes (131-134) with phenyl (135) were found to follow [4+2] cycloaddition pathway resulting in excellent yields of previously unknown pyrimidinones (136-138)[88] (Scheme-25). It was also observed that the reactions of diphenylketene with 1,3-diazabutadiene (131) followed [2+2] cycloaddition pathway yielding β-lactams 139 whereas 1,3-diazabutadiene 132 gave pyrimidinone 140 as [4+2] cycloadduct. Further it was found that the reactions of 1,3-diazabutadienes 133 with chloroketene followed [4+2] cycloaddition pathway accompanied by novel 1,2-alkylthioshifts yielding pyrimidinones 14 (Scheme-26).

Keeping these observations in view and in order to rationalise and to have deeper insight into the mechanistic aspects of ketenes1,3-diazabutadienes cycloadditions, we have further investigated such cycloadditions with a variety of ketenes and the results of these investigations form main body of this dissertation.



Scheme-25



Scheme-26

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CHAPTER-II

The Reactions Of 1,3-Diaza-1,3-Butadienes With Various Monosubstituted Ketenes: Some Mechanistic Considerations

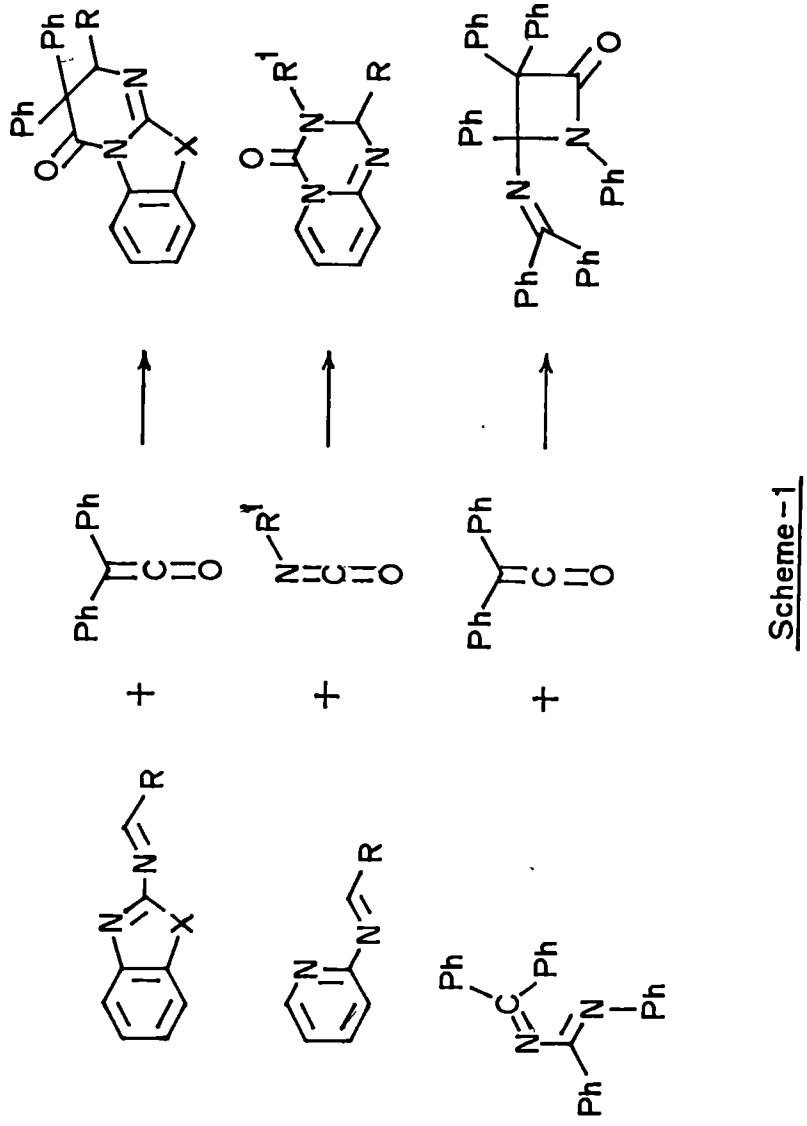
---

II.1 Introduction

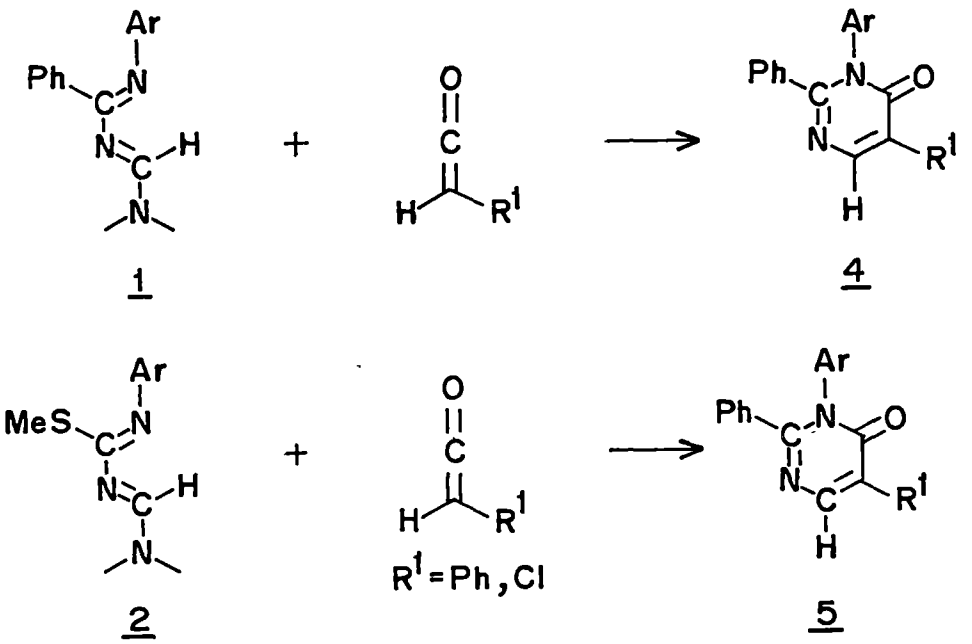
The ketene chemistry is dominated by [2+2] cycloadditions which over the years has been established as a well documented route to the synthesis of four membered carbocyclic and heterocyclic systems. There are numerous eports concerning [2+2] cycloaditions of imines with various ketenes, extended recently to vinyl/isopropenyl ketenes[1-4], leading to a variety of substituted β-lactams[5-8], which in certain cases have even been converted to important penicillin derivatives. This cycloaddition mode has also been reported to be preferred even in case of reactions of ketenes with various conjugated azines viz. monoaza and diazabutadienes.

Even though there are several literature reports concerning the participation of 1,2-and 1,4-diazabutadienes participate as an effective 4π-component in Diels-Alder Cycloadditions but such reports in case of 1,3-diaza-1,3-butadienes are very rare[9]. The reported reactions in this category correspond exclusively to heterocyclic 1,3-diaza-1,3-butadienes.[10] The reactions of acyclic 1,3-diaza-1,3-butadienes with diphenyl ketene yielded exclusively [2+2] cycloadducts[11] (Scheme-1). However, the reactions of recently synthesised and highly polarised 1,3-diaza-1,3-butadienes (1, 2) with phenylketene and chloroketene have recently been reported to give very good yields of pyrimidinones[12] (4,5) (Scheme-2). The formation of which were attributed to the elimination of dimethylamine from initially formed [4+2] cycloadducts as intermediates.

Since the ketene chemistry is dominated by [2+2] cycloadditions the observed formation of [4+2] cycloadducts has led to a number of speculation concerning the mechanistic aspects of such cycloadditions and to establish the most probable mechanistic pathway is thought to be an interesting scientific enquiry. The probable mechanistic pathways leading to the formation of pyrimidones are outlined in Scheme-3. In this scheme, it is assumed that the initial attack of N-1 of polarizable 1,3-diaza-1,3-butadienes (6) on ketene carbonyl (7) leads to the formation of zwitterionic intermediate 8 and because of its enhanced stability it prefers to undergo ring closure to yield [4+2] cycloadducts (9) which on elimination of secondary

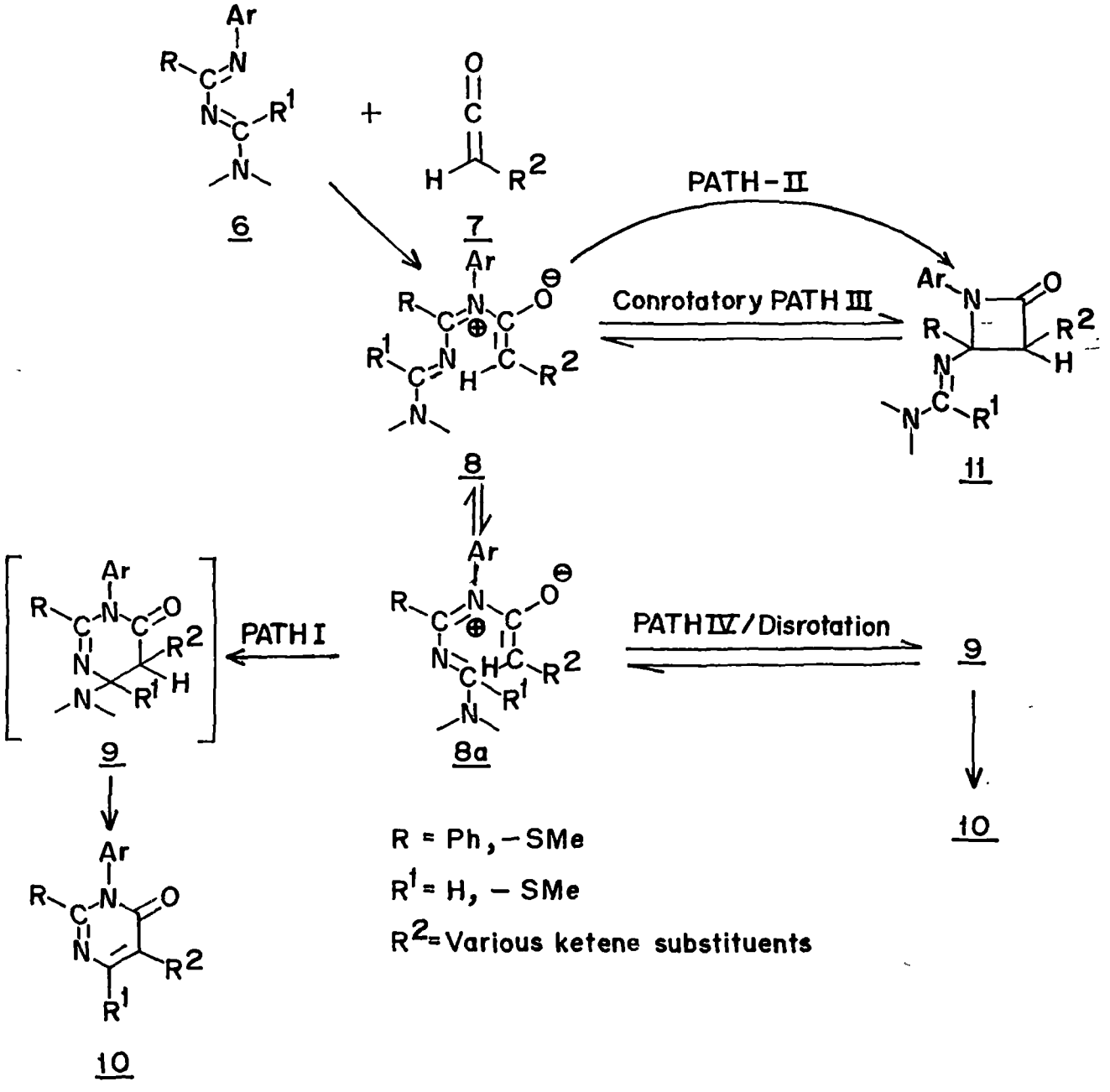


Scheme-1


Ar
Ph
N
C
N
H
C
N
1
+
O
C
H
R1
Ar
Ph
C
N
O
N
R1
H
4
Ar
MeS
C
N
N
H
C
N
2
+
O
C
H
R1
R1 = Ph, Cl
Ar
Ph
C
N
O
N
C
R1
H
5

Scheme-2

amine/methane thiol lead to possibly thermodynamically more stable pyrimidinones (10) (Path-I). It is also reasonable to assume that the β-lactam 11 may be formed initially via kinetic controlled and well documented [2+2] cycloaddition pathway-II or conrotatary ring closure pathway III, but these pathways are reversible if β-lactams are unstable and then they can exist only in small stationary concentrtion. The reversal of β-lactams to zwitterionic intermediate allows for formation of [4+2] cycloadducts 9, which may or may not be thermodynamically more stable, which in any case, is removed from consideration by the elimination of secondary amine/methane thiol. It is even conceivable that the formation of β-lactams, as shown later, is actually preferred in some cases and this preference may be marked using monosubstituted ketenes. It is also possible that the pyrimidones (10) may arise via the disrotatory ring closure of zwitterionic intermediate (8a) pathway-IV. It may also be assumed that the presence of volumunous group(s), either at C-4 of 1,3-diaza 1,3-dibutadienes or at ketene carbon, may force zwilternonic intermediate to exist predominantly in S-trans form 8 leading β-lactams (11). Whereas, the presence of less bulkier monosubstituents on ketene carbon may prefer S-*cis* form 8a leading to [4+2] cycloadducts 10. It is also felt that in case, the stability of the zwitterionic intermediate plays an important role in determining the cycloaddition pathway. Then the presence of stabilising/destabilising functions in the cationic/anionic

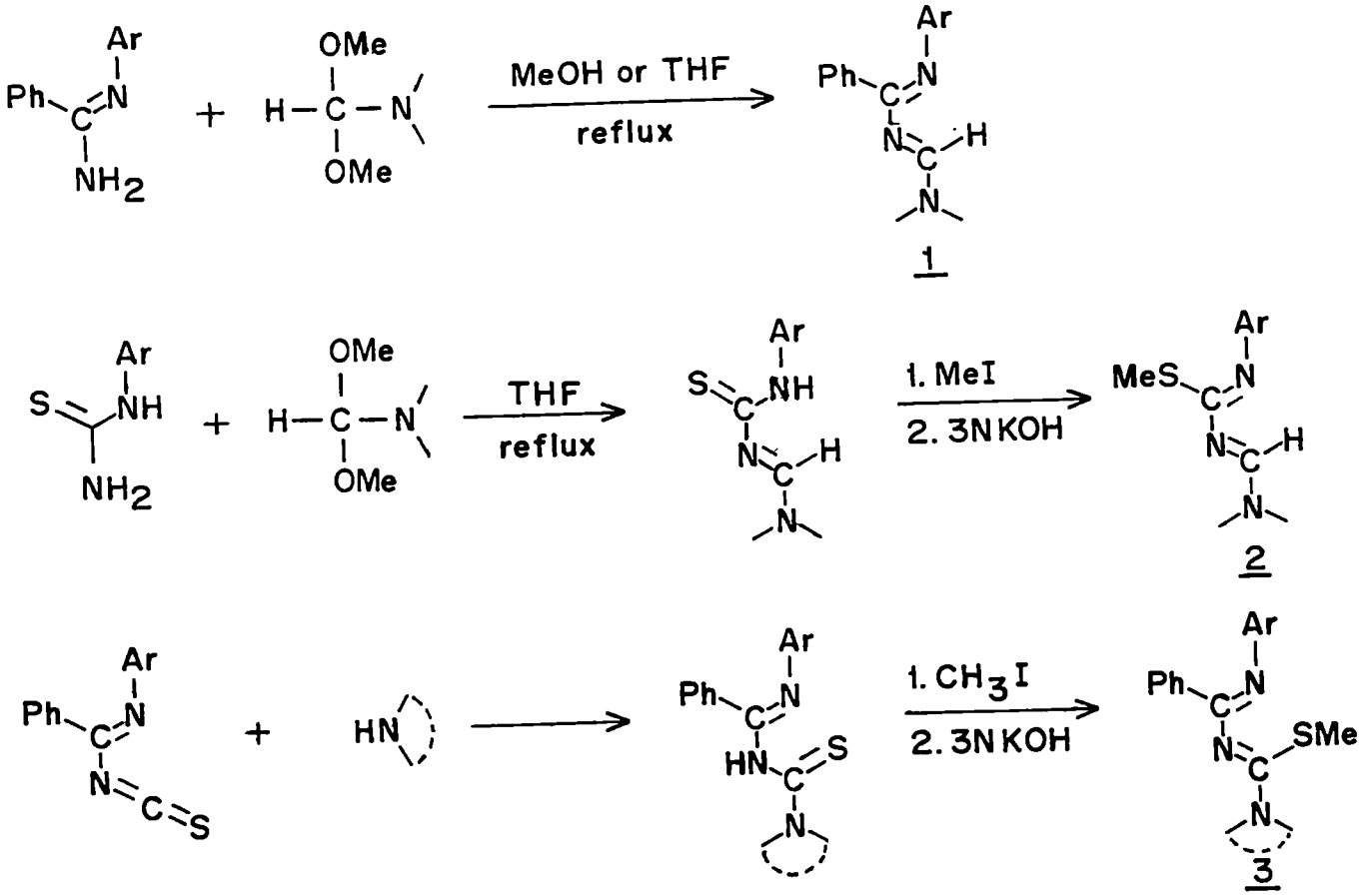

PATH-II
Conrotatory PATH III
PATH I
PATH IV / Disrotation
R = Ph, -SMe
R1 = H, - SMe
R2 = Various ketene substituents

Scheme-3

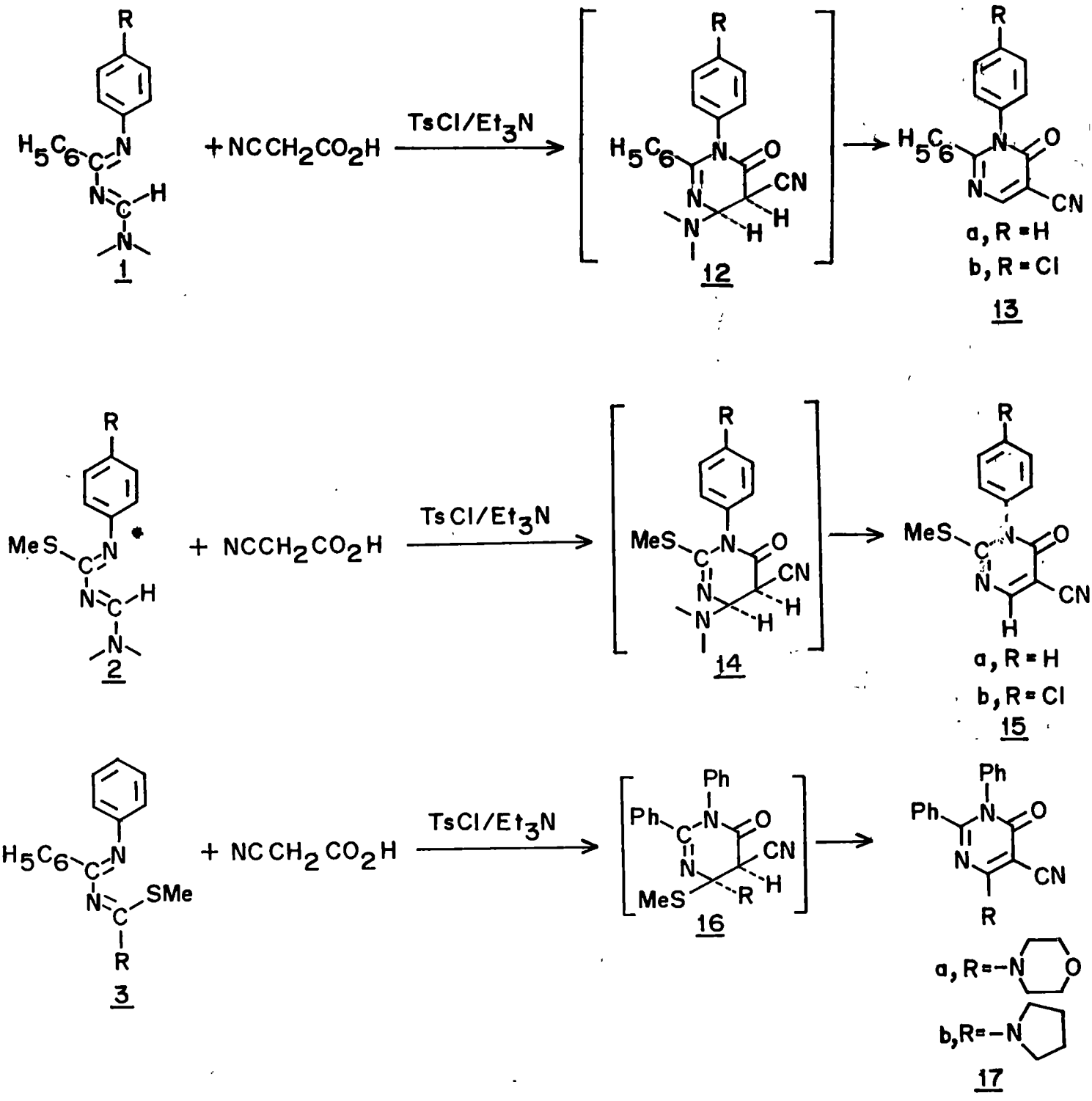
components of the zwitterion should perhaps effect the cycloaddition pathway followed in these reactions. Keeping this in view, we have examined, in this chapter, the reactions of various 1,3-diaza-1,3-butadienes with monosubstituted viz cyano, p--nitrophenyl-, succinimido-, phthalimido-, and phenoxy ketenes. The 1,3-diaza-1,3-butadienes used for this purpose have been prepared by the procedures reported recently[13] (Scheme-4).

Results and Discussions

The reactions of 1,3-diaza-1,3-butadienes (1 & 2) with cyanoketene, generated *in situ* from cyanoacetic acid/p-toluenesulphonyl chloride/triethylamine, where anionic component of the zwitterionic intermediate could be stabilised by conjugatively electron withdrawing cyano group, followed the expected [4+2] cycloaddition pathway leading to good yields of previously unknown pyrimidinones 13 and 15. The products have been assigned the pyrimidinone structures 13 and 15 on the basis of analytical results and spectral data. Their I.R. spectra (KBr) showed strong absorption band at *ca* 1690 cm^{-1} due to α,β-unsaturated carbonyl group (C=O) and another peak at around 2250 cm^{-1} due to cyano (CN) group. The ^1H NMR signatures also attest to the assigned structres, which exhibited the absence of $-N(CH_3)_2$ protons and presence of a singlet at *ca* 8.4 due to olefinic proton (=N-CH=C-). Thus compound 13a, for example, showed I.R peak at 1700 cm^{-1} and 2250 cm^{-1} due to α,β-unsaturated carbonyl group and cyanogroups, respectively and its ^1H NMR did


Ar
Ph
N
C
NH2
+
OMe
H
C
N
OMe
MeOH or THF
reflux
1
S
NH
THF
reflux
1. MeI
2. 3N KOH
MeS
2
HN
1. CH3I
2. 3N KOH
HN
SMe
3

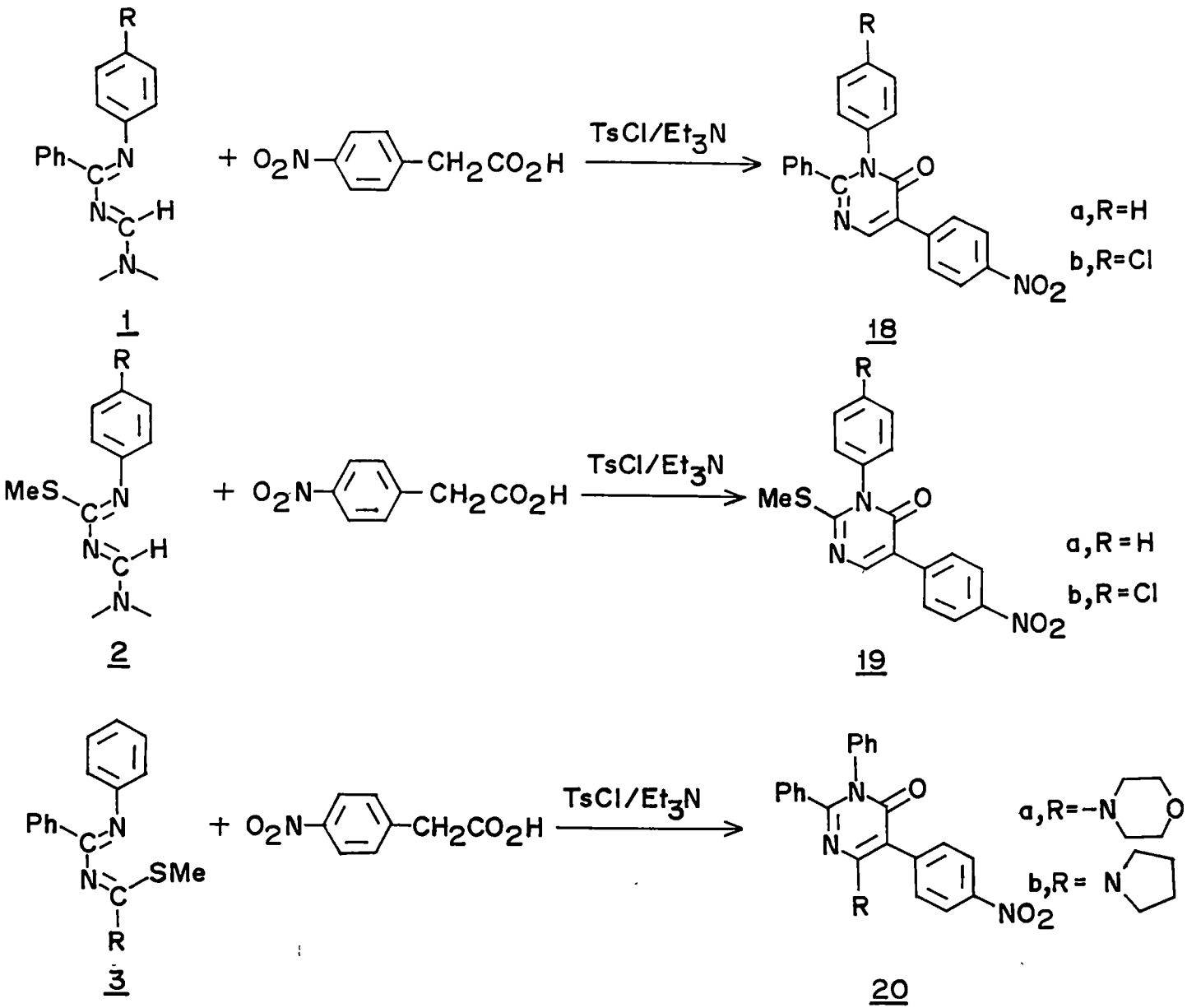
Scheme-4


R
H5C6
N
C
N
H
N
1
+NCCH2CO2H
TsCl/Et3N
12
CN
H
13
a, R = H
b, R = Cl
MeS
2
14
15
Ph
SMe
3
16
17
a, R=-N O
b, R=-N

Scheme-5

not show the presence of $-N(CH_3)_2$ protons whereas multiplet at 7.20-7.53 (10H) and singlet at 8.56 (1H) were typical of aromatic and lone olefinic protons. Conceivably these pyrimidinones arise from the base induced elimination of dimethylamine from the initially formed [4+2] cycloadducts 12 and 145 (Scheme-5). The intermediates 12 and 145 with the desired stereochemical arrangement of hydrogen and dimethylamino functions on adjacent carbons is obtained either through highly stereoselective [4+2] cycloaddition and/or via the equilibration of these intermediates either involving acidic hydrogen next to carbonyl or through zwitterionic intermediate.

The steric factors have been reported to alter the nature of the cycloaddition pathway, in case of reactions of 1,3-diaza-1,3-butadienes with diphenylketene.[11] In order to ascertain the influence of steric factors on the nature of zwitterionic intermediate and in turn on the nature of cycloaddition pathway, we have also carried out the reactions of cyanoketene with 1-aryl-4-methylthio-2-phenyl-4-secondaryamino(morpholino, pyrrolidino)-1,3-diaza-1,3-butadienes, (3). The reactions of 3 with cyanoketene gave very good yields of pyrimidinones 17, which proceed through the initial formation of [4+2] cycloadduts 16, as an intermediate and as expected these undergo preferential elimination of methylmercaptan yielding 179. similarly, the reactions of 1,3-diaza-1,3-butadienes 1, 2 and 3 with *p*-nitrophenylketene, as expected followed [4+2] cycloaddition leading to good yields of another set of novel pyrimidinones 18,

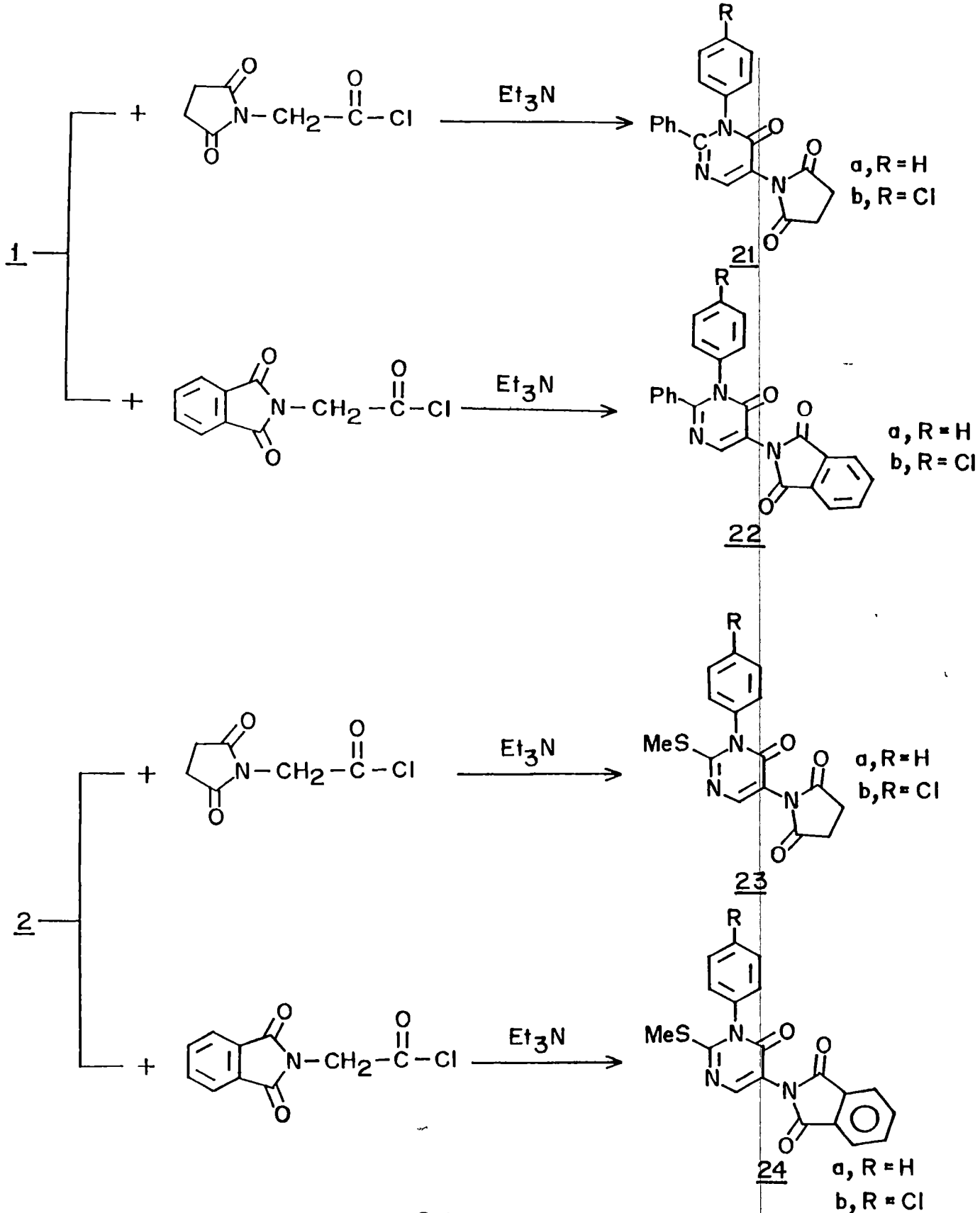

R
Ph
N
C
N
H
N
1
+ O2N
CH2CO2H
TsCl/Et3N
O
NO2
a,R=H
b,R=Cl
18
MeS
2
19
SMe
3
20
a,R=-N O
b,R= N

Scheme-6

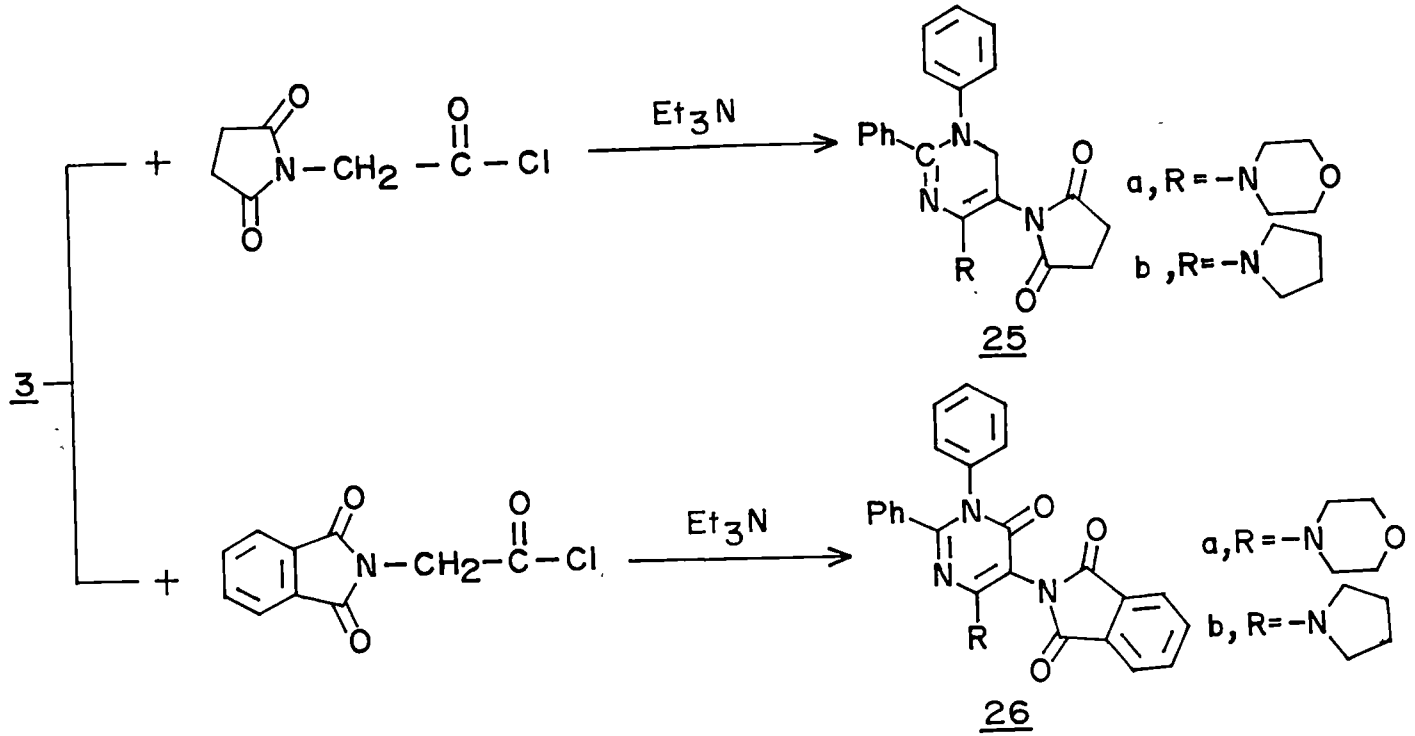
19 and 20, respectively. These products were characterised with the help of their analytical data and spectral evidences (Scheme-6). All the pyrimindinones 17, 18 and 19 showed the absence of secondary amino groups and the presence of olefinic proton along with aromatic protons in their ^{1}H NMR spectra.

Now, it was thought worthwhile, to investigate the reactions of 1,3-diaza-1,3-butadienes 1, 2 and 3 with ketenes bearing the substituents which are not that efficient stabilisers of the anionic component of zwitterion. The ketenes selected for the purpose are succinimido and phthalimido ketenes. Thus, the reactions of 1,3-diaza-1,3-butadienes 1, with succinimido - and phthalimido ketenes, generated *in situ* from the corresponding acetyl chloride in the presence of triethylamine, were found to result in very good yields of previously unknown 5-succinimidyl- and 5-phthalimidyl pyrimidinone derivatives 21 and 22, respectively.

Thus the compounds 22 and 22 were characterised as 2,3-diphenyl-5-succinimidoyl pyrimidin-4 (3H)-one and 2,3-diphenyl-5-phthalimidoyl pyrimidin-4(3H)-one respectively on the basis of analytical data and spectral evidences. These compounds, as mentioned earlier showed α,β-unsaturated carbonyl stretching frequency *ca* 1680 cm^{-1} in the I.R. spectra and multiplet for aromatic protons at *ca* 7.2-7.50, and olefinic proton at *ca* 8.30 in ^{1}H NMR spectra. The pyrimidinones 21 and 22 obviously arise via the elimination of dimethylamine from the initially



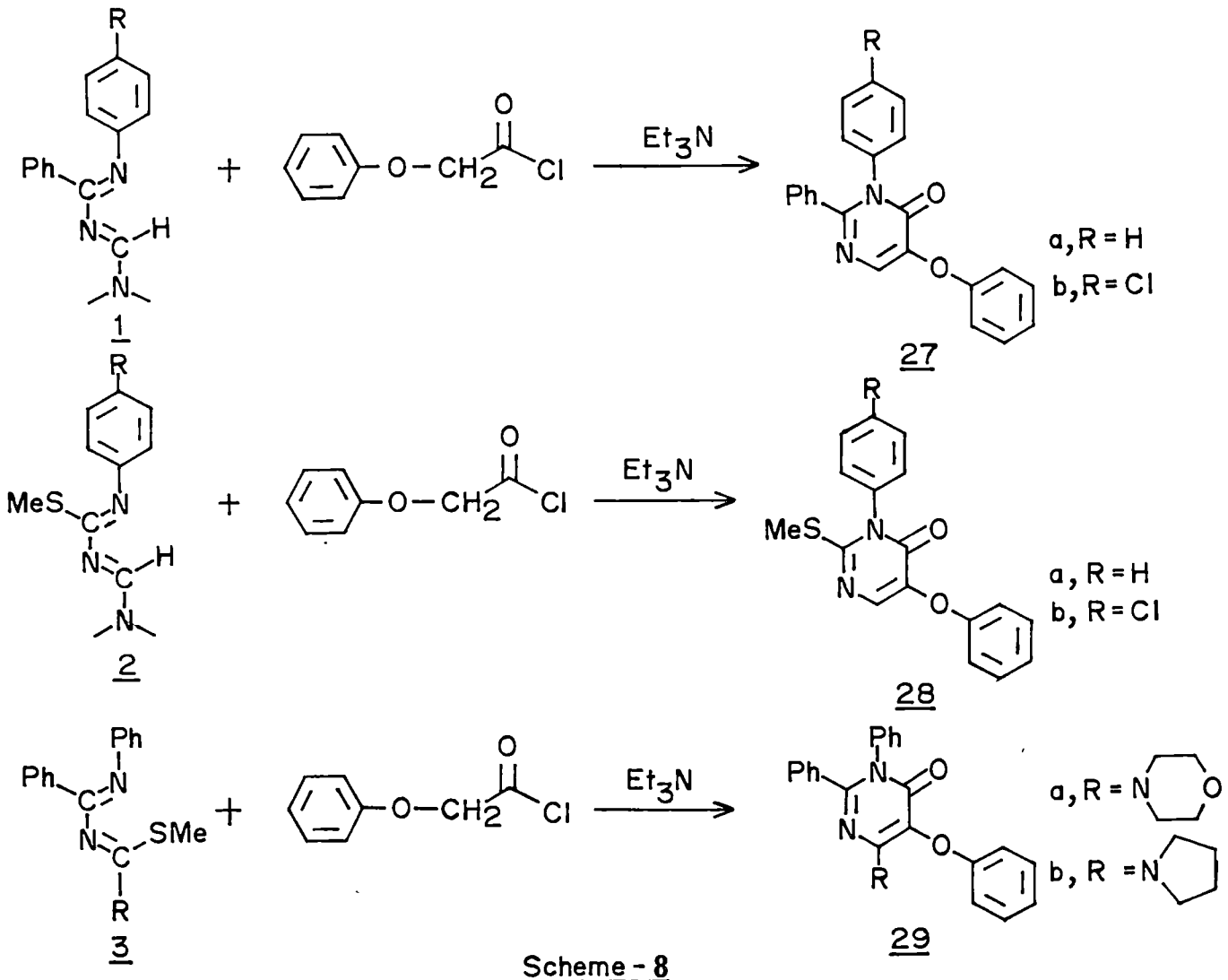
Scheme-7


3
+
N–CH2–C–Cl
Et3N
Ph
N
C
N
R
O
a, R = –N O
b, R = –N
25
+
N–CH2–C–Cl
Et3N
Ph
N
R
O
a, R = –N O
b, R = –N
26

Scheme-7

formed [4+2] cycloadducts, as intermediates. The reactions of 2 with these ketenes, similarly followed the same reaction pathway resulting in pyrimidinones 23 and 24 (Scheme-7). Interestingly even the reactions of 1,3-diaza-1,3-butadienes (3), bearing two bulkier substituents at position-4, with these ketenes having bulkier succinimidoyl/phthalimidoyl substituent, were also found to follow [4+2] cycloaddition pathway leading to pyrimidinones 25 and 26. Hence, it may be inferred that the steric factors perhaps do not play any significant role in the predominance of one zwitterionic form over the other and are perhaps not so important in determining the nature of cycloaddition pathway followed. The structures of the pyrimidinones 25 and 26 were also confirmed on the basis of analytical data and spectral evidences. The compounds 21-25 appear to be an important class of pyrimidinone derivatives since these can be easily hydrolysed to pyrimidinones having latent 5-amino substituent.

Finally, it was decided to investigate the reactions of 1,3-diaza-1,3-butadienes (1-3) with phenoxyketene, having conjugatively electron donating phenoxy group, which can contribute towards the destabilisation of the anionic component of the zwitterionic intermediate. The reactions in this case also were found to follow the [4+2] cycloaddition pathway yielding 5-phenoxy-pyrimidin-4(3H)-ones (27-29), which presumably again are formed via the elimination of dimethylamine/methyl mercaptan from the initially formed [4+2] cycloadducts as intermediates (Scheme-8). The analytical and spectral data for


R
Ph
N
C
N
H
N
1
+
O
O–CH2
Cl
Et3N
R
Ph
N
O
N
O
a, R = H
b, R = Cl
27
R
MeS
N
C
N
H
N
2
+
O
O–CH2
Cl
Et3N
R
MeS
N
O
N
O
a, R = H
b, R = Cl
28
Ph
Ph
N
C
N
SMe
R
3
+
O
O–CH2
Cl
Et3N
Ph
Ph
N
O
N
R
O
a, R = N O
b, R = N
29

Scheme - 8

these compounds given in the experimental section, are in conformation with the assigned structures.

Conclusion

In case of reactions of 1,3-diaza-1,3-butadienes with various, monosubstituted ketenes, it may be concluded from the above observations, the stability of the anionic component of the zwitterionic intermediate does not play any important role in determining the mode of cycloaddition. Further, the steric factors either do not contribute much to the predominance of zwitterionic form **77a**, or the predominance of one zwilterionic form over the other perhaps does not influence the course of the reactions. From above it also follows that the peri-selectivity i.e. conrotatory and/or disrotatory ring closure pathways III & IV may also be ruled out for these reactions. In subsequent chapter, attempts will be made to throw further light on the mechanistic aspects.

Experimental

Melting points were determined on a Toshniwal melting point apparatus and are uncorrectd. ^{1}H NMR spectra were recorded on a varian EM 390 90 MHz spectrometer and chemical shift values are expressed in (ppm) downfield from $(CH_3)_4$ Si as internal standard. I.R. and Mass spectra were recorded on a Perkin-Elmer 297 I.R. spectrophotometer and Jeol-D 300 mass spectrometer respectively. Carbon, Hydrogen and Nitrogen analysis were done at RSIC, Central Drug Research Institute, Lucknow and North-Eastern Hill University, Shillong. Elemental analysis of the representative compounds were only carried out.

Starting Materials and Solvents

All the 1,3-diaza-1,3-butadienes used here were prepared by the procedure reporrted earlier.[13] All the monosubstituted acetic acid e.g. cyanoacetic acid, p-nitrophenylacetic acid, succinimidyl acetic acid, phthalimidyl- acetic acid and phenoxyacetic acid were prepared by stand and procedures. The acid chlorides whereever used were prepared by treating acid with phosphorous pentachloride in anhydrous benzene. The acid chlorides were purified by distillation or recrystallization. The p-toluenesulphonyl chloride was purified from a mixture of chloroform and hexane (1:5) and its further recrystallisation from anhydrous hexane. The thiophene free benzene and triethylamine used were dried over sodium wire.

Reactions of 1,3-Diaza-1,3-Butadienes with ketenes :

Method-A: A solution of acid (cyanoacetic acid 2 and *p*-nitrophenylacetic acid) (4 mmol) and triethylamine (10 mmol) in dry benzene (30 ml) was stirred for half an hour. To this a solution of 1,3-diaza-1,3-butadiene (1, 2 or 3) (in dry benzene 10 ml) (4 mmol) was added. A solution of *p*-toluensulphenyl chloride (6 mmol) in benzene (30 ml) was then added dropwise (1h) and the reaction mixture was stirred for a period of 4 hours. On completion of the reaction, it was diluted with benzene, washed with water (3 x 50 ml), 5% sodium hydroxide (2x30 ml), brine (2 x 50 ml) and finally dried over anhydrous magnesium sulphate. The crude products obtained by stripping of solvents under reduced pressure were purified by recrystallisation from appropriate solvent(s).

Method-B: A solution of 1,3-diaza-1,3-butadienes (4 mmol) and dry triethylamine (10 mmol) in dry benzene (30 ml) was stirred in round bottom flask. To this a solution of acid chloride (6 mmol) in benzene (30 ml) was added dropwise over a period of 2 hr. After completion of the reaction it was diluted with benzene, washed several times with water (4x50 ml), sodium hydrogen carbonate (2x30 ml), water (2x50 ml) and finally dried over anhydrous sodium sulphate. Removal of solvent under reduced pressure yielded the crude products which were purified by recrystallion from a mixture of benzene-hexane or chloroform-hexane.

2,3-Diphenyl-5-cyano-pyrimidin-4(3*H*)-one(13a): yield, 65%, white solid; m.p. 164-5°C. (Found: C, 74.70; H, 4.02; N, 15.30, $C_{17}H_{11}N_3O$ requires C, 74.71; H, 4.06; N, 15.37) ν_{max} (KBr): 2250 cm^{-1} (C≡N) and 1700 Cm^{-1} (C=0). δH: 7.20-7.53 (m, 10H, arom) and 8.56 (S, 1H, olefinic). M^+273.

3-(4-Chlorophenyl)-5-cyano-2-phenyl pyrimidin-4(3*H*)-one (13b): Yield, 78%; white solid; m.p. 178°C. ν_{max} (KBr): 2250 cm^{-1} (C≡N) and 1680 Cm^{-1} (C≡0). H: 706-7.43 (m, 9H, arom) and 8.53 (s, 1H, olefinic). M^+ 307.

5-Cyano-2-methylthio-3-phenyl-pyrimidin-4(3*H*)-one (15a): yield, 87%; white solid; m.p. 172°C. ν_{max} (KBr): 2250 cm^{-1} (CN) and 1700 Cm^{-1} (C=0). δH: 2.53 (S, 3H,-SCH_3); 7.16-7.33 (m, 2H, arom); 7.50-7.66 (m, 3H, arrom) and 8.26 (S, 1H, olefinic). M^+ 243.

3-(4-chlorophenyl)-5-cyano-2-methylthio pyrimidin-4(3*H*)-one (15b): yield, 70%; white solid; m.p. 203-4°C.ν_{max} (KBr) : 2225 cm^{-1} (C≡N) and 1700 cm^{-1} (C=0). δH: 2.53 (S, 3H,-SCH_3); 7.16-7.33 (m, 2H, arom); 7.50-7.70 (m, 2H, arom) and 8.36 (s, 1H, olefinic). M^+ 277.

2,3-Diphenyl-5-cyano-6-morpholino pyrimidin-4(3*H*)-one (19a) : yield, 77%; white solid; m.p. 258-9°C. ν_{max} (KBr):2225 c^{-1} (C≡N) and 1680 cm^{-1} (C=0). δH : 3.76-3.93 (bd, 4H,-CH_2-N-CH_2-), 4.10-4.26 (bd, 4H,-CH_2-O-CH_2-) and 7.20-7.50 (m, 10H, arom). M^+ 358.

2,3-Diphenyl-5-cyano-6-pyrrolidino pyrimidin-4(3*H*)-one (17b): yield, 85%; white solid; m.p. 266°C, ν_{max} (KBr): 2225 cm^{-1} (C≡N) and 1700 cm^{-1} (C=O). δH: 1.83-2.06(m,4H,$-CH_2-CH_2-$); 3.80-4.03 (m, 4H,$-CH_2-N-CH_2-$) and 7.16-7.36 (m, 10H, arom) M^+ 342.

2,3-Diphenyl-5-(4-nitrophenyl)pyrimidin-4(3*H*)-one (18a): yield, 60%; yellow solid; m.p. 206-7°C. (Found: C, 70.83; H, 4.02; N, 11.36. $C_{22}H_{15}N_3O_3$ requies C, 71.54; H, 4.09; N, 11.38). νmax (KBr): 1690 cm^{-1} (C=O) and 1510 Cm^{-1} (NO_2). H; 7.25-7.43 (m, 8H, arom); 7.50-7.66 (m, 4H, arom); 8.13 (s, 1H, olefinic) and 8.30-8.46 (m, 2H, arom). M^+369.

3-(4-chlorophenyl)-5-(4-nitrophenyl)-2-phenylpyrimidin-4(3*H*)-one (18b): yield, 72%; yellow solid; m.p. 252°C. νmax (KBr):1700 Cm^{-1} (C≡O) and 1510 Cm^{-1} (NO_2). δH: 7.13-7.46 (m, 11H, arom), 8.10 (s, 1H, olefinic) and 8.30-8.46 (m, 2H, arom).M^+403.

2-Methylthio-5-(4-nitrophenyl)-3-phenylpyrimidin-4(3*H*)-one (19a): yield, 60%; pale yellow solid; m.p. 198°C. νmax (KBr): 1690 cm^{-1} (C≡O) and 1500 cm^{-1} (NO_2). δH:2.00 (s,3H,$-SCH_3$); 7.36-7.50 (m,3H, arom), 7.56-7.63 (m, 4H, arom); 8.10 (s, 1H, olefinic) and 8.26-8.43 (m, 2H, arom). M^+339.

2,3-Diphenyl-6-morpholino-5-(4-nitrophenyl)pyrimidin-4(3*H*)-one (20a): yield, 80%, yellow solid; m.p. 234°C.νmax (KBr): 1670 cm^{-1} (C≡O) and 1530 cm^{-1} (NO_2). H: 3.36-3.50 (m, 4H,$-CH_2-N-CH_2$); 3.63-3.76 (m, 4H,$-CH_2-O-CH_2-$); 7.20-7.46 (m, 10H, arom); 7.80-7.93 (m, 2H, arom) and 8.30-8.43 (m, 2H, arom). M^+454.

2,3-Diphenyl-6-pyrrolidino-5-(4-nitrophenyl)pyrinidin-4(3*H*)one (20b): yield, 65%, yellow solid; m.p. 228-9°C. ν_{max} (KBr): 1680 cm^{-1} (C=O) and 1530 cm^{-1} (NO_2). δH: 1.76-2.13 (m, 4H,-CH_2-CH_2-); 3.20-3.40 (m, 4H,-CH_2-N-CH_2-); 7.16-7.40 (m, 10H, arom). 7.60-7.73 (m, 2H, arom) and 8.20-8.33 (m, 2H, arom). M^+ 438.

2,3-Diphenyl-5-succinimidylpyrimidin-4(3*H*)-one (21a): yield, 66%; white solid; m.p. 276°C. (Found C: 68.88; δH, 4.40; N, 11.92. $C_{20}H_{15}N_3O_3$ requires C, 69.56; H, 4.38; N, 12.17). ν_{max} (KBr): 1720 cm^{-1} and 1620 cm^{-1} (C=O). H: 2.86-3.00 (bs, 4H,-CH_2-CH_2-); 7.26-7.50 (m, 10H arom) and 8.20 (S, 1H, olefinic). M^+ 345.

3-(4-chlorophenyl)-2-phenyl-5-succinimidyl pyrimidin-4(3*H*)-one (21b): yield, 70%; white solid, m.p. 285-6°C. ν_{max} (KBr): 1720 and 1620 cm^{-1} (C=O). δH: 2.76-2.93 (bs, 4H, -CH_2-CH_2-); 7.26-7.53 (m. 9H, arom) and 8.30 (s, 1H, olefinic). M^+ 379.

2-Methylthio-3-phenyl-5-succinimidyl pyrimidin-4(3*H*)-one (23a): yield, 75%; white solid, m.p. 200-202°C. ν_{max} (KBr): 1700 Cm^{-1} and 1640 Cm^{-1} (C=O).δH: 2.50(s, 3H,-SCH_3); 2.86 (s,4H,-CH_2-CH_2-); 7.36-7.53 (m, 2H, arom); 7.63-7.73 (m, 3H, arom) and 7.95 (s, 1H, olefinic). M^+ 315.

3-(4-Chlorophenyl)-2-methylthio-5-succinimidyl-pyrimidin-4(3*H*)-one (23b): yield, 85%; white solid; m.p-204°C ν_{max} (KBr): 1720 cm^{-1} and 1640 cm^{-1} (C=O). δH: 2.60 (s, 3H,-SCH_3): 2.90-3.03 (d, 4H, -CH_2-CH_2-); 7.10-7.26 (m, 2H, arom), 7.43-7.53 (m, 2H, arom)

and 7.93 (s, 1H, olefinic). M^+ 349.

2,3-Diphenyl-6-morpholino-5-succinimidyl pyrimidin-4(3*H*)-one (25a): yield, 80%, white solid; m.p. 242°C. ν_{max})KBr): 1725 cm^{-1} and 1670 Cm^{-1} (C=O). δH: 276-2.93 (m, 4H,$-CH_2-CH_2-$); 3.73 (bs, 8H, morpholine), 7.20-7.40 (m, 8H, arom) and 7.86-8.06 (m, 2H, arom). M^+ 430.

2,3-Diphenyl-6-pyrrolidino-5-succinimidyl pyrimidin-4(3*H*)-one (25b): yield, 85%; white solid; m.p. 228-9°C. ν_{max} (KBr): 1730 cm^{-1} and 1670 cm^{-1} (C=O). H: 1.80-2.00 (m, 4H,$-CH_2-CH_2-$); 2.80-3.00 (m, 4H,$-CH_2-CH_2$), 3.56-3.66 (m, 4H,$-CH_2-N-CH_2-$), 7.23-7.46 (m, 8H, arom) and 7.80-8.13 (m, 2H, arom). M^+ 414.

2,3-Diphenyl-5-phthalimidyl-pyrimidin-4(3*H*)-one (22a): yield, 70%, white solid, m.p-207. (Found: C, 69.50; H, 5.32; N, 13.43. $C_{24}H_{15}N_3O_3$ requires C, 69.55; δH, 5.35; N, 13.52). ν_{max} (KBr): 1700 Cm^{-1} and 1610 Cm^{-1} (C=O). H: 7.43-7.53 (m, 2H, arom); 7.56-7.66 (m, 4H, arom), 7.70-7.96 (m, 8H, arom) and 8.40 (s, 1H, olefinic). M^+ 393.

3-(4-Chlorophenyl)-2-phenyl-5-phthalimidylpyrimidin-4(3*H*)-one (22b): yield, 60%; white solid, m.p. 216°C. ν_{max} (KBr): 1710Cm^{-1} and 1620 Cm^{-1} (C=O). H: 7.23-7.60 (m, 8H, arom); 7.80-8.13 (m, 5H, arom) and 8.36 (s, 1H, olefinic). M^+ 427.

2-Methylthio-3-phenyl-5-phthalimidyl-pyrimidin-4(3*H*)-one (24a): yield, 60%, white solid, m.p. 133-4°C. ν_{max} (KBr): 1720 cm^{-1} and

1620 cm^{-1} (C=O). H: 2.43, (s, 3H,-SCH_3); 7.33-7.60 (m, 5H, arom); 7.80-8.00 (m, 4H, arom) and 8.10 (s, 1H, olefinic). M^+ 363.

2,3-Diphenyl-6-morpholino-5-phthalimidylpyrimidin-4(3*H*)-one(27a): yield, 74%, white solid, m.p. 159-160°C ν_{max} (KBr): 1720 Cm^{-1} and 1670 Cm^{-1} (C=O). H: 2.73-2.96 (bs, 4H,-CH_2-N-CH_2-); 3.63-3.93 (bs, 4H,-CH_2-O-CH_2); 7.16-7.43 (m, 12H, aom) and 7.80-8.06 (m, 2H, arom). M^+ 478.

2,3-diphenyl-5-phthalimidyl-6-pyrrolidino-pyrimidin-4(3*H*)-one (26b): yield, 80%, white solid, m.p. 255-6°C ν_{max} (KBr): 1720 Cm^{-1} and 1680 Cm^{-1} (C=O). H: 1.80-2.63, (m,4H,-CH_2-CH_2-); 2.73-2.93 (bs, 4H,-CH_2-N-CH_2-), 7.30-7.36, (m, 12H, arom) and 7.80-8.15 (m, 2H, arom). M^+ 462.

2,3-Diphenyl-5-phenoxy-pyrimidin-4(3*H*)-one (27a): yield, 70%; white solid, m.p. 165-6°C. (Found: C, 77.75; H, 4.72; N, 8.18. $C_{22}H_{16}N_2O_2$ requires C, 77.63; H, 4.74; N, 8.23). ν_{max} (KBr): 1690 cm^{-1} (C=O). H: 7.00-7.13 (m, 2H, arom); 7.43-7.63 (m, 11H, arom); 8.13-8.23 (m, 2H, arom) and 8.30 (s, 1H, olefinic). M^+ 340.

3-(4-Chlorophenyl)-5-phenoxy-2-phenyl-pyrimidin-4(3*H*)-one (27b): yield, 70%, white solid, m.p. 171°C. ν_{max} (KBr): 1690 cm^{-1} (C=O). H: 7.00-7.13 (m, 2H, arom) 7.30-7.43 (m, 4H, arom), 7.50-7.60 (m, 5H, arom), 8.13-8.23 (m, 2H, arom) and 8.30 (s, 1H, olefinic). M^+ 374.

2-Methylthio-5-phenoxy-3-phenyl-pyrimidin-4(3*H*)-one (28a): yield, 64%, white solid, m.p. 141.2°C. ν_{max} (KBr): 1700 Cm^{-1} (C=O). 6H: 2.43 (s, 3H,-SCH_3); 7.06-7.20 (m, 2H, arom); 7.26-7.43 (m, 5H, arom); 7.53-7.63 (m, 2H, arom) and 7.80 (s, 1H, olefinic). M^+ 310.

3-(4-Chlorophenyl)-2-methylthio-5-phenoxypyrimidin-4(3*H*)-one (28b): yield, 65%, white solid, m.p. 170°C. ν_{max} (KBr): 1700 cm^{-1} (C≡O). δH: 2.43 (s, 3H,-SCH_3); 7.03-7.16 (m, 2H, arom); 7.20-7.33 (m, 5H, arom), 7.46-7.63 (m, 2H, arom) and 7.76 (s, 1H, olefinic). M^+ 344.

2,3-Diphenyl-6-morpholino-5-phenoxy pyrimidin-4 (3*H*)-one (29a): yield, 65%, white solid; m.p. 204-5°C. ν_{max} (KBr): 1690 C^{-1} (C=O). H: 3.13-3.30 (m, 4H,-CH_2-N-CH_2-); 3.40-3.46 (m, 4H,-CH_2-O-CH_2-); 6.96-7.13 (m, 2H, arom); 7.23-7.50 (m, 11H, arom) and 8.10-8.30 (m, 2H, arom). M^+ 425.

2,3-Diphenyl-5-phenoxy-6-pyrrolidinopyrimidin-4 (3*H*)-one (29b): yield, 60%, white solid; m.p. 243°C ν_{max} (KBr): 1690 cm^{-1} (C=O). δ_H: 1.70-1.90 (m, 4H,-CH_2-CH_2-), 3.06-3.26 (m, 4H,-CH_2-N-CH_2-); 7.00-7.13 (m, 2H, arom), 7.23-7.56 (m, 11H, arom) and 8.10-8.30 (m, 2H, arom). M^+ 409.

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CHAPTER-III

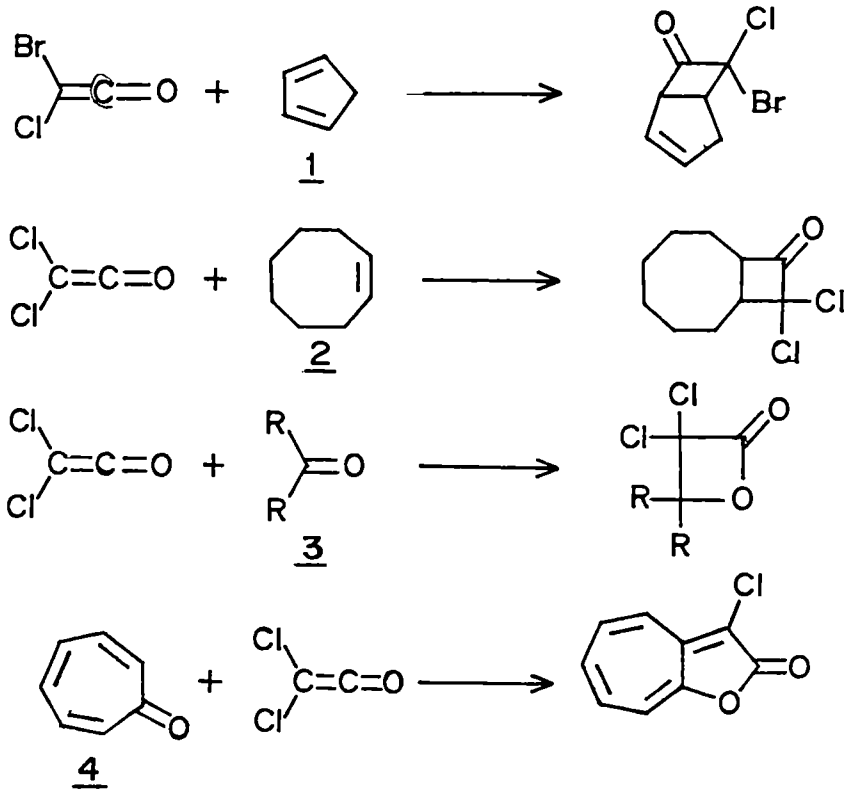
REACTIONS OF 1,3-DIAZA-1,3-BUTADIENES WITH HALOKETENES

INTRODUCTION

Ketenes have been known since the synthesis of diphenyl ketene by Staudinger in 1905.[1] This development led to the beginning of careful investigations of ketene chemistry. Halogenated ketenes were unknown until the first report of difluoroketene as late as 1957 and subsequent report of dichloroketene in 1965-66[2] and the earlier attempts towards generation of haloketenes always led to polymerized product even at low temperatures. The two methods successfully employed for the generation of haloketenes with the varying degree of success[3-5] were either zinc assisted dehalogenation haloacetyl halide or base assisted dehydrohalogenation of haloacetyl halide having at least one α-hydrogen atom.

Ketenes in general are susceptible to polymerization but halogenated ketenes perhaps surpass all of them and most reactions involving these compounds are accompanied by the formation of significant amount of tarry materials. The most common olefin for trapping the elusive halogenated ketene has been cyclopentadiene(1) and although a 1,4- cycloaddition is possible, the cycloaddition was shown to occur exclusively in 1,2-manner as in case of cycloalkenes(2). Dichloroketene could be effectively trapped by activated carbonyl compounds (3). However, it underwent 1,3-cycloaddition with tropone[6] (4) (Scheme-1).

There are quite a few reports of addition of halogenated ketenes to carbon-nitrogen double bonded systems. Dibromo- and dichloroketenes were found to add readily to dialkyldiimides (5) to yield the β-imino-β-lactams.[7-9] The cycloadditions of imines (6) and dihaloketenes were shown to result almost in quantitative yields of α,α-dihalo-β-lactams.[10] Whereas, the α,β-unsaturated imines, for example, 1-aza-1,3-buta-1,3-dienes (7) yielded both 1,2- and 1,4-cycloadducts[10] (Scheme-2). This was shown to be possible since it is well established that cycloadditions across C=N is a two step process involving a dipolar intermediate.[11,12] The lack of any further information concerning the cycloadditions of haloketenes with other monoaza and diazabutadienes stimulated us to investigate the cycloadditions of 1,3-diaza-1,3-butadienes with various haloketenes. Thus, the reactions of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Cl
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+
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O
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Br
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Cl
C=C=O
+
2
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Cl
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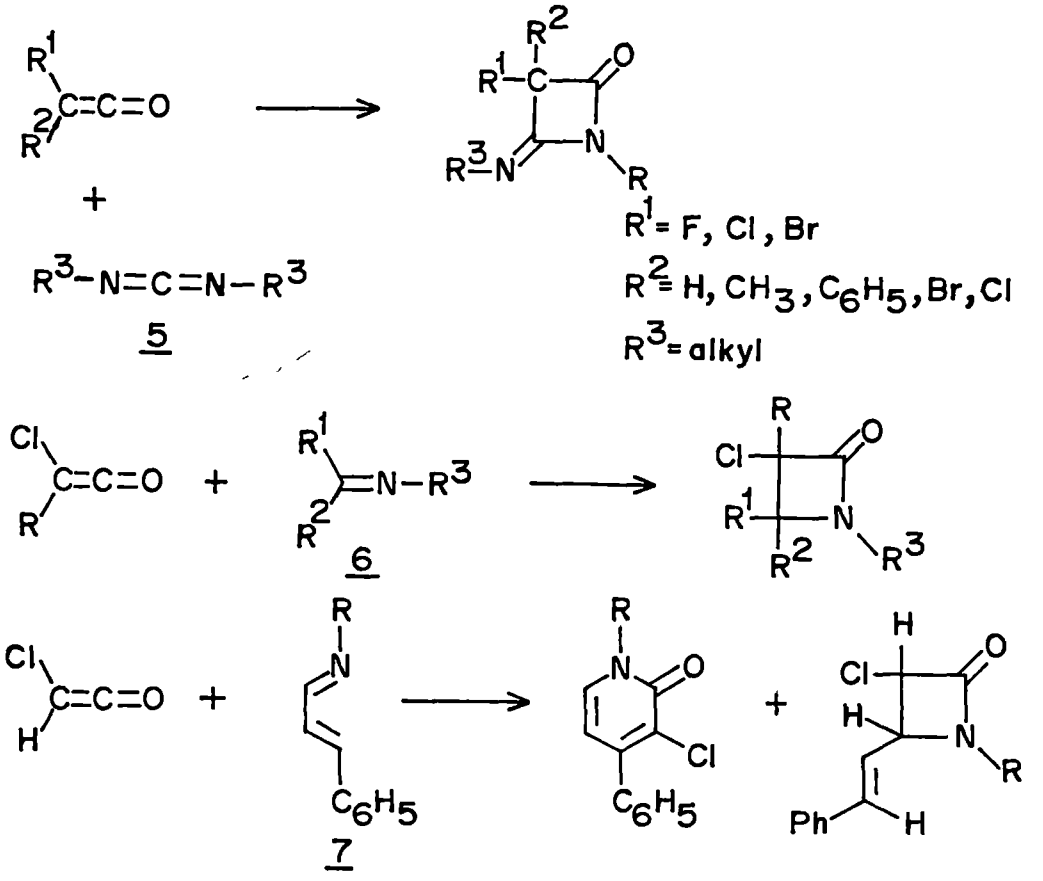
Cl
Cl
C=C=O
+
R
R
O
3
Cl
Cl
O
R
O
R
4
+
Cl
Cl
C=C=O
Cl
O
O

Scheme-1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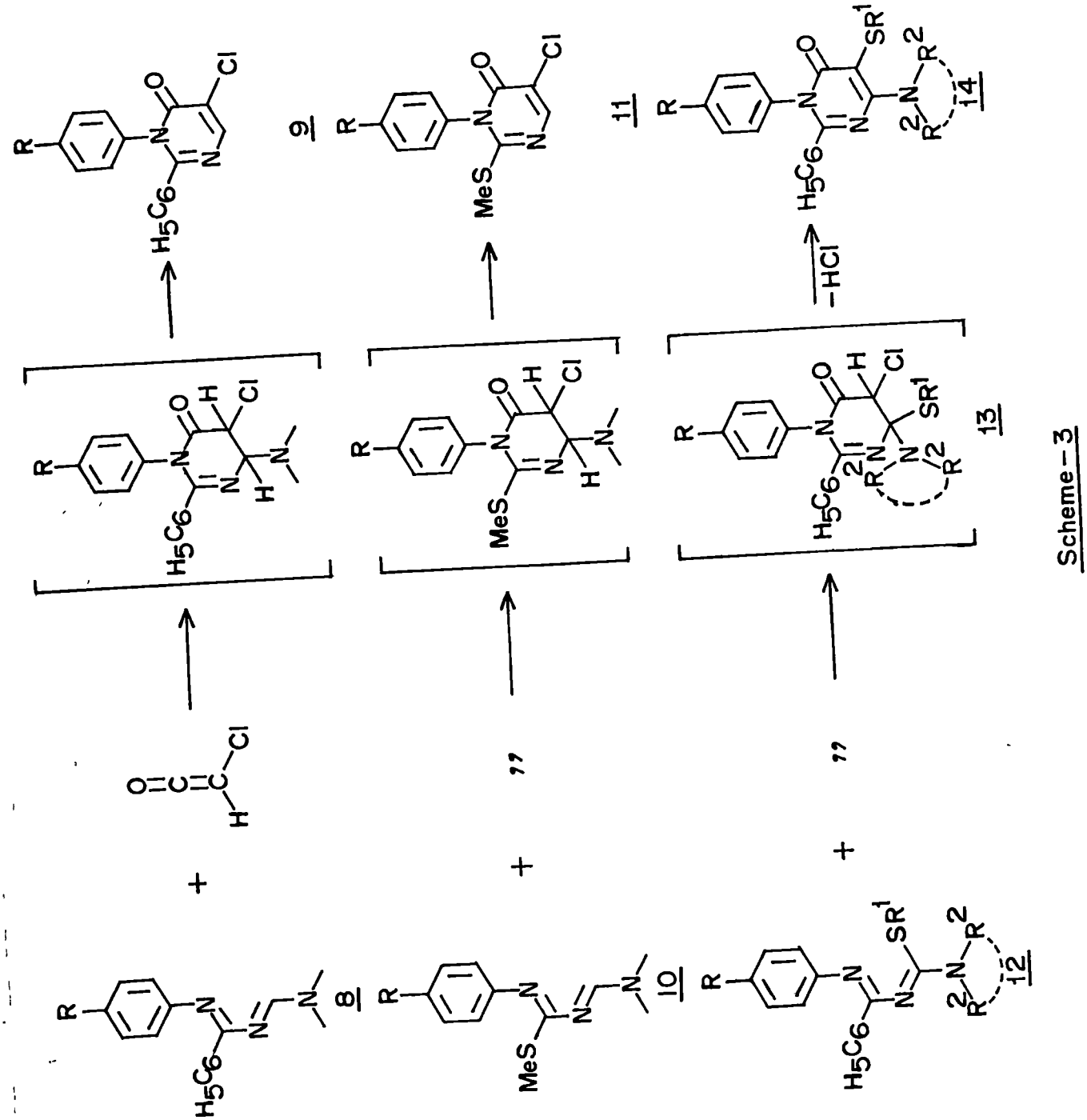
C=C=O
R2
+
R3-N=C=N-R3
5
R2
R1-C
O
R3=N
N
R
R1= F, Cl, Br
R2= H, CH3, C6H5, Br, Cl
R3= alkyl
Cl
C=C=O
R
+
R1
=N-R3
R2
6
R
Cl
O
R1
N
R2
R3
Cl
C=C=O
H
+
R
N
C6H5
7
R
N
O
Cl
C6H5
+
H
Cl
O
H
N
R
Ph
H

Scheme-2

monochloroketene with various activated 1,3-diaza-1,3-butadienes were carried out in our laboratory.[13]. These reactions were found to follow exclusively 1,4-addition mode resulting in high yields of previously unknown pyrimidinones. Thus, the reactions of 1,3-diaza-1,3-butadienes 8 and 10 with chloroketene gave pyrimidinones 9 and 11 formed via base induced elimination of dialkyl-amine from initially formed [4+2] cycloadduct as an intermediate. The higher polarisability of 1,3-diaza-1,3-butadienes could be considered as one of the reasons for the formation of δ-lactam in preference to β-lactam as in case of 1-aza-1,3-butadienes.[10] Interestingly, the reactions of 1,3-diazabutadienes (12) with monochloroketene resulted in products which indicated the presence of methylthio as well as sec-amino functions and loss of hydrogen chloride. The products were characterized as pyrimidinones (14) and involved transposition of -SMe from position 6- to position 5- of initially formed [4+2] cycloadducts (13) as an intermediate (Scheme-3).[14]. The probable mechanistic pathways proposed for the formation of rearranged pyrimidinones (14) are outlined in Scheme-4. In this scheme it is proposed that 1,3-diazabutadienes (12) undergoes cycloaddition with chloroketene to yield [4+2] cycloadduct intermediate (13) either directly or on reversal of [2+2] cycloadduct (15). This intermediate may then follow three different pathways. The pathway I assumes that the intermediate 13, in presence of excess triethylamine, may result in a carbene intermediate 16 leading to



Scheme-3

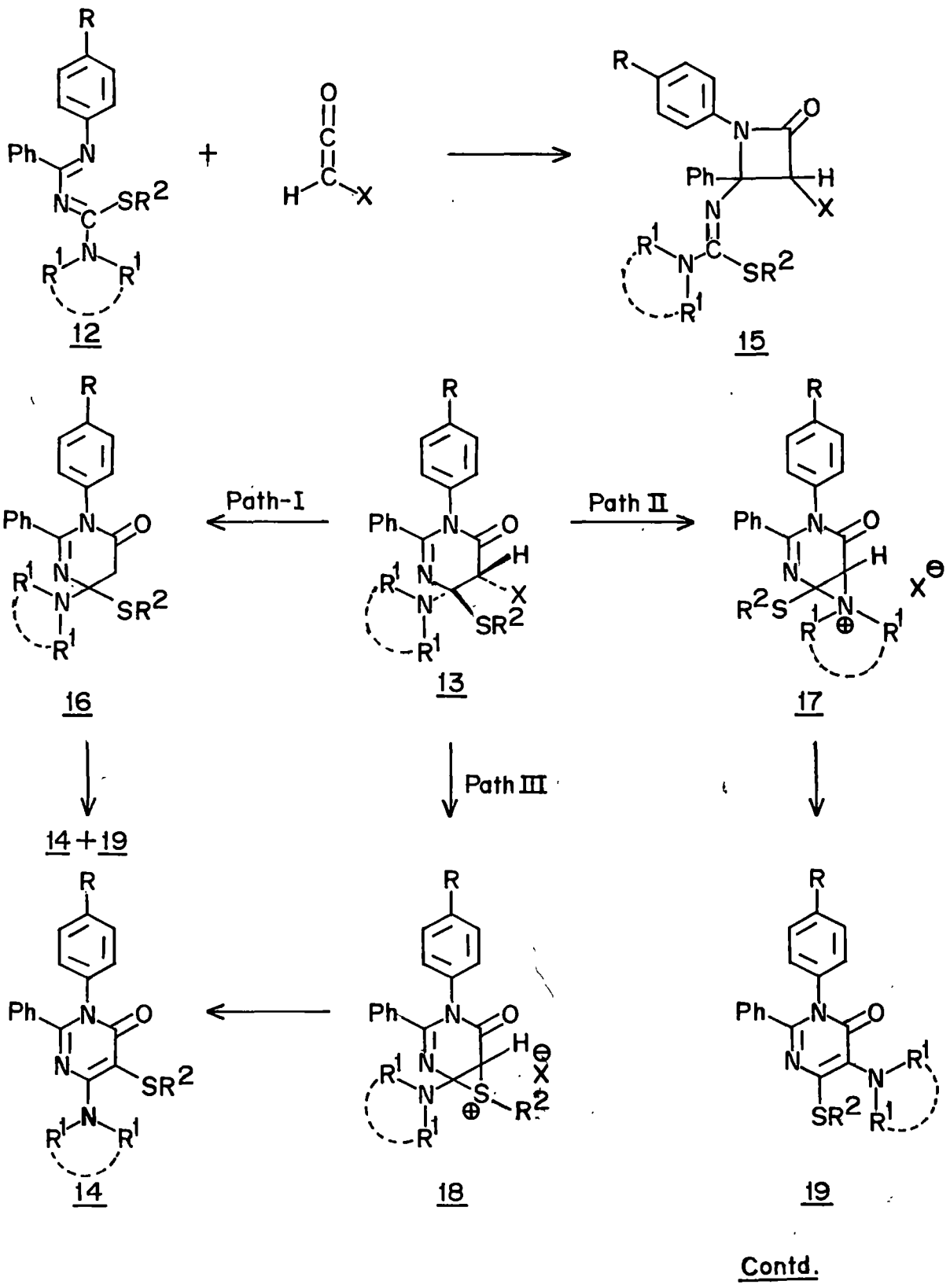
products. This pathway may be ruled out since such an intermediate should have resulted in a mixture of pyrimidinones **14** and **19**, containing at least a small proportion of **19** due to lower nucleophilicity of nitrogen as compared to sulfur. The formation of carbene intermediate may further be ruled out since no such rearranged pyrimidinone was observed in the reactions of 1,3-diazabutadienes **8** and **10** with chloroketene. The pathway II leading to the formation of pyrimidinone **19** *via* aziridinium intermediate **17** could also be ruled out since it involves the attack of lesser nucleophilic nitrogen at c-5 bearing a leaving group. Also no such rearrangement was observed in cycloadditions of chloroketene with 1,3-diaza-butadienes **8** and **10**. The most likely pathway III involves the transformation of intermediate **13** into an episulfonium intermediate **18**. This intermediate then rearranges by the loss of a proton and migration of an alkyl thio function to give pyrimidinones **14**.

In order to generalise such molecular rearrangements accompanying the cycloaddition reactions of 1,3-diazabutadienes with haloketenes and to have a deeper insight into the mechanistic aspects it was thought worthwhile to carry out the detailed investigations of the reactions of 1,3-diazabutadienes with various haloketenes. The results of such investigations with bromo-, iodo-,2-chloro-2-methyl- and 2,2-dichloroketenes along with suitable mechanistic explanations are described as follows:

Results and Discussion:

The reactions of 1-aryl-2-phenyl-4-secondaryamino-4 thioalkyl-1,3-diaza-1,3-butadienes with bromo- and iodoketenes have been investigated since it was thought that the mechanistic pathway followed in their cycloadditions may be influenced by their larger size and better leaving group ability. In case of these cycloadditions, it was thought possible that the intermediate 13, because of better leaving group ability of bromideiodide, may lead by base induced elimination of hydrogen halide to a carbene intermediate 16 which then may lead to some extent to the formation of aziridinium ion intermediate 17 and subsequently to the corresponding pyrimidinone 19. However, the reactions of 1,3-diazabutadienes (12) with monobromoketene, generated *in situ* from bromo-acetyl bromide and triethylamine, also led to the very good yields (73-90%) of 5-alkylthio-3-aryl-6-sec.amino-2-phenyl-4(3*H*)-pyrimidinones (14). The products have been characterised on the basis of analytical and spectral evidences. The compound 14, for example, was analysed for $C_{19}H_{19}N_3OS$ and its mass spectrum showed a molecular ion peak at m/z 337. Its IR spectrum showed an α,β-unsaturated carbonyl peak at 1670 cm^{-1}. The ^1H and ^{13}C NMR spectra exhibited signals both for dimethylamino and methylthio groups. On the basis of above analytical and spectral data the products could be assigned the structures 14 or 19. The structure 19 could be ruled out on the basis of mechanistic arguements advanced earlier. Similarly, the reactions of 1,3-diaza-1,3-butadienes (12) with iodoketene,

generated *in situ* from iodoacetic acid in presence of p-toluenesulfonyl chloride and triethylamine, resulted in the isolation of identical pyrimidinones **14**. The pyrimidinones obtained in case of reactions of bromo and iodoketenes showed undepressed mp and super imposable i.r. spectra with the corresponding samples obtained in case of chloroketene reactions. The formation in good yields of identical pyrimidinones **14** in cases of chloro, bromo- and iodoketenes clearly indicated the presence of a common intermediate in all these reactions. These results clearly rule out the the presence of carbene **16** or aziridinium **17** intermediates in case of reactions of 1,3-diazabutadiene with bromo- and iodoketenes. It may be concluded that the reactions of 1,3-diazabutadienes (**12**) with mono haloketenes irrespective of the nature of halogen atom, proceed *via* episulfonium intermediate **18** leading to pyrimidinones **14** (Scheme-4). The preferential migration of alkylthio group in all these cases requires trans arrangement of halogen and alkylthio groups in the intermediate **13**. This intermediate with the desired stereochemical arrangement of alkylthio and halogen groups may be obtained either through highly stereoselective [4+2] cycloadditions of 1,3-diazabutadienes (**12**) with haloketenes or via the equilibration of the intermediate **13** either involving acidic hydrogen at C-5 or through zwitterionic intermediate (Scheme-5). Another logistic mechanistic possibility for the formation of pyrimidinones **14** in above reactions, is that the


Path-I
Path II
Path III
12
15
16
13
17
14+19
14
18
19
Contd.

a: R = H, R^1 =  , $R^2 = CH_3$

b: R = H, R^1 =  , $R^2 = CH_3$

c: R = H, R^1 =  , $R^2 = CH_3$

d: R = H, R^1 = , $R^2 = CH_3$

e: R = H, R^1 = , $R^2 = CH_2CH_3$

f: R = H, R^1 = , $R^2 = CH_2CH_3$

g: R = H, R^1 = , $R^2 = CH_2CH_3$

h: R = H, R^1 = , $R^2 = CH_2CH_3$

i: R = CH_3, R^1 = , $R^2 = CH_3$

j: R = CH_3, R^1 = , $R^2 = CH_3$

k: R = CH_3, R^1 = , $R^2 = CH_3$

l: R = CH_3, R^1 = , $R^2 = CH_3$

m: R = CH_3, R^1 = , $R^2 = CH_3$

n: R = CH_3, R^1 = , $R^2 = CH_3$

o: R = CH_3, R^1 = , $R^2 = CH_3$

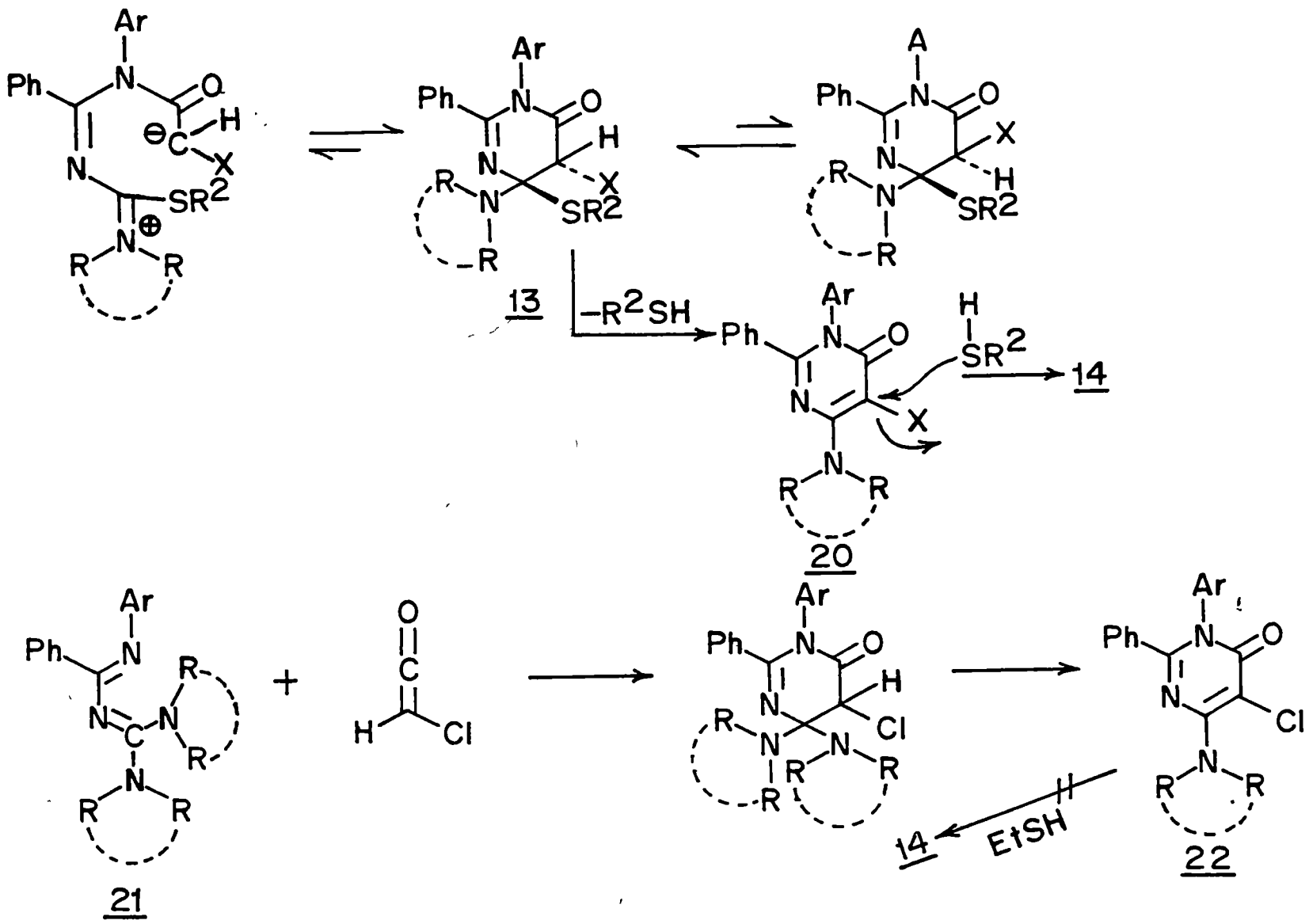
p: R = CH_3, R^1 = , $R^2 = CH_3$

Scheme-4

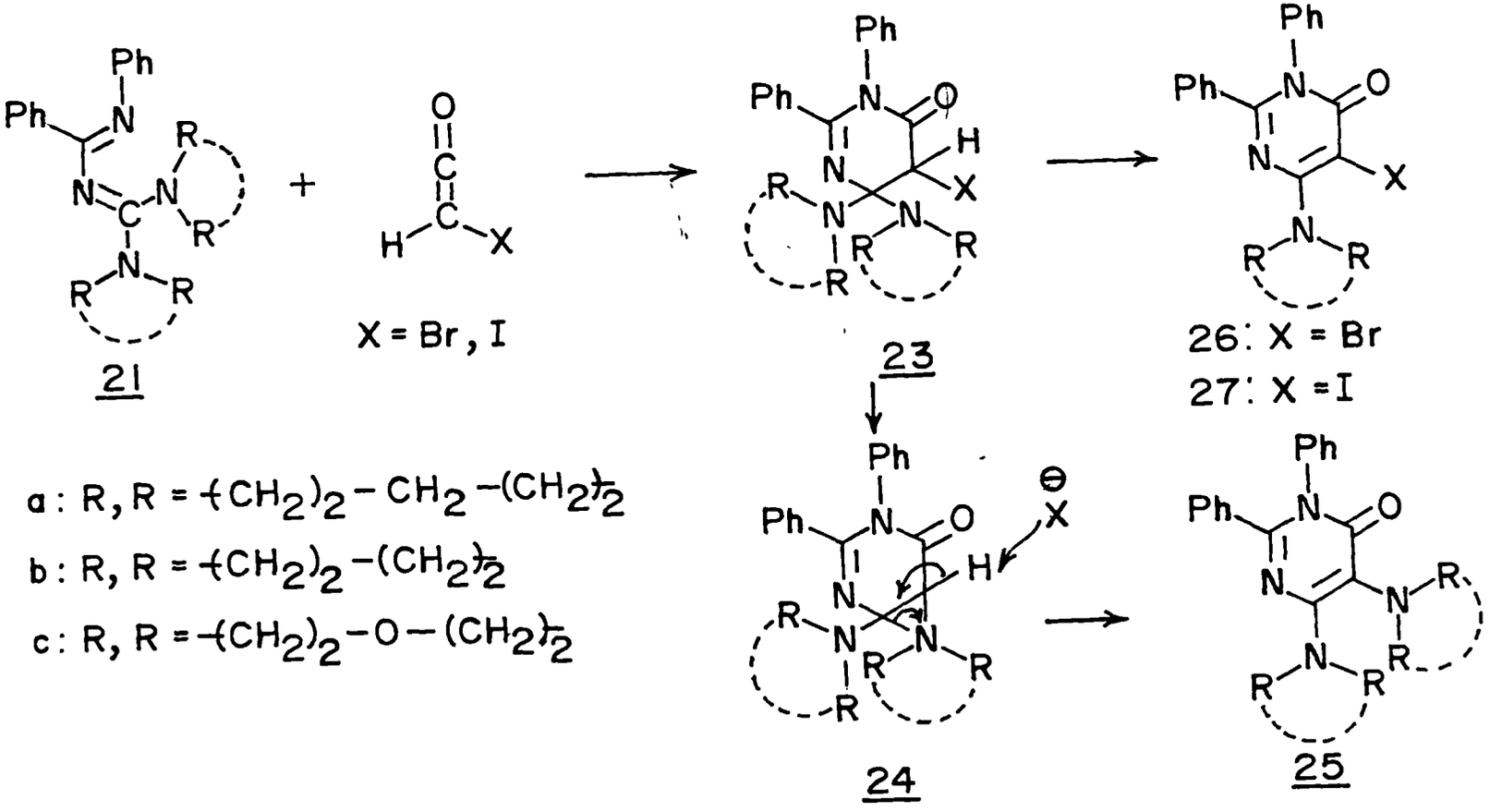
intermediate 13 may undergo base assisted elimination of alkylmercaptan yielding pyrimidinone 20 which then may react with the eliminated alkylmercaptan to give pyrimidinones 14. This possibility was also ruled out since the reaction of ethylmercaptan with 5-chloropyrimidinones (22), obtained by the rections of 1,3-diazabutadienes (21) with chloroketene[13] under identical reaction conditions did not result in the displacement of chloride by alkylthio and the starting pyrimidinones 22 was recovered unchanged (Scheme-5).

In continuation of our investigations we have investigated the reactions of 1,3-diazabutadienes (21), having bis-sec. aminofunctions at position 4-, with bromo- and iodoketenes. It was thought that initially formed [4+2] cycloadduct intermediate 23 in these cases, having a better leaving group bromide/iodide at C-5, may invoke an aziridinium intermediate 24 leading ultimately to rearranged pyrimidinones 25 (Scheme-6). However, the intermediate 23 also underwent the usual elimination of secondaryamines, as observed earlier in case of chloroketene reactions, resulting in 2,3-diphenyl-5-bromo-6- sec. amino-pyrimidin-4 (3*H*)-one (26) and 2,3-diphenyl-5-iodo-6-piperidino-pyrimidin-4 (3*H*)-one (27a) respectively. The pyrimidinones 26 and 27 were characterised on the basis of analytical data and spectral evidences.

It has been reported earlier[14] that the reactions of 1-aryl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadienes (8) and 1-aryl-

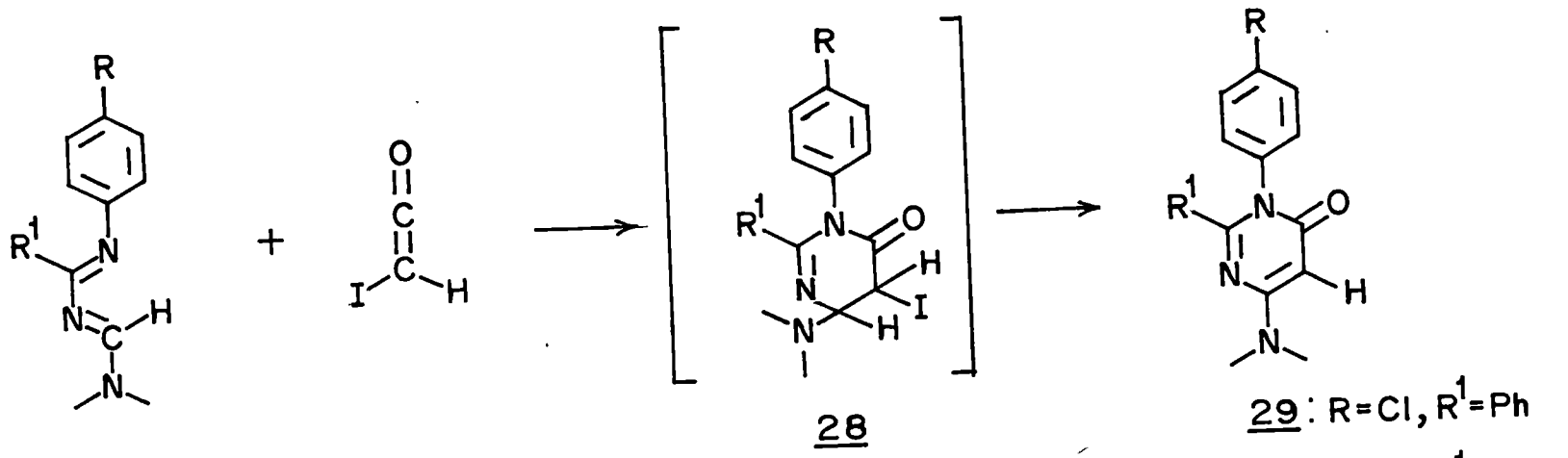


Scheme-5


Ph
Ph
N
N
C
N
R
R
R
R
R
R
21
+
O
C
C
H
X
X = Br, I
Ph
Ph
N
O
H
X
N
R
N
N
R
R
R
23
Ph
Ph
N
O
H
X
N
R
N
N
R
R
R
24
Ph
Ph
N
O
X
N
R
N
N
R
R
R
26: X = Br
27: X = I
25
a: R, R = -(CH2)2-CH2-(CH2)2-
b: R, R = -(CH2)2-(CH2)2-
c: R, R = -(CH2)2-O-(CH2)2-

Scheme-6

4-dimethylamino-2-thiomethyl-1,3-diaza-1,3-butadienes (10) with monochloroketene yielded good yields of 3-aryl-5-chloro-2-phenyl-pyrimidin-4(3*H*)-one (9) and 3-aryl-5-chloro-2-thiomethyl-pyrimidin-4 (3*H*)-ones (11), respectively. The pyrimidinones 9 and 11 in these cases were thought to arise via the elimination of dimethylamine from the initially formed [4+2] cycloadducts. Further to these investigations, it was thought worthwhile to exmaine the reactions of 1,3-diaza-1,3-butadienes 8 and 10 with bromo- and iodoketenes. It was felt that the [4+2] cycloadducts formed in these cases having better leaving groups bromide/iodide at C-5 may undergo preferential elimination of hydrohalous acids rather than dimethylamine elimination observed in case of chloroketene reactions. Thus, the reactions of 1,3-diaza-1,3-butadienes 8 and 10 with monoiodoketene resulted in the formation of 3-p-chlorophenyl-6-dimethylamino-2-phenyl-pyrimidin-4(3*H*)-one (29) and 6-dimethylamino-3-phenyl-2-thiomethyl-pyrimidin-4(3*H*)-one (30) respectively. These pyrimidinones are formed by the elimination, as expected, of hydroiodic acid from the [4+2] cycloadduct intermediate 28 (Scheme-7). On the other hand, the intermediate 31 in case of the cycloaddition reactions of 1,3-diazabutadienes 8 and 10 with bromoketene underwent loss both of dimethylamine and hydrobromic acid resulting in pyrimidinones 32, 33 and 29, 30 respectively. The mixtures of pyrimidinones 29 & 32 and 30 & 33, were separated with the help of silica gel column chromatography using a mixture (1:10) of ethylacetate hexane, as



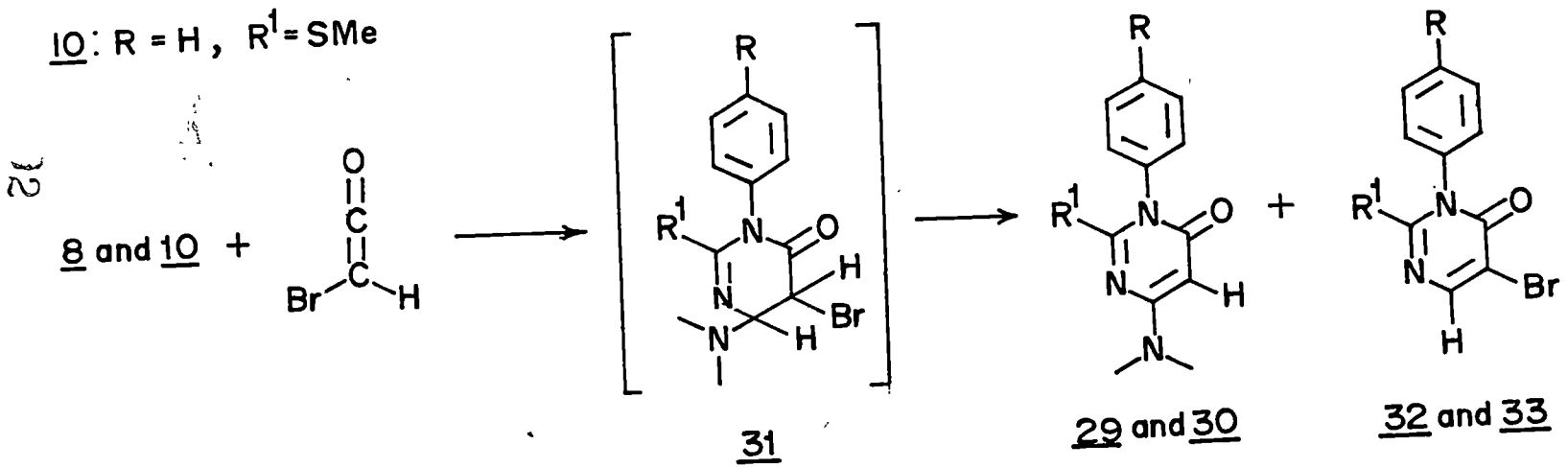
28

29 : R = Cl, R^1 = Ph

30 : R = H, R^1 = SMe

8 : R = Cl, R^1 = Ph

10 : R = H, R^1 = SMe



31

29 and 30

32 and 33

R = Cl, R^1 = Ph : 29 : 38% 32 : 32%

R = H, R^1 = SMe : 30 : 42% and 33 : 36%

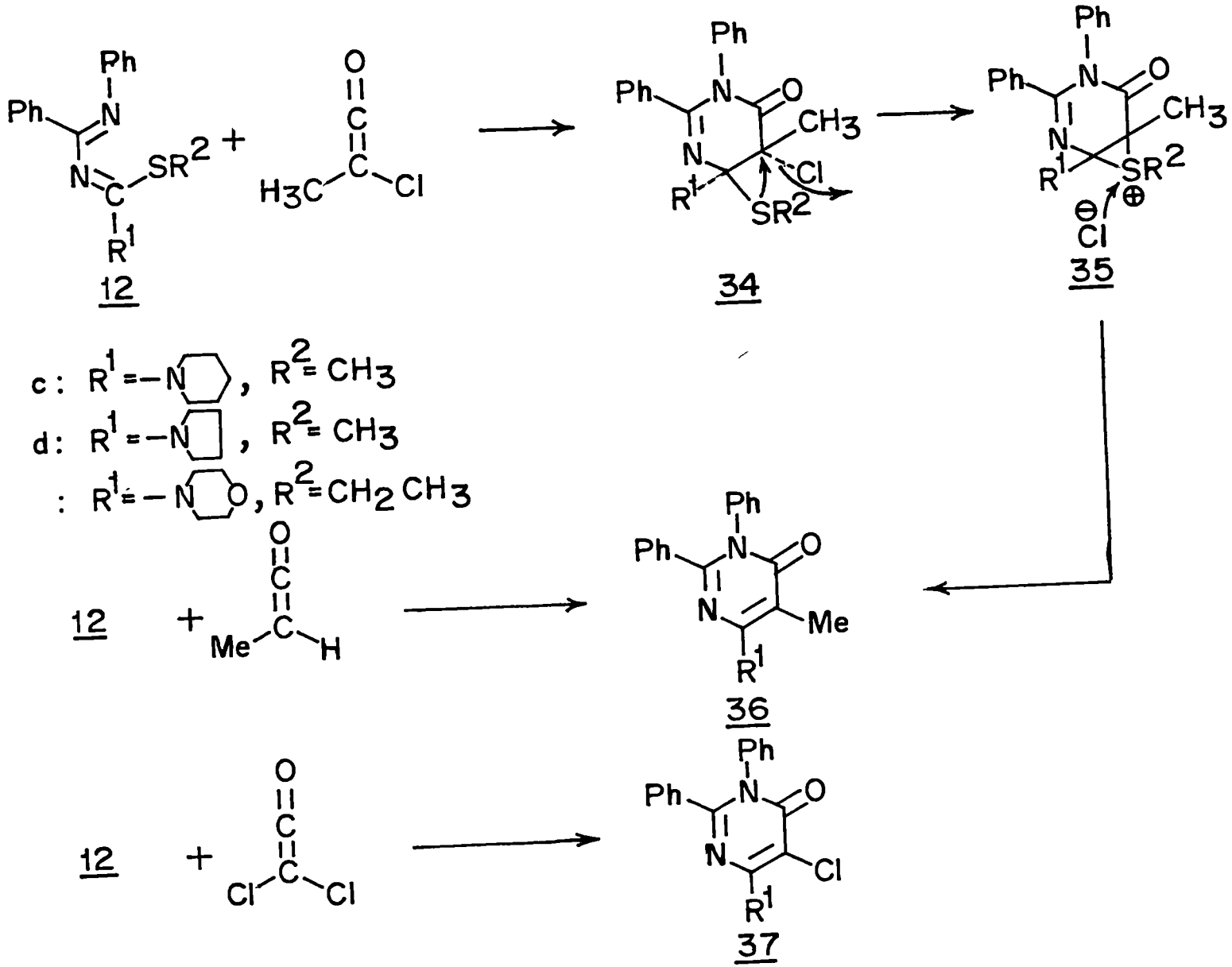
Scheme-7

eluent. The ratio of the isolated pyrimidinones (29:32:: 38:32%) and (30:33:: 42:36%) indicates that the loss both of dimethylamine and hydrobromic acid perhaps takes place with almost equal ease from the intermediate 31. The ^{1}H NMR spectra exhibited vinylic protons *Ca* 8.00 and *Ca* δ5.20 for pyrimidinones 32, 33 and 29, 30, respectively.

In Scheme-4, it is assumed that the presence of a hydrogen atom at C-5 in intermediate 18 is perhaps essential for the formation of rearranged pyrimidinones 14. In order to investigate this and the efficacy of episulfonium ion intermediate for such rearrangements it was thought worthwhile to examine the reactions of 1,3-diaza-1,3-butadienes 12 with 2-chloro-2-methylketene and 2,2-dichloroketene. It was also felt that the examination of these reactions will possibly help in distinguishing between the two most probable mechanistic pathways *viz.* (i) that the highly polarised 1,3-diazabutadienes prefer to follow directly the [4+2] cycloaddition pathway (ii) that these reactions initially undergo [2+2] cycloadditions yielding β-lactams which subsequently change to pyrimidinones. It is because in case of these reactions the intermediate [4+2] cycloadducts, in contrast to earlier mentioned [4+2] cycloadduct intermediates, in the absence of any hydrogen at C-5 will perhaps not have any chance either to undergo elimination of alkylmercaptan or alkyl thio shift and hence the [2+2] cycloaddition may be the only observed pathway, yielding exclusively the β-lactams.

Thus, the reactions of 2,3-diphenyl-4-secondaryamino (morpholino-, piperidino-, pyrrolidino-)-4-thioalkyl(methyl, ethyl)-1,3-diaza-1,3-butadienes (12) with 2-chloro-2-methylketne, generated *in situ* form α-chloropropionic acid in presence of p-toluenesulfonyl chloride and triethylamine, resulted interestingly in another set of rearranged pyrimidinones 36. These pyrimidinones were characterised as 2,3-diphenyl-5-methyl-6-sec. amino-pyrimidin-4(3*H*)-ones on the bsis of analytical data and spectral evidences. The ^{1}H NMR spectra of these compounds showed the presence of secondary amino and methyl protons and the absence of alkylthio protons. Their IR spectra exhibited a strong absorption *ca.* 1660 cm^{-1} which could be assigned α,β-unsaturated carbonyl of pyrimidinones 36. Further confirmation for the structure 36c was derived from the superimposable IR spectra and undepressed mixed melting point with a sample prepared by the reaction of 12c with methylketene, generated *in situ* from propionic acid in presence of p-toluenesulfonyl chloride and triethylamine.

The probable mechanism leading to the formation of pyrimidinones 36 is outlined in scheme-8.. Here again, it is assumed that the initial [4+2] cycloadduct intermediate 34 leads to episulfonium intermediate 35, by involving attack of sulfur of thioalkyl at C-5 bearing chloride as a leaving group. The intermediate 35 then, as depicted, undergoes elimination of alkylsulfenyl chloride to yield pyrimidinones 36. Clearly again,



Scheme-8

the formation of episulfonium intermediate 35 requires the trans stereochemical arrangement of thioalkyl and chloride in intermediate 34 and it may be possible either *via* stereoselective [4+2] cycloaddition of 12 with 2-chloro-2-methylketene or via the equilibration of the intermediate 34 involving zwitterion. Further the absence of hydrogen at C-5 in intermediate 34 rules out the involvement of such a hydrogen, for possible equilibration as assumed earlier. Similarly, the treatment of 1,3-diaza-1,3-butadienes (12c & 12d) with dichloroketene, generated *in situ* from trichloroacetyl chloride and *zinc*, resulted in the formation of 5-chloro-6-sec. amino-2,3-diphenyl-pyrimidin-4(3*H*)-one (37 c & d) arising via the loss of methylsulfenyl chloride from an intermediate of type 35.[15]

The above results clearly establish the involvement of episulfonium intermediates for the formation of rearranged pyrimidinones and it is still not possible to distinguish between the two most probable mechanistic pathways in case of 1,3-diaza-1,3-butadienes-ketenes cycloadditions. It may still be assumed that the highly polarised 1,3-diaza-1,3-butadienes at our hands either prefer to undergo direct [4+2] cycloadditions or [2+2] cycloadducts formed initially equilibate, via zwitterion, with [4+2] adducts which undergo either elimination of alkylmercaptan/sec. amines or undergo rearrangement to yield stable pyrimidinones.

In order to distinguish between the above mentioned mechanistic aspects and to firmly establish the mechanism in the next chapter it is proposed to investigate the rreactions with disubstituted ketenes where the proposed [4+2] cycloadduct intermediate will have neither elimination nor rearrangement possibility.

3-4 h. On completion of the reaction (TLC), it was diluted with chloroform, washed with water (5x50 ml), 5% sodium hydroxide solution (2x30 ml), brine (2x50 ml) and dried over anhydrous magnesium sulphate. The crude product obtained after removal of solvent under reduced pressure were purified by passing them through silica gel column.

6-Dimethylamino-2,3-diphenyl-5-methylthio-4(3*H*)-pyrimidone (14a): 90%, m.p. 128-30°C. (Found: C,67.50; H,5.68;N,12.40.$C_{19}H_{19}N_3OS$ requires C,67.66;H,5.64;12.46) ν_{max}: 1670 cm^{-1} (C=O). δ_H:2.28 (s,3H,$-SCH_3$);3.26(s,6H,$-N(CH_3)_2$) and 7.13-7.33(m,10H, arom). δ_C: 17.68($-SCH_3$); 41.10 ($-N(CH_3)_2$); 91.48(C-5);127.62,128.48.128.97, 129.11 (C-2′,3′,6′,7′); 127.87,129.43(C-4′,8′); 134.85,137.75(C-1′,5′);164.87(C-2);163.52(C-4,6). M^+ 363.

2,3-Diphenyl-5-methylthio-6-morpholino-4(3*H*)-pyrimidone (14b): 90%, m.p. 176°C. (Found: C,66.36;H,5.52;N,11.10.$C_{21}H_{21}N_3O_2S$ requires C,66.49;H,5.54;N,11.02). ν_{max} 1670 cm^{-1} (C=O) δ_H: 2.36(s,3H,$-SCH_3$); 3.86-3.92(m, 8H, morpholine) and 7.10-7.33(m, 10H, arom). M^+ 379.

2,3-Diphenyl-5-methylthio-6-piperidino-4(3*H*)-pyrimidone (14c): 88%, m.p. 126-7°C. (Found: C,69.97;H,6.00;N,11.00.$C_{22}H_{23}N_3OS$ requires C,70.03;H,6.10;N,11.14). ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.63-1.80(m, 6H,$-CH_2-CH_2-CH_2-$);2.33 (s, 3H, $-SCH_3$); 3.66-3.86(m, 4H, $-CH_2-N-CH_2-$) and 7.10-7.36 (m, 10H, arom). M^+ 377.

Experimental

Melting points were determined with a Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer, using KBr disc. ^{1}H NMR were recorded in $CDCl_3$, with a Varian 390, 90 MHz spectrometer using TMS as the internal standard. Mass spectra were obtained by electron impact at 70 eV.

Reactions of 1,3-Diaza-1,3-Butadienes[4] with ketenes:

Method A: To a well stirred solution of 1,3-diaza-1,3-butadiene (4 mmol) and triethylamine (10 mmol) in dry chloroform (30 ml), was added gradually a solution of acid halide (6 mmol) in dry chloroform (30 ml) over a period of 1.5-2 h at room temperature. After completion of the reaction (TLC), it was further diluted with chloroform and washed several times with water (5x50 ml), sodium hydrogen carbonate (2x30 ml), water (2x50 ml) and finally dried over anhydrous magnesium sulphate. Removal of solvent under reduced pressure yielded the crude product, which was purified by silica gel column chromatography.

Method B: A solution of acid (6 mmol)in dry chloroform (30 ml) was stirred for half an hour. To this solution, 1,3-diaza-1,3-butadiene (4 mmol) was added and stirring was continued. A solution of p-toluenesulfonylchloride (6 mmol) in chloroform (30 ml) was added dropwise over a period of 1h and the reaction mixture was stirred at room temperature for a further period of

2,3-Diphenyl-5-methylthio-6-pyrrolidino-4(3*H*)-pyrimidone (14d): 88%, m.p. 152°C. (Found: C,69.43;H,5.85;N,11.50.$C_{21}H_{21}N_3OS$ requires C,69.47;H,5.79;N,11.57).ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.80-2.03(m,4H, $-CH_2-CH_2-$); 2.33(s,3H, SCH_3); 3.80-4.02(m, 4H, $-CH_2-N-CH_2-$) and 7.10-7.30(m, 10H, arom). M^+ 363.

6-Dimethylamino-2-3-diphenyl-5-ethylthio-4(3*H*)-pyrimidone (14e): 74% m.p. 107-8°C (Found: C,68.01;H,6.11;N,11.90.$C_{20}H_{21}N_3OS$ requires C,68.38;H,5.98;N,11.97).ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.13-1.30(t, 3H, $-CH_3$); 2.70-2.93(q. 2H, $-SCH_2-$); 3.30 (s, 4H, $-N(CH_3)_2$); and 7.06-7.36(m, 10H, arom). M^+ 351.

2,3-diphenyl-5-ethylthio-6-morpholino-4(3*H*)-pyrimidone (14f): 80%, m.p. 183°C. (Found: C,67.00;H,5.74;N,10.62.$C_{22}H_{23}N_3O_2S$ requires C,67.18;H,5.85;N,10.69).ν_{max}: 1670 cm^{-1} (C=O). δ_H:1.19-1.30 (t, 3H, $-CH_3$); 2.73-3.00(q, 2H, $-SCH_2-$); 3.70-3.86 (m, 8H, morpholine) and 7.06-7.28(m, 10H, arom). M^+ 393.

2,3-Diphenyl-5-ethylthio-6-piperidino-4(3*H*)-pyrimidone (14g): 80%, m.p. 137-8°C. (Found: C,70.40;H,6.30;N,10.70.$C_{23}H_{25}N_3OS$ requires C,70.59;H,6.39;N,10.74).ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.16-1.33(t,3H, $-CH_3$); 1.66-1.80(m 6H, $-CH_2-CH_2-CH_2-$); 2.80-3.95(q, 2H, $-SCH_2-$); 3.73-390 (m, 4H, $-CH_2-N-CH_2-$) and 7.06-7.36(m, 10H, arom). M^+ 391.

2,3-Diphenyl-5-ethylthio-6-pyrrolidino-4(3*H*)-pyrimidone (14h): 78%, m.p. 164°C. (Found: C,69.30;H,6.17;N,11.07.$C_{22}H_{23}N_3OS$ requires C,70.03;H,6.10;N,11.14).ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.16-

1.33 (t, 34, $-CH_3$); 1.83-2.00(m, 4H, $-CH_2-O$, 2.68-2.93 (,2H, $-SCH_2$); 3.83-4.00 (m, 4H, $-CH_2-N-CH_2$) and 7.06-7.36 (m, 10H, arrom). M^+ 377.

6-Dimethylamino3-(4-methylphenyl)-5-methylthio-2-phenyl-4(3H)-pyrimidone(14i): 87%, m.p. 129-30°C. (Found: C,66.58; H,5.98; N,11.88. $C_{20}H_{21}N_3OS$ requires C,66.38;H,5.98;N,11.97). ν_{max} 1660 cm^{-1} (C=O). δ_H: 2.30(s, 3H,$-CH_3$);2.33(s,3H,$-SCH_3$);3.30(s, 6H,$-N(CH_3)_2$); 6.97-7.06(m, 4H, arom) and 7.16-7.26(m, 5H, arom). M^+ 351.

3-(4-Methylphenyl)-5-methylthio-6-morpholino-2-phenyl-4(3H)-pyrimidone (14j): 90%, m.p. 168-70°C. (Found: C,67.70; H,5.80; N,10.72.$C_{22}H_{23}N_3O_2S$ requires, C,67.18;H,5.85;N,10.69).ν_{max}: 1660 cm^{-1} (C=O). δ_H:2.22(s,3H,$-CH_3$); 2.35(s,3H,$-SCH_3$); 3.73-3.88(m, 8H, morpholine); 7.00-7.10(m,4H, arom) and 7.20-7.40(m, 5H, arom). M^+ 393.

3-(4-Methylphenyl)-5-methylthio-2-phenyl-6-piperidino-4(3H)-pyrimidone (14k): 86%, m.p. 174-5°C. (Found: C,70.40 H, 6.30;N,H, 6.30;10.72). $C_{23}H_{25}N_3OS$ requires C, 70.59; H, 6.39; N, 10.74. ν_{max}: 1660 cm^{-1} (C=O). δ_H: 1.66-1.82(m, 6H, $-CH_2-CH_2-CH_2-$); 2.28 (s,3H,CH_3); 2.33 (s,3H,$-SCH_3$); 3.70-3.90 (m,4H,$-CH_2-N-CH_2-$); 7.00-7.10(m,4H, arom) and 7.23-7.33(m, 5H, arom). M^+ 391.

3-(4-Methylphenyl)-5-methylthio-2-phenyl-6-pyrrolidino-4(3*H*)-pyrimidone (14l): 81%, m.p. 164°C. (Found: C,69.70; H,6.08; N,11.08;.$C_{22}H_{23}N_3OS$ requires C,70.03;H,6.10;N,11.14). ν_{max}: 1660

cm^{-1} (C=O). δ_H: 1.83-2.03(m,4H, $-CH_2-CH_2-$); 2.33 (s, 6H, $-CH_3$ and $-SCH_3$); 3.80-3.98(m,4H, $-CH_2-N-CH_2-$); 7.00-7.08 (m, 4H, arom) and 7.13-7.33 (m, 5H, arom). M^+ 377.

3-(4-Chlorophenyl)-6-dimethylamino-5-methylthio-2-phenyl-4(3*H*)-pyrimidone(14m):Yield 78%, m.p. 127°C. (Found: C,61.90; H,4.80;N,11.34.$C_{19}H_{18}ClN_3OS$ requires C,61.37;H,4.85;N,11.31). ν_{max}: 1670 cm^{-1} (C=O). δ_H: 2.32(s,3H,$-SCH_3$); 3.33(s,6H, $-N(CH_3)_2$) and 7.00-7.33(m, 9H, arom). M^+ 371.

3-(4-Chlorophenyl)-5-methylthio-6-morpholino-2-phenyl-4(3*H*)-pyrimidone(14n): Yield: 73%, m.p. 233°C. (Found: C,60.50; H,4.74; N,10.12. $C_{21}H_{20}ClN_3OS$ requires C,60.94;H,4.84;N,10.16).ν_{max}: 1670 cm^{-1} (C=O). δ_H: 2.26(s,3H,$-SCH_3$); 3.68-3.90 (m, 8H, morpholine) and 7.00-7.36 (m, 9H, arom). M^+ 413.

3-(4-Chlorophenyl)-5-methylthio-2-phenyl-6-piperidino-4(3*H*)-pyrimidone (14o): Yield: 76%, m.p. 195°C. (Found: C,64.04; H,5.32; N, 10.30. $C_{22}H_{22}ClN_3OS$ requires C,64.16; H,5.35; N,10.21).ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.60-1.76(m,6H,- $CH_2-CH_2-CH_2$-); 2.32(s, 3H, $-SCH_3$); 3.70-3.86(m, 4H, $-CH_2-N-CH_2-$) and 7.00-7.36(m, 9H, arom). M^+ 411.

3-(4-Chlorophenyl)-5-methylthio-2-phenyl-6-pyrrolidino-4(3*H*)-pyrimidone (14p): Yield: 75%, m.p. 169-71°C. (Found: C,64.40; H,5.00; N, 11.50. $C_{21}H_{20}ClN_3OS$ requires C,63.40;H,5.03; N, 11.57). ν_{max}: 1660 cm^{-1} (C=O). δ_H: 1.83-2.00(m, 4H,$-CH_2-CH_2-$); 2.30(s, 3H, $-SCH_3$); 3.80-4.00(m, 4H, $-CH_2-N-CH_2$)-) and 7.00-

7.33(m, 9H, arom). M^+ 397.

5-Bromo-2,3-diphenyl-6-piperidino-4(3*H*)-pyrimidone (26a): 83% m.p.148-50°C. (Found: C,61.01; H, 4.85; N, 10.20. $C_{21}H_{20}BrN_3O$ requires C, 61.47;H,4.91;N,10.24). ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.60-1.76 (m, 6H, $-CH_2-CH_2-CH_2-$); 3.60-3.83(m, 4H, $-CH_2-N-CH_2-$) and 7.13-7.43(m, 10H, arom). M^+ 410.

5-Bromo-2,3-diphenyl-6-pyrrolidino-4(3*H*)-pyrimidone (26b): 70%, m.p. 160-62°C. (Found: C,60.37; H,4.53; N,10.60. $C_{20}H_{18}BrN_3O$ requires C,60.62; H, 4.58; N,10.60). ν_{max}: 1660 cm^{-1} (C=O). δ_H: 1.90-2.06(m, 4H, $-CH_2-CH_2-$); 3.90-4.06(m, 4H, $-CH_2-N-CH_2-$) and 7.23-7.46(m, 10H, arom). M^+ 396.

5-Bromo-2,3-diphenyl-6-morpholino-4(3*H*)-pyrimidone (26c): 76%, m.p. 199-201°C. (Found: C,58.00; H,4.32; N,10.10.$C_{20}H_{18}BrN_3O_2$ requires C,58.26; H,4.40; N,10.19). ν_{max}: 1680 cm^{-1} (C=O). δ_H: 3.90(s, 8H, morpholine) and 7.26-750(m, 10H, arom). M^+ 412.

2,3-Diphenyl-5-iodo-6-piperidino-4(3*H*)-pyrimidone (27a): 66%, m.p. 157-59°C. (Found: C,55.10; H,4.38; N,9.10.$C_{21}H_{20}IN_3O$ requires C,55.16; H,4.41; N,9.19). ν_{max}: 1680 cm^{-1} (C=O) δ_H: 1.63-1.83(bs, 6H, $-CH_2-CH_2-CH_2-$); 3.70-3.90(bs, 4H, $-CH_2-N-CH_2-$) and 7.16-7.40(m, 16H, arom). M^+ 457.

3-(4-Chlorophenyl)-6-dimethylamino-2-phenyl-4(3H)-pyrimidone (29) 76% (Iodoketene), 38% (Bromoketene), m.p. 168-69°C. (Found: C,66.20; H,4.92; N,12.86. $C_{18}H_{16}ClN_3O$ requires C66.36; H,4.95;

N,12.90). ν_{max}: 1670cm^{-1}(C=O). δ_H: 3.10(s, 6H, -N(CH_3)$_2$); 5.40(s, 1H, olefinic); 7.03-7.16(m, 2H, arom) and 7.26-7.40(m, 7H, arom). M^+ 325.

6-Dimethylamino-2-methylthio-3-phenyl-4(3*H*)-pyrimidone (30): 72% (Iodoketene), 42% (Bromoketene), m.p. 119-20°C. (Found: c,59.63; H,5.75; N, 16.00. $C_{13}H_{15}N_3OS$ requires C,59.75; H,5.78; N,16.08). ν_{max}: 1645 cm^{-1} (C=O). δ_H: 2.43(s, 3H, -SCH_3); 3.13(s, 6H, -N(CH_3)$_2$); 5.26(s, 1H, olefinic); 7.26-7.43(m, 2H, arom) and 7.53-7.63(m, 3H, arom). M^+ 261.

5-Bromo-3-(4-Chlorophenyl)-2-phenyl-4(3*H*)-pyrimidone (32): 32%, m.p. 209-10°C. (Found: C,52.92; H,2.76; N,7.82.$C_{16}H_{10}BrClN_2O$ requires C,53.14; H,2.79; N,7.75).ν_{max}: 1690 cm^{-1} (C=O). δ_H: 7.27-7.40(m, 4H, arom); 7.47-7.60(m, 5H, arom) and 8.18(s, 1H, olefinic). M^+ 361.

5-Bromo-2-methylthio-3-phenyl-4(3H)-pyrimidone (33): 36%, m.p. 178-9°C. (Found: C,43.43; H,3.00; 7.30-7.43(m, 2H, arom);Found: C, 43.43; 4,3.00; N, 9.41. $C_{11}H_9BrN_{20}$ requires C, 44.46; 4,3.05; N,9.43) ν_{max}: 1700 cm^{-1} (C=O) δ_H: 2.43 (S,34,-SCH_3); 7.30-7.43 (m, 24, arom);7.73(m, 3H, arom) and 8.26(s, 1H, olefinic). M^+ 297.

2,3-Diphenyl-5-methyl-6-piperidino-4(3*h*)-pyrimidone(36c): 74%, m.p. 184-8°C. δ_H: 1.60-1.76(m, 4H,- CH_2-N-CH_2-); 2.06(s, 3H, -CH_3); 3.36-3.56(m, 4H, -CH_2-N-CH_2-) and 7.10-7.40(m, 10H, arom). M^+ 347.

2,3-Diphenyl-5-methyl-6-pyrrolidino-4(3*H*)-pyrimidone(36d): 84%, m.p. 234-6°C. (Found: C,75.86; H,6.35;N,12.60. $C_{21}H_{21}N_3O$ requires C, 76.11; H,6.39;N,12.68). ν_{max}: 1660 cm^{-1} (C=O). δ_H: 1.76-2.00(m, 4H, $-CH_2-CH_2-$); 2.23(s, 3H $-CH_3$); 3.66-3.93 (m, 4H, $-CH_2-N-CH_2-$) and 7.13-7.40(m, 10H, arom). M^+ 331.

2,3-Diphenyl-5-methyl-6-morpholino-4(3*H*)-pyrimidone(36e): 83%, m.p. 207-8°C. (Found: C,72.72; H,6.02; N,12.14. $C_{21}H_{21}N_3O_2$ requires C,72.60;H,6.0;N,12.10). ν_{max}: 1675 cm^{-1} (C=O). δ_H: 2.13(s, 3H, $-CH_3$); 3.43-3.60(m, 4H, $-CH_2-N-CH_2-$); 3.76-3.93(m, 4H,$-CH_2-O-CH_2-$) and 7.13-7.40(m, 10H, arom). M^+ 347.

5-Chloro-2,3-diphenyl-6-piperidino-4(3*H*)-pyrimidone (37c): 81%, m.p. 200-201°C. (Found: C,68.52; H,5.40;N,11.60.$C_{21}H_{20}ClN_3O$ requires C,68.95;H,5.47;N,11.49). ν_{max}: 1670 cm^{-1} (C=O). δ_H:1.60-176 (m,6H,$-CH_2-CH_2-CH_2-$); 3.65-3.82(m, 4H, $-CH_2N-CH_2-$) and 6.98-7.35 (m, 10H, arom). M^+ 365.

5-Chloro-2,3-diphenyl-6-pyrrolidino4(3*H*)-pyrimidone (37d): 76%, m.p. 210-12°C. (Found: C,69.03; H,5.16; N,12.10.$C_{20}H_{18}ClN_3O$ requires C,68.28; H,5.12; N,11.95). ν_{max}: 1670 cm^{-1} (C=O). δ_H: 1.83-2.03(m, 4H, $-CH_2-CH_2-$); 3.80-4.00(m, 4H, $-CH_2-CH_2-$) and 6.93-7.42(m, 10H, arom). M^+ 351.

5-Chloro-2,3-diphenyl-6-morpholino-4(3*H*)-pyrimidone (37e): 83%, m.p. 222-3°C. (Found: C,66.02;H,4.88;N,11.40.$C_{20}H_{18}ClN_3O_2$ requires C,65.31;H,4.90;N,11.43).ν_{max}: 1680 cm^{-1} (C=O). δ_H: 3.66-3.94(m,8H, morpholine) and 7.15-7.50(m, 10H, arom). M^+ 367.

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CHAPTER-IV

The Reactions of 1,3-Diaza-1,3-Butadienes with Diphenyl and Dimethyl Ketenes

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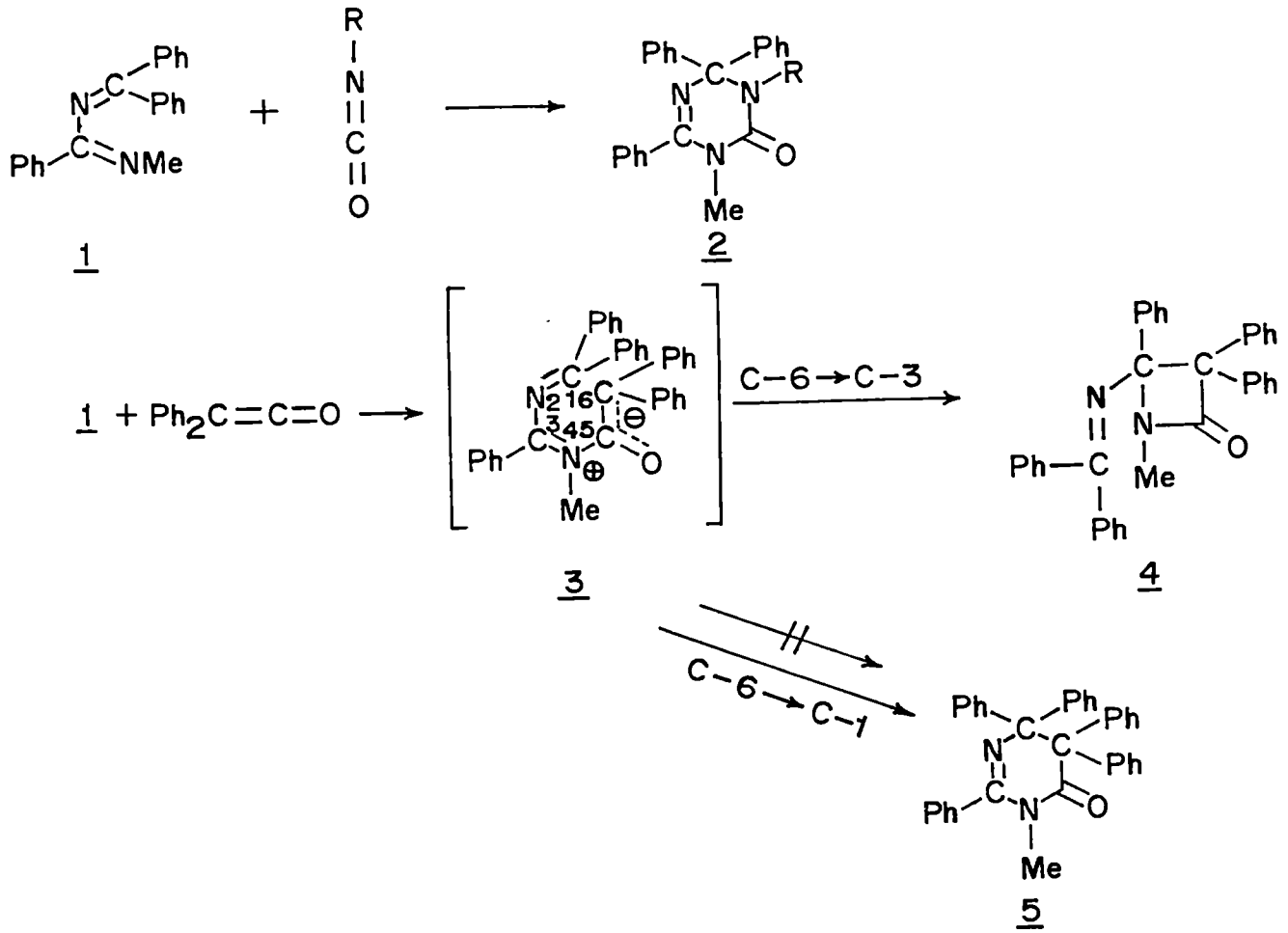
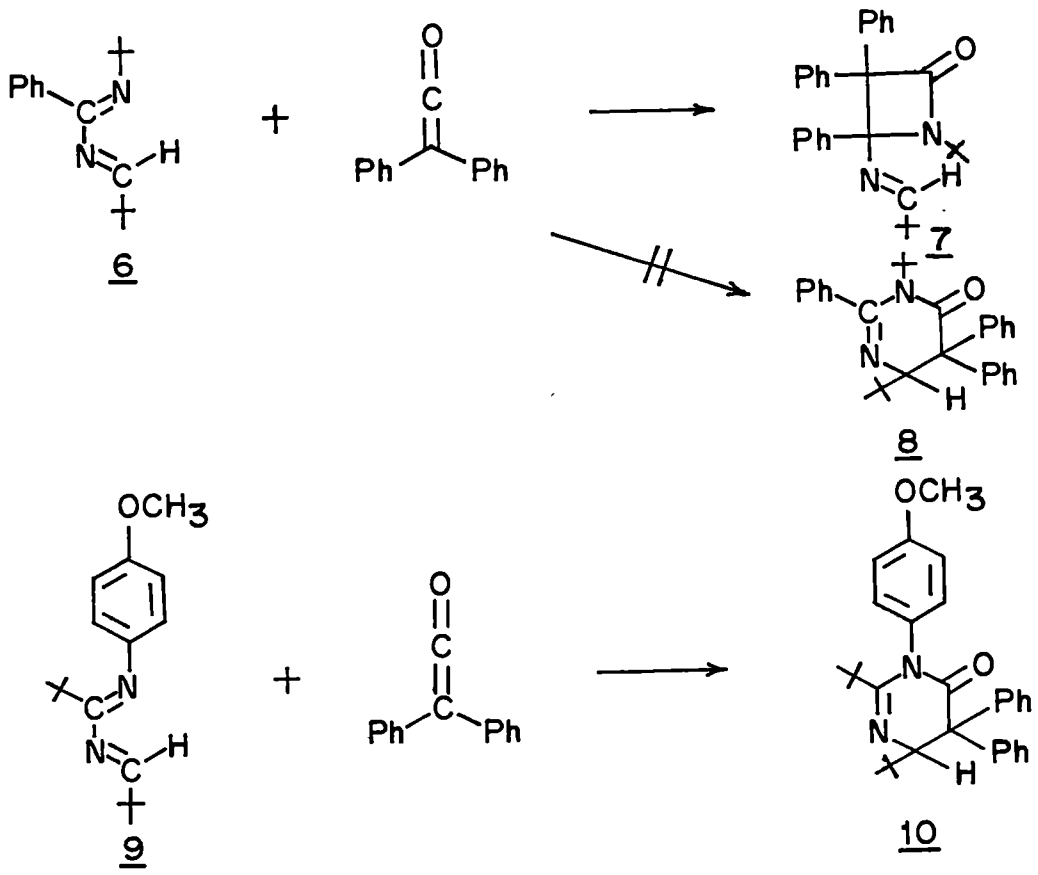
Cycloadditions of 1,3-diazabutadienes with heterocumulenes were initiated by Matsuda, Yamamoto and Ishii.[1] As the first example of a [4+2] cycloaddition reaction they found the formation of dihydrotriazinones (2) as products from an isolated 1,3-diazabutadiene (1) derivative and isocyanates. However, the reaction of 1,3-diazabutadienes derivative (1) with 1 equiv. of diphenylketene proceeded smoothly at room temperature to give quantitatively azetidinone , as [2+2] cycloadduct (Scheme-1).


Ph
Ph
N
C
Ph
Ph
C
NMe
1
+
R
N
C
O
Ph
Ph
C
R
N
N
Ph
C
N
O
Me
2
1 + Ph2C=C=O
Ph
Ph
Ph
N2
1
6
C
Ph
3
4
5
C
Ph
C
N
O
Me
3
C-6→C-3
Ph
Ph
C
C
Ph
N
N
Ph
C
Me
O
Ph
4
C-6→C-1
Ph
Ph
Ph
C
C
Ph
N
Ph
C
N
O
Me
5

Scheme-1

The formation of [2+2] adduct from zwitterionic intermediate 3 and the absence of [4+2] cycloadduct (5) was explained by steric factors. The nucleophilic attack of C-6 at C-3 to yield azetidinone (4) with three vicinal phenyl substituents was preferred, since the attack of C-6 at C-1 to form (5) would be inhibited by the four vicinal phenyl substituents.

Subsequently, Wurthwein et.al[2] reported that the reaction of 1,3-diazabutadiene (6), having bulky tert-butyl functions at 1- and 4-positions, with diphenylketene followed [2+2] cycloaddition pathway yielding azetidinone (7). This was explained on the basis of steric reasons since it was felt that [2+2] cycloaddition mode leading to azetidinone (7) having three vicinal phenyl groups suffers much less steric hindrance compared to the alternative [4+2] cycloaddition mode leading to pyrimidone (8) with one bulky tert-butyl and two phenyl groups in vicinal positions (Scheme-2). It was further reported that the reaction of sterically strained tert.butyl substituted 1,3-.diaza-1,3-butadiene (9) with diphenylketene followed [4+2] cycloaddition pathway leading to pyrimidone (10). The formation of pyrimidone (10) in this case was also explained on the basis of steric factors, since the alternative [2+2] cycloaddition of (9) would give rise to azetidinone with one tert.butyl and two phenyl groups in vicinal positions, suffering from severe steric hindrance. Thus they confirmed the explanation of Matsuda et.al. that steric reasons are decisive for the mode of cycloaddition.



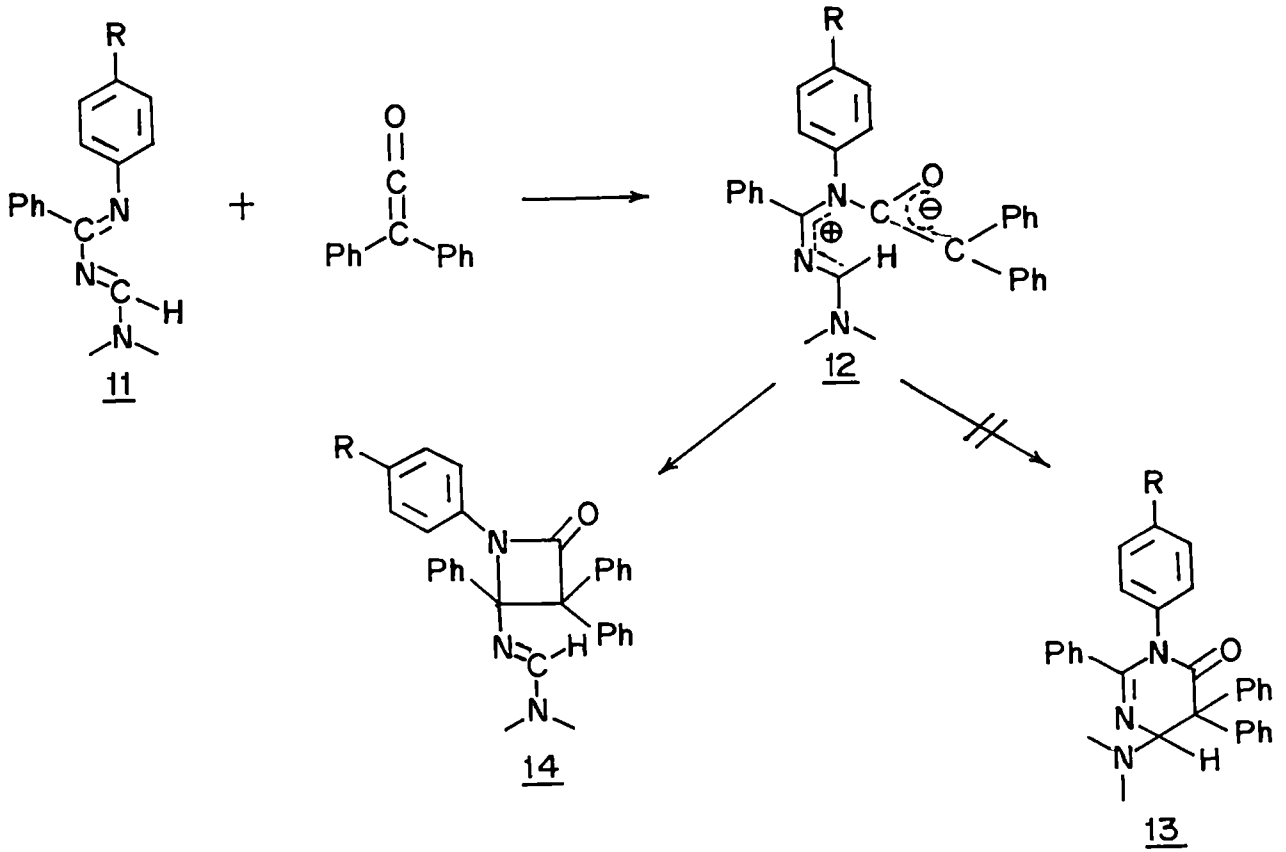
Scheme-2

Wurthwein et.al[2,3] supplemented their experimental results by abinitio 3-21G model calculations for the parent compounds,[4,5] and the best conformer of 1,3-diazabutadienes was found to be the s-trans form with z-configuration at the C=NH Unit (ECRHF) = -185.85376 au, E rel = 0.00 Kcal/mol; a gauche minimum ($_{C=N-C=N=60}$) is 2.75 Kcal/mol higher in energy. For the isomers with E- C+NH-Unit a gauche a gauche conformer ($_{C=N-C=N}=30°$) was predicted to be the global minimum (E rel = 1.31 Kcal/mol); the s-trans form corresponds to a local minimum, 3.48KCal/mol higher energy (E rel = 4.79 Kcal/mol). Both S-cis-conformers are maxima (transition states of the C-N-rotation). Since the barriers for the rotation around C-N-;bond for both series are small (4-6 Kcal/mol); sterically and electronically favourable [2+2] and [4+2] cycloaddition reactions may be expected.

Wurthwein et.al[2] further reported that the formation of azetidinone is a kinetically governed process, since this β-lactam derivative was found to be *ca.* 32 Kcal/mol higher in energy than the corresponding 4,5-dihydro-6-pyrimidinone systems. From such a data and from the total energy of ketene heats of reaction for the formation of four-membered ring of *ca.* -34 Kcal/mol and for the six-membered ring of -66 Kcal/mol were predicted, both reactions being fairly exothermic processes. Further, because of the substantial differences in electronegativity of the reacting atoms a non-synchronous concerted or even stepwise mechanism for such cycloaddition

reactions[6] was proposed. The [2+2] cycloaddition of 1,3-diaza-butadiene along the 3,4-N=C-double bond with ketenes would lead to a regioisomeric N-substituted β-lactam, which according to AM1[7] is *ca.* 6Kcal/mol higher in energy than the observed β-lactam. Similarly, other possible four and six-membered isomers within $C_4H_6N_2O$ group of substances were calculated to be more energy rich using the AM1 method.

In our laboratories it was observed that reactions of 1-aryl-4-dimethylamino-2-phenyl-1,3-diaza-1,3-butadienes-(11) with diphenylketene yielded good yields of products, which initially were thought to be [4+2] cycloadducts the pyrimidinones (13), and later identified as azetidinones (14) arising presumably *via* Zwitterionic intermediates (12)[8] (Scheme-3). The formation of azetidinone (14) in this reaction was further confirmed by Wurthwein et.al. with the help of additional 13_C spectral data. The preferred formation of [2+2] cycloadduct in this case was explained by Wurthwein et.al[2] on the basis of steric reasons, since it was felt that the formation of pyrimidinone (13) with one dimethylamino and two phenyl groups in vicinal positions suffers from much more steric hindrance as compared to azetidinone (14) having three vicinal phenyl groups. Obviously the three vicinal phenyl groups in (14) are not prohibitive for such a [2+2] cycloaddition whereas one dimethylamino and two phenyl groups in vicinal positions are prohibitive for [4+2] cycloaddition thus Wurthwein et.al[2] confirmed the explanation proposed by Matsuda et.al., that steric



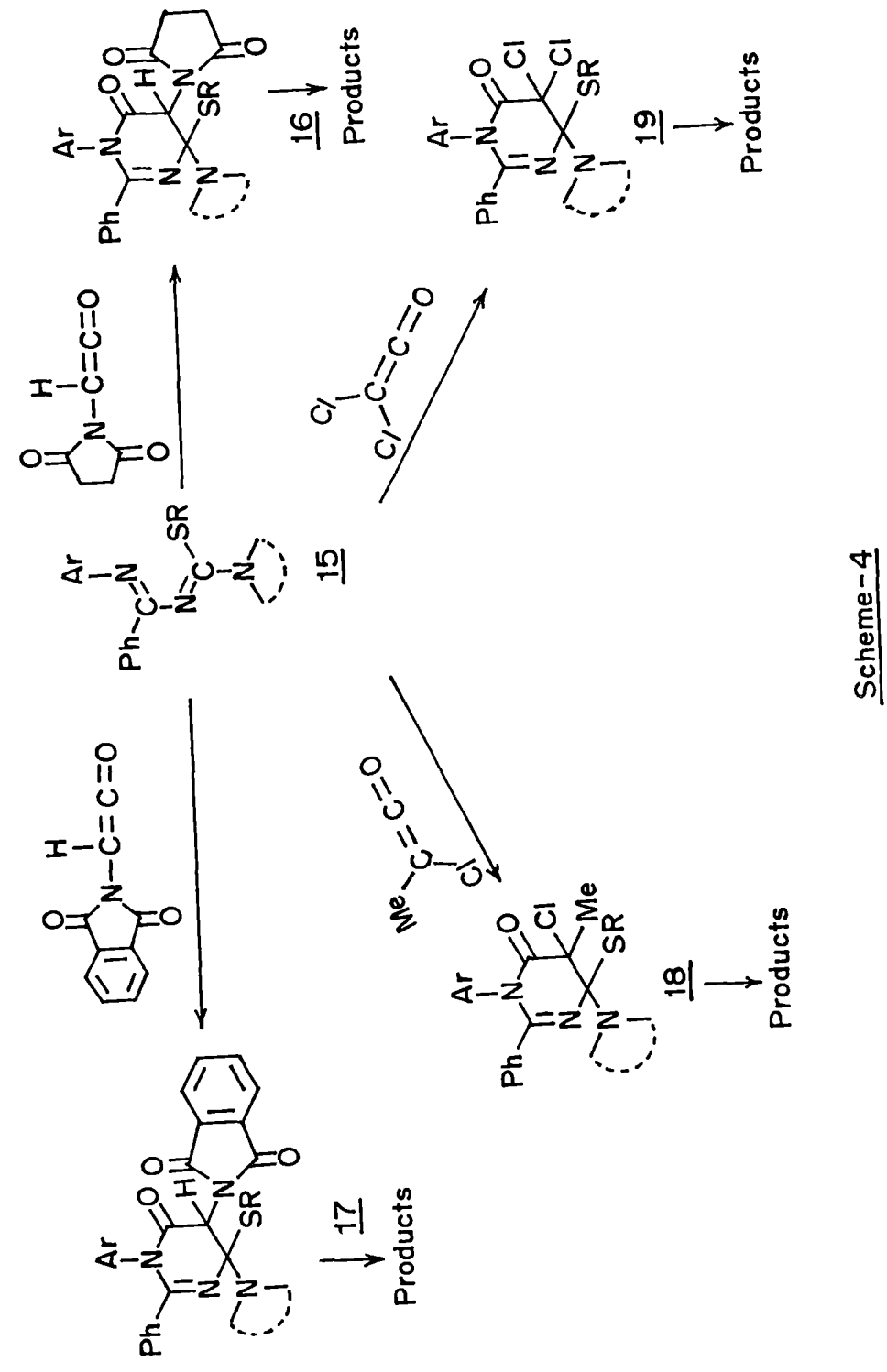
Scheme - 3

factors are decisive for the mode of cycloaddition.

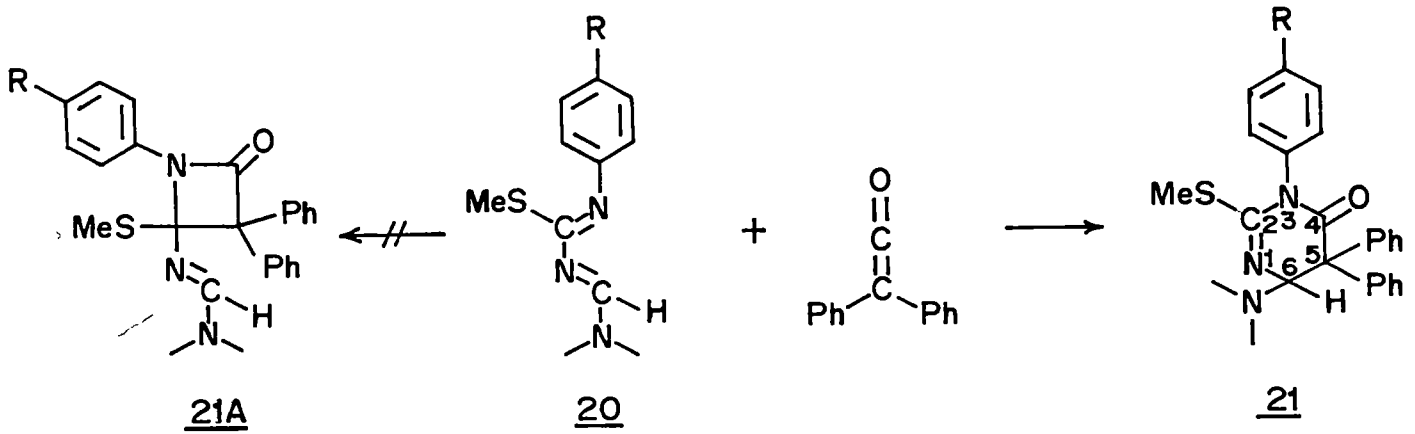
We felt that explaining the cycloaddition mode purely by steric reasons is perhaps oversimplification of the problem since the observed formation of [4+2] cycloadduct in case of 1,3-diazabutadienes/ketenes reactions reported in earlier chapters perhaps cannot easily be explained in this manner. For example, the reactions of 1,3-diazabutadiene (15) with bulkier succinimidoyl-phathalimidoylketenes and dichloro-/chloromethyl ketenes were shown to follow [4+2] cycloaddition mode even though the intermediate [4+2] cycloadducts (16-19) clearly suffer from severe steric hindrance as compared to the steric hindrance of alternative azetidinones (Scheme-4). Further, the reactions of 1,3-diazabutadienes (20) with diphenylketene were shown to follow [4+2] cycloaddition mode leading to pyrimidinones (21), even though it may be expected that one dimethylamino and two phenyl groups in vicinal positions may offer more steric hindrance than vicinal one methylthio and two phenyl groups in case of alternative azetidinone (22) (Scheme-5).

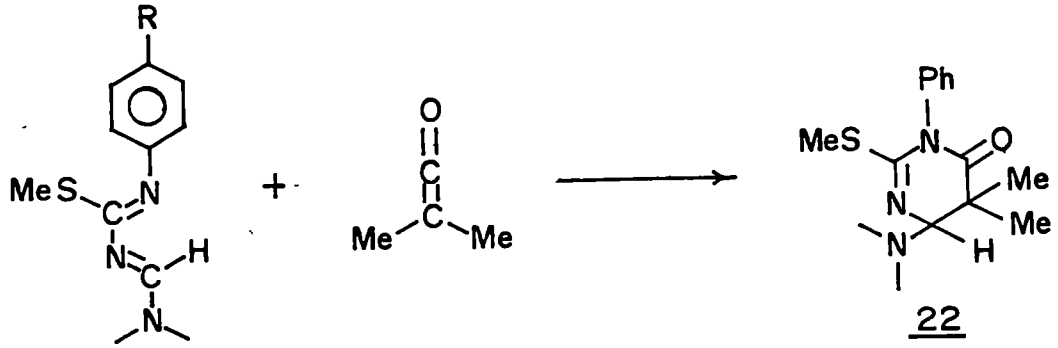
Thus, in order to understand further the factors influencing the mode i.e. [4+2] versus [2+2] cycloaddition and to firmly establish the mechanism of cycloadditions it was thought worthwhile to further investigate the reaction of various 1,3-diazabutadienes with diphenylketene.

To begin with the reaction of 4-dimethylamino-1-*p*-tolyl-2-thiomethyl-1,3-diaza-1,3-butadiene (20 : R = CH_3) with



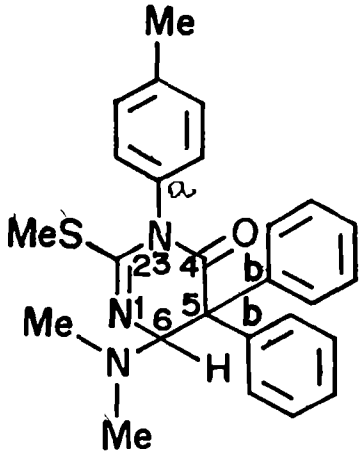
Scheme-4


R
MeS
Ph
Ph
N
O
H
Ph
Ph
21A
20
21
R = H, CH3, Cl, OCH3


R
MeS
H
Me
Me
Ph
Me
Me
H
20 : R = H
22

Scheme-5

diphenylketene, generated *in situ*, was reinvestigated and the product isolated was identified as 6-dimethylamino-5-diphenyl-2-thiomethyl-3-*p*-tolyl-3,4,5,6-tetrahydro-pyrimidin-4-one (21; R = CH_3) on the basis of TR and ^1H NMR spectral, which was identical and superimposable with the earlier obtained sample. Its IR spectrum (KBr) showed a strong peak around 1700 cm^{-1} due to carbonyl absorption which is comparable with the literature value for such systems.[2] Its ^1H NMR spectrum (300 MHz, $CDCl_3$) exhibited singlets at δ2.30(3*H*), δ2.37(6*H*) and δ5.20(1*H*) and were assigned to -SMe,-$N(CH_3)_2$ protons and methine protons, respectively. The aromatic protons appeared as a multiplet at δ7.19-7.50 (14*H*). Further confirmation for its structure was derived from its ^{13}C NMR signals which showed peaks at δ58.3 (C-5), 81.5 (C-6), 153.8 (C-2) and 170.4 (C-4), the values which are comparable with the literature values for such a system.[2] Other peaks in this spectrum appeared at δ15.2 (SMe), 21.3(Me), 41.5(-$N(CH_3)_2$), 126.1, 127.2, 127.7, 128.3, 128.7, 129.0, 129.5, 129.7, (aromatic), 133.4 (C-a), 139.5 (C-b) and 141.3(C-b).



 21

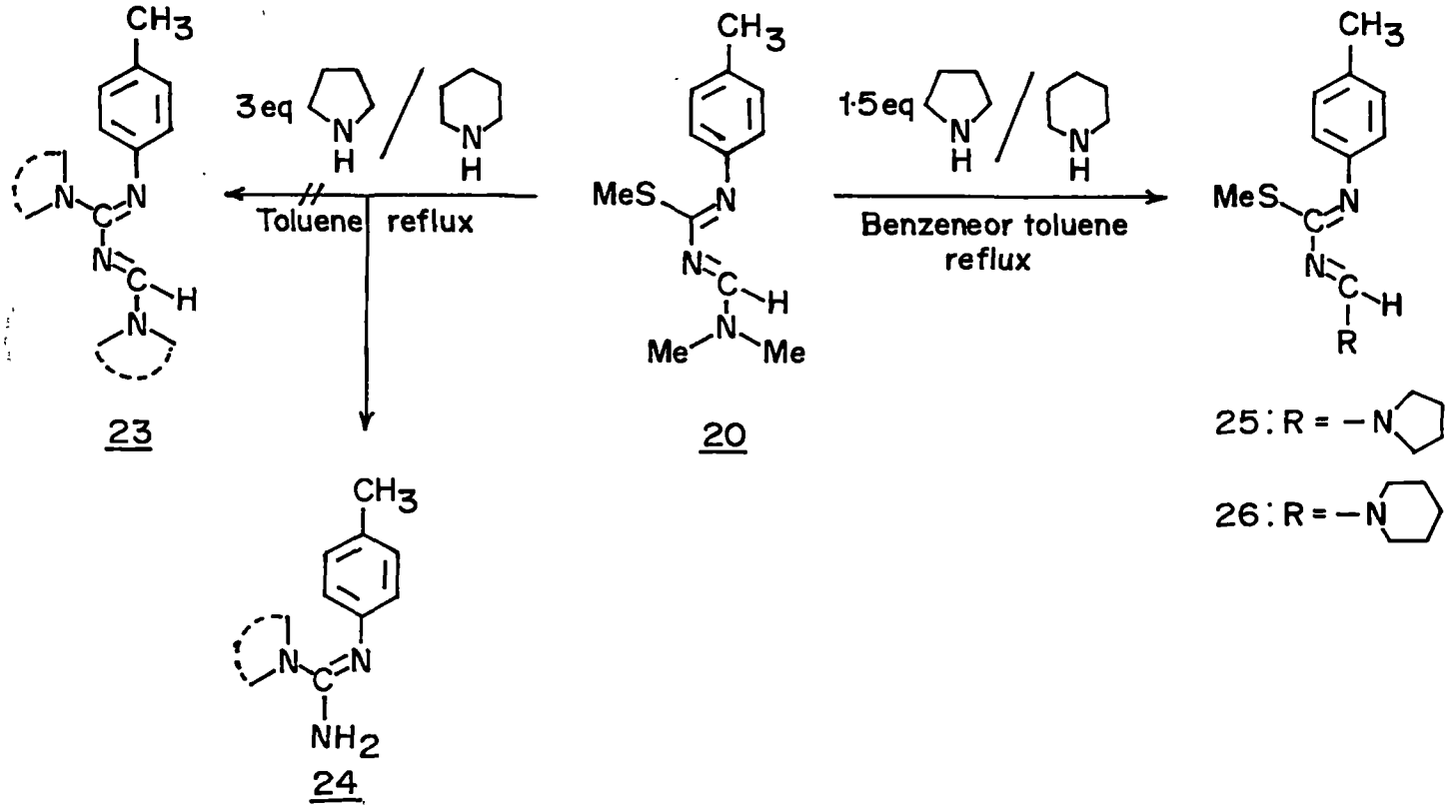
Keeping in view the lesser steric requirements of methyl group as compared to phenyl, we have investigated the reaction of 4-dimethylamino-1-phenyl-2-thiomethyl-1,3-diaza-1,3-butadiene (20; R=H) with dimethylketene in order to understand the nature of cycloaddition pathway followed in this case. Thus the treatment of 20 (R=H) with dimethylketene, generated *in situ* from isobutrylchloride and triethylamine, resulted in a product formed *via* [4+2] cycloaddition and characterised as 5,5-dimethyl-6-dimethylamino-3-phenyl-2-thio-methyl-3,4,5,6-tetrahydro-pyrimidin-4-one (22) (Scheme-5). Its IR spectrum (KBr) showed strong absorption at 1700 cm^{-1} due to carbonyl and its ^{1}H NMR spectrum (300 MHz, $CDCl_3$) exhibited signals at δ1.28 and 1.37 (s, 6H, $N(Me)_2$), δ2.29(s,3H, SMe), δ2.37 (s,6H, $N(Me)_2$), δ4.27(s,1H, 6H), δ7.15 (m,2H, arom) and δ7.42 (m, 3H, arom) Its ^{13}C NMR exhibited characteristic peaks for the proposed structure at δ14.9 (s Me), 19.3 and 26.5 (5-gem-dimethyl), 40.84 & 40.89 ($-N(Me)_2$ and C-5), 83.3 (C-6), 153.1 (C-2) and 175.1 (C=O) in addition to aromatic carbons at 129.0, 129.2 and 136.1.

In continuation of our investigations it was thought worthwhile to examine the mode of cycloadditions of diphenylketene with 1,3-diazabutadienes having similar/different polarising functions at 2- and 4- positions. For this purpose attempts were made to prepare 2,4-bis-pyrrolidino/piperidino by refluxing a mixture of 20 and pyrrolidine/piperidine (3 eq) which resulted only in guanidine 24. However, the reaction of 20 with

1.5 eg of pyrrolidine/piperidine in refluxing benzene/toluene resulted in the selective attack of nucleophile at position 4- and selective removal of dimethyl amine, a poorer leaving group as compared to methylmercaptain, yielding 4-pyrrolidino- and 4-piperdino suibstituted 1,3-diazabutadienes 25 & 26, respectively (Scheme-6).

In order to generalise the earlier observed [4+2] cycloaddition mode for similar 1,3-diazabutadienes (20: R=H, Me) we have carried out the reactions of 4-pyrrolidino-2-thiomethyl-1-p-toyl-1,3-diaza-1,3-butadiene (25) and 4-piperidino-2-thiomethyl-1-p-tolyl-1,3-diaza-1,3-butadiene (26) with diphenylketene.

These reactions were also found to [4+2] cycloaddition mode resulting in good yields of previously unknown 5,5-diphenyl-6-pyrrolidino-2-thiomethyl-3-p-tolyl-3,4,5,6-tetrahydro-pyrimidin-4-one (27) and 5,5-diphenyl-6piperidino-2-thiomethyl-3-*p*-tolyl-3,4,5,6-tetrahydro-pyrimidin-4-one (28), respectively. These structures were assigned on the basis of analytical data and spectral evidences. Their IR spectra (KBr) showed strong peaks at *ca.* 1695 cm^{-1} and 1620 cm^{-1} due to carbonyl and C=N absorption respectively. ^1H NMR spectrum (300 MHz, $CDCl_3$) of 27 exhibited signals at δ1.59 (s, 4H, $-CH_2-CH_2-$), δ 2.24 (S, 3H, CH_3), δ2.36 (S, 3H, SMe), δ2.48 (bm, 2H, $-NCH_2-$), δ2.95 (bm, 2H,$-NCH_2-$), δ5.34 (S, 1H, H-6), and the aromatic protons appeared as multiplet at 7.16-7.29 (14b). The nonequivalence of $-CH_2-N-CH_2-$ protons in case of 27 and 28 may be due to the hinderred rotation

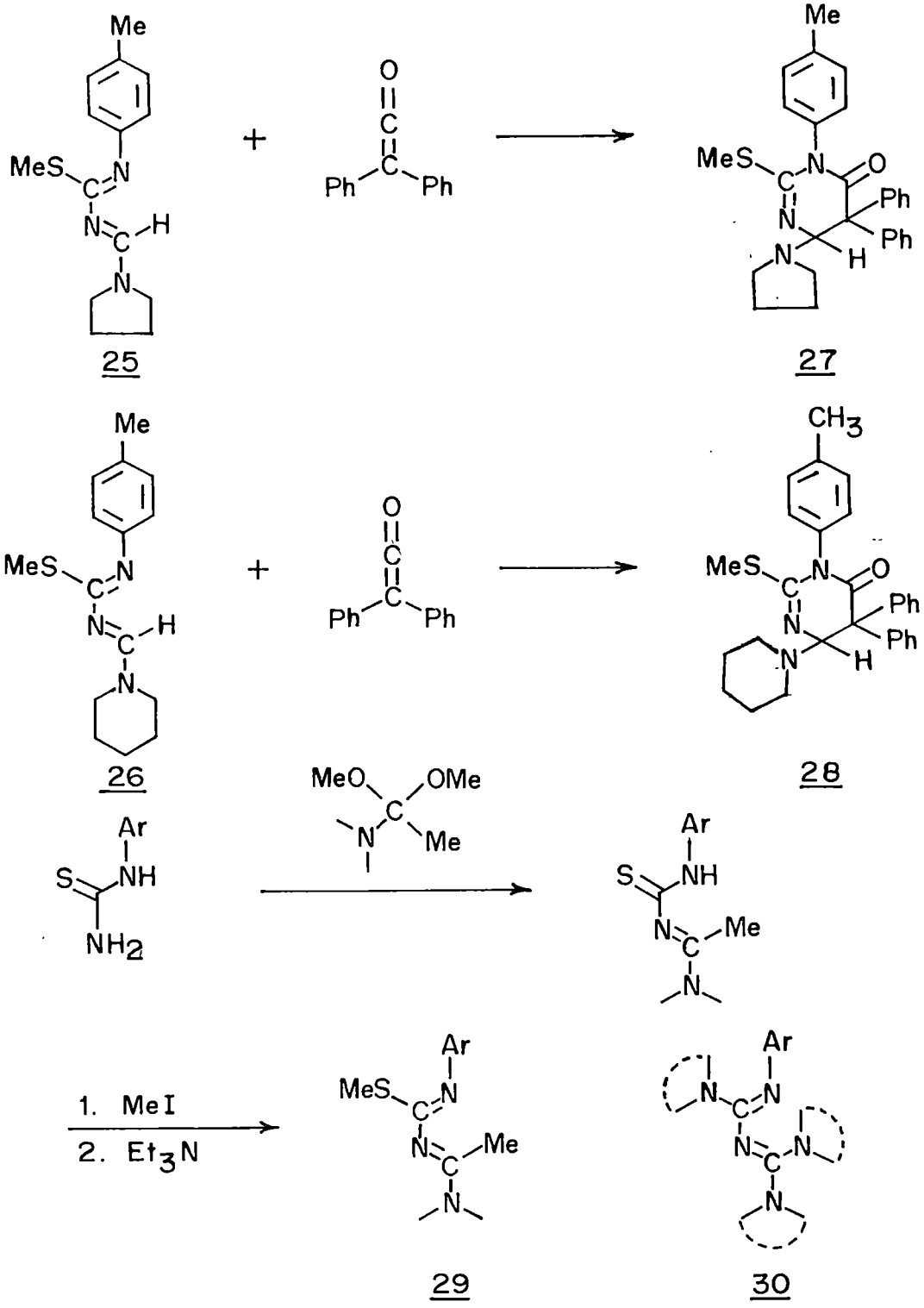

CH3
3eq
N
H
Toluene
reflux
MeS
Me
Me
1·5eq
Benzeneor toluene
reflux
R
NH2
23
20
24
25: R = –N
26: R = –N

Scheme–6

of pyrrolidine/piperidine moiety because of the bulkier phenyl groups at adjacent carbon. ^{13}C NMR spectra of **27** and **28**, in addition to other carbons showed characteristic signals due to C-2, C-4, C-5 and C-6.

The observance of [4+2] cycloaddition mode in reactions of 1,3-diazabutadienes (**20**, **25** & **26**) with dimethyl- and diphenylketene clearly indicates that steric factors alone perhaps do not determine the cycloaddition mode in such cases. Since, on steric grounds the formation of alternative azetidinone should perhaps be preferred over observed pyrimidinone. Thus it may be proposed that in addition to steric factors the electronic factors also play an important role in determining the mode of such cycloadditions. Further it may be said that [4+2] cycloadducts may always be formed exclusively in reactions of diphenylketene with 1,3-diazabutadienes having conjugatively donating functions at 2-position. In view of this it was thought worthwhile to carry out the reactions of 1,3-diazabutadiene **29**, having additional function at position 4- and prepared as shown in Scheme-7, with dimethyl- and diphenylketenes. Despite a number of attempts no isolable product could be isolated in these cases, however, the attempts are still being made to synthesise diazabutadienes of type **30** and to examine their mode of cycloadditions with these ketenes.

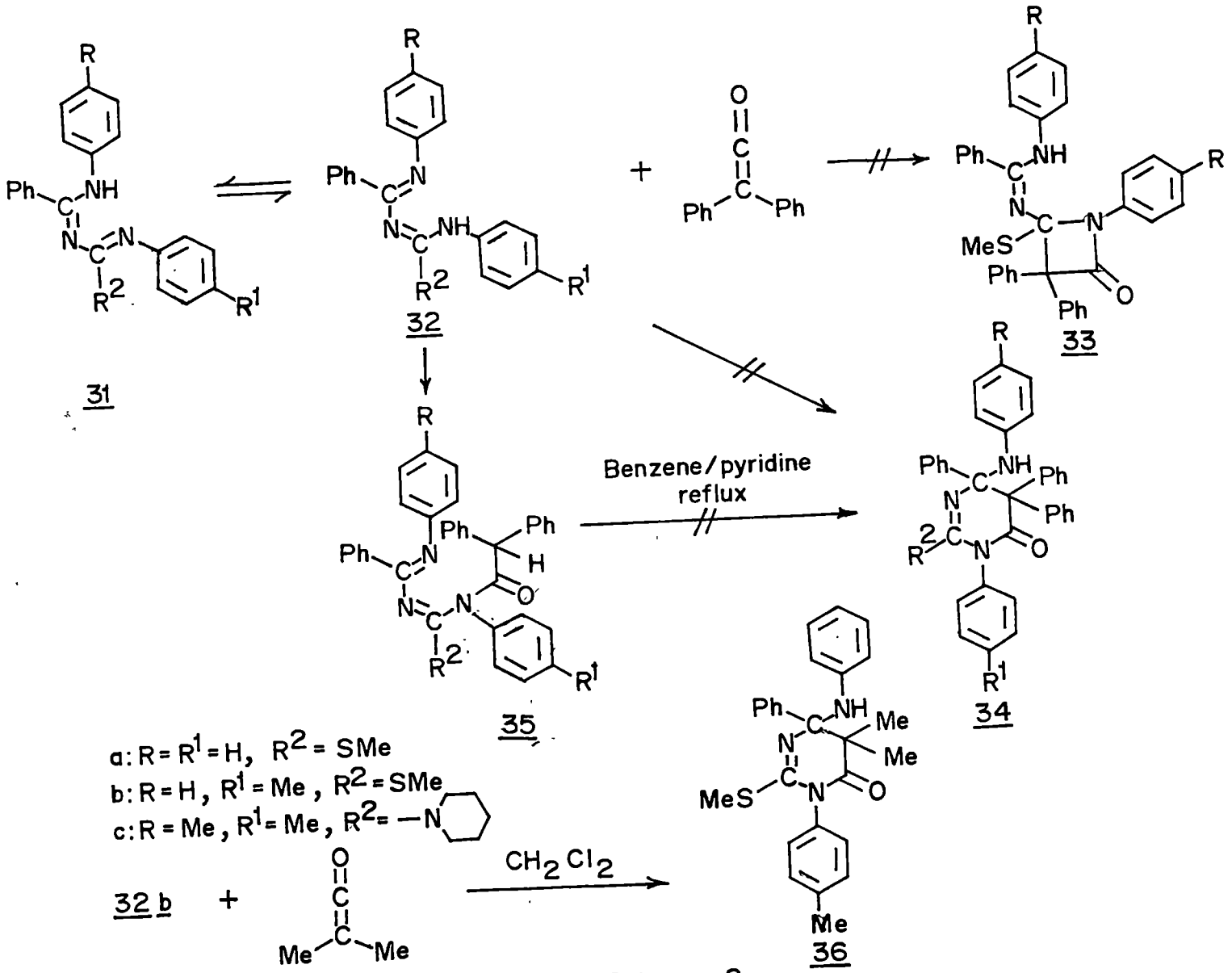
In continuation of our investigations concerning the mechanistic aspects involved in the reactions of disubstituted


Me
MeS
N
C
N
H
N
25
+
O
C
C
Ph
Ph
Me
MeS
N
O
C
N
Ph
Ph
N
H
27
Me
MeS
N
C
N
H
N
26
+
O
C
C
Ph
Ph
CH3
MeS
N
O
C
N
Ph
Ph
N
H
28
MeO
OMe
C
N
Me
Ar
S
NH
NH2
Ar
S
NH
N
C
Me
N
1. MeI
2. Et3N
Ar
MeS
N
C
N
C
Me
N
29
Ar
N
C
N
N
C
N
N
30

Scheme-7

ketenes with 1,3-diazabutadienes and to further substantiate the inference drawn above, we have investigated the reactions of various N-arylamino-1,3-diazabutadienes (32). In case of N-arylamino-1,3-diazabutadienes, which can exist in tautomeric form 31 and 32, the terminal nitrogen (-NH-aryl) of the form 32 has been shown to be more nucleophilic and has been shown to attach preferentially at ketene carbonyl.[9] Interestingly, the reactions of 1,3-diazabutadienes with diphenylketene did not yield any of the expected products i.e. azetidinones 33 and pyrimidinones 34, but resulted in the formation of substituted acyclic 1,3-diazabutadienes 35. The structure 35 was assigned to these prodeucts on the basis of analytical and spectral evidences. However, the reaction of 1,2-diphenyl-4-thiomethyl-4-(*N*-tolyl)-1,3-diaza-1,3-butadiene (32b) with dimethylketene generated *in situ* from dimethylacetyl chloride and triethylamine, was found to result in 5,5-dimethyl-2-thiomethyl-3-(p-tolyl)-6-phenyl-6-anilino-3,4,5,6-tetrahydropyrimidine-4-one (36) (Scheme-8(. The IR spectrum (KBr) of 36 showed characteristic carbonyl absorption at 1683 cm^{-1}. Its ^1H NMR spectrum ($CDCl_3$) showed the absence of methine proton and presence of C-5 gemdimethyl protons as singlets at δ2.35 and δ2.43 due to $Ar-CH_3$ and SCH_3 in addition to aromatic protons. It may be mentioned here that acyclic 1,3-diazabutadiene derivatives 35 failed to cyclise to pyrimidinone 34 even in refluxing benzene in presence of pyridine as a base.

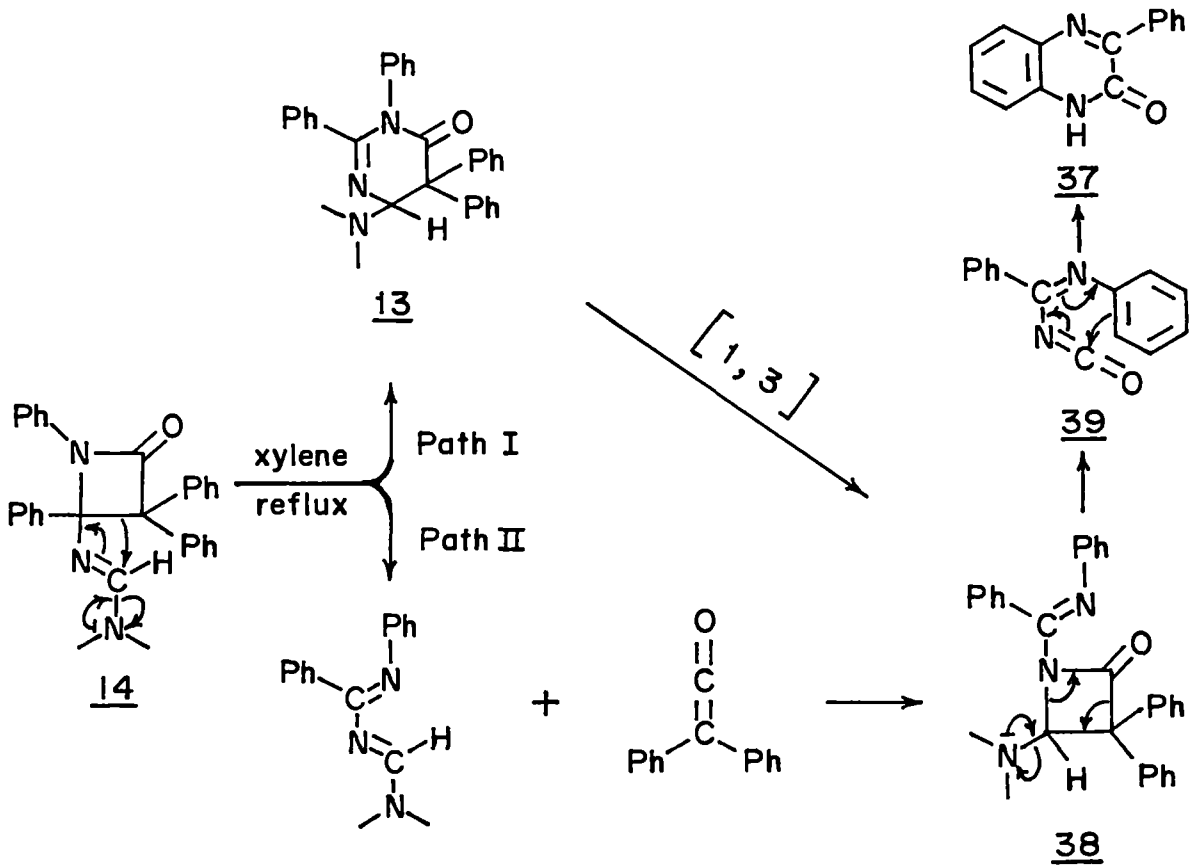
Also, it was reported[2] that the formation of β-lactam in such cycloadditions is a kinetically governed process and the


31
32
33
34
35
36
Benzene/pyridine
reflux
a: R = R1 = H, R2 = SMe
b: R = H, R1 = Me, R2 = SMe
c: R = Me, R1 = Me, R2 = —N
32 b
CH2 Cl2

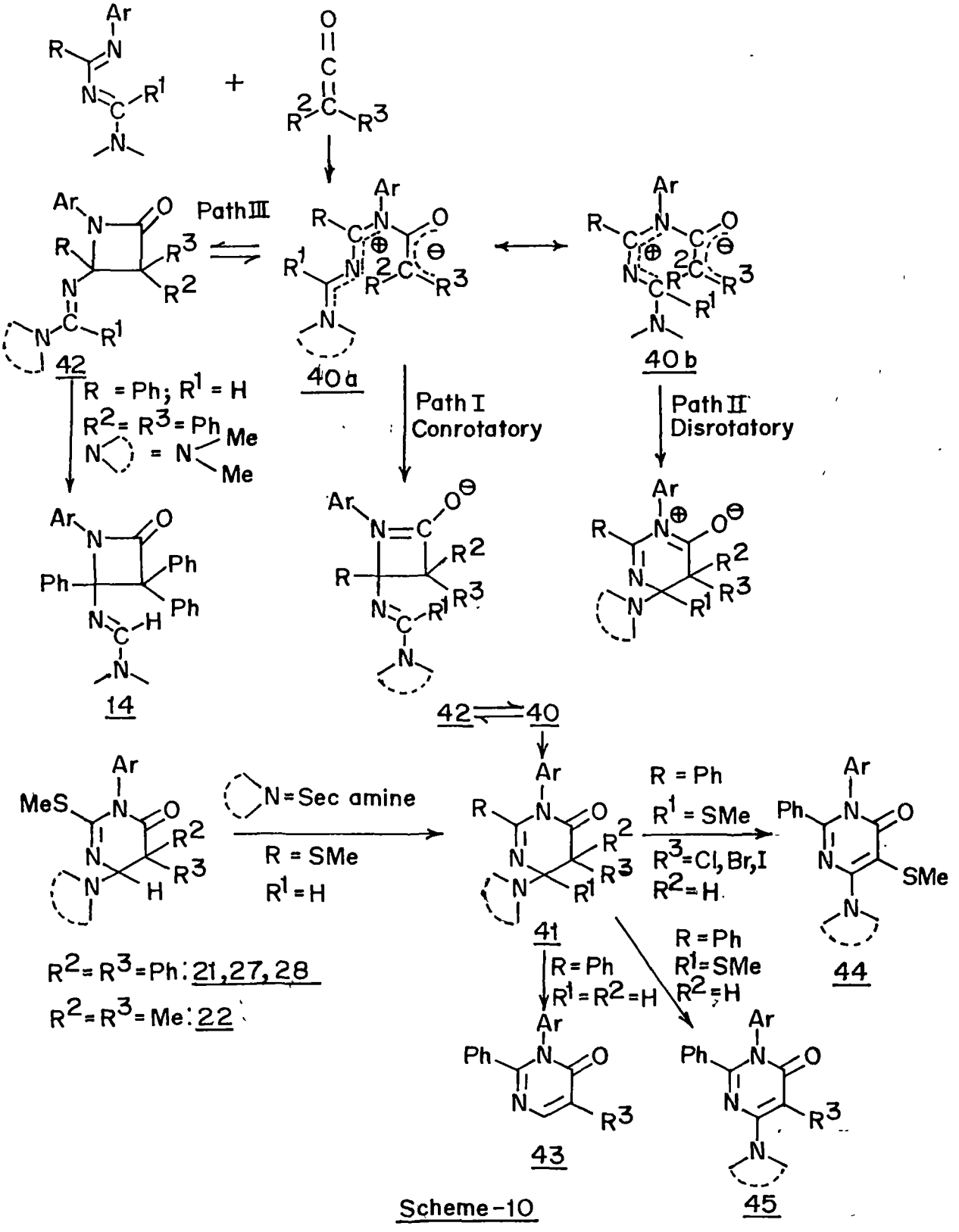
Scheme-8

β-lactam was predicted to be *ca.* 32KCal/mol higher in energy than the corresponding pyrimidinone system. Thus it was felt that the thermolysis of azetidinone (14), prepared as described in Scheme-3, may probably yield pyrimidinones (13). Interestingly, refluxing a xylene solution of azetidinone (14, R=H) for 2 hrs yielded a product which was characterised as 2-phenyl quinazolin-4-one (37). On the basis of analytical data, spectral evidences and its comparable m.pt (235-236°c) with the reported m.pt (236°C). Probable mechanistic pathways leading to the formation of 37 are outlined in Scheme-9. In this scheme it is assumed that β-lactam (14) may initially undergo rearrangement to pyrimidinone (13) (path I) which by [1,3] aryl shift may lead to another β-lactam (38) as intermediate. The intermediate 38 then by facile enamine elimination may yield iminoisocyanate intermediate 39, which then follows usual electrocyclic ring closure to yield 37. The more likely pathway II involves reversion of β-lactam 14 to 1,3-diazabutadiene and diphenylketene so generated then adds across 3,4-imino bond to yield β-lactam 38, as intermediate, which then follows the route mentioned above to yield 37.

[2+2] versus [4+2] cycloadditon Reactions of 1,3-diazabutadienes-with ketenes - Mechanistic considerations: The probable mechanistic pathways leading to the formation of [2+2] or [4+2] cycloadducts in case of reactions of 1,3-diazabutadienes with various ketenes are outlined in Scheme-10. In this scheme it is


Ph
Ph
N
O
Ph
N
Ph
N
H
13
[1, 3]
N
Ph
C
N
H
C
O
37
Ph
N
Ph
C
N
C
O
39
Ph
Ph
N
Ph
O
N
Ph
N
H
Ph
38
Ph
O
N
Ph
xylene
reflux
Path I
Path II
14
Ph
N
Ph
C
N
H
C
N
+
O
C
C
Ph
Ph

Scheme - 9


Path III
42
R = Ph; R¹ = H
R² = R³ = Ph
Me
N = N
Me
40a
40b
Path I
Conrotatory
Path II
Disrotatory
14
42 ⇌ 40
MeS
N=Sec amine
R = SMe
R¹ = H
R = Ph
R¹ = SMe
R³ = Cl, Br, I
R² = H
41
44
R = Ph
R¹ = R² = H
R = Ph
R¹ = SMe
R² = H
43
45
R²=R³=Ph: 21, 27, 28
R²=R³=Me: 22

Scheme-10

assumed that the initial nucleophilic attack of N-1 of 1,3-diazabutadienes at ketene carbonyl results in the formation of stabilised zwitterionic intermediate **40**, which can exist in forms *40a* and *40b* due to smaller barrier to rotation across C-N bond. Some of the mechanistic possibilities discussed earlier viz (i) the highly stabilised zwitterionic intermediate *40* always prefer to give pyrimidinones say *41* (ii) the conrotatory ring closure of zwitterionic form (40 a) (path I) gives β-lactams and (iii) the disrotatory ring closure of zwitterionic form *40b* (path II) leads to pyrimidinones may be ruled out on the basis of observed variance in the products formed with different substituted diazabutadienes and ketenes. The most reasonable mechanism which can explain the formation of various products assumes that kinetic control leads to the ring closure of zwitterionic intermediate to give initially β-lactam **42** (path III) but this path is reversible due to the presence of polar donating formamidine moiety. Thus reversal to **40** allows for the formation of [4+4] adduct **41** which may or may not be thermodynamically more stable but which, in any case, is removed from consideration by the elimination (of HN < to give 43 and of MeSH to give *45*) and by rearrangement (to give *44*) from even a small stationary concentration of [4+2] adduct (41) to give the observed stable products. In case such elimination and rearrangement is not possible then *41* reverts to 42 *via* zwitterion *40* to give β-lactam **14** as stable isolable products. In case of 1,3-diazabutadienes

having polar donating thiomethyl function at 2-position the initially formed β-lactam becomes still more unstable then there is only a small stationary concentration and reverts faster to 41 via *40* and the observed products are [4+2] cycloadducts (21,22,27 & 28). if it does not impose very severe steric hindrance. In reactions of *N*-aryl-substituted-1,3-diazabutadienes (39) with diphenylketene the products neither assume [2+2] structure 33 (these β-lactams being unstable due to the presence of amidine and thiomethyl functions) and nor pyrimidone structure 34 due to severe steric hindrance of three phenyl and one arylamino functions at vicinal positions. However, in case of reaction of 32b with dimethylketene [2+2] cycloadduct is not observed due to reasons discussed above and [4+2] cycloadduct the pyrimidinone 36 could be isolated due to lesser steric hindrance of one phenyl, one arylamino and two methyl groups at vicinal positions.

Experimental

Melting points were determined on a Toshniwal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian EM 390 90 MHz and Bruker ACF 300 MHz spectrometers and ^{13}C spectra on a Bruker ACF 300 spectrometer in $CDCl_3$. Chemical shift values are expressed in δ ppm downfield from TMS as internal standard. IR spectra were recorded on Perking-Elmer 983 spectrophotometer and Mass spectra were obtained by electon impact at 70eV.

Starting Materials:

1,3-Diaza-1,3-butadienes 20[12] and 32[9] and diphenyl acetyl chloride[13] were prepared by the reported procedures.

Preparation of 1-aryl-2-thiomethyl-4-pyrrolidino/piperidino-1,3-diaza-1,3-butadienes 25 and 26:

General Procedure: A mixture of 1-aryl-2-thiomethyl-4-dimethylamino-1,3-diaza-1,3-butadiene (4 mmol) and pyrrolidine/ piperidine (6 mmol) was reluxed in dry benzene for 4 h. Removal of solvent under reduced pressure yielded the rude product, which was purified by passing through silica gel calumn using a mixture (1:9) of ethyl acetate and hexane.

1-(p-methylphenyl)-2-thiomethyl-4-pyrroldino-1,3-diaza-1,3-butadiene (25): Yield : 86%; viscous liquid. (Found: C, 64.30; H, 7.31; N, 16.09; $C_{14}H_{19}N_3S$ requires C, 64.33; H, 7.32; N, 16.08). ν_{max}: 1615, 1538, 1440, and 1359 cm^{-1}.δ_H (300 MHz, $CDCl_3$): 1.91

olefinic). M^+ 261.

1-(p-methylphenyl)-2-thiomethyl-4-pyrrolidino-1,3-diaza-1,3-butadine (26) : Yield: 81%, viscous liquid (Found: C, 65.43; H, 7.68; N, 15.29. $C_{15}H_{21}N_3S$ requires C, 65.41; H, 7.68; N, 15.26). ν_{max}: 1612, 1540, 1445, and 1360 cm^{-1}. δ_H (90 MHz, $CDCl_3$): 1.67 (br s, 6H,$-CH_2-CH_2-CH_2-$) 2.33(s, 3H, $-CH_3$); 2.40(s, 3H,$-SCH_3$); 3.26-3.46 (brs, 2H,$-N-CH_2-$); 3.60-3.80(brs, 2H,$-CH_2-N-$); 6.76-7.27 (m, 4H, arom); 8.33 (s, 1H, olefinic). M^+ 275.

Reactions of 1,3-diaza-1,3-butadienes with disubstituted ketenes: General Procedure : To a well stirred solution of 1,3-diaza-1,3-butadienes (4mmol) and triethylamine (10 mmol) in dry dichloromethane (30 ml), was added gradually a solution of diphenyl/dimethyl acetyl chloride (6 mmol) in dry dichloromethane (30 ml) over a period fo 1h at room temperature. After the completion of the reaction, the reaction mixture was washed with sodium bicarbonate (2x30 ml) and then with water (5x50 ml) and finally dried over anhydrous sodium sulfate. The crude product obtained after removal of solvent under reduced pressure was purified by passing through a silica gel column.

5,5-Dimethyl-6-dimethylamino-2-thiomethyl-3-phenyl-5*H*, 6*H*-pyrimidin-4(3*H*)- one (22): Yield, 45%, m.p. 144-145° (Found: C, 61.81; H, 7.26; N, 14.44. $C_{15}H_{21}N_3OS$ requires C, 61.82; H, 7.26; N, 14.42).ν_{max}: 1700 (C=O) and 1613 (C=N) cm^{-1}; δH (300 MHz, $CDCl_3$),: 1.28 (s, 3H,$-CH_3$); 1.36 (s, 3H, $-CH_3$); 2.29(s,3H,$-SCH_3$); 2.37(s,6H, $-N(CH_3)_2$); 4.27(s,1H, methine); 7.12-7.18

(m,2H, arom); 7.37-7.46(m,3H, arom). δ_C(75.46 MHz, $CDCl_3$); 14.89 (SCH_3); 19.30, 26.47, 40.84,(C-5), 40.89 ($-N(CH_3)_2$), 83.26 (C-6), 129.03, 129.25, 136.12 (arom); 153.13, (C-2), 175.07 (C-4). M^+ 291.

5,5-Diphenyl-3-(p-methylphenyl)-2-thiomethyl-6-pyrrolidino-5*H*, 6H-pyrimidin-4(3H)-one (27) : Yield : 86%; m.p. 144°C-145°C. (Found : C, 77.77; H,6.43; N, 9.20. $C_{28}H_{29}N_3OS$ requires C, 73.81; H, 6.41; N, 9.22). ν_{max}:1689 (C=O), 1620, 1510, 1438 cm^{-1} δ_H (300 MHz, $CDCl_3$): 1.59 (brs, 4H-CH_2-CH_2-), 2.24(s,3H, CH_3); 2.36 (s,3H,-SCH_3); 2.48(d, J = 7.0 Hz, with fine splitting, 2H-CH_2-N-); 2.95 (d, J = 70 Hz, with fine splitting, 2H, -CH_2-N) 5.34(s, 1H, methine); 7.11-7.23 (m, 9H, arom); 7.27-7.35 (m, 3H, arom); 7.46 (d, J = 8.1 Hz, with fine splitting, 2H, arom). δ_C (75.46 MHz); 15.1 (-SCH_3), 21.3 (-CH_3), 23.7 (-CH_2-CH_2-), 48.8 (-CH_2-N-), 59.3 (-N-CH_2-), 96.1, 126.1, 126.9, 127.5, 128.1, 128.6, 128.9, 129.0, 129.1, 129.6, 129.7, 133.4, 139.3, 140.6, 153.6, 170.7 (C=O). M^+ 455.

5,5-Diphenyl-3-(p-methylphenyl)-2-thiomethyl-6-piperidino-5H, 6H-pyrimidin-4(3*H*)-one (28): Yield: 89%; m.p. 158°-160°C. (Found: C,74.19; H, 6.63; N,8.94. $C_{29}H_{31}N_3OS$ requires C, 74.16; H, 6.65; N, 8.95). ν_{max}: 1694 (C=O), 1622, 1505, 1444 cm^{-1} δH (300 MHz, $CDCl_3$); 1.29(br s, 6H,-CH_2-CH_2-CH_2-); 2.24(s,3H,-CH_3); 2.34 (s,3H, -SCH_3), 2.43 (d, J=11.1 Hz, 2H, -N-CH_2-); 2.87 (d, J = 11.1 Hz; 2H, -CH_2-N-); 4.98 (s,1H, methine); 7.05-7.16(m, 9H, arom); 7.25-7.30 (m,3H, arom); 7.44(d, J = 8.2 Hz, with fine splitting, 2H, arom); δ_C (75.5 MHz, $CDCl_3$); 14.9 (-SCH_3), 21.2(-CH_3), 24.0, 25.9, 50.1, 58.1, 82.8, 95.9, 125.5, 126.7, 127.4,

(br s, 4H,-CH_2-CH_2-); 2.29(s, 3H,-CH_3); 2.34(s,3H,-SCH_3), 3.48-3.54 (m, 2H, -CH_2-N-CH_2-); 6.70-7.18 (m, 4H, arom); 8.38 (s, 1H, olefinic). M^+ 261.

1-(p-methylphenyl)-2-thiomethyl-4-pyrrolidino-1,3-diaza-1,3-butadine (26) : Yield: 81%, viscous liquid (Found: C, 65.43; H, 7.68; N, 15.29. $C_{15}H_{21}N_3S$ requires C, 65.41; H, 7.68; N, 15.26). ν_{max}: 1612, 1540, 1445, and 1360 cm^{-1}. δ_H (90 MHz, $CDCl_3$): 1.67 (br s, 6H,-CH_2-CH_2-CH_2-) 2.33(s, 3H, -CH_3); 2.40(s, 3H,-SCH_3); 3.26-3.46 (brs, 2H,-N-CH_2-); 3.60-3.80(brs, 2H,-CH_2-N-); 6.76-7.27 (m, 4H, arom); 8.33 (s, 1H, olefinic). M^+ 275.

Reactions of 1,3-diaza-1,3-butadienes with disubstituted ketenes: General Procedure : To a well stirred solution of 1,3-diaza-1,3-butadienes (4mmol) and triethylamine (10 mmol) in dry dichloromethane (30 ml), was added gradually a solution of diphenyl/dimethyl acetyl chloride (6 mmol) in dry dichloromethane (30 ml) over a period fo 1h at room temperature. After the completion of the reaction, the reaction mixture was washed with sodium bicarbonate (2x30 ml) and then with water (5x50 ml) and finally dried over anhydrous sodium sulfate. The crude product obtained after removal of solvent under reduced pressure was purified by passing through a silica gel column.

5,5-Dimethyl-6-dimethylamino-2-thiomethyl-3-phenyl-5*H*, 6*H*-pyrimidin-4(3*H*)- one (22): Yield, 45%, m.p. 144-145° (Found:

C, 61.81; H, 7.26; N, 14.44. $C_{15}H_{21}N_3OS$ requires C, 61.82; H, 7.26; N, 14.42). ν_{max}: 1700 (C=O) and 1613 (C=N) cm^{-1}; δH (300 MHz, $CDCl_3$),: 1.28 (s, 3H,-CH_3); 1.36 (s, 3H, -CH_3); 2.29(s,3H,-SCH_3); 2.37(s,6H, -$N(CH_3)_2$); 4.27(s,1H, methine); 7.12-7.18 (m,2H, arom); 7.37-7.46(m,3H, arom). δ_C(75.46 MHz, $CDCl_3$); 14.89 (SCH_3); 19.30, 26.47, 40.84,(C-5), 40.89 (-$N(CH_3)_2$), 83.26 (C-6), 129.03, 129.25, 136.12 (arom); 153.13, (C-2), 175.07 (C-4). M^+ 291.

5,5-Diphenyl-3-(p-methylphenyl)-2-thiomethyl-6-pyrrolidino-5*H*, 6H-pyrimidin-4(3H)-one (27) : Yield : 86%; m.p. 144°C-145°C. (Found : C, 77.77; H,6.43; N, 9.20. $C_{28}H_{29}N_3OS$ requires C, 73.81; H, 6.41; N, 9.22). ν_{max}:1689 (C=O), 1620, 1510, 1438 cm^{-1} δ_H (300 MHz, $CDCl_3$): 1.59 (brs, 4H-CH_2-CH_2-), 2.24(s,3H, CH_3); 2.36 (s,3H,-SCH_3); 2.48(d, J = 7.0 Hz, with fine splitting, 2H-CH_2-N-); 2.95 (d, J = 70 Hz, with fine splitting, 2H, -CH_2-N) 5.34(s, 1H, methine); 7.11-7.23 (m, 9H, arom); 7.27-7.35 (m, 3H, arom); 7.46 (d, J = 8.1 Hz, with fine splitting, 2H, arom). δ_C (75.46 MHz); 15.1 (-SCH_3), 21.3 (-CH_3), 23.7 (-CH_2-CH_2-), 48.8 (-CH_2-N-), 59.3 (-N-CH_2-), 96.1, 126.1, 126.9, 127.5, 128.1, 128.6, 128.9, 129.0, 129.1, 129.6, 129.7, 133.4, 139.3, 140.6, 153.6, 170.7 (C=O). M^+ 455.

5,5-Diphenyl-3-(p-methylphenyl)-2-thiomethyl-6-piperidino-5H, 6H-pyrimidin-4(3*H*)-one (28): Yield: 89%; m.p. 158°-160°C. (Found: C,74.19; H, 6.63; N,8.94. $C_{29}H_{31}N_3OS$ requires C, 74.16; H, 6.65; N, 8.95). ν_{max}: 1694 (C=O), 1622, 1505, 1444 cm^{-1} δH (300 MHz,

$CDCl_3$); 1.29(br s, 6H,-CH_2-CH_2-CH_2-); 2.24(s,3H,-CH_3); 2.34 (s,3H, -SCH_3), 2.43 (d, J=11.1 Hz, 2H, -N-CH_2-); 2.87 (d, J = 11.1 Hz, 2H, -CH_2-N-); 4.98 (s,1H, methine); 7.05-7.16(m, 9H, arom); 7.25-7.30 (m,3H, arom); 7.44(d, J = 8.2 Hz, with fine splitting, 2H, arom); δ_C (75.5 MHz, $CDCl_3$); 14.9 (-SCH_3), 21.2(-CH_3), 24.0, 25.9, 50.1, 58.1, 82.8, 95.9, 125.5, 126.7, 127.4, 127.9, 128.5, 129.1, 129.3, 133.3, 138.5, 141.1, 141.3, 153.1, 169.6 (C=O).

1-2-Diphenyl-4-thiomethyl-4[N-phenyl-N-(2,2-diphenylacetyl)]-1,3-diza-1,3-butadiene (35a): Yield = 38%; m.p. 175°C. (Found: C,77.86; H,5.39; N,7.81. $C_{35}H_{29}N_3OS$ require C,77.89; H,5.42; N, 7.79 ; ν_{max} 1687 (C=O); 1588, 1490 cm^{-1}. δ_H (300 MHz, $CDCl_3$): 2.09(s,3H,-SCH_3); 4.92(s,1H, methine); 6.66(d, J = 7.5, 1H, arom); 6.73(d, J=7.3, 1H, arom); 6.83-7.51(m,22H, arom); 8.02(dd, J= 8.1 and 1.9, 1H, arom). M^+ 539.

1,2-Diphenyl-4-thiomethyl-4-[N-(4-methylphenyl)-N-(2,2-diphenylacetayl)]-1,3-diaza-1,3-butadiene (35b): Yield = 40%, m.p. = 173°C; (Found: C, 78.13; H,5.63; N,7.56. $C_{36}H_{31}N_3OS$ requires C,78.09; H,5.64; N,7.59; ν_{max} 1683 (C=O), 1602, 1589 cm^{-1}; δ_H(300 MHz, $CDCl_3$): 2.10(s,3H,-SCH_3);2.28(s,3H,-CH_3),4.92(s,1H, methine), 6.51(d, J = 7.8, 1H, arom); 6.71(d, J = 7.6, 1H, arom); 6.85-7.43(m,21H, arom), 8.03(d,1H, arom). δ_C(75.46 MHz, $CDCl_3$), 15.39(-SCH_3); 21.08 (-CH_3), 54.88 (methine C), 121.2, 121.9, 123.0, 127.2, 127.3, 128.0, 128.2, 128.3,

128.4, 128.5, 128.6, 128.65, 128.7, 128.8, 128.9, 129.2, 129.9, 130.7, 134.2, 135.3, 138.6, 138.7, 148.8 (aromatic), 155.1 (C-2)157.1 (C-4), 171.9 (C=O). M^+ 553.

1-(4-methylphenyl)-2-piperidino-4-[N-(4-methylphenyl)-N-(2,2-diphenylacetyl)]-1,3-diaza-1,3-butadiene (35c) : Yield = 35%; m.p. 124-125°C, (Found: C, 81.39; H,6.70; N,9.30 $C_{41}H_{40}N_4O$, requires C,81.42; H,6.67; N, 9.26; ν_{max} 1683 (C=O), 1621, 1598, 1577 cm^{-1}.δ_H(300 MHz, $CDCl_3$) : 1.40-1.51 (m, 6H,$-CH_2-CH_2-CH_2-$), 2.23(s,3H,$-CH_3$), 2.32(s,3H,$-CH_3$), 3.18-3.25(m,4H,$-CH_2-N-CH_2-$), 4.93 (s,1H, methine), 6.37 (d, J = 8.1 Hz, 2H, arom), 6.70-6.82 (m,8H, arom), 6.95(d, J= 8.0 Hz, 2H, arom), 7.00-7.50(m, 10H, arom), 7.96 (d, J = 7.0 Hz, 2H, arom), δ_C(75.5 MHz $CDCl_3$) : 20.9($-CH_3$), 21.1($-CH_3$), 24.3($-CH_2-CH_2-CH_2-$), 25.3($-CH_2-CH_2-CH_2-$); 46.7 ($-CH_2-N-CH_2$), 53.7(CH), 122.2, 127.0, 127.1, 127.9, 128.1, 128.3, 128.5, 128.8, 129.0, 129.7, 129.9, 131.6, 135.8, 138.0, 138.3, 138.6, 144.2, 146.7 (arom), 158.1 (C-2), 159.6 (C-4), 171.7 (C=O). M^+ 604.

5-5-Dimethyl-2-thiomethyl-3-(p-tolyl)-6-phenyl-6-anilno-3,4,5,6-tetrahydropyrimidin-4-one (36): Yield = 41%; m.p. 181°C. (Found: C, 72.66; H, 6.32; N,9.81. $C_{26}H_{27}N_3OS$ requires C,72.69; H, 6.33; N, 9.78). ν_{max} : 1683 (C=O), 1608, 1507 cm^{-1}. δ_H(90 MHz, $CDCl_3$): 1.03(s,3H,$-CH_3$); 1.30(s,3H,$-CH_3$), 2.35(s,3H,$-CH_3$); 2.43(s,3H,$-SCH_3$), 7.10-7.51(m, 12H, arom), 7.62-7.80(m,2H, arom). M^+ 429.

2-phenyl quinazolin-4-one (37) : (1 g, 2.25 mmol) of β-lactam **14** was refluxed in dry xylene for 2 h. The solvent was removed under reduced pressure and the crude product was pruified by passing through a silica gel column using a mixture (1:9) of ethyl acetate: hexane to yield quinazolinone **37** (0.35 g, 70.5%). m.p. , 235-236°C; Found: C, 75.64; H, 4.53; N, 12.63 $C_{14}H_{10}N_2O$ requires C, 75.66; H, 4.53; N,12.60). ν_{max} : 1666 (C=O), 1601, 1476, 1556 cm^{-1}. δ_H(300MHz, $CDCl_3$): 7.49-7.54(m,1H, arom); 7.56-7.64(m,3H, arom); 7.78-7.86 (m, 2H, arom); 8.25-8.28 (m,2H, arom); 8.32-8.35(d, J = 7.6, with fine splitting, 1H, arom); 11.72 (bs, 1H, exchangable with D_2O,-NH-). δC(75.46MHz): 120.8, 126.4, 126.8, 127.4, 128.0, 129.1, 131.7, 132.8; 134.9, 149.3, 151.8, 163.9 (C=O). M^+ 222

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