CYCLOADDITION REACTIONS OF VARIOUS 1, 3-DIAZA-1, 3-BUTADIENES AND IMINES IN HETEROCYCLIC SYNTHESIS

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SEPTEMBER 1996

DEDICATED TO

MY

PARENTS

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Professor of Chemistry
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I certify that the Thesis entitled *"Cycloaddition Reactions of Various 1,3-Diaza-1,3-Butadienes and Imines in Heterocyclic Synthesis"* submitted by Mr. Arun Kumar Sharma for the degree of Doctor of Philosophy of the North-Eastern Hill University, Shillong, embodies the record of original investigation carried out by him under my supervision. He has been duly registered and the Thesis is worthy of being considered for the Ph.D. Degree. This work has not been submitted for any Degree of any other University.

Place : Shillong
Date : 30 September 1996

Signature of the Supervisor

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ARUN KUMAR SHARMA

CONTENTS

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CHAPTER—I

Cycloaddition Reactions of various 1,3-Diaza-1,3-Butadienes with Conjugated and Chloroketenes

I.1: *General Introduction*

The Diels-Alder cycloaddition reaction, discovered in 1920s by Otto Diels and Kurt Alder in Germany,[1] is the most widely used and best known pericyclic reaction which turned out to be an important tool in synthetic organic chemistry.[2] It has been the subject of extensive preparative,[3-10] theoretical,[11,12] and mechanistic[13] studies contributing towards the ease and predictability with which these reactions may be carried out. For the recent dramatic advances in organic synthesis which have been accompanied by ever increasing pressures to attain greater levels of stereochemical control, the Diels-Alder cycloaddition has proved to be extremely useful. For many years, the capture of a diene by a dienophile was recognised to be capable of generating as many as four contiguous stereogenic centers in a single

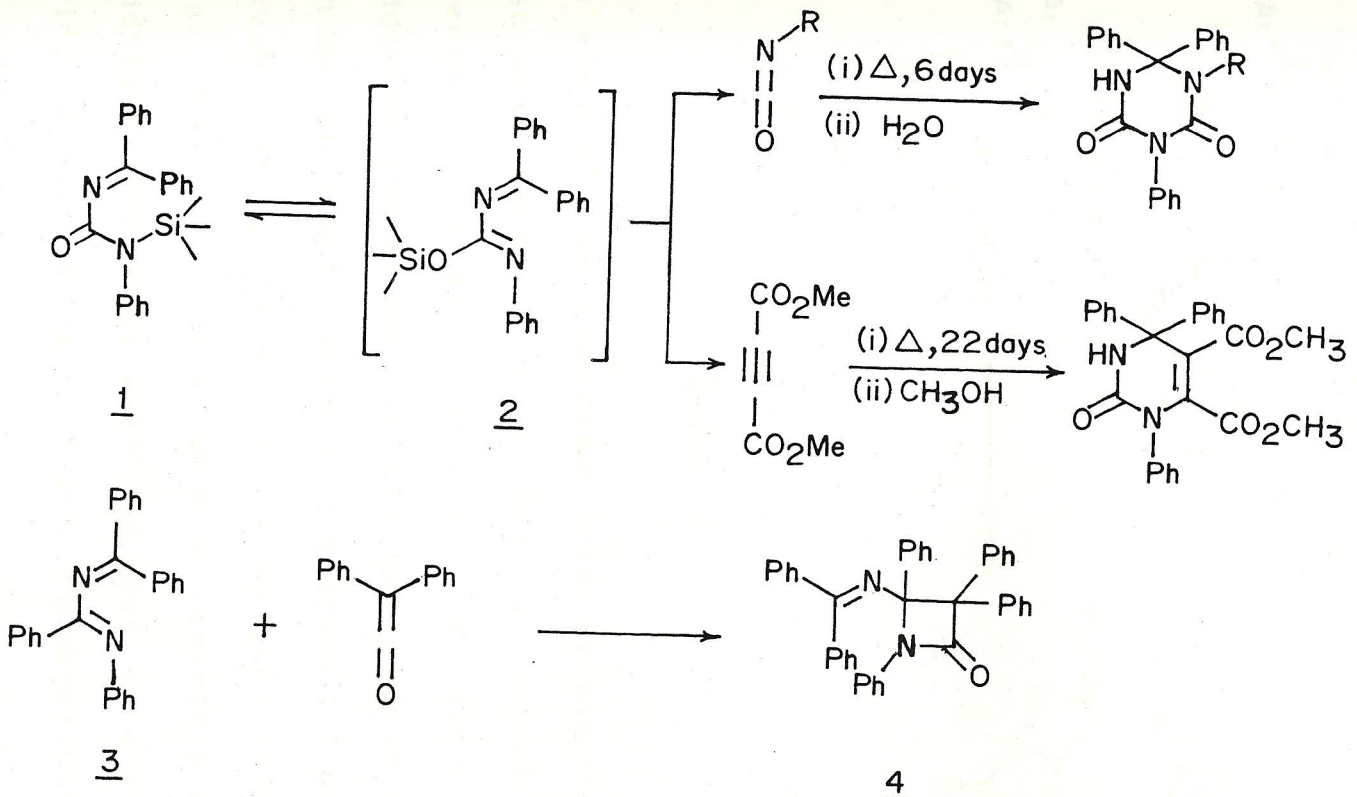
laboratory step.[14-15] Subsequently asymmetric,[16] and intramolecular variants[17] of this process came to the fore and have been accorded widespread attention. To a significant extent the operating controlling factors in these modifications are quite well understood.

Heterodienes have proved to be of great potential in heterocyclic synthesis. Extensive studies have been carried out on the Diels-Alder cycloadditions involving heterodienes containing one or more heteroatoms and some comprehensive reviews have appeared on oxazines,[5] nitrosoalkenes,[18] heterodienophiles[19] and about intra- and intermolecular cycloaddition reactions in the synthesis of heterocyclic natural products.[20] The observation that the azadienes[3,4,6,9,11,18,21,22] show diminished reactivity towards electron deficient dienophiles, lends credence to the electrophilic nature of such systems. These observations together with the recongnised shortcomings in attempting cycloaddition reactions with 2π and 4π components of similar electrophilic nature led to the development of several general approaches for useful azadiene Diels-Alder cycloadditions.

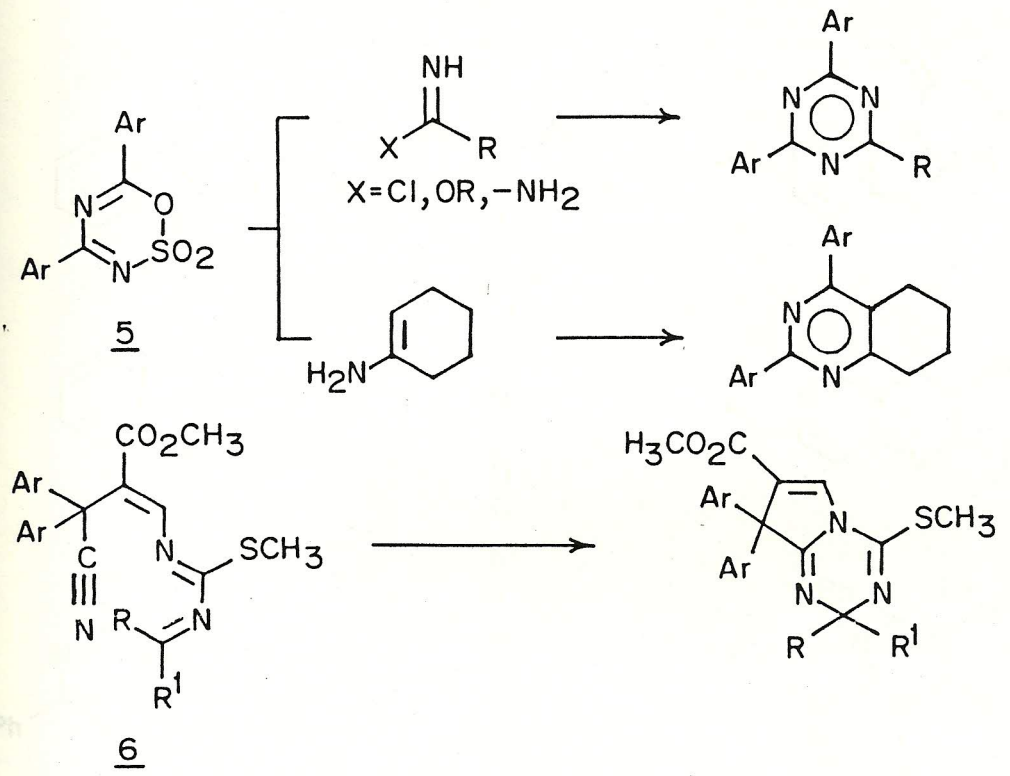
There are numerous reports concerning [4+2] cycloaddition reactions of 1,2- and 1,4-diazabutadienes. In contrast, such cycloaddition reactions with 1,3-diaza-1,3-butadienes, especially, with their acyclic counterparts, are very rare and have not been much exploited in heterocyclic synthesis.[13-15a] This may be atrributed to (i) the lack of suitable methods available for the preparation of stable 1,3-diaza-1,3-butadienes

and (ii) their reluctance to participate in Diels-Alder reaction because of their inverse electron demand tendency due to the unfavourable position of second nitrogen at position 3- of butadiene system. The successful attempts in this direction include the thermal isomerisation of an unsaturated *N*-Silylurea **1** to 2-trimethylsilyloxy-1,3-diaza-1,3-butadiene **2** and their subsequent Diels-Alder reaction. Their efficiency towards the cycloaddition reactions was soon considered doubtful since such reactions involved long reaction times, poor yields etc.[23] Matsuda *et al.* observed that a similar 1,3-diaza-1,3-butadiene **3**, failed to react with dimethyl acetylene dicarboxylate and formed [2+2] cycloadducts **4** with diphenylketene (Scheme 1).[23] Weidinger *et al.* reported the [4+2] cycloaddition reactions of 4,6-diaryl-1,2,3,5-oxathiadiazine-2,2-dioxides **5** with nucleophilic heterodienophiles[24] and electron-rich olefins[25] (Scheme 2). More *et al.* reported recently, *in situ* generation and subsequent intramolecular Diels-Alder reactions of 2-methylthio-1,3-diaza-1,3-butadienes **6**[26] (Scheme 2).

Few reports of the successful participation of heterocyclic 1,3-diaza-1,3-butadienes as 4π component in Diels-Alder cycloaddition reactions with dienophiles are also available in literature[27-31] (Scheme-3). Recently, there have been reports concerning the [4+2] cycloaddition reactions of simple, yet isolable and stable, 1,3-diaza-1,3-butadienes that concern the reactions of **7** and **8** with isocyanates[32a] substituted nitriles[32b,c] (Scheme-3) and ketenes.[33]


Ph
N
Ph
O
N
Si
Ph
1
Ph
N
Ph
SiO
N
Ph
2
R
N
O
(i) △, 6 days
(ii) H2O
Ph
Ph
HN
N
R
O
N
O
Ph
CO2Me
CO2Me
(i) △, 22 days
(ii) CH3OH
Ph
Ph
CO2CH3
HN
O
N
CO2CH3
Ph
Ph
N
Ph
Ph
N
Ph
3
+
Ph
Ph
O
Ph
Ph
Ph
N
Ph
Ph
Ph
N
O
4

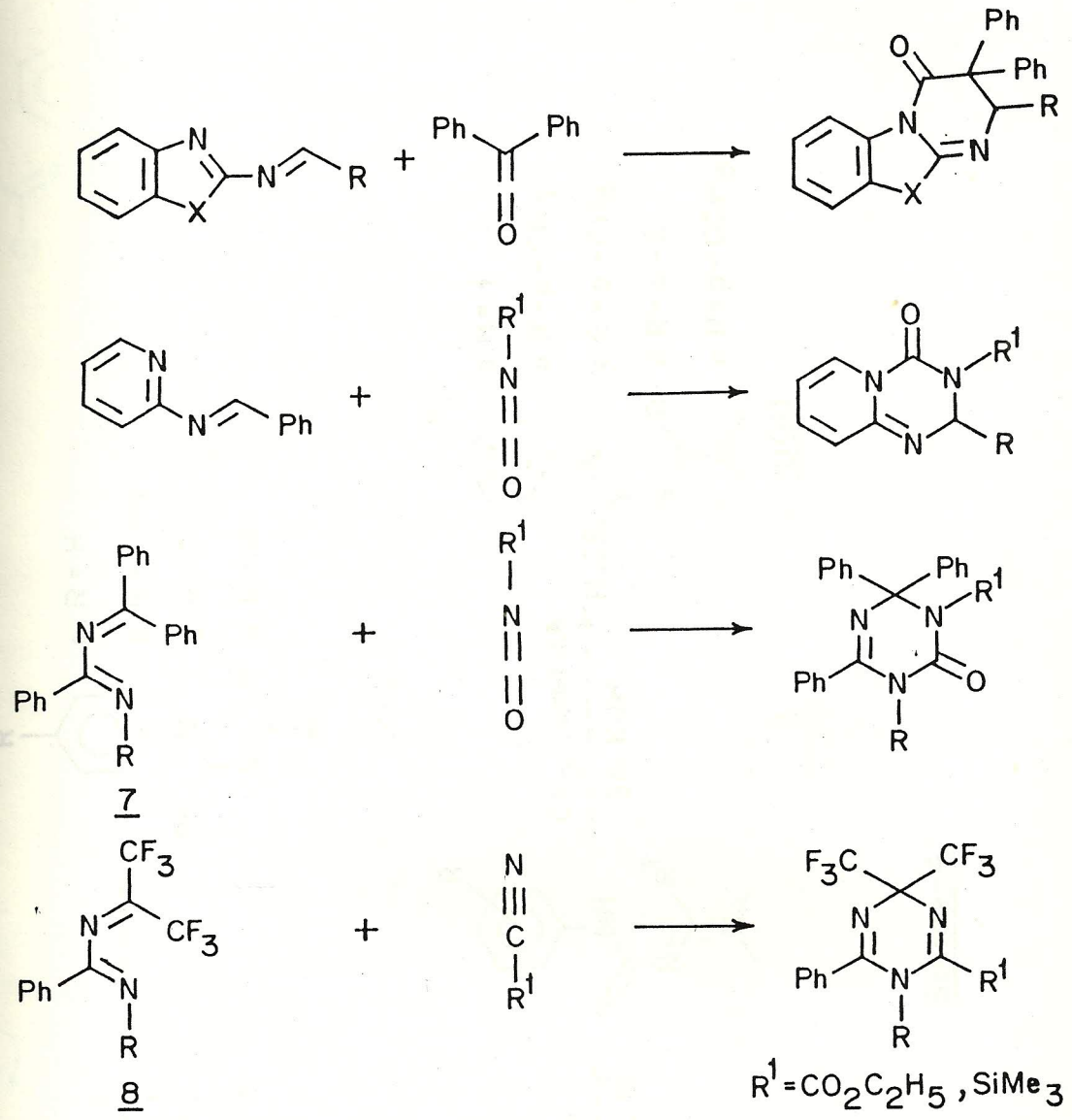
Scheme-1



Scheme - 2

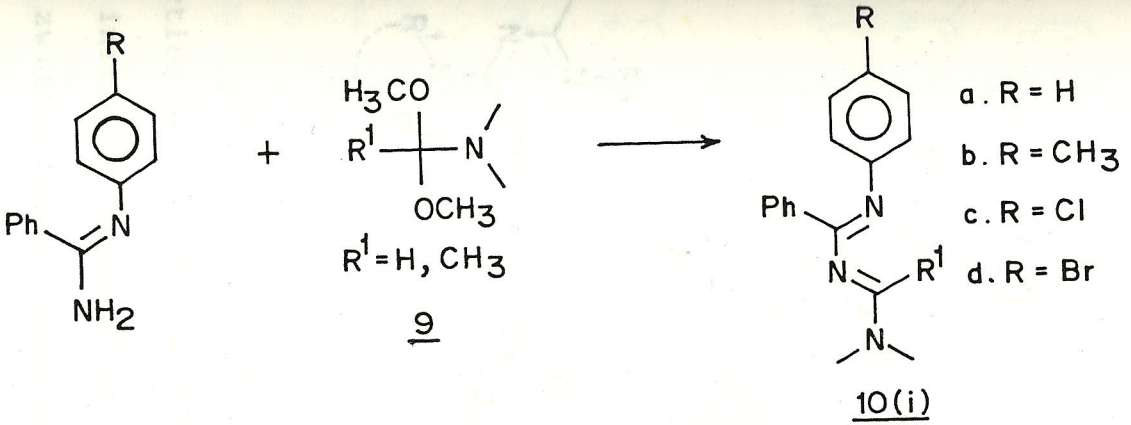
In view of the reported lack of synthetic approaches together with reports of failure of acyclic 1,3-diaza-1,3-butadienes as an effective 4π component in Diels-Alder cycloaddition reactions, we devised simple methods for the preparation of stable acyclic 1,3-diaza-1,3-butadienes.[34] Such 1,3-diazabutadienes with polarising functions at 4 and 2/4-positions (Schemes 4 and 5) were successfully utilised in [4+2] cycloaddition reactions with various ketenes e.g. phenyl-, diphenyl-, chloro-, bromo-, iodo-, chloromethyl-, dichloro- and various other ketenes.

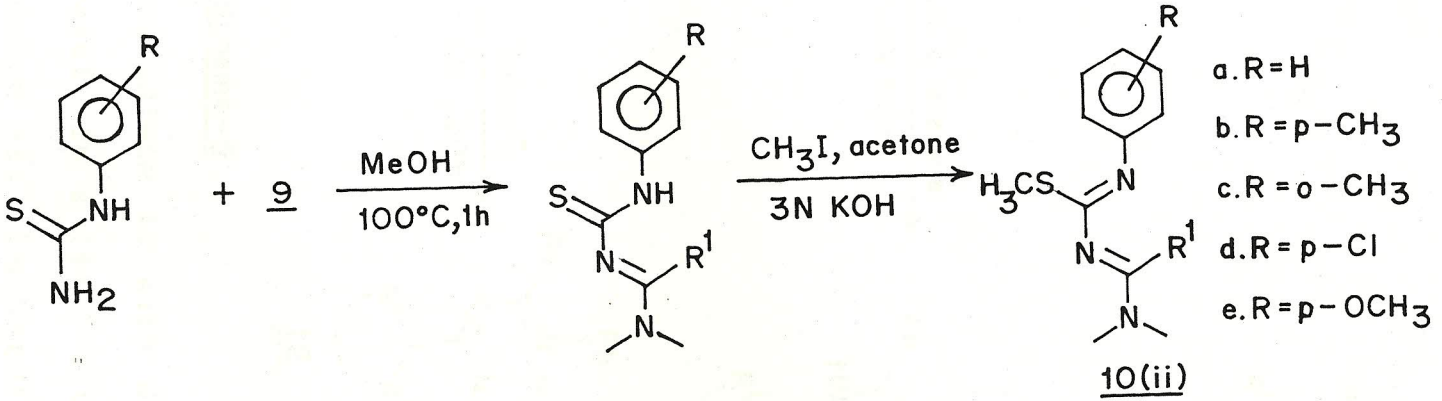
The reaction of 1,3-diaza-1,3-butadienes 10 with monophenyl ketene 13 resulted in the formation of [4+2] cycloadduct 3-aryl-



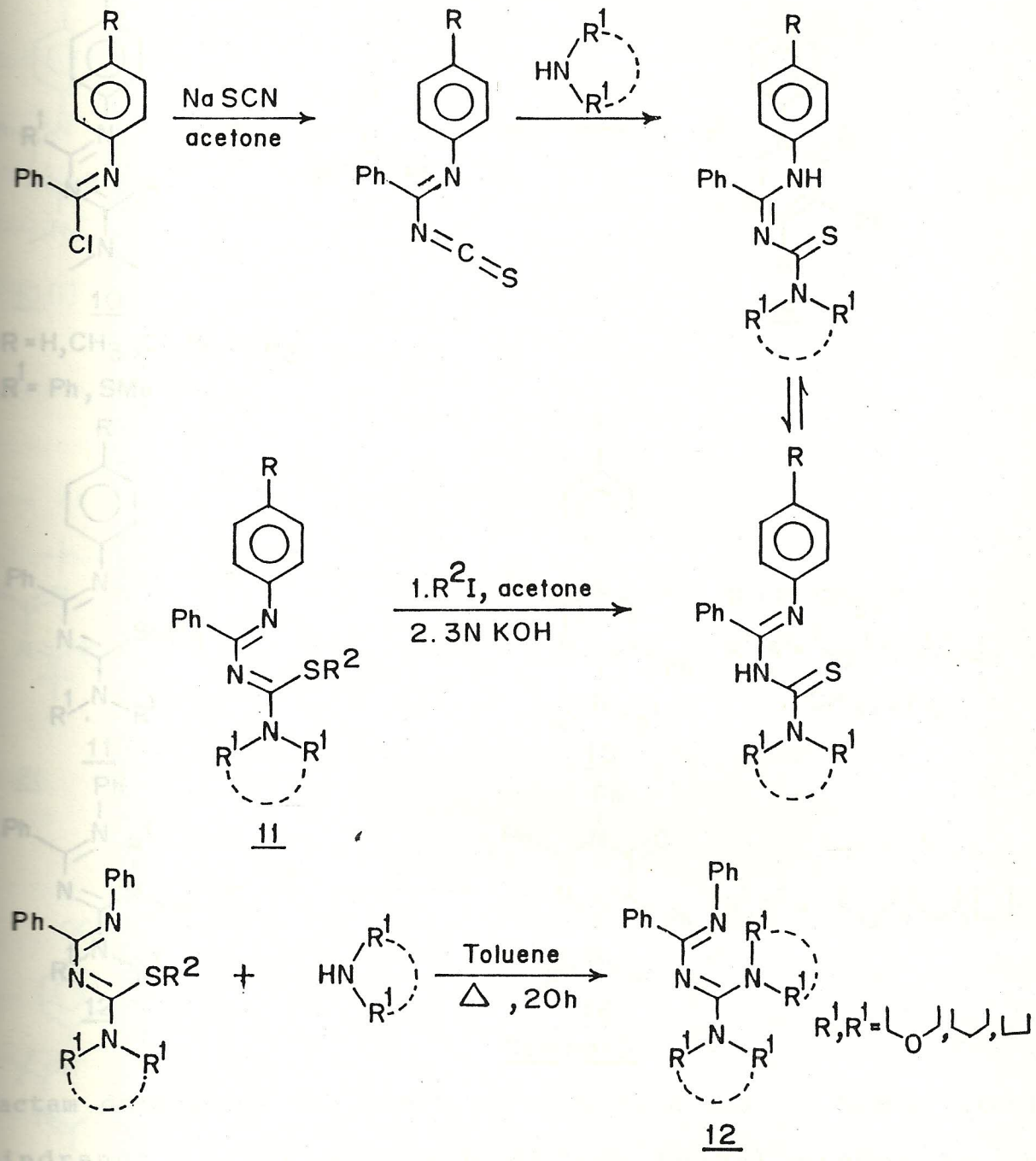
Scheme-3

5-phenyl-2-phenyl/methylthio-4(3*H*)-pyrimidinone 14 *via* the elimination of dimethylamine function. Similar reactions with 1,3-diaza-1,3-butadienes 11 and 12 resulted in the isolation of pyrimidinone 15 and 16 *via* the elimination of methylthio and secondary amine functions respectively[35] (Scheme 6). The


R
Ph
N
NH2
+
H3CO
R1
N
OCH3
R1=H, CH3
9
R
Ph
N
N
R1
N
a. R = H
b. R = CH3
c. R = Cl
d. R = Br
10(i)

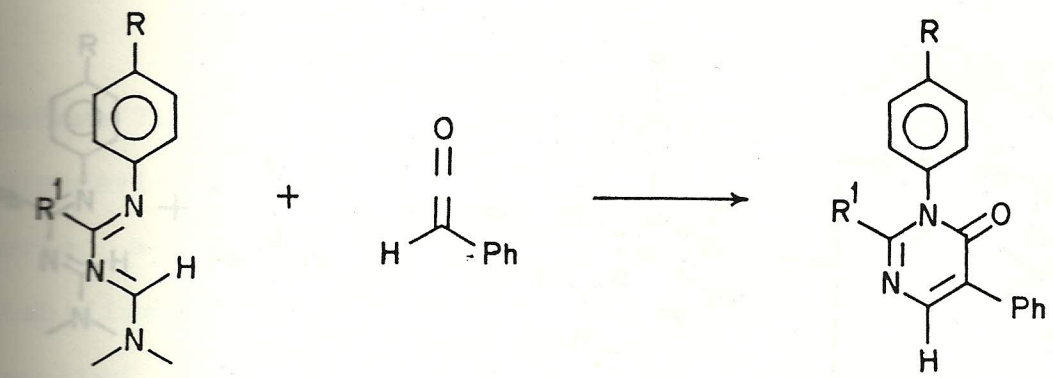

R
S
NH
NH2
+ 9
MeOH
100°C,1h
R
S
NH
N
R1
N
CH3I, acetone
3N KOH
R
H3CS
N
N
R1
N
a. R=H
b. R=p-CH3
c. R=o-CH3
d. R=p-Cl
e. R=p-OCH3
10(ii)

Scheme-4



Scheme-5

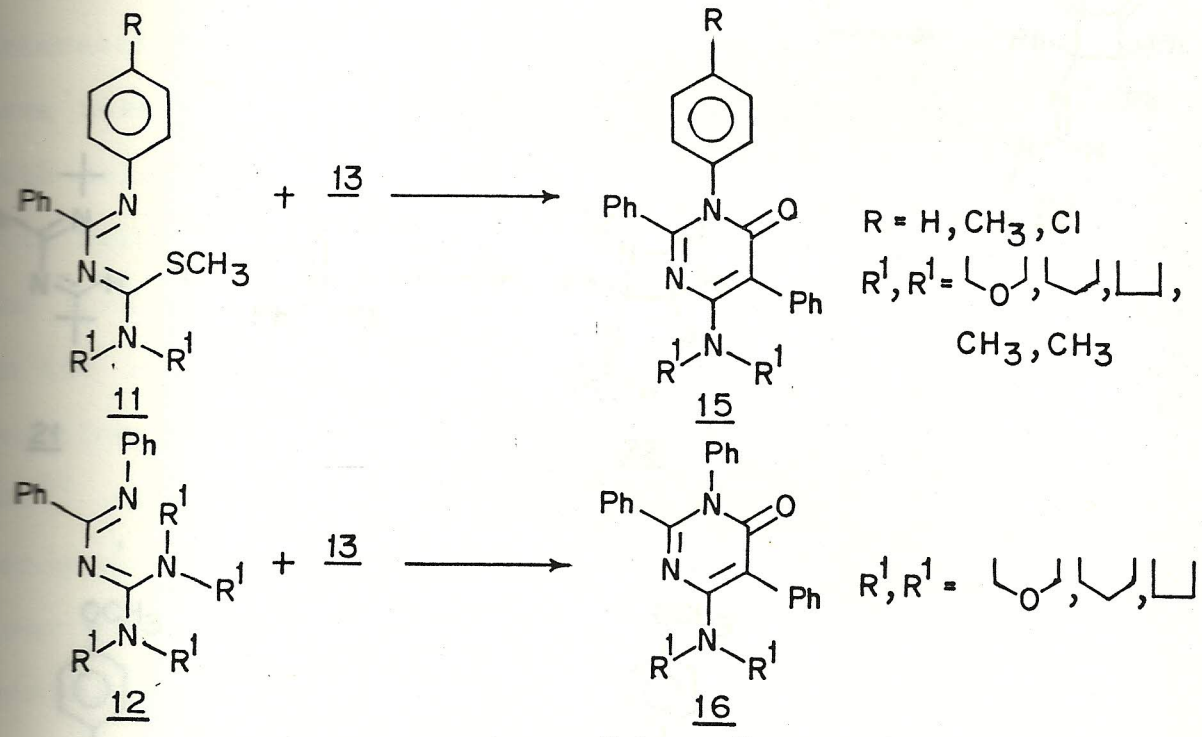
reaction of 1,3-diaza-1,3-butadiene 10 with diphenyl ketene 17 was initially assumed to result in a [4+2] cycloadduct 19[36] *via* the zwitterrionic intermediate 18. Luthardt and Wurthwein[37] reported that the intermediate 18 prefers the formation of β-



10 13 14

R = H, CH_3, Cl, Br, OCH_3

R^1 = Ph, SMe



11 15

R = H, CH_3, Cl

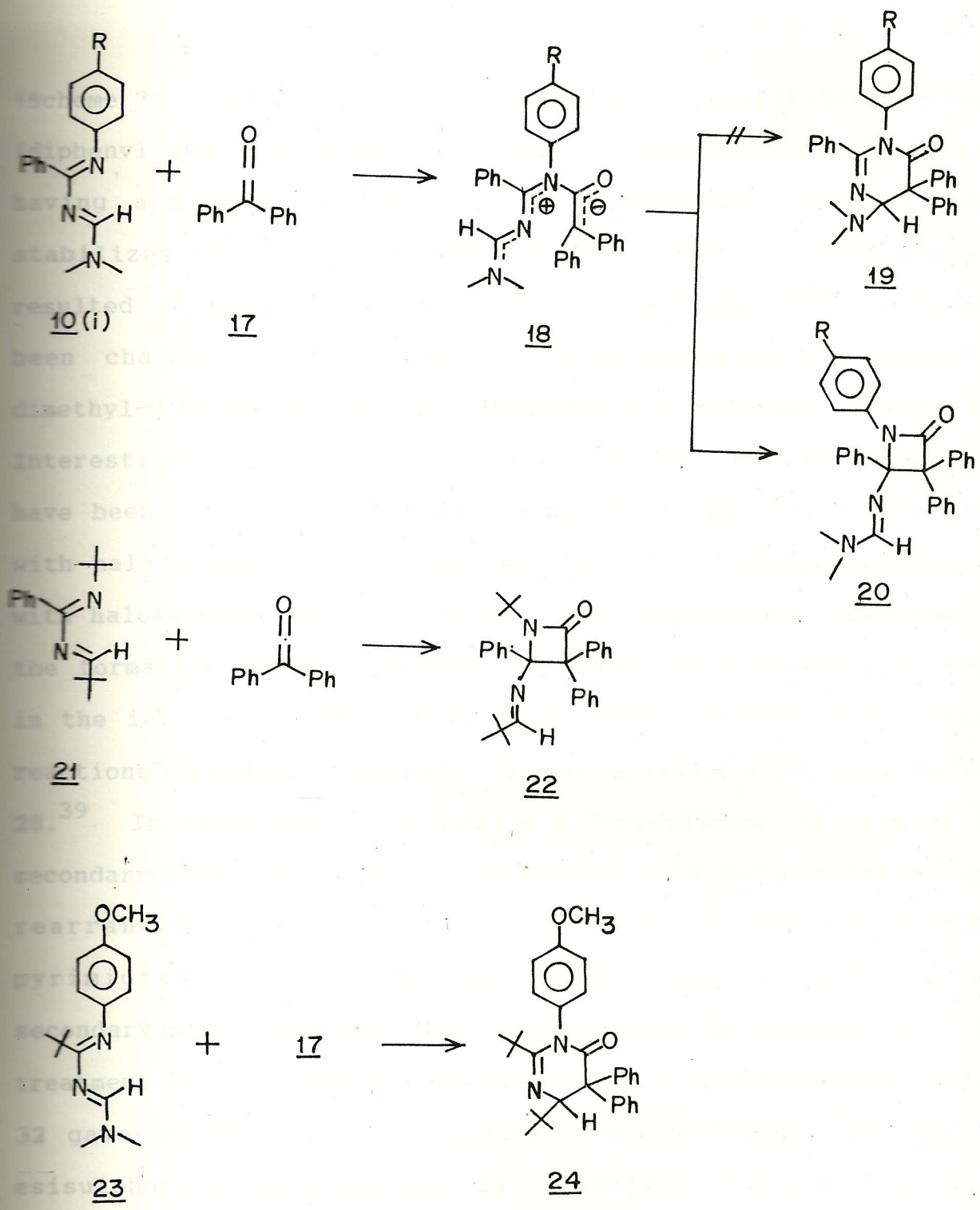
R^1, R^1 = ⌓O⌓, ⌓⌓, ⌓⌓, CH_3, CH_3

12 16

R^1, R^1 = ⌓O⌓, ⌓⌓, ⌓⌓

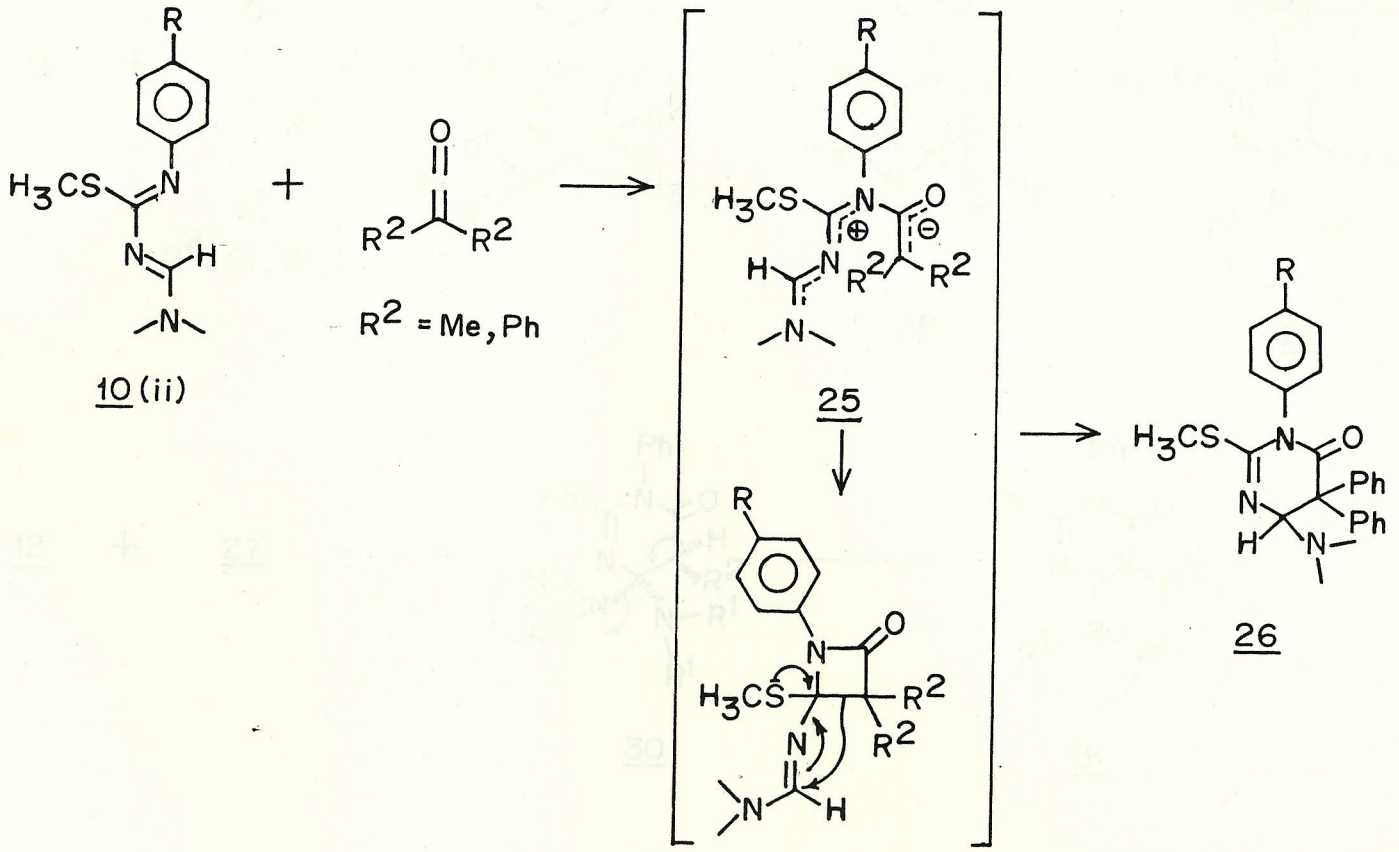
Scheme-6

lactam derivative *via* [2+2] cycloaddition due to higher steric hindrance to the approach of two phenyl groups to the dimethylamine function leading to [4+2] cycloadduct **19** as compared to the approach of two phenyl groups to C-2, leading to [2+2] cycloadduct **20** (Scheme-7). They extended the steric arguments to the formation of **22** and **24** in the reaction of diphenylketene **17** with 1,3-diazabutadiene **21** and **23** respectively

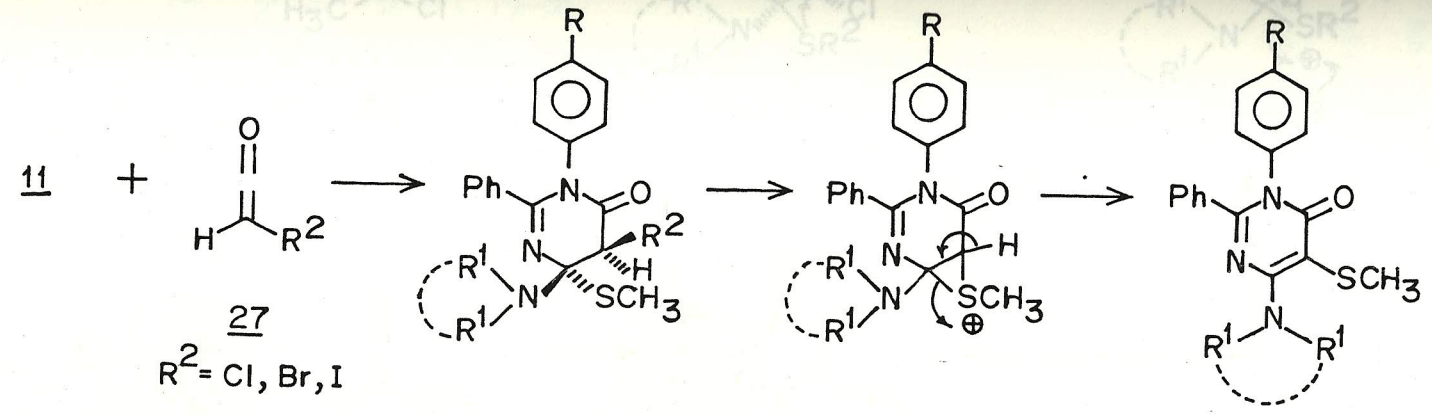


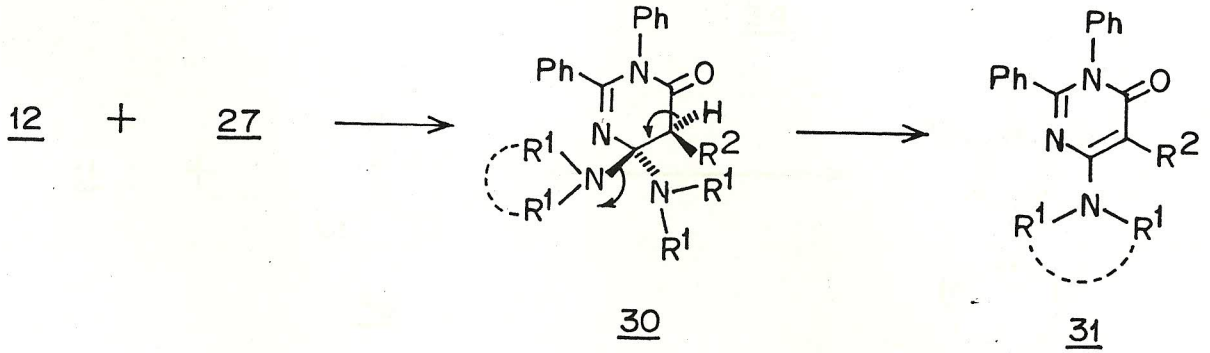
Scheme – 7

(Scheme 7). Interestingly, the reaction of disubstituted ketenes (diphenyl and dimethylketene), with 1,3-diaza-1,3-butadiene **10ii** having a polarising function at 2-position, which further stabilizes the initially found zwitterionic intermediate **25**, resulted in good yields of [4+2] cycloadducts **26**[38] which have been characterised as 3-aryl-6-dimethylamino-5,5-diphenyl/dimethyl-2-methylthio-3,5,6-trihydropyrimidin-4-ones (Scheme 8). Interesting 1,2-alkylthio shift accompanying [4+2] cycloadditions have been reported in the reactions of 1,3-diaza-1,3-butadienes with halo ketenes. Thus the reaction of 1,3-diazabutadienes **11** with haloketenes (chloro-, bromo-, and iodoketenes) resulted in the formation of pyrimidinones **29** involving 1,2-alkylthio shift in the initially formed [4+2] cycloadduct intermediates. These reactions presumably proceed *via* an episulphonium intermediate **28**.[39] In reactions of 1,3-diaza-1,3-butadienes **12**, having two secondaryamine functions at 4-position, with haloketenes no such rearrangement was observed and these reactions yielded pyrimidinones **31** with the elimination of one of the secondaryamine functions from intermediate **30** (Scheme 9). The treatment of 1,3-diaza-1,3-butadienes **11** with chloromethyl ketene **32** gave another set of rearranged pyrimidinones **34** *via* the esisulphonium intermediate **33**. Further information about structure **34** was derived from the superimposable IR spectra and undepressed mixed melting point with a sample prepared from the reaction of **11** with methylketene **35**. Similar reaction of **11** with dichloroketene **36** resulted in pyrimidinone **37** *via* the loss of

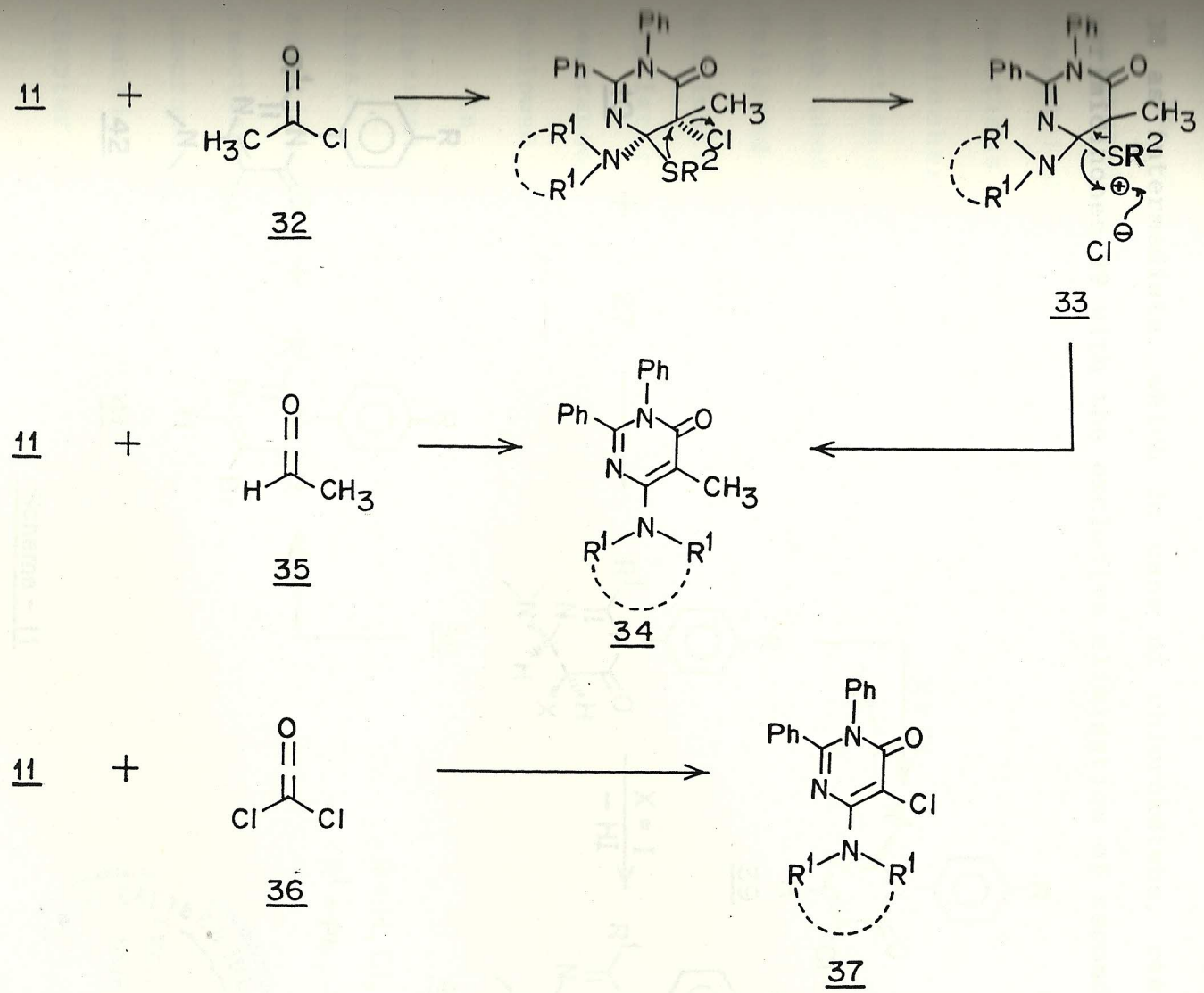


Scheme-8



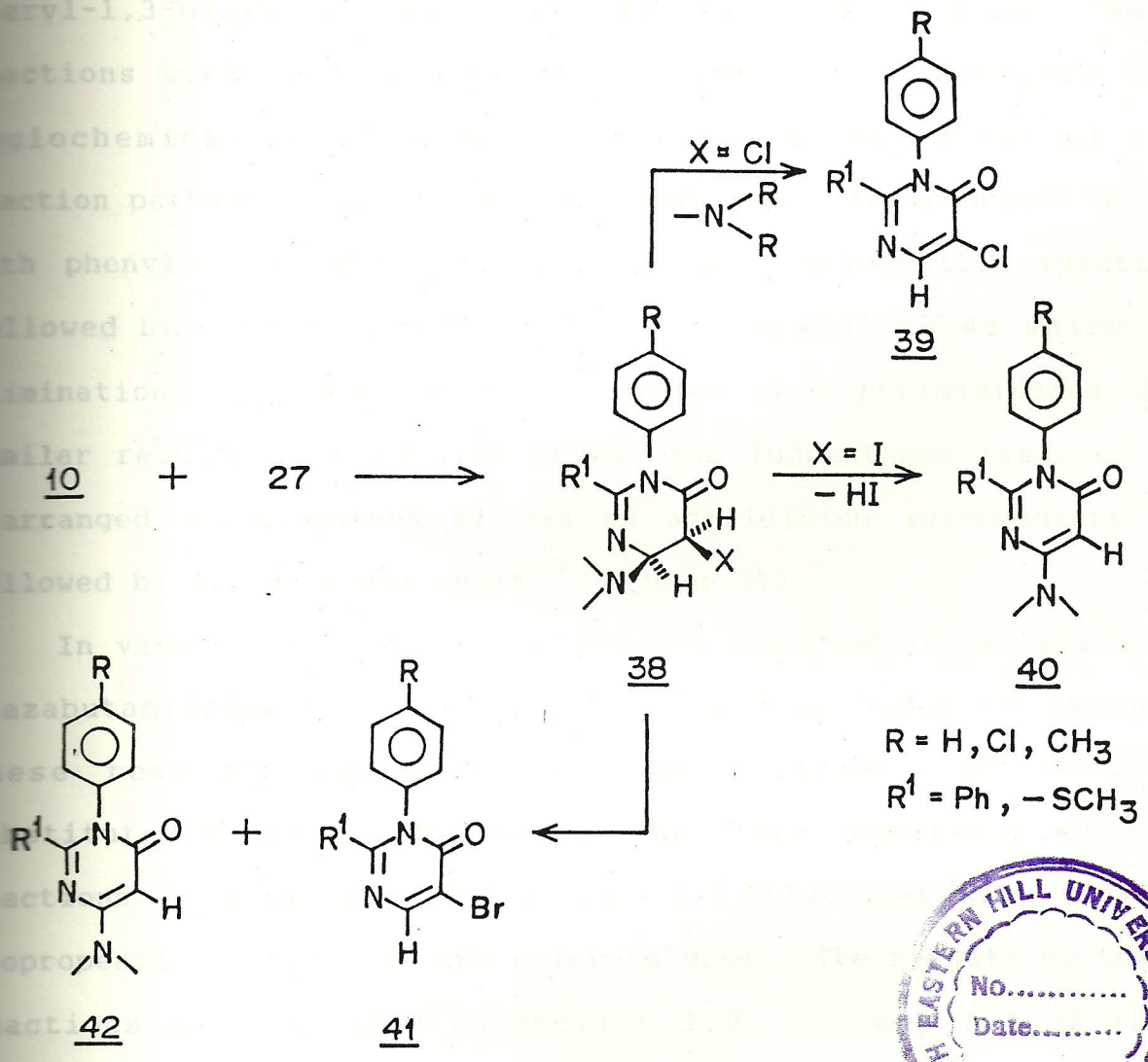


Scheme – 9



Scheme – 10

methyl sulphenyl chloride from an intermediate of the type 33 (Scheme 10). The reactions of 1,3-diaza-1,3-butadienes 10 with various haloketenes were assumed to proceed *via* [4+2] cycloadduct 38 as intermediate, which in case of chloroketene, resulted in pyrimidinones 39 with the exclusive elimination of secondaryamine



10 + 27 → 38 → 40 (X = I, − HI) ; 38 → 39 (X = Cl) ; 38 → 42 + 41

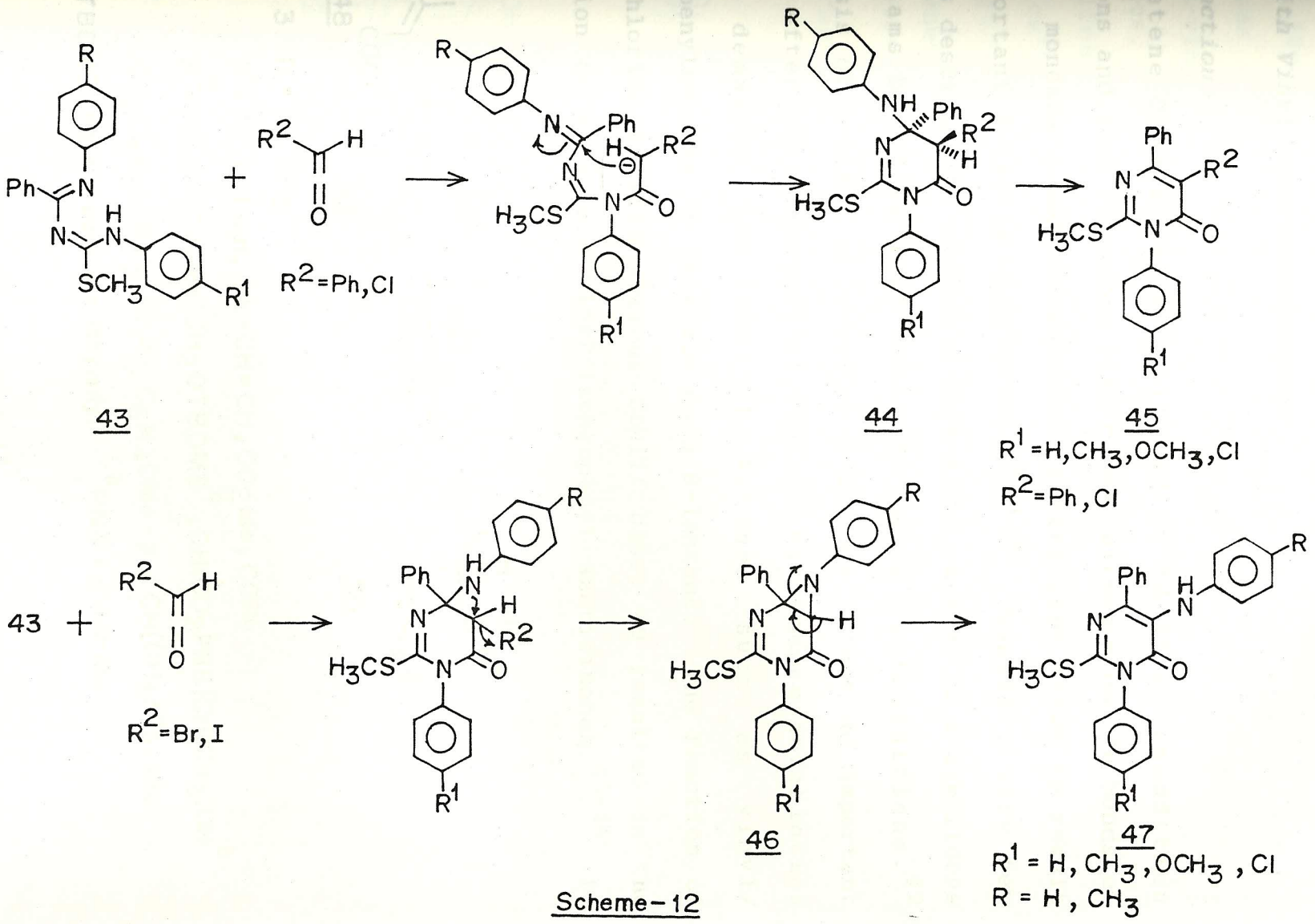
Scheme – 11

functions and pyrimidinones 40 in case of iodoketene with the exclusive elimination of HI. In case of bromoketene, the

intermediate **38** underwent loss, both of dimethylamine and hydrobromic acid resulting in pyrimidinones **41** (34%) and **42** (40%) respectively[39] (Scheme 11).

In continuation of our studies concerning 1,3-diazabutadiene-ketene cycloadditions, we have synthesised various N-aryl-1,3-diaza-1,3-butadienes **43**[40] and carried out their reactions with various ketenes in order to investigate the regiochemical aspects and to understand the nature of the reaction pathway followed in these reactions. The reaction of **43** with phenyl- and chloroketenes underwent nucleophilic reaction followed by cyclisation to yield an intermediate **44** which on elimination of primary aromatic amines gave pyrimidinones **45**. Similar reactions of **43** with bromo- and iodoketenes resulted in rearranged pyrimidinones **47** *via* an aziridinium intermediate **46** followed by 1,2-(N-aryl) shift[40] (Scheme 12).

In view of the interesting results observed in various 1,3-diazabutadiene-ketene cycloadditions and in order to exploit these reaction pathways for the synthesis of various substituted/fused pyrimidinones, we have investigated the reactions of a variety of 1,3-diaza-1,3-butadienes with vinyl-, isopropenyl-, butadienyl and chloroketenes. The results of these reactions are described in Section I.2, I.3 and I.4 of this Chapter.


R
Ph
N
H
N
SCH3
R1
R2
H
O
R2=Ph,Cl
H3CS
Ph
H
Θ
NH
43
44
45
R1=H,CH3,OCH3,Cl
R2=Ph,Cl
43 +
R2=Br,I
46
47
R1 = H, CH3, OCH3, Cl
R = H, CH3

Scheme-12