INVESTIGATIONS ON OXOKETENE S,S-ACETALS : NEWER SYNTHETIC METHODS FOR NOVEL CARBOCYCLES AND HETEROCYCLES

ABSTRACT

By

BISWAJIT DEB

DEPARTMENT OF CHEMISTRY
SCHOOL OF PHYSICAL SCIENCES

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

DOCTOR OF PHILOSOPHY

To

NORTH-EASTERN HILL UNIVERSITY

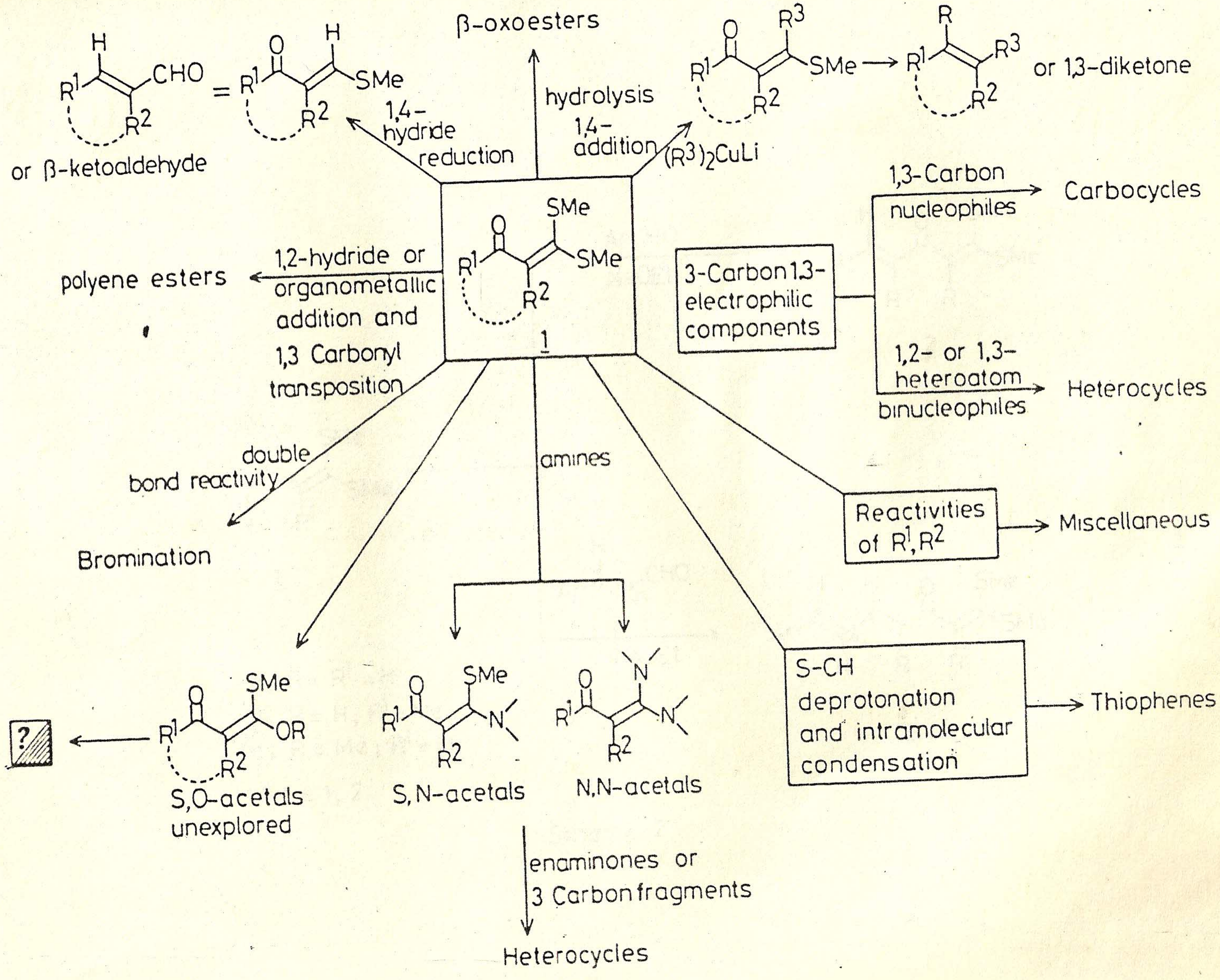
SHILLONG-793001

INDIA

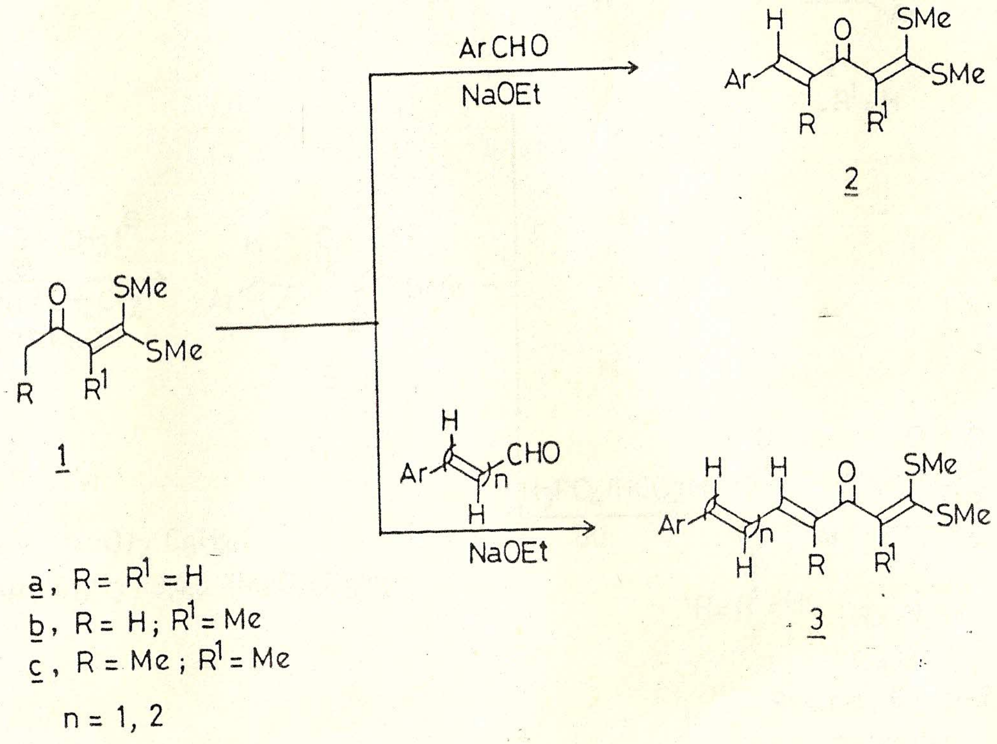
1990

The synthesis of α-oxoketene dithioacetals of general formula 1 was first reported in 1910, by Kelber and coworkers^{1}. This class of compounds can be easily prepared from a wide variety of active methylene compounds and carbon disulfide in presence of a suitable base followed by alkylation. Many experimental variations of this method have been developed$^{2-4}$ in order to improve the yields of dithioacetals 1 evolving the overall process to be a one pot transformation. They are known to be versatile synthones and have been recognized as useful building block in various synthetic transformations^{5}. The α-oxoketene dithioacetals posses 1,3-electrophilic centers with differing electrophilicity, this property has been extensively exploited for the construction of new bonds involving 1,2, 1,4 or both nucleophilic additions leading to a number of new synthetic methodologies for a wide range of organic molecules. (Scheme 1)

Among other uses of these compounds, the oxoketene dithioacetals 1 derived from aliphatic ketones (Scheme 2) are of particular interest, as they can be condensed with various aromatic aldehydes to afford the corresponding cinnamoyl ketene dithioacetals 2 and 3 in excellent yields^{6}. In the present study, it was proposed to undertake some of the important transformations based on α-cinnamoyl ketene dithioacetals 3. The second chapter deals with the synthesis of substituted cyclopentanones 5, 6 and 7 obtained by acid catalyzed ring opening of the cyclopropyl ketene^{7} 4 (Scheme 3). The cyclopropyl ketone 4


β-oxoesters
hydrolysis
1,4-addition
(R3)2CuLi
or 1,3-diketone
1,4-hydride reduction
or β-ketoaldehyde
SMe
R1
R2
R3
CHO
1
1,2-hydride or organometallic addition and 1,3 Carbonyl transposition
polyene esters
double bond reactivity
Bromination
3-Carbon 1,3-electrophilic components
1,3-Carbon nucleophiles
Carbocycles
1,2- or 1,3-heteroatom binucleophiles
Heterocycles
Reactivities of R1,R2
Miscellaneous
S-CH deprotonation and intramolecular condensation
Thiophenes
amines
S,O-acetals unexplored
S,N-acetals
N,N-acetals
enaminones or 3 Carbon fragments
Heterocycles
?

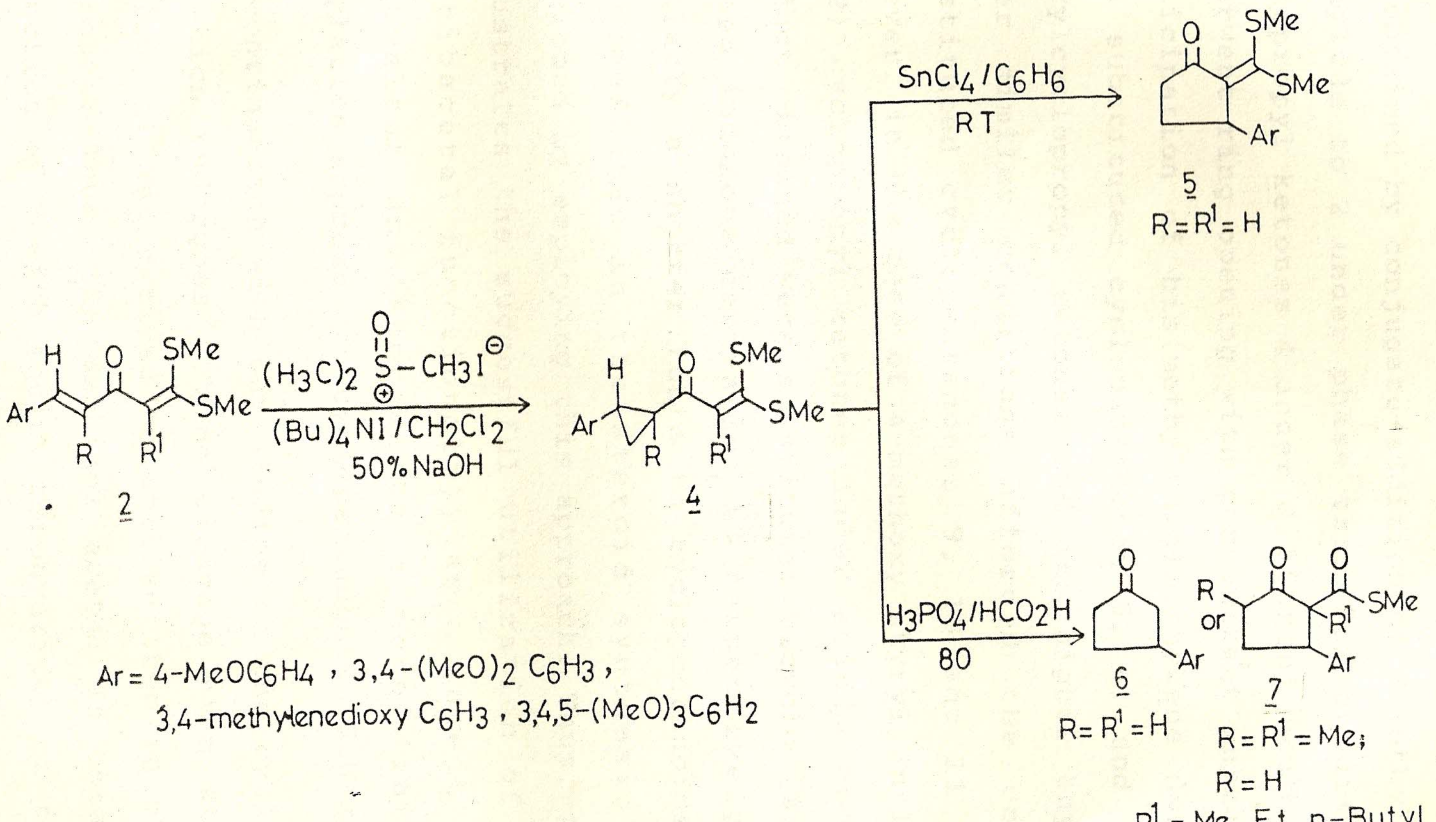
Scheme-1



a, $R = R^1 = H$
b, $R = H; R^1 = Me$
c, $R = Me; R^1 = Me$

$n = 1, 2$

Scheme- 2



$R = R^1 = H$ (5)

$R = R^1 = H$ (6)

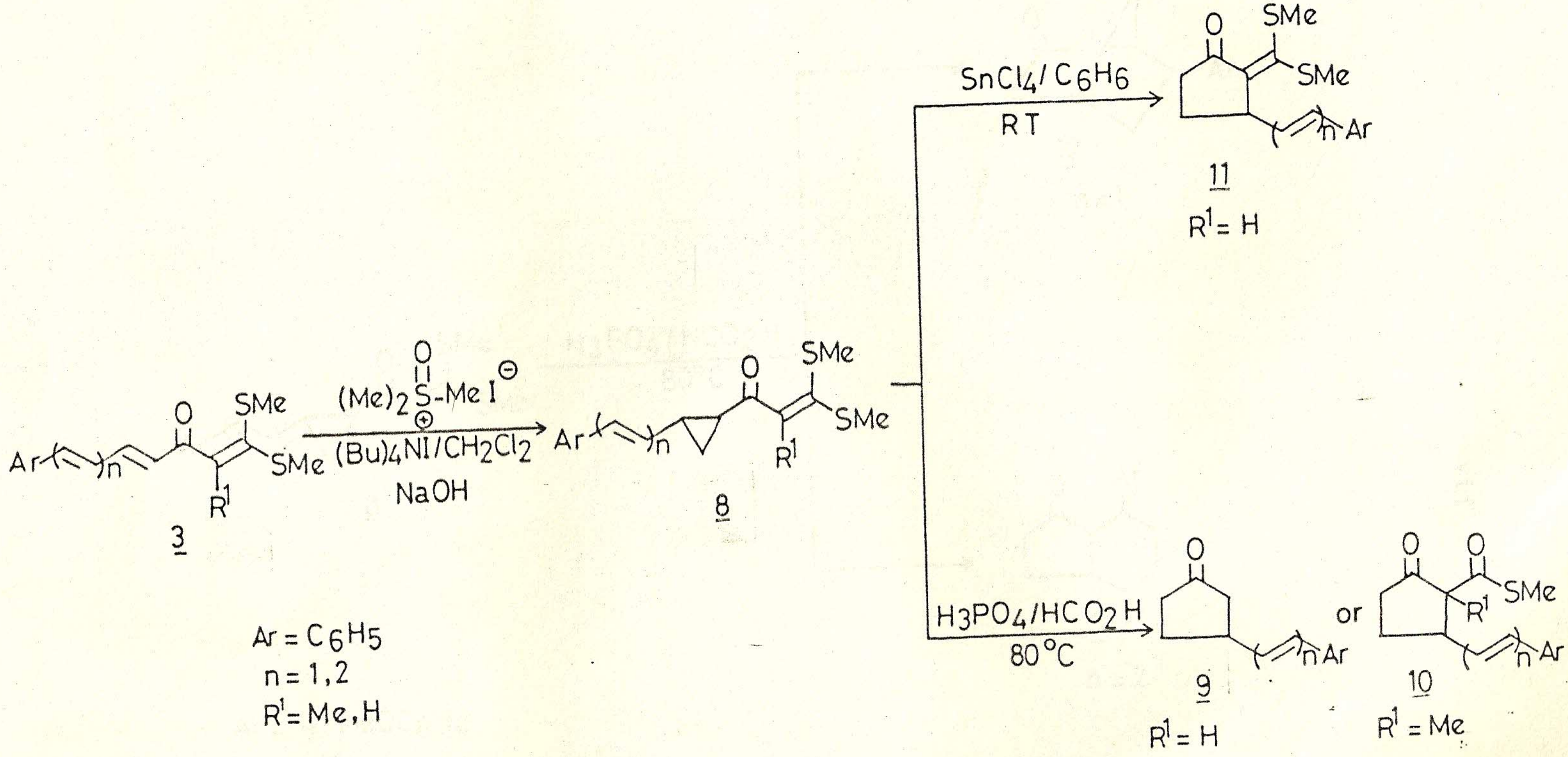
$R = R^1 = Me$; $R = H$, $R^1 = Me$, Et, n-Butyl, n-neptyl (7)

Ar = 4-MeOC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4-methylenedioxy C$_6$H$_3$, 3,4,5-(MeO)$_3$C$_6$H$_2$

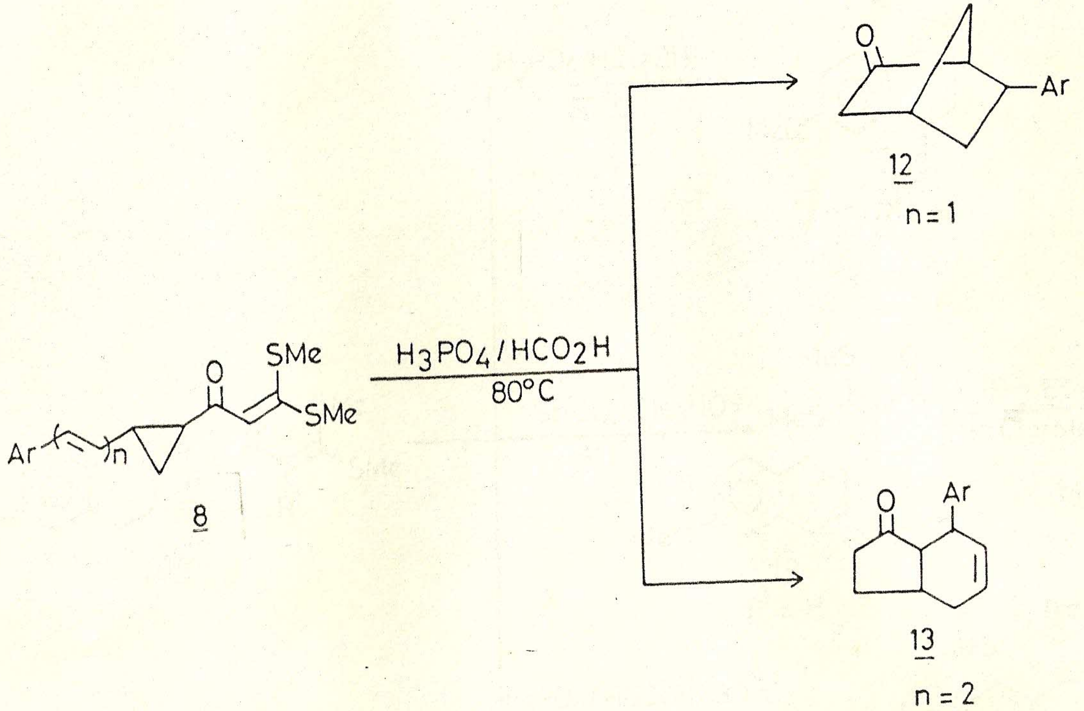
Scheme-3

was obtained by conjugate addition of dimethylsulphoxonium methylide to 2 under phase transfer conditions. These cyclopropyl ketones 4 under different acidic conditions underwent ring opening with concomitant intramolecular π-participation of bis(methylthio)methylene double bond to give substituted cyclopentanones 5, 6, and 7. Similarly styrylcyclopropyl ketones and its higher enyl homologs 8 under similar conditions afforded the corresponding substituted cyclopentanones 9, 10 and 11 (Scheme 4). However, in the case of 4-methoxy styryl (n=1) and dienyl (n=2) cyclopropyl ketones under acidic condition, the product obtained were substituted bicyclo [2.2.1] heptane 12 and indanone derivative 13 respectively.(Scheme 5) Similarly a shorter route to cyclopentanoids 17 and 18, intermediates in the steroid synthesis[8], has been developed by employing this approach. Thus, these methods illustrates the successful utilization of α-oxoketene dithioacetal functionality as a latent β-ketoester equivalent and represents a novel intramolecular alkylative approach to cyclopentanones (Scheme 6).

In continuation with our studies on the cyclopropylketones 8, which undergoes a ring cleavage even at mild acidic medium, it was decided to utilize them in more synthetic purposes. Thus, the carbinol acetal 19 obtained by 1,2-reduction of 8 with sodium borohydride, on treatment with pyridinium tosylate underwent dehydration followed by ring opening to give 1,1 bis(methylthio)polyene acetals 20. On

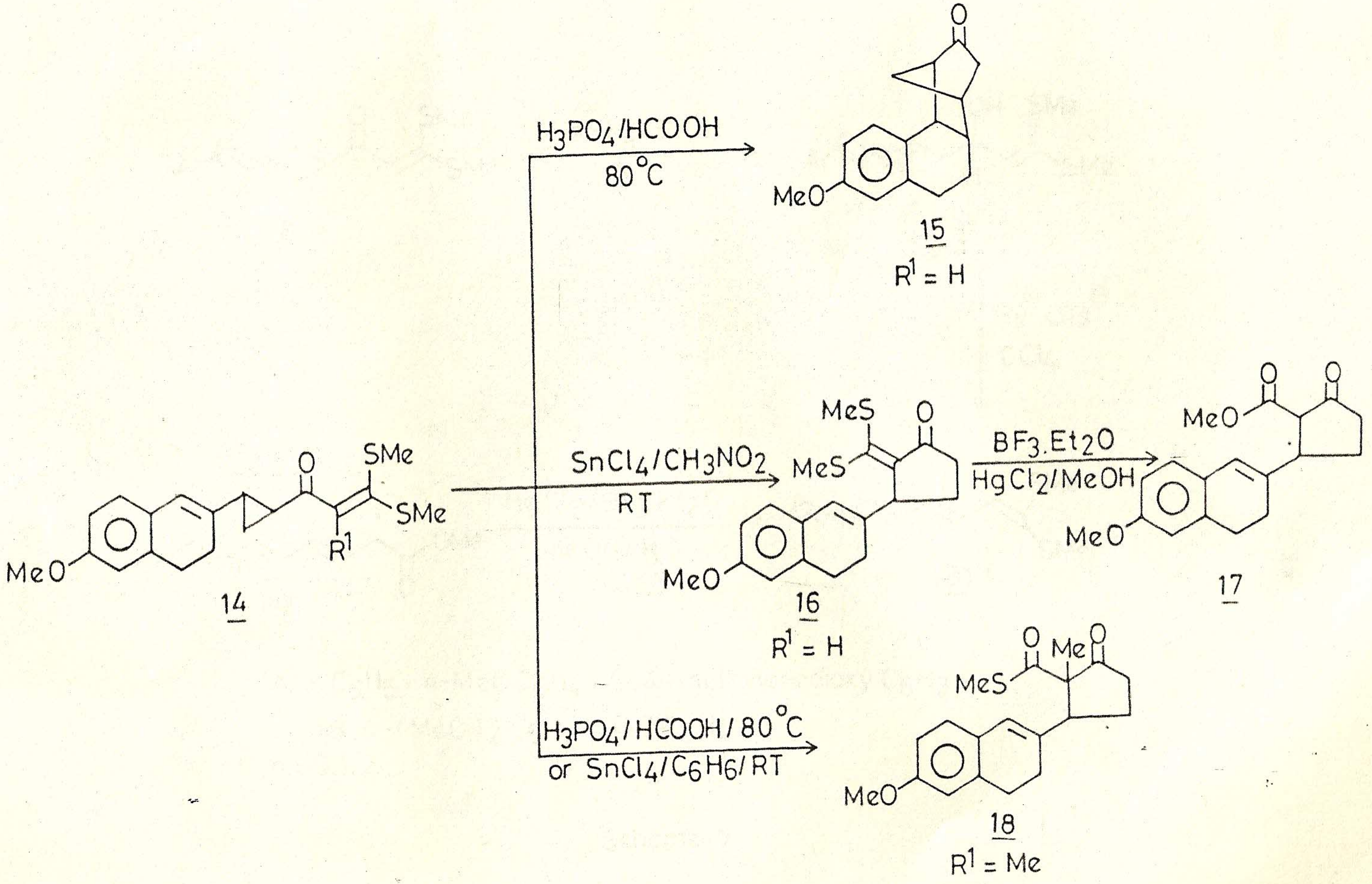

SMe
SMe
O
Ar
n
R1
3
(Me)2 S-Me I
(Bu)4NI/CH2Cl2
NaOH
8
SnCl4/C6H6
RT
11
R1 = H
H3PO4/HCO2H
80°C
9
R1 = H
or
10
R1 = Me
Ar = C6H5
n = 1,2
R1 = Me,H

Scheme-4

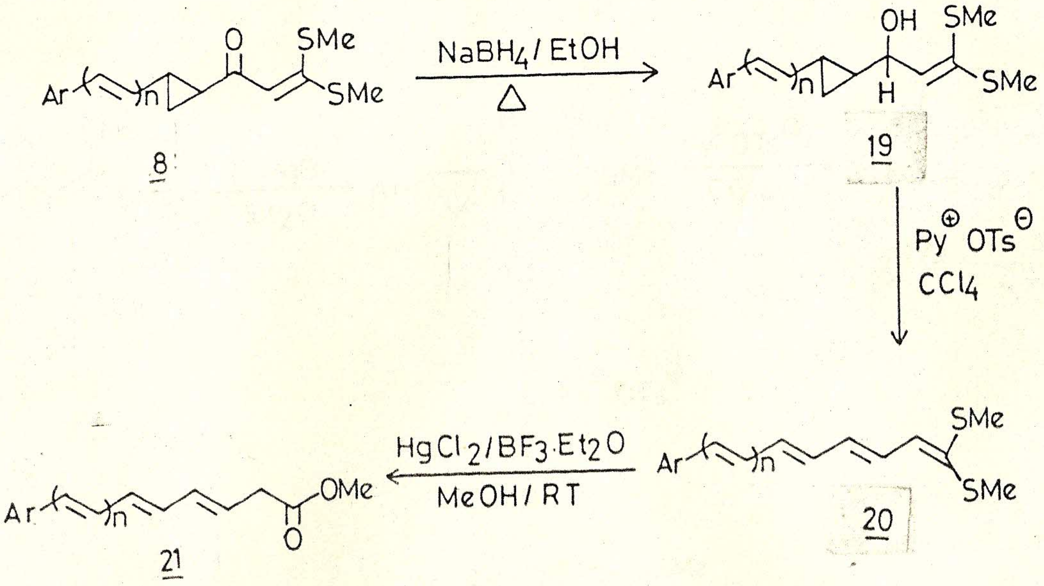


Ar = 4-MeOC$_6$H$_4$

Scheme-5

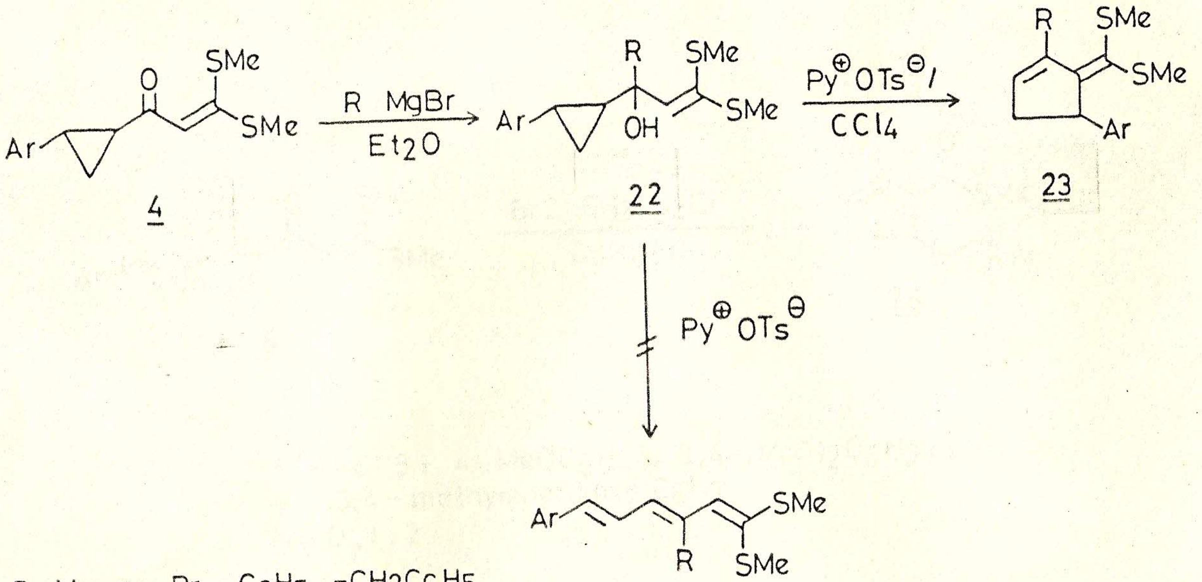

H3PO4/HCOOH
80°C
15
R1 = H
SnCl4/CH3NO2
RT
MeS
MeS
16
R1 = H
BF3.Et2O
HgCl2/MeOH
MeO
17
MeO
SMe
SMe
R1
14
H3PO4/HCOOH/80°C
or SnCl4/C6H6/RT
MeS
Me
18
R1 = Me

Scheme-6



Ar = C_6H_5, 4-MeOC_6H_4, 3,4-methylenedioxy C_6H_3,
3,4-$(MeO)_2$ C_6H_3, 4-ClC_6H_4
n = 0,1,2

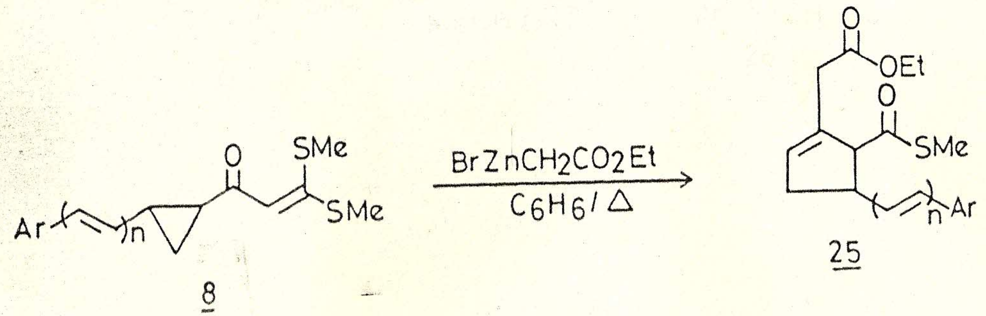
Scheme-7



$R = Me, n-Pr, C_6H_5, -CH_2C_6H_5$

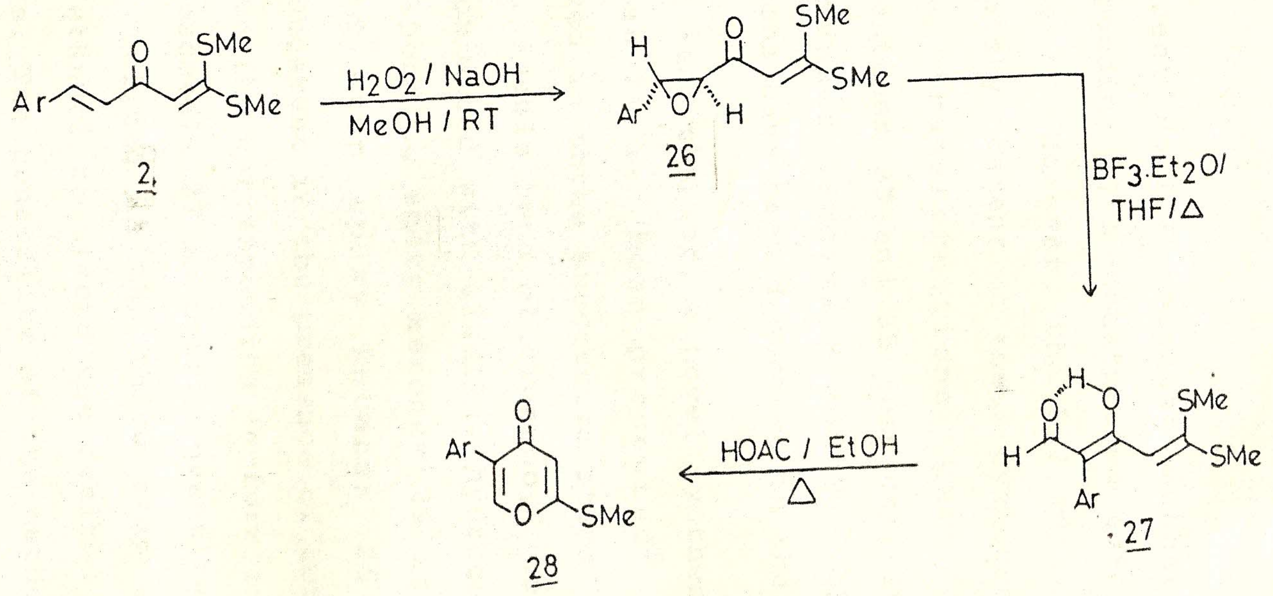
$Ar = C_6H_5, 4-MeOC_6H_4$

Scheme-8



Ar = C_6H_5 , 4-MeOC_6H_4 , 3,4-$(MeO)_2C_6H_3$,
3,4- methylene dioxy C_6H_3
n = 0 ,1 , 2

Scheme- 9



Ar= C_6H_5 ; 4-MeC_6H_4 ; 4-ClC_6H_4 ; 4-MeOC_6H_4 , 3-MeOC_6H_4 ;
3,4-$(MeO)_2C_6H_3$; 3,4,5-$(MeO)_3C_6H_2$; 3,4- methylenedioxy C_6H_3

Scheme- 10

subsequent Hg(II) assisted methanolysis 20 gave the corresponding β, γ-unsaturated esters 21 in good yields (Scheme 7). However, the 1,2-addition of Grignard and Reformatsky reagent to these cyclopropyl ketones and their future transformations gave the corresponding cyclopentenes 23 and 25 respectively, cyclized in *5-exo-trig* manner (Scheme 8 and 9). The details of these reactions have been described in the third chapter.

In the last chapter, a novel synthesis of substituted γ-pyrones 28 has been presented[9]. This synthesis was achieved in three successive steps. In the first step the styryl double bond of cinnamoyl ketene dithioacetals 2 were oxidized with alkaline hydrogenperoxide to give the corresponding epoxy ketones 26 in good yields. In the second step epoxy ketones 26 were subjected to rearrangement in the presence of borontrifluoride etherate to give the corresponding (α-formyl-α-phenylacetyl) ketene dithioacetals 27 in nearly quantitative yield, which were then cyclized in the third step by refluxing in acetic acid/ethanol to afford the desired pyran-4-one 28 in good yields. The generality of the method have been studied in greater details which is described in the present chapter.

REFERENCES

1. Kelber, C., *Chem.Ber.* 1910, *43*, 1252.
2. Thuillier, A.; Vialle, J., *Bull.Soc.Chim.Fr.*, 1962, 2187.
3. Chauhan, S.M.S.; Junjappa, H., *Tetrahedron*, 1976 *32*, 1779.
4. Dieter, R.K.; Jenkitkasemwong, L.; Dieter, J.W. *J.Org.Chem.*, 1984, *49*, 3183.
5. Dieter, R.K., *Tetrahedron*, 1986, *42*, 3029.
6. Thuillier, A.; Vialle, J., *Bull.Soc.Chim.Fr.*, 1962, 2182.
7. Deb, B.; Ila, H.; Junjappa, H. *Tetrahedron Lett.*, 1988, *29*, 2111.
8. Trost, B.M. *Chem.Soc.Rev.*, 1982, *11*, 141.
9. Deb, B.; Asokan, C.V.; Ila, H.; Junjappa, H. *Synthesis* 1987, 893.