REACTIONS OF 1,4-DICHLOROBUT-2-YNE DERIVATIVES LEADING TO HETEROCYCLES

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Abstract - This short review summarizes the syntheses of various types of chrom-3-ene derivatives by hydration of acetylenic linkage and polyheterocycles such as benzofuro[3,2-*c*]benzopyrans, benzofuro[3,2-*b*]benzofurans, benzofuro[2,3-*b*]-benzofurans and a number of other heterocyclic systems by [3,3] sigmatropic rearrangements from 1,4-dichlorobut-2-yne derivatives.

CONTENTS :

[1]benzopyran

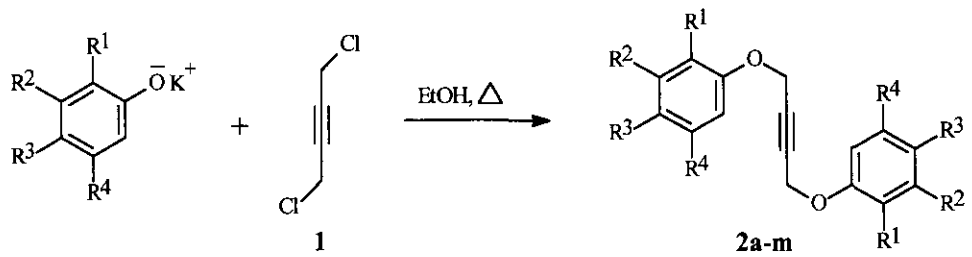
4.3 Synthesis of polyheterocycles by sequential [3,3] sigmatropic rearrangements.

1. INTRODUCTION

Quite a good amount of work has been carried out on the reactions of 1,4-dichlorobut-2-yne (**1**) derivatives since its preparation[1] from but-2-yn-1,4-diol by Johnson. For synthesis of heterocyclic compounds mainly two different reactions were utilized *viz.* (i) Claisen rearrangement of various 1,4-diaryloxybut-2-ynes and 4-aryloxybut-2-yn-1-yloxyheterocycles, (ii) hydration of various 1,4-disubstituted derivatives of 1,4-dichlorobut-2-yne. In 1963 Thyagarajan *et al.* initiated the work on 1,4-diaryloxybut-2-yne and subsequently developed it into a reaction of synthetic utility for the synthesis of heterocycles *viz.* chrom-3-ene derivatives, benzofuro[3,2-*c*][1]benzopyrans (11a-methylpterocarpans), benzofuro[3,2-*b*]benzofurans and benzofuro[2,3-*b*]benzofurans. The reactions are fascinating because the but-2-ynyl derivatives in most of their reactions *viz.* hydration followed by cyclization, or Claisen rearrangement followed by cyclization give isomeric products. Consequently various heterocycles can be synthesized in an unconventional manner by simple molecular reorganizations. This short review is limited to present only the aforesaid two reactions of 1,4-dichlorobut-2-yne derivatives yielding heterocycles. This part does not include the amine oxide and sulfoxide rearrangements of *N*-alkylanilino and arylthio derivatives which will form part two of the review and will be communicated later.

2. Preparation of 1,4-dichlorobut-2-yne derivatives.

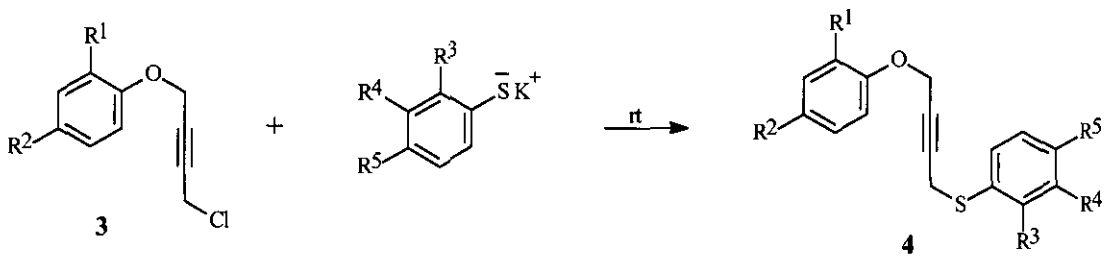
1,4-Bis-derivatives of 1,4-dichlorobut-2-yne are generally prepared from 1,4-dichlorobut-2-yne (**1**) by the nucleophilic displacement of chlorides by aryloxy anion. 1,4-Diaryloxybut-2-ynes (**2**) are prepared according to the procedure[1] of Johnson *et al.*



1 **2a-m**

1-Aryloxy-4-arylthiobut-2-ynes (**4**) were prepared by the addition a solution of 1-aryloxy-4-chlorobut-2-yne (**3**) in ethanol to a solution of arylmercaptan and potassium hydroxide in ethanol under nitrogen at room temperature.[2,3]

Corresponding sulfoxides and sulfones were prepared by selective oxidation with one or two equivalents of *m*-chloroperoxybenzoic acid in dichloromethane.



Other unsymmetrical 1,4-disubstituted but-2-ynes are usually prepared from 1-aryloxy-4-chlorobut-2-ynes[4,5] (**3**) by replacing the chloride with an oxy anion on a heterocyclic moiety. This may be achieved by classical alkylation procedure[6] *i.e.* by refluxing 1-aryloxy-4-chlorobut-2-yne (**3**) and the appropriate heterocyclic compound with a hydroxy group at a suitable position in acetone in the presence of anhydrous potassium carbonate or by phase transfer catalyzed alkylation condition[7] *i.e.* by stirring a solution of 1-aryloxy-4-chlorobut-2-yne (**3**) and the appropriate heterocyclic compound with a hydroxy group at a suitable position in dichloromethane and sodium hydroxide solution at room temperature in the presence of a phase transfer catalyst (PTC) such as benzyltriethylammonium chloride or tetrabutylammonium bromide.[8] Classical alkylation proved to be better for obtaining *O*-alkylated products in case of ambident nucleophiles. In some cases PTC condition resulted *C*-alkylation, *C,C*-dialkylation in preference to *O*-alkylation.[8,9]

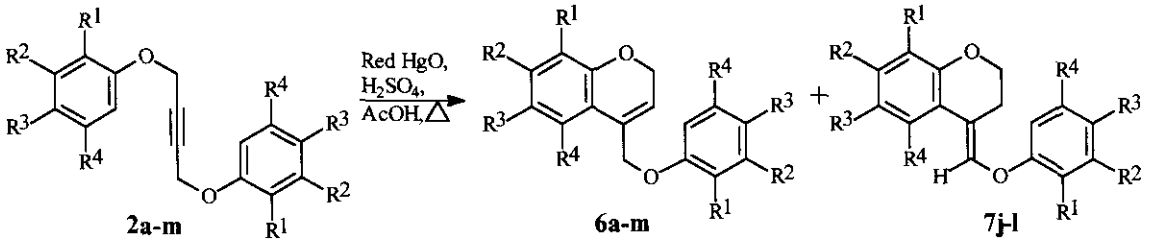
3. Synthesis of heterocycles by hydration of acetylenic linkage of 1,4-bis-derivatives of 1,4-dichlorobut-2-yne.

Hydration of alkynes has long evoked interest as a synthetic reaction of value[10-12] catalyzed by mineral or Lewis acids and mercuric ion, the products of such hydration have variously afforded ketones,[13] enol acetates,[14] ketols[15] and heterocyclic ring products.[16] This reaction has been successfully employed for the synthesis of 4-substituted chrom-3-ene from 1,4-dichlorobut-2-yne derivatives *viz.* 1,4-bis(aryloxy)but-2-ynes (**2a-m**), 1-aryloxy-4-arylthiobut-2-ynes (**4a-o**) and 1-aryloxy-4-arylsulfonylbut-2-ynes (**5a-o**).

3.1 Hydration of 1,4-diaryloxybut-2-ynes (2).

Hydration of 1,4-diaryloxybut-2-ynes[17] (**2a-m**) with red mercuric oxide in refluxing acetic acid in the presence of concentrated sulfuric acid afforded 4-aryloxymethylchrom-3-ene (**6a-m**) (Scheme 1). Hydration of **2** with mercuric oxide and sulfuric acid was remarkable because simple phenyl propargyl ether (**8**) affords only phenoxyacetone (**9**) under identical condition. Other route[18] for the syntheses of 4-aryloxymethylchrom-3-ene is a much longer one starting from 4-chlorobut-2-yn-1-ol[19] (Scheme 2).

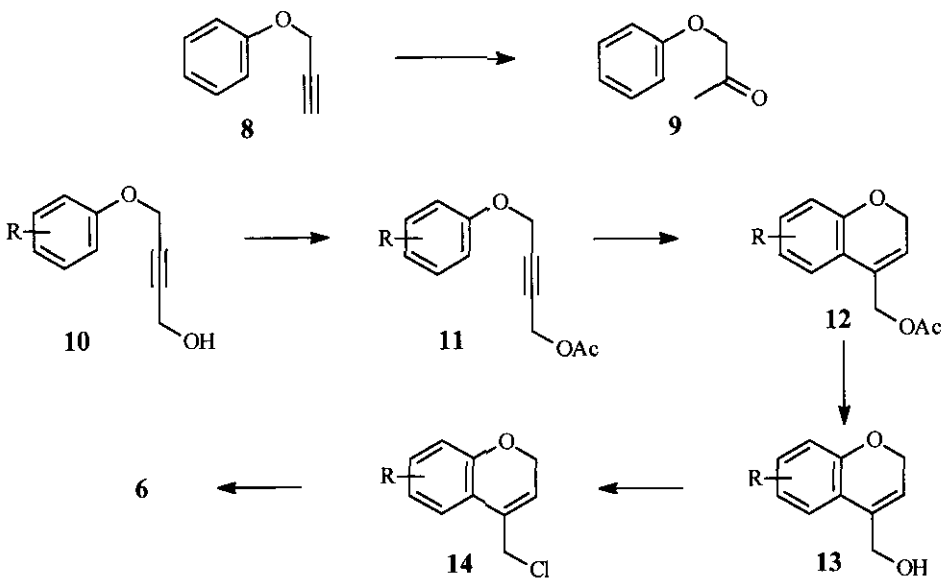
This approach of synthesis of aryloxymethylchrom-3-ene derived additional interest in view of a report on the biological activity of 1-aryloxymethyl-3,4-dihydroisoquinolines (**15**). The latter compounds have been



	R^1	R^2	R^3	R^4	Yield (%)
a,	H	H	Cl	H	26
b,	H	H	H	H	30
c,	Cl	H	Cl	H	30
d,	Me	H	Cl	H	20
e,	Br	H	H	H	24
f,	H	H	Br	H	30
g,	OMe	H	H	H	60
h,	Ph	H	H	H	26
i,	H	H	Ph	H	41
j,	Me	H	H	H	58
k,	Me	H	H	Me	60
l,	H	H	Me	H	58
m,	Cl	H	H	H	31

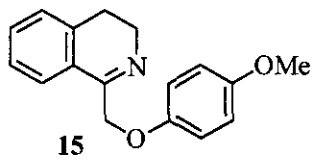
	R^1	R^2	R^3	R^4	Yield (%)
j,	Me	H	H	H	15
k,	Me	H	H	Me	20
l,	H	H	Me	Me	15

Scheme 1



Scheme 2

shown to possess strong inhibitory effect on the component enzyme, viral neuraminidase, present in common respiratory pathogenic viruses.[20] So the potential of analogous systems were investigated.[17]

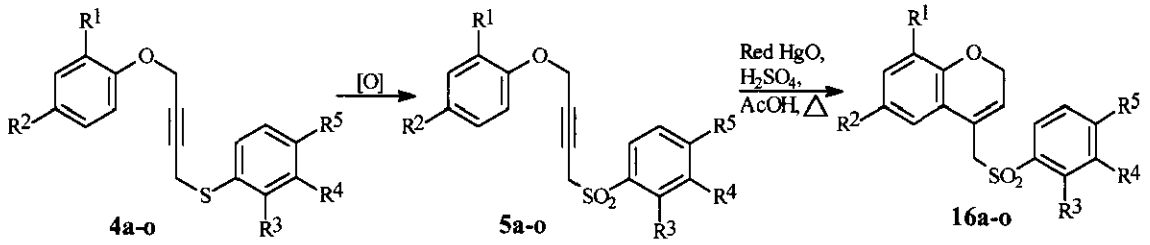


15

Contrary to earlier experience at hydration of the acetylenes utilizing mercuric sulfate as the preferred catalyst, it was found that a combination of red mercuric oxide and a few drops of sulfuric acid in acetic acid medium afforded more clean and better products.[17] The 4-aryloxymethylchrom-3-enes (**6a-m**) were unstable to prolonged heating in acid.[17] There is an optimal reaction time for the hydration to proceed without much destruction of the product formed. Of the several 1,4-diaryloxybut-2-ynes (**2a-m**) studied, there were three which not only gave the chromens (**6a-m**) but also the thermally equilibrated exomethylene isomers (**7j-l**) (Scheme 1).[17]

3.2 Hydration of 1-aryloxy-4-arylsulfonylbut-2-ynes (5).

The aforesaid one step synthesis of chrom-3-enes (**6a-m**) was extended to the hydration of 1-aryloxy-4-arylsulfonylbut-2-ynes (**5a-o**).[21] The availability of of two different modes of cyclization to these unsymmetrical substrates (**5a-o**) generated additional interest.



4a-o **5a-o** **16a-o**

	R^1	R^2	R^3	R^4	R^5	Yield (%)		R^1	R^2	R^3	R^4	R^5	Yield (%)
a,	H	Cl	H	H	Cl	64	**i,**	H	Cl	H	H	NO_2	44
b,	H	Me	H	H	Cl	66	**j,**	Cl	H	H	H	Cl	70
c,	H	Me	Me	H	H	74	**k,**	Me	H	H	H	Cl	62
d,	H	H	H	H	Cl	60	**l,**	Me	H	H	phenylene		53
e,	Me	H	Me	H	H	62	**m,**	H	Cl	H	H	t-Bu	44
f,	H	Cl	H	H	Br	52	**n,**	H	Cl	H	phenylene		52
g,	H	Cl	H	H	OMe	50	**o,**	H	Cl	H	H	H	58
h,	Cl	Cl	H	H	Cl	26							

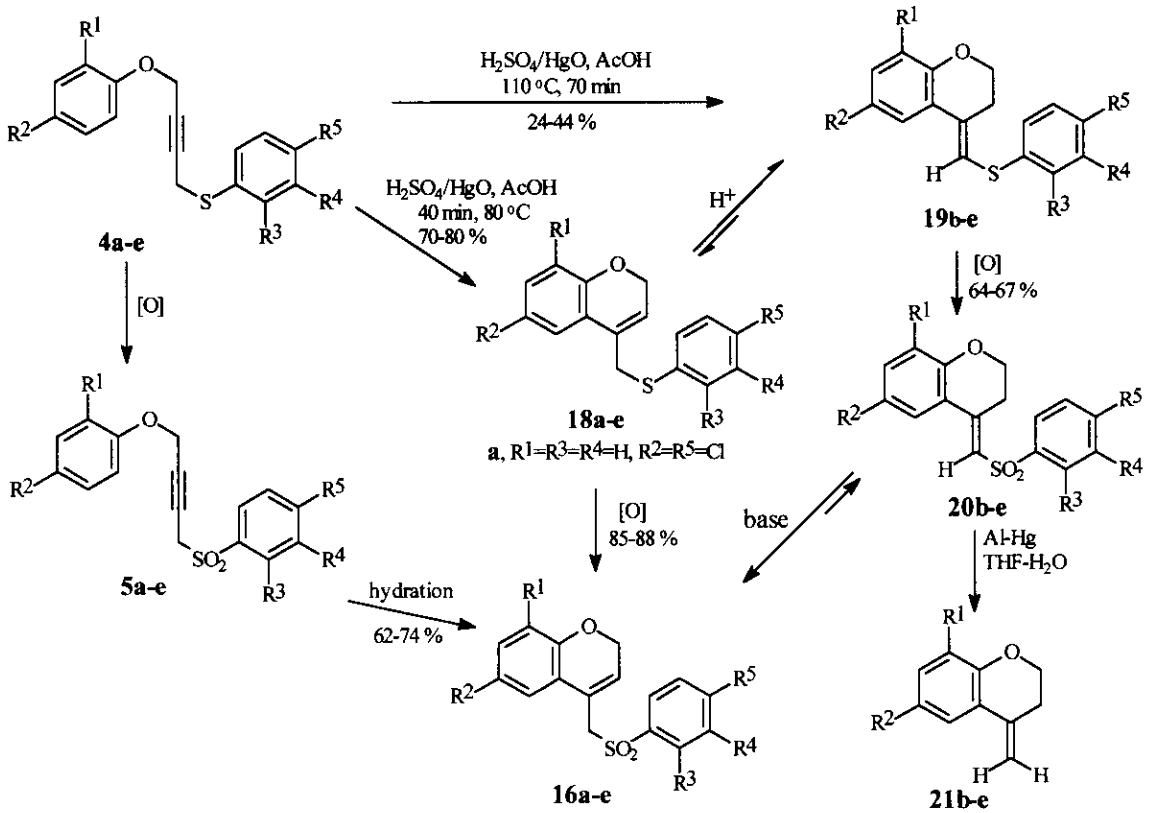
Scheme 3

Treatment of the substrates (**5a-o**) with red mercuric oxide and sulfuric acid in refluxing acetic acid gave only one type of products (**16a-o**) of cyclization out of the two different possibilities.[21] When compared with the corresponding 1,4-diaryloxybut-2-ynes (**2a-m**), the sulfones (**5a-o**) gave higher yields of chrom-3-enes[22] (**16a-o**) because of varying stabilities of the respective chrom-3-enes in the acidic reaction

medium. Perhaps, the sulfone function has directive influences on the mode of cyclization to give only one type of products (Scheme 3).

3.3 Hydration of 1-aryloxy-4-arylthiobut-2-ynes (4).

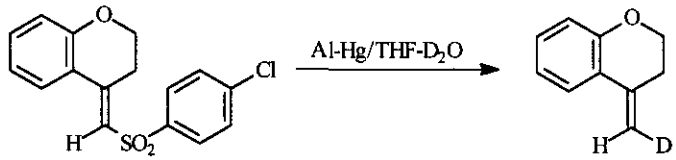
The facility of cyclization of **2a-m** and **5a-o** to chromenes in the aforesaid reactions, prompted further investigation[23] on the analogous synthesis of thiochromenes from 1-aryloxy-4-arylthiobut-2-ynes (**4a-e**) and 1,4-bis(arylthio)but-2-ynes (**17**). The hydration of 1-aryloxy-4-arylthiobut-2-ynes (**4a-e**) was investigated using hot glacial acetic acid as solvent alongwith red mercuric oxide and a trace of concentrated sulfuric acid as catalysts.[24] Of the five substrates (**4a-e**) examined each gave a single product. One of these was readily identified as the chromene (**18a**) by its facile oxidation to **16a** reported[21] earlier. Each of the other four products (**19b-e**) on oxidation with *m*-chloroperoxybenzoic acid afforded corres-ponding sulfones (**20b-e**). Interestingly, chromatography of these sulfones over basic alumina (or treatment of a d^3-chloroform solution with dilute alkali in an NMR tube) resulted in a quantitative conversion into the chrom-3-enes (**16b-e**). The sulfones (**20b-e**) were, however, quite stable to chromatography over neutral alumina. Isomerization of a vinylic sulfone into the corresponding allylic



Scheme 4

sulfone during chromatography has been reported[25,26] previously. Additional corroboration of vinyl sulfone structure in the sulfone (**20b-e**) was readily obtained by an aluminum amalgam reduction of the vinyl sulfone to the 4-methylenechroman (**21b-e**) (Scheme 4).[23]

An interesting observation in the formation of the chrom-3-ene is the fact that, both with sulfides (**4a-e**) and the sulfones (**5a-o**), the initial product of the cyclization is the chrom-3-ene.[23] Acid catalyzed equilibration of the sulfide, however, results in conversion to the exomethylene product.[23] The geometrical disposition of the sulfone with respect to the benzene ring of the chrom-3-ene was fund to be *trans* by the reduction of sulfone (**20d**) with aluminum amalgam in deuterium oxide at low temperature. This led to the cleavage of the sulfone function and incorporated a deuterium atom in its place. The ^{1}H-NMR spectrum of this product (**22**), readily revealed the site of the deuterium atom as shown in Scheme 5.[23]



20d **22**

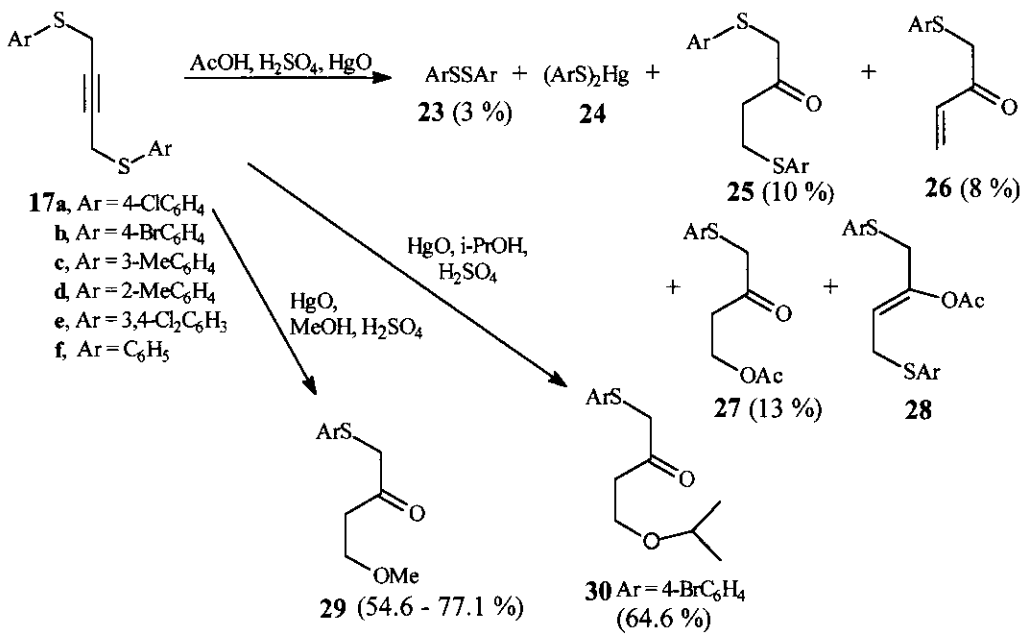
Scheme 5

The specific location of deuterium was found to be temperature dependent. Reduction of the sulfone (**20d**) at temperature above 0 ^{0}C resulted in scrambling of the deuterium on the terminal methylene leading to mixtures of **22** and its geometrical isomer. The hydration of 1-aryloxy-4-arylthiobut-2-ynes (**4a-e**) demonstrated a well-defined preference for formation of a 6-membered oxygen heterocycle and none of possible thiochrom-3-ene derivative.[23]

3.4 Hydration of 1,4-bis(arylthio)but-2-ynes (17).

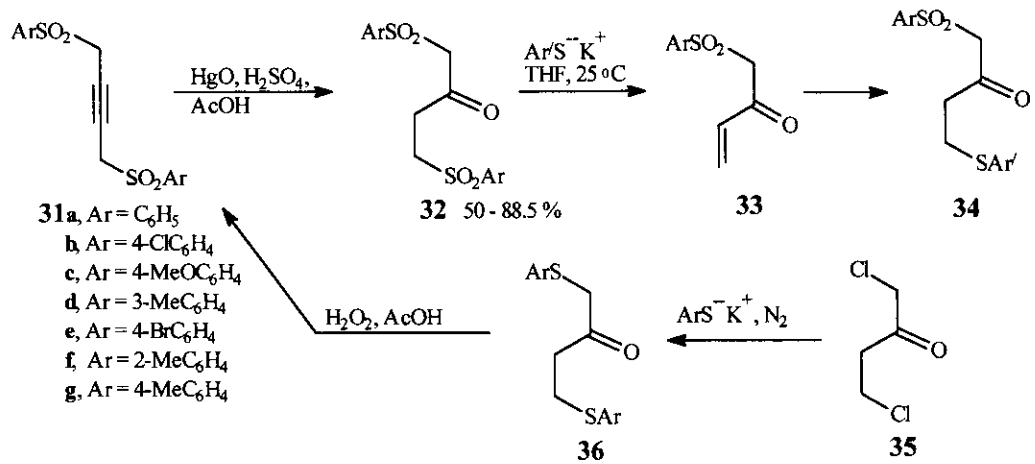
The mercuric ion-catalyzed hydration of 1,4-bis(arylthio)but-2-ynes (**17a-f**) under the same reaction conditions as stated earlier, revealed a different picture, no cyclic product was obtained even in the absence of any competing aryloxy function. This reaction afforded a variety of products in acetic acid among which are : 1,4-bis(arylthiomethyl)vinylacetate (**28**), 1,4-bis(arylthio)-2-butanone (**25**), 1-arylthio-3-buten-2-one (**26**) and 1-arylthio-4-acetoxy-2-butanone (**27**).[23] Ketone (**25**) eliminates aryl thiol[27-30] in an acidic medium yielding **26** which undergoes Michael addition of solvent to give **27**. Hydration of **17a-f** in methanol cleanly gave 1-arylthio-4-methoxy-2-butanones (**29**) (Scheme 6).[23]

Thus a study of the hydration of 1,4-bis(arylthio)but-2-ynes (**4a-e**) has failed to reveal formation of any thiochrom-3-enes. The failure indicates relatively less activation of the site of ring closure by the sulfide sulfur than oxygen in the aryl propargyl ethers. To examine this point, the hydration of 1,4-bis(arylsulfonyl)but-2-ynes[31] (**31a-g**) was investigated. The hydration of the alkyne (**31a-g**) is found to be



Scheme 6

straightforward and simple. The products from hydration of **31a-g** are ketones (**32a-g**) obtained in high yields and purity. This result provides emphatic evidence for the need for an activating function in the alkyne to observe any ring closure. Ketones (**32a-g**) are extremely stable to the acidic hydration conditions, although under mildly alkaline conditions, they are susceptible to elimination-addition sequence (Scheme 7).[27]

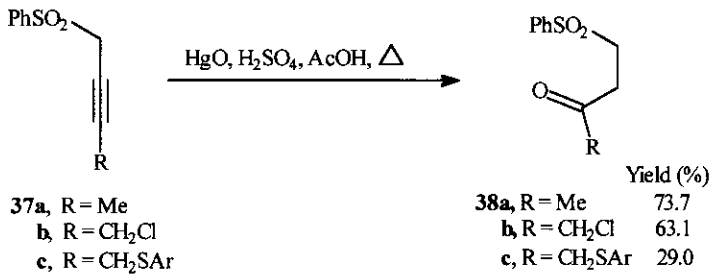


Scheme 7

3.5 Hydration of 1-arylsulfonylbut-2-ynes.

Similar results implicating the need for an activating function in the alkyne to undergo any ring closure,

were observed in a study of hydration directed to the regiospecific hydration in arylsulfonylbut-2-ynes (**37a-c**) (Scheme 8). Mercuric ion catalyzed hydration of 1-arylsulfonylbut-2-yne (**37a**), 1-arylsulfonyl-4-chlorobut-2-yne (**37b**) and 1-arylsulfonyl-4-arylthiobut-2-yne (**37c**) leads to a single ketonic products (**38a-c**) (Scheme 8). Evidence has been provided to show that the reaction is truly regiospecific, with consistent placement of the carbonyl ω- to the sulfonyl group.

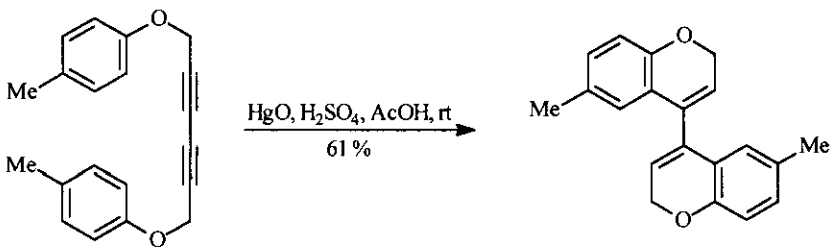


37a, R = Me
b, R = CH_2Cl
c, R = CH_2SAr

Yield (%)
38a, R = Me 73.7
b, R = CH_2Cl 63.1
c, R = CH_2SAr 29.0

Scheme 8

An interesting hydration of 1,6-diaryloxy-2,4-hexadiyne (**39**) to give 4,4′-bichrom-3-ene (**40**) was reported[32] by Balasubramanian *et al.* (Scheme 9).

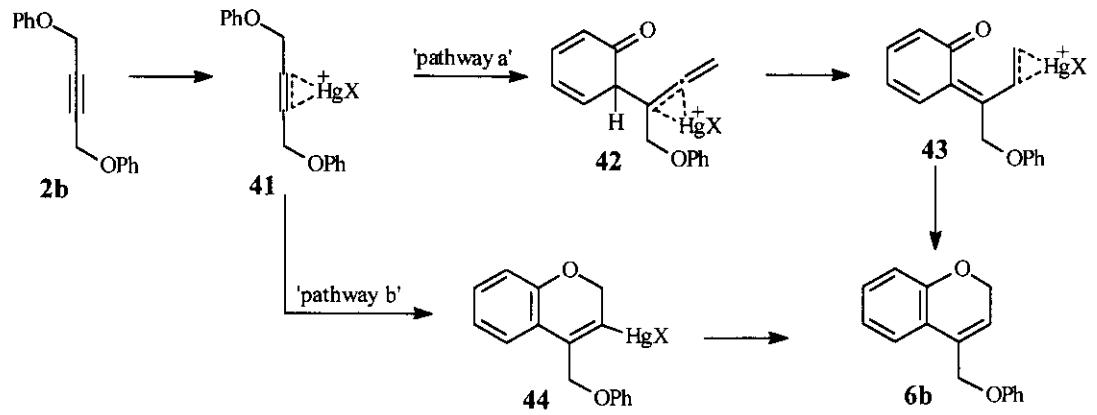


39 **40**

Scheme 9

Despite variations of results, the butynyl bis(sulfides) (**17a-f**) offer some clue to the overall mechanism of the ring closure under hydration conditions. Although ketonic products are obtained from bis(sulfides) (**17a-f**), no ring closure derivatives are detected.[23] This is in contrast to the fact that ring closed products are obtained from 1-aryloxy-4-arylthiobut-2-ynes (**4a-e**) and their sulfones (**5a-o**), but no ketonic products are detected among the hydration products.[21,23] Thus formation of the ketones and the chrom-3-enes may be by entirely separate pathways. This has been verified by Bates ans Jones[33] by preparing a number of 1,4-diaryloxy-2-butanone and subjecting them to hydration conditions and found that none produce 4-aryloxymethylchrom-3-ene (**6**). Bates *et al.* proposed an additional mechanism involving concerted sigmatropic rearrangement triggered by the charge induced π-complex formation.[34]

Another possibility involving a σ-complex, cyclization of this ion (**41**), and protonolysis of the C-Hg bond[35] produced a "two-step" sigmatropic mechanism which may be viewed as a metal ion catalyzed



Scheme 10

Friedel-Crafts alkenylation of an aromatic ring by an alkyne.[36] However, 'pathway b' was discarded on the basis of experimental evidences.[33]

4 [3,3] Sigmatropic rearrangements of 1,4-dichlorobut-2-yne derivatives.

1,4-Diaryloxybut-2-ynes (**2**) can undergo two consecutive Claisen rearrangements.[37,38] Usually these give products of two sequential rearrangements wheras 1-aryloxy-4-vinyloxybut-2-ynes afford products of the first Claisen rearrangement at a relatively much lower temperature (100-130 ^{0}C). However, the products of the second Claisen rearrangements can be obtained at a much higher temperature (above 200 ^{0}C).

4.1 Regioselective synthesis of 2*H*-pyrano- and furoheterocycles

So far we have seen that the formation of 2*H*-pyran ring fused to aryl ring can be achieved by mercury(II) catalyzed hydration of 1,4-diaryloxybut-2-ynes (**2**).[17] If the aryloxybut-2-ynyloxy function is attached to a vinyl group, the activation energy requirement is much less compared to that of aryl propargyl ether and the first [3,3] sigmatropic rearrangement occurs at a much lower temperature *ca.* 132 ^{0}C. This has been utilized for the synthesis of 2*H*-pyran ring or furan ring fused to a number of heterocycles *viz.* coumarin, quinolone, uracil etc.

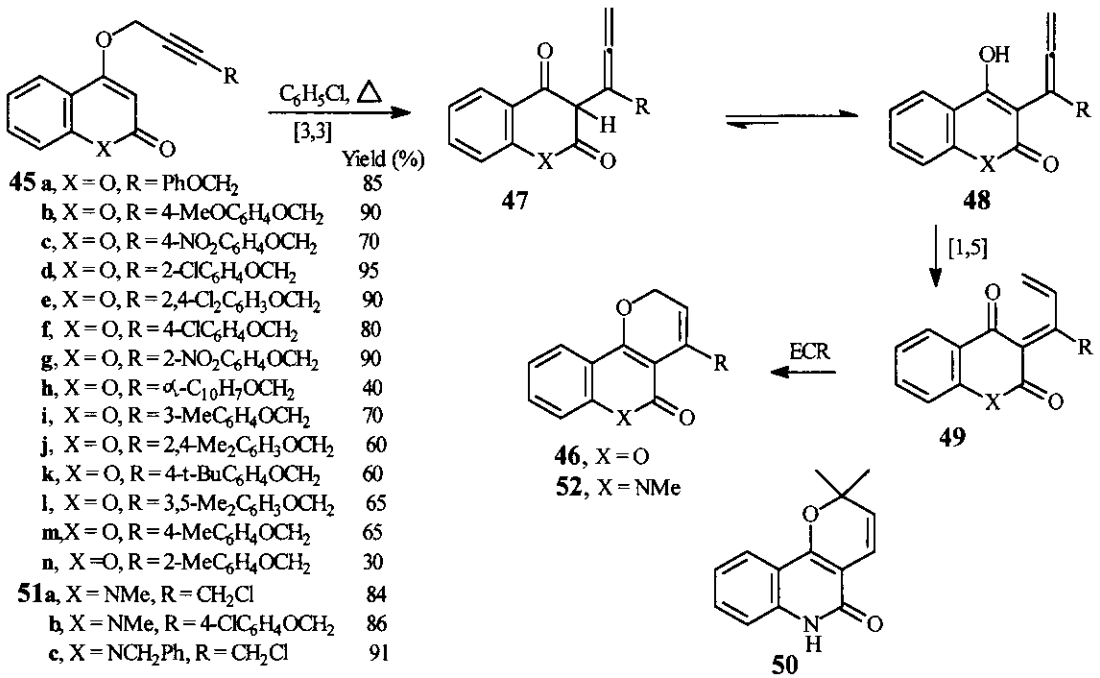
4.1.1 Regioselective synthesis of 2*H*-pyranoheterocycles.

The synthesis of 2*H*-pyranoheterocycles from the 1,4-dichlorobut-2-yne derivatives by the application of [3,3] sigmatropic rearrangement at a relatively low temperature is simple and has been proved to be a general method.[39] The following 2*H*-pyranoheterocycles have been synthesize by this protocol.

Regioselective Synthesis of Pyrano[3,2-*c*][1]benzopyran-5(2*H*)-ones (46) and Pyrano[3,2-*c*]quinolin-5(2*H*)-ones (52).

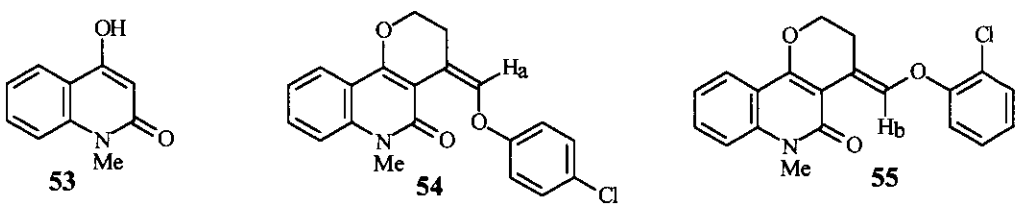
The ethers, 1-aryloxy-4-(4′-coumarinyloxy)but-2-ynes (**45a-h**) were heated in refluxing chlorobenzene to

give pyrano[3,2-*c*][1]benzopyran-5(2*H*)-ones (**46a-h**) in almost quantitative yields. All the forteen butyne derivatives studied expectedly underwent [3,3] sigmatropic rearrangement at the 4-(4′-coumarinyloxy)propynyl part to give pyranocoumarin derivatives (**46a-h**) and no furocoumarin was formed at all[39] (Scheme 11).



Scheme 11

Flindersine, 2,2-dimethylpyrano[3,2-*c*]quinolin-5(2*H*)-one (**50**) and various substituted flindersine derivatives are widely distributed in nature.[40-45] A good deal of work has been reported on the synthesis of flindersine[46-49] and its analogs with various substitution in the aromatic ring.[50-52] A simple methodology for the regioselective synthesis of flindersine analogues, pyrano[3,2-*c*]quinolin-5(2*H*)-ones (**52a-c**) with variation in the dihydropyran ring has recently been reported[53] (Scheme 11) *via* the thermolysis of 4-(1-aryloxybut-2-ynyloxy)quinolin-2(1*H*)-ones (**51a-c**). This method is perhaps the simplest route for the synthesis of these heterocycles. It is remarkable to note that even when 4-hydroxy-1-methylquinolin-2(1*H*)-ones (**53**) are refluxed with 1-aryloxy-4-chlorobut-2-ynes in acetone /1-butanol, cyclic products[53]

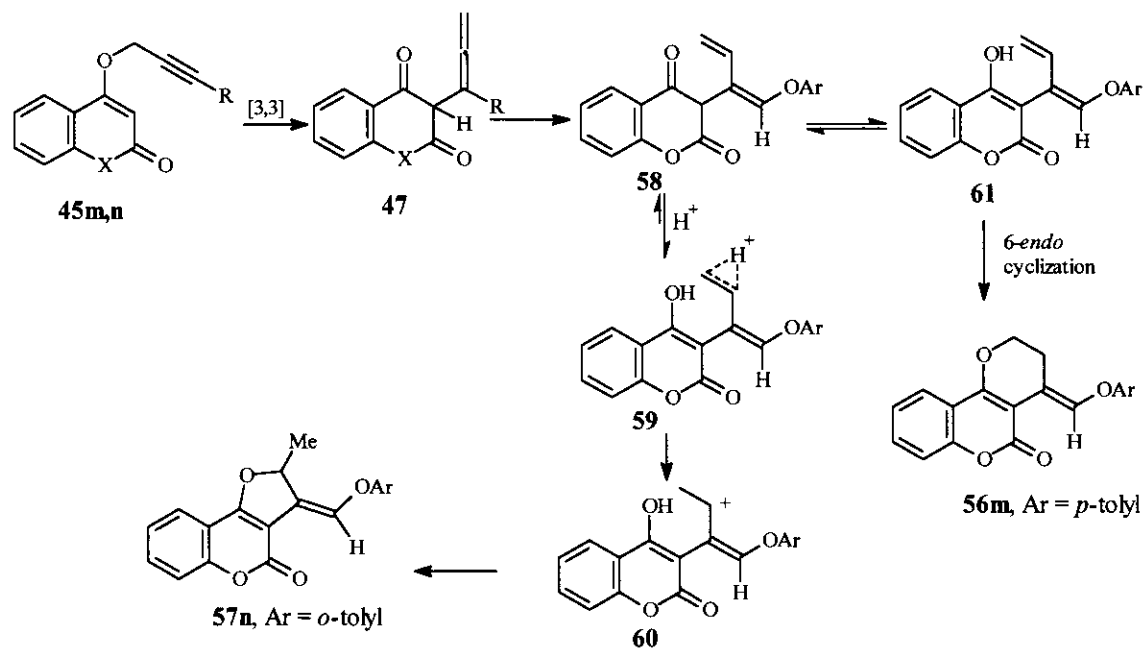


such as **54** and **55** are obtained. The geometrical disposition of the vinylic hydrogens H_a and H_b of

products (**54**) and (**55**) respectively has been established from their ^{1}H-NMR chemical shifts.

The butyne derivative containing aryloxy moiety carrying a methyl group[54] at the *para*-position (**45m**) afforded the normal pyranocoumarin (**46m**) along with its isomer (**56m**). The one with the methyl group at the *ortho*-position (**45n**) also gave the normal pyranocoumarin (**46n**) along with its isomer (**57n**) (Scheme 12). However, other substrates containing aryloxy moiety carrying methyl substitutents (**45i-l**) afforded the normal pyranocoumarin (**46i-l**) (Scheme 11).

The formation of **57n** from **45n** may be explained by an initial [3,3] sigmatropic rearrangement to give **47** followed by isomerization of the allene moiety to butadiene (**58**) by a 1,3-H$^+$ shift[55,56] and acid catalyzed cyclization (enol may also act as an acid) of **59** to **57n** (Scheme 12). The products (**46**) and (**52**) are also formed from intermediate (**47**) *via* enolization followed by [1,5] H shift and electrocyclic ring closure (ECR) (Scheme 11). Compound (**57n**) is formed in preference to product (**46n**), product ratio is not altered even if the reaction is carried out in purified chlorobenzene or in the presence of hydroquinone or *p*-toluenesulfonic acid. The formation of **56m** from **45m** may be rationalized *via* the formation of butadiene (**58**) followed by enolization and 6-*endo* cyclization to give **56m**.

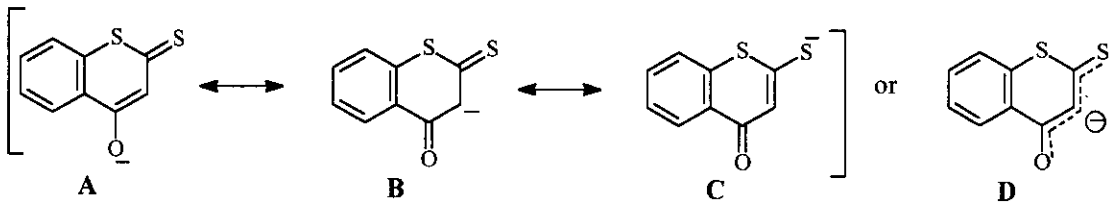


Scheme 12

Regioselective Synthesis of Thiopyrano[2,3-*b*][1]benzothiopyran-5(2*H*)-ones (65).

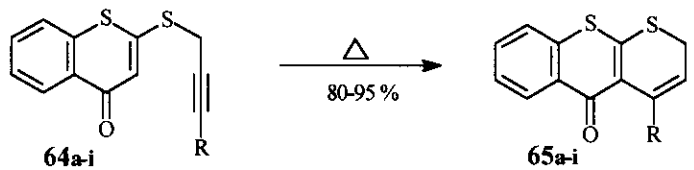
Efforts towards the synthesis of pyrano[3,2-*c*][1]benzothiopyran-5(2*H*)-thione (**62**) starting from 4-hydroxydithiocoumarin[57] (**63**) were unsuccessful. Any attempts to secure *O*-alkylated products from 4-hydroxydithiocoumarin (**63**) and allyl halides or but-2-ynyl halides by classical alkylation or phase-transfer

catalyzed alkylation failed.[58] Only product obtained was 2-allylthio[1]benzothiopyran-4-ones[59] or 2-(4′-aryloxybut-2-ynylthio[1]benzothiopyran-4-ones (**64**) in almost quantitative yields. Mainly *S*-alkylation was observed, *C*-alkylation to a limited extent and virtually no *O*-alkylation although compound (**63**) is capable of forming an ambident anion with several canonical forms **A**, **B**, and **C**, or delocalized **D**.



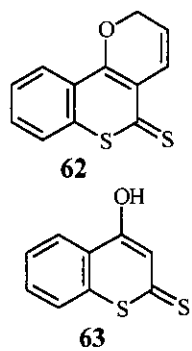
A **B** **C** **D**

For achieving *O*-alkylation the Mitsunobu reaction[60,61] was attempted. Here too the nucleophilicity of sulfur became the deciding factor and only the *S*-alkylation was observed. The *S*-alkylated products, 2-but-2-ynylthio[1]benzothiopyran-4-ones (**64a-i**) on refluxing in chlorobenzene furnished 4-substituted methylthiopyrano[2,3-*b*][1]benzothiopyran-5(2*H*)-ones[58,62] (**65a-i**) in excellent yields (Scheme 13).



64a-i **65a-i**

	Yield (%)		Yield (%)
a, R = CH_2Cl	82	**f**, R = 4-$MeOC_6H_4OCH_2$	85
b, R = CH_2OH	80	**g**, R = 2-$ClC_6H_4OCH_2$	85
c, R = 2-$MeC_6H_4OCH_2$	80	**h**, R = 2,4-$Cl_2C_6H_3OCH_2$	95
d, R = 4-$ClC_6H_4OCH_2$	90	**i**, R = $PhOCH_2$	90
e, R = 4-$BrC_6H_4OCH_2$	90		



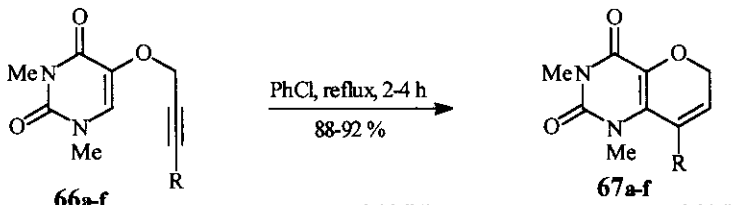
62 **63**

Scheme 13

The synthesis of thiopyrano[2,3-*b*]benzothiopyran-5(2*H*)-ones (**65**) is very much related to the synthesis of thieno[2,3-*b*]benzothiopyran-4-one reported earlier by a longer route.[63] Thieno[2,3-*b*]benzothiopyran-4-one skeleton has been used as an intermediate for the synthesis of a series of drugs[64] which are useful for the treatment of Psychotic disturbances.

Regioselective Synthesis of Pyrano[3,2-*d*]pyrimidine-2,4-dione.

8-Aryloxymethyl-1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-diones (**67a-f**) were synthesized[65] in 88-92 % yields by the thermal [3,3] sigmatropic rearrangement of 5-(4-aryloxybut-2-ynyloxy)-1,3-dimethylpyrimidine-2,4-diones (**66a-f**) in refluxing chlorobenzene (purified) for 2-4 h (Scheme 14). This method is better than that of Otter *et al.* who reported the varying proportions of furo[3,2-*d*]pyrimidine-2,4-dione and 6*H*-pyrano[3,2-*d*]pyrimidine-2,4-dione (**67**, R = H) from the thermal reaction[66] of 5-(2-propynyłoxy)uracil (**66**, R = H).



66a-f **67a-f**

	Yield (%)		Yield (%)
a, R = $PhOCH_2$	92	**d**, R = $2\text{-}MeC_6H_4OCH_2$	88
b, R = $4\text{-}ClC_6H_4OCH_2$	89	**e**, R = $2\text{-}ClC_6H_4OCH_2$	92
c, R = $4\text{-}MeOC_6H_4OCH_2$	88	**f**, R = $2,4\text{-}Me_2C_6H_3OCH_2$	89

Scheme 14

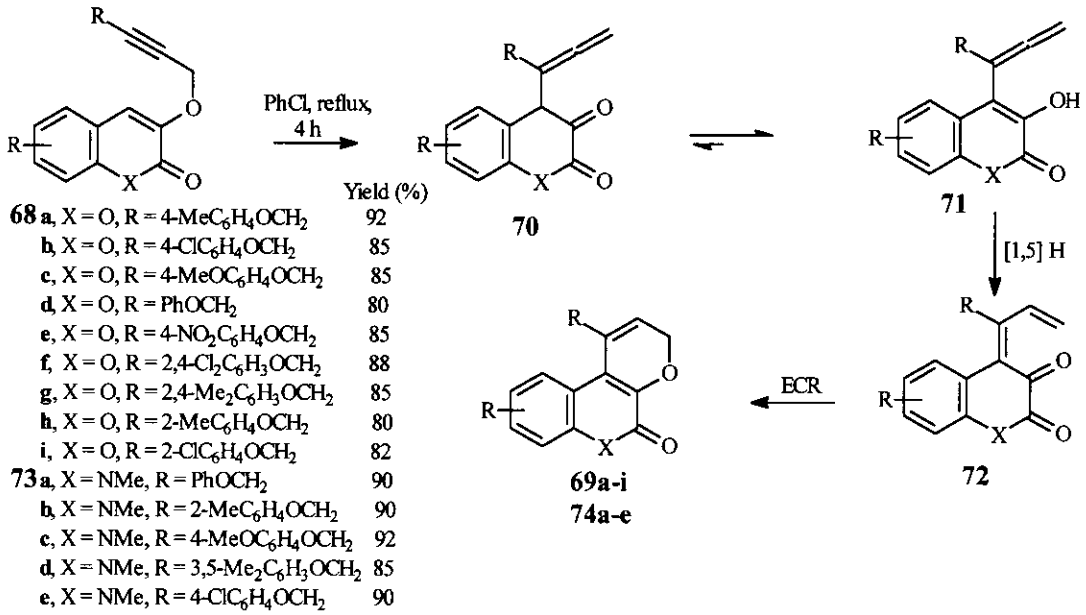
Regioselective Synthesis of Pyrano[2,3-*c*][1]benzopyran-5(3*H*)-ones (69) and 3*H*-Pyrano[2,3-*c*]quinolin-5(6*H*)-ones (74).

These heterocycles are also synthesized by the thermal sigmatropic rearrangement of propargyl and but-2-ynyl ethers of 3-hydroxycoumarin[67] and 3-hydroxyquinolone.[68] A regioselective synthesis of pyrano[2,3-*c*][1]benzopyran-5(3*H*)-one derivatives (**69a-i**) from 3-(4-aryloxybut-2-ynyloxy)[1]benzo-pyran-2-ones (**68a-i**) has been achieved *via* the pericyclic pathway.[69,70] If ionic or radical pathway is allowed to follow then the corresponding 2-methylfuro[2,3-*c*][1]benzopyran-4-one derivatives are obtained. Substrates (**68a-i**) in refluxing chlorobenzene undergo an initial [3,3] sigmatropic rearrangement followed by enolization to give the allenyl enols (**71**). In the absence of any other agents (acid, base or radical initiator) normally the pericyclic pathway[71,72] (*i.e.* [1,5] H shift followed by electrocyclic ring closure) is followed to give 1-aryloxymethylpyrano[2,3-*c*][1]benzopyran-5(3*H*)-ones (**69a-i**) in almost quantitative yields (Scheme 15). When this reaction was conducted in commercial chlorobenzene without further purification, a mixture of furo- and pyranocoumarins are obtained. The products are characterized by the application of spectroscopic methods *e.g.* high resolution ^{1}H-NMR and ^{13}C-NMR spectra.[73]

The same methodology has been successfully utilized for the synthesis of a number of 3*H*-pyrano[2,3-*c*]quinolin-5(6*H*)-ones (**74a-e**) in almost quantitative yields.[74] While 3-propynyloxyquinolin-2(1*H*)-ones gave exclusively the pyranoquinolones,[68] the 3-(4-aryloxybut-2-ynyloxy)-1-methylquinolin-2(1*H*)-ones (**73a-e**) in refluxing chlorobenzene generated pyranoquinolones (**74a-e**) or furoquinolones or a mixture of both. Addition of azoisobutyronitrile as a radical initiator or hydroquinone as a radical scavenger showed no effect on the formation of products.

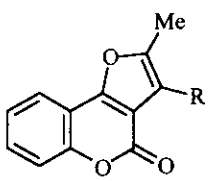
4.1.2 Synthesis of 2*H*-Furoheterocycles

Instances of synthesis of furoheterocycles from 1,4-bis-derivatves of 1,4-dichlorobut-2-yne are less abundant in literature compared to that of pyranoheterocycles. Synthesis of 2-methyl-3-aryloxymethyl-



Scheme 15

furo[3,2-*c*][1]benzopyran-4-ones (**76**) from 4-(4-aryloxybut-2-ynyloxy)[1]benzopyran-2-ones (**45**) has not been reported so far although numerous examples of 2-methylfuro[3,2-*c*][1]benzo-pyran-4-one (**75**) are known.[75-77] However, a number of furoheterocycles furo[2,3-*c*][1]-benzopyran-4-ones (**81**), furo[3,2-*c*]quinolin-4(5*H*)-one (**78**), furo[2,3-*c*]quinolin-4(5*H*)-ones (**85**), furo-[3,2-*d*]pyrimi-dine-2,4-diones (**89**) etc. have been synthesized from 1,4-bis-derivatives of 1,4-dichlorobut-2-yne.[78]

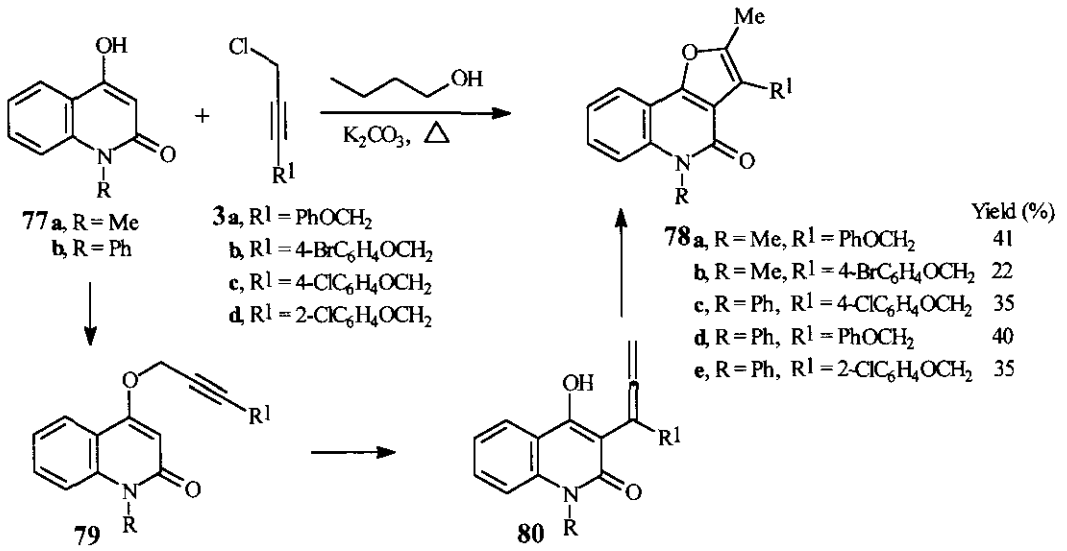


75, R = H
76, R = CH_2OAr

Synthesis of furo[3,2-*c*]quinolin-4(5*H*)-ones (78).

Various substituted furo[3,2-*c*]quinolin-4(5*H*)-ones are abundant in the plant[79] and a number of synthesis[80-84] for these compounds are reported. Furo[3,2-*c*]quinolin-4(5*H*)-ones[78] (**78a-e**) were obtained in moderate yields by simply refluxing 1-alkyl-4-hydroxyquinolin-2(1*H*)-ones (**77a,b**) with 1-aryloxy-4-chlorobut-2-ynes (**3**) in 1-butanol in the presence of anhydrous potassium carbonate (Scheme 16). This seems to be the simplest method for the synthesis of these heterocycles.

The facile formation of furo[3,2-*c*]quinolin-4(5*H*)-ones (**78a-e**) may be explained by the replacement of chlorine of 1-aryloxy-4-chlorobut-2-yne (**3**) by quinolin-2(1*H*)-one-3-oxy anion to give ethers (**79**) (not



Scheme 16

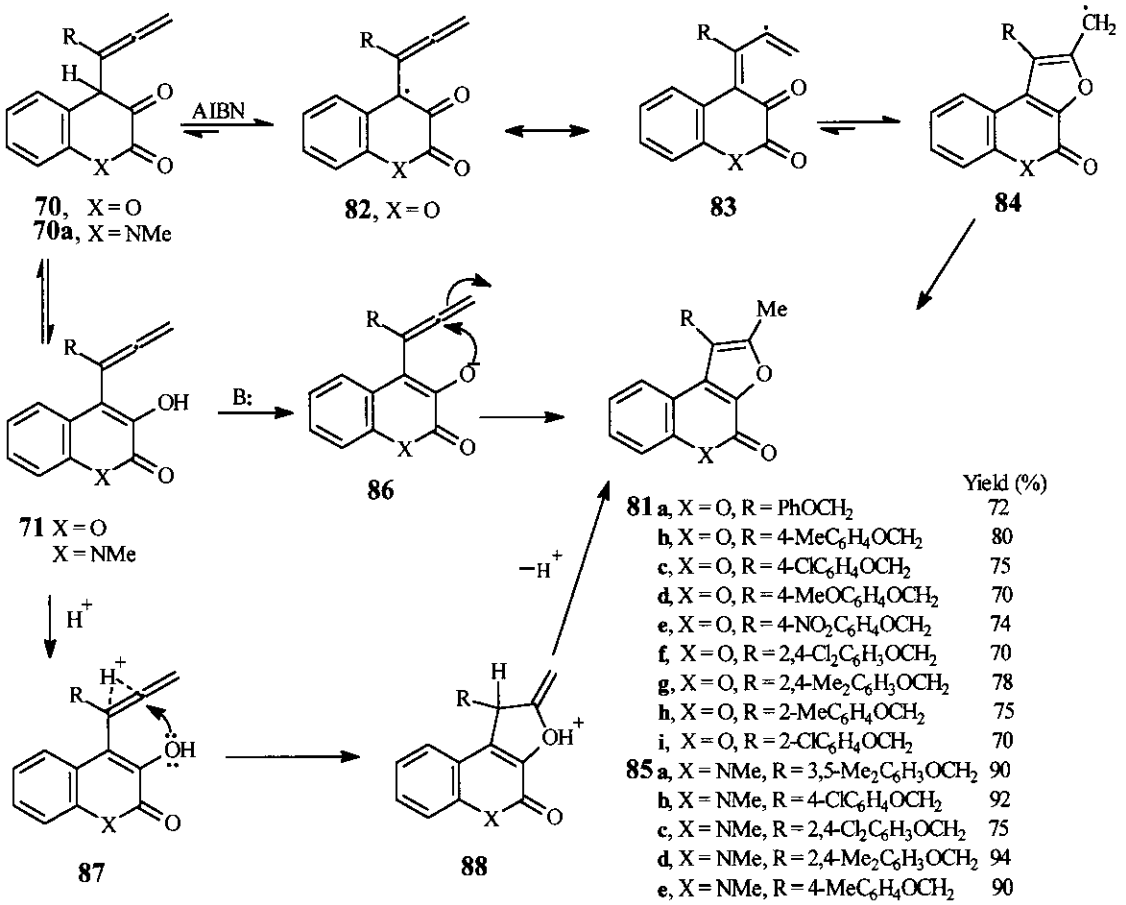
isolated) which under the reaction conditions suffered a [3,3] sigmatropic rearrangement to give allenyl enols (**80**). These intermediates under base catalysis afforded the furo[3,2-*c*]quinolin-4(5*H*)-ones (**78a-e**) (Scheme 16).

Furo[2,3-*c*][1]benzopyran-4-one and furo[2,3-*c*]quinolin-4(5*H*)-ones.

Simple 2-methylfuro[2,3-*c*][1]benzopyran-4-ones have been synthesized from 3-propynyloxy[1]-benzopyran-2-one[75] or 3-(2-chloroprop-2-enyloxy)[1]benzopyran-2-one[75] or by dehydrogenation of 1,2-dihydrofuro[2,3-*c*][1]benzopyran-2-one.[85]

Recently it has been demonstrated[70,71] that the intermediate allenyl enols (**80**) from the thermal [3,3] sigmatropic rearrangement of 3-(4-aryloxybut-2-ynyloxy)[1]benzopyran-2-ones (**68a-i**) may be cyclized regioselectively following a pericyclic pathway to give pyranocoumarins (**69a-i**), a radical pathway as well as an ionic pathway to give 1-aryloxymethyl-2-methylfuro[2,3-*c*][1]benzopyran-4-ones (**81**) (Scheme 17). This is the first instance where it has been shown that the intermediate allenylenols from Claisen rearrangement can be cyclized regioselectively following a radical pathway.[69,70]

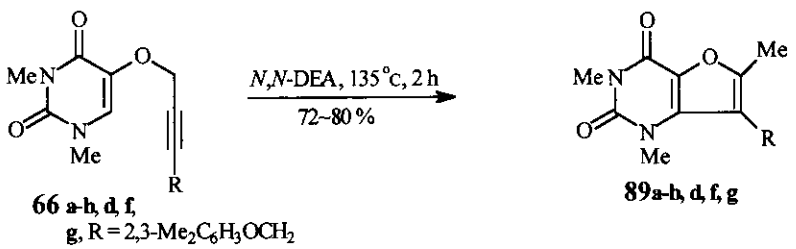
The *synthesis of simple* furo[2,3-*c*]quinolin-4(5*H*)-ones have been recently reported.[68] The thermal [3,3] sigmatropic rearrangement of 3-(4-aryloxybut-2-ynyloxy)quinolin-2(1*H*)-ones[74] (**73a-e**) in the presence of a base or *p*-toluenesulfonic acid afforded 1-aryloxymethyl-2-methylfuro[2,3-*c*]quinolin-4(5*H*)-ones (**85a-e**) (Scheme 17). Interestingly 1-aryloxymethyl-3*H*-pyrano[2,3-*c*]quinolin-5(6*H*)-ones (**74a-e**) on *heating in refluxing N,N-diethylaniline also provided* 1-aryloxymethyl-2-methylfuro[2,3-*c*]quinolin-4(5*H*)-ones[86] (**85a-e**).



Scheme 17

Synthesis of furo[3,2-*d*]pyrimidine-2,4-diones.

Synthesis of 1,3-dimethyl-6-methylfuro[3,2-*d*]pyrimidine-2,4-diones has been reported.[66,87] Substrates 5-(4-aryloxybut-2-ynyloxy)-1,3-dimethylpyridimidine-2,4-diones (**66a-b, d, f, g**) on heating in basic solvent *e.g. N,N*-diethylaniline at 130 ^{0}C furnished 7-aryloxymethyl-1,3-dimethyl-6-methylfuro[3,2-*d*]pyri-midine-2,4-diones (**89a-b, d, f, g**) in 72-80 % yields[88,89] (Scheme 18). The formation of products **89a-b, d, f, g** from **66** has been rationalized by a mechanism similar to that given for the formation of products **81** and



Scheme 18

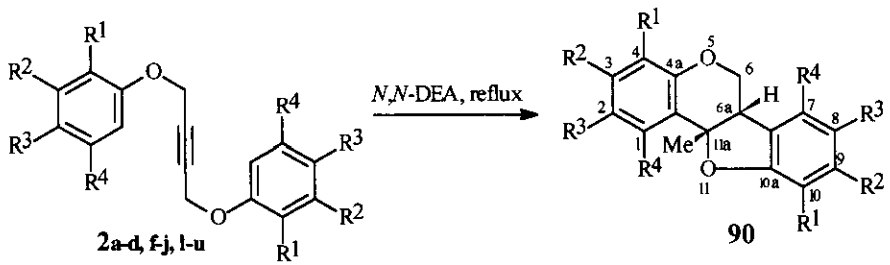
85 from **68** and **73** respectively in Scheme 17.

4.2 Double Claisen rearrangement of 1,4-diaryloxybut-2-ynes.

Syntheses of benzofuro[3,2-*c*][1]benzopyran, benzofuro[3,2-*b*]benzofuran and benzofuro[2,3-*b*]benzofuran have been achieved by thermal double (two consecutive) Claisen rearrangement of 1,4-diaryloxybut-2-ynes (**2**).[37,38,90] We like to call this "**Thyagarajan reaction**" after the name of B. S. Thyagarajan for his outstanding contribution to the chemistry of derivatives of 1,4-dichlorobut-2-yne.

4.2.1 Synthesis of benzofuro[3,2-*c*][1]-6a,11a-dihydro-11a-methylbenzopyrans from 1,4-diaryloxybut-2-ynes.

Successful Claisen rearrangement of 1,4-bis(4-chlorophenoxy)but-2-yne (**2a**) in refluxing *N,N*-diethylaniline for 10-12 h was first reported by Thyagarajan and co-workers.[37] The product of the rearrangement is the benzofuro[3,2-*c*][1]-6a,11a-dihydro-11a-methylbenzopyran (**90a**). Later the same group reported[38] the rearrangement of a number of 1,4-diaryloxybut-2-ynes (**2b-d, f-j, l-u**) for the synthesis of the tetracyclic compounds resembling pterocarpans, more specifically 11a-methylpterocarpans (**90b-d,f-j,l-u**) (Scheme 19).



	R1	R2	R3	R4	Yield (%)		R1	R2	R3	R4	Yield (%)
a,	H	H	Cl	H	40	**m**,	Cl	H	H	H	67
b,	H	H	H	H	60	**n**,	H	H	OMe	H	64
c,	Cl	H	Cl	H	40	**o**,	H	phenylene		H	60
d,	Me	H	Cl	H	57	**p**,	H	Me	Cl	H	34
f,	H	H	Br	H	40	**q**,	Me	Me	H	H	45
g,	OMe	H	H	H	38	**r**,	H	Me	Me	H	37
h,	Ph	H	H	H	65	**s**,	Cl	H	Ph	H	59
i,	H	H	Ph	H	71	**t**,	H	H	SMe	H	57
j,	Me	H	H	H	50	**u**,	H	H	t-Bu	H	70
l,	H	H	Me	H	50						

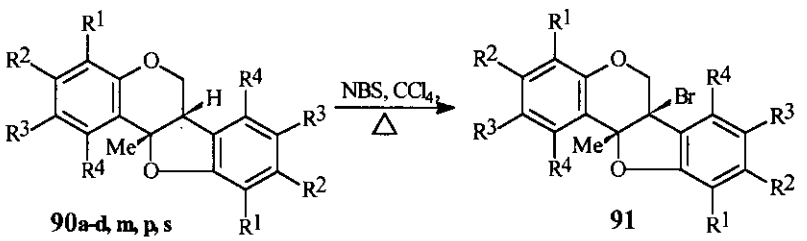
Scheme 19

Although the reaction is general for the synthesis of benzofuro[3,2-*c*]benzopyrans (**90**), 1,4-bis(4-nitrophenoxy)but-2-yne and 1,4-bis-(4-formylphenoxy)but-2-yne fail to give any tractable product, except tarry material perhaps due to the presence of aryloxy group with electron withdrawing substitutents demanding higher activation energy.

The stereochemistry of the ring junction in the tetracyclic system can be surmised from molecular models

which show a strain-free *cis* arrangement. The stereochemistry of the ring fusion of two oxygen heterocyclic ring in petrocarpan series was concluded to be *cis* from Dreiding models.[91,92]

The ^{1}H-NMR spectrum of benzofuro[3,2-*c*]benzopyran (**90a-d, f-j, l-u**) is interesting especially a multiplet between 3.35 and 4.50 ppm for the benzylic and *O*-methylene protons which shows a typical ABC pattern with a total of 11 lines. The nonequivalence of the OCH_2 protons shows for a coupling between themselves with J = 11 Hz while the benzylic proton shows a small coupling constant of 5 Hz with one of them and 8.5 Hz with the other. This feature was further confirmed when the benzylic proton was replaced with a bromine atom. In these the OCH_2 showed an AB quartet in the region 4.3-5.2 ppm with J = 12 Hz. The replacement of the benzylic proton by bromine (Scheme 20) aids in the determination of the geminal and vicinal coupling constants in the parent molecule. Such a bromination has not been reported in the pterocarpan derivatives.[38] Extensive proton magnetic resonance study of several other pterocapan derivatives by Pachler and Underwood[93,94] also showed that the stereochemistry of the ring junction is *cis*.



90a-d, m, p, s

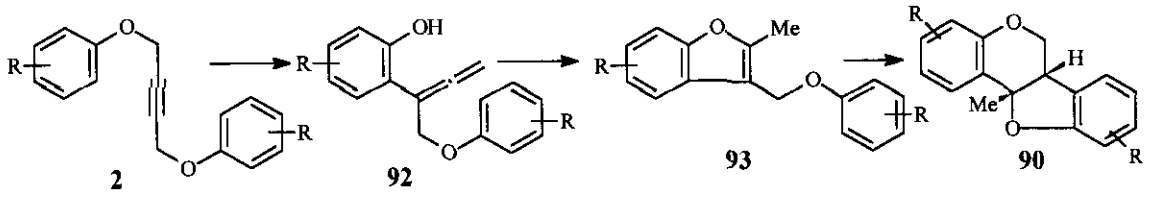
	R1	R2	R3	R4	Yield (%)
a,	H	H	Cl	H	83
b,	H	H	H	H	80.5
c,	Cl	H	Cl	H	83
d,	Me	H	Cl	H	87
m,	Cl	H	H	H	95
p,	H	Me	Cl	H	90.2
s,	Cl	H	Ph	H	83

Scheme 20

These 11a-methylpterocarpans can undergo unusul ring contraction to benzofurobenzofuran (coumaranocoumaran) or a novel ring expansion to benzofurobenzoxepinone.[95]

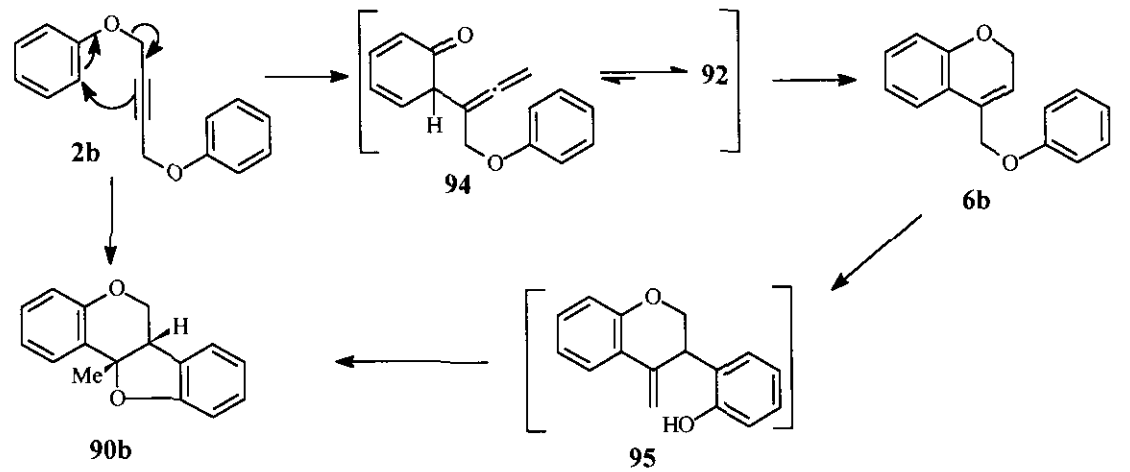
Mechanism

Initially Thyagarajan *et al.* proposed the following mechanism due to the presence of the coumaran moiety in the final products (**90a**). Two sequential Claisen rearrangements were considered leading to the formation of benzofuro[3,2-*c*][1]-6a,11a-dihydro-11a-methylbenzopyrans or shortly 11a-methylpterocarpans **90** (Scheme 21).



Scheme 21

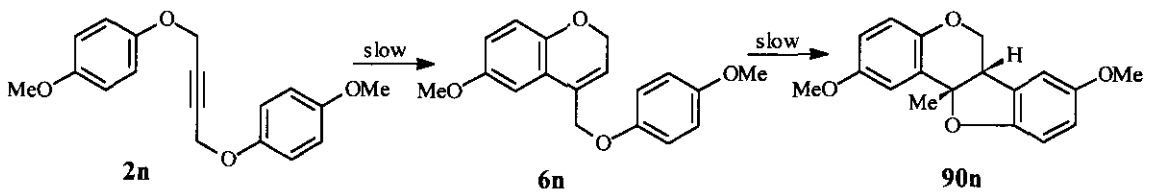
The well-established equilibrium between the anion of *ortho*-allenylphenol[96] and 2-methylbenzofuran was suggestive of such a mechanism. Again, instances are known where an allylic unsaturation forming part of a ring system participates in a Claisen rearrangement.[97,98] This suggestion was tested by synthesizing the intermediate (**93**) from 3-chloromethyl-2-methylbenzofuran[99] and also by another route from 1,4-diaryloxybut-2-enes[90] and subjecting this to the condition of the rearrangement. However, the so called intermediate 2-methyl-3-phenoxymethylbenzofuran (**93**) was recovered unchanged. 4-Phenoxymethyl-chrom-3-ene (**6b**) has been described earlier from the hydration of 1,4-bis(phenoxy)but-2-yne (**2b**).[17] This has also been synthesized from 4-chloromethylchrom-3-ene (**14**) (described earlier by propargylic Claisen rearrangement[100]) by the nucleophilic displacement of halogen by phenoxide anion (Scheme 2). This compound **6b** on refluxing in *N,N*-diethylaniline afforded the same product 11a-pterocarpan as obtained from the direct rearrangement of 1,4-bis(phenoxy)but-2-yne[38] (**2b**) and thus establishing the intermediacy of 4-aryloxymethylchrom-3-ene (**6b**) in the Claisen rearrangement of 1,4-diaryloxybut-2-ynes (**2**) (Scheme 22). Later intermediate allene (**92**) has been postulated by Schmidt *et al.* by the first [3,3] sigmatropic rearrangement[101] of 1,4-diaryloxybut-2-yne.



Scheme 22

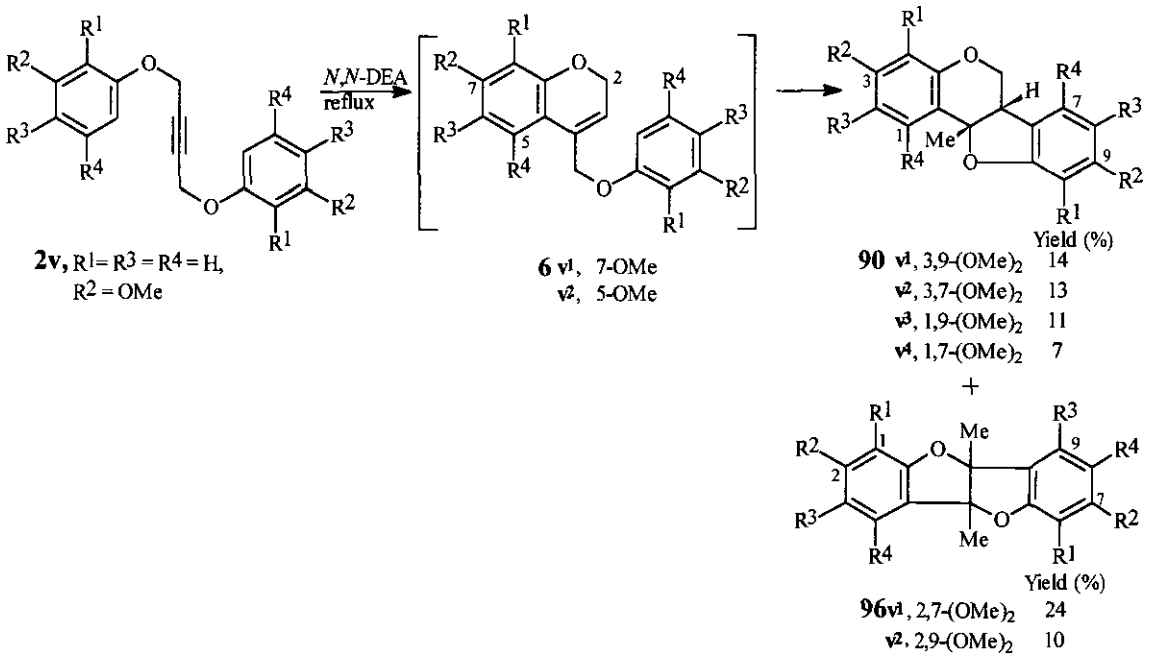
Detailed mechanistic studies[102] have been carried out by Balasubramanian *et al.* A ^{1}H-NMR follow up provided conclusive evidence for the involvement of two sequential Claisen rearrangements in the thermal

rearrangement of 1,4-diaryloxybut-2-ynes (**2n**) to 11a-methylpterocapans (**90n**).



2n **6n** **90n**

Kielman and co-workers[103] in an attempt to synthesize 11a-methyl analogs of natural phytoalexins, such as methylhomopterocapin (**90v**[1]) to investigate their chemical and biological properties[104,105] studied the thermal Claisen rearrangement of 1,4-bis(*m*-methoxyphenoxy)but-2-yne (**2v**) in detail. Substrate (**2v**) was subjected to refluxing in *N*,*N*-diethylaniline for several hours to give heterocyclic isomers (**90v**[1], **90v**[2], **90v**[3] and **90v**[4]), whose ratio is a function of reaction time and temperature (Scheme 23). The individual compounds were isolated by liquid chromatography and the composition was verified by integration of the peak areas of the methoxy and angular methyl protons (3.8 and 1.7 ppm respectively) in the ^{1}H-NMR spectrum.



2v, R[1]= R[3] = R[4] = H, R[2] = OMe

6 v[1], 7-OMe
v[2], 5-OMe

Yield (%)

90 v[1], 3,9-(OMe)$_2$ 14
v[2], 3,7-(OMe)$_2$ 13
v[3], 1,9-(OMe)$_2$ 11
v[4], 1,7-(OMe)$_2$ 7

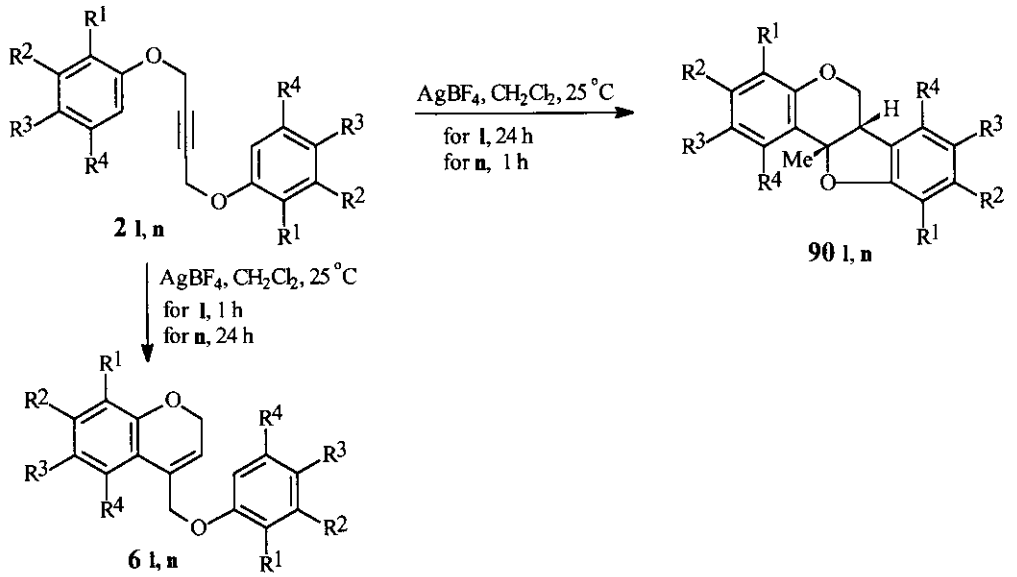
+

Yield (%)

96v[1], 2,7-(OMe)$_2$ 24
v[2], 2,9-(OMe)$_2$ 10

Scheme 23

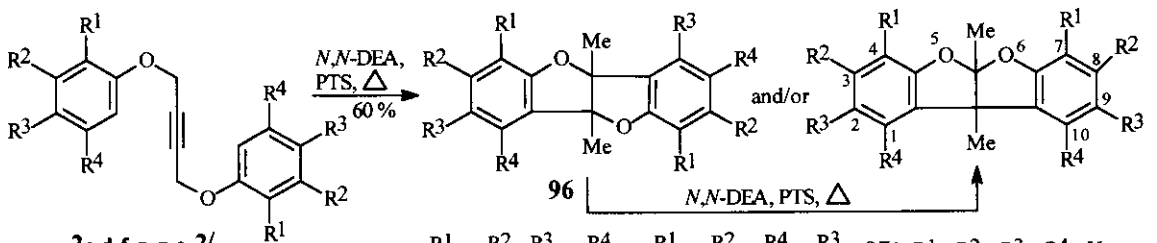
Charge-induced Claisen rearrangement[106] has been utilized by Bates and Jones[33] for the synthesis of 11a-methylpterocarpan (**90**). Charge formation by co-ordination to C-C multiple bond of substrate (**2**) by soft Lewis acid[107-109] $AgBF_4$ in dichloromethane at 25 ^{0}C afforded selectively 4-aryloxymethylchrom-3-ene (**6**) or 11a-methylpterocarpan (**90**) depending on the substrate and the reaction time (Scheme 24).



Scheme 24

4.2.2 Synthesis of benzofuro[3,2-*b*]benzofurans and benzofuro[2,3-*b*]benzofurans.

The rearrangement of butynyl ethers (**2**) was sensitive to the reaction temperature, as only solvents boiling above 200 ^{0}C were found to be effective. Diethylaniline (bp 216 ^{0}C) is effective. However, addition of HCl, $HClO_4$ or such other acids which caused a lowering of bp of the reaction medium, failed to effect the rearrangement.[110] This problem was overcome by the addition of a soild acid *e.g.* 4-toluenesulfonic acid. All except four of the fourteen different ethers rearranged smoothly to give benzofurobenzofurans in good yields[110] (Scheme 25). These results are unique in the sense that the Claisen rearrangement is carried out in a basic medium in the presence of a proton donar, leading to



	R1	R2	R3	R4	R1	R2	R4	R3
96 a,	H	H	Cl	H	H	H	Cl	H
c,	Cl	H	H	H	Cl	H	H	H
d,	Me	H	H	H	Me	H	H	H
f,	H	H	Br	H	H	H	Br	H
g,	OMe	H	H	H	OMe	H	H	H
n,	H	H	OMe	H	H	H	OMe	H
o,	H	H	phenylene		H	H	phenylene	
#96/,	H	H	Cl	H	H	H	Me	H

97 b, R1 = R2 = R3 = R4 = H
l, R1 = R2 = R4 = H, R3 = Me

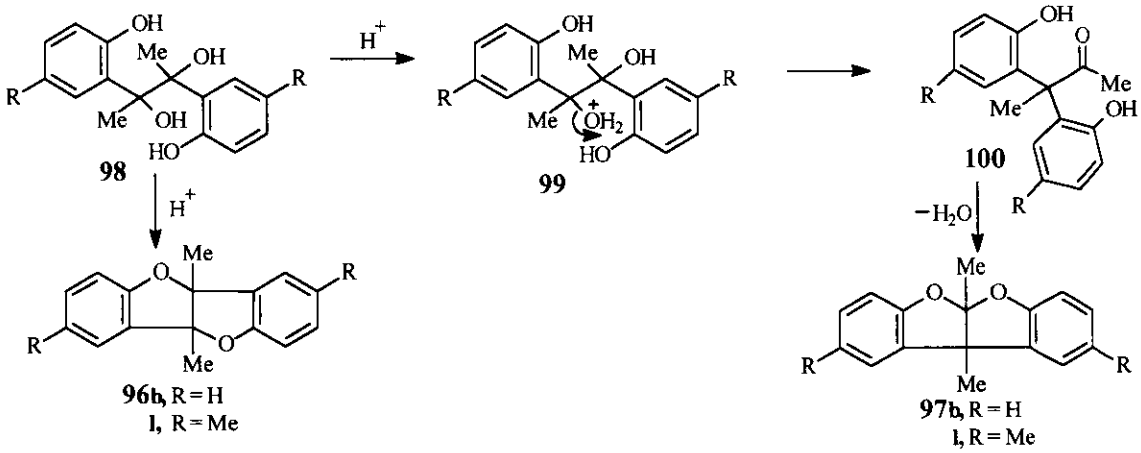
#from an unsymmetrical 1-(4/-chlorophenoxy)-4-(4/-methylphenoxy)but-2-yne

Scheme 25

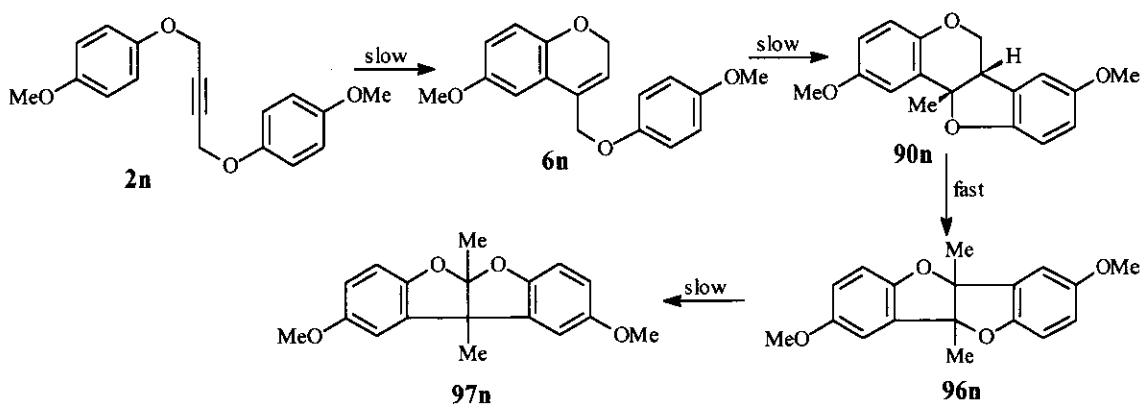
formation of benzofurobenzofuran system. The benzofuro[3,2-*b*]benzofuran (**96**) and benzofuro[2,3-*b*]benzofuran (**97**) may be easily distinguished from their ^{1}H-NMR spectra. Compound (**96d-e**) shows only a single CH_3 signal (δ 1.7) whereas compound (**97b-l**) exhibits two distinct peaks (between δ 1.68 and δ 1.7 with a separation of 6 Hz) for the aliphatic methyls suggesting their non-equivalence in the structure.

Compounds (**97b**) and (**97l**) have also been described[111,112] as resulting from acid-catalyzed dehydration of 2,3-bis(*o*-hydroxyphenyl)-2,3-dihydroxybutanes (**98**). The formation of **97** from dihydroxybutanes (**98**) may be explained by acid catalyzed pinacol rearrangement prior to cyclization with phenolic groups (Scheme 26). It may be mentioned here that benzofuro[2,3-*b*]benzofuran (**97**) has also been synthesized by the condensation of *p*-cresol with glyoxal.[113]

A number of benzofuro[3,2-*b*]benzofuran (**96**) and benzofuro[2,3-*b*]benzofurans have also been synthesized from 4-aryloxymethylchrom-3-enes (**6**).



Scheme 26

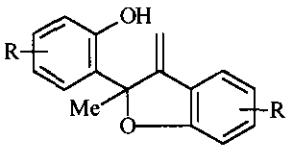


Scheme 27

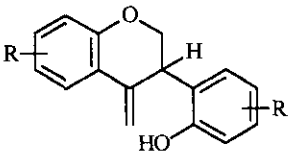
Table : Pyrolysis of 1,4-bis(4-methylphenoxy)but-2-yne (**2n**) in PEG-200 at 270 °C

Reaction time (min)	**96n** (% ratio)	**97n** (% ratio)
30	46.9	53.1
60	18.2	81.8
90	9.0	91.0
150	0.0	100.0

Independent pyrolysis of **6n**, **90n** and **96n** in PEG-200 at 270 °C for 4 h yielded **97n**. It was also shown that the pyrolysis of suspected intermediates, 2-(*o*-hydroxyphenyl)-2-methyl-3-methylenedihydrobenzofuran (**101**) and 3-(*o*-hydroxyphenyl)-4-methylenedihydrobenzopyran (**102**) also yielded **97n** (75 %) within 2 h. Thus involvement of these intermediates in the conversion of **2** into **97** was clearly shown.

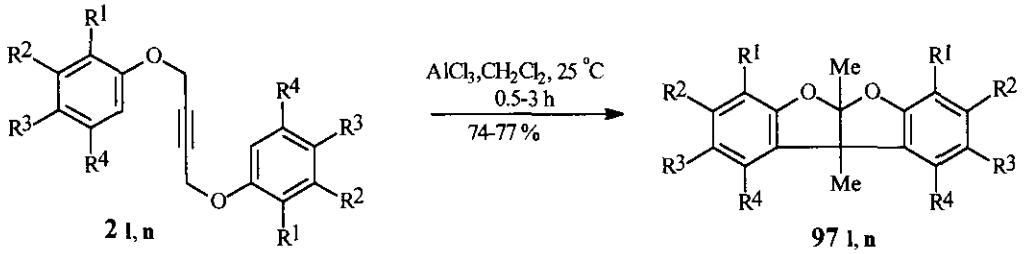


101



102

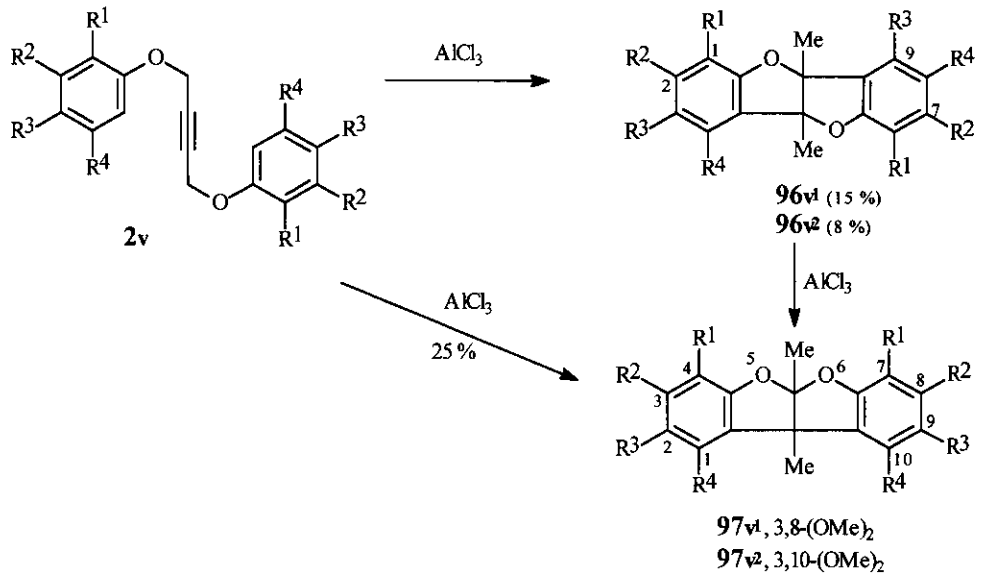
Charge formation by heteroatom complexation of substrate (**90**) with a hard Lewis acid[114] $AlCl_3$ gave benzofuro[2,3-*b*]benzofuran[33] (**97**) (thermodynamic product). No benzofuro[3,2-*b*]benzofuran (**96**) (kinetic product) was obtained (Scheme 28). Although isolation or detection of intermediates in the $AlCl_3$ catalyzed conversion of **2** into **97** was impossible it is reasonable to assume that **2** proceeds to **97** in a stepwise manner *via* 4-aryloxymethylchrom-3-ene (**6**) and benzofuro[3,2-*c*][1]-6a,11a-dihydro-11a-methylbenzopyran (**90**). These transformations may be charge-induced Claisen rearrangements similar in mechanism to the process reported for BCl_3.[106]



2 l, n **97 l, n**

Scheme 28

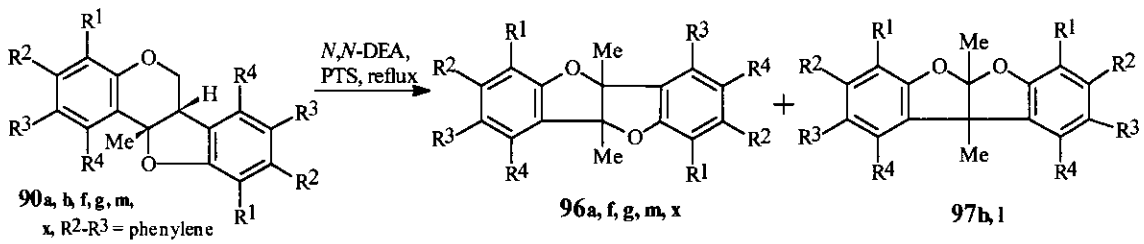
With aluminum chloride as catalyst 1,4-bis(*m*-methoxyphenoxy)but-2-yne (**2v**) in refluxing dichloromethane rearranged smoothly to a mixture of **96v**[1], **96v**[2] and the corresponding cyclic ketols[103] (more stable) **97v**[1] (major product) and **97v**[2] (Scheme 29).



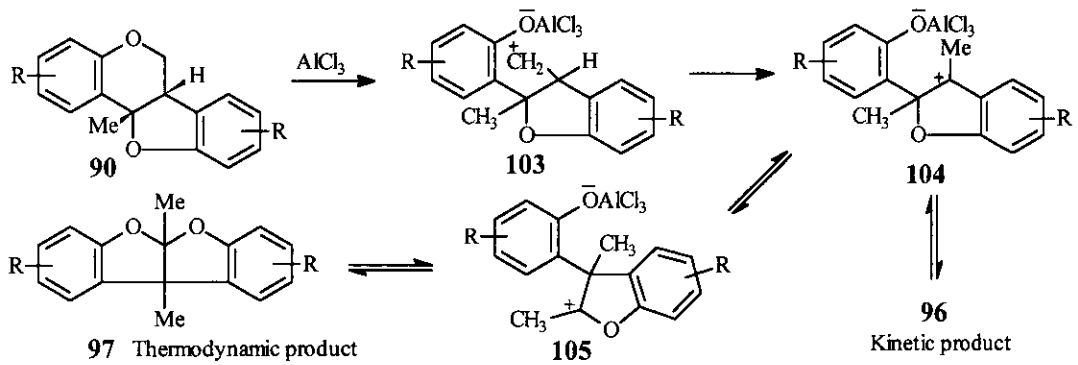
Scheme 29

4.2.3 Unusual ring contraction of benzofuro[3,2-*c*][1]benzopyran.

It has been reported that benzofuro[3,2-*c*][1]benzopyrans (**90**) undergo a novel ring contraction[115,116] to give benzofuro[3,2-*b*]benzofurans (**96**) or benzofuro[2,3-*b*]benzofurorans (**97**) in 55-80 % yields under thermal condition in the presence of *p*-toluenesulfonic acid in boiling *N*,*N*-diethylaniline (Scheme 30).



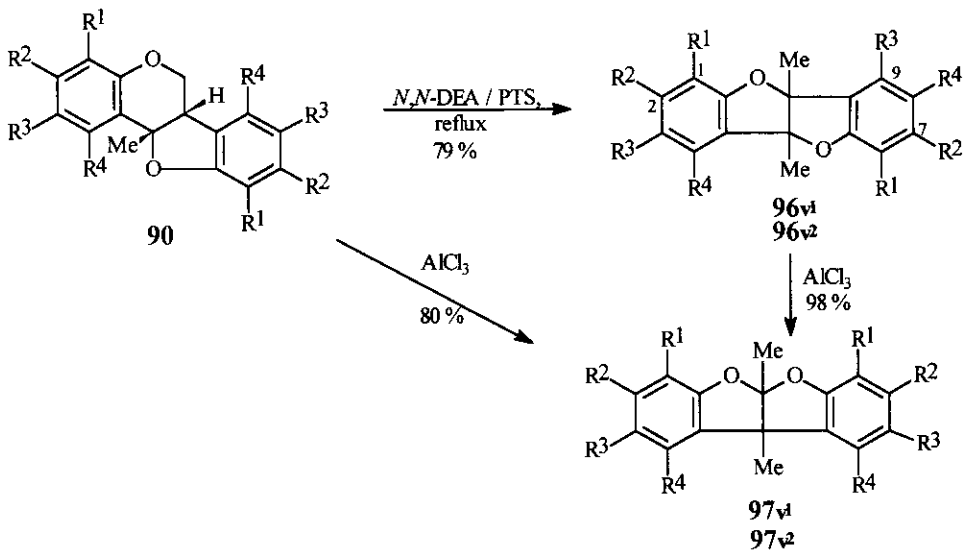
Scheme 30



Scheme 31

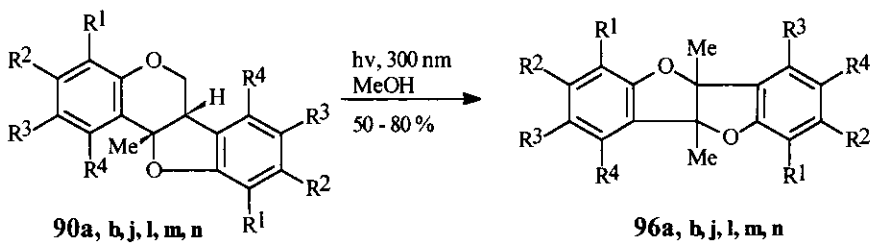
This novel ring contraction was also observed when 11a-methylpterocarpans (**90**) were subjected to hard Lewis acid ($AlCl_3$) catalysis.[33] A plausible mechanism accounting for the transformation of **90** into **97** is outlined in Scheme 31.

Kielman *et al.* reported[103] the convertion of 11a-methylpterocarpans (**90v**^{1} and **90v**^{2}) into benzofuro[3,2-*b*]benzofurans (**97v**^{1}, major product and **97v**^{2}) by treatment with anhydrous $AlCl_3$ in CH_2Cl_2 (Scheme 32).

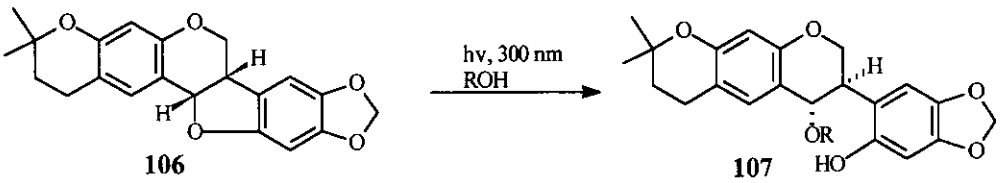


Scheme 32

Balasubramanian *et al.* have shown that the 11a-methylpterocarpans (**90**) undergo this novel ring contraction under photochemical condition[117] to give 4b,9b-dihydro-4b,9b-dimethylbenzofuro[3,2-*b*]benzofurans (**96**) in 50-78 % yields (Scheme 33). This result is different from that obtained by Rall *et al.*[118,119] from the photolysis of natural pterocarpan (**106**) who observed the formation of isoflavan derivatives (**107**) (Scheme 34). It may also be noted that the photolysis of totally different substrates *viz.* anthracene endoperoxides also lead to the formation of **96**.[120,121]

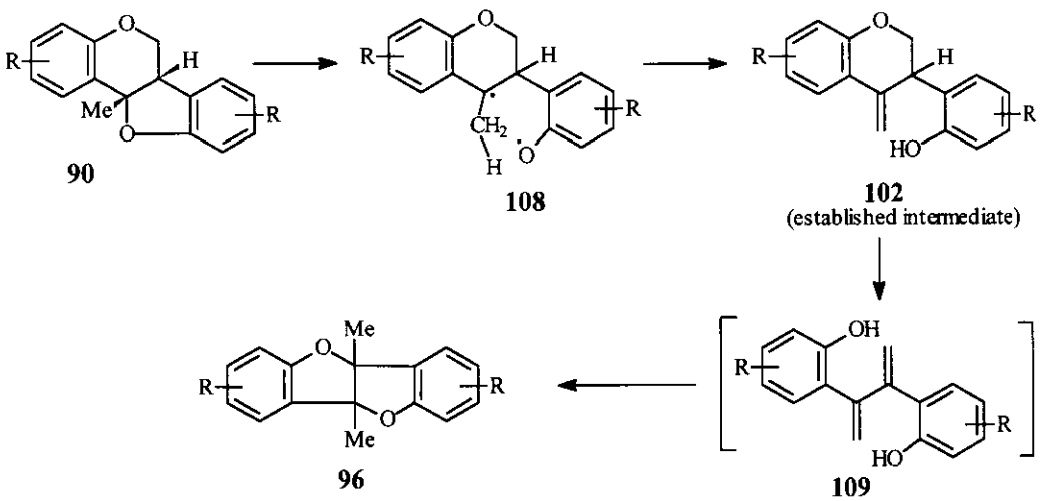


Scheme 33



Scheme 34

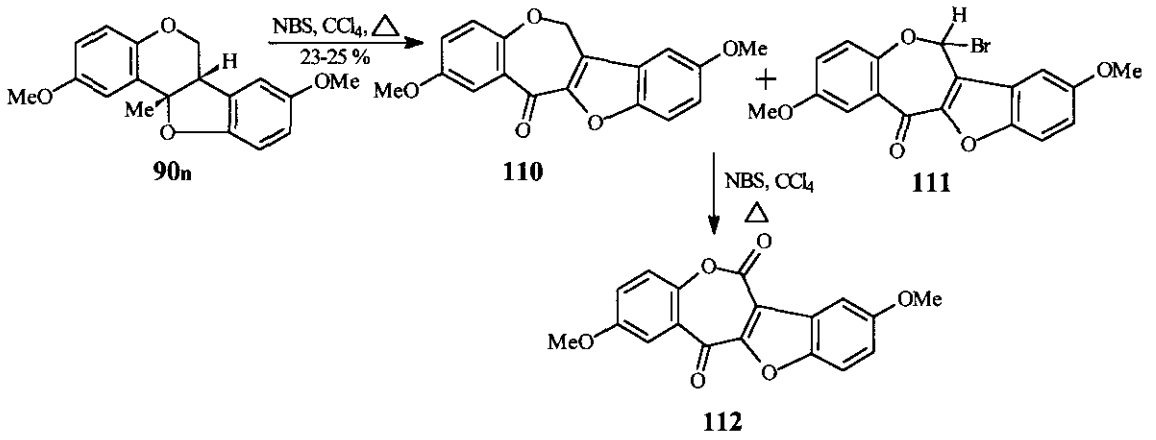
Detailed mechanistic studies were carried out[117] by Balasubramanian *et al.* on this photochemical ring contraction. An unusual acceleration of this novel photochemical rearrangement by bases has been observed. Based on literature report[118,119,122-125] five different mechanisms were considered to rationalize this photochemical transformation. On the basis of exhaustive experimentation all the five machanisms were discarded and a sixth mechanism was established for this novel photochemical rearrangement (Scheme 35). They could not offer any evidence for the butadiene intermediate (**109**). However, this hitherto unknown class of 2,3-bis(2-hydroxypheny)butadienes (**109**) can be expected to be highly photoreactive and that is perhaps the reason for their failure to detect them in the photochemical transformation of **90** to **96**.



Scheme 35

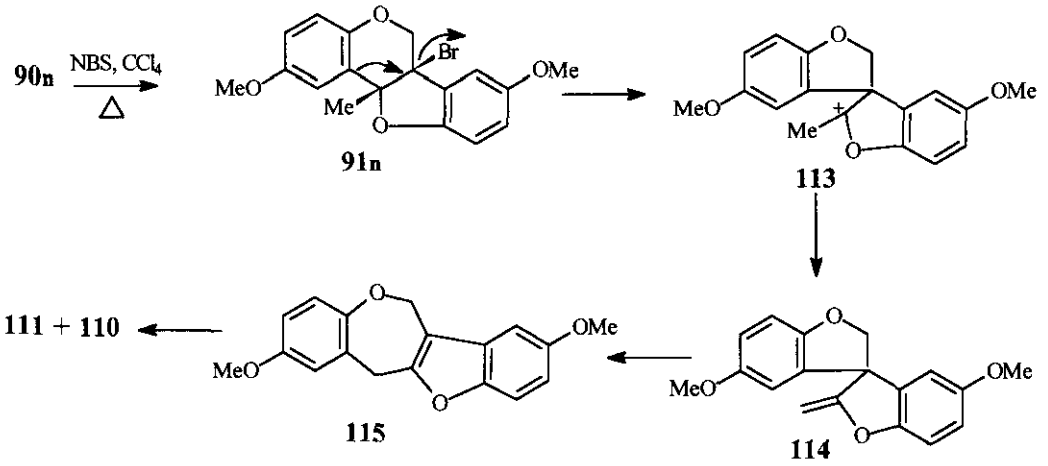
4.2.4 Synthesis of benzofurobenzoxepinone derivatives by unusual ring expansion of benzofuro[3,2-*c*][1]benzopyran.

11a-Methylpterocarpans (**90**) on bromination at 6a-position with *N*-bromosuccinimide in carbon tetrachloride may undergo an unusual ring expansion[95] to 2,8-dimethylbenzofuro[3,2-*c*][1]benzoxepinone (**110**) and its 12-bromo dervative **111** (Scheme 36). These benzofurobenzoxepinones (**110** and **111**) on further oxidation with *N*-bromosuccinimide afforded the lactone (**112**).



Scheme 36

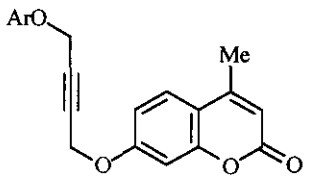
The formation of benzoxepinones (**110**) and (**111**) has been rationalized bearing in mind the *cis*-stereochemistry of the ring junction in **90**. Benzylic bromination followed by its intramolecular displacement by the benzylic bond results in the formation of a stable cation (**113**). The latter (**113**) could lose a proton, undergo an allylic migration and give the ring expanded product (**115**). Oxidation of the benzylic and allylic methylene by *N*-bromosuccinimide[126-128] affords **110** and further bromination at C-12 gives the bromo derivative (**111**) (Scheme 37).



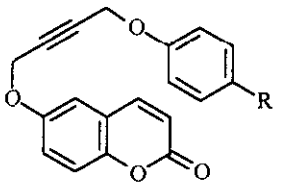
Scheme 37

4.3 Synthesis of polyheterocycles by sequential [3,3] sigmatropic rearrangements.

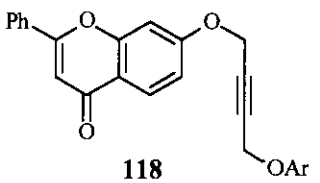
Synthesis of tetracyclic oxygen heterocycles has so far been discussed. Recently the synthesis of a number of polyheterocycles from unsymmetrical 1,4-bis(substituted)but-2-ynes *e.g.* substrates (**116**, **117**, **118** and **45**) by two consecutive [3,3] sigmatropic rearrangement has been reported. The second [3,3] sigmatropic rearrangement step has been useful in substrates like **66** and **68** for the synthesis of polyheterocycles.



116



117



118

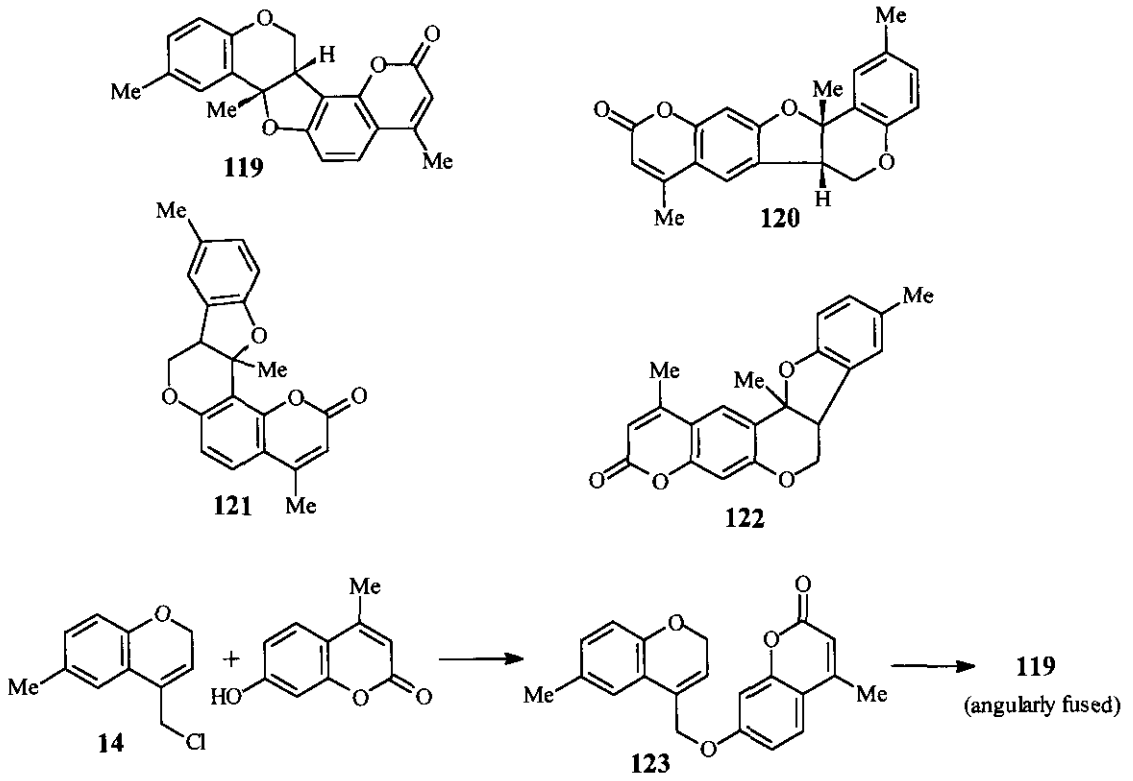
Synthesis of polyheterocycles from 4-methyl-7-(4-tolyloxybut-2-ynyloxy)[1]benzopyran-2-one (116).

4-Methyl-7-(4-tolyloxybut-2-ynyloxy)[1]benzopyran-2-one (**116**) is a unique substrate for comparing the relative ease of [3,3] sigmatropic rearrangement as it possesses two comparable aryloxypropynyl moieties devoid of isolated double bond character. Substrate (**116**) on refluxing in *N,N*-diethylaniline for 20 h afforded[129,130] two products (**119**) (35 %) and (**120**) (15 %) which were separated by column chromatography over silica gel. The products are isomeric with the starting butyne derivative (**116**). On the basis of spectral data and also from mechanistic considerations, two of the four structures (**119**, **120**, **121** and **122**) were tentatively proposed for the products.

The structure of the major product was established to be 4,7a,9-trimethyl-7a*H*,13*H*[1]benzopyrano[4,3-*b*]furano[2,3-*b*][1]benzopyran-2-one (**119**) by its independent synthesis from the thermal rearrangement of **123** (Scheme 38). The other product was found to be linearly fused from the analysis of the aromatic region of its 400 MHz ^{1}H-NMR spectrum including homo decoupling. NOE studies on this product clearly indicated the choice of 2,8,13a-trimethyl-6*H*,13a*H*[1]benzopyrano[6,7-*b*]furano[3,2-*c*][1]benzopyran-10-one (**120**). A first [3,3] sigmatropic rearrangement of **116** followed by enolization, [1,5] H shift and electrocyclic ring closure may give a chromenylmethoxycoumarin (**123**) which then undergoes a second [3,3] sigmatropic rearrangement at the 8-position of the coumarin followed by cyclization to give the major product (**119**) (angularly fused) or at the 6-position of the coumarin followed by cyclization to give the minor product (**120**) (linearly fused) (Scheme 38). The formation of the angularly cyclized product (**119**) as the major and the linearly cyclized product (**120**) as the minor product follows the normal pattern of the reactions[131-134] of derivatives of 7-hydroxycoumarin. However, a remarkable point to note here is that the first [3,3] sigmatropic shift has taken place at the aryloxypropynyl moiety in preference to the coumarinyloxypropynyl moiety.

Synthesis of polyheterocycles from 6-(4-aryloxybut-2-ynyloxy)[1]benzopyran-2-ones (117).

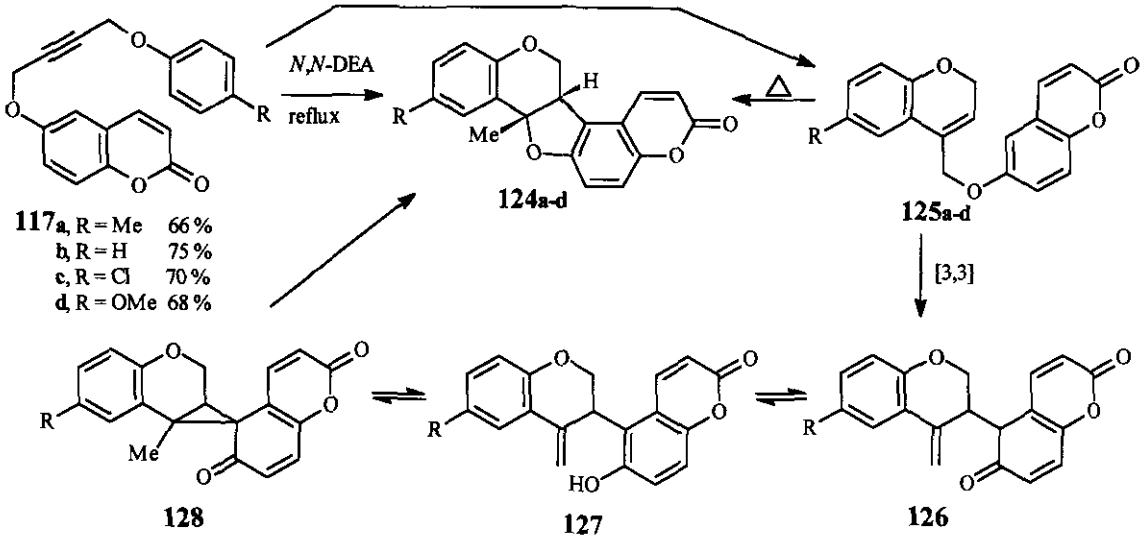
These substrates (**117a-d**) are also unique as they offer scope for comparing the relative ease of [3,3] sigmatropic rearrangements of the aryloxypropynyl moiety versus the coumarinyloxypropynyl moiety.



Scheme 38

6-Aryloxybut-2-ynyloxy)[1]benzopyran-2-ones (**117a-d**) when heated in refluxing *N,N*-diethylaniline for 15 h furnished 7a-methyl-13,13a-dihydro-7a*H*-furo[3,2-*c*:5,4-*f*]bis[1]benzopyran-3-ones[135,136] (**124a-d**) in 66-75 % yields (Scheme 39).

The structure of the product (**124a-d**) was deduced from elemental analysis and spectral data and confirmed by its independent synthesis from **125** (Scheme 39). The formation of products (**124**) from **117** may be explained by a [3,3] shift at the aryloxypropynyl part of substrates (**117**) followed by cyclization to provide intermediate 4-(6-coumarinyloxymethyl)chrom-3-enes (**125**) (not isolated but synthesized by another route) which may then suffer a second [3,3] sigmatropic shift at the C-5 position of the coumarin followed by enolization to give phenol (**127**). Transformation of phenol (**127**) to product (**124a-d**) may then occur *via* a spirodienone-coumaran rearrangement[137,138] (Scheme 39). The formation of angularly cyclized product in preference to the linearly cyclized product follows the normal pattern for reactions of 6-hydroxycoumarin derivatives.[139] The nature of the product formation is unaffected by the addition of *p*-toluenesulfonic acid although it improves the yields (80-85 %) and reduced the reaction time (10 h). It is also interesting to note that the first [3,3] sigmatropic shift has occurred at the aryloxypropynyl moiety in preference to the coumarin-6-oxypropynyl moiety of the substrates (**117a-d**).



Scheme 39

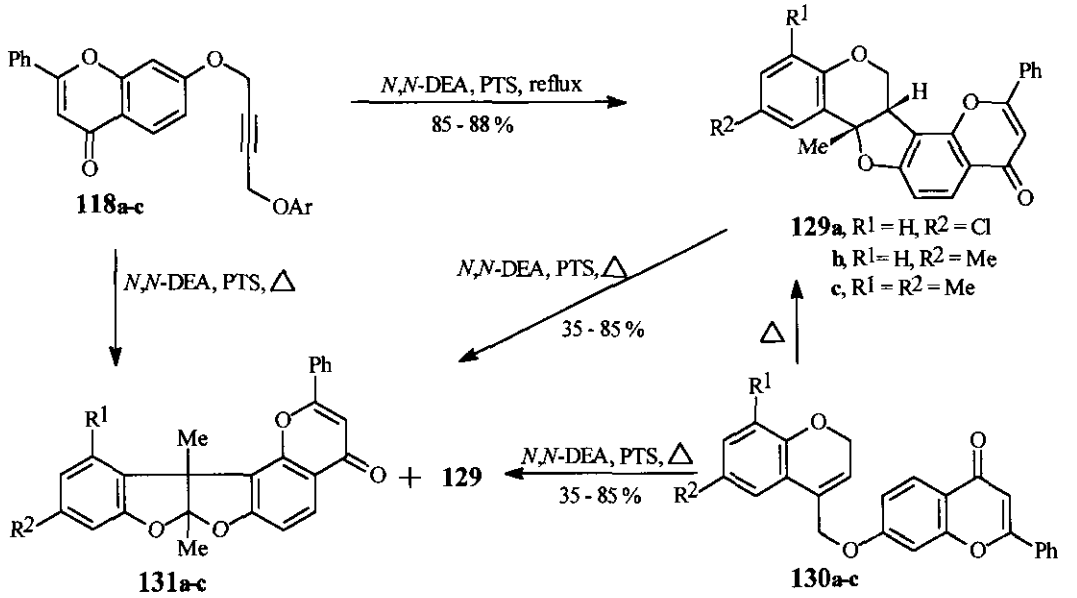
Synthesis of polyheterocycles from 7-(4-aryloxybut-2-ynyloxy)-2-phenyl[1]benzopyran-4-ones (118).

Thermal rearrangements of another set of substrates (**118a-c**) providing a scope for comparing the relative ease of first [3,3] sigmatropic rearrangements of the aryloxypropynyl moieties with those of flavonyloxypropynyl species were studied.[140] 7-(4-Aryloxybut-2-yn-1-yloxy)-2-phenyl[1]benzopyran-4-ones (**118a-c**) when heated in refluxing *N,N*-diethylaniline for 18 h gave regioselectively 7a-methyl-2-phenyl-13,13a-dihydro-7a*H*-furo[3,2-*a*:5,4-*h*']bis[1]benzopyran-4-ones (**129a-c**) in excellent yields (Scheme 40). The structural assignment was made on the basis of spectral data, mechanistic considerations and also from an independent synthesis starting from 4-aryloxybut-2-yn-1-ol through a sequence of reactions *e.g.* (i) acetate formation, (ii) Claisen rearrangement, (iii) deacetylation (iv) conversion of OH into Cl, (v) replacement of Cl by flavone-7-oxide anion to give **130a-c**.

The formation of product (**129a-c**) from substrates (**118a-c**) has been rationalized by a mechanism similar to that presented in case of formation of products (**124a-d**) (Scheme 39). The formation of angularly cyclized product in this case follows the normal pattern for reactions of derivatives of 7-hydroxyflavone.[141,142]

The addition of p-toluenesulfonic acid[110] *(2 mol equivalents) to the thermolysis solution of* **118a** *did not* change product formation but the reaction time was reduced (11 h). An increase in the amount of *p*-toluenesulfonic acid (to 10.8 mol equivalents) furnished a new product with a furo[2,3-*b*]furan skeleton (**131a**) admixed with **129a** in the ratio 65:35 (total yield 68 %). If the reaction is conducted for longer period (19 h), a tendency to decomposition was observed as 7-hydroxyflavone was isolated from the

reaction mixture. Increasing the reaction time to 28 h caused total destruction and no tractable product could be isolated. Substrates (**118b**) and (**118c**) were similarly treated with *p-toluenesulfonic acid*, **118b** giving a mixture of **129b** and **131b** in the ratio 20:80 (total yield 71 %) and **118c** furnishing a mixture of **129c** and **131c** in the ratio 15:85 (total yield 78 %). Compounds (**129a-c**) and (**131a-c**) with *p*-toluenesulfonic acid under the same reaction condition behaved similarly to give mixture of **129** and **131** in the same ratio as stated earlier (Scheme 40).



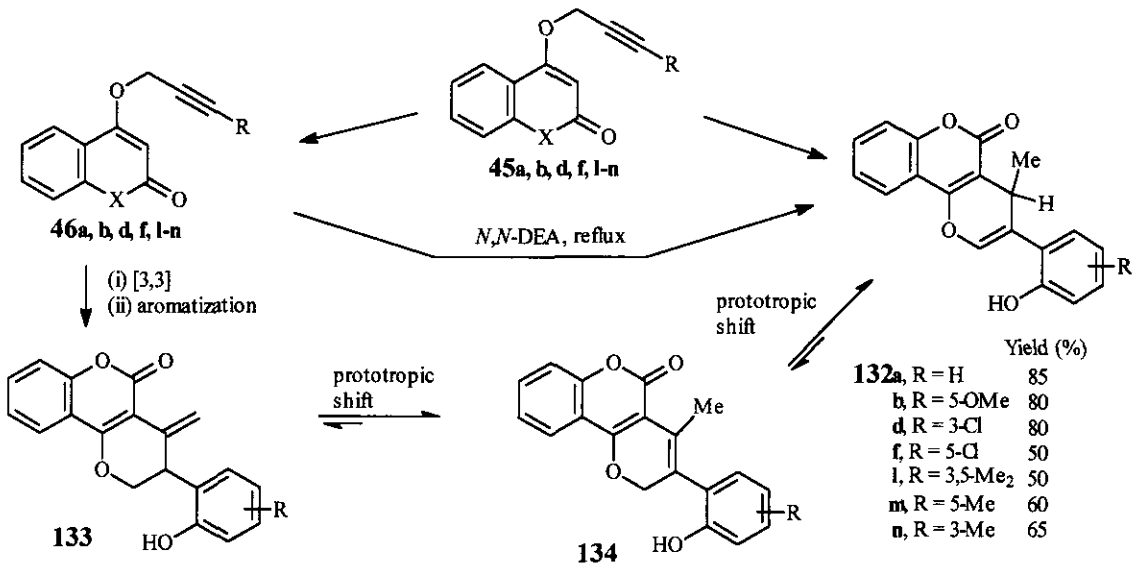
Scheme 40

Synthesis of heterocycles from the sequential [3,3] rearrangement of 1-aryloxy-4-(4′-coumarinyloxy)but-2-ynes (45).

1-Aryloxy-4-coumarinyl-4-oxybut-2-ynes (**45a, b, d, f, l-n**) when subjected to thermal rearrangement in refluxing *N,N*-diethylaniline gave 4-methyl-3-(2-hydroxyphenyl)pyrano[3,2-*c*][1]benzopyran-5(4*H*)-ones (**132a, b, d, f, l-n**). The same products (**132**) are obtained when 4-aryloxymethylpyrano[3,2-*c*][1]benzopyran-5(2*H*)-ones (**46**) were refluxed in *N,N*-diethylaniline for 5 h. Addition of *p*-toluenesulfonic acid during the thermal rearrangement of **45** or **46** showed no effect on the formation of the products. Another striking difference is that the products of the second Claisen rearrangement follow a different course and resisted cyclization to give a polyheterocycle.[143]

The formation of **132** is evidently *via* **46** as **46** also provides **132** under similar treatment. The formation of **132** from **46** may be explained by a second Claisen rearrangement to give phenolic products (**133**). One prototropic shift may convert **133** to **134**. Intermediate (**134**) seems to be unstable due to unfavourable structure of >C=O and $-CH_3$ on a SP^2 carbon. Here phenyl conjugation may not be

important, the coplanarity may be lost. Intermediate (**134**) may undergo a second prototropic shift to give finally the stable product (**132**) (Scheme 41).



Scheme 41

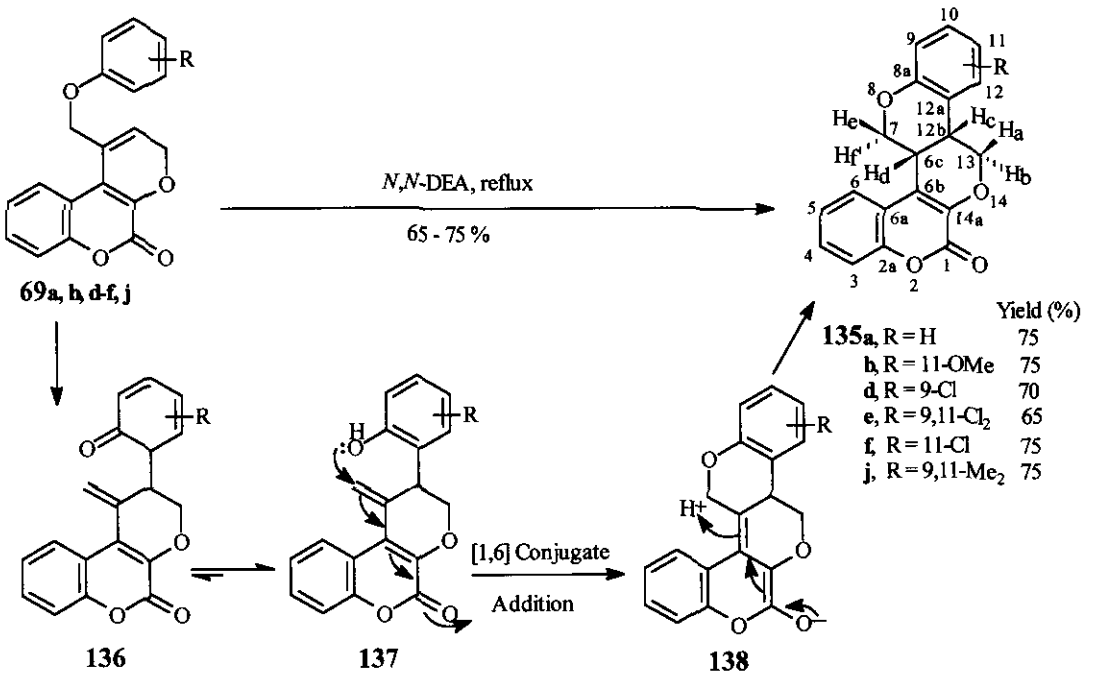
Synthesis of [6,6]pyranopyran

Recently there has been a flurry of activity on the synthesis of pyranopyrans.[144-150] It became possible to synthesize two different series of pyranopyrans from 1,4-bis(derivatives) of 1,4-dichlorobut-2-ynes by the application of sequential [3,3] sigmatropic rearrangements. Substrates (**66**) and (**68**) on first Claisen rearrangement furnished pyranoheterocycles (**67**) and (**69**). A close examination of the products of second Claisen rearrangement of these substrates (**67**) and (**69**) reveal the possibility of an [1,6] internal conjugate addition to give a cyclized product. The results are noted below.

Regioselective Synthesis of [6c,12b,-*cis*]-6c,7,12b,13-tetrahydro-1*H*-chromeno[3=B4,4=B4:4,5]-pyrano[2,3-*c*]chromen-1-ones (135).

1-Aryloxymethylpyrano[2,3-*c*][1]benzopyran-5(3*H*)-ones (**69a, b, d-f, j**) still possess an allyl aryl ether moiety and may undergo a second Claisen rearrangement. Substrates (**69a, b, d-f, j**) on heating in *N,N*-diethylaniline indeed afforded the pentacyclic polyheterocycles, [6c,12b-*cis*]-6c,7,12b,13-tetrahydro-1*H*-chromeno[3=B4, 4=B4 : 4,5]pyrano[2,3-*c*]chromen-1-ones (**135a, b, d-f, j**) in 65-75 % yields.[136,151] The structures of these complex molecules were established from their elemental analyses, high resolution ^{1}H-NMR and other spectral data including 2D, DEPT, HETCOR and NOE experiments. The pyranopyran ring junction stereochemistry is found to be *cis* from ^{1}H-NMR studies and also from molecular mechanics calculations. The formation of the products (**135**) from **69** may be rationalized by [3,3] sigmatropic

rearrangement of **69** to **136** followed by enolization to give **137**. The phenol (**137**) in *N,N*-diethylaniline base may then add to the diene-lactone moiety by a [1,6] conjugate addition to give finally the [6,6] pyranopyran (**135**) (Scheme 42).

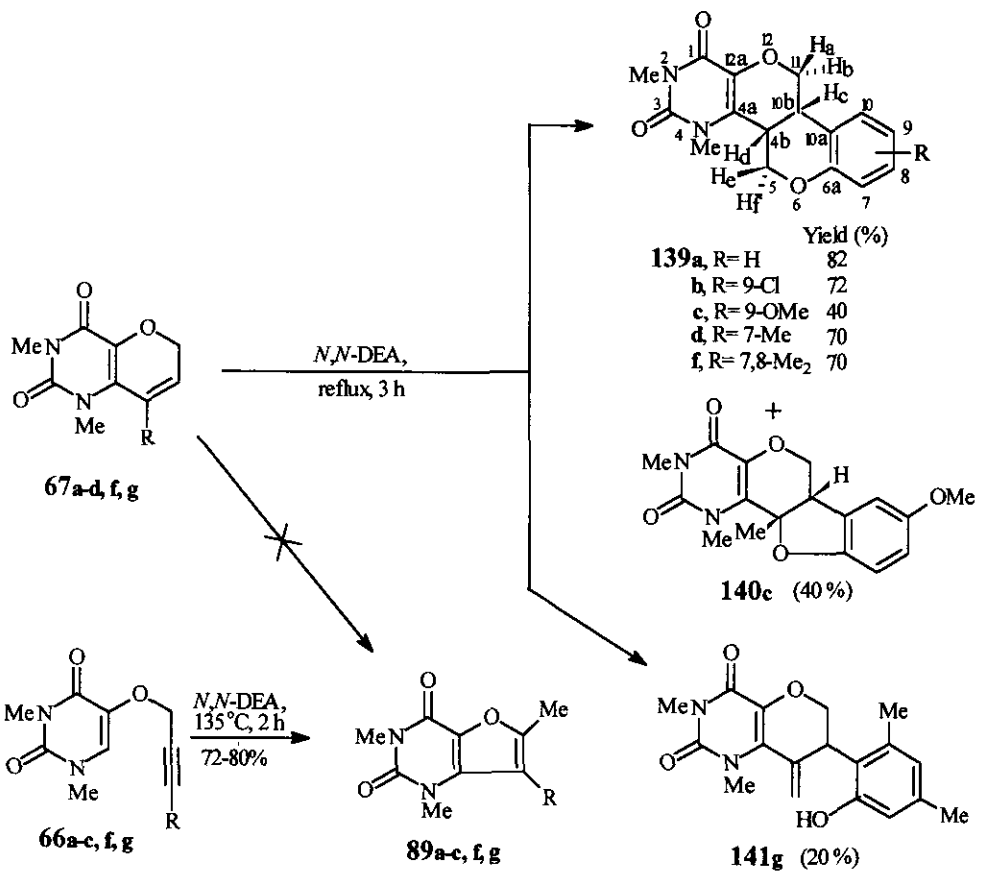


Scheme 42

Regioselective synthesis of [6,6] pyranopyran from 8-aryloxymethyl-1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-diones (67).

The synthesis of 8-aryloxymethyl-1,3-dimethyl-6*H*-pyrano[3,2-*d*]pyrimidine-2,4-diones (**67**) has been described earlier. These substrates also posses an allyl aryl ether moiety and in principle should undergo a second Claisen rearrangement. To test this, the substrates (**67a-d, f, g**) were refluxed in *N,N*-diethylaniline for 3 h and new products were obtained. The structure of the products were assigned **139a-d, f, 140c, 141g** on the basis of elemental analyses and spectral data including ^{13}C, DEPT, ^{1}H-^{1}H COSY and HETCOR. The aliphatic protons were identified by combination of HMBC and HMQC experiments in $CDCl_3$ solution. The *cis*-stereochemistry of the ring junction was established from decoupling, NOE experiments and molecular mechanics calculations.[88,89] The *cis*-isomer was found to be more stable than the *trans*-isomer by ~3.76 kcals/mol. Substrate (**67g**) did not provide a product arising out of cyclization but an intermediate (**141g**) was isolated only in 20 % yield. Substrate (**67c**) gave a mixture of two products (**139c**) (40 %) and the furopyran (**140c**) (40 %) (Scheme 43).

Uracil moiety is present in these heterocycles. 5-Substituted uracils have been developed as drugs[152-158]



Scheme 43

and enzyme inhibitors[159-161] but functionalization of uracil at C-5 and C-6 usually requires rather tedious and sophisticated reaction conditions.[162-164] These pyranopyran derivatives have the potential to be useful. However, no biological evaluation of these compounds have been made so far. The methodology described is simple as well as facile for the synthesis of these compounds. Attempt to synthesize pyranopyran from 3*H*-pyrano[2,3-*c*]quinolin-5(6*H*)-ones (**73**) were of no avail. On heating in *N*,*N*-diethylaniline the substrates (**73a, b, d-i**) were converted to 1-aryloxymethyl-2-methylfuro[2,3-*c*]quinolin-4(5*H*)-ones (**85a, b, d-i**) in 66-79 % yields by an unusual ring contraction. However, synthesis of furo[2,3-*c*]quinolin-4(5*H*)-one derivatives has also been reported earlier in low yields.[165-168]

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