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ON THE CLAISEN REARRANGEMENT OF 1,4-DIARYLOXY-2-BUTYNES[+]

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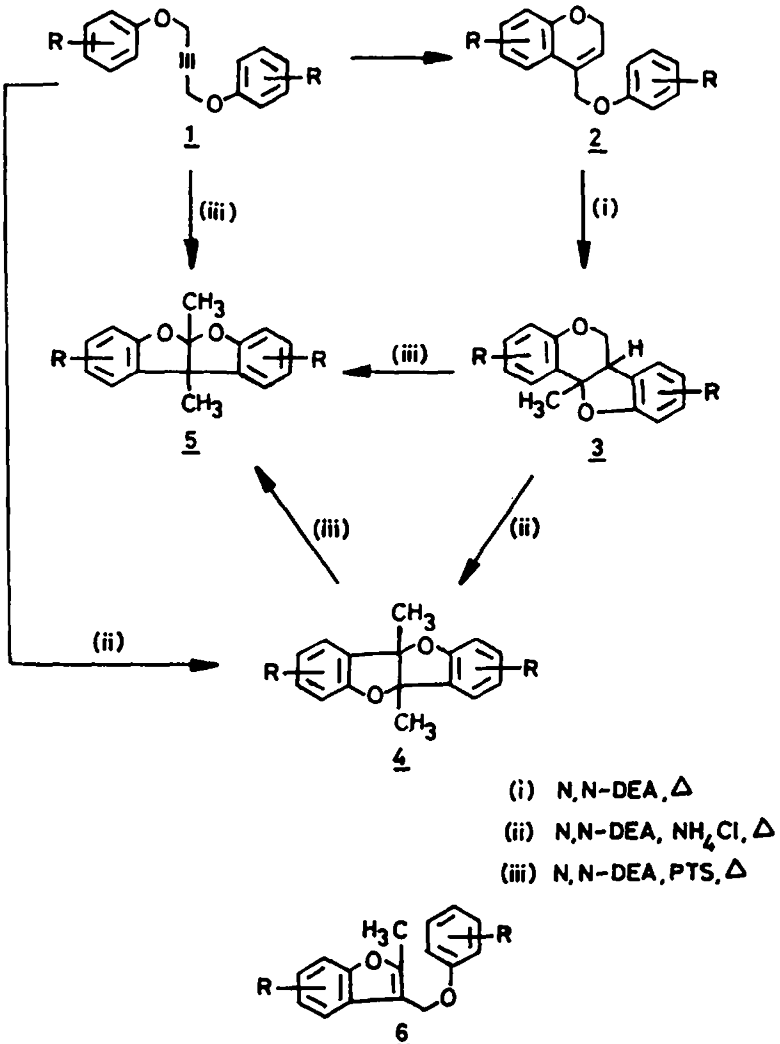
Abstract - A proton nmr follow-up provided conclusive evidence for the involvement of two sequential Claisen rearrangements in the thermal rearrangement of 1,4-diaryloxy-2-butynes 1 to 11a-methylpterocarpans 3. A detailed study of the rearrangement of 1,4-diaryloxy-2-butynes 1 in polyethyleneglycol-200 (PEG-200), indicated a definite possibility of selective synthesis of either benzofuro(3,2-b)-benzofuran 4 or benzofuro(2,3-b)benzofuran 5, by varying the temperature of the reaction alone.

The Claisen rearrangement is one of the very well-studied name reactions in organic chemistry and continues to attract considerable attention.[1] Various modifications have been made to improve the utility of this versatile reaction.[2] The thermal rearrangement of 1,4-diaryloxy-2-butynes 1 is one such instance, where two sequential Claisen rearrangements were encountered leading to the formation of benzofuro(3,2-C)(1)-6a-11a-dihydro-11a-methylbenzopyrans or shortly, 11a-methylpterocarpans 3. This novel rearrangement was discovered and fairly well-investigated by Thyagarajan et al.[3] Initially, two different mechanisms involving either 4-aryloxymethylchrom-3-ene 2 or 2-methyl-3-aryloxymethylbenzofuran 6 were proposed. Later the study of the thermolysis of the proposed intermediates 3 and 6, synthesised independently, indicated the involvement of 4-aryloxymethylchrom-3-ene 2 and not the 2-methyl-3-aryloxymethylbenzofuran 6.[4] Further, the thermal rearrangement of 1 in presence of ammonium chloride in refluxing N,N-diethylaniline(N,N-DEA) yielded 4b,9b-dihydro-4b,9b-dimethylbenzofuro(3,2-b)benzofuran 4, while under similar conditions, in the presence of p-toluenesulphonic acid, the product obtained was the isomeric 5a-10b-dihydro-5a,10b-dimethylbenzofuro(2,3-b)-benzofuran 5 (Scheme 1).

[+] Dedicated to Prof. S. Swaminathan, University of Madras, on the occasion of his 60th Birthday.



(i) N,N-DEA, Δ
(ii) N,N-DEA, NH_4Cl, Δ
(iii) N,N-DEA, PTS, Δ

SCHEME 1

$$\underline{1a} \xrightarrow{\text{slow}} \underline{2a} \xrightarrow{\text{slow}} \underline{3a} \xrightarrow{\text{fast}} \underline{4a} \xrightarrow{\text{slow}} \underline{5a}$$

It was also observed by these workers that independent pyrolysis of chrom-3-ene 2, 11a-methylpterocarpan 3 and benzo(3,2-b)benzofuran 4 in refluxing N,N-DEA, in presence of PTS led to the formation of benzofuro(2,3-b)-benzofuran 5, thus indicating the involvement of 2, 3 and 4 in the conversion of 1 ⟶ 5.[5]

Later Bates and Jones,[6] have achieved similar transformations to a limited extent under Lewis acid catalysis under mild conditions. These transformations were highly dependent on the nature of the aromatic substituents. Recently, Donnelly et al.[7] have reported the formation of a mixture of benzofuro-benzofurans 4 and 5 from the pyrolysis of 2-butyne 1 in ethylene glycol.

The mass spectra of 2-butyne 1, chrom-3-ene 2, 11a-methylpterocarpan 3, benzofuro(2,3-b)benzofuran 5 and benzofuro(3,2-b)benzofuran 4 exhibited strikingly similar fragmentation patterns, thus indicating the occurrence of rearrangement of all these compounds viz., 1, 2, 3 and 4 to 5 under electron-impact conditions, as in thermal rearrangement. For example, the mass spectra of 1,4-bis(4-methylphenoxy)-2-butyne 1a and its rearrangement products, viz., 2a, 3a, 4a and 5a indicate the presence of peaks at 266, 251, 249, 223, 165, 159, etc., with 251 ($M-CH_3$) always being the base peak.[8]

Recently, we have found that 11a-methylpterocarpans 3 undergo photochemical ring contraction to yield benzofuro(3,2-b)benzofurans 4.[9] The partial transformation of 4 to the isomeric benzofuro(2,3-b)benzofuran 5, has also been noticed when 4 was irradiated with a 254 nm light source in methanol.[10]

Results and Discussion

As can be seen from the earlier discussion, there is no direct evidence for the formation of chrom-3-ene 2, in the rearrangement of 1,4-diaryloxy-2-butyne 1 to 11a-methylpterocarpan 3, other than the fact that chrom-3-ene 2 also yields 11a-methylpterocarpan 3, under identical conditions. So, to obtain more information about the nature of the intermediates involved in the 1 ⟶ 3, transformation, the reaction of 1a in refluxing N,N-DEA was monitored with proton nmr. In this experiment nmr spectra were recorded for the samples collected after every 30 mts. of the reaction over a period of 6 hrs.

The proton nmr spectra of these samples unmistakably indicated the formation of 4-aryloxymethylchrom-ene 2a ($O-CH_2$ at $\delta 4.8$ and olefinic H at $\delta 5.8$) and also the formation of 4-methylene-3-(o-hydroxyphenyl)dihydrobenzopyran 7 (exomethylene protons at $\delta 4.8$ and $\delta 5.7$). In fact, one could see the formation of chrom-3-ene 2 and exomethylene pyran 7 simultaneously after the first half-an-hour. However, the percentage of 2 and 7 in the mixture was found to be always less than 10%. Thus, the nmr monitoring of the rearrangement of 2-butyne 1a provided conclusive evidence for the involvement of two sequential Claisen rearrangement steps, via chrom-3-ene 2 in the 1 ⟶ 3 transformation.

Further, the pyrolysis of 1,4-bis(p-methylphenoxy)-2-butyne 1a in quinoline/acetic anhydride under reflux for 8 hrs. led to the isolation of 4-methylene-3-(2 '-hydroxy-5'-methylphenyl)dihydrobenzopyran 7a. This product was compared with an authentic sample, prepared from pyrolysis of chrom-3-ene 2a under similar conditions. It is of interest to note that the first Claisen rearrangement product viz., o-allenylphenol did not get trapped as acetate and only the second Claisen rearrangement product was trapped. Apparently the intramolecular 1,5-sigmatropic shift of the o-allenylphenol is very much faster than the acylation of the phenolic group, under these conditions.

In view of the successful ring contraction of 11a-methylpterocarpans 3 and of isomerisation of benzofuro(3,2-b)benzofuran 4 to benzofuro(2,3-b)benzofuran 5 under acid-catalysis and photolytic conditions, it was felt worthwhile to attempt to tune the rearrangement of 2-butyne 1 to a particular product, either 2, 3, 4 or 5 by just modifying the temperature or the reaction time in a single solvent.

To meet these requirements, a solvent should have the following attributes:

1. High boiling point, to manoeuvre the temperature of the reaction.
2. Work-up should be convenient.
3. Total yield of the products should be high.

Rearrangement of 2-butyne 1a in refluxing N,N-DEA (b.p. 218°C) for 5 hrs. afforded pure 3a as a solid m.p. 131°C in 55% yield whereas in refluxing quinoline (b.p. 232°C) a mixture of 3a and 4a were formed in the ratio of 60:40 respectively. Prolonged heating of 1a in quinoline for 12 hrs. gave rise to pure 4a in 62% yield. Heating of 1a in diphenyl ether (b.p. 250°C) resulted in the formation of a mixture of 3a and 4a in 68% yield in the ratio of 65:35 respectively.

After the few experiments in the above mentioned solvents like, N,N-DEA, quinoline and diphenyl ether, it was found that polyethyleneglycol-200 (PEG-200) was most suitable for the present purpose. PEG-200 offers a wide range of temperature to study the rearrangement, the work-up is very simple and yield of products is quite high (75%-80%).

The temperatures at which the rearrangement was studied were, 195°C, 225°C and 270°C. To maintain the desired temperature, a salt bath (KNO_3 + $NaNO_3$ + $LiNO_3$) was employed, whose melting point was around 175°C. Before the substrate, 1,4-bis(4-methylphenoxy)-2-butyne 1a was introduced into the solvent, the temperature of the solvent was allowed to attain and maintain at the desired temperature. The reactions were carried out on 1.0 g. scale using 10 ml. of PEG-200. Equal aliquots were drawn after every 30 mts., from the reaction mixture. They were worked-up by pouring into water and extracting with ether. Evaporation of the dried ether extract yielded the product, which was analysed by an EM-390 proton NMR spectrometer. The relative ratios of each of the compounds were calculated by integration of characteristic signals (for 2-butyne 1a δ4.7, (O-CH_2), chrom-3-ene 2a, δ4.8 (O-CH_2) and δ5.8 (olefinic-H), 11-a-methylpterocarpan 3a, δ1.69 (11a-CH_3), benzofuro(3,2-b)-benzofuran 4a, δ 1.74 (4b, 9b-di CH_3-) and benzofuro(2,3-b)benzofuran 5a, δ1.74 and δ1.54 (singlets due to 5a and 10b CH_3)).

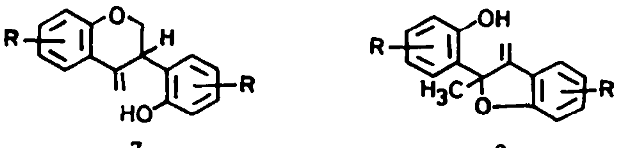
The analysis of the crude product of rearrangement of 1a at 195°C, indicated the presence of starting material 1a even after 5 hrs. of the reaction, in addition to the presence of the products, viz., 3a and 4a with the latter in majority. The ratio of 1a:3a:4a at 195°C after 5 hrs. was found to be 40:17.7:42.2 respectively. It is important to note the simultaneous formation of 11a-methylpterocarpan 3a and benzofuro(3,2-b)benzofuran 4a even at 195°C.

A similar proton nmr analysis of the crude products obtained from the rearrangement of 1a at 225°C, revealed the disappearance of 1a within 30 mts. of the commencement of the reaction. After 90 mts. no 11a-methylpterocarpan 2a could be seen and only benzofuro(3,2-b)benzofuran 4a was present. It is interesting to note that even after 4.5 hrs. no further isomerisation of 4a to 5a was noticed. The results of a similar nmr analysis of the reaction of 2-butyne 1a at 270°C are shown in table 1. The formation of a mixture of 4a and 5a could be noticed even at the end of the first 30 mts. As the time proceeded, the percentage of 5a gradually increased and the percentage of 4a decreased. Finally after 2.5 hrs. only 5a could be seen.

Table 1. Pyrolysis of 1,4-bis(4-methylphenoxy)-2-butyne 1a in PEG-200 at 270°C

Reaction time	Products 4a(%)	 5a(%)
30 mts.	46.9	53.1
60 mts.	18.2	81.8
90 mts.	9.0	91.0
150 mts.	0	100.0

Independent pyrolysis of 2a, 3a and 4a in PEG-200 at 270°C for 4 hrs. yielded 5a. Further the pyrolysis of suspected intermediates, 2-methyl-2-(o-hydroxyphenyl)-3-methylenedihydrobenzofuran 8a and 4-methylene-3-(o-hydroxyphenyl)dihydrobenzopyran 7a also yielded 5a within 2 hrs., thus indicating the involvement of all these intermediates in 1a ⟶ 5a conversion. The findings from the above experiments point to the following mechanism (scheme 2).



7

8

SCHEME 2

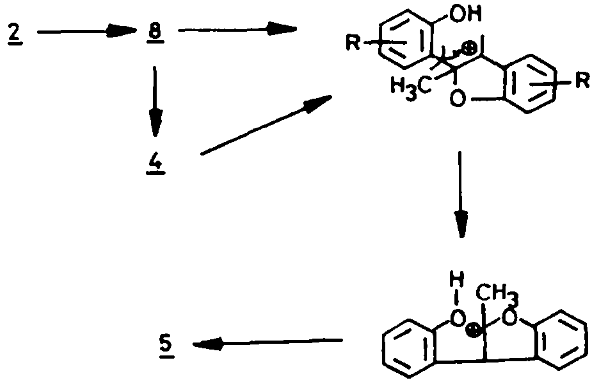
The conversion of 1a to 3a was considered to be slow compared to that of 3a to 4a because of the presence of 2-butyne 1a, 11a-methylpterocarpan 3a and benzofuro(3,2-b)benzofuran 4a in the ratio of 40:17.7:42.2 at 195°C, after 5 hrs. The observed stability of 4a at 225°C for 5 hrs. speaks of the slowness of the subsequent isomerisation of 4a to 5a. The pyrolysis of other substituted 1,4-diaryloxy-2-butynes 1b to 1d in PEG-200 at 270°C afforded the corresponding 5a,10b-dihydro-5a,10b-dimethylbenzofuro(2,3-b)benzofuran 5 (table 2).

Table 2. Synthesis of 5a,10b-dihydro-5a,10b-dimethylbenzofuro(2,3-b)-benzofuran 5

S.No.	R	Starting Material 1	Product 5	Yield %
1.	CH_3	1a	5a	75
2.	Cl	1b	5b	76
3.	OCH_3	1c	5c	80
4.	H	1d	5d	78

The significant feature, to be noted here is that the ring contraction of 11a-methylpterocarpan 2a was negligible in N,N-DEA (b.p. 218°C), while it is appreciable in PEG-200, even at 195°C, thereby indicating the important role played by PEG-200 in the ring contraction of 11a-methylpterocarpans 3.

With a view to get some insight into the subtler aspects of these transformations, particularly with regard to the concerted or non-concerted nature, the pyrolysis of 3-deutero-4-(4'-methylphenoxy)methyl-6-methylchrom-3-ene 10 was carried out in PEG-200 at 270°C for 6 hrs. The product isolated in 70% yield was a white solid melting at 198°C. The nmr and mass spectrum of this product showed the absence of deuterium indicating the exchange of deuterium with the protic solvent medium. The structure of the product was confirmed to be benzofuro(2,3-b)benzofuran 5a by the mixed melting point determination with the authentic sample. This observation supports the mechanism involving phenolic intermediates as shown in scheme 3.



SCHEME 3

Conclusion

The present study clearly demonstrates the solvent effect on the Claisen rearrangement of 1,4-diaryloxy-2-butynes 1 and provides the possibility of selective synthesis of either of benzofuro-benzofurans 4 or 5 by varying the temperature of the reaction alone in PEG-200.

Acknowledgement

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EXPERIMENTAL

1. General considerations: Melting points reported are uncorrected. Infrared spectra were recorded on a Perkin-Elmer (257 and 1310 models) instruments. NMR spectra were recorded on a Varian EM-390 spectrometer, with CDCl$_3$ as solvent and tetramethylsilane (TMS) as the internal standard. The chemical shifts reported are in δ scale.

The compounds 1,4-diaryloxy-2-butynes 1, 4-aryloxymethylchrom-3-ene 2, 11a-methylpterocarpan 3, benzofuro(3,2-b)benzofuran 4 and benzofuro(2,3-b)-benzofuran 5 were prepared as per the reported procedures[3,4]. The salt bath employed in the present investigation was prepared by the mixture of equimolar quantities of sodium nitrate, potassium nitrate and lithium nitrate. The melting point of the bath was around 175°C.

2. Rearrangement of 1,4-bis(4-methylphenoxy)-2-butyne 1a in N,N-diethylaniline - NMR follow-up: The compound 1a (2.0 g, 7.4 mmoles) was introduced into 10 ml. of N,N-DEA, which was heated to reflux in a salt-bath maintained at 225°C. After every 30 mts. over a period of 5 hrs. a one ml. aliquot of the reaction mixture was withdrawn and worked-up by pouring into ice-cold 1N HCl solution followed by extraction with ether (2 x 25 ml.). The ether layer was further washed with 2N HCl (25 ml.) and water. The dried ethereal layer on evaporation under reduced pressure yielded the crude product 120 mg., which was analysed by NMR.

3. Pyrolysis of 1a in quinoline/acetic anhydride mixture: The compound 1a (1.3 g.) (1.26 mmoles) was dissolved in quinoline (8 ml.) containing acetic anhydride (1.2 ml) and sodium acetate (0.5 g.). The mixture was pyrolysed for 8 hrs. The reaction mixture was cooled and extracted with ether. The ethereal layer was washed with saturated sodium bicarbonate solution and dried with anhydrous sodium sulphate. The removal of ether and quinoline under reduced pressure yielded the crude product 7a (1.2 g.), which was purified by passing it over either neutral alumina or basic alumina, using hexane as eluent. Yield after purification was 1.0 g. (65%) (viscous liquid, homogeneous on tlc).

^{1}H-NMR (CDCl$_3$) δ : 2.1 (s, 3H), 2.2 (s, 3H), 2.3 (s, 3H), 4.2-4.4 (m, 3H), 4.7 (d, 1H, J = 1 Hz), 4.56 (d, 1H, J = 1 Hz), 6.8-7.5 (m, 6H).

IR (cm^{-1}) neat : 3100(m), 2980(s), 2960(s), 1720(s), 1560(m), 1450(m), 1320(m).

UV (nm) CH$_3$OH :

λ max	ϵ
312	(1924.5)
285	(2340.2)
254.6	(3958.0)

4. Synthesis of 6-methyl-4-methylene-3-(2'-acetoxy-5'-methylphenyl)dihydrobenzopyran 7a: The 6-methyl-4-(4'-methylphenoxy)methylchrom-3-ene 2a (1.3 g.) (1.26 mmoles) was dissolved in quinoline (8 ml.) containing acetic anhydride (1.2 ml.) and sodium acetate (0.5 g.). The mixture was pyrolysed for 4 hrs. The product was worked-up as in the previous experiment. The purified product exhibited the same spectral characteristics as in experiment 3.

5. Pyrolysis of 1a in Quinoline: The compound 1a (1.0 g., 3.7 mmoles) was dissolved in quinoline (5 ml.) and refluxed for 6 hrs. The reaction mixture was worked-up as described in experiment 2. The product, a colourless solid, m.p. 152°C (600 mg, 60%) was found to be a mixture of 2,8-dimethyl-11a-methylpterocarpan 3a and benzofuro(3,2-b)benzofuran 4a in the ratio of 60:40 by proton nmr analysis. In another experiment under identical conditions, prolonged heating for 12 hrs. yielded only 4a as solid m.p. 174°C (620 mg., 62%).

6. Pyrolysis of 1a in diphenyl ether: The butynyl ether 1a (1.0 g., 3.7 mmoles) was dissolved in diphenyl ether (5 ml.) and refluxed in a salt bath for 6 hrs. The solvent was removed under reduced pressure. The crude product was triturated with hexane to remove traces of diphenyl ether. The solid m.p. 162°C (650 mg., 65%) thus obtained was found to be a mixture of 3a and 4a in the ratio of 40:60, as indicated by proton nmr.

7. Pyrolysis in Polyethylene Glycol - 200 (PEG-200) : General procedure: The commercially available PEG-200 (laboratory grade) was employed as such for the rearrangement studies. It was found to boil at 270°C. PEG-200 (10 ml.) was taken in a two-necked flask and heated in a salt bath until the desired temperature is reached. The solvent was allowed to attain the constant temperature. The compound 1a (1.0 g.) was added to the pre-heated solvent and samples of 1 ml. aliquots were collected after every 30 mts. over a period of 5 hrs. These aliquots were poured into water and extracted with ether. The ether layer was washed with water and dried. On evaporation it yielded 72 mg. of solid product. The proton nmr spectra were recorded for these samples.

7. a) Rearrangement of 1a at 195°C in PEG-200: The compound 1a (1.0 g.) was dissolved in a pre-heated PEG-200 (10 ml.), which was maintained at 195°C. The proton nmr spectra were recorded for the samples collected over a period of 5 hrs. These spectra indicated the presence of 1a, 3a and 4a at various proportions. The sample at the end of the 5th hr. indicated the presence of 1a, 3a and 4a ratio to be 40:17.7:42.2 respectively.

b) Thermolysis of 1a at 225°C in PEG-200: The pyrolysis of 1a was carried out at 225°C, by following the same method described in the previous experiment. The product analysis indicated disappearance of 1a within 30 mts. of the commencement of the reaction and complete conversion of 1a to 4a within 2.5 hrs.

c) Thermolysis of 1a at 270°C in PEG-200: At this temperature the different intervals of time indicated the isomerisation of 4a to 5a and 11a-methylpterocarpan 3a was detected only in the first 30 mt. sample. The product analysis is given in table 1. At the end of 2.5 hrs. only benzofuro(2,3-b)-benzofuran 5a was present (refer to table 1).

8. Pyrolysis of 2-butynes 1 in PEG-200 at 270°C: The butynyl ether 1 (3.7 mmoles) was dissolved in PEG-200 (10 ml.) and heated to 270°C and maintained at this temperature for 4 hrs. The work-up of the reaction product yielded crude benzofuro(2,3-b)benzofurans 5, which were recrystallised from methanol and characterised by spectral data and compared with the authentic samples.[3] (Table 2).

9. Pyrolysis of suspected intermediates in PEG-200 at 270°C : General Procedure: The suspected intermediate 2a or 3a or 4a or 7b (6-methyl-4-methylene-3-(2'-hydroxy-5'-methylphenyl)dihydrobenzopyran, prepared from the base-catalysed hydrolysis of the corresponding acetate 7a, or 8a[7] (0.37 mmoles) was dissolved in PEG-200 (3 ml.) and pyrolysed for the given interval time (table 3) and the product 5a was isolated after usual work-up.

Table 3. Preparation of 5a from the suspected intermediates

S.No.	Starting Material	Number of hr. of reflux	Yield of 5a (%)
1.	2a	3	72
2.	3a	3	70
3.	4a	3	73
4.	7b	2	75
5.	8a	1	76

10. Synthesis of 6-methyl-3-deutero-4-(4'-methylphenoxy)methylchrom-3-ene 10: To the acetic acid-d_1 (prepared from the hydrolysis of acetic anhydride in presence of D_2O and D_2SO_4), under anhydrous conditions, 2.2 g. of (0.01 moles) of red mercuric oxide and 10 g. (0.037 moles) of 1,4-bis(4-methylphenoxy)-2-butyne 1a was added. The mixture was refluxed for 40 mts. in an oil bath. Then the reaction mixture was cooled and the acetic acid was neutralised by the addition of solid sodium carbonate. The solid reaction mixture was extracted with ether, washed with 5% sodium hydroxide (3 x 50) and water. The ethereal layer was dried and evaporated to yield crude chrom-3-ene 10 6.2 g. which on passing through an alumina column using hexane as eluent yielded pure 10, 6.0 g. (60%) - m.p. 74-75°C. The proton nmr analysis using the relative ratios of 3-H proton signal at δ 5.8 to the O-CH_2 signal at δ 4.8 and the mass spectral

analysis indicated the deuterium incorporation to be 78% (while analysing the mass spectrum the contribution due to undeuterated 2a was taken into consideration).

11. Pyrolysis of deuterochrom-3-ene 10 in PEG-200: The deutero compound 10 (100 mg., 0.37 mmoles) was dissolved in PEG-200 (3 ml.) and heated to 270°C. It was maintained at this temperature for 4 hrs. The mass spectrum analysis of the product 5a indicated total absence of deuterium.

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