A Short Synthesis of 4-Aryloxymethyl-Δ^3-chromenes and 3-(β-Aryloxy)ethylbenzofurans

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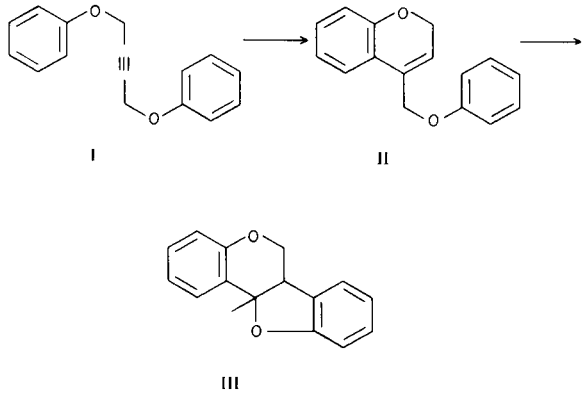
A direct and short route to the synthesis of 4-aryloxymethyl-Δ^3-chromenes and 3-(β-aryloxy)-ethylbenzofurans is described. Hydration of 1,4-diaryloxy-2-butynes with mercuric oxide and sulfuric acid affords, instead of a ketone, the cyclization product of the ketone. In three of the diaryloxy-butynes studied, the corresponding aryloxyethylbenzofurans are formed. In no instance could the ketone be isolated from the hydration reaction.

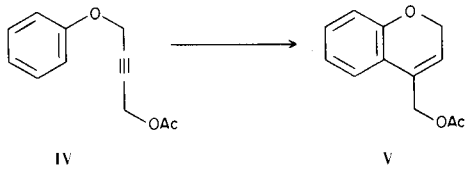
We have earlier published on the sequence of reactions involved in the thermal isomerization of 1,4-diaryloxy-2-butynes into the corresponding benzofurobenzopyrans shown below (1,2).



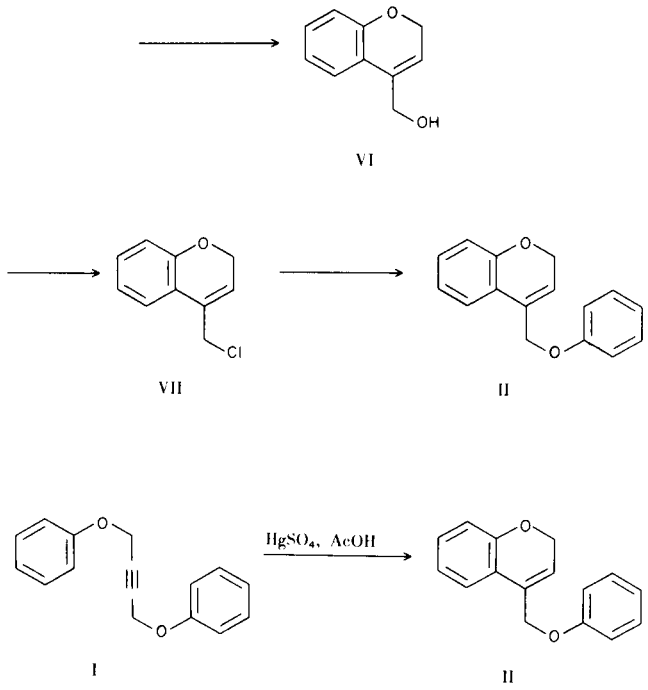
I II III

The 4-aryloxymethyl-Δ^3-chromene was clearly shown to be an intermediate in this reaction by its conversion to the same tetracyclic product under identical conditions.

The aryloxymethylchromene was synthesized by two different approaches shown below:



IV V

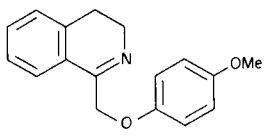


VI VII II I II

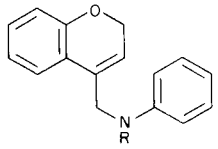
Of the two routes indicated, the hydration of the butyne with mercuric sulfate-acid was a pleasant surprise in the turn of events because simple phenyl propargyl ether itself affords only phenoxyacetone (2) under identical conditions.

VIII IX

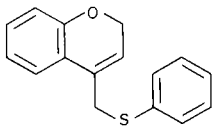
In view of this and in view of possible potential application of this reaction as a general one-step synthesis of aryloxymethylchromenes, we have now investigated this cyclization with a variety of 1,4-diaryloxy-2-butynes. The results of this study are presented here. This general approach to such systems derives additional interest in view of a recent publication on the biological activity of 1-aryloxymethyl-3,4-dihydroisoquinolines. The latter compounds have recently been shown to possess strong inhibitory effect on the component enzyme, viral neuraminidase, present in common respiratory pathogenic viruses (3). It is, therefore, of interest to investigate the potential of analogous systems like the aryloxymethylchromenes, arylaminomethylchromenes, aryloxymethylthiochromenes and arylaminomethylthiochromenes. The most active compound reported in the aryloxymethylisoquinolines is illustrated below (X) along with the other systems we are currently investigating:



X



XI

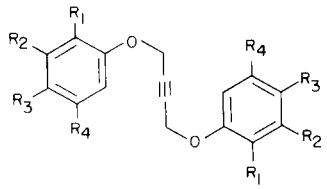


XII

The 1,4-diaryloxy-2-butynes required in this study were synthesized according to our earlier published procedures (4,5). In addition to butynes described earlier, we have now synthesized seven new different butynes.

TABLE I

1,4-Bis-aryloxy-2-butynes



	R_1	R_2	R_3	R_4	M.p. (°C)	Formula	Analysis, % Calcd. C	Calcd. H	Found C	Found H
1. (a)	Cl	H	H	H						
2. (a)	CH_3	H	H	H						
3. (a)	H	H	Cl	H						
4. (a)	H	H	Br	H						
5. (a)	H	H	CH_3	H						
6. (a)	$-OCH_3$	H	H	H						
7.	Cl	H	Cl	H	112	$C_{16}H_{10}Cl_4O_2$	51.06	2.66	50.75	2.59
8.	CH_3	H	Cl	H	112.5	$C_{18}H_{16}Cl_2O_2$	64.47	4.77	64.69	4.79
9.	Br	H	H	H	86	$C_{16}H_{12}Br_2O_2$	48.52	3.05	48.78	3.14
10.	CH_3	H	H	CH_3	99	$C_{20}H_{22}O_2$	81.63	7.48	81.74	7.58
11.	H	H	C_6H_5	H	168	$C_{28}H_{22}O_2$	86.13	5.68	86.03	5.74
12.	C_6H_5	H	H	H	95	$C_{28}H_{22}O_2$	86.13	5.68	86.28	5.74
13.	Cl	H	C_6H_5	H	156	$C_{28}H_{20}Cl_2O_2$	73.21	4.39	73.48	4.36

(a) Compounds 1-6 reported by B. S. Thyagarajan, *et al.*, *Tetrahedron*, **21**, 2289 (1965).

TABLE II

Butyne Used (10 g.)	Amount of Red Mercuric Oxide (g.)	Conc. H_2SO_4 Used (drops)	Time of Reflux (hour)	Product Obtained	Solvent of Crystallization	% Yield
1	2.6	3	1	Chromene	Pet. ether (30-60°)	31
2	2.6	3	0.75 hr. water bath at 70°	Chromene	Distilled (b)	58
	2.6	3	2	Benzofuran	Distilled (b)	15
3	2.6	3	1	Chromene	Ethanol	26
4	2.6	3	1	Chromene	Ethanol	30
5	2.6	3	2.5	Benzofuran	Ethanol	11
	2.6	3	0.83	Chromene	Ethanol	58
6	1.5 g. $HgSO_4$	6	4 hr. on water bath	Chromene	Ethanol	60
7	2.6	3	2	Chromene	Ethanol	30
8	7.8	12	3	Chromene	Ethanol	20
9	2.6	3	1	Chromene	Ethanol	24
10	2.6	3	0.83	Chromene	Distilled (b)	60
	2.6	3	2.5	Benzofuran	Distilled (b)	20
11	5.2	8	3.5	Chromene	Acetone	41
12	2.6	3	1	Chromene	Pet. ether (30-60°)	26
13	7.8	10	3	Chromene	Ethanol-Acetone	26

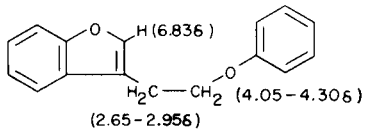
(a) Hydration of (6) was done by Dr. Bhima Rao (Ph.D. thesis), University of Madras, 1966. (b) Distilled using a short-path distillation apparatus.

Contrary to our earlier experience at hydration of the butynes utilizing mercuric sulfate as the preferred catalyst, we found during the course of the present study that a combination of red mercuric oxide and a few drops of sulfuric acid in acetic acid medium afforded cleaner and better products. The experimental section describes the conditions employed with different butynes.

The chromenes were characterized by their elemental analysis, mass spectra and nmr spectra. Unlike the starting butynes, the chromenes showed the presence of vinyl protons between 5.85 and 6.15 δ. Indeed the percentage of chromene formed could be readily estimated from the relative ratios of the vinyl protons to that of the OCH_2 protons. Although both the starting butynes and the product chromenes contain OCH_2 functions, the chromene methylenes are flanked by a double bond and show a slightly larger deshielding and appear at lower fields, than the methylenes of the butynes.

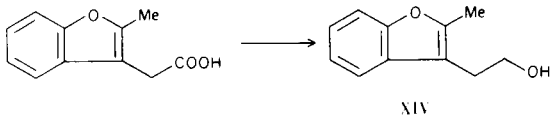
The aryloxymethylchromenes were instable to prolonged heating in acid. There is, therefore, an optimal time limit for the hydration reaction to proceed to completion without the destruction of the product formed. This is indicated in the experimental section.

Of the several butynes studied here, there were three which showed additionally interesting features on hydration. These butynes gave not only the chromenes but also the benzofurans (XIII). Two of these products were liquids, distillable without decomposition while the third was a solid. They all gave elemental analyses isomeric with the starting butynes and the chromenes. However, their nmr spectra differed completely from those of the chromenes. Proton signals were found at 2.65 to 2.95 δ and 4.05 to 4.3 δ as triplets. These signals are absent in the chromenes. These could be attributed to the allylic methylenes and *O*-methylenes, respectively, each being coupled to the other. The allylic methylenes showed further signs of coupling with another proton, so that the triplet was actually a doublet of triplets. A search for this single proton producing such a coupling revealed that it was buried in the aromatic proton signals. When a decoupling was made saturating the odd proton signal, the doublet of triplets collapsed into a simple triplet, confirming that it was indeed coupled to the allylic methylenes. Based on this, we concluded these new compounds are the 3-phenoxyethylbenzofurans illustrated below.

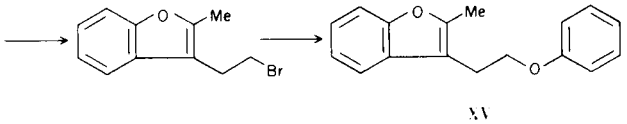


XIII

As additional confirmation of the benzofuran structure, we synthesized 2-methyl-3-(β-phenoxy)ethylbenzofuran by the following approach (see experimental).



XIV



XV

Compound XV lacks the 2-proton on the benzofuran and so shows a simple pattern of two triplets for the allylic and *O*-methylene protons as XIII does.

The formation of the benzofuran products is not surprising because any intermediary ketone formed as a result of the hydration of the butynes should be capable of cyclizing onto the aromatic rings on either side of the four carbon chain. Cyclization on one side should lead to chromenes and on the other side should give the benzofurans. The experimental data show, in general there appears to be a preference for the formation of chromenes over the benzofurans. The present study has concerned itself only with *symmetrical* 1,4-diaryloxy-2-butynes where cyclization on either end would have the same directive effect. We are currently studying the behavior of *unsymmetrical* 1,4-diaryloxy-2-butynes and the corresponding sulfur and nitrogen systems to investigate any possible directive influences in these cases.

EXPERIMENTAL

The melting points were determined with an ordinary thermometer and were not corrected. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer and Varian HA-100 spectrometer using carbon tetrachloride or deuteriochloroform as solvents and tetramethylsilane (TMS) as an internal standard. Mass spectral data were obtained on a Hitachi Perkin-Elmer MOdel RMU-6E mass spectrometer.

Synthesis of 1,4-Bis-aryloxy-2-butynes.

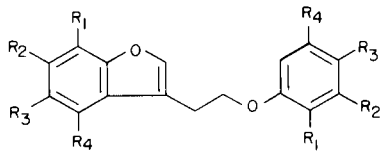
The symmetrical 1,4-bis-aryloxy-2-butynes were prepared according to the earlier published procedure (4,5,6). The butynyl ethers obtained are listed in Table I. Most of the ethers were recrystallized from ethanol or from a mixture of benzene-petroleum ether (60-80°). Compounds 11 and 13 were recrystallized from chloroform.

Procedure for Hydration.

The butyne (10 g.) in glacial acetic acid (50 ml.), red mercuric oxide (2.6-7.8 g.), and concentrated sulfuric acid (3 to 12 drops) were refluxed for 3/4 hour to 4 hours, cooled and filtered. The filtrate was neutralized with sodium carbonate and extracted with diethyl ether. The ether extract was washed with water, 10% sodium hydroxide solution (twice, 250 ml. each time) and once

TABLE III

3-Phenoxyethylbenzofurans

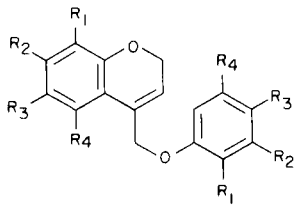


							Analysis, % Calcd.		Found	
	R_1	R_2	R_3	R_4	B.p. or M.p.	Formula	C	H	C	H
1.	H	H	CH_3	H	71-72° (m.p.)	$C_{18}H_{18}O_2$	81.17	6.81	80.99	6.87
2.	CH_3	H	H	H	70-72°/ .02 mm (a)	$C_{18}H_{18}O_2$	81.17	6.81	81.33	6.95
3.	CH_3	H	H	CH_3	88-95°/ .03 mm (a)	$C_{20}H_{22}O_2$	81.63	7.48	81.67	7.58

(a) The compounds were distilled using a short-path distillation apparatus and the b.p.'s were not corrected.

TABLE IV

4-Aryloxymethyl-Δ^3-chromenes



	R_1	R_2	R_3	R_4	M.p. or B.p. (°C)	Formula	Analysis, % Calcd. C	Calcd. H	Found C	Found H
1.	Cl	H	H	H	83-84	$C_{16}H_{12}Cl_2O_2$	62.55	3.91	62.61	3.99
2.	H	H	Cl	H	71-72	$C_{16}H_{12}Cl_2O_2$	62.55	3.91	62.63	3.85
3.	Cl	H	Cl	H	130-131	$C_{16}H_{10}Cl_4O_2$	51.06	2.66	51.14	2.74
4.	Me	H	Cl	H	95	$C_{18}H_{16}Cl_2O_2$	64.47	4.77	64.69	4.74
5.	Br	H	H	H	62	$C_{16}H_{12}Br_2O_2$	48.52	3.03	48.70	3.14
6.	H	H	Br	H	97	$C_{16}H_{12}Br_2O_2$	48.52	3.03	48.61	3.07
7.	$-OCH_3$	H	H	H	103-104	$C_{18}H_{18}O_4$	72.46	6.05	72.50	6.24
8.	C_6H_5	H	H	H	115	$C_{28}H_{22}O_2$	86.13	5.68	86.17	5.79
9.	H	H	C_6H_5	H	129-130	$C_{28}H_{22}O_2$	86.13	5.68	86.44	5.74
10.	Cl	H	C_6H_5	H	107-108	$C_{28}H_{20}Cl_2O_2$	73.21	4.39	73.49	4.45
11.	CH_3	H	H	H	150°/.02 mm	$C_{18}H_{18}O_2$	81.17	6.81	79.79	6.72
12.	CH_3	H	H	CH_3	168°/.05 mm	$C_{20}H_{22}O_2$	81.63	7.48	80.60	7.53
13.	H	H	CH_3	H	71-72	$C_{18}H_{18}O_2$	81.17	6.81	79.06	6.74

Compounds (11), (12), and (13) were converted into known benzofurobenzopyrans (III). The liquid compounds were distilled using a short-path distillation apparatus and the b.p.'s were not corrected.

with water again. An emulsion formed at this stage was removed by shaking with rock-salt solution, followed by another water-wash. The ether extract was then dried (sodium sulfate) and distilled. The dark red viscous liquid thus obtained was dissolved in 10-15 ml. of benzene and passed through a neutral alumina column (20 x 2 cms). It was eluted with petroleum ether (30-60°), and for compounds 11 and 13 (Table II) were eluted with benzene-petroleum ether (30-60°) 1:1.

The first 2 to 3 fractions (350 ml. each) was stripped of solvent and the residue triturated with 10 ml. of ethanol to give a solid.

Butynes 11 and 13 were not sufficiently soluble in glacial acetic acid even under reflux. Therefore, these two butynes required 100 ml. of glacial acetic acid per 10 g. of the butyne. For some of the butynes, the quantities of red mercuric oxide, concentrated sulfuric acid and time of reflux varied. These are indicated in the accompanying Table II.

The products of hydration are listed in Table III (benzofurans) and IV (chromenes).

In three of the chromenes, out of thirteen reported here, elemental analyses were erratic. Repeated purification indicated tenacious occlusion of mercury salts as impurities. Despite repeated purifications, these compounds did not give accurate elemental analyses, although their nmr spectra and mass spectra fully corroborated their structures. As additional proof of their structures, we have successfully converted them into the corresponding benzofurobenzopyrans (*vide* page 1, experimental section).

Synthesis of 3-(β-*p*-Chlorophenoxy)ethylbenzofuran (XV).

2-Methyl-3-benzofuryl Acetic Acid.

This compound was synthesized according to the procedure of R. Gaertner (7).

Reduction of 2-Methyl-3-benzofurylacetic Acid with Lithium Aluminum Hydride.

The above acid (5.0 g.) in dry diethyl ether (150 ml.) was refluxed with lithium aluminum hydride (1.0 g.) for 6 hours. Excess lithium aluminum hydride was destroyed by adding moist ether. Then it was acidified with dilute hydrochloric acid and more ether (250 ml.) was added. The ether layer was separated, washed once with 5% sodium carbonate solution, thrice with saturated sodium chloride solution and once with water (100 ml.). The ether solution was dired over anhydrous sodium sulfate and stripped of the solvent. The clear liquid was distilled under reduced pressure using a short-path distillation apparatus, b.p. 100-105°/0.5 mm (not corrected); yield 3.60 g., 77.7%, nmr (carbon tetrachloride): 2.26 δ (S, 3H), 2.72 δ (t, 2H, J = 6.5 cps), 3.20 δ (S, 1H), 3.68 δ (t, 2H, J = 6.5 cps), 7.00-7.50 δ (m, 4H), ir (neat): 3380 cm^{-1}, molecular ion peak at 176.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.00; H, 6.81. Found: C, 75.18; H, 6.81.

Conversion of the Alcohol (XIV) to the Corresponding Bromide.

The above alcohol (3.0 g.) in anhydrous ether (70 ml.) and pyridine (5 drops) was stirred with phosphorus tribromide (1.80 g.) in anhydrous ether (30 ml.) at 0-5° for 5 minutes. Then more ether (150 ml.) was added to the reaction mixture, the ether solution was washed once with water (50 ml.) once with a 5% solution of sodium bicarbonate, twice with saturated sodium chloride solution and finally once with water (50 ml.). It was dried (sodium sulfate) and ether removed *in vacuo*. The pale yellow liquid (crude yield 2.60 g., 60%) could not be purified by distillation or by chromatography. It tended to decompose. So it was used as such for the next step.

Condensation of the Above Bromide with *p*-Chlorophenoxide.

p-Chlorophenol (1.0 g.) and potassium hydroxide (0.44 g.) in DMF (10 ml.) was heated on a steam bath for 15 minutes and cooled to room temperature. Then the bromide (2.0 g.) in DMF (10 ml.) was added slowly to the stirred solution of the phenoxide and the stirring was continued for 20 hours. DMF was removed under a vacuum. The residue was extracted with chloroform (100 ml.). The chloroform extract was washed once with 10% sodium hydroxide solution, thrice with water and dried (sodium sulfate). Removal of ether gave a pale yellow liquid, 0.9 g. This liquid was chromatographed through a neutral alumina column (20 x 2.5 cms). Petroleum ether (30-60°, 1 liter) elute was discarded. The next eluate (20% benzene-petroleum ether, 600 ml.) gave the desired clear liquid. It was distilled under reduced pressure using a short path distillation apparatus, b.p. 105-110°/0.03 mm (uncorrected), yield 15.5%; nmr (carbon tetrachloride): 2.40 δ (S, 3H), 2.95 δ (t, 2H, J = 6.5 cps), 4.05 δ (t, 2H, J = 6.5 cps), 6.65-7.50 δ (m, 8H); molecular ion peak at 286, 288.

Anal. Calcd. for $C_{17}H_{15}ClO_2$: C, 72.10; H, 5.25. Found: C, 71.12; H, 5.25.

Acknowledgments.

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(6) Use of aqueous ethanol (80-85%) was found to be advantageous for this nucleopholic displacement reaction.

(7) R. Gaertner, *J. Am. Chem. Soc.*, **74**, 5319 (1952).