Studies in the Claisen Rearrangement. Part XII (1). Synthesis of Benzofuro[3,2-*c*][1]-6a,11a-dihydro-11a-methylbenzopyrans from 1,4-Diaryloxy-2-butynes

*K. C. Majumdar and B. S. Thyagarajan**

Chemistry Department, University of Idaho, Moscow, Idaho 83843

and

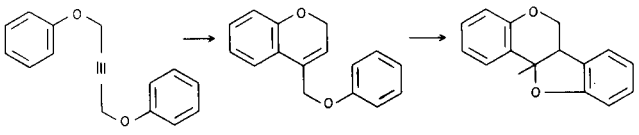
K. K. Balasubramanian (2)

Chemistry Department, Indian Institute of Technology, Madras-36, India

Received November 15, 1972

Successful Claisen rearrangement of a number of 1,4-diaryloxy-2-butynes is reported. The products of such a rearrangement are the benzofuro[3,2-*c*]benzopyrans. This novel rearrangement offers a facile synthetic route to tetracyclic derivatives resembling the naturally occurring pterocarpans.

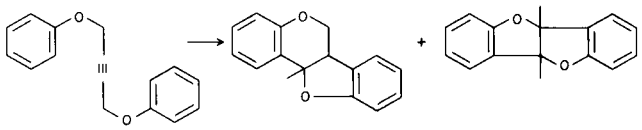
In a preliminary communication (3), we described the rearrangement of 1,4-diaryloxy-2-butynes into the title compounds. Subsequently, we discussed possible mechanistic pathways for this novel rearrangement establishing the following sequence for the molecular reorganization (4).



1 2 3

However, until the present, we have not presented the other salient features of the rearrangement nor the experimental efforts in elucidating the possible intermediates. In this paper we present the experimental details of the rearrangement, its general synthetic utility as extended to several other new 1,4-diaryloxy-2-butynes and the spectral features relevant to the structure and stereochemistry of the benzofurobenzopyrans.

The rearrangement of 1,4-diaryloxy-2-butynes could be carried out under a variety of conditions. In the absence of a solvent at *ca.* 200°, with most butynes the rearrangement proceeds to give the benzofurobenzopyrans in excellent yields. However, with certain butynes such conditions lead to the formation of benzofuro[3,2-*b*]-benzofurans (8) (**4**), in addition to the benzofurobenzopyrans.



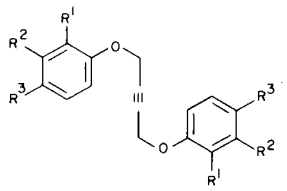
1 3 4

Many different solvents have been tried in studies relating to the rearrangement of aryl allyl ethers (5). Correspondingly, we tried some eleven solvents to study their influence on the course of the rearrangement. The only important criterion for a solvent to be effective in this rearrangement was that its boiling point had to be 200° or above. Of all the solvents investigated, *N,N*-diethylaniline proved to be the best in terms of yields of rearrangement products and ease of workup of the reaction mixture. The basic solvent could be easily removed by acid treatment at the end of the reaction.

The boiling point requirement mentioned above, expressed itself in an interesting manner in another aspect of the rearrangement which we discuss below. One of the simple methods to trap an intermediary phenol in Claisen rearrangements of aryl allyl ethers is to employ quantities of acetic anhydride or benzoic anhydride in the solvent medium. Any phenolic intermediate is then trapped as its acetate or benzoate. Thus, 2,6-diallyloxyanthracene, when rearranged in diethylaniline in presence of acetic anhydride, afforded the *diacetate* of 1,5-diallyl-2,6-dihydroxyanthracene (6). When 1,4-diaryloxy-2-butynes were treated similarly with diethylaniline and acetic anhydride,

TABLE I

1,4-Diaryloxy-2-butynes



	R¹	R²	R³	M.p., °C	Molecular Formula	Analysis % Calcd. C	Calcd. H	Found C	Found H
1 (b)	H	H	H						
2 (a)	Cl	H	H						
3 (a)	OCH_3	H	H						
4 (a)	CH_3	H	H						
5 (a)	H	H	Cl						
6 (a)	H	H	Br						
7 (a)	H	H	CH_3						
8 (a)	H	H	OCH_3						
9 (a)	H	H	NO_2						
10 (a)	H	H	CHO						
11 (b)	H	3,4-phenylene							
12 (c)	Cl	H	Cl						
13 (c)	Br	H	H						
14 (c)	CH_3	H	Cl						
15 (c)	H	H	C_6H_5						
16 (c)	C_6H_5	H	H						
17 (c)	Cl	H	C_6H_5						
18	CH_3	CH_3	H	71	$C_{20}H_{22}O_2$	81.63	7.48	81.83	7.37
19	H	H	SCH_3	103-104	$C_{18}H_{18}O_2S_2$	65.45	5.45	65.76	5.56
20	H	H	$C(CH_3)_3$	66-68	$C_{24}H_{30}O_2$	82.24	8.63	82.43	8.48
21	H	CH_3	CH_3	80	$C_{20}H_{22}O_2$	81.63	7.48	81.34	7.40
22	H	CH_3	Cl	76	$C_{18}H_{16}Cl_2O_2$	64.47	4.77	64.50	4.84

(a) Reported by B. S. Thyagarajan, K. K. Balasubramanian, R. Bhima Rao (8). (b) Reported by A. W. Johnson (15). (c) Reported by B. S. Thyagarajan and K. C. Majumdar (16).

there was no rearrangement at all. The starting butynes were recovered quantitatively. Even in decalin, upon addition of varying amounts of acetic anhydride, the diaryloxybutynes failed to undergo any rearrangement.

An earlier publication in the literature refers to the use of benzoic anhydride in the rearrangement of the diallyl ether of stilbestrol (7) when the corresponding dibenzoate was isolated. Similar efforts in the case of the diaryloxy butynes gave no benzoates of any sort. Instead, the rearrangement led to the formation of benzofurobenzofurans (**4**).

This observation led to the interesting rearrangement of the 1,4-diaryloxybutynes into benzofurobenzofurans (**4**) which we have described elsewhere (8).

Thus, all attempts to trap any phenolic intermediates in the rearrangement of aryl propargyl ethers were futile.

The application of spectral data in the elucidation of the structures of the benzofurobenzopyrans also led to another interesting feature less frequently noted in the literature. The structure proof for the tetracyclic compounds rests on the following data:

1. Elemental analyses and molecular ion peaks indicate

TABLE II

Solvent	B.P. (C)	Compound (Table I) Studied	Reaction Time (Hours)	Results
1. Dimethylformamide	153	9	20	(a)
2. Bromobenzene	155	7	10	(a)
3. *p*-Cymene	176	7	10	(a)
4. *o*-Dichlorobenzene	180	7	10	(a)
5. Dimethylsulfoxide	184	5	10	(a)
6. Dimethylaniline	192	1	10	(a)
		5	10	(b)
		7	10	(e)
		8	10	(c)
		9	10	(d)
7. Decalin	189	5	5	(b)
		5	10	(d)
		7	5	(b)
		7	10	(d)
8. *N*-Methylaniline	196	5	5	(b)
		7	10	(e)
		7	5	(b)
		5	10	(c)
		9	10	(d)
9. Ethyleneglycol	196	5	10	(e)
		7	10	(e)
		2	10	(e)
		6	10	(a)
		9	10	(b)
10. Diphenyl ether	258	2	10	(e)
		5	10	(e)
		6	10	(e)
11. Diethylaniline	215	(+)	10	(e)
12. No Solvent	190-200	2	8	(e)

(a) Denotes nearly quantitative recovery. (b) Denotes partially recovered. (c) Denotes no characteristic solid obtained. (d) Denotes tarry material obtained. (e) Product obtained. (+) All except 9 and 10 are rearranged, 9 and 10 gave tarry material.

the compounds are isomeric with the butynes so that no atoms are lost or gained in the rearrangement.

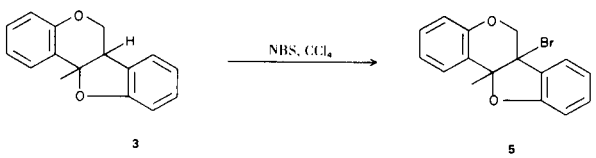
2. The compounds are completely saturated as determined by hydrogenation (9), addition of bromine or oxidation with permanganate.

3. The compounds are unaffected by ozonolysis.

While all this chemical evidence pointed to lack of unsaturation, the ir spectra of the benzofurobenzopyrans revealed the presence of new bands in the region of 900-1000 cm^{-1} which were not found in the starting butynes. Normally, bands in this region are attributed to olefinic bonds; however, in the present instance, they account for the cyclic ether bands of the tetracyclic system.

The nmr spectrum of the benzofurobenzopyrans have some unique features which go to establish its structure unequivocally. The 1,4-diaryloxy-2-butynes show only two signals arising from the aromatic ring protons and from the propargylic *O*-methylene protons.

In contrast, the nmr spectra of the benzofurobenzopyrans show a multiplet between 6.5-7.40 ppm for the aromatic protons, a multiplet between 3.35 and 4.50 ppm for the benzylic and *O*-methylene protons and a sharp singlet at 1.74 ppm for the angular methyl group. The multiplet in the region 3.35 to 4.50 ppm shows a typical ABC pattern with a total of 11 lines. The nonequivalance of the *O*-methylene protons allows for a coupling between

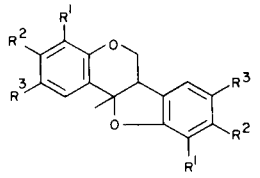


3 5

themselves with a coupling constant of 11 cps while the benzylic proton shows a small coupling constant of 5 cps with one of them and a coupling constant of 8.5 cps with

TABLE III

Benzofuro[3,2-c][1]-6a,11a-dihydro-11a-methylbenzopyrans



	R¹	R²	R³	M.p., °C	% Yield	Molecular Formula	Analysis % Calcd. C	Calcd. H	Found C	Found H
1 (a)	H	H	H	124						
2 (a)	H	H	Cl	164						
3	Cl	H	H	190	67	$C_{16}H_{12}Cl_2O_2$	62.55	3.91	62.77	3.89
4	OCH_3	H	H	126-128	38	$C_{18}H_{18}O_4$	72.47	6.09	72.20	5.96
5	CH_3	H	H	149-154	50	$C_{18}H_{18}O_2$	81.17	6.81	81.19	7.01
6	H	H	Br	169-170	40	$C_{16}H_{12}Br_2O_2$	48.48	3.03	48.68	3.24
7	H	H	CH_3	138-140	50	$C_{18}H_{18}O_2$	81.17	6.81	81.28	6.69
8	H	H	OCH_3	145	64	$C_{18}H_{18}O_4$	72.47	6.08	72.46	6.05
9	H	3,4-phenylene		168	60	$C_{24}H_{18}O_2$	85.18	5.36	85.06	5.62
10	H	CH_3	Cl	192	34	$C_{18}H_{16}Cl_2O_2$	64.47	4.77	64.18	4.76
11	Cl	H	Cl	160	40	$C_{16}H_{10}Cl_4O_2$	51.06	2.66	50.99	2.74
12	CH_3	CH_3	H	154	45	$C_{20}H_{22}O_2$	81.63	7.48	81.32	7.36
13	CH_3	H	Cl	180	57	$C_{18}H_{16}Cl_2O_2$	64.47	4.77	64.47	4.75
14	H	CH_3	CH_3	203	37	$C_{20}H_{22}O_2$	81.63	7.48	81.63	7.44
15	C_6H_5	H	H	209-210	65	$C_{28}H_{22}O_2$	86.13	5.68	86.40	5.62
16	H	H	C_6H_5	223	71	$C_{28}H_{22}O_2$	86.13	5.68	86.45	5.67
17	Cl	H	C_6H_5	230	59	$C_{28}H_{20}Cl_2O_2$	73.21	4.39	73.47	4.47
18	H	H	SCH_3	155-156	57	$C_{18}H_{18}O_2S_2$	65.45	5.45	65.62	5.57
19	H	H	$C(CH_3)_3$	127-128	70	$C_{24}H_{30}O_2$	82.24	8.63	82.50	8.73

(a) Reported by B. S. Thyagarajan, K. K. Balasubramanian, R. Bhima Rao (3,4).

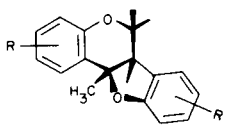
the other. This feature was further confirmed when the benzylic proton was replaced with a bromine atom.

Seven different bromo compounds were prepared (see Experimental) and in these the *O*-methylene protons showed an AB quartet in the region 4.3-5.2 ppm with a coupling constant of 12 cps. There was also a noticeable deshielding effect (0.30 ppm) on the angular methyl group by the bromine. The replacement of the benzylic proton by bromine 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.

The stereochemistry of the ring fusion in the tetracyclic system can only be surmised from molecular models which show a strain-free *cis* arrangement.

In connection with the stereochemistry of the two oxygen heterocyclic rings in the pterocarpan series, it was concluded from Dreiding models that the ring was *cis*-fused (10,11). A more extensive proton magnetic resonance study of several other pterocarpan derivatives has also been made by Pachler and Underwood (12,13). It has been concluded based on the nmr spectra that the stereochemistry at the ring junction is *cis*.

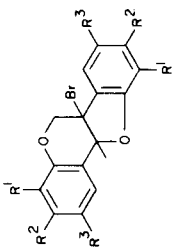
Extending this argument to the pterocarpan derivatives obtained in this study, these compounds could therefore be represented as **6**.



6

TABLE IV

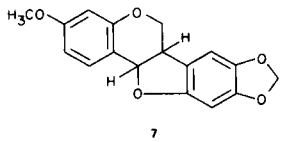
Benzofuro[3,2-*c*][1]-6a,11a-dihydro-6a-bromo-11a-methylbenzopyrans



No.	R^1	R^2	R^3	M.p., °C	Yield %	Formula	Analysis Calcd. C	Calcd. H	Found C	Found H	Nmr ($CDCl_3$) a (AB quartet)	Nmr ($CDCl_3$) b (Singlet)
1	H	H	H	98 (d)	80.5	$C_{16}H_{13}BrO_2$	60.56	4.10	60.57	4.07	4.30-5.00	2.05
2	Cl	H	Cl	206-208 (d)	83	$C_{16}H_9BrCl_4O_2$	42.20	1.97	42.50	2.09	4.40-5.10	2.10
3	Me	H	Cl	153 (d)	87	$C_{18}H_{15}BrCl_2O_2$	52.17	3.62	52.01	3.61	4.30-5.00	2.10
4	H	Me	Cl	136 (d)	90.2	$C_{18}H_{15}BrCl_2O_2$	52.17	3.62	52.38	3.79	4.25-4.95	2.05
5	Cl	H	H	162 (d)	95	$C_{16}H_{11}BrCl_2O_2$	49.80	2.87	49.72	2.94	4.47-5.20	2.15
6	H	H	Cl	135 (d)	83	$C_{16}H_{11}BrCl_2O_2$	49.80	2.87	49.73	2.89	4.30-5.00	2.03
7(a)	Cl	H	C_6H_5	197 (d)	83	$C_{28}H_{19}BrCl_2O_2$	62.44	3.53	62.53	3.65		

(a) This compound was not soluble enough to permit nmr spectral determination in solvents like benzene, chloroform, DMSO, *etc.*

The easy accessibility of the 1,4-diaryloxy-2-butynes from simple phenols and 1,4-dichloro-2-butynes makes the present approach a very facile process for preparing derivatives related to pterocarpan (14) (**7**).



7

Several of the benzofurobenzopyrans prepared in this study were examined for possible antifertility activity and antimicrobial properties. However, none showed encouraging biological activities.

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 chloroform-d_1 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-Diaryloxy-2-butynes.

The symmetrical 1,4-diaryloxy-2-butynes were prepared according to the earlier published procedure (8,15,16). 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°).

General Procedure for the Rearrangement of 1,4-Diaryloxy-2-butynes to Benzofuro[3,2-*c*]benzopyrans.

The 1,4-diaryloxy-2-butyne (**5g**) was refluxed in *N,N*-diethylaniline (25 ml.) for 10-12 hours under nitrogen. The reaction mixture was cooled and poured into ice-cold 1:1 hydrochloric acid and extracted with excess ether. The ether extract was washed with more of dilute hydrochloric acid to remove the basic aniline, then with 5% aqueous sodium hydroxide and finally with water. The neutral ether extract was dried (sodium sulfate) and evaporated. The solid obtained was triturated with ethanol (15-20 ml.) and filtered. The product was crystallized from any of the following solvents: ethanol or petroleum ether (60-80°) or benzene-ethanol mixture or chloroform-benzene mixture. The benzofuro[3,2-*c*]benzopyrans obtained by this procedure are listed in Table III.

The rearrangement products of 2-butynes **15** and **17** (Table I) were not ether soluble so they were extracted with chloroform from their acidified reaction mixture.

2-Butynes (**4**, **7**, and **19** of Table I) when refluxed with *N,N*-diethylaniline gave a mixture of approximately 80% benzofuro[3,2-*c*]benzopyran and 20% benzofuro[3,2-*b*]benzofuran (**4**). When these three butynyl ethers (**4**, **7**, and **19** of Table I) were refluxed in *N*-methylaniline they gave only benzofuro[3,2-*c*]-benzopyrans.

Table II shows the results obtained with different solvents for the rearrangement.

Attempted Rearrangement of 1,4-Bis(*p*-methylphenoxy)-2-butyne in the Presence of Acetic Anhydride.

1,4-Bis(*p*-methylphenoxy)-2-butyne (3 g.) was refluxed in a mixture of diethylaniline (25 ml.) and acetic anhydride (12 ml.) for 30 hours. The solution was concentrated under reduced pressure to about 10 ml. After decomposing the mixture with ice-cold dilute hydrochloric acid, the aqueous solution containing the precipitated solid was filtered. The solid material was crystallized from ethanol. It was found to be the starting material as revealed by the mixed melting point determination with an authentic sample, m.p. 82.5-83° mixed m.p. with pure starting material, 82-83°, recovery 2.8 g. (96%).

An attempted rearrangement of the same butyne in decalin in the presence of acetic anhydride resulted in the quantitative recovery of the starting material.

In both experiments, the temperature of the reaction mixture was found to be lowered to 140-150° as soon as acetic anhydride was added.

Rearrangement of 1,4-Bis(*p*-chlorophenoxy)-2-butyne in the Presence of Benzoic Anhydride.

The 2-butyne (2 g.) was refluxed with benzoic anhydride (4 g.) in diethylaniline (20 ml.) for 10 hours. The cooled basic solution was extracted with ether. The ether extract was washed with excess dilute hydrochloric acid, then with a saturated solution of sodium bicarbonate and finally with water. The neutral ether solution was dried (magnesium sulfate) and the solvent was removed. A thick pleasant smelling liquid was obtained, yield 5.2 g.

The above liquid was dissolved in a minimum amount of benzene and chromatographed over alumina, the column being made in petroleum ether (30-60°). The first fraction of the petroleum ether elution (100 ml.) gave a red liquid containing crystalline solid, yield 3.8 g. This liquid-solid mixture was triturated well with ethanol (10 ml.) and filtered. The solid thus obtained from three similar petroleum ether elutions was crystallized from benzene-petroleum ether mixture, m.p. (1st crop) 204-205°, yield 1.0 g., m.p. (2nd crop) 196-201°, yield 0.3 g.

The crystals obtained in the 1st crop did not depress the melting point of authentic 4b,9b-dihydro-4b,9b-dimethyl-3,8-dichlorobenzofuro[3,2-*b*]benzofuran (*i.e.*, the product of rearrangement of starting butyne in the presence of *p*-toluene sulphonic acid) (8), mixed m.p. with an authentic sample 206-208°.

General Procedure for Bromination.

The benzofuro[3,2-*c*]benzopyran (0.01 *M*), *N*-bromosuccinimide (1.78 g., 0.01 *M*) and benzoylperoxide (5 mg., catalyst) were slowly refluxed in carbon tetrachloride (150 ml.) on a steam bath for 4 hours when all the *N*-bromosuccinimide was completely converted to succinimide. The mixture was cooled and filtered free of succinimide. The pale yellow filtrate was then washed with freshly prepared ferrous sulfate solution and with water. The solution was dried (sodium sulfate) and the solvent was removed at 40-45° under a vacuum. The residue was triturated with 10 ml. of ether and collected on a filter. All bromo compounds (except **7**, Table IV) were crystallized from ether. Compound **7** (Table IV) is insoluble in ether and sparingly soluble in warm chloroform, benzene, or DMSO. Compound **1** (Table IV) is very unstable, and decomposes at room temperature. Therefore, removal of the solvent was done at room temperature under a vacuum. Then petroleum ether (30-60°) was added and the solid obtained was stored inside the freezer. The relatively stable bromo compounds prepared by this procedure are listed in Table IV.

Acknowledgements.

We are grateful to the Warner-Lambert Research Institute, Morris Plains, New Jersey, for the pharmacological data.

Table IV

REFERENCES

(1) K. C. Majumdar and B. S. Thyagarajan, *Int. J. Sulfur Chem.*, A, 2, 93 (1972).

(2) Part of this work was carried out at the Department of Organic Chemistry, University of Madras and was incorporated in the Ph.D. dissertation of K. K. B. (1965).

(3) B. S. Thyagarajan, K. K. Balasubramanian, and R. Bhima Rao, *Tetrahedron Letters*, 1393 (1963).

(4) B. S. Thyagarajan, K. K. Balasubramanian, and R. Bhima Rao, *Tetrahedron*, **23**, 1893 (1967).

(5) D. S. Tarbell, *Organic Reactions*, edited by Roger Adams, Vol. II, 1 (1944).

(6a) L. Fieser, *J. Am. Chem. Soc.*, **58**, 749 (1936); (b) L. Fieser, *ibid.*, **61**, 2215 (1939).

(7) E. Kaiser, A. L. Anderson Jr., and J. J. Svara, *ibid.*, **70**, 1243 (1965).

(8) B. S. Thyagarajan, K. K. Balasubramanian, and R. Bhima Rao, *Tetrahedron*, **21**, 2289 (1965).

(9) Hydrogenation was attempted in a Paar hydrogenator with platinum oxide catalyst for 8 hours.

(10) H. Suginome, *Experientia*, **18**, 161 (1962).

(11) H. Suginome and T. Iwadare, *ibid.*, 18, 163 (1962).

(12) K. G. R. Pachler and W. G. E. Underwood, *Tetrahedron*, **23**, 1817 (1967).

(13) S. H. Harper, A. D. Kemp, and W. G. E. Underwood, *Chem. Ind. (London)*, 562 (1965).

(14) J. B. Bredenberg and J. N. Shoolery, *Tetrahedron Letters*, 285 (1961).

(15) A. W. Johnson, *J. Chem. Soc.*, 1009 (1946).

(16) K. C. Majumdar and B. S. Thyagarajan, *J. Heterocyclic Chem.*, **9**, 489 (1972).