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ARENE SYNTHESES BY DEHYDRATION OF 7-OXABICYCLO[2.2.1]HEPTENE SYSTEMS

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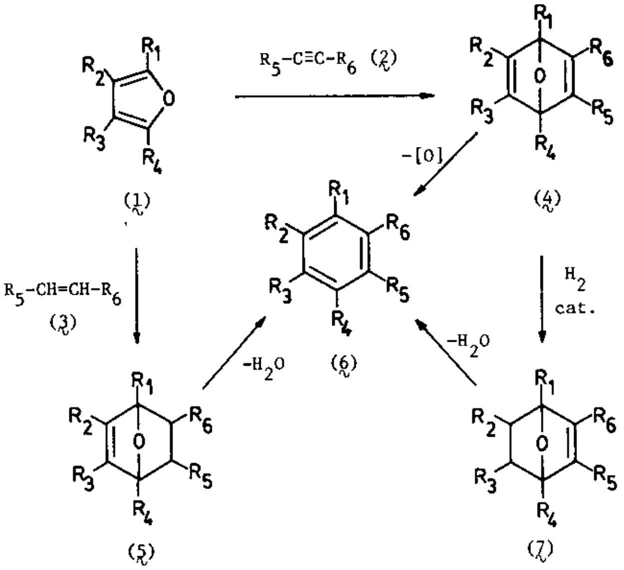
Abstract — Aromatization by dehydration of 7-oxabicyclo[2.2.1]heptene systems is an efficient method, which would provide benzene, napthalene, anthracene as well as phenanthrene derivatives in acceptable yields.

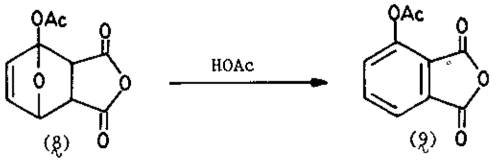
Introduction

Furans (1) behave as characteristic dienes in Diels-Alder cycloaddition reaction. Electron-deficient alkynes (2) or alkenes (3) would add facilely to furans (1), and afford 7-oxabicyclo-[2.2.1]hepta-2,5-dienes (4) or 7-oxabicyclo[2.2.1]hept-2-enes (5). The direct extrusion of oxygen moiety from (4) would lead to polysubstituted arenes (6). Various aspects of this serviceable extrusion strategy have been reviewed recently.[2] Alternatively, oxygen-bridged olefins (5) can also yield synthetically useful arenes upon treatment with acids as well as other suitable reagents. These reactions are formally dehydration reactions. On the other hand, the catalytic hydrogenation of the slightly electron-rich double bond of (4) (where R_5 and R_6 are electron-withdrawing groups) would give (7), which can then be converted to (6) through acid catalyzed dehydration. The dehydration route is generally rather beneficial because the oxygen atom in (4) is usually very difficult to remove. In this review, we will briefly discuss the syntheses of benzene, naphthalene, anthracene as well as phenanthrene derivatives by applying this dehydration methodology.

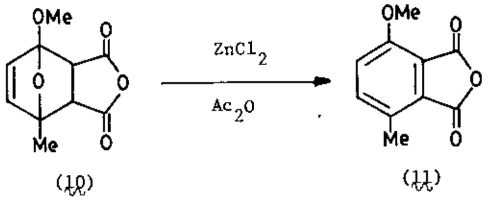


Syntheses of Benzene Derivatives

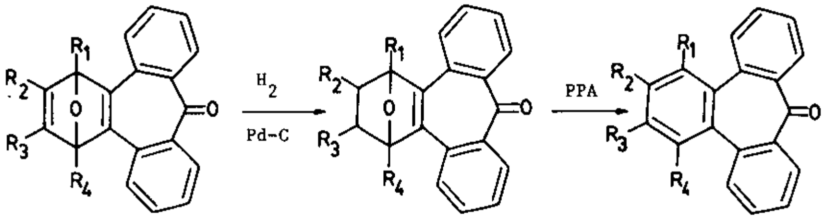
3-Acetoxy-3,6-epoxy-Δ^4-tetrahydrophthalic anhydride (**8**) can be converted to 3-acetoxyphthalic anhydride (**9**) by reaction with acetic acid at 125°C.[3]



When 3-methyl-6-methoxy-3,6-endoxo-1,2,3,6-tetrahydrophthalic anhydride (**10**) was allowed to react with anhydrous zinc chloride in boiling acetic anhydride for 4.5 h, 48% yield of the anhydride (**11**) was resulted. On the other hand, the reaction between (**10**) and polyphosphoric acid (PPA) provided (**11**) only in 20% yield. However, when (**10**) was recrystallized from warm methanol, 75% yield of (**11**) was obtained.[4,5]



Catalytic hydrogenation would convert the endoxide (12) to (13), which would then yield (14) by heating at 150°C with polyphosphoric acid for 2 h[6] (Table 1).

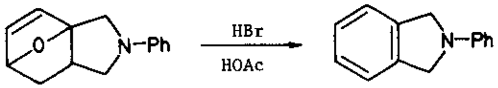


(12) (13) (14)

Table 1

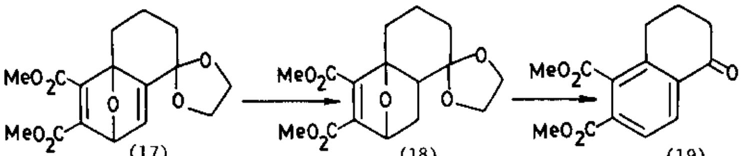
R_1	R_2	R_3	R_4	Yield
H	H	H	H	70-80%
Me	H	H	H	45%
Me	H	H	Me	50%

N-Phenyl-4H-5,7a-epoxyisoindoline (15) was efficiently dehydrated to give N-phenylisoindoline (16) in good yield by reaction with a solution of hydrobromic acid in glacial acetic acid at 60°C.[7]

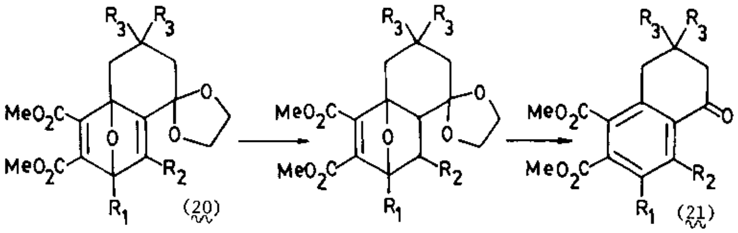


(15) (16)

The oxanorbornadiene (17) was hydrogenated to the compound (18), which was then dehydrated with concentrated hydrochloric acid in refluxing methanol to the compound (19).[8] Similarly, this method was later extended to the oxanorbornadienes (20), from which their corresponding aromatic products (21) were obtained[9] (Table 2).



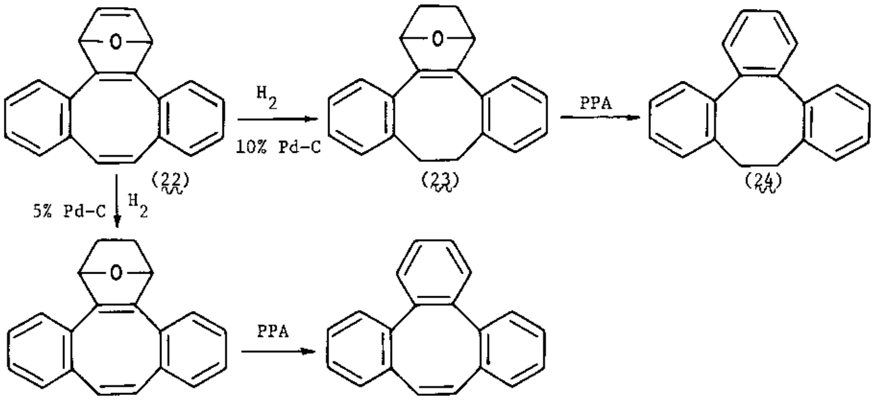
(17) (18) (19)



(20) (21)

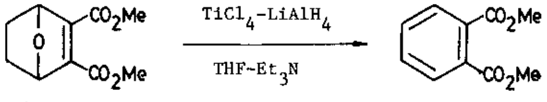
Table 2	R_1	R_2	R_3	Yield
(19)	H	H	H	65%
(21b)	H	H	Me	57%

The endoxide (22) underwent hydrogenation over 10% Pd-C to furnish the tetrahydro compound (23), which reacted with polyphosphoric acid to provide 13,14-dihydrotribenzo[*a,c,e*]cyclooctene (24).[10] On the other hand, the exdoxide (22) would be hydrogenated smoothly over 5% Pd-C to give the dihydro compound (25), which would undergo dehydration to yield tribenzo[*a,c,e*]cyclooctene (26).[11]



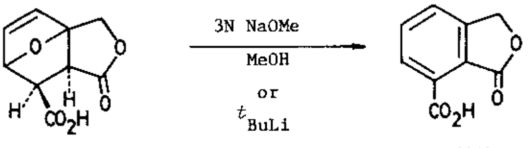
(22) (23) (24) (25) (26)

In the excess of triethylamine, low valent forms of titanium reagent was able to effect the dehydration of the compound (27) to afford dimethyl phthalate (28).[12]



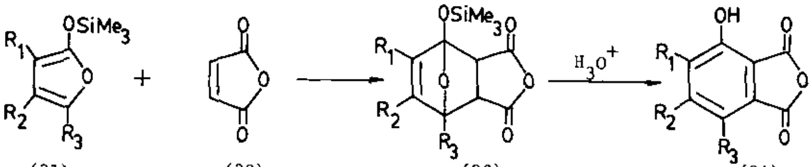
(27) (28)

The compound (29) would not yield (30) upon treatment with acid and it was finally found out that either sodium methoxide in methanol or *tert*-butyllithium was able to effect the dehydration and the compound (30) was obtained in fair yields.[13]



(29) (30)

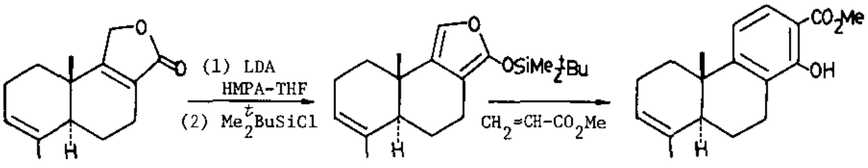
Trimethylsiloxyfurans (31) reacted smoothly with maleic anhydride (32) to give the adducts (33), which was dehydrated by acid to the 3-hydroxyphthalic anhydrides (34),[14] whose yields are listed in Table 3.



(31) (32) (33) (34)

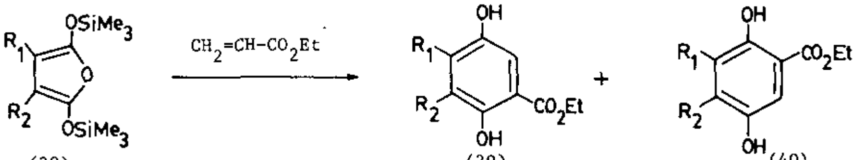
Table 3	R_1	R_2	R_3	Temperature (°C)	Time (h)	Yield
	H	H	H	-20 ∿ 0	0.5	5%
	H	H	Me	r.t.	0.25	53%
	H	H	Me	-20 ∿ 0	0.5	67%
	Me	H	Me	0 ∿ r.t.	2.0	95%
	H	H	Et	0 ∿ 40	5.0	90%

A similar strategy was reported[15], in which the siloxyfuran (36) was generated from (35) by reaction successively with lithium diisopropylamide in hexamethylphosphoramide-tetrahydrofuran and dimethyl-*tert*-butylsilyl chloride. When the compound (36) was allowed to react with methyl acrylate, compound (37) was isolated.[15]



(35) (36) (37)

Bis-(trimethylsiloxy)furan (38) has also been utilized for the preparation of phenolic compounds.[16] The hydroquinones (39) and (40) were obtained by reacting (38) with ethyl acrylate. The yields as well as ratios of the products (39) and (40) were shown in Table 4.[16]

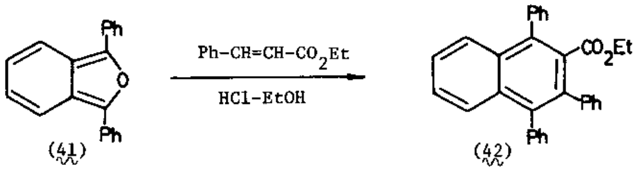


(38) (39) (40)

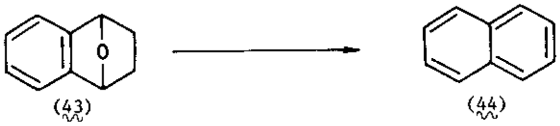
Table 4	R_1	R_2	Ratio (39):(40)	Total Yield
	Me	H	4 : 1	87%
	Ph	H	13 : 1	97%

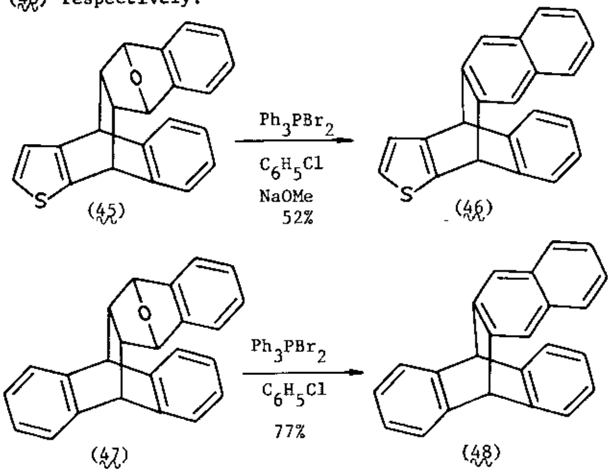
Syntheses of Naphthalene Derivatives

A typical example of these dehydration reactions has been recorded in as early as 1932.[17] When 1,3-diphenylisobenzofuran (41) was allowed to react with ethyl cinnamate in absolute ethanol which had been saturated with hydrogen chloride, the naphthalene (42) was obtained.[17]

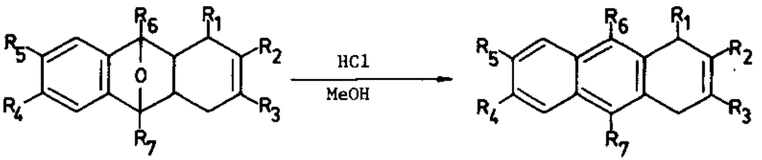


1,4-Endoxo-1,2,3,4-tetrahydronaphthalene (43) can be converted to naphthalene (44) by treatment with either acid[18] or triphenylphosphonium dibromide in chlorobenzene.[19] Triphenylphosphonium dibromide was also effective in the transformation of the compounds (45) and (47) to the bicyclic compounds (46) and (48) respectively.[19]





Dehydration of methyl-substituted 9,10-endoxo-1,4,4a,9,9a,10-hexahydroanthracenes (49) to 1,4-dihydroanthracenes (50) was accomplished by reaction with concentrated hydrochloric acid in methanol for 2 h at reflux temperature (Table 5).[20]



(49) (50)

Table 5	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield
(50a)	H	Me	H	H	H	H	H	73%
(50b)	H	Me	Me	H	H	H	H	63%
(50c)	Me	H	Me	H	H	H	H	49%
(50d)	H	Me	Me	H	H	Me	H	90%
(50e)	H	Me	Me	H	H	Me	Me	94.5%
(50f)	H	Me	Me	Me	H	H	H	48.5%
(50g)	H	Me	Me	Me	Me	H	H	47%
(50h)	H	Me	Me	Me	Me	Me	Me	96.5%

The naphthalenes (52) were prepared from the Diels-Alder adducts (51) in the presence of acid.[21] The yields and reaction conditions are depicted in Table 6.

(51) (52)

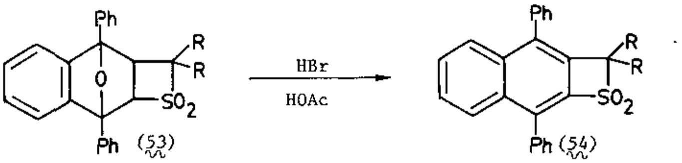
Table 6

R	Reagents	Condition	Yield
-CHO	HOAc + HCl	1 h, r.t.	58%
$-CO_2Me$	HOAc + p-$C_7H_7SO_3H$	12 h, r.t.	45%
$-CONH_2$	HOAc + HBr	12 h, r.t.	65%

The oxygen-bridged compound (53) would yield the 2H-naphtho[2,3-*b*]thiete 1,1-dioxide (54) by reaction with a solution of hydrobromic acid in glacial acetic acid at reflux temperature[22] (Table 7).

Table 7

R	Yield
Me	96.7%
H	98.6%



The Diels-Alder adducts (55) underwent catalytic hydrogenation with high yields to produce the partially saturated endoxides (56). These compounds were then dehydrated by acid to form the corresponding naphthalenes (57)[23] (Table 8).

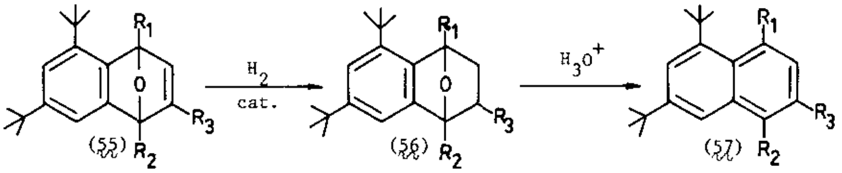


Table 8

R_1	R_2	R_3	Condition	Overall Yield
H	H	H	(1) H_2, cat., EtOH (2) HCl, EtOH, reflux	75%
Me	Me	H	(1) H_2, cat., EtOH (2) HCO_2H, 100°C	40%
^{t}Bu	^{t}Bu	H	(1) H_2, cat., EtOH (2) HCO_2H, HCO_2Na, 55°C	86%
^{t}Bu	H	^{t}Bu	(1) H_2, cat., EtOH (2) HCl, EtOH, 25°C	57%

Similarly, the oxygen-bridged compounds (58) were hydrogenated and aromatized to compounds (60) via (59)[24] (Table 9).

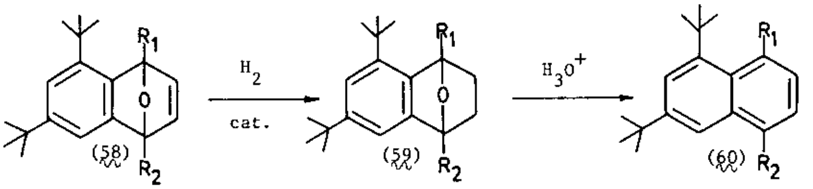
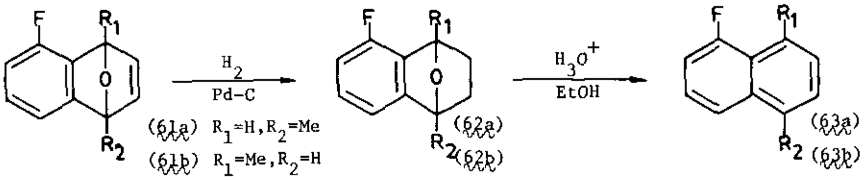


Table 9

R_1	R_2	Reaction Condition	Overall Yield
^{t}Bu	^{t}Bu	(1) H_2, EtOH, EtOAc, Pd-C, 12.5h (2) HCl, EtOH, 2min	85%
H	^{t}Bu	(1) H_2, EtOH, Pd-C, 1h (2) HC, EtOH, 2.5h	74.5%
CH_2Ph	H	(1) H_2, EtOH, Pd-C, 2h (2) HCl, EtOH, 2h	61%
H	CH_2Ph	(1) H_2, EtOH, Pd-C, 2h (2) HCl, EtOH, 2h	61%
^{t}Bu	CH_2Ph	(1) H_2, EtOH, EtOAc, Pd-C, 1h (2) HCl, EtOH, 3min	74%

1-Methyl-5-fluoro-1,4-dihydro-1,4-epoxynaphthalene (61a) and 1-methyl-8-fluoro-1,4-dihydro-1,4-epoxynaphthalene (61b) can be converted to their corresponding naphthalenes (63a) and (63b), respectively, under similar condition in 60% and 63% yield.[25] Moreover, the tetrafluorinated compounds



(64) and (66) can also be aromatized to the naphthalenes (65) and (67), respectively, by reaction with a refluxing solution of hydrobromic acid and acetic acid[26] (Table 10 and 11).

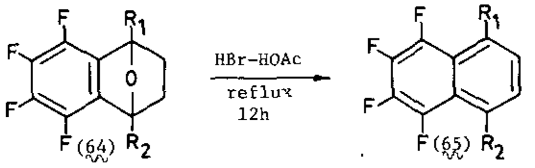


Table 10

R_1	R_2	Yield
Me	H	95%
Me	Me	48%

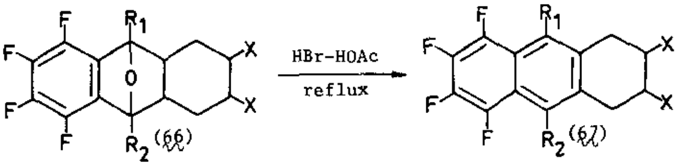


Table 11

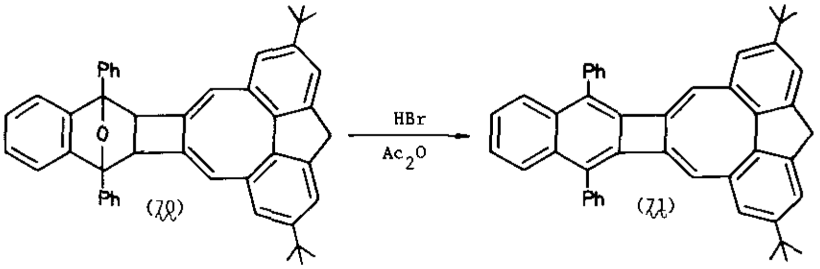
R_1	R_2	X	Yield
Me	H	H	95%
Me	H	Br	65%
Me	Me	H	92%
Me	Me	Br	84%

5,10-Diphenylbenzo[*b*]biphenylene (69) can be conveniently prepared from 5,10-diphenyl-5,10-oxido-5,5a,9b,10-tetrahydrobenzo[*b*]bipyenylene (68) through various reaction conditions as shown in Table 12.[27]

Table 12

Reaction Condition	Yield
HCl	97%
P_4S_{10}, CS_2, r.t., 4 days	82%
PPA, CH_2Cl_2, 140°C, 80 min then 125±15°C, 3 h	25%

The compound (70) was dehydrated by reacting with hydrogen bromide in acetic anhydride to give the hydrocarbon (71) in 72% yield.[28]

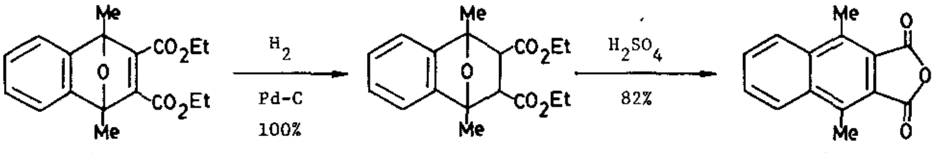


(70) (71)

4,9-Diphenyl-4,9-oxido-1,3,3a,4,9,9a-hexhydronaphtho[2,3-*c*]thiophene 2,2-dioxide (72) can be converted to 4,9-diphenyl-1,3-dihydronaphtho[2,3-*c*]thiophene 2,2-dioxide (73) in 94% yield by reaction with 48% hydrobromic acid in acetic acid at 100°C for 7 h.[27]

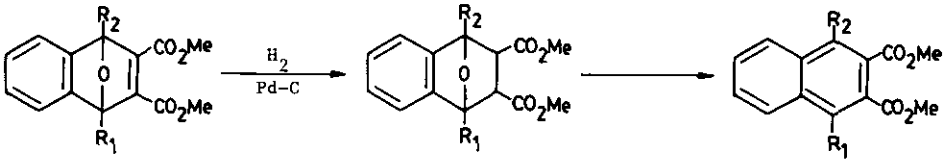
(72) (73)

Catalytic hydrogenation of 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,4-dihydronaphthalene (74) over 10% Pd-C in ethyl acetate provided quantitatively 2,3-dicarbethoxy-1,4-dimethyl-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (75). The aromatization of (75) with concentrated sulfuric acid at 0°C afforded 82% yield of 1,4-dimethyl-2,3-naphthalic anhydride (76).[29]



(74) (75) (76)

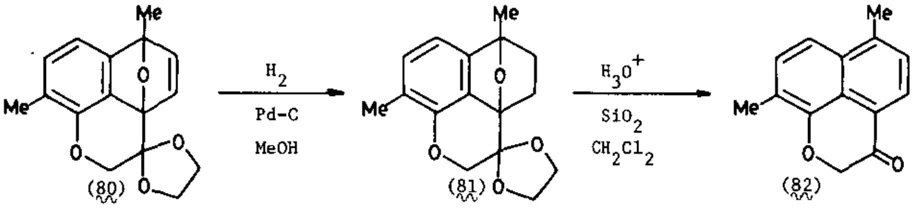
The Diels-Alder adducts (77) can be hydrogenated catalytically to (78), which were then subjected to acid treatment at reflux temperature to provide the naphthalene derivatives (79)[30] (Table 13).



(77) (78) (79)

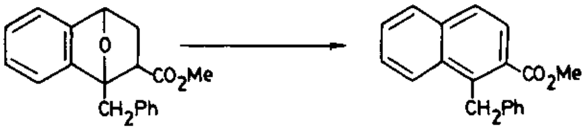
Table 13	R_1	R_2	Reagent	Yield
(78a)	CH_2Ph	H	p-$C_7H_7SO_3H$, C_6H_6	70%
(78b)	CH_2Ph	Ph	MeOH, HCl	93%

The compound (80) would lead to the naphthalene (82) in 72% overall yield by catalytic hydrogenation to (81), which was subsequently dehydrated.[31]



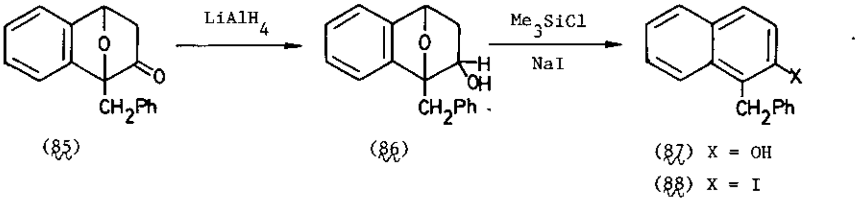
(80) (81) (82)

It is important to point out that strong acidic condition does not always produce desired aromatic products. In some particular cases, the dehydration was accomplished by using a catalytic quantity of toluenesulfonic acid in refluxing benzene or toluene. For example, 1-benzyl-2-(carbomethoxy)-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (83) was aromatized by p-toluenesulfonic acid monohydrate in refluxing toluene to give methyl 1-benzyl-2-naphthoate (84) in 65% yield.[32]

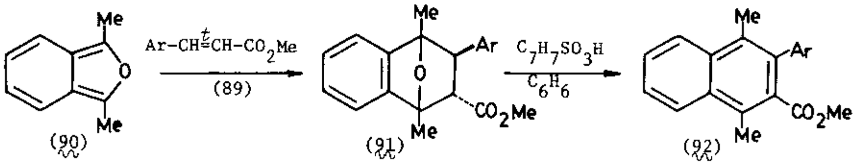


(83) (84)

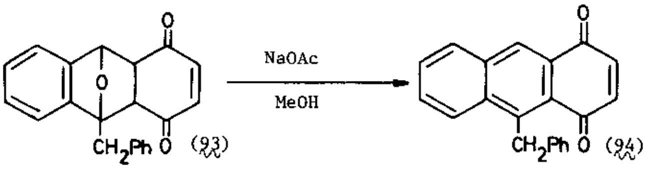
Alternatively, a mixture of trimethylsilyl chloride and sodium iodide was found to be superior in those cases where acid catalysis condition was unsatisfactory.[32] For instance, 1-benzyl-1,4-epoxy-3,4-dihydro-2(1H)-naphthalenone (85) was first reduced by lithium aluminum hydride to give the endo alcohol (86), which was aromatized by trimethylsilyl chloride and sodium iodide to give a mixture of 1-benzyl-2-naphthol (87) and 1-benzyl-2-iodonaphthalene (88) in 40% and 25% yield respectively. Obviously, conversion of the naphthol (87) to its iodide (88) is competitive with the cleavage of the oxygen bridge.[32]

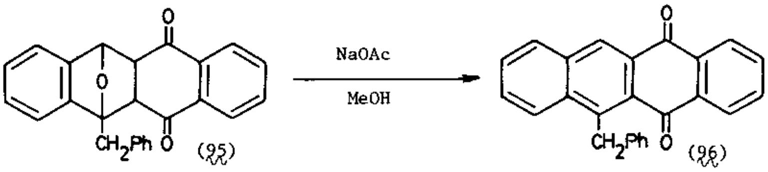


Recently, the substituted cinnamic ester (89) was found to react with 2,5-dimethylisobenzofuran (90) to give the endoxide (91). *p*-Toluenesulfonic acid in benzene was effective in the conversion of (91) to the naphthalene derivative (92).[33]

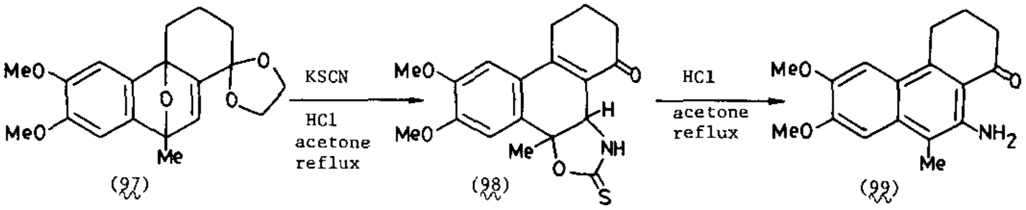


However, the Diels-Alder adducts formed by the reaction with quinones should be aromatized under basic conditions. For example, the acid catalyzed aromatization of 9-benzyl-9,10-epoxy-exo-4a,9-exo-9a,10-tetrahydro-1,4-anthraquinone (93) and 5-benzyl-6,11-epoxy-6,11-dihydro-5,12-naphthacenedione (95) failed and complex reaction mixtures resulted. Sodium acetate in refluxing methanol efficiently aromatized (93) and (95) to 9-benzyl-1,4-anthraquinone (94) and 6-benzyl-5,12-naphthacenedione (96) in 90% and 76% yield, respectively.[32]



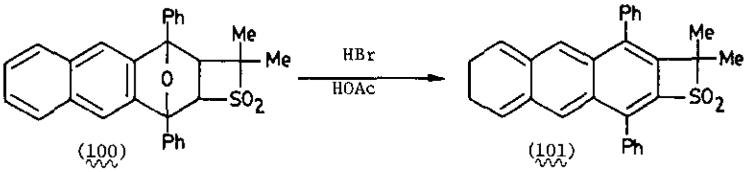


Treatment of the oxygen-bridged compound (97) with potassium thiocyanate in hydrochloric acid afforded the heterocyclic compound (98), which upon subsequent acid hydrolysis, could be converted to the amino compound (99) in 45% overall yield.[34]

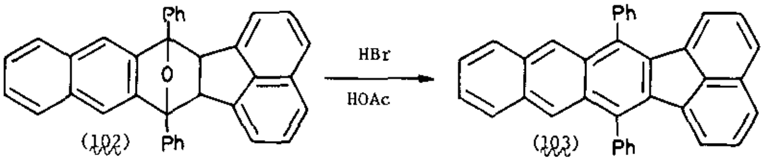


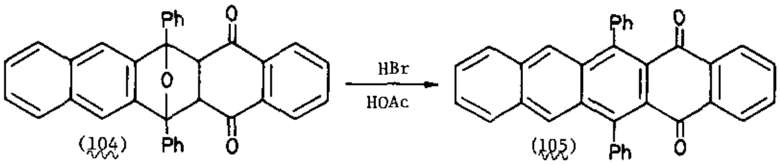
Syntheses of Anthracene and Phenanthrene Derivatives

Hydrobromic acid in glacial acetic acid was capable to convert 2a,3,10,10a-tetrahydro-2,2-dimethyl-3,10-diphenyl-3,10-epoxy-2H-anthra[2,3-*b*]thiete 1,1-dioxide (100) to 2,2-dimethyl-3,10-diphenyl-2H-anthra[2,3-*b*]thiete 1,1-dioxide (101) in quantitative yield.[22]

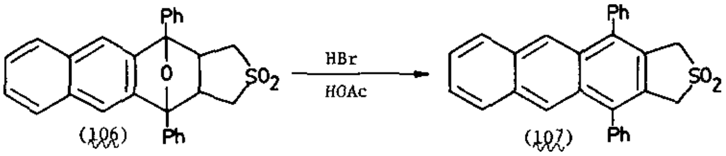


7,14-Diphenyl-7,14-oxido-6b,7,14,14a-tetrahydronaphtho[2,3-*k*]fluoranthrene (102) reacted with acetic acid in 48% hydrobromic acid at 100°C for 19.5 h to yield 96% of 7,14-diphenylnaphtho-[2,3-*k*]fluoranthrene (103).[27] When 6,13-diphenyl-6,13-oxido-5,5a,6,13,13a,14-hexahydropentacene-5,14-dione (104) was reacted under similar condition for 12 h, 6,13-diphenylpentacene-5,14-quinone (105) was obtained in 48% yield.[27]



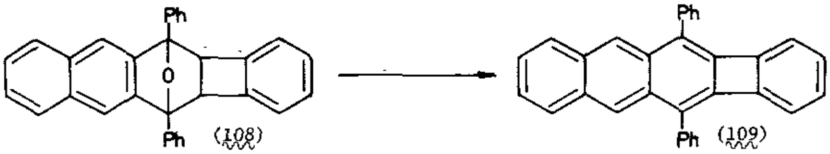


Similarly, 4,11-diphenyl-4,11-oxido-1,3,3a,4,11,11a-hexahydroanthra[2,3-*c*]thiophene 2,2-dioxide (106) can be converted to 4,11-diphenyl-1,3-dihydroanthra[2,3-*c*]thiophene 2,2-dioxide (107) in 82% yield by reacting with 48% hydrobromic acid and acetic acid at 100°C.[27]



(106) (107)

On the other hand, 5,12-diphenyl-naphtho[2,3-*b*]biphenylene (109) can be obtained from 5,12-diphenyl-5,12-oxido-4b,5,12,12a-tetrahydronaphtho[2,3-*b*]biphenylene (108) through various conditions as depicted in Table 14.[27]

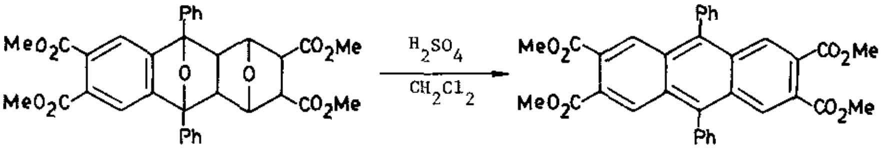


(108) (109)

Table 14

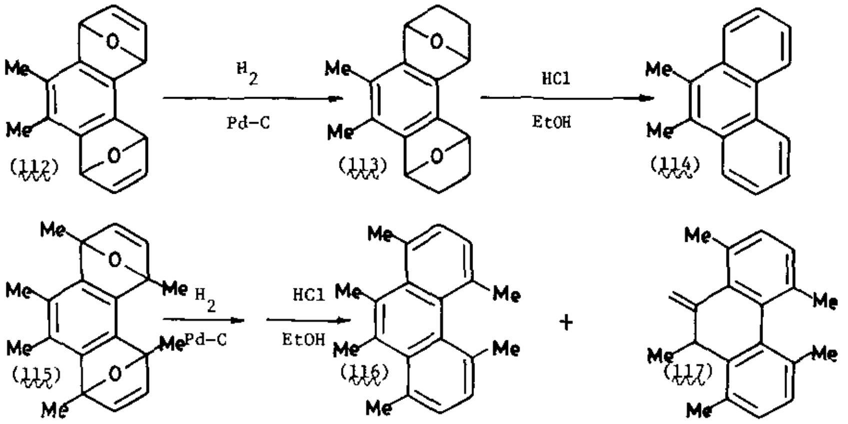
Reaction Condition	Yield
P_4S_{10}, CS_2, r.t., 70 min	61%
PPA, 130-170°C, 3 h	59% (mixture of isomers)

A recent report showed that the *bis*-oxygen-bridged ester (110) can undergo double debridging by reaction with sulfuric acid in methylene chloride when stirred under ultrasonic agitation below 10°C for 6 h.[35]



(110) (111)

The aromatization of 9,10-dimethyl-1,4,5,8-tetrahydrophenanthrene-1,4:5,8-diendoxide (112) was achieved by catalytic hydrogenation, which was followed by dehydration with ethanol saturated with hydrogen chloride to give 9,10-dimethylphenanthrene (114) in 95% yield.[36] However, when 1,4,5,8,-9,10-hexamethyl-1,4,5,8-tetrahydrophenanthrene-1,4:5,8-diendoxide (115) was allowed to react under similar conditions, the major product was not the desired 1,4,5,8,9,10-hexamethylphenanthrene (116) but its tautomer (117). The yield of (116) was merely 2.5% whilst (117) was obtained in 7.5% yield.[36]



Conclusion

The synthetic approach towards arenes via the cycloaddition between furans and alkynes or alkenes are not without shortcomings. In particular, the reaction rates of Diels-Alder cycloaddition of furans and alkenes connecting to electron-withdrawing groups are generally only moderate. These reactions usually require prolonged heating. Moreover, it is almost impossible to drive the reaction to completion when furans react with unactivated alkenes. Heating at elevated temperature would only help to promote the cycloreversion of the adducts to their corresponding starting materials. Several methods have been proposed to either increase the rates or to facilitate the completion of these reactions. For example, Diels-Alder reaction between furans and unactivated alkenes under high pressure have been found to be most satisfactory.[37] Lewis acids have also been used to promote the reaction rate between furans and unactivated alkenes.[38] Cyclodextrin catalysis was also suggested to be effective.[39] On the other hand, the Diels-Alder reaction between furans and alkynes are seldom reversible. The only disadvantage that remains is that one more step, i.e. catalytic hydrogenation is required. This two step procedure can be useful when the reaction between furans and alkenes fails. It is noteworthy to state that most of the aromatization steps demand acid catalyzed conditions, which are objectionable when acid labile functional groups are present.

Nevertheless, these dehydration reactions of compounds such as (5) and (7) would serve excellently as a complementary procedure for the preparation of arenes. This is due to the fact that universal and practical reagents which would extrude oxygen atoms from compounds such as (4) have so far been unknown and these deoxygenation reagents are still being actively pursued in several laboratories.[2]

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