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Isobenzofuran

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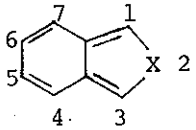
The preparation of isobenzofuran and its thermal and photochemical reactions are reviewed. The chemistry of heterocycles related to isobenzofuran is discussed.

1. Introduction

Isoindole (1, benzo[c]pyrrole) and isothianaphthene (2, benzo[c]thiophene) have been reviewed[1,2]. The purpose of this review is to survey the recent progress in the chemistry of isobenzofuran (3, benzo[c]furan)[3]. The relevant literature is covered through mid-1977.



1, X = NH

2, X = S

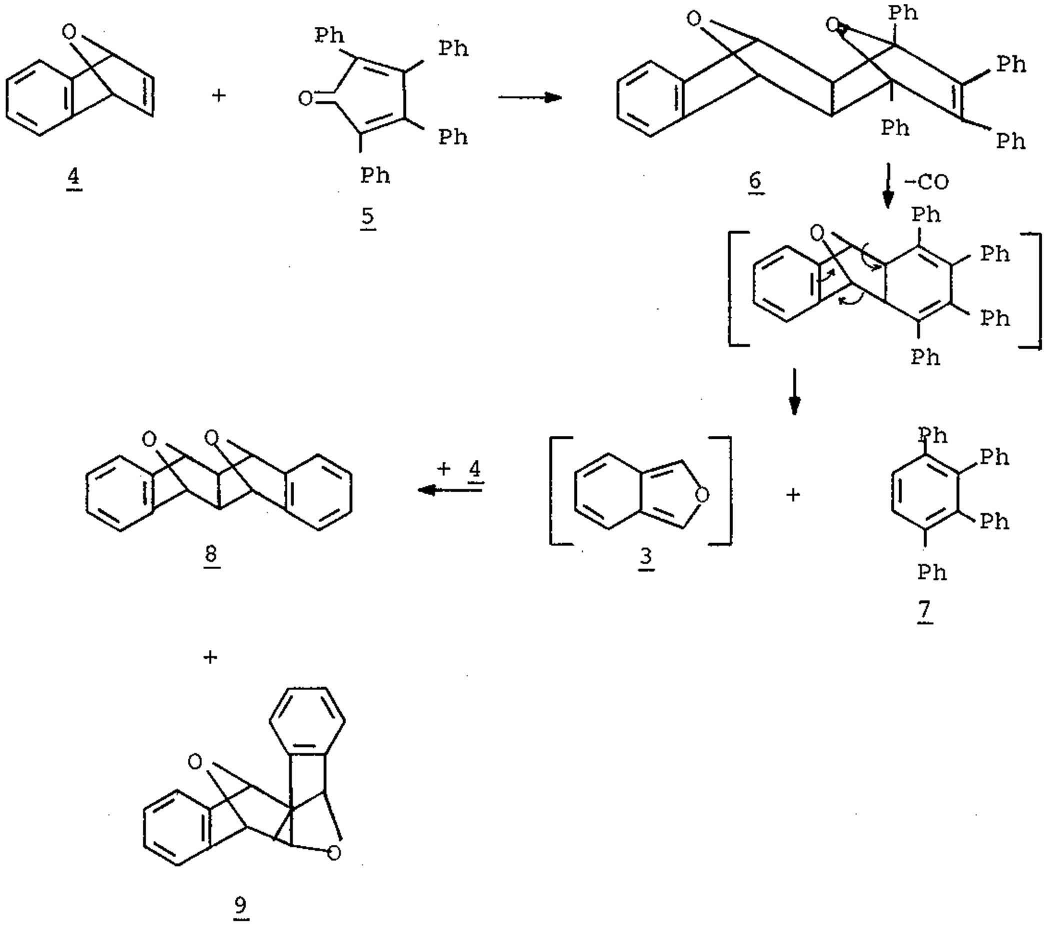
3, X = O

The chemical abstracts name for 3 is isobenzofuran (IBF), however, the unambiguous name benzo[c]furan is used as well[2,4]. The ring system is numbered as shown in 3.

2. IBF - Generation and Isolation

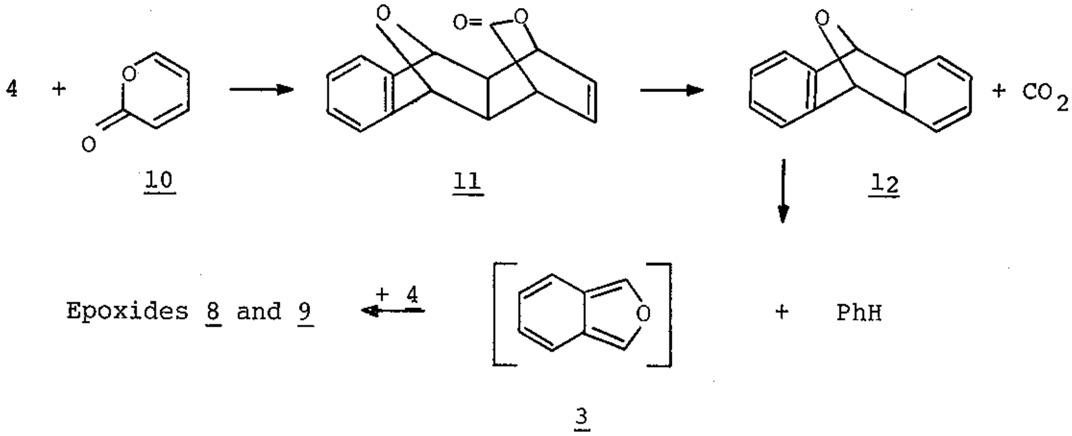
Due to its instability, the parent compound, IBF (3), remained unknown until 1964 when Fieser and Haddadin[5a,b] trapped it as a transient intermediate which resulted from a retro-Diels-Alder reaction as shown in Scheme A.

Scheme A

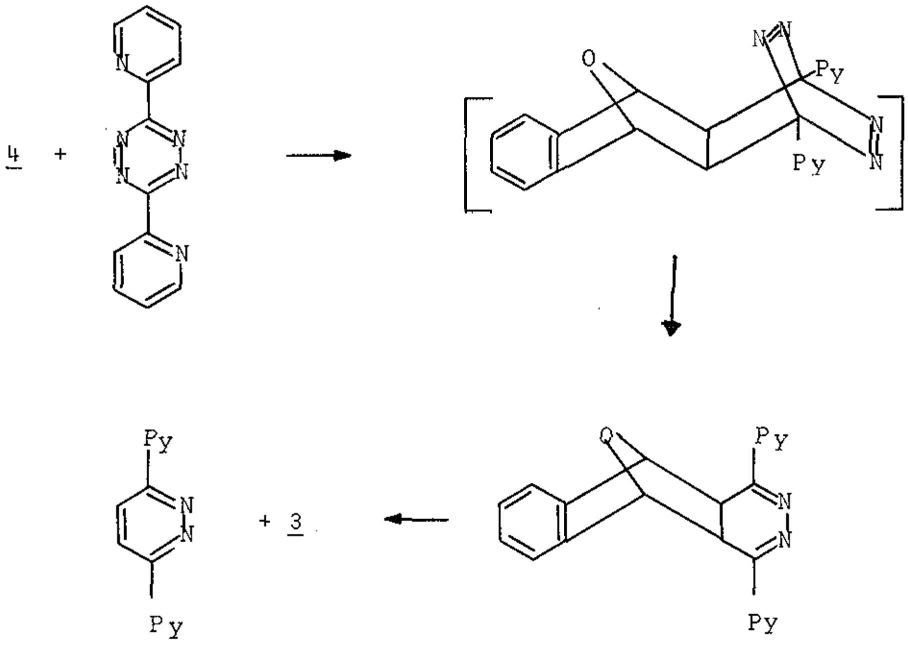


IBF (3) was formed by the heating of either dieneophile 4 and diene 5, or intermediate 6. The transient IBF was trapped by excess 1,4-dihydronaphthalene-1,4-epoxide (4) to give epoxides 8 and 9 in high yield. Furthermore, 3 was generated by an analogous path using α-pyrone (10) as the diene (Scheme B)[5a,b].

Scheme B



The idea of a retro-Diels-Alder reaction as a source for IBF was admirably utilized recently by three groups of workers. Almost simultaneously, Warrener[6] on one side and Wege[7] on the other reported the isolation and characterization of the elusive IBF (3). Warrener[6] reacted dieneophile 4 with 3,6-di(2'-pyridyl)-1,2,4,5-tetrazine in dimethyl sulfoxide at room temperature. The rapid reaction proceeded to precipitate the yellow dihydro derivative 13. Controlled pyrolysis of 13 at 120° under reduced



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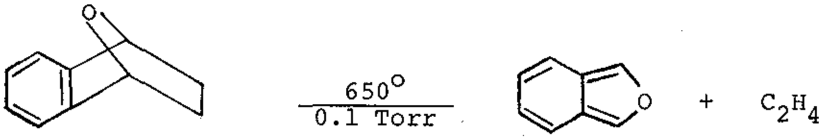
Py = 2'-pyridyl

pressure (0.1 mm) gave pure crystalline IBF which was collected on a cold finger at -80°, m.p. ca 20°. Wege[7] used lactone 11 (Scheme B) which was adsorbed on celite and sublimed at 10^{-2} mm through a tube heated at 130°. IBF was collected in a cold trap. Wege succeeded in isolating intermediate 12 (Scheme B) as a colorless crystalline solid. It remained for Wiersum and Mijis[8] to achieve the preparation of IBF (3) in 100% yield by the technique of flash-vacuum thermolysis. This method provides

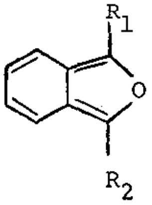


3

for the preparation of pure 3 from 1,2,3,4-tetrahydronaphthalene-1,4-epoxide in relatively large quantities. Warrener's method appears to yield 3 contaminated with 3,6-di(2'-pyridyl)pyridazine[9].

1-Alkyl and 1,3-Dialkyl Derivatives of IBF

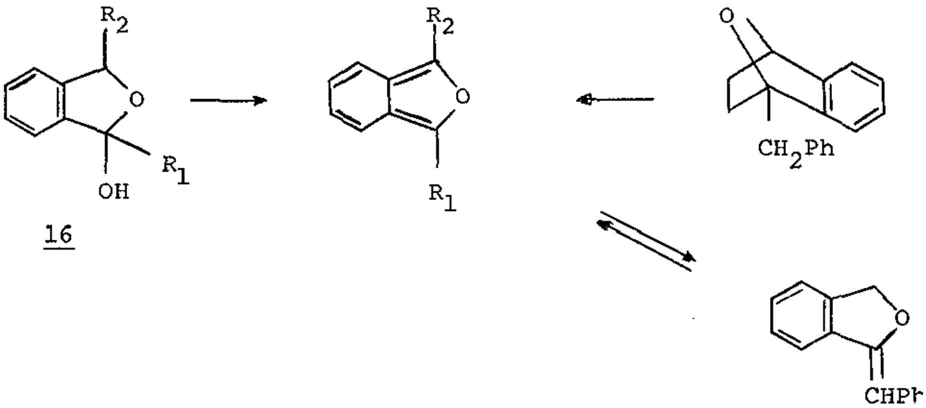
1-Alkyl and 1,3-dialkyl substituted isobenzofurans are unstable at room temperature. 1,3-Dimethylisobenzofuran (14) was trapped



14, $R_1 = R_2 = CH_3$

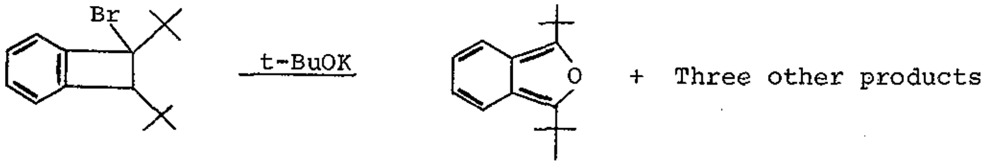
15, $R_1 = H$, $R_2 = CH_3$

by Fieser and Haddadin[5a,b]. *1-Methylisobenzofuran (15),* 1,3-dimethylisobenzofuran (14) and benzylisobenzofuran (17) were obtained recently by Bornstein and coworkers[10] who employed Wiersum's flash-vacuum thermolysis technique. The yields of these isobenzofurans were essentially quantitative. Earlier, Smith and Wikman[11] *generated 17, 18 and 19 through* the dehydration of hemiketal 16. Isobenzofurans 17 and 18 could be detected by trapping them with dimethyl acetylenedicarboxylate. IBF 19 was isolated as a reactive yellow oil.



17, R_1 = CH_2Ph
R_2 = H
18, R_1 = CH_2Ph
R_2 = Ph
19, R_1 = tert-Bu
R_2 = Ph

While Smith and Wikman[11] could not observe directly the 17 to 20 equilibrium by nmr or uv spectra, Bornstein and coworkers[9] corroborated this claim by measuring the conversion of the isolated 17 to 20; their nmr spectral study showed that equilibrium, at room temperature in $CDCl_3$, was established predominantly toward 20 in about 4 hr. Isobenzofurans 13 and 14 did not exhibit such a tautomeric equilibrium. 1,3-Ditertiary-butylisobenzofuran (22) was observed by Nenitzescu and coworkers[12] "in some experiments" on 1-bromo-1,2-ditertiary-cyclobutene (21). IBF 22, which presumably was obtained as a minor product, was converted by oxygen into 1,2-dipivalylbenzene.



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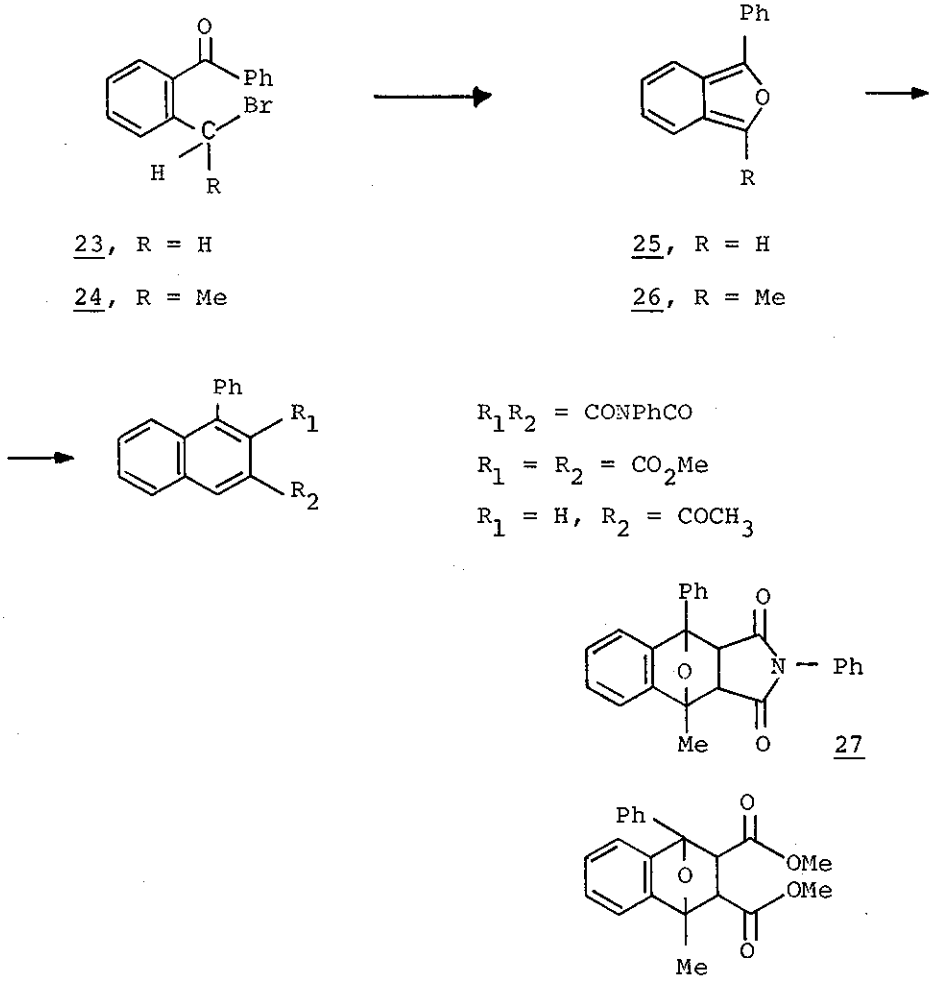
22

A monoaryl substituent at position 1 does not seem to stabilize the IBF nucleus significantly. Faragher and Gilchrist[13] generated 1-phenylisobenzofuran (25) and 1-phenyl-3-methylisobenzofuran (26) by the irradiation of bromoketones 23 and 24 with a 300 W Sunlamp. Isobenzofurans 25 and 26 were trapped by a variety of dieneophiles. Under the reaction conditions, IBF 25 reacted with dimethyl acetylenedicarboxylate, N-phenylmaleimide, dimethyl fumarate, and methyl vinyl ketone to give directly the corresponding naphthalene derivatives (Scheme C).

Scheme C



23, R = H

24, R = Me

25, R = H

26, R = Me

R_1R_2 = CONPhCO

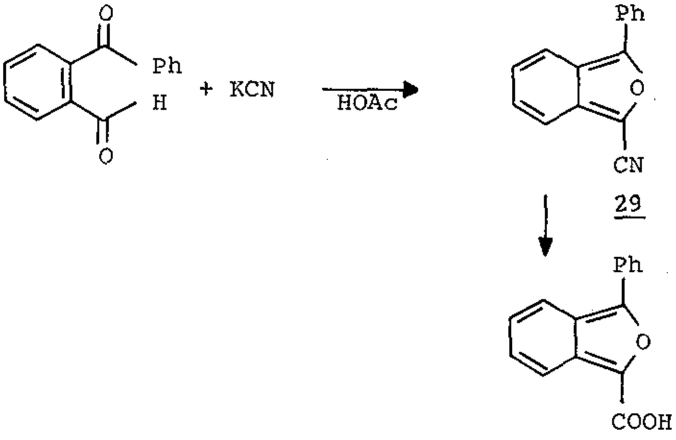
$R_1 = R_2 = CO_2Me$

R_1 = H, $R_2 = COCH_3$

27

28

Intermediates 27 and 28, which cannot lose water, were isolated. The above dehydrohalogenation reaction proceeds thermally in some cases[13]. The introduction of a cyano group and a phenyl group in the 1,3-positions gives a stable IBF (29) as shown by Roberts and coworkers[14]. The yellow 29 was hydrolyzed by base to acid 30.



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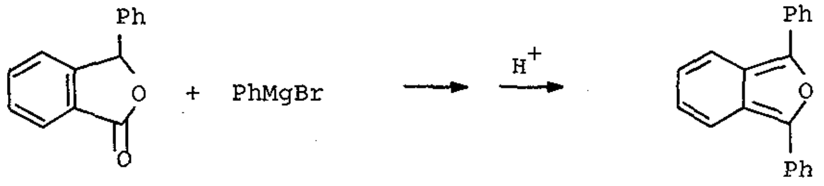
30

1,3-Diarylisobenzofurans have been known for a long time. Elderfield[3] has reviewed their methods of preparation. Useful modifications of these methods have been introduced. Newman[15] studied the addition of phenylmagnesium bromide to 2-phenylphthalide and noticed that the reaction is sensitive to solvent and to the order of addition of reagents. Nevertheless, 1,3-diphenylisobenzofuran (1,3-DPIBF, 31) was prepared in 87% yield.



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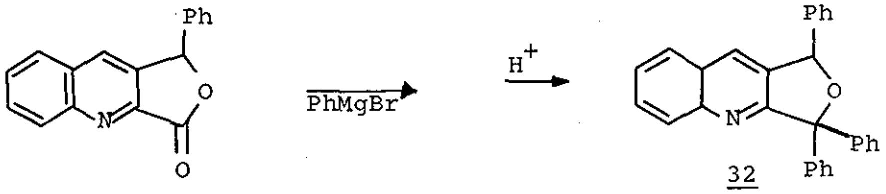
This method does not seem to be versatile. Our attempt to use it in the synthesis of 1,3-diphenylfuro[3,4-b]quinoline (33) resulted



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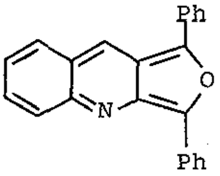

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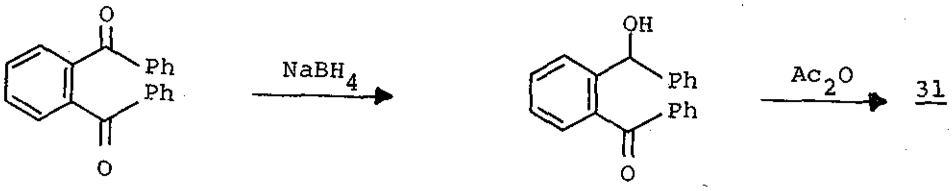
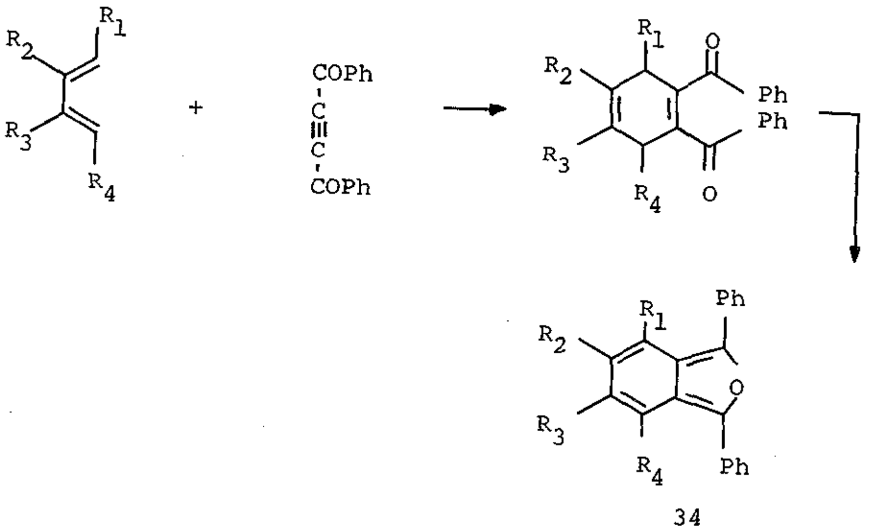
in the formation of furan 32 instead. It appears that the hemiketal intermediate is not stable and undergoes ring opening and subsequent addition of another mole of the Grignard reagent[16].

Potts and Elliot[17] reported an improvement on the preparation of 31 from o-dibenzoylbenzene. Reduction of the latter with excess sodium borohydride followed by treatment with hot acetic anhydride gave 31 in 70% yield.



Several substituted 1,3-diarylisobenzufurans (34) were prepared by Ried and Bonnighausen[18] as shown in Scheme D.

Scheme D



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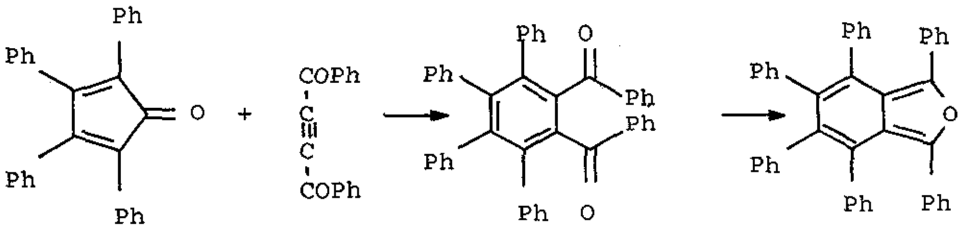
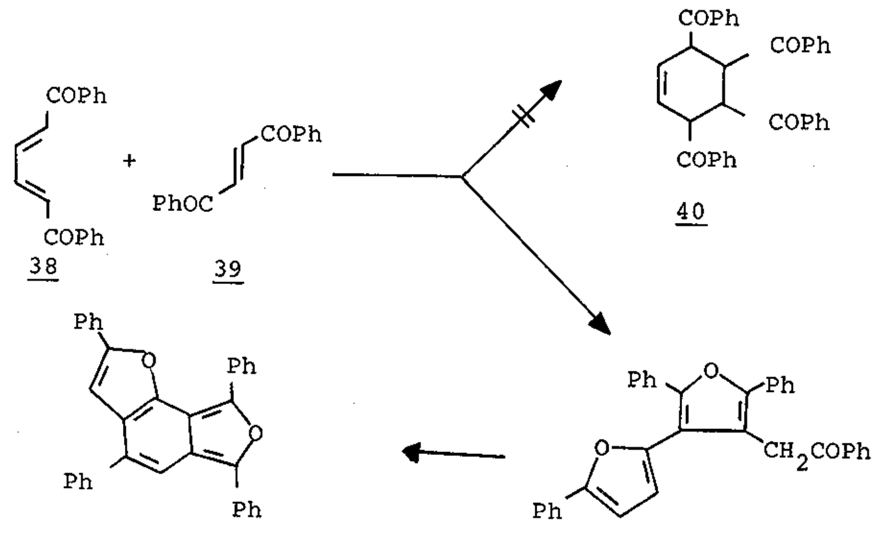
While these workers used hot acetic anhydride as a dehydrating agent, White and coworkers[19] found p-toluenesulfonic acid more useful. However, neither dehydrating agent worked in the case where $R_2 = R_3 = H$, $R_1 = R_4 = CH_3$. Hexaphenylisobenzofuran 37 was prepared[18] by the Diels-Alder reaction of tetracyclone (35) and dibenzoylacetylene to yield 1,2-dibenzoyl-3,4,5,6-tetraphenylbenzene 36 which was reduced with zinc to give 37.



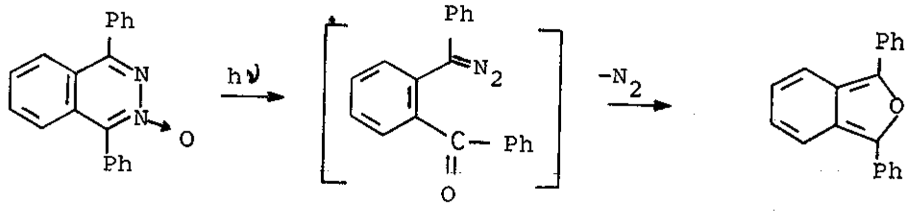
35 36 37

In an attempt to perform a reaction analogous to the classic reaction of Adams and Gold[20], Preslon and Lepage[21] reported that diene 38 and dieneophile 39 did not give the expected 3,4,5,6-tetrabenzoylcyclohexene (40) but yielded difuran 41 which was easily converted to IBF 42 on treatment with



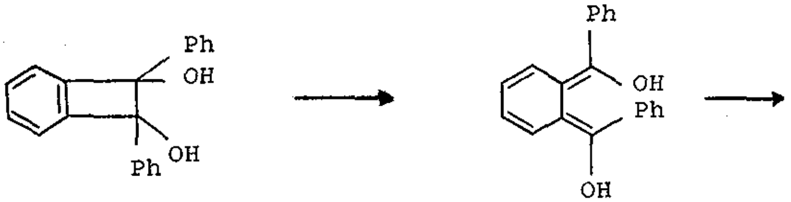
38 39 40 41 42

acid. Of particular interest is the formation of 1,3-DPIBF (31) from the photolysis[22] of phthalazine-N-oxide 43 and the



43 31

thermolysis[23] of benzocyclobutenediol 44.



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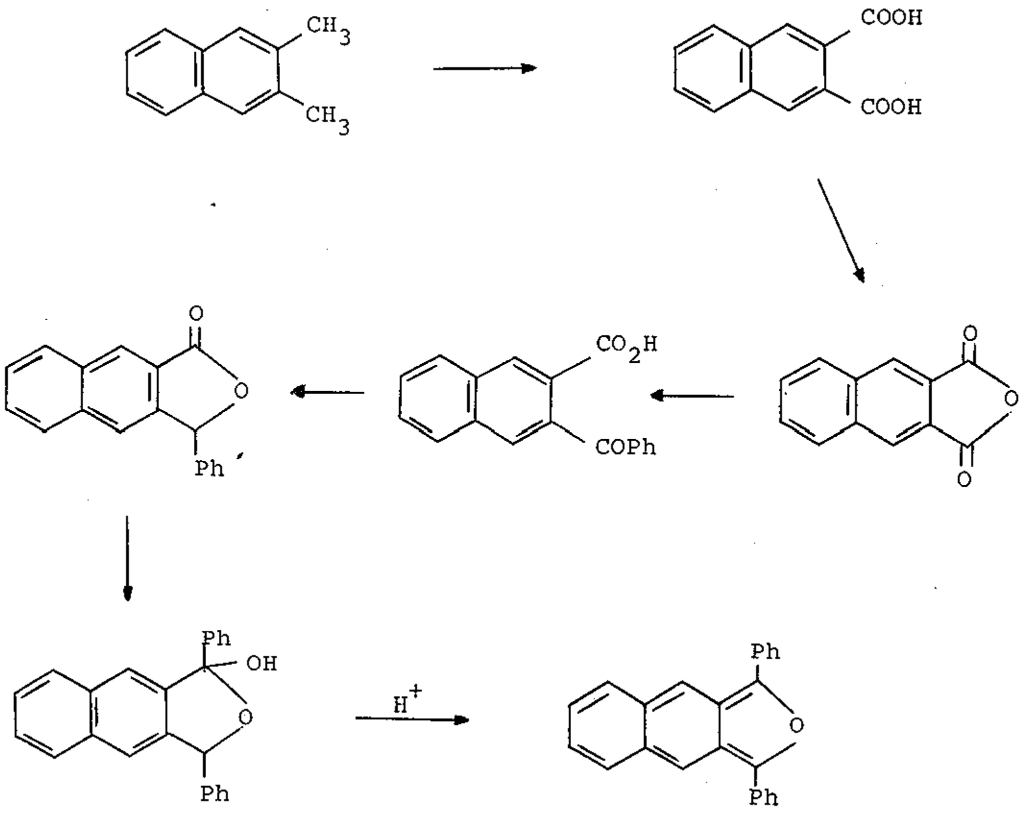
Although 1,3-diarylisobenzofurans are stable, the linear benzo-annelation of 1,3-DPIBF destabilizes the system yet increases its reactivity (vida infra). Cava and VanMeter[24] reported an elegant multi-step synthesis of 1,3-diphenylnaphtho-[2,3-c] *furan* (45), Scheme E. Compound 45 which was obtained as deep red glistening plates is stable in the solid state but decolorizes slowly, on standing, in organic solvents.

Scheme E



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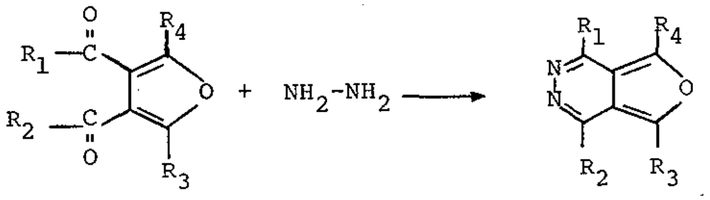
3. Quinonoidal Heterocycles Related to IBF

The introduction of the proper heteroatom in the benzo-part of the structure of IBF resulted in the stabilization of the system. This was demonstrated in the synthesis of furo[3,4-d]pyridazine (47) from dialdehyde 46 and anhydrous



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47, $R_1 = R_2 = R_3 = R_4 = H$

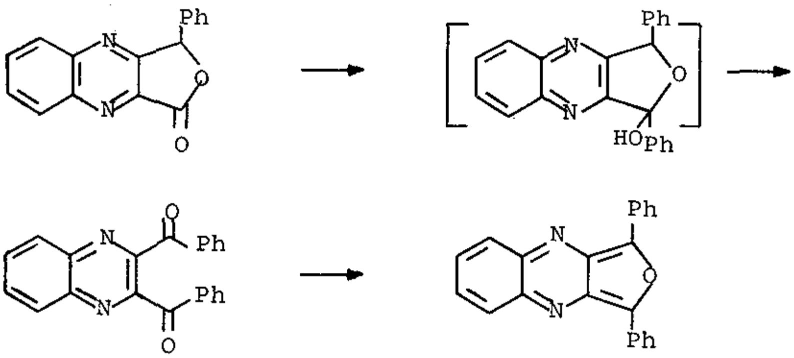
48, $R_1 = R_2 = R_3 = R_4 = CH_3$

49, $R_1 = R_2 = R_3 = H$, $R_4 = CH_2OH$

hydrazine in dry methanol. 47 is described as a yellow solid that melts at 161°, a very high melting point when compared with that of IBF (ca 20°). Robba and Zaluski[25] reported the ir and nmr spectra of 47. The chemical shift of the protons at C_4 and C_7 ($R_1=R_2=H$) are reported to be at 9.29 ppm. The same workers prepared 1,4-dichlorofuro[3,4-d]pyridazine (50) which

50

they claim to be colorless! The furo derivatives 48 and 49 were prepared by Mosby[26] and Adembri and coworkers[27] respectively. It is interesting to note that Mosby reported 48 as a monohydrate whereas Robba and Zaluski showed that the parent system 47 is apparently resistent to a reaction with methanol. Another example of the stabilizing effect of nitrogen in this regard is the finding by Haddadin and coworkers[28] that the greenish-blue 1,3-diphenylfuro[3,4-b]quinoxaline (51) is quite stable in contrast with 1,3-diphenylnaphtho[c]furan (45). Furan 51 was



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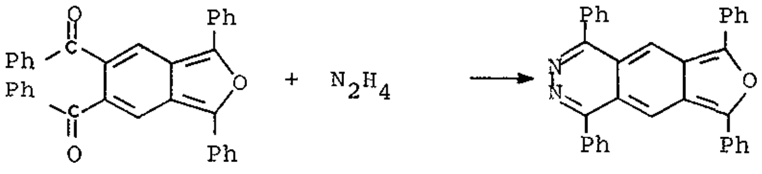
also obtained in low yield (10%) by the treatment of 2,3-dibenzoylquinoxaline with triethyl phosphite[29].

Lepage and Lepage[30] recently described the preparation of 1,4,6,8-tetraphenylfuro[3,4-g]phthalazine (52) as a violet solid.



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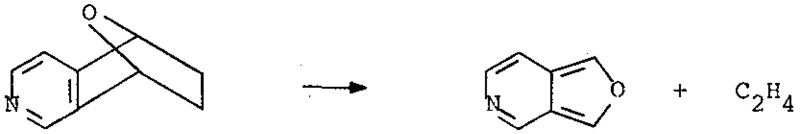
More recently, Wiersum and coworkers[31] used their most efficient method of flash-vacuum thermolysis, at 600-650°, in the first preparation of parent furo[3,4-c]pyridine (53)



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as a white solid which melts with polymerization below room temperature, and immediately turns reddish brown in contact with air, a behavior analogous to that of the parent IBF (3).

4. Theoretical Consideration

Dewar and coworkers[32] calculated the resonance energy of IBF (3) and 1,3-DPIBF (31) using a semiempirical SCF MO approximation method. They predicted that IBF (3) is almost non-aromatic (resonance energy = 2.4 Kcal/mole), and therefore unstable, while 31 has a resonance energy of 48.8 Kcal/mole which explains its stability. Recently, Palmer and Kennedy[9] reported a detailed study of the electronic structure of isoindole, isobenzofuran, and benzo[c]thiophene. IBF (3) is reported to possess resonance energy even lower than benzene itself.

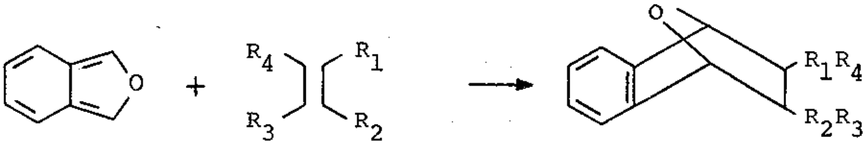
The values of resonance energy used by Palmer and Kennedy are based on a different definition of resonance energy than that used by Dewar[32], nonetheless, the value for IBF does not show purely polyolefinic character as Dewar predicted. Palmer and Kennedy concluded that "There seems little doubt that the quinonoid heterocycles 1, 2, and 3 still retain some resonance energy in the ground state; however, the numerical values are low, and as long suspected, well below that of Kekule series benzo[b]pyrrole, benzo[b]thiphene and benzo[b]furan. The lack of stability of the molecules is readily attributed to the low resonance energy and to the low lying triplet state".

Recently, Sardella et al[63], suggested that "the heterocycles 1, 2, and 3 consist of contiguous but virtually noninteracting π systems, with their aromaticity deriving largely from the five-membered ring and their reactivity stemming from the adjacency of the butadiene moiety".

5. Reactions of IBF

a) Thermal Reactions

The reactivity of isobenzofurans lies in their o-quinonoidal structure with the driving force of reaction being the production of a benzenoid structure. Isobenzofurans are excellent 4π electron substrates in $4\pi + 2\pi$ cycloaddition reactions as demonstrated by the numerous Diels-Alder reactions (tables I, II). IBF (3) is extremely reactive with the typical dieneophiles. It reacts instantaneously with maleic anhydride[8],



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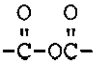
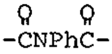
54, $R_1 = R_2 =$ 
$-\overset{O}{\overset{\|}{C}}-O\overset{O}{\overset{\|}{C}}-$

$R_3 = R_4 = H$

55, $R_1 = R_2 =$ 
$-\overset{O}{\overset{\|}{C}}NPh\overset{O}{\overset{\|}{C}}-$

$R_3 = R_4 = H$

56, $R_1 = R_2 = R_3 = H$

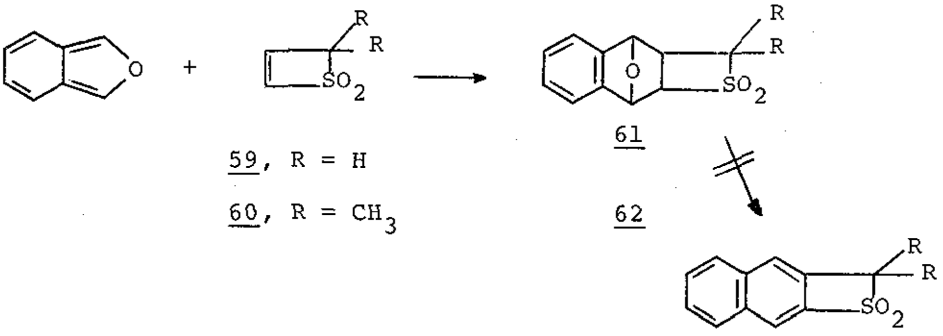
$R_4 = COCH_3$

57, $R_1 = R_2 = H$

$R_3 = R_4 = CO_2Me$

58, $R_1 = R_2 = R_3 = R_4 = CN$

N-phenylmaleimide[6,8], methyl vinyl ketone[8], dimethyl fumarate[7], and tetracyanoethylene[6] to give adducts 54, 55, 56, 57 and 58 respectively. Paquette and Phillips[33] reacted thiete sulfone (59) with IBF generated from the Fieser-Haddadin precursor and obtained thiete sulfone 61 which could not be dehydrated to naphtho[2,3-b]thiete-1,1-dioxide (63). Thiete sulfone 62 behaved similarly[34].



59, R = H

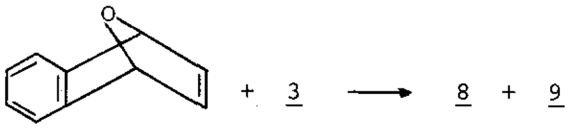
60, R = CH_3

61

62

63

The exo/endo ratio of adducts from the various cycloaddition reactions of IBF seems to vary. Whereas Fieser and Haddadin reported that olefin 4 adds to IBF (3) from the exo side



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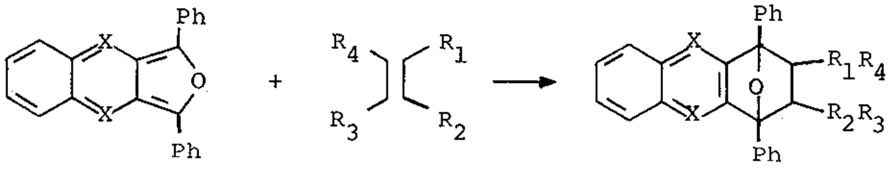
exclusively, Paquette[33,34] obtained 68% of exo 61 and 15% of endo 61, however, adduct 62 was 98% exo. The exo/endo ratio was determined by nmr spectral analysis in all cases where the dieneophile is cyclic. The geometry in the exo adduct prevents the coupling of the protons at the bridge junction and the adjacent proton in nmr spectrum. Such coupling is observed in the endo adducts. Wiersum[8] and Mijis found an exo/endo ratio of 1:3 in adducts 54 and 55. Mixtures of an exo and endo adduct 57 were also reported[7]. Bornstein and coworkers[9] isolated exo and endo adducts from the reactions of 1-methylisobenzofuran and 1,3-dimethylisobenzofuran with N-phenylmaleimide. Although it appears that no clear cut rule can be formulated for such reactions, the steric effect of the substituents in both the diene and dieneophile seems to play a major role in the control of the stereochemistry of the adducts.

It is evident that the availability and the high reactivity of IBF and its derivatives serve as a versatile method in the synthesis of a variety of naphthalenes and their azanaphthalene derivatives. Of special interest is the recent report of Kende et al, who employed intermediate 11 in the elegant synthesis of some anthracyclinones[62].

1,3-DPIBF (31) has been widely used as a reactive diene especially in the trapping of the relatively unstable compounds listed in Table 1. The various types of dieneophiles that have been reported to undergo cycloaddition reactions with 1,3-DPIBF are shown in Table II. Linear annelation of 1,3-DPIBF increases both the instability and the reactivity of the system. Cava and VanMeter[24] reported that 1,3-diphenylnaphtho-[2,3-c]furan (45) reacted instantaneously, at room temperature, with N-phenylmaleimide, maleic anhydride, and within a few minutes with dimethyl acetylenedicarboxylate, ω-nitrostyrene, 1,4-naphthoquinone, and 1,4-benzoquinone. The latter reacted with two moles of the diene. Similarly, Haddadin and coworkers[28] observed the same trend in the reaction of 1,3-diphenylfuro-[3,4-b]quinoxaline (51) with a variety of dieneophiles.



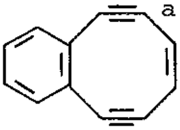
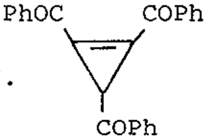
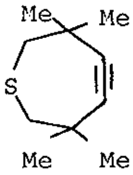
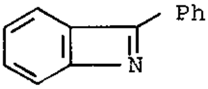
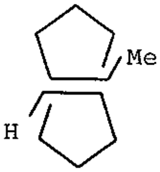
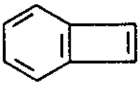
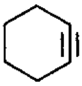
45, X = CH

51, X = N

<u>Table I</u>

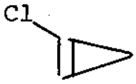
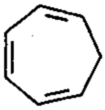
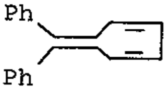
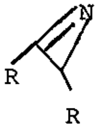
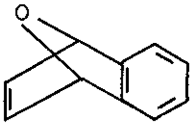
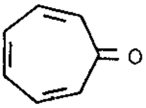
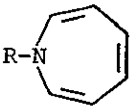
Transient intermediates and

relatively unstable compounds trapped by 1,3-DPIBF

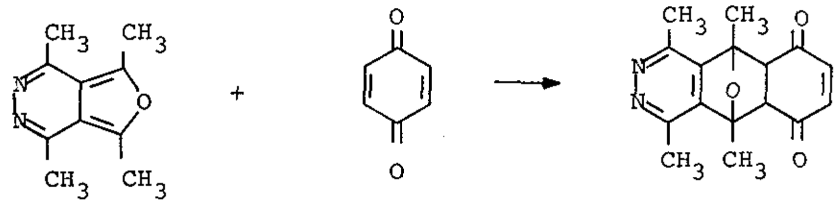
		Ref.			Ref.
1.	 [a]	35	6.		40
2.		36	7.		41
3.		37	8.		42
4.		38	9.		43
5.		39	10.		44
			11.		45
			12.		46

a) Reacted with 2 moles of 1,3-DPIBF.

Table II

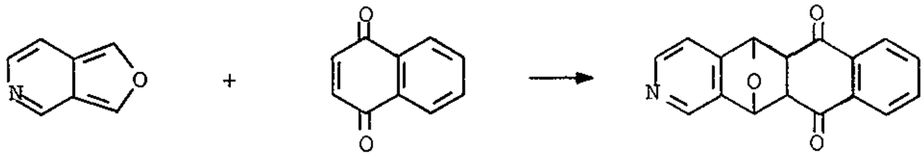
	Dieneophile	Ref.		Dieneophile	Ref.
1.		47	5.		51
2.		48	6.		52
3.		49	7.		53
4.		50			

Lomme and Lepage[54] reported the reaction of 1,4,5,7-tetramethylfuro[3,4-d]pyridazine (48) with p-benzoquinone to yield dihydroquinone 64.



48 64

It seems that the most reactive hetero-derivative of IBF is furo[3,4-c]pyridine which was found to react instantaneously and quantitatively with maleic anhydride and N-phenylmaleimide to yield adducts in *ca* 3:1 endo/exo ratio[30]. It reacted with 1,4-naphthoquinone to give pure 8-aza-6,11-epoxy-6,11-dihydro-5,12-naphthoquinone (65) in an endo/exo ratio of 10:1.



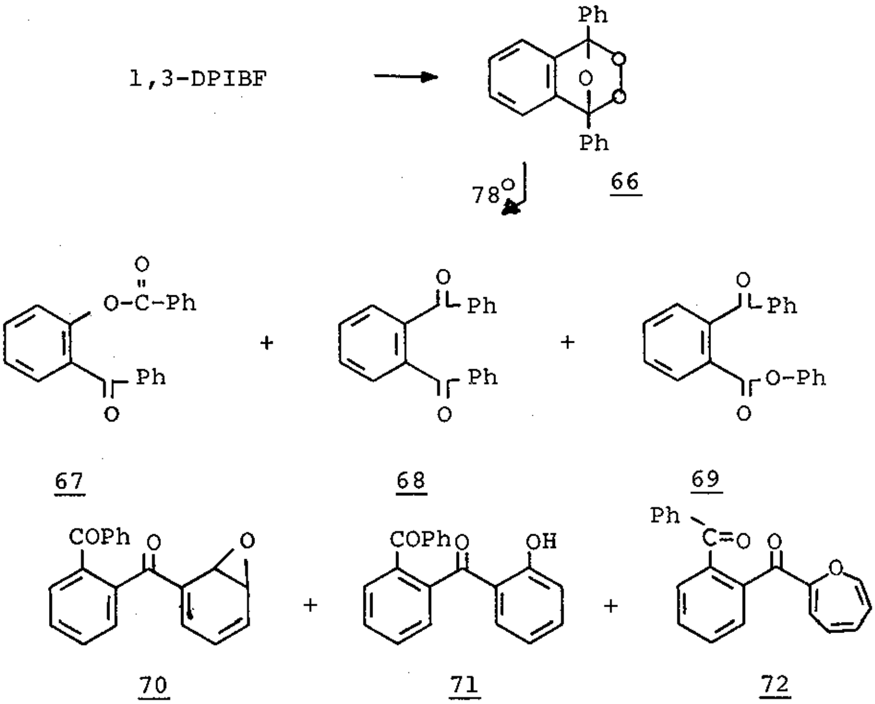
65

b) Photochemical Reactions of IBF

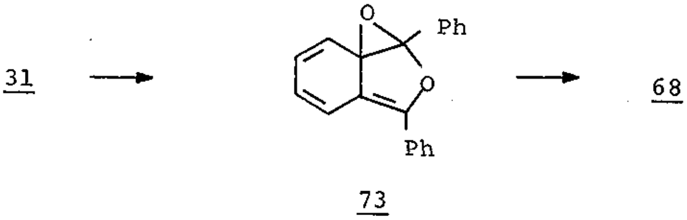
The photochemical reactions of the parent IBF (3) and its alkyl derivatives are virtually unknown. However, extensive work has been done on 1,3-DPIBF (31) which has been recognized as one of the best singlet oxygen acceptors[55]. It is claimed to have the largest rate constant, $8 \times 10^8\ M^{-1}\ sec^{-1}$, for quenching singlet oxygen[56]. The details of the kinetics and the mechanisms of the photooxidation of 1,3-DPIBF (31) lie beyond the scope of this review. The photo dimer of 1,3-DPIBF has been known since 1906[57]. A host of products from the photooxidation of 1,3-DPIBF (31) have been identified by Rio and Scholl,[58] who isolated the photooxide 66 in high yield from a methylene blue sensitized photooxidation at -50° (Scheme F).

Photooxide 66 produces products 67, 68, 69, 70, 71, and 72 in various conditions. The nature of the products was found to be dependent on the polarity of solvent. Reduction of peroxide 66 with KI-AcOH; PPh_3; CS_2; (PhCl, 78°) produced diketone 68. A kinetic and product study of the autoxidation and photooxidation of 1,3-DPIBF (31) was carried out by Howard and Mendenhall[59] who found no proof for the intermediacy of singlet oxygen during molecular oxygen oxidation. The main product of the photooxidation in CCl_4 was 68. These results are closely related to those of Boyer and coworkers[60] who

Scheme F

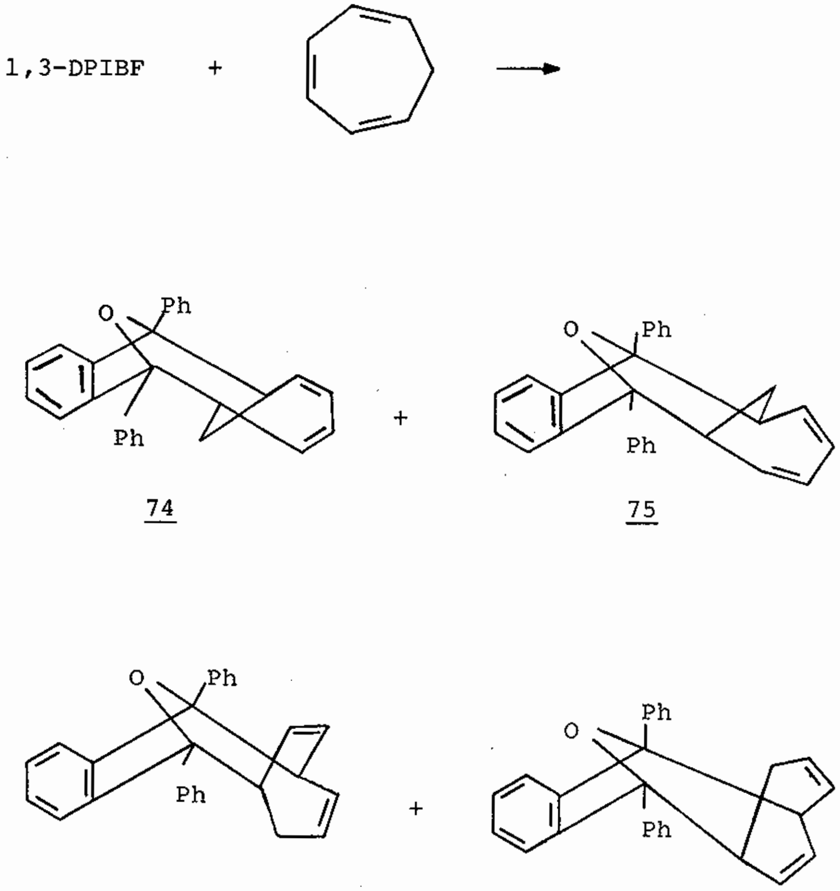

1,3-DPIBF
Ph
O
Ph
66
78°
O-C-Ph
Ph
Ph
Ph
Ph
O-Ph
67
68
69
COPh
OH
Ph
C=O
70
71
72

reported that thermal treatment of 1,3-DPIBF (31) with m-chloroperbenzoic acid in CH_2Cl_2 gave 68. It is postulated that 31 is converted to epoxide 73 which undergoes a rapid rearrangement to produce 68. Singlet oxygen involvement is ruled out.



Sasaki and coworkers[51] found that irradiation (Pyrex, 290 nm) of 1,3-DPIBF (31) with a large excess of cycloheptatriene gave a mixture of formal [6 + 4] and [4 + 4] adducts with exo and endo configurations 74, 75, 76, and 77, Scheme G. It is proposed that the formation of the [4 + 4] adducts proceeds by a concerted manner via an exciplex intermediate in $\pi - \pi^*$ singlet state, and the [6 + 4] adducts are thought to arise from the excited $\pi - \pi^*$ triplet state of 1,3-DPIBF indicating a stepwise mechanism.

Scheme G



74

75

76

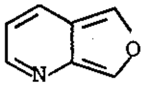
77

6. Spectroscopic Properties of IBF

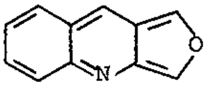
Despite its instability at or below room temperature the, uv spectra of IBF, 1-methylisobenzofuran, 1,3-dimethylisobenzofuran, and 1-benzylisobenzofuran have been determined[6,7,8,10]. The fluorescence spectrum at 77°K has been reported[6]. The nmr spectra of the above compounds have been measured[6,7,8,10]. IBF (3) shows a singlet at ca δ 7.88 and an AA' BB' pattern at 7.22 and 6.7. An analysis of coupling constants has been reported recently[9]. The ratio $J_{4,5}/J_{5,6}$ for IBF is 0.7 (0.7 for 2, 0.74 for 1, X = NCH_3). This value lies in the expected position based upon aromatic character consideration (the ratio for benzene is 1, naphthalene 0.82, and cyclohexa-1,3-diene 0.52). The photoelectron spectrum for IBF and the ionization potentials are assigned in the light of non-empirical calculations[9]. The uv and fluorescence spectra of 1,3-diarylisobenzofurans have been known for a long time[19,20]. A high resolution mass spectrum of IBF was determined by Warrener[6] (parent peak at m/e 118.04196, as well as major peaks at 90 and 89). The mass spectrum of 1,3-DPIBF showed the molecular ion as the base peak and little fragmentation occurred. A peak at m/e 241 is attributed to $[M\text{-}H\text{-}CO]^+$ [61].

Conclusion

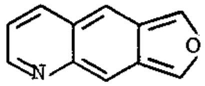
The chemistry of IBF has received considerable attention in the last ten years, however, there are a number of challenging problems to be tackled. To name a few, the synthesis of the parent and/or alkyl derivatives of the systems 78-83 is yet to be realized. These and other variations should be useful intermediates in the synthesis of various heterocycles otherwise inaccessible or more difficult to make by other methods.



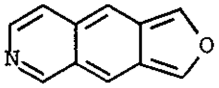
78



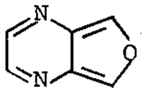
79



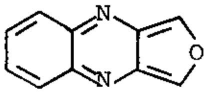
80



81



82



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