

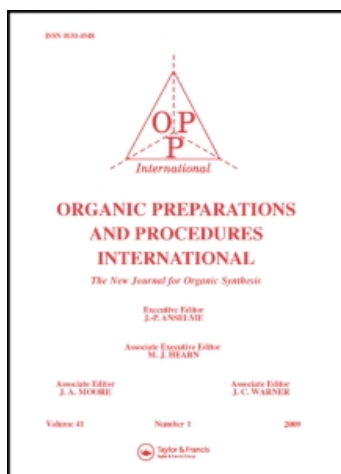
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SYNTHETIC APPLICATIONS OF DIARYL ETHER PHOTOCHEMISTRY. A REVIEW

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SYNTHETIC APPLICATIONS OF DIARYL ETHER PHOTOCHEMISTRY. A REVIEW

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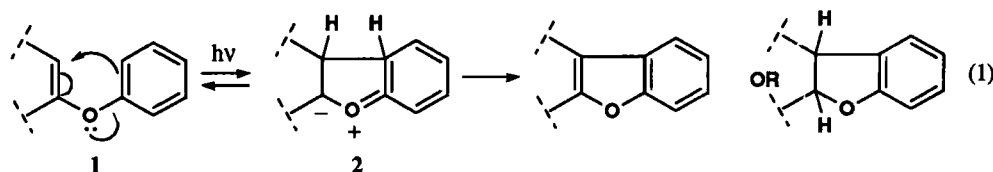
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INTRODUCTION

Photochemical reactions have been successfully used in organic synthesis for many years and books on the subject have appeared.¹⁻³ These and other books have reviewed photochemical reactions involving a variety of functional groups with emphasis on the most commonly studied moieties in organic photochemistry: the carbonyl group, alkenes, and aromatic compounds. Since carbon-carbon bond formation is central to organic synthesis, photocycloaddition reactions-in which there are several different types-have received the most attention. This review summarizes those photochemical reactions of diaryl ethers, and to a lesser extent aryl vinyl ethers, which have synthetic potential. By their nature, photochemical reactions are selective and readers should keep this in mind when deciding on using a photochemical step in a synthetic scheme. This review will not attempt to describe the required apparatus and all the associated intricacies when carrying out a photochemical reaction. The above mentioned books¹⁻³ provide good introductions to practical aspects of organic photochemistry.



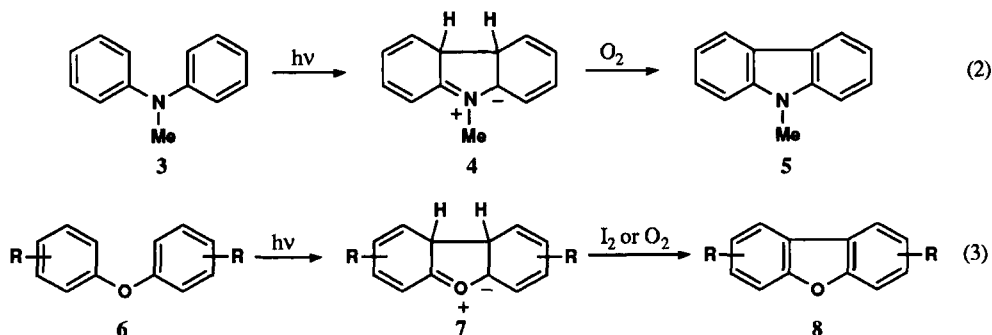
To our knowledge, an explicit review of the photochemistry of diaryl ethers has not appeared in the literature. However, Schultz⁴ and Schultz and Motyka⁵ have summarized photochemical heterocyclization reactions of aryl vinyl ethers and diaryl ethers (Eq. 1), as part of a broader review of such types of reactions. Because photocyclization reactions are probably the most useful for organic synthesis, this review will begin with a summary of photoheterocyclizations of diaryl and aryl vinyl ethers, with emphasis on recent applications to synthesis. This will be followed by a section dealing with photochemical reactions initiated by aryl-oxygen bond homolysis and ending with a section of miscellaneous reaction types. An understanding of mechanism is important for deciding on the possible application of a photochemical reaction to a related system. Therefore, the current under-

standing of the mechanisms of the reactions to be discussed will be presented, but only in enough detail as to provide insight into the possible generality of the transformation. The reader will need to refer to the original literature for a more complete mechanistic discussion.

I. ELECTROCYCLIC RING CLOSURE

1. Mechanism

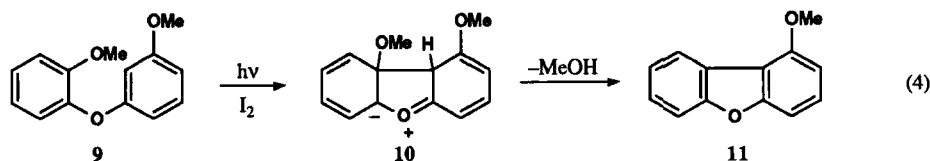
Photochemical reactions of diaryl ethers and diarylamines may involve a 6π electrocyclic ring closure leading to products.^{4,5} In these systems, the heteroatom is connected to two carbon-carbon double bonds **1** and photocyclization results directly in the formation of a reactive ylide intermediate **2** (Eq. 1). It has now been established⁶ that the photocyclization for *N*-methyldiphenylamine (**3**) proceeds via the ylide **4** (Eq. 2), which has been characterized by flash photolysis studies (absorption maxima at 370 and 610 nm).^{7,8} The ylide intermediate may return to starting material or react *via* dehydrogenation (in the presence of an oxidizing agent) to give *N*-methylcarbazole (**5**). From mechanistic studies of diphenyl ether⁹ (**6**, $R = p\text{-Me}$), it is believed that the primary photochemical step is also the formation of a ylide intermediate **7**, which can be oxidized by I_2 or O_2 to give dibenzofuran **8** (Eq. 3).



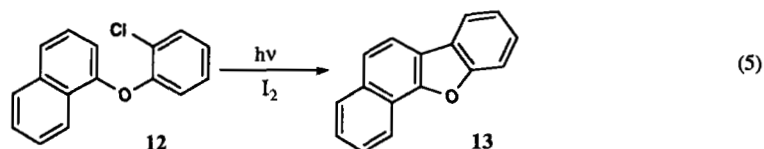
Photocyclization of aryl vinyl ethers reportedly also proceeds *via* a six-electron rearrangement to provide a ylide intermediate.⁴ In the absence of other effects such as proton transfer from the solvent, these systems rearrange by a process involving a 1,4-(6π) hydrogen shift to give dihydrofurans (Eq. 1, first product) without the use of an oxidizing agent.

2. Diaryl Ethers

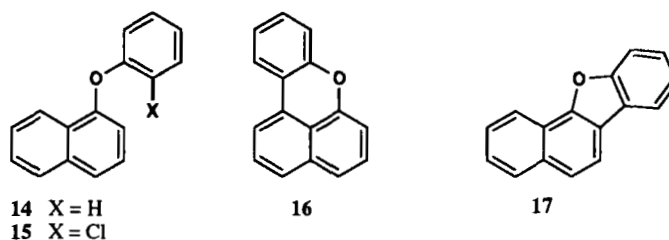
A series of dimethyl-substituted diphenyl ethers **6** has been shown to undergo photocyclization to benzofurans **8** in the presence of I_2 (Eq. 3) in yields of 40-61%.⁹ When there is a photolabile substituent at the *ortho* position, diaryl ethers can undergo eliminative photocyclization (Eqs. 4 and 5).¹⁰ It has been shown that a low yield of dibenzofuran **11** is observed on irradiation of ether **9**¹⁰ and



o-chlorophenyl-1-naphthyl ether (**12**) can be photolyzed to produce benzo[*b*]naphtho[2,1-*d*]furan (**13**) in 45% yield.^{5,10,11} It is presumed that the reaction proceeds through a similar ylide intermediate **10** and that not only does the photolabile substituent *ortho* to the ether direct the closure, but the subsequent loss of methanol ensures that the cyclization is irreversible and electron redistribution leads to stable dibenzofuran products.

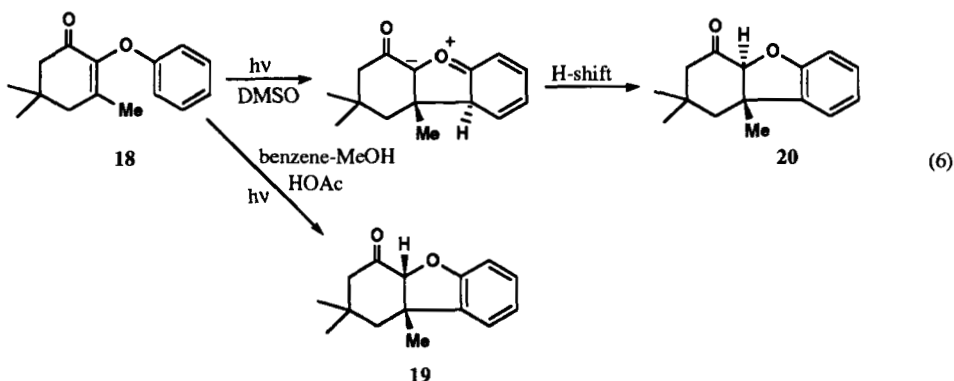


Similar photocyclizations can occur for phenyl-1-naphthyl ether (**14**) and *o*-chlorophenyl-1-naphthyl ether (**15**).¹¹ These compounds have two available modes of photocyclization: closure at the 8-position of the naphthalene ring to give **16**, or closure at the 2-position of the naphthalene ring to give **17**. However, photolysis of **14** did not produce either of the expected products while the photoreaction of **15** gave pure **17** in 45% yield. Presumably in these systems the directing influence of the chloro substituent is required for efficient reaction.

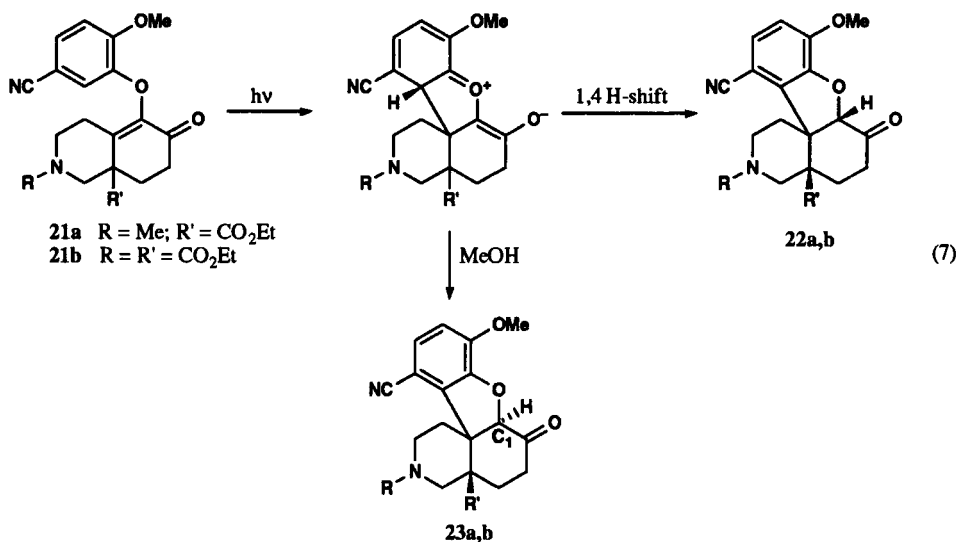


3. Aryl Vinyl Ethers

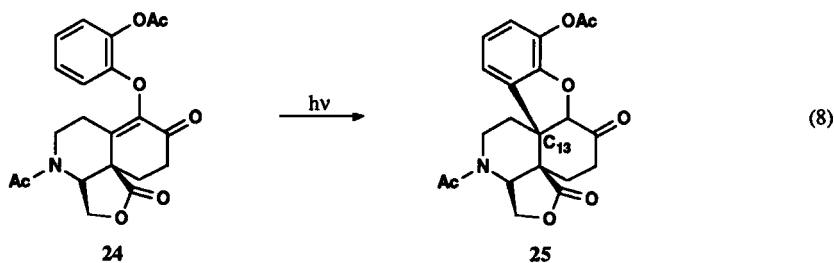
Aryl vinyl ether **18** (derived from isophorone epoxide) and related compounds can be photolyzed in benzene-methanol-acetic acid solution to give photocyclization product **19** with the cis-dihydrofuran ring fusion (Eq. 6).^{4,5} Yields are generally high (> 50 %) and are quantitative for several compounds (e. g., when Ar = *m*-tolyl, *m*-carboxyphenyl and 4-chloro-5-methylphenyl). If instead the



photolysis of **18** is carried out in an aprotic solvent such as DMSO, the *trans*-dihydrofuran product **20** is obtained in high yield. Ring fused aryloxyenones **21** undergo a similar stereoselective photocyclization in benzene: **21a** and **21b** gave the *trans* products **22a** and **22b**, respectively, in 80-90% yields (Eq. 7).^{4,5} The product stereochemistry is consistent with a reaction mechanism involving a conrotatory

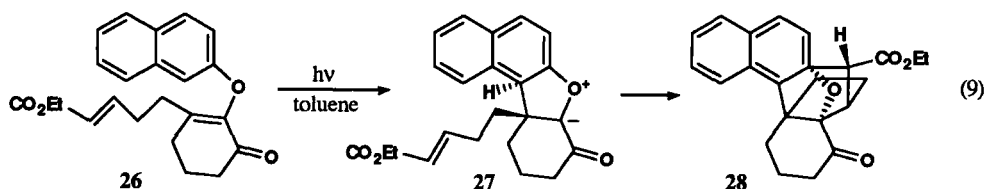


electrocyclic process to give an intermediate ylide, followed by suprafacial 1,4-hydrogen shift to give the product. If the reaction is carried out in methanol, proton transfer from the solvent to the anion will compete to give the *cis*-dihydrofurans **23**, in addition to **22**. The proton transfer mechanism was substantiated when irradiation of **21** in methanol-*O-d* gave **22** with no incorporation of deuterium and **23** with complete deuterium incorporation at C-1. It is noteworthy that protonation of the ylide occurs to give the more stable epimer. Recent flash photolysis studies support the presence of the ylide in the photocyclization process.^{12,13} The cyclization of fused-ring aryloxyenones has also been used to synthesize a morphine ring system **25** from precursor **24** in 90% yield (Eq. 8).^{4,5} This reaction provides a high degree of stereochemical control at C-13. Other medicinally important alkaloids such as lycoramine and analogues of codeine, vindrosine, and vindoline may be synthesized in relatively high yields using the same approach (overall stereospecific photoarylation).

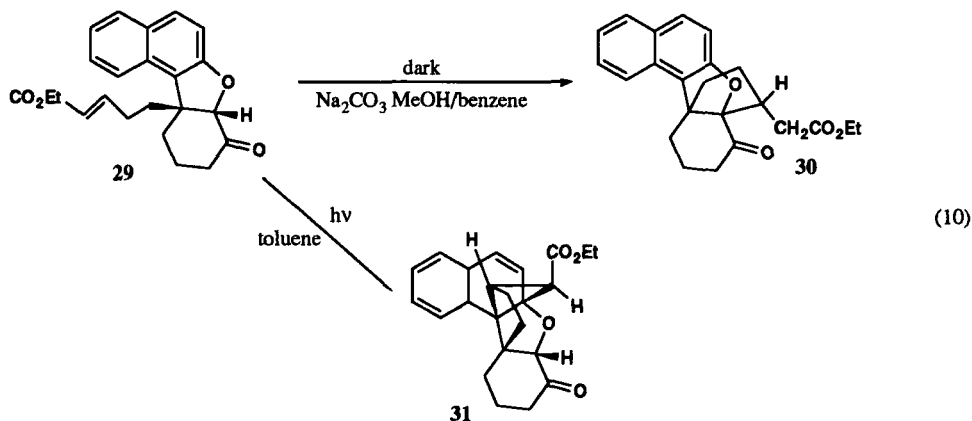


The intermediate *trans*-fused carbonyl ylide **27**, formed *via* six electron conrotatory photocyclization of aryl vinyl ether **26**, undergoes intramolecular [3+2] dipolar cycloaddition to the side chain

olefin to give **28** in 85% yield (irradiation for 25 minutes at temperatures ranging from -78° to 110°) (Eq. 9).¹⁴⁻¹⁶ However, irradiation of **26** in protic media gave **29** in relatively high yield (trapping of the



ylide by proton transfer). Further reaction of **29** in the dark at room temperature with sodium carbonate in methanol/benzene gave the Michael adduct **30** in 70% yield while photolysis in toluene at room temperature gave the [2+2] adduct **31** in 76% yield (Eq. 10). Therefore, the combined photocyclization-intramolecular addition reactions of aryl vinyl ethers offers considerable flexibility in the formation of complex systems from relatively simple achiral starting materials. In addition, the thioether analogs also undergo these types of photocyclizations.¹⁴⁻¹⁶ Although the products formed in each one of these reactions are racemates, further investigation into the use of precursors with a chiral auxiliary can be anticipated in the synthesis of optically pure materials. The above reactions have applications in the synthesis of biologically active compounds.

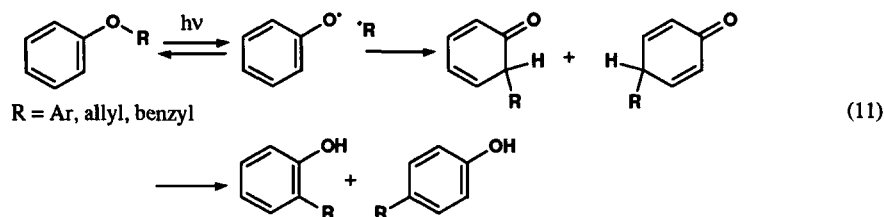


II. PHOTOREARRANGEMENT

1. Mechanism

In addition to electrocyclic ring closure, diaryl ethers (and some aryl alkyl ethers; aryl vinyl ethers do not react via this pathway) can react via initial aryl-oxygen bond homolysis (as the primary photochemical step), to give a radical pair, which can escape or recombine to give *o*- and *p*-substituted phenols.¹⁷⁻²¹ In general, the yield of escape products is much lower than rearrangement products, which is consistent with the accepted *intramolecular* pathway shown in Eq. 11.^{20,21} The overall mechanism is similar to the well-known photo-Fries rearrangement of aryl esters.²² It is reasonable to assume that electrocyclic ring closure (discussed above) and photorearrangement via aryl-oxygen bond homolysis are *competing* photoreactions of diaryl ethers. The electrocyclic ring closure pathway

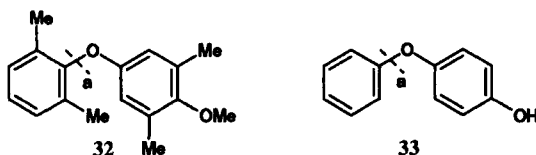
in general requires the presence of an oxidizing agent to take it to completion and when such an agent is lacking, photorearrangement becomes the dominant pathway.



The photorearrangement is known to be highly sensitive to the presence of hydroxylic solvents. When they are used, the rearrangement yields are generally high^{20,21} but when non-polar solvents such as benzene and cyclohexane are used, much lower photorearrangement yields are observed. The mechanism shown in Eq. 11 can account for these observations. The initially photogenerated phenoxyl-aryl (alkyl) radical pair can revert back to starting material or recombine at the ortho and para positions to give the corresponding cyclohexadienones. These intermediates are significantly more polar (due to the carbonyl group) than the radical pair. Hence the presence of a hydrogen bonding solvent should help the rearrangement. Okata *et al.*²⁰ have offered a different explanation for the solvent effect. They proposed that a hydroxylic solvent enhances the efficiency of the initial homolysis step by hydrogen bonding to the oxygen in a polar transition state.

2. Photo-Fries Type Rearrangements

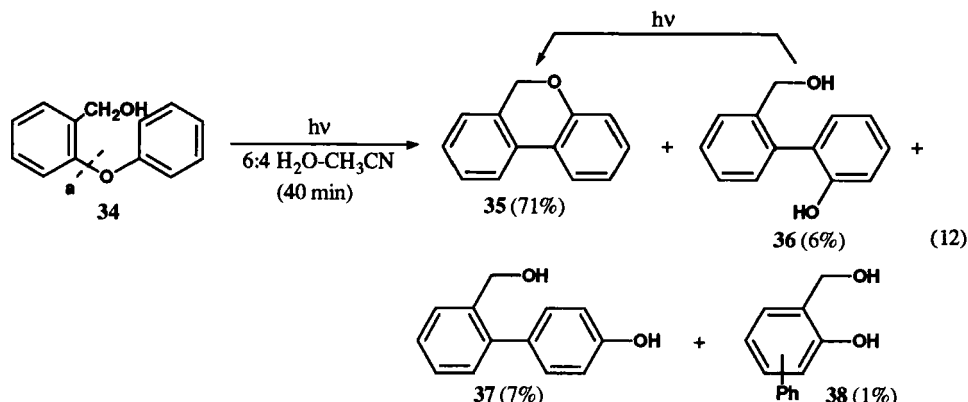
As indicated above, the photo-Fries type photorearrangement of diaryl ethers (and some aryl alkyl ethers) in general gives a mixture of the *o*- and *p*-substituted phenols. However, the photochemical reaction can be performed under mild conditions and may be synthetically useful if a thermal rearrangement was originally planned for the substrate. Only a limited number of examples has been studied photochemically. The parent diphenyl ether is reported²¹ to give *o*-phenylphenol and *p*-phenylphenol in 30% and 24% yields, respectively, on photolysis in 2-propanol. Of the non-symmetrically substituted diaryl ethers studied to date, a high degree of regioselectivity is observed. For example, photolysis of **32**²¹ and **33**¹⁹ gave products arising mostly from homolysis of bond a. These two examples indicate that the ether bond which breaks should give the more stable phenoxyl radical.



3. Photocyclization of *o*-Phenoxybenzyl Alcohol

Recently, Huang *et al.*²³ reported that photolysis of *o*-phenoxybenzyl alcohol **34** gave dibenzopyran **35** (cannabinol ring system) as the major product (71%; $\Phi = 0.002$ in 100% CH₃CN and

0.007 in 6:4 H₂O-CH₃CN), along with a mixture of biphenyls **36-38** (Eq. 12). What is surprising here

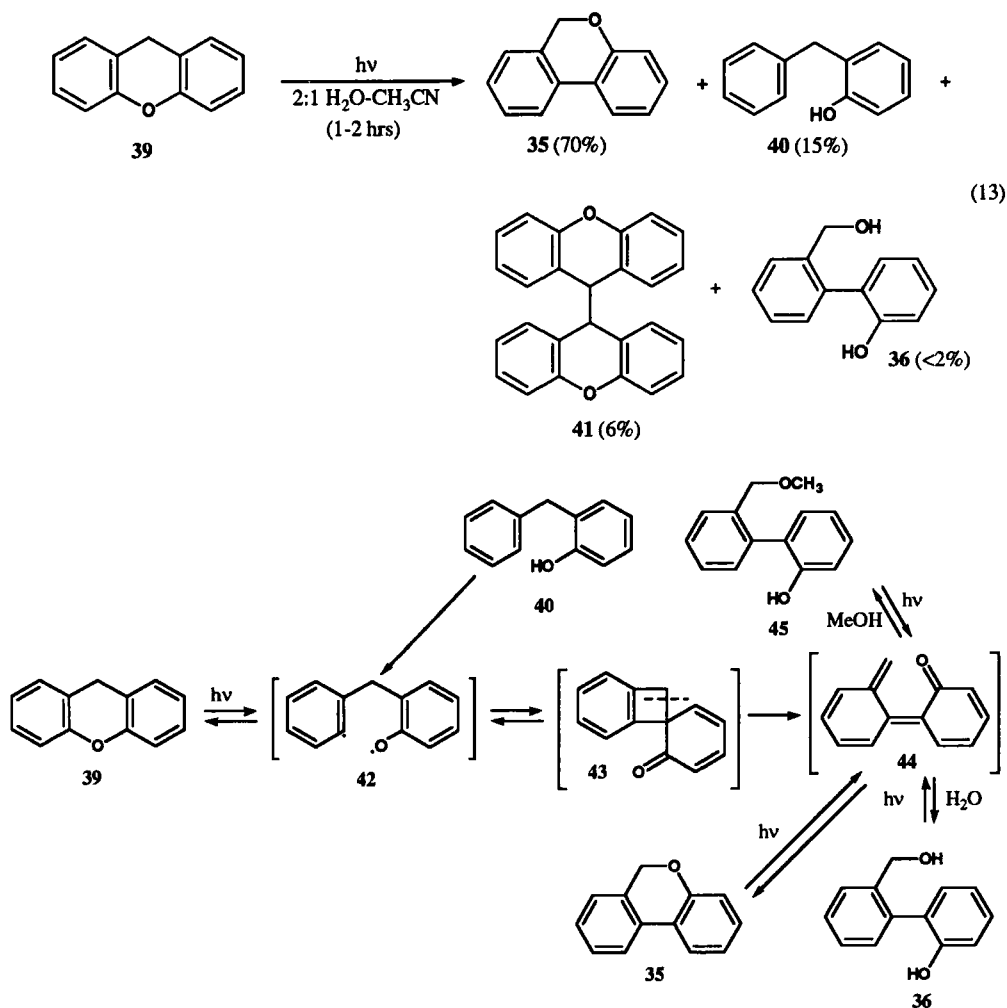


is that the expected photo-Fries type rearrangement products **36-38** are formed in such low yields. However, in a related paper²⁴, Huang et al. reported that biphenyl alcohol **36** is photochemically very reactive. Photolysis of this alcohol gave pyran **35** with high quantum yield ($\Phi = 0.25$ in 1:1 H₂O-CH₃CN, pH ~ 7). Thus it appears that the mechanism of reaction involves initial aryl-oxygen homolysis which is regioselective at the aryl-oxygen bond on the ring containing the CH₂OH group (bond **a**). Subsequent rearrangement gives biphenyls **36** and **37**. Secondary photolysis converts **36** to pyran **35** via a mechanism involving a biphenyl-*o*-quinonemethide intermediate.²⁴ The high yield of **35** indicates that the initially generated radical pair couples mostly at the ortho position (to give **36**). In addition, the higher quantum yields observed in aqueous solution is consistent with what is known about the effect of a polar solvent on the photoisomerization of diaryl ethers (*vide supra*). The overall conversion of a simple phenoxybenzyl alcohol to a pyran is appealing for synthesis. The parent system gives acceptable yields. However, attempts at extending the reaction to the α -methyl substituted derivative (at the benzylic position) of **34** gave only a low yield of the corresponding pyran derivative due to the photolability of the product.²³

4. Photoisomerization of Xanthene

Xanthene (**39**), which may be regarded as a simple diaryl ether derivative, is readily converted to xanthone on photolysis in the presence of oxygen. However, on photolysis in aqueous solution in the absence of oxygen, pyran **35** is again formed (70%; $\Phi = 0.0014$ in 100% CH₃CN and 0.0035 in 7:3 H₂O-CH₃CN), along with some minor side products (Eq. 13).²⁵ The observation of products **40** and **36** is indicative of a mechanism which involves initial aryl-oxygen bond homolysis (Scheme 1). Trapping of the initially generated biradical **42** gives phenol **40** (hydrogen donor being the solvent). This phenol was the exclusive product (> 90%) when **39** was photolyzed in 100% 2-PrOH, which is consistent with the mechanistic scheme. The biradical **42** may revert back to substrate or re-bond at the ortho position of the phenoxy moiety to give the benzocyclobutane/cyclohexadienone intermediate **43**. As discussed before, this step should be enhanced by a polar hydroxylic solvent such as water resulting in higher quantum yield of reaction, which was observed. Intermediate **43** may ring open to

give the biphenyl-*o*-quinonemethide **44**, which is known to cyclize to pyran **35**²⁴ or it can be trapped by solvent (H₂O to give **36** or MeOH when it is used, to give ether **45**). Both of these latter products may be photochemically converted to **35**.²⁴ Photolysis of 9-methylxanthene failed to give significant yields of the corresponding pyran due to the photolability of the substituted pyran product.²⁴



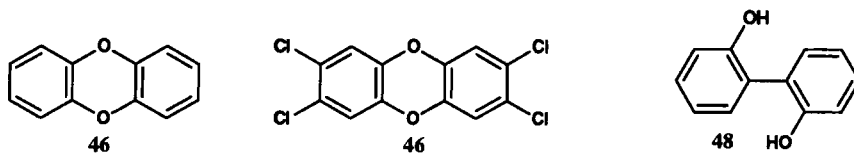
Scheme 1

5. Photolysis of Dibenzo-*p*-dioxin

Dibenzo-*p*-dioxin (**46**) is another simple diaryl ether, in this case with two ether moieties. The 2,3,7,8-tetrachloro-substituted derivative (**47**), more commonly known as dioxin, has received much publicity due to its high toxicity in laboratory animals and its common occurrence in chemical wastes. Photochemical degradation of dioxin has been considered as a viable method for its conversion to less toxic materials.²⁶⁻³⁰ Photodegradation of dioxin gives a complex mixture of products and hence is synthetically not useful. However, the photochemical behaviour of the parent system **46** has not been

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explored extensively. Massé and Pelletier³¹ reported that photolysis of **46** in oxygenated organic solvents gave a complex mixture of products, one of them being 2,2'-dihydroxybiphenyl (**48**). However, based on what we already know for xanthene (**39**) photochemistry, photolysis of **46** might

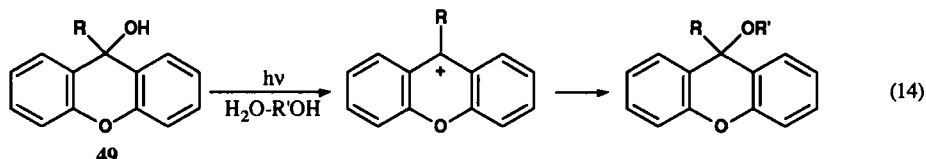


be more selective under deaerated conditions in a hydroxylic solvent. Thus, Guan and Wan³² have discovered that irradiation of **46** in $\text{H}_2\text{O}-\text{CH}_3\text{CN}$ mixtures gave **48** as the only product (yield 20–40%). Moreover, when NaBH_4 was present during the photolysis, the yield of **48** increased to > 70%. The mechanism of reaction is similar to that proposed for xanthene (**39**) although additional studies are required to delineate the enhancing effect of NaBH_4 .

III. MISCELLANEOUS PHOTOREACTIONS

1. Photosolvolytic of Xanthenols

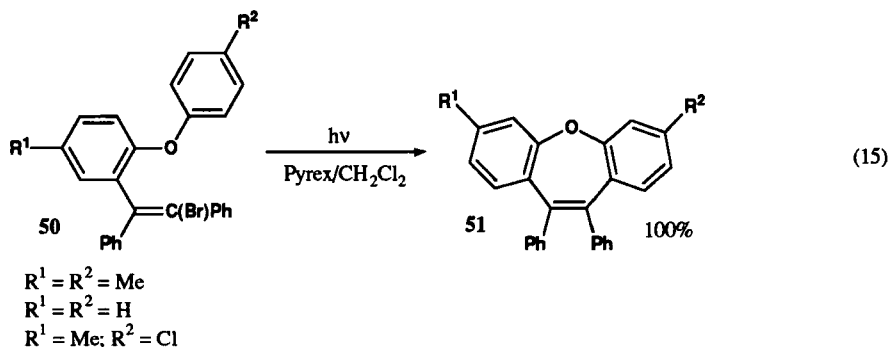
Xanthenols **49** photosolvolyze readily in neutral aqueous alcohol solution, to give the corresponding xanthenyl cations, which may be trapped by alcohol to give high yields (> 50%) of the corresponding ethers (Eq. 14).³³ The mechanism of reaction has been studied by several groups using



classical photochemical techniques as well as via laser flash photolysis.^{33–35} These studies have confirmed that the primary photochemical step is heterolytic C–OH bond cleavage from the singlet excited state. Although it is also possible to accomplish the solvolysis under more traditional thermal conditions in the presence of acid, the photochemical method can be done in neutral or even basic media and hence may be useful when acidic medium is to be avoided.

2. Formation of Oxepins

A potentially useful photochemical reaction of a compound containing a diaryl ether moiety is the recent work of Kitamura *et al.*³⁶ who reported that photolysis of vinyl bromides **50** (which have a diaryl ether moiety nearby) resulted in formation of dibenzoxepins **51** in quantitative yield (Eq. 15). This reaction is general when the diaryl ether moiety is kept simple. When it is a dibenzofuran group, the photocyclization fails and only the photosolvolytic product was isolated. The mechanism of reaction involves initial C–Br bond cleavage, to generate a vinyl cation, which is trapped by the phenyl ring of the diaryl ether, to generate the dibenzoxepin ring system.



IV. SUMMARY

In this review we have attempted to present those photochemical reactions of diaryl ethers and some aryl alkyl ethers which might have synthetic utility. The electrocyclic ring closure reactions have already been shown to be useful synthetic transformations. The other types of reactions discussed do not have the same potential. As with most photochemical transformations, generality cannot be expected. In synthesis, one uses a photochemical reaction to carry out a very specific transformation which cannot be done easily using known thermal pathways. However, recent discoveries of new reactions of diaryl ethers have increased the utility of this functionality in synthesis and this trend can only be expected to continue.

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