Diaryl Ketones as Photoactivators

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Abstract: The lowest lying triplet excited states of diaryl ketones are usually long lived and can be photochemically generated with high quantum yields. Hence, compounds of this type are efficient triplet photosensitizers. Three major mechanisms, namely hydrogen abstraction, energy transfer and electron transfer, can be involved in the photosensitized processes. This paper reviews recent examples on the relevance of diaryl ketones as triplet photosensitizers in synthesis. In addition, a number of applications are also presented. In general, the literature coverage has been limited to the publications that appeared during the last five years.

Keywords: Diary ketones, photosensitizer, hydrogen abstraction, energy transfer and electron transfer.

INTRODUCTION

In the ground state, the basic chemistry of the carbonyl chromophore is to a large extent independent on the nature of the groups (aryl, heteroaryl, alkyl) attached to the carbonyl carbon. However, these substituents have a strong influence on the behavior of the carbonyl chromophore excited state [1-8].

The electrons that are of importance in determining the photoreactivity of the carbonyl chromophore are the oxygen lone pair and the π electrons of the C=O group. For dialkyl ketones, intersystem crossing from S_1 to T_1 and radiative transition from S_1 to S_0 are competitive processes. Under favorable conditions, reactions can take place from both S_1 and T_1. The energy difference between nπ* and ππ* states is relatively large and the reactive excited triplet states are of nπ* character.

In the case of aromatic ketones, conjugation reduces the energy gap between the singlet and the triplet levels, leading to an appreciable increase of the rate coefficients for intersystem crossing, whose quantum yields become close to the unity. Hence, diaryl ketones react mainly from T_1, as reactions from S_1 must compete with the very fast intersystem crossing process ($> 10^{10}$ s^{-1}). Besides, they have a lower energy gap between nπ* and ππ* states as compared to dialkyl ketones. This can have an impact on the ordering of the states in the triplet manifold, resulting in some cases in ^{3}ππ* excited states below ^{3}nπ* states (see Fig. (**1**)) [2-8]. Thus, depending on the nature of the aryl group (i.e. phenyl, thienyl, pyridyl,…) [2,3], the nature of the substituents (electron-donating *vs.* electron-withdrawing) [2,5,6] or position of substituents on the aromatic rings [2,5], the electronic configuration of the lowest triplet states can change, and this will influence the ketone photoreactivity. Also, solvent effects [4,5,7] as well as the degree of planarity of the system [8] can switch the order of the two lowest-lying triplet excited states of aryl ketones. In general, increasing the solvent polarity or the dihedral angles that each of the aryl rings makes with the C_{arom}-(C=O)-C_{arom} plane destabilizes the nπ* states.

Moreover, in describing the electronic configuration of excited states of aromatic ketones with nearby T_1 and T_2 states, it could be necessary to consider the contribution of both ^{3}nπ* and ^{3}ππ* character [8]. Since, nπ* states have higher radiative rates than ππ* states, the former can control the emission properties, resulting in a more structured emission. When T_1 has mainly ππ* character, the emission could originate from the ππ* T_1 state and/or the nπ* T_2 state, depending on the competition between the thermal activation of T_1 (to T_2) and its decay.

In the n→π* transition, the electron density moves away from the oxygen, and the double bond character of the carbonyl chromophore decreases compared to that in the ground state. This is reflected in a lower carbonyl stretching frequency for the excited state, and gives rise to electrophilic and radical-like properties of the nπ* excited state, leading to hydrogen abstraction, radical addition and electron transfer reactions.

In the π→π* transition, the electron density is shifted from the aryl ring to the carbonyl chromophore, but the electron distribution in the π and π* orbitals is unequal due to the different electronegativity of the carbon and oxygen atoms of the carbonyl group. Thus, the stretching frequency of T_1 ππ* excited states is reduced compared to that in the ground state, but not to the same degree as in T_1 nπ* states. Because of the delocalization, the ππ* triplet is in general less reactive than the nπ* triplet, although electron transfer is little affected [2-6].

From above data, it is worth noting that diaryl ketones can be very useful as triplet photosensitizers, due to their long-wavelength absorptions, their high efficiencies of intersystem crossing and their usually long-lived triplet excited states. This paper reviews recent reports on the interest of these compounds in synthesis, as well as in industrial applications, such as crosslinking of resins and

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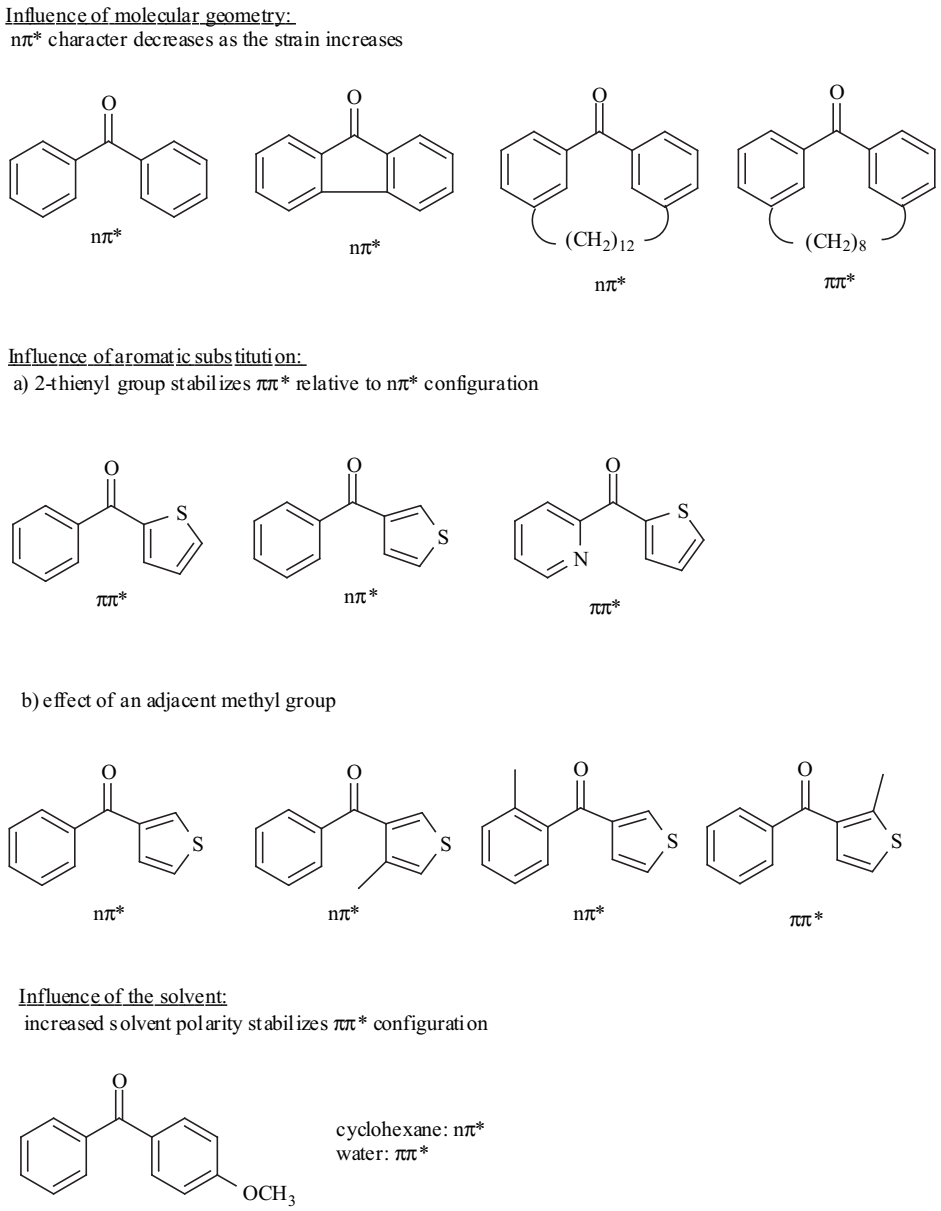


Fig. (1). Some factors influencing the nature of the configuration of the lowest excited triplet state of diaryl ketones.

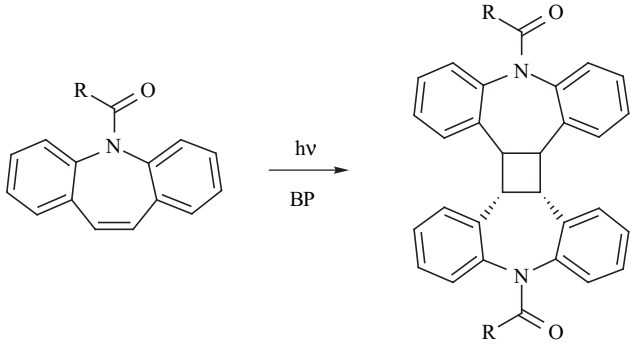
desulfuration of diesel fuel. The biological relevance of benzophenone-derived compounds is also presented.

DIARYL KETONES AS PHOTOSENSITIZERS IN SYNTHESIS

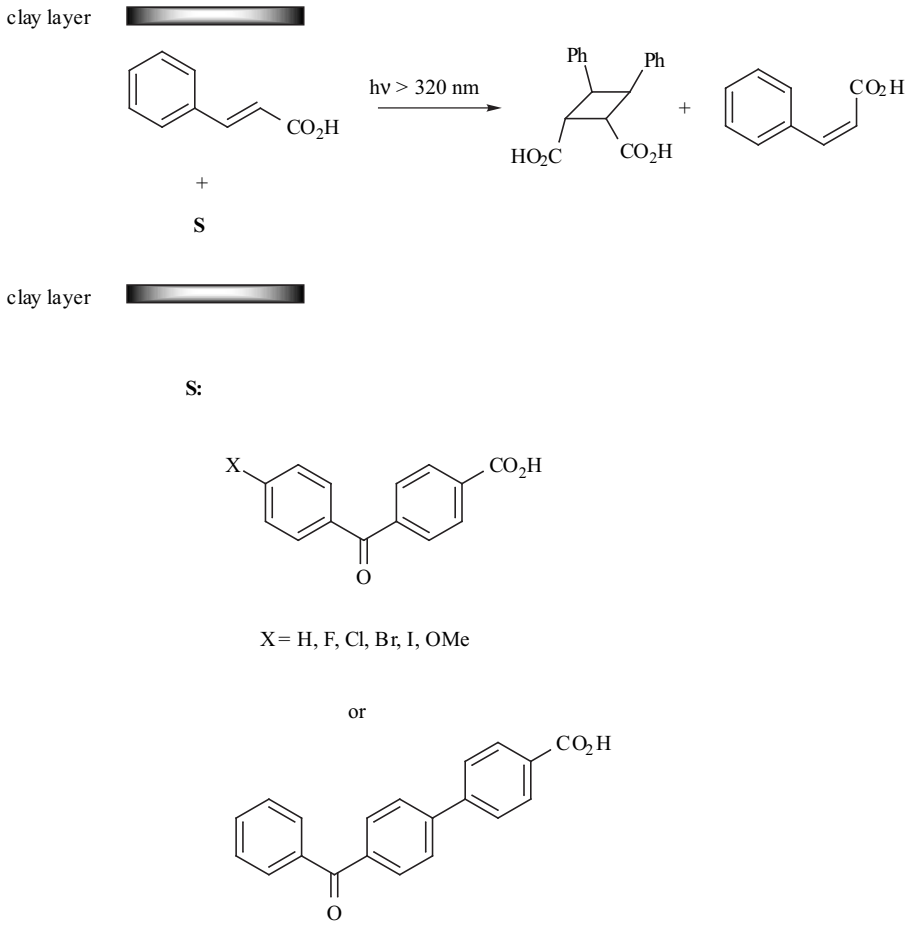
Photocycloadditons

In solution, benzophenone (BP) can photosensitize dimerization of stilbene derivatives if the central double bond is fixed in a ring system (to avoid *cis-trans* isomerization and photocyclization to dihydrophenanthrene). This is the case of *N*-acyldibenz[e,f]azepine, whose photosensitized irradiation leads to only one photodimer (Scheme **1**) [9].

When the central double bond is not part of a ring system, aryl olefins can still photocyclodimerize when they are intercalated in the interlayers of clay minerals. Thus, stilbene-4-carboxylate ions give rise to efficient formation of *syn*-head-to-head and *syn*-head-to-tail cyclodimers upon irradiation in the presence of hydrotalcites. However, only the *syn*-head-to-head dimer is obtained when benzophenone derivatives and *trans*-cinnamate are coadsorbed in the clay



Scheme 1. BP-sensitized cyclodimerization of *N*-acyldibenz[e,f] azepines.

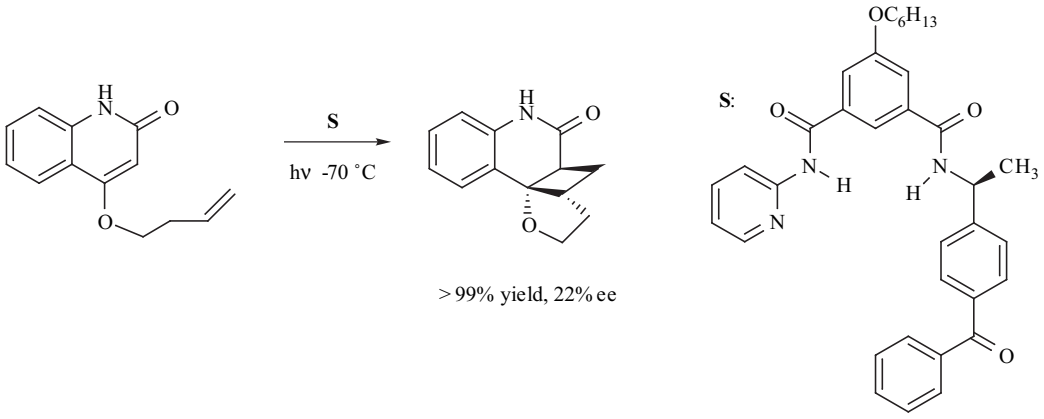


Scheme 2. Benzophenones-sensitized cyclodimerization of cinnamic acid in hydrotalcite interlayers.

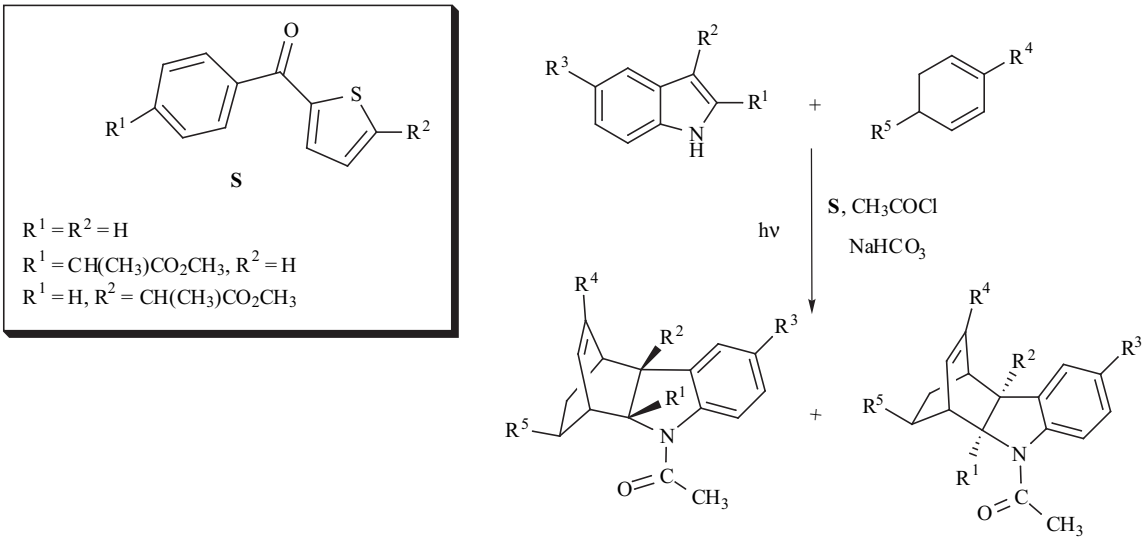
interlayers (Scheme **2**) [10]. By comparison, only *Z-E* photoisomerization is observed in the absence of the clay. Though the possibility of triplet sensitization has not been ruled out, the reaction efficiency and its stereoselectivity seem to agree with a mechanism involving the intermediacy of an exciplex between the benzophenone singlet excited state and the ground state cinnamate.

A chiral molecular receptor possessing an appendant benzophenone moiety has been used as a strategy for enantioselective BP-photosensitized [2+2]-cycloaddition (Scheme **3**) [11]. The rate of triplet-triplet energy transfer to a quinolone could be rate enhanced through binding to the chiral receptor, allowing catalytic asymmetry induction in the intramolecular enone-alkene cycloaddition.

In general, the Diels-Alder reaction is inefficient when both diene and dienophile components are electron-rich compounds. However, [4+2]-cycloaddition reactions between indoles and cyclohexadienes can be photocatalyzed by benzoylthiophenes (Scheme **4**) [12]. Although diene dimerization is also observed, the results provide a novel method for promoting the [4+2] cross-cycloaddition reaction between electron-rich components. Experimental and



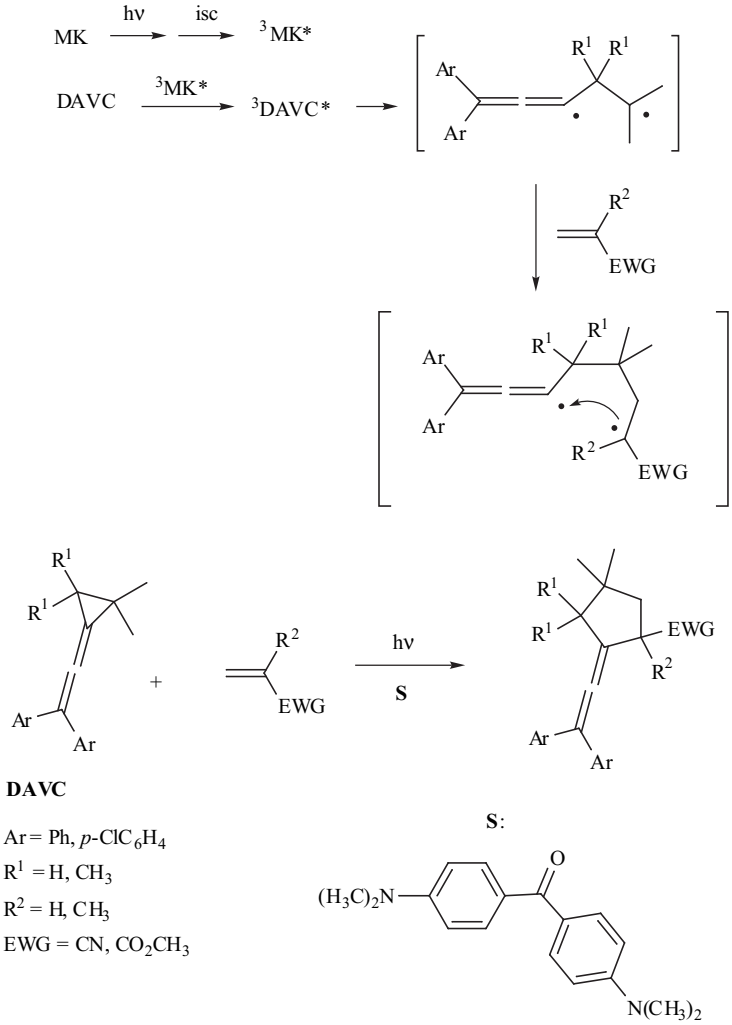
Scheme 3. A chiral BP-derived receptor as photosensitizer in a [2+2]-cycloaddition of a quinolone.



Scheme 4. Diels-Alder reaction photocatalyzed by 2-benzoylthiophenes.

theoretical studies agree well with the involvement of triplet ketone-indole exciplexes, which are quenched by the diene to afford intermediate ternary complexes, leading finally to the Diels-Alder cycloadducts.

Irradiation of a benzene solution containing diarylvinylidenecyclopropanes (DAVC) and electron-deficient alkenes in the presence of Michler´s ketone (MK) affords the [3+2]-cycloaddition products in high yield (Scheme **5**) [13]. No

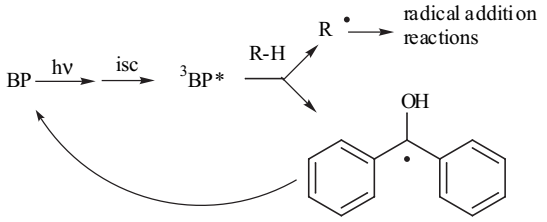


Scheme 5. Michler´s ketone sensitized [3+2]-cycloaddition.

reaction occurs in the absence of the photosensitizer. The result is explained through the involvement of a 1,3-biradical generated from the DAVC triplet upon bond cleavage.

Photoadditions

It is well-known that BP triplet excited state is capable of abstracting a hydrogen atom from various donors (R-H), such as alcohols, amines, ethers and hydrocarbons (Scheme **6**). This fact has been used with synthetic purposes; the more recent examples are described below.



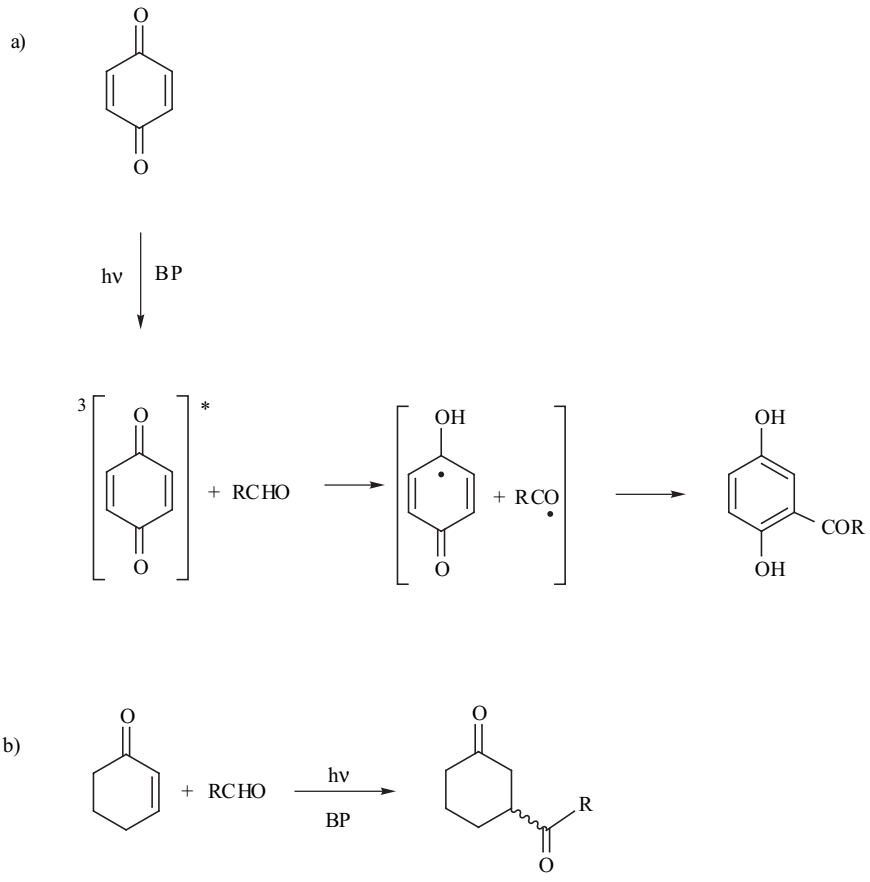
Scheme 6. General scheme for photosensitized H-abstraction reactions.

The BP-mediated addition of aldehydes to α,β-unsaturated carbonyl compounds in benzene as solvent is an established reaction (Scheme **7**) [14]. It proceeds from the enone triplet excited state, which abstracts a hydrogen from the C-H bond of the aldehyde. Radical-radical coupling, followed by enolization, yields the acylated derivatives. Tanko *et al.* have reported an environmentally benign and effective modification of the method by using supercritical-CO_2 (SC-CO_2) [15]. Solubility of the polar material in the non-polar SC-CO_2 is improved by increasing the pressure and by using *t*-ButOH as co-solvent. This method allows an effective synthesis of 2-acyl-1,4-hydroquinones from quinones. The use of 2-cyclohexen-1-one as the α,β-unsaturated compound leads to 1,4-diketones.

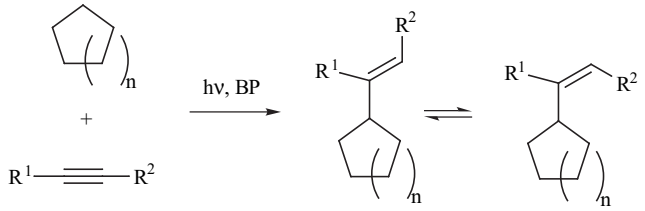
Cycloalkanes can be functionalized by irradiation with electron deficient alkynes in the presence of benzophenone, either in solution or bound to a polymer (Scheme **8**) [16]. As the reaction can be carried out using solar radiation, and the polymer-bound photosensitizer is potentially recyclable, this constitutes an environmentally benign method of functionalizing unactivated cycloalkanes.

Photosensitized hydrogen abstraction from 2-alkyl-1,3-dioxolanes gives the corresponding 1,3-dioxolan-2-yl radical, which after reaction with α,β-unsaturated ketones yields monoprotected 1,4-diketones (Scheme **9**) [17]. This is a versatile method with cyclic enones, but shows low efficiency with open chain ketones.

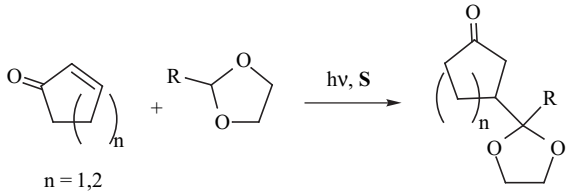
Furthermore, 1,3-dioxolan-2-yl radicals add to fumaric amides, providing a diastereoselective synthesis of 2-substituted chiral succinic acid derivatives when using chiral oxazolidine as aminyl source (Scheme **10**) [18]. The ratio of the two diastereoisomers varies from 89:11 to 95: 5. These products can be of interest as suitable building blocks in organic synthesis.



Scheme 7. BP-mediated addition of aldehydes to α,β-unsaturated carbonyl compounds in supercritical CO_2.

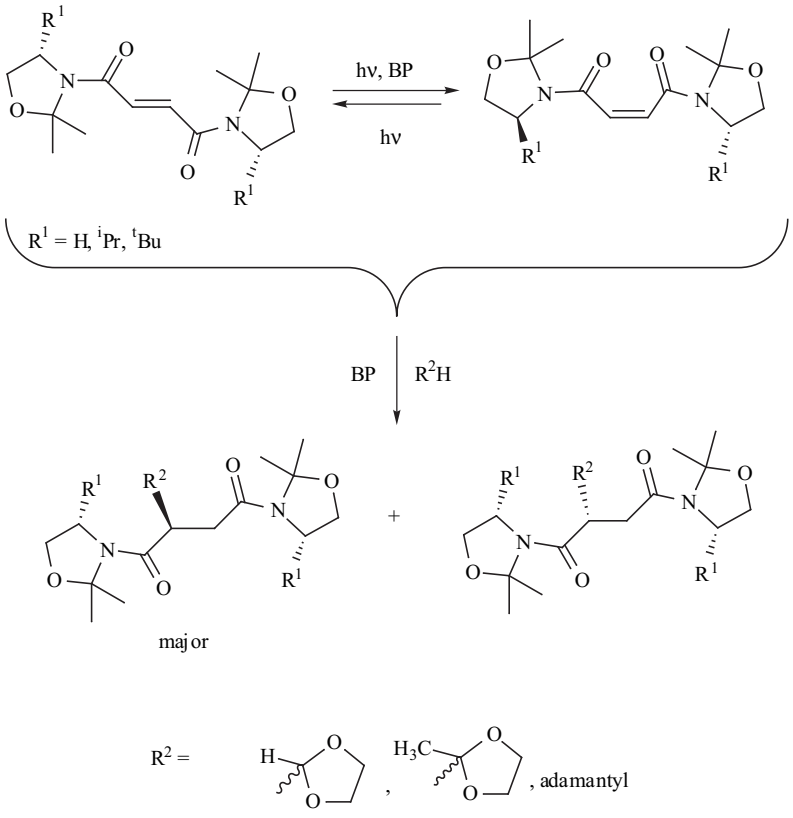


Scheme 8. Photosensitized functionalization of cycloalkanes.



S: benzophenone, benzophenone sodium sulfonate

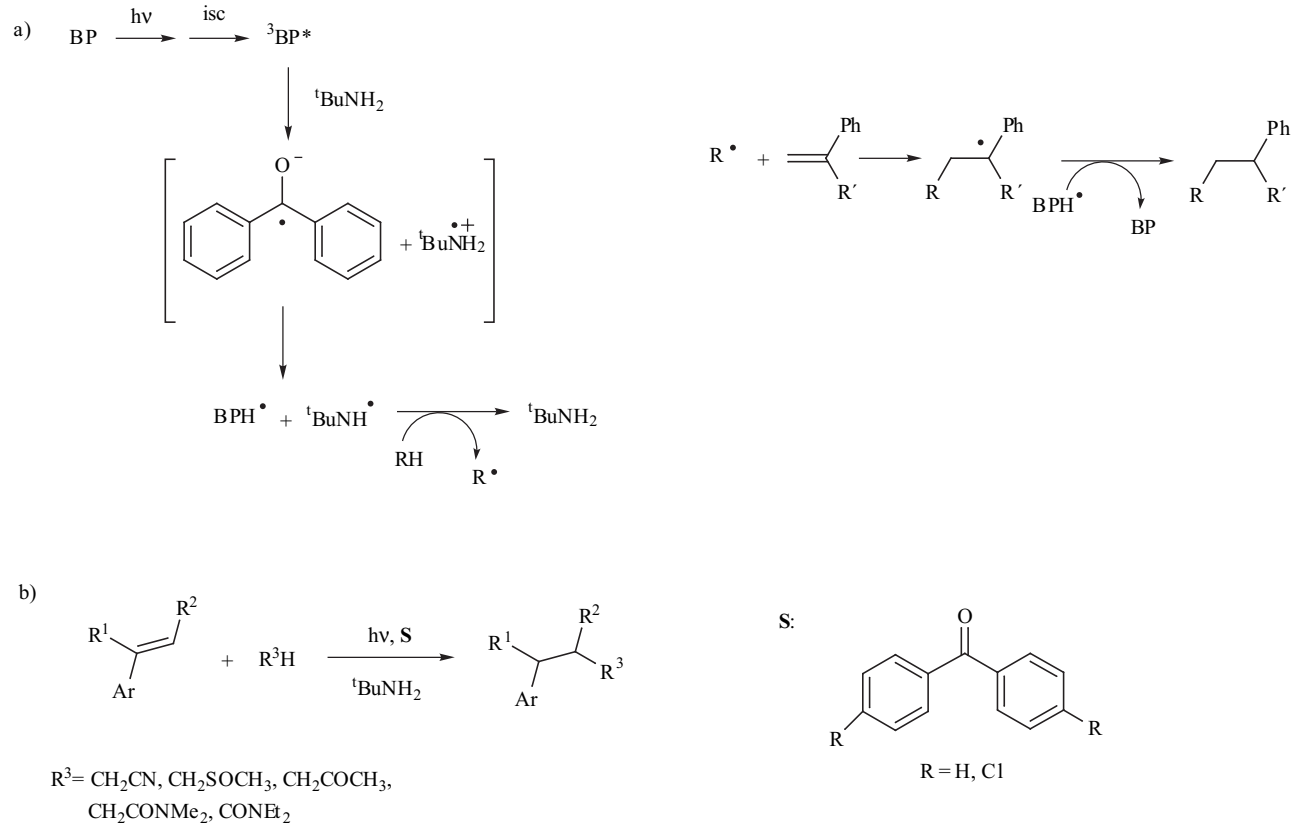
Scheme 9. Photosensitized synthesis of monoprotected 1,4-diketones.



Scheme 10. Photosensitized radical addition to fumaric acid derivatives.

The H-abstraction by triplet benzophenone from alkyl groups attached to electron-withdrawing moieties (cyano and chloro, etc.) is very slow, and the corresponding radical addition to olefins is low-yielding. However, in the presence of tert-butylamine alkylation of diphenylethenes, stilbenes and anethole takes place efficiently with alkylating agents such as methyl ketones, dimethyl sulfoxide and N,N-dialkylamides (Scheme **11**) [19]. Since the presence of the amine is essential for high yield alkylation, the intermediacy of aminyl radicals has been proposed.

A somewhat related process is the regio- and stereoselective addition of tertiary amines to electron-deficient chiral alkenes described by Pete *et al.* [20]. It is based on the generation of α-aminyl radicals by a coupled electron/proton transfer from the amine to the triplet excited state of an aromatic ketone (Scheme **12**). When 4,4′-dimethoxy-benzophenone or 4,4′-dimethylaminobenzophenone are used instead of benzophenone, no sensitizer-derived coupling products are formed. Furthermore, addition of *N*-alkylpyrrolidines to (5*R*)-5-menthyloxy-2-(5*H*)-furanone can



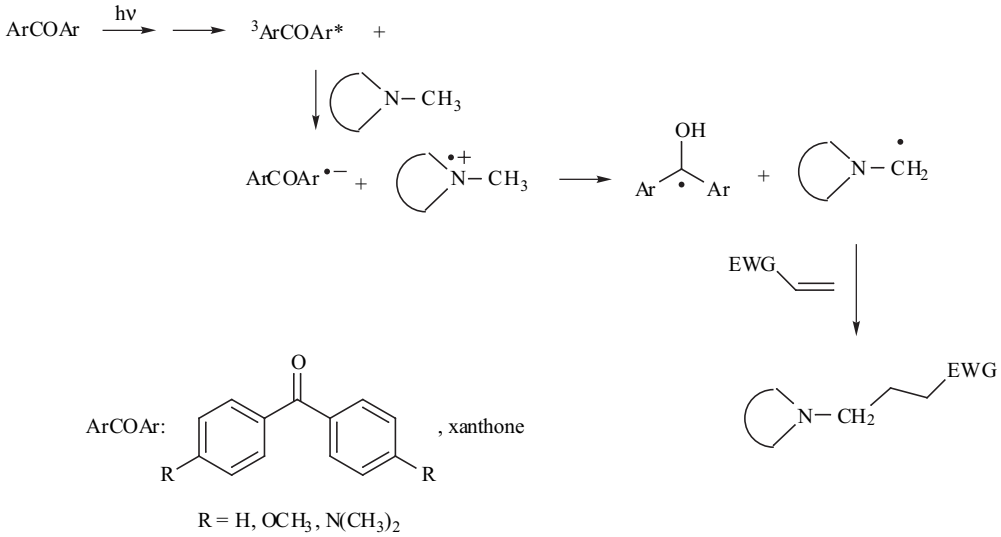
Scheme 11. BP-photosensitized alkylation of arylalkenes using alkyl groups attached to electron-withdrawing moieties.

occur with a complete facial selectivity and in high yield (94%). This method has been applied to the expedient and enantio-selective synthesis of natural products.

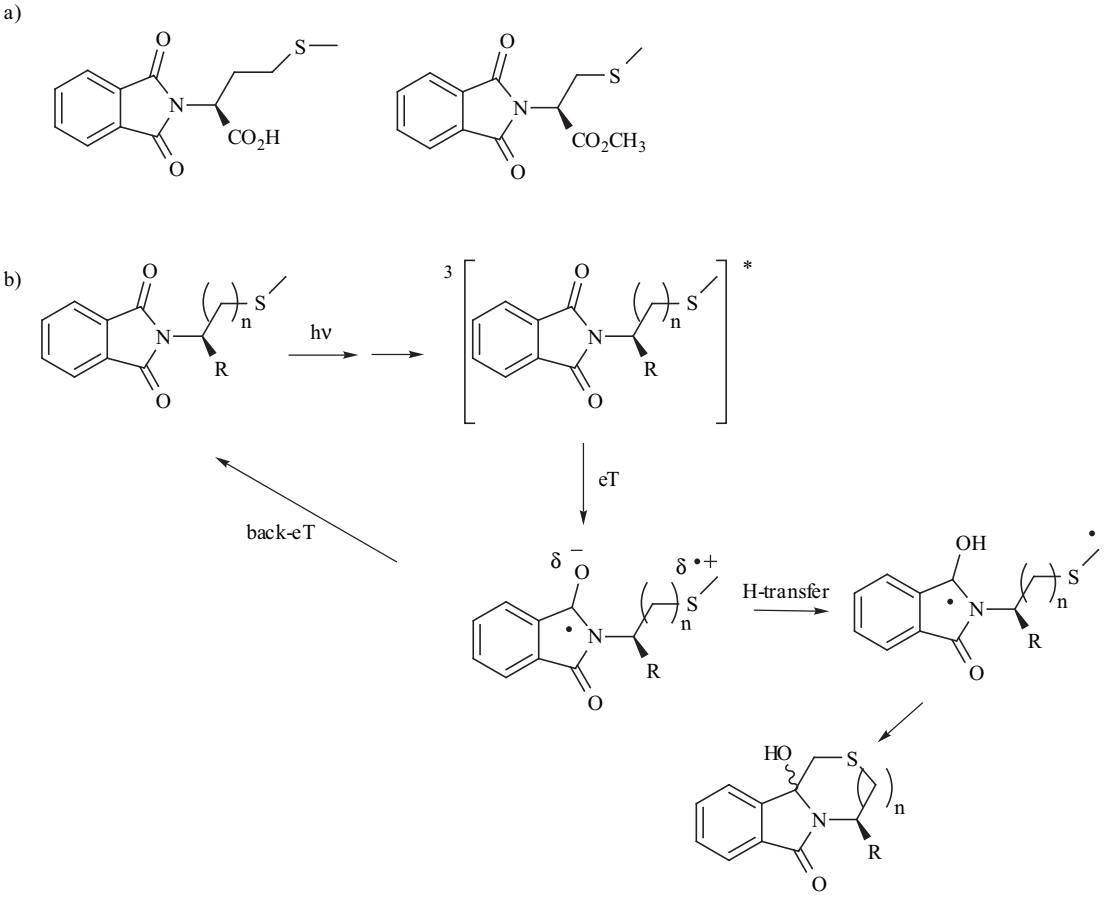
In some cases, benzophenone can generate alkyl radicals through mechanisms different from H-abstraction. Thus, it can mediate the photolysis of 1-iodoperfluorohexane due to the low dissociation energy of the CF_2-I bond, leading to the formation of $C_6F_{13}\cdot$ radicals [21]. Addition of these radicals to 3-propen-1-ol affords $C_6F_{13}CH_2CHICH_2OH$ in 40% yield, which after reduction with tributylstannate gives $C_6F_{13}CH_2CH_2CH_2OH$. This two-step procedure can be extended to the preparation of fluorinated telechelic diols.

Photocyclizations

The photochemical and photophysical behavior of *N*-phthaloylmethionine and *S*-methyl-*N*-phthaloylcysteine methyl ester has been studied by time-resolved spectroscopy (Scheme **13**) [22]. Their lowest excited triplet state seems to have a π,π^* character. However, it has been postulated that photoinduced charge separation taking place in an upper

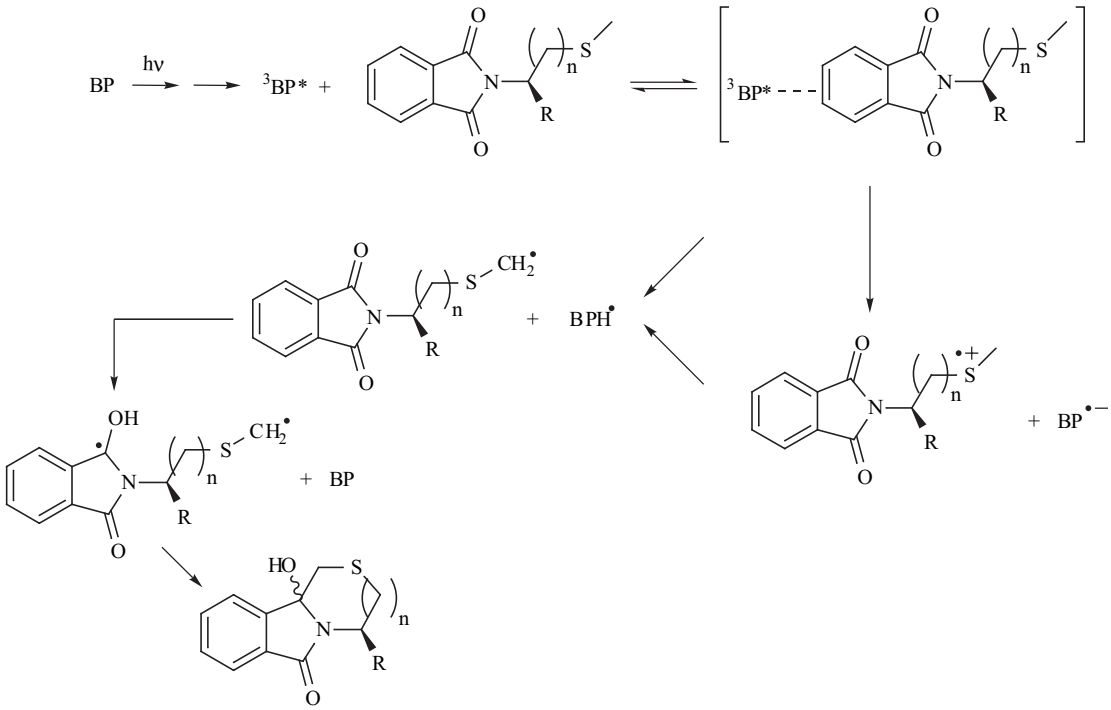


Scheme 12. BP-sensitized addition of tertiary amines to electron-deficient alkenes.



Scheme 13. Cyclization of sulfur- and carboxy-substituted *N*-alkylphthalimides.

n,π* triplet excited state is responsible for their cyclization. Inefficient triplet population and low decompositon quantum yield (< 0.05) has been explained by intramolecular back electron transfer as a major effect.



Scheme 14. BP-sensitized cyclization of sulfur- and carboxy-substituted *N*-Alkylphthalimides.

However, product formation is enhanced under ketone photosensitization. Quenching of the triplet states of acetophenone, xanthone, 4-carboxybenzophenone and benzophenone by these sulfur-containing *N*-alkylphtalimides has been studied in aqueous or acetonitrile solutions. After quenching, practically no phthalimide π,π^* triplet is generated (Scheme **14**). Formation of the photoproduct has been explained as a result of intermolecular electron transfer from thioether to the ketone triplet. This is confirmed by observation of the BP (or 4-carboxybenzophenone) ketyl radical and radical anion.

Photofragmentations: N-O Bond Cleavage

The benzophenone-sensitized photolysis of *O*-benzoyl-*N*-(1-naphthoyl)-*N*-phenylhydroxylamine in organic solvents gives 1-naphthanilide and benzoic acid. These compounds are obtained after fragmentation of the hydroxylamine triplet to give amidyl-benzoyloxy radical pairs, followed by decarboxylation to amidyl-phenyl radical pairs. However, in compartmentalized media, benzoyloxy- and phenyl-migrated products are also formed (Scheme **15**) [23]. Thus, in hexadecyltrimethylammonium chloride (HTAC) micelles, the hydrophobicity of the radical pairs, combined with the high intramicellar viscosity, reduces the rate of cage escape so that intersystem crossing to the singlet pairs becomes competitive, leading to efficient geminate recombination. The same is observed in an anionic micellar medium, such as sodium dodecyl sulfate (SDS), although the 1,5-benzoyloxy-rearranged products are hydrolyzed to *N*-(1-naphthoyl)aminophenols.

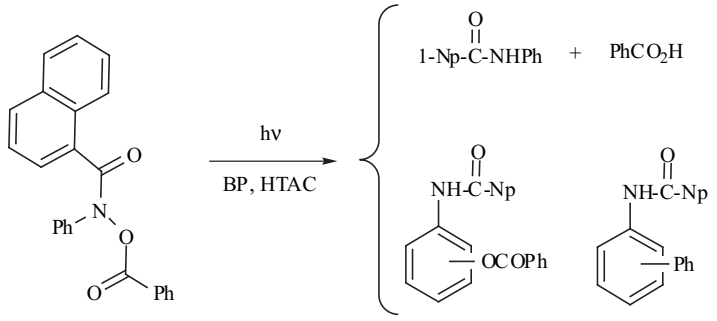
Photocleavage of Dithiane-Carbonyl Adducts

Irradiation of dithiane-carbonyl adducts in the presence of BP leads to C-C bond cleavage with regeneration of the carbonyl compound (Scheme **16**) [24]. The mechanism of this reaction involves electron transfer from the dithiane moiety to the BP triplet excited state. The C-C cleavage in the generated radical-cation is assisted by the BP radical-anion. This protection is compatible with organometallic reagents and constitutes a practical photoremovable group for aldehydes and ketones.

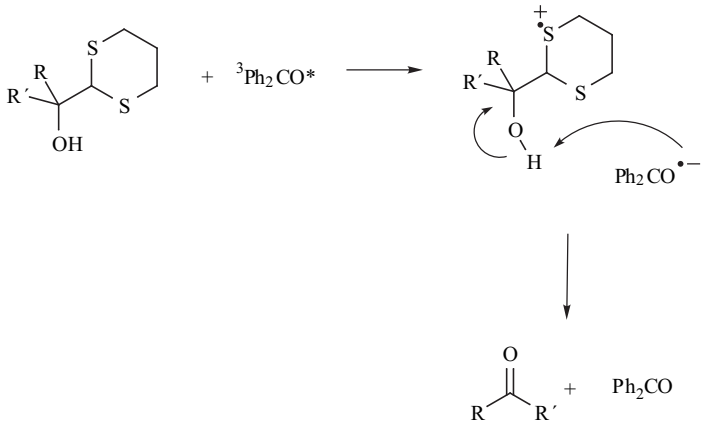
Photosensitized Ring-Opening

Energy transfer from BP triplet to 3-(1-naphthyl)-2-(1-naphthalenemethyl)oxaziridine affords 1-naphthaldehyde and 1-(1-naphthoyl)-1-naphthalenemethylamine as main products (Scheme **17**) [25]. Cleavage of the N-O bond in the oxaziridine triplet gives rise to a biradical whose fragmentation leads to the aldehyde and the triplet nitrene; alternatively, intersystem crossing to the singlet followed by hydrogen shift affords the amide.

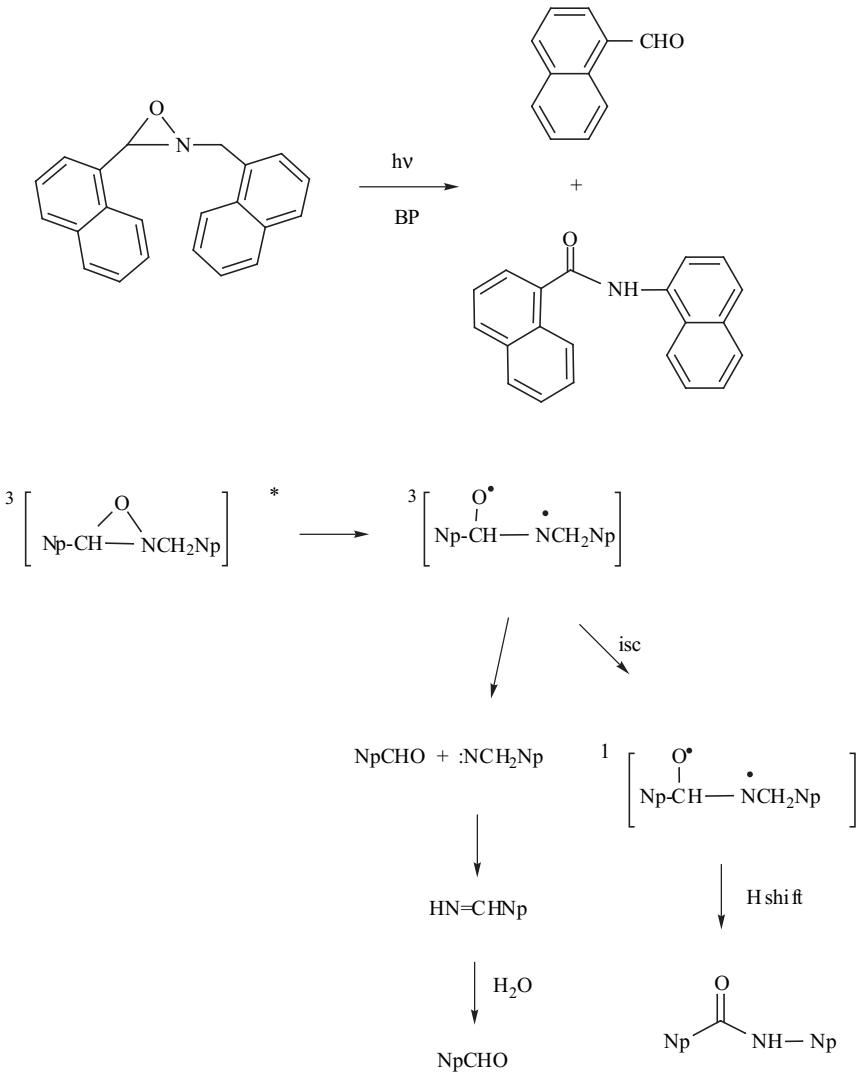
In low-temperature matrices (Ar matrix, 10 K), BP-photosensitized rearrangement of 3-methyl-2-(1-naphthyl)-2*H*-azirine leads to a ketene imine, involving the formation of a hot biradical by C-N bond cleavage of the azirine triplet (Scheme **18**) [26]. In the presence of oxygen, the formation of the ketene imine was quenched and the corresponding aldehyde and acetonitrile oxide is obtained. However, in solution, the hot biradical relaxes to the vibrationally ground state, by collisional interaction with solvent molecules, and



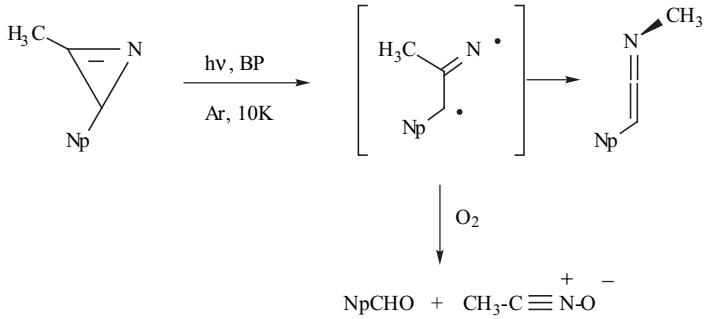
Scheme 15. BP-sensitized photolysis of hydroxylamines in cationic micellar media.



Scheme 16. Photoremovable protecting groups of ketones and aldehydes.



Scheme 17. Photosensitized ring-opening of an oxaziridine.

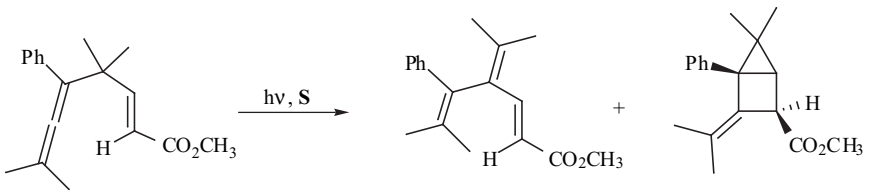


Scheme 18. Photosensitized rearrangement of 2*H*-azirines in low-temperature matrices.

reverts to the starting material. Then, no products derived from the ketene imine are obtained.

Photoisomerizations

Direct photolysis of γ-(3-methyl-1-phenyl-1,2-butadienyl)-substituted α,β-unsaturated esters and nitriles gives the [2+2]cycloadduct, cross-conjugated trienes and several other photoproducts arising from intramolecular processes (Scheme **19**) [27]. By contrast, triplet–sensitization with aromatic ketones leads only to the cycloadduct and the triene. The photochemoselectivity of the photosensitized process depends on the substituents of the vinyl group and the energy of the triplet sensitizer. Thus, in the case of the 1,1-bismethoxycarbonyl-3,3,6-trimethyl-4-phenyl-1,4,5-heptatriene, acetophenone sensitization (E_T = 310 *k*J mol^{-1}) produces isomerization to the triene and the cycloadduct, while benzophenone (E_T = 287 *k*J mol^{-1}) leads mainly to the triene. With 2-benzoylpyridine as photosensitizer (E_T = 279 *k*J mol^{-1}), only formation of the



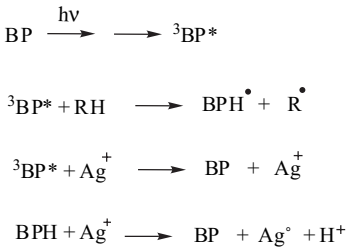
S:	Φ	Φ
Acetophenone	0.37	0.016
Benzophenone	0.29	0.0018
2-Benzoylpyridine	0.16	<0.0001

Scheme 19. Ketone-photosensitized processes of allenyl(vinyl)methanes.

trienes is observed in significant amounts. This behavior is rationalized by assuming that the triplet excited states of the allene or vinyl moiety give rise selectively to the cross-conjugated triene or the [2+2]cycloadduct, respectively.

Photoreduction

BP photosensitizes the reduction of Ag^+ ions in BP-$AgClO_4$-SDS micellar solutions (Scheme **20**) [28]. The mechanism and kinetics of this process have been recently elucidated. It has been found that upon hydrogen abstraction from SDS, the resulting benzophenone ketyl radical reduces Ag^+ ions by an electron transfer process. However, the yield of colloidal Ag nanoparticle formation decreases remarkably with the increase of Ag^+ concentration due to efficient quenching of BT triplet by the Ag^+ ions.



Scheme 20. Ketone-photosensitized formation of colloidal Ag nanoparticles.

DIARYL KETONES AS PHOTOSENSITIZERS IN PHOTOCROSSLINKING

Photoinitiated Radical Polymerization

The photochemical crosslinking of acrylated coatings by ultraviolet or visible light has become an established technology for many industrial applications, including wood coatings, lithographic inks, textile industry or optical fibre coatings. Several types of photoinitiators have been developed for this purpose. After light absorption, radical photoinitiators give rise to free radicals that add to the monomer, inducing a chain process and leading to a highly crosslinked film. Diaryl ketones, such as benzophenone, undergo hydrogen atom abstraction from the environment, with the resin or a solvent acting as donors. In general, addition of tertiary amines enhances their efficiency (Scheme **21**) [29]. In this case, it has been suggested that the ketone forms an exciplex with the amine; then electron transfer occurs, leading to the main initiating radicals, namely the α-aminyl radicals. Alkyl- and arylthio-substituted benzophenones exhibit much higher activity than benzophenone, which has been associated with their higher extinction coefficients, longer wavelength absorption maxima in the near UV region above 300 nm and additional radical formation arising from side chain scission [30].

Development of polymeric photoinitiators based on binding of benzophenone to pre-polymers, in order to overcome the problems of initiator migration, lower volatiles and food contamination, is a subject of industrial interest. Photocuring studies indicate that binding of 4-hydroxybenzophenone to melamine and urethane acrylate prepolymers enhances its efficiency as photoinitiator, Fig. (**2**) [31].

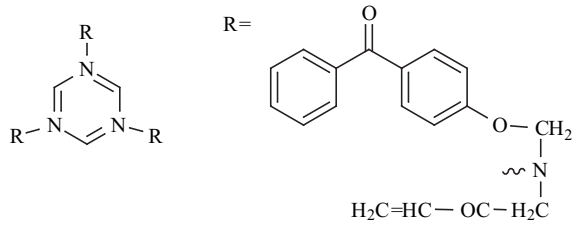
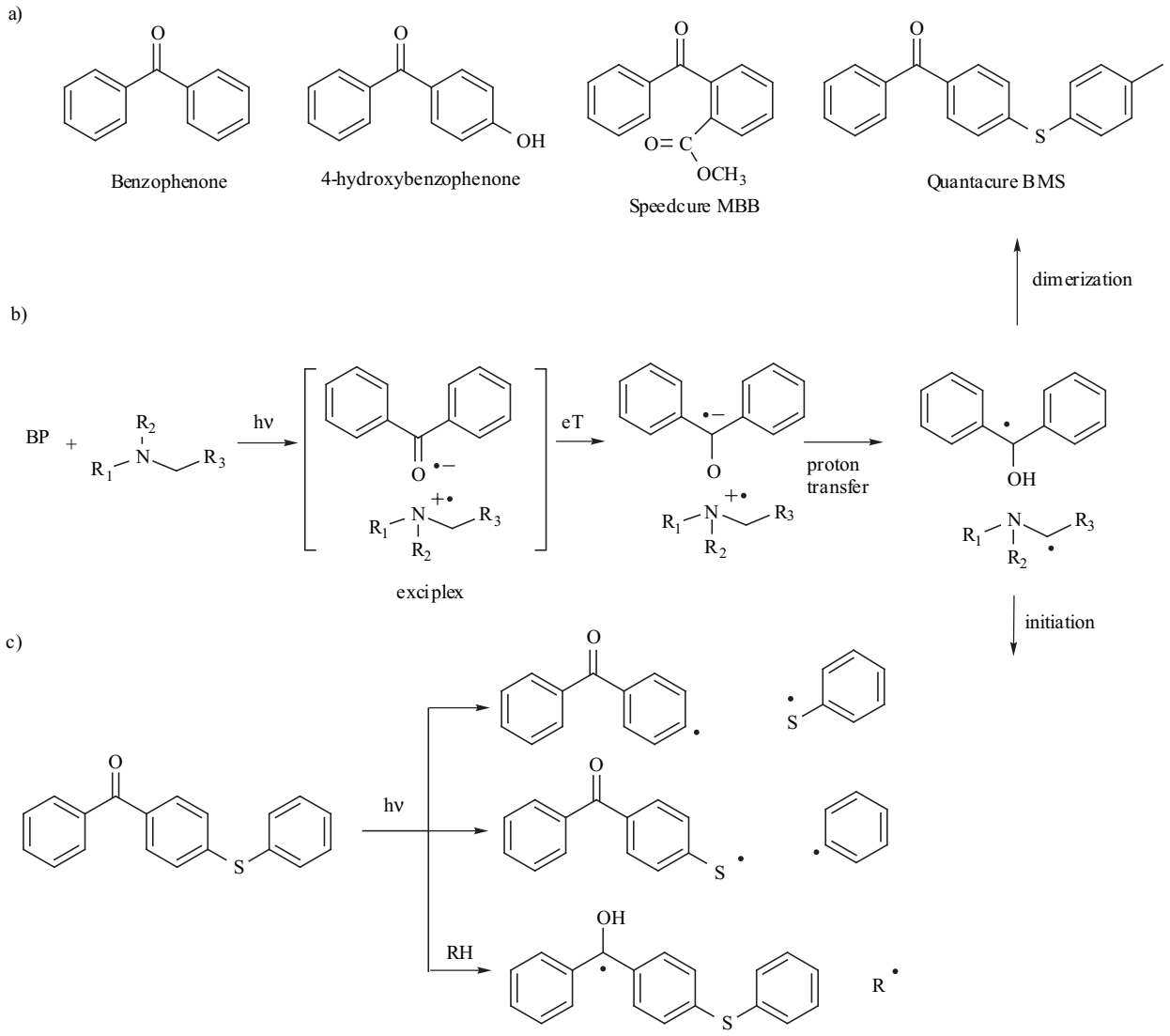


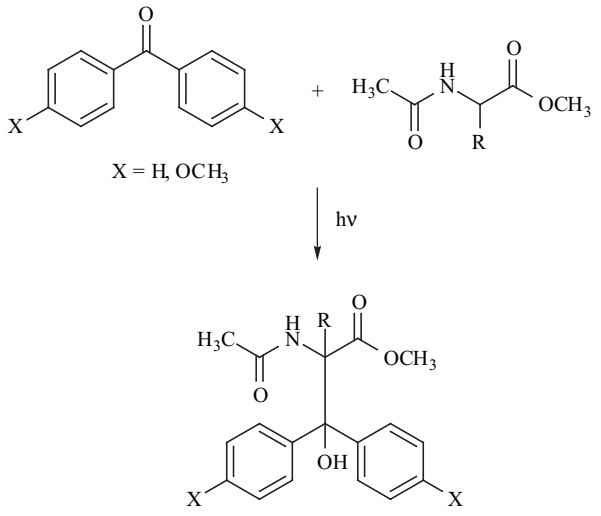
Fig. (2). 4-Hydroxybenzophenone modified melamine acrylate.

Benzophenones have also been extensively used as crosslinkers to study the structure, function and interactions of proteins. The strategy is based on radical coupling after hydrogen atom abstraction by the benzophenone triplet excited state from protein constituents (Scheme **22**) [32]. Sequencing of the resulting linked peptides under mild conditions allows to determine the site of photoprobe (benzophenone) incorporation, process known as photolabeling. Thus, in order to elucidate the topography of glycophorin A in membranes, a systematic study of the photoalkylation of 10 lipophilic amino acids by benzophenone has been performed. A rank order of relative chemical reactivities has been established; methionine stands out because of its reactivity and the chemical stability of the photocross-linked products.

A benzophenone dimer, connected by a flexible diamine tether, has been found to present photophysical properties different from those of benzophenone, Fig. (**3**) [33]. It displays a new absorption band at λ_{max} *ca.* 370 nm arising from charge transfer interaction. This dimer has shown high efficiency in achieving cross-linking of collagen (sluggishly reactive towards that process) to form robust structures that may have biomedical applications.



Scheme 21. Ketone-photosensitized radical polymerization.



Scheme 22. Photochemical reaction between amino acids and benzophenones.

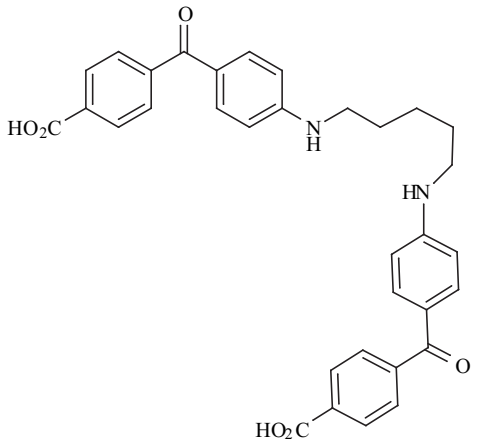
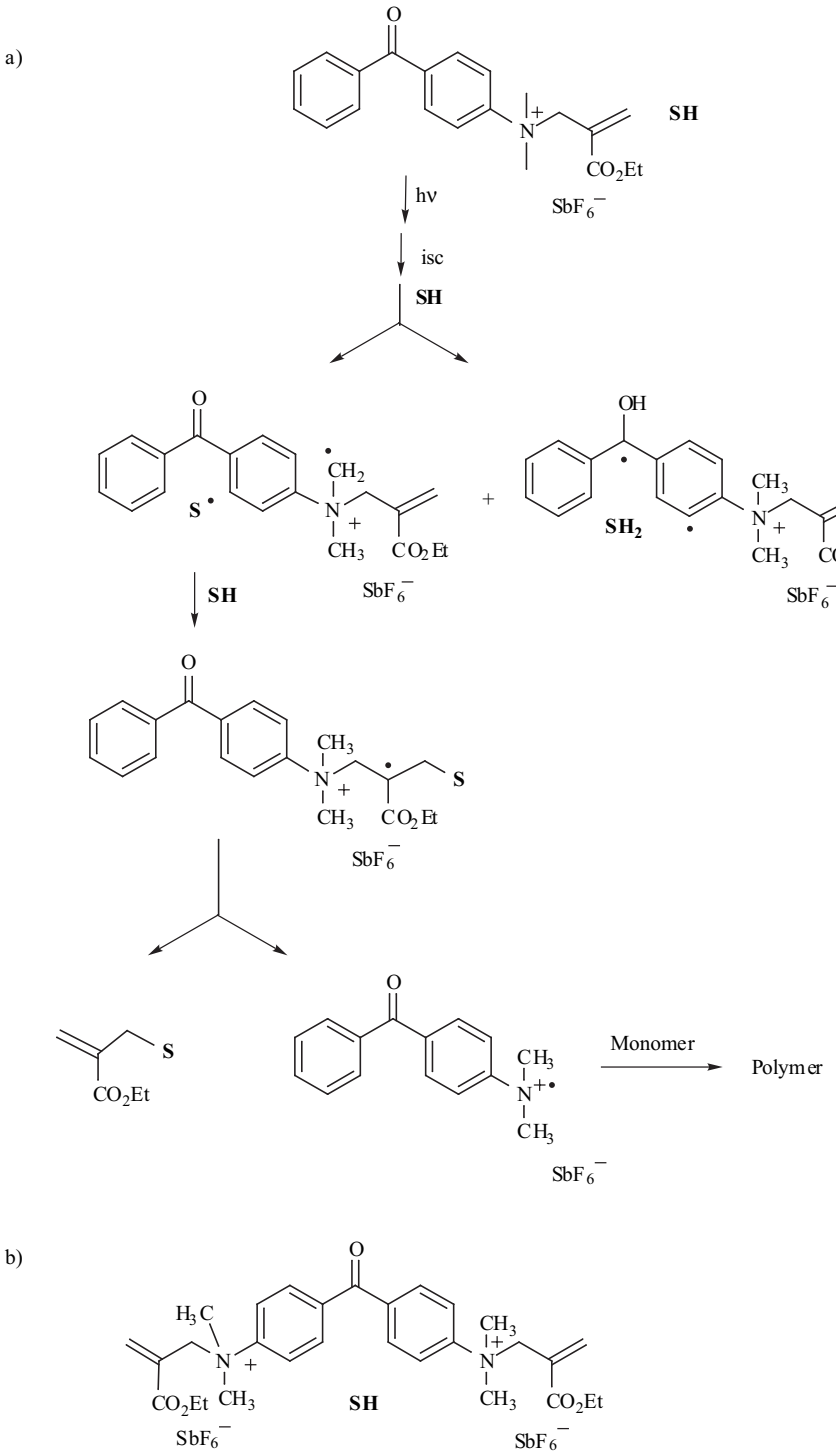


Fig. (3). Benzophenone dimer conneted by a flexible diamine tether.

Photoinitiated Cationic Polymerization

This type of polymerization can be performed using allyl onium salts in the presence of benzophenone as sensitizer.



Scheme 23. A benzophenone containing allyl ammonium salt as photosensitizer in cationic polymerization.

However, photosensitization may be disadvantageous in that sensitizer diffusion becomes slower as the viscosity of the system increases. To overcome this problem, a benzophenone containing allyl ammonium salt in its structure has been used as a self-initiating addition fragmentation agent in the cationic polymerization of oxiranes (i.e., cyclohexene oxide) and vinyl monomers (butylvinyl ether or *N*-vinyl carbazole). The bifunctional initiator was more active in inducing crosslinking process than the monofunctional one (Scheme **23**) [34].

DIARYL KETONES AS PHOTOSENSITIZERS IN THE DESULFURATION OF DIESEL FUEL

A deep desulfurization of light oil has been reported based on benzophenone photosensitized oxidation using a two-phase oil/aqueous H_2O_2 system [35]. Although benzophenone is capable of sensitizing the formation of excited dibenzothiophenes (DBTs), desulfurization hardly proceeds in the presence of naphthalene (NP) due to triplet energy transfer from either photoexcited DBT or benzophenone to ground-state NP (Scheme **24**). Hydrogen

peroxide oxidizes the excited DBT and thus interrupts the energy transfer to NP. In this way, the sulfur content of commercial light oil reduces from 0.2 to 0.05 wt % after 48 h of irradiation. The photodecomposed sulfur-containing compounds are extracted by the water phase; there they are removed using column adsorption with aluminum oxide so that the recovered H_2O_2 solution is reusable. This system is also able to remove nitrogen-containing compounds present in light oil simultaneously with sulfur-containing compounds [36].

$$^3BP^* + DBT \longrightarrow BP + {}^3DBT^*$$

$$^3BP^* + NP \longrightarrow BP + {}^3NP^*$$

Scheme 24. Energy transfer from BP triplet to DBT or NP.

Benzophenone-modified silica gel (SG-BP) has been used as a heterogeneous triplet photosensitizer [37]. Although the efficiency of SG-BP is relatively lower than that of homogeneous BP, the sulfur content of light oil is reduced from 0.18 to less than 0.05 wt% after 60 h of photoirradiation.

DIARYL KETONES AS PHOTOSENSITIZERS IN THE DRUG-MEDIATED MODIFICATION OF BIOMOLECULES

Benzophenone-derived drugs, Fig. (**4**) can photosensitize modification of biomolecules ultimately producing phototoxic side effects in patients [38]. The ketone triplet excited state can be involved in hydrogen abstraction and electron or energy transfer processes (Scheme **25**). In some cases, such as amiodarone, aryl radicals generated by photodehalogenation from the triplet are responsible for the observed adverse effects.

Photosensitized Modification of Unsaturated Lipids

Photooxidation of unsaturated lipids is claimed to be responsible for cell-damaging processes. Model fatty acids containing double allylic systems (linoleic acid and 1,4-cyclohexadienes) have been used to distinguish between photoperoxidation occurring *via* radicals (b and c in Scheme **25**) or singlet oxygen (d in Scheme **25**) [39]. Product studies show that drugs with the 2-benzoylthiophene (BT) chromophore photosensitize lipid peroxidation by both types of mechanisms, although the former contributes to a higher extent (Scheme **26**) [40]. By contrast, only the radical mechanism operates in the case of the analogous benzophenone drug. The results are attributed to the different nature of the lowest-lying triplet state of the BT chromophore (π,π^*) as compared to BP ($n\ \pi^*$). Thus, BT triplet abstracts hydrogen from suitable donors with rate constants *ca* two orders of magnitude lower than BP triplet; however, it efficiently sensitizes singlet oxygen production.

Photosensitized Modification DNA

Studies on DNA photooxidation induced by BPs have shown that these compounds promote DNA damage through energy transfer, hydrogen abstraction and one-electron oxidation [41]. By using 2´-deoxyguanosine (dGuo), it has been shown that at high dGuo concentrations, BP photooxidation occurs *via* electron transfer, through the nucleoside radical cations (Scheme **27**). These radical cations are subsequently transformed into the final products by well-established steps. The predominanting formation of oxazolone has been rationalized as due to rapid deprotonation of the dGuo radical cation before nucleophilic attack by water. Although no 8-oxodGuo was detected, its generation cannot be rejected.

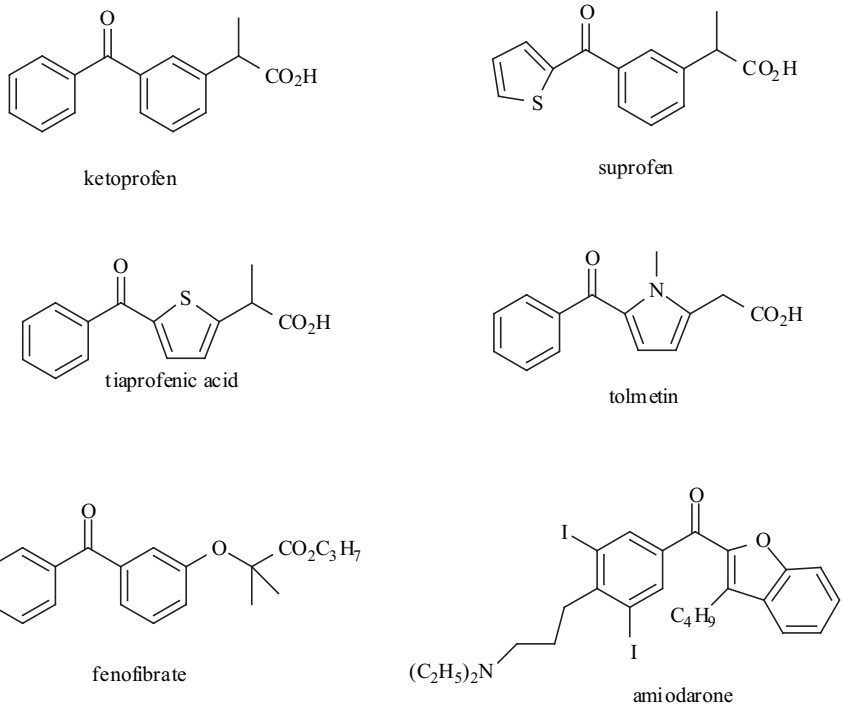
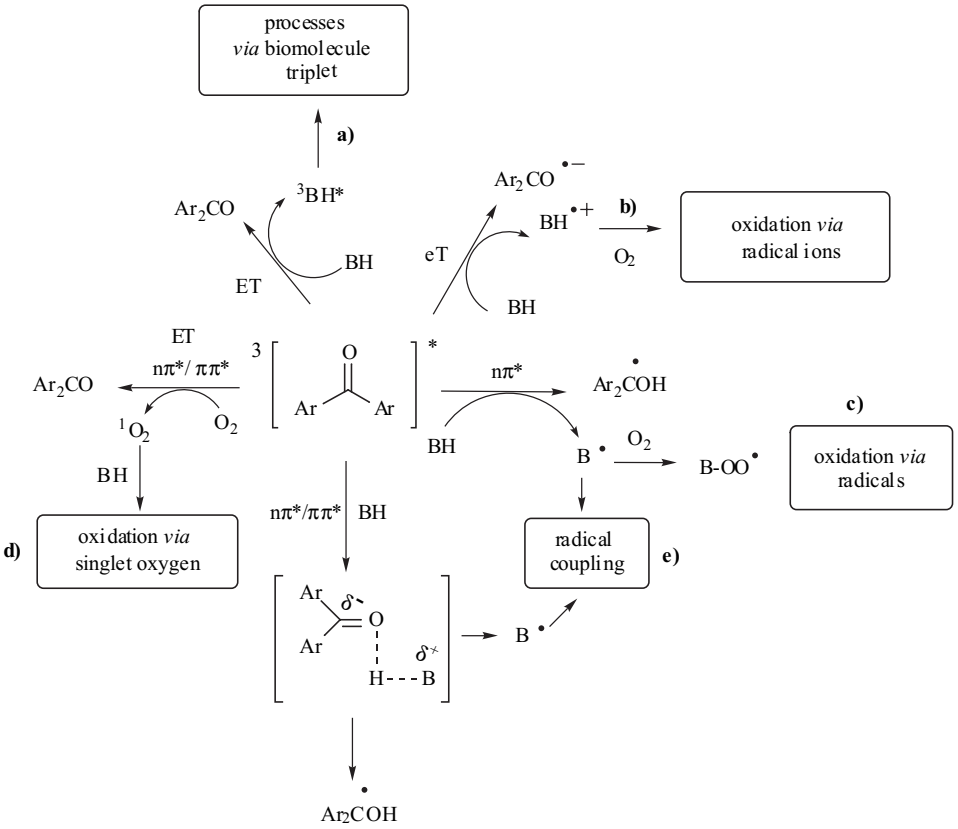
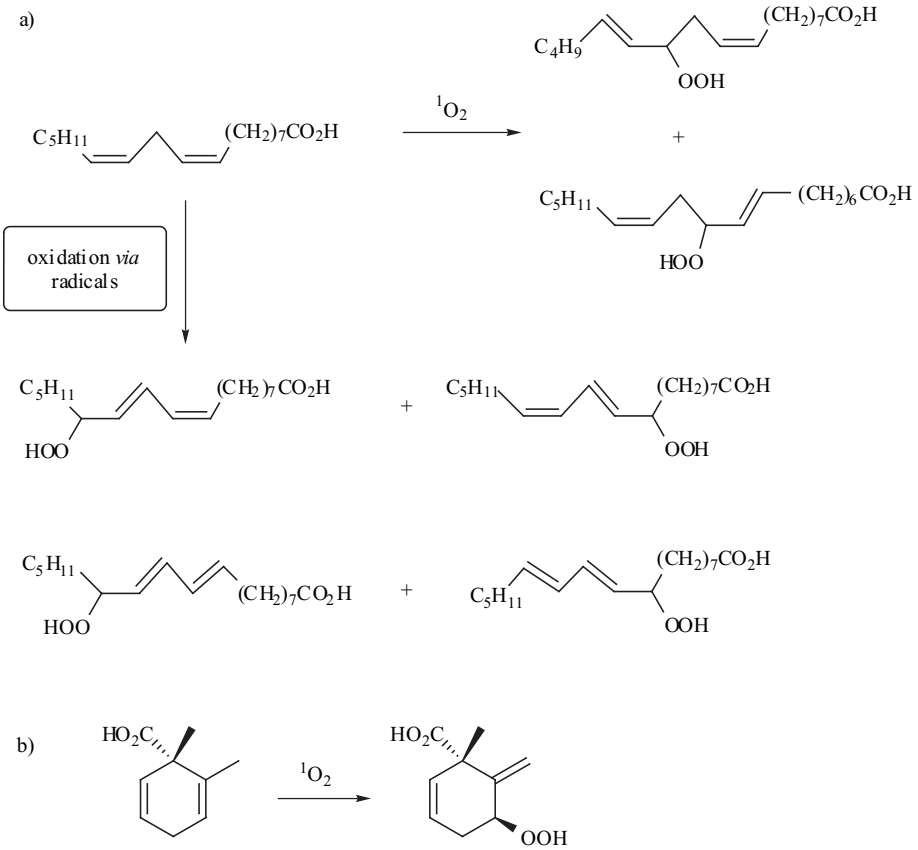


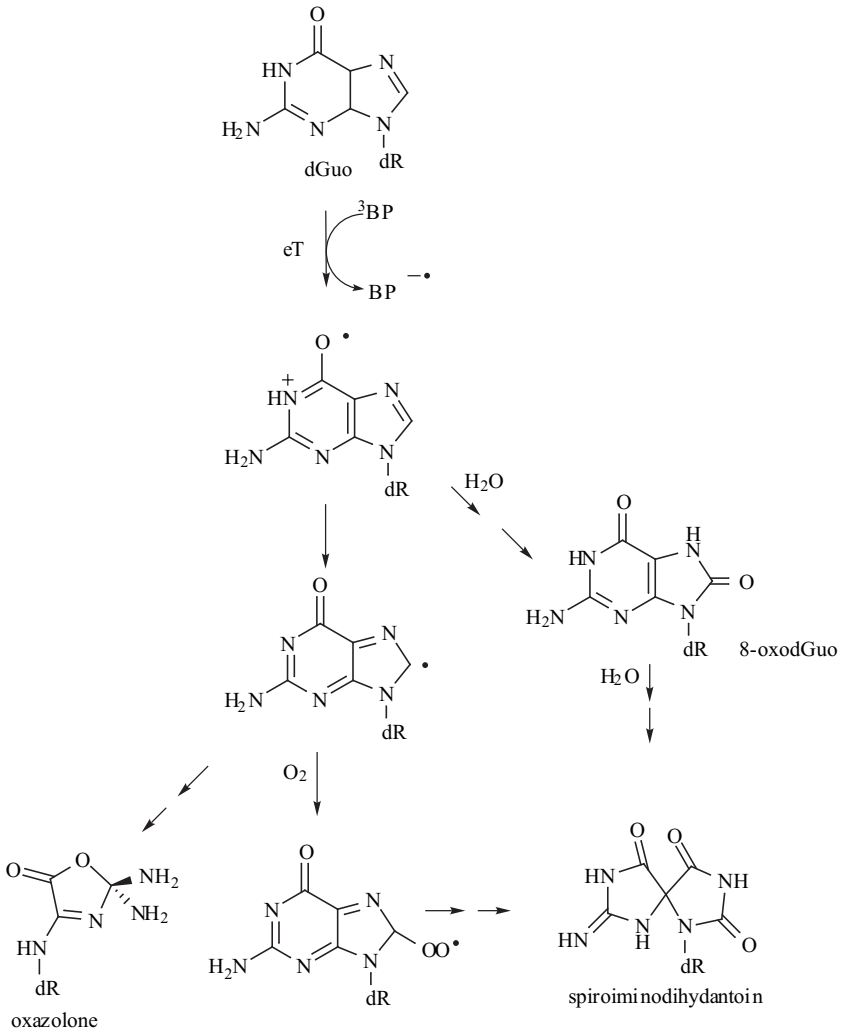
Fig. (4). Benzophenone-derived drugs.



Scheme 25. Processes involved in biomolecules modification photosensitized by diarylketones.



Scheme 26. Lipid photoperoxidation of model unsaturated lipids induced by the BT chromophore.



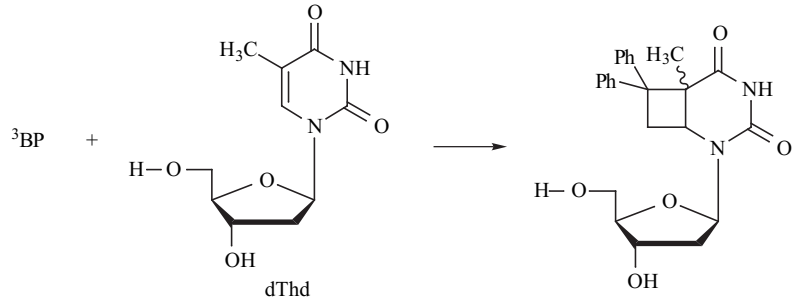
Scheme 27. Proposed mechanism for the photooxidation of dGuo.

On the other hand, studies on photosensitization of thymine nucleobase by benzophenone derivatives (benzophenone, ketoprofen and fenofibrate, Fig. (**4**)) have shown that although there is a strong interaction between the BP triplet and the base, neither triplet-triplet energy transfer nor electron transfer appear to play a major role [42]. Indeed, a Paterno-Büchi cycloaddition is the predominanting process (Scheme **28**). The same is true in thymidine; however, in the DNA, the contribution of energy transfer could be higher, due to the lower energy of the base triplet in the macromolecule. Hence, formation of dimers might be the predominanting process in DNA [43].

Photosensitized Modification of Proteins

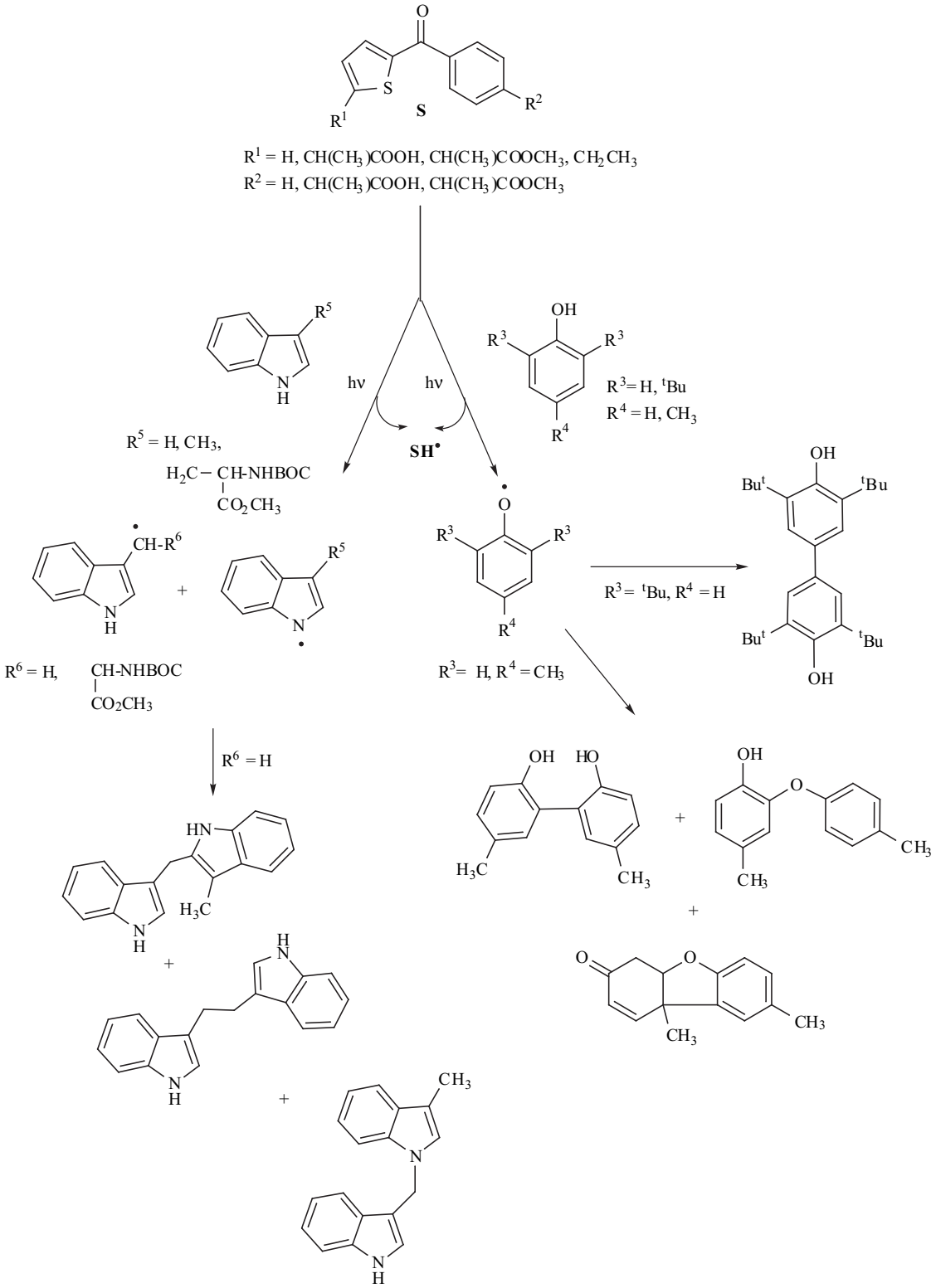
As mentioned above, the diaryl ketones have been extensively used as crosslinkers to study the structure, function and interactions of proteins, due to their ability to abstract hydrogen from the C-H bonds of amino acids. Besides, as in the case of the 2-benzoylthiophene chromophore, they can photosensitize protein modification by electron-transfer processes.

Thus, His, Tyr and Trp have been found to be the reactive sites of model protein (serum albumin) upon photosensitization with tiaprofenic acid (Fig. (**4**)) [44]. In



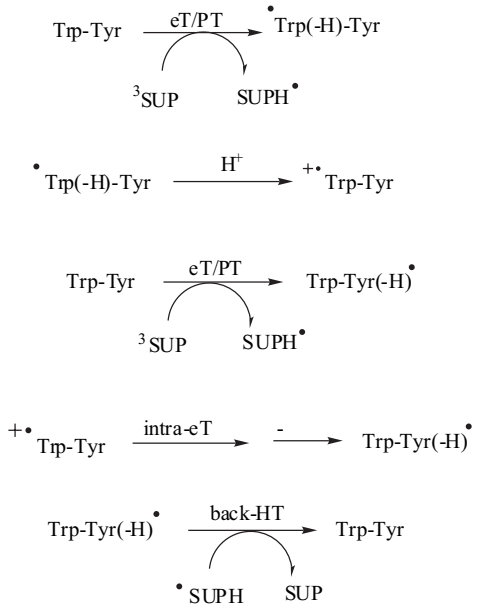
Scheme 28. Formation of oxetanes by irradiation of BP and dThd.

this context, studies have been performed to determine the nature of the chemical changes taking place upon irradiation of phenols and indoles, models for the protein modification (Scheme **29**) [45]. It has been shown that phenoxy radicals and ketyl radicals are formed through a concerted electron and proton transfer, where a hydrogen-bonded exciplex BT---HOPh is involved. The main products derived from the phenolic substrates are homodimers, though cross-coupling products between the ketone and the phenolic derivatives are also isolated. In the case of the indolic substrates, besides the indolyl radical, formation of skatolyl radicals has also been evidenced by means of time-resolved and product studies.



Scheme 29. Promoted modification of protein models by BTs chromophores.

Furthermore, it has been recently demonstrated that suprofen (Fig. (**4**)) photosensitizes the intra-eT reactions in Trp-Tyr and Trp-Gly-Tyr peptides (Scheme **30**) [46]. Besides, the influence of the photosensitizer configuration on the involved processes has been studied using the enantiomerically pure compounds. The obtained data show that the photosensitizer chirality influences the concentration of the radicals formed after triplet quenching, what could be of biological relevance.



Scheme 30. Benzoylthiophenes as photosensitizers in intramolecular eT reactions in Trp-Tyr peptides.

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REFERENCES

[1] Gilbert, A.; Baggot, J. In *Essentials of Molecular Photochemistry,* Blackwell Scientific Publications, Oxford, **1991**.

[2] Arnold, D.R.; Hadjiantoniou, C.P. *Can. J. Chem.*, **1978**, *56*, 1970; Arnold, D.R.; Birtwell, R.J.; Clarke, Jr. B.M. *Can. J. Chem.*, **1974**, *52*, 1681; Romani, A.; Ortica, F.; Favaro, G. *Chem. Phys.*, **1998**, *237*, 413; Ortica, F.; Romani, A.; Favaro, G. *J. Phys. Chem. A.*, **1999**, *103*, 1335.

[3] Coenjarts, C.; Scaiano, J.C. *J. Am. Chem. Soc.*, **2000**, *122*, 3635.

[4] Boscá, F.; Cosa, G.; Miranda, M.A.; Scaiano, *J.C. Photochem. Photobiol. Sci.*, **2002**, *1*, 704.

[5] Bhasikuttan, A.C.; Singh, A.K.; Palit, D.K.; Sapre, A.V.; Mittal, J.P. *J. Phys. Chem. A.*, **1998**, *102*, 3470

[6] Wagner, P.J.; Kemppainen, A.E.; Schott, H.N. *J. Am. Chem. Soc.*, **1973**, *95*, 5604.

[7] Pownall, H.J.; Huber, J.R. *J. Am. Chem. Soc.*, **1971**, *93*, 6429.

[8] Turro, N.J.; Gould, I. R.; Liu, J.; Jenks, W.S.; Staab, H.; Alt, R. *J. Am. Chem. Soc.,* **1989**, *111*, 6378.

[9] Querner, J.; Scheller, D.; Wolff, T. *J. Photochem. Photobiol. A: Chem.*, **2002**, *150*, 85.

[10] Shichi, T.; Takagi, K.; Sawaki, Y. *Clay Science*, **1999**, *10*, 503.

[11] Cauble, D.F.; Lynch, V.; Krische, M.J. *J. Org. Chem.*, **2003**, *68*, 15.

[12] Pérez-Prieto, J.; Stiriba, S.E.; González-Béjar, M.; Domingo, L.R.; Miranda, M.A. *Org. Lett.*, **2004**, *6*, 3905.

[13] Mizuno, K.; Sugita, H.; Hirai, T.; Maeda, H.; Otsuji, Y.; Yasuda, M.; Hashiguchi, M.; Shima, K. *Tetrahedron Lett.*, **2001**, *42*, 3363.

[14] Kraus, G.A.; Kirihara, M. *J. Org. Chem.*, **1992**, *57*, 3256.

[15] Pacut, R.; Grimm, M.L.; Kraus, G.A.; Tanko, J.M. *Tetrahedron Lett.*, **2001**, *42*, 1415.

[16] Geraghty, N.W.A.; Hannan, J.J. *Tetrahedron Lett.*, **2001**, *42*, 3211.

[17] Mosca, R.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron*, **2001**, *57*, 10319; Manfrotto, C.; Mella, M.; Freccero, M.; Fagnoni, M.; Albini, A. *J. Org. Chem.*, **1999**, *64*, 5024.

[18] Campari, G.; Fagnoni, M.; Mella, M.; Albini, A. *Tetrahedron: Asymmetry*, **2000**, *11*, 1891.

[19] Yamashita, T.; Watanabe, M.; Kojima, R.; Shiragami, T.; Shima, K.; Yasuda, M. *J. Photochem. Photobiol. A: Chem.*, **1998**, *118*, 165.

[20] Bertrand, S.; Hoffmann, N.; Pete, J.P. *Eur. J. Org. Chem.*, **2000**, 2227; Wang, Z.Y.; Jian, T.Y.; Chen, Q.H. *Chin. Chem. Lett.*, **1999**, *10*, 889.

[21] Lahiouhel, D.; Ameduri, B.; Boutevin, B. *J. Fluorine C.*, **2001**, *107*, 81.

[22] Görner, H.; Griesbeck, A.G.; Heinrich, T.; Kramer, W.; Oelgemöller, M. *Chem. Eur. J.*, **2001**, *7*, 1530.

[23] Kaneko, T.; Tokue, T.; Kubo, K.; Sakurai, T. *Bull. Chem. Soc. Jpn.,* **1999**, *72*, 2771; Kaneko, T.; Tokue, T.; Kubo, K.; Sakurai, T.J. *Chem. Res.*, **1999**, 644.

[24] McHale, W.A.; Kutateladze, A.G. *J. Org. Chem.*, **1998**, *63*, 9924.

[25] Ohba, Y.; Kubo, K.; Sakurai, T. *J. Photochem. Photobiol. A, Chem.*, **1998**, *113*, 45.

[26] Inui, H.; Murata, S. *Chem. Phys. Lett.*, **2002**, *359*, 267.

[27] Tsuno, T.; Hoshino, H.; Okuda, R.; Sugiyama, K. *Tetrahedron*, **2001**, *57*, 4831.

[28] Kometani, N.; Doi, H.; Asami, K.; Yonezawa, Y. *Phys. Chem. Chem. Phys.*, **2002**, *4*, 5142.

[29] Allen, N.S.; Marin, M.C.; Edge, M.; Davies, D.W.; Garret, J.; Jones, F.; Navaratnam, S.; Parsons, B.J. *J. Photochem. Photobiol. A: Chem.*, **1999**, *126*, 135.

[30] Allen, N.S.; Corrales, T.; Edge, M.; Catalina, F.; Blanco-Pina, M.; Green, A. *Polymer*, **1998**, *39*, 903; Li, H.; Gu, J.; Yu, S. *J. Radiat. Res. Radiat. Proces.*, **2000**, *18*, 81.

[31] Wu, Q.; Qu, B. *J. Appl. Polym. Sci.*, **2002**, *85*, 1581.

[32] Deseke, E.; Nakatani, Y.; Ourisson, G. *Eur. J.Org. Chem*., **1998**, 243.

[33] Pitts, J.D.; Howell, A.R.; Taboada, R.; Banerjee, I.; Wang, J.; Goodman, S.L.; Campagnola, P.J. *Photochem. Photobiol*., **2002**, *76*, 135.

[34] Yurteri, S.; Onen, A.; Yagci, Y. *Eur. Polym. J*., **2002**, *38*, 1845.

[35] Hirai, T.; Shiraishi, Y.; Ogawa, K.; Komasawa, I. *Ind. Eng. Chem. Res.*, **1997**, *36*, 530; Shiraishi, Y: Hara, H.; Hirai, T.; Komasawa, I. *Ind. Eng. Chem. Res.*, **1999**, *38*, 1589.

[36] Shiraishi, Y.; Hirai, T.; Komasawa, I. *Solv. Extr. Res. Dev. Japan*, **2002**, *9*, 121.

[37] Shiraishi, Y.; Hirai, T. *Solv. Extr. Res. Dev. Japan*, **2003**, *10*, 79.

[38] Boscá, F.; Miranda, M.A. *J. Photochem. Photobiol.*, **1998**, *43*, 1.

[39] Samadi, A.; Martínez, L.A.; Miranda, M.A.; Morera, I.M. *Photochem. Photobiol.*, **2001**, *73*, 359

[40] Bosca, F.; Miranda, M.A.; Morera, I.M.; Samadi, A. *J. Photochem. Photobiol. B: Biol.*, **2000**, *58*, 1; De la Peña, D.; Martí, C.; Nonell, S.; Martínez, L.A.; Miranda, M.A. *Photochem. Photobiol*., **1997**, *65*, 828

[41] a) Starrs, S.M.; Davies, J.H. **2000**, *72*, 291; Adam, W.; Arnold, M.A.; Nau, W.M.; Pischel, U.; Saha-Möller, C.R. *J. Am. Chem. Soc*., **2002**, *124*, 3893; b) Lhiaubet, V.; Paillous, N.; Chouini-Lalanne, N. *Photochem. Photobiol.*, **2001**, *74*, 670; c) Delatour, T.; Douki, T.; D´Ham, C.; Cadet, J. *J. Photochem. Photobiol. B: Biol*., **1998**, *44*, 191.

[42] Encinas, S.; Belmadoui, N.; Climent, M.J.; Gil, S.; Miranda, M.A. *Chem. Res. Toxicol.*, **2004**, *17*, 857

[43] Delatour, T.; Douki, T.; D´Ham, C.; Cadet, J. *J. Photochem. Photobiol. B: Biol*., **1998**, *44*, 191.

[44] Miranda, M.A.; Castell, J.V.; Hernández, D.; Gómez-Lechón, M.J.; Boscá, F.; Morera, I.M.; Sarabia, Z. *Chem. Res. Toxicol*., **1998**, *11*, 172.

[45] Miranda, M.A.; Pérez-Prieto, J.; Lahoz, A.; Morera, I.M.; Sarabia, Z.; Martínez-Maña, R.; Castell, J.V. Eur. *J. Org. Chem*., **1999**, 497; Pérez-Prieto, J.; Boscá, F.; Galian, R.E.; Lahoz, A.; Domingo, L.R.; Miranda, M.A. *J. Org. Chem*., **2003**, *68*, 5104; Pérez-Prieto, J.; Galian, R.E.; Morant-Miñana, M.C.; Miranda, M.A. *Photochem. Photobiol. Sci*., **2003**, *2*, 1; Pérez-Prieto, J.; Morant-Miñana, M.C.; Galian, R.E.; Miranda, M.A. *Photochem. Photobiol.*, **2005**, in press.

[46] Galian, R.E.; Pastor-Pérez, L.; Miranda, M.A.; Pérez-Prieto, J. *Chem. Eur. J.,* **2005**, *11*, 3443.

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