Photolabile protecting groups and linkers

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1 Introduction

Protecting groups are a painful necessity in organic synthesis, despite all the drawbacks associated with their use.[1–3] Indeed, in addition to the fact that their introduction and cleavage require two synthetic steps (usually in yields markedly lower than the expected quantitative yield for such "trivial" transformations), they complicate a synthetic plan by their incompatibility with some organic reagents. The complication increases rapidly with the number of different protecting groups on the same molecule. The conditions necessary for their cleavage have to be very specific for a given group, in order to leave intact all the others (the so-called "orthogonality").[4] Photolabile protecting groups bring an interesting feature: they don't require any reagent for their cleavage, just light. This category of protecting groups opens the possibility of dealing with extremely sensitive molecules, otherwise incompatible with acids or bases.

The possibility of breaking bonds smoothly without the need of any reagent is also very appealing for solid-phase organic synthesis (SPOS), where an organic substrate is bound to a polymeric matrix (*e.g.* polystyrene bead, glass surface, soluble polymer) through a linker. This linker is usually cleaved in the very last step of the sequence, in order to liberate the desired product. Relatively harsh conditions are frequently required (strong acids or nucleophiles), and photochemical cleavage can solve some of the problems associated with sensitive compounds.

Very good general reviews have been published in this field,[5,6] together with more specific articles.[7] However, in the last fifteen years or so, considerable progress has been made, and new families of photolabile protecting groups have been developed. A testament to their importance in organic synthesis and in biochemistry is that thousands of examples of their use have emerged in the literature. By no means does this review aim at cataloguing them all. We will rather focus on the fundamental work resulting on either the development of new groups, or the understanding and improvement of existing ones. Photolytic cleavage of a chemical bond is, by essence, the consequence of the absorption of a photon by the substrate, and can occur through a limited number of pathways. Hence, we attempted to classify the known groups according to their mechanism of cleavage, distributed over seven general classes. This review covers the literature until the end of April 2001.

2 Norrish-type II reactions

The excitation of an organic chromophore can lead to the formation of a highly reactive diradical species. Among all its possible reaction pathways, hydrogen abstraction in the γ-position is quite common, and was identified very early on by Norrish.[8] This process is now commonly described for carbonyl compounds as a Norrish-type II reaction.

2.1 *o*-Nitrobenzyl alcohol derivatives

The most popular photolabile protecting group is undisputedly the 6-nitroveratroyloxycarbonyl group (NVOC), originally introduced by Patchornik, Amit and Woodward.[9] It is based on the photochemically-induced photoisomerisation of *o*-nitrobenzyl alcohol derivatives into *o*-nitrosobenzaldehyde (Scheme 1).

Carbamates, carbonates and esters are thus converted into an acetal derivative that spontaneously collapses into an aldehyde and the liberated fragment. In the case of carbamates, spontaneous decarboxylation leads to the free amine. Although the vast majority of the systems involve the *ortho* isomer, photoisomerisation of *meta* and *para* nitrobenzyl alcohols has been observed.[10]

The original study was based on the veratryl-derived carbamates of amino acids (nitroveratryloxycarbonyl, NVOC). The two methoxy groups were introduced to increase the absorbance at wavelengths longer than 320 nm. Under these conditions, even the most light-sensitive amino acid, tryptophan, was not affected (Scheme 2).

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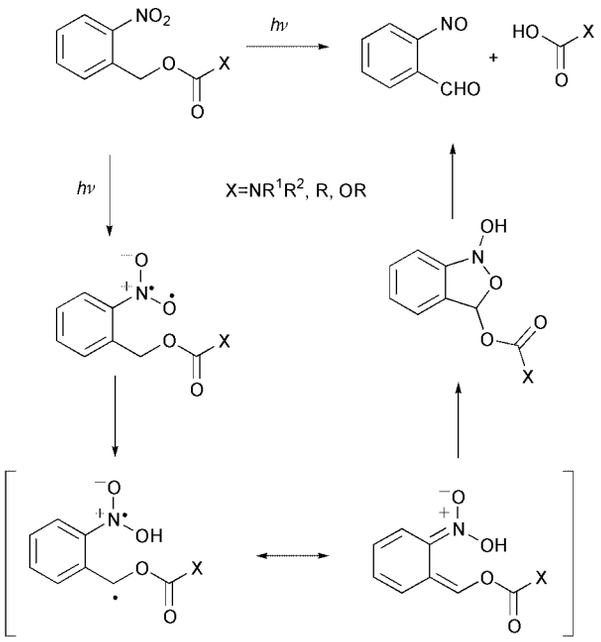
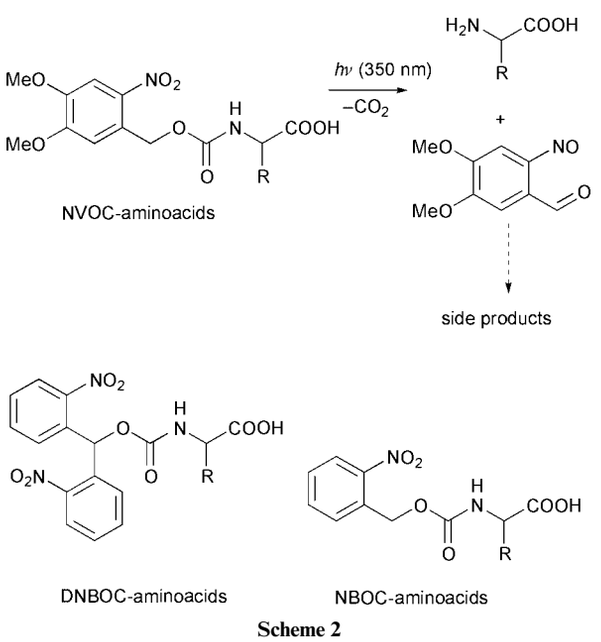


Scheme 1

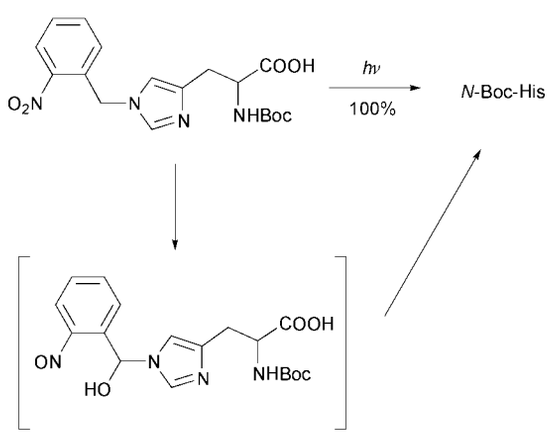


Scheme 2

However, although the carbon dioxide evolution was quantitative, the recovery of the amino acids was significantly lower than expected. A serious side-reaction was the formation of an imine, resulting from the reaction of the released amine with the aldehyde photoproduct. This could be suppressed by adding a carbonyl scavenger, such as semicarbazide hydrochloride, to the reaction mixture. With this additive, the yields were consistently quantitative. Another solution, circumventing the use of additives, is to substitute the benzylic methylene group with another *o*-nitrophenyl group (the symmetry preventing the formation of diastereoisomers). In this case, the photolysis led to the release of a ketone, much less prone to imine formation than aldehydes. Hence, the di(nitrobenzyl)oxycarbonyl (DNBOC) group gave yields higher than 70%. It was also tested for the protection of carboxylic acids as the corresponding esters. The yields of the recovered acids were consistently quantitative. Another very attractive method to trap the reactive nitroso photoproduct was proposed by Pirrung, substituting the benzylic centre with a pentadienyl chain. An intramolecular Diels–Alder reaction between the diene and the nitroso group efficiently inactivated the side-product.[11]

In a study directed towards the photogeneration of bases, Cameron and Fréchet examined in detail the effects of the substituents on the nitrobenzyloxycarbonyl (NBOC) group.[12] Despite expectations, due to the higher stability of a tertiary benzylic radical, the introduction of an α-methyl group did not increase the quantum yield ($\Phi = 0.11$, $\Phi = 0.13$ for the unsubstituted). It has, however, to be taken into account that there is only one hydrogen remaining. On the other hand, adding a nitro group in the other *ortho* position boosted the quantum yield ($\Phi = 0.62$); this was attributed to the fact that more hydrogen abstraction-capable species were present. The DNBOC quantum yield was also higher than the parent compound ($\Phi =$ 0.26). In general, quantum yields are higher for carbamates than for esters. The exact influence of the substituents at the benzylic centres on the quantum yield has been described as "a complex combination of both steric and electronic effects, as well as the statistics of the hydrogen atom abstraction". Substituent effects were also examined on esters (instead of carbamates) and a similar trend was observed except for a significant increase in quantum yield for the α-methyl derivative.[13] Other groups have also studied the mechanism in great detail, in particular by using flash photolysis at the picosecond time scale.[14,15] Most of the studies focus on the photolysis efficiency. Nevertheless, the ease of introduction of a protecting group is at least as important as its removal. In many cases, the NVOC chloride (a chloroformate) is used to protect amines or alcohols; when other analogues are not commercially available or unstable, a mild method using 1,1′-carbonyldiimidazole can be used.[16] In the case of extreme steric hindrance, the preparation is less straightforward. For example, the conventional methods failed for the preparation of the 2,2,6,6-tetramethylpiperidine carbamate;[17] it was, however, possible to first treat the amine with phosgene, and *then* to add the *o*-nitrobenzyl alcohol. The presence of at least 50% of dioxane as co-solvent was found to be crucial.

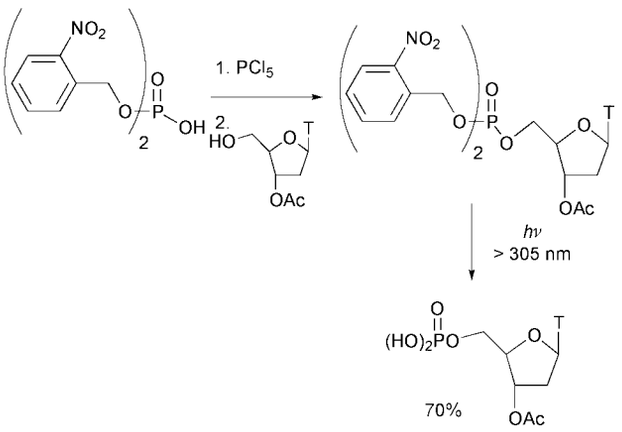
The *o*-nitrobenzyl group was also used for the direct protection of the imidazole side-chain of histidine, by *N*-alkylation with the corresponding bromide (Scheme 3).[18] The photolysis (medium-pressure Hg-lamp with pyrex filter) liberated back quantitative yields of histidine, and no racemisation was detected.



Scheme 3

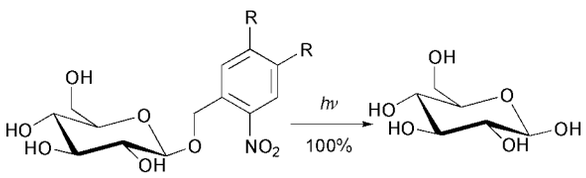
ortho-Nitrobenzyl alcohol derivatives were used for the protection of the phosphate group in nucleotide synthesis (Scheme 4).[19] Protection and deprotection were efficient. In the initial attempts, the nitrosoaldehyde-derived side-products caused a significant darkening of the solution, acting as an internal filter preventing efficient light absorption, but the ingenious use of polymer-bound semicarbazide allowed the recovery of the nucleotides in yields greater than 70%.

The NVOC/NBOC groups were also used for the protection of the hydroxy groups in carbohydrates.[20,21] For example, the



Scheme 4

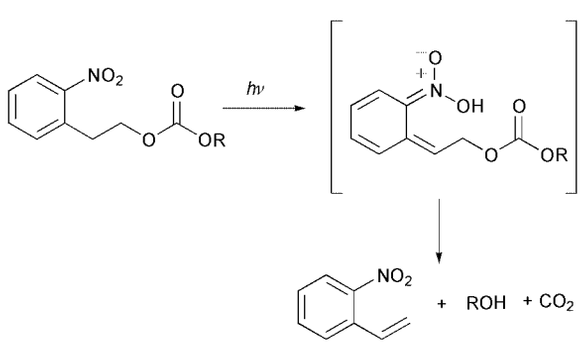
hemiacetal of glucose was protected as a mixed acetal. Photolysis gave quantitative yields of glucose, for both types of photolabile groups (Scheme 5).



Scheme 5

Ethers of this type were also used to protect the 2′-OH group in ribonucleosides. The protection was performed by reacting the free alcohol with *o*-nitrophenyldiazomethane in the presence of tin dichloride (a mixture of 3′ and 2′ ethers was obtained and separation was necessary).[22] The photolysis was also quantitative. This 2′-OH protection was very valuable in the preparation of oligoribonucleotides, for both solution- and solid-phase synthesis.[23–26] An interesting orthogonal scheme for RNA synthesis using an acetal-derived analogue was developed by Pitsch and Gough.[27–29]

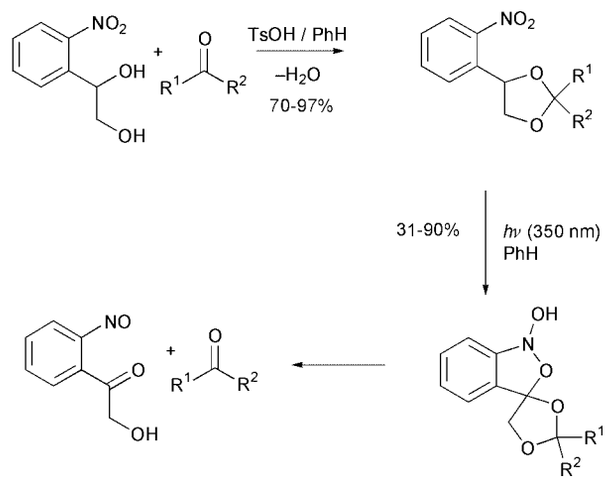
The functional group to be protected could also be linked to the *o*-nitrobenzyl group at the β position, as shown in recent work by Hasan with nucleoside carbonates (Scheme 6).[30] However, the variation in quantum yields according to the substituents paralleled those for the α-bound carbonates; this makes the direct β-H abstraction improbable, and an alternative mechanism was proposed.



Scheme 6

The same study showed additional influence of the substituents on the aromatic ring on the quantum yield, for both α- and β-bound carbonates. *o*-Halogen compounds showed an increase in quantum yield, except for the fluorine. Interestingly, electron-releasing groups such as the methoxy (*e.g.* the 4,5-dimethoxy pattern from the original NVOC group) drastically reduced the quantum yield ($\Phi = 0.0013$, to be compared to the completely unsubstituted NBOC, analog: $\Phi = 0.033$. Note that these measurements were performed on the thymidine carbonates, and not on cyclohexyl carbamates as above).[12] The high reactivity at 320 nm observed by Patchornik was clearly due to a large increase in absorbance, compensating the decrease in quantum yield.

An interesting modification by Gravel allowed the use of a similar protecting group for ketones (Scheme 7).[31] Indeed, such



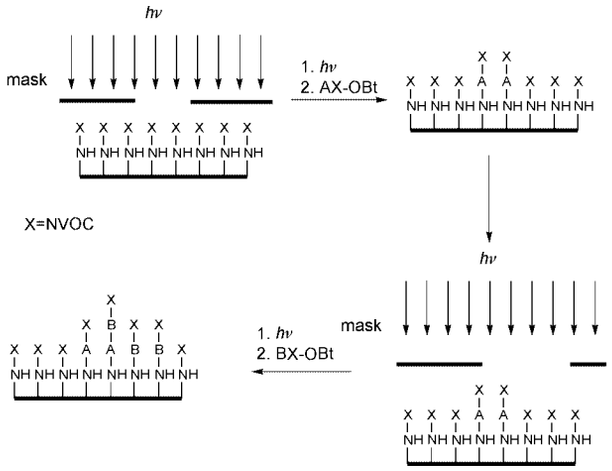
Scheme 7

photolabile groups are still scarce. The *o*-nitrophenylethyleneglycol was thus used. The standard ketalisation procedure (TsOH, PhH, Dean–Stark) gave high yields of the ketal. The cleavage was equally efficient, and photolysis at 350 nm in benzene gave up to 97% of the ketone back. One of the drawbacks of this protecting group was its rather poor stability against many reagents; these ketals were unstable towards sodium hydride in polar solvents, and strong reducing agents such as lithium aluminium hydride. On the other hand, a surprisingly high stability towards acids was observed, even surviving brief exposure to HCl in THF or sulfuric acid. The proposed photolysis mechanism, following the lines of the NVOC cleavage, was confirmed by the isolation and identification of the nitroso hydroxyketone.

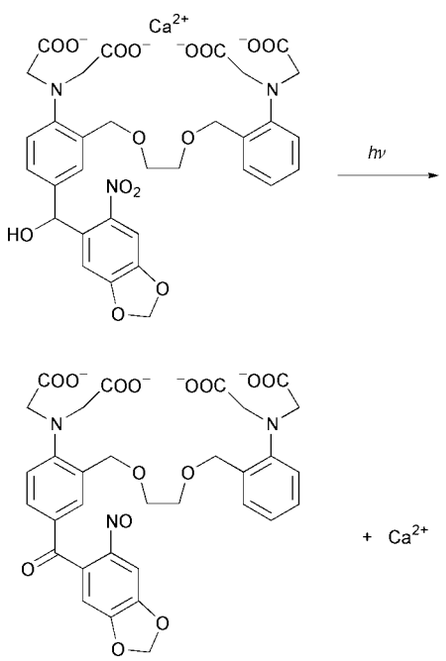
A major application of the NVOC-protected amino acid in peptide synthesis was developed at Affymax, for light-directed spatially addressable parallel chemical synthesis. In this strategy, NVOC-protected amino groups are attached to a glass plate through an amino linker. Photochemical deprotection with masks followed by reaction with NVOC-protected activated esters of amino acids allowed the coupling of amino acids at certain positions of the plate only. Variation in the mask position and iterations allowed the synthesis of a large number of different (in size and sequence) peptides on the plate (Scheme 8).[32] Binding properties could then be directly evaluated on the plate. The same strategy was applied to oligonucleotide synthesis, using a slightly modified α-Me-NVOC-type group.[33–36]

"Caged" compounds are compounds with specific properties (usually biological) that are inactivated by the protection of the relevant functional group. The original activity is restored upon photolysis. This strategy is very convenient to deliver *in-situ* reactive compounds, for example in living cells or in solid-state polymers.

Adams designed chelating ligands that release Ca^{2+} upon irradiation, based on substituted *o*-nitrobenzyl alcohols (Scheme 9).[37] Other systems have been designed to take Ca^{2+} upon illumination, although the *o*-nitrobenzyl alcohol-derived ligands showed low efficiencies.[38] Photoliberation of phosphates such as ATP, cAMP or cGMP,[39–41] and neurotransmitters has also been performed.[42]



Scheme 8



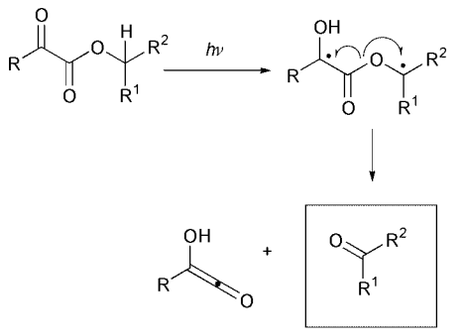
Scheme 9

The use of the NVOC-type protecting group has also been cleverly proposed for fluorescent probes. Indeed, the fluorescence of aromatic amines was quenched when linked to an *o*-nitrobenzyl alcohol derivative (by resonant energy transfer). Photolysis was expected to restore the amine fluorescence.[43]

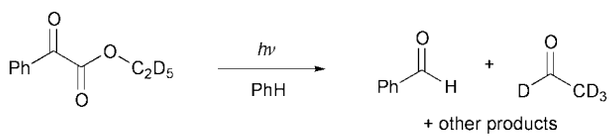
2.2 α-Ketoester derivatives

Photolabile protecting groups were used as potential delivery system for fragrances. Interesting work by Herrmann described the use of α-ketoesters as photoliberators of aldehydes or ketones, using sunlight as a promoter.[44] The system was unaffected by the presence of ambient oxygen. The mechanism was described as a Norrish-type II fragmentation (Scheme 10).

Strictly speaking, it is not a protecting group, since the alcohol moiety is oxidised during the process. A detailed mechanistic study was published by Neckers, emphasising the importance of this reaction for stereolithographic applications.[45] The absence of hydrogen in the γ-position (such as the *tert*-butylphenylglyoxylate) led to no reaction at all; evidence of a Norrish-type II reaction rather than type I. A competitive process, however, could be the intermolecular hydrogen abstraction, as shown by the experiment with a d_5-ethyl phenylglyoxylate in benzene, leading to non-deuterated benzaldehyde (Scheme 11). A multiple pathway mechanism is thus likely.



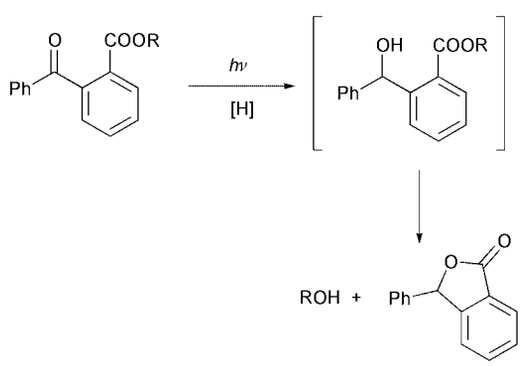
Scheme 10



Scheme 11

2.3 Benzophenone reduction

Porter recently described an original approach, based on the photoreduction of a benzophenone ester by a hydrogen or electron donor [isopropanol (propan-2-ol) or cyclohexylamine].[46] The unmasked hydroxy group spontaneously lactonised with the benzoate ester, thus liberating the free alcohol (Scheme 12).



Scheme 12

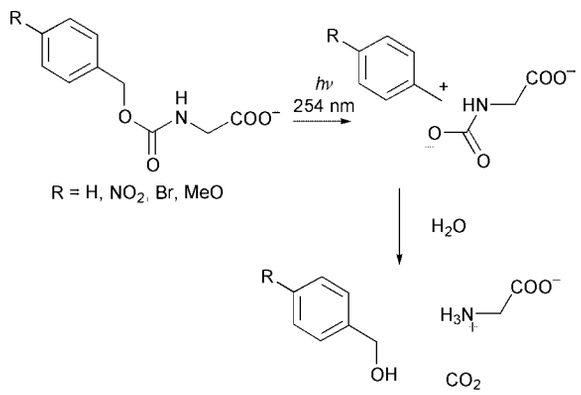
With light below 330 nm, the yields were reduced, probably due to secondary photochemical reactions on the ring, and a uranium-filtered light (366 nm) was found to be optimal. The reactants were transparent above 390 nm.

3 Photosolvolysis-related reactions

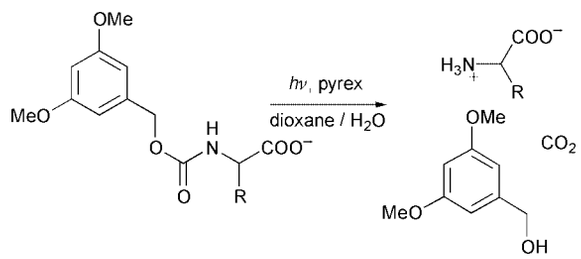
3.1 Benzyl alcohol derivatives

The first observation of photolability was reported by Barltrop and Schofield in 1962.[47,48] It was indeed found that the *N*-benzyloxycarbonyl (Cbz) protected glycine was deprotected upon irradiation at 254 nm (Scheme 13), in significant chemical and quantum yields (75%, $\Phi = 0.15$). A heterolytic mechanism was proposed, mainly based on the observation of benzyl alcohol as a major by-product, strong pH-dependence and the increase in quantum yield when the ring was substituted with electron-releasing groups. The quantum yield also showed a significant increase when water was added to the solvent.

The introduction of two methoxy groups in the *meta*-positions was found, by Chamberlin, to have a dramatic increase in reactivity.[49] Several amino acids and peptides were tested (Scheme 14). The typical yields (in aqueous dioxane, with a high-pressure mercury lamp and Vycor filter) varied between



Scheme 13



Scheme 14

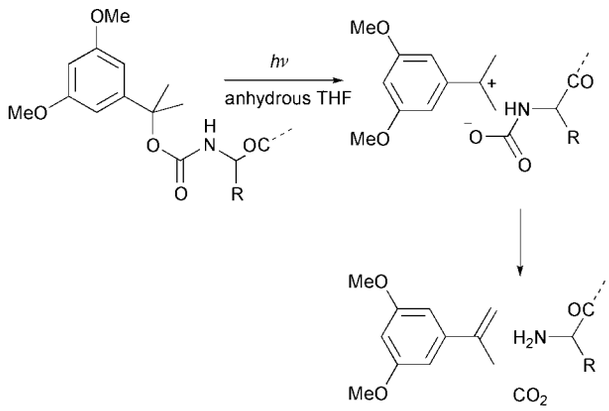
42 and 85%. Interestingly, under these conditions, the Cbz groups were cleaved only up to 10%; a lysine N_{α}-protected with the 3,5-dimethoxybenzyloxycarbonyl group and the N_{ε}-Cbz could be cleaved selectively at the N_{α}-position.

No explicit mention of the mechanism was given, except a reference to a study by Zimmerman, where the effect of a *meta*-methoxy group was investigated.[50,51] The heterolytic nature of the cleavage was again established by the presence of a benzylic alcohol as by-product, which was considered as highly improbable to be formed by the recombination of a benzylic radical and a hydroxyl radical. A molecular orbital-based discussion brought some ground to this explanation, showing that *meta*-substituents could efficiently stabilise a carbocation at the excited state. A detailed revision of this mechanism was later proposed by Pincock *et al.*, suggesting that the dominant photochemical step was in fact a homolytic cleavage of the benzylic–heteroatom bond, leading to a ground-state radical pair.[52] Subsequent electron-transfer *then* occurs, to give the ion pair proposed in the earlier mechanisms. However, the controversy remains, high-level calculation recently performed confirmed the original mechanism.[53]

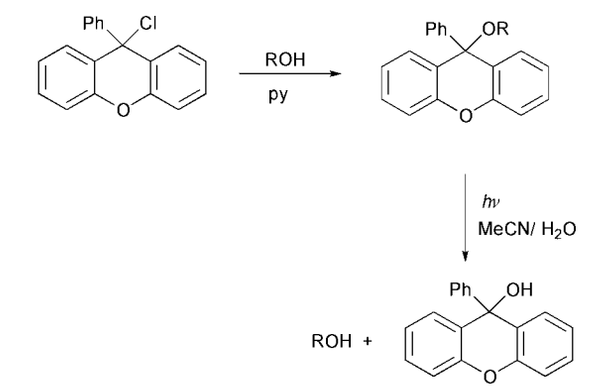
Regardless of the exact nature of the mechanism, if a benzylic radical or carbocation is formed in the rate-determining step, stabilising groups are expected to facilitate the reaction. For example, the two methyl groups in the α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl group (Ddz) were introduced by Birr in 1972 (Scheme 15).[54] This group showed an interesting dual reactivity, first as an acid-labile group (half-life of 1 hour in AcOH–H_2O 80% at 20 °C, and quantitative cleavage in 5% TFA–CH_2Cl_2: k_{rel} Boc/Ddz: 1 : 1400). Photochemically, the Ddz-protected amino acids were more reactive than the 3,5-dimethoxybenzoin derivatives (see section 3.2). In this case, the by-product was not the benzyl alcohol, but the α-methylstyrene or its dimer (by photocycloaddition [2 + 2]), formed by direct elimination. This is an advantage, since non-aqueous conditions can be used.

This increased reactivity was later exploited by Cameron and Fréchet, as a new way of photogenerating bases for imaging systems.[55]

Other types of benzylic carbocation-driven photolysis have been used, such as the 9-phenylxanthen-9-yl, or pixyl (px), group (Scheme 16).[56] The moderately acidic conditions used to



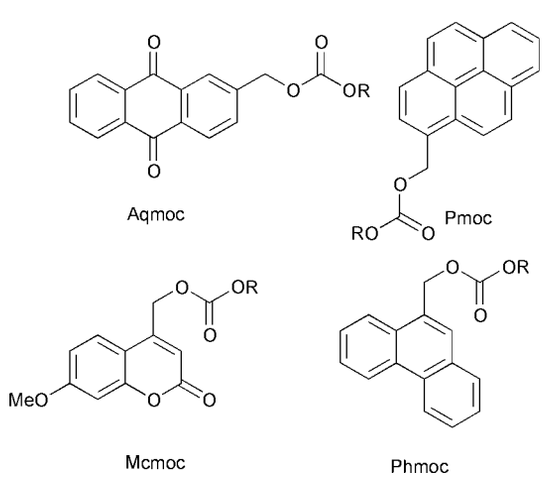
Scheme 15



Scheme 16

cleave it from the 5′-position of nucleosides unfortunately led to partial deprotection of THP groups at the 2′-position, limiting its use in oligoribonucleotide synthesis. Recent work however showed that it was possible to carry out photolysis in aqueous acetonitrile (the more water, the more efficient the process) with a low-pressure Hg-lamp in quartz glassware. The photolysis was quite efficient (78%–97%), whereas the protection yields were slightly lower (66%–74%).

Recently, polycyclic aromatic hydrocarbons bearing benzylic methylene groups were also found to be good photolabile protecting groups for alcohols (Scheme 17).[57] The anthraquinon-



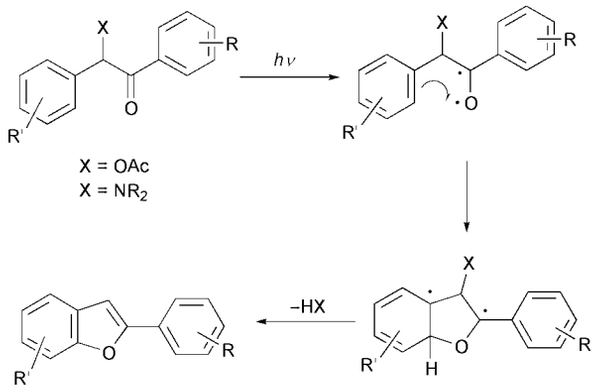
Scheme 17

2-ylmethoxycarbonyl (Aqmoc), pyren-1-ylmethoxycarbonyl (Pmoc), 7-methoxycoumarin-4-ylmethoxycarbonyl (Mcmoc) and phenanthren-9-ylmethoxycarbonyl (Phmoc) groups were tested, with decreasing reactivity at 350 nm (the Phmoc was found unreactive). The Aqmoc was tested in more detail. Stern–Volmer quenching experiments suggest a mechanism through a

long-lived triplet excited state. The presence of THF was essential to maintain high yields. The deprotection of a carbohydrate derivative was disturbed by the re-attack of the liberated alcohol to form a symmetrical carbonate, but in the case of adenosine, 91% yield was obtained. Analogues of Mcmoc have also been used as phosphate photoreleasing agents.[58,59]

3.2 Benzoin esters

In 1964, Sheehan showed that benzoin acetate (also called desyl acetate) could cyclise into a 2-substituted benzofuran, upon irradiation (high-pressure Hg-lamp, pyrex filter) (Scheme 18).[60]

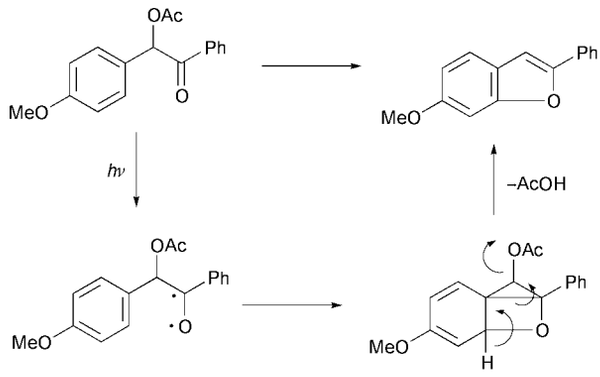


Scheme 18

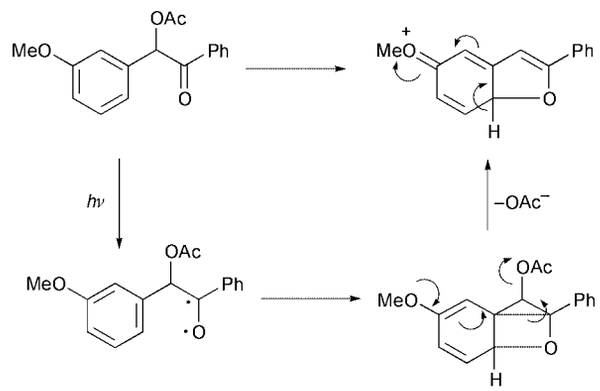
The yield of benzofuran was dependent on the solvent (15% in benzene, 10% in dioxane or isopropanol), but also on the leaving group X (more than 70% if an amine). The mechanism was rationalised by a diradical process, initiated by an n–π* transition of the carbonyl group.

The effects of the substituents were investigated in a preliminary study, and the 4,4′-dimethoxybenzoin acetate gave only trace amounts of the benzofuran. This was attributed to an intense charge-transfer transition at 282 nm (MeO > CO) reducing the amount of light available to the n–π*. This reaction was applied in protecting group chemistry in 1971, also by Sheehan.[61] Substitution on the benzylic ring was then found to significantly accelerate the reaction, the optimal substitution being located at the 3′ and 5′-positions. Hence the photolysis of the 3′,5′-dimethoxybenzoin acetate led to a remarkably smooth and fast cyclisation, releasing the acetate moiety as acetic acid in very high yields. On the other hand, substitution on the benzoyl ring only had detrimental effects. The 4′-methoxybenzoin acetate also led to the liberation of acetic acid, but was found unreactive in a 1 M solution of piperylene (penta-1,3-diene) in benzene. This quenching was a clear evidence for a mechanism *via* a triplet excited state. On the other hand, the 3′,5′-dimethoxybenzoin acetate cleavage was very fast, and there was no interference neither by a naphthalene solution or neat piperylene. One can conclude that the reaction occurs within 10^{-10} seconds after the absorption of the photon; this suggests a short-lived n–π* excited state, probably a singlet, although a triplet arising from a very fast intersystem crossing (known to be fast for aryl ketones) cannot be totally ruled out. The near quantitative release of acetic acid and the very high quantum yield (Φ = 0.644) makes this system very attractive for the protection of carboxylic acids. A noteworthy drawback is the presence of a chiral centre, potentially problematic with chiral carboxylic acids. The mechanism proposed in 1971 was somewhat different to the one proposed in the earlier work,[60] this time involving the formation of a tricyclic "hausane" by a Paterno–Buchi type reaction (*i.e.* the [2 + 2] olefin/carbonyl photocycloaddition). The rate of decomposition of the intermediate was rationalised on the basis of the position of the methoxy substituent (Schemes 19 and 20).

The substituted benzoins were also utilised as photoremovable groups for phosphates. Their very high quantum yields and

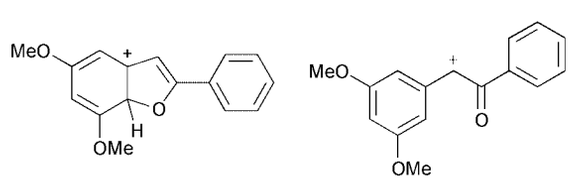


Scheme 19



Scheme 20

extremely short-lived excited states made them attractive for intracellular release of biologically active substances. However, the intrinsic chirality of trisubstituted phosphates raises the issue of diastereomeric mixtures if the racemic benzoin was used. Hence, Pirrung prepared an enantiopure (>97% ee) dimethoxybenzoin, by the addition of phenylmagnesium bromide to an optically pure *o*-trimethylsilyl dimethoxybenzyl cyanohydrin and subsequent acidic hydrolysis.[62] In this study, an alternative mechanism was proposed, involving the photosolvolysis of the benzylic phosphate, strongly favoured by the stabilisation of a benzylic cation by the *meta*-methoxy groups at the excited state (as shown by Zimmerman).[50,51] Here again, the photodeprotection was not quenched by a 30 mM methylnaphthalene solution, suggesting a singlet excited state. The deprotection operates at 350 nm, a wavelength where the ring responsible for the photosolvolysis does not absorb. One hypothesis would be that the initial absorption by the benzoyl moiety is followed by an energy-transfer into the other ring. This solvolysis mechanism was investigated by Corrie.[63] Laser flash-photolysis experiments showed that cation **A** (Scheme 21)

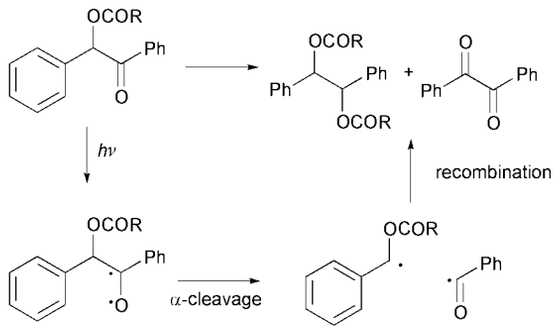


Scheme 21

was formed within the laser pulse (*ca.* 10 ns), and thus confirms its presence in the reaction pathway. A mechanism through cation **B** is not excluded, but no alcohol was detected, even in the presence of 1 : 1 water–acetonitrile.

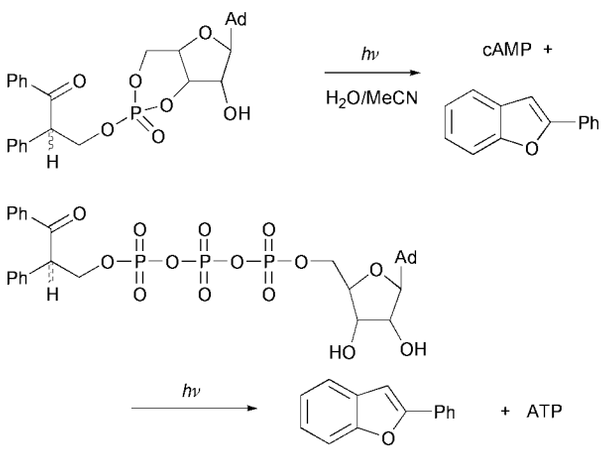
In fact, the large amount of experimental data, sometimes in apparent contradiction, shows that many different reaction pathways operate, strongly depending on the substituents,

solvent and leaving group. For example, the unsubstituted benzoins were shown by Lewis,[64] Turro,[65] and others, to react *via* an α-cleavage of the diradical, resulting from the carbonyl excitation (Scheme 22).



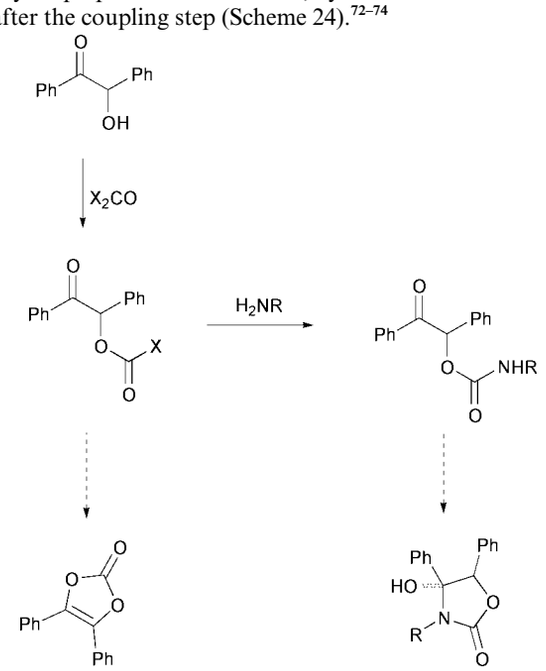
Scheme 22

Applications in caged-phosphates were quite thoroughly investigated by the groups of Baldwin,[66] Corrie,[67,68] Pirrung[62] and Givens.[59,69,70] For example, the release of cAMP and ATP is shown in Scheme 23.[71]



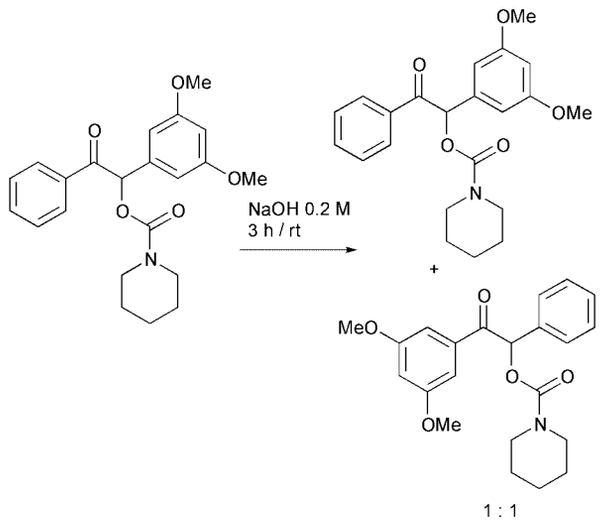
Scheme 23

On the other hand, amine protection as the carbamates was more problematic, for several reasons. The first was the difficulty to prepare the carbamates; cyclisation occurred during or after the coupling step (Scheme 24).[72–74]



Scheme 24

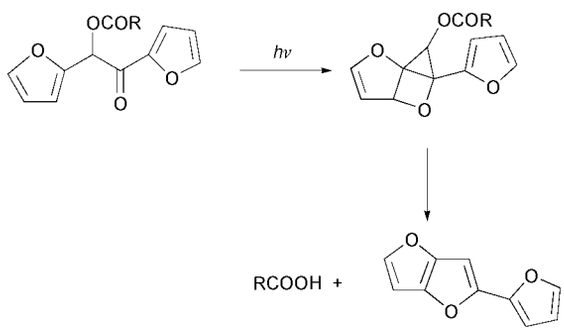
In addition the unsymmetrical benzoins had a propensity to isomerise in basic medium (Scheme 25).[73,75–79]



Scheme 25

These problems could eventually be circumvented.[72,79,80] A more serious drawback for applications in caged amine-containing neurotransmitters was the intrinsically slow rate of decarboxylation of carbamic acids (much slower than the photolysis). Systems requiring fast release of the amine (generally the species responsible for the biological response) could thus not be based on benzoin carbamates.

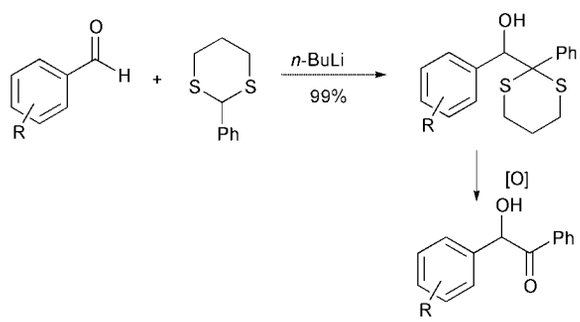
Analogues to benzoins, furoins, were proposed as photolabile groups (Scheme 26).[81] Photolysis of furoin esters indeed



Scheme 26

occurred, but much slower than for the 3′,5′-dimethoxybenzoin (by one order of magnitude).

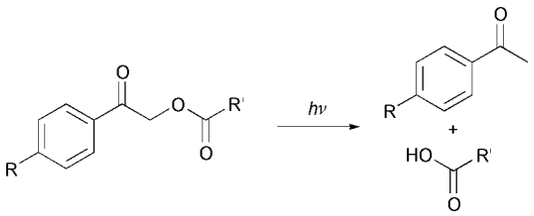
The efficient preparation of unsymmetrical benzoins was developed, for both solution- and solid-phase (Scheme 27).[82,83]



Scheme 27

3.3 Phenacyl esters

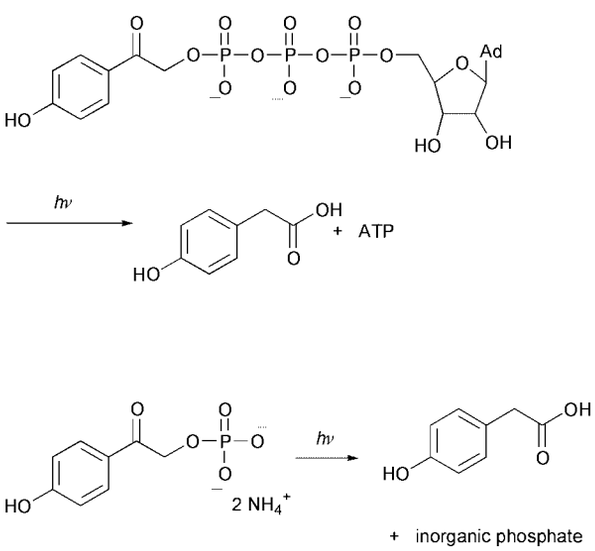
The phenacyl esters were also capable of liberating an acid upon photochemical activation (Scheme 28).[84,85] Interestingly, Sheehan reported a good chemical reactivity for simple



Scheme 28

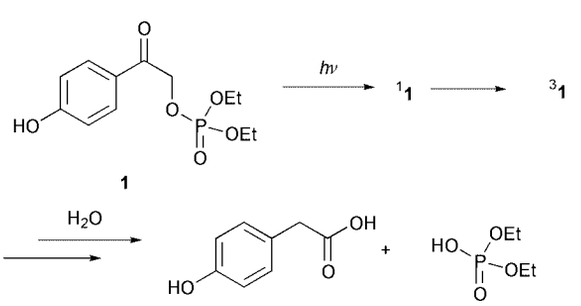
phenacyl esters with sodium thiophenoxide, and proposed it as a *chemical* protecting group.[86]

The use of phenacyl groups in organic synthesis is not very common. On the other hand, they were widely used in caged phosphates.[69,70] For example, the *para*-hydroxyphenacyl group (pHP) is a fast-release trigger for biological stimulants.[87] The side products are generally biologically inert and transparent at wavelengths longer than 300 nm. It provides a high efficiency of ATP release, has no chiral centres, and is very soluble in water (Scheme 29). The rearranged *para*-hydroxyphenylacetic acid has



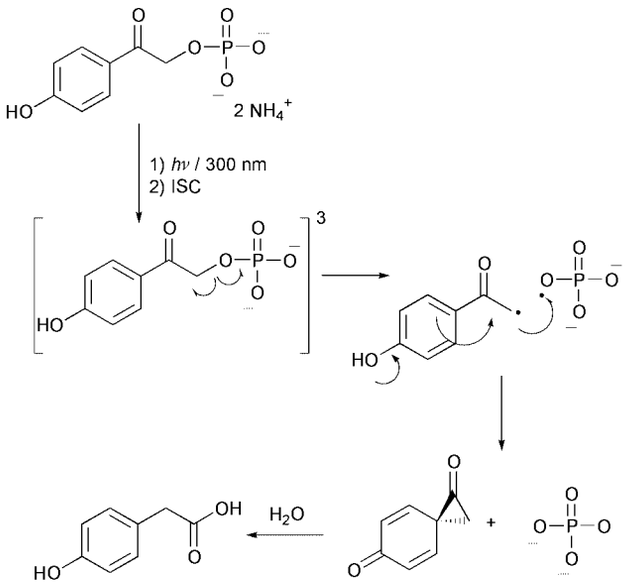
Scheme 29

a hypochromic shift that prevents photochemical interference. Other substituents on the aromatic ring were less efficient; a *para* amino group was less effective and did not lead to the rearrangement. The knowledge of the release rate is crucial. Givens proposed a short-lived triplet as the reactive excited state. This assertion was later questioned,[88] and a singlet was proposed. Recent work by Wirtz and Givens tends to confirm that it is indeed a very short-lived triplet (Scheme 30).[89]



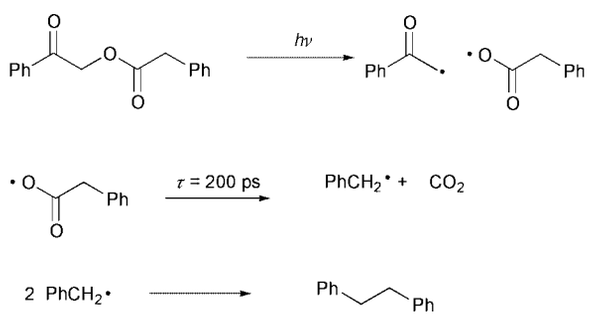
Scheme 30

Water has been shown to accelerate the reaction (5% of water led to an acceleration factor of 5), but piperylene (0.5 mM) or air slowed the process down by a factor of 4. The quantum yield was very high (Φ = 0.94 at 313 nm), and reduced by the presence of piperylene (Φ = 0.37 with 10 mM piperylene). The following mechanism was proposed (Scheme 31).[87]



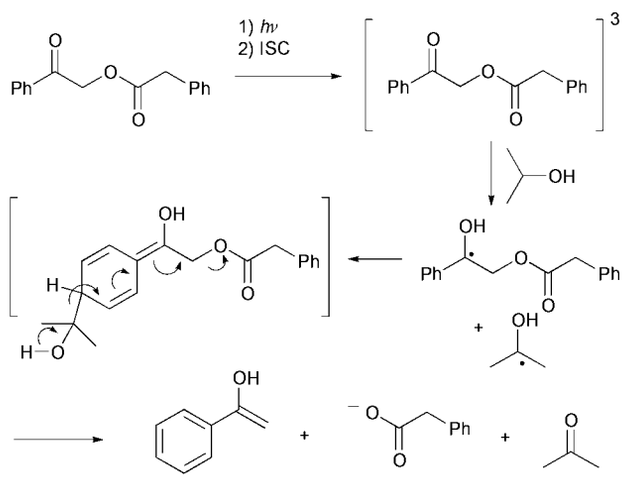
Scheme 31

For esters of unsubstituted phenacyl groups, the mechanism might be more complicated. Indeed, in order to liberate a carboxylic acid, the hydrogen abstraction should be very fast, otherwise decarboxylation would occur (Scheme 32). In



Scheme 32

acetonitrile, no traces of bibenzyl were detected, but high yields of acetophenone and phenylacetic acid were observed. These inconsistencies led Falvey to propose an alternative mechanism when a hydrogen donor was present in the medium (*e.g.* isopropanol) (Scheme 33).[90]

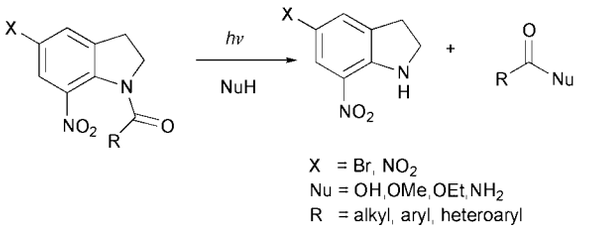


Scheme 33

3.4 Acylating agents

Traditionally, the carboxy group is protected as an ester and rarely as an amide, due to the chemical resistance towards

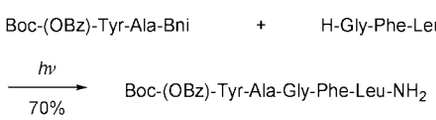
hydrolysis. An early account of photolabile *ortho*-nitroanilines was published in 1973, but this group was rarely used.[91] A modification of this group lead to a new family of light-sensitive amides,[92] the 5-bromo-7-nitroindolines (Bni), which undergo smooth photolysis, also with wavelengths longer than 400 nm (Scheme 34). The only by-product was the deacylated indoline.



Scheme 34

The most interesting observation was that, in a nucleophilic solvent such as methanol or ethanol, the ester instead of the acid was obtained. The 7-nitro group was crucial for this reactivity. Other substitution patterns also lead to photolysis, but without incorporation of the solvent. Interestingly, increasing the size of the fused ring changed the properties;[93] *N*-acyltetrahydroquinolines were also photolytically hydrolysed, but without solvent incorporation; more importantly from the mechanistic point of view, the aromatic nitro group was reduced into a nitroso group. The Bni group was used as a carboxy protecting group for peptide fragment condensation,[94] or as a fast-releasing agent of neurotransmitter amino acids in biological media (*e.g.* L-glutamate).[95,96] During the latter study, essentially carried out in aqueous media, it was observed that the nitro group was reduced into a nitroso group, and the oxygen of the carboxy group did not originate from the solvent, but rather from the nitro group (established by isotope labelling). The nature of the photolysis mechanism thus seems to be solvent-dependant. In order to improve the efficiency of the release, the substituents around the aromatic ring were modified. The replacement of the bromo group in the Bni by a methoxycarbonylmethylene was beneficial (in water, 2.5 times more efficient). Removing the bromo at C-5 and adding a methoxy at C-4 was also beneficial (3 times). On the other hand, the simultaneous presence of a methoxy group at C-4 and a methyl at C-5 reduced the efficiency, probably due to a steric interaction distorting the optimal orbital alignment between the oxygen lone pairs and the aromatic ring. In order to further increase the electron-donation, a dimethylamino group was introduced at C-4, leading this time to a photochemically inert compound; this lack of reactivity was attributed to a low-lying triplet state.

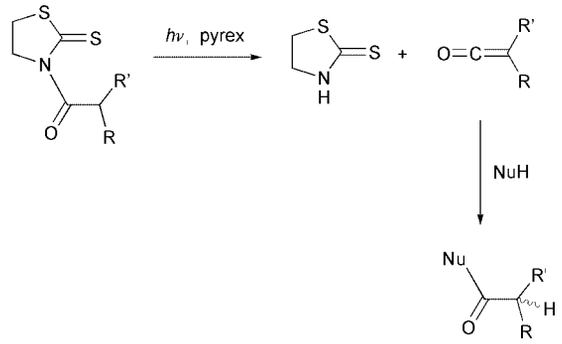
The possibility of adding a nucleophile during the cleavage step was exploited by Pass, Amit and Patchornik to perform peptide segment coupling (Scheme 35).[97] No racemisation was



Scheme 35

observed on the amino acid moiety, but the introduction of the Bni group to the amino acid was somewhat problematic. Many different routes were investigated, including nitration of the indoline after the acylation with the amino acid.[94] The most practical procedure finally involved heating the acid and the nitroindoline in toluene with thionyl chloride.[97] This very attractive strategy has, however, received little attention until very recently.[98]

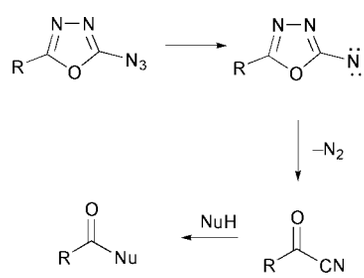
Another interesting apparent solvolysis reaction was proposed by White.[99] The carboxy group was masked as a *N*-acyl-2-thionothiazolidine, and released upon irradiation (Scheme 36). When a nucleophile was present, a new bond was formed



Scheme 36

(*e.g.* ethyl ester when ethanol was used). However, the lack of reactivity when the carboxy chain had no α-H (γ to the sulfur) suggested a Norrish-type II mechanism leading to a ketene intermediate; indeed, it was observed that substrates bearing a chiral center at this position underwent total racemisation.

A related reaction was described by Confalone and Woodward.[100] The photolysis of 5-azido-1,3,4-oxadiazoles was able to generate an acylcyanide, which was then trapped by a nucleophile (or the solvent). This heterocycle is in fact a masked photoreleasable carboxy group (Scheme 37). Its cumbersome

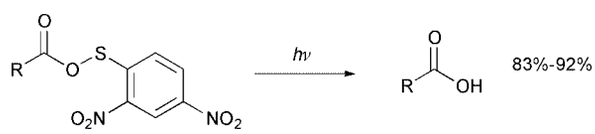


Scheme 37

preparation, however, limits its utility in protecting group chemistry.

3.5 Miscellaneous solvolyses

Another type of solvolysis was described very early on by Barton, with the use of 2,4-dinitrobenzenesulfenyl esters as masked carboxylic acids (Scheme 38).[101,102] The photolysis proceeded



Scheme 38

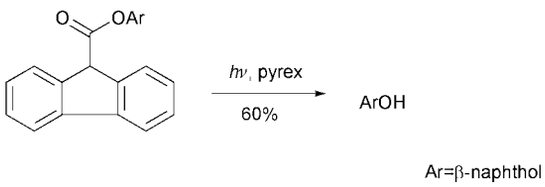
with high yields. The mechanism was proposed as a heterolysis, with formation of the carboxylate anion and benzenesulfenyl cation. This hypothesis was mainly based on the absence of the decarboxylation that would have been characteristic of a carboxyl radical. The addition of cyclohexylamine did not lead to the formation of any amide.

4 Norrish-type I reactions

Carbonyl compounds are excited by the absorption of a photon, and the homolysis of the (C=O)–R bond may result. The two radical fragments evolve according to their intrinsic reactivity, but the carbonyl radical frequently undergoes first a decarbonylation. This process was also observed by Norrish,[8] and is now described as a Norrish-type I reaction.

4.1 Fluorenecarboxylates

One of the earliest accounts of a photolabile protecting group was published by Barton, with the use of fluoren-9-ylcarboxylates as protecting groups for phenols (Scheme 39).[101,102] The



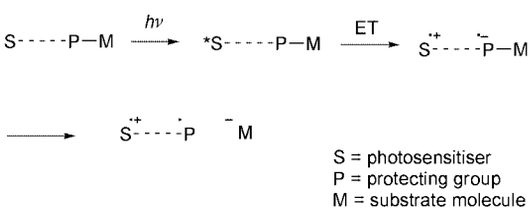
Scheme 39

mechanism was believed to occur through a homolysis of the carboxy–fluorenyl bond, followed by decarbonylation and formation of an aryloxy radical. This reaction however did not work with *p*-cresol, unless quartz glassware was used. This article mentions for the first time the crucial importance of the wavelength.

5 Photo-electron transfer

5.1 Arylamines as photo-reductors

In a series of papers, Falvey introduced an interesting strategy.[90,103–105] He proposed a modular approach, separating the light absorption and the cleavage phases, in order to better optimise each step. This general strategy was based on the photoinduced electron transfer (PET, Scheme 40). The ultimate



Scheme 40

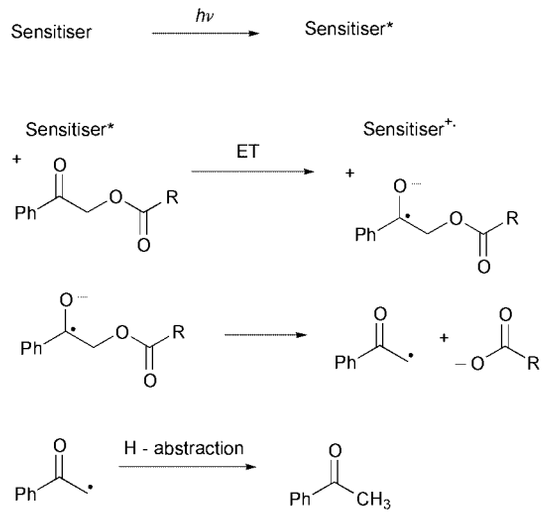
goal is to develop systems capable of working at higher wavelengths than 350 nm, and which are responsive to different wavelengths. The chromophore should be an electron-donating species (reducing agent) at the excited state.

In this scenario, an anion is liberated, whereas other approaches liberate a cation or a radical, frequently unstable and prone to rearrangement. An example of this strategy was shown with the phenacyl protecting group as the labile unit, and a sensitiser such as *N,N*-dimethylaniline (DMA), tetramethylbenzidine (TMB), or tetramethylphenylenediamine (TMPD) (Scheme 41). The photolysis was carried out in acetonitrile, with a 150 W Hg-vapour lamp. Various carboxylic acids (aromatic, aliphatic, *N*-Boc-amino acids) were deprotected by this method. Low yields were obtained when using esters with easily reduced functionalities (*e.g.* acrylates).

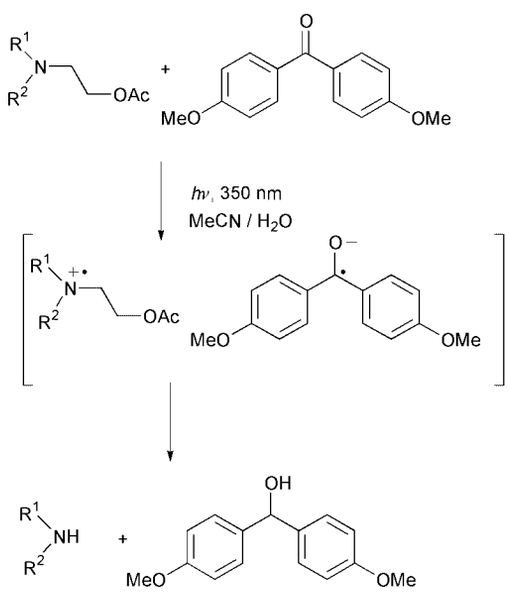
Other types of functionality were deprotected by this method: alcohols (from carbonates), phosphates and diacids (from diesters). For example, methanol or nucleosides were liberated with yields typically higher than 80%; in some cases, the yield to protect these alcohols were somewhat modest (38–48% for nucleic acids); *N*-Bocglutamic acid or malonic acid were released with 87% and 83% yields. An intramolecular version, where both donors and acceptors were covalently linked, was recently published.[106]

5.2 Benzophenone as photooxidant

A related strategy was employed by Cossy, but this time by using a light-induced photooxidation (Scheme 42).[107] In this work, the *N*-(2-acetoxyethyl) group was used as an amine photolabile group. The protection procedure was practical, by



Scheme 41



Scheme 42

the simple reaction of an amine with 2-acetoxyethyl bromide in the presence of potassium carbonate. The deprotection required a stoichiometric amount of 4,4′-dimethoxybenzophenone (the electron acceptor), and irradiation at 350 nm for 3 hours in aqueous acetonitrile.

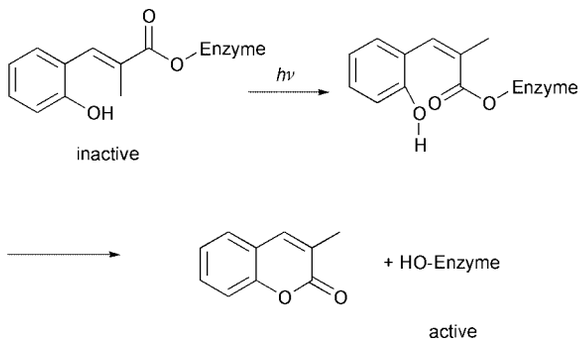
This reaction is very specific to tertiary amines; if R^1 or R^2 is hydrogen, no reaction occurred. The cleavage regioselectivity is also very high, always occurring on the acetoxyethyl moiety and never on the other substituents, regardless of their nature (even benzylic). When substituents included an α-chiral centre as in α-methylbenzylamine, no racemisation was detected.

6 Photoisomerisation *trans–cis*

6.1 Cinnamyl esters

Olefins are known to isomerise upon irradiation with UV-light. This strategy in protecting group chemistry was used by Porter.[108,109] Enzymes (*e.g.* human α-thrombin) could be inactivated by acylation with a photolabile group. The activity could be restored by irradiation with UV-light (medium-pressure Hg-Xe lamp, pyrex filter) (Scheme 43).

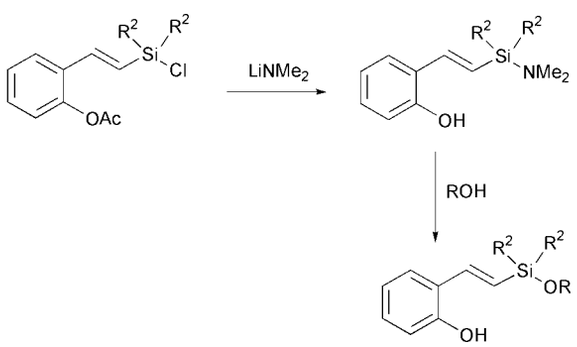
The limitations reside in the extensive overlap between enzyme and inhibitor absorbance spectra; the intensity of the light source had to be high, but long irradiations degraded the enzyme. On the other hand, the use of a monochromator provided insufficient intensity.



Scheme 43

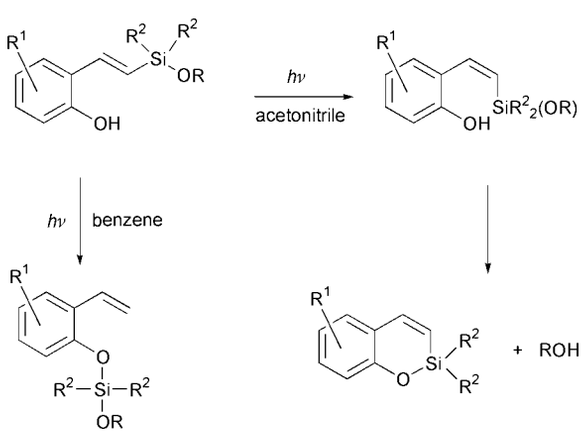
6.2 Vinylsilanes

An interesting silicon-based protecting group was introduced by Pirrung *et al.*, also using the *trans–cis* photoisomerisation of alkenes.[110,111] Indeed, the drawback of existing silicon-based protecting groups (sisyl, see Section 8) is the requirement of harsh, short-wavelength light (254 nm). Based on the work of Porter,[108,109] vinylic phenols were used. The silylethers were prepared by the condensation with the silyldimethylamide (Scheme 44).



Scheme 44

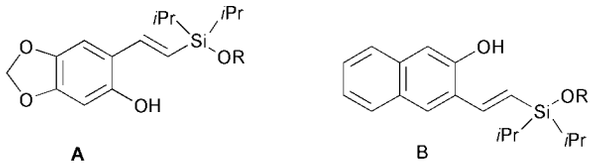
The photolysis was carried out in a Rayonet apparatus at 254 nm, and cleanly gave 84% of liberated alcohol when using acetonitrile (Scheme 45); on the other hand, the reaction took



Scheme 45

an abnormal course in benzene, where 91% of a rearranged product was obtained. Yields were generally good with primary, secondary and allylic alcohols (in acetonitrile), as well with 3′- and 5′-protected nucleosides, with a stability close to the triisopropylsilyl group (for R^2 = Me).

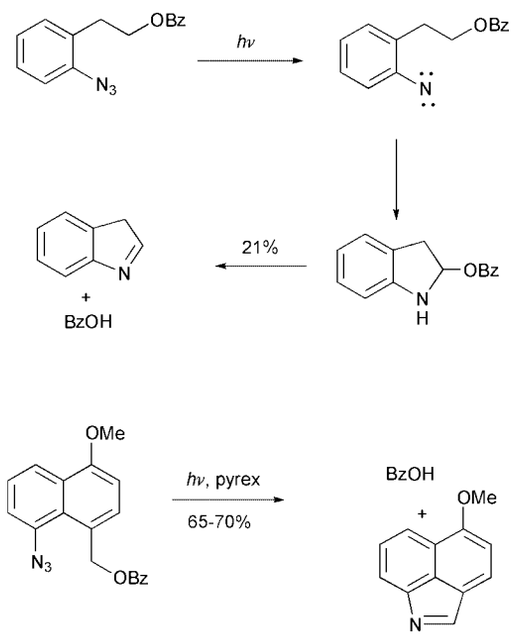
In an attempt to move the absorption towards higher wavelengths, a methylenedioxy group was added (**A**), but without success (only the rearranged product was obtained). On the other hand, the naphthalene derivative **B** was efficient at 350 nm in methanol (Scheme 46).



Scheme 46

7 Nitrene insertions

The ability of nitrene to undergo C–H insertions was exploited by Barton.[112] Hence, the photolysis of an arylazide generated a nitrene intermediate, which underwent an insertion into the C–H bond adjacent to an ester function. The resulting hemiaminal spontaneously collapsed to liberate a carboxylic acid (Scheme 47).

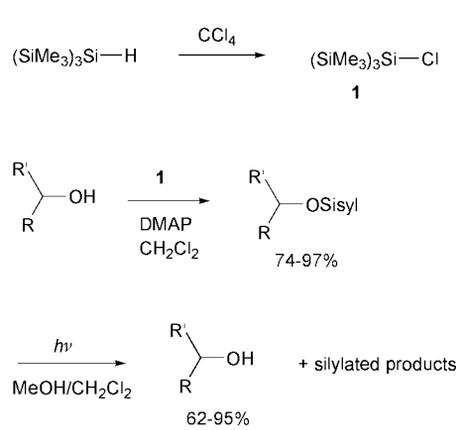


Scheme 47

The simple benzoic system failed to react efficiently, but the *peri* interaction in 1,8-disubstituted naphthalenes was judiciously used to facilitate the nitrene insertion on the C–H bond and the liberation yields were acceptable (65–70%).

8 Miscellaneous mechanisms

The photoremoval of silyl protecting groups is quite rare. First reported by Brook in 1997,[113,114] the sisyl (tris(trimethylsilyl)-silyl) group is a photolabile, but fluoride resistant, protecting group (Scheme 48). Despite the absence of π-systems,



Scheme 48

polysilanes absorb UV-light. The wavelength and extinction coefficient vary with the length of the Si–Si bond (this is due to σ-conjugation). Sisyl ethers absorb at 204 and 254 nm.

The photolysis is carried out with a medium-pressure Hg-lamp with pyrex filter. In the absence of light, the sisyl ethers are unstable towards BuLi, $LiAlH_4$ (strong nucleophiles) and TBAF. Remarkably, they are stable towards CsF and KF–18-crown-6, but also MeMgBr, Wittig reagents, TsOH or HCl.

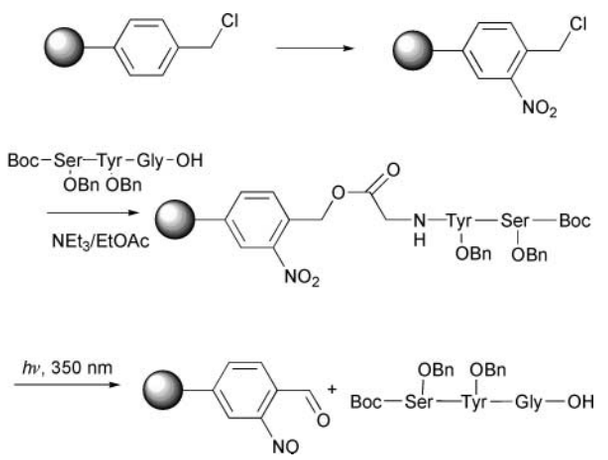
9 Photolabile linkers and resins

9.1 Introduction

In solid-phase organic synthesis (SPOS), the substrate to be synthesised or transformed is bound to the solid phase either directly (functionalised resin) or through a binding unit called a *linker*. Regardless of the ambiguity in defining what belongs to the linker category or the functionalised resin, this unit can be considered as a protecting group that has to be removed at some point in the course of the synthesis. All the advantages associated with photochemical removal can be transposed to the solid-phase, and it is not surprising that there has been great efforts paralleling those for the conventional solution-phase.[115–117]

9.2 Norrish-type II reactions

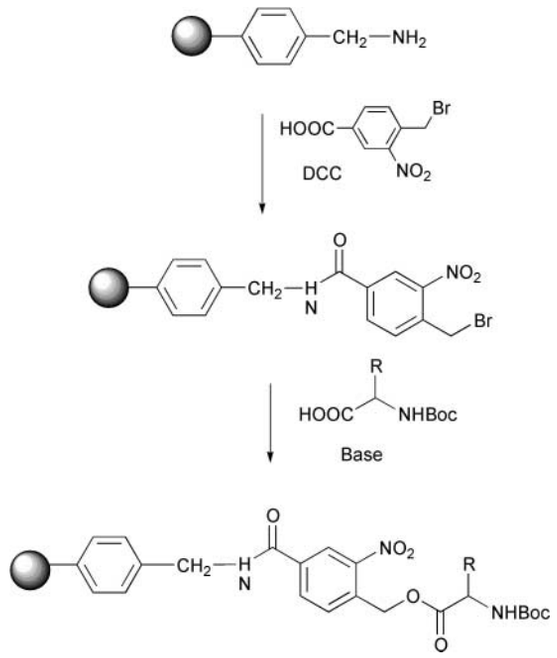
The first account of a photolabile linker to bind a substrate to a solid support was published in 1973 by Rich *et al.*,[118] and was based on the *o*-nitrobenzyl alcohol derivatives introduced by Patchornik.[9] Its preparation was extremely easy, and took advantage of the already present chloromethyl group on the resin aromatic framework: simple nitration of chloromethylated polystyrene beads was followed by heating the resulting benzylic chloride with an amino acid (or a peptide fragment) and a base (Scheme 49).



Scheme 49

Photolysis (350 nm) gave a tripeptide with an overall yield of 62%. However, longer peptides led to significantly lower yields (32% for a tetrapeptide). Poor swelling properties due to the increase in polarity by the numerous nitro groups were invoked to rationalise this problem. This limitation was overcome by not nitrating the resin itself, but rather by introducing a proper photolabile linker, thus ensuring that only the required number of nitro groups were present (Scheme 50).[119]

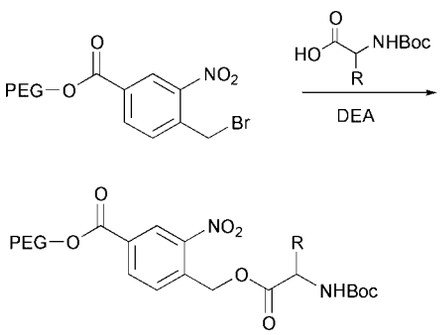
This new resin showed satisfactory swelling properties in common organic solvents, and liberated high yields of peptides as free C-terminal carboxylic acids upon photolysis (64% for a decapeptide). Photolysis was performed at 350 nm in degassed methanol (the presence of oxygen decreased both the yield and purity). A modification of this resin involved the replacement of the benzylic bromide by an amine, thus linking the peptide to the resin through an amide bond. Photolysis leads to



Scheme 50

the C-terminal carboxamide, which is also present in many biologically active peptides.[120,121]

Solid phase synthesis can present some drawbacks over solution-phase synthesis; a compromise is found with soluble-polymers, such as poly-ethyleneglycol (PEG). This polymer can be considered as a simple protecting group allowing solubilisation of the peptide, and the separation from side-products can be performed by membrane filtration.[122,123] Photolabile linkers of the type seen above were developed for PEG-supported synthesis (Scheme 51). It must be mentioned that this case presents

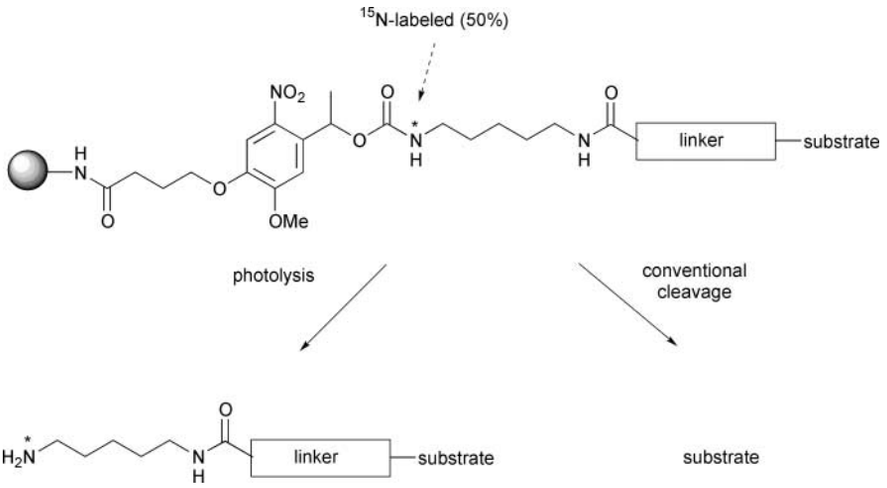


Scheme 51

the additional advantage that the photolysis will exclusively cleave the linker-bound peptide, and not peptides accidentally bound to the polymer through an unfunctionalised free hydroxy group. It thus avoids the necessity of blocking the remaining free sites by acetylation.[124]

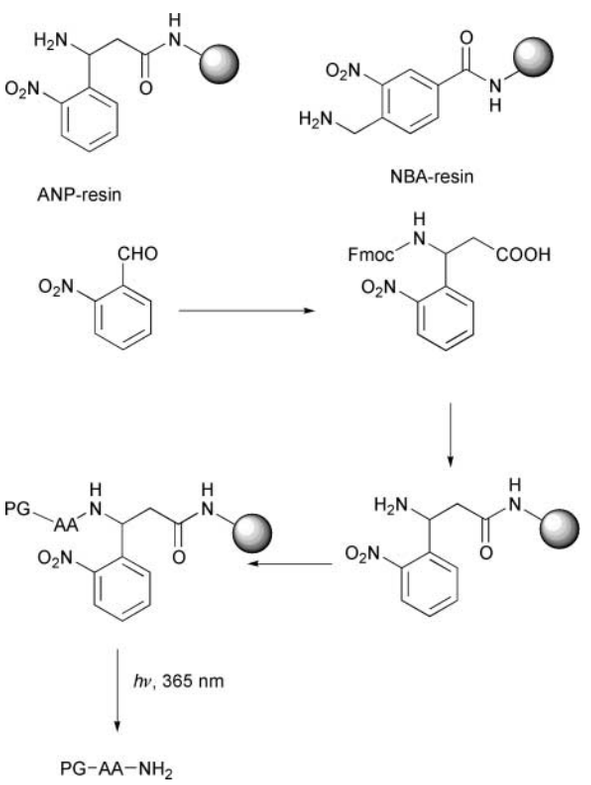
The peptide could also be liberated from the polymer by hydrazinolysis,[125] or catalytic hydrogenation.[126] The linker was also bound to the polymer through an amide bond rather than an ester.[127] Both C-terminal free acids or carboxamides (with an N-modified linker) were obtained by this strategy.[128]

A photolabile linker was also used to provide convenient orthogonality for analytical purposes by McKeown.[129] An easily ionisable amine was introduced on the linker to provide a characteristic ESI-MS signal. As an additional feature, ^{15}N labelling was used to distinguish specific signals from background noise. Thus, the substrate could be liberated from the resin by conventional hydrolytic cleavage, whereas a single bead, when photolyzed at 365 nm, provided a solution that could be directly analysed by ESI-MS (Scheme 52).



Scheme 52

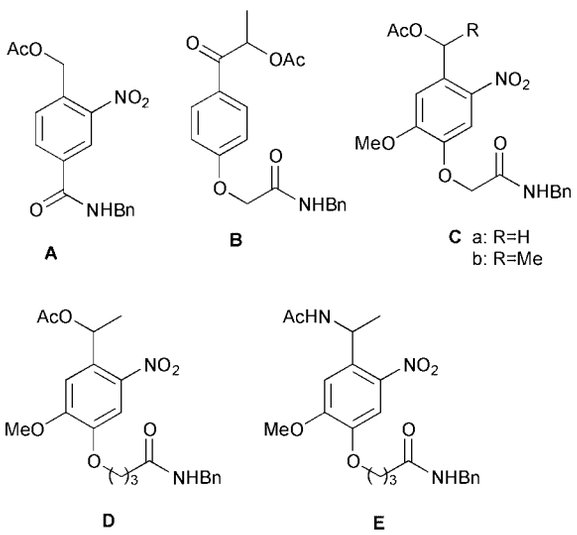
Another single-bead decoding strategy by ESI-MS was used by Brown.[130] The ANP-resin (3-amino-3-(2-nitrophenyl)propionic acid) was utilised for its improved characteristics (high cleavage yields and shorter half-lives under irradiation). The photolysis liberated the C-terminal peptides as carboxamides (Scheme 53). The linker is very easily prepared and coupled to the solid support (in this example, TentaGel 88 was used).



Scheme 53

Fmoc-Arg(Tos)-NH_2 was liberated in 83% yield after 20 hours photolysis at 365 nm. A tripeptide (Fmoc-Asp-Arg(Tos)-Val-NH_2) was also cleaved and analysed by ESI-MS.

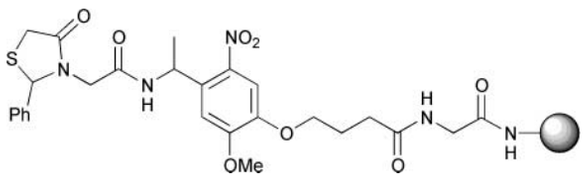
Very extensive studies have been carried out by Holmes, on the effect of the substituents at various positions on the linker.[131,132] The classical linkers (*e.g. o*-nitrobenzyl or phenacyl) suffer from slow cleavage rate; during the time required for the photolysis, unwanted photo-oxidations may occur (such as oxidation of methionine into methionine sulfoxide).[121] Another drawback is the formation of a nitrosoaldehyde that can react or act as a filter. The properties of different linkers were compared (Scheme 54).[131] The NBA resin was efficiently used in



Scheme 54

oligonucleotide synthesis, with photochemical deprotection conditions which minimised thymine–thymine photodimerisation.[133] The phenacyl linker carbonyl group (as in **B**) can participate in a cyclisation (as diketopiperazine at the dipeptide stage); it is also quite sensitive to nucleophiles.[134] The addition of an α-methyl group to *o*-nitrobenzyl alcohol-derived linkers (as in **C**, **D**, and **E**) led to poor release in peptides longer than five residues due to poor swelling of the resin.[135] An α-aryl substituent improved the efficiency, and decapeptides were prepared.[136] However, the introduction of the α-methyl group increased the reaction rate and diminished the reactivity of byproducts (a nitrosoacetophenone). The high photolysis rates allowed the release of methionine-containing peptides.

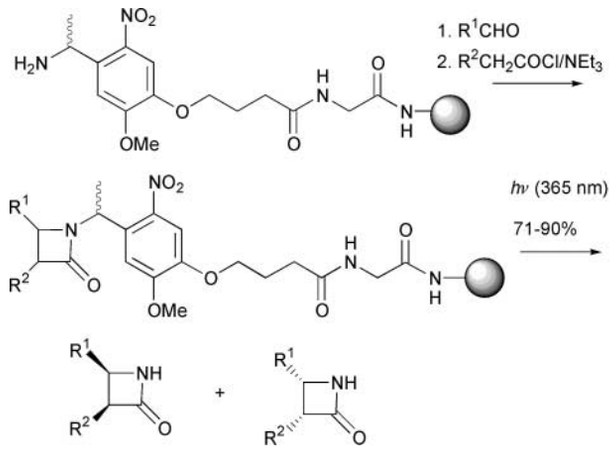
The photolysis rate of all these linkers was quite solvent-dependent. **A** is the standard NBA-resin. **B** was ineffective in organic solvents, whereas **C** and **D** were rapidly photolyzed, presumably due to increased absorbance in the 365 nm region. **Cb** was *ca.* five times faster than **Ca**, and **E** was the fastest of all these linkers. The attachment on the solid support (polystyrene beads) was provided by a glycine unit (Scheme 55). The beads



Scheme 55

could be analysed by gel-phase ^{13}C-NMR spectroscopy, with ^{13}C-enriched glycine, and showed doubled signals because of the diastereomeric mixture. The linker was stable upon treatment with 95% TFA–H_2O, but 95% cleavage was observed after 3 hours photolysis. The photolysis of the supported linker was slower than in the solution-phase, for light scattering, shielding or shadowing effects of the resin, as well as the swelling and solvation properties of the support.

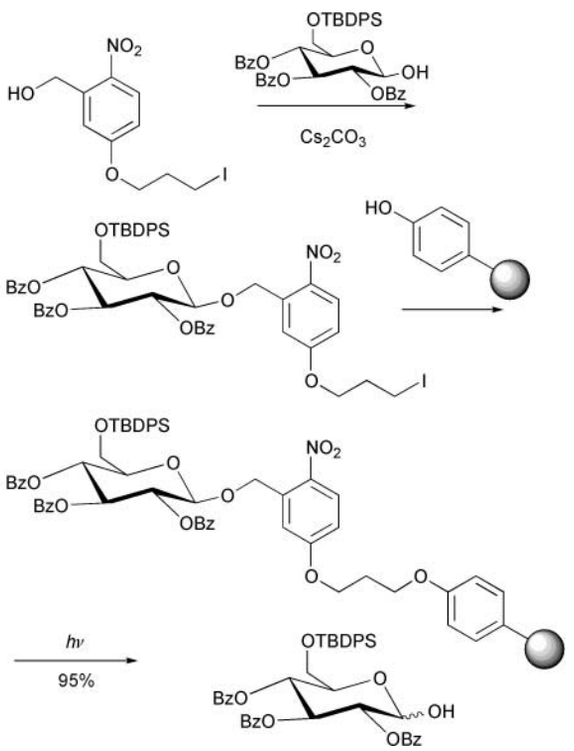
The amine function from the Holmes linker was used as the nitrogen source in a combinatorial synthesis of β-lactams (Scheme 56).[137] This strategy, in addition to the mildness of



Scheme 56

cleavage conditions, allows the formation of *N*-unsubstituted β-lactams.

Nicolaou also used a photolabile linker, in the solid-phase synthesis of polysaccharides.[138] In a first example, the carbohydrate was coupled to the *o*-nitrobenzyl alcohol derivative at the benzylic position, and then attached to the resin through a phenyl-ether link. Iterative synthesis was then performed on the bound sugar, up to a heptasaccharide. Photolysis smoothly released the saccharide (Scheme 57).



Scheme 57

The drawbacks of this strategy (both α and β anomers at the cleavage site, and the need to reactivate the released saccharide for subsequent coupling steps) were addressed in a more recent work.[139] A *p*-hydroxybenzoic acid spacer was inserted between the photolabile linker and the carbohydrate unit (Scheme 58). Cleavage released the carbohydrate *p*-hydroxybenzoate, with the β anomeric configuration. Treatment of the resin with $PhSSiMe_3$ and zinc iodide formed a free carbohydrate donor, that can be immediately used as a building block. In this example, the resin was simply the chloromethylated Merrifield-resin, directly attached to the photolabile unit. A dodecasaccharide was prepared using this strategy.

Nitrobenzyl alcohol- or amine-derived linkers have also been optimised for other types of solid support, such as aminopropylsiloxane-grafted controlled pore glass (amino-CPG), and very short and efficient preparative strategies have been developed by Harran.[140]

Other side-reaction as seen above can actually occur during photolysis of *o*-nitrobenzyl linkers. It was observed that a peptidase remained active upon irradiation, and in the presence of the linker, but lost significantly its activity upon photolysis in the presence of the linker. The presence of DTT (dithioerythrol) accelerates the cleavage. In the presence of semicarbazide, there was no loss of activity. Clearly the photolysis nitroso by-products interact detrimentally with the release enzyme.[141]

9.3 Photosolvolysis

A phenacyl-type linker (handle) for polymer-supported peptide synthesis was developed by Mutter (Scheme 59).[134] There was at that time a lack of systems that were labile towards nucleophilic attack. This linker was based on propionylphenoxyacetic acid, and was totally stable under acidic conditions (6 hours in TFA, 1.2 M HCl–HOAc or 33% HBr–HOAc). On the other hand, it was very sensitive to nucleophiles (triton, NH_3, hydrazine, NaOH, Et_3N–MeOH). Its photolability was increased compared to the *para*-unsubstituted parent, probably due to the bathochromic shift induced by the *para*-methoxy substituent.[85] Hence, 80% of cleavage was observed after 10 hours of irradiation at 350 nm. It was also very easily prepared. An application was shown with the synthesis of Leu-Enkephalin (biologically active pentapeptide).

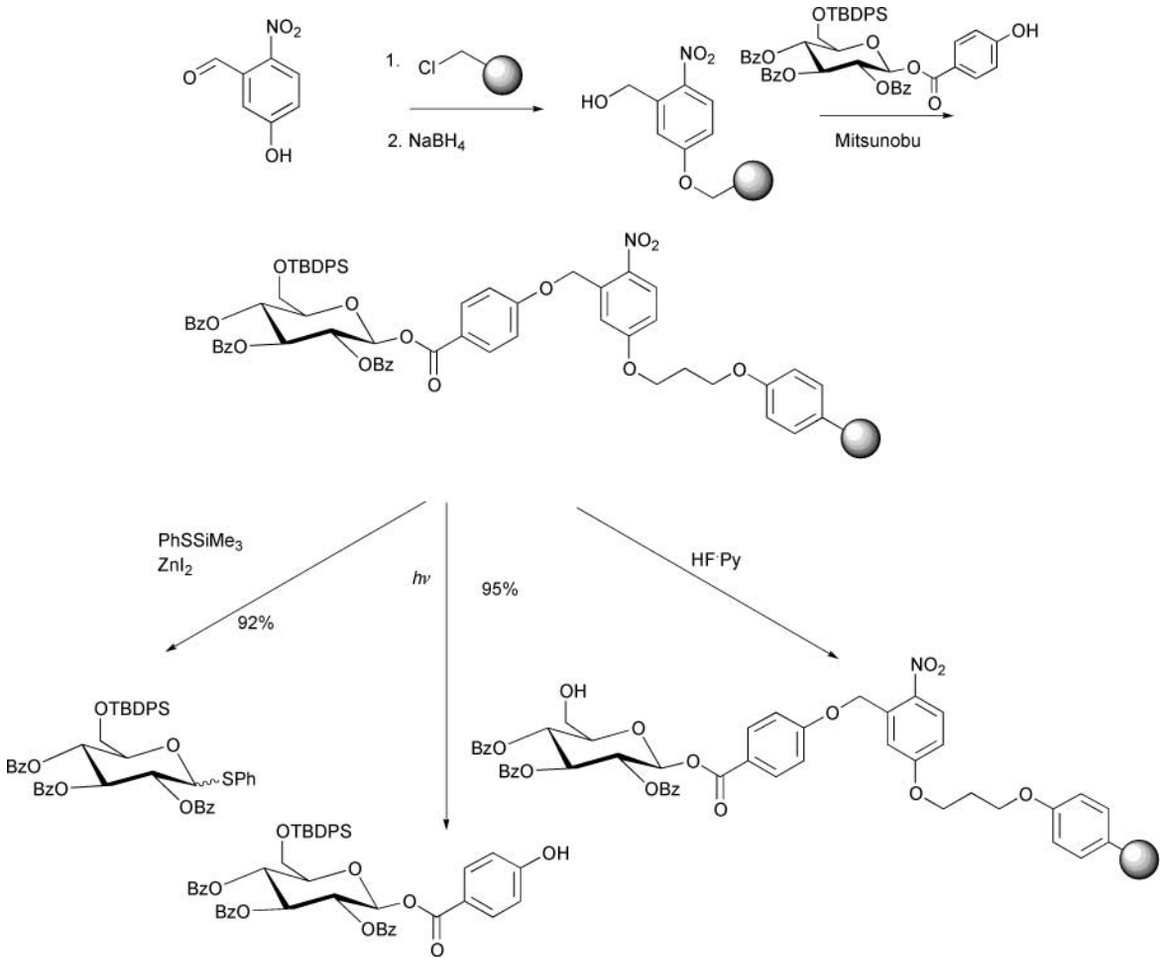
A functionalised resin (no linker, **A**), based on the same principle, but lacking the benefit of the *para*-ether induced bathochromic shift, had been described by Wang (Scheme 60).[142] A photosensitivity at 350 nm was observed, but very long irradiation times were required; its efficiency was found to be somewhat disappointing, and traditional chemical cleavage was later proposed. Indeed, a potassium cyanide–18-crown-6 was used to selectively cleave the peptide from the resin, without cleavage of the side-chains benzyl esters (as hydrazine does).[143] Another variation was resin **B** (using a linker).[144]

As mentioned above (Section 3.2), Chan used the benzoin photolabile group as a linker.[145] In this case, the linker was used to link parts of a peptide, and not to attach it to a solid support (Scheme 61).

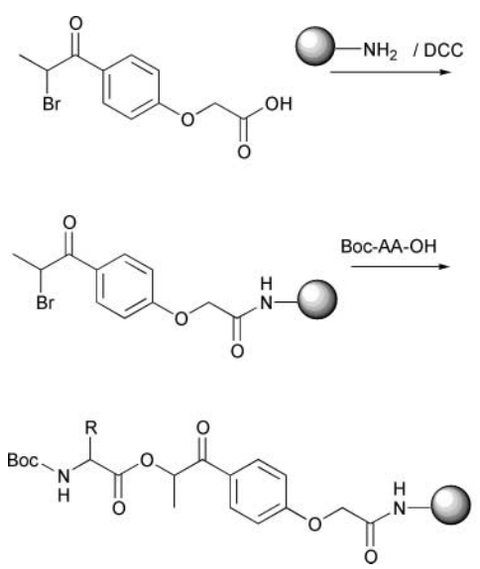
Balasubramanian used an interesting "safety-catch" strategy (Scheme 62).[83] To prevent unwanted photolysis during the course of the synthesis, the dithiane used for the preparation of the benzoin was kept intact. This linker is thus totally photostable. Prior to the cleavage, the hydrolysis of the dithiane restored the photosensitivity.

9.4 Norrish-type I reactions

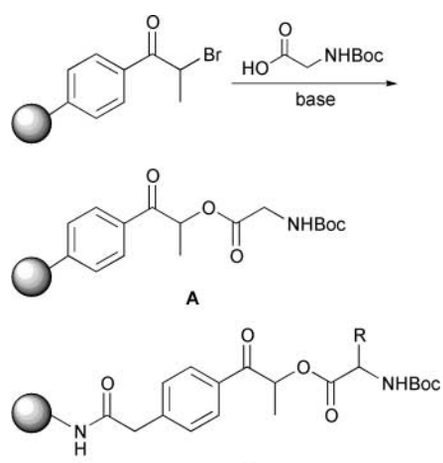
Giese developed a new linker based on the pivaloyl fragment (Scheme 63).[146] The carboxylic acid is liberated upon irradiation with light below 340 nm, and the reaction works equally well regardless of the solvent (except acetonitrile). This linker is very resistant to chemical reactions: Suzuki or Stille couplings are compatible, but it is also stable to harsh acidic media (TsOH, PhMe, 80 °C) and strong bases (KHMDS, −78 °C). As an example, Leu-Enkephalin was synthesised, with a loading of



Scheme 58



Scheme 59



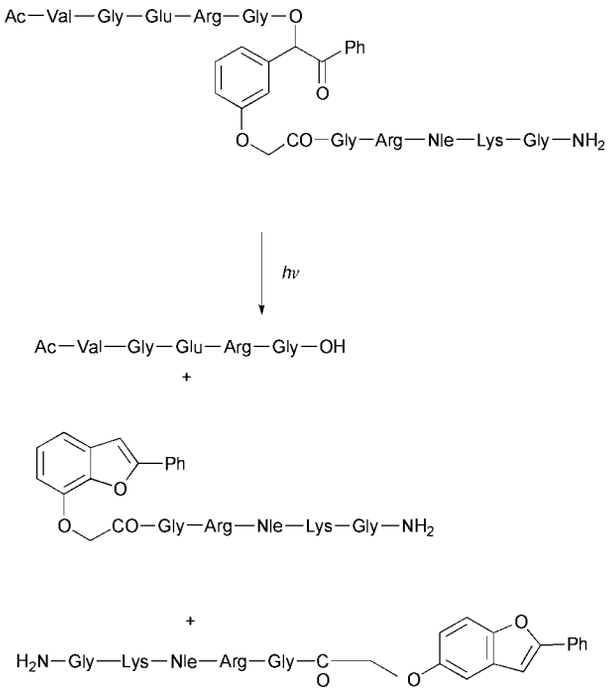
Scheme 60

0.147 mmol g^{-1} after four steps. The photolysis reaction rate and the light intensity did not increase proportionally, as frequently found in SPOS. This is attributed to light scattering, shielding or shadowing effects from the beads. The mechanism for this unprecedented reaction is proposed to be initiated by a Norrish-type I reaction, followed by a radical-induced β-C–O bond cleavage.

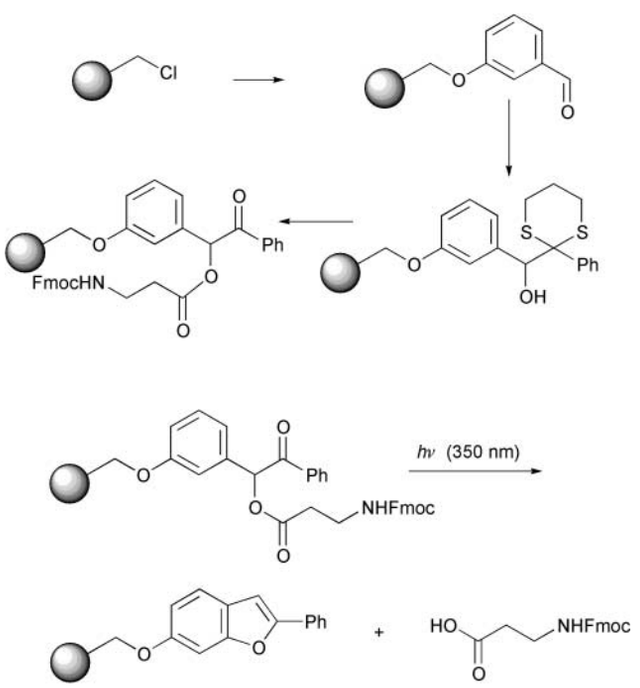
A variation of this linker was later described, allowing the anchorage of an alcohol through an ether bond (Scheme 64).[147] The absence of ester makes this linker exceptionally resistant towards aggressive compounds, such as $LiAlH_4$, hydrazine or potassium *tert*-butoxide. Photolysis (between 280 and 340 nm) smoothly released the alcohol in yields up to 80%. As in the previous case, all the by-products are gaseous or resin-bound.

9.5 Traceless resins and linkers

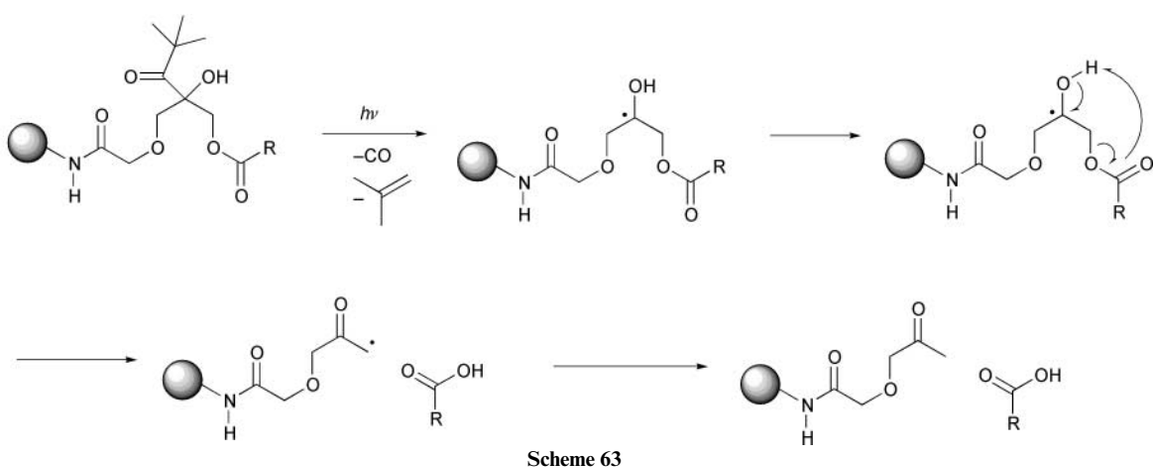
A traceless linker is a linker leaving a C–H bond on the substrate upon cleavage. An arylsilane is frequently used, because of its easy protodesilylation. On the other hand, the formation of an aliphatic C–H bond is more difficult. Such a linker could be made in the family of photolabile linkers, based on the Barton photolabile thiohydroxamate (Scheme 65).[148] The drawback of this approach is the requirement of an external hydrogen donor (Bu_3SnH, TMS_3SiH or *t*-BuSH).



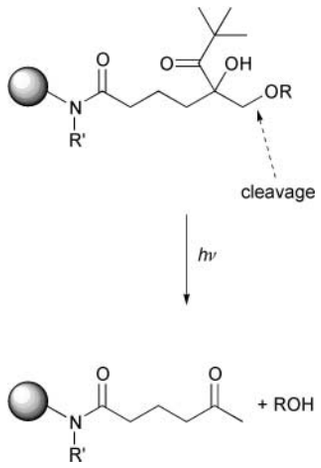
Scheme 61



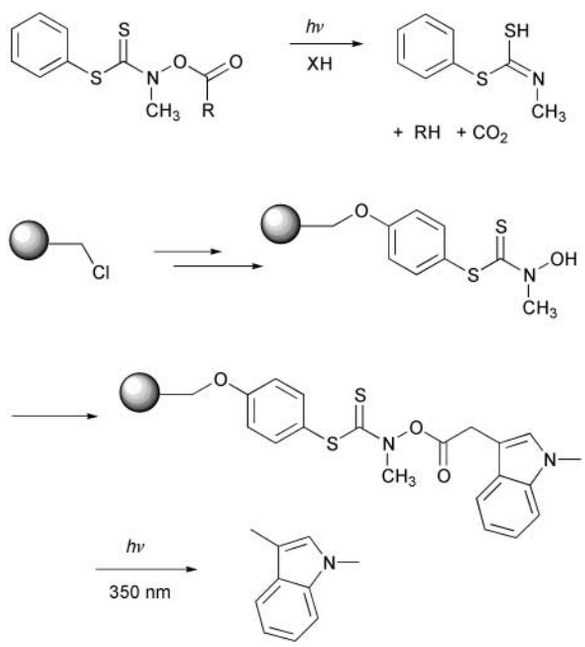
Scheme 62



Scheme 63



Scheme 64

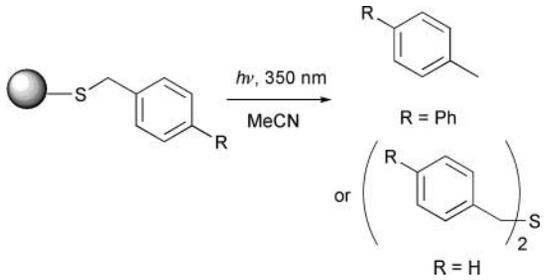


Scheme 65

Another potentially traceless linker for non-peptidic molecules was proposed in 1994, based on a thioether linkage (Scheme 66).[149]

10 Experimental aspects

Photochemical reactions are usually very easily carried out using normal Pyrex reaction vessels (for specific cases requiring short-wavelength light, quartz glassware is nevertheless

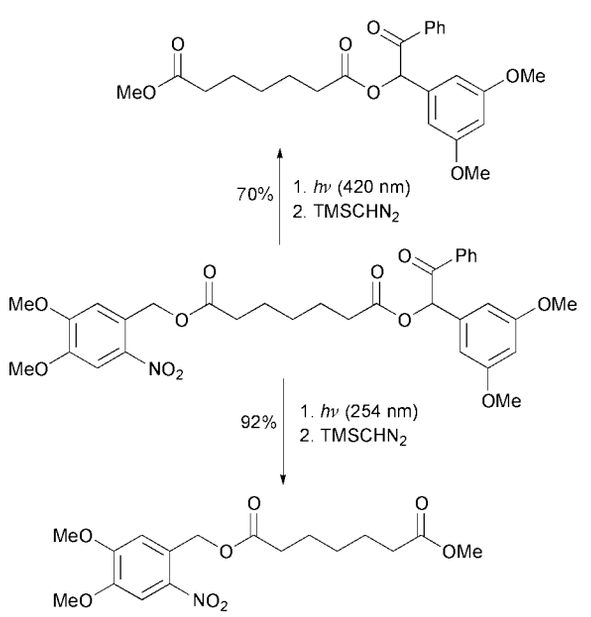


Scheme 66

required). As ambient oxygen can be an efficient quencher, it is recommended to briefly deaerate the reaction mixtures immediately before the irradiation. Simply bubbling argon through the solution for a few minutes is in most of the cases sufficient. There are a vast variety of different light sources available, ranging from expensive lasers to inexpensive common slide projectors.[27] For many applications, a medium- or high-pressure mercury lamp with an appropriate cut-off filter is the simplest source. For a more precise control of the wavelength, a Rayonet apparatus equipped with monochromatic bulbs at 254, 300, 350 or 419 nm will be required.[150]

11 Perspectives

All the work discussed above shows that there is indeed a great variety of photolabile protecting groups, and that they can provide an attractive solution whenever an orthogonality issue is raised. There is however an aspect that has not been addressed until very recently. Would it be possible to use the wavelength to exploit the concept of orthogonality *within the set of photolabile protecting groups*, and selectively remove one of several groups at a given wavelength, and another at a different wavelength? Preliminary work in our laboratory showed that *o*-nitrobenzyl alcohol derivatives reacted at various rates according to the photolysis wavelength.[151] When two different chromophores have to be independently excited, there is always the risk of energy transfer, suppressing the initial discrimination. Further work showed that energy transfer can be minimised (if not suppressed), and that chromatic orthogonality is indeed possible (Scheme 67).[150]



Scheme 67

This new approach is still in its infancy, but it clearly opens new perspectives in protecting group chemistry, solid-phase synthesis, release of caged-substances and material science.

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