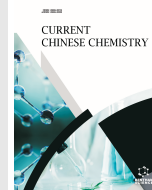


The Recent Developments and Applications of Photoremovable Protecting Groups in Organic Chemistry

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Abstract: A photoremovable protecting group (PRPG) is an organic molecular framework that may be cleaved when exposed to light. It allows spatial as well as temporal control over the release of various substances such as neurotransmitters, cell signalling molecules, acids, bases, Ca²⁺ ions, oxidants, insecticides, pheromones, and perfumes, etc. This mini-review highlights the history and current state of the art of several PRPGs in organic chemistry. Synthesis, application and mechanism of cleavage process of PRPGs were also discussed thoroughly in this article.

Keywords: Photoremovable protecting groups, photoreleasable protecting groups, photocleavable protecting groups, photoactivatable protecting groups, photochemistry, neurotransmitter.

1. INTRODUCTION

Selective functionalization of poly-functional molecules is an essential and desired characteristic in multi-step organic synthesis since it allows the creation of new functionalities. It is possible to introduce a protecting group (PG) onto a specific functional group (FG) in a poly-functional molecule in order to inhibit its reactivity under the reaction conditions required to make modifications elsewhere in the molecule. The deactivation of functional groups in synthetic organic chemistry that are reactive towards nucleophilic or electrophilic reagents and whose selective transformation may face difficulties is a regular phenomenon. This deactivation is accomplished by covering the functional group with a protecting group. The protecting group should possess certain unique properties, including the ability to react readily with the functional group being protected under mild conditions, (ii) stability to the reaction conditions following protection, and (iii) ease of removal without impacting other parts of the molecule [1].

For a long time, the chemical community has been aware of photoremovable (also known as photoreleasable, photocleavable, or photoactivatable) protecting groups (PRPGs). Photoremovable protecting groups are identical to conventional protecting groups used in organic synthesis, with the exception that the deprotection process is activated by light irradiation. Since light is used to deprotect, it has many benefits, including (i) the capacity to precisely regulate processes in time and space, (ii) the absence of reagents other than light, and (iii) the ability to be carried out under moderate and neutral reaction conditions. A decent PRPG should meet many requirements, the most essential of which are as follows [2]:

First, a smooth and uniform photoreaction with a reasonably high quantum efficiency and a rapid rate of release is a general requirement. Second, the deprotection of the substrate from the protective group should be the first photochemical step in the process of photochemistry. Third, photolysis products should not absorb light at the wavelength of the PRPG's irradiation, thereby avoiding competition for incoming light. Additionally, they must be biologically compatible. Fourth, the wavelengths used for excitation should be longer than 300 nm and should not be absorbed by the solvent, photoproducts, or substrate. Fifth, after photolysis, the PRPGs should not produce any stereogenic centres. Sixth, for biological investigations, the protective group, caged compounds, and photoproducts should be soluble in water. This criterion is waived for synthetic applications. Seventh, there must be a generic, high-yielding synthetic method for attaching the PRPG to the substrate. Notably, no one PRPG can meet all of these criteria. Even if a PRPG lacks one or two of these characteristics, it is still helpful. *o*-nitrobenzyl esters, α -substituted acetophenones, benzoin, benzyl groups, cinnamate esters, and coumaryl groups are all examples of photoremovable protecting groups that are often employed. Photoremovable protective groups have been referred to in the literature as "phototrigger," "photolabile group," and "caging group".

2. THE CHEMISTRY OF PHOTOREMOVABLE PROTECTING GROUPS

2.1. 2-Nitrobenzyl (2-NB) Based PRPGs

PRPGs based on nitrobenzyl are often considered the most commonly utilized PRPGs. Since Norrish originally described the mechanism of these PRPGs in 1935, they are often referred to as Norrish Type II reactions. Barltrop and

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co-workers [3] demonstrated the photorelease of benzoic acid for the first time in 1966, utilising the 2-nitrobenzyl group as indicated in Scheme 1.

The photorelease of the 2-nitrobenzyl group occurs in five distinct steps (Scheme 2): excitation, photoredox to the aci-nitro intermediate, cyclization to the benzisoxazole, ring-opening to the hemiacetal, and collapse of the hemiacetal with substrate release. Though the 2-nitrobenzyl group has been widely investigated as a PRPG, it does have some limitations, including the following: (i) During photolysis, a reactive o-nitrosoaldehyde (**3**) is formed as a by-product, which can be harmful, especially in biological studies [4, 5]; (ii) a secondary photoproduct, azobenzene-2,2'-dicarboxylic acid (**4**), is also formed from the reactive 2-nitrosoaldehyde, (iii) short-wavelength UV light is necessary for deprotection, which resulted in undesired by-product formation. To address the aforementioned disadvantages of the 2-nitro-benzyl group, several structural analogues were synthesized, including the 4,5-dimethoxy analogue (DMNB) [6], 1-(2-nitrophenyl) ethyl (NPE) [7] and its 4,5-dimethoxy analogue (DMNPE) [8], and the α -carboxy-2-nitrobenzyl (CNB) [9] groups. Kaplan and co-workers used the 2-nitrobenzyl PRPG to release ATP for the first time in 1978 [10]. After photochemical cleavage, the inorganic phosphate and ATP were released from the corresponding 1-(2-nitrophenyl) ethyl (NPE) and 2-nitrobenzyl (NB) carbonyl compounds, respectively (Scheme 3).

Following the successful introduction of 2-nitrobenzyl caged ATP into physiological media, it gained widespread acceptance, and the majority of caged biologically active compounds, such as caged phosphates [6, 7], caged proteins [11], caged calcium [6, 12], and caged fluorophores [13] have been synthesized using 2-nitrobenzyl derivatives.

2.2. Benzoin Based PRPGs

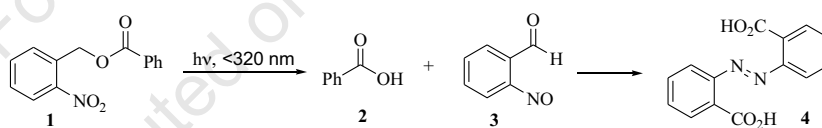
Sheehan and Wilson [14] investigated the photochemical rearrangement of various benzoin compounds to produce 2-

phenyl benzofuran (**18**) for the first time in 1971. They established that when benzoin esters are exposed to light, they undergo photocyclization, releasing carboxylic acids concurrently (Scheme 4). Additionally, Corrie and Trentham [15] demonstrated that the photorelease efficiency of benzoin is highly dependent on the nature and position of the substituents. It has been found that 3', 5'-dimethoxy benzoin esters demonstrate the highest quantum efficiency of 0.78.

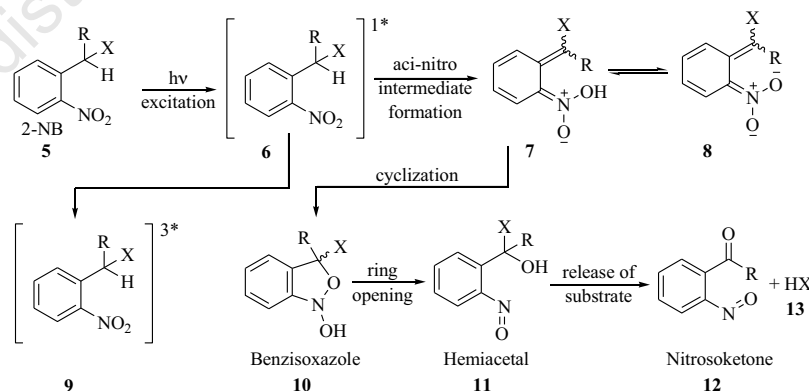
The photorelease mechanism was assigned based on the quenching of benzofuran formation by naphthalene and piperylene (Scheme 5). [16-18] Benzoin protecting groups exhibit several important properties, including the following: (i) rapid release of the protected compound with a high chemical and quantum yield (ii), solubility in a wide range of solvents (iii), formation of biologically compatible side products and (iv) absorption in the longer wavelength region (300 nm). As a result, the benzoin group became particularly appealing, and caged benzoin phosphates were utilized as a suitable substituent of the previously used nitrobenzyl caged phosphates. Givens and colleagues investigated the utility of benzoin esters as phototriggers for biologically active molecules such as cAMP [16-18], GABA [19] and glutamate [19, 20]. Research reports from other groups have also found the utility of benzoin esters as photo-triggers [14, 15].

2.3. Phenacyl Based PRPGs

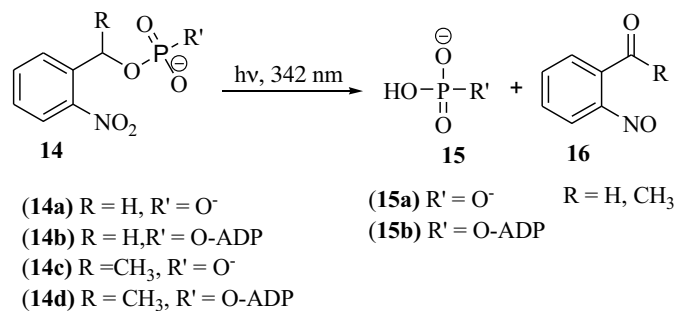
Sheehan and Umezawa introduced the use of the phenacyl group as a PRPG in 1973 [20]. They observed that irradiating p-methoxyphenacyl benzoate (**27**) in ethanol or dioxane gave benzoic acid in a good yield with the formation of the photoproduct para-methoxyacetophenone. Initially, it was proposed that photorelease would occur *via* simple homolysis of the carbon-oxygen bond in the triplet excited state, as shown in Scheme 6.



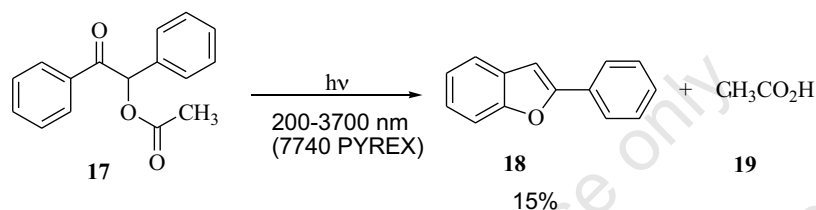
Scheme 1. Photorelease of benzoic acid from the 2-nitrobenzyl group.



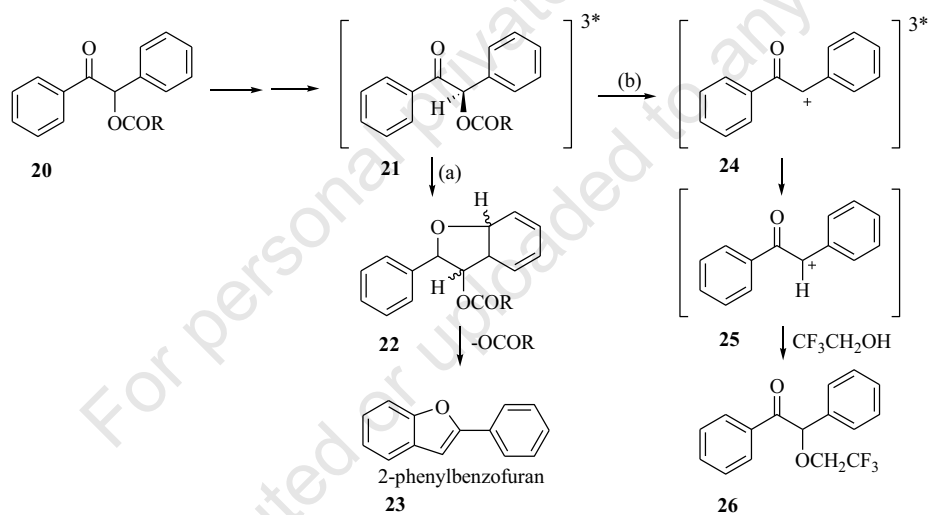
Scheme 2. 2-nitrobenzyl group photorelease mechanism.



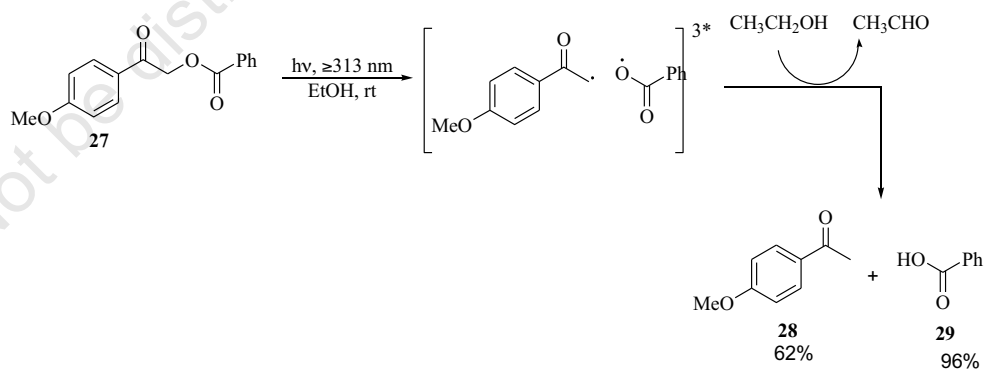
Scheme 3. Photorelease of phosphate from the 2-nitrobenzyl group.



Scheme 4. Photorelease of carboxylic acid by benzoin group.



Scheme 5. Benzoin photorelease mechanism.

Scheme 6. Photorelease of benzoic acid, amino acids, and peptides by the *p*-methoxyphenacyl group.

Anderson and Reese [21] described in 1962 that ortho- and para-methoxyphenacyl chloride, as well as para-hydroxyphenacyl chloride, undergo a Favorskii-like rearrangement in 1% aqueous ethanol to form two most important photoproducts, namely para-hydroxyacetophenone and ethyl para-hydroxyphenyl acetate, through a spiro intermediate (31). (Scheme 7).

Givens and co-workers [22] developed the para-hydroxyphenacyl group as an effective PRPG for carboxylic acid release. The para-hydroxyphenacyl group has several attractive properties that make it a potential photo-trigger, including the following: (i) It is easily synthesized from commercially available para-hydroxyacetophenone *via* a simple synthetic route, (ii) it is water soluble, (iii) photorelease occurs quickly, (iv) photorelease quantum yields are high, and (v) the main photoproduct, para-hydroxyphenyl acetic acid, is non-toxic compound. As a result, it does not compete for light absorption with the reactant substrate, and (vii) the para-hydroxyphenacyl group does not introduce a chiral centre. Apart from the benefits mentioned before, the primary disadvantage of the para-hydroxyphenacyl protecting group is its poor molar extinction coefficient above 320 nm wavelengths.

Conrad and co-workers [23] addressed the aforementioned issue by adding extra methoxy substituents to the aromatic ring of the para-hydroxyphenacyl chromophore. They described a novel PRPG, 3,5-dimethoxy-para-hydroxyphenacyl ester, with an absorption wavelength of up to 400 nm (Scheme 8). However, this modification resulted in a significant decrease in the quantum yields of photorelease of the substrate as a result of the modification. The para-hydroxyphenacyl PRPG has been shown to release the substrate through direct neighboring group participation, which results in the formation of the spirodienedione intermediate (44) [19, 24]. The nucleophilic hydrolysis of the spirodienedione intermediate results in the formation of the photoproduct, para-hydroxyphenylacetic acid (Scheme 9).

Givens and co-workers [18, 21] discovered that the para-hydroxyphenacyl group is a powerful photo-trigger for the release of active biomolecules such as α -amino acids, phosphates, nucleotide derivatives, peptides, and oligopeptides, as well as Bradykinin, a naturally occurring, potent modulator of pain, inflammation, and vasodilator response.

According to Zabadal and co-workers [25], in the year 2001, a new class of phenacyl group, namely the 2,5-dimethylphenacyl (DMP) group, was introduced as a PRPG. The DMP group was introduced as a PRPG on the basis of the highly efficient photoenolisation reaction of *o*-alkylaryl ketones to carry out the release of various functional groups. The photoirradiation of DMP ester results in the release of free carboxylic acid as well as the photoproduct 6-methylindan-1-one (48) (Scheme 10).

Following this discovery in 2005, the Klan [26] group demonstrated that the 2,5-dimethylphenacyl (DMP) group can also be used as a PRPG for alcohols and phenols (Scheme 11). They also looked into the effect of solvent on the photolysis of 50a-e and discovered that the photolysis in a nonpolar solvent (cyclohexane) proceeds more quickly than the photolysis in a polar solvent like methanol.

In order for the photorelease to occur, a mechanism [27] that includes photo-enolization of the DMP chromophore in its singlet excited state is suggested, as presented in Scheme 12.

2.4. Coumarinyl Based PRPGs

Newly discovered photo-triggers, coumarin-4-ylmethyl groups, have been utilized to create caged compounds of phosphates, carboxylates, carbonyl compounds, phenolic compounds, alcohols, and amines. It is generally accepted that the photochemistry of the coumarin chromophore is comparable to that of an arylalkyl-type photoremovable protecting group.

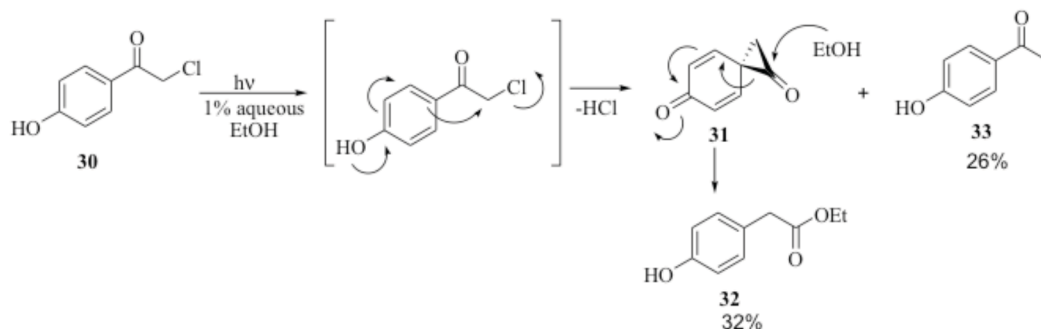
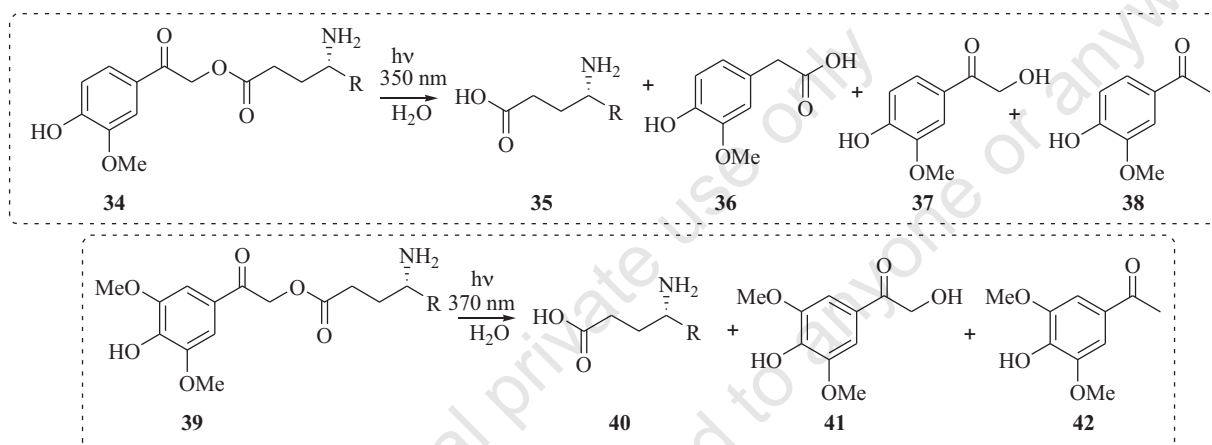
Givens and co-workers [28] conducted the first study on the photochemical reactivity of 7-methoxycoumarin-4-ylmethyl (MCM) esters in 1984. When MCM esters in aqueous medium were photolyzed, it resulted in the release of free carboxylic acid, as well as the production of the photoproduct hydroxymethylcoumarin (58).

Schade and colleagues [29] investigated the photochemical and photophysical behaviour of 4-(hydroxymethyl)-7-methoxycoumarin (MCM) caged esters under physiological conditions and discovered that the quantum efficiencies for the photolysis of MCM caged esters ranged between 0.0043 and 0.0064, as shown in Scheme 13.

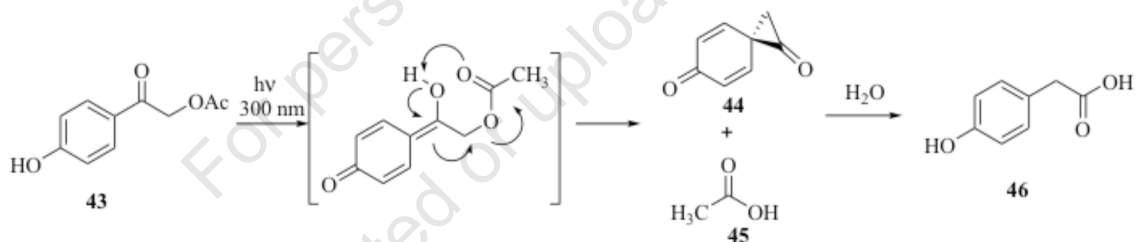
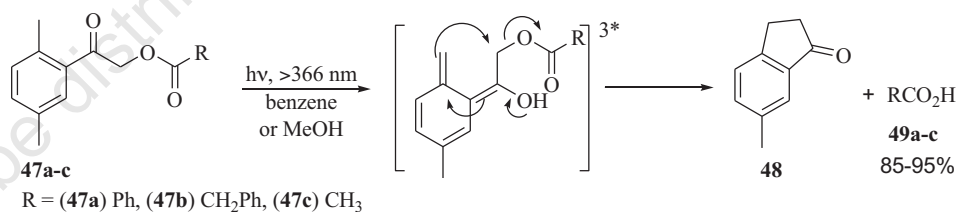
Scheme 14 shows the possible mechanism for the photolysis of MCM esters, which involves a singlet excited state followed by either direct heterolytic C-O bond cleavage or homolytic cleavage of C-O bond followed by electron transfer to generate the ion pair. Finally, in an aqueous solvent, the resultant ion pair escapes from the solvent cage and reacts with the photoproducts to form the desired outcome. Schade and coworkers report the quantum efficiency and the polarity of the solvent employed in the experiment are related [29].

Despite the fact that the first report of MCM ester as a PRPG was published in 1984, the usage of coumarin derivatives as caging groups was only discovered ten years later. Two-nitrobenzyl type cages were explored as a possible alternative for the coumarin caging group. Photolysis of MCM-cAMP [30, 31] at 340 nm in a simulated physiological conditions resulted in a high yield of parent cAMP in a quantitatively significant amount. The coumarin caging group offers numerous benefits in addition to its high quantum yield, including (i) having a high molar-extinction coefficient, (ii) having absorption in the visible region, with the absorption maxima being red shifted by introducing appropriate substituents into the aromatic ring, (iii) having a fast rate of photorelease, (iv) having improved stability in darkness, and (v) having a high two-photon absorption cross section that is very useful for biological investigations.

In order to produce several caged compounds of bioactive molecules such as second messengers, [30, 32, 33] neurotransmitters, DNA and RNA, an inhibitor of nitric oxide synthesis, and an inhibitor of protein synthesis, MCM [34, 35] and their structural variants (Fig. 1) were synthesized with improved properties and have been explored for their potential to produce several caged compounds of bioactive molecules. Caged compounds have recently been effectively used in the study of cell chemistry, and this is an exciting development.

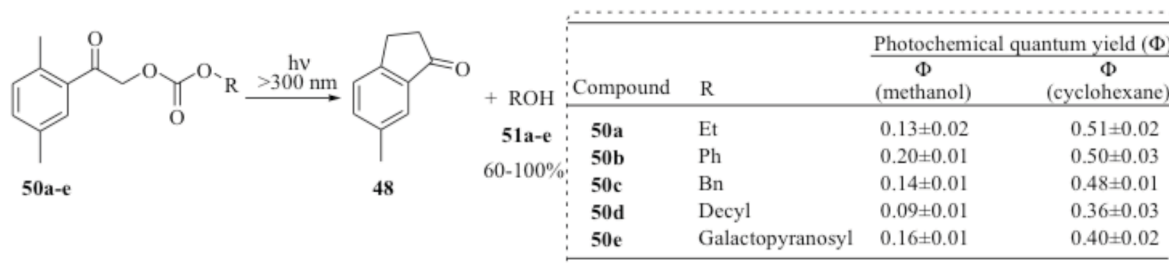
Scheme 7. Reaction mechanism of the *p*-hydroxyphenacyl chloride.

Scheme 8. Photorelease of amino acids from methoxy and dimethoxy phenacyl groups.

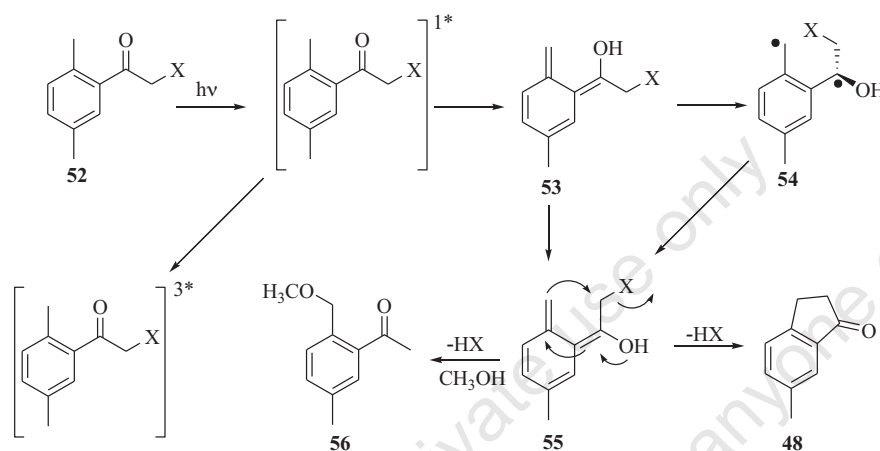
Scheme 9. Photorelease of acetic acid from the *p*-hydroxy phenacyl group.

Ester	Solvent	Φ_p
47a	benzene	0.23 ± 0.02
	methanol	0.09 ± 0.01
47b	benzene	0.18 ± 0.02
	methanol	0.11 ± 0.01
47c	benzene	0.25 ± 0.01
	methanol	0.14 ± 0.02

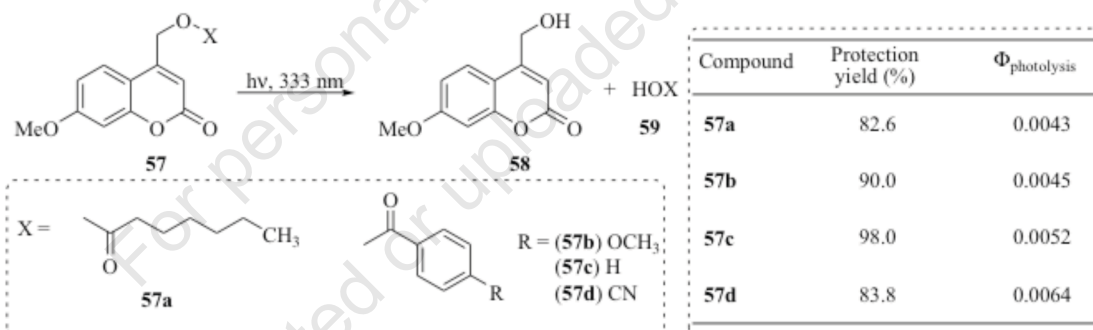
Scheme 10. Photorelease of carboxylic acids by 2,5-dimethylphenacyl group.



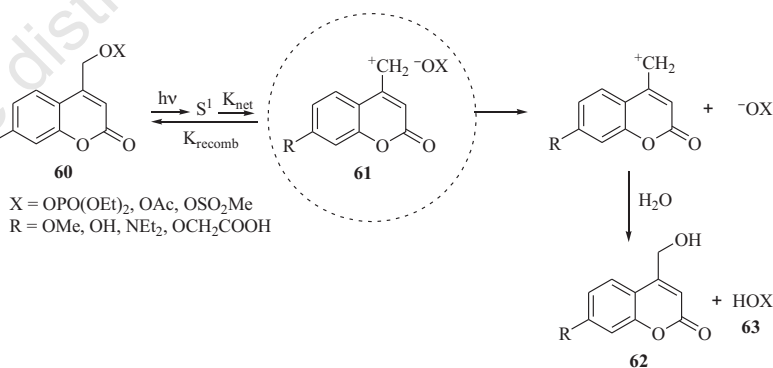
Scheme 11. Photorelease of alcohols and phenol by 2,5-dimethylphenacyl group.



Scheme 12. 2,5-dimethylphenacyl photorelease mechanism.



Scheme 13. Release of carboxylic acids from 4-(hydroxymethyl)-7-methoxycoumarin PRPG.



Scheme 14. The photorelease mechanism of the coumarinyl group.

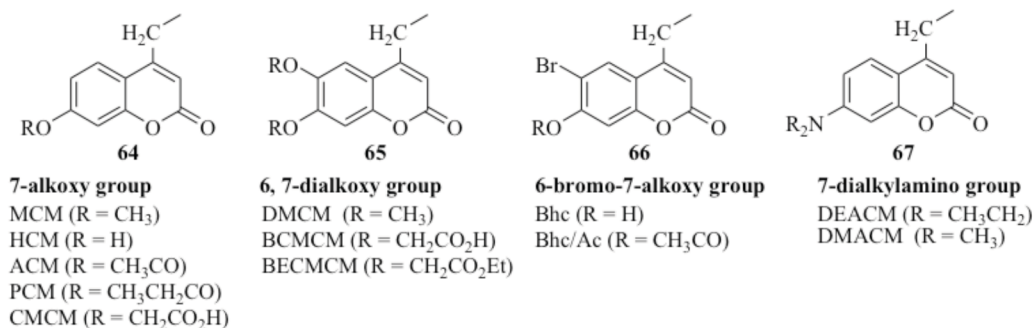


Fig. (1). Structures of coumarin group.

The MCM PRPGs have a few drawbacks, such as the fact that some of the derivatives are not stable in neutral aqueous environments for an extended period of time and that none of the coumarin caged compounds are commercially available.

2.5. 8-Bromo-7-Hydroxyquinoline Based PRPG

Fedoryak and co-workers [36] investigated the photochemical properties of the 8-Bromo-7-hydroxyquinoline (BHQ) group (**68**) in 2002 and discovered that it is efficiently photolyzed by both one photon excitation (365 nm) and two photon excitation (740 nm) under aqueous buffer to release carboxylic acids (Scheme 15).

Zhu and co-workers [37] used the BHQ group in 2006 to liberate carboxylates, phosphates, and diols functional groups from a variety of organic compounds (Scheme 16). The researchers further propose that photolysis occurs *via* a solvent-assisted photoheterolysis (S_N1 type) reaction mechanism on the sub-microsecond time scale, which is supported by Stern-Volmer quenching, time-resolved infrared (TRIR), and ¹⁸O labelling studies. The high quantum efficiency of the BHQ group for photolysis, as well as its excellent solubility in aqueous buffers is the primary advantage of this PRPG.

2.6. Oxazole Based PRPGs

One decade ago, in 2010, Soares and co-workers [38] examined the photochemical characteristics of fused oxazole derivatives and discovered that they may be utilised as novel photoremovable protective groups for the release of amino acids.

The photosensitivity of ester conjugates was investigated using irradiation at wavelengths of 254, 300, and 350 nm, respectively. At 254 and 300 nm (Scheme 17), photolysis of oxazole conjugates resulted in full release of the amino acid, with the best results achieved for naphtho[2,3-d]oxazole.

2.7. Anthraquinon-2-Yl-methoxycarbonyl (Aqmoc) PRPG

As revealed by Furuta and co-workers [39], anthraquinon-2-ylmethoxycarbonyl may act as a PRPG for alcohols. Compound **77** was exposed to 350 nm photolysis, which resulted in the release of the alcohol in 50% aqueous THF (Scheme 18). The results of the Stern-Volmer analysis revealed that the triplet excited state is implicated in the release of ethanol.

2.8. 2-Benzoylbenzoate PRPG

Photolysis of 2-benzoylbenzoate esters **78** in 2-propanol produced the alcohol and lactone **81**, according to Porter and co-workers [40], whereas irradiation of **78** in the presence of the electron donor cyclohexylamine not only produced the alcohol but also resulted in the formation of lactone **80**. Photoreduction of **78** produces a 2-(R-hydroxyphenylmethyl)-benzoic ester, which then undergoes intramolecular lactonization to liberate the alcohol, which is thought to be the cause of these reactions. The reaction will only proceed as expected in the presence of electron donors or H-donating solvents (Scheme 19).

It was recently discovered that a derivative of 2-benzoylbenzoate esters **82** with an ortho to the ketone isopropyl substituent that allows for intramolecular H-atom abstraction and, as a result, can release alcohol regardless of the reaction medium was synthesised by Gudmundsdottir and co-workers (Scheme 20) [41].

2.9. Fluorescent Photoremovable Protecting Groups

Among the many PRPGs, some are fluorescent and thus have a competitive advantage over their non-fluorescent counterparts. As previously stated, fluorescent PRPGs not only allow for the controlled release of bioactive molecules at a desired site for a specific period of time, but they also allow for visualization, quantification, and follow-up of the spatial distribution, localization, and depletion of the released molecules [29, 42-46]. The strategy described above, fluorescent PRPGs, has been successfully employed for the controlled release of bioactive molecules in the study of a variety of diseases. First and foremost, it allows the detection of small aliphatic amino acids that are neither fluorescent nor have strong absorption in the UV/vis region using a far more sensitive technique than conventional UV absorption [47-52]. Second, it allows for the visualisation of amino acids involved in biological processes [53, 54]. Finally, because the amino acids are tagged with fluorescent PRPG, they can be released for a specific period of time at a deuterated concentration. It has been reported that the use of fluorescent PRPGs in the treatment of neuropsychiatric diseases can result in the release of neuroactive amino acids (*e.g.* gamma-aminobutyric acid, glycine, glutamic acid, *etc.*). [55] Despite the fact that FPRPGs are of great utility, only a few have been reported in the literature, as shown in Fig. (2) [56-64].

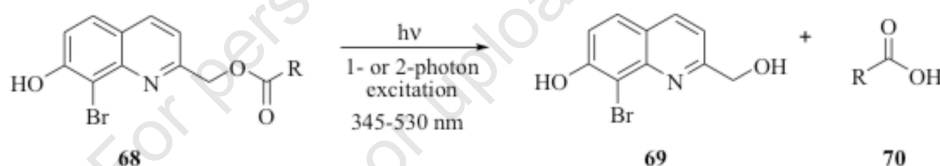
FPRPGs for biological applications should have certain essential characteristics, including (i) a high uncaging cross section over 350 nm wavelength, (ii) fluorescence enhancement after uncaging, and (iii) versatile chemistry for bioconjugation as well as intracellular delivery. Aiming for new fluorescent PRPGs with larger uncaging cross sections is desired since it can effectively switch on their fluorescence while reducing the negative effects of ultraviolet light on living specimens. As a result, the discovery of novel fluorescent PRPGs and the use of these compounds in biological applications is a highly challenging area of chemical and pharmaceutical chemistry.

2.10. Applications in Total Synthesis of Natural Products

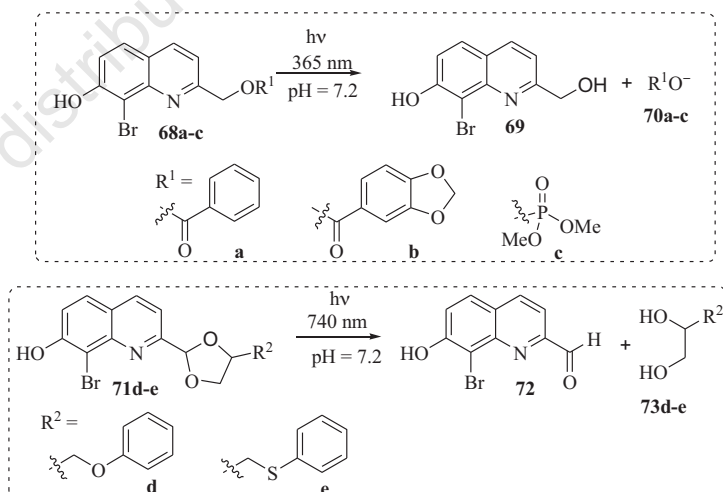
Despite their many advantages, PRPGs are seldom used in total syntheses in spite of their significant advantages. Total synthesis of natural products is one of the important fields in organic chemistry [65-69]. Although PRPGs' "orthogonality" to conventional synthetic reagents has been demonstrated in the synthesis of natural products; their capacity to conduct a "traceless reagent process" has also been demonstrated to be successful. *o*-Nitrobenzyl PPGs have also been shown to be useful in the synthesis of natural products. Its use in the total synthesis of Calicheamicin γ 1 was reported by Nicolaou and co-workers, and it was established that it was highly compatible with other classical polycyclic aromatic hydrocarbons and their functionalities (Scheme 21) [70]. Another elegant example is the usage of *o*-Nitrobenzyl PPGs in the synthesis of an analogue of leukotriene C₄, which was discovered by chance (LTC₄, Scheme 22) [71]. In the final steps, deprotection of the nitrobenzyl derivative by irradiation at 350 nm results in the

formation of the secondary amine in 74% yield. It is worth noting that photolysis did not result in any isomerization of the triene part or any racemization. Another natural product ent-Fumiquinazoline [72] (Scheme 23), whose synthesis included the use of PRPGs. The syntheses necessitated the use of irradiation at a 254 nm wavelength to cleave the *o*-Nitrobenzyl PRPG.

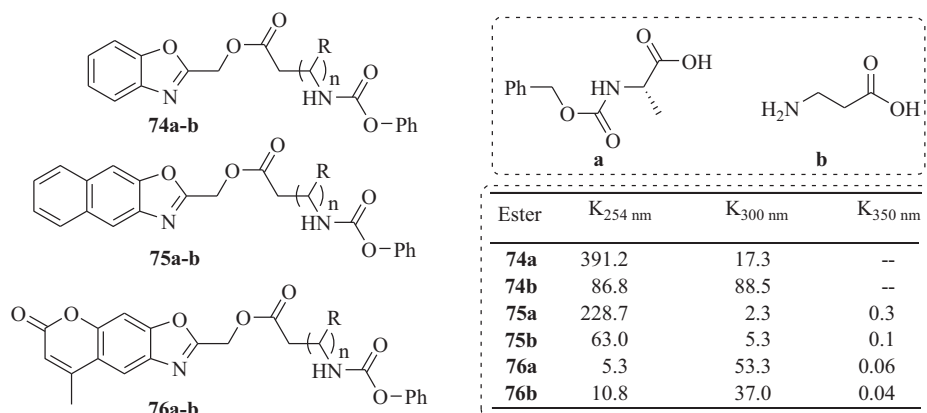
The *o*-nitrobenzyl series has been expanded to include a wide range of photoremovable protective groups. Each new group was created to address the *o*-nitrobenzyl group's deficiencies or add features such as faster release rates, absorption range extension into the near UV-visible region, enhanced solubility, increased efficiency, better conversions and yields, and more mild photoproducts from the protecting group. This chemistry's modifications and applications to two photon excitation methods, traceless reagents in chemical synthesis and photolithography, orthogonal reagents in synthesis, and time-resolved spectroscopic techniques will place even greater demands on the design, synthesis, and development of new photoremovable protecting groups. However, no one photoremovable protective group currently meets all nine requirements proposed by Sheehan and Lester. Despite this, significant progress has been made, as indicated by the increasing number of applications described for several of these photoremovable groups, particularly in biological research. Synthesis, combinatorial chemistry, microarrays, and photolithography will all benefit from this technology. As current systems are improved and novel photoactive protective groups are discovered, these disciplines have benefited and will continue to pique the scientific community's attention.



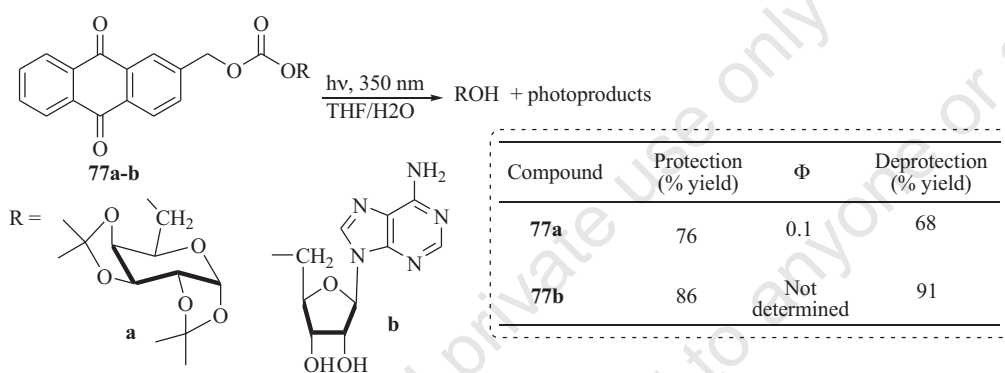
Scheme 15. Release of carboxylic acids from 8-Bromo-7-hydroxyquinoline PRPG.



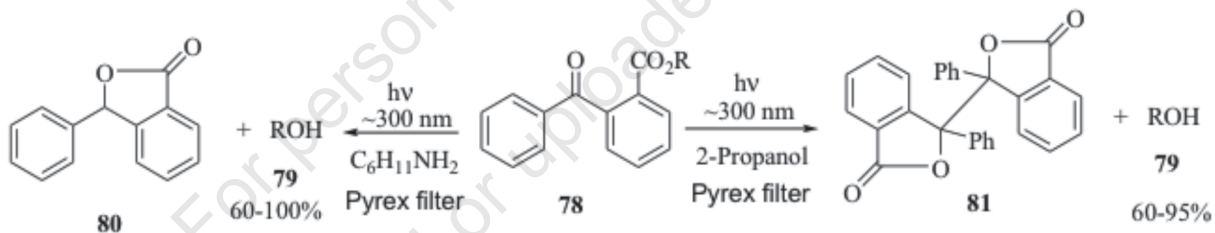
Scheme 16. Release of functional groups by 8-Bromo-7-hydroxyquinoline (BHQ) PRPG.



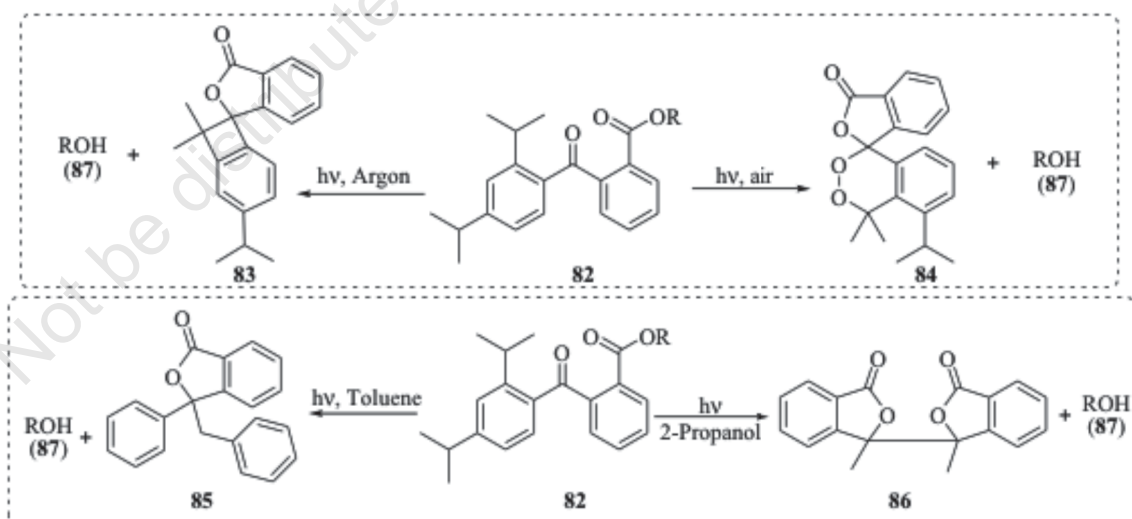
Scheme 17. Release of amino acids by Oxazole-based PRPGs.



Scheme 18. Release of alcohols by Anthraquinon-2-ylmethoxycarbonyl (Aqmoc) PRPG.



Scheme 19. Release of alcohols from 2-benzoylbenzoate PRPG.



Scheme 20. Release of alcohols by 2-benzoylbenzoate esters.

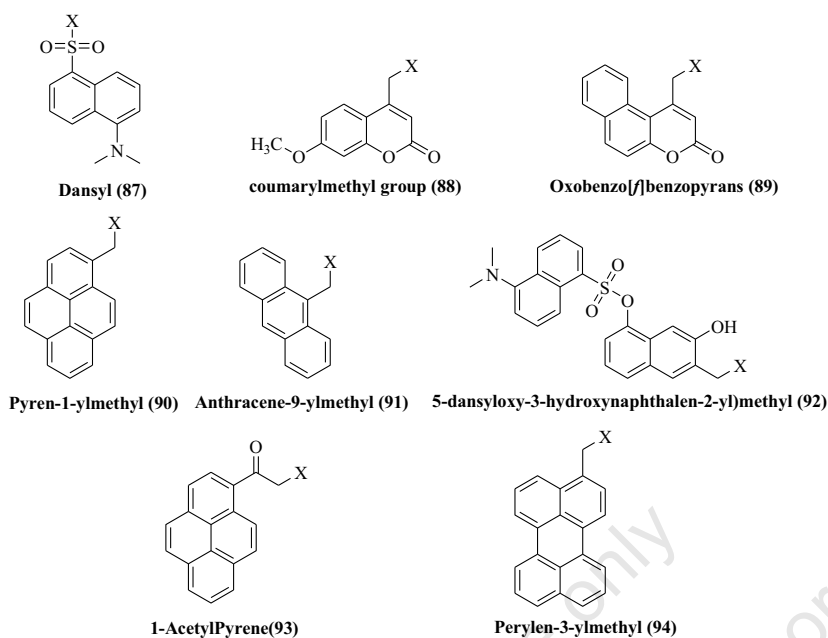
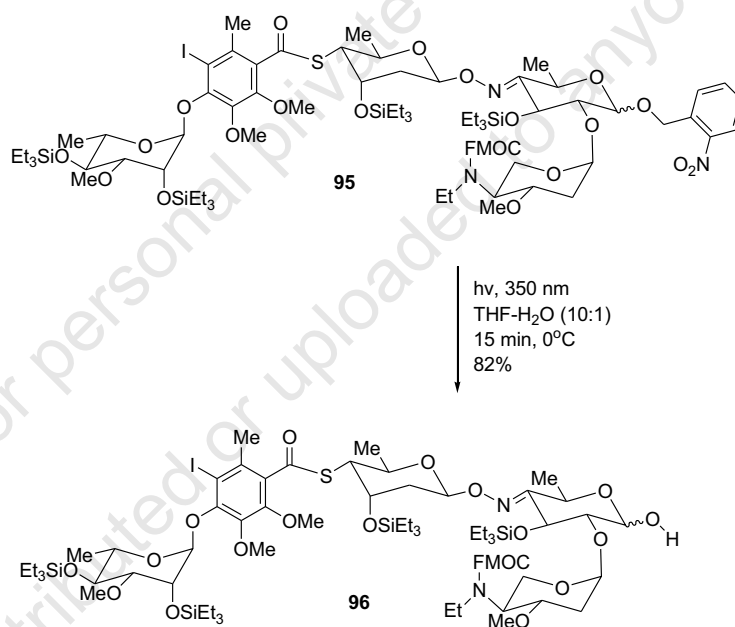
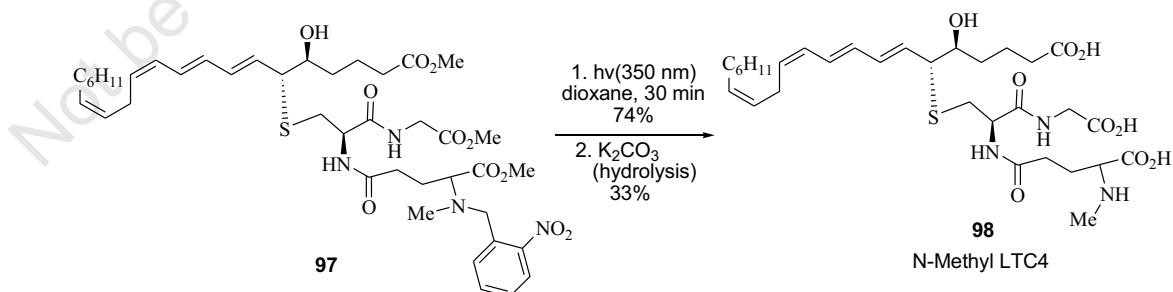
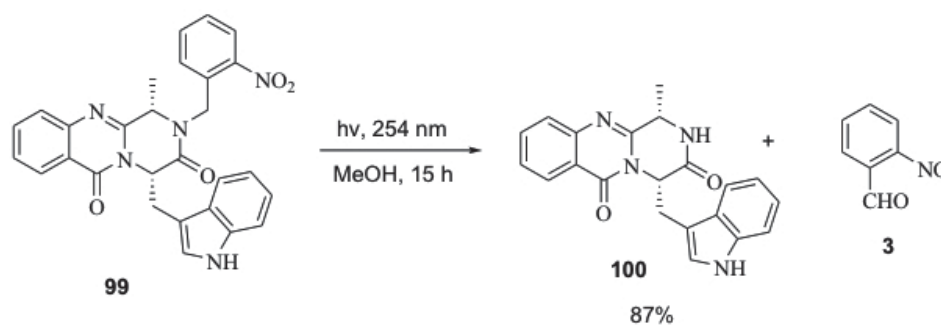


Fig. (2). Some well explored FPRPG.

Scheme 21. Removal of a 2-nitrobenzyl PRPG in Nicolaou's synthesis of Calicheamicin γ 1.

Scheme 22. Final Steps in the total synthesis of N-Methyl LTC4.



Scheme 23. Removal of a 2-nitrobenzyl PRPG in the final step of Busuyek's synthesis of ent-Fumiquinazoline.

CONCLUSION

It has been discovered that photoremovable protecting groups are very helpful in the development of biological and pharmaceutical chemistry, and in particular, in the investigation of a wide range of biological processes. Many research groups have invented protective groups that are easily removable in the presence of light and have high effectiveness, which they have used to a range of chemical transformations in recent years. There has been a significant increase in interest in PRPGs over the last decade. This has resulted in a significant increase in the number of creative designs and the development of both unique and known PRPGs to fulfill the standards for higher sensitivity, faster kinetics, and much more specific bioanalytical applications. As a consequence of the many recent discoveries, the synthesis, thermal stability, solubility, and absorption characteristics of PRPGs, as well as their efficiencies and removal rates, have all been substantially enhanced. Many important research objectives, such as expanding the wavelength range for activation of PRPGs with visible and infrared light while also improving the absorption abilities for wavelength-selective, orthogonal activation, and combining these attributes with the inherent photoactivation benefits that PPGs exhibit, as illustrated at the outset of this study, are still unmet. In order to aid researchers in the implementation of these methods, as well as to encourage and inspire their interest in this rapidly expanding area, the main goal is to support and assist them. The goal of this mini-review is to offer an overview of the chemistry of various photoremovable protecting groups, which have played a significant role in the development of organic and bio-organic chemistry, as well as in the delivery of medicines.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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