Handbook of Synthetic Photochemistry

Edited by
Angelo Albini and Maurizio Fagnoni
Handbook of Synthetic Photochemistry

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Angelo Albini and Maurizio Fagnoni
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Handbook of Synthetic Photochemistry

Edited by
Angelo Albini and Maurizio Fagnoni
From its origin over a century ago, organic photochemistry has undergone a transformation from an area of science populated by a few specialized organic and physical chemists to a field that now attracts the interest of members of the broad synthetic organic chemistry community. Along the way, the basic chemical and physical foundations of the science were developed and the full synthetic potential of photochemical reactions of organic substrates has been realized.

The science of organic photochemistry can be traced back to observations made in the nineteenth century, which showed that ultraviolet irradiation of certain organic substances leads to formation of products that have unique and sometimes highly strained structures. An example of this is found in studies in the early 1800s, which demonstrated that irradiation of the naturally occurring, cross-conjugated cyclohexadienone, α-santonin, in the crystal state induces a deep-seated, multisteped rearrangement reaction. It is fair to conclude that at that time observations like this could only have been attributed to the magic of Nature, since little if anything was known about the fundamental principles of the light absorption process and the relationships between structures and decay pathways of electronic excited states.

The science of organic photochemistry experienced a significant transformation in the middle part of the twentieth century when it began to attract the interest of organic chemists, who were skilled in the use of valence bond theory, and physical chemists, who were able to probe and theoretically analyze the properties of electronic excited states. These efforts led to a basic mechanistic framework for understanding and predicting how electronic excited states of organic substrates undergo reactions to form products. Clear examples of the insight provided by organic chemists during this era are found in ground-breaking investigations performed independently by Zimmerman and Chapman that probed the photochemistry of simple, cross-conjugated cyclohexadienones. The realization that these processes could be described by utilizing Lewis electron-dot-line structures of excited states and reactive intermediates brought organic photochemistry into the intellectual sphere of organic chemists, who already had learned the benefits of writing arrow-pushing mechanisms for ground-state reactions.

Another important contribution to the field of organic photochemistry arose from investigations of excited state redox processes in the latter part of the twentieth
century. These efforts showed that when the oxidation and reduction potentials and excited state energies of interacting electron donors and acceptors are appropriate, thermodynamically and kinetically favorable excited state single electron transfer (SET) will take place to produce ion radical intermediates. This phenomenon expanded the vista of organic photochemistry, since it enabled the unique and predictable reactivity profiles of charged radicals to be included in the concept library used to design new photochemical transformations. Many examples of the exceptional impact that SET has had on the field of organic photochemistry came from the pioneering work of Arnold and a cadre of other organic chemists who developed synthetic applicable SET photochemical processes.

It is clear that studies in the area of organic photochemistry have led to the discovery of a large number of novel reactions, and that some of these processes meet the high standards needed for use as preparative methodologies. The compilation in this Handbook, which begins with a useful chapter describing practical experimental methods used in photochemistry, reviews several of the more synthetically prominent photochemical reactions of organic substrates.

There is no doubt that the field of organic photochemistry was subjected to intense scrutiny in the latter half of the twentieth century, and that efforts during this period led to a firm understanding of basic photochemical principles and to the discovery of a wealth of highly unique chemical reactions. Moreover, during this period members of the synthetic organic chemistry community recognized that several photochemical processes could be applied as key steps in routes for the construction of complex target molecules. It is likely that activity in the area of organic photochemistry will not diminish in the twenty-first century where it will be used in finding matchless solutions to challenging chemical problems. Thus, rather than being caused by the need to prepare sophisticated organic substances made by Nature, problems in the new century are likely to revolve about the search for green methods for promoting chemical reactions and for processes that can be performed in confined spaces (e.g., cells), defined patterns (e.g., lithography), and precisely controlled time domains (e.g., triggers). Organic photochemistry is uniquely applicable to these types of challenges and, as a result, it should continue to be an interesting area in which to work.

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Preface

Practitioners of organic photochemistry feel that this science has a great potential for synthesis. Indeed, nowadays many reactions are known that lead to useful transformations and have been exploited as key steps in complex synthetic plans. These achievements attract the interest of synthetic chemists. However, photochemical methods are probably less often adopted than they may be, and are still less familiar to the broad chemical community than other methods. In the present handbook it has been attempted to offer an easy approach to the use of photochemical methods in synthesis. Thus, rather than discussing the chemistry of the various chromophores, as usual in photochemistry books, reactions have been grouped according to the molecular transformation involved and care has been given that experimental aspects (much less elaborate with many other methods) are clearly presented. We are convinced that a more general application in nonspecialized laboratories will lead to the discovery of new applications and even new reactions.

It was chosen to have a multiauthor book because this allows a breadth of approaches that could not otherwise be reached. The distinguished photochemists who accepted to participate in this project patiently tolerated the long work required to avoid the risk of discontinuity. We thank them heartily and any deficiency in the book is certainly not their fault. Thanks go to Dr. Heike Nöthe, a friendly and capable help during both the preparation and production phases and to Davide Ravelli and Matteo Albini for the pictures.

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1
Photochemical Methods

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1.1
Photochemical Methods

1.1.1
Photochemistry and Organic Synthesis

A cursory look to the literature shows that only about 1% of the published papers classed as organic syntheses by Chemical Abstracts involve a photochemical step. On the other hand, in photochemistry courses it is often stated that excitation by light multiplies by 3 the accessible reaction paths, because the chemistry of the excited singlet and triplet states are added to that of the ground state. It thus appears that photochemical reactions are less used as they may be. As it has been again recently remarked, this limited diffusion may be due to ill-founded prejudices [1].

Two conditions should be verified in order that the potential of photochemical reactions is more extensively exploited. These are:

- That the knowledge of the main classes of such reactions is more largely diffused among synthetic practitioners, so that a photochemical step comes more often into consideration when discussing a synthetic plan.

- That the prejudice that photochemical reactions are mostly unselective, experimentally cumbersome and at any rate difficult to generalize is overcome, so that there is no hesitation in considering the introduction of a photochemical step on the basis of the analogy with known examples, just as one would do with a thermal reaction.

The connection between synthesis and photochemistry is vital. As long as photochemistry is felt as a “sanctuary” of the small group of “professional” photochemists, many synthetic perspectives will be ignored, and this is a negative impact also on mechanistic photochemistry that loses part of its interest. As a matter of fact, this remark is not new. In a talk in Leipzig in 1908, Hans Stobbe, a pioneer of photochemistry (well known for his innovative studies on the photochromism of
fulgides), stressed the importance of devising new photochemical applications in organic chemistry [2]. “Then probably…” he hoped “…organic chemists would become interested and take into account the effect of light on their experiments. Known photoreaction would become better known and new photoreactive compounds will be looked for. Final products and intermediates would be isolated, their structure demonstrated and on the basis of the chemical structure the process will be understood. In this way the physical chemist would always have in his hands a wealth of material for his favorite studies of kinetics and for investigating the relation between radiation and chemical energy.”

Stobbe’s wish has been only partially fulfilled in the century which has elapsed in the meantime. Whilst many photochemical reactions have been discovered, certainly many more wait to be uncovered, and it still holds true that more photochemistry carried out by synthetic chemists would contribute to the growth of photochemistry as a whole. This Handbook represents a modest attempt to contribute towards this aim and to foster the synthetic use of photochemistry. The presentation is referred to the small-scale laboratory synthesis of fine chemicals. In this aspect, the photochemical literature does not differ from the large majority of published synthetic work, most of which is carried out on the 100 mg scale for exploratory studies. However, there is no reason to think that a photochemical reaction is unfit for scaling up. As will shown below, an increase up to the 100 g scale can be obtained in the laboratory by simple arrangements. Furthermore, while the presently running industrial applications are limited in number, they are nonetheless rather important [3]. Some of these are well established, an example being the synthesis of vitamin D₃ which has been produced at the several tons level each year for several decades, and for which dedicated plants continue to be built. This indeed demonstrates that photochemical syntheses are commercially viable.

1.2
Irradiation Apparatus

1.2.1
General

As the name implies, photochemical reactions result from the absorbance of light by the starting reagent. Conditions for a successful course of the photoreaction are that:

- There is good matching between the emission of the light source and the absorption by the reagent; that is, the wavelength emitted by the lamp falls within the absorption band of the reagent.
- Nothing interferes with the photons before they reach the target molecule; for example, the wall of the vessel and the solvent are transparent to \( \lambda_{ex} \).
- Nothing interferes with the electronically excited states and quench them before they react (see Scheme 1.1).
In other cases, rather than irradiating the reagent ("direct" excitation), a photosensitizer or photocatalyst is irradiated and activates the reagent by some mechanism (energy transfer, a redox step, hydrogen abstraction). In this case, the above conditions apply to the sensitizer.

Today, there are several companies which supply lamps as well as complete photochemical reactors (lamp + power supply + reaction flask with accessories, e.g. for gas inlet). However, the complete set may be rather expensive and not necessarily provide the most convenient solution. The most widely used light sources are mercury vapor arcs, both in photochemistry and in indoor and outdoor illumination, and which are classed according to the operating pressure. It is important that the wattage on the lamp label is not confused with the amount of light emitted. The efficiency of conversion into light is low, and the lamp output is dispersed over a range of wavelengths and towards all directions; thus, only a part of the light emitted (in turn, a fraction of the electrical power dissipated) is absorbed. Therefore, it is important to take care of the geometry of the lamp/reaction vessel system as well as of the wavelength matching between lamp emission and reagent absorption, because these factors are at least as important as the lamp power in determining how many molecules of the reagent will be excited. The quantum yield then indicates the fraction of excited states that reacts \( \Phi = \text{molecules reacted}/\text{photons absorbed} \), provided that no competitive quenching occurs. The main characteristics of lamps used for photochemical synthesis are presented in the following sections.

### 1.2.2 Low-Pressure Mercury Arcs

The most widely used lamps are low-pressure \( (10^{-5} \, \text{atm under operating conditions}) \) Hg arcs, of 6–16 W, that are often identified as germicidal lamps or mercury resonance lamps. These are supplied as quartz (or rather “fused silica,” a synthetic amorphous SiO\(_2\)) tubes of various lengths, typically 20–60 cm (although lamps >1 m long are available), and with 1.0–2.4 cm diameter (see Figure 1.1). In these lamps, >80% of the emission occurs at 254 nm (and a fraction at 185 nm, a wavelength to which the common “quartz” is not transparent and thus is available only if a high-purity “UV-grade” quartz is used).

Under these conditions, the excitation of most classes of organic compounds (including many solvents!) is ensured. It must be taken into account that, given the large size of the lamp, the amount of photons emitted per surface unity is low. Therefore, these lamps are most useful for external irradiation by using (quartz!) tubes for the irradiated solutions. The heating under operating conditions is modest.
Multilamp apparatus are commercially available where between eight and 12 lamps are arranged in a circular fashion (40–60 cm diameter), with room inside to accommodate the vessel in which the solution to be irradiated is contained. These were initially marketed by the Southern New England Ultraviolet Co. under the name of “Rayonet,” now the name is often used for similar devices by other companies. These units are fitted with a fan which maintains the temperature below 40°C; otherwise, this might increase in such a confined space (see Figure 1.2).

Figure 1.1 Lamps used for photochemical syntheses. (a) Low-pressure mercury arc; (b, c) phosphor-coated lamps, emission centered at 305 and 370 nm; (d, e) medium- and high-pressure mercury arcs, respectively.

Figure 1.2 Multilamp apparatus fitted with low-pressure mercury lamps and a rotating “merry-go-round” that ensures the uniform illumination of several test tubes. Alternatively, test tubes or other vessel(s) containing the solution to be irradiated can be accommodated.
However, anybody can build an “amateur” version of the irradiation apparatus, simply by placing one to three pairs of lamps (with each pair mounted on a normal lamp holder for household “fluorescent” lamps) around a small space where two to four test tubes or a single cylindrical vessel of larger diameter can be placed. This home-made apparatus can be easily installed (but well separated from the laboratory, in order to maintain appropriate safety precautions, or better still under a ventilated hood to remove ozone; see below and Figure 1.3). In order to maximize the fraction of light absorbed, it is convenient that the tubes are as long as the lamps, or even slightly shorter. The manufacturers can provide lamps of this type in different shapes (U-shaped, coiled) with a more concentrated emission; this makes their use possible in different set-ups, an example being an immersion well apparatus with internal irradiation (see Figure 1.4).

Figure 1.3 Two pairs of lamps used for external irradiation. In the arrangement shown, only a small fraction of the light flux is used.
Low-pressure mercury arcs are manufactured for much more widespread use than preparative photochemistry, and therefore are by far the cheapest light source (particularly if buying them from companies selling optical components can be avoided). Furthermore, these lamps are long-lived (>10,000 h, depending on how they are used), consume less energy, and require only an inexpensive transformer and a starter for operation.

Whilst there is no doubt that these are the most convenient sources, their geometric optimization is difficult and part of the lamp emission may be lost. In the external irradiation set-up, the most convenient choice is to use tubes which are about the same length as the lamps, and contain 20 ml of solution. In fact, this set-up works very well for small-scale photochemical syntheses, with irradiated volumes in the region of 100 ml distributed in a number of quartz test tubes or in a single cylindrical vessel. This set-up is also convenient for optimizing the reactions, since results can easily be compared under different conditions but constant irradiation when placing different solutions in the tubes. One available accessory for these multilamp apparatuses is a “rotating merry-go-round”; this can hold several tubes and ensures equivalent irradiation in all positions (see Figure 1.2).

The lamp emission can be changed by means of a coating made from a phosphor (or a combination of phosphors) that absorbs the almost monochromatic Hg radiation and emits a range of longer wavelengths. Phosphor-coated lamps maintain the same advantages of “quartz” lamps (including price, due to their large-scale manufacture for different uses, including household illumination), and are available in a variety of wavelength ranges. Apart from “fluorescent” lamps for household illumination, which emit over most of the visible (and are useful for dye-photosensitized irradiations), lamps with emission centered at 305, 350 and 370 nm (half-height width 20–40 nm; the last one is known as “Wood” or “black light” lamp) that are most useful for photochemical applications are commercially available (as well as lamps with the emission centered at various wavelengths in the visible). Except for the 305 nm type, Pyrex glassware (transparency limit 300–310 nm, but take into account that the transparency changes somewhat with the use) [4] can be used with phosphor-coated lamps, as there is no emission below that wavelength. The phosphor coating does not alter the electrical characteristics, and these lamps can be interchanged with germicidal lamps in all of the settings mentioned above. Having available three to four pairs each of 254, 305, and 350 (or 370) nm lamps, as well as lamps emitting in the visible range, allows one to carry out any type of small-scale photochemical reaction with negligible financial investment.

One subcategory of low-pressure lamp that might become more important in the future is the electrodeless discharge lamp, which is energized by an external field. These lamps comprise a quartz tube that has been evacuated, leaving behind a small pressure of argon and mercury or other metal or metal halide. Emission is obtained by placing the lamp in a microwave field, for example. Whilst these lamps are available commercially, they may also be built in-house rather easily [5].
1.2.3 Medium- and High-Pressure Mercury Arcs

Medium-pressure (sometimes dubbed “high pressure,” 1–10 atm) mercury arcs are available in different types, ranging from 100 to 1000 W. They are supplied as small ampoules (from 3 to 15 cm in length, depending on the power; see Figure 1.1). The emission consists of a range of lines (the most prominent are those at 313, 366, 405, and 550 nm) over a continuum, while the 254 nm line is strongly diminished. The emission from these lamps is at least 10-fold stronger than that of low-pressure arcs, and occurs over a much smaller surface. In contrast to the previous type, these sources develop a considerable amount of heat, and require several minutes to achieve their optimal temperature, where the emission reaches full intensity. Cooling is required, but running tap water is normally sufficient to maintain the temperature at about 20 °C. Due to these characteristics, these lamps are typically used in an immersion well apparatus with circulating water. If the cooling well is made from Pyrex, the (small) fraction of emission below 300 nm is lost, which may make a difference (see below and Figure 1.4a). The most powerful lamps require a forced circulation for cooling. A suitable power supply is also required for operation, the lifetime is limited, and overall the system is considerably more expensive than the low-pressure lamps. There may also be some concern regarding safety aspects; it is suggested that the reactor is provided with a switch that will cut the power supply in case of an increase in temperature.

Figure 1.4 (a) Immersion well irradiation apparatus; (b) a refrigerated apparatus for conducting reactions at low temperature.
These compact and rather powerful sources are convenient for internal irradiation of volumes of between 100 and 1000 ml, where the emission in any direction is exploited (obviously within the range of absorbed $\lambda$); and are well suited for preparative irradiations up to the gram scale. The apparatus can be easily adapted to low-temperature experiments (e.g., at $-80^\circ$C) by circulating a refrigerant liquid through the lamp jacket (in this case, the lamp must be ignited outside and placed in position when lit, otherwise it will not function) and adding an external cooling bath (see Figure 1.4b) [6]. Lamps doped with different metals are also available; these yield an emission which is richer in some regions of spectrum, and may be better suited to particular photoreactions, although they are generally more expensive.

High-pressure (or “very high” pressure, 200 atm; see Figure 1.1) arcs, ranging from 150 to 1000 W and above, operate at higher temperatures. In this case, the contribution of the continuum is much more important than that at a lower pressure, although the maxima may still be distinguished. The optimal temperature requires several minutes before it is reached, and must be maintained by appropriate cooling. These Hg-lamps are the most powerful and the smallest sources, with a distance between the electrodes of only a few millimeters. In view of the severe operating conditions, such lamps are used in explosion-proof cases (finned for cooling, unless forced cooling is required) that are fitted with mirror and lenses. In this way a collimated emission is obtained, typically 5 cm in diameter, and the lamp is mounted on a optical bench where other optical components can be added (see Figure 1.5).

By inserting either an interference filter or a colored filter, it is possible to select a more or less extended region of the spectrum; likewise, by adding an optical fiber it is possible to direct the beam where desired. This set-up best exploits the characteristics of these powerful lamps, and offers an excellent choice for the irradiation of small surfaces. Consequently, spectrophotometric cuvettes or cylindrical cuvettes are used for the irradiation, which involves small volumes. Such restrictions, as well as the high price and short lifetime of the lamp and its accessories, favors the use of these arcs for kinetics studies and quantum yield measurements, rather than for preparative photochemistry.

![Figure 1.5](image.png)