



Handbook of Synthetic Photochemistry

Edited by
Angelo Albini and Maurizio Fagnoni



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The Editors

Prof. Dr. Angelo Albini

University of Pavia
Department of Organic Chemistry
Via Taramelli 10
27100 Pavia
Italy

Prof. Dr. Maurizio Fagnoni

Department of Organic Chemistry
University of Pavia
Via Tamarelli 10
27100 Pavia
Italy

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Foreword

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.

Patrick S. Mariano
Department of Chemistry and Chemical Biology
University of New Mexico
Albuquerque, NM, USA

Contents

Foreword V

Preface XV

List of Contributors XVII

- 1 Photochemical Methods** 1
Angelo Albini and Luca Germani
- 1.1 Photochemical Methods 1
- 1.1.1 Photochemistry and Organic Synthesis 1
- 1.2 Irradiation Apparatus 2
- 1.2.1 General 2
- 1.2.2 Low-Pressure Mercury Arcs 3
- 1.2.3 Medium- and High-Pressure Mercury Arcs 7
- 1.2.4 Other Light Sources 9
- 1.3 Further Experimental Parameters 11
- 1.3.1 Concentration and Scale 11
- 1.3.2 Effect of Impurities, Oxygen, and Temperature 15
- 1.3.3 Safety 17
- 1.3.4 Planning a Photochemical Synthesis 17
- 1.4 Photochemical Steps in Synthetic Planning 19
- References 22
- 2 Carbon–Carbon Bond Formation by the Photoelimination of Small Molecules in Solution and in Crystals** 25
Saori Shiraki and Miguel A. Garcia-Garibay
- 2.1 Introduction 25
- 2.1.1 Synthesis of Unstable Molecules 27
- 2.2 Photochemical C–C Bond Formation in Solution 30
- 2.2.1 Concerted Reactions 30
- 2.2.2 Photoelimination of N₂ 31
- 2.2.2.1 Synthesis of Three-Membered Rings 31

2.2.2.2	Synthesis of Cyclobutanes and Polycyclic Compounds	33
2.2.3	Photoelimination of CO from Ketones in Solution	35
2.2.4	Photoelimination of CO ₂ from Lactones	39
2.2.5	Photoelimination of Sulfur from Sulfides, Sulfoxides, and Sulfones	40
2.3	Reactions in the Solid State	41
2.3.1	Reactivity and Stability in the Solid State	42
2.3.2	Restricting the Fate of the Radical Intermediates in Solids	43
2.3.3	Crystalline Diacyl Peroxides	44
2.3.4	Decarbonylation of Crystalline Ketones	50
2.3.4.1	Early Observations	50
2.3.4.2	Reactivity and Stability	51
2.3.4.3	The RSE > 11 kcal mol ⁻¹ Condition	53
2.3.4.4	Scope of the Reaction	55
2.3.4.5	Reaction Enantiospecificity	56
2.3.4.6	Synthesis of Natural Products	57
2.3.4.7	Quenching Effects	57
2.3.4.8	Reaction Scale and Experimental Conditions	59
2.4	Concluding Remarks	60
	References	60
3	Intermolecular Addition Reactions onto C–C Multiple Bonds	67
	<i>Valentina Dichiarante and Maurizio Fagnoni</i>	
3.1	Introduction	67
3.1.1	Scope and Mechanism	68
3.2	Addition to C–C Double Bonds	69
3.2.1	H–C Addition (Hydroalkylation Reactions)	69
3.2.1.1	Addition of Alkanes	70
3.2.1.2	Addition of Alcohols (Hydrohydroxymethylation), Ethers, and (2-substituted) 1,3-Dioxolane(s)	71
3.2.1.3	Addition of Amines (Hydroaminomethylation) or Amides	72
3.2.1.4	Hydrofluoromethylation	74
3.2.1.5	Addition of Nitriles or Ketones	75
3.2.1.6	Hydroacylation and Hydrocarboxylation Reactions	75
3.2.1.7	Hydroarylation (Photo-EOCAS)	76
3.2.2	H–N Addition (Hydroamination)	76
3.2.3	H–P Addition	78
3.2.4	H–O Addition	80
3.2.5	H–S Addition	82
3.2.6	Addition of X–Y Reagents to Alkenes	83
3.2.6.1	Halogenation	84
3.2.6.2	Addition with the Formation of C–C Bonds	84
3.3	Addition to C–C Triple Bonds	86
3.3.1	Hydroalkylation Reactions	87
3.3.2	Addition of X–Y Reagents	87

3.4	Concluding Remarks	88
	References	89
4	Formation of a Three-Membered Ring	95
	<i>Takashi Tsuno</i>	
4.1	Introduction	95
4.2	Di- π -Methane Rearrangement	96
4.2.1	Di- π -Methane Rearrangement of Barrelene, Benzobarrelene, Dibenzobarrelene, and Related Derivatives	96
4.2.2	Di- π -Methane Rearrangement of Acyclic Systems	100
4.2.3	Di- π -Methane Rearrangement in Natural Compounds	103
4.3	Oxa-di- π -Methane Rearrangement and Related Rearrangements	105
4.3.1	Oxa-di- π -Methane Rearrangement of β,γ -Unsaturated Ketones and Aldehydes	105
4.3.2	Aza-di- π -Methane Rearrangement	109
4.3.3	Synthetic Applications of Oxa-di- π -Methane Rearrangement	110
4.4	[2+1] Cycloaddition of Alkenes with Carbenes	111
4.4.1	Intramolecular [2+1] Cycloaddition	111
4.4.2	Novel Triplet Sensitizers for the Generation of Carbenes	111
4.4.3	Metal-Catalyzed Cyclopropanation-Supported Photochemistry	112
4.4.4	Novel Precursors of Carbenes	113
4.5	Formation of a Cyclopropane via Intramolecular Hydrogen Abstraction	114
4.5.1	Formation of Cyclopropanol via Intramolecular β -Hydrogen Abstraction	115
4.5.2	Formation of Cyclopropane Ring via Intramolecular γ -Hydrogen Abstraction	117
4.6	[3+2] Cycloaddition of Arenes with Alkenes	119
4.6.1	Intermolecular [3+2] Cycloaddition	119
4.6.2	Intramolecular [3+2] Cycloaddition	119
4.6.3	Application of the Photochemical [3+2] Cycloaddition in the Synthesis of Natural Products	122
4.7	Photochemical Synthesis of Three-Membered Heterocycles	123
4.7.1	Epoxides	123
4.7.2	Aziridines	123
	References	126
5	Formation of a Four-Membered Ring	137
	<i>Norbert Hoffmann</i>	
5.1	Introduction	137
5.2	[2+2]-Photocycloaddition of Nonconjugated Alkenes	137
5.3	[2+2]-Photocycloaddition of Aromatic Compounds	144
5.4	Photochemical Electrocyclic Reactions	150
5.5	Intramolecular γ -Hydrogen Abstraction (Yang Reaction)	153

5.6	Metal-Catalyzed Reactions	156
5.7	Other Methods	157
5.8	Concluding Remarks	160
	References	160
6	Formation of a Four-Membered Ring: From a Conjugate Alkene	171
	<i>Jörg P. Hehn, Christiane Müller, and Thorsten Bach</i>	
6.1	Introduction	171
6.2	[2+2]-Photocycloaddition of Enones (Substrate Type A1)	173
6.2.1	Cyclopentenones	173
6.2.2	Cyclohexenones	177
6.2.3	<i>para</i> -Quinones and Related Substrates	181
6.3	[2+2]-Photocycloaddition of Vinylogous Amides and Esters (Substrate Classes A2 and A3)	182
6.3.1	Endocyclic Heteroatom Q in β -Position (Substrate Class A2)	183
6.3.1.1	4-Hetero-2-Cyclopentenones	183
6.3.1.2	4-Hetero-2-Cyclohexenones	185
6.3.2	Exocyclic Heteroatom Q in β -Position (Substrate Class A3)	186
6.4	[2+2]-Photocycloaddition of α,β -Unsaturated Carboxylic Acid Derivatives (Substrate Classes A4, A5, and A6)	189
6.4.1	No Further Heteroatom Q in β -Position (Substrate Class A4)	189
6.4.1.1	α,β -Unsaturated Lactones	189
6.4.1.2	α,β -Unsaturated Lactams	192
6.4.1.3	Coumarins	193
6.4.1.4	Quinolones	194
6.4.1.5	Maleic Anhydride and Derivatives	196
6.4.1.6	Sulfur Compounds	197
6.4.2	Endocyclic Heteroatom Q in β -Position (Substrate Class A5)	198
6.4.2.1	1,3-Dioxin-4-Ones	198
6.4.2.2	4-Pyrimidinones	200
6.4.3	Exocyclic Heteroatom Q in β -Position (Substrate Class A6)	201
6.4.3.1	Lactones	202
6.4.3.2	Lactams	203
6.5	Concluding Remarks	205
	References	205
7	Formation of a Four-Membered Ring: Oxetanes	217
	<i>Manabu Abe</i>	
7.1	Introduction	217
7.2	The Generally Accepted Mechanism of the Paternò–Büchi Reaction	220
7.3	Regioselective and Site-Selective Syntheses of Oxetanes	221
7.4	Stereoselective Syntheses of Oxetanes	226
7.5	Concluding Remarks	233
	References	233

8	Formation of a Five-Membered Ring	241
	<i>Ganesh Pandey and Smita R. Gadre</i>	
8.1	Introduction	241
8.2	Formation of Five-Membered Rings: Intramolecular δ -H Abstraction	241
8.2.1	Formation of Cyclopentanol Ring System	242
8.2.1.1	Synthesis of Indanols	243
8.2.2	Synthesis of Tetrahydrofuranols	247
8.2.2.1	Formation of Benzofuranols	250
8.2.3	Synthesis of Pyrrolidine Derivatives	250
8.3	Formation of Five-Membered Rings via [3+2]-Cycloadditions	254
8.3.1	Photofragmentation of Oxiranes to Carbonyl Ylides: Synthesis of Tetrahydrofurans	254
8.3.2	Generation of Azomethine Ylides by the Photolysis of Aziridines: Synthesis of the Pyrrolidine Framework	258
8.3.3	Vinyl Cyclopropane to Cyclopentene Rearrangement	260
8.4	Photochemical Electrocyclization Reactions: Synthesis of Fused, Five-Membered Ring Compounds	261
8.5	Photoinduced Electron Transfer-Mediated Cyclizations: Synthesis of Five-Membered Carbocyclic and Heterocyclic Ring Systems	266
8.5.1	Radical Cation-Mediated Carbon–Carbon Bond Formation	266
8.5.2	Radical Anion-Mediated Cyclizations	272
8.5.3	Intramolecular Trapping of Radical Cations by Nucleophiles	276
	References	279
9	Formation of Six-Membered (and Larger) Rings	287
	<i>Julia Pérez-Prieto and Miguel Angel Miranda</i>	
9.1	Introduction	287
9.2	Photoelectron Transfer-Initiated Cyclizations	287
9.2.1	Phthalimides as Electron Acceptors	287
9.2.2	Aromatic Ketones as Electron Acceptors	291
9.2.3	Chloroacetamides as Electron Acceptors	292
9.2.4	Electron-Deficient Aromatic Compounds as Electron Acceptors	293
9.3	Photoinduced 6π -Electrocyclization	295
9.3.1	Stilbene-Like Photocyclization	295
9.3.2	Vinyl-Biphenyls Photocyclization	299
9.3.3	Anilides and Enamides Photocyclization	299
9.4	Photocycloaddition Reactions	300
9.4.1	Photochemical Diels–Alder Reaction	301
9.4.2	Photoenolization/Diels–Alder Reaction	302
9.4.3	[4+4]-Photocycloaddition	302
9.4.4	Transition Metal Template-Controlled Reactions	304
9.5	Remote Intramolecular Hydrogen Abstraction	307
9.6	Ring Contraction and Ring Enlargement	308
9.7	Other Reactions	311

- 9.7.1 Intramolecular [2+2]-Cycloadditions 311
- 9.7.2 Photocyclization of Cinnamylanilides 311
- 9.7.3 Photocycloaddition of Aromatic Compounds 311
- 9.8 Concluding Remarks 313
- References 313

10 Aromatic and Heteroaromatic Substitution by $S_{RN}1$ and S_N1 Reactions 319

Alicia B. Peñeñory and Juan E. Argüello

- 10.1 Introduction 319
- 10.2 General Mechanistic Features 320
 - 10.2.1 $S_{RN}1$ Mechanism 320
 - 10.2.2 S_N1 Mechanism 322
- 10.3 Carbon–Carbon Bond Formation 323
 - 10.3.1 Carbanions from Ketones, Esters, Acids, Amides, and Imides as the Nucleophiles 323
 - 10.3.2 Alkenes, Alkynes, Enols, and Vinyl Amines as the Nucleophiles 326
 - 10.3.3 Aryl Alkoxide and Aryl Amide Anions as the Nucleophiles 329
 - 10.3.4 Cyanide Ions as the Nucleophile 331
- 10.4 Carbon–Heteroatom Bond Formation 332
 - 10.4.1 Tin Nucleophiles 332
 - 10.4.2 Sulfur Nucleophiles 333
- 10.5 Synthesis of Bi-, Tri-, and Polyaryls 334
 - 10.5.1 Consecutive $S_{RN}1$ -Pd(0)-Catalyzed Crosscoupling Reactions 334
 - 10.5.2 Photo- S_N1 as an Alternative to Metal Catalysis 336
- 10.6 Synthesis of Carbocycles and Heterocycles 338
 - 10.6.1 Carbocycles 338
 - 10.6.2 Nitrogen Heterocycles 341
 - 10.6.3 Oxygen Heterocycles 344
 - 10.6.4 Sulfur Heterocycles 346
- References 346

11 Singlet Oxygen as a Reagent in Organic Synthesis 353

Matibur Zamadar and Alexander Greer

- 11.1 Introduction 353
- 11.2 Dioxetanes 354
 - 11.2.1 Background Information 354
 - 11.2.2 Adamantyl-Substituted Alkenes 355
 - 11.2.3 Alkoxy-Substituted Alkenes 356
 - 11.2.4 Phenyl- or Methyl-Substituted Alkenes 357
 - 11.2.4.1 Diphenylindene Photooxidation 357
 - 11.2.4.2 Electron-Transfer Photooxidation 357
 - 11.2.5 Summary 358
- 11.3 Endoperoxides 358
 - 11.3.1 Background Information 358

11.3.2	Arenes	359
11.3.2.1	Benzenes	359
11.3.2.2	Naphthalenes	361
11.3.2.3	Anthracenes, Polyacenes, and Carbon Nanotubes	362
11.3.3	Electron-Transfer Photooxidation	364
11.3.4	Conjugated Dienes	364
11.3.4.1	Acyclic Dienes	364
11.3.4.2	Cyclopentadienes and Cyclohexadienes	364
11.3.4.3	Heterocycles and Cyclohexatriene	365
11.3.5	Summary	368
11.4	Allylic Hydroperoxides	368
11.4.1	Background Information	368
11.4.2	Simple Alkenes	368
11.4.3	“Ene” Reactions Confined in Zeolites	370
11.4.4	Summary	370
11.5	Tandem Singlet Oxygen Reactions	371
11.5.1	Background Information	371
11.5.2	Bisperoxides	371
11.5.2.1	Phenyl-Substituted Alkenes	371
11.5.2.2	Cyclic Alkenes	372
11.5.3	Rearrangement to a Hemiketal Hydroperoxide	374
11.5.4	Rearrangements to Spiro Compounds	374
11.5.5	Summary	376
11.6	Concluding Remarks	377
	References	377
12	Synthesis of Heteroaromatics via Rearrangement Reactions	387
	<i>Nicolò Vivona, Silvestre Buscemi, Ivana Pibiri, Antonio Palumbo Piccionello, and Andrea Pace</i>	
12.1	Introduction	387
12.2	Synthesis of Five-Membered Rings with One Heteroatom	388
12.2.1	Pyrroles	388
12.2.2	Furans	391
12.2.3	Thiophenes	392
12.3	Synthesis of Five-Membered Rings with Two Heteroatoms	393
12.3.1	Pyrazoles	393
12.3.2	Imidazoles	394
12.3.3	Oxazoles	398
12.3.4	Thiazoles	400
12.4	Synthesis of Five-Membered Rings with Three Heteroatoms	402
12.4.1	Oxadiazoles	402
12.4.2	Triazoles	404
12.4.3	Thiadiazoles	405
12.5	Synthesis of Six-Membered Rings	406
12.6	Synthesis of Seven-Membered Rings	406

12.6.1	Azepines	406
12.6.2	Diazepines	407
12.6.3	Oxazepines	409
12.7	Concluding Remarks	410
	References	411
13	Photolabile Protecting Groups in Organic Synthesis	417
	<i>Christian G. Bochet and Aurélien Blanc</i>	
13.1	Introduction	417
13.2	Photolabile Protecting Groups	418
13.2.1	Ortho-Nitrobenzyl Alcohol Derivatives	418
13.2.2	Benzyl Alcohol Derivatives	421
13.2.3	Other Types of Protecting Group	423
13.2.3.1	Norrish Type II	423
13.2.3.2	Norrish Type I	424
13.2.3.3	Thioketals	424
13.2.3.4	Silicon Ethers	424
13.2.4	Z/E Photoisomerization	425
13.2.4.1	Cinnamyl Esters	425
13.2.5	Phenacyl Derivatives	426
13.2.5.1	Mechanism	426
13.2.6	Benzoin Derivatives	428
13.2.6.1	Mechanism	428
13.2.7	Indolines	429
13.3	Chromatic Orthogonality	430
13.4	Two-Photons Absorption	431
13.5	Concluding Remarks	432
13.6	Appendix	433
	References	439
	Index	449

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.

Angelo Albini and Maurizio Fagnoni

List of Contributors

Manabu Abe

Hiroshima University (HIRODAI)
Graduate School of Science
Department of Chemistry
1-3-1 Kagamiyama
Higashi-Hiroshima
Hiroshima 739-8526
Japan

Angelo Albini

University of Pavia
Department of Organic Chemistry
Via Taramelli 10
27100 Pavia
Italy

Juan E. Argüello

Universidad Nacional de Córdoba
Facultad de Ciencias Químicas
INFIQC – Dpto Química Orgánica
Ciudad Universitaria
5000 Córdoba
Argentina

Thorsten Bach

Technische Universität München
Lehrstuhl für Organische Chemie I
85747 Garching
Germany

Aurélien Blanc

University of Strasbourg
Institut de Chimie, UMR 7177/CNRS
Laboratoire de Synthèse et Réactivité
Organiques
4 rue Blaise Pascal
67000 Strasbourg
France

Christian G. Bochet

University of Fribourg
Department of Chemistry
9 Ch. du Musée
1700 Fribourg
Switzerland

Silvestre Buscemi

Università degli Studi di Palermo
Dipartimento di Chimica Organica
“E. Paternò”
Viale delle Scienze, Parco d’Orleans II
Edificio 17
90128 Palermo
Italy

Valentina Dichiarante

University of Pavia
Department of Organic Chemistry
Via Taramelli 10
27100 Pavia
Italy

Maurizio Fagnoni

University of Pavia
Department of Organic Chemistry
Via Taramelli 10
27100 Pavia
Italy

Smita R. Gadre

National Chemical Laboratory
Division of Organic Chemistry
Dr. Homi Bhabha Road
Pune 411008
India

Miguel A. Garcia-Garibay

University of California
Department of Chemistry and
Biochemistry
Los Angeles, CA 90095
USA

Luca Germani

University of Pavia
Department of Organic Chemistry
Via Taramelli 10
27100 Pavia
Italy

Alexander Greer

Graduate Center and
The City University of New York
(CUNY)
Brooklyn College
Department of Chemistry
Brooklyn, NY 11210
USA

Jörg P. Hehn

Technische Universität München
Lehrstuhl für Organische Chemie I
85747 Garching
Germany

Norbert Hoffmann

Université de Reims Champagne-
Ardenne, CNRS
Institut de Chimie Moléculaire de
Reims, UMR 6229
Groupe de Photochimie, UFR Sciences
B.P. 1039
51687 Reims
France

Patrick S. Mariano

University of New Mexico
Department of Chemistry and
Chemical Biology
Albuquerque, NM 87131
USA

Miguel Angel Miranda

Universidad Politécnica de Valencia
Instituto de Tecnología
Química UPV-CSIC
Departamento de Química
Camino de Vera sn
46071 Valencia
Spain

Christiane Müller

Technische Universität München
Lehrstuhl für Organische Chemie I
85747 Garching
Germany

Andrea Pace

Università degli Studi di Palermo
Dipartimento di Chimica Organica
"E. Paternò"
Viale delle Scienze, Parco d'Orleans II
Edificio 17
90128 Palermo
Italy

Ganesh Pandey

National Chemical Laboratory
Division of Organic Chemistry
Dr. Homi Bhabha Road
Pune 411008
India

Alicia B. Peñéñory

Universidad Nacional de Córdoba
Facultad de Ciencias Químicas
INFIQC – Dpto Química Orgánica
Ciudad Universitaria
5000 Córdoba
Argentina

Julia Pérez-Prieto

Universidad de Valencia
Instituto Ciencia Molecular
Polígono La Coma sn
46980 Paterna, Valencia
Spain

Ivana Pibiri

Università degli Studi di Palermo
Dipartimento di Chimica Organica
“E. Paternò”
Viale delle Scienze, Parco d’Orleans II
Edificio 17
90128 Palermo
Italy

Antonio Palumbo Piccionello

Università degli Studi di Palermo
Dipartimento di Chimica Organica
“E. Paternò”
Viale delle Scienze, Parco d’Orleans II
Edificio 17
90128 Palermo
Italy

Saori Shiraki

University of California
Department of Chemistry and
Biochemistry
Los Angeles, CA 90095
USA

Takashi Tsuno

Nihon University
College of Industrial Technology
Department of Applied Molecular
Chemistry
Narashino, Chiba 275-8575
Japan

Nicolò Vivona

Università degli Studi di Palermo
Dipartimento di Chimica Organica
“E. Paternò”
Viale delle Scienze, Parco d’Orleans II
Edificio 17
90128 Palermo
Italy

Matibur Zamadar

Graduate Center and
The City University of New York
(CUNY)
Brooklyn College
Department of Chemistry
Brooklyn, NY 11210
USA

1

Photochemical Methods

Angelo Albini and Luca Germani

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 be 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

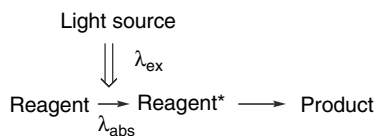
Irradiation Apparatus

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 λ_{exc} .
- Nothing interferes with the electronically excited states and quench them before they react (see Scheme 1.1).



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} 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.



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.

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).

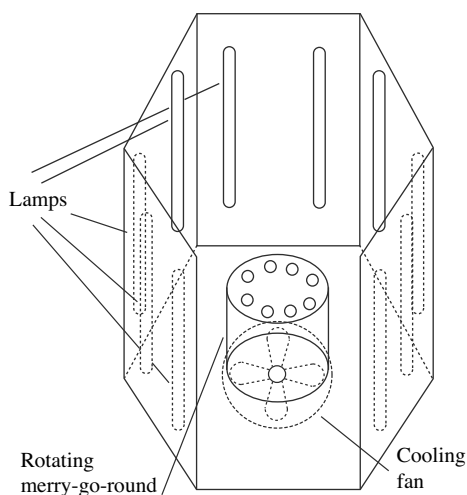


Figure 1.2 Multilamp apparatus fitted with low-pressure mercury lamps and a rotating “merry-go-round” that ensures the uniform illumination of several test tubes. Alternatively, test tubes or other vessel(s) containing the solution to be irradiated can be accommodated.

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.

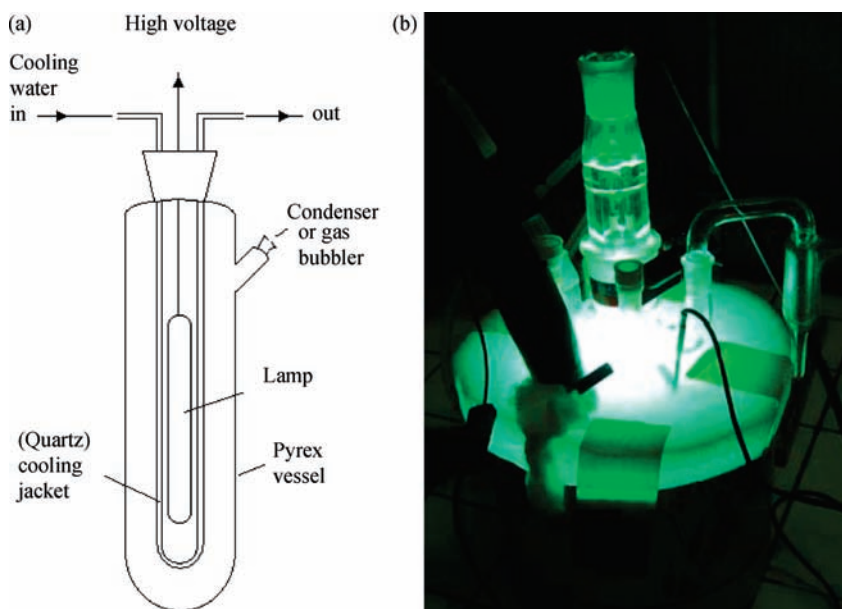


Figure 1.4 (a) Immersion well irradiation apparatus; (b) a refrigerated apparatus for conducting reactions at low temperature.

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 λ); 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°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 an 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.

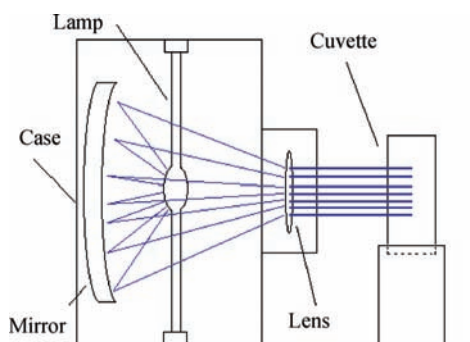


Figure 1.5 High-pressure mercury arc mounted on an optical bench.