



# Photoinduced decarboxylation reactions

## Radical chemistry in water

Axel G. Griesbeck,\* Wolfgang Kramer and Michael Oelgemöller

Institute of Organic Chemistry, University of Cologne, Greinstr. 4, D-50939 Köln, Germany.

E-mail: griesbeck@uni-koeln.de

Received 24th June 1999

### Summary

*Intramolecular* photodecarboxylation reactions of potassium  $\omega$ -phthalimido carboxylates in water or mixtures of water and organic solvents (acetone, acetonitrile) were investigated using an incoherent XeCl excimer radiation source emitting at 308 nm. Electron transfer induced *intermolecular* addition of alkyl carboxylates to phthalimides likewise proceeded efficiently under these conditions. The reactions can be performed in multigram (*i.e.* 10–30 g product) quantities using easily available substrates such as glutamic acid (for the synthesis of **3**), leucine (for **8**, **9**) or simple alkyl carboxylates (for **11**). The advantages of this methodology are: clean and high-yielding reactions, solvent and waste minimization, water-based processes and efficient utilization of photons of defined energy.

### Introduction

Photons are the environmentally most friendly reagents in chemistry. They can be tuned in order to selectively excite one part of a molecule or a bimolecular entity either by wavelength adaptation or by intensity variation (one- *versus* two-photon chemistry). Another aspect which makes photochemistry attractive is that solar radiation is the source of life on earth and still is the most powerful and productive way to produce organic molecules. Thus, use of this natural energy reservoir to perform chemical reactions would be highly desirable in order to approach the noble goals of sustainable chemistry.

Many photochemical reactions, however, suffer from their very special reaction conditions, *i.e.* the use of a limited number of organic solvents which are photostable during the reaction, low concentrations of substrates, sophisticated substrate and/or product structures, complex product mixtures, special prerequisites for the performance of the reactions (wavelength and filters), *etc.* It is therefore highly desirable to develop photochemical processes which come nearer to 'natural' photochemistry, *i.e.* aqueous media, oxygen tolerable and long-wavelength irradiation. Not all conditions will be reached immediately but a step-wise modification of efficient photochemistry might lead to these goals.

We have investigated in the last decade the photochemistry of N- and C-activated  $\alpha$ -amino acids. The motivation for this project was the search for new and efficient amino acid transformations which might be useful additions to known organometallic or electrochemical methods. Concerning the nature of the chromophoric group, one has to take into account that any oligopeptide with  $n$  amino acid residues has at least  $(n - 1)$  chromophoric groups which can be electronically excited under short-wave-

length excitation beside the terminal carboxylate. Thus, light must be concentrated and collected into a selective molecular trap, either directly linked to the amino acid (or the peptide) or by energy or electron transfer using external sensitizing agents. Covalently linked chromophores which show highly selective photochemistry include aromatic ketones (C-terminal),<sup>1</sup> pyruvamides (N-terminal)<sup>2</sup> and especially the phthalimide group.<sup>3</sup> The advantages of all these chromophores were as follows: absorption in the 310–350 nm region, rapid intersystem crossing (ISC) to give relatively long-lived triplet excited states, selective activation of proximate C–H bonds (for aromatic ketones or pyruvamides) or photoinduced electron-transfer activity (for phthalimides).

An especially attractive photochemical reaction was discovered when C-unprotected  $\omega$ -phthalimido carboxylic acids were irradiated. Applied as the free acids, only  $\alpha$ -phthalimido carboxylic acids were prone to decarboxylation in a variety of solvents giving rise to the corresponding *N*-alkyl phthalimides.<sup>4</sup> This reaction was successfully applied by Mariano and Yoon for the generation of 1,3-dipoles which were trapped with dipolarophiles.<sup>5</sup> Remote carboxy groups, however, were unreactive under these reaction conditions. A major improvement came with the use of potassium salts of the carboxylates.<sup>6</sup>

### Results and discussion

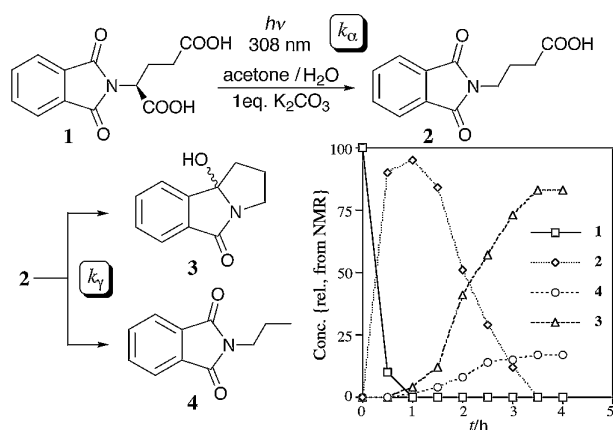
In earlier experiments we used acetone solutions with small amounts of water added in order to improve the solubility of the potassium salt. Actually, higher water concentrations diminished the chemoselectivity, *i.e.* more 'simple' decarboxylation products were formed.<sup>7</sup> Another step forward was made when we found that preparing the potassium salts prior to photolysis made the reaction more selective and even higher water concen-

### Green Context

Aqueous photochemistry represents a potentially very interesting technique for the selective and clean transformation of organic chemicals. This contribution outlines the use of photochemistry in water for the highly selective and high-yielding decarboxylation of carboxylic acids, leading to polycyclic compounds. It also contributes to the growing body of organic reactions which can be advantageously carried out using water as solvent (see *e.g.* *Green Chemistry*, 1999, 1, 167).  
DJM

trations could now be tolerated.<sup>8</sup> The reaction principle is shown in Scheme 1 with *N*-phthaloyl glutamic acid as a model substrate.

NMR spectroscopic investigation of the reaction progress revealed that  $k_{\alpha}/k_{\gamma}$  must be higher than 10. This reaction was performed using solely water as solvent in which the bis-potassium salt of the starting material **1** as well as the product mixture was soluble in concentrations up to 0.1 M. In order to optimize also the light source and the geometry of the reactor, we investigated a new setup for photodecarboxylation in aqueous media. As the light source we used a 3 kW XeCl excimer lamp<sup>9</sup> in a falling film apparatus with a 2–5 liter reservoir. This incoherent excimer radiation source emits a narrow line centered at 308 nm and can be used also in an immersion well configuration. About 10% of the electric power is converted into light emission. There is only little heat release and water cooling is sufficient.<sup>10</sup> For conversion of 50 mmol of substrate **1** ca. 10 kW h are necessary. The excimer radiation setup is shown in Fig. 1.



Scheme 1

The use of aqueous solvent mixtures or pure water as solvent is advantageous also in the sense that pH measurement could be used as an analytical tool to follow the reaction progress. As shown in Scheme 2 the decarboxylative photocyclization of a 0.05 M solution of the bis-potassium salt **1-K<sub>2</sub>** in water can be monitored by pH which starts at 6.4 and levels off at 7.45.

Two other photocyclization reactions which involve the formation of CO<sub>2</sub> were also investigated under the reaction conditions described above: the macrocyclization of substrate **5** to give the twelve-membered annulated amide **6**<sup>7</sup> (Scheme 3) and the cyclization of the anthranilic acid derivative **7** to give the isoindolo benzodiazepine **8**.<sup>11</sup> Both reactions proceeded smoothly when performed with mercury low pressure lamps (phosphor coated with an emission maximum at 300 nm) in acetone solutions. Relatively long irradiation times were needed to run the reaction to complete conversion (ca. 20 h for 5 mmol conversion using 800 W mercury low pressure lamps).

In contrast to this, 3 kW XeCl excimer irradiation gave complete conversion of 50 mmol of **5** in 2 liter of water after only 4.5 h. In a first experiment, 200 ml of acetonitrile were added in order to solubilize the substrate; however, the product precipitated during photolysis. In order to circumvent the use of organic solvents, we irradiated a suspension of **5-K** in water and produced a suspension of **6** in water. Workup of the reaction mixture was extremely easy: after evaporation of 75% of the solvent, the product precipitated and was isolated by filtration in 82% yield. The purity of **6** was even higher than that from 'traditional' irradiation.<sup>7</sup>

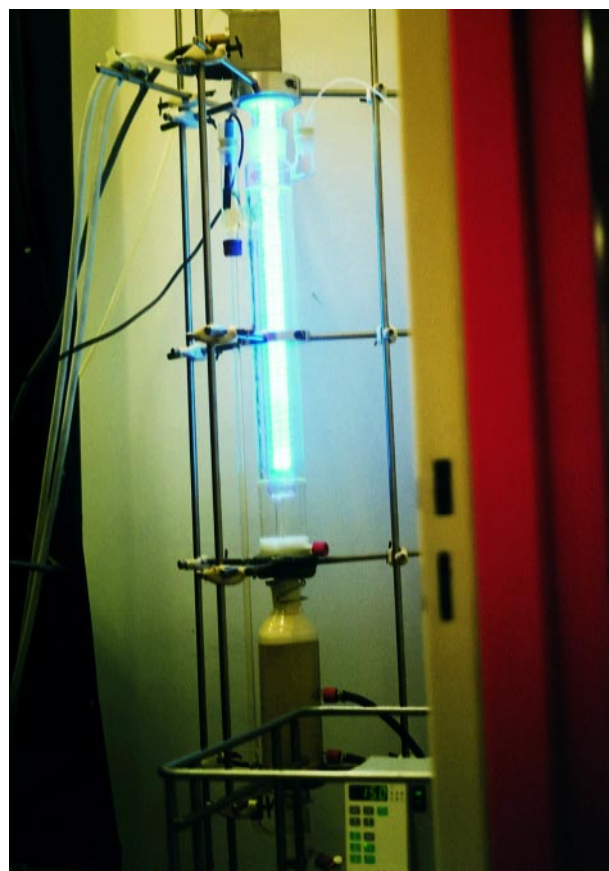
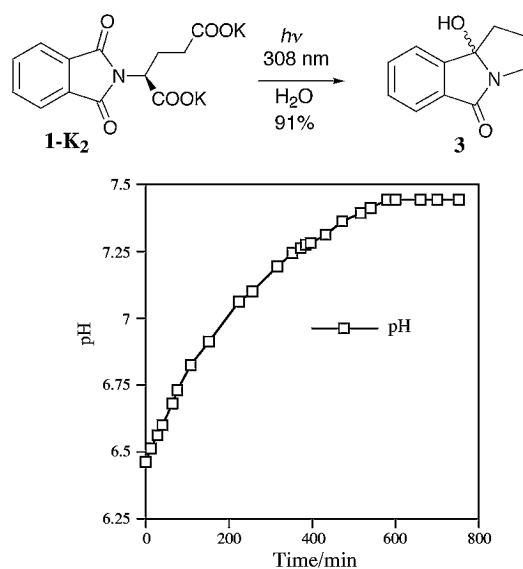
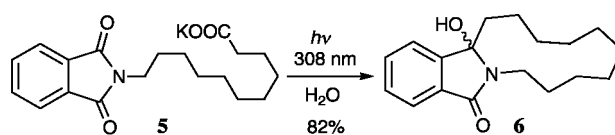


Fig. 1 Excimer radiation reactor: falling-film configuration with pH control (left) and N<sub>2</sub>/Ar inlet

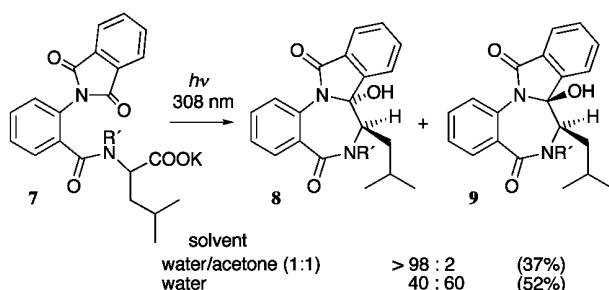


Scheme 2



Scheme 3

A highly surprising result was obtained with the anthranilic acid-based substrate **7**: when irradiated in water–acetone mixtures selectively the *trans*-diastereoisomeric cyclization product **8** was formed from **7-K**, whereas irradiation in pure water led to a 60:40 mixture of *trans*- and *cis*-isomers **8** and **9** (Scheme 4).



Scheme 4

Obviously, an increase in solvent polarity and protic conditions favor less tight donor–acceptor structures which lead to less stereoselective C–C coupling reactions. The yield was strongly enhanced from 37% to 52% when switching from solvent mixtures to purely aqueous conditions.

Also intermolecular addition reactions could be performed in aqueous media, e.g. the photodecarboxylative addition of potassium isobutyrate to *N*-methylphthalimide **10** (Scheme 5).<sup>12</sup> This reaction proceeded smoothly in a 3:1 (vol%) water–acetone mixture using 6 equivalents of alkyl carboxylate and a 0.02 M solution of **10**. The reaction progress was monitored by continuous pH control and gas chromatographic determination of the substrate/product ratio. The pH change for this reaction was similar to that for the intramolecular photodecarboxylations described above: the initial pH value was 6.66 and the final value 8.02. Until ca. 80% conversion of **10** the reaction progress was linear which indicates a pseudo-first order reaction with the alkyl carboxylate as an excess component (which seems not be consumed other than by radical addition). On the other hand, the pH/time correlation showed sigmoidal behaviour in contrast to the intramolecular reactions. This unusual behaviour can be rationalized by assuming a competition between radical addition and catalytic decarboxylation with the formation of Kolbe products which has been already shown for 1-adamantane carboxylic acid.<sup>12</sup>

In summary, intra- and intermolecular photodecarboxylation is a versatile method for radical addition reactions and proceeds efficiently in water by using XeCl excimer based technology. These processes minimize the use of toxic solvents and of organic waste materials.

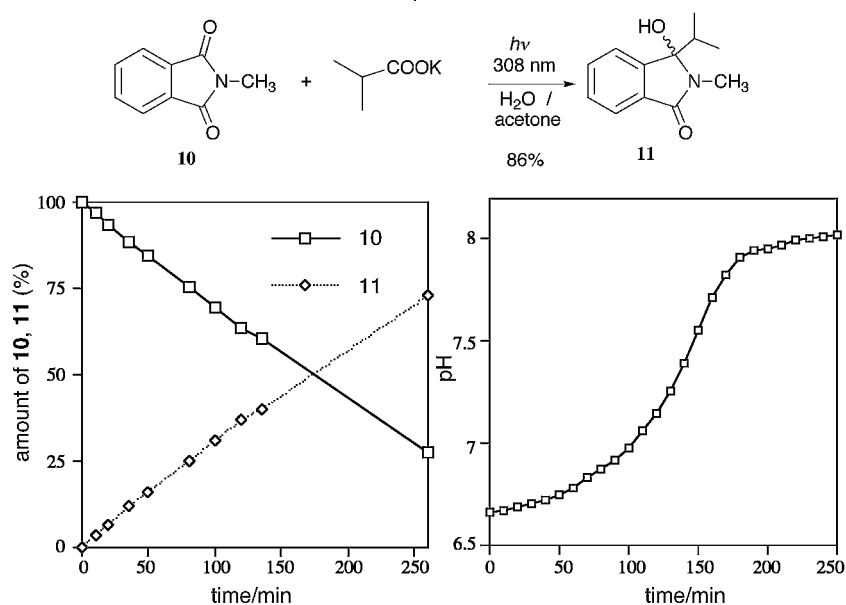
## Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft (GR 881/7-3) and the Fonds der Chemischen Industrie.

## References

- 1 A. G. Griesbeck, H. Heckroth and J. Lex, *Chem. Commun.*, 1999, 1109.
- 2 A. G. Griesbeck and H. Heckroth, unpublished results.
- 3 A. G. Griesbeck, *Chimia*, 1998, **52**, 272; A. G. Griesbeck, *EPA Newsletters*, 1998, 3; A. G. Griesbeck, *Liebigs Ann. Chem.*, 1996, 1951.
- 4 A. G. Griesbeck and A. Henz, *Synlett*, 1994, 931.
- 5 Y. Takahashi, T. Miyashi, U. C. Yoon, S. W. Oh, M. Mancheno, Z. Su, D. F. Falvey and P. S. Mariano, *J. Am. Chem. Soc.*, 1999, **121**, 3926; U. C. Yoon, S. J. Cho, Y.-J. Lee, M. J. Mancheno and P. S. Mariano, *J. Org. Chem.*, 1995, **60**, 2353.
- 6 A. G. Griesbeck, A. Henz, K. Peters, E.-M. Peters and H. G. von Schnering, *Angew. Chem.*, 1995, **107**, 498; *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 474.
- 7 A. G. Griesbeck, A. Henz, W. Kramer, J. Lex, F. Nerowski, M. Oelgemöller, K. Peters and E.-M. Peters, *Helv. Chim. Acta*, 1997, **80**, 912.
- 8 A. G. Griesbeck, F. Nerowski and J. Lex, *J. Org. Chem.*, 1999, **64**, 5213.
- 9 U. Kogelschatz, *Pure Appl. Chem.*, 1990, **62**, 1667; B. Eliasson and U. Kogelschatz, *Appl. Phys. B.*, 1988, **46**, 299.
- 10 Synthetic application described: T. Oppenländer and T. Hennig, *Chem. Ing. Tech.*, 1995, **67**, 594.
- 11 A. G. Griesbeck, W. Kramer and J. Lex, unpublished results.
- 12 A. G. Griesbeck and M. Oelgemöller, *Synlett*, 1999, 492.

Paper 9/05076K



Scheme 5

# ORDER FORM

I wish to order Green Chemistry

☐ Full rate for printed journal  
Sterling £250.00 US dollars \$412.00

☐ Personal rate\* for printed journal  
Sterling £38.00 US dollars \$63.00

\*Only available if there is a full rate subscription at the same address.

To order, please complete the following: My organisation already subscribes to Green Chemistry, which is sent to the following address:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

☐ Electronic Subscription rate:  
Sterling £250.00 US Dollars \$412.00

Please send me details of how to access the electronic journal

Name \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

E-mail \_\_\_\_\_

## Methods of Payment

☐ I enclose a cheque made payable to  
**The Royal Society of Chemistry** for £/\$ \_\_\_\_\_  
(All cheque payments should be in £ sterling drawn on a UK bank or US dollars drawn on a US bank).

☐ Please send me a pre-payment invoice for £/\$ \_\_\_\_\_

☐ Please charge my: Visa/Access/MasterCard/Amex  
(Please delete as appropriate) for £/\$ \_\_\_\_\_

Account No \_\_\_\_\_

Signature \_\_\_\_\_

Expiry date \_\_\_\_\_

## Cardholder's or Invoice address

Name \_\_\_\_\_

Position \_\_\_\_\_

Organization \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

## Delivery Address (if different)

Name \_\_\_\_\_

Position \_\_\_\_\_

Organization \_\_\_\_\_

Address \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

†Credit cards may be used for orders up to £1,000.

All prices subject to change without notice. Non-RSC members' prices quoted.

## Value Added Tax

In certain circumstances we may be obliged to charge Value Added Tax (VAT) on sales to other EU member countries.

In order to avoid this possibility we need your VAT registration number. Could you, therefore, please complete the following as appropriate.

I am registered for VAT and my

VAT Number is: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

## Please complete and return to:

The Royal Society of Chemistry,  
Turpin Distribution Services Limited,  
Blackhorse Road, Letchworth,  
Herts SG6 1HN, United Kingdom.

Telephone: +44 (0) 1462 672555

Fax: +44 (0) 1462 480947

*Turpin Distribution Services Limited is wholly owned by The Royal Society of Chemistry.*

**RSC Members ordering for their own personal use should obtain members prices and order from:**

Membership Administration Department  
The Royal Society of Chemistry  
Thomas Graham House, Science Park  
Milton Road, Cambridge, CB4 0WF,  
United Kingdom.

Telephone: +44 (0) 1223 420066

Fax: +44 (0) 1223 432133

E-mail: waldenn@rsc.org

URL: www.rsc.org

The Royal Society of Chemistry may include your address in its computerized mailing system in order that information about its products and services may be sent to you.

If you **DO NOT** wish to receive details please tick this box ☐.

**RS•C**

ROYAL SOCIETY OF CHEMISTRY