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Photochemistry of N-Phthaloyl Derivatives of Methionine

Axel G. Griesbeck*, Harald Mauder and Ingrid Müller
Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-8700 Würzburg, Germany

Eva-Maria Peters, Karl Peters and Hans Georg von Schnering
Max-Planck-Institut für Festkörperforschung, Heisenbergstraße 1, D-7000 Stuttgart 80, Germany

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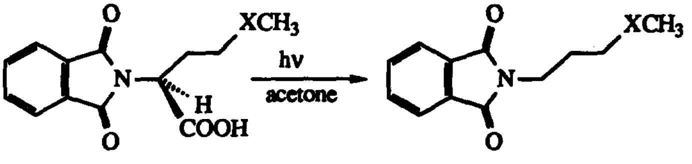
ABSTRACT : Photodecarboxylation of N-phthaloyl derivatives of methionine sulfoxide **1b** and methionine sulfone **1c** was observed in acetone as the major reaction. For **1a** a fast electron transfer initiated cyclization which leads to the bicyclization product **3** (X-ray structure) was observed in the sensitized photolysis. Direct photolysis of **1a** leads preferentially to the tricyclic product **4** and the decarboxylation product **5**. The methionine methyl esters **6a-c** showed electon transfer initiated cyclization (for **6a**) and disproportionation (for **6b**), whereas **6c** proved to be photostable.

The photochemistry of N-phthaloyl α-amino acids has been intensively investigated by Kanaoka et al.[1] Decarboxylation was described to be the exclusive primary reaction pathway for a series of substrates.[2] During our investigations of photochemical amino acid transformations[3,4] we also got interested in electron-transfer initiated reactions. Heteroatoms such as sulfur[5], oxygen[6], or nitrogen[7] in the side-chain of amino acids are potential donors for intramolecular ET thus generating radical ion pairs which could further react to new amino acid derivatives. We tested a series of enantiomerically pure methionine derivatives as potent substrates: N-phthaloyl methionine **1a**, its sulfoxide **1b**[8], the sulfone **1c**[9], and the corresponding methyl esters **6a-c**.[10] The free acids **1b** and **1c** underwent efficient decarboxylation during irradiation in acetone (300 nm).(Scheme 1).

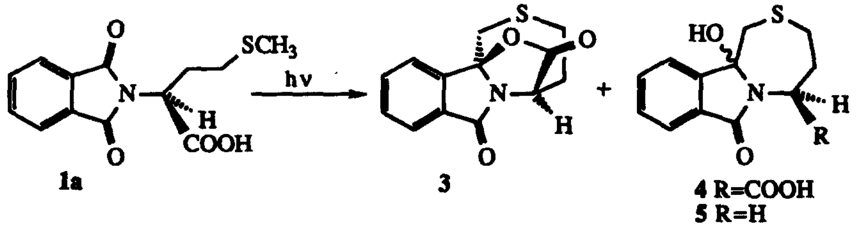


1b,c **2b,c**

b : X = SO
c : X = SO$_2$

Scheme 1

1a showed a completely different product spectrum. When the irradiation of **1a** was performed in acetone as major component the bicyclization product **3** (75-85% yield) was isolated (Scheme 2, Table 1) besides minor amounts of the tricyclic compound **4** and the product of a decarboxylation/ cyclization sequence **5**.[2,11] Under analogous conditions the irradiation in acetonitrile did not lead to a detectable conversion. Photolysis in acetonitrile in the presence of benzophenone (entry 3) gave the idential product composition as in entry 1, thus proving the triplet excited state of **1a** being the reactive intermediate.



Scheme 2

Table 1. Photolysis of **1a** - product composition

entry	solvent[a]	conditions	conversion (%)[b]	**3** (%)[b]	**4** (%)[b]	**5** (%)[b]
1	acetone	pyrex	100	80	5	15
2	acetonitrile	pyrex	< 5	-	-	-
3	acetonitrile	pyrex/BP[c]	63	83	2	15
4	benzene	pyrex	10	50	30	20
5	benzene	quartz	40	58	25	17
6	benzene	pyrex/BP[c]	70	71	14	15

[a] 0.05 M solution of **1a** / 30°C / 3000 Å / 10 h / RPR-208 Rayonet photoreactor; [b] ^{1}H NMR (250 MHz) normalized to 100%; [c] 0.02 M solution of benzophenone (BP).

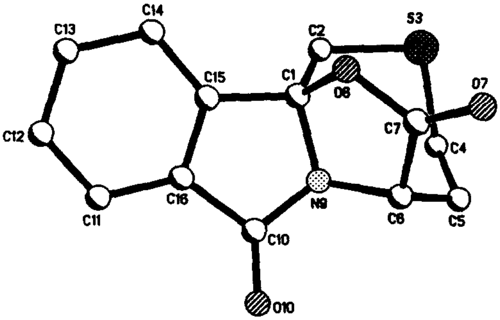
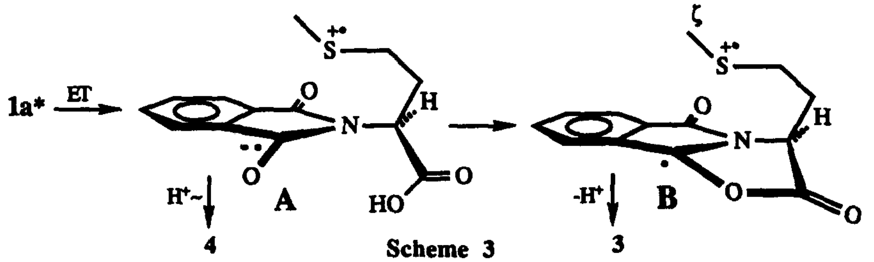


Figure 1. Crystal structure of **3** selected bond lengths (pm) and angles (°): C1-C2: 153.3, C2-S3: 180.6, S3-C4: 181.3, C4-C5: 151.6, C5-C6: 153.9, C6-N9: 144.8, N9-C1: 146.3, C1-O8: 144.3, O8-C7: 137.5. S3-C2-C1: 114.2, C2-S3-C4: 101.2, S3-C4-C5: 114.9, C4-C5-C6: 113.4, C5-C6-N9: 114.1, C5-C6-C7: 113.2, C1-O8-C7: 107.7, C6-C7-O8: 109.7.

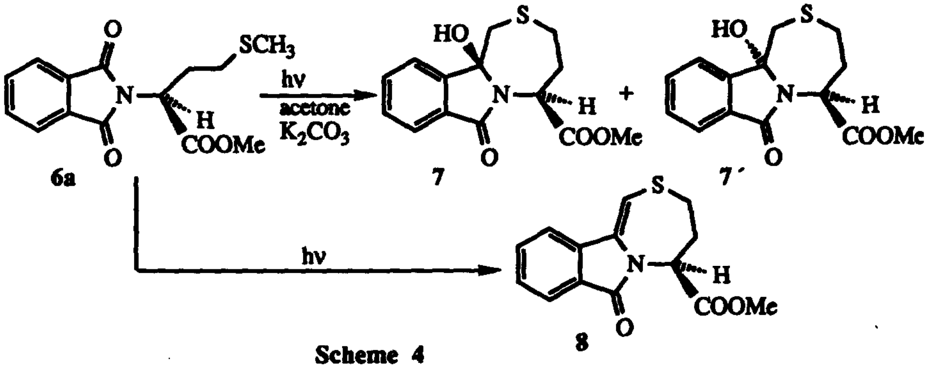
Compound **3** and **4** are highly unusual products in the sense that the normal decarboxylation route is not followed here. Obviously the first reaction event must be an electron transfer from the sulfur atom to the phthalimide group. Subsequently the phthalimide radical anion forms the lactone ring *via* nucleophilic attack at the carboxy group.[12] Loss of a proton from the radical cation part of the molecule **B** and radical recombination leads to **3** (Scheme 3).The structure of **3** was established by a X-ray analysis (Figure 1).[13] Alternatively proton transfer from the radical cation part of the intermediate **A** can proceed which generates a 1,7-biradical capable of direct radi-cal recombination to give product **4**. This compound is unable to undergo photodecarboxylation and does *not* form the lactone **3** under the reaction conditions.



Scheme 3

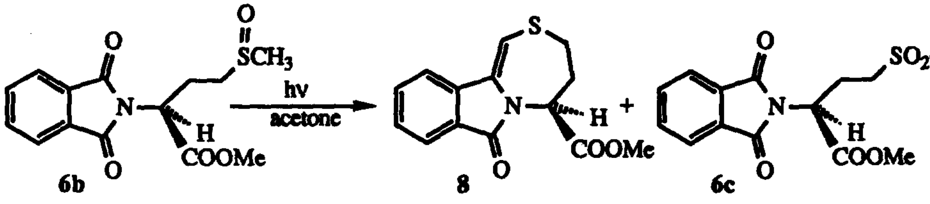
When benzene was used as solvent (entry 4,5) the reaction efficiency dropped remarkably. After a more than ten-fold prolonged irradiation time a 5:3:2 mixture of **3**,**4** and **5** was isolated.The addition of benzophenone (entry 6) again accelerated the reaction and leads to a similar product ratio as in entry 1 and 3. Obviously the triplet energy of benzophenone is sufficient to generate triplet excited **1a** which is well in accord with the energy of the lowest phthalimides triplet state (ca. 68.5 kcal/ Mol).[14]

The photochemisty of the N-phthaloyl methionine methyl ester **6a** was already described by Kanaoka and coworkers.[2] We found the ring annulation and dehydration product **8** as sole compound when irradiation was performed in the absence of a base. In the presence of sodium carbonate, the electron transfer initiated cyclization products **7**,**7'** were isolated as a 45:55 diastereomeric mixture in 84% yield (Scheme 4). Corresponding to **1a** the photoreaction of **6a** was most efficient in acetone.



Scheme 4

In case of sulfone **6c** no conversion was observed even after prolonged irradiation. This is in agreement with the missing electron donor function for intramolecular ET. It is, however, astonishing when compared with the behaviour of alkyl-chain substituted amino acid derivatives[4] which showed efficient γ-hydrogen abstraction in unpolar solvents. The photochemical behaviour of the sulfoxide **6b** again was striking: a ca. 1:1 mixture of the sulfone **6c** and the annulation product **8** was formed after a ca. fourty-fold prolonged irradiation time compared to its analogue **6a**.



Scheme 5

This product composition must be due to a electron-transfer initiated disproportionation, where the sulfoxide moiety of **6b** acts as electron donor in a intra- *or* intermolecular electron transfer step. Its radical cation can subsequently attack another sulfoxide unit which transfers one oxygen atom to give the sulfone **6c** and a sulfide radical cation. After back electron transfer compound **6a** is generated and is converted after second excitation to product **8**. Indeed when the reaction was stopped after 20% conversion about 5% of the sulfide **6a** could be detected in the reaction mixture. A similar electron-transfer initiated disproportionation has been described by Fox et al. in the photolysis of dialkyl sulfides in acetone.[15]

ACKNOWLEDGEMENTS

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8. Sulfoxide **1b** was synthesized from methionine-S-oxide and phthalic anhydride in 57% yield.
9. Sulfone **1c** was synthesized from **1a**[2] with a three molar excess of hydrogen peroxide (24 h, R.T.) in 31% yield after column chromatography.
10. Methyl esters **6a-c** were synthesized from **1a-1c** by acid catalyzed esterification (MeOH / HCl, 1h, 5°C) in 85-93% yield.
11. In ref. 2 the spectral and analytical data for product **3** obviously were misinterpreted.
12. Analogous lactonizations with intermediate radical cations are well documented; e.g.: Wilson, R. M., Musser, A. K., *J. Am. Chem. Soc.* **1980**, *102*, 1720; Gassman, P. G., Bottorff, K. J., *J. Am. Chem. Soc.* **1987**, *109*, 7547; Gassman, P. G., De Silva, S. A., *J. Am. Chem. Soc.* **1991**, *113*, 9870, and lit. cited therein.
13. Complete results have been deposited and are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftliche Information mbH, D-7514 Eggenstein-Leopoldshafen 2, on quoting the depository number CSD-56596, the names of the authors and the journal citation. The crystals of **3** (acetone, m.p. 188-189°C) are orthorhombic, $P2_12_12_1$, $a = 867.5(2)$, $b = 1895.8(5)$, $c = 704.6(1)$ pm; $V = 1158.8(6)\times10^6$ pm^3; $Z = 4$; $d_{calc} = 1.497$ g/cm^3; 1957 independent reflections, 1783 with $F > 3\sigma(F)$; $R = 0.042$, $R_W = 0.034$.
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