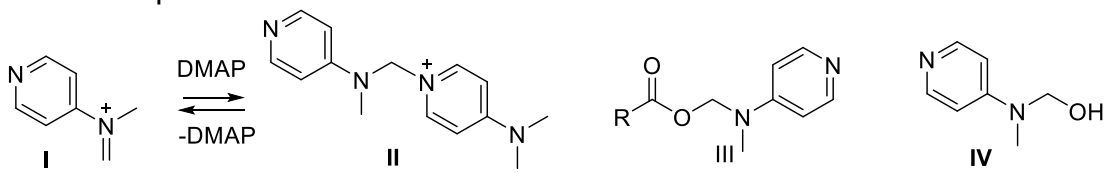
Study of the UVA-light-mediated Synthesis of Hydroxamic Acids From Carboxylic Acids by High Resolution Mass Spectromery

Christiana Mantzourani,[*] Olga G. Mountanea,[*] Maroula G. Kokotou,[**] Christoforos G. Kokotos,* George Kokotos*

*****Department of Chemistry and Center of Excellence for Drug Design and Discovery, National and Kapodistrian University of Athens, Panepistimiopolis, Athens 15771, Greece

******Laboratory of Chemistry, Department of Food Science and Human Nutrition, Agricultural University of Athens, Iera Odos 75, Athens 11855, Greece. chrmantz@chem.uoa.gr

Direct infusion−high resolution mass spectrometry (DI−HRMS) is an alternative approach to chromatography−MS-based techniques, which finds various applications in non-targeted metabolomics. The direct injection of a sample into ESI-HRMS offers a rapid and simplified approach, avoiding time-consuming chromatography and possible decomposition of sensitive to solvents analytes, and offering the possibility for acquiring the MS information of all analytes in a defined scan range and for the follow-up retrospective analysis. Most recently, we have applied DI−HRMS to unravel the mechanism of the catalyst-free light-mediated aerobic oxidation of aldehydes to carboxylic acids [1]. In the present study, adopting a DI−HRMS method, we studied the mechanism of the UVA-light-mediated synthesis of hydroxamic acids from carboxylic acids in the presence of 4-dimethylaminopyridine (DMAP) and $BrCCl_3$ [2]. Upon mixing, DMAP and $BrCCl_3$ form a charge transfer complex (CTC) and after irradiation, homolytic cleavage of the excited CTC leads to iminium intermediate **I** and its adduct with DMAP **II,** which both were observed by HRMS in high intensity. The carboxylic acid reacts with **I** (or/and **II**), leading to hemiaminal ester **III**. Nucleophilic attack of a hydroxylamine derivative to **III** provides the coupling product, liberating compound **IV**. The study of the reaction mechanism using DI-HRMS has provided experimental evidence for the co-existence of various intermediate species and pathways and may help in designing new efficient light-mediated syntheses of pharmacologically active compounds.



Selected Intermediates Observed by HRMS

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1. C. S. Batsika, C. Koutsilieris, G. S. Koutoulogenis, M. G. Kokotou, C. G. Kokotos, G. Kokotos, *Green Chem.*, **2022**, *24*, 6224-6231.
2. O. G. Mountanea, C. Mantzourani, M. G. Kokotou, C. G. Kokotos, G. Kokotos, *Eur. J. Org.*, **2023**, doi.org/10.1002/ejoc.202300046.