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Photooxygenation of 5-Dialkylamino-4-pyrrolin-3-ones. Synthesis of Highly Functionalized Ureas, 2-Oxazolidinones and 2-Oxazolinones[§]

Ihsan Erden^{*}, Galip Özer, Christophe Hoarau, Weiguo Cao, Jiangao Song, and Christian Gärtner

San Francisco State University, Department of Chemistry and Biochemistry, 1600 Holloway Avenue, San Francisco, CA 94132 USA

Ingmar Baumgardt[‡] and Holger Butenschön[‡]

Leibniz Universität Hannover, Institut für Organische Chemie, Schneiderberg 1B, D-30167 Hannover, Germany

Abstract

5-Dialkylamino-4-pyrrolin-3-ones, available from cyclocondensation of amidines with dimethyl acetylenedicarboxylate (DMAD) undergo rapid singlet oxygenation to give highly functionalized ureas by way of a 1,2-dioxetane cleavage of the initially formed [2+2] cycloadducts. These latter compounds undergo cyclization to 2-oxazolidinones in MeOH. Catalytic hydrogenation of the ureas in EtOAc gives 2-oxazolinones. The DBU-DMAD adduct undergoes photooxygenation by an entirely different pathway to give a large ring heterocycle.

The reactions of enamines with singlet oxygen have been extensively studied and the mechanisms involved elucidated.^{1–8} In these reactions it has been shown that singlet oxygen combines with enamines by way of an electron transfer or charge transfer mechanism to 1,2-dioxetanes before the latter collapse to carbonyl fragments. Exocyclic enaminoketones and lactones have been reported by Wasserman and Ives to react with ¹O₂ to give 1,2-diones, presumably by way of a 1,2-dioxetane.^{9–11} We have extensively studied the singlet oxygenations of the C=N containing compounds in the past and found that by contrast to enaminoketones, α-oximinoketones undergo in the presence of base oxidative C–C cleavage to give esters and carboxylic acids.^{12–16} We recently reported the synthesis of 5-dialkylamino-4-pyrrolin-3-ones of the type **3** through a cyclocondensation of amidines with dimethyl acetylenedicarboxylate (DMAD).¹⁷ We also showed that the 4-demethyl analog serves as an excellent precursor of 2-acyltetramic acids, a naturally occurring class of antibiotics and antitumor agents¹⁸ and now report the singlet oxygenations of these compounds.

Singlet oxygenations of the enaminoketones (or vinylogous amides) **4** at -78 °C in CH₂Cl₂ using a high-pressure sodium lamp and tetraphenylporphyrin as sensitizer proceeded rapidly, resulting in quantitative formation of a single product in each case. Based on ¹H and ¹³C NMR, as well as elemental analysis, MS spectra and FT-IR data, the products were identified as the vinylogous ureas of the type **6** (Table 1).

[§]This paper is dedicated to Professor Dieter Kaufmann on the occasion of his 60th birthday.

ierden@sfsu.edu.

[‡]Authors to whom correspondence regarding the X-ray crystallography should be addressed.

The urea structure **6c** was further confirmed by X-ray crystallography (Fig.1, Supporting Information).

Ureas **6** underwent cyclization to the 2-oxazolidinones **9** when stirred in MeOH at room temperature. Alternatively, when the photooxygenations of **4a** and **4c** were conducted in methanol solution instead of CH₂Cl₂, the corresponding ureas immediately underwent cyclization to the 2-oxazolidinone derivatives **9a** and **9c**, respectively. Scheme 2 depicts the mechanism that appears to be plausible for the intramolecular cyclization pathway in the presence of methanol.

Upon catalytic hydrogenation of the ureas in an aprotic solvent such as ethyl acetate, the sole products that were obtained after chromatography on silicagel were the 4-oxazolin-2-ones **11a-c** in yields of 74-82%. These results are in accord with the expectation that once the exocyclic double bond in **6** is reduced, the resulting saturated 1,2-dione would undergo intramolecular cyclization in a manner similar to that shown in Scheme 2, by way of attack of adventitious H₂O at the carbonyl group; the resulting 5-hydroxy-2-oxazolidinone would undergo spontaneous dehydration to give the 4-oxazolin-2-one derivatives **11** as outlined in Scheme 3. Alternatively, the cyclization to **11** could occur directly *via* the enol derived from **10**. In one case, the starting 4-pyrrolin-3-one **4a** was selectively reduced at the exocyclic double bond (Pd/H₂, EtOAc) and the resulting 4-pyrrolin-3-one **12** was photooxygenated in CH₂Cl₂ at -78 °C. Under these conditions, the 2-oxazolinone **11a** was directly formed and was isolated by column chromatography. Compounds of the type **11** with the substitution pattern shown are unknown.

In one case the reduced urea intermediate **10b** was identified in the crude ¹H NMR spectrum of the hydrogenolysis mixture. Compound **10b** exhibited a characteristic triplet at 4.8 ppm (J= 6.75 Hz) for the tertiary hydrogen α to the carbonyl group, an AB system at 2.9 and 2.6 ppm (dd, J= 6.75 and 16.0 Hz) for the diastereotopic hydrogens adjacent to the carbomethoxy group, as well as the singlets at 2.5 ppm for the NMe₂ group and 2.3 ppm for the acetyl group, respectively. Upon chromatography on silica gel, urea **10b** underwent cyclization followed by dimethylamine elimination to give oxazolidinone **11b**.

The question was whether the tricyclic 4-pyrrolin-3-one **13a** derived from the cyclocondensation between DBU and dimethyl acetylenedicarboxylate^{19,20} would undergo a similar transformation reaction upon singlet oxygenation. Under the same condition (-78 °C, CH₂Cl₂), the crimson color of the starting material **13a** disappeared within a short time, and the singlet oxygenation terminated, the solvent removed in vacuo, to give a colorless product. To our surprise, the product from this reaction did not exhibit any of the characteristic features in the NMR spectrum displayed by the 2-oxazolidinones obtained from the monocyclic analogs. Based on all spectral data as well as elemental analysis, the product turned out to be the bridged heterocycle **18**. It obviously stems from an alternative singlet oxygenation pathway; the initial 1,2-dioxetane undergoes a "walk" to the alternative dioxetane **14**, and after C-C-cleavage, the resulting tricyclic heterocycle **15** suffers ring opening in the presence of H₂O. Intramolecular conjugate addition of the enol **17** onto the remote α,β -unsaturated ester group delivers the interesting macrocyclic compound **18** containing a 1,3-oxazolidin-4-one unit. Scheme 4 depicts a plausible mechanism for the aforementioned transformation.

Compound **18** is formally an amino acid and is soluble in H₂O as well as organic solvents. Although intermediate **15** was never observed spectroscopically, a white solid appeared upon rotaevaporation of the solvent from the photooxygenation mixture, and as soon as vacuum was cut off and moist air was let in, the crystals melted and a waxy solid was formed. We postulate, that at that stage compound **15** was converted to **18** by way of **16** and **17**. The characteristic AB doublets at 3.3 and 3.4 (J_{AB}= 17.4 Hz) for the CH₂ group due to the carbomethoxy group

and the triplet at 6.0 ppm for the olefinic hydrogen in the ^1H NMR spectrum were of diagnostic value in the characterization of the **18**. Endoperoxide-dioxetane rearrangements are relatively common,²¹⁻²⁵ however, dioxetane-dioxetane rearrangements are extremely rare. To our knowledge, there is one other case similar to the one described herein, where an enaminoketone undergoes with $^1\text{O}_2$ an analogous dioxetane-dioxetane rearrangement and oxidative C-C-cleavage giving rise to a ketolactone, analogous to the intermediate **15**.²⁶ This transformation was implemented in a total synthesis of a rhoeadin alkaloid by the authors. Whereas the spiro lactone **21** was stable, in our case, the strained tricyclic nature of **15** as well as the presence of the additional nitrogen facilitates the fragmentation of the 1,3-oxazolidin-5-one unit.

In conclusion, we have shown that 5-dialkylamino-4-pyrrolin-2-ones, readily available by our amidine-DMAD cyclocondensation reactions exhibit exceptional reactivity toward singlet oxygen. The 1,2-dioxetane cleavage products from these reactions serve as precursors of uniquely functionalized ureas as well as 2-oxazolidinones and 2-oxazolinones. The tricyclic analog **13** (*Z* and *E* isomers) exhibits divergent behavior in the photooxygenation due to strain reasons and undergoes C-C cleavage followed by rearrangement to large ring heterocycles. Currently we are investigating the cycloadditions of pyrrolinones of the type **3** toward a variety of other cycloaddends, and will shortly disclose our results from these reactions.

Experimental Section

Typical Procedure for the photooxygenations of 5-dimethylamino-4-pyrroline-3-ones

100 mg (0.35 mmol) of **4** was dissolved in 5 mL of CH_2Cl_2 , 3 mg of the sensitizer (TPP, tetraphenylporphyrin) was added, and the solution was irradiated with a 250 W high-pressure Na vapor lamp at -78°C under a positive pressure of dry oxygen. The reaction was monitored by TLC, and in most cases it was over after 20 min of irradiation. The solvent was rotaevaporated to give a quantitative yield of the urea **6** (by NMR). Further purification for analytical samples was achieved by either recrystallization in the case of solid products, or column chromatography on silica gel, eluting with EtOAc/MeOH (99:1).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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20. In our hands, this compound is formed as a mixture of both *E* (**13b**) and *Z* (**13a**) isomers (separable by column chromatography), depending on the reaction temperature and solvent used. Moreover, we cannot account for the singlet at 3.33 ppm for the methoxy group as reported in ref.18^b; rather, it appears at 3.71 ppm in the case of the (*Z*) isomer (**13a**) and 3.82 ppm in the case of **13b**. Both (*Z*) and (*E*) isomers afford **18** upon photooxygenation. Upon catalytic hydrogenation, both yield the same partially reduced product (**19**). The experimental details are given in the Supporting Information.

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SCHEME 1. Amidine-DMAD cyclocondensations

SCHEME 2. Mechanism of 2-oxazolidinone formation from 3

SCHEME 3. 2-Oxazolinone formation from 6 or 12

SCHEME 4. Photooxygenation of the DBU-DMAD cyclocondensation product

SCHEME 5. A Similar photooxidation mechanism

Table 1
Singlet Oxygenation of 5-dimethylamino-4-pyrrolin-3-ones

entry	subst.	R ₁	R ₂	Prod.	Yield% ^a
1	4a	Me	Bn	6a	85
2	4b	Me	Ph	6b	86
3	4c	Ph	Bn	6c	90
4	4d	Me	<i>n</i> -Bu	6d	83
5	4e	<i>n</i> -Hex	Bn	6e	89
6	4f	<i>n</i> -Hex	<i>n</i> -Bu	6f	92

^a Isolated yields by chromatography and/or crystallization