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

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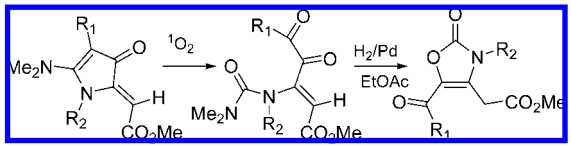
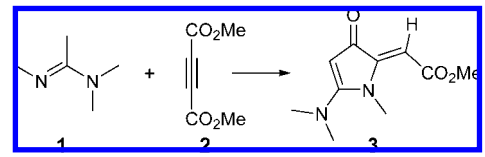


5-Dialkylamino-4-pyrrolin-3-ones, available from cyclocondensation of amidines with dimethyl acetylenedicarboxylate (DMAD), undergo rapid singlet oxygenation to give highly functionalized ureas by way of a 1,2-dioxetane cleavage of the initially formed [2 + 2] cycloadducts. These latter compounds undergo 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.

Introduction

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 $^1O_2$ to give 1,2-diones, presumably by way of a 1,2-dioxetane.[9−11] We have extensively studied the singlet oxygenations of C=N-containing compounds in the past and found that in 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** (Scheme 1) 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 agents,[18] and now report the singlet oxygenations of these compounds.

SCHEME 1. Amidine-DMAD Cyclocondensations



Singlet oxygenations of the enaminoketones (or vinylogous amides) **4** at −78 °C in CH_2Cl_2 using a high-pressure sodium lamp and tetraphenylporphyrin as sensitizer proceeded rapidly, resulting in quantitative formation of a single product in each case. On the basis of ^1H and ^{13}C 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).

The urea structure **6a** was further confirmed by X-ray crystallography (Figure 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 CH_2Cl_2, 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 silica gel 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

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

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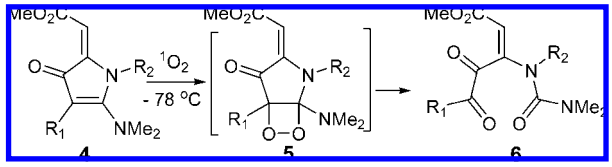
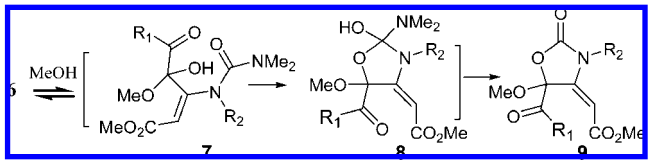
TABLE 1. Singlet Oxygenation of 5-Dimethylamino-4-pyrrolin-3-ones



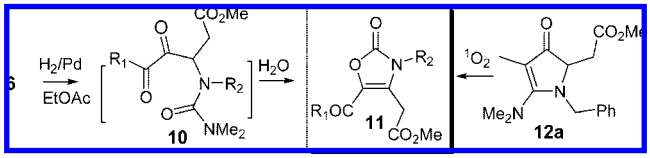
entry	substrate	R_1	R_2	product	yield, %[a]
1	**4a**	Me	Bn	**6a**	85
2	**4b**	Me	Ph	**6b**	86
3	**4c**	Ph	Bn	**6c**	90
4	**4d**	Me	*n*-Bu	**6d**	83
5	**4e**	*n*-Hex	Bn	**6e**	89
6	**4f**	*n*-Hex	*n*-Bu	**6f**	92

[a] Isolated yields by chromatography and/or crystallization.

SCHEME 2. Mechanism of 2-Oxazolidinone Formation from 3



SCHEME 3. 2-Oxazolinone Formation from 6 or 12



intramolecular cyclization in a manner similar to that shown in Scheme 2, by way of attack of adventitious H_2O 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/H_2, EtOAc), and the resulting 4-pyrrolin-3-one 12 was photooxygenated in CH_2Cl_2 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 caharacteristic 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, and singlets at 2.5 ppm for the NMe_2 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, CH_2Cl_2), the crimson color of the starting material

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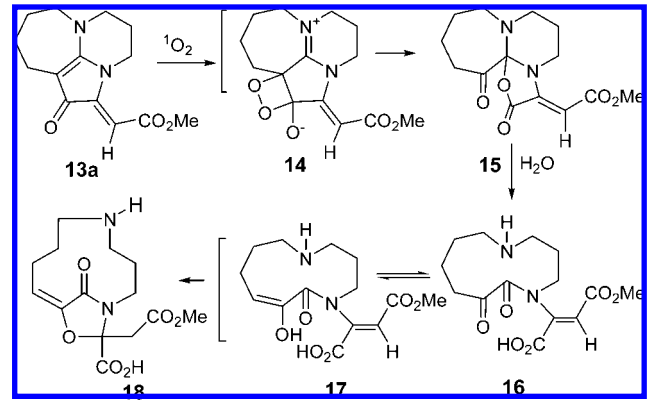
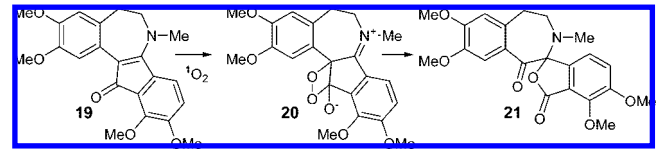
SCHEME 4. Photooxygenation of the DBU-DMAD Cyclocondensation Product



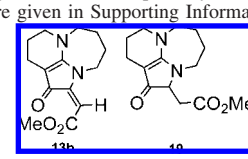
SCHEME 5. Similar Photooxidation Mechanism



13a disappeared within a short time, and the singlet oxygenation was 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. On the basis of 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 H_2O. 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 H_2O as well as organic solvents. Although intermediate **15** was never observed spectroscopically, a white solid appeared upon rotary evaporation 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 CH_2 group attached to the carbomethoxy group and the triplet at 6.0 ppm for the olefinic

(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 18b; 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 Supporting Information.



hydrogen in the ^{1}H 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 $^1O_2$ 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 spirolactone **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.

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Experimental Section

Typical Procedure for the Photooxygenations of 5-Dimethylamino-4-pyrroline-3-ones. A 100 mg (0.35 mmol) portion 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 rotary evaporated 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).

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Supporting Information Available: Synthetic procedures; analytical and spectral data for the ureas **6e−f**, 2-oxazolidinones **9a−d**, 2-oxazolinones **11a−c**, and compounds **12a**, **13a,b**, **18** and **19**; and X-ray crystallography data for **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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