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AZETIDINE-2,4-DIONES VIA PHOTOCHEMICAL REACTION OF N-FORMYL-α-OXOAMIDES

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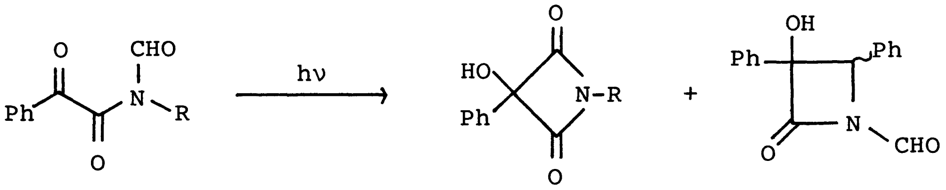
Photochemical reaction of N-formyl-α-oxoamides gave 3-hydroxyazetidine-2,4-diones in good yields. In the case of N-benzyl-N-formylamide, N-formyl-β-lactam was obtained accompanied by the azetidine-2,4-dione. Intramolecular hydrogen abstraction mechanisms were postulated.

It is well-known that azetidine-2,4-diones, four membered cyclic imides, are pharmacollogically highly active. However, the yields of the previously reported syntheses were generally poor.[1)] Recently, photocyclization involving formyl hydrogen abstraction has received considerable attention.[1,2)] In relation to our previous studies on photocyclization of α-oxoamides[3)] and their derivatives,[4)] we now report the facile synthesis of 3-hydroxyazetidine-2,4-diones via photocyclization of N-formyl-α-oxoamides (1).

Irradiation of a benzene solution of N-formyl-N-methylbenzoylformamide (1a) with a high pressure mercury lamp under argon gave a cyclization product, 3-hydroxy-1-methyl-3-phenylazetidine-2,4-dione (2a) in 32% yield. When other N-formyl-α-oxoamides (1b-1e) were irradiated under the same conditions, the corresponding cyclic imides (2b-2e) were obtained (Table). In the case of N-benzyl-N-formyl-α-oxoamide (1d), an N-formyl-β-lactam (3d) was obtained in 16% yield in addition to the azetidine-2,4-dione (2d)



1 2 3d

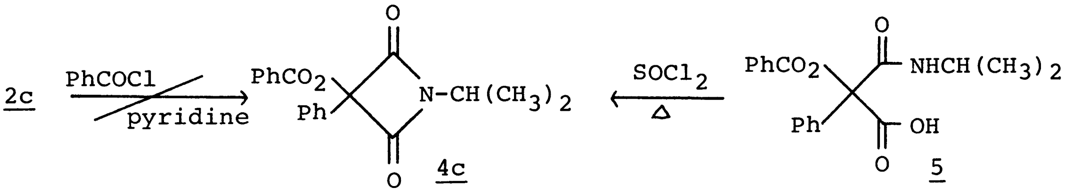
The structure of 2c was confirmed by the fact that benzoylation of 2c gave 3-benzoyloxy-1-isopropyl-3-phenylazetidine-2,4-dione (4c) which was identified by the independent synthesis from 5c.[4)] The structures of other photoproducts were determined by means of the spectral data and elemental analyses.

Table. Azetidine-2,4-diones from 1

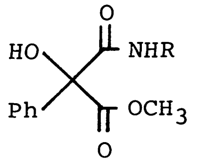
	Yield/%	
	in benzene	in t-butyl alcohol
a:R=CH_3	32	63
b:R=CH_2CH_3	24	50
c:R=$CH(CH_3)_2$	34	57
d:R=CH_2Ph	44 (16)*	56 (17)*
e:R=Ph	47	87

*Yield of 3d

The use of tert-butyl alcohol as a solvent resulted in a significant increase of the yields of 2 as shown in Table, while photolysis of 1 in methyl alcohol gave the ring opening products (6) formed by methanolysis of 2.



The formation of 2 is rationalized in terms of hydrogen abstraction by the ketone carbonyl from the formyl group and subsequent cyclization of the resulting 1,4-diradical (7), whereas the β-lactam is apparently formed via a diradical (8) produced by benzylic hydrogen abstraction. The photocyclization reaction of the N-benzyl-N-formyl-α-oxoamide (1d) was sensitized by 3-methoxyacetophenone (E_T=73 kcal/mol)[5] but not by Michler's ketone (E_T=62 kcal/mol).[5] The quenching of the reaction by stilbene was inefficient. These results suggest that the cyclization involves a rapid triplet-state reaction, although a singlet-state reaction can not be excluded from the available data.



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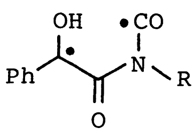

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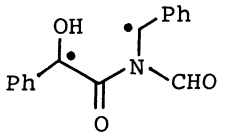

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In conclusion, photoreaction of N-formyl-α-oxoamides gave 3-hydroxyazetidine-2,4-diones in good yields irrespective of the substituents on the nitrogen atom. The starting materials (1a-1d) can be easily prepared from N-substituted formamides and phenylglyoxalyl chloride. Further, the hydroxy group of 2 is easily acylated by a usual method as described above. Therefore, the present reaction provides a useful synthesis of azetidine-2,4-diones bearing various oxygen functions at the 3-position.

References

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2) H. Wehrli, Helv. Chim. Acta, 1980, 63, 1915.

3) (a) H. Aoyama, T. Hasegawa, M. Watabe, H. Shiraishi, and Y. Omote, J. Org. Chem., 1978, 43, 419. (b) H. Aoyama, T. Hasegawa, and Y. Omote, J. Am. Chem. Soc., 1979, 101, 5343. (c) H. Aoyama, M. Sakamoto, and Y. Omote, J. Chem. Soc., Perkin Trans. 1, 1981, 1357.

4) H. Aoyama, M. Sakamoto, and Y. Omote, J. Chem. Soc., Chem. Commun., 1982, 119.

5) S. L. Murov, "Handbook of Photochemistry", Marcel Dekker: New York, 1973. tert-Butyl alcohol-benzene (3:1) was used as a solvent in the sensitized reactions. Concentrations of the sensitizers were adjusted so that 95% or more of the incident light was absorbed by the sensitizers. In the case of 3-methoxyacetophenone, the sensitized reaction was more efficient than the direct photolysis ($\Phi_{sens}/\Phi \approx 3$)

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