PHOTOCHEMICAL SYNTHESIS OF 2-AZETIDINONE DERIVATIVES

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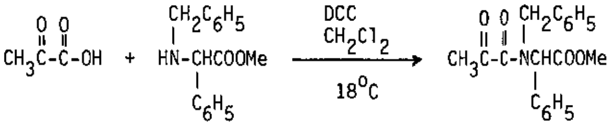
Abstract —— Irradiation of N-Pyruvoyl-N-benzyl phenylglycine methyl ester (1) yields 1-(α-methoxycarbonyl)benzyl-3-hydroxy-4-phenyl-2-azetidinone (4) in 85% yield.

Synthesis of the new families of 2-azetidinone derivatives, β-lactams, has generated strong interest because of their diverse biological activities such as antibiotic[1], antitumor[2], insecticidal[3], and herbicidal activities[4-5]. The β-lactams possessing side chains of 3-amino-nocardicinic acid[6] and aromatic or heteroaromatic substituents at the 4-position are particularly interesting.

We report here the synthesis of 1-(α-methoxycarbonyl)benzyl-3-hydroxy-4-aryl-2-azetidinone through type II photocyclization of N-benzyl-N-pyruvoylphenylglycine methyl ester. Coupling of pyruvic acid with N-benzylphenylglycine methyl ester using dicyclohexylcarbodiimide (DCC), followed by silica gel chromatography, led to 65% yield of N-benzyl-N—pyruvoylphenylglycine methyl ester, m.p. 75.5 - 78°C (recrystallized from isopropyl ether).



$$CH_3\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-OH + \overset{\overset{CH_2C_6H_5}{|}}{HN}-\underset{\underset{C_6H_5}{|}}{CH}COOMe \xrightarrow[18^{\circ}C]{DCC,\ CH_2Cl_2} CH_3\overset{\overset{O}{\|}}{C}-\overset{\overset{O}{\|}}{C}-\overset{\overset{CH_2C_6H_5}{|}}{N}\underset{\underset{C_6H_5}{|}}{CH}COOMe$$

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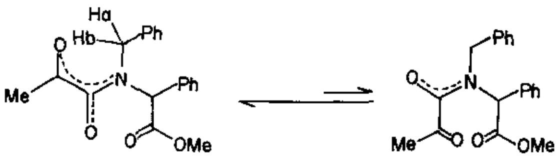
Inspection of the pmr spectrum reveals that the pyruvamide exists in two conformational isomers, s-cis 2 and s-trans 3 in the ratio of ca. 82% to 18%. pmr; 2($CDCl_3$) δ 1.95(s, $\underline{CH_3}\overset{\overset{O}{\|}}{C}O$), 3.78(s, $O\underline{CH_3}$), 4.5(dd, $\underline{CH_2}\phi$), 5.97(s, $N\overset{\overset{\phi}{|}}{\underline{CH}}COO$), 6.8-7.3(m, phenyls); 3($CDCl_3$) δ 2.43(s), 3.68(s), 4.7(s), 5.8(s), 6.8-7.3(phenyls).

It is well known that amide groups are planar and α-dicarbonyl compounds can also exist in coplanar dicarbonyl geometry in the ground state. Thus two carbonyl groups and amide group in 2 are coplanar and the benzyl group in 2 is not free from rotation because of the steric hindrance, and such facts are well supported by the chemical shifts and the splittings of benzylic protons H_a and H_b into



s - cis

2 (82 %)

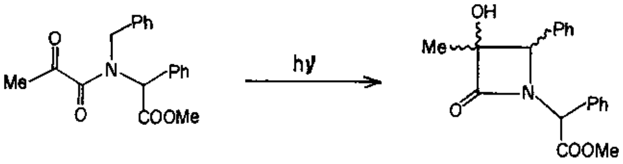
s - trans

3 (18 %)

doublets in 2. In the case of 3, however, coplanarity of dicarbonyl geometry cannot be retained because of the steric repulsion of methoxycarbonyl group against the terminal acetyl group, maintaining the coplanarity only in the amide group. The protons of acetyl group which is out of conjugation show the chemical shift at δ 2.43 ppm in 3 compared to 1.95 ppm in 2.

Aoyama *et al*. have studied the reaction of the α-oxoamides in the solution phase[7] and in the crystalline state[8]. The authors suggest that the conformation of the oxoamides is planar and the carbonyl groups are transoid, and the intramolecular γ-hydrogen abstraction resulted only in this conformation. The restraints on molecular motions and restrictions on the biradicals formed by γ-hydrogen abstraction imposed by the crystal lattice on its consituents apparently increase the type II photoreactivities.

From these facts, it can be easily seen that the methoxycarbonyl group plays an important role to restrict the molecular motion, and a favorable conformation for type II reaction is retained both in the solution phase and the solid state in s-cis conformation of N-benzyl-N-pyruvoylphenylglycine.



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4

Irradiation* of (1) in benzene or cyclohexane solution under nitrogen atmosphere gave (4) in 85% yields as four diastereomeric mixtures. The progress of the reaction was monitored by measuring the carbonyl stretching band in the infrared spectrum. The carbonyl absorption of the amide group (1650 cm^{-1}) gradually disappeared during the course of the reaction and showed an intense new band

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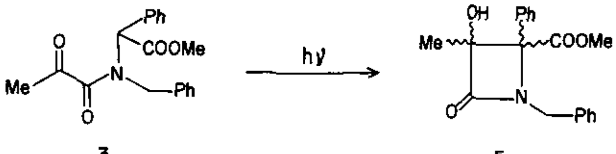
* A solution of (1) in a Pyrex tube purged with N_2 for 0.5 hr was irradiated in a Rayonet Photochemical Reactor (The Southern New England Ultraviolet Company) Model RPR-208 equipped with 350 nm fluorescent lamps.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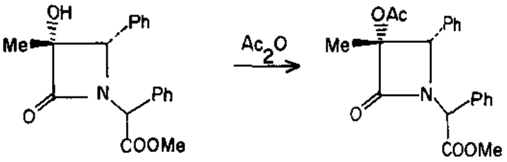
at 1730-1770 cm^{-1}*, characteristic of β-lactam carbonyl group. The irradiated solution was* evaporated under vacuum and the residue was dissolved in CCl_4. Standing the solution for 24 hrs at room temperature, a single isomer (6) was precipitated as crystals (m.p. 142-146°C). The pmr spectrum of the isolated single isomer (6) showed δ 1.70(s, 3-Me), 2.65(s, -O$\underline{H}$), 3.80(s, 4-H), 5.55(s, $\overset{\phi}{\mathrm{N}}$-C$\underline{\mathrm{H}}$-COO), and 7.0-7.2(two phenyl groups); IR(film); 3350 cm^{-1}, 1740-1775 cm^{-1}. Acetylation of the irradiated mixture with acetic anhydride and p-toulenesulfonic acid in acetic acid showed four constituents of diastereoisomers in the ratio of 45%, 32%, 20% and 2% in GC analysis. The pmr spectra of 7 showed δ 1.46(s, $\mathrm{O\overset{O}{\overset{\|}{C}}C\underline{H}_3}$), 1.89(s, 3-C$\underline{H}_3$), 3.68(s, -OC$\underline{H}_3$), 4.99(s, 4-$\underline{H}$), 5.47(s, $\mathrm{N\overset{\phi}{C}\underline{H}COO}$), and 6.97-7.05(m, two phenyl groups).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Configuration of the isolated single isomer (6), 3-hydroxy-4-phenyl-2-azetidinone, was assigned unequivocally on the basis of its pmr spectra; the isomer (7) with the higher chemical shifts (δ, 1.46) for the O-acetyl group must have the 4-phenyl and 3-O-Acetyl group cis to each other. Since acetylation should not affect (invert) the stereochemistry of 3-hydroxy-β-lactam (6), the 3-acetoxy-β-lactam is assigned as cis-configuration. Product (5) was not detected. If the product (5) is formed, the pmr signals of benzylic protons(ϕC$\underline{H}_2$) should appear similar to those of compound (3) and the coupling patterns should be also similar to those of (3) since the magnetic and electronic *environments of benzyl group in (3) and (5) are almost same. However, the pmr* spectra of the irradiated mixtures (4) did not show such benzylic proton signals. Irradiation of N-pyruvoylphenylglycine methyl ester under the same condition did not give any type II photoproduct implying the low reactivity of phenylmethoxycarbonylmethine proton of (3). Furthermore, (5) should come from the configuration of (3) and the concentration of (3) is always 18% of (1) diminishing the chance of (5) to be formed even if (3) is photoreactive. Thus the failure of the detection of (5) is justified.

In view of these results, it is evident that the photocyclization of α-oxoamide of N-substituted amino acids by retaining the suitable conformation in the solution phase can be used for the synthesis of various substituted 3-hydroxy-4-aromatic or heteroaromatic substituted 2-azetidinone analogous to nocardicin nucleus, thienamycin nucleus, and bleomycins. The stereochemical outcome of the β-lactam formation by the type II photochemical reaction can be used for the mechanistic studies. The scope and mechanistic studies of these reactions are in progress.

The authors wish to thank the Korea Advanced Institute of Science and Technology and the Korea Research Institute of Chemical Technology for the financial support of this research.

REFERENCES

1. T. Takita, Y. Muraoka, T. Yoshioka, A. Fujii, K. Maeda, and H. Umezawa, J. Antibiot., 25, 755 (1972).
2. M.S. Manhas, S.G. Amin, and R.D. Glaza, J. Heterocycl. Chem., 16(2), 285 (1979).
3. K. Clauss, K. Juehlein, L. Emmel, and A. Walteradorfer, Ger. Pat., 2,715,675 (1978); CA,90 67741U (1979).
4. a) R.D. Hoyz, U.S. Pat., 3,958,974 (1976); CA,85, 10850s (1976).
   b) R.F. Abdulla, J. Med. Chem., 18(c), 625 (1975).
5. a) G. Pifferi, Brit. Pat., 1,192,952; CA 73, 55961b (1970).
   b) L. Fontanella, L. Mariani, and Z. Testa, Farmaco, Ed. Sci., 28 448 (1973); CA,79 105015 (1973).
6. T. Kamiya, in "Recent Advances in the Chemistry of β-Lactam Antibiotics" (J. Elks, Ed), Special Publication No. 28, p281, The Chemical Society, 1977.
7. H. Aoyama, T. Hasegawa, M. Watabe, H. Shiraishi, and Y. Omote, J. Org. Chem., 43, 419 (1978).
8. H. Aoyama, T. Hasegawa, and Y. Omote, J. Am. Chem. Soc., 101, 5343 (1979).

Received, 29th November, 1982