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A NEW SYNTHESIS OF 2-AMINO-γ-LACTONES INVOLVING PHOTOCHEMICAL ADDITION REACTION OF ALCOHOLS TO ENAMIDE

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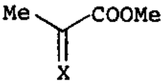
Abstract——Photochemical addition reaction of alcohols to the enamide (**2**) prepared from pyruvic acid ester has provided a new synthetic method of the 2-amino-γ-lactones (**6a-d**).

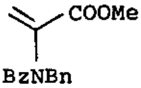
During the course of studies on the cyclization of enamides with various types of structures,[1,2] we have investigated the photochemical behavior of the enamide (**2**) which was prepared from pyruvic acid ester and found that a new photochemical addition reaction of alcohols to the enamide provides a new and general synthetic method of the 2-amino-γ-lactones.

Though photocyclization of the N-benzoylenamine type of enamides derived from either cyclic or acyclic ketones has been well known to proceed smoothly to give the isoquinolones,[1,2] photochemical study of the enamide derived from α-keto-ester hitherto has not been investigated except the intramolecular [2+2]photocycloaddition of the corresponding N-allylenamide.[3,4]

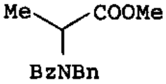
Benzoylation of the imine (**1b**), which was prepared by condensation[5] of methyl pyruvate (**1a**) and benzylamine, gave the enamide (**2**) in 58% yield [ir($CHCl_3$)cm^{-1}: 1725 and 1645; nmr($CDCl_3$) δ:5.90 and 5.23(each s)(CH_2=C<)]. Attempted reductive photocyclization of the enamide (**2**) in the presence of sodium borohydride was unsuccessful due to susceptibility to reduction of the double bond leading to the formation of the corresponding methyl derivative (**3**). Thus, irradiation of the enamide (**2**) in methanol under non-oxidative condition with low pressure mercury lamp was carried out. The product was a mixture of two photo-products (**4**)(10%) and (**5a**)(20%) which were readily separated by chromatography and characterized by the following spectral analysis and chemical conversion. The first eluted product (**4**) was found to be the expected photocyclized lactam [m/z: 295 (M^+); nmr($CDCl_3$) δ:8.20(m, 8-H) and 4.22(dd, J=6 and 2.5Hz, 3-H)].



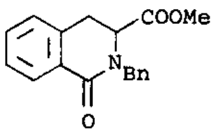
(1a) X=O
(1b) X=NBn



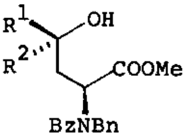
(2)



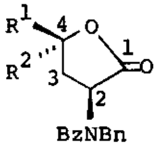
(3)



(4)

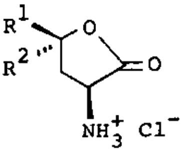


(5a-d)

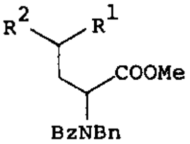


(6a-d)

	R^1	R^2
a:	H	H
b:	Me	H
c:	H	Me
d:	Me	Me



(7a) R^1=Me, R^2=H
(7b) R^1=H, R^2=Me



(8a) $R^1{=}{-}O(CH_2)_3{-}{=}R^2$
(8b) $R^1{=}{-}(CH_2)_3O{-}{=}R^2$
(8c) $R^1{=}{-}(CH_2)_5{-}{=}R^2$

(Bn=CH_2Ph)
(Bz=COPh)

The second product **(5a)** exhibited unassignable broad nmr spectrum. The structure of **(5a)** was deduced from its chemical conversion by treatment with p-toluenesulfonic acid into the 2-amino-γ-lactone **(6a)** which exhibited the following spectra [m/z: 295 (M^+); ir($CHCl_3$) cm^{-1}:1780 and 1640; nmr($CDCl_3$) at 51°C δ:4.56 (br td, J=8.5 and 3.5Hz, 4-H), 4.22(q, J=8.5Hz, 4-H), and 4.14(m, 2-H)]. Thus, it has been found that the enamide **(2)** undergoes photoaddition reaction of methanol used as solvent. In order to establish the generality of this photoaddition reaction, we investigated photochemical reaction of the enamide **(2)** in other alcohols. On irradiation in ethanol, the enamide **(2)** gave the adducts **(5b)** and **(5c)** which were also characterized by their conversion to the corresponding 2-amino-γ-lactones **(6b)**(24%)[nmr($CDCl_3$) at 52°C δ:4.94(sext, J=6.5Hz, 4-H) and 2.62(dt, J=13 and 8Hz, 3-H) and 1.94(ddd, J=13, 10.5, and 4.5Hz, 3-H) and **(6c)**(25%)[nmr($CDCl_3$) at 51°C δ:4.45(sext, J=6.5Hz, 4-H) and 2.33(t-like, J=8Hz, 3-H_2)]. Their stereochemistry was deduced by comparison of their nmr spectra with the authentic 2-amino-γ-lactones[6] **(7a)** and **(7b)** of which the cis-lactone **(7a)** exhibited two signals at δ:3.43(ddd, J=12, 8.5, and 5.5Hz) and 2.55(td, J=12 and 10Hz) due to two hydrogens at the 3-position while the trans-lactone **(7b)** exhibited a single signal at δ:3.06(m) due to the same two hydrogens.

Similarly, on irradiation in isopropanol, the adduct (**5d**) was obtained and characterized as its 2-amino-γ-lactone (**6d**) in 49% yield. Further, in addition to alcohols, two organic solvents such as tetrahydrofuran and cyclohexane were found to be photochemically incorporated into the enamide (**2**). Two adducts (**8a**)(24%) and (**8b**)(20%) were obtained by irradiation of (**2**) in tetrahydrofuran and a single adduct (**8c**)(27%) in cyclohexane, respectively, though the stereochemistry of the former two adducts (**8a**) and (**8b**) was not established.
These 2-amino-γ-lactones (**6a-d**) synthesized in this work are derivatives of biologically important γ-hydroxyamino acids, such as homoserine (constituent of toxic marine cyanophyte),[7-9] γ-hydroxynorvaline (constituent of Boletus satanas Lenz),[6,9] and γ-hydroxyleucine (constituent of mushroom toxin phalloin).[9]

Thus, we have established a new synthetic method of the 2-amino-γ-lactones involving photochemical addition reaction of alcohols to the enamide followed by acidic lactonization though mechanistic study of the initial photochemical addition reaction has not been clarified.

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