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INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS OF IMINES OF GLYCINE ESTERS BEARING AN ALKYNYL FUNCTION[1)]

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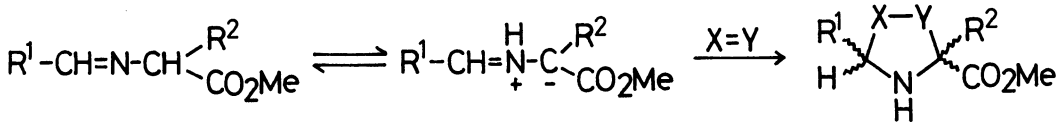
Imines of glycine methyl esters, o-propargyloxybenzylidene(methoxycarbonyl)-methylamines, undergo an intramolecular cycloaddition via their 1,3-dipolar tautomers, azomethine ylides, to an alkynyl group. Initial cycloadducts were thermally converted to dehydrogenated compounds with concurrent migration of methoxycarbonyl group.

As recently reviewed,[2,3)] 1,3-dipolar substrates containing a dipolarophile function can undergo intramolecular 1,3-cycloadditions leading to fused or bridged heterocycles. In the course of some other studies with o-substituted benzylidene derivatives of glycine esters, we have found that a o-propargyloxybenzylidene derivative of glycine ester undergoes an intramolecular 1,3-cycloaddition.[4)] Recently, two groups[5,6)] have demonstrated the intermolecular 1,3-dipolar cycloadditions of imines of α-amino acid esters via their 1,3-dipolar tautomers as shown in the following scheme.



R^1: Ph, p-substituted phenyl, 2-furyl, 2-thienyl
R^2: H, alkyl, Ph, indol-3-ylmethyl
X=Y: double and triple bonds

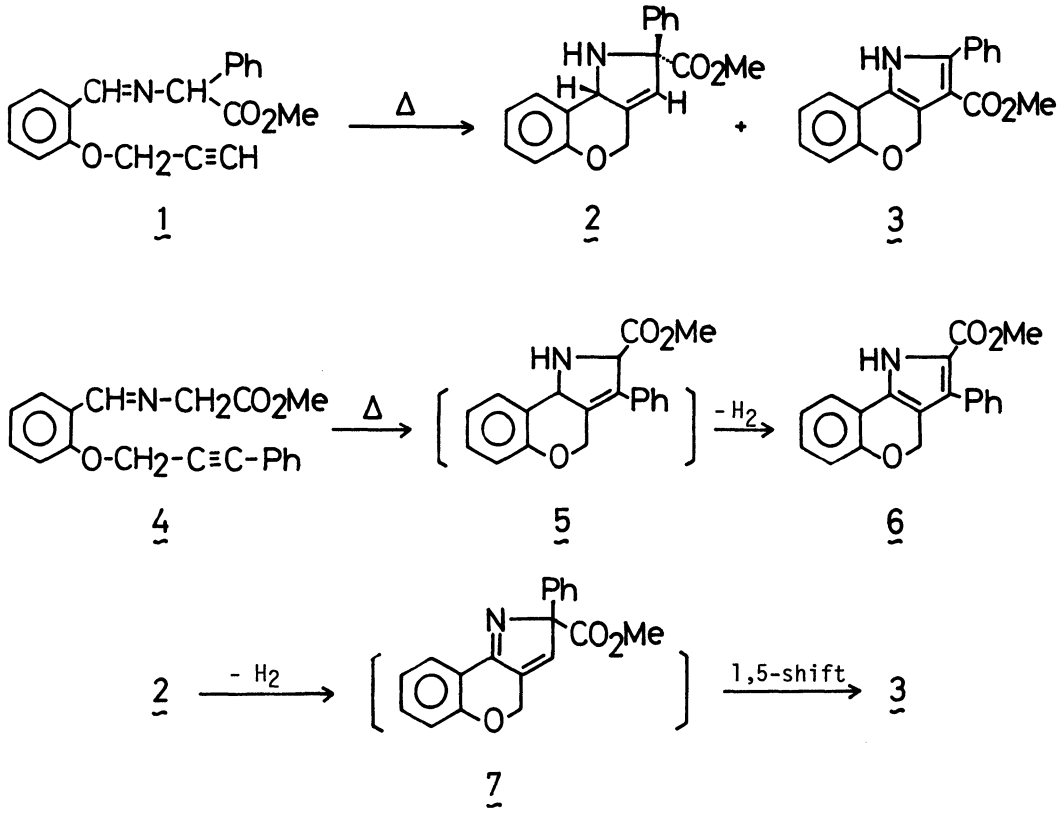
In the present paper we wish to report our findings concerning the intramolecular 1,3-dipolar cycloaddition of o-propargyloxybenzylidene derivatives of glycine esters.

A solution of imine 1[7)] in xylene was refluxed for 3 h, and then chromatography (SiO_2, hexane-benzene) of the reaction mixture afforded two crystalline products 2 and 3 in 39 and 2% yields respectively, together with o-propargyloxybenzaldehyde arising from the hydrolysis of unchanged 1.

Structural elucidation of the intramolecular 1,3-cycloadduct 2 was accomplished on the basis of spectral data: mp 93-94°C, colorless prisms; IR (KBr) 3300, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.90 (br, 1H, NH), 3.63 (s, 3H), 4.63, 4.88 (each dd, 1H, J=14, 2 Hz), 4.89 (pseudo s, 1H), 6.22 (d, 1H, J=2 Hz), 6.74-7.80 (m, 9H); MS m/e 307 (M^+). Although it is difficult to learn the stereochemistry of 2 from the spectral data, it was assumed that 2-phenyl group and 9b-hydrogen atom in 2 are cis from the viewpoint described below.

On the other hand, the molecular formula of 3 corresponded to that of a dehydrogenated compound of 1. When a solution of 2 in xylene was refluxed without or with Pd-charcoal (5% Pd) for 5 h, 3 was formed in 7 or 37% yield respectively, together with unchanged 2. Thus, it is reasonable to conclude that 3 is derived from the dehydrogenation of 2. From the above result and spectral data

indicating the presence of NH group, 3-methoxycarbonyl-2-phenyl- and 2-methoxycarbonyl-3-phenyl-4H-pyrro[2,3-d]benzo[b]pyran are possible for the structure of 3.



Scheme 1

However, 3 was assigned to be the 3-methoxycarbonyl-2-phenyl isomer by comparison with 2-methoxycarbonyl-3-phenyl isomer 6 prepared from imine 4[7] as shown in Scheme 1. Although imine 4 was less reactive toward the intramolecular cycloaddition, upon heating in xylene for 3 h 4 directly gave the desired compound 6 in 3% yield, probably via dehydrogenation of the initial cycloadduct 5.

3: mp 217-218°C, colorless prisms; IR (KBr) 3320, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 5.56 (s, 2H), 6.80-7.60 (m, 9H), 8.75 (br, 1H, NH); MS m/e 305 (M^+).

6: mp 213-214 C, colorless prisms; IR (KBr) 3300, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 5.26 (s, 2H), 6.90-7.50 (m, 9H), 9.60 (br, 1H, NH); MS m/e 305 (M^+).

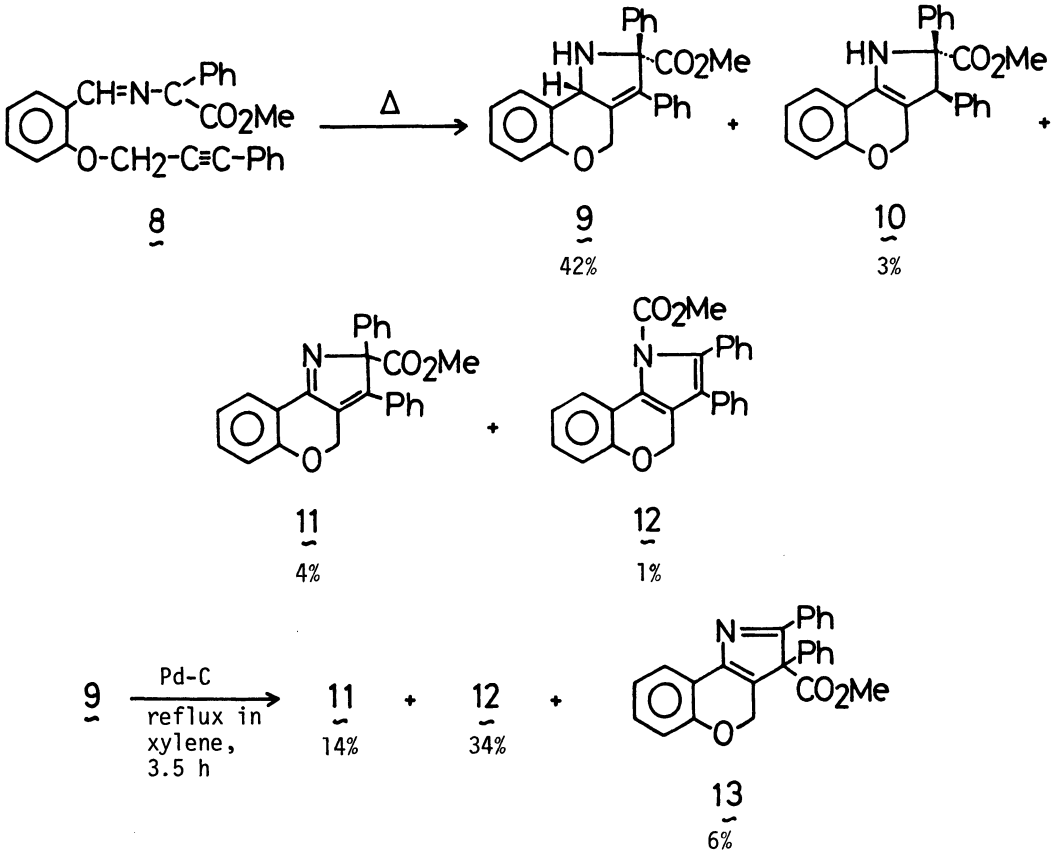
The formation of 3 from 2 might be interpreted as arising from a thermally-allowed 1,5-shift of methoxycarbonyl group in the initial dehydrogenated compound 7.

A similar treatment of imine 8[7] afforded four crystalline products 9, 10, 11, and 12, accompanied by o-phenylpropargyloxybenzaldehyde. On the basis of spectral data and analytical values, 9 and 10 were assumed to be 2-methoxycarbonyl-2,3-diphenyl-4H-2,9b-dihydropyrro[2,3-d]benzo[b]pyran and its isomeric 4H-2,3-dihydro derivative respectively.

9: mp 117-118°C, colorless prisms; IR (KBr) 3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (br, 1H, NH, exchanged with D_2O), 3.52 (s, 3H), 4.75 (s, 2H), 5.00 (pseudo s, 1H, changed to a sharp singlet when treated with D_2O), 6.73-7.60 (m, 14H); MS m/e 383 (M^+).

10: mp 114-115°C, colorless prisms; IR (KBr) 3300, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (br, 1H, NH), 3.76 (s, 3H), 4.36, 4.80 (each dd, 1H, J=16, 2 Hz), 5.28 (d, 1H, J=2 Hz), 6.48-7.20 (m, 14H); MS m/e 383 (M^+).

Again it was supposed that 2-phenyl group and 9b-hydrogen atom in 9 are cis from the viewpoint described below. On the other hand, the stereochemistry of 10 was assumed on the basis of its ^{1}H NMR spectrum.[8]



Scheme 2

Both the products 11 and 12 corresponded to dehydrogenated compounds of 9 or 10. In fact, when a solution of 9 in xylene was refluxed with Pd-charcoal (5% Pd) for 3.5 h, a mixture of 11, 12 and a new dehydrogenated compound 13 was obtained together with recovery of 9. Upon heating in xylene for 12 h, 10 was converted into 12. Thus interconversions among dehydrogenated compounds 11, 12, and 13 were next investigated. As shown in Scheme 2, 11 isomerized to 12 and 13, but 12 was unchanged. On the other hand, 13 was converted into 12.

11: mp 144-145°C, colorless needles; IR (KBr) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 5.12 (s, 2H), 6.80-7.40 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 52.97, 65.49, 93.31 (quart. C), 165.82 (C=N), 169.62 (CO_2Me); MS m/e 381 (M^+).

12: mp 184-186°C, colorless needles; IR (KBr) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H), 5.27 (s, 2H), 6.98-7.50 (m, 13H), 8.08-8.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 54.23, 64.66, 153.45 (CO_2Me); MS m/e 381 (M^+).

13: mp 165-167°C, yellow prisms; IR (KBr) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3H), 4.30, 5.23 (each d, 1H, J=11 Hz), 6.80-8.15 (m, 14H); ^{13}C NMR ($CDCl_3$) δ 53.11, 67.73, 71.97 (quart. C), 156.85

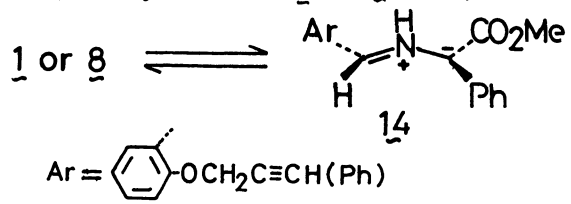
(C=N), 167.09 (CO_2Me); MS m/e 381 (M^+).

Structures of 11, 12, and 13 were deduced on the basis of their spectral data. It is evident that 12 has a N-methoxycarbonylpyrrole structure from the chemical shift of CO_2Me in the ^{13}C NMR spectrum.[9] By comparison of the chemical shifts of quart. carbon atoms in the ^{13}C NMR spectra of 11 and 13, it was assumed that 11 and 13 are 2H- and 3H-pyrrole structures respectively.

On the basis of results shown in Scheme 2, the processes leading to the dehydrogenated compounds from 9 or 10 can be interpreted as proceeding via 11, followed by 1,5- and 1,3-shift of methoxycarbonyl group to give the most stable compound 12.

$$\underset{9 \text{ or } 10}{} \xrightarrow{-H_2} \underset{11}{} \xrightarrow[\text{shift}]{1,5-} \underset{13}{} \xrightarrow[\text{shift}]{1,3-} \underset{12}{}$$

It seems to be reasonable to conclude that the intramolecular cycloaddition proceeds via a 1,3-dipolar cycloaddition reaction involving a prototropic equilibrium of the imine 1 or 8 with its 1,3-dipolar isomer, azomethine ylide 14. As described above, the cycloadducts 2 and 9 were produced as single diastereoisomers. This fact suggests that the initial cycloaddition reaction proceeds via a concerted process rather than a stepwise process. Inspection of the Dreiding models indicated that 14 in which aryl (Ar) and phenyl groups are trans is the most preferable geometry for 14.[10] On the basis of the above concepts, the stereochemistry of 2 and 9 were deduced as shown above.



References and Notes

1) Studies on Intramolecular 1,3-Cycloadditions. Part 2. Part 1: O. Tsuge, K. Ueno, and A. Inaba, Heterocycles, 4, 1 (1976).
2) A. Padwa, Angew. Chem., 88, 131 (1977).
3) W. Oppolzer, ibid., 89, 10 (1978).
4) O. Tsuge, K. Ueno, and K. Oe, presented at the 36th Spring Meeting of the Chemical Society of Japan, Osaka, April 1977, No. 3R-13.
5) R. Grigg and J. Kemp, J. C. S. Chem. Comm., 1977, 125; ibid., 1978, 109.
6) M. Joucla and J. Hamelin, Tetrahedron Lett., 1978, 2885.
7) All compounds in this paper gave satisfactory elemental analyses. By the reaction of the corresponding o-propargyloxybenzaldehyde with glycine ester imines 1, 4, and 8 were obtained in almost quantitative yields respectively. 1: pale yellow oil; IR (neat) 3300, 1740, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (t, 1H, J=2.5 Hz), 3.50 (s, 3H), 4.68 (d, 2H), 5.18 (s, 1H), 6.80-7.60 (m, 8H), 8.05-8.23 (m, 1H), 8.78 (s, 1H, CH=N). 4: pale yellow oil; IR (neat) 2230, 1740, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3H), 4.44 (s, 2H), 5.00 (s, 2H), 7.00-8.10 (m, 9H), 8.83 (s, 1H, CH=N). 8: pale yellow oil; IR (neat) 2310, 1730, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H), 4.93 (s, 2H), 5.20 (s, 1H), 6.05-7.60 (m, 9H), 8.83 (s, 1H, CH=N).
8) The stereochemistry of 10 was assumed from the comparison with reported chemical shifts of CH_3 of methoxycarbonyl groups in two isomeric 1,3-cycloadducts[6] obtained from benzylidene(methoxycarbonyl)-methylamine and methyl α-cyano-β-phenylacrylate.
9) The carbon atom CO_2Me of N-methoxycarbonylpyrrole was observed at δ 150.82 in the ^{13}C NMR spectrum.
10) The alternative geometry with CO_2Me interchanged with phenyl group suffers much higher van der Waals strain.

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