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SYNTHESIS OF FULLY UNSATURATED MONOCYCLIC 1,2,5-TRIAZEPINES FROM 4-AZIDOPYRIDAZINES

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Photolysis of the 3-methoxy-4-azidopyridazines (1) in the presence of a base such as methoxide ion and diethylamine resulted in ring-expansion to form the corresponding unstable 1H-1,2,5-triazepines (3 and 4), which were tautomerized to the relatively stable 4H-isomers 5 and 6 by further treatment with sodium methoxide. Treatment of the 1H-triazepines (3 and 4) with acetyl chloride in pyridine gave the stable 1-acetyl-1H-1,2,5-triazepines (7 and 8). The products 5-8 are the first examples of isolated 1,2,5-triazepines.

KEYWORDS ——— 4-azidopyridazine; photolysis; ring-expansion; azirine intermediate; 1H-1,2,5-triazepine; 4H-1,2,5-triazepine

Much effort has recently been devoted to the synthesis of new fully unsaturated seven-membered heterocyclic rings with two or more heteroatoms.[1] With regard to monocyclic triazepines,[2] 1,2,4-triazepines have been prepared by the cycloaddition[3] of 1-azirines to 1,2,4,5-tetrazines or by a photochemical walk-rearrangement[4] of 3,4,7-triaza-2,4-norcaradienes. However, all other possible three isomers, 1,2,3-, 1,2,5-, and 1,3,5-triazepines, have remained unknown, although some reactions[2,5] involving such triazepines as unisolable intermediates and the syntheses[1,2] of di- and per-hydrotriazepines are known. We report here the synthesis of fully unsaturated 1,2,5-triazepines from 4-azidopyridazines.

The singlet arylnitrenes generated from arylazides either by photolysis or by thermolysis are known to undergo ring-expansion.[6] We have already reported the formation of 1,3- and 1,4-diazepines from azidopyridines.[7] These results prompted us to examine the photolysis of azidodiazines, but attempts to obtain ring-expansion products such as triazepines were unsuccessful. 5-Azidopyrimidines gave only substitution products.[8] Photolysis of unsubstituted and methyl-substituted 4-azidopyridazines in the presence of methoxide ions afforded 4-amino and/or 4-methoxy-pyridazines but no ring-expansion products. However, the 4-azidopyridazines (1) having a methoxy group in the 3-position gave the desired novel 1,2,5-triazepines.

Irradiation (400 W, high-pressure Hg lamp; Pyrex filter) of the 3-methoxy-4-azidopyridazines[9] (1a-c; ca. 0.5 g) in methanol-dioxane (1:1; 100 ml) containing sodium methoxide (ca. 1 mol eq) for 50-60 min under ice cooling resulted in ring-expansion to form the 3,4-dimethoxy-1H-1,2,5-triazepines (3)[10]

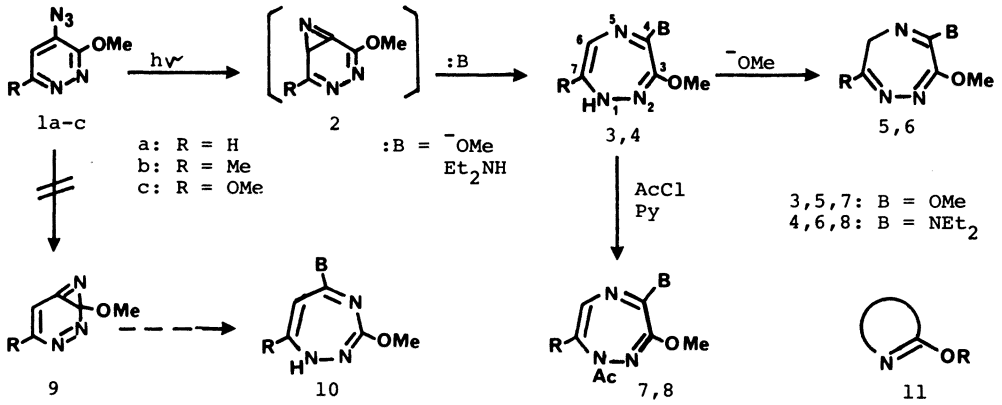

Chart 1

in 50-60% yields. Similarly, the 4-diethylamino-1H-1,2,5-triazepines (4)[10] were obtained by the photolysis of 1a-c in dioxane containing diethylamine. But the 1H-triazepines (3 and 4) were unstable and readily decomposed when passed through a silica gel or alumina column, and thus were characterized only by spectral analysis without isolation. However, further treatment of 3 and 4 with sodium methoxide in methanol at room temperature for 5-6 h resulted in tautomerization to give the relatively stable 6H-1,2,5-triazepines (5 and 6)[11] in 30-50% yields from the starting azides (1). The 6H-isomers 5 were also obtained directly from 1 by irradiation in the presence of a large excess of sodium methoxide.

Treatment of the 1-unsubstituted 1H-isomers 3 and 4 with acetyl chloride in pyridine afforded the 1-acetyl-1,2,5-triazepines (7 and 8)[12] in ca. 60% yields as stable crystals. It is known that the CH-forms of diazepines such as 4H-1,2-[13] and 6H-1,4-diazepines[7] and 5H-2,3-benzodiazepines[14] undergo acylation with tautomerization, giving rise to the corresponding N-acyl derivatives. However, attempts to convert the 4H-isomers 5 and 6 (CH-forms) into the 1-acetyl-1H-triazepines (7 and 8) have been unsuccessful.

The formation of 3 and 4 from 1 may proceed via the azirine intermediates 2 derived from the initially formed singlet 4-pyridazinylnitrenes, but that of 1,2,4-triazepines (10) expected from the another possible azirine intermediates 9 was not observed in the present photolysis. This direction of azirine formation is analogous to that of 2-substituted phenylnitrenes,[15] which are known to cyclize preferentially at the vacant α-position. Although the effect of the methoxy group is not clear at present, we assume that the electron-donating methoxy group may provide assistance for the cyclization of the initially formed pyridazinylnitrenes to the azirines, and for the stabilization of the triazepine ring obtained. It has been observed that diazepine rings are stabilized by an iminoether structure 11.[7]

The ^{1}H-NMR spectra of the a-series (R = H) of the 1H-triazepines (3, 4, 7, and 8) showed AB pairs of doublets (J = 6 Hz) at around δ 6.0 assignable to 6-H and 7-H, while those of the 6H-isomers (5 and 6) showed methylene signals around

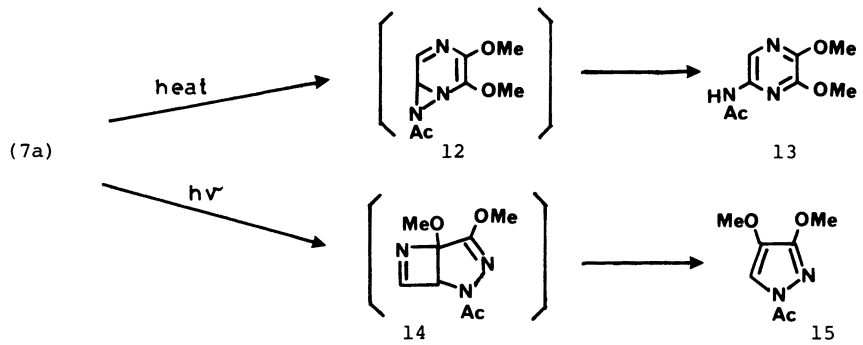

Chart 2

δ 3.7-3.8. The ^{13}C-NMR spectra of 5 and 6 showed signals due to sp^3 carbons at δ 40-45 (t), but those of 7 and 8 showed no sp^3 ring carbons. These spectral data and the results of the following chemical studies are consistent with the proposed 1,2,5-triazepine structures for 3-8.

Heating the 1-acetyl-1H-triazepine (7a) in o-dichlorobenzene at 190 °C for 60 h in a sealed tube gave the 2-aminopyrazine derivative 13 in 76% yield, probably via the aziridine intermediate 12. Irradiation of 7a in benzene at room temperature for 5 h afforded the pyrazole derivative 15 in 70% yield, presumably via the bicyclic intermediate 14. These results are analogous to those observed for a variety of fully unsaturated seven-membered heterocyclic rings.[16]

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8) For example, irradiation of 2,4-dialkoxy-5-azidopyrimidines in the presence of sodium methoxide gave 5-amino-2,4-dialkoxy-6-methoxypyrimidines, and 6-methyl-

2,4-dialkoxy-5-azidopyrimidines afforded 5-amino-2,4-dialkoxy-6-methoxymethylpyrimidines.

9) 4-Azidopyridazines (1) were prepared from the corresponding 4-nitropyridazine 1-oxides by treatment with sodium azide followed by deoxygenation.

10) For example, compound 3a: ^{1}H-NMR ($CDCl_3$) δ : 3.68 and 3.80 (each 3H, s, OMe), 5.15 (1H, br, NH), 5.80 (1H, d, 7-H), 5.97 (1H, d, 6-H), $J_{6,7}$= 6 Hz; 4a: ^{1}H-NMR ($CDCl_3$) δ : 1.12 and 3.10-3.40 (6H, t, and 4H, m, NEt_2), 3.60 (3H, s, OMe), 4.88 (1H, br, NH), 5.76 (1H, d, 7-H), 6.10 (1H, d, 6-H), $J_{6,7}$= 6 Hz.

11) Satisfactory elemental analyses and spectral data were obtained for the products 5-8, e.g., 5a: oil, ^{1}H-NMR δ : 3.72 (2H, br, 6-H_2), 3.72 and 3.92 (each 3H, s, OMe), 7.50 (1H, t, J=5 Hz, 7-H); ^{13}C-NMR δ : 43.65 (t, 6-C), 54.00 and 54.29 (each q, OMe), 151.30 (d, 7-C), 152.36 and 154.53 (each s, 3- and 4-C); 6a: oil. ^{1}H-NMR δ : 1.04 and 2.94-3.34 (6H, t, and 4H, m, NEt_2), 3.80 (3H, s, OMe), 3.81 (2H, br, 6-H_2), 7.40 (1H, t, J=6 Hz, 7-H).

12) Compound 7a: mp 112-113 °C, IR (KBr): 1684 (C=O), 1640 (C=N) cm^{-1}; ^{1}H-NMR δ : 2.21 (3H, s, COMe), 3.82 and 3.89 (each 3H, s, OMe), 6.20 (1H, d, 7-H), 6.34 (1H, d, 6-H), $J_{6,7}$= 6 Hz. ^{13}C-NMR δ : 21.06 (q, COMe), 54.06 and 55.88 (each q, OMe), 120.88 and 128.41 (each d, 6- and 7-C), 157.24 and 158.00 (each s, 3- and 4-C), 172.30 (s, COMe); 7b: mp 101.5-103.5 °C; 8a: mp 60-61 °C; 8b: mp 87-89 °C.

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