NEW SYNTHETIC ROUTES TO FULLY UNSATURATED 1,4-BENZODIAZEPINES FROM QUINOLYL AZIDES

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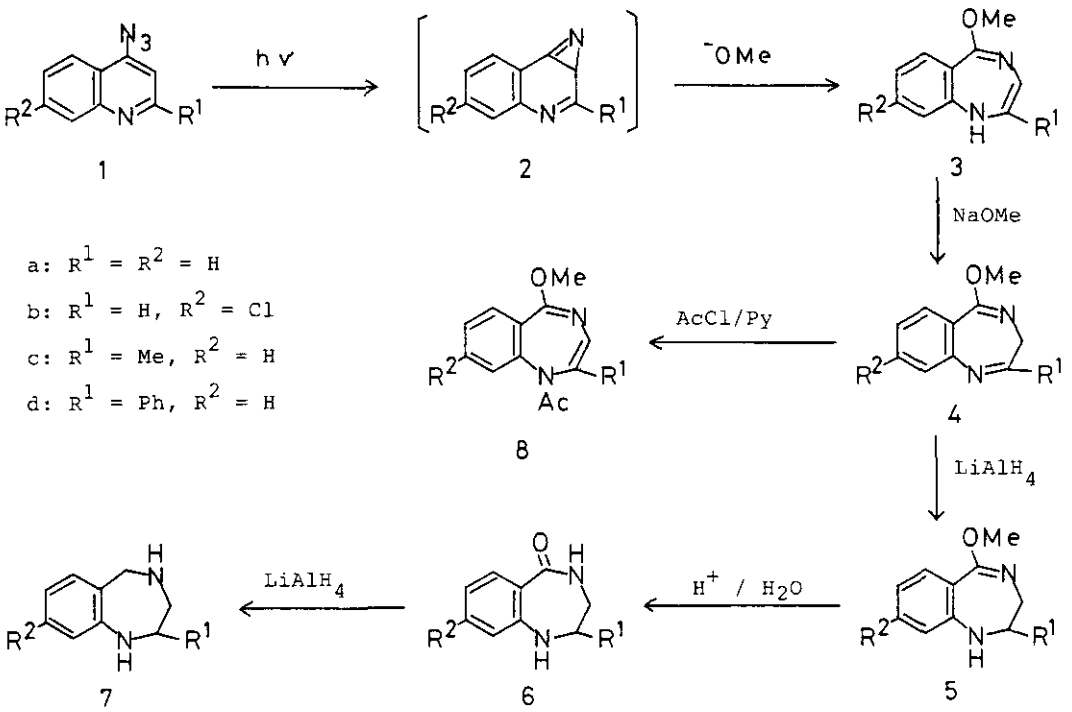
Abstract —— Photolysis of 4-azidoquinolines (1) in the presence of methoxide ions resulted in ring-expansion to give the 1H-1,4-benzodiazepines (3), which were tautomerized to the 3H-isomers (4) by further treatment with sodium methoxide. Similarly, 3-azidoquinolines (9) afforded the 3H-1,4-benzodiazepines (11), which were converted to the 5H-isomers (14) by treatment with sodium methoxide.

Much effort has recently been devoted to the synthesis of new fully unsaturated seven-membered heterocyclic rings.[1] We have already reported the syntheses of novel fused 1,2-,[1c] 1,3-,[1d] 2,3-,[2] and 2,4-diazepines[3] condensed with aromatic rings such as benzene, pyridine, thiophene, furan, or pyrrole. Among the six theoretically possible benzodiazepines, the 1,4-benzodiazepines have been most widely investigated owing to their biological activities.[1a] However, it is surprising that there are only several examples of fully unsaturated 3H-[1a] and 5H-1,4-benzodiazepines[4] and no 1H-isomers. We report here the new synthetic routes to all three tautomers of fully unsaturated 1,4-benzodiazepines.

The singlet arylnitrenes generated from phenyl,[5] pyridyl,[6] and isoquinolyl azides[3] are known to undergo ring-expansion to give azepine derivatives *via* azirine intermediates upon photolysis or thermolysis in the presence of bases. Therefore, we examined the photolysis of quinolyl azides under such conditions.

The 4-azidoquinolines (1a-d) were irradiated (400 W, high-pressure Hg lamp; Pyrex filter) in methanol-dioxane (1:1) containing sodium methoxide (1.5-2.0 mol eq) for *ca*. 30 min under ice cooling resulted in ring-expansion to form the desired 5-methoxy-1H-1,4-benzodiazepines (3)[7] in high yields as yellow oil, presumably *via* the azirine intermediates (2). The diazepines (3) are the first examples of

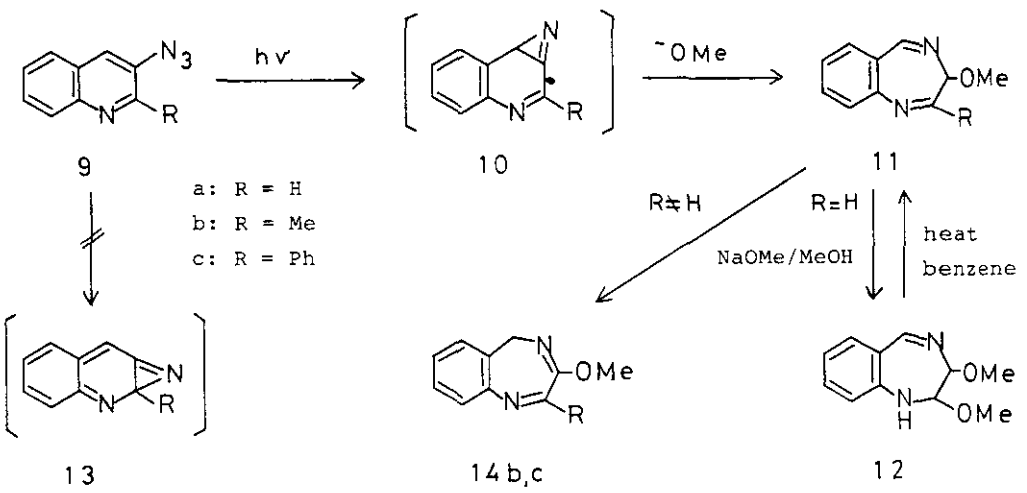
1H-1,4-benzodiazepines, but they were too unstable to be isolated. However, the 1H-diazepines (3) were further treated with sodium methoxide at room temperature for 7-8 h to result in tautomerization giving the stable 3H-1,4-benzodiazepines (4)[8] as yellow oil in ca. 50% yields from the azides (1).



Scheme 1

The structures of the diazepines (4) were confirmed by the results of various chemical studies, besides by their spectral data. For example, lithium aluminum hydride (LAH) reduction of 4 afforded the 1,2-dihydro compounds (5), which were hydrolyzed to give the 5-oxo compounds (6). Treatment of 6 with LAH gave the tetrahydro-1,4-benzodiazepines (7); the compound (7a) was identical with an authentic sample prepared by the reported method.[9] The 3H-diazepines (4) were treated with acetyl chloride in pyridine to give the 1-acetyl-1H-1,4-benzodiazepines (8) in ca. 20% yields.

Next, the 3-azidoquinolines (9a-c) were irradiated under the similar conditions. The 2-substituted 3-azidoquinolines (9b,c) gave directly the 3-methoxy-3H-1,4-benzodiazepines (11b,c)[10] in 40-50% yields as crystals via the azirine intermediates (10), whereas the 2-unsubstituted 3-azidoquinoline (9a) afforded the methanol adduct (12) in 45% yield as the sole product. However, heating the



Scheme 2

adduct (12) in refluxing benzene resulted in the formation of the 3H-diazepine (11a)[10] in 80% yield by elimination of methanol. The formation of 1,3-benzodiazepines derived from the azirine intermediates (13) was not observed in the photolysis of 9. The 1,4-benzodiazepine structure of the 3H-diazepines (11) was also confirmed by the fact that treatment of 11 with LAH afforded the known tetrahydro-1,4-benzodiazepines (7).

It should be noted that treatment of the 2-substituted 3H-1,4-diazepines (11b,c) with sodium methoxide in refluxing methanol resulted in tautomerization to afford the 5H-1,4-benzodiazepines (14) in 85-95% yields.[11] However, in the case of 11a (R = H), the base-induced addition of methanol occurred predominantly over the tautomerization to yield only the adduct (12). The 5H-diazepine (14a) could not be obtained, even though 11a was treated with various bases such as t-amines and t-butoxide. In contrast to the 5-methoxy-3H-diazepines (4), the 3-methoxy-3H-diazepines (11) did not give 1-acetyl-1H-diazepines by acetylation.

The difference between 5-methoxy- and 3-methoxy-1,4-benzodiazepines toward tautomerizations may depend on the different position of the methoxy group, but at present no plausible explanation can be offered to account for the differences. In order to examine the tautomerism, attempts to prepare the fully unsubstituted parent 1,4-benzodiazepine ring are in progress.

In conclusion, the results reported provide new synthetic methods for fully unsaturated 1,4-benzodiazepines and their derivatives.

REFERENCES AND NOTES

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7. The structures of the unstable 1H-1,4-benzodiazepines (3) were confirmed by their NMR spectra; e.g., (3a): δ (CD_3OD, compounds 3 decomposed rapidly in $CDCl_3$): 3.72 (3H, s, OMe), 5.46 (1H, d, J=6 Hz, 3-H), 5.66 (1H, d, J=6 Hz, 2-H), 5.10 (1H, br, NH), 7.4-8.4 (4H, m, Ar-H); (3b): δ (CD_3OD): 3.68 (3H, s, OMe), 4.7 (1H, br, NH), 5.30 (1H, d, J=6 Hz, 3-H), 5.60 (1H, d, J=6 Hz, 2-H). Suschitzky et al. reported the synthesis of 3b by a method similar to that described in the present work. [F. Hollywood, Z.U. Khan, E.F.V. Scriven, R.K. Smalley, H. Suschitzky, D.R. Thomas, and R. Hull, J. Chem. Soc., Perkin Trans. 1, 1982, 431]. But the data given for their compound are quite different from those of the 1H-diazepine (3b) or the 3H-diazepine (4b) obtained by us.
8. Satisfactory elemental analyses and spectral data were obtained for the new diazepines reported; e.g., (4a): ^{1}H-NMR δ ($CDCl_3$): 3.62 (2H, d, J=4 Hz, 3-H_2), 3.85 (3H, s, OMe), 7.2-7.85 (4H, m, Ar-H), 8.01 (1H, t, J=4 Hz, 2-H); ^{13}C-NMR δ ($CDCl_3$): 46.42 (t, 3-C), 54.06 (q, OMe), 161.01 (d, 5-C), Ph-C [124.18 (s), 125.54 (d), 127.01 (d), 128.36 (d), 131.19 (d), 147.54 (s), 136.71 (s)]; (4b): ^{1}H-NMR δ ($CDCl_3$): 3.60 (2H, d, J=4 Hz, 3-H_2), 3.84 (3H, s, OMe), 7.20 (1H, dd, J=8 and 1 Hz, 7-H), 7.37 (1H, d, J=1 Hz, 9-H), 7.55 (1H, d, J=8 Hz, 6-H), 7.96 (1H, t, J=4 Hz, 2-H).
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10. Compound (11a): mp 46-49 °C, ^{1}H-NMR δ ($CDCl_3$): 3.61 (3H, s, OMe), 3.96 (1H,dd, J=2 and 2, 3-H), 7.2-7.6 (5H, m, 2-H and Ar-H), 8.35 (1H, d, J=2 Hz, 5-H); (11b): mp 78-79 °C; (11c): mp 90-92 °C.
11. Compound (14b): mp 42-43 °C, ^{1}H-NMR δ ($CDCl_3$): 2.38 (3H, s, 2-Me), 3.53 (3H, s, OMe), 3.96 (2H, s, 5-H_2), 6.8-7.2 (4H, m, Ar-H); (14c): mp 128-129 °C.

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