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THERMAL INTRAMOLECULAR CYCLIZATION OF 2-ETHYNYLPYRIDINE N-YLIDES TO INDOLIZINES AND CYCLAZINES

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Treatment of 2-ethynyl-1-phenacylpyridinium bromides (1a-c), prepared from 2-ethynylpyridines and phenacyl bromide, with a base, DBU, in refluxing benzene gave 3-benzoylindolizines (2), whereas heating the salts (1) in refluxing acetic acid afforded 1-benzoylindolizines (3). Upon similar treatment with the base, 2-ethynyl-6-methyl-1-phenacylpyridinium bromides (10a-c) gave 2-phenylcycl[3.2.2]azines (12), together with 3-benzoylindolizines (11). However, the reaction of 6-amino-2-ethynylpyridines (17a-c) with phenacyl bromide resulted in the formation of 1-azaindolizines (18), which were treated with the base to give 1-azacycl[3.2.2]azines (19). The mechanisms for these intramolecular cyclization via pyridine N-ylide intermediates are discussed.

KEYWORDS ——— intramolecular cyclization; rearrangement; 2-ethynylpyridine N-ylide; indolizine; 3-azaindolizine; cycl[3.2.2]-azine; 1-azacycl[3.2.2]azine

Ylides have been widely used as reactive intermediates in organic syntheses,[1-3] particularly in reactions involving either thermal[2] or photochemical[3] intramolecular rearrangements and intermolecular cycloadditions.[1,2] As for aromatic amines, the intermolecular 1,3-dipolar cycloaddition[2] of azine N-ylides and N-imides to olefins or acetylenes and the intramolecular 1,5-dipolar cyclization[4] of azine N-vinylimides have been well investigated. However, few such reactions of pyridines having an unsaturated substituent in the 2-position of the pyridine ring were known. Therefore, we were interested in examining the thermal behavior of 2-ethynyl- and 2-vinyl-pyridinium ylides in connection with studies of the thermal sigmatropic rearrangements of aliphatic allyl-[5,6] and propynyl-amine N-ylides and N-imides,[7] and have already reported that the 2-ethynylpyridine N-imides and related compounds undergo thermal intramolecular cyclization to give 3-azaindolizines.[8] We report here the thermal intramolecular cyclization of 2-ethynylpyridine N-ylides.

The starting 2-ethynyl-1-phenacylpyridinium bromides (1a-c and 10a-c) were prepared in high yields from the corresponding 2-ethynylpyridines by treatment with phenacyl bromide.[9] The 2-ethynylpyridines used in the present work were prepared from the corresponding 2-bromopyridines and acetylenes according to the reported method.[8,10]

Treatment of the 6-unsubstituted pyridinium salts (1a-c) with 1,5-diaza-

bicyclo[5.4.0]undec-5-ene (DBU) or potassium tert-butoxide in refluxing benzene gave the 3-benzoylindolizines (2)[11] in 60-70% yields. Unexpectedly, heating the salts (1) in refluxing acetic acid also resulted in cyclization to give the 1-benzoylindolizines (3)[11] in 50-70% yields, but no 3-benzoyl isomers (1).

Possible mechanisms for these reactions are shown in Chart 1, although none of the intermediates could be isolated. The N-ylides (4) initially formed from the salts (1) by the base treatment may cyclize to give the 1-benzoyl products (2) via the zwitter ionic intermediates (5) and the cyclic ylides (6) successively. The propynylamine N-ylides and N-oxides are known to undergo a thermal [2,3]-sigmatropic rearrangement to generate allenic compounds.[7] However, a concerted mechanism for the present reaction seems unlikely because of prohibitive ring strain in the corresponding five-membered cyclic allenic intermediates. This behavior is analogous to that observed for 2-ethynylpyridine N-imides.[8] On the other hand, the formation of the 1-benzoylindolizines (3) from 1 by the acid treatment may proceed via the addition of an acetoxy anion to the triple bond to produce allenic intermediates followed by cyclization to 7, which may give the ylide intermediates (8) by ring fission. The ylides (8) may undergo [2,3]-sigmatropic rearrangement to the bicyclic intermediates (9), which then give the products (3) by elimination of acetic acid.

However, the 6-methylpyridinium salts (10a-c), upon treatment with the base, gave the 2-phenylcycl[3.2.2]azines (12)[12] in 10-15% yields, together with the 3-benzoylindolizines (11) in ca. 60% yields. In this case, the initial base-induced deprotonation from the methyl group to 14 may also occur in competition

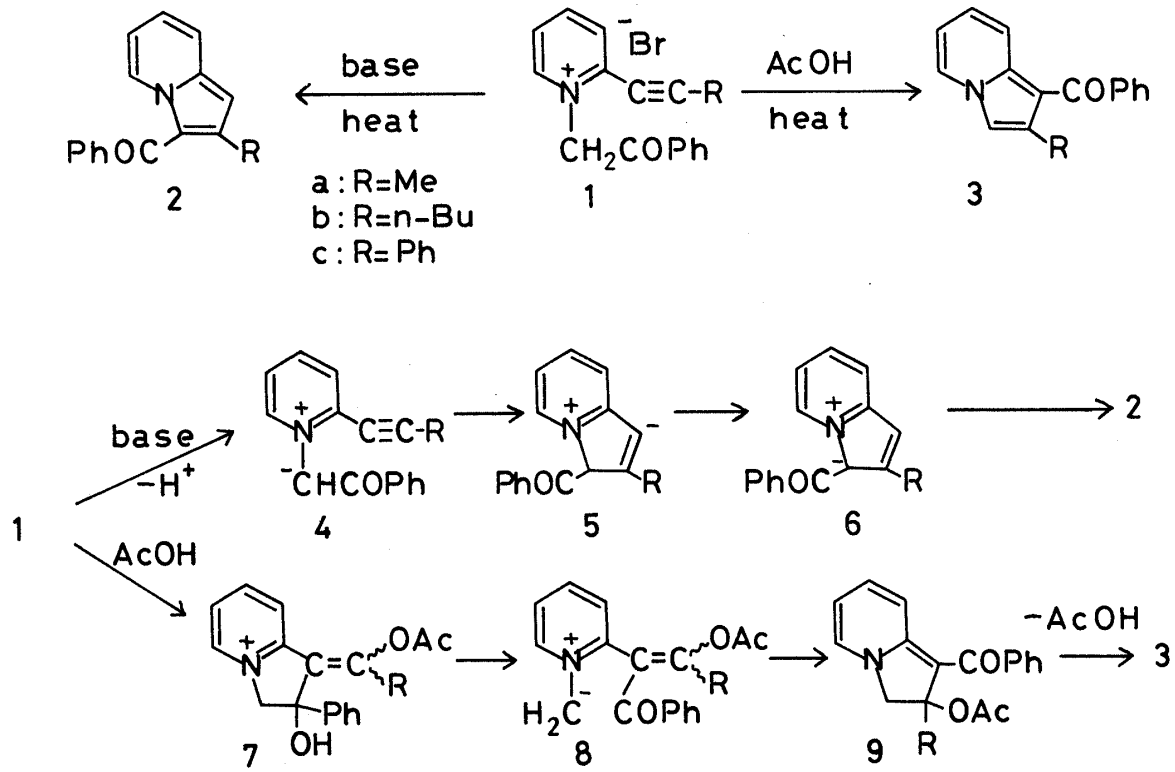

Chart 1

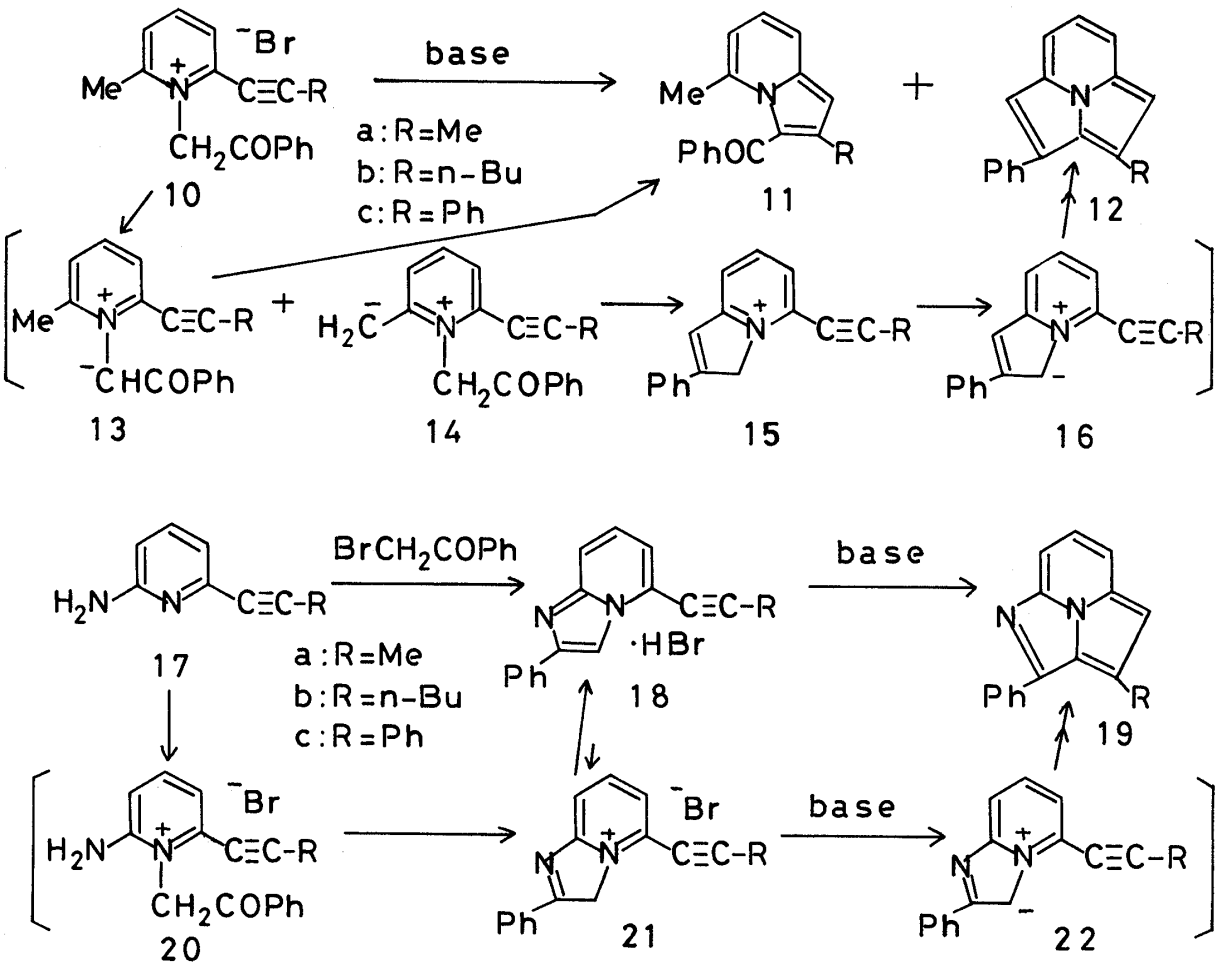

Chart 2

with the deprotonation from the phenacyl group to the ylides (13). The intermediates (14) may cyclize to give the cyclic ylides (16) via 15. The cyclic ylides (16) may further cyclize to the tricyclic products (12), analogously to the formation of 2 from 4. In addition, further treatment of the 3-benzoylindolizines (11) with the base did not give the cyclazines (12) and heating the salts (10) in acetic acid also gave the 1-benzoyl isomers of 11, but no cyclazines.

In contrast to the cases of 6-unsubstituted and 6-methylpyridines, treatment of the 6-amino-2-ethynylpyridines (17) with phenacyl bromide did not afford the 1-phenacylpyridinium salts (20) and gave the 1-azaindolizine hydrobromides (18)[13] in 85-95% yields, presumably via the salts (20) and their Schiff bases (21). The azaindolizines (18) were treated with sodium carbonate in water to give the 1-azacycl[3.2.2]azines (19)[14] in 80-90% yields. The formation of the cyclazines (19) from 18 may also involve the cyclic ylide intermediates (22) via 21, as in the formation of 12.

In conclusion, the present results provide useful new methods for preparing indolizines[15] and cyclazines,[16] although many synthetic routes for these heterocyclic rings are known. Studies on applications of these results to other systems are in progress.

REFERENCES AND NOTES

1) For reviews, see W.J. McKillip, E.A. Sedor, B.M. Culbertson, and S. Wawzonek, Chem. Rev., 73, 255 (1973); T.L. Glichrist and C.J. Moody, ibid., 77, 409 (1977); T. Nakai and K. Mikami, Yuki Gosei Kagaku Kyokai Shi, 38, 381 (1981).
2) For reviews, see Y. Tamura, Yakugaku Zasshi, 100, 1 (1980); Y. Tamura and M. Ikeda, "Advances in Heterocyclic Chemistry," Vol. 29, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, London, 1981, p. 71.
3) For reviews, see M. Nastasi, Heterocycles, 4, 1509 (1976); T.Tsuchiya, Yakugaku Zasshi, 103, 373 (1983); Yuki Gosei Kagaku Kyokai Shi, 39, 99 (1981); 41, 641 (1983).
4) Y. Tamura, N. Tsujimoto, Y. Sumida, and M. Ikeda, Tetrahedron, 28, 21 (1971); T. Sasaki, K. Kanematsu, and A. Kakehi, J. Org. Chem., 37, 3106 (1972); A. Kakehi, S. Ito, K. Uchiyama, Y. Konno, and K. Kondo, ibid., 42, 443 (1977).
5) A.R. Lepley and A.G. Giumani, "Mechanisms of Molecular Migrations," Vol. 3. ed. by B.S. Thyagrajan, Wiley Intersciences, New York, 1971, p. 207; I.D. Brindle and M.S. Gibson, J. Chem. Soc., Perkin Trans. 1, 1979, 517; R.W. Jemsen, T. Laird, W.D. Ollis, and I.O. Sutherland, ibid., 1980, 1450.
6) E. Vadjes, M.J. Arco, D.W. Powell, J.M. Renga, and S.P. Singer, J. Org. Chem., 43, 4831 (1978); T. Tsuchiya, H. Sashida, and H. Sawanishi, Chem. Pharm. Bull., 26, 2880 (1978); T. Tsuchiya and H. Sashida, ibid., 29, 1887 (1981).
7) S. Mageswaran, W.D. Ollis, D.A. Southan, I.O. Sutherland, and Y. Thebtranonth, J. Chem. Soc., Perkin Trans. 1, 1981, 1969; H. Sashida and T. Tsuchiya, Heterocycles, 19, 281 (1982).
8) T. Tsuchiya, H. Sashida, and A. Konoshita, Chem. Pharm. Bull., 31, 4568 (1983).
9) Satisfactory elemental analyses and spectral data were obtained for all new compounds reported.
10) K. Sonogashira, Y. Tohda, and H. Hagihara, Tetrahedron Lett., 1975, 4467.
11) The 2-phenylindolizines (2c, 3c) are known [T. Melton and D.G. Wibberley, J. Chem. Soc., 1967, 983] and the other indolizines (2 and 3) obtained were characterized by spectral comparison with 2c and 3c.
12) The 2,3-diphenyl compound (12c) is known [R.J. Windgassen, W.H. Saunders, and V. Boekelheid, J. Am. Chem. Soc., 81, 1459 (1959)] and the compounds (12a,b) were characterized by spectral comparison with 12c.
13) The salts (18a: mp 213-215 °C; 18b: mp 114-116 °C; 18c: mp 214-216 °C) were chracterized by spectral data.
14) The compounds (19a: mp 123-124 °C; 19b: oil; 19c: mp 125-126 °C) were characterized by comparison with the related compounds reported [V. Boekelheid and A. Miller, J. Org. Chem., 26, 431 (1961); O. Fuentes and W.W. Paudler, ibid., 40, 1210 (1975)].
15) For reviews, see F.J. Swinbourne, J.H. Hunt, and G. Klinkert, "Advances in Heterocyclic Chemistry," Vol. 23, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, London, 1978, p. 103; T. Uchida and K. Matsumoto, Synthesis, 1976, 209.
16) W. Flitsch and U. Krämer, "Advances in Heterocyclic Chemistry," Vol. 22, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, London, 1978, p. 321.

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