NOVEL RING CONTRACTION OF 4,6-DIHYDRO-3,7-DIPHENYL-5-(p-TOSYL)-1,2,5-TRIAZEPINE VIA A CHLORINATION

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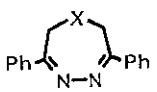
Abstract ——— In the chlorination 4,6-dihydro-3,7-diphenyl-5-(p-tosyl)-1,2,5-triazepine undergoes a novel ring contraction in methanol to afford pyrrolidines and morpholines which are arisen from the extrusion of nitrogen, in contrast to the formation of the 4-(p-tosylamino)pyridazine and/or 4,6-dichlorodihydrotriazepine in an aprotic solvent.

In the course of a survey of halogenations of seven-membered cyclic 1,2-diaza systems 1, it has been found that ring contraction reactions remarkably depend upon the reaction conditions as well as the nature of X in 1[1-4].



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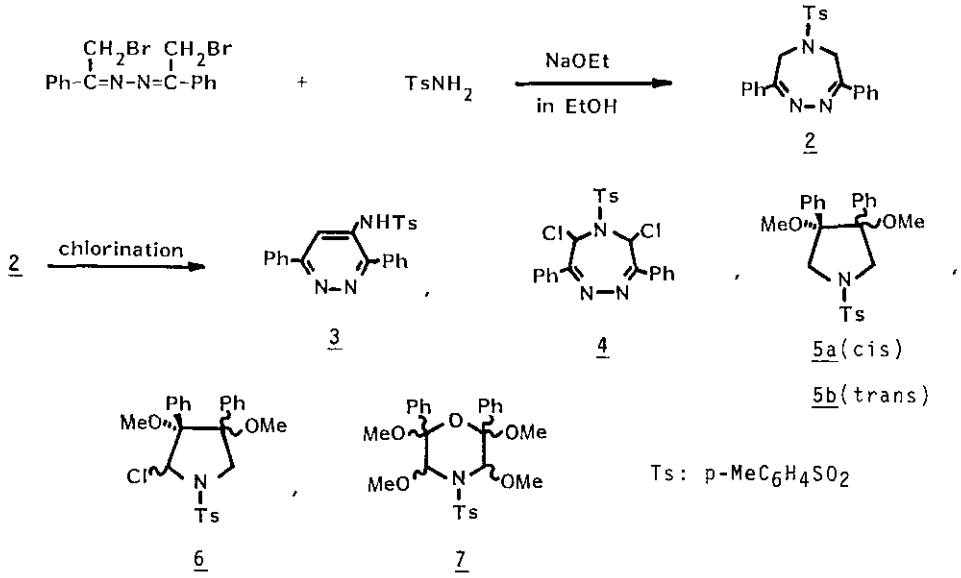
We have previously reported that the bromination of 5-benzyl-4,6-dihydro-3,7-diphenyl-1,2,5-triazepine 1 (X=NCH_2Ph) afforded either 1-benzyl-4-phenylimidazole or 3,6-diphenylpyridazine as the main product depending upon the reaction conditions, whereas 4-benzylamino-3,6-diphenylpyridazine was formed in the chlorination[1]. In these halogenations, however, no halogenated dihydrotriazepines were isolated. In order to compare the mode of halogenation of a dihydrotriazepine bearing an electron-withdrawing substituent on the 5-position with that of the benzyldihydrotriazepine 1 (X=NCH_2Ph), we planned to investigate halogenations of 4,6-dihydro-3,7-diphenyl-5-(p-tosyl)-1,2,5-triazepine 2. We report here a novel ring contraction of 2 via a chlorination.

The dihydrotriazepine 2 (mp 137-138 °C)[5] was prepared in 80% yield by the reaction of α-bromoacetophenone azine[6] with p-toluenesulfonamide in the presence of sodium ethoxide in ethanol under reflux (Scheme 1).

In the reaction of 2 with sulfuryl chloride or chlorine gas in dichloromethane or with N-chlorosuccinimide (NCS) in carbon tetrachloride, 3,6-diphenyl-4-(p-tosylamino)pyridazine 3 (mp 251-252 °C) and/or 4,6-dichloro-4,6-dihydro-3,7-diphenyl-5-(p-tosyl)triazepine 4 (mp 168-169 °C dec) were obtained[7]: the relative yields of products depended upon the reaction conditions (Scheme 1)[8]. The ring contraction of 2 to 3 is closely similar to that of 1 (X=NCH_2Ph) to the 4-benzylaminopyridazine[1]. It should be emphasized, however, that the dichloride 4 retained seven-membered ring was formed in this case[9].

A dramatic change was observed in the chlorination in methanol. No 3 and 4 were obtained, but instead six novel ring-contracted products arisen from the extrusion of nitrogen from 2 were isolated in low yields, accompanied with intractable tarry materials. On the basis of spectral data[10], these products were assigned as two stereoisomeric 3,4-dimethoxy-3,4-diphenyl-1-(p-tosyl)pyrrolidines, 5a (mp 174-175



SO_2Cl_2 (equimolar) in CH_2Cl_2 (Method A), r.t., 1h 3 (58%), 4 (15%)

SO_2Cl_2 (2 times mol) in CH_2Cl_2 (Method B), r.t., 30 min 4 (83%)

Cl_2 (excess) in CH_2Cl_2, r.t., 20 min 4 (81%)

NCS (equimolar) in CCl_4, reflux, 2 h 3 (86%), 4 (15%)

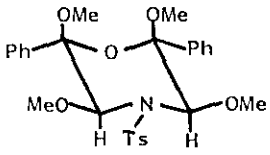
Cl_2 (excess) in MeOH, 0-5 °C, 2 h 5a (13%), 5b (6.5%), 6 (5%), 7a (3%), 7b (5.5%)

Scheme 1

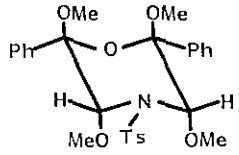
°C) and 5b (mp 195-196 °C), 2-chloro-3,4-dimethoxy-3,4-diphenyl-1-(p-tosyl)-2,3,5,6-tetramethoxymorpholines, 6a (mp 188-189 °C) and 6b (mp 173-174 °C).

The configurations of 3- and 4-positions in isomers 5a and 5b were identified to be the cis and trans, respectively, on the basis of ^{1}H NMR spectra: the methoxy protons (δ 2.76) in 5b appear upfield of those (δ 2.84) in 5a owing to the shielding effect of the adjacent phenyl groups in 5b. However, the stereochemistry of 6 is not fully solved[11].

Although several configurations are possible for morpholines 7, spectral data indicate that both 7a and 7b have a symmetrical structure, respectively. An inspection of molecular models shows that preferable configurations of 7 having a symmetrical structure are the following ones, 7-1 and 7-2; steric interactions among substituents in 7-2 are more significant than those in 7-1.



7-1 (=7a)

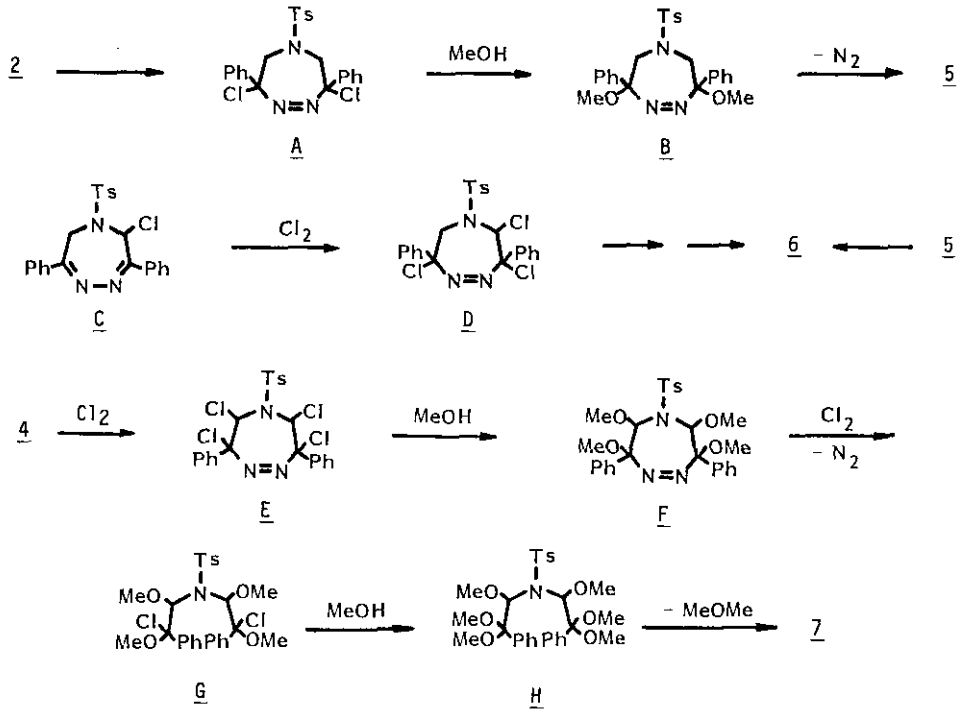


7-2 (=7b)

It is known that steric interactions, mostly arising from touching or overlapping of van der Waals radii of closely spaced hydrogens usually causes a shielding of the carbons attached to these hydrogens[12]. In the ^{13}C NMR spectra the methoxy- and ring-carbons, especially 3- and 5-carbons, in 7b appear upfield of those in 7a, respectively. Thus, two stereoisomeric morpholines 7a and 7b can be assigned as 7-1 and 7-2, respectively. The ^{1}H NMR spectra also supported the assigned structures. The treatment of dichloride 4 with chlorine gas in methanol at 0-5 °C gave a mixture of morpholines, 7a (30%) and 7b (1%)[13]. This fact strogly indicates that morpholines 7 are formed via a dichloride like 4.

The pathways for the above novel ring contractions are not clear, but we wish to tentatively suggest the probable ones. Since it has been reported that chlorine reacts with acyclic ketazines to give α,α'-dichloroazoalkanes via a 1,4-addition manner[14], pathways via chlorinated cyclic azo intermediates might be thought for the formation of the products 5-7.

As shown in Scheme 2, chlorine adds to 2 to yield a cyclic dichloroazo intermediate A. A nucleophilic substitution of A with methanol produces a dimethoxy derivative B, followed by the elimination of nitrogen with concurrent ring closure to give stable pyrrolidines 5. The chloride 6 is formed via either a trichloroazo inter-



Scheme 2

mediate D formed from monochloride C[15] or the chlorination of an isomer of 5. On the other hand, a tetramethoxyazo intermediate F formed from a tetrachloroazo compound E is probably involved in the formation of morpholines 7. The intermediate F yields an acyclic chlorinated amine G via the elimination of nitrogen with concurrent chlorination. Subsequent nucleophilic substitution of G with methanol yields a hexamethoxy-substituted amine H, and then ring closure of H with the elimination of methyl ether finally gives 7.

REFERENCES AND NOTES

1. O. Tsuge and K. Kamata, Heterocycles, 1975, 3, 547.
2. O. Tsuge and K. Kamata, ibid., 1975, 3, 15.
3. O. Tsuge, K. Kamata, and S. Yogi, Bull. Chem. Soc. Jpn., 1977, 50, 2153.
4. K. Kamata and O. Tsuge, Heterocycles, 1984, 22, 1497.
5. 2: colorless prisms; ^{1}H NMR ($CDCl_3$) δ 2.31 (3H, s, CH_3), 4.26 (4H, s, CH_2), 6.9-7.9 (14H, m, ArH); MS m/z 403 (M^+).
   All the new compounds in this communication gave satisfactory elemental analyses.
6. O. Tsuge, M. Tashiro, K. Kamata, and K. Hokama, Org. Prep. & Proced., 1971, 3, 289.

7. 3: colorless prisms; IR (KBr) 3230 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.33 (3H, s, CH_3), 7.2-8.0 (15H, m, ArH); MS m/z 401 (M^+).
   4: colorless prisms; ^1H NMR ($CDCl_3$) δ 2.39 (3H, s, CH_3), 6.98 (2H, s, CH), 7.2-7.9 (14H, m, ArH); MS m/z 471, 473, 475 (M^+).
8. In Scheme 1 Method A or B represents the following procedure, respectively. Method A: a solution of sulfuryl chloride in CH_2Cl_2 was added, drop by drop, over a period of 60 min to a solution of 2 in CH_2Cl_2. Method B: a solution of sulfuryl chloride in CH_2Cl_2 was added all at once to a solution of 2 in the same solvent. The brominations under similar conditions gave 3 and/or 4,6-dibromodihydrotriazepine; the results are closely similar to those in the chlorinations.
9. Contrary to the formation of diazanorcaradiene from the 4,6-dihalide of 1 (X= $C(COOEt)_2$)[3], the dichloride 4 decomposed to a mixture of 3,6-diphenylpyridazine (78%) and p-toluenesulfonamide (39%) on heating with sodium iodide in refluxing acetone.
10. 5a: colorless prisms; ^1H NMR ($CDCl_3$) δ 2.46 (3H, s, CH_3), 2.84 (6H, s, OCH_3), 3.86, 4.05 (each 2H, d, CH_2, J=10.2 Hz), 6.9-7.5 (12H, m, ArH), 7.85-8.0 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 21.5 (q, CH_3), 51.0 (t, 2-, 5-C), 52.4 (q, OCH_3), 88.1 (s, 3-, 4-C), 127.4, 127.6, 127.9, 129.8 (each d), 134.8, 135.6, 143.5 (each s); MS m/z 437 (M^+), 405 (M^+ - MeOH), 374 (405^+ - OMe).
    5b: colorless prisms; ^1H NMR ($CDCl_3$) δ 2.46 (3H, s, CH_3), 2.76 (6H, s, OCH_3), 3.89, 4.30 (each 2H, d, CH_2, J=10.8 Hz), 6.75-7.5 (12H, m, ArH), 7.85-8.05 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 21.6 (q, CH_3), 49.8 (t, 2-, 5-C), 50.6 (q, OCH_3), 89.4 (s, 3-, 4-C), 127.2, 127.5, 127.8, 128.9, 129.8 (each d), 133.3, 135.2, 143.5 (each s); MS m/z 437 (M^+), 405 (M^+ - MeOH), 374 (405^+ - OMe).
    6: colorless prisms; ^1H NMR ($CDCl_3$) δ 2.42 (3H, s, CH_3), 2.82 (3H, s, 4-OCH_3), 3.73 (3H, s, 3-OCH_3), 3.68, 3.93 (each 1H, d, CH_2, J=11.1 Hz), 5.59 (1H, s, >CH), 6.9-7.4 (12H, m, ArH), 7.9-8.1 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 21.5 (q, CH_3), 47.3 (t, 5-C), 52.2, 60.9 (each q, OCH_3), 82.5, 87.7 (each s, 3-, 4-C), 96.4 (d, 2-C), 127.5, 127.8, 128.3, 128.5, 129.5 (each d), 133.7, 137.2, 137.5, 143.5 (each s); MS m/z 471, 473 (M^+), 440, 442 (M^+ - OMe), 436 (M^+ - Cl), 435 (M^+ - HCl).
    7a: colorless prisms; ^1H NMR ($CDCl_3$) δ 2.40 (3H, s, CH_3), 2.83 (6H, s, 2-, 6-OCH_3), 3.12 (6H, s, 3-, 5-OCH_3), 5.11 (2H, s, >CH), 7.15-7.75 (12H, m, ArH), 7.85-8.05 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 21.5 (q, CH_3), 49.5, 58.7 (each q,

OCH_3), 89.4 (d, 3-, 5-C), 101.3 (s, 2-, 6-C), 127.5, 127.9, 128.0, 128.6, 129.1 (each d), 138.4, 138.5, 142.8 (each s); MS m/z 482 (M^+ - OMe), 450 (482^+ - MeOH).

7b: colorless prisms; ^1H NMR ($CDCl_3$) δ 2.42 (3H, s, CH_3), 2.76 (6H, s, 2-, 6-OCH_3), 3.24 (6H, s, 3-, 5-OCH_3), 5.11 (2H, s, $\geq CH$), 7.05-7.70 (12H, m, ArH), 7.90-8.10 (2H, m, ArH); ^{13}C NMR ($CDCl_3$) δ 21.5 (q, CH_3), 51.0, 56.5 (each q, OCH_3), 86.6 (d, 3-, 5-C), 100.8 (s, 2-, 6-C), 126.6, 128.0, 128.8 (each d), 137.9, 138.7, 142.7 (each s); MS m/z 482 (M^+ - OMe), 450 (482^+ - MeOH).

11. It was assumed that the methoxy groups in 6 have a cis configuration, because the value of chemical shift of the 4-methoxy protons is closely similar to that in 5a.
12. E. Bretmaier and W. Voelter, '^{13}C NMR Spectroscopy Monographs in Modern Chemistry 5', Verlag Chemie, Weinheim, New York, 1978, p. 74.
13. The chlorination of the 4,6-dimethoxyldihydrotriazepine, which was obtained in the reaction of 2 with bromine in methanol, under similar conditions afforded again a mixture of 7a (16%) and 7b (trace).
14. D. S. Malament and J. M. McBride, J. Am. Chem. Soc., 1970, 92, 4586, 4593. See also the references cited therein.
15. In an aprotic solvent the monochloride C undergoes dehydrochlorination to give 3 via a triazanorcaradiene intermediate or further chlorination to afforde 4. Further investigation concerning solvent effects on halogenations of 2 is in progress.

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