SEQUENTIAL INTRAMOLECULAR DIELS-ALDER REACTION AND INTERMOLECULAR 1,3-DIPOLAR CYCLOADDITION REACTION: ONE-POT [6.6.5]ANNELATION REACTION LEADING TO THE FORMATION OF POLYAZA-STEROID TYPE SKELETONS

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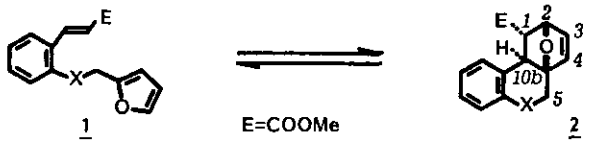
Abstract ——— The reaction of methyl o-(2-furylmethyloxy)- and o-[N-ethyl-N-2-(furylmethyl)amino]cinnamate with phenyl azide provided the one-pot [6.6.5]annelation reaction leading to the formation of polyaza-steroid type skeletons through an intramolecular Diels-Alder reaction, followed by an intermolecular 1,3-dipolar cycloaddition reaction.

As we have reported earlier, the multiple sequence of cycloaddition reaction including a 1,3-dipolar cycloaddition and/or the Diels-Alder reaction constitutes an extremely useful and facile way for the synthesis of polycyclic compounds[1]. In connection with our program directed toward the further synthetic development of sequential cycloaddition reactions, we decided to explore a new approach to heterocyclic steroidal skeletons.

Our approach involves the initial intramolecular Diels-Alder reaction of the system where a furan ring as a diene and a dienophile moiety are properly located through an aromatic ring, and the subsequent intermolecular 1,3-dipolar cycloaddition to a strained double bond newly formed. During the course of the investigation along this line, we found a one-pot [6.6.5]annelation reaction leading to the formation of polyaza-steroid type skeletons.

Methyl o-(2-furylmethyloxy)- (1a) and o-[N-ethyl-N-2-(furylmethyl)amino]cinnamate (1b)[2] gave, upon heating, the corresponding intramolecular Diels-Alder adducts, 2a (mp 103-104 °C) and 2b (mp 126-127 °C), respectively. However, their yields were poor because they thermally underwent a retro cycloaddition reaction; 1a (reflux in xylene, 47 h) or 1b (reflux in toluene, 7 h) gave 2a or 2b in 8 or 34% yield, and when heated in toluene under reflux for 5 h, 2a or 2b was converted into a mixture

of 1a and 2a (9:1) or 1b and 2b (2:1), respectively.



1 E=COOMe 2

a: X=O; b: X=NEt

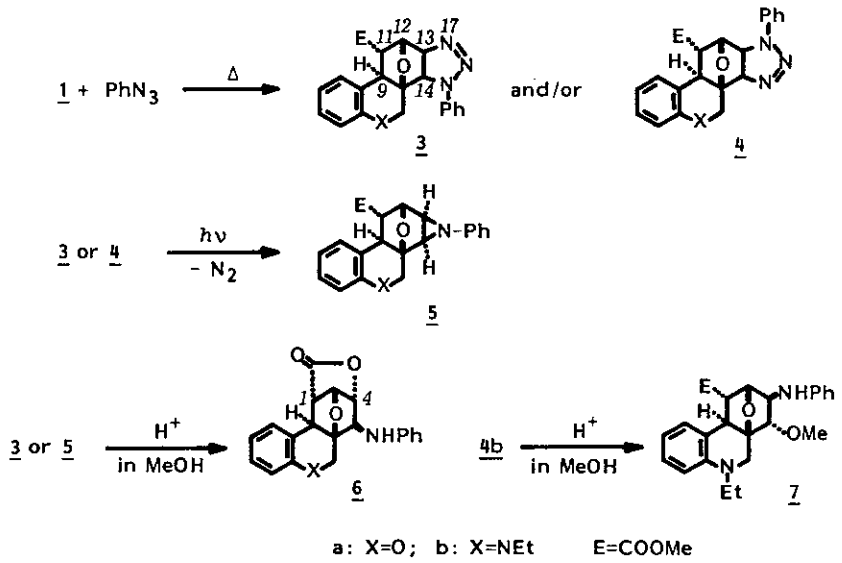
Structural elucidation of 2 was accomplished on the basis of spectral data[3], althoughthe endo-configuration of the ester group will be described later.

Thus, we investigated the one-pot reaction of cinnamates 1 with phenyl azide in order to trap the thermally unstable 2 as a 1,3-dipolar cycloadduct. A solution of 1a (6.4 mmol) and phenyl azide (9.6 mmol) in dry toluene (50 ml) was refluxed for 18 h to give the expected triazoline 3a (mp 151-152 °C dec) as the sole product in 43% yield, together with recovery of 1a (28%). In the reaction of 1b with the azide under similar conditions (4.5 h), however, two isomeric triazolines, 3b (mp 158-159 °C dec) and 4b (mp 176-178 °C dec), were isolated in 25 and 37% yields, respectively. In both cases no adducts of azide to 1 were isolated.

On the basis of spectral data[4] and chemical conversions, the structures of 3 and 4 were assigned as 15-phenyl- and 17-phenyl-substituted exo-adducts of phenyl azide to the Diels-Alder adducts 2, respectively. The coupling constants of $J_{12,13}$ (0 Hz) and $J_{13,14}$ (9.0 Hz) in 3 and 4 are compatible with those of the exo-adducts of azides to norbornene systems[5].

Irradiation of a solution of 3a in benzene with a 100W high pressure mercury lamp under cooling for 2 h gave the aziridine 5a (mp 139-140 °C) in 95% yield. Similar photolysis of 3b and 4b afforded the same aziridine 5b (mp 96-97 °C) in 32 and 22% yields, respectively, together with intractable resinous materials; this fact indicates that 3b and 4b are regioisomers having the same stereochemistry[6].

When a solution of 3a (0.53 mmol) in methanol (4 ml) was stirred with a catalytic amount (20 mg) of p-toluenesulfonic acid at room temperature for 1.5 h, the lactone 6a (mp 224-225 °C) was obtained in 46% yield. The similar acidic methanolysis of 3b gave also the lactone 6b (mp 278-279 °C dec) in 72% yield. Structural elucidation of the lactones 6 was accomplished on the basis of spectral data[7]. The formation of 6 from 3 strongly indicates that the phenyl group is located at the 15-position in 3, and that the ester group has the endo-configuration in 3 and thereby in 2. The lactones 6a and 6b were also obtained from the similar acidic methanol-



ylis of aziridines 5a and 5b in both 60% yields, respectively.

On the other hand, the isomer 4b did not form a lactone under similar acidic methanolysis, but instead 3-anilino-4-methoxy derivative 7[8] was obtained in 70% yield; the formation of 7 strongly supports the assigned structure for 4b.

The study of the synthesis of heterocyclic steroidal compounds using the reaction of intramolecular Diels-Alder adducts like 2 with various 1,3-dipoles is now in progress.

REFERENCES AND NOTES

1. For example, O. Tsuge, S. Kanemasa, and S. Takenaka, Bull. Chem. Soc. Jpn., 1983, 56, 2073; O. Tsuge, K. Ueno, and S. Kanemasa, Chem. Lett., 1984, 797; O. Tsuge, E. Wada, S. Kanemasa, and H. Sakoh, Bull. Chem. Soc. Jpn., 1984, 57, 3221; O. Tsuge, S. Kanemasa, H. Sakoh, and E. Wada, ibid., 1984, 57, 3234.
2. All the new compounds reported herein gave satisfactory elemental analyses. The cinnamates 1a and 1b were prepared in quantitative yields by the Wittig-Horner reaction of the corresponding benzaldehyde with methyl diethylphosphonoacetate, respectively: 1a (mp 40-41 °C) and 1b (yellow oil).
3. 2a: ^{1}H-NMR ($CDCl_3$) δ 3.12-3.23 (2H, m, 1- and 10b-H), 4.20, 4.65 (each 1H, d, 5-H, J=13.0 Hz), 5.21 (1H, dd, 2-H, J=4.0, 2.0 Hz), 6.37 (1H, d, 4-H, J=6.0 Hz), 6.50 (1H, dd, 3-H, J=6.0, 2.0 Hz); MS m/z 258 (M^+). 2b: ^{1}H-NMR ($CDCl_3$) δ 3.10-

3.35 (2H, m, 1- and 10b-H), 4.52, 4.76 (each 1H, d, 5-H, J=12.0 Hz), 5.13 (1H, dd, 2-H, J=3.0, 1.5 Hz), 6.33 (1H, d, 4-H, J=6.0 Hz), 6.43 (1H, dd, 3-H, J=6.0, 1.5 Hz); MS m/z 285 (M^+).

4. 3a: ^{1}H-NMR ($CDCl_3$) δ 3.10 (1H, t, 11-H, J=6.0 Hz), 3.56 (1H, d, 9-H, J=6.0 Hz), 4.40 (1H, d, 14-H, J=9.0 Hz), 4.47, 4.73 (each 1H, d, 7-H, J=14.0 Hz), 4.88 (1H, d, 13-H, J=9.0 Hz), 4.92 (1H, d, 12-H, J=6.0 Hz); MS m/z 349 (M^+).

   3b: ^{1}H-NMR ($CDCl_3$) δ 2.94-3.24 (4H, m, 7-, 11-H and N-CH_2Me), 3.43 (1H, d, 7-H, J=13.0 Hz), 3.56 (1H, 9-H, J=9.0 Hz), 5.02 (1H, d, 12-H, J=6.0 Hz), 5.02 (1H, d, 13-H, J=9.0 Hz); MS m/z 404 (M^+).

   4b: ^{1}H-NMR ($CDCl_3$) δ 3.08 (1H, t, 11-H, J=5.0 Hz), 3.52 (1H, d, 9-H, J=5.0 Hz), 3.56, 3.70 (each 1H, d, 7-H, J=12.0 Hz), 4.32 (1H, d, 13-H, J=9.0 Hz), 4.82 (1H, d, 14-H, J=9.0 Hz), 4.83 (1H, d, 12-H, J=5.0 Hz); MS m/z 404 (M^+).

5. For example, S. McLean and D. M. Findlay, Tetrahedron Lett., 1969, 2219.

6. 5a: ^{1}H-NMR ($CDCl_3$) δ 2.60, 2.88 (each 1H, d, 2a- or 3a-H, J=5.0 Hz), 3.06 (1H, t, 1-H, J=5.0 Hz), 3.37 (1H, d, 9b-H, J=5.0 Hz), 4.24, 4.65 (each 1H, d, 4-H, J=12.0 Hz), 4.82 (1H, d, 2-H, J=5.0 Hz); MS m/z 349 (M^+).

   5b: ^{1}H-NMR ($CDCl_3$) δ 2.48, 2.85 (each 1H, d, 2a- or 3a-H, J=5.0 Hz), 3.05-3.62 (6H, m, 1-, 4-, 9b-H and NCH_2Me), 4.80 (1H, d, 2-H, J=6.0 Hz); MS m/z 376 (M^+).

7. 6a: IR (KBr) 3350, 1790 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.93 (1H, d, 1-H, J=6.0 Hz), 3.53 (1H, s, 11-b-H), 3.80 (2H, br. s, 5-H and NH), 4.17, 4.65 (each 1H, d, 6-H, J=13.0 Hz), 4.53 (1H, d, 4-H, J=6.0 Hz), 5.28 (1H, t, 1a-H, J=6.0 Hz); MS m/z 335 (M^+).

   6b: IR (KBr) 3360, 1795 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.82 (1H, dd, 1-H, J=5.0, 2.0 Hz), 3.00-3.78 (6H, m, 5-, 6-, 11b-H and NCH_2), 4.46 (1H, d, 4-H, J=5.0 Hz), 5.33 (1H, t, 1a-H, J=5.0 Hz), 5.50 (1H, br, NH); MS m/z 362 (M^+).

8. 7: mp 132-133 °C; IR (KBr) 3430, 3410, 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.36-2.80 (2H, m, 1- and 10b-H), 3.34 (3H, s, OCH_3), 3.63 (3H, s, $COOCH_3$), 3.00-3.80 (5H, m, 2-, 5-H and NCH_2), 3.95 (1H, d, 3-H, J=8.0 Hz, turned to singlet with D_2O), 4.59 (1H, s, 4-H), 5.20 (1H, d, NH, J=8.0 Hz); MS m/z 408 (M^+).

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