

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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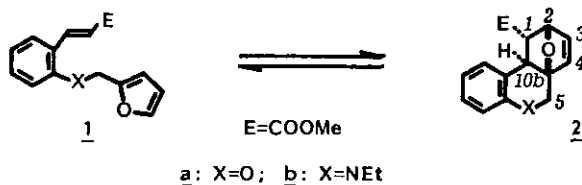
Abstract — The reaction of methyl *o*-(2-furylmethoxy)- and *o*-[N-ethyl-N-2-(furylmethyl)amino]cinnamate with phenyl azide provided the one-pot [6.6.5]annelation reaction leading to the formation of polyaza-steroid type skeletons through an intramolecular Diels-Alder reaction, followed by an intermolecular 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 compounds¹. 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-furylmethoxy)- (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.



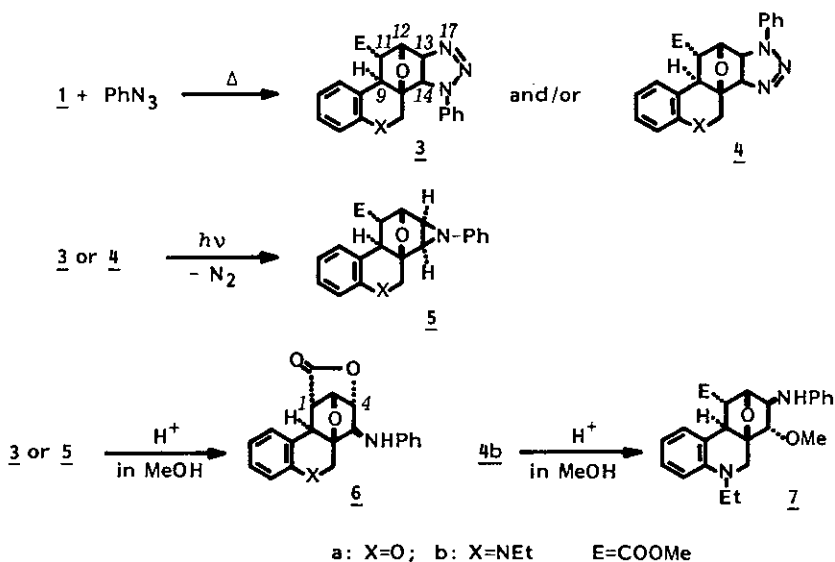
Structural elucidation of 2 was accomplished on the basis of spectral data³, although the endo-configuration of the ester group will be described later.

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 data⁴ 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 systems⁵.

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 stereochemistry⁶.

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 data⁷. 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 7⁸ 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

- 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.
- 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).
- 2a: ¹H-NMR (CDCl₃) 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: ¹H-NMR (CDCl₃) 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: $^1\text{H-NMR}$ (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: $^1\text{H-NMR}$ (CDCl_3) δ 2.94-3.24 (4H, m, 7-, 11-H and $\text{N-CH}_2\text{Me}$), 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: $^1\text{H-NMR}$ (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: $^1\text{H-NMR}$ (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: $^1\text{H-NMR}$ (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} ; $^1\text{H-NMR}$ (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} ; $^1\text{H-NMR}$ (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 $^\circ\text{C}$; IR (KBr) 3430, 3410, 1725 cm^{-1} ; $^1\text{H-NMR}$ (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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