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INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS TO A FURAN RING

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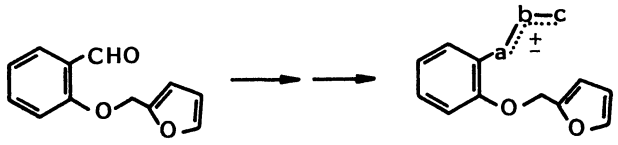
1,3-Dipolar systems derived from o-(2-furylmethyloxy)benzaldehyde undergo an intramolecular cycloaddition to the furan ring, giving the corresponding cycloadducts; this provides the first example for the intramolecular 1,3-dipolar cycloaddition to a furan ring.

Although the cycloadditions where furans enter as 4π components are well known, the study of thermally induced cycloadditions to furans as 2π components has been relatively scanty to date. Since the 1,3-dipolar cycloaddition of nitrile oxides to furan has first been demonstrated in 1966,[1] the dipolarophilic activity of furan has become of interest in recent years. The 1,3-dipolar cycloadditions of nitrile oxides,[1,2] nitrile imines,[3,4] and nitrones[5-7] to furans have so far been reported: In general furans are slightly reactive toward 1,3-dipoles. However, it should be noted that the cycloaddition of a nitrone to furan has been used as a key step in the total synthesis of nojirimycin.[7]

As recently reviewed,[8] intramolecular 1,3-dipolar cycloadditions are a very powerful tool in the synthesis of structurally complex fused heterocyclic compounds. An intramolecular Diels-Alder reaction in which a furan moiety reacted as the dienophile has recently been observed,[9] and to our knowledge this is the only example for the thermally induced intramolecular cycloaddition to a furan ring as the 2π component.

In this communication we wish to report the intramolecular cycloaddition of 1,3-dipolar systems derived from o-(2-furylmethyloxy)benzaldehyde 1[10]; this provides the first example for the intramolecular 1,3-dipolar cycloaddition to a furan ring as the dipolarophile.



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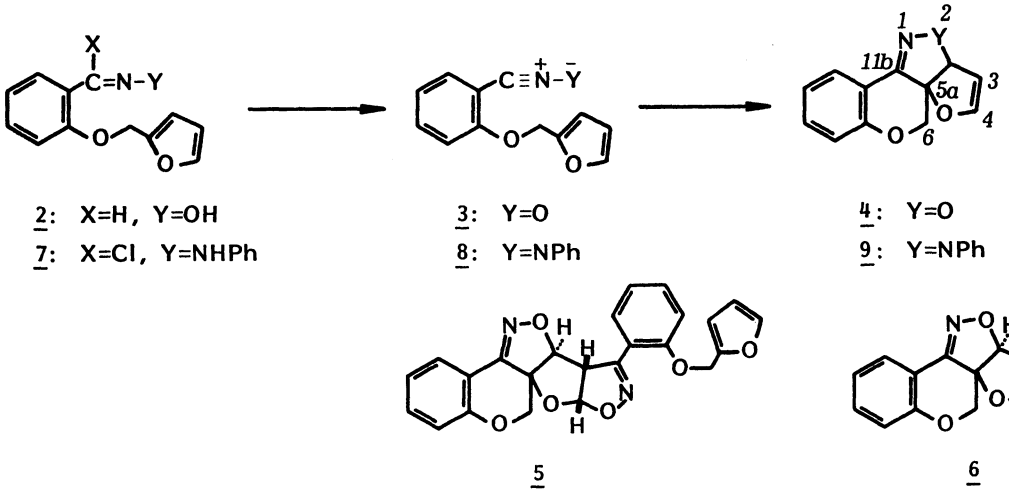
We have first investigated the intramolecular cycloaddition of the systems bearing nitrile betaine dipoles. o-(2-Furylmethyloxy)benzonitrile oxide 3 was generated according to the Lee's method.[11] To a mixture of o-(2-furylmethyloxy)benzaldoxime 2[12] (9.2 mmol) and triethylamine (50 mg) in dichloromethane (40 mL), 10% aqueous sodium hypochlorite (16 mL) was added dropwise at room temperature. After the reaction mixture was vigorously stirred at the same temperature for 5 h, the reaction phases were separated and the aqueous phase was extracted with dichloromethane (20 mL). The combined organic layers were dried over magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel using benzene as an eluent to give 4 (mp 142-143.5 °C) and 5 (mp 136-138 °C) in 83 and 10% yields, respectively.

On the basis of spectral data, especially showing the presence of a methine, a quaternary carbon and two vinylic carbons,[13] the major product 4 was assigned as the expected cycloadduct, 2aH-furo[2,3-d][1]benzopyrano[4,3-c]isoxazole, and the minor product 5 as the bisadduct derived from a further cycloaddition of 3 to 4. The major product 4 reacted with benzonitrile oxide under similar conditions to give a 49% yield of the cycloadduct 6 (mp 250-251 °C), whose spectral data[13] are comparable of those of 5 (Scheme 1).



2: X=H, Y=OH
7: X=Cl, Y=NHPh

3: Y=O
8: Y=NPh

4: Y=O
9: Y=NPh

5

6

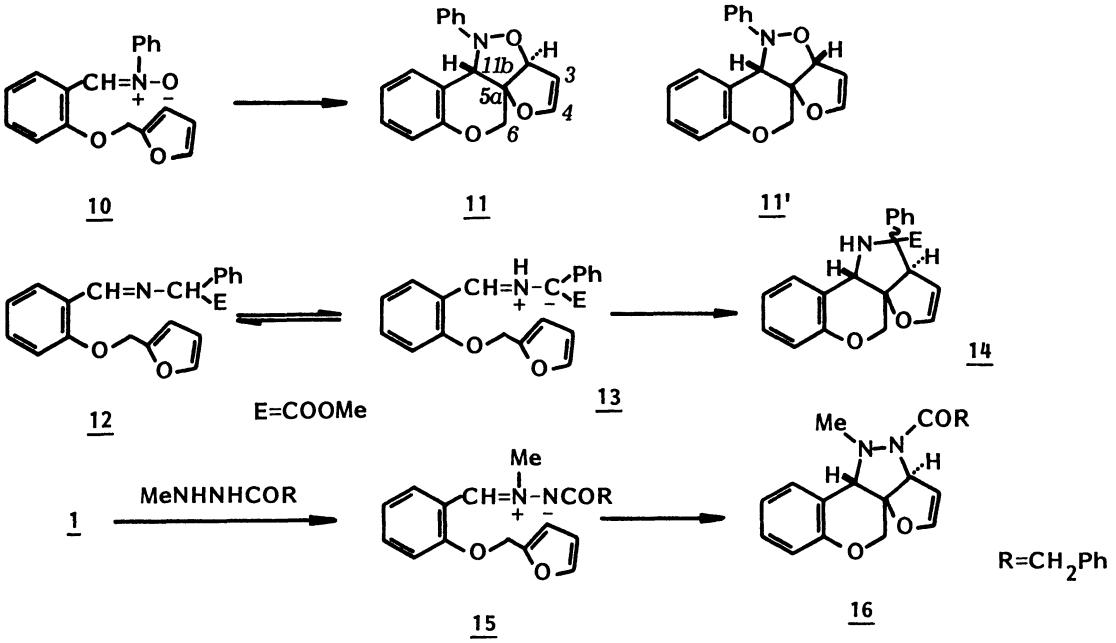
Scheme 1.

The intramolecular cycloaddition of o-(2-furylmethyloxy)benzonitrile N-phenylimine 8 has next been investigated. When a solution of the hydrazonyl chloride 7 in benzene was refluxed with triethylamine,[14] the expected cycloadduct, 2aH-2-phenylfuro[2,3-d][1]benzopyrano[3,4-c]pyrazole 9 (mp 167-168 °C), was obtained in 44% yield. Structural elucidation of 9 was again accomplished on the basis of spectral data.[15] On the other hand, irradiation of 3-phenyl-5-[o-(2-furylmethyloxy)-phenyl]tetrazole which is a precursor of 8 with a high-pressure mercury lamp in benzene afforded an isomer (mp 128-129 °C) of 9 in 30% yield. When irradiated under similar conditions, 9 was readily transformed into the isomer whose structure is not clear yet.[16]

Next, the intramolecular cycloaddition of systems bearing nitrone, azomethine ylide and imine dipoles has been investigated. On heating in toluene under reflux for 5 h, the nitrone 10[17] gave the cycloadduct, 2aH-1-phenyl-1,11b-dihydrofuro[2,3-d][1]benzopyrano[4,3-c]isoxazole (mp 108-109 °C), as the sole product in 76% yield. Although it is difficult to determine the stereochemistry from spectral data,[18] it seemed reasonable to assume that the cycloadduct is 11 in which 2a-H and 11b-H are trans, but not 11' which has a cis configuration on the basis of inspections of the transition states leading to cycloadducts[19] (Scheme 2).

Imines of α-amino acid esters undergo inter-[20] and intramolecular[21] cycloadditions via their 1,3-dipolar tautomers, azomethine ylides. Thus, the imine 12[22] was used as a precursor of the azomethine ylide 13. When a solution of 12 in xylene was refluxed for 30 h, an intramolecular cycloadduct, 1aH-2-methoxycarbonyl-2-phenyl-2a,11b-dihydrofuro[3,2-c][1]benzopyrano[3,4-d]pyrrole 14 (mp 196-198 °C), was isolated in 9% yield, together with a complex mixture of products. The spectral data of 14 were compatible with the assigned structure.[23] Although 2a-H and 11b-H were assumed to be trans like those in 11, the stereochemistry could not be fully solved.

Finally, we have investigated the intramolecular cycloaddition of an azomethine imine. When a solution of equivalents of the aldehyde 1 and 1-methyl-2-phenylacetylhydrazine in toluene was



Scheme 2.

refluxed with molecular sieve 4A for 7 h, the expected cycloadduct derived from the azomethine imine 15, 2aH-1-methyl-2-phenylacetyl-1,11b-dihydrofuro[3,2-c][1]benzopyrano[3,4-d]pyrazole 16 (mp 135 °C), was obtained in 60% yield. Structural elucidation of 16 was again accomplished on the basis of spectral data.[24)]

It should be emphasized that the last two reactions provide the first example for the 1,3-dipolar cycloadditions of azomethine ylide and imine dipoles to a furan ring. In contrast to the intermolecular 1,3-dipolar cycloadditions to furans which used in large excess,[1-7)] the intramolecular ones reported here which are entropically favored, proceeded smoothly to give the cycloadducts in fairly good yields.

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12) The aldoxime 2 was prepared from the aldehyde 1 and hydroxylamine: mp 110-111 °C; ^{1}H-NMR ($CDCl_3$) δ 8.42 (1H, s, CH=N); MS m/e 217 (M^+).
All new compounds in this communication gave satisfactory elemental analyses.

13) 4: ^{1}H-NMR ($CDCl_3$) δ 4.16, 4.55 (each 1H, d, CH_2, J=12.0 Hz), 5.37 (1H, t, 3-H, J=2.8 Hz), 5.54 (1H, d, 2a-H, J=2.8 Hz), 6.56 (1H, d, 4-H, J=2.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 70.22 (t), 84.95 (d, 2a-C), 93.82 (s, 5a-C), 101.27 (d, 3-C), 149.71 (d, 4-C), 154.40 (s, 11b-C); MS m/e 215 (M^+).

5: ^{1}H-NMR ($CDCl_3$) δ 3.97, 4.34 (each 1H, d, CH_2, J=12.0 Hz), 4.74 (1H, s, 2a-H), 4.93 (1H, d, 2b-H, J=9.0 Hz), 5.12 (2H, s, CH_2), 6.27 (1H, d, 5a-H, J=9.0 Hz); MS m/e 430 (M^+).

6: ^{1}H-NMR (DMSO-d_6) δ 4.13, 4.41 (each 1H, d, CH_2, J=12.0 Hz), 5.18 (1H, s, 2a-H), 5.22 (1H, d, 2b-H, J=9.0 Hz), 6.48 (1H, d, 5a-H, J=9.0 Hz); MS m/e 334 (M^+).

14) o-(2-Furylmethyloxy)benzaldehyde phenylhydrazone (mp 125-126 °C) was prepared from 1 and phenylhydrazine. After a solution of the hydrazone (1.0 mmol) and N-chlorosuccinimide (1.5 mmol) in carbon tetrachloride (20 mL) was heated at 45-50 °C for 1 h, the reaction mixture was filtered. The filtrate was concentrated in vacuo, and the obtained hydrazonyl chloride 7 without purification was heated with triethylamine (0.5 mL) in benzene (10 mL) under reflux for 2 h.

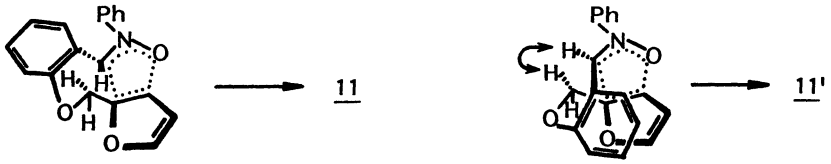
15) 9: ^{1}H-NMR ($CDCl_3$) δ 4.13, 4.57 (each 1H, d, CH_2, J=12.0 Hz), 5.03 (1H, dd, 2a-H, J=3.0, 1.0 Hz), 5.40 (1H, dd, 3-H, J=3.0, 3.0 Hz), 6.53 (1H, dd, 4-H, J=3.0, 1.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 68.40 (d, 2a-C), 69.81 (t), 91.39 (s, 5a-C), 99.39 (d, 3-C), 148.42 (d, 4-C), 154.23 (s, 11b-C); MS m/e 290 (M^+).

16) The spectral data of the isomer are as follows: ^{1}H-NMR ($CDCl_3$) δ 4.15, 4.36 (each 1H, d, CH_2, J=12.0 Hz), 5.25 (1H, d, J=3.0 Hz), 6.06 (1H, s), 6.51 (1H, d, J=3.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 62.00 (s), 71.69 (t), 98.99 (d), 101.39, 146.31 (each d), 155.17 (s); MS m/e 290 (M^+). Further investigation of the photoisomerization is in progress.

17) The nitrone 10 (mp 89-90 °C) was prepared from 1 and phenylhydroxylamine: ^{1}H-NMR ($CDCl_3$) δ 8.31 (1H, s, CH=N); MS m/e 293 (M^+).

18) 11: ^{1}H-NMR ($CDCl_3$) δ 4.10, 4.28 (each 1H, d, CH_2, J=12.0 Hz), 5.24 (1H, s, 11b-H), 5.24 (1H, dd, 2a-H, J=3.0, 0.8 Hz), 5.42 (1H, dd, 3-H, J=2.7, 3.0 Hz), 6.50 (1H, dd, 4-H, J=2.7, 0.8 Hz); ^{13}C-NMR ($CDCl_3$) δ 64.99 (t), 67.80 (d, 11b-C), 87.84 (d, 2a-C), 94.54 (s, 5a-C), 101.24 (d, 3-C), 154.96 (d, 4-C); MS m/e 293 (M^+).

19) The transition state A leading to 11 has more preferable geometry than B leading to 11' because of a significant steric interaction between the azomethine hydrogen and methylene in B.



A B

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22) The imine 12 was prepared from 1 and phenylglycine methylester: yellow oil; ^{1}H-NMR ($CDCl_3$) δ 5.12 (1H, s, CH), 8.67 (1H, s, CH=N); MS m/e 349 (M^+).

23) 14: IR (KBr) 3300 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.25 (1H, br, NH), 3.62 (3H, s), 3.72 (1H, dd, 2a-H, J=2.8, 1.5 Hz), 4.06, 4.44 (each 1H, d, CH_2, J=11.0 Hz), 4.01 (1H, br, 11b-H), 5.03 (1H, t, 3-H, J=2.8 Hz), 6.30 (1H, dd, 4-H, J=2.8, 1.5 Hz); ^{13}C-NMR ($CDCl_3$) δ 59.71 (d, 2a-C), 60.30 (d, 11b-C), 72.57 (t), 81.26 (s, 5a-C), 93.94 (s, 2-C), 100.75 (d, 3-C), 147.01 (d, 4-C); MS m/e 349 (M^+).

24) 16: ^{1}H-NMR ($CDCl_3$) δ 2.92 (3H, s), 3.44, 4.07 (each 2H, s), 4.53 (1H, 11b-H), 5.46 (2H, s and d, $J_{3,4}$=2.0 Hz), 6.34 (1H, d, 4-H, J=2.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 64.46 (t, 6-C), 66.05 (d, 11b-C), 69.51 (d, 2a-C), 93.58 (s, 5a-C), 104.21 (d, 3-C), 148.00 (d, 4-C); MS m/e 348 (M^+). The stereochemistry was assumed on the basis of inspections of transition states.[19]

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