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# FURAN DERIVATIVES AS 4 π -COMPONENTS IN [4 π + 2 π] CYCLOADDITION REACTIONS WITH 3-CYANOCYCLOPROPENE

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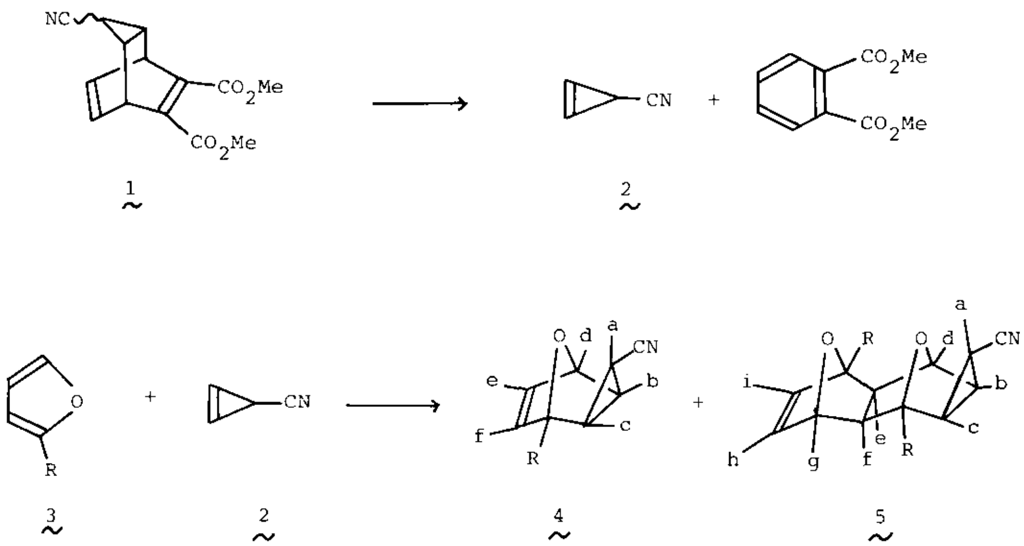
Abstract —— [4 π + 2π]-Type cycloaddition reactions of 2-methoxycarbonyl-, 2-acetyl-, and 2-methylfurans with 3-cyanocyclopropene generated in situ from tricyclo[3.2.2.$0^{2,4}$]nonadiene derivative afforded 8-oxatricyclo[3.2.1.$0^{2,4}$]oct-6-ene derivatives, which further reacted with the furans to give [4 π + 2π]-type cycloadducts.

While furan derivatives are known to be as active partners in cycloaddition reactions to yield many types of cyclic compounds interesting from pharmaceutical point of view,[1] the researches on the reactions with cyclopropenes seem to be few in number. One of the reason for this seems to be the tedious preparation methods and the unstabilities of cyclopropenes.[2] However, considering the high strain energies, cyclopropenes are expected to behave as active dienophiles to furans.[3] As a part of a series of our study on the addition reactions of heterocyclic compounds,[4] we investigated thermal addition reactions of furan derivatives with 3-cyanocyclopropene to obtain 1:1 and 2:1 cycloadducts. Here the results will be discussed.

3-Cyanocyclopropene (2) was generated accompanied by dimethyl phthalate through a thermal decomposition of an adduct (1) of 7-cyano-1,3,5-cycloheptatriene and dimethyl acetylenedicarboxylate.[5] The adduct (1) was reacted with four molar equivalent amounts of methyl 2-furancarboxylate (3a) at 200 °C for 48 h. Separation and purification of the reaction mixture using silica gel chromatography afforded 1:1 and 1:2 cycloadducts (4a) and (5a) in 8 and 47% yields, respectively.[6] The similar reaction using 2-acetylfuran (3b) at 200°C for 10 h gave the corresponding cycloadducts (4b) and (5b) in 41 and 14% yields, respectively. Under a prolonged heating (200°C for 16 h) no 1:1 adduct (4b) was obtained but

48% yield of a 1:2 adduct (5b) was afforded. Reaction of 2 with 2-methylfuran (3c) at 200°C for 24 h afforded a 1:2 adduct (5c) in 58% yield but no 1:1 adduct was detected.[7]



a:R=$CO_2Me$
b:R=COMe
c:R=Me

Figure 1

The structures of the adducts were deduced on the basis of their spectral properties and confirmed by the resemblance of them to those of the analogous compounds[8] as follows. The coupling constants between $H_a$ and $H_b/H_c$ in 4 and 5 shown in the Table 1 teach the anti-configurations of the cyano groups on the cyclopropane moieties.[9] The exo-conformation of the cyclopropane moieties is confirmed by the coupling constants (ca. 0 Hz) between the protons $H_b$ and $H_d$.[10] These facts determine the structures of 4a and 4b to be as shown in the Figure 1.

Table 1. Coupling Constants of 5a∼c in Hz.

| | $J_{ab}$ | $J_{ac}$ | $J_{bc}$ | $J_{de}$ | $J_{fg}$ | $J_{gh}$ | $J_{hi}$ |
|---|---|---|---|---|---|---|---|
| 5a | 3.5 | 3.5 | 7.0 | 0.0 | 0.0 | - | - |
| 5b | 3.3 | 3.3 | 6.8 | 0.0 | 0.0 | 1.6 | 5.4 |
| 5c | 2.7 | 2.7 | 7.0 | 0.0 | 0.0 | 2.0 | 6.6 |

Two possible planar structures (A and B in the Figure 2) can be proposed for the 1:2 adducts (5a-c). A measurement of nuclear Overhauser effect in the nmr spectra of 5c taught the structure (A) to be the correct one as follows. An irradiation of the protons of one of the two methyl groups ($Me_1$) caused a 10% enhancement of the signal of $H_g$ but the peak of $H_d$ showed no change. On the other hand, the irradiation of the other methyl protons ($Me_2$) resulted in a 11% glowth of the signal of $H_d$ but no effect was observed in the peak of $H_g$. This fact shows that $Me_1$ is located close to $H_g$ but not to $H_d$ and that $Me_2$ is near to $H_d$, supporting the plausible structure to be the type A.

Both the coupling constants $J_{de}$ and $J_{fg}$ are ca. 0 Hz, suggesting the dihedral angles between the corresponding protons to be both ca. 90°.[11] Four possible structures (I-IV) of the 1:2 adducts are depicted in the Figure 3. Dreiding models teach that the structure which has both dihedral angles between $H_d$ and $H_e$ and $H_f$ and $H_g$ as 90° is only IV. McCulloch et al. have reported that the coupling constants between $H_a$ and $H_b$ are 0 Hz in the structure (VI) but 4.5 Hz in V, well supporting the above consideration.[12] These facts conclude that the plausible structures of the 1:2 adducts are as shown in the Figure 1.

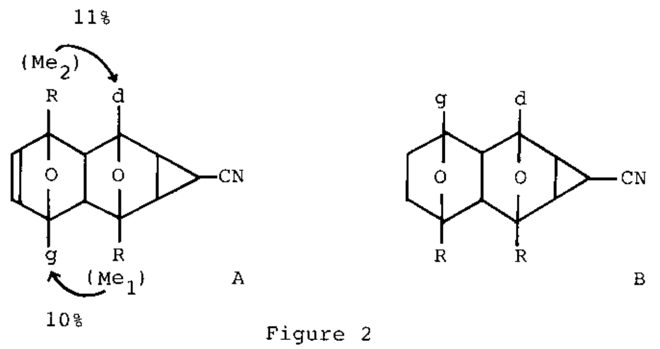


Figure 2

The reaction is considered to proceed via a thermally allowed [4 π + 2 π]-type cycloaddition to form the 1:1 adduts (4), which further reacted with furans to give the 1:2 adducts (5) again through a [4 π + 2 π]-type cycloaddition. The predominance of the exo-addition of the cyclopropene is explained by the absence of the secondary orbital interaction, which stabilizes the endo-type transition states,[13] resulting in a formation of the sterically stable exo-adducts. The anti-configuration of the cyano group is considered to be the result of the steric and electrostatic repulsions between the cyano group and the oxygen atom in the furan moieties.

In the transition states to form the 1:2 adducts also the secondary orbital interactions can not exist, thus the sterically most stable structure is considered to be formed. Dreiding models teach that in the transition states for the possible structures (I-IV), the most stable one is that for the structure (IV).

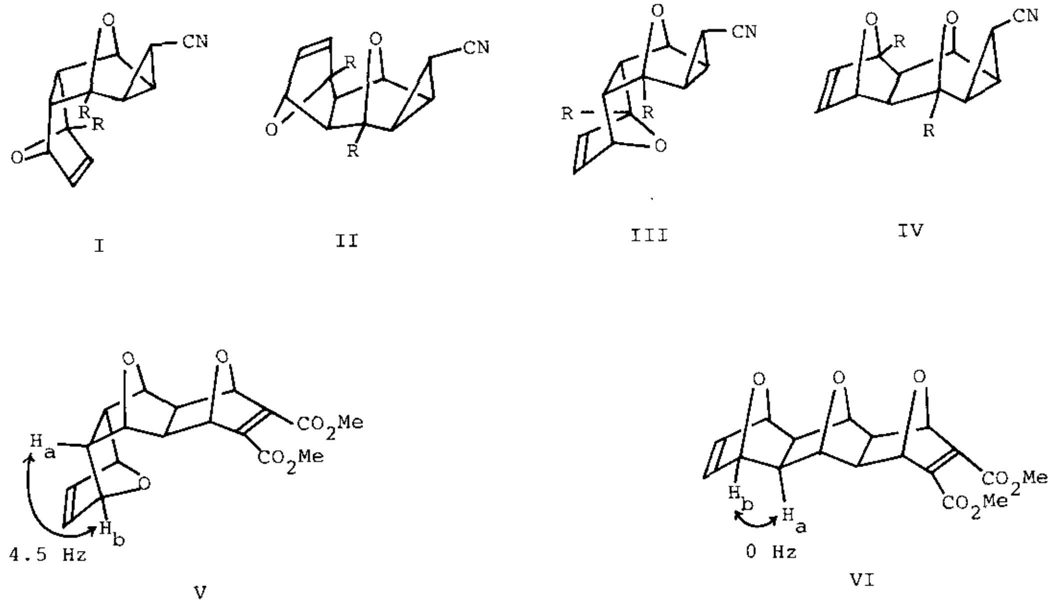


Figure 3

The above mentioned results show that both types of furans bearing electron-attracting substituents (**3a**, **3b**) and electron-donating one (**3c**) proceeded additions suggesting that the reactions are not so much influenced by substituents on the furans.[14,15]

EXPERIMENTAL

Melting points were recorded on a Yanagimoto Micro Melting Point Apparatus and are uncorrected. Nmr spectra were measured with a Varian XL 200 or a Hitachi R-20B spectrometers with tetramethylsilane as an internal standard. Uv and ir spectra were measured with a Hitachi 220A and JASCO A-102 spectrophotometers, respectively. Mass spectra were measured with a Hitachi M-52 or a Hitachi M-2000S spectrometers. Wakogel B-5 F and Wakogel C-200 were used for thin layer and column chromatography, respectively.

Reaction of 2-Methoxycarbonylfuran (3a) with 3-Cyanocyclopropene (2). A mixture of 3a (1500 mg, 12 mmol) and 1 (780 mg, 3 mmol) was heated at 200°C for 48 h in a sealed tube. The reaction mixture was chromatographed on silica gel to give recovered 3a (860 mg, benzene), a mixture (680 mg, benzene-ether 8:2) of dimethyl phthalate and a 1:1 adduct (4a), and a 1:2 adduct (5a) (210 mg, 47%, benzene-ether 1:1). The mixture was further separated by thin layer chromatography on silica gel using benzene-ether (1:1) as a developing solvent to give an oil 4a (23 mg, 8%, $R_f$=0.40).

4a: Hrms: 191.0584. Calcd for $C_{10}H_9NO_3$: 191.0583. Ms m/z (rel intensity): 191 ($M^+$, 50), 161 (50), 129 (100). Ir (oil): 3000, 2250, 1720 $cm^{-1}$. $^1$H Nmr ($CDCl_3$) $\delta$ ppm: 2.12 (dd, $J_{ab}$=3.1, $J_{bc}$=7.3 Hz, 1H, $H_b$), 2.35 (dd, $J_{ac}$=3.1, $J_{bc}$=7.3 Hz, 1H, $H_c$), 2.58 (dd, $J_{ab}$=$J_{ac}$=3.1 Hz, 1H, $H_a$), 3.92 (s, 3H, Me), 5.00 (br s, 1H, $H_d$), 6.68 (br s, 2H, $H_e$, $H_f$). $^{13}$C Nmr ($CDCl_3$) $\delta$ ppm: 14.0, 29.6, 31.2, 52.8, 77.8, 97.0, 117.6, 137.4, 138.4.

5a: Hrms: 317.0893. Calcd for $C_{16}H_{15}NO_6$: 317.0887. Ms m/z (rel intensity): 317 ($M^+$, 42), 284 (56), 197 (100). Ir (oil): 3010, 2950, 2240, 1750, 1740 $cm^{-1}$. $^1$H Nmr ($CDCl_3$) $\delta$ ppm: 1.95 (dd, $J_{ab}$=3.5, $J_{bc}$=7.0 Hz, 1H, $H_b$ ), 2.00 (dd, $J_{ab}$= $J_{ac}$=3.5 Hz, 1H, $H_a$), 2.52 (br s, 2H, $H_e$, $H_f$), 3.88 (s, 3H, Me), 3.89 (s, 3H, Me), 4.47 (br s, 1H, $H_d$), 4.96 (br s, 1H, $H_g$), 6.52 (br s, 2H, $H_h$, $H_i$). $^{13}$C Nmr ($CDCl_3$) $\delta$ ppm: 1.1, 25.5, 27.9, 52.7, 52.9, 53.6, 53.7, 75.5, 79.6, 84.1, 88.4, 118.6, 137.7, 137.8, 168.2, 168.9.

Reaction of 2-Acetylfuran (3b) with 3-Cyanocyclopropene (2). A mixture of 3b (1210 mg, 12 mmol) and 1 (780 mg, 3 mmol) was heated at 200°C for 10 h in a sealed tube. The reaction mixture was chromatographed on silica gel to give recovered 3b (770 mg, 64%, benzene), dimethyl phthalate (210 mg, 35%, benzene), a mixture of recovered 1, dimethyl phthalate, and a 1:1 adduct (4b) (330 mg, benzene-ether 8:2), and a mixture of recovered 1 and a 1:2 adduct (5b) (270 mg, benzene-ether 7:3). The former mixture was further separated by thin layer chromatography on silica gel using chloroform-benzene (9:1) as a developing solvent to give recovered 1 (90 mg, $R_f$=0.17), dimethyl phthalate (33 mg, 6%, $R_f$=0.28), and an oil 4b (170 mg, 41%, $R_f$=0.24). The latter mixture was also separated by thin layer chromatography on silica gel using benzene-ether (1:1) as a developing solvent to give recovered 1 (77 mg, $R_f$=0.68) and an oil 5b (90 mg, 14%, $R_f$=0.41).

**4b**: Hrms: 175.0629. Calcd for $C_{10}H_9NO_2$: 175.0632. Ms m/z (rel intensity): 175 ($M^+$, 61), 145 (100), 131 (51). Ir (oil): 3010, 2950, 2240, 1720 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ ppm: 2.10 (dd, $J_{ab}$=3.0, $J_{bc}$=6.8 Hz, 1H, $H_b$), 2.28 (dd, $J_{ac}$=3.0, $J_{bc}$=6.8 Hz, 1H, $H_c$), 2.29 (s, 3H, Me), 2.68 (dd, $J_{ab}$=$J_{ac}$=3.0 Hz, 1H, $H_a$), 4.99 (br s, 1H, $H_d$), 6.64 (br s, 2H, $H_e$, $H_f$). $^{13}C$ Nmr ($CDCl_3$) $\delta$ ppm: 14.1, 26.8, 29.5, 30.8, 77.8, 91.3, 118.0, 137.2, 138.3.

**5b**: Hrms: 285.0998. Calcd for $C_{16}H_{15}NO_4$: 285.0995. Ms m/z (rel intensity): 285 ($M^+$, 14), 242 (32), 214 (100), 131 (79). Ir (oil): 3010, 2950, 2240, 1710 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ ppm: 1.82 (dd, $J_{ab}$=$J_{ac}$=3.3 Hz, 1H, $H_a$), 1.98 (dd, $J_{ab}$=3.3, $J_{bc}$=6.8 Hz, 1H, $H_b$), 2.12 (dd, $J_{ac}$=3.3, $J_{bc}$=6.8 Hz, 1H, $H_c$), 2.35 (s, 3H, Me), 2.36 (s, 3H, Me), 2.46 (br s, 2H, $H_e$, $H_f$), 4.39 (br s, 1H, $H_d$), 4.86 (d, $J_{gh}$=1.6 Hz, 1H, $H_g$), 6.42 (d, $J_{hi}$=5.4 Hz, 1H, $H_i$), 6.48 (dd, $J_{gh}$=1.6, $J_{hi}$=5.4 Hz, 1H, $H_h$). $^{13}C$ Nmr ($CDCl_3$) $\delta$ ppm: 1.6, 25.4, 27.7, 28.1, 28.6, 53.1, 53.4, 75.3, 79.0, 89.3, 94.1, 118.5, 137.8, 138.0.

Reaction of 2-Methylfuran (**3c**) with 3-Cyanocyclopropene (**2**). A mixture of **3c** (980 mg, 12 mmol) and **1** (780 mg, 3 mmol) was heated at 200°C for 24 h in a sealed tube. The reaction mixture was chromatographed on silica gel to give dimethyl phthalate (270 mg, 45%, ethyl acetate-n-hexane 1:19), recovered **1** (570 mg, ethyl acetate-n-hexane 3:7), and an oil containing mainly a 1:2 adduct **5c** (350 mg, ethyl acetate-n-hexane 7:3). The oil was further purified by thin layer chromatography on silica gel using ethyl acetate-n-hexane (3:1) as a developing solvent to give crystals **5c** (110 mg, 58%, $R_f$=0.37).

**5c**: mp 132.5-133.5°C. Hrms: 229.1105. Calcd for $C_{14}H_{15}NO_2$: 229.1107. Ms m/z (rel intensity): 229 ($M^+$, 100), 211 (16), 185 (27), 157 (51). Ir (KBr): 3050, 2950, 2240 $cm^{-1}$. $^1H$ Nmr ($CDCl_3$) $\delta$ ppm: 1.50 (s, 3H, Me), 1.59 (s, 3H, Me), 1.69 (dd, $J_{ab}$=$J_{ac}$=2.7 Hz, 1H, $H_a$), 1.72 (dd, $J_{ac}$=2.7, $J_{bc}$=7.0 Hz, 1H, $H_c$), 1.81 (dd, $J_{ab}$=2.7, $J_{bc}$=7.0 Hz, 1H, $H_b$), 2.01 (br s, 2H, $H_e$, $H_f$), 4.37 (br s, 1H, $H_d$), 4.83 (d, $J_{gh}$=2.0 Hz, 1H, $H_g$), 6.22 (d, $J_{hi}$=6.6 Hz, 1H, $H_i$), 6.39 (dd, $J_{gh}$=2.0, $J_{hi}$=6.6 Hz, 1H, $H_h$). $^{13}C$ Nmr ($CDCl_3$) $\delta$ ppm: 0.5, 14.7, 15.4, 26.9, 29.6, 54.2, 55.2, 73.6, 77.9, 82.1, 85.8, 120.2, 137.7, 141.3.

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6. All the yields were calculated on the basis of the starting materials really consumed.
7. Despite repeated experiments, the sole formation of the 1:1 adducts (**4**) was not realized probably because of the similar or bigger reactivity of **4** to furans (**3**) than that of 3-cyanocyclopropene (**2**) under the reaction conditions.
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14. Contrary to the present reslts, in the reactions of **2** with pyrrole deriva-

tives, a remarkable substituent effects have been observed. Only pyrroles having electron-attracting groups at the 1-position gave the cycloadducts. These facts suggest that the electrons on the nitrogen atom of the pyrroles are very mobile, and contrary to this, that the electronic structures of the furans are not so much influenced by substituents.

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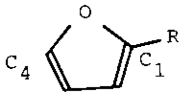
15. The MNDO molecular orbital calculations gave the results depicted in the Table 2, which shows that the energy differences between HOMO of **3** and LUMO of **2** are almost same as those of between LUMO of **3** and HOMO of **2**. The values, the squares of the coefficients of the frontier orbitals at the reacting points/the energy differences in these frontier orbitals, were caluculated as shown in the Table 3, which are more favorable for the combination of LUMO of **2** and HOMO of **3**. These values, however, teach that any considerable differences in the reactivities can not be found.

Table 2. Coefficients and Energy Levels of the Frontier Orbitals of the Reaction Sites

| Compounds | Frontier Orbitals | Energies | Coefficients $C_1$ | $C_4$ |
|---|---|---|---|---|
| 2-Methoxycarbonylfuran (**3a**) | HOMO | -9.614 | -0.5729 | 0.6131 |
| | LUMO | -0.352 | 0.4604 | 0.4643 |
| 2-Acethylfuran (**3b**) | HOMO | -9.481 | -0.5742 | 0.6080 |
| | LUMO | -0.291 | 0.4156 | 0.4457 |
| 2-Methylfuran (**3c**) | HOMO | -9.025 | -0.5770 | 0.5924 |
| | LUMO | 0.553 | 0.5419 | 0.5772 |
| | | | $C_1$ | $C_2$ |
| 3-Cyanocyclopropene (**2**) | HOMO | -10.679 | 0.6567 | 0.6567 |
| | LUMO | 0.378 | -0.7044 | 0.7044 |

Table 3. Values of $S(C_rC_s)^2$/(LUMO-HOMO)

| Interaction | Values |
|---|---|
| (**2**) LUMO - (**3a**) HOMO | 0.035 |
| (**2**) LUMO - (**3b**) HOMO | 0.035 |
| (**2**) LUMO - (**3c**) HOMO | 0.036 |
| (**3a**) LUMO - (**2**) HOMO | 0.018 |
| (**3b**) LUMO - (**2**) HOMO | 0.015 |
| (**3c**) LUMO - (**2**) HOMO | 0.024 |



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