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THERMAL $[4\pi + 2\pi]$-TYPE CYCLOADDITION REACTIONS OF PYRROLE DERIVATIVES WITH 3-CYANOCYCLOPROPENE GENERATED IN SITU

Katsuhiro Saito,* Kazuaki Ito, and Kensuke Takahashi
Department of Applied Chemistry, Nagoya Institute of Technology,
Gokiso-cho, Showa-ku, Nagoya 466, Japan

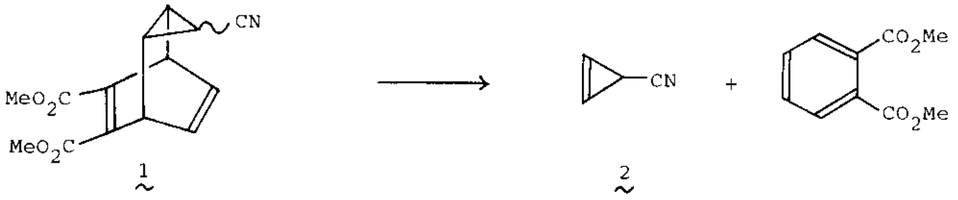
Abstract — Thermal reactions of 3-cyanocyclopropene with 1-methoxycarbonyl-, 1-benzoyl-, and 1-phenylpyrroles afforded $[4\pi + 2\pi]$-type cycloaddition products, while 1-methyl- and 1-methyl-3-acetylpyrroles did not give any adducts. The adduct of 1-benzoylpyrrole existed as a mixture of two rotamers because of the hindered rotation of the carbamate group.

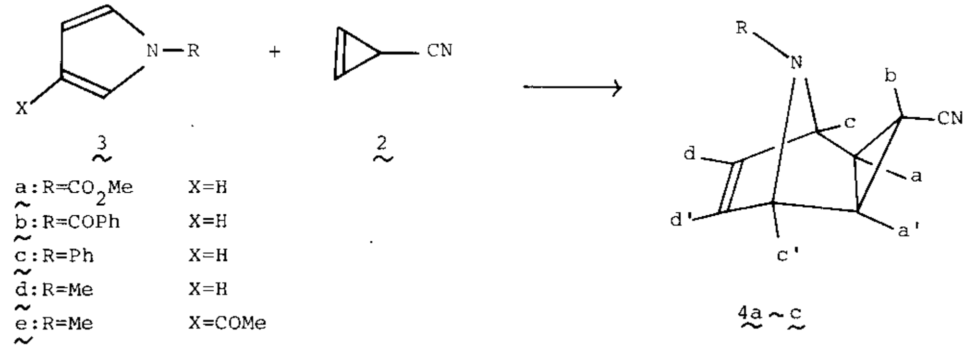
Because of a contribution of 6π-electrons aromatic structure, pyrroles are known to have a tendency to undergo substitution reactions rather than addition reactions.[1,2] Much attention has been paid to the reactions of pyrroles with olefins from the viewpoint of the synthetic utility for medicinally interesting compounds and the elucidation of the electronic natures of pyrroles.[1,2,3] While cyclopropenes behave as reactive dienophiles and are known to be efficient building units for cyclopropane moieties, we are unaware of any reports which have documented the reactions of pyrroles with cyclopropenes.[4]

Several papers have reported that cyclopentadiene reacted with cyclopropenes to give endo-type $[4\pi + 2\pi]$ cycloadducts predominantly,[5] while furans mainly afforded exo-type $[4\pi + 2\pi]$ cycloadducts.[6] We investigated the reactions of pyrroles with 3-cyanocyclopropene in order to clarify the following points; whether pyrroles undergo addition reactions with 3-cyanocyclopropenes or not; whether the additions proceed in an exo- or endo-manner. Here the results are reported.

3-Cyanocyclopropene (2) was generated in situ by Alder-Rickert cleavage of the adduct of 7-cyanotropilidene and dimethyl acetylenedicarboxylate (1).[7] A mixture of 1 and ten-molar equivalent amount of 1-methoxycarbonylpyrrole (3a) was heated in a sealed tube at 200°C for 20 h. The reaction mixture was separated and purified with thin-layer chromatography on silica gel to give the adduct **4a** in 27.6% yield. The similar reaction using 1-benzoylpyrrole (**3b**) afforded the corresponding adduct **4b** in 10.0% yield. The reaction with 1-phenylpyrrole (**3c**) under the similar reaction conditions resulted in the quantitative recovery of 3c, however, the reaction at the elevated temperature (280°C) gave the corresponding adduct **4c** in 13.0% yield. The reactions using 1-methylpyrrole (**3d**) and 1-methyl-3-acetylpyrrole (**3e**) yielded no addition products and resulted in the quantitative recoveries of **3d** and **3e**, respectively, even in the reactions at 280°C.[8]

The structures of the adducts were deduced on the basis of their spectral, especially nmr spectral properties and confirmed by comparison of these properties with those of the analogous compounds.[5,6] The *anti*-configuration of the cyano group on the cyclopropane ring is confirmed by the coupling constant values (2.4 or 2.8 Hz) between the vicinal protons H_b and H_a/H_a'.[9] The chemical shift values of the methine protons H_b (CO_2CH_3: 2.51 ppm, COPh: 2.49 ppm, Ph: 2.94 ppm) are influenced by the substituents on the nitrogen atom of the pyrrole moieties suggesting that H_b and the nitrogen atom are located closely each other indicating the cyclopropane moiety to be in an *exo*-configuration. The *exo*-cofigura-

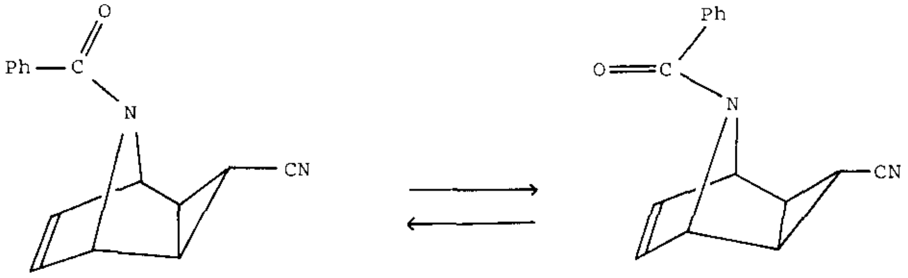




a:R=CO_2Me X=H
b:R=COPh X=H
c:R=Ph X=H
d:R=Me X=H
e:R=Me X=COMe

tion was further confirmed by the coupling constant values (ca. 0 Hz) between the bridgehead protons H_c and H_a/H_a'.[10]

In the nmr spectrum of 4b, the signals of the bridgehead protons (H_c and H_c') and the olefinic protons (H_d and H_d') are split into two pairs of signals. This fact is considered to be the result of the hindered rotation around the C-N bond of the carbamate group as documented in the analogous compounds.[11] In the nmr spectrum of 4b measured in toluene-d_8 at the elevated temperatures these phenomena disappeared to coalesce to the peaks at 4.44 ppm (53.0 °C, H_c) and 5.93 ppm (59.0 °C, H_d), respectively.



4b

The reaction is considered to proceed *via* a thermally allowed [4π + 2π]-type cycloaddition process, in which pyrroles act as 4π-components.[12] The dominant formation of the *exo*-type adduct 4 is explained by the steric repulsion, which is bigger in the transition state of the *endo* adducts[5] because the secondary orbital interaction which stabilizes the *endo*-form transition state can not be expected in this case.[12] The *anti*-configuration of the cyano group on the cyclopropane ring is also attributable to the steric repulsion between the cyano group and the nitrogen atom which is expected in the transition state leading to the *syn*-configuration adducts.

It is known that the aromaticity of pyrroles are influenced by the substituents as follows. The electrn releasing groups on the nitrogen atoms strengthen the aromaticity of the pyrroles, which undergo mainly substitution reactions but not addition reactions. On the contrary, the electron attracting groups weaken the aromaticity of the pyrroles, which react as 4π-components in [4π + 2π]-type cycloaddition reactions.[1,2,3]

The low reactivity of 3c and the failure of the formation of the adducts of 3d and 3e are considered to be the result of the bigger aromaticity of these pyrroles comparing to the other pyrroles (3a,b) because of the electron releasing effect of the phenyl and methyl groups of 3c-e.[1,2,3]

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EXPERIMENTAL

Melting points were recorded on a Yanagimoto micro melting point apparatus and were uncorrected. Nmr spectra were measured with a Varian XL 200 or Hitachi R-20B spectrometers with tetramethylsilane as an internal standard. Ir and uv sectra were measured with a JASCO A-102 and Hitachi 200-10 spectrophotometers, respectively. Mass spectra were measured with a Hitachi M-52 or JMX-DX300 spectrometers. Wako gel B5F and Wako gel C200 were used for thin-layer and column chromatography, respectively.

Reaction of 1-Methoxycarbonylpyrrole (3a) with 3-Cyanocyclopropene (2). A mixture of 3a (2206 mg, 17.6 mmol) and 1 (479 mg, 1.85 mmol) was heated at 200°C for 20 h in a sealed tube. The reaction mixture was chromatographed on silica gel column to give the recovered 3a (1756 mg, 79.6%, n-hexane-benzene 7:3), dimethyl phthalate (178 mg, 49.6%, benzene-ether 8:2), and a mixture of dimethyl phthlate, 1, and 4a (202 mg, benzene-ether 7:3). The mixture was subjected to thin-layer chromatography on silica gel using benzene-ether (7:3) as a developing solvent to give dimethyl phthalate (31 mg, 8.6%, R_f=0.75), 1 (63 mg, 13.1%, R_f=0.63), and 4a (97 mg, the total yield was 27.6%, R_f=0.44).

4a: Hrms: 190.0753. Calcd for $C_8H_{10}N_2O_2$: 190.0743. Mass m/z (rel intensity): 190 (M^+, 11), 149 (31), 140 (58), 138 (100). Ir (oil): 3020, 2980, 2250, 1720 cm^{-1}. ^{1}HNmr ($CDCl_3$) δ ppm: 1.94 (d, 2H, H_a, H_a', J=2.4 Hz), 2.51 (t, 1H, H_b, J=2.4 Hz), 3.63 (s, 3H, Me), 4.80 (bs, 2H, H_c, H_c'), 6.60 (bs, 2H, H_d, H_d'). J_{ab}=2.4 Hz, J_{ac}=ca. 0.0 Hz, J_{cd}=ca. 0.0 Hz.

Reaction of 1-Benzoylpyrrole (3b) with 3-Cyanocyclopropene (2). A mixture of 3b (1007 mg, 6 mmol) and 1 (766 mg, 3 mmol) was heated at 200°C for 24 h in a sealed tube. The reaction mixture was chromatograhed on silica gel column to give the recovered 3b (831 mg, 82.5%, benzene), dimethyl phthalate (574 mg, 100.0%, benzene-ethe , 9:1) and an oil containing 4b (125 mg), which was further purified by thin-layer chromatography on silica gel using ether-benzene (2:1) as a developing solvent to give 4b (70 mg, 10.0%, R_f=0.50).

4b: Hrms: 236.0940. Calcd for $C_{15}H_{12}N_2O$: 236.0934. Mass m/e (rel intensity): 236 (M^+, 10), 131 (12),105 (100). Ir (oil): 3050, 2250, 1655, 1600 cm^{-1}. ^{1}HNmr ($CDCl_3$) δ ppm: 2.04 (d, 2H, H_a, J=2.8 Hz), 2.49 (t, 1H, H_b, J=2.8 Hz), 4.80 (bs, 1H, H_c or H_c'), 5.25 (bs, 1H, H_c' or H_c), 6.49 (bs, 1H, H_d or H_d'), 6.80 (bs, 1H, H_d' or H_d), 7.40-7.60 (m, 5H, Ph).

Reaction of 1-Phenylpyrrole (3c) with 3-Cyanocyclopropene (2). A mixture of 3c (4294 mg, 30 mmol) and 1 (774 mg, 3 mmol) was reacted at 280°C for 10 min in a sealed tube. The reaction mixture was filtered to remove the recovered 3c (2393 mg, 55.7%). The filtrate was chromatograhed on silica gel column to give the recovered 3c (756 mg, 17.6%, n-hexane-benzene 6:4), a mixture of 4c and dimethyl phthalate (280 mg, benzene), and the recovered 1 (405 mg, 52.3%, benzene-ether 8:2). The mixture was further separated with thin-layer chromatography on silica gel using benzene as a developing solvent to give 4c (81 mg, 13.0%, R_f=0.56) and dimethyl phthalate (170 mg, 29.3%, R_f=0.24).

4c: Hrms: 208.1000. Calcd for $C_{14}H_{12}N_2$: 208.0999. Mass m/z (rel intensity): 208 (M^+, 100), 207 (62), 181 (20). Ir (oil): 3060, 2250, 1600 cm^{-1}. ^{1}HNmr ($CDCl_3$) δ ppm: 1.97 (d, 2H, H_a, H_a', J=2.4 Hz), 2.94 (t, 1H, H_b, J=2.4 Hz), 4.58 (bs, 2H, H_c, H_c'), 6.36 (bs, 2H, H_d, H_d'), 6.60-7.30 (m, 5H, Ph).

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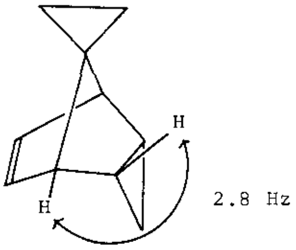
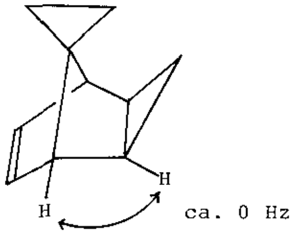
The coupling constant values between the cyclopropane protons and the bridgehead protons of the analogous compounds (endo- (A) and exo-type compound (B)) are known to be as shown bellow.



A



B

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