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TWO TRICYCLIC ADDUCTS FROM CONSECUTIVE ADDITIONS OF DIMETHYL ACETYLENE-DICARBOXYLATE TO 2,4-DI-*t*-BUTYL-3a,5a-DIHYDRO-3*H*-CYCLOBUTA[*b*]PYRROLE: A NOVEL FORMATION OF CYCLOBUTA[1',2'-*f*]PYRROLO-[1,2-*b*]OXAZINE DERIVATIVE

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Abstract - The tricyclic heterocycles (**2**) and (**3**) were newly synthesized by the addition reaction between 2,4-di-*t*-butyl-3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrrole (**1**) and dimethyl acetylenedicarboxylate (DMAD). The structures were confirmed by the X-Ray structural analyses, and the pathway affording them was also proposed.

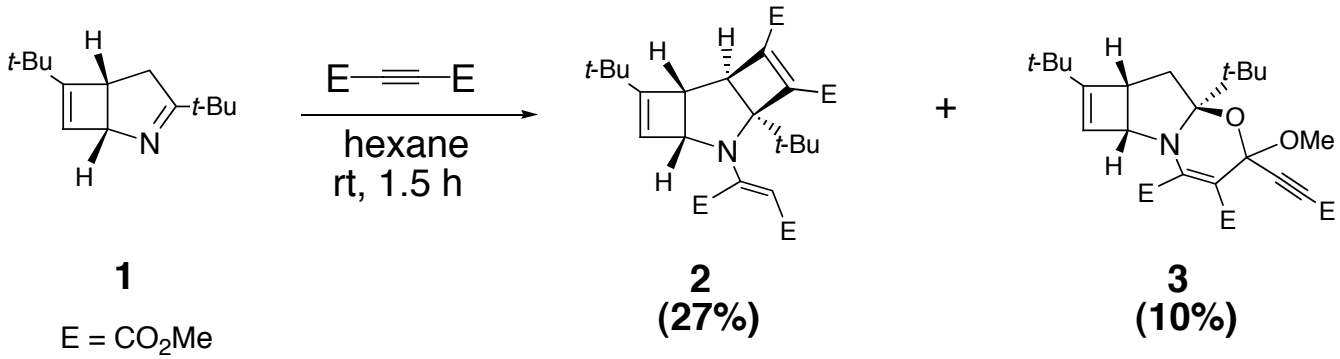
The isomerization between *N*-protected 1*H*-azepine and 3a,5a-dihydro-1*H*-cyclobuta[*b*]pyrrole has been well established.[1] We have already reported the synthesis of 2,4-di-*t*-butyl-3a,5a-dihydro-3*H*-cyclobuta-[*b*]pyrrole (**1**) from photochemical reaction of *N*-methoxycarbonyl-2,5-di-*t*-butyl-1*H*-azepine, followed by a demethoxycarbonylation using alcoholic-alkali.[2] The dihydro-3*H*-cyclobuta[*b*]pyrrole (**1**) found to be a good precursor for the dialkyl-3*H*-azepine, because the thermal reaction of **1** in benzene at 150°C gave 2,5-di-*t*-butyl-3*H*-azepine as a single product *via* a disrotatory cyclobutene ring opening.[2] According to our knowledge, the chemistry of 3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrrole system has been rarely explored. In order to investigate the chemistry of this ring system, the reaction with dimethyl acetylenedicarboxylate (DMAD) was examined.

Recently, the cycloaddition reaction of heterocyclic diene with DMAD is widely employed for the synthesis of bicyclic heterocycles.[3] Additionally, the reactions of a variety of heterocycles such as imidazole and 4,5-dihydrocyclobuta[*c*]pyrrole derivatives with DMAD have been also developed as a novel synthetic method for 7*H*-pyrrolo[1,2-*a*]imidazoles and azepine derivative, respectively.[4] We found that the consecutive addition reaction of DMAD with **1** under mild conditions gave tricyclic heterocycles, 3-(1',2'-

bismethoxycarbonylvinyl)-2a,5-di-*t*-butyl-1,2-bismethoxycarbonyl-2a,3a,5a,5b-tetrahydropyrrol[2,3:4,5]-bicyclobutene (**2**) and 7,8a-di-*t*-butyl-2-methoxy-3,4-bismethoxycarbonyl-2-methoxycarbonylethynyl-5a,7a,8,8a-tetrahydrocyclobuta[1',2'-*f*]pyrrolo[1,2-*b*]oxazine (**3**). We report here the detailed results of the reaction and the structural features of obtained tricyclic heterocycles.

A hexane solution of the cyclobuta[*b*]pyrrole (**1**) and an excess DMAD was stirred for 1.5 h at ambient temperature. After the solvent was removed *in vacuo*, subsequent chromatography on silica gel gave colorless solids (**2**) and (**3**) in 27 and 10% yields, respectively. (Scheme 1)

MS (FAB) data in *m*-nitrobenzyl alcohol for **2** (*m/z* 490.3 (M^++1, 100%)) and **3** (*m/z* 490.3 (M^++1, 7%)) suggested the reaction is 2 : 1 addition of DMAD to the substrate (**1**). The consecutive additions of DMAD to the substrate was also confirmed by the ^{1}H NMR spectral data for these adducts showed respective four singlet methyl peaks at δ 3.60, 3.80, 3.86 and 3.88 for **2** and δ 3.55, 3.71, 3.78 and 3.85 for **3**. In the IR spectrum the ethynyl absorption of **3** characterically appeared at 2200 cm^{-1}.



Scheme 1

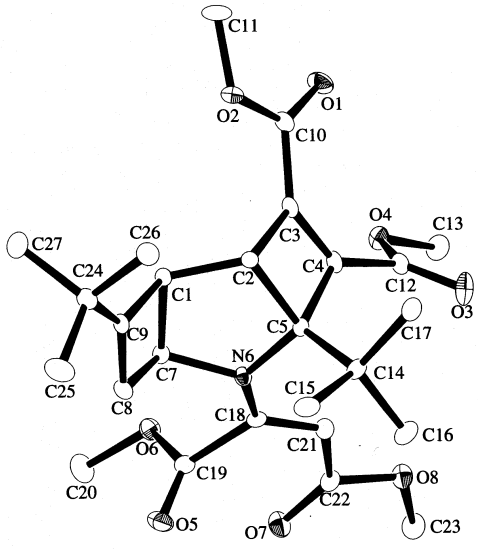


Figure 1. The ORTEP drawing of the molecular structure of **2** as 30% probability ellipsoids

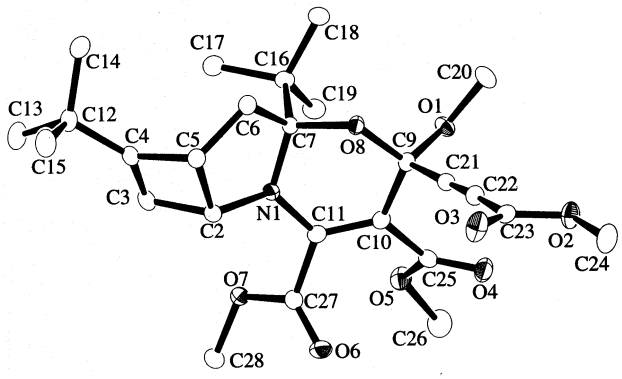


Figure 2. The ORTEP drawing of the molecular structure of **3** as 50% probability ellipsoids

The X-Ray study was performed to elucidate the structure of these 2 : 1 adducts between DMAD and **1**. The single crystal suitable for the X-Ray structural analysis in each case was obtained by recrystallization from hexane. The tricyclic structures are shown in Figures 1 and 2 along with the appropriate atom-labeling.

In the crystal structure of **2**, the two of cyclobutene rings have anti orientation. In the case of **3**, cyclobuta[1',2'-*f*]pyrrolo[1,2-*b*]oxazine is a new ring system. The oxazine ring (N1, C7, O8, C9, C10, C11) has almost an envelope conformation. The dihedral angle between planes 1 (C7/O8/N1) and 2 (N1/O8/C9/C10/C11) is 143.64∞. In the case of least square plane of plane 2, mean deviation and X^2 are 0.0431 and 6966.0. For the space group, $Pna2_1$ for **2** and $P2_1/n$ for **3** exhibits racemic crystals owing to the racemate of precursor (**1**), which was formed by the photoreaction of *N*-methoxycarbonyl-2,5-di-*t*-butyl-1*H*-azepine.[2]

We wish to propose a mechanism which leads to the tricyclic compounds (**2**) and (**3**) (Scheme 2). The formation of a common intermediate (**4**) is rationalized by an ene reaction[5] between DMAD and **1**. In general, a orbital interactions for an ene reaction have been known as the interaction of the HOMO of allyl compounds and the LUMO of an olefin.[5a] According to the AM1 calculations[6] of the substrate (**1**), the NHOMO, which is assignable to the azaallyl moiety on the five-membered ring, shows preferable in-phase interaction with the LUMO of DMAD on the ene reaction. The orbital profiles and coefficients are illustrated in Figure 3.

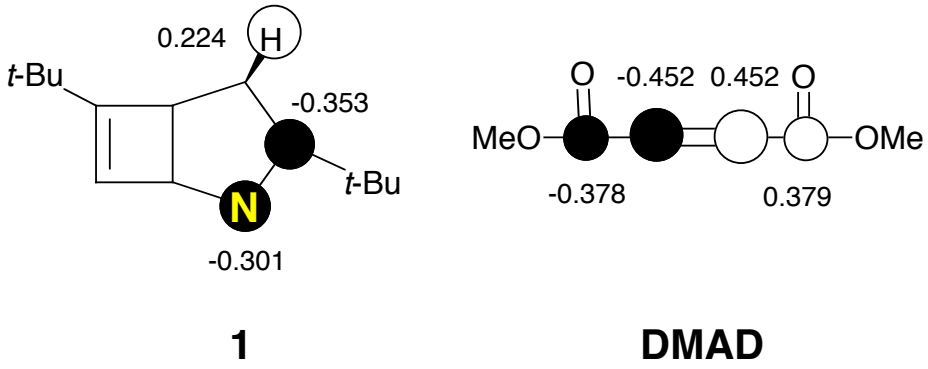
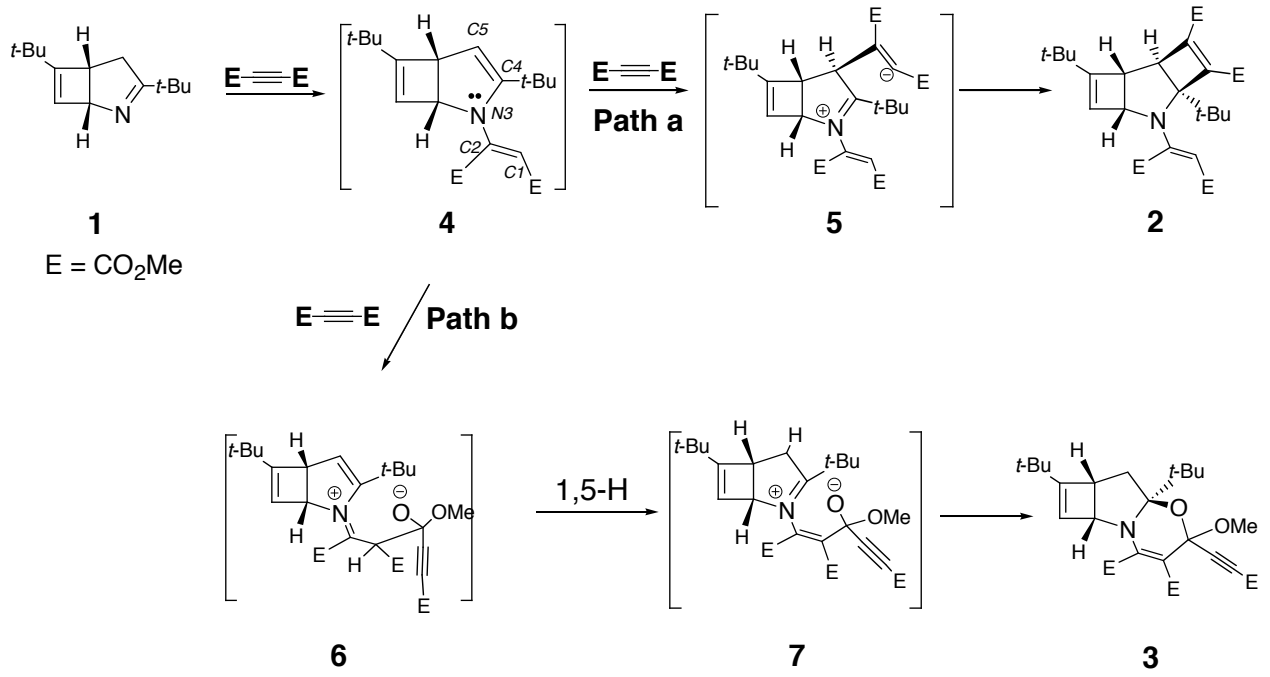


Figure 3. AM1[6] caluculated HOMO-1 of 1, and LUMO of DMAD

Then the nucleophilic Michael-type addition at the *C5* carbon, the β-position of the enamine part with a second DMAD, occurs to form a charge-separated intermediate (**5**). Tricyclic ring is completed by a nucleophilic cyclization between the resulting anion and the iminium cation part of **5** (path a) to give the tricyclic compound (**2**). The formation of **2** from **4** can be also considered as a thermal [2+2] cycloaddition reaction.[7] On the other hand, nucleophilic attack from the carbon *C1*, which is the other enamine β-carbon of the intermediate (**4**), on the carbonyl carbon of DMAD, and a subsequent [1,5] hydrogen shift results in the formation of charge separated intermediate (**7**) *via* (**6**). Further intramolecular nucleophilic cyclization between anionic oxygen and iminium carbon gives tricyclic adduct (**3**) (path b). Interestingly, formation of oxazine 6-membered ring was rare in the reaction of heterocyclic imine C=N derivative with DMAD. The difference of nucleophilicity between the carbon *C5* and *C1* of the intermediate (**4**) was ascribed for the formation of these two regioisomeric adducts with a 3:1 ratio.



Scheme 2

EXPERIMENTAL

The melting points are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz, and the ^{13}C NMR spectra were recorded at 67 MHz in $CDCl_3$ solution. IR spectra were recorded on a JASCO FT-IR 5000 spectrophotometer. Electronic spectra were measured in ethyl alcohol. MS spectrometry was performed on a JEOL JMS-DX300 mass spectrometer coupled to a JMA-3100 data analysis system. The high-resolution MS spectral data were obtained on a Hewlett-Packard 5890 SERIES II mass spectrometer. Elemental analyses were performed by the Microanalytical Laboratory centre at the Department of Chemistry, Faculty of Science, Kyushu University. The computations was performed with MOPAC program, graphically facilitated CAChe ver. 3.22 from Fujitsu Limited.

Reaction of 2,4-Di-*tert*-butyl-3a,5a-dihydro-3*H*-cyclobuta[*b*]pyrrole (1) with DMAD

A solution of **1** (94 mg, 0.46 mmol) and an excess of DMAD (647 mg, 4.56 mmol) in hexane (5 mL)was stirred for 1.5 h at ambient temperature. The reaction mixture, which was concentrated under reduced pressure and purified by column chromatography (5% to 20% EtOAc/hexane) over silica gel, gave **2** (61 mg) in 27% yield and **3** (20 mg) in 10% yield as colorless solids. Both **2** and **3** were recrystallized from hexane to give colorless needles in both cases.

3-(1',2'-Bismethoxycarbonylvinyl)-2a,5-di-*t*-butyl-1,2-bismethoxycarbonyl-2a,3a,5a,5b-tetrahydropyrrol[2,3:4,5]bicyclobutene (**2**): Colorless needles; mp 143-145°C. ^{1}H NMR δ = 5.83 (d, *J* = 1.5 Hz, 1H), 5.00 (s, 1H), 4.73 (d, *J* = 4.0 Hz, 1H); 3.88 (s, 3H), 3.86 (s, 3H), 3.80 (s, 3H), 3.60 (s, 3H), 3.55 (d, *J* = 1.5 Hz, 1H), 3.50 (td, *J* = 4.0 and 1.5 Hz, 1H), 1.15 (s, 9H), 1.08 (s, 9H); ^{13}C NMR δ = 167.7 (s), 166.5 (s), 164.3 (s), 161.2 (s), 159.8 (s), 153.1 (s), 147.7 (s),

140.1 (s), 130.2 (d), 91.6 (d), 88.9 (s), 69.2 (d), 52.8 (q), 52.5 (q), 52.1 (q), 50.9 (q), 49.5 (d), 43.6 (d), 37.9 (s), 33.3 (s), 29.4 (q), 27.5 (q); IR (KBr) 2954, 1723, 1657 cm^{-1}; MS (FAB) *m/z* 490 (M^+; 100%), 430 (56), 57 (16); UV λmax (EtOH) 288 (log ε 4.27) nm. Anal. Calcd for $C_{26}H_{35}NO_8$: C, 63.79; H, 7.21; N, 2.86. Found: C, 63.90; H, 7.25; N, 2.89.

Crystal Data: $C_{26}H_{35}NO_8$, orthorhombic, space group $Pna2_1$, a = 12.3126(2) Å, b = 13.0845(3) Å, c = 16.2827(3) Å, V = 2623.21(8) $Å^3$, Z = 4, Dc = 1.240 g/cm^3, $F(000)$ = 1048, T = 93 K, λ(Mo Kα) = 0.71069 Å, 3105 reflections measured, 3103 observed (I >-10σ(I)), 318 variables,R = 0.044, R_w = 0.065, GOF = 0.51.

7,8a-Di-*t*-butyl-2-methoxy-3,4-bismethoxycarbonyl-2-methoxycarbonylethynyl-5a,7a,8,8a-tetrahydrocyclobuta[1',2'-*f*]pyrrolo[1,2-*b*]oxazine (**3**): Colorless needles; mp 141.5-142°C; ^1H NMR δ = 5.79 (br d, J = 1.5 Hz, 1H), 4.34 (d, J = 4.5 Hz, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.71 (s, 3H), 3.55 (s, 3H), 3.55 (m, J = 10.8, 4.5 and 1.5 Hz, 1H), 2.60 (dd, J = 14.7 and 3.0 Hz, 1H), 2.20 (dd, J = 14.7 and 10.8 Hz, 1H), 1.04 (s, 9H), 0.99 (s, 9H) ; IR (KBr) 2960, 2200, 1719, 1622 cm^{-1}; MS (FAB) *m/z* 490 (M^+; 7%), 458 (100), 406 (18), 57 (14); UV λmax (EtOH) 308 (log ε 4.00) nm. Anal. Calcd for $C_{26}H_{35}NO_8$: C, 63.79; H, 7.21; N, 2.86. Found: C, 63.67; H, 7.21; N, 2.85.

Crystal Data: $C_{26}H_{35}NO_8$, monoclinic, space group $P2_1/n$, a = 9.9328(2) Å, b = 24.2546(6) Å, c = 11.0896(2) Å, β = 108.4264(4)∞, V = 2534.70(10) $Å^3$, Z = 4, Dc = 1.283 g/cm^3, $F(000)$ = 1048, T = 93 K, λ(Mo Kα) = 0.71069 Å, 5716 reflections measured, 3923 observed (I >1.5σ(I)), 317 variables, R = 0.049, R_w = 0.079, GOF = 0.74.

X-Ray Crystallographic Analysis of Tricyclic Compounds (2) and (3).

The X-Ray data were collected on a *MSC/RAXIS-RAPID* Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71069 ≈). Data reduction and cell refinement were carried out with the *TEXSAN PROCESS*[8] and *MSC/RAXIS-RAPID* Imaging Plate Diffractometer. The structure was determined and refined using the *TEXSAN SHELXS-97*.[9] Molecular graphics: *TEXSAN ORTEP II*.[10] All non-H atoms were found by difference Fourier synthesis. Anisotropic displacement parameters were used for all the non-H atoms. H atoms attached to the C atoms were found by the difference Fourier synthesis. These H atoms were given an isotropic displacement parameter equal to 1.2 times the equivalent isotropic displacement parameter of the C atom to which it is attached. After the initial refinement cycle, difference Fourier synthesis was carried out in order to put the residual H atoms at the correct positions. Finally, the H atoms were treated as the fixed molecular displacement parameter after the positional refinement.

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