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Cyclization reaction of cyclopentadienone with prop-2-yn-1-ol in priority to Diels–Alder reaction

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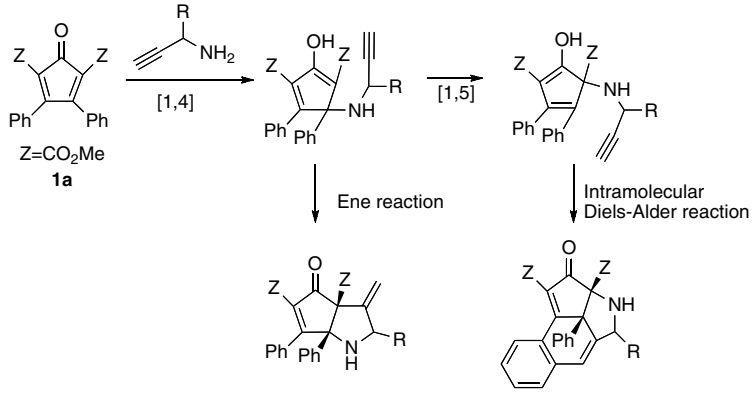
Abstract—2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1a**) reacts with prop-2-yn-1-ols (**2**) to give 3-methylene-2,3,3a,6a-tetrahydrocyclopenta[*b*]furan-4-one derivatives in the presence of trialkylamines.

Recently, we reported a novel cyclization of electron-deficient cyclopentadienone with 2-alkenyl and 2-alkynylamines via sequential pericyclic reaction pathway, in which the reaction proceeded via initial formation of the 1,4-adducts followed by the ene cyclization and/or sequential reactions (1,5-sigmatropic rearrangement and intramolecular Diels–Alder (DA) reactions) depending upon the structures of the amines (Scheme 1).[1]

The reaction of **1a** with propargyl alcohol was known to give the substituted benzene derivative via the decarbonylation of the DA adducts. Based on the MO calculation data of prop-2-ylamine and prop-2-yn-1-ol, we thought that the occurrence of the 1,4-addition leading to the cyclization is closely related to the relative orbital energy levels between the π HOMO and n HOMO of propargyl alcohol. The inversion of these π and n orbital energy levels by conversion to its conjugate base (alkoxide) may realize the 1,4-addition reaction in preference to the Diels–Alder reaction (Fig. 1).

To generate the alkoxide anion, we used trialkylamines as catalysts. Of all the trialkylamines used, DABCO (1,4-diazabicyclo[2.2.2]octane) is an efficient catalyst. The reactions were carried out using DABCO as catalyst under essentially the same reaction condition as that used for the DA reaction. The experimental results are shown in Table 1.

The reaction of **1a** with **2a** gave the bicyclic compound (**4a**) in good yield. The absence of amines only gave



Scheme 1.

Keywords: Cyclopentadienone; Prop-2-yn-1-ol; Cyclization; X-ray analysis; Pericyclic reaction; MO calculation.
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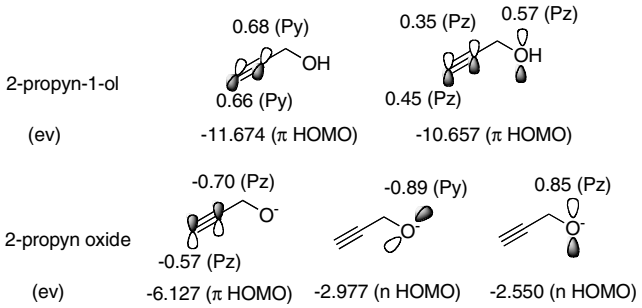


Figure 1. PM3-calculated FMO energy levels and coefficient.

the dehydrogenated DA adduct (**3a**). Use of a large excess of triethylamine (TEA) as solvent did not improve the yield of **4a**, giving rise to the DA reaction. The mass spectrum of **4a** showed a 1:1 adduct of **1a** and **2a**. The IR spectrum showed a conjugated carbonyl absorption band at 1742 and 1710 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra of **4a** indicated the presence of the exocyclic vinyl protons and the three sp^3 carbon atoms except for the two methoxy groups. The methyl protons of a methoxycarbonyl group and one of the C(2) methylene protons showed a high-field shift [δ 3.11 for C(3a)–CO_2Me, δ 4.55 for C(2)–Hβ] compared with another methyl group [δ 3.84 for C(1)–CO_2Me, δ 4.90 for C(2)–Hα], implying that the ester plane and the C(6a)-phenyl ring are in a nearly face-to-face disposition and Hβ is located on the C(5), C(6)-double bond. To clarify the full structure of **4a**, a single crystal X ray analysis was performed (Fig. 2).[2]

First of all, we considered that the cyclization is initiated by isomerization of prop-2-yn-1-ol (acetylene structure) to propa-1,2-dien-1-ol (allene structure), because **4a** can be derived from both structures (Scheme 2).

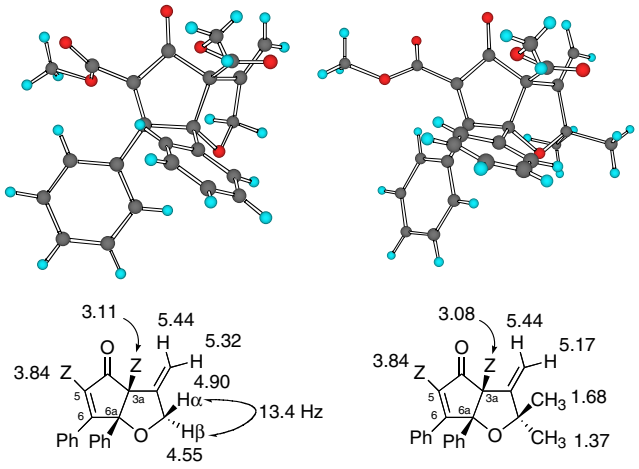
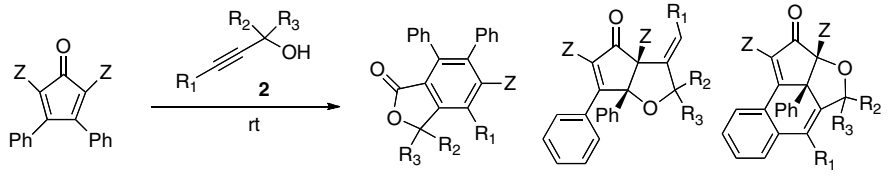


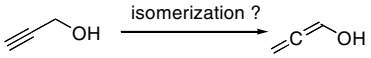
Figure 2. Computer-generated representation of X-ray structure of **4a** (left), **4c** (right): the thermal ellipsoids are omitted for clarity.

Table 1. Product distribution for the reaction of **1a** with prop-2-yn-1-ols



Substrate (R_1, R_2, R_3)	Solvent	Base	Time	Yield		
				3	**4**	**5**
2a (H, H, H)	$CHCl_3$	DABCO[c]	1	0	84	0
	$CHCl_3$	TEA[c]	1	0	70	0
	TEA	TEA	3	0	67	0
	TEA[a]	TEA	1	5	30	0
	$CHCl_3$[b]		1	83	0	0
2b (H, Me, H)	$CHCl_3$	DABCO[d]	3	14	54	0
2c (H, Me, Me)	THF	LDA[e]	7	0	4	14
	$CHCl_3$[b]		5	48	0	0
2d (Me, H, H)	$CHCl_3$	DABCO[d]	6	34	0	16
2e (Et, H, H)	$CHCl_3$	DABCO[d]	4	39	0	13
2f (CH_2OH, H, H)	$CHCl_3$	DABCO[c]	1	0	82	0
	$CHCl_3$	TEA[c]	1	0	78	0
	TEA	TEA	1	0	61	0
	$CHCl_3$		3	43	0	0
2g (CH(Me)OH, Me, H)	$CHCl_3$	DABCO[d]	5	0	70	0
2h ($C(Me)_2OH$, Me, Me)	THF	LDA[e]	6	0	6	0
2i (H, –$(CH_2)_4$–)	THF	LDA[e]	2	0	5	10

[a] 80 °C.
[b] 60 °C.
[c] Substrate:base = 24:1.
[d] Substrate:base = 5:1.
[e] Substrate:base = 2:1.



Scheme 2.

However, formation of the bicyclic compound in the reaction with 1,1-dimethylpro-2-yn-1-ol under the same reaction condition implies that isomerization of prop-2-yn-1-ol to propa-1,2-dien-1-ol did not occur during the cyclization process (Scheme 3).

As shown in **2b**, introduction of a methyl group at the α-position retarded the formation of **4b**. 1-Dimethyl-prop-2-yn-ol did not give any cyclization products. Insertion of methylene unit(s) adjacent to the OH group did not produce the corresponding cyclization products.

In the reaction of 3-methyl and 3-ethyl substrates (**2d** and **2e**), the tetracyclic compounds (**5d**,**5e**) were also isolated. The mass spectrum of **5e** showed a dehydrogenated 1:1 adduct of **1a** and **2e**. The ^{1}H NMR spectrum exhibited the absence of characteristic exocyclic vinyl group for the bicyclic compounds. The structure of **5e** was confirmed by the X-ray analysis (Fig. 3).[3]

The isolation of tetracyclic compound **5e** is the first example except for the use of terminal alkyne groups. But the yields of **5** were not enough, the optimization of the reaction condition seems to be necessary.

A characteristic difference of reactivity was found between **2e** and but-2-yne-1,4-diol (**2f**). Compound **2f** readily underwent cyclization to give the bicyclic compound in high yield, implying that the hydrogen bond due to the hydroxymethyl group might promote the cyclization. The X-ray structure of the adduct (**4h**) from 2,5-dimethylhex-3-yne-2,5-diol (**2h**) is depicted in Figure 4.[4]

1-Ethynylcyclopentanol (**2i**) gave both bicyclic (5%) and tetracyclic compounds (10%) in poor yield, in sharp contrast to the cases of the corresponding amine substrates. The reactions with 1-ethynylcyclohexylamine (**2m**) gave bicyclic **4m** (51%) and tetracyclic compounds **5m** (8%) (Scheme 4). The X-ray structure of **4m** is shown in Figure 5.[5] The difference in reactivity between the amines and the alcohols is attributable to steric hindrance in the alkoxide formation.

The bicyclic compounds have been considered to be derived from intramolecular ene reaction. However, this concerted cyclic mechanism cannot explain the stereochemical outcome of the reaction of **1a** with but-2-yne-1,4-diol (**2h**). Intrinsic reaction coordinate (IRC) calculation on the anionic species by PM3[6,7] method suggests

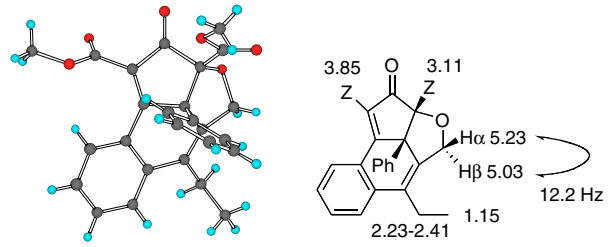


Figure 3. Computer-generated representation of X-ray structure of **5e**: the thermal ellipsoids are omitted for clarity.

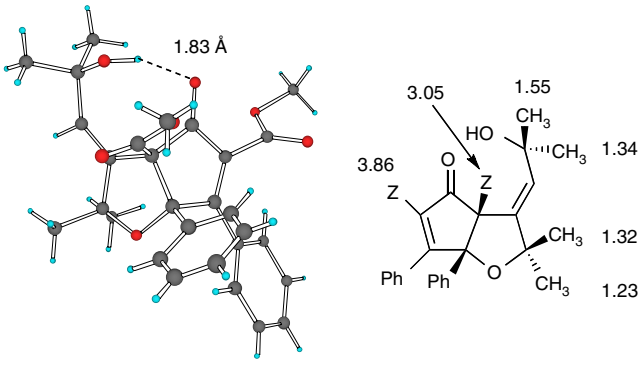
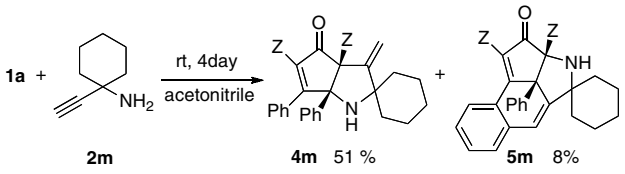


Figure 4. Computer-generated representation of X-ray structure of **4h**: the thermal ellipsoids are omitted for clarity.



Scheme 4.

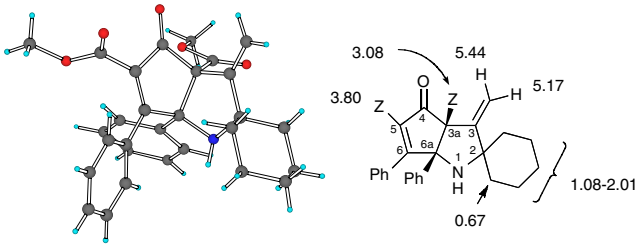
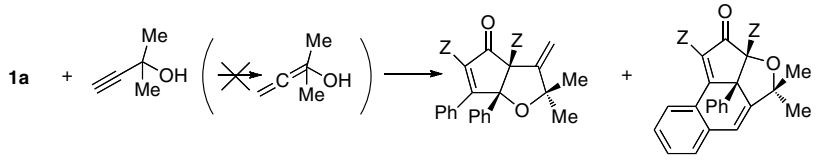


Figure 5. Computer-generated representation of X-ray structure of **4m**: the thermal ellipsoids are omitted for clarity.

that the cyclization proceeds in a stepwise mechanism in which the presence of the hydroxy group stabilizes the



Scheme 3.

post-TS structure by intramolecular hydrogen-bond formation between the hydroxy group and enolic oxygen. The X-ray structure of **4h** is consistent with the one derived from the stepwise mechanism (Fig. 6 and Scheme 5).

In summary, we have demonstrated that the bicyclic compounds **4** are derived from the stepwise [2π+2π+2σ] reaction of the 1,4-adducts of **1a** and **2** and the tetracyclic compounds **5** are formed from the intramolecular [4+2]π cycloadditions of the [1,5]-sigmatropic rearrangement products of the 1,4-adducts of **1a** and **2**, followed by the [1,5]-sigmatropic rearrangement of the hydrogen and by dehydrogenation. The one-pot multistage sequential pericyclic reactions were discussed based on the X-ray crystallographic structures and the MO calculation data.

On the basis of this study, we are currently investigating the cascade reactions between cyclopentadienones and several substituted but-2-yne-1,4-diols. Also, to detail the reaction mechanism, full structure of the density functional theory (DFT)[8] calculations at B3LYP/6-31G(d) are used.

X-ray crystallographic data: Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 295071-295074 and 246953. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

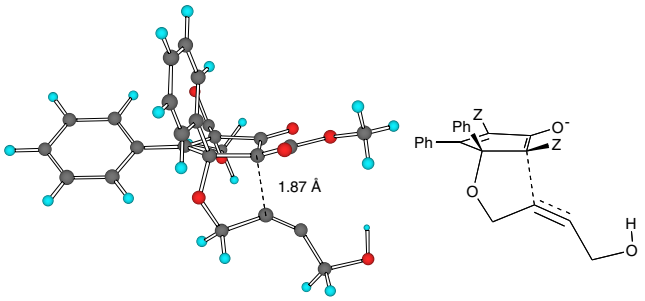


Figure 6. PM3 transition structure of the intramolecular cyclization of the 1,4-adduct of **1a** and **2f**.

References and notes

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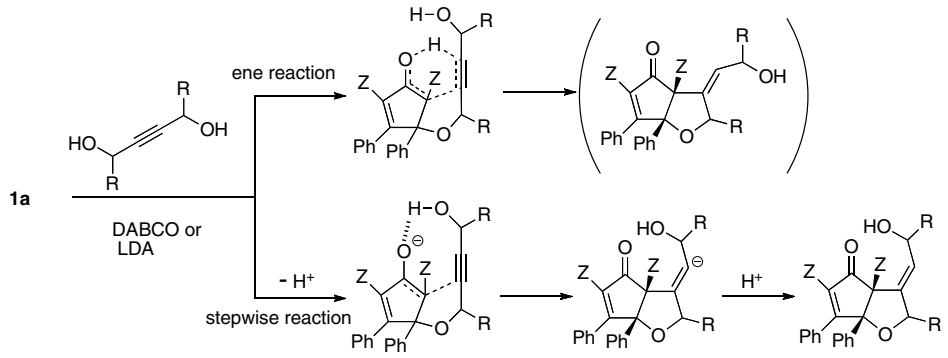
2. X-ray crystallographic study (general procedure): Single crystals of the compounds were prepared by slow evaporation of an ethanol–ethyl acetate solution at room temperature. The cell constants were found by a least-squares procedure using the values of the Bragg angles of 20 reflections. All measurements were made on a Rigaku AFC-7 four-circle automatic diffractometer with a graphite monochromated Mo-Kα radiation. The reflection data were collected using ω-2θ scan technique to a maximum 2θ value of 55.0. All of the unique reflections were used for the calculation of normalized structure factors. The structures were solved by direct method.[9] The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were refined isotropically. Some hydrogens of the methoxycarbonyl groups were located on the calculated positions and refined. The full-matrix least square refinement was used and the unweighted (R) and weighted agreement factors (R_w) are given. Neutral atom scattering factors were taken from International Tables for X-ray Crystallography.[10] All calculations were performed on a Silicon Graphics O2 workstation with teXsan Crystal Structure Analysis Package.[11] Crystal Data of **4a**; $C_{24}H_{20}NO_6$, $M = 404.42$, triclinic, space group $P1(-1)$, $a = 9.989(2)$ Å, $b = 12.817(3)$ Å, $c = 8.652(1)$ Å, $\alpha = 99.03(1)°$, $\beta = 108.87(2)°$, $\gamma = 96.59(1)°$, $V = 1018.8(3)$ Å^3, $Dc = 1.318$ g cm^{-3}, $Do = 1.328$ g cm^{-3}, $Z = 2$, $R = 0.075$, $R_w = 0.140$, CCDC reference number 295071. **4c**; $C_{26}H_{24}O_6$, $M = 432.47$, monoclinic, space group $P2_1/n$, $a = 15.096(9)$ Å, $b = 17.211(7)$ Å, $c = 8.737(5)$ Å, $\beta = 97.99(5)°$, $V = 2248(2)$ Å^3, $Dc = 1.278$ g cm^{-3}, $Do = 1.275$ g cm^{-3}, $Z = 4$, $R = 0.115$, $R_w = 0.118$, CCDC reference number 295072.
3. Crystal data of **5e**; $C_{26}H_{22}O_6$, $M = 430.46$, monoclinic, space group $P2_1/n$, $a = 14.898(8)$ Å, $b = 13.117(1)$ Å, $c = 11.492(2)$ Å, $\beta = 103.75(1)°$, $V = 2181.0(7)$ Å^3, $Dc = 1.311$ g cm^{-3}, $Do = 1.314$ g cm^{-3}, $Z = 4$, $R = 0.087$, $R_w = 0.089$, CCDC reference number 295073.
4. Crystal data of **4h**; $C_{29}H_{30}O_7$, $M = 490.55$, monoclinic, space group $P2_1/n$, $a = 17.649(8)$ Å, $b = 15.054(4)$ Å, $c = 10.031(3)$ Å, $\beta = 98.93(4)°$, $V = 2632.0(2)$ Å^3, $Dc = 1.237$ g cm^{-3}, $Do = 1.238$ g cm^{-3}, $Z = 4$, $R = 0.103$, $R_w = 0.105$, CCDC reference number 295074.
5. Crystal data of **4m**; $C_{29}H_{29}NO_5$, $M = 471.55$, orthorhombic, space group $P2_12_12_1$, $a = 14.858(3)$ Å, $b = 14.905(4)$ Å, $c = 11.273(4)$ Å, $V = 2496.4$ (10) Å^3, $Dc = 1.255$ g cm^{-3}, $Do = 1.250$ g cm^{-3}, $Z = 4$, $R = 0.048$, $R_w = 0.066$, CCDC reference number 246953.



Scheme 5.

6. Semiempirical molecular orbital calculations were performed using MOPAC 2002; Stewart, J. J. P. *QCPE Bull.* **1990**, *10*, 86 and *MOPAC 2002*; Fujitsu Ltd.: Tokyo, Japan, 1998.
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