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DABCO-triggered mild cascade reaction of electron-deficient cyclopentadienone: facile and efficient synthesis of condensed carbocycles

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ABSTRACT

2,5-Bis(methoxycarbonyl)-3,4-diphenylcyclopentadienone (**1**) reacts with 4-phenylbut-3-yn-2-one (**2b**) in the presence of DABCO to give the bicyclic carbocycles (**6b**) and the tetracyclic carbocycle (**7b**) under extremely mild reaction conditions.

1. Introduction

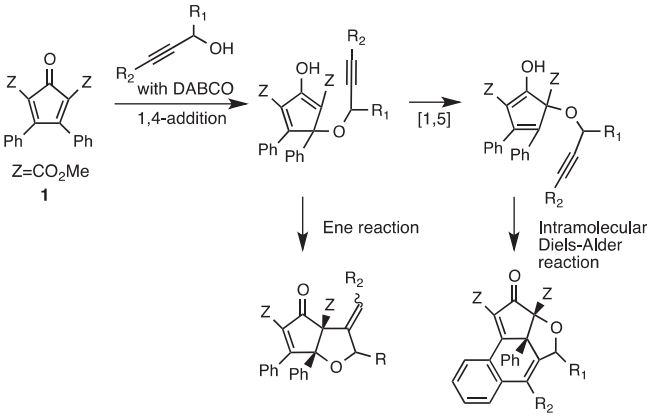
A cascade reaction, which consists of sequential chemical transformations, is a useful synthetic method for the construction of complex polycyclic systems. The transformations take place in one synthetic operation under the same reaction conditions, without adding additional reagents. The advantages are that the reaction is generally fast and stereoselective owing to its intramolecular nature and does not need the isolation of many intermediates generated in the process.[1–4] Studies on the application of a cascade reaction to natural products synthesis have been widely reported.[5] Additionally, the synthetic method has become increasingly important from the ecological and economical viewpoints.

Recently we reported a novel cyclization reaction of 2,5-bis(methoxycarbonyl)-3,4-diphenylcyclopenta-dienone (**1**) with 2-alkynylamines and 2-alkynylalcohols via a cascade reaction pathway.[6–8]

For example, the reaction of **1** with prop-2-yn-1-ol in the presence of a catalytic amount of DABCO (1,4-diaza-bicyclo[2.2.2] octane) gave the bicyclic heterocycle, which is derived from the stepwise [2π+2π+2σ] reaction (intramolecular ene reaction) of the initial formation of 1,4-adduct. When 3-methyl- or 3-ethyl-prop-2-yn-1-ol was used, the tetracyclic compound formed from the intramolecular Diels–Alder (IMDA) reaction of the [1,5]-sigmatropic rearrangement product of the 1,4-adduct, followed by the [1,5]-sigmatropic rearrangement of hydrogen and by dehydrogenation (Scheme 1). In this reaction, DABCO acts as an efficient base to generate the alkoxide anion.

On the basis of this connection, we considered that but-3-yn-2-ones (**2**) would show a similar reaction behavior under the presence of DABCO resulting in carbon–carbon bond formation via an enolate.

This Letter deals with the reaction of **1** with several but-3-yn-2-ones (**2**) via the initial formation of the 1,4-adducts followed by the ene reaction and/or the cascade pericyclic reactions.



Scheme 1. Cyclization reaction of cyclopentadienone (**1**) with pop-2-yn-1-ol in the presence of DABCO.

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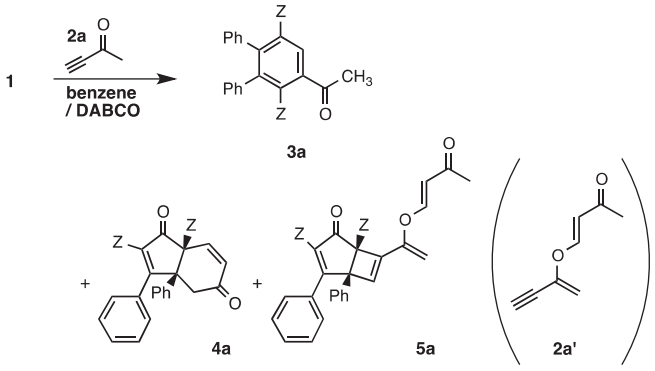
2. Results and discussion

Based on the background described above, the reaction of **1** with but-3-yn-2-one (**2a**) was carried out first. A benzene solution of **1** and an excess amount of **2a** in the presence of a catalytic amount of DABCO was allowed to stand at room temperature until **1** could not be recognized on the thin layer chromatogram (TLC). Purification using normal phase column chromatography afforded three cyclization products **3a**, **4a**, and **5a** with 7%, 22%, and 18% yields, respectively (Scheme 2 and Table 1).

Compound **3a** exhibited an M^+ ion peak at *m*/*z* 388 in the mass spectrum, suggesting that the decarbonylated 1:1 cycloadduct is obtained through the Diels–Alder reaction of **1** with the triple bond of **2a** followed by the aromatization.

The mass spectrum of **4a** showed a 1:1 adduct (*m*/*z* 416) of **1** and **2a**. The IR spectrum showed a conjugated carbonyl and an ester carbonyl absorption band at 1766 and 1732 cm^{-1}. The ^1H NMR spectrum exhibited characteristic doublet signals at δ 6.29 and δ 6.74 (*J* 9.8 Hz ascribable to the *cis* olefin) (Fig. 1). The methyl protons of a methoxycarbonyl group showed a high-field shift (δ 3.20), suggesting that the methyl protons are shielded by the electronic ring current of the neighboring C_{3a}-phenyl group. The structure of **4a** was unambiguously confirmed by X-ray crystallographic analysis.[9]

The mass spectrum of **5a** showed an M^+ ion peak at *m*/*z* 484, suggesting that **1** reacts with twice the molar amount of **2a**. The ^1H NMR spectrum of **5a** indicated the presence of the characteristic five olefinic hydrogens and a methyl group derived from *E*-3-(1-buten-3-yn-2-oxy)-buten-2-one (**2a′**). Ramanchandran et al., reported that but-3-yn-2-one (**2a**) condenses itself in the presence of a catalytic amount of DABCO providing **2a′** in high yield.[10] The ^{13}C NMR spectrum of **5a** exhibited two sp^3 carbon signals at δ 72.1 and δ 67.3, assignable to the tetrahedral carbons of the fused ring position. These results strongly suggest the formation of bicyclic compound (**5a**) bearing a cyclobutene ring.[11]



Scheme 2. Cyclization reaction of **1** with but-3-yn-2-one (**2a**).

Table 1
Reaction conditions and product ratio for the reaction of **1** with 4-substituted-but-3-yn-2-one (**2**) in the presence of DABCO

Compd	Time (d)	Total yield (%)	Yield (%)				
			3	**4**	**5**	**6**[a]	**7**
2a	3	47	7	22	18	—	—
2b	3	68	—	—	—	42	26
2c	4	37	—	—	—	24	13
2d	7	86	49	—	—	32	5
2e	3	48	—	—	—	48	—
2f	7	58	—	—	—	47	11

[a] Mixture of *E*- and *Z*-isomer.

Without DABCO, the reaction only gave the decarbonylated Diels–Alder adduct (**3a**) with 72% yield, indicating that DABCO acts as a trigger for altering the reaction behavior of **2a**. Thus, the expected carbocycles could not be obtained in the reaction of **1** and **2a**.

Next, we tried to use 4-arylsubstituted-but-3-yn-2-one (**2b–f**) as reactants. A mixture of **1** and 4-phenylbut-3-yn-2-one (**2b**) in the presence of a catalytic amount of DABCO in benzene was allowed to stand at room temperature for 3 days. After purification, two major cyclization products **6b** and **7b** were obtained (Scheme 3).

The mass spectrum of **6b** indicated a 1:1 adduct of **1** and **2b** [*m*/*z* 515 (M^++Na)]. The ^1H NMR spectrum showed a duplicated signal pattern, suggesting that the product is a mixture of *E*- and *Z*-adduct (***E*-6b** and ***Z*-6b**). The ^{13}C NMR spectrum of ***E*-6b** showed a characteristic exocyclic vinyl group (δ 143.5) and a low-field shift of methylene group (δ 47.7), supporting the formation of the bicyclic compound. The methyl signals of the methoxycarbonyl groups are δ 2.84 and 3.83 for the *E*-form, showing the high field shift compared to those in ***Z*-6b** (δ 3.18 and δ 3.77) (see Fig. 1). The upfield

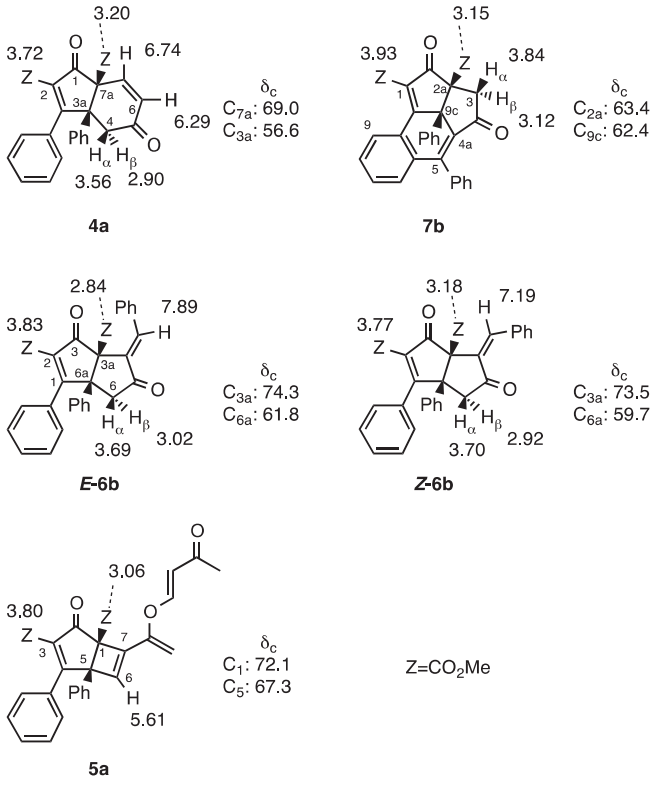
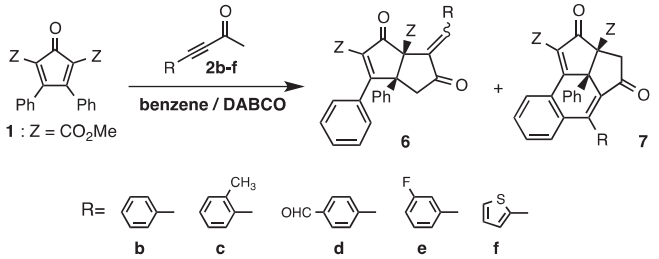


Figure 1. Characteristic ^1H and ^{13}C NMR Chemical Shifts (δ) of **4a**, **5a**, ***E*-6b**, ***Z*-6b,** and **7b**.



Scheme 3. Cyclization Reaction of **1** with 4-arylsubstituted-but-3-yn-2-one (**2b–f**).

shift of the OMe signal observed in ***E*-6b** is assigned to the anisotropic effect of the neighboring *cis*-oriented C_{6a}-phenyl and the phenyl ring of the styrene moiety. Just after separation of **6b** by silica gel column chromatography, the *E*:*Z* ratio was 45:55. However, the amount of *E*-form increased with time, suggesting that the isomerization from the *Z*-form to the *E*-form gradually takes place in the solution (After 80 days, the *E*:*Z* ratio changed to 88:12).

Inspite of the isomerization, the mixture could be further separated by reverse-phase HPLC. Both structures of the bicyclic carbocycles ***E*-6b** and ***Z*-6b** were confirmed by X-ray analysis.[9]

The mass spectrum of **7b** showed a dehydrogenated 1:1 adduct of **1** and **2b** [*m*/*z* 513 (M^++Na)]. The ^{1}H NMR spectrum exhibited the absence of characteristic exocyclic vinyl group found in the bicyclic compounds. The ^{1}H detected heteronuclear multiple bond connectivity (HMBC) spectrum and the numbers of aromatic protons (9H) suggested that the terminal alkynic carbon was connected to the 2-position of the phenyl group. The methyl protons of the methoxycarbonyl group showed high-field shift (δ 3.15) compared with another methyl group (δ 3.93), suggesting that the methyl group is located above the plane of the C_{2a}-phenyl group. The structure of **7b** was confirmed as a tetracyclic carbocycle by the X-ray analysis.

Similar reaction behavior was observed in 4-aryl-substituted-but-3-yn-2-ones (**2c–f**). The reaction conditions and the product distribution are summarized in Table 1.

The reaction of **1** with **2d** gave the decarbonylated DA adduct (**3d**) in 49% yield besides **6d** and **7d**. Increase in the DA cycloaddition reactivity can be explained in terms of the frontier molecular orbital (FMO) theory.[12] The π-HOMO and π-LUMO energy levels of **2d** are lowered by introducing the electron-withdrawing group on the benzene ring, resulting in the fact that both HOMO–LUMO interactions may be operative (i.e., neutral-type cycloaddition[13]).[14]

The highest yield of tetracyclic compounds (**7**) was obtained when the unsubstituted phenyl derivative (**2b**) was used. The presence of either electron-withdrawing or -donating group on the phenyl ring tends to decrease the yield.

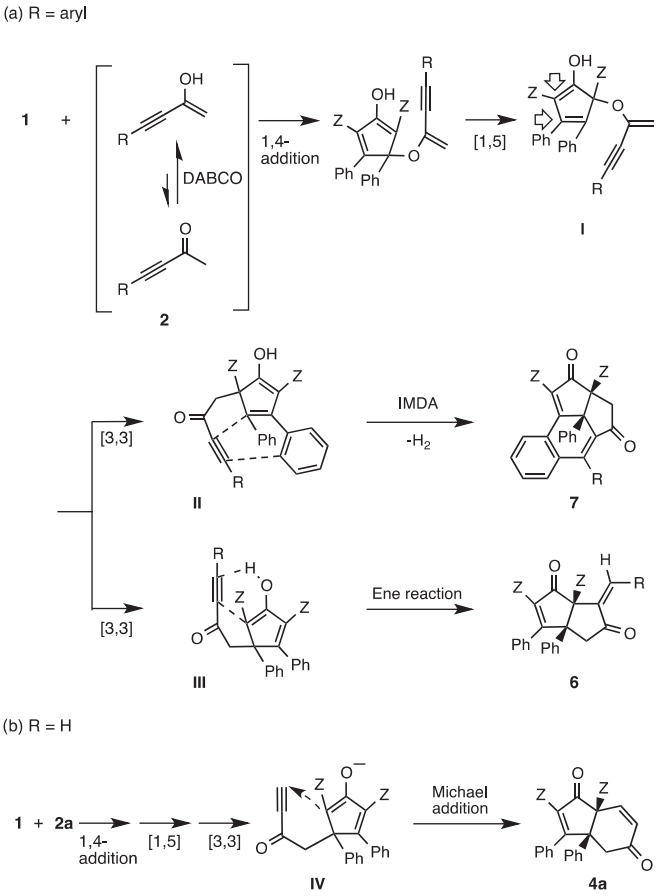
Based on these structural features of the reaction products and the reaction behavior of **1** toward propargyl alcohols[8] and propargyl amines[6], we considered a possible reaction pathway of **1** and **2** as follows (Scheme 4).

Initially, DABCO catalyzed an enolization of **2**, followed by a 1,4-addition reaction of the enolate oxygen toward **1**. Then, the 1,4-adduct rearranges to give the [1,5]-sigmatropic rearrangement product. In this stage, there are two [3,3]-sigmatropic rearrangement pathways that arise from the two olefines of the cyclopentadiene moiety.

The transition structures of the [3,3]-sigmatropic rearrangement from the [1,5]-sigmatropic rearrangement product (**I**) were successfully located by semi-empirical MO (PM6[15]) calculation (Fig. 2). The estimated reaction barriers (ΔΔHf) of **I**→**II** and **I**→**III** are 39.9 and 40.3 kcal/mol, respectively. These values are much lower than that of the initial [1,5]-sigmatropic rearrangement (59.2 kcal/mol), suggesting that the formation of tetra- and bicyclic compounds might be formed via [3,3]-sigmatropic rearrangement.[16]

The tetracyclic compound **7** is considered to be formed from the IMDA reaction (styrene as diene) of the [3,3]-sigmatropic rearrangement product (**II**), followed by the [1,5]-sigmatropic rearrangement of the hydrogen and dehydrogenation. In spite of the loss of the aromatic resonance stabilization of the styrene moiety at the initial step, the IMDA reaction takes place under extremely mild conditions. The regaining of aromaticity of the benzene ring seems to play an important role in the progress of subsequent reactions.[6]

The bicyclic compounds **6** were considered to be derived from the intramolecular [2π+2π+2σ] (ene) reaction of the [3,3]-sigmatropic rearrangement product (**III**).[6]



Scheme 4. Possible pathway of cyclization reaction of **1** with 4-arylsubstituted-but-3-yn-2-one (**2**).

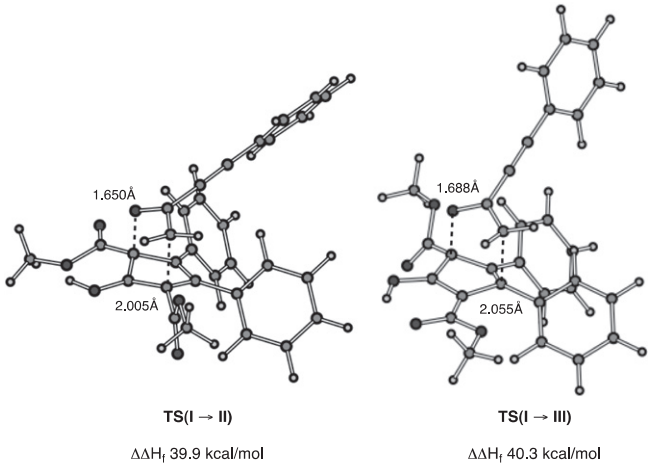


Figure 2. PM6-Transition structures and the reaction barriers for the [3,3]-sigmatropic rearrangement of the [1,5]-sigmatropic rearrangement product (**I**).

When the acetylene terminus of **2** is free (i.e., **2a**), **4a** is considered to be formed via sequential [1,5]- and [3,3]-sigmatropic rearrangements of the initial 1,4-adduct, followed by the intramolecular Michael addition of the enolate to the acetylene terminus of the butynone moiety.[17] The terminal acetylenic ketones tend to act as efficient Michael acceptor[18] with the result that the intramolecular Michael addition of intermediate **IV** might occur prior to ene or IMDA reactions.[19]

In summary, we have demonstrated that **1** reacts with but-3-yn-2-ones (**2**) in the presence of DABCO to give the bicyclic (**4**, **5** and **6**) and the tetracyclic carbocycles (**7**) under room temperature. The reactions seem to provide a new synthetic method featuring sequential carbon–carbon bond formation using organic amine under extremely mild conditions.

Further experiments including the density functional theory (DFT) calculations to elucidate the formation mechanisms of these condensed carbocycles are in progress.

Acknowledgments

We thank Mr. K. Watanabe, Miss Y. Jikumaru and Miss E. Tanaka for experimental assistance.

Supplementary data

Supplementary data (experimental procedures, detailed characterization data, copies of the spectral data, and ORTEP drawings) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.002.

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9. All measurements were performed on a Rigaku RAXIS RAPID imaging plate area detector with graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å). The data were collected at a temperature of 23 ± 1 °C to a maximum 2θ value of 55°. The structures were solved by direct method (SIR92[20]), and all hydrogen atoms were located at calculated positions. The structure was refined by a full-matrix least-squares technique using anisotropic thermal parameters for non-hydrogen atoms and a riding model for hydrogen atoms. All calculations were performed using the crystallographic software package Crystal Structure.[21] These X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Crystal Data of ***E*-6b**; $C_{31}H_{24}O_6$, M = 492.5, orthorhombic, space group $P2_12_12_1$, a = 9.294 (3), b = 15.894 (4), c = 16.704 (5) Å, V = 2468 (2) Å^3, Dc = 1.326 gcm^{-3}, Do = 1.325 g cm^{-3}, Z = 4, R = 0.036, Rw = 0.049. CCDC reference number 831661. ***Z*-6b**; $C_{31}H_{24}O_6$, M = 492.5, monoclinic, space group $P2_1/c$, a = 11.8334 (6), b = 12.9679 (8), c = 16.7754 (9) Å, β = 101.810 (1)° V = 2519.8 (3) Å^3, Dc = 1.298 g cm^{-3}, Do = 1.300 g cm^{-3}, Z = 4, R = 0.077, Rw = 0.111. CCDC reference number 831662. **7b**; $C_{31}H_{22}O_6$, M = 490.5, monoclinic, space group $P2_1/n$, a = 11.508 (3), b = 12.864 (4), c = 16.479 (6) Å, β = 97.68 (1)°, V = 2418 (2) Å^3, Dc = 1.348 g cm^{-3}, Do = 1.347 g cm^{-3}, Z = 4, R = 0.051, Rw = 0.086. CCDC reference number 831663. **4a**; $C_{25}H_{20}O_6$, M = 416.4, monoclinic, space group $P2_1/n$, a = 8.543 (3), b = 16.115 (5), c = 15.571 (6) Å, β = 98.49 (2)°, V = 2120 (2) Å^3, Dc = 1.305 g cm^{-3}, Do = 1.304 g cm^{-3}, Z = 4, R = 0.050, Rw = 0.091. CCDC reference number 831660.
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11. Compound **5a** is presumably formed via a thermally forbidden reaction pathway, that is, [2+2] cycloaddition of **1** and **2a**′, or 1,3-sigmatropic rearrangement of the DA adduct.
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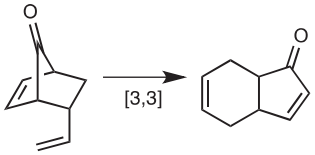
16. (a) The PM6 calculated reaction barriers for Claisen rearrangements are *ca.* 20 kcal/mol higher than the actual values. We previously reported that PM3 and MP2/6-31G(d) calculated reaction barriers for [3,3]-sigmatropic rearrangement of **A** are 50.1 and 29.0 kcal/mol, respectively.[16b] The PM6 and B3LYP/6-31G(d) calculations gave the similar results 48.9 and 27.9 kcal/mol, respectively;



A

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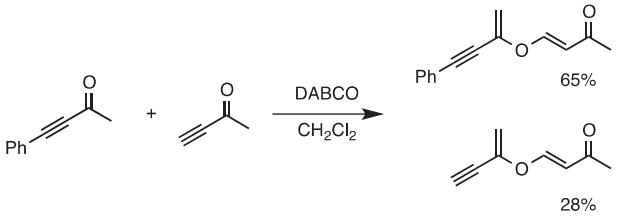
17. (a) Lavalleé, J.-F.; Berthiaume, G.; Desiongchamps, P.; Grein, F. *Tetrahedron Lett.* **1986**, *27*, 5455–5458; (b) Deslongchamps, P.; Roy, C. L. *Can. J. Chem.* **1986**, *64*, 2068–2075.
18. But-3-yn-2-one serves as a Michael addition donor as well as a Michael acceptor and condenses with itself in the presence of DABCO providing *E*-3-(1-buten-3-yn-2-oxy)-buten-2-one (**2a**′). 4-Phenylbut-3-yn-2-one (**2b**) did not undergo self-condensation but serves as a good Michael addition donor reacting with but-3-yn-2-one to provide the cross-coupled product.[10]



19. The TS structure for the intramolecular Michael addition of **IV** is located by PM6-calculation. The reaction barrier is 27.1 kcal/mol and the forming bond distance is 1.813 Å.
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