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# Thermal and catalytic isomerization of exomethylenecycloheptadienes. Experimental and theoretical studies

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ABSTRACT

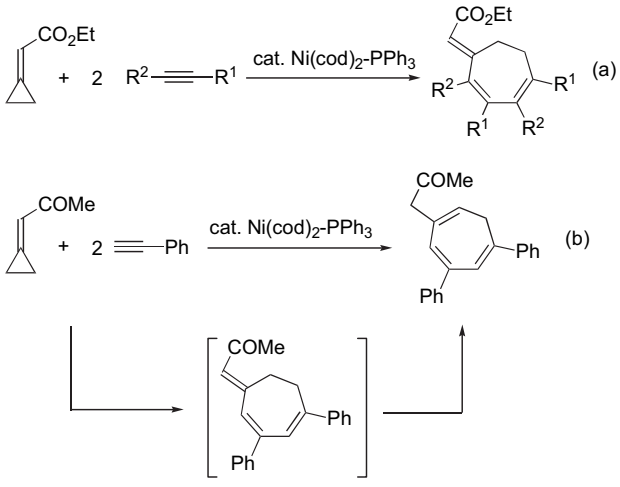
The intermolecular [3+2+2] cycloaddition reaction of ethyl cyclopropylideneacetate with alkynes proceeded in the presence of a Ni(0)/$PPh_3$ catalyst, and cycloheptadiene derivatives were obtained. However, in the reaction of 1-cyclopropylidene-2-propanone with phenylacetylene, a cycloheptatriene derivative was isolated. It was anticipated that the isomerization of the initially formed cycloheptadiene derivative led to the formation of the cycloheptatriene derivative. In this paper, we report the isomerization of cycloheptadiene derivatives under thermal, acidic and basic conditions. The stability of the products was also studied by theoretical calculations. The effects of substituents and the mechanism of the isomerization were discussed.



## 1. Introduction

The isomerization of cycloheptadienes and cycloheptatrienes proceeds via various pathways and the mechanism has been studied in depth. For example, the 1,5-sigmatropic shift of cycloheptatriene derivatives has been extensively studied.[1] This rearrangement is closely related to the frontier orbital interaction between the $\sigma^*$ orbital of the migrating group and the $\pi_{HOMO}$ of a conjugated diene system. The conformation of the starting material can affect the rates and the product distributions of the process. In addition, the interconversion of norbornadiene, norcaradiene, cycloheptadiene, and toluene has been reported.[2] There have been several studies related to the isomerization of cycloheptadiene derivatives to cycloheptatrienones under basic or acidic conditions.[3] In most examples, the tautomerization of imine-enamine or cycloheptadienone–cycloheptatrienol was discussed.[3a,b]

We have previously reported that a new intermolecular [3+2+2] cycloaddition reaction of ethyl cyclopropylideneacetate with alkynes proceeded in the presence of a Ni(0)/$PPh_3$ catalyst, and cycloheptadiene derivatives were obtained (Scheme 1a).[4] However, in the reaction of 1-cyclopropylidene-2-propanone with phenylacetylene, a cycloheptatriene derivative was isolated (Scheme 1b).[4a,4c]




**Scheme 1.**

It was anticipated that the isomerization of the initially formed cycloheptadiene derivative led to the formation of the cycloheptatriene derivative. Since conjugated enoates are generally more stable than non-conjugated enoates, we were interested in the formation of a cycloheptatriene, instead of the expected cycloheptadiene derivative, in this reaction. Herein, we describe the isomerization of cycloheptadiene derivatives, which were generated by the [3+2+2] cycloaddition reactions of electron-deficient

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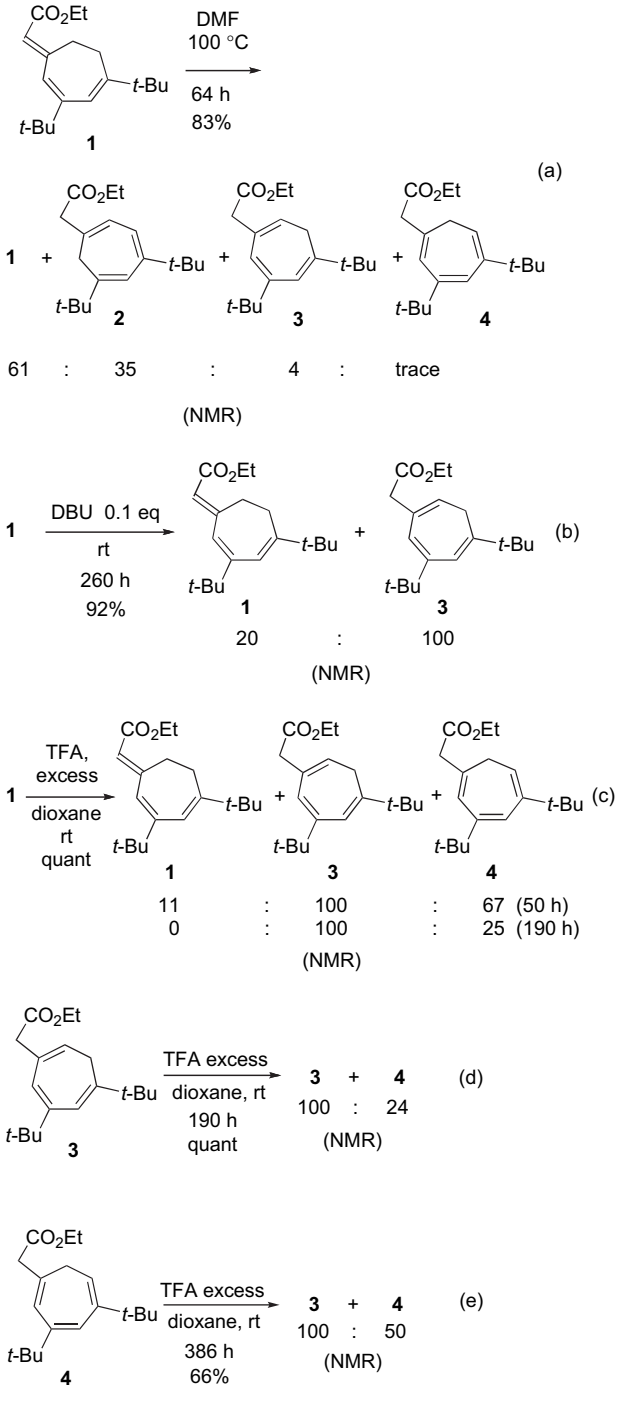
methylenecyclopropanes and alkynes. The mechanism of the reactions as well as the substituent effects was discussed. We also studied the stability of the isomers by density functional theory (DFT) calculations and compared the experimental and theoretical results.

## 2. Results and discussion

### 2.1. Synthesis and isomerization of cycloheptadienes

We selected two cycloheptadienes and studied the isomerization reactions under thermal, acidic, and basic conditions. We initiated our study by carrying out the isomerization of **1**, which has two electron-donating groups (*t*-Bu groups). The results are summarized in Scheme 2.




**Scheme 2.**

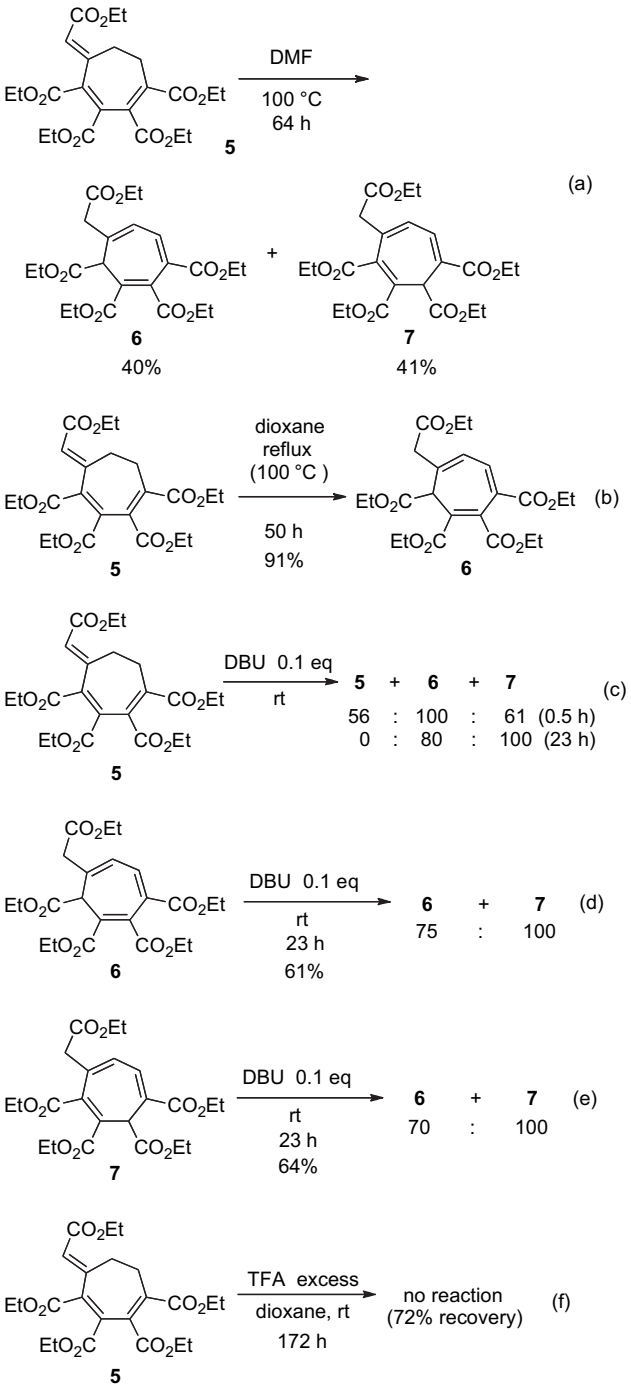
The slow isomerization of **1** proceeded at 100 °C in DMF, and a mixture of **1** and isomers (**2**–**4**) were obtained (Scheme 2a). Compound **2** was identified as the major product.[5] On the other hand, the treatment of **1** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for a long period (260 h) at room temperature afforded the isomer **3**, which was obtained as a minor product under thermal conditions (Scheme 2b).[6] The structure of **3** was similar to the product isolated by the nickel-catalyzed reaction of 1-cyclopropylidene-2-propanone with alkynes (Scheme 1b).[4a,4c] To examine the possibility of the formation of other isomers, we also carried out the isomerization reaction under acidic conditions. Thus, the reaction of cycloheptadiene **1** at room temperature for 50 h in the presence of trifluoroacetic acid (TFA) afforded two isomers (**3** and **4**) in addition to the starting material. When the reaction time was extended to 190 h, the amount of **4** decreased and compound **3** was isolated as the major product (Scheme 2c). The result indicated that compound **3** was formed by the isomerization of the initially formed isomer **4**. We next studied the acid-catalyzed interconversion between **3** and **4** to examine the existence of the equilibrium between the isomers. Treatment of the isomer **3** with TFA at room temperature for 190 h afforded a mixture of **3** and **4** (**3**:**4**=100:24, Scheme 2d). Similarly, the isomer **4** was treated under acidic conditions for 386 h to afford a mixture of **3** and **4** (**3**:**4**=100:50, Scheme 2e).[7,8]

Subsequently, we investigated the isomerization of cycloheptadiene **5** (Scheme 3). Thermal reaction (100 °C) of **5** in DMF gave the isomers **6** and **7** (Scheme 3a).[9] When the thermal reaction was carried out in dioxane, the isomer **6** was isolated in high yield (Scheme 3b). It is noteworthy that a single isomer was isolated in this reaction. On the other hand, the exposure of **5** to DBU afforded **6**, together with another isomer **7** (Scheme 3c). To examine the existence of the equilibrium between the isomers, compounds **6** and **7** were isolated and exposed to the same reaction conditions. Both compounds were converted to a mixture of **6** and **7**, and the ratios of the isomers were similar (Scheme 3d–e). When lithium diisopropylamide (LDA) was used as a base, the decomposition of **5** was observed. Meanwhile, compound **5** was not reactive under acidic conditions: the reaction of **5** did not proceed in the presence of TFA at room temperature, and the starting material was recovered (Scheme 3f).

### 2.2. DFT calculations

Density functional theory calculations were performed in order to estimate the relative energies of the cycloheptatriene derivatives. The Gaussian03[10] software program with B3LYP/6-311+G* basis set was employed to estimate the energy of the cycloheptadiene **1** and the cycloheptatriene isomers **2**–**4**. The energy of a structurally similar compound **8** and a supposed intermediate **9** (vide infra) was also calculated.[11] We performed the geometry optimization and thermochemistry analysis at 298.15 K. The initial structure used for the geometry optimization of **1** was referred to the crystal structure of a cycloheptadiene (**A**).[4a,4c] The structural information of cycloheptatriene (**B**) was utilized for the optimization of **2**–**4**, and **8** (Fig. 1).[12] The structures with the global minimum energy were determined by DFT calculations. The optimized structures of the compounds and the relative energies are shown in Figure 2.

In the optimized structure of **1**, the π-bonds of cycloheptadiene and the exomethylene groups were coplanar, so that compound **1** has a long π-conjugated system. At the same time, compound **1** would be destabilized by the steric interaction between the bulky ethoxycarbonyl group and the methylene group located at the cycloheptadiene ring. The small dihedral angle between the C–H bonds of the $-CH_2CH_2-$ group might also




**Scheme 3.**

reduce the stability of **1**. On the other hand, these unfavorable interactions are not present in the cycloheptatrienes (**2**–**4**,and **8**). The higher stability of **2**–**4** compared to **1** could be reasonably explained by considering these interactions. The optimized structure of the isomers **2**–**4** and **8** adopted boat conformation, which is generally considered as the most stable conformation for the cycloheptatrienes.[13] Based on the relative energies of the compounds, the calculated order of the isomer stability was **2**>**3**>**4**>**8**. We assume that the substituents might cause the deformation of the structure and make the most stable boat conformation strained (and less stable). Thus, the order of the nonplanarity angle ($\alpha$),[13d] which is a benchmark for the planarity of the cycloheptatriene ring, was **4**>**3**>**2**>cycloheptatriene

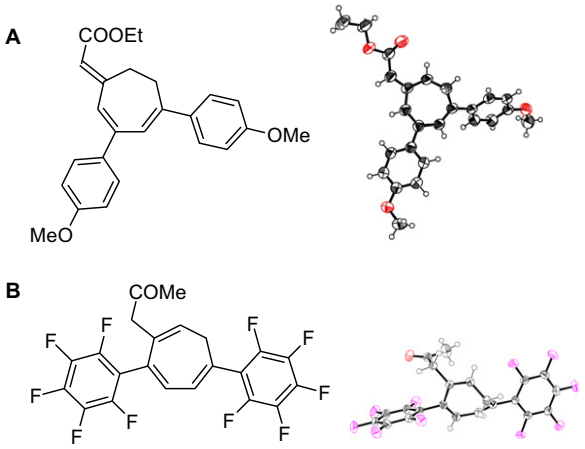


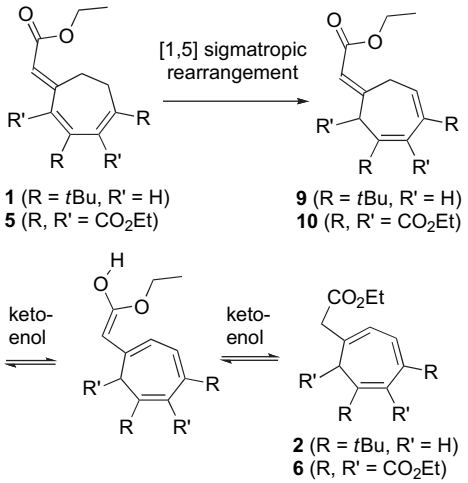

**Figure 1.** The structures and ORTEP views of compounds **A**–**B**.

(CHT)>**8** (Fig. 2). Especially, large substituents bound to C2 or C5 atom might induce the deformation of the structure (compare **2** vs **3** or **4**). A notable exception is **8**, of which the ring is more planar to reduce the unfavorable interaction between the bulky *t*-Bu groups at C1 and C6 positions.

The observed isomer distribution by the isomerization reactions generally reflects the relative energies of the isomers by DFT calculation. Thus, compound **2** was isolated as the major product under thermal conditions (Scheme 2a) and the formation of **3** (and **4**) was observed in the acid- or base-catalyzed isomerization of **1** (Scheme 2b–e). As expected, a very unstable isomer (**8**) was not detected throughout our study. At the same time, the most stable isomer (**2**) was not always isolated as the major product because of the high activation energy required for the conversion (vide infra).

### 2.3. Mechanistic consideration

The proposed mechanism of the isomerization[14,15] of cycloheptadienes under thermal condition is shown in Scheme 4. The [1, 5] sigmatropic rearrangement[1] of **1** would proceed at 100 °C, and compound **9** would be generated as an intermediate. The rapid keto-enol tautomerization of **9** would proceed because of the high acidity of the methylene protons, and cycloheptatriene **2** would be isolated as the final product.[16] The instability of **9** was also indicated by the




**Scheme 4.**

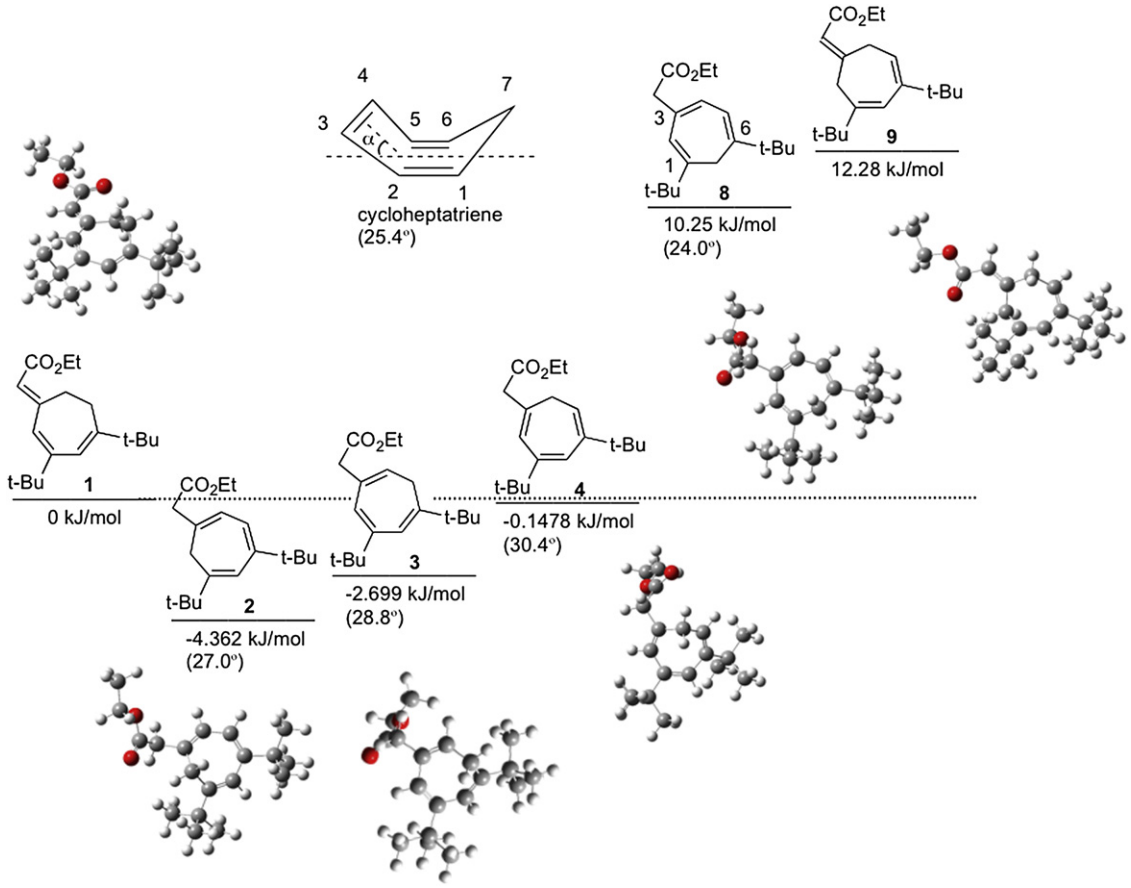



**Figure 2.** The optimized structures, relative energies, and $\alpha$ values (in parentheses) of compounds **1**–**4**, **8**–**9** and CHT.

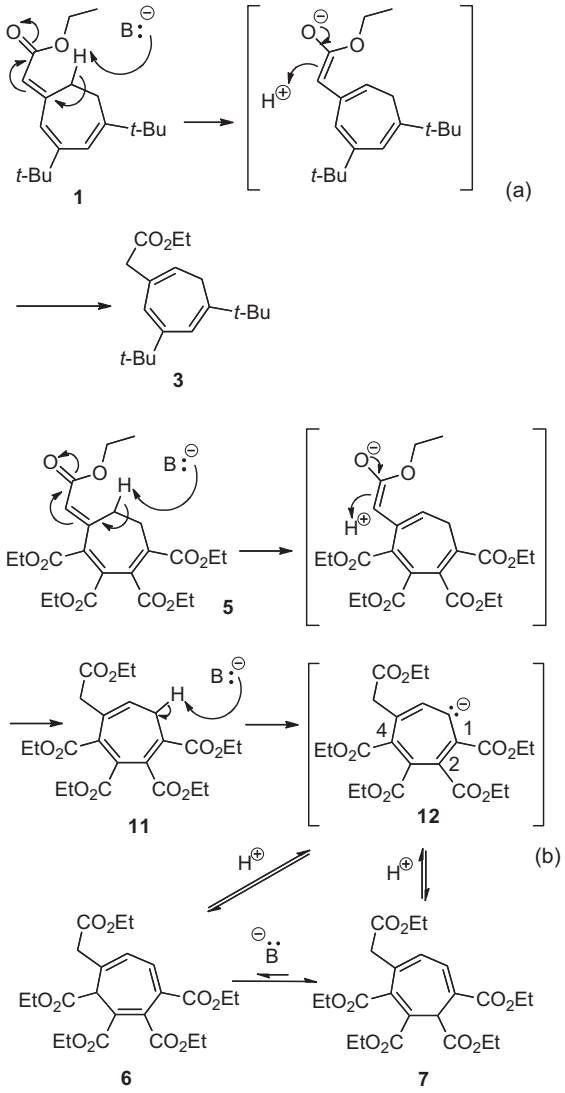
result of the DFT calculation (Fig. 2). A similar mechanism could be postulated for the thermal isomerization of the pentaester **5**.[17] The isomerization of the initially formed isomer (**6**) might proceed to give **7** when the reaction was carried out in DMF.

The proposed mechanism of the isomerization of cycloheptadienes under basic condition is shown in Scheme 5. The cycloheptadiene **1** would be deprotonated by base (DBU) to give the enolate and then protonated to afford the isomer **3** (Scheme 5a). The trisubstituted exoolefin structure of **1** is strained because of the 1,3-allylic strain among the substituents. On the other hand, the cycloheptatriene **3** would adopt boat conformation and the ethoxycarbonylmethyl group of **3** would rotate freely to remove the strain. Consequently, compound **3** would be more stable compared to **1**. Since the acidity of **3** is much lower than the acidity of **1**, the deprotonation of **3** would not proceed and the most stable isomer (**2**) would not be formed under the reaction conditions. It is possible to explain the formation of a cycloheptatriene in the reaction of 1-cyclopropylidene-2-propanone (Scheme 1b) based on the observed results. Thus, the initially formed cycloheptadiene would isomerize rapidly under the reaction conditions because a base ($PPh_3$) is present in the reaction mixture. The presence of the acetyl group instead of the ethoxycarbonyl group would enhance the acidity of the cycloheptadiene and accelerate the isomerization reaction.

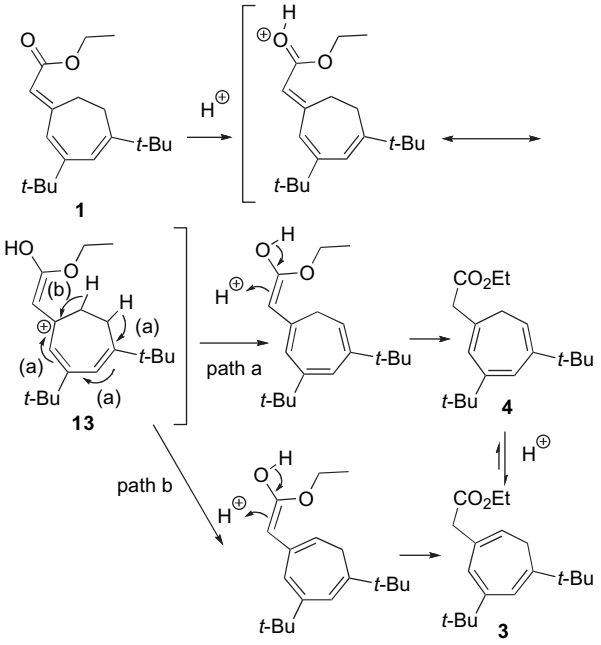
The initial step of the reaction of the cycloheptadiene **5** proceeds via similar deprotonation-protonation, and the intermediate **11** would be generated (Scheme 5b). The acidity of **11** is much higher compared to that of **3**, and the deprotonation of **11** would proceed smoothly in the presence of DBU. The protonation of the anion **12** affords a mixture of **6** and **7**. The results shown in Scheme 3 indicate that the formation of **6** proceeded faster, and the base-catalyzed isomerization proceeded to give **7** as the major product. The formation of **6** as a kinetic product might be explained by postulating that the protonation of the anion **12** proceeded selectively. Thus, the protonation of C4, which is located between the ethoxycarbonylmethylene group and the ethoxycarbonyl group, is a kinetically favorable process, while the protonation of C2 is slow because of the presence of three bulky ethoxycarbonyl groups close to C2.

The proposed mechanism of the isomerization of **1** under acidic condition is shown in Scheme 6. The cycloheptadiene **1** would be protonated to give a cation (**13**),[18] which is converted to a mixture of **3** and **4**. When the reaction proceeded via path (a), the kinetically favored isomer **4** would be generated. On the other hand, the thermodynamic product **3** would be isolated when the reaction proceeded via path (b). Since the acid-catalyzed interconversion between **3** and **4** under acidic conditions was observed, the isomer **3** would become the major product when a mixture of **3** and **4** was treated with an acid (TFA) for a long period. The recovery of the starting material (**5**) under acidic conditions could be explained in terms of the low basicity of **5**.

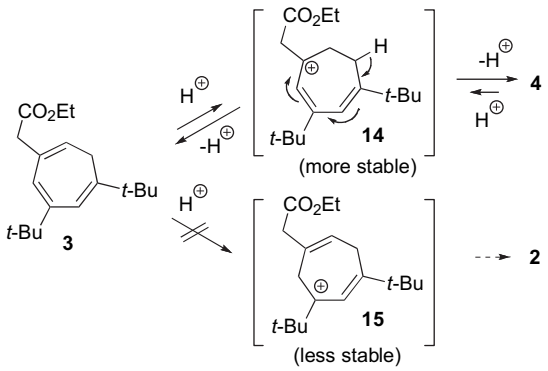
Though compound **2** was assumed to be the most stable isomer based on the theoretical study, the formation of **2** was not observed under the acidic conditions. The result could be explained in terms of the high energy barrier for the conversion of **3** (or **4**) to **2** (Scheme 7). Thus, the acid-catalyzed isomerization of **3**–**4** (or **4**–**3**) would proceed via cation **14**,[19] while the generation of the cation **15** is essential for the formation of **2**. Since the cation **15** is less stable compared to **14**, which has a longer $\pi$-conjugated system, the formation of **2** would be suppressed. The structures and relative energies of **14** and **15** were calculated, and we confirmed that the cation **15** is 32.83 kJ/mol less stable than **14**.




Scheme 5.




Scheme 6.




Scheme 7.

## 3. Conclusion

In conclusion, we studied the isomerization of cycloheptadiene derivatives, which was prepared by the intermolecular [3+2+2] cycloaddition reaction of ethyl cyclopropylideneacetate with alkynes, under thermal, basic and acidic conditions. The relative stability of the products was calculated and the results were compared with the observed isomer distributions. The mechanism of the isomerization was discussed in detail. The study will contribute to the understanding of the structure and stability, and reactivity of cycloheptatriene derivatives.

## 4. Experimental

### 4.1. Typical experimental procedures

*4.1.1. Isomerization of **1** under thermal conditions.* A solution of **1** (59 mg, 0.2 mmol) in dry DMF (2 mL) was heated at 100 °C for 64 h. The reaction mixture was purified by a silica gel column chromatography (hexane/AcOEt 40:1) to give a mixture of products (48.9 mg, 83%). The ratio was estimated by $^1$H NMR analysis.

*4.1.2. Isomerization of **1** under basic conditions.* A mixture of **1** (290 mg, 1 mmol) and DBU (15.0 μl, 0.1 mmol) was stirred at room temperature under Ar. The progress of the reaction was monitored by TLC. The mixture was purified by silica gel column chromatography (hexane/AcOEt 100:1) to give **3**.

*4.1.3. Isomerization of **1** under acidic conditions.* To a solution of cycloheptadiene **1** (29 mg, 0.1 mmol) in dioxane (10 mL) was added TFA (5 mL, 64.9 mmol) under Ar and the mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. The residue was purified by silica gel column chromatography (hexane/AcOEt 60:1) to give **3** and **4**.

*4.1.3.1. Compound **2**.* Colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) 6.30 (d, $J$=5.8 Hz, 1H), 6.11 (s, 1H), 5.93 (d, $J$=5.8 Hz, 1H), 4.17 (q, $J$=7.2 Hz, 2H), 3.22 (s, 2H), 2.38 (s, 2H), 1.27 (t, $J$=7.2 Hz, 3H), 1.15 (s, 9H), 1.13 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) 171.7, 152.3, 146.3, 128.6, 125.4, 121.2, 118.0, 60.7, 42.2, 36.3, 36.2, 32.1, 30.6, 29.4, 14.2; IR (neat) 2964, 1738, 1626, 1463, 1362, 1249, 1155, 1034 cm$^{-1}$. HRMS (ESI) Calcd for $[C_{19}H_{30}O_2+Na]^+$: 313.2138. Found: 313.2136.

*4.1.3.2. Compound **3**.* Pale yellow oil; $^1$H NMR (400 MHz, $CDCl_3$) 6.34 (s, 1H), 5.99 (s, 1H), 5.23 (t, $J$=6.9 Hz, 1H), 4.10 (q, $J$=7.2 Hz, 2H), 3.08 (s, 2H), 2.19 (d, $J$=6.6 Hz, 2H), 1.21 (t, $J$=7.2 Hz, 3H), 1.14 (s, 9H) 1.11 (s, 9H); $^{13}$C NMR (150 MHz, $CDCl_3$) 172.2, 152.8, 147.9, 130.6, 122.7, 121.3, 116.6, 60.4, 41.4, 36.4, 35.9, 30.7, 29.8, 28.8, 14.2; IR (neat) 2964, 2905, 2870, 1736, 1626, 1551, 1476, 1463, 1389, 1362, 1328, 1297, 1250,

1153, 1096, 1034, 933, 864, 794, 731, 648, 440, 412 $cm^{-1}$. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.3; H, 10.6.

*4.1.3.3. Compound **4**.* Pale yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) 6.62 (s, 1H), 6.00 (d, *J*=1.2 Hz, 1H), 5.23 (t, *J*=6.9 Hz, 1H), 4.12 (q, *J*=7.2 Hz, 2H), 3.21 (d, *J*=0.9 Hz, 2H), 2.19 (d, *J*=6.9 Hz, 2H), 1.24 (t, *J*=7.2 Hz, 3H), 1.15 (s, 9H), 1.05 (s, 9H); $^{13}C$ NMR (150 MHz, $CDCl_3$) 171.6, 150.9, 146.5, 130.5, 123.7, 123.2, 115.0, 60.6, 43.6, 36.3, 34.9, 31.5, 30.6, 30.3, 14.2; IR (neat) 3452, 3048, 2965, 2869, 2360, 1739, 1637, 1464, 1389, 1364, 1330, 1248, 1154, 1036, 866, 822, 669, 468, 406 $cm^{-1}$. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.3; H, 10.7.

*4.1.3.4. Compound **6**.* Pale yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) 7.72 (d, *J*=6.3 Hz, 1H), 6.43 (d, *J*=6.3 Hz, 1H), 4.70 (s, 1H), 3.87–4.33 (m, 10H), 3.48 (d, *J*=15.3 Hz, 1H), 3.35 (d, *J*=15.9 Hz, 1H), 1.03–1.32 (m, 15H); $^{13}C$ NMR (150 MHz, $CDCl_3$) 171.7, 150.8, 146.5, 130.5, 123.7, 123.2, 114.9, 60.6, 43.6, 36.3, 34.8, 31.4, 30.7, 30.65 30.60, 30.3, 29.8, 14.2; IR (neat) 3629, 3433, 2983, 2940, 2905, 1732, 1627, 1556, 1466, 1446, 1391, 1368, 1253, 1178, 1095, 1055, 1027, 958, 918, 863, 841, 772, 729, 471 $cm^{-1}$. Anal. Calcd for $C_{23}H_{30}O_{10}$: C, 59.2; H, 6.48. Found: C, 59.0; H, 6.48.

*4.1.3.5. Compound **7**.* Pale yellow oil; $^1H$ NMR (300 MHz, $CDCl_3$) 7.42 (d, *J*=6.0 Hz, 1H), 6.81 (d, *J*=6.3 Hz, 1H), 5.59 (s, 1H), 3.91–4.36 (m, 10H), 3.36 (d, *J*=16.2 Hz, 1H), 3.29 (d, *J*=16.2 Hz, 1H), 1.11–1.31 (m, 15H); $^{13}C$ NMR (150 MHz, $CDCl_3$) 169.5, 168.6, 167.1, 164.7, 164.3, 139.3, 136.0, 134.4, 133.2, 128.0, 124.9, 62.1, 61.9, 61.6, 61.3, 61.1, 41.5, 40.7, 14.2, 14.1, 14.0, 14.0, 13.8; IR (neat) 3648, 2983, 2939, 2906, 1738, 1616, 1541, 1467, 1446, 1391, 1368, 1331, 1258, 1176, 1097, 1082, 1053, 1028, 937, 862, 803, 766, 441 $cm^{-1}$. Anal. Calcd for $C_{23}H_{30}O_{10}$: C, 59.2; H, 6.48. Found: C, 59.1; H, 6.47.

## Acknowledgements

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## Supplementary data

Experimental procedures and characterization data (pdf), and the details of the X-ray structural determination of **B** (CIF) are available. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.065.

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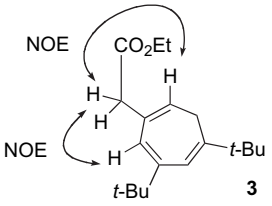
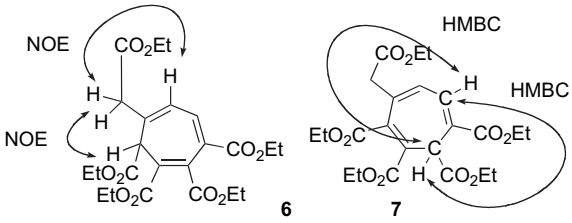
5. When the thermal reaction of **1** was carried out at higher temperature (130 °C) or for a longer period (150 h), the amount of **1** decreased and compound **2** was formed as the major product. However, the formation of unidentified products precluded the detailed analysis of the reaction. When the thermal reaction was carried out in toluene, the reaction was very sluggish. The total yield of the isomers was 31% and the starting material still remained when the reaction was carried out at 100 °C for 231 h. The decomposition of **1** was observed when the reaction of **1** was carried out in dioxane at 100 °C.
6. Exposure of **1** to a solution of DBU in dioxane for a long period at room temperature also afforded **3**. The structure of **3** was confirmed by an NOESY experiment as shown below.




**3**

7. We also monitored the isomerization of **1** in dioxane-$d_8$-TFA by $^1H$ NMR and confirmed that compounds **3** and **4** were formed and isomerized in the reaction mixture.
8. Though we carried out the isomerization of several substrates to examine the effect of the substituents, the isolation and analysis of the products turned out to be extremely difficult.
9. The structures of **6** and **7** were confirmed by an NOESY experiment and an HMBC experiment as shown below.




**6** **7**

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11. The theoretical calculation of **5** and the isomers was not carried out since the compounds were expected to adopt various conformations and the analysis would be very difficult.
12. Compound **B** was synthesized by the [3+2+2] cocyclization and an X-ray crystallographic analysis was carried out. The details are described in Supplementary data.
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16. We assume that the [1, 5] sigmatropic rearrangement of **1** is a faster process compared to the keto-enol tautomerization of **1**, since only a small amount of compound **3** was isolated: if the keto-enol tautomerization is a faster process, a significant amount of **3** would be isolated.
17. Alternatively, the thermal isomerization of **5** might proceed via the repeated keto-enol tautomerization of **5**. Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449.
18. Calculation indicated that the stability of **13** was comparable to that of **15** (vide infra).
19. Attempted observation of the cation **14** in TFA was unsuccessful, probably due to the low basicity of **3**. Alternatively, the formation of another cationic species, which was tentatively assigned as a tropylium ion, was observed. As for the basicity of cycloheptatriene, see: Salpin, J.-Y.; Mormann, M.; Tortajada, J.; Nguyen, M.-T.; Kuck, D. *Eur. J. Mass Spectrom.* **2003**, *9*, 361–376.