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[6+2] Cycloaddition of *N*-phenyltriazolinedione with cycloheptatriene derivatives mediated and stereodirected by a chiral 3-oxy substituent

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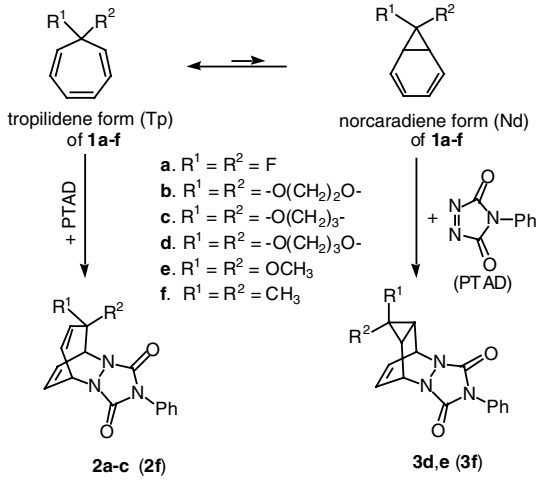
Abstract—The addition of *N*-phenyltriazolinedione to a 7,7-dimethylcycloheptatriene derivative afforded a [6+2] adduct, which was found to be produced by the rearrangement of an initially formed [4+2] adduct. The regioselectivity of the initial addition was controlled by the 3-oxy-substituent, which also mediates the PTAD addition to the tropilidene form. The chiral 3-substituent also controlled the stereoselectivity of the addition to a high degree.

The reaction of cycloheptatriene with a dienophile is a classic example that a minor component in a quick equilibration of the reactant is more reactive than a major component overcoming its low content. Tautomerization of a cycloheptatriene derivative between the tropilidene form (Tp) and norcaradiene form (Nd) is quick, and Tp is generally predominant, while dienophiles add to the minor but more reactive Nd in most cases. The reaction of 7,7-disubstituted cycloheptatrienes **1** with *N*-phenyltriazolinedione (PTAD) serves as some exceptional examples.[1,2] When the external bond angle at C7 is as small as that in **1a**–**c**, the addition selectively proceeds via Tp to give **2**.[3,4] The small angle forces the ring conformation to be flatter, which enhances its reactivity as a diene in addition to suppression of the Nd content in the tautomerization.[5] In contrast, **3** was solely obtained from cycloheptatrienes **1d** and **1e** in spite of the similarity of the 7-substituents to **1b**, but with a slightly larger external angle at C7.[3] With limited examples so far studied, the generality of the mode-switching rule as well as the stereoselectivities observed in the formation of **2c** and its analogues are not totally understood (Scheme 1).[4]



Scheme 1. Modes of PTAD addition to 7,7-disubstituted cycloheptatrienes.

For the synthetic purpose, cycloadditions with **1f** and its derivatives are important since these products, derivatives of **2f** and **3f**, have a *gem*-dimethyl unit, and serve as synthons for varied terpenoids, though the **3f** products through Np are less valuable due to the availability of other preparation methods for the *gem*-dimethylcyclopropyl unit including asymmetric synthesis.[6] In this study, substrate **4a** was employed to attain the regio- and stereoselective addition of PTAD, since the optically active 2,4-pentanediol moiety introduced at C3 of **4a** is a promising stereocontroller for the PTAD addition to a π-system,[7] and it can be a functional group to use the adduct as a chiral synthon. The observed addition was smooth and quantitative via Tp under sufficient stereocontrol to afford an unexpected [6+2] cycloadduct.

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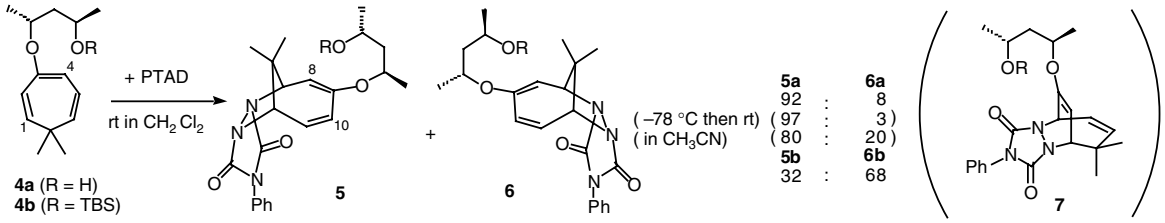


Scheme 2. PTAD addition with **4a** and **4b**, and diastereomeric ratios of **5a**,**b** versus **6a**,**b**.

Substrate **4a** was prepared by a reported method.[8] When a dichloromethane solution of **4a** (0.2 mM) was mixed with PTAD (1.4 equiv) at room temperature, **4a** was immediately consumed to give **5a** and its diastereomer **6a** (Scheme 2). The spectral properties of **5a/6a** are similar to those expected for a simple [4+2] adduct **7** in showing three olefinic protons, but the formation of **7** by the present addition was clearly discarded by a detailed NMR analysis of the product including the HMBC measurement; for example, the coupling constant of $J_{8,10} = 2.1$ Hz in **5a** cannot explain the structure of **7**. To determine the stereodirection of the addition, **5a** was converted to the acetal **8** by the acid treatment (TsOH·pyridine/rt, 67% yield). The NMR analysis by NOE measurements of **8** indicates a relative stereochemistry between the pentanediol and newly formed moieties as well as the concaved *endo*-structure at the PTAD moiety (shown in Fig. 1).

The diastereomer ratio **5a/6a** = 92/8 obtained at room temperature was improved to 97/3 when **4a** and PTAD was mixed at −78 °C and then warmed up to rt. The poorer selectivity of 80/20 observed in acetonitrile indicates that the stereocontrol is sensitive to the conditions, and the mechanism may include weak interactions such as hydrogen bonding. In fact, when the hydroxy group of **4a** was protected by a TBS group, the PTAD addition proceeded smoothly in dichloromethane at room temperature as was **4a**, but the selectivity was the inverse; the reaction with **4b** was resulted in **5b/6b** = 32/68.[9]

The [6+2] cycloaddition is known for PTAD addition with some ring-fused cycloheptatrienes,[5a] but unknown for the reaction with monocyclic cycloheptatrienes. These formal forbidden mode as a thermal electrocyclic addition suggests the existence of an intermediate during the formation of **5/6**. The initial addition mode as well as its selectivity was clarified by performing the reaction at low temperatures. That is, **4a** and PTAD were mixed in $CDCl_3$ at −90 °C, and the reaction was monitored by ^1H NMR at low temperatures. The consumption of **4a** was immediate even at −70 °C to produce a new adduct **9a** with a small amount of **5a**. By warming the mixture to −20 °C, **5a** was increased with a decrease in **9a**. The planar structure of **9a** could be determined by NMR analyses, of which the results clearly removed the possibility of [2+2] PTAD addition at the 3,4-bond of **4a**; for example, the dimethylated C8 has HMBC signals with N-α H7 as well as olefinic H9. By the same experiment except for the use of **4b**, the ^1H NMR spectrum at −70 °C showed the formation of two products in a ratio of 17/83. Their spectra are similar to each other, and the minor one is almost identical with **9a**. When warming this mixture, **6b** was produced as a major product accompanied by **5b** as a minor component. There is no stereochemical information for **9** (and its diastereomer **10**), but if the rearrangement of **9/10** to **5/6** is a stereospecific 1,3-rearrangement, the stereochemistries of **9** and **10** are assigned as shown in Scheme 3.

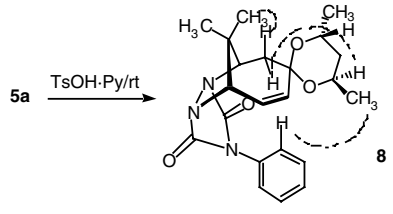
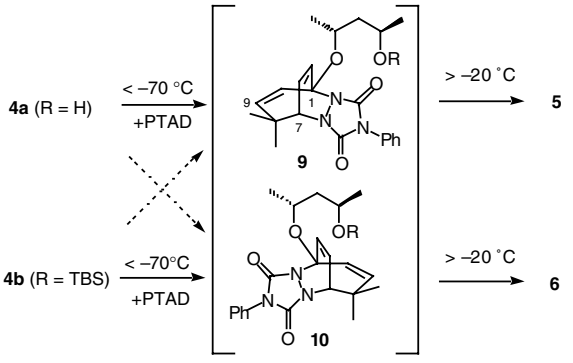


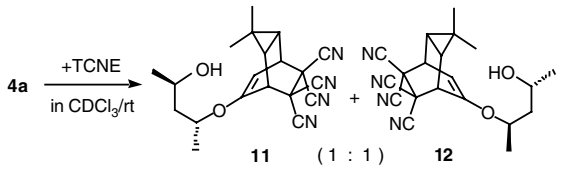
Figure 1. Selected NOE data for **8** derived from **5a**.

The reaction of **4a** with PTAD was found to consist of the regio- and stereoselective [4+2] addition and the rearrangement of the adduct. Rearrangements of the PTAD adduct are known for several cases, but detection of the primary adduct as the intermediate during the thermal addition is not known except for one case, where the primary [4+2] adduct rearranges to the [2+2] adduct.[10]

Other than the regio- and stereoselectivities of the initial addition of PTAD and the succeeding quick rearrangement, the present reaction is still distinctive because PTAD adds at Tp. The external angles at C7 of 7,7-dimethylcycloheptatriene **1f** and its analogues including **4a** are large and thus classified in a group of **1d** and **1e**.[11] This means that PTAD is expected to add at Nd to give **3**[12] in contradiction to the observed results with **4a**. The



Scheme 3. Overall stepwise process for PTAD addition to **4a** and **4b**.



Scheme 4. TCNE addition to **4a** at room temperature.

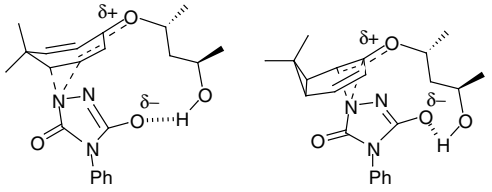


Figure 2. Expected transition states for PTAD addition with **4a** through Tp (left) and Nd (right).

existence of Nd in the tautomerization of **4a** and reactivity of the Nd against the dienophile were proved using tetracyanoethylene (TCNE), another strong dienophile.[13] The reaction of **4a** with TCNE in $CDCl_3$ proceeded smoothly at room temperature to quantitatively give a mixture of **11** and **12** (=1:1) (Scheme 4). The NMR spectra as well as their ESI-MS spectra indicate predominant addition through Nd with no stereoselectivity.

All features found in the reaction with **4a** with PTAD are reasonably understood if the initial [4+2] cycloaddition proceeded through a polar transition state.[14] The 3-oxy substituent of **4a** increases the electron density of the triene π-system to enhance or to induce electrophilic (but not electrocyclic) addition of PTAD to make the transition state polar. Such an addition does not require a flat conformation of the π-system. Although the oxy substituent effect is also possible to work with the Nd of **4a**, the effect is not large as that in Tp where the developing cation is delocalized (Fig. 2). The anion concurrently produced at the PTAD part can be used for making hydrogen bond with the hydroxy group in the chiral pentanediol moiety, which determines the stereodirection of the addition. The 3-oxy group after formation of the initial adducts **9/10** works to weaken the C1–N2 bond to make **9/10** less stable than stereo congested **5/6**.[15] In conclusion, the regio- and stereoselective functionalization of the 7,7-dimethylcycloheptatriene derivatives at the sterically crowded 1- and 6-positions was achieved by the PTAD addition.

References and notes

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9. Relative stereochemistry between **5a** and **5b** (**6a** and **6b**) was assigned by their interconversion via silylation and desilylation processes.
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11. The potential energy difference between the tautomers of **1f** calculated by Gaussian 98W at the B3LYP/6-31G* level is 3.4 kcal mol^{-1} (Tp is more stable than Nd), which is similar to 7.1 kcal mol^{-1} for **1d**, but is distinguishable from 14.9 for **1a** and 12.0 for **1b**. The torsional angle for the diene part in **1f** is 25.4°, which is also similar to 25.6° of **1d** (see Ref. 5c for the calculations of **1a**, **1b**, and **1d**). Introduction of a methoxy substituent at the 3-position of **1f** mimicing **4a** does not have a large affect and results in 3.6 kcal mol^{-1} for the potential difference and 26.8° for the 1,4-diene part and 25.8° for the 3,6-diene part.
12. The reaction of **1f** with PTAD has not been reported, but is strongly suggested to give **3f** through Nd. Singlet oxygen ($^1O_2$) addition is Tp favored compared to PTAD addition. The $^1O_2$ addition to the unsubstituted cycloheptatriene mainly gives a Tp adduct (Tp:Nd = 95:5), while PTAD only gives an Nd adduct. Since $^1O_2$ addition to **1f** results in both Tp and Nd adduct (Tp:Nd = 60:40), PTAD addition to **1f** should predominantly give the Nd adduct **3f**. See: Adam, W.; Adamsky, F.; Klarner, F. G.; Peters, E. M.; Peters, K.; Rebollo, H.; Rungeler, W.; Schnering, H. G. *Chem. Ber.* **1983**, *116*, 1848–1859.
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15. Thermodynamic stability of **5a** is 8.8 kcal mol^{-1} more stable than that of **9a** estimated by using a simplified model at the B3LYP/6-31G* level (methoxy instead of 2,4-pentanediol moiety and methyl instead of phenyl).