CHEMISTRY LETTERS, pp. 855-858, 1992.

Concomitant Formation of Isomeric 1-, 2-, and 3-Substituted Heptafulvenes from 2-Substituted Tropones and Active Methylene Compounds

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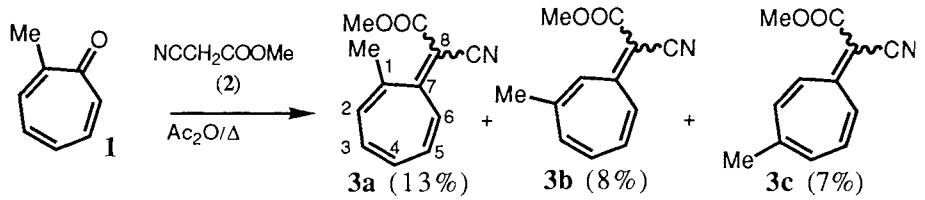
Condensations of methyl cyanoacetate and 4-nitrobenzyl cyanide with 2-isopropyl-, 2-methyl-, and 2-phenyltropones in Ac_2O gave isomeric 1-, 2-, and 3-substituted heptafulvene derivatives. The mechanism of reaction was explained in terms of a remote nucleophilic attack of the active methylene compounds to acetoxycycloheptatrienylium salt, followed by [1,5] sigmatropic hydrogen shift and elimination of acetic acid.

The most convenient method of synthesizing 8,8-disubstituted heptafulvenes is the Ac_2O-mediated condensation of active methylene compounds with tropones.[1] In connection to other synthetic project,[2] we have carried out the condensation of 2-methyltropone (**1**) with methyl cyanoacetate (**2**) in refluxing Ac_2O solution. Surprisingly, the products isolated via silica-gel column chromatographically were, along with 8-cyano-8-(methoxycarbonyl)-1-methylheptafulvene (**3a**), isomeric 2-methyl and 3-methyl derivatives (**3b** and **3c**) (Scheme 1).[3]

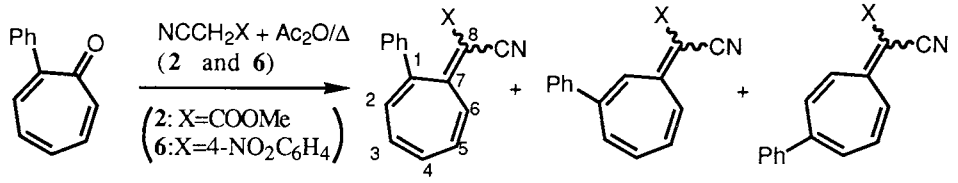


Scheme 1.

Therefore, we have extended the study to a few tropone derivatives and obtained results as reported herein. It should be noted that the carbonyl carbon of the starting **1** is transformed into hydrogen-carrying sp^2-carbons in **3b** and **3c**.

When an Ac_2O solution of 2-phenyltropone (**4**) and **2** was refluxed for 30 min, the products obtained were 8-cyano-8-(methoxycarbonyl)-2-phenylheptafulvene (**5b**) and 8-cyano-8-(methoxycarbonyl)-3-phenylheptafulvene (**5c**) via chromatographic separation. No 1-phenyl derivative (**5a**) was detected.

Parallel results were observed in the reaction of **4** with 4-nitrobenzyl cyanide (**6**) to afford 8-cyano-8-(4-nitrophenyl)-2-phenylheptafulvene (**7b**) and 8-cyano-8-(4-nitrophenyl)-3-phenylheptafulvene (**7c**) (Scheme 2).



Scheme 2.

Through fractional recrystallizations of **7b** from EtOAc, pure *Z*-**7b** was isolated. Thermal isomerization of *Z*-**7b** in refluxing benzene for 10 h did not proceed at all, but in $CDCl_3$, an *E,Z*-equilibration occurred at 20 °C in 5 h. Consequently, a trace amount of acid residue facilitated the isomerization. The ^1H NMR spectrum of *Z*-**7b** is illustrated in Fig. 1.

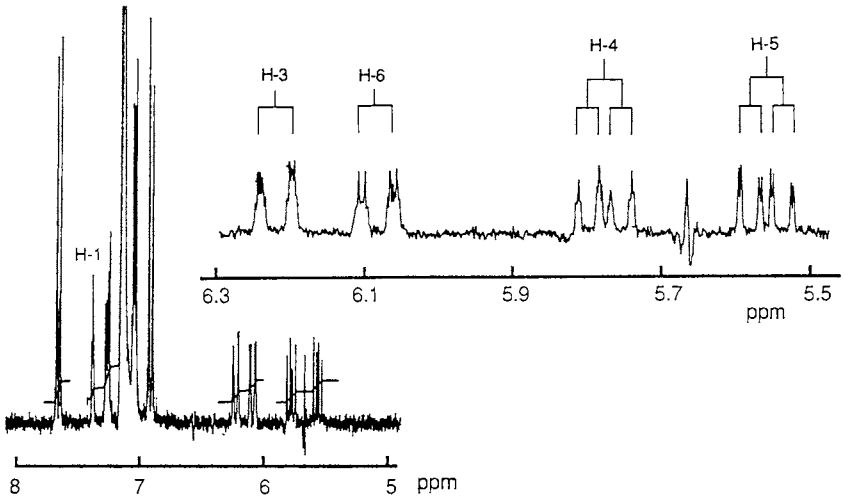
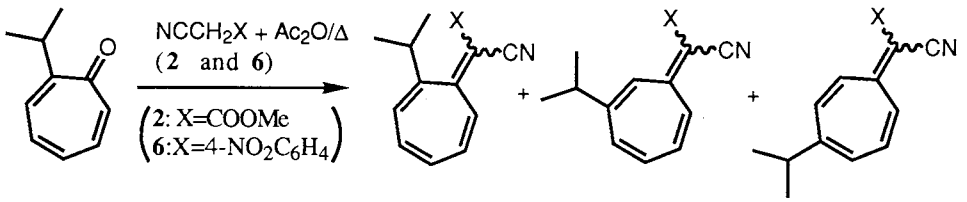


Fig. 1. The ^1H NMR Spectrum (270 MHz) of *Z*-**7b**.

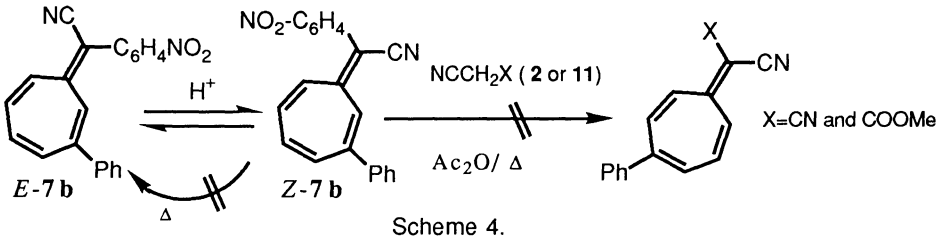
Similarly, the reaction of 2-isopropyltropone (**8**) and **2** afforded regio-isomeric mixture of respective heptafulvenes, 8-cyano-2-isopropyl-8-(methoxycarbonyl)heptafulvene (**9b**), and 8-cyano-3-isopropyl-8-(methoxycarbonyl)heptafulvene (**9c**), but no 1-isopropyl derivative (**9a**), while the reaction of **8** and **6** afforded all possible three 8-cyano-8-(4-nitrophenyl)heptafulvenes, i.e., 1-, 2-, and 3-isopropyl derivatives (**10a**, **10b**, and **10c**) (Scheme 3).



Scheme 3.

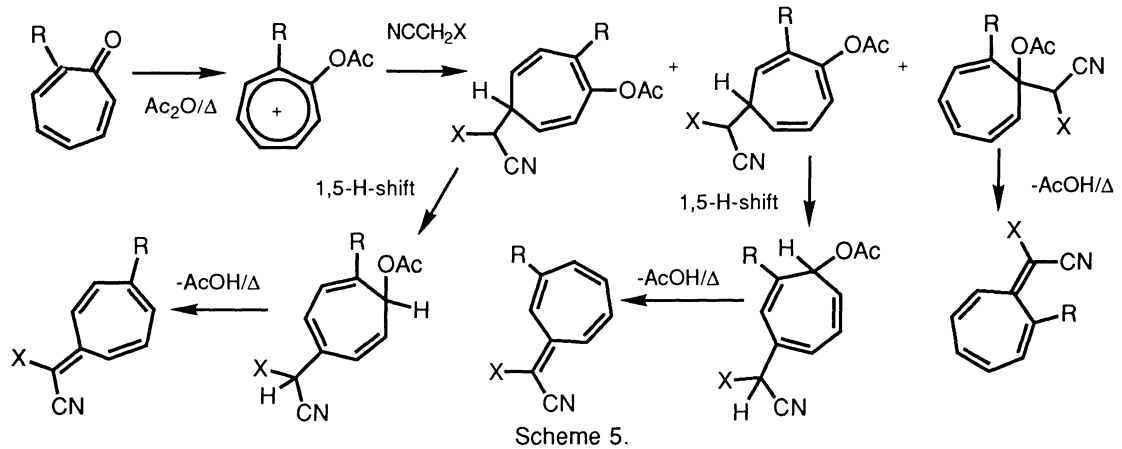
When a mixture of the heptafulvene and the active methylene compound was

further heated under the reaction conditions, no regio-isomerization of the starting heptafulvene occurred; e.g., heating **7b** with either **6** or malononitrile (**11**) in Ac_2O for 5 h caused a quantitative recovery of the starting material. Thus, the products are not mutually interconvertible, and formed in parallel and independent manner (Scheme 4).



Scheme 4.

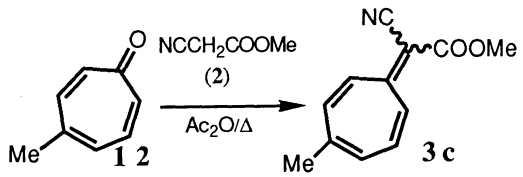
To explain the present results, a remote attack of the active methylene derivatives to acetoxycycloheptatrienylium ions can be proposed as the most plausible mechanism; the subsequent [1,5] sigmatropic hydrogen shift of the resultant cycloheptatriene system and the elimination of acetic acid should give the products as depicted (Scheme 5).



Scheme 5.

Consequently, the condensation of active methylene compounds with tropones in Ac_2O is not so simple as has been considered.

The occurrence of the conjugate addition might be due to a steric hindrance of the bulky substituent on the tropone ring toward nucleophilic attack of the bulky active methylene reagents.

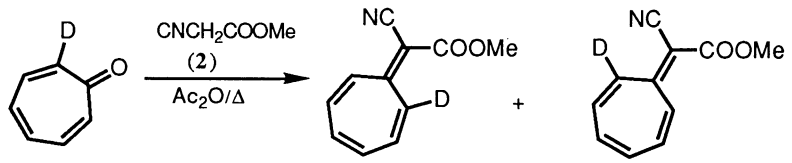


Scheme 6.

Being consistent with this, 4-methyltropone (**12**) exclusively condensed with **2** to give **3c** (Scheme 6).

In addition, the reaction of tropone-2-*d* (**13**-2-*d*) with **2** gave *E*- and *Z*-8-cyano-8-(methoxycarbonyl)heptafulvenes-2-*d* (**14**-*d*). The deuterium distribution of **14** indicated essentially the carbonyl carbon attack of **2** according to ^1H NMR spectral

analysis.



13-2-*d* *Z*-**14**-2-*d* *E*-**14**-2-*d*

Scheme 7.

Therefore, the remote attack observed in the substituted tropones is attributable to a sterical reason.

Nevertheless, several ring-substituted 8,8-dicyanoheptafulvenes are reported to be formed via normal substitution mechanism; Kitahara synthesized 8,8-dicyano-1,6-dimethylheptafulvene from 2,7-dimethyltropone and **11**,[1] and the X-ray analysis determined its structure,[4] and we ourselves investigated the condensation of **11** with 2,5-dioxygenated tropones to obtain only normal products.[5] Obviously, **11**, the most frequently used active methylene compound, is not sufficiently bulky to cause the conjugate addition.

We thank The Ministry of Education, Culture and Science, Japanese Government, for financial assistance through the Grant-in-Aid for Scientific Research (03214107 to H. T.).

References

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3) The ^{13}C NMR spectra (in $CDCl_3$) of heptafulvenes revealed geometrical isomerism. However, detailed discussion will be a subject of a forthcoming full paper. Due to limited space available, only the chemical shift data of **3a**, **3b**, and **3c** are listed. The asterisked figures indicate overlapped signals for both isomers.
3a: {24.7, 25.0}, {52.4, 52.5}, {95.8, 97.7}, {116.4, 117.4}, {125.6, 126.6}, {131.0, 131.1}, {132.2*}, {132.4, 132.6}, {133.4*}, {133.5, 136.9}, {162.6, 163.1}, and {163.4, 164.5}.
3b: {27.8, 28.1}, {51.9, 52.0}, {88.2, 88.4}, {118.9*}, {133.4, 134.8}, {135.1, 135.5}, {135.6, 136.5}, {137.3, 137.4}, {139.8, 140.7}, {149.4, 150.0}, {160.9, 161.0}, and {165.1*}.
3c: {25.9, 26.0}, {52.0*}, {88.5*}, {118.6*}, {132.8, 133.8}, {134.7, 134.8}, {135.6, 136.2}, {137.5, 138.1}, {141.2, 141.9}, {148.2, 149.1}, {161.2*}, and {165.0*}.

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(Received March 3, 1992)