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Why Are the Troponoid Rings of the Mesylate and Tosylate of Tropone Oxime Cleaved Easily by Nucleophiles?†

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Abstract: The molecular orbital (MO) calculations predict that the the reaction of the mesylate (**2**) of tropone oxime with nucleophiles will lead to the ring opening of the substrate. In accord with this MO prediction we have found experimentally that the facile ring opening of **2** occurs while the oxime **3** is inert to nucleophiles. Thus, **2** reacts with nucleophiles under mild conditions and gives stereoselectively a variety of (*Z,Z,Z*)-trienes, as the sole products in high yields. The reaction is similar to that of the tosylate **1**. The reaction has been found to be caused by the intramolecular (HOMO $\rightarrow \sigma^*$) charge transfer in the Meisenheimer tetrahedral intermediate. A hyperconjugation plus E2 mechanism is proposed for the facile ring opening. The MO theory interprets why the troponoid rings of the mesylate and tosylate are cleaved easily by nucleophiles.

We have recently reported a novel and surprisingly facile ring opening of the tosylate (**1**) of tropone oxime by a variety of nucleophiles.[1] The reaction produces thermodynamically unstable *all-cis* trienes (Scheme 1). Although extensive reactions on troponoid compounds have been reported,[2] the troponoid-ring skeleton has been retained in both nucleophilic and electrophilic reactions.[3] In contrast, the ring opening of **1** proceeds smoothly under mild conditions at low temperatures. The reaction has the following synthetic advantages: (i) products are *Z,Z,Z*-trienes with high stereoselectivity, which are usually difficult to synthesize; (ii) the ring cleavage can be smoothly achieved under mild conditions; (iii) the short reaction time, simple procedure and high yields are also technical merits.

† Dedicated to Professor Tetsuo Nozoe in the memory of his life-long career for non-benzenoid aromatic chemistry. He has deceased on the 4th of April in 1996, one month before his 94th birthday. For his biography and research history, see: (a) Nozoe, T. In *Seventy Years in Organic Chemistry*; Seeman, J. I., Ed.; *Profiles, Pathways, and Dreams: Autobiographies of Eminent Chemists*; American Chemical Society: Washington, DC, 1991. (b) *Heterocycles* **1978**, *11*(1): Special Issue for celebration of his 77th birthday.

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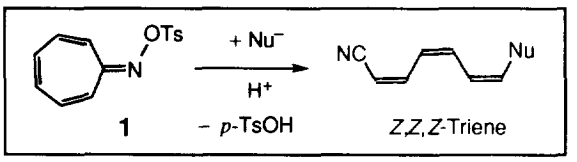


Scheme 1. Ring Opening of Tropone Oxime Tosylate (**1**) by Nucleophiles.[1]

It is a logical concern to examine whether the unprecedented reaction can be interpreted in terms of patterns of established ionic reactions such as S_N2 and E2. In this paper we will examine theoretically why the σ bond of troponoid compounds is cleaved in spite of coexistence of their highly reactive conjugated π bonds in the compounds. Various leaving groups are adopted, and the possibility of the reaction will be tested. Then, based on the theoretical result, we will perform some experiments. It will be shown that theoretical calculations can predict correctly the ring-opening reactivities.

RESULTS AND DISCUSSION

Theoretical Choice of Substrates for Ring Opening of Troponoid Compounds.

In the preceding paper of the ring opening of tropone oxime tosylate (**1**),[1] two questions still remained. One is possibility of whether other substrates than the tosylate **1** may undergo the similar concerted ring opening. The other is the classification of the novel reaction pattern. In order to solve these two questions, we have carried out molecular orbital (MO) calculations.

First, we have considered the following four substrates **1**–**4**. PM3 calculations[4] have been carried out for nucleophilic reactions between the substrates **1**–**4** and methoxide ion [Nu^- = MeO^- in Schemes 1 and 2].

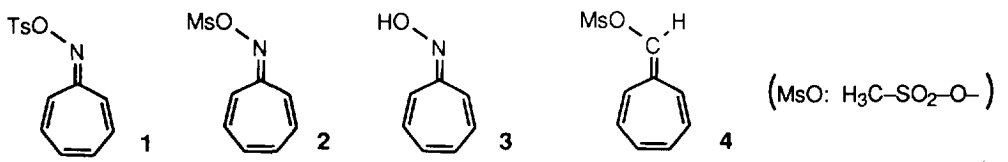


Table 1 displays the computed results of selected bond distances, net electronic charges and activation energies. Among these four substrates, the tosylate **1** and methanesulfonate (mesylate) **2** have low (ca. 27 kcal/mol) activation energies. The charge migration (ρ) and the synchronous bond elongation (R_{C-C} and R_{X-L}) are also reasonable only in these two substrates. Thus, the cleavage of the troponoid ring is feasible in the substrate with combination of the exo imine bond and the OTs (tosyloxy) [or OMs (mesyloxy)] leaving group. The PM3 calculation also indicates that the ring-opening reaction gives the (Z,Z,Z)-triene by the rotation around the bold C–C bond (TS) as shown in the following scheme.

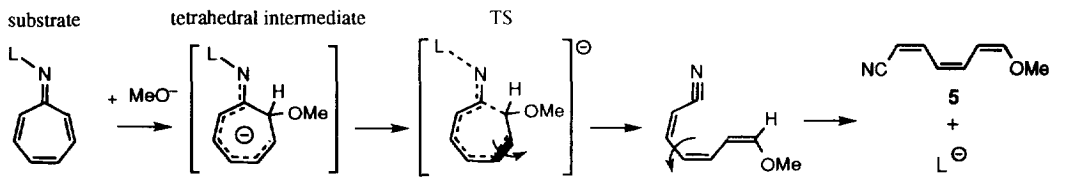
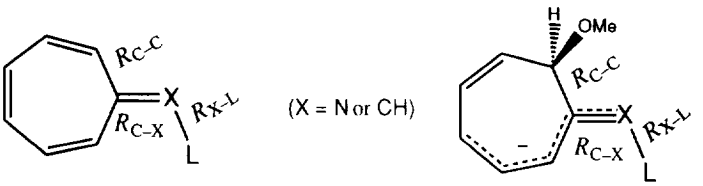


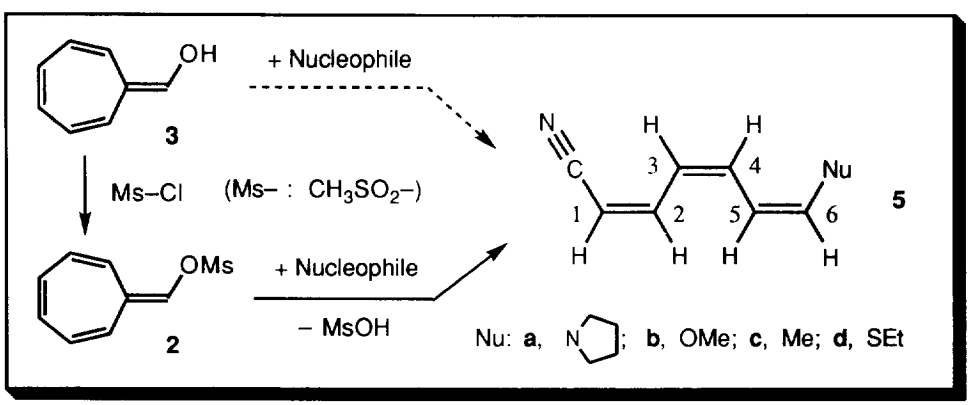
Table 1. Changes of Bond Distances (R's), Net Charges (ρ's) of Leaving Groups (L's) and Activation Eneries (E_a) along Reaction Paths Calculated by the PM3 Method.[a]

X–L		R_{C-C}	R_{C-X}	R_{X-L}	ρ on L	E_a
N–OTs	substrate (**1**)	1.462	1.316	1.402	–0.124	
	intermediate	1.526	1.338	1.532	–0.304	
	TS ($\nu^{\ddagger}$ = 817.8*i*)	1.968	1.233	1.778	–0.665	**26.9**
N–OMs	substrate (**2**)	1.462	1.316	1.405	–0.124	
	intermediate	1.526	1.337	1.528	–0.303	
	TS ($\nu^{\ddagger}$ = 790.0*i*)[b]	1.980	1.233	1.775	–0.658	**27.3**
N–OH	substrate (**3**)	1.462	1.316	1.397	–0.045	
	intermediate	1.525	1.327	1.442	–0.123	
	TS ($\nu^{\ddagger}$ = 279.4*i*)	2.359	1.255	1.580	–0.281	**45.1**
CH–OMs	substrate (**4**)	1.456	1.362	1.365	–0.121	
	intermediate	1.516	1.383	1.354	–0.288	
	TS ($\nu^{\ddagger}$ = 320.7*i*)	2.348	1.311	1.400	–0.301	**48.6**



substrate (tetrahedral) intermediate and TS

[a] Bond distances R's in Å, net electronic charges ρ's (negative, anionic) on leaving groups L's, and activation energies E_a's in kcal/mol relative to energies of tetrahedral intermediates. In *X*–L, for example, *N*–OMs means that a leaving group mesylate $-OSO_2CH_3$ is attached to the imine nitrogen atom. For transition states (TS's), the sole imaginary frequencies ($\nu^{\ddagger}$'s, cm^{-1}) are given in parentheses. The nucleophile is MeO^-. [b] These data are also shown in Figure 2.



Scheme 2. Ring Opening of Tropone Oxime (**3**) and Tropone Oxime Mesylate (**2**) by the Nucleophiles.

Experimental Verification of Ring-Opening Reaction of Tropone Oxime Mesylate (2) by Nucleophiles.

On the basis of the theoretical data in Table 1, we may expect that tropone oxime mesylate (**2**) (E_a = 27.3 kcal/mol) undergoes easily the ring opening similarly to the tosylate **1** (E_a = 26.9 kcal/ mol). However, tropone oxime (**3**) will not give the ring opening easily, since the calculated result has shown the activation energy (E_a = 45.1 kcal/mol) for **3** is larger than those for the mesylate **2** and tosylate **1**.

Table 2. Reaction of Tropone Oxime Mesylate (**2**) or Tropone Oxime (**3**) with Various Nucleophiles in Scheme 2 to give 6-Substituted (*Z,Z,Z*)-1,3,5-Hexatrienecarbonitriles (**5**).

Entry	Substrate	Nucleophile	Solvent	Conditions	Product	Yields[a]
1	**3**, *N*–OH	Pyrrolidine	CH_2Cl_2	room temp., 2 days	—[b]	—
2	**3**, *N*–OH	MeONa	THF	room temp., 2 days	—[b]	—
3	**3**, *N*–OH	MeMgI	THF	room temp., 2 days	—[b]	—
4	**3**, *N*–OH	EtSNa	THF	room temp., 2 days	—[b]	—
5	**2**, *N*–OMs	Pyrrolidine	CH_2Cl_2	−20 °C, 1 h	**5a**	99
6	**2**, *N*–OMs	MeONa	THF	0 °C, 3 h	**5b**	97
7	**2**, *N*–OMs	MeMgI	THF	0 °C, 4 h	**5c**	68
8	**2**, *N*–OMs	EtSNa	THF	−20 °C, 1 h	**5d**	98

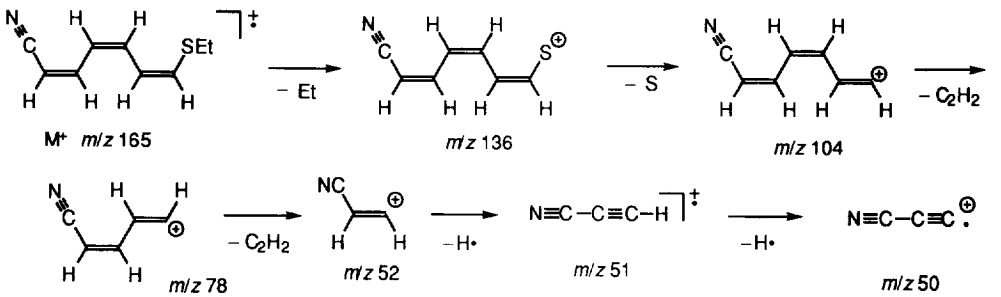
[a] Isolated yield (%). [b] No reaction occurred.

In order to assess the theoretical result (Table 1), we have prepared the mesylate **2** from the reaction of tropone oxime **3** and methanesulfonyl chloride (MsCl) under the presence of pyridine in a high yield. In Table 2, both the substrates, **2** and **3**, were subject to the nucleophilic reaction with pyrrolidine, sodium methoxide, and methylmagnesium iodide under the conditions similar to those of the tosylate **1**.[1] A new nucleophile, sodium ethanethiolate, was also examined toward **2** and **3** (entries 4 and 8 in Table 2). Tropone oxime **3** was mixed with pyrrolidine, NaOMe, MeMgI, or NaSEt. But the substrate **3** was recovered unchanged (no reaction) in accordance with the theoretical prediction. On the other hand, the mesylate **2** reacted with the same four nucleophiles to yield 6-1'-pyrrolidinyl- (**5a**), 6-methoxy- (**5b**), 6-methyl- (**5c**), and 6-ethylthio-1,3,5-hexatrienecarbonitrile (**5d**) in high yields in Table 2 (see also Scheme 2).

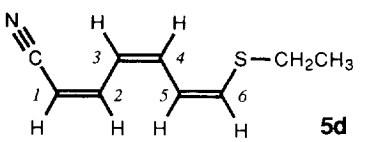
Experimental Identification of the Products.

The products **5a–d** in the above section (Scheme 2 and Table 2) are found to be identical (see Experimental section) with those authentic samples which were obtained from the reactions of the tosylate **1**.[1] We have elucidated the structure of the new product **5d** as follows. IR spectrum of **5d** displays ν_{max} of conjugated cyano group at 2198 cm^{-1}. Microanalytical and molecular weight data from mass spectrometry of **5d** indicate the molecular formula of the product. In the mass spectra of the products **5d**, the molecular ion (M^+ *m/z* 165) appears as the base peak. The following fragmentation strongly suggests that the product **5d** is a hexatrienecarbonitrile. There is an intense fragment peak at *m/z* 104 due to loss of the substituent, EtS, and due to the trienecarbonitrile cation radical. The fragment loses acetylene (HC≡CH) stepwisely to

form C_5H_4N (*m/z* 78) and C_3H_2N (*m/z* 52). Then the *m/z*-52 fragment loses hydrogen radical to form C_3NH (*m/z* 51) and C_3N (*m/z* 50) species.



^{1}H NMR spectrum of the product **5d** exhibits a well resolved pattern. To accomplish full assignment and accurate analysis, we have used modern techniques of the following NMR (^{1}H and ^{13}C) spectroscopies. In the one-dimensional (1D) NMR, resolution-enhanced spectra with Gaussian- and sine-bell wind functions[5] have been employed separately. In the two-dimensional (2D) NMR, ^{1}H–^{1}H shift-correlation spectroscopy (COSY),[6] ^{1}H–^{1}H shift-correlation spectroscopy by long-range couplings (COLOC),[7] ^{13}C–^{1}H COSY,[8] ^{13}C–^{1}H COLOC[9] with an aid of composite decoupling, gated decoupling, ^{13}C–^{1}H selective decoupling (SEL), and ^{13}C–^{1}H long-range selective decoupling (LSPD)[10] have been used. The ^{1}H–^{1}H vicinal coupling constants ($^3J_{H-H}$) strongly suggest *Z,Z,Z*-configuration for **5d** (see Experimental section).



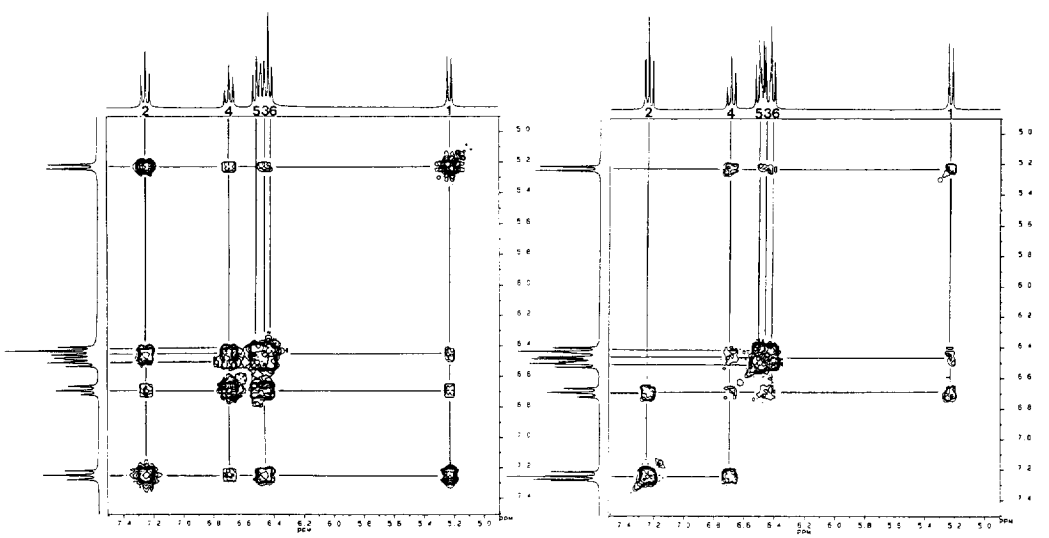


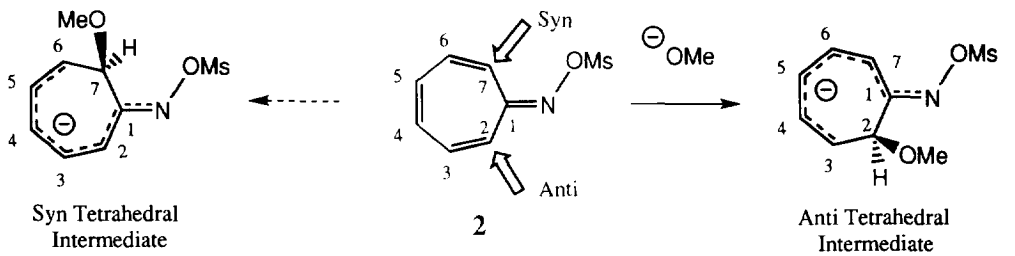
Fig. 1. 2D NMR ^{1}H–^{1}H COSY (left) and ^{1}H–^{1}H COLOC (right) Spectra for **5d**.

Figure 1 displays expanded contour maps of downfield region covering olefinic protons. The left view shows five intense contours between H(1) and H(2), H(2) and H(3), H(3) and H(4), H(4) and H(5) and H(5) and H(6) in accordance with the *Z,Z,Z*-configuration. The configuration is supported by the right chart displaying intense contours between H(1) and H(4) as well as between H(3) and H(6) due to long-range $^5J_{H-H}$ (zig-zag) interactions.

The ^{13}C NMR spectra of **5d** show one cyano carbon and six olefinic carbons at δ 117 and 97–144, respectively, together with those of a substituent ethylthio group. The former signals appear as singlets and the latter six olefinic carbons do all as doublets, respectively, by an off-resonance experiment. The ^{13}C–^1H vicinal coupling constants[11] ($^3J_{C-H}$) also support *Z,Z,Z*-configuration for **5d** (Experimental section). All these data indicate that the product **5d** is a Z,Z,Z-1,3,5-hexatrienecarbonitrile.

Theoretical Inspection of the Ring Opening.

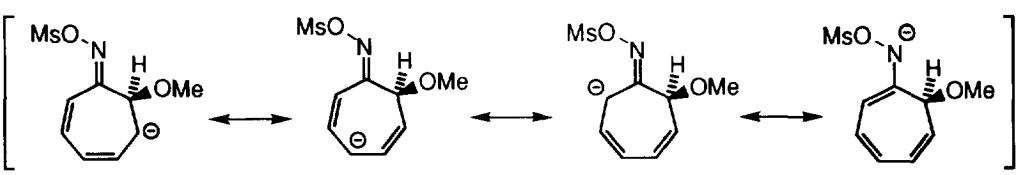
In order to elucidate the reaction mechanism of Scheme 2, we have analyzed the results of PM3 calculations for a nucleophilic reaction between the substrate (mesylate) **2** and methoxide ion [Nu = (**b**) MeO in Scheme 2]. The first step of the reaction is formation of an anti tetrahedral intermediate in the left side of Figure 2. The substrate **2** has the same-type LUMO as that of tropone (and hexatriene). According to its largest extension, the nucleophile MeO^- attacks C-2 (anti) or C-7 (syn) of **2**. The *anti* intermediate is by 2.9 kcal/mol more stable than the *syn* one in Figure 2.



The next step is either the concerted C(1)–C(2) and N–O bond scission or the N–O bond scission producing a nitrene intermediate. Each transition state is shown in the right side of Figure 2. The concerted C–C bond-cleavage path is much more favorable than the nitrene-forming (N–O bond cleavage) path (the E_a difference = 9.1 kcal/mol). Thus, PM3 calculations demonstrate the concerted mechanism for the ring opening. Here, one question remains. It is the classification of our novel reaction to the established concerted nucleophilic reactions such as S_N2 and E2.

Origin of the Ring Opening and Assignment of the Reaction Pattern.

At the first step of the reaction, the tetrahedral intermediate is formed and has the following anionic centers. Figure 3 shows the electronic charge densities and the shape of HOMO of the intermediate in the mesylate **2**. They reflect the canonical resonance structures.



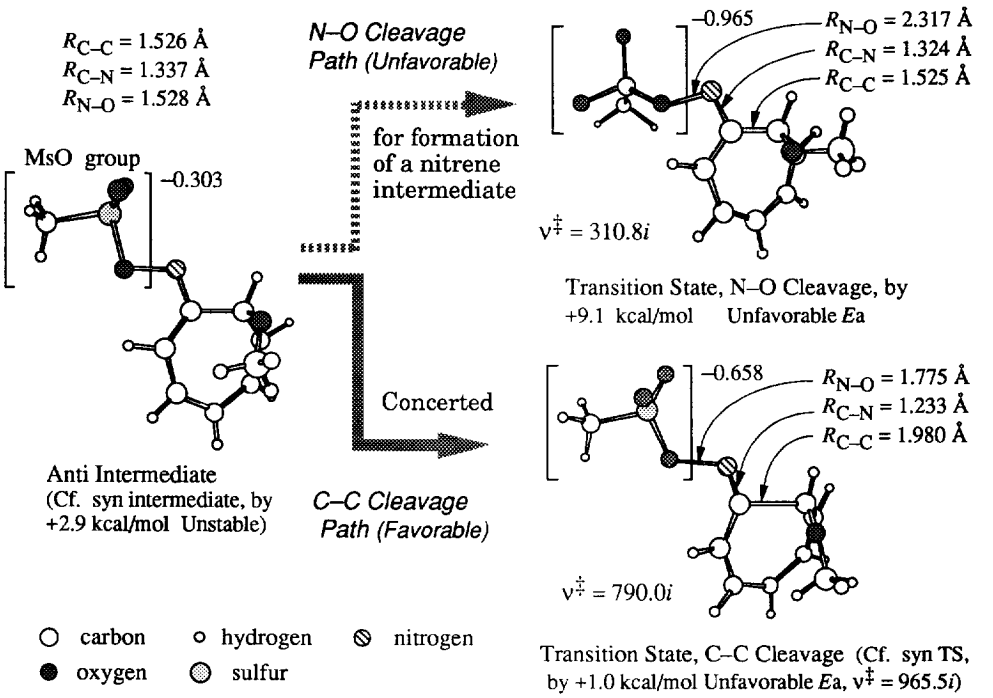


Fig. 2. The Tetrahedral Intermediate and Two Transition States in the Anti Reaction Path of Scheme 2 Computed with the PM3 Method.[4]

The tetrahedral intermediate is composed of the mesylate 2 and methoxide ion MeO^-. Positive energy values indicate that anti intermediate and anti concerted transition state (TS) are more favorable than the corresponding syn ones. The N–O bond-cleavage TS for formation of a nitrene intermediate is by 9.1 kcal/mol less favorable than the concerted ring-opening C–C bond-cleavage TS. At TS's, sole imaginary frequencies $\nu^{\ddagger}$'s are shown in cm^{-1}. Frames attached to the OMs moiety denote net electronic charges (negative, anionic).

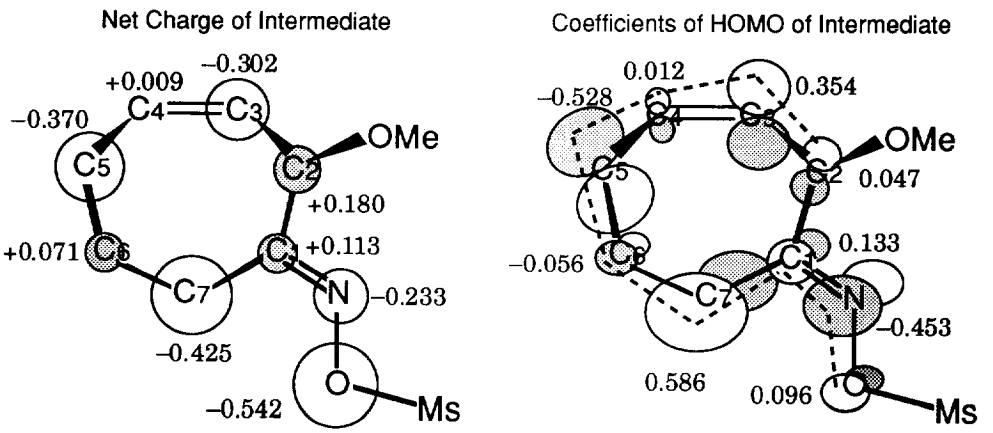
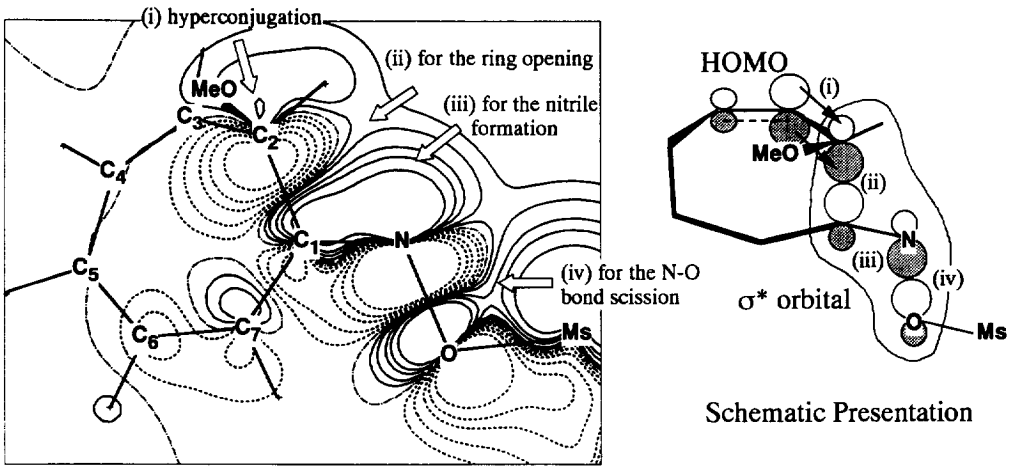


Fig. 3. Net Electronic Charges (positive, cationic) and a Shape of HOMO of the Anti Tetrahedral Intermediate in the Mesylate, **2**.

The broken lines in HOMO show the upper side of the molecular skeleton.

The HOMO electronic density is available for the intramolecular charge transfer. The target vacant MO should be of the σ*-type for the C(1)–C(2) and N–O bond scission. This σ* type MO [C(1)–C(2) σ*] can be found in the intermediate (Figure 4). A decisive point is found in Figure 4. In the intermediate, the antibonding nature becomes localized at the C(1)–C(2) and N–O regions. *The charge acceptance of the intermediate σ* orbital leads naturally to the scission of C(1)–C(2) and N–O bonds!* In addition, at the C(1)–N region, the large π-type bonding extension has appeared in the intermediate. This in-phase extension gives formation of the cyano group through the charge acceptance. The nodal properties of this σ* orbitals is similar to that of the frontier orbital for E2 reactions.[12] It is expected that the HOMO→σ* excitation, i.e., charge reorganization is the driving force of the ring opening. The HOMO→σ* charge-transfer takes place in a hyperconjugation between the p_π orbital on C(3) and the sp^3-type σ* on C(2) as the empty bold arrow (i) shown in Figure 4.



THE DRIVING FORCE OF RING OPENING

Fig. 4. The σ* (anti bonding in σ skeleton) Frontier Orbital Demonstrating the Concerted Ring Opening, C(1)–C(2) Bond Cleavage, Nitrile-Bond Formation and N–O Bond Cleavage.

Interrupted lines stand for null (zero) orbital contours. Noteworthy is localization of bond-interchange character for an E2-type mechanism induced by hyperconjugation in the intermediate. This orbital is the third σ* one, and the first and the second σ* orbitals are σ* (S–O) ones.

The combination of cleavage of C(1)–C(2) and N–O bonds and conversion of the imine bond to the nitrile bond is of the E2 reaction. Thus, the present ring opening is regarded as an E2-type mechanism induced by hyperconjugation.

The substrate **3** was found not to react with the nucleophiles. The C(1)–C(2) σ* orbital of the intermediate derived from **3** is different from the frontier orbital for E2 reactions. That is, in this σ* orbital, the antibonding nature localizes at the C(1)–C(2) region and is small at the N–O region. The HOMO → σ* charge transfer causes only the cleavage of the C(1)–C(2) bond as Table 1 shows. Therefore, **3** is not suitable for the concerted C(1)–C(2) and N–O bond scission.

The magnitude of the HOMO → C(1)–C(2) σ* intramolecular charge transfer depends on their energy gap. The smaller gap corresponds to the larger magnitude. For the mesylate (–OMs) and tosylate (–OTs), small energy gaps and accordingly small activation energies are obtained (Figure 5).

SUMMARY AND CONCLUDING REMARKS

Troponoid ring skeletons are rigid and cannot be broken usually. In this sense the facile ring-opening reaction is really surprising and has needed theoretical elucidation. We have tested why the σ bond of the troponoid ring is cleaved in spite of coexistence of their highly reactive conjugated π bonds. The following mechanistic consequences in the framework of the kinetic control have been obtained.

1) There is an exo imine bond and a tosyloxy or mesyloxy leaving group in the substrate **1** or **2**. This combination may provide a low-lying σ* MO ready for the bond scission. 2) The σ* MO is a vacant frontier MO and becomes localized effectively at bond-breaking parts when a tetrahedral intermediate is formed. 3) The HOMO → σ* internal charge transfer in the intermediate is the driving force for the concerted ring opening in an E2-type mechanism induced by hyperconjugation.

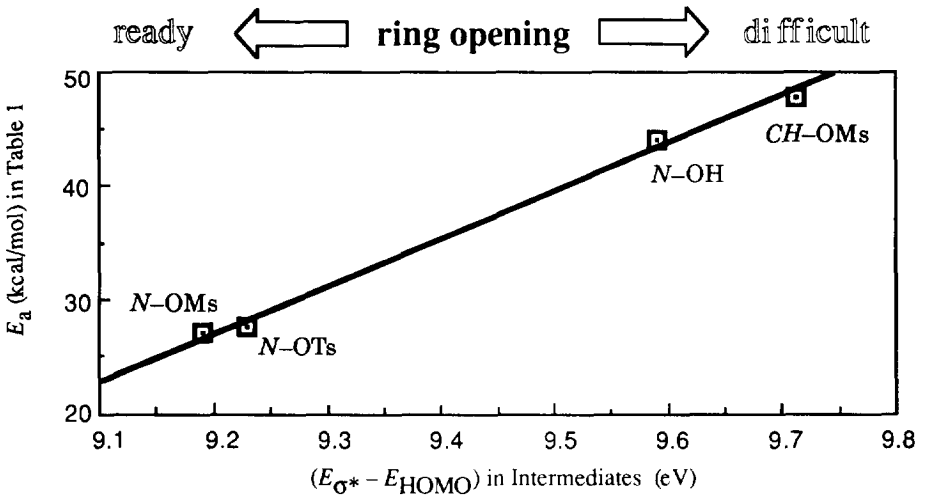


Fig. 5. A correlation between differences of FMO energies in the tetrahedral intermediate and computed activation energies (E_a's).

E_a values are shown in the right edges of Table 1. *N*–OMs means the intermediate between tropone oxime mesylate (**2**) and methoxide ion. Other similar notations are explained below Table 1.

EXPERIMENTAL SECTION

Computational Methods. Semiempirical PM3 MO[4] calculations were carried on a CONVEX C-220 computer in the Information Processing Center of Nara University of Education and on a CONVEX C-3420 computer in the Computer Center of Nara University.

Reagents and Starting Material. The starting material, tropothione[13] was prepared from tropone[14] as described previously. Tropone oxime (**3**) was obtained starting from tropone via tropothione according to a previously published procedure.[1] The solvents used were freshly distilled under nitrogen from appropriate drying agents. Pyrrolidine was freshly distilled over CaH_2 (solid). Dichloromethane was freshly distilled at reduced pressure to remove HCl. Evaporations were carried out at 0 °C or lower by using an aspirator or oil vacum pump. Solids were dried at room temperature (0.2 mmHg).

Instrumentation/Analytical Procedures. Melting points were determined on a Büchi 510 apparatus in open capillary tubes and were uncorrected. Elemental analyses were performed at the Analytical Laboratory, Chemical Analysis Center, Saitama University. IR spectra were recorded on a Hitachi 260-50 grating spec-

trometer using KBr disks. UV–visible spectra were taken with a Hitachi U-3300 recording spectrometer using 1-cm quartz cells. Electron impact mass spectra (MS) were obtained with a JEOL DX 303 double focusing spectrometer at ionizing potential of 70 eV. The values of *m/z* in significant ions were reported with relative intensities in parentheses (percent for the base peak) for low resolution analyses. NMR (^{13}C and ^{1}H) spectra were recorded on a Bruker AM-400 (400 MHz for ^{1}H, 100.6 MHz for ^{13}C) instruments in $CDCl_3$ with tetramethylsilane as the internal standard. The assignments of NMR spectra are based on $^{1}H\{^{1}H\}$ homonuclear decoupling and $^{13}C\{^{1}H\}$ heteronuclear 1D and 2D NMR experiments. The nuclear Overhauser effect (NOE) measurements were performed at 400 MHz on the AM-400 instrument in degassed $CDCl_3$ solutions at 27 °C. The enhancements of NOE were obtained from quantitative difference $^{1}H\{^{1}H\}$ NOE spectra. 1D ^{13}C NMR spectra were recorded without and with the resolution enhancement by Gaussian wind function, independently, at 128K data points.

Preparation of Tropone Oxime (3). A solution of tropothione[13] (2.24 g, 18.4 mmol) in 100 mL of chloroform was cooled to 0 °C and then was added a solution of hydroxylamine (1.77 g, 53.6 mmol) in 20 mL of ethanol. The mixture was stirred at 0 °C for 5 h. The resultant deep red solution was washed with 100 mL of water then was dried over anhydrous $MgSO_4$. Evaporation gave 2.07 g (17.1 mmol, 93%) of **3**.

3: deep red prisms, mp and mixed mp 71–72 °C (Lit.[1] 71.5–72 °C); IR ν_{max} 3160s, 3075s, 1600s, 1575s, 1550s, 1020s, 980s, 750s cm^{-1}; ^{1}H NMR δ 9.10 (br s, 1 H, OH), 6.96 (dd, 1 H, $J_{2,3}$ 12.5 and $J_{2,7}$ 2.1 Hz, H-2), 6.39 (dt, 1 H, $J_{6,7}$ 10.7, $J_{2,7} = J_{5,7}$ 2.1 Hz, H-7), 6.27 (dd, $J_{2,3}$ 12.5, $J_{3,4}$ 6.7 Hz, H-3), and 6.21–6.10 (complex m, 3 H, H-4 ~ H-6); ^{13}C NMR δ 156.70 (s, C-1), 133.84 (d, C-7), 132.76 (d, C-6), 132.17 (d, C-3), 130.39 (d, C-5/C-6), 129.69 (d, C-6/C-5), 125.08 (d, C-2); MS *m/z* 121 (M^+, 28), 104 (11), 78 (100), 77 (25), 51 (20).

Preparation of Tropone Oxime Mesylate (2). A solution of 2.00 g (16.5 mmol) of tropone oxime (**3**) in 5.5 mL of pyridine was added slowly 1.4 mL (18 mmol) of methanesulfonyl chloride over a period of 10 min. The reaction mixture was stirred at 0 °C for 7 h, then was added of ice–water, and yellow precipitation was obtained. The mixture was filtrated to afford yellow crystalline solid (3.08 g, 94 %), which was purified by recrystallization from ethanol giving **2**. Analytical samples were obtained by further recrystallization.

2: yellow needles, mp 54–55 °C; IR ν_{max} 1533s, 1343s, 1160s, 805s, 745s cm^{-1}; UV–vis λ_{max} (Hexane) 230 (log ε 4.23), 284 (3.84), 296 (3.91), 308 (3.89), 322 (3.64), 364 nm (3.01); ^{1}H NMR δ 7.03 (dd, 1 H, $J_{2,3}$ 12.5, $J_{2,4}$ 2.2 Hz, H-2), 6.68–6.50 (m, 3 H, H-3, -6, and -7), 6.53 (ddt, 1 H, $J_{4,5}$ 9.5, $J_{5,6}$ 8.1, $J_{3,5} = J_{5,7}$ 2.0 Hz, H-5), 6.47 (dddd, 1 H, $J_{4,5}$ 9.5, $J_{3,4}$ 8.1, $J_{2,4}$ 2.2, $J_{4,6}$ 1.7 Hz, H-4), 3.17 (s, 3 H, Me); ^{13}C NMR δ 162.29 (s, C-1), 135.67 (d, C-6/7), 134.16 (d, C-5), 133.89 (d, C-7/6), 131.76 (d, C-4), 131.29 (d, C-3), 124.31 (d, C-2), 36.33 (q, Me); MS *m/z* (70 eV) 199 (M^+, 10), 120 (53), 104 (10), 103 (40), 90 (100), 89 (99), 78 (76), 77 (75), 76 (36), 65 (21), 64 (30), 52 (57). Anal. Calcd for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03; S, 16.10. Found: C, 48.52; H, 4.54; N, 6.96; S, 16.01.

General Procedure for Reaction of Tropone Oxime (3) with Nucleophile. A solution of tropone oxime (1.00 g, 8.26 mmol) and a nucleophile(40 mmol) in 30 mL of a solvent (pyrrolidine in dichloromethane; NaOMe or MeMgI in THF) was stirred at room temperature for 2 days. A usual workup followed by solvent removal recovered almost quantitatively the oxime **3** unreacted. The reaction was performed using pyrrolidine, sodium methoxide and methylmagnesium iodide (Table 2). IR and ^{1}H NMR were identical with those of an authentic sample.

Reaction of Tropone Oxime Mesylate (2) with Pyrrolidine. A solution of the mesylate (**2**) of tropone oxime (1.03 g, 5.18 mmol) and pyrrolidine (1.78 g, 25.0 mmol) in 20 mL of dichloromethane (or chloroform) was stirred keeping the temperature below –20 °C for 1 h. The solution changed from yellowish brown to dark reddish brown. After evaporation of volatile material at –20 °C, cold dichloromethane or ether (10 mL) was added to the residue. The resulted solution was washed with saturated aqueous NaCl solution (4 × 3 mL), then was dried over $MgSO_4$. Solvent removal in vacuo at –20 °C left the crude product. The product was purified by recrystallization from ether to give 6-1'-pyrrolidinyl-(*Z,Z,Z*)-1,3,5-hexatrienecarbonitrile (**5a**) (891 mg, 99 %).

5a: yellow prisms, mp and mixed mp 53–54 °C (dec) (Lit.[1] 53–54 °C); IR ν_{max} 3040w, 2945m, 2850m, 2190s, 1615s, 1565 brs, 1380s, 1232s, 1124m, 705m cm^{-1}; UV–vis λ_{max} (MeOH) 244 (log ε 3.56), 270 (3.51), 399 nm (4.57); λ_{max} (Hexane) 236 (3.51), 264 (3.45), 377 nm (4.52); MS *m/z* 174 (M^+, 100), 108 (51), 104 (23), 78 (18), 52 (11), 51 (6), 50 (11); ^{1}H NMR δ 7.29 (ddd, 1 H, $J_{2,3}$ 11.9, $J_{1,2}$ 10.8, $J_{2,4}$ 1.1 Hz, H-2), 6.90 (ddq 1 H, $J_{4,5}$ 13.2, $J_{3,4}$ 10.6, $J_{2,4} = J_{4,6} = J_{1,4}$ 1.1 Hz, H-4), 6.23 (dt, 1 H, $J_{5,6}$ 9.1, $J_{4,6}$ $J_{3,6}$

1.1 Hz, H-6), 5.97 (ddt, 1 H, $J_{2,3}$ 11.9, $J_{3,4}$ 10.6, $J_{1,3} = J_{3,6}$ 1.1, $J_{3,5}$ <1.0 Hz, H-3), 5.12 (dd, 1 H, $J_{4,5}$ 13.2, $J_{5,6}$ 9.1, $J_{3,5}$ < 1.0 Hz, H-5), 4.88 (dt, 1 H, $J_{1,2}$ 10.8, $J_{1,3} = J_{1,4}$ 1.1 Hz, H-1), 3.46 (t, 4 H, J 6.6 Hz, H-2',5'), 1.90 (m, 4 H, H-3',4'); quantitative difference NOE experiment: irr δ 7.29 (H-2), enhanced δ 4.88 (20%, H-1), 5.12 (21%, H-5); irr δ 6.90 (H-4), enhanced δ 5.97 (20%, H-3); irr δ 6.23 (H-6), enhanced δ 5.12 (22%, H-5); irr δ 5.97 (H-3), enhanced δ 6.90 (22%, H-4); irr δ 5.12 (H-5), enhanced δ 7.29 (15%, H-2), 6.23 (24%, H-6); irr δ 4.88 (H-1), enhanced δ 7.29 (26%, H-2).

Reaction of Tropone Oxime Mesylate (2) with Sodium Methoxide. The above procedure was followed using **2** (1.03 g, 5.18 mmol) in 30 mL of anhydrous tetrahydrofuran (THF) and sodium methoxide (10.4 mmol) in 5 mL of methanol keeping the temperature below 0 °C. The solution changed from yellowish brown to deep purple almost instantaneously. The reaction mixture was stirred at 0 °C for 3 h. The completion of this reaction was confirmed by TLC on alumina (benzene elution). A 100 mL of cold water was added to the reaction mixture, and the aqueous mixture was extracted with ether repeatedly. Solvent removal gave reddish brown solid. Recrystallization from ether gave 6-methoxy-(*Z,Z,Z*)-1,3,5-hexatrienecarbonitrile (**5b**) (678 mg, 97%).

5b: colorless needles, mp and mixed mp 54–55 °C (Lit.[1] 54–55 °C); IR ν_{max} 3050w, 2930m, 2840m, 2200s, 1625s, 1595m, 1265s, 1100s, 1025m, 740s cm^{-1}; UV–vis λ_{max} (MeOH) 226 (log ε 3.54), 260 (3.72), 325 nm (4.38); λ_{max} (Hexane) 221 (3.51), 264 (3.82), 314 nm (4.48); MS, *m/z* 135 (M^+, 93), 120 (15), 104 (21), 78 (18), 66 (30), 65 (100), 52 (18), 51 (18), 50 (15); ^1H NMR δ 7.21 (ddd, 1 H, $J_{2,3}$ 12.2, $J_{1,2}$ 10.8, $J_{2,4}$ 1.0 Hz, H-2), 6.81 (ddddd, 1 H, $J_{4,5}$ 12.2, $J_{3,4}$ 10.8, $J_{1,4}$ 1.6, $J_{4,6}$ 1.2, $J_{2,4}$ 1.0 Hz, H-4), 6.31 (dddt, 1 H, $J_{2,3}$ 12.2, $J_{3,4}$ 10.8, $J_{3,6}$ 1.7, $J_{1,3} = J_{3,5}$ 1.0 Hz, H-3), 6.18 (ddd, 1 H, $J_{5,6}$ 6.4, $J_{3,6}$ 1.7, $J_{4,6}$ 1.2 Hz, H-6), 5.46 (ddd, 1 H, $J_{4,5}$ 12.2, $J_{5,6}$ 6.4, $J_{3,5}$ 1.0 Hz, H-5), 5.15 (ddd, 1 H, $J_{1,2}$ 10.8, $J_{1,4}$ 1.6, $J_{1,3}$ 1.0 Hz, H-1), 3.75 (s, 3 H, OMe); Quantitative difference NOE experiment: irr δ 7.21 (H-2), enhanced δ 5.15 (22%, H-1), 5.46 (20%, H-5); irr δ 6.81 (H-4), enhanced δ 6.31 (19%, H-3); irr δ 6.18 (H-6), enhanced δ 5.46 (25%, H-5); irr δ 6.31 (H-3), enhanced δ 6.81 (20%, H-4); irr δ 5.46 (H-5), enhanced δ 7.21 (16%, H-2), 6.18 (18%, H-6); irr δ 5.15 (H-1), enhanced δ 7.21 (18%, H-2).

Reaction of Tropone Oxime Mesylate (2) with Methyl Magnesium Iodide. The general procedure was followed, using **2** (3.00 g, 15.1 mmol) in 50 mL of THF and an ethereal solution (16.3 mL) of methyl magnesium iodide (22.7 mmol). The reaction mixture was stirred at 0 °C for 4 h. The mixture was added 60 mL of aqueous ammonium chloride solution (0.39 mol) at once at −18 °C. The resultant ethereal solution was washed with cold saturated solution of sodium chloride several times until a neutral solution was obtained. Solvent removal left brownish oily residue. The residue was passed through short florisil column chromatography eluted with dichloromethane, then was purified by silica gel column chromatography eluted with benzene to give yellowish crystals (1.22g, 68%). Recrystallization from ether gave (*Z,Z,Z*)-1,3,5-heptatrienecarbonitrile (**5c**).

5c: colorless needles, mp and mixed mp 42–43 °C (Lit.[1] 42–43 °C); IR ν_{max} 3055m, 3015m, 2915m, 2220s, 1620m, 1597s, 724s cm^{-1}; UV–vis λ_{max} (MeOH) 298 nm (log ε 4.44); λ_{max} (hexane) 295 nm (4.49), MS *m/z* 119 (M^+, 67), 118 (54), 104 (56), 92 (35), 91 (100), 78 (15), 52 (19), 51 (22), 50 (14); ^1H NMR δ 7.31 (ddd, 1 H, $J_{2,3}$ = 12.2, $J_{1,2}$ = 10.9, $J_{2,4}$ = 1.1, $J_{2,6}$ < 1.0 Hz, H-2), 6.74 (ddddd, 1 H, $J_{4,5}$ 11.9, $J_{3,4}$ 11.0, $J_{4,6}$ 1.8, $J_{1,4}$ 1.6, $J_{2,4}$ 1.1, $J_{4,Me}$ < 1.0 Hz, H-4), 6.48 (ddqdd, 1 H, $J_{4,5}$ 11.9, $J_{5,6}$ 10.7, $J_{5,Me}$ 1.8, $J_{3,5}$ 1.6, $J_{1,5}$ 1.1 Hz, H-5), 6.47 (ddddd, 1 H, $J_{2,3}$ 12.2, $J_{3,4}$ 11.0, $J_{1,3}$ 1.8, $J_{3,5}$ 1.6, $J_{3,6}$ 1.1 Hz, H-3), 5.88 (dqdd, 1 H, $J_{5,6}$ 10.7, $J_{6,Me}$ 7.2, $J_{4,6}$ 1.8, $J_{3,6}$ 1.1, $J_{2,6}$ < 1.0, $J_{1,6}$ < 1.0 Hz, H-6), 5.24 (dtd, 1 H, $J_{1,2}$ 10.9, $J_{1,3} = J_{1,4}$ = 1.6, $J_{1,5}$ 1.1, $J_{1,6}$ <1.0 Hz, H-1), 1.85 (dd, 3 H, $J_{6,Me}$ 7.2, $J_{5,Me}$ 1.8, $J_{4,Me}$ <1.0 Hz, Me); Quantitative difference NOE experiment: irr δ 7.31 (H-2), enhanced δ 5.24 (18%, H-1), 6.48 (18%, H-5); irr δ 6.74 (H-4), enhanced δ 6.47 (20%, H-3); irr δ 5.88 (H-6), enhanced δ 6.48 (18%, H-5); irr δ 6.47 (H-3), enhanced δ 6.74 (18%, H-4); irr δ 6.48 (H-5), enhanced δ 7.31 (22%, H-2), 5.88 (17%, H-6); irr δ 5.24 (H-1), enhanced δ 7.31 (21%, H-2).

Reaction of Tropone Oxime Mesylate (2) with Sodium Ethanethiolate. A mixture of solution of the mesylate **2** (3.00 g, 15.1 mmol) in 90 mL of anhydrous THF and sodium ethanethiolate (18.1 mmol) in 10 mL of ethanol was stirred at –20 °C for 1 h. Workup similar to the above case of sodium methoxide left yellowish crystalline residue (2.44 g, 98%). Recrystallization from ether–hexane (95:5) gave 6-(ethylthio)-(*Z,Z,Z*)-1,3,5-hexatrienecarbonitrile (**5d**).

5d: pale yellow prisms, mp 49–50 °C; IR ν_{max} 3045w, 2950w, 2910w, 2198m, 1585s, 1570m, 1443w, 755s, 702s cm^{-1}; UV–vis λ_{max} (MeOH) 258 (log ε 3.83), 273 (3.73), 353 nm (4.22); λ_{max}

(Hexane) 257 (4.04), 272 (3.91), 345 nm (4.40); ^{1}H NMR δ 7.25 (ddd, 1 H, $J_{2,3}$ 12.0, $J_{1,2}$ 10.8, $J_{2,4}$ 1.1 Hz, H-2), 6.68 (ddddd, 1 H, $J_{4,5}$ 11.7, $J_{3,4}$ 10.9, $J_{1,4}$ 1.5, $J_{4,6}$ 1.3, $J_{2,4}$ 1.1 Hz, H-4), 6.51 (ddd 1 H, $J_{4,5}$ 11.7, $J_{5,6}$ 9.3, $J_{3,5}$ 0.9 Hz, H-5), 6.45 (dddt, 1 H, $J_{2,3}$ 12.0, $J_{3,4}$ 10.9, $J_{1,3}$ 1.1, $J_{3,5}$ =$J_{3,6}$ 0.9 Hz, H-3), 6.41 (ddd, 1 H, $J_{5,6}$ 9.3, $J_{4,6}$ 1.3 , $J_{3,6}$ 0.9 Hz, H-6), 5.22 (ddd, 1 H, $J_{1,2}$ 10.8, $J_{1,4}$ 1.5, $J_{1,3}$ 1.1 Hz, H-1), 2.79 (q, 2 H, J 7.4 Hz, SC*H*$_2$CH$_3$), 1.33 (t, 3 H, J 7.4 Hz, SCH$_2$C*H*$_3$); ^{13}C NMR δ 143.61 (ddt, $^1J_{CH}$ 157.9, $^3J_{CH(4)}$ 10.6, $^2J_{CH(1)}$ = $^2J_{CH(3)}$ 2.5 Hz, C-2), 135.68 (dtd $^1J_{CH}$ 172.9, $^3J_{CH(4)}$ = $^3J_{CH(CH_2)}$ 5.4, $^2J_{CH(6)}$ 1.9 Hz, C-6), 132.89 (dddd, $^1J_{CH}$ 153.0, $^3J_{CH(6)}$ 18.1, $^3J_{CH(2)}$ 8.0, $^2J_{CH(5)}$ 3.5 Hz, C-4), 123.33 (dddd, $^1J_{CH}$ 159.5, $^3J_{CH(1)}$ 10.6, $^3J_{CH(5)}$ 3.3, $^2J_{CH(2)}$ 1.9 Hz, C-3), 120.21 (dtd, $^1J_{CH}$ 161.8, $^2J_{CH(4)}$ = $^3J_{CH(3)}$ 9.0, $^2J_{CH(6)}$ 2.9 Hz, C-5), 116.52 (dd, $^3J_{CH(2)}$ 14.9, $^2J_{CH}$(1) 3.1 Hz, CN), 96.90 (ddd, $^1J_{CH}$ 177.6, $^3J_{CH(3)}$ 5.4, $^2J_{CH(2)}$ 1.9 Hz, C-1), 28.48 (tquin, $^1J_{CH}$ 140.2, $^2J_{CH(Me)}$ = $^3J_{CH(6)}$ 4.6 Hz, SC*H*$_2$), 15.59 (qt, $^1J_{CH}$ 128.8, $^2J_{CH(CH2)}$ 3.5 Hz, SCH$_2$C*H*$_3$); MS *m/z* 165 (M^+, 100), 136 (85), 104 (53), 78 (45), 52 (54), 51 (34), 50 (19). Anal. Calcd for $C_9H_{11}NS$: C, 65.41; H, 6.71; N, 8.48; S, 19.40. Found: C, 65.37; H, 6.70; N, 8.47; S, 19.35.

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