Highly Stereoselective Ring Opening Reaction of Tropone Oxime Tosylate with Nucleophiles

Takahisa Machiguchi,*[a] Toshio Hasegawa,[a] Megumi Ohno,[a] (the late) Yoshio Kitahara,[b] Makoto Funamizu,[b] and Tetsuo Nozoe*[c]

[a] *Department of Chemistry, College of Liberal Arts and Science, Saitama University, Shimo-Ohkubo, Urawa, Saitama 338, Japan*
[b] *Department of Chemistry, Faculty of Science, Tohoku University, Aramaki-Aoba, Sendai, Miyagi 980, Japan*
[c] *Tokyo Research Laboratories, Kao Corporation, Bunka, Sumida-ku, Tokyo 131, Japan*

The tosylate (**1**) of tropone oxime undergoes a novel ring-opening reaction under mild conditions with secondary amines, alkoxides, and Grignard reagents affording stereoselectively 6-substituted (1*Z*,3*Z*,5*Z*)-hexa-1,3,5-trienecarbonitriles (**2a—h**) as sole products in high yields; these are easily converted into *Z,Z,E*-isomers (**3a—h**) with acids and further into *E,E,E*-isomers (**4a—h**) as the final form by stronger acid or by passing the solution over a column of alumina.

Although troponoid compounds are known to isomerize to the corresponding benzenoid compounds,[1] cleavage of the troponoid skeleton has rarely been observed. In fact, the only recorded example is the thermal decomposition of 2-azidotropone in aqueous dioxane, methanol, or aniline to give a mixture of conjugated dienecarboxylic acid and derivatives.[2] We report that the tosylate (**1**) of tropone oxime† undergoes a highly stereoselective rearrangement with a variety of nucleophiles to form 6-substituted hexa-1,3,5-trienecarbonitriles.

The tosylate (**1**) reacted smoothly with a variety of secondary amines at low temperature to give only the ring-cleavage products (**2a—d**) with *Z,Z,Z*-configuration, in high yields. With sodium alkoxides and Grignard reagents in tetrahydrofuran (THF), the products were (**2e** and **f**) or (**2g** and **h**), respectively.‡ Results are summarized in Table 1.

† Obtained from the oxime as yellow needles, m.p. 94—95 °C. Tropone oxime was obtained from cyclohepta-2,4,6-triene-1-thione (tropothione)[3] with hydroxylamine in chloroform (65%) at room temperature or from tropone[4] with hydroxylamine hydrochloride in refluxing methanol (98%). When hydroxylamine itself is used, tropone does form the oxime but only as a minor product in competition with the formation of 2-aminotropone.[5]

‡ Satisfactory combustion microanalytical data were obtained for all new compounds reported.

Spectral data for representative compounds are as follows: (**2a**) yellow prisms, i.r. ν_{max} (KBr) 2190s, 1615s, and 1565br. s cm^{-1}; u.v.–visible λ_{max} (MeOH) 244 (log ε 3.56), 270sh (3.51), 286sh (3.43), 301sh (3.24), and 399 nm (4.57); ^{1}H n.m.r. (90 MHz; $CDCl_3$) δ 1.91 (4H, m, $N[CH_2]_2$-$[CH_2]_2$), 3.46 (4H, m, $N[CH_2]_2$), 4.87 (1H, d, *J* 10.8 Hz, 1-H), 5.11 (1H, dd, *J* 13.2, 9.0 Hz, 5-H), 5.97 (1H, dd, *J* 11.8, 10.6 Hz, 3-H), 6.23 (1H, d, *J* 9.0 Hz, 6-H), 6.90 (1H, dd, *J* 13.2, 10.6 Hz, 4-H), and 7.29 (1H, dd, *J* 11.8, 10.8 Hz, 2-H); ^{13}C n.m.r. (22.5 MHz; $CDCl_3$) δ 25.62 ($N[CH_2]_2$-$[CH_2]_2$), 52.28 ($N[CH_2]_2$), 89.98 (C-1), 92.86 (C-5), 114.52 (C-3), 118.10 (CN), 135.87 (C-4), 139.28 (C-6), and 144.00 (C-2); (**2e**) colourless needles, i.r. ν_{max} (KBr) 2200s, 1620s, and 1100s cm^{-1}; u.v.–visible λ_{max} (MeOH) 226 (log ε 3.54), 260sh (3.72), and 325 nm (4.38); ^{1}H n.m.r. (90 MHz; $CDCl_3$) δ 3.75 (3H, s, OMe), 5.14 (1H, d, *J* 11.0 Hz, 1-H), 5.46 (1H, dd, *J* 12.0, 6.2 Hz, 5-H), 6.19 (1H, d, *J* 6.2 Hz, 6-H), 6.30 (1H, dd, *J* 11.0, 10.7 Hz, 3-H), 6.82 (1H, dd, *J* 12.0, 10.7 Hz, 4-H), and 7.21 (1H, t, *J* 11.0 Hz, 2-H); ^{13}C n.m.r. (22.5 MHz; $CDCl_3$) δ 60.68 (OMe), 95.51 (C-1), 101.69 (C-5), 116.69 (CN), 120.92 (C-3), 131.05 (C-4), 143.78 (C-2), and 151.96 (C-6); (**2g**) colourless needles, i.r. ν_{max} (KBr) 2220s, 1597s, and 724s cm^{-1}; u.v.–visible λ_{max} (MeOH) 298 nm (log ε 4.44); ^{1}H n.m.r. (400 MHz; $CDCl_3$) δ 1.85 (3H, d, *J* 7.3 Hz, Me), 5.23 (1H, d, *J* 10.7 Hz, 1-H), 5.87 (1H, dq, *J* 11.2 Hz, 7.3 Hz, 6-H), 6.48 (2H, t, *J* 11.2 Hz, 3-H, 5-H), 6.74 (1H, t, *J* 11.2 Hz, 4-H), and 7.31 (1H, dd, *J* 11.2, 10.7 Hz, 2-H); ^{13}C n.m.r. (22.5 MHz; $CDCl_3$) δ 13.52 (Me), 97.08 (C-1), 116.41 (CN), 123.67 (C-3, C-5), 132.62 (C-4), 133.27 (C-6), and 143.54 (C-2).

The n.m.r. assignments (atom numbering in Scheme 1) were based on ^{1}H{^{1}H} and ^{13}C{^{1}H} (selective heteronuclear decoupling) data.

The products (**2**) are thermodynamically unstable and rearrange to their more stable isomers (**3**) and (**4**), respectively.§ Thus, the amino derivatives (**2a—d**) were easily isomerized with aqueous 0.05% acetic acid at 0 °C to the *Z,Z,E*-isomers (**3a—d**). Likewise, (**2e** and **f**) were converted into their *Z,Z,E*-isomers (**3e** and **f**) with toluene-*p*-sulphonic acid (TsOH). The rearrangement of (**2g** and **h**) to their *Z,Z,E*-isomers (**3g** and **h**) was effected with acetic acid. The *Z,Z,E*-isomers (**3a—h**) were further isomerized to the respective most stable *E,E,E*-isomers (**4a—h**). Similarly, the initial *Z,Z,Z*-products (**2a—h**) were converted into (**4a—h**). The conditions and yields for these isomerizations are summarized in Scheme 1.

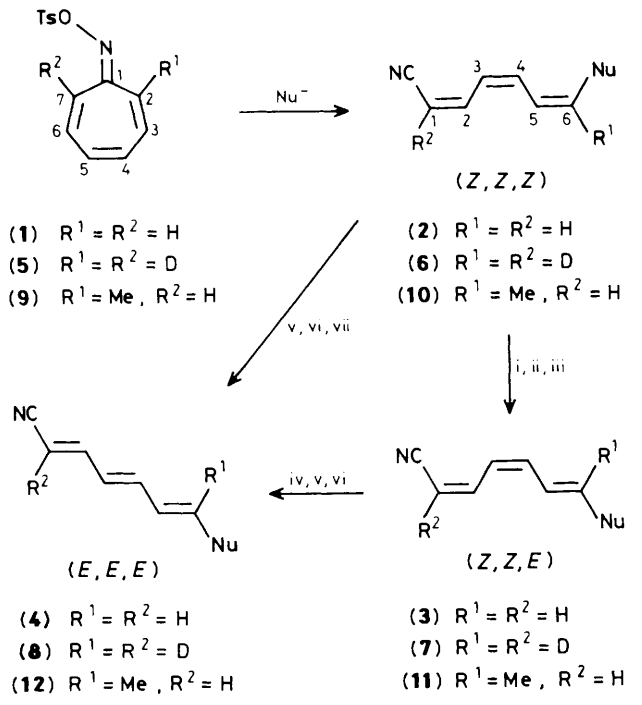
In order to determine the attacking position of the nucleophiles, the tosylate (**5**) of [2,7-^{2}H$_2$]tropone oxime (isotopic purity 93.2% $^2H_2$, 6.8% $^2H_1$, from mass spec-

Table 1. Reactions of the tosylate (**1**) with secondary amines, alkoxides, and Grignard reagents to give 6-substituted (1*Z*,3*Z*,5*Z*)-hexa-1,3,5-trienecarbonitriles (**2**).

Entry	Nucleophile	Conditions	Product (**2**)[a]	Yield[b] (%)
1	Pyrrolidine	CH_2Cl_2, −20 °C, 1 h[c]	(**2a**)	97
2	Me_2NH	CH_2Cl_2, −20 °C, 2 h[c]	(**2b**)	96
3	Me_2NH	—, −20 °C, 30 min[c]	(**2b**)	98
4	Et_2NH	—, 0 °C, 2.5 h[c]	(**2c**)	97
5	Morpholine	—, 0 °C, 40 min[c]	(**2d**)	92
6	MeONa	THF, 0 °C, 4 h	(**2e**)	96
7	EtONa	THF, 0 °C, 30 min	(**2f**)	98
8	MeMgI[d]	THF, 0 °C, 4 h	(**2g**)	34
9	PhMgBr[d]	THF, 0 °C, 3 h	(**2h**)	45

[a] M.p. or b.p.: (**2a**) 53—54 °C (decomp.); (**2b**) 56—57 °C (decomp.); (**2c**) 20 °C at 0.02 mmHg; (**2d**) 44—45 °C (decomp.); (**2e**) 54—55 °C; (**2f**) 42—43 °C; (**2g**) 42—43 °C; (**2h**) 35—36 °C. [b] Yield at isolated material. [c] The tosylate (**1**) reacted with amines at temperatures above 20 °C to give a mixture of *Z,Z,Z*- (main product) and *Z,Z,E*-isomers. Compound (**1**) was recovered unchanged when treated with ammonia at room temperature overnight in a sealed tube. [d] When methyl- or phenyl-lithium was used the yields were significantly lower.

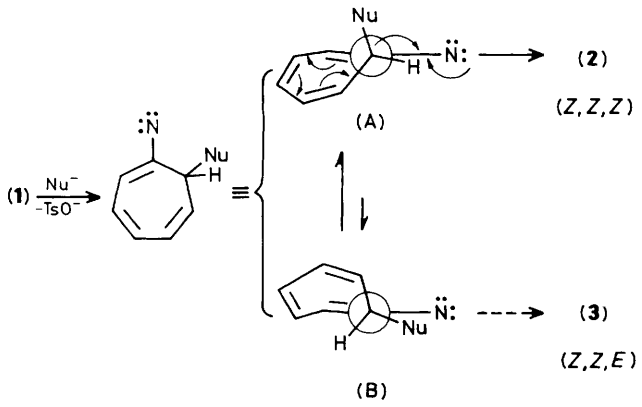
§ ^{1}H N.m.r. vicinal coupling constants (in Hz) in the order of $J_{1,2}$, $J_{3,4}$, $J_{5,6}$: (**2a**) 10.8, 10.6, 9.0; (**3a**) 10.6, 10.5, 12.2; (**4a**) 15.5, 14.0, 12.7; (**2b**) 10.7, 10.3, 9.3; (**3b**) 11.1, 10.3, 12.3; (**4b**) 15.6, 14.3, 12.7; (**2c**) 10.6, 10.3, 9.6; (**3c**) 10.4, 10.2, 12.9; (**4c**) 15.4, 14.0, 13.1; (**2d**) 10.8, 10.7, 8.9; (**3d**) 10.5, 10.5, 12.9; (**4d**) 15.7, 14.7, 13.2; (**2e**) 11.0, 10.7, 6.2; (**3e**) 11.0, 11.4, 12.1; (**4e**) 15.7, 14.8, 12.3; (**2f**) 10.8, 10.4, 6.3; (**3f**) 11.0, 11.0, 12.1; (**4f**) 15.7, 14.7, 12.2; (**2g**) 10.7, 11.2, 11.2; (**3g**) 11.0, 10.3, 14.7; (**4g**) 15.8, 15.0, 14.7; (**2h**) 10.7, 11.7, 11.7; (**3h**) 10.6, 10.6, 15.4; (**4h**) 16.1, 14.7, 15.1; (**10b**) 10.8, 10.2; (**11b**) 10.5, 10.4; (**12b**) 15.6, 13.7.



Nu: **a**, N⬠; **b**, NMe_2; **c**, NEt_2; **d**, N⬡O;

e, OMe; **f**, OEt; **g**, Me; **h**, Ph.

Scheme 1. *Reagents and conditions*: i, aq. 0.05% AcOH, 0 °C, 3 h, 95—99% for (**2a—c**), and 12 h, 96% for (**2d**); ii, TsOH (1 equiv.), dioxane, reflux, 5—8 h, 25—30% for (**2e** and **f**); iii, AcOH (10 equiv.), CCl_4, reflux, 10—18 h, 92—96% for (**2g** and **h**); iv, aq. 5% AcOH, 10 °C, 4 h, 92—96% for (**3a—c**), and 8 h, 42% for (**3d**); v, TsOH (1 equiv.), $CHCl_3$, reflux, 2 h, 22—27% for (**2e** and **f**) and (**3e** and **f**); vi, HCl gas, MeCN, 0 °C, 1—2 days, 66—98% for (**2g** and **h**) and (**3g** and **h**); vii, alumina column, CH_2Cl_2, room temp., 75—86% for (**2a—c**), 57% for (**2d**).



Scheme 2

trometry), synthesized from [2,7-$^2H_2$]cycloheptatrienethione,[3c] was subjected to the reaction with pyrrolidine, affording [1,6-$^2H_2$]hexatrienecarbonitrile (**6a**) (isotopic purity 92.8% $^2H_2$, 7.2% $^2H_1$). The product (**6a**) was converted into (**7a**) and finally into (**8a**). Similarly, reaction of the tosylate (**9**) of 2-methyltropone oxime with dimethylamine gave (**10b**), which was further isomerized to (**11b**) and (**12b**).¶ These results show that the nucleophiles attack at C-2 from the side *anti* to the tosyl group in (**1**), (**5**), and (**9**), despite steric hindrance by the methyl group in the last case. The reaction path shown in Scheme 2 represents a possible interpretation of the stereoselective initial formation of the *Z,Z,Z*-isomers. A conformation (A) with the substituent in the axial position in the nitrene intermediate is preferred to (B) with the substituent in the equatorial position according to a MINDO/3 calculation.**

Thus, the ring opening reaction and subsequent conversions gave each geometrical isomer of the 6-substituted hexatrienecarbonitriles [(**2a—h**), (**3a—h**), and (**4a—h**)]. The high yields, mild experimental conditions, and high stereoselectivity of this reaction promise a synthetically useful method leading to conjugated hexatrienes.

One of the authors (T. M.) thanks the Ministry of Education, Science and Culture, Japan and the Suntory Institute for Bioorganic Research for grants. We also thank Professor Satoru Masamune (Massachusetts Institute of Technology, U.S.A.) for discussions.

Received, 17th March 1988; Com. 8/01089G

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¶ Compound (**9**) was synthesized from 2-methyltropone oxime[6] in a similar way to (**1**) in 93% yield. The *E*-configuration was confirmed by both nuclear Overhauser enhancement (n.O.e.) (between the H-7 in the seven-membered ring and an *ortho*-H in the tosyl ring) and an *X*-ray analysis (details to be published elsewhere). The configuration of the C(5)—C(6) bond in (**10b**), (**11b**), and (**12b**) was verified by n.O.e. (enhancement > 22% each between 4-H or 5-H and C-Me or N-Me).

** The calculations and geometry optimization of the nitrene intermediates (A) and (B) were carried out for (**2b, e,** and **g**) at the Computer Centre, University of Tokyo, by use of the MOPAC program.[7]