A Novel Synthesis of Bicyclic Isoxazolines *via* Sequential Michael and Intramolecular 1,3-Dipolar Additions

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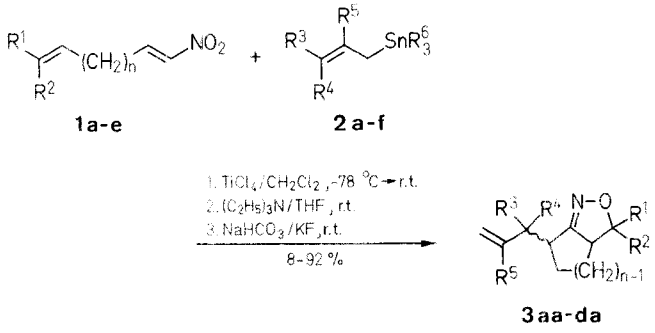
Bicyclic isoxazolines are obtained in good yields by the titanium tetrachloride-mediated reaction of allylic stannanes with 1-nitroalkadienes. Titanium tetrachloride converts stannyl nitronates generated in the Michael addition step to nitrile oxide equivalents which, on adding triethylamine, undergo intramolecular 1,3-dipolar cycloaddition to give the isoxazolines.

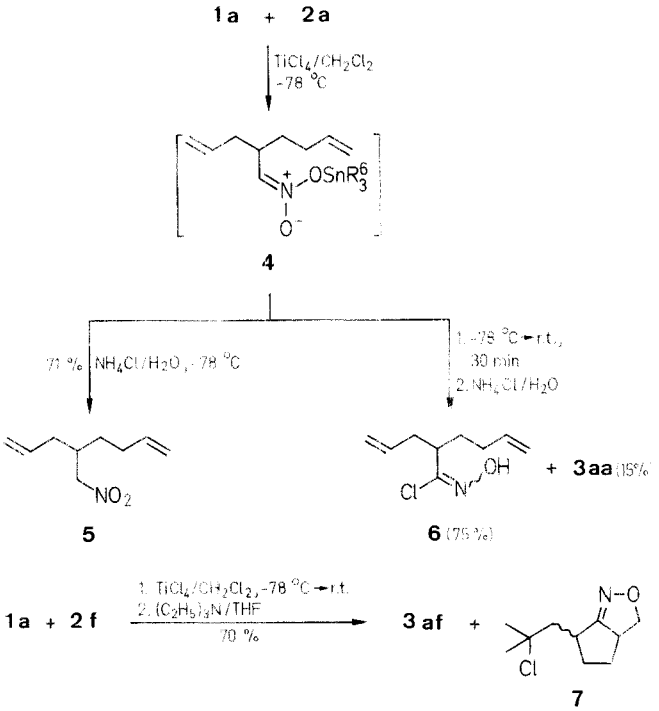
The chemistry of isoxazolines continues to attract interest because their versatile ring functions as a masked aldol, γ-amino alcohol, or unsaturated carbonyl group.[1] In addition, isoxazoline derivatives could be utilized in order to regulate the stereo- and regiochemistry in natural product syntheses.[2] Preparation of the isoxazoline derivatives is usually carried out by 1,3-dipolar cycloaddition of nitrile oxides which are generated from nitro, oxime, or hydroxyimino chloride compounds.[3] Isoxazolines are also prepared by the cycloaddition of silyl nitronates.[4] In this paper, we report a new synthesis of bicyclic isoxazolines **3** based on the intramolecular 1,3-dipolar cycloaddition of nitrile oxides (or their equivalents) generated in the Lewis acid-mediated reaction of 1-nitroalkadienes with allylic stannanes.



1	R^1	R^2	n
a	H	H	2
b	C_6H_5	H	2
c	CH_3	CH_3	2
d	H	H	3
e	$H_2C=CH$	H	2

2	R^3	R^4	R^5	R^6
a	H	H	H	CH_3
b	H	H	H	C_6H_5
c	CH_3	H	H	C_6H_5
d	CH_3	CH_3	H	C_6H_5
e	C_6H_5	H	H	CH_3
f	H	H	CH_3	C_6H_5

Michael addition of allyltrimethylstannane (**2a**) to 1-nitro-1,5-hexadiene (**1a**)[5] was induced by addition of titanium tetrachloride at −78 °C to give nitronate **4** which could be isolated as nitro form **5** in 71% yield[8] if the reaction was quenched immediately at −78 °C. The nitronate **4** was converted by titanium tetrachloride to hydroxyimino chloride **6** (or metallooxyimino chloride) when the reaction mixture was allowed to warm to room temperature.[9] A nitrile oxide generated by subsequent addition of triethylamine underwent intramolecular cycloaddition to give bicyclic isoxazoline **3aa** as a diastereomeric mixture (ca 3:2, determined by ^{13}C-NMR). Reactions of various 1-nitroalkadienes **1** and allylic stannanes **2** were examined and the results are listed in Table 1. Allyl groups were introduced with allylic transposition to give the corresponding isoxazolines **3** in good yields (entries 1–5), except for 2-methyl-2-propenylstannane **2f**, where hydrochlorination of the double bond occurred partially to give a mixture of **3af** and **7** under the standard conditions (**3af**:**7** = ca 1:2, the combined yield was 70%). The side-reaction could be overcome by using 2 equivalents of **2f** to **1a**. Thus, isoxazoline **3af** was obtained in 74% yield (entry 6). When the dipolarophilic site was sterically hindered or labile under the acidic conditions employed, the reactions were greatly suppressed yielding complexed mixtures (entries 8 and 10). Laborious chromatographic separation gave a low yield of isoxazoline **3ca** (8%, entry 8), while no identifiable compounds were obtained in entry 10. Isoxazoline **3da** with a 6-membered fused ring was also obtained in 78% yield from 1-nitro-1,6-heptadiene (**1d**).[5] In contrast to **3aa**, isoxazoline **3da** obtained was diastereomerically pure and its stereochemistry was assigned to be *cis* by diagnosis of the 400 MHz ^{1}H-NMR spectra. Allylic silanes could be utilized instead of stannanes, although yields were somewhat lower due to byproduct formation. Thus, the reaction of **1a** with allyltrimethylsilane performed under similar conditions afforded **3aa** (80%) and chlorinated isoxazoline **8**[10] (10%).



Other Lewis acids such as aluminium trichloride and tin tetrachloride were not so effective for this purpose, although they are known as good activators of conjugated nitro olefins.[11] In the presence of tin tetrachloride, instead of titanium tetrachloride, the reaction of **1a** with **2a** led to a complex mixture, while an unexpected compound, to which cyclohexanone oxime structure

9 was assigned, was obtained in 74% yield when aluminium trichloride was employed. On standing overnight at room temperature, the oxime **9** underwent both dehydrochlorination and deoximation to give a conjugated cyclohexenone **10.** A marked contrast between the reactions using titanium tetrachloride and aluminium trichloride could be attributed to the difference of their Lewis acidity if a hydroxyimino chloride derivative as an intermediate is assumed. The use of aluminium trichloride (stronger Lewis acid than titanium tetrachloride) would bring about an intramolecular Friedel-Crafts type reaction of the hydroxyimino chloride derivative to give **9.**

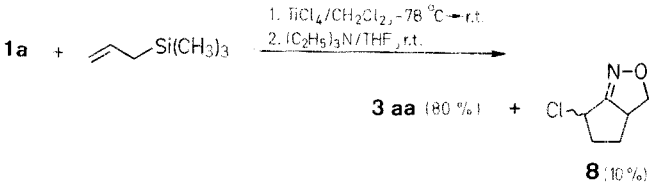
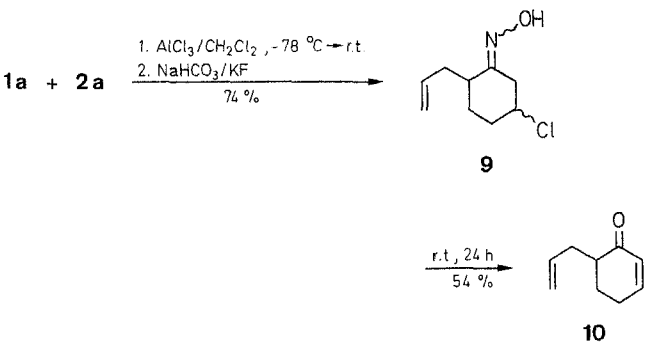


Table 1. Titanium Tetrachloride-Promoted Reaction of 1-Nitroalkadienes with Allylic Stannanes

Entry	Reactants	Product	Yield (%)	b.p. (°C)/mbar[a]	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)[c]	IR (Neat) ν (cm^{-1})[d]	MS (20 eV)[e] *m/e* (%)
1	**1a + 2a**	**3aa**[f]	92	75/0.4	$C_9H_{13}NO$ (151.2)	1.4–2.6 (m, 6H); 2.8 (m, 1H); 3.77 (m, 2H); 4.50 (m, 1H); 5.10 (m, 2H); 5.80 (m, 1H or major); 5.90 (m, 1H of minor)	1642, 1464, 916	151 (M^+, 7); 135 (7); 120 (30); 118 (27); 110 (62); 94 (48); 80 (100)
2	**1a + 2b**	**3aa**[f]	88					
3	**1a + 2c**	**3ac**[g]	64	96/0.4	$C_{10}H_{15}NO$ (165.2)	1.15 (m, 3H); 1.60–2.90 (m, 6H); 3.6–4.2 (m, 2H); 4.2–5.5 (m, 3H); 5.5–6.2 (m, 1H)	1644, 1450, 896	165 (M^+, 24); 150 (17); 135 (26); 134 (64); 120 (38); 110 (100)
4	**1a + 2d**	**3ad**[g]	63	75/0.3	$C_{11}H_{17}NO$ (179.3)	1.15 (m, 6H); 1.17–2.4 (m, 4H); 2.45–2.8 (m, 1H); 3.75 (m, 2H); 4.50 (m, 1H); 4.8–5.2 (m, 2H); 5.60 (m, 1H)	1640, 1466, 916	179 (M^+, 7); 149 (7); 134 (13); 120 (3); 111 (100); 110 (20)
5	**1a + 2e**	**3ae**[g]	84	173/0.4	$C_{15}H_{17}NO$ (227.3)	1.05–2.55 (m, 4H); 3.0–4.0 (m, 4H); 4.30–4.65 (m, 1H); 4.90–5.40 (m, 2H); 5.80–6.60 (m, 1H); 7.30 (m, 5H)	1640, 1602, 1496, 920	227 (M^+, 5); 211 (24); 210 (10); 195 (11); 194 (14); 117 (100)
6	**1a + 2f**	**3af**[g,h]	74	88/0.4	$C_{10}H_{15}NO$ (165.2)	1.1–2.65 (m, 6H); 1.80 (s, 3H); 2.65–3.2 (m, 1H); 3.75 (m, 2H); 4.55 (m, 1H); 4.80 (m, 2H)	1650, 1450, 896	165 (M^+, 39); 150 (100); 135 (30); 134 (65); 120 (37); 118 (23); 110 (66)
7	**1b + 2a**	**3ba**[g]	66	oil[i]	$C_9H_{13}NO$ (151.2)	1.1–3.0 (m, 7H); 3.4–4.0 (m, 1H); 4.9–5.4 (m, 3H); 5.5–6.2 (m, 1H); 7.30 (m, 5H)	1642, 1496, 916	227 (M^+, 16); 226 (8); 210 (5); 168 (6); 136 (14); 121 (12); 105 (100)
8	**1c + 2a**	**3ca**[g]	8	oil[i]	$C_{11}H_{17}NO$ (179.3)	1.2–3.5 (m, 13H); 4.51 (m, 1H); 4.8–5.2 (m, 2H); 5.3–6.0 (m, 1H)	1634, 1456, 916	(CI)[j]; 180 (M^+ + 1, 14); 164 (50); 149 (46); 109 (100)
9	**1d + 2a**	**3da**[k]	78	90/0.4	$C_{10}H_{15}NO$ (165.2)	1.13 (qd, 1H, J = 12, 3 Hz); 1.32 (qd, 1H, J = 13, 3 Hz); 1.46 (qt, 1H, J = 13, 3 Hz); 1.87 (d-quint, 1H, J = 13, 3 Hz); 2.07 (m, 1H); 2.13 (m, 1H); 2.20 (dt, 1H, J = 14, 7 Hz); 2.32 (m, 1H); 2.70 (dt, 1H, J = 14.6 Hz); 3.15 (m, 1H); 3.79 (dd, 1H, J = 10.4, 9.6 Hz); 4.47 (dd, 1H, J = 10.4, 7.9 Hz); 5.03 (m, 1H); 5.09 (m, 1H); 5.91 (dddd, 1H, J = 17.0, 10.2, 7.5, 6.2 Hz)	1642, 1448, 916	165 (M^+, 100); 136 (49); 134 (52); 120 (24); 107 (37)
10	**1e + 2a**	–[l]	–	–	–	–	–	–

[a] Oven temperatures of Kugelrohr are given.
[b] Satisfactory microanalyses (C, H, N ±0.3) or accurate mass determinations (±0.002 mass units) were obtained.
[c] Recorded on a Hitachi R-600 spectrometer or a JEOL GX-400 spectrometer.
[d] Measured using a Hitachi 270-30 spectrometer.
[e] Obtained on a Hitachi M-80B spectrometer.
[f] Diastereomer ratio was determined to be ca. 3 : 2 by ^{13}C-NMR ($CDCl_3$): (major isomer: δ = 27.82; 33.71; 35.23; 37.37; 54.76; 74.38; 116.88; 134.89; 173.74 ppm. Minor isomer: δ = 26.06; 33.94; 36.21; 37.41; 55.06; 74.70; 116.39; 135.73; 173.65 ppm). The stereochemical assignment could not be done.
[g] Diastereomer ratio was not determined.
[h] Two equivalents of **2f** to **1a** were used.
[i] Distillation was not carried out.
[j] Methane was employed as CI gas.
[k] Only one diastereomer was obtained. ^{13}C-NMR ($CDCl_3$): δ = 24.23; 32.37; 32.44; 35.39; 37.62; 48.96; 73.12; 116.16; 135.98; 162.13 ppm.
[l] No identifiable products were obtained (see text).



6-Allyl-3a,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isoxazole (3aa); Typical Procedure:

To a stirred solution of 1-nitro-1,5-hexadiene (**1a**; 1.27 g, 10 mmol) and allyltrimethylstannane (**2a**; 2.46 g, 12 mmol) in dry dichloromethane (25 ml) is added a 2 normal dichloromethane solution of titanium tetrachloride (6 ml) at −78 °C by a syringe. After the addition, the greenish yellow solution is allowed to warm to room temperature and then stirred for 1 h. Dry tetrahydrofuran (25 ml) followed by triethylamine (4.2 ml, 30 mmol) are added and stirred for another 1 h. The mixture is quenched by successive addition of saturated aqueous sodium hydrogen carbonate (20 ml) and 10% aqueous potassium fluoride (20 ml). After saturation of the resultant mixture with sodium chloride, the mixture is filtered through a Celite pad and the pad is washed with ethyl acetate (2 × 20 ml). The filtrate is extracted with ethyl acetate (3 × 30 ml). The organic phase is washed with saturated brine (50 ml) and dried with sodium sulfate. After the solvent is evaporated, the residue is chromatographed on silica gel (hexane/dichloromethane = 1:1–0:1) to give **3aa** as a diastereometric mixture; yield: 1.39 g (92%). Kugelrohr distillation (oven temperature 75 °C/0.4 mbar) gives an analytically pure sample.

$C_9H_{13}NO$	calc.	C 71.49	H 8.66	N 9.26
(151.2)	found	71.61	8.68	9.08

4-Nitromethyl-1,7-octadiene (5):

To a stirred solution of **1a** (127 mg, 1 mmol) and **2a** (246 mg, 1.2 mmol) in dry dichloromethane (10 ml) is added a 2 normal dichloromethane solution of titanium tetrachloride (0.5 ml) at −78 °C by a syringe. After stirring for 5 min at −78 °C, the reaction is quenched by successive addition of saturated aqueous ammonium chloride (10 ml) and 10% aqueous potassium fluoride (10 ml). After saturation of the mixture with sodium chloride, it is filtered through a Celite pad, which is washed with ether (2 × 10 ml). The filtrate is extracted with ether (3 × 10 ml) and the organic phase is washed with saturated brine (10 ml) and dried with sodium sulfate. After evaporation of the solvent, the residue is chromatographed on silica gel (hexane/dichloromethane = 3:1–1:1) to give **5** as a colorless oil; yield: 135 mg (71%) (Table 2).

3-Allyl-5-hexenehydroximic Chloride (6):

To a stirred solution of **1a** (127 mg, 1 mmol), and **2a** (246 mg, 1.2 mmol) in dry dichloromethane (10 ml) is added a 2 normal dichloromethane solution of titanium tetrachloride (0.5 ml) at −78 °C by a syringe. After the addition, the mixture is allowed to warm to room temperature and stirred for 30 min. The mixture is extracted with ethyl acetate (3 × 10 ml) and the organic phase is washed with saturated brine (10 ml) and dried with sodium sulfate. After evaporation of the solvent, the residue is chromatographed on silica gel (hexane/dichloromethane = 1:1–0:1) to give **3aa** (less polar fraction); yield: 25 mg (15%) and **6** (polar fraction); yield: 151 mg (75%) (Table 2).

6-(2-Chloro-2-methylpropyl)-3a,4,5,6-tetrahydro-3*H*-cyclopent[*c*]isoxazole (7):

The reaction of **1a** (127 mg, 1 mmol) and **2f** (486 mg, 1.2 mmol) is carried out as given under typical procedure. Chromatographic purification (silica gel) of the crude product gives a mixture of **3af** and **7**, **3af/7** = ca 1:2 determined by GLC, OV-1, 1 m; yield: 132 mg (~70%). Preparative GLC [Japan Analytical Industry, LC-08, JAI-1H (20 mmID × 60 cm) + JAI-2H (20 mmID × 60 cm)] of the mixture gives pure **7**; yield: 58 mg (29%) (Table 2).

Reaction of 1a with Allyltrimethylsilane:

The reaction of **1a** (127 mg, 1 mmol) and allyltrimethylsilane (140 mg, 1.2 mmol) is performed similar to the typical procedure. The crude product is chromatographed on silica gel to give **3aa** (polar fraction): yield: 121 mg (80%) and **8** (less polar fraction); yield: 15 mg (10%) (Table 2).

Table 2. Spectroscopic Data of Compounds **5–10**

Product	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)	IR (Neat) ν (cm^{-1})	MS (20 eV) *m/e* (%)
5	1.50 (m, 3H); 2.15 (m, 4H); 4.31 (d, 2H, J = 6 Hz); 4.9–5.2 (m, 4H); 5.4–6.2 (m, 2H)	1642, 1552, 1386	169 (M^+, 22); 156 (16); 107 (15); 93 (66); 67 (100)
6	1.4–3.0 (m, 7H); 4.8–5.3 (m, 4H); 5.4–6.2 (m, 2H); 8.09 (br s, 1H)	3288, 1644	189 (M^+ + 2, 1); 187 (M^+, 2); 172 (5); 170 (8); 151 (43); 120 (31); 79 (100)
7[a]	1.58 (br s, 6H); 1.6–3.5 (m, 7H); 3.80 (m, 2H); 4.52 (m, 1H)	2976, 1652	203 (M^+ + 2, 1); 201 (M^+, 3); 186 (13); 166 (55); 150 (55); 136 (39); 110 (100)
8[b]	1.5–2.3 (m, 2H); 2.3–3.0 (m, 2H); 3.3–4.4 (m, 2H); 4.4–5.0 (m, 2H)	1646, 824, 784	147 (M^+ + 2, 10); 145 (M^+, 43); 110 (53); 109 (28); 79 (84); 54 (100)
9[c]	1.1–2.8 (m, 8H); 3.50 (m, 1H); 4.00 (m, 1H); 4.8–5.3 (m, 2H); 5.4–6.2 (m, 1H); 8.5 (br, 1H)	3304, 1642, 1450, 762	189 (M^+ + 2, 3); 187 (M^+, 10); 172 (15); 170 (16); 134 (100); 120 (73)
10	1.7–2.9 (m, 7H); 4.8–5.3 (m, 2H); 5.66 (m, 1H); 6.00 (dt, 1H, J = 10, 1 Hz); 6.91 (dt, 1H, J = 10, 4 Hz)	1680, 1642, 1390	136 (M^+, 39); 121 (6); 108 (5); 107 (7); 95 (24); 68 (100)

[a] Diastereomer ratio was estimated to be ca 3:2 by ^{13}C-NMR spectra ($CDCl_3$). Major isomer: δ = 27.7; 31.4; 31.9; 33.2; 37.8; 49.5; 54.3; 69.7; 74.5; 174.1 ppm. Minor isomer: δ = 27.6; 32.1; 32.3; 33.4; 35.9; 47.2; 53.0; 70.2; 74.4; 174.2 ppm.

[b] Diastereomer ratio was determined to be 1:1 by GC (OV-1, 1 m).

[c] Diastereomer ratio was not determined.

2-Allyl-5-chlorocyclohexanone Oxime (9) and 6-Allyl-2-cyclohexenone (10):

To a suspension of aluminium chloride (267 mg, 2 mmol) in dry dichloromethane (10 ml) are added **1a** (146 mg, 1.1 mmol) and **2a** (276 mg, 1.3 mmol) at −78 °C. After the addition, the mixture is allowed to warm to room temperature and stirred for 2 h. The reaction is quenched by successive addition of saturated aqueous sodium hydrogen carbonate (10 ml) and 10% aqueous potassium fluoride (10 ml). After being saturated with sodium chloride, the mixture is filtered through a Celite pad, which is washed with ether (2 × 10 ml). The filtrate is extracted with ether (3 × 10 ml) and the organic phase is washed with saturated brine (30 ml) and dried with sodium sulfate. After the solvent is evaporated, the residue is chromatographed on silica gel (dichloromethane) to give **9**; yield: 159 mg (74%). Compound **9** (136 mg, 0.72 mmol) is left overnight at room temperature, rechromatography of the material on silica gel (hexane/dichloromethane = 1:1–0:1) affords 54 mg (54%) of **10**; yield: 54 mg (54%) (Table 2).

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(5) These compounds were prepared from the corresponding aldehydes *via* the following two steps: (1) CH_3NO_2 10% aqueous NaOH;[6] (2) $CH_3SO_2Cl/(C_2H_5)_3N$.[7] Yields of **1a, 1b, 1c, 1d,** and **1e** were 67%, 58%, 42%, 45%, and 50%; respectively.

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(9) When the reaction was quenched at this stage by adding saturated aqueous ammonium chloride solution, hydroxyimino chloride **6** and **3aa** were obtained in 75% and 15% yields, respectively.

(10) This compound (1:1 diastereomeric mixture) could be obtained in 51% yield from the reaction of **1a** and chlorotrimethylsilane.

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