

Silyl Nitronates in Organic Synthesis. Routes to Heterocycles

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The preparation and properties of silyl nitronates are described. Their usefulness as intermediates in preparative organic chemistry is demonstrated in the synthesis of some heterocycles such as isoxazolidines, 2-isoxazolines, isoxazoles, pyrazoles, and pyrrolidones. The structures of some pyrazoles were solved by analysis of coupled ^{13}C NMR spectra.

The chemistry of silyl and alkyl nitronates has been investigated and reviewed.¹⁻⁷ They add in a 1,3-dipolar fashion to the double bond with formation of isoxazolidines. In a preceding paper⁸ a method was worked out for the preparation of trimethylsilyl nitronates from primary nitro compounds. As observed earlier, they add readily in a regioselective manner to vinyls carrying electron withdrawing groups such as CN, COOR, and phenyl. Several rearrangements were observed which in conjunction with selective reduction of the *N*-*O* bond may open new routes to a variety of compounds.

Preparation and properties of silyl nitronates.

The simple primary nitro compounds, nitromethane, nitroethane, nitropropane, give the corresponding silyl nitronates in satisfactory yields by treatment with chlorotrimethylsilane and triethylamine in benzene at room temperature. The silyl ester of *aci*-nitromethane is very unstable; it could not be isolated, but was directly reacted *in situ*. When higher homologues, e.g. 1, or sterically hindered primary nitro compounds, 2, are reacted, the yield of silyl nitronate is lower and considerable amounts of unreacted nitro compounds are present; 3 and secondary nitro compounds do not react at all. The silyl esters are obtained practically quantitatively by using *N,O*-bis(trimethylsilyl)-

acetamide (BSA),⁷ *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA), or lithium diisopropylamidechlorotrimethylsilane (LDA-CS)⁸ in tetrahydrofuran at -75°C . In 2 and 6 the OH group was also silylated. The silyl nitronates can be reacted directly as crude material. The lower boiling derivatives are purified by distillation but are sometimes difficult to separate from the accompanying acetamide reagents. They decompose slowly on standing with formation of trimethylsilanol and a polymerized intractable material but are stabilized by triethylamine. The silyl nitronates condense on heating⁸ or even better in a fluoride ion catalyzed reaction⁸ at low temperature with aldehydes to nitro alcohols. Water, acids, alcohols, thiols, and amines rapidly hydrolyze silyl nitronates back to nitro compounds. The silyl nitronates are unreactive towards unactivated double bonds, e.g. cyclohexene, but if the double bond is located in the same molecule as in 5, intramolecular cyclization takes place. When 5 was silylated with BSTFA, 1 h reflux, no olefinic protons were visible in the ^1H NMR spectrum of the crude product.

Isoxazolidines, 2-isoxazolines, isoxazoles, 2-pyrrolidones, and pyrazoles. Thorough accounts of the chemistry of isoxazoles, isoxazolines, and isoxazolidines are given by Kochetkov and Solokov⁹ and Takeuchi and Furusaki.¹⁰

N-Silyloxy-isoxazolidines obtained by the addition of silyl nitronates to olefins, are quantitatively transferred into 2-isoxazolines on treatment with toluenesulfonic acid (TsOH). Catalytic hydrogenation of the acrylic ester adduct, 8, gives 3-hydroxy-5-alkyl-2-pyrrolidones, 9, and/or 2-hydroxy-4-ketoesters.⁶ Acrylonitrile shows a slightly different reaction

Table 1. ^{13}C NMR data for 1-phenyl-3-methylpyrazole and 1-phenyl-5-methylpyrazole in CDCl_3 .

Compound	Shifts ppm from TMS			$\text{C}_{1\text{Ar}}$	$\text{C}_{2,6\text{Ar}}$	$\text{C}_{3,5\text{Ar}}$	$\text{C}_{4\text{Ar}}$	CH_3
	C^3	C^4	C^5					
1-Phenyl-3-methylpyrazole ^b	151.2	108.2	126.6	140.9	119.5	130.0	126.6	14.4
1-Phenyl-5-methylpyrazole	140.4 ^a	107.5	140.4	139.3 ^a	125.5	129.6	128.2	13.0
	Coupling constants (Hz)							
1-Phenyl-5-methylpyrazole	$J_{\text{C}^3\text{H}^4}$	$J_{\text{C}^4\text{CH}_3}$	$J_{\text{C}^5\text{H}^6}$	$J_{\text{C}^1\text{H}^2}$	$J_{\text{C}^2\text{CH}_3}$	$J_{\text{C}^3\text{H}^4}$		
	5.65	0.9	184.4	10.35	3.65	174.7		

^a Can be reversed. ^b Cf. Ref. 12.

more hindered isomer, Scheme 1. The shifts and coupling constants are collected in Table 1 for 1-phenyl-3-methylpyrazole and 1-phenyl-5-methylpyrazole. The ^{13}C NMR spectra as well as the ^1H NMR data (Ar-H, broad multiplet for the 3-methyl derivative and Ar-H, singlet for the 5-methyl derivative) show that the aromatic ring is turned out of the plane in the sterically crowded 5-methyl derivative. These data are confirmed by the assignment of $^3J_{\text{C}^3\text{H}^4} = +8.38$ Hz, $^2J_{\text{C}^3\text{H}^4} = +5.78$ Hz, $^2J_{\text{C}^4\text{H}^6} = +10.6$ Hz, $^2J_{\text{C}^5\text{H}^6} = +8.9$ Hz, $^2J_{\text{C}^1\text{H}^2} = +9.0$ Hz, and $^3J_{\text{C}^1\text{H}^2} = +4.65$ Hz for 1-methylpyrazole.¹¹

Methyl vinyl ketone adds rapidly with evolution of heat to the silyl ester of *aci*-nitropropane, and elimination of trimethylsilanol gives 3-ethyl-5-acetyl-2-isoxazoline 17. The 3-propyl derivative is obtained similarly from nitrobutane.

EXPERIMENTAL

Trimethylsilyl ester of 1-aci-nitromethylcyclohexanol, 2. A solution of 2 (1.59 g, 0.01 mol), BSA (5.0 g, 0.025 mol) and a few drops of triethylamine in benzene (10 ml) was refluxed for 4 h. The solvent was evaporated and the remainder was distilled *in vacuo*, first at ca. 60 °C (oil bath temperature)/0.5 mmHg, whereby large quantities of the acetamide sublimed into the condenser. The ester distilled at 100 °C/0.5 mmHg (1.98 g, 69 %). (Found: C 53.63; H 9.41. Calc. for $\text{C}_{13}\text{H}_{20}\text{Si}_2\text{O}_3$: C 53.97; H 10.03 %). ^1H NMR (CDCl_3): δ 0.13 (9 H, s), 0.30 (9 H, s), 1.2–2.0 (10 H, m), 6.03 (1 H, s).

Trimethylsilyl ester of 3-methoxycarbonyl-1-aci-nitropropane. A solution of methyl 4-nitrobutyrate,¹³ 4, (2.94 g, 0.02 mol) in benzene (20

ml) was silylated with BSFTA (7.7 g, 0.03 mol) and a few drops of triethylamine at 80 °C for 2 h. The solvent was evaporated and the silyl ester was distilled *in vacuo* at 92–94 °C/1 mmHg (4.0 g, 91 %). ^1H NMR (CDCl_3): δ 0.30 (9 H, s), 3.46 (4 H, br.d), 3.69 (3 H, s), 6.2 (1 H, m). Less silylating agent (<1.5 mol) gave incomplete reaction.

Silylation of 5 with BSTFA (1.5 mol) in benzene, 80 °C for 1 h gave a product the ^1H NMR spectrum of which was devoid of any olefinic protons. Intramolecular cyclization had probably occurred.

Silylation of 6 with BSA (3 mol) in benzene at 80 °C for 2 h gave quantitatively the nitronate ester. It was difficult to separate it from the acetamide by distillation. ^1H NMR (CDCl_3 , crude distillate): δ 0.33 (9 H, s), 4.38 (2 H, d, J 5.6 Hz), 6.29 (1 H, t, J 5.6 Hz).

Silylation of 7 according to the same method gave quantitatively the corresponding silyl nitronate that decomposed on attempted distillation. ^1H NMR (CDCl_3 , crude product): δ 0.33 ($\text{Si}(\text{CH}_3)_3$, s), 2.38 (CH_3 , s).

2-Trimethylsilyloxy-5-cyanoisoxazolidine, 11, ($\text{R}' = \text{H}$). To acrylonitrile (10.6 g, 0.2 mol), triethylamine (21.2 g, 0.21 mol) and chlorotrimethylsilane (21.6 g, 0.2 mol) in benzene (200 ml) nitromethane (12.2 g, 0.2 mol) was added dropwise at room temperature with stirring. After 18 h the solution was filtered, evaporated, and distilled *in vacuo* at 0.8 mmHg, b.p. 58–60 °C. The yield of 11 (isomeric mixture, $\text{R}' = \text{H}$) was 30.9 g or 85 %. ^1H NMR (CDCl_3): δ 0.18 and 0.23 (9 H, s), 2.4–3.6 (4 H, m), 4.8–5.1 (1 H, m).

2-Trimethylsilyloxy-3-ethyl-5-cyanoisoxazolidine, 11, ($\text{R}' = \text{C}_2\text{H}_5$, *cis-trans* forms). A mixture of crude trimethylsilyl ester of *aci*-nitropropane (8.05 g, 0.05 mol) in benzene (50 ml) and acrylonitrile (2.65 g, 0.05 mol) was kept overnight at room temperature, then filtered, evaporated, and distilled *in vacuo* at 56–58 °C/0.2 mmHg

(7.05 g, 67 %, lit.⁶ b.p. 56–58 °C/0.2 mmHg).

5-Cyano-2-isoxazoline, 12, (R'=H). To acrylonitrile (2.65 g, 0.05 mol), trimethylamine (5.05 g, 0.05 mol) chlorotrimethylsilane (5.40, 0.05 mol) in benzene (50 ml), nitromethane (3.05 g, 0.05 mol) was added dropwise with stirring at room temperature. The mixture was refluxed for 20 min, filtered, cooled and TSOH (100 mg) was added with stirring. Heat evolved and after ca. 1 h the solvent was evaporated and the remainder distilled at 90 °C/3 mmHg. Yield: 1.58 g, 40 %. ¹H NMR (CDCl₃): δ 3.46 (2 H, dd, J 8.5, 1.6 Hz), 5.24 (1 H, t, J 8.5 Hz), 7.38 (1 H, t, 1.6 Hz).

3-Ethyl-5-cyano-2-isoxazoline, 12, (R'=C₂H₅). To 2-trimethylsilyloxy-3-ethyl-5-cyanoisoxazolidine (4.28 g, 0.02 mol) in benzene (25 ml), TsOH (100 mg) was added. The temperature rose in the mixture which was stirred for 1 h, washed aqueous sodium bicarbonate, dried over sodium sulfate, evaporated, and distilled *in vacuo*, b.p. 91 °C/1.5 mmHg, 1.80 g, 73 % (lit.⁶ b.p. 91 °C/1.5 mmHg).

5-Trimethylsilyloxy-2-isoxazoline, 13, (R'=H). To 2-trimethylsilyloxy-5-cyanoisoxazolidine (10.92 g, 0.06 mol) was added solid KF (500 mg) in small portions with cooling. Large amounts of hydrocyanic acid were evolved and a good hood must be used for the reaction. When the reaction had subsided, the product was distilled *in vacuo*. The yield of 13 (R'=H) was 7.6 g, 82 %, b.p. 58 °C/0.5 mmHg, identical to the product described earlier.⁶

3-Methyl-5-trimethylsilyloxy-2-isoxazoline, 13, (R'=CH₃). Nitroethane (10 g, 0.133 mol), triethylamine (13.5 g, 0.133 mol) and chlorotrimethylsilane (14.4 g, 0.133 mol) were stirred for 1 h and acrylonitrile (6.9 g, 0.133 mol) was added. The stirring was continued for 18 h and the mixture refluxed for 1 h, filtered, and evaporated. Tetrabutylammonium fluoride (500 mg) was added in small portions while cooling with tap-water and stirring. Hydrocyanic acid was evolved. When the reaction had subsided, the product, 13, (R'=CH₃) was distilled *in vacuo*, b.p. 54–56 °C/0.9 mmHg, identical to the product described earlier.⁶ The yield was 6.0 g or 47 %.

3-Ethyl-5-trimethylsilyloxy-2-isoxazoline, 13, (R'=C₂H₅). Potassium fluoride (200 mg) was added in small portions with stirring to 2-trimethylsilyloxy-3-ethyl-5-cyanoisoxazolidine (8.4 g, 0.04 mol) cooled with tap-water. Hydrocyanic acid was evolved. When the reaction had subsided, the product was distilled *in vacuo*. The yield of 13 (R'=C₂H₅) was 80 %, b.p. 45 °C/0.3 mmHg, identical to the product described.⁶

3-Ethylisoxazole, 14, (R'=C₂H₅). 3-Ethyl-5-trimethylsilyloxy-2-isoxazoline (550 mg, 0.003 mol) in chloroform (5 ml) was refluxed for 2 h with TsOH (50 mg). The reaction mixture was washed with aqueous sodium bicarbonate (2 ml), and the aqueous phase was extracted several times with chloroform. The combined

organic phase was dried over anhydrous Na₂SO₄ and evaporated *in vacuo*. 200 mg (69 %) of almost pure liquid, 14 (R'=C₂H₅) remained. ¹H NMR (CDCl₃): δ 1.26 (3 H, t, J 7.5 Hz), 2.70 (2 H, q, J 7.5 Hz), 6.15 (1 H, d, J 2.6 Hz), 8.23 (1 H, d, J 2.6 Hz).

Isoxazole, 14, (R'=H) was prepared from 5-trimethylsilyl-2-isoxazoline according to the same method. The aqueous phase was extracted with ether. The yield was 83 %.

3-Methylisoxazole, 14, (R'=CH₃) was prepared from 3-methyl-5-trimethylsilyl-2-isoxazoline, 13 (R'=CH₃) in a yield of 63 % according to the same method. ¹H NMR (CDCl₃): δ 2.32 (3 H, s), 6.20 (1 H, d, J 1.6 Hz), 8.33 (1 H, d, J 1.6 Hz).

1-Phenyl-5-methylpyrazole and 1-phenyl-3-methylpyrazole. 3-Methyl-5-trimethylsilyloxy-2-isoxazoline (0.520 g, 0.003 mol), phenylhydrazine (0.330 g, 0.003 mol), and TsOH (50 mg) in dry methanol (5 ml) were refluxed for 4 h. Evaporation of methanol *in vacuo*, addition of chloroform, washing with saturated aqueous sodium bicarbonate, drying with anhydrous sodium sulfate, and evaporation gave a mixture of isomeric pyrazoles (300 mg). They were separated on TLC (silica gel, CHCl₃) giving 180 mg, 38 %, of 1-phenyl-5-methylpyrazole and 30 mg, 6 %, 1-phenyl-3-methylpyrazole. ¹H NMR, see Table 1. Both compounds are liquids.

1-Phenyl-5-ethylpyrazole and 1-phenyl-3-ethylpyrazole. 3-Ethyl-5-trimethylsilyloxy-2-isoxazoline (0.28 g, 0.0015 mol) in dry methanol (5 ml) was refluxed for 4 h with phenylhydrazine (0.162 g, 0.0015 mol) and a catalytic amount of TsOH (25 mg). Evaporation and TLC of the product on silica gel (CHCl₃) gave a band consisting of an inseparable mixture of the 5- and 3-isomers (~2:1, 0.20 g, 80 %, liquid). The structures were determined by analysis of the coupled ¹³C NMR spectrum. ¹³C NMR (CDCl₃): ²J_{C-H}=10 Hz, ³J_{C-H}=6 Hz (calc. for the 5-isomer ~10 and 6 Hz, respectively; major), ²J_{C-H}~²J_{C-H}=8 Hz (calc. for the 3-isomer ~9 Hz; minor).

Pyrazole. 5-Trimethylsilyloxy-2-isoxazoline, 13, (R'=H) (4.57 g, 0.03 mol) in methanol (20 ml) was refluxed for 4 h with hydrazine (1.15 g, 0.036 mol) and TsOH (250 mg). The methanol was evaporated *in vacuo*. The product was neutralized with saturated NaHCO₃ and the aqueous phase washed several times with ether, dried over anhydrous Na₂SO₄ and evaporation of ether gave a white crystalline compound, m.p. 70 °C. The yield of pyrazole was 1.80 g, 88 %.

1-Phenylpyrazole was prepared from 13 (R'=H) and phenylhydrazine according to the same method. The yield was 90 %.

3-Methylpyrazole. 3-Methyl-5-trimethylsilyloxyisoxazoline (0.520 g, 0.003 mol) in dry methanol (5 ml) was refluxed for 4 h with hydrazine (0.115 g, 0.0036 mol) and TsOH (50 mg). Evaporation of methanol *in vacuo*, neutralization of

TsOH with NaHCO_3 and extraction with ether gave 3-methylpyrazole (0.15 g, 61%), m.p. 36–37 °C after evaporation of ether.

3-Ethylpyrazole. 3-Ethyl-5-trimethylsilyloxy-2-isoxazoline (0.28 g, 0.0015 mol) in dry methanol (5 ml) was refluxed for 4 h with hydrazine (0.058 g, 0.0018 mol) and TsOH (25 mg) and evaporated. Ether was added and TsOH extracted with a small amount of saturated sodium bicarbonate solution. The aqueous phase was extracted several times with ether, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The remainder was chromatographed on TLC (silica gel, ether and a few drops of NH_3) and gave pure 3-ethylpyrazole (80 mg, 55%). $^1\text{H NMR}$ (CDCl_3): δ 1.0 (3 H, t, J 6 Hz), 2.19 (2 H, q, J 6 Hz), 4.81 (1 H, d, J 2 Hz), 5.94 (1 H, d, J 2 Hz), 7.4 (1 H, br.s.).

Preparation of 3-ethyl-5-acetyl-2-isoxazoline, 17, ($\text{R}' = \text{C}_2\text{H}_5$). To the trimethylsilyl ester of *aci*-nitropropane⁶ (8.05 g, 0.05 mol) in benzene (25 ml), methyl vinyl ketone (3.5 g, 0.05 mol) was added with stirring and cooling under tap-water. After 12 h at room temperature TsOH (200 mg) was added in small portions with cooling. The solution was stirred for an additional hour, washed with sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated. 17 (3.90 g, 55%) distilled at 104–106 °C/10 mmHg. $^1\text{H NMR}$ (CDCl_3): δ 1.17 (3 H, t, J 7.4 Hz), 2.29 (3 H, s), 2.39 (2 H, q, J 7.4 Hz), 3.16 (2 H, br.d, J ca. 9 Hz), 4.85 (1 H, dd, J 7.9 and 10.0 Hz).

3-Propyl-5-acetyl-2-isoxazoline, 17, ($\text{R}' = \text{CH}_2\text{CH}_2\text{CH}_3$). To crude trimethylsilyl ester of *aci*-nitrobutane prepared from nitrobutane (1.03 g, 0.01 mol) and BSA (4.0 g, 0.02 mol) in benzene (10 ml) methyl vinyl ketone (1.0 g, 0.01 mol) was added. The reaction mixture was stirred overnight at room temperature and then TsOH (50 mg) was added. After 1 h the organic phase was washed with water dried over anhydrous calcium chloride and evaporated. Distillation at 116–118 °C/10 mmHg gave 3-propyl-5-acetyl-2-isoxazoline (0.48 g, 42%). $^1\text{H NMR}$ (CDCl_3): δ 0.97 (3 H, t, J 6.8 Hz), 1.3–2.0 (4 H, m), 2.29 (3 H, s), 2.37 (2 H, t, J 7 Hz), 3.16 (2 H, br.d., J ca. 9 Hz).

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