A Novel Intramolecular Silyl Nitronate Cycloaddition Route to Dihydrofuraldehydes and Dihydropyranaldehydes

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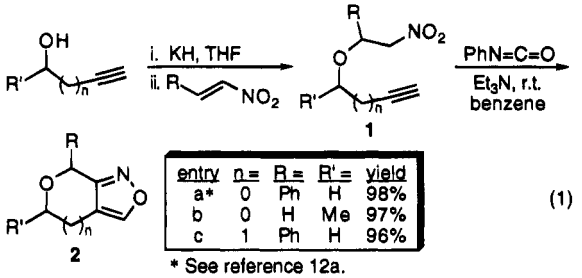
The novel transformation (**1** → **3**) of propargylic or homopropargylic nitroethers to dihydrofuraldehydes (n = 0) or dihydropyranaldehydes (n = 1) is reported. The transformation proceeds by a silyl nitronate olefin cycloaddition to an *N*-[(trimethylsilyl)oxy]isoxazolidine intermediate which, upon acid workup, undergoes desilylation with subsequent elimination of hyponitrous acid to **3**.

In connection with our interests in the intramolecular nitrile oxide–olefin cycloaddition[2] and intramolecular silyl nitronate cycloaddition[3] reactions, we report here an interesting product anomaly in the intramolecular silyl nitronate cycloaddition of propargylic and homopropargylic nitro ethers which delivers novel heterocycles of general structure **3**. The intramolecular nitrile oxide–olefin cycloaddition reaction provides a particularly powerful means of relative stereochemical control[4] as it delivers heterocyclic products with a wide variety of functionality.[5] Applications in the synthesis of new drugs[6] and agrochemicals[7] containing substituted isoxazoles are numerous.[8]

We have observed that the intramolecular nitrile oxide–olefin cycloaddition reaction of a propargylic or homopropargylic nitro ether is facile and proceeds reliably to the isoxazole. Thus, nitro ether **1**, prepared by Michael addition of the appropriate alkoxide and nitro olefin reaction partners,[9] undergoes dehydrative cyclization to dihydrofuro- and dihydropyrano-heterocycle **2**. Indeed, as bracketed by entries a–c (eq 1), this procedure delivers the targeted isoxazoles in excellent yield (96–98%).

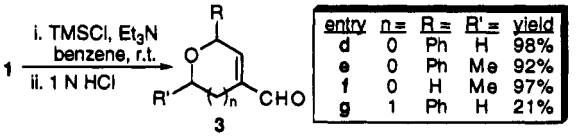


entry	n =	R =	R' =	yield
a*	0	Ph	H	98%
b	0	H	Me	97%
c	1	Ph	H	96%

* See reference 12a.

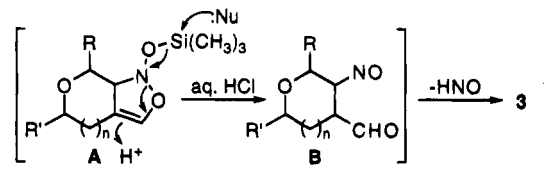
(1)

Silyl nitronates are easily prepared by deprotonation of the acidic α-proton of a primary or secondary nitroalkane followed by *O*-silylation of the resulting nitronate.[10] These silyl nitronates hold important synthetic potential in nitro-aldol and 1,3-dipolar cycloaddition reactions and, in the latter, the resulting *N*-[(trimethylsilyl)oxy]isoxazolidines are readily converted to 2-isoxazolines upon treatment with acid.[11] With this literature precedence and our results with **1** → **2** in hand, we were quite surprised to find that the intramolecular silyl nitronate cycloaddition of **1** (eq 2) delivered a very different final product from that of intramolecular nitrile oxide–olefin cycloaddition (eq 1). It was immediately evident from spectral analysis that the targeted isoxazole **2** was not present in any of the crude reaction mixtures. Rather, spectral data indicated that the product in each case was an α,β-unsaturated aldehyde [^{1}H-NMR C(=O)*H* singlet at 9–10 ppm; ^{13}C-NMR *C*=*C*C(=O)H at ≈140/145/190 ppm; FT-IR C(=*O*)H at ≈2700 cm^{-1}]. Further investigation established that the product from each intramolecular silyl nitronate cycloaddition was the dihydrofurancarbaldehyde (n = 0) or dihydropyrancarbaldehyde (n = 1) **3**.



entry	n =	R =	R' =	yield
d	0	Ph	H	98%
e	0	Ph	Me	92%
f	0	H	Me	97%
g	1	Ph	H	21%

(2)



On the basis of previous studies of diastereoselectivity in intramolecular silyl nitronate cycloadditions,[12b] we noted several similarities between these novel transfor-

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(2) (a) Padwa, A. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; J. Wiley and Sons, New York, 1984; Vol 2, Chapter 12. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(3) The pioneering work of Torssell and co-workers has established that silyl nitronates can be synthetic equivalents of nitrile oxides in 1,3-dipolar cycloaddition reactions. See for example: (a) Torssell, K.; Zeuthen, O. *Acta Chem. Scand.* **1978**, *B33*, 379. (b) Das, N. B.; Torssell, K. B. G. *Tetrahedron* **1983**, *39*, 2227. (c) Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569.

(4) (a) For a recent report from our laboratory concerning double diastereoselectivity in the INOC reaction, see: Kim, H. R.; Kim, H. J.; Duffy, J. L.; Olmstead, M. M.; Ruhlandt-Senge, K.; Kurth, M. J. *Tetrahedron Lett.* **1991**, *32*, 4259. (b) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 10061.

(5) For recent reviews, see: (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH Publishers: New York, 1988. (b) See ref 2.

(6) Fosa, P.; Menozzi, G.; Schenone, P.; Filippelli, W.; Russo, S.; Lucarelli, C.; Marmo, E. *Farmaco* **1991**, *46*, 789.

(7) For example, see: (a) Lang, A.; Lin, Y. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed; Pergamon Press: Oxford, 1984; Vol. 6, pp 1–130. (b) Otsuji, Y.; Mizuno, K. Jpn. Patent, JP 01070476 A2; *Chem. Abstr.* **1989**, *111* (15), 134134r. (c) For a recent report from our laboratories, see: Kim, H. J.; Lee, J. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6513.

(8) Boyd, G. V. *Prog. Heterocycl. Chem.* **1991**, *3*, 166.

(9) Duffy, J. L.; Kurth, J. A.; Kurth, M. J. *Tetrahedron Lett.* **1993**, *34*, 1259.

(10) (a) Colvin, E. W.; Seebach, D. *J. Chem. Soc. Chem. Commun.* **1978**, 689. (b) Olah, G. A.; Gupta, B. G. B.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 4272. (c) Colvin, E. W.; Beck, A. K.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 2264. (d) Feger, H.; Simchen, G. *Synthesis*, **1981**, 378.

(11) (a) Dehaen, W.; Hassner, A. *Tetrahedron Lett.* **1990**, *31*, 743. (b) Kim, B. H.; Lee, J. Y. *Tetrahedron: Asymmetry* **1991**, *2*, 1359.

0022-3263/94/1959-3783$04.50/0

mations and the corresponding allylic and homoallylic nitro ether cycloadditions. First, like the homoallylic system, homopropargylic nitro ether **1g** apparently undergoes 1,3-dipolar cycloaddition only slowly, hence, the low yield of dihydropyran **3g** after a 1-week dipolar cycloaddition. Second, the corresponding allylic and propargylic nitro ethers both undergo cycloaddition cleanly and in high yield. Third, Michael addition of a secondary potassium alkoxide to a β-substituted nitro olefin results in the formation of a diastereomeric mixture of nitro ethers. For example, reacting the potassium alkoxide of 3-butyn-2-ol with β-nitrostyrene gives an inseparable 2:1 diastereomeric mixture of nitro ether **1e**. Subsequent silyl nitronate olefin cycloaddition with acidic workup delivers **3e** where the diastereomeric ratio is unchanged from the starting nitro ether (entry **e**; **3e** obtained as a 2:1 mixture of diastereomers **3e**^{a} and **3e**^{b}).

We believe the novel transformation depicted in eq 2 proceeds via *N*-[(trimethylsilyl)oxy]isoxazolidine **A**, the anticipated product of silyl nitronate olefin cycloaddition from nitro ether **1**. Upon acid workup, intermediate **A** presumably undergoes desilylation to β-nitroso carboxaldehyde **B** instead of the anticipated loss of trimethylsilanol (i.e., **A** → **2**). Subsequent spontaneous elimination of hyponitrous acid from **B** delivers the observed dihydrofurancarbaldehyde (n = 0) or dihydropyrancarbaldehyde (n = 1) **3**.

Experimental Section

General Procedure A. To a stirred solution of nitro ether **1** (1 equiv) in dry benzene was added triethylamine (3 equiv) followed by phenyl isocyanate (3 equiv). A white precipitate formed and the resulting mixture was allowed to stir under nitrogen at room temperature for 24 h, at which point TLC showed complete disappearance of starting material. Water (2.2 mL/mmol **1**) was then added and the reaction allowed to stir for an additional 12 h. The solution was filtered and the precipitate washed with ether (5.4 mL/mmol **1**). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography gave **2**.

(±)-6-Phenyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (2a). By general procedure **A**, (±)-2-[2-propyn-1-oxy]-1-nitro-2-phenylethane (190 mg, 0.921 mmol), dry benzene (5 mL), triethylamine (390 μL, 2.76 mmol), phenyl isocyanate (310 μL, 2.76 mmol), and purification by column chromatography (1:15 EtOAc:hexanes) gave **2a** in 98% yield (169 mg) as a clear colorless oil which turned brown upon standing [R_f = 0.25 (1:6 EtOAc:hexane); FT-IR (neat) 3061, 3029, 2890, 1720, 1665, 1630, 1600, 1069, 1013, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.96 (dd, J = 1.1, 10.8 Hz, 1H), 5.03 (dd, J = 1.1, 10.8 Hz, 1H), 6.11 (s, 1H), 7.44 (m, 5H), 8.04 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 63.9, 76.4, 122.9, 126.3, 128.5, 128.7, 137.9, 148.1, 172.4; HRMS calcd for $C_{11}H_9NO_2$ 187.0633, found 187.0633].

(±)-4-Methyl-4*H*,6*H*-furo[3,4-*c*]isoxazole (2b). By general procedure **A**, (±)-2-[3-butyn-2-oxy]-1-nitroethane (120 mg, 0.840 mmol), dry benzene (5 mL), triethylamine (270 μL, 2.52 mmol), phenyl isocyanate (350 μL, 2.52 mmol), and purification by column chromatography (1:15 EtOAc:hexanes) gave **2b** in 97% yield (92 mg) as a clear colorless oil which turned brown upon standing [R_f = 0.18 (1:6 EtOAc:hexane); FT-IR (neat) 3064, 3033, 2933, 2879, 1633, 1448, 1065, 927, 723 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, J = 6.3 Hz, 3H), 4.86 (d, J = 13.3 Hz, 1H), 4.97 (dd, J = 1.0, 13.3 Hz, 1H), 5.18 (q, J = 6.3 Hz, 1H), 8.01 (d, 1.0 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.7, 63.4, 72.2, 129.2, 147.8, 170.8; HRMS calcd for $C_6H_7NO_2$ 125.0477, found 125.0479].

(±)-4,5-Dihydro-7-phenyl-7*H*-pyrano[3,4-*c*]isoxazole (2c). By general procedure **A**, (±)-2-[3-butyn-1-oxy]-1-nitro-2-phenylethane (200 mg, 0.908 mmol), dry benzene (5 mL), triethylamine (380 μL, 2.71 mmol), phenyl isocyanate (300 μL, 2.71 mmol), and purification by column chromatography (1:10 EtOAc:hexanes) gave **2c** in 96% yield (175 mg) as a clear yellow oil [R_f = 0.22 (1:6 EtOAc:hexane)]; FT-IR (neat) 3063, 3033, 2975, 2862, 1602, 1444, 1094, 930, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.80 (m, 2H), 3.80 (ddd, J = 4.3, 8.5, 11.8 Hz, 1H), 4.10 (ddd, J = 4.7, 5.2, 11.8 Hz, 1H), 5.84 (s, 1H), 7.39 (m, 5H), 8.22 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 19.8, 63.1, 75.1, 112.1, 127.5, 128.5, 129.0, 138.1, 153.4, 180.0; HRMS calcd for $C_{12}H_{11}NO_2$ 201.0790, found 201.0791].

General Procedure B. To a stirred solution of nitro ether **1** (1 equiv) in dry benzene was added triethylamine (3 equiv) followed by trimethylsilyl chloride (3 equiv). A white precipitate formed and the resulting mixture was allowed to stir under nitrogen at room temperature for 24 h, at which point TLC showed complete disappearance of starting material. Aqueous HCl (1 N) was added and the layers were separated. The aqueous layer was extracted with ether (3 × 5 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by column chromatography gave **3**.

(±)-2,5-Dihydro-2-phenyl-4-furancarbaldehyde (3d). By general procedure **B**, (±)-2-[2-propyn-1-oxy]-1-nitro-2-phenylethane (280 mg, 1.36 mmol), dry benzene (7 mL), triethylamine (570 μL, 4.07 mmol), trimethylsilyl chloride (530 μL, 4.07 mmol), aqueous HCl (1 N, 7 mL), and purification by column chromatography (1:10 EtOAc:hexanes) gave **3d** in 98% yield (149 mg) as a clear yellow oil [R_f = 0.28 (1:6 EtOAc:hexane); FT-IR (neat) 3066, 3031, 2859, 2724, 1683, 1173, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (ddd, J = 2.2, 3.9, 12.9 Hz, 1H), 5.05 (ddd, J = 1.9, 5.7, 12.9 Hz, 1H), 6.00 (m, 1H), 6.86 (d, J = 1.9 Hz, 1H), 7.34 (m, 5H), 9.83 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 73.0, 88.2, 126.3, 128.5, 128.8, 139.5, 142.4, 146.9, 186.9; HRMS calculated for $C_{11}H_{10}O_2$ 174.0681, found 174.0681].

(±)-2,5-Dihydro-2-phenyl-5-methyl-4-furancarbaldehyde (3e). By general procedure **B**, (±)-2-[3-butyn-2-oxy]-2-phenyl-1-nitroethane (2:1 mixture of diastereomers; 168 mg, 0.763 mmol), dry benzene (5 mL), triethylamine (410 μL, 2.29 mmol), trimethylsilyl chloride (380 μL, 2.29 mmol), aqueous HCl (1 N, 5 mL), and purification by column chromatography (1:10 EtOAc:hexanes) gave **3e** in 92% yield (2:1 mixture of diastereomers **3e**^{a} and **3e**^{b}; 132 mg) as a clear yellow oil [R_f = 0.27 (1:6 EtOAc:hexane); FT-IR (neat) 3064, 3030, 2975, 2927, 2829, 2719, 1681, 1173, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (d, J = 6.4 Hz, 2H, **3e**^{a}), 1.61 (d, J = 6.4 Hz, 1H, **3e**^{b}), 5.28 (dq, J = 1.6, 6.4 Hz, 0.33H, **3e**^{b}), 5.42 (dq, J =1.6, 6.4 Hz, 0.66H, **3e**^{a}), 5.96 (dd, J = 1.6, 4.0 Hz, 0.33H, **3e**^{b}), 6.06 (dd, J = 1.6, 5.4 Hz, 0.66H, **3e**^{a}), 6.88 (m, 1H), 7.37 (m, 5H), 9.90 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.0 (**3e**^{a}), 21.5 (**3e**^{b}), 80.0 (**3e**^{b}), 81.1 (**3e**^{a}), 86.5 (**3e**^{a}), 87.0 (**3e**^{b}), 126.7, 127.0, 128.8, 128.9, 129.1, 146.0 (**3e**^{b}), 148.0 (**3e**^{a}), 148.5, 186.0; HRMS calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0838].

(±)-2,5-Dihydro-2-methyl-3-furancarbaldehyde (3f). By general procedure **B**, (±)-2-[3-butyn-2-oxy]-1-nitroethane (185 mg, 1.30 mmol), dry benzene (7 mL), triethylamine (540 μL, 3.90 mmol), trimethylsilyl chloride (490 μL, 3.90 mmol), and aqueous HCl (1 N, 7 mL) gave **3f** in 97% yield (143 mg) as a clear yellow oil [R_f = 0.11 (1:6 EtOAc:hexane); FT-IR (neat) 3034, 2957, 2926, 2857, 2720, 1690, 1194 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (d, J = 6.3 Hz, 3H), 4.78 (ddd, J = 1.9, 3.6, 17 Hz, 1H), 4.88 (ddd, J = 1.9, 5.4, 17 Hz, 1H), 5.14 (m, 1H), 6.93 (dd, J = 2.0, 3.5 Hz, 1H), 9.83 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 20.5, 73.9, 80.1, 137.0, 145.8, 186.7; HRMS calcd for $C_6H_8O_2$ 112.0524, found 112.0521].

(±)-5,6-Dihydro-2-phenyl-2*H*-pyran-4-carbaldehyde (3g). By general procedure **B**, (±)-2-[3-butyn-1-oxy]-1-nitro-2-phenylethane (200 mg, 0.908 mmol), dry benzene (5 mL), triethyl-

(12) (a) Compound **2a** is a known compound: Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M.; Hassner, A.; Murthy, K. S. K. *Tetrahedron Lett.* **1988**, *29*, 4169. (b) Hassner, A.; Murthy, K. S. K.; Padwa, A.; Chiacchio, U.; Dean, D. C.; Schoffstall, A. M. *J. Org. Chem.* **1989**, *54*, 5277.

amine (380 μL, 2.71 mmol), trimethylsilyl chloride (350 μL, 2.71 mmol), aqueous HCl (1 N, 5 mL), and purification by column chromatography (1:15 EtOAc:hexanes) gave **3g** in 21% yield (36 mg) as a clear yellow oil [R_f = 0.28 (1:6 EtOAc:hexane); FT-IR (neat) 3063, 3032, 2930, 2859, 2722, 1687, 1163, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43, (m, 2H), 3.77 (ddd, J = 4.7, 8.6, 11.6 Hz, 1H), 4.13 (ddd, J = 3.5, 5.2, 8.6 Hz, 1H), 5.37 (m, 1H), 6.83 (d, J = 1.5 Hz, 1H), 7.37 (m, 5H), 9.51 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.8, 62.9, 76.3, 127.3, 128.5, 128.8, 138.5, 139.0, 149.2, 192.5; HRMS calcd for $C_{12}H_{12}O_2$ 188.0837, found 188.0839].

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Supplementary Material Available: ^1H- and ^{13}C-NMR spectra for **2a–c** and **3d–g** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.