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Six-membered cyclic nitronates as Brönsted bases: protonation and rearrangement into butyrolactone oximes

Vladimir O. Smirnov, Yulia A. Khomutova and Sema L. Ioffe*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 499 135 5328; e-mail: iof@ioc.ac.ru

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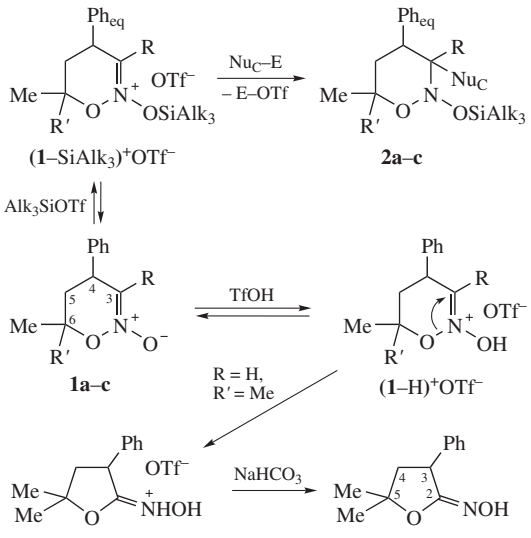
The protonation of six-membered cyclic nitronates (SMCNs) was studied by low-temperature NMR spectroscopy, and an efficient preparative procedure for acid-induced rearrangement of SMCNs into oximes of substituted butyrolactones was developed.

Six-membered cyclic nitronates **1** can be considered as Lewis bases that formed ionic pairs (**1**–$SiAlk_3$)$^+OTf^-$ upon interaction with powerful silyl Lewis acids such as trialkylsilyltriflates. These oxazinium cations were studied in detail by low-temperature NMR spectroscopy.[1] The cations (**1**–$SiAlk_3$)$^+$ undergo C,C-coupling with π-nucleophiles Nu_C–E to give nitrosoacetals **2** (Scheme 1).[1,2] However, the ability of nitronates **1** to interact as bases with protic acids to give *N*-hydroxy-5,6-dihydro-4*H*-1,2-oxazinium ions (**1**–H)$^+$ is still unexplored.

Here we report preliminary data on the interaction of protic acids with nitronates **1**. The previously described procedure[1] was applied to the generation and low-temperature NMR monitoring of cations (**1**–H)$^+$. The signals of the cation (**1a**–H)$^+$ were observed after addition of 2 equiv. of TfOH to a precooled (–40 °C) NMR sample of **1a** in CD_2Cl_2.† For the most of signals in ^{1}H and ^{13}C NMR spectra strong downfield shift accompanies the transformation of nitronate **1a** into cation (**1a**–H)$^+$. The differences of chemical shifts of analogous signals in (**1a**–H)$^+$ and **1a** spectra (Δδ) are similar to those of previously obtained for silylated ion (**1a**–$SiAlk_3$)$^+$ and nitronate **1a**, respectively.[1] In contrast to silylated cation (**1a**–$SiAlk_3$)$^+$, under incomplete formation of (**1a**–H)$^+$ (in case of TfOH deficiency) only one set of peaks can be observed, obviously, due to rapid proton exchange, and chemical shifts are between the chemical shifts of nitronate **1a** and cation (**1a**–H)$^+$.



Scheme 1

Consequently, the rate of exchange for the **1a** + TfOH ⇄ ⇄ (**1a**–H)$^+OTf^-$ system is much greater than that for the **1a** + $TfOSiAlk_3$ ⇄ (**1a**–$SiAlk_3$)$^+OTf^-$ system. The dependence of Δδ (for characteristic peaks) on the ratio **1a**:TfOH indicates that the equilibrium **1a** + TfOH ⇄ (**1a**–H)$^+OTf^-$ is shifted completely to the right even in the presence of 2 equiv. of TfOH. Indeed, the increase of TfOH excess does not affect Δδ values noticeably (Figure 1).

Upon heating of (**1a**–H)$^+OTf^-$ to room temperature, the cation undergoes quantitative rearrangment to protonated butyrolactone oxime (**3a**–H)$^+OTf^-$. The structure of the latter was confirmed, along with spectral characteristics, with preparative isolation of parent oxime **3a**, after treatment of the NMR sample with an aqueous solution of $NaHCO_3$. Note that, in contrast to (**1a**–H)$^+$ cation, separate peaks of NH, OH and TfOH protons are observed

† For the calibration of NMR spectra on the solvent residual peak, the data for chemical shifts of CH_2Cl_2 in $CDCl_3$ were taken (^{1}H: 5.30 ppm; ^{13}C: 53.52 ppm).[5]

Nitronate **1a** (230 K, 10.8 mg in 0.50 ml CD_2Cl_2). ^{1}H NMR (200 MHz) δ: 7.38–7.16 (m, 5H, Ph), 6.35 (d, 1H, H-3, *J* 2.5 Hz), 3.87–3.73 (m, 1H, H-4), 2.04 (dd, 1H, H-5, *J* 13.6 and 7.7 Hz), 1.73 (t, 1H, H-5, *J* 13.0 Hz), 1.42 (s, 3H, Me), 1.36 (s, 3H, Me). ^{13}C NMR (50 MHz, 230 K, CD_2Cl_2) δ: 139.7 (*i*-Ph), 128.6, 127.3, 127.2 (*o*,*m*,*p*-Ph), 113.0 [C(3)], 82.1 [C(6)], 38.3, 38.1 [C(4) and C(5)], 27.0, 21.6 (2Me).

1a with 2.0 equiv. TfOH. ^{1}H NMR (200 MHz, 230 K, CD_2Cl_2) δ: 13.05 (br. s, 2H, TfOH + NOH), 7.83 (br. s, 1H, H-3), 7.46–7.33 (m, 3H, Ph), 7.29–7.18 (m, 2H, Ph), 4.29–4.14 (m, 1H, H-4), 2.31 (dd, 1H, H-5, *J* 14.2 and 7.4 Hz), 2.03 (t, 1H, H-5, *J* 13.1 Hz), 1.55 (s, 6H, 2×Me). ^{13}C NMR (50 MHz, 230 K, CD_2Cl_2) δ: 139.9 [C(3)], 133.6 (*i*-Ph), 129.3, 128.7, 128.2 (*o*,*m*,*p*-Ph), 119.7 (q, CF_3, *J* 318 Hz), 92.3 [C(6)], 38.4, 35.7 [C(4) and C(5)], 26.1, 21.3 (2Me).

1a with 5.0 equiv. TfOH. ^{1}H NMR (200 MHz, 230 K, CD_2Cl_2) δ: 12.1 (br. s, 5H, TfOH + NOH), 7.90 (br. s, 1H, H-3), 7.48–7.36 (m, 3H, Ph), 7.29–7.16 (m, 2H, Ph), 4.31–4.14 (m, 1H, H-4), 2.38 (dd, 1H, H-5, *J* 14.5 and 7.3 Hz), 2.09 (t, 1H, H-5, *J* 12.9 Hz), 1.59 (s, 3H, Me), 1.55 (s, 3H, Me). ^{13}C NMR (50 MHz, 230 K, CD_2Cl_2) δ: 139.6 [C(3)], 132.8 (*i*-Ph), 129.5, 129.1, 127.7 (*o*,*m*,*p*-Ph), 117.8 (q, CF_3, *J* 317 Hz), 94.2 [C(6)], 38.5, 35.5 [C(4) and C(5)], 25.9, 21.3 (2Me).

(**3a**–H)$^+OTf^-$. ^{1}H NMR (300 MHz, 298 K, CD_2Cl_2) δ: 11.65 and 9.82 (2br. s, 2×1H, NH, OH), 7.51–7.43 (m, 3H, Ph), 7.31–7.24 (m, 2H, Ph), 4.75 (dd, 1H, H-3, *J* 11.9 and 9.0 Hz), 2.87 (dd, 1H, H-4, *J* 13.2 and 9.2 Hz), 2.51 (t, 1H, H-4, *J* 12.5 Hz), 1.85 and 1.70 (2s, 2×3H, 2Me). ^{13}C NMR (75 MHz, 298 K, CD_2Cl_2) δ: 177.0 [C(2)], 130.9, 130.4, 128.4 118.2 (Ph), 118.6 (q, CF_3, *J* 317 Hz), 104.3 [C(5)], 49.5 [C(3)], 44.5 [C(4)], 27.9, 25.8 (2Me).

Table 1 Characteristic NMR peaks for nitronates **1a–c** and respective cations (**1**–H)$^+$.

Nitronate/ cation	^{1}H NMR, δ		^{13}C NMR, δ	
	1	(**1**–H)$^+$OTf$^-$	**1**	(**1**–H)$^+$OTf$^-$
1a	6.35 (d, H-3, *J* 2.5 Hz) 3.87–3.73 (m, H-4) 2.04 (dd, H-5$_{eq}$, *J* 13.6 and 7.7 Hz) 1.73 (t, H-5$_{ax}$, *J* 13.0 Hz)	7.83 (br. s, H-3) 4.29–4.14 (m, H-4) 2.31 (dd, H-5$_{eq}$, *J* 14.2 and 7.4 Hz) 2.03 (t, H-5$_{ax}$, *J* 13.1 Hz)	113.0 [C(3)] 82.1 [C(6)]	139.9 [C(3)] 92.3 [C(6)]
1b	1.73 [s, C(3)Me] 3.67 (dd, H-4, *J* 10.9 and 8.0 Hz) 2.06 (dd, H-5$_{eq}$, *J* 13.8 and 7.8 Hz) 1.85 (t, H-5$_{ax}$, *J* 12.6 Hz)	2.17 [s, C(3)Me] 4.07 (dd, H-4, *J* 11.0 and 7.5 Hz) 2.32 (dd, H-5$_{eq}$, *J* 14.6 and 7.5 Hz) 2.15 (dd, H-5$_{ax}$, *J* 14.3 and 11.0)	123.7 [C(3)] 82.0 [C(6)]	153.8 [C(3)] 89.9 [C(6)]
1c	6.33 (d, H-3, *J* 3.0 Hz) 3.96 (ddd, H-4, *J* 12.5, 7.0 and 3.0 Hz) 2.25 (dd, H-5$_{eq}$, *J* 13.5 and 7.0 Hz) 1.79 (t, H-5$_{ax}$, *J* 13.0 Hz)	7.85 (d, H-3, *J* 1.5 Hz) 4.40–4.26 (m, H-4) 2.49 (dd, H-5$_{eq}$, *J* 14.5 and 7.5 Hz) 2.12 (dd, H-5$_{ax}$, *J* 11.8 and 14.5 Hz)	113.9 [C(3)] 104.3 [C(6)]	140.8 [C(3)] 113.7 [C(6)]

in the spectra of the (**3a**–H)$^+$OTf$^-$ + TfOH system even at room temperature.

The kinetic investigation of the rearrangement (**1a**–H)$^+$OTf$^-$ → → (**3a**–H)$^+$OTf$^-$ was studied at 252–281 K according to a previously described procedure,[1] following (**1a**–H)$^+$OTf$^-$ concentration. It was shown that the decrease of the amount of (**1a**–H)$^+$ corresponds to the increase of the amount of (**3a**–H)$^+$, and no other intermediates were observed in proton spectra during the rearrangement. This reaction follows first-order rate law [based on (**1a**–H)$^+$]. After processing of kinetic data according to the Eyring equation, the activation parameters for the rearrangement were determined as $\Delta H^{\neq}$ = 74.8±2.8 kJ mol^{-1} and $\Delta S^{\neq}$ = = –26.5±10.6 J mol^{-1} K^{-1}. From these data, the stability of **1a**–H$^+$ (in terms of half-life period) is estimated as 11 h at –30 °C, 36 min at –10 °C, 3 min at 10 °C and 21 s at 30 °C.

The addition of 3.5 equiv. of weaker trifluoroacetic acid (TFA) (procedure[1]) to the NMR sample of nitronate **1a** also leads to a downfield shift of nitronate signals, but to less extent than with the use of TfOH.‡ As for TfOH, further addition of TFA does not lead to any substantial changes of chemical shifts (Figure 1). However, upon heating of the resulting NMR sample to room temperature only a complex mixture of unidentified products forms, that contains no traces of (**3a**–H)$^+$$CF_3CO_2^-$. These facts allow us to assume that the treatment of TFA with nitronate **1a** does not give rise to (**1a**–H)$^+$$CF_3CO_2^-$. Probably, other species, for example complex **1a**·TFA or 1,3-adduct **1a** with TFA, are formed in this interaction.

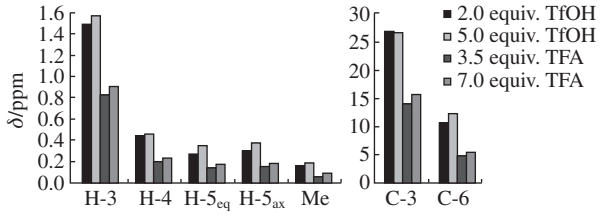


Figure 1 Difference of chemical shifts (Δδ) for characteristic peaks in ^{1}H and ^{13}C NMR spectra of a mixture of nitronate **1a** with TfOH or TFA.

‡ **1a** with 3.5 equiv. TFA. ^{1}H NMR (200 MHz, 230 K, CD_2Cl_2) δ: 11.52 (s, 3.5H, Ac_FOH, NOH), 7.42–7.30 (m, 3H, Ph), 7.22 (d, 2H, *o*-Ph, *J* 6.4 Hz), 7.17 (s, 1H, H-3), 4.05–3.90 (m, 1H, H-4), 2.18 (dd, 1H, H-5, *J* 14.2 and 7.3 Hz), 1.88 (t, 1H, H-5, *J* 13.0 Hz), 1.44 (s, 6H, 2Me). ^{13}C NMR (50 MHz, 230 K, CD_2Cl_2) δ: 158.7 (q, CO_{TFA}, *J* 41.6 Hz) 136.6 (*i*-Ph), 129.0, 128.0, 127.5 (*o*,*m*,*p*-Ph), 126.9 [C(3)], 114.1 (q, CF_3, *J* 285.7 Hz), 86.5 [C(6)], 38.2, 37.0 [C(4), C(5)], 26.5, 21.5 (2Me).

1a with 7.0 equiv. TFA. ^{1}H NMR (200 MHz, 230 K, CD_2Cl_2) δ: 11.64 (s, 7H, Ac_FOH, NOH), 7.43–7.31 (m, 3H, Ph), 7.29–7.19 (m, 3H, *o*-Ph, H-3), 4.11–3.92 (m, 1H, H-4), 2.20 (dd, 1H, H-5, *J* 14.6 and 6.0 Hz), 1.90 (t, 1H, H-5, *J* 12.4 Hz), 1.45 (s, 6H, 2Me). ^{13}C NMR (50 MHz, 230 K, CD_2Cl_2) δ: 160.0 (q, CO_{TFA}, *J* 42.5 Hz), 136.3 (*i*-Ph), 129.0, 128.1, 127.5 (*o*,*m*,*p*-Ph), 128.3 [C(3)], 113.9 (q, CF_3, *J* 285.0 Hz), 87.1 [C(6)], 38.2, 36.8 [C(4), C(5)], 26.5, 21.4 (2Me).

Upon treatment of NMR samples of nitronates **1b**,**c** with an excess of TfOH according to a described procedure,[1] the corresponding cations (**1b**–H)$^+$ or (**1c**–H)$^+$ were obtained (Scheme 1).

Their characteristic peaks are listed in Table 1. The dominant conformations of nitronates **1a–c** and respective cations (**1**–H)$^+$ were similar since the vicinal coupling constants of both species have close values.

Upon heating to room temperature, ionic intermediates (**1b**,**c**–H)$^+$TfO$^-$ decompose to a complex mixture of unidentified products. Obviously, the presence of acetal moiety at C(6), as well as the absence of a proton at C(3), makes impossible the rearrangement of (**1**–H)$^+$ into (**3**–H)$^+$.

At the same time, other nitronates **1**, that meet the above restrictions, can be smoothly converted into the corresponding oximes **3** after treatment with triflic acid using a convenient procedure (Scheme 2).§ A possible pathway of rearrangement is shown in Scheme 2.

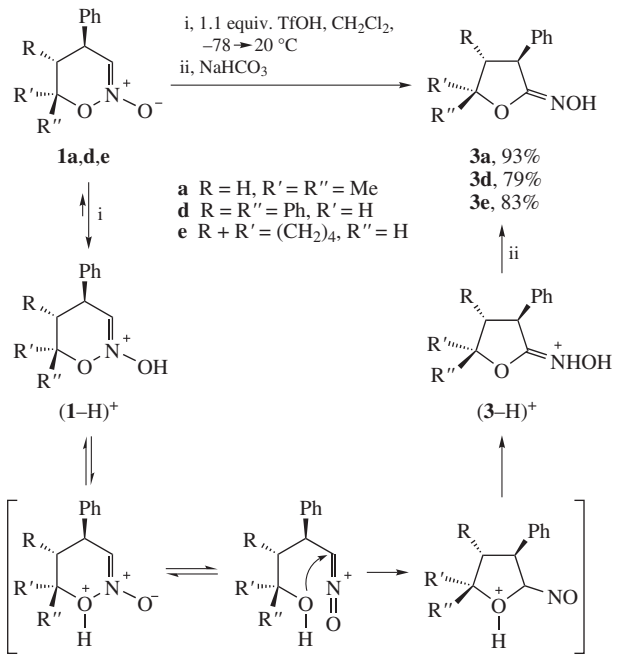
Quantitative generation of the ionic species (**1**–H)$^+$OTf$^-$ from nitronates **1** is the crucial point for successful proton-induced rearrangement of nitronate **1** into **3**. The addition of only a catalytic

§ *General procedure for the preparation of butyrolactone oximes* **3a**,**d**,**e**. To a stirred solution of nitronate **1** in dry CH_2Cl_2 (3.0 ml mmol^{-1}), TfOH (1.1 equiv.) was added at –78 °C. The cooling bath was removed after 5 min, and the reaction mixture was allowed to reach ambient temperature. After additional 5 min, a saturated aqueous sodium bicarbonate solution (3.0 ml mmol^{-1}) was added to the reaction mixture. The aqueous layer was separated and washed with an equal volume of CH_2Cl_2. Combined organic layers were washed with brine, dried over sodium sulfate and evaporated. Crystalline residue was recrystallised from toluene.

3a: yield 93%, colourless crystals, mp 148–152 °C. ^{1}H NMR (300 MHz, 298 K, $CDCl_3$) δ: 7.37–7.21 (m, 5H, Ph), 6.87 (br. s, 1H, OH), 4.20 (dd, 1H, C*H*Ph, *J* 11.3 and 8.6 Hz), 2.44 (dd, 1H, *H*–C–H′, *J* 12.5 and 8.5 Hz), 2.14 (t, 1H, *H*′–C–H, *J* 12.0 Hz), 1.57 (s, 3H, Me), 1.48 (s, 3H, Me). ^{13}C NMR (75 MHz, 298 K, $CDCl_3$) δ: 161.0 (C=N), 138.5 (*i*-Ph), 128.9, 128.1 (*o*,*m*-Ph), 127.5 (*p*-Ph), 86.4 (Me_2CO), 46.3 (CH_2), 45.9 (*C*HPh) 28.5, 27.1 (2Me). Found (%): C, 70.12; H, 7.55; N, 6.85. Calc. for $C_{12}H_{15}NO_2$ (%): C, 70.22; H, 7.37; N, 6.82.

3d: yield 79%, colourless crystals, mp 168–170 °C. ^{1}H NMR (300 MHz, 298 K, $CDCl_3$) δ: 7.82 (br. s, 1H, OH), 7.40–7.25 (m, 5H, Ph), 7.24–7.05 (m, 6H, Ph), 6.95–6.65 (m, 4H, Ph), 5.87 (d, 1H, O–C*H*Ph, *J* 7.2 Hz), 4.33 [d, 1H, N=C(O)C*H*Ph, *J* 7.6 Hz], 3.87 (t, 1H, C*H*Ph, *J* 7.3 Hz). ^{13}C NMR (75 MHz, 298 K, $CDCl_3$) δ: 160.0 (C=N), 137.9, 135.35, 135.28 (3×*i*-Ph), 129.0, 128.8, 128.6 (3×*o*,*m*-Ph), 128.5 (*p*-Ph), 128.2, 128.1 (2×*o*,*m*-Ph), 127.4, 127.2 (2×*p*-Ph), 125.8 (*o*,*m*-Ph), 86.2 (Ph*C*H–O), 57.3 (*C*HPh), 50.9 (*C*HPh). Found (%): C, 80.52; H, 5.91; N, 4.12. Calc. for $C_{22}H_{19}NO_2$ (%): C, 80.22; H, 5.81; N, 4.25.

3e, yield 83%, colourless crystals, mp 126–128 °C. ^{1}H NMR (300 MHz, 298 K, $CDCl_3$) δ: 7.82 (br. s, 1H, OH), 7.36–7.15 (m, 5H, Ph), 4.60 (q, 1H, HCO, *J* 5.3 Hz), 3.80 (d, 1H, C*H*Ph, *J* 6.4 Hz), 2.38 (m, 1H, *H*CCHPh), 1.94–1.30 [m, 8H, $(CH_2)_4$]. ^{13}C NMR (75 MHz, 298 K, $CDCl_3$) δ: 160.9 (C=N), 138.0 (*i*-Ph), 128.7, 127.9 (*o*,*m*-Ph), 127.2 (*p*-Ph), 80.1 (HCO), 50.0, 44.7 (2×CH), 28.3, 25.7, 22.0, 21.2 (4CH_2). Found (%): C, 73.00; H, 7.57; N, 5.89. Calc. for $C_{14}H_{17}NO_2$ (%): C, 72.70; H, 7.41; N, 6.06.

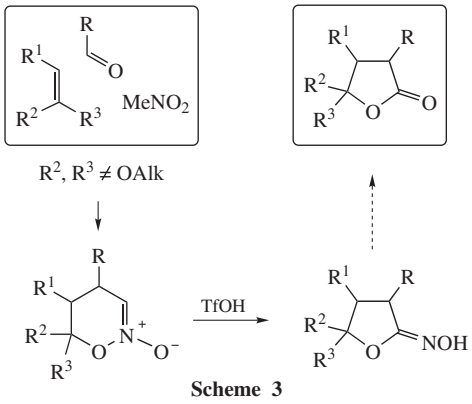


Scheme 2

amount of triflic acid (5%) to the solution of **1a** leads to a complex mixture of products, which contains the target oxime only in trace amounts (detection by TLC).

Previously,[3,4] it was shown with several examples that the above mentioned nitronates can be converted into target oximes in modest yields upon treatment with potassium *tert*-alcoholates. The effective procedure for deoximation of **3** into substituted butyrolactones was described.[3,4] The above procedure for the rearrangement of **1** into **3** upon treatment with triflic acid seems more convenient and effective.

The acid-induced rearrangement of **1** to **3** can be used as a new convenient strategy of the stereocontrolled assembly of substituted butyrolactones from very simple precursors (Scheme 3).



Scheme 3

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References

1 Yu. A. Khomutova, V. O. Smirnov, H. Mayr and S. L. Ioffe, *J. Org. Chem*., 2007, **72**, 9134.
2 V. O. Smirnov, S. L. Ioffe, A. A. Tishkov, Yu. A. Khomutova, I. D. Nesterov, M. Yu. Antipin, W. A. Smit and V. A. Tartakovsky, *J. Org. Chem*., 2004, **69**, 8485.
3 S. E. Denmark, M. S. Dappen and C. J. Cramer, *J. Am. Chem. Soc*., 1986, **108**, 1306.
4 S. E. Denmark, Y.-C. Moon, C. J. Cramer, M. S. Dappen and C. B. W. Senanayake, *Tetrahedron*, 1990, **46**, 7373.
5 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem*., 1997, **62**, 7512.

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