

# Studies on the chemistry of the chiral nitronic acid and nitronic esters

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**Abstract:** Some new chemistry of the chiral nitronic acid and nitronic esters is described. Conversions with retention of configuration are found among the chiral nitronic acid, oxime, nitronic esters and *O*-alkyloximes.  $\alpha,\beta$ -Elimination reactions of nitronic esters are observed for the first time. Novel and enantiopure chiral bisheterocyclic compounds are obtained via highly diastereoselective 1,3-dipolar cycloaddition of the chiral nitronic esters with ethyl acrylate. © 1997 Elsevier Science Ltd

## Introduction

The chemistry of nitronic acids and nitronic esters remains relatively unknown due to their well instability.<sup>1</sup> In our recent publications,<sup>2</sup> we described progress in the study of nitronic acids and nitronic esters, that is (1) the first stable nitronic acid and nitronic esters were obtained, (2) nitronic esters were synthesized for the first time via *O*-alkylation of the alkali metal nitronate with alkyl halides and (3) enantiopure nitronic esters were prepared for the first time by way of asymmetric *O*-alkylation. Moreover, these achievements have led to other interesting findings, the empirical correlation rule of chiral  $\gamma$ -butyrolactones<sup>3</sup> and the first stable axial conformers of monosubstituted cyclohexanes at room temperature.<sup>4</sup> Here we report some new chemistry of the chiral nitronic acid and nitronic esters (Scheme 1).

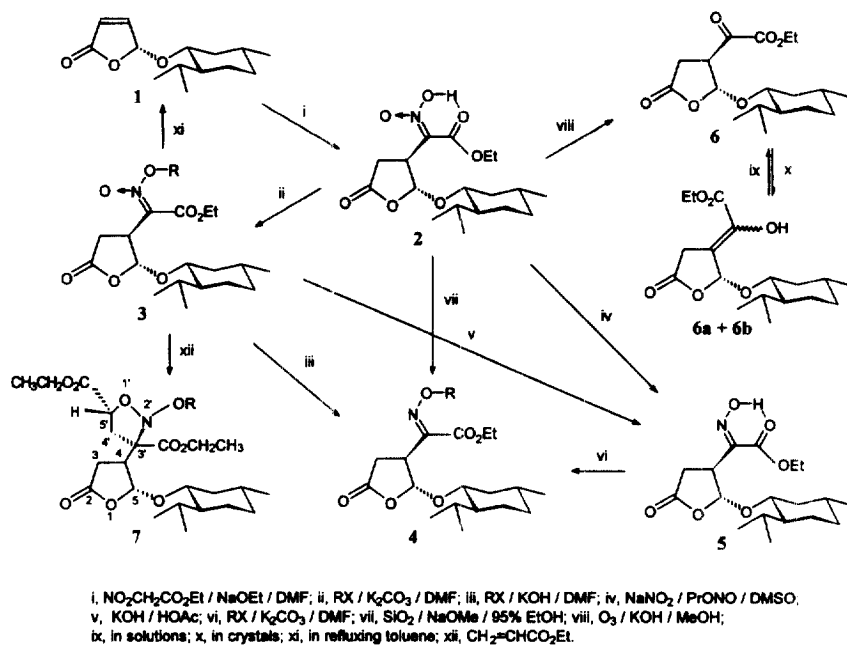
## Results and discussion

Stable, enantiopure, and crystalline nitronic acid **2** is synthesized via asymmetric Michael addition of ethyl nitroacetate to the chiral synthon **1**.<sup>5</sup> Stable, enantiopure, and crystalline nitronic esters **3** are obtained when **2** is treated with various alkyl halides in the presence of  $K_2CO_3$  and DMF.<sup>2</sup> NOE experiments<sup>2</sup> and  $^{13}C$  NMR spectral analyses (the nitronate carbons of **2** and **3** all appearing at 103 ppm) confirm that **3** has the *Z* configuration. Interestingly, when secondary alkyl or allyl halides are used, enantiopure and oily *O*-alkyloximes **4** are produced as minor byproducts.<sup>2</sup> NOE experiments<sup>2</sup> and  $^{13}C$  NMR spectral analyses (the oxime carbon of **4** and **5** all emerging at 153 ppm) suggest that **4** also possesses the *Z* configuration.

Compound **4** is presumed to result from the partial decomposition<sup>6</sup> of **3** under the basic conditions, and the subsequent *O*-alkylation of the resulting oxime with the unreacted alkyl halide. This hypothesis is confirmed by the following experiments. The reaction mixture of **3** and KOH in DMF is quenched with a cold dilute acid (HOAc) to give **5**, and *iso*-propyl nitronic ester **3** is treated with KOH and  $CH_3I$  to furnish *O*-methyloxime **4**. Enantiopure and crystalline oxime **5** is afforded when **2** is treated with  $NaNO_2$  and PrONO in DMSO,<sup>7</sup> and the spectroscopic data reveal the presence of a six-membered intramolecular hydrogen bond similar to that of **2**. In order to prove further that **4** has the *Z* configuration, **5** is reacted with alkyl halides in the presence of  $K_2CO_3$  and DMF to give **4**, which are identical in every aspect with the same compounds from **3**.

Unexpectedly, *O*-methyloxime **4** is obtained when a mixture of **2** and the basic silica gel<sup>8</sup> (prepared by NaOMe) is eluted with 95% ethanol, which is identical in every aspect with the same compound from **3** and **5**. Mild ozonolysis<sup>9</sup> of **2** in the presence of KOH and methanol at 0°C generates the  $\alpha$ -ketoester **6** which, to our surprise, is found to have different structures in its different states, namely,

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Scheme 1. The chemistry of the chiral nitronic acid and nitronic esters.

the keto form **6** exists in a solution whereas the enol forms **6a** and **6b** exist in crystals.<sup>10</sup> Though **3** is found to be stable in boiling water,<sup>11</sup> it is found that  $\alpha,\beta$ -elimination occurs when **3** is heated in refluxing toluene to give **1**. To the best of our knowledge, this is the first observation of such a chemical property of nitronic esters, for it is well known that nitronic esters tend to decompose into oximes and carbonyl compounds.<sup>1</sup>

Like nitrones, nitronic esters can also undergo 1,3-dipolar cycloadditions with olefinic compounds,<sup>1</sup> however no information has been reported about nitronic esters involved in asymmetric 1,3-dipolar cycloadditions. The first and highly diastereoselective 1,3-dipolar cycloaddition of the chiral nitronic ester **3** with ethyl acrylate was achieved when it was treated with ethyl acrylate at 30–40°C in the absence of solvents, giving the novel chiral bisheterocyclic compound, enantiopure and oily **7**, as the single product. The absolute configuration of the  $\text{C}_{3'}$  and  $\text{C}_{5'}$  atoms is tentatively assumed to be *R* on the basis of the following considerations: from the point of view of steric hindrance, ethyl acrylate is expected to approach to **3** from the opposite direction of menthyloxy, and 1,3-dipolar cycloadditions of nitronic esters usually give *endo* adducts.<sup>12</sup>

Though it has been stated that there seems to be no relationship between stability and structure of nitronic esters,<sup>6</sup> the anomalous stability of the chiral nitronic acid and nitronic esters prompts us to study the correlation between stability and structure of these special species in organic compounds. Our recent research work demonstrates that the reactions of ethyl nitroacetate, the synthetic precursor of **2**, with benzyl chloride and benzyl bromide, respectively, fail to produce nitronic esters. Interestingly however, the former affords the thermodynamically controlled *O*-alkylated product 4-phenyl-3,5-biscarbethoxyisoxazoline *N*-oxide, while the latter furnishes the kinetically controlled *C*-alkylated product ethyl 2-nitro-2-benzyl-3-phenylpropionate.<sup>13</sup>

Further investigations on this subject and the possible mechanisms of some of the new chemistry described above are underway.

### Experimental section

Elemental analyses were performed on a Perkin–Elmer 240C microanalyzer. Infrared spectra were recorded on a Hitachi 260-50 spectrometer.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained at 200 MHz on a Varian-200 spectrometer in  $\text{CDCl}_3$  with chemical shifts in ppm downfield from TMS and coupling constants in Hz. Optical rotations were measured on a Perkin–Elmer 241MC polarimeter. Melting points (uncorrected) were taken on a Yanaco MP-500 apparatus. The syntheses and characterization of compounds 1–3 are reported in a previous paper.<sup>2b</sup>

*(Z)-(+)-O-Methyloxime of (4S,5R)-4-(1'-nitroso-1'-carbethoxymethyl)-5-[(1R,2S,5R)-menthyloxy]-3,4-dihydro-2(5H)-furanone 4*

**Method 1.** *iso*-Propyl nitronic ester **3** (0.5 g, 1.2 mmol) was treated with KOH (0.07 g, 1.2 mmol) and  $\text{CH}_3\text{I}$  (0.15 mL, 2.4 mmol) in DMF (8 mL). The reaction mixture was stirred at room temperature for 6 h. The progress of the reaction was monitored by TLC. The reaction mixture was dissolved in ether and washed with water, brine and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent furnished the crude product. Column chromatography on silica gel using a mixture of light petroleum ether and ethyl acetate (7:1) gave **4** in 66% yield.

**Method 2.** Compound **5** (0.5 g, 1.4 mmol) was treated with  $\text{CH}_3\text{I}$  (0.17 mL, 2.8 mmol) and  $\text{K}_2\text{CO}_3$  (0.19 g, 1.4 mmol) in DMF (10 mL). After being stirred at room temperature for 48 h, the reaction mixture was dissolved in ether and washed with water, brine and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent under reduced pressure afforded **4** in 71% yield.

**Method 3.** The basic silica gel was readily prepared by mixing chromatographic grade silica gel (100 g) with a methanolic solution of sodium methoxide (0.25 N, 300 mL) followed by evaporation to dryness and heating at 400°C for several hours. Compound **2** (0.5 g, 1.3 mmol) was mixed with the activated basic silica gel (20 g) and the mixture was stirred at 50°C in a closed bottle for 48 h. Elution of the resulting mixture with 95% ethanol gave a light yellow residue which was purified by column chromatography on silica gel using a mixture of light petroleum ether and ethyl acetate (6:1) as the eluent to furnish **4** in 22% yield.

A colorless oil;  $[\alpha]_{578}^{25} +230.5$  (*c* 1.0, hexane); IR (neat) 1740, 1720, 1650, 1580  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  0.65–1.35 (m, 14H), 1.38 (t, 3H), 1.63 (m, 2H), 2.19 (m, 2H), 2.38 (dd, 1H, *J*=16.6, 11.4 Hz), 2.86 (dd, 1H, *J*=16.6, 3.6 Hz), 3.45 (dd, 1H, *J*=10.6, 4.2 Hz), 3.62 (ddd, 1H, *J*=11.4, 3.6, 1.5 Hz), 3.72 (s, 3H), 4.35 (q, 2H), 5.52 (d, 1H, *J*=1.5 Hz);  $^{13}\text{C}$  NMR  $\delta$  13.5, 15.6, 20.4, 21.6, 22.6, 24.9, 31.0, 31.9, 33.7, 42.4, 47.7, 49.0, 51.4, 61.4, 81.0, 110.3, 152.8, 159.3, 169.9; Anal. Calcd for  $\text{C}_{19}\text{H}_{31}\text{NO}_6$ : C, 61.79; H, 8.40; N, 3.79. Found: C, 61.92; H, 8.22; N, 3.73.

*(4S,5R)-(+)-4-(1'-Nitroso-1'-carbethoxymethyl)-5-[(1R,2S,5R)-menthyloxy]-3,4-dihydro-2(5H)-furanone 5*

**Method 1.** Compound **2** (5.4 g, 15 mmol),  $\text{NaNO}_2$  (10 g, 0.15 mol) and  $\text{PrONO}$  (12 g, 0.15 mol) were mixed in DMSO (40 mL) under nitrogen. After being stirred in subdued light at 23–28°C for 48 h, the reaction mixture was quenched with ice and water (400 mL) to give the crude product. Recrystallization from ether and light petroleum ether afforded **5** in 78% yield.

**Method 2.** An alkyl nitronic ester **3** (1.5 mmol) was treated with KOH (0.08 g, 1.5 mmol) in DMF (8 mL). The reaction mixture was stirred at room temperature for 12 h. Then it was quenched with ice (150 g) and 5% HOAc (50 mL), and a white solid was precipitated on standing. Recrystallization from ether and light petroleum ether generated **5** in 52–74% yields.

Colorless crystals; mp 121–122°C;  $[\alpha]_{578}^{25} +118$  (*c* 1.0,  $\text{CHCl}_3$ ); IR (KBr) 3250, 1745, 1725, 1688, 1590  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\delta$  0.66–1.14 (m, 14H), 1.29 (t, 3H), 1.55 (m, 2H), 2.11 (m, 2H), 2.36 (dd, 1H, *J*=17.2, 11.5 Hz), 2.88 (dd, 1H, *J*=17.2, 3.2 Hz), 3.35 (dd, 1H, *J*=10.5, 4.1 Hz), 3.53 (dd, 1H, *J*=11.5, 3.2 Hz), 4.26 (q, 2H), 5.74 (s, 1H), 11.35 (br s, 1H);  $^{13}\text{C}$  NMR  $\delta$  14.2, 16.2, 21.2, 22.4, 23.4, 25.7, 31.9, 32.5, 34.7, 43.5, 46.8, 50.1, 62.1, 81.6, 111.4, 153.9, 160.3, 171.7; Anal. Calcd for  $\text{C}_{18}\text{H}_{29}\text{NO}_6$ : C, 60.81; H, 8.23; N, 3.94. Found: C, 60.92; H, 8.26; N, 3.95.

*(4R,5R)-(-)-4-Ethoxyoxalyl-5-[(1R,2S,5R)-menthyloxy]-3,4-dihydro-2(5H)-furanone 6*

Compound **2** (2.0 g, 5.4 mmol) in methanol (25 mL) was treated with potassium hydroxide (0.33 g, 5.9 mmol) and stirred for 5 min to form the nitronate salt. Then the solution was cooled to 0°C, and a stream of ozone-oxygen was passed through it. The progress of the reaction was monitored by TLC. Soon after the completion of the reaction, the mixture was concentrated by rotary evaporation to a residue, which was dissolved in ether and washed with 20% NaOH, water, brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of solvent gave crude product. Recrystallization from a mixture of light petroleum ether and methylene chloride led to **6** in 83% yield.

Colorless crystals; mp 58–61°C; [ $\alpha$ ]<sub>589</sub><sup>25</sup> –134.3 (c 0.83, CH<sub>2</sub>Cl<sub>2</sub>); IR (in nujol) 1790, 1760, 1750, 1730 cm<sup>-1</sup>; <sup>1</sup>H NMR  $\delta$  0.7–1.3 (m, 14H), 1.40 (t, 3H), 1.65 (m, 2H), 2.10 (m, 2H), 2.78 (dd, 1H, *J*=18.0, 4.8 Hz), 2.97 (dd, 1H, *J*=18.0, 9.4 Hz), 3.55 (dd, 1H, *J*=10.6, 4.2 Hz), 3.93 (ddd, 1H, *J*=9.4, 4.8, 2.2 Hz), 4.38 (q, 2H), 5.86 (d, 1H, *J*=2.2 Hz); <sup>13</sup>C NMR  $\delta$  13.9, 15.5, 20.8, 22.1, 22.9, 25.3, 29.2, 31.2, 34.1, 39.6, 47.5, 50.4, 63.3, 77.8, 99.4, 159.6, 173.5, 189.5; Anal. Calcd for C<sub>18</sub>H<sub>28</sub>NO<sub>6</sub>: C, 63.53; H, 8.24. Found: C, 63.48; H, 8.21.

*(4S,5R)-(+)-4-[(3'R\*,5'R\*)-N-Ethoxy-3',5'-biscarbethoxy-3'-isoxazolidinyl]-5-[(1R,2S,5R)-menthyloxy]-3,4-dihydro-2(5H)-furanone 7*

Ethyl nitronic ester **3** (1.3 mmol) was dissolved in excessive ethyl acrylate (3 mL), and the reaction mixture was stirred at 30–40°C for 24 h. Removal of the unreacted acrylate under reduced pressure gave the crude product which was purified by column chromatography on silica gel using a mixture of light petroleum ether and ethyl acetate (6:1) as the eluent to furnish **7** in 53% yield. (Compounds **7** where R is CH<sub>3</sub> (42%) and C<sub>9</sub>H<sub>19</sub> (46%) are to be characterized.) The purity of compounds **7** was demonstrated by TLC.

A colorless oil; [ $\alpha$ ]<sub>589</sub><sup>25</sup> +22 (c 0.79, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) 1760–1740 cm<sup>-1</sup> (C<sub>2</sub>, C<sub>8'</sub> and C<sub>11'</sub> carbonyls); <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>)  $\delta$  0.6–1.6 (m, 25H), 2.34 (m, 2H, H<sub>7</sub>, H<sub>12</sub>), 2.63 (d, 2H, *J*=8.4 Hz, H<sub>4'</sub>), 3.14 (d, 2H, *J*=8.2 Hz, H<sub>3</sub>), 3.20 (m, 1H, H<sub>6</sub>), 3.33 (t, 1H, *J*=8.2 Hz, H<sub>4</sub>), 3.90 (br q, 6H, H<sub>6'</sub>, H<sub>9'</sub>, H<sub>12'</sub>), 5.17 (s, 1H, H<sub>5</sub>), 5.35 (t, 1H, *J*=8.4 Hz, H<sub>5'</sub>); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>)  $\delta$  13.8, 13.9, 14.0, 16.5, 21.2, 22.2, 23.5, 26.0, 31.7, 34.1, 34.4, 41.5, 42.9, 48.5, 52.9, 60.8 (C<sub>6'</sub>), 61.4 (C<sub>12'</sub>), 61.9 (C<sub>9'</sub>), 79.7 (C<sub>6</sub>), 82.6 (C<sub>5'</sub>), 84.5 (C<sub>3'</sub>), 110.3 (C<sub>5</sub>), 169.0 (C<sub>11'</sub>), 169.1 (C<sub>8'</sub>), 170.8 (C<sub>2</sub>). Anal. Calcd for C<sub>25</sub>H<sub>41</sub>NO<sub>9</sub>: C, 60.12; H, 8.22; N, 2.81. Found: C, 60.25; H, 8.14; N, 2.79.

 *$\alpha$ , $\beta$ -Elimination reactions of nitronic esters 3*

An alkyl nitronic ester **3** (0.5 g) was refluxed in toluene (20 mL) for 48 h. Removal of solvent under reduced pressure and recrystallization from light petroleum ether gave compound **1** in 72–86% yields.

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7. This reaction condition was reported for the conversion of nitro to carbonyl, see: Kornblum, N.; Wade, P. *J. Org. Chem.* **1973**, *38*, 1418, but in this case the reaction gives **5** rather than **6**.
8. This reaction condition was described for the transformation of nitro to carbonyl, see: Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3861, however in this case the reaction produces **4** rather than **6**.
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10. Complete tautomerization between **6** and **6a+6b** is confirmed by their spectroscopic analyses. The keto form **6**: IR (nujol) 1790, 1760, 1745, 1730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.94 (ddd, 1H,  $J=9.4$ , 4.8, 2.2 Hz,  $\text{H}_4$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  189.5 (C=O). The enol forms **6a** and **6b**: mp  $58-61^{\circ}\text{C}$ ; IR (KBr) 3500, 3375, 1770, 1725, 1630  $\text{cm}^{-1}$ .
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