General Method for the Synthesis of Isoxazoline N-Oxides from Aliphatic Nitro Compounds

Roman A. Kunetsky, Alexander D. Dilman,* Marina I. Struchkova, Pavel A. Belyakov, Vladimir A. Tartakovsky, Sema L. Ioffe
N. D. Zelinsky Institute of Organic Chemistry, 119991 Moscow, Leninsky prosp. 47, Russian Federation
Fax +7(495)1355328; E-mail: adil25@mail.ru
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Abstract: A method for the synthesis of isoxazolines N-oxides from primary aliphatic nitro compounds and olefins based on the 1,3-dipolar cycloaddition of intermediate 1-halo-substituted silyl nitronates, followed by halosilane elimination has been described. The nature of the halogen atom plays a key role in determining the stability and reactivity of all intermediates of this process. Bromonitro compounds can be conveniently used in reactions with terminal alkenes, while fluorinated derivatives must be employed for internal olefins.

Key words: aliphatic nitro compounds, silyl nitronates, 1-halo-substituted nitro compounds, 1,3-dipolar cycloaddition

In contrast to the six-membered nitronates, which proved to be valuable intermediates in organic synthesis,1 their lower homologs, five-membered nitronates (isoxazoline N-oxides), have much narrower synthetic applications. This is primarily associated with the lack of convenient methods for their synthesis. Indeed, there has been only one well known strategy towards isoxazoline N-oxides based on the cyclization of γ-functionalized nitro compounds,2 while the latter require tedious preparation themselves.

Recently we reported completely different approach to isoxazoline N-oxides starting from simple primary aliphatic nitro compounds and terminal olefins (Scheme 1).3 The method includes bromination of nitro compounds 1 (step 1), silylation of α-bromo derivatives (step 2), cycloaddition of bromosilyl nitronates with alkenes (step 3), and elimination of bromosilane from N-silyloxyisoxazolidine (step 4). Steps 2–4 proceed within one synthetic operation.

The major disadvantage of this procedure is very slow cycloaddition (step 3) requiring up to one month at room temperature, which precludes employment of less reactive internal olefins, thereby rendering 4-substituted isoxazoline N-oxides inaccessible by this method. There are also additional shortcomings such as the need for large excess of alkene (up to five equiv) and utilization of expensive silylating reagent t-BuMe2SiCl.

The major focus of the present work is to reduce the reaction time of cycloaddition in order to broaden the scope of the approach shown on Scheme 1. First of all we decided to improve previously reported procedure3 by using cheaper silylating reagent Me3SiCl at step 2 and performing the process at higher concentration (1 M) of the nitro substrate. Under these conditions the reaction can be carried out with only 1.5 equivalents of the alkene (Table 1). Importantly, these modifications allow increasing the reaction scale up to 50 mmol of α-bromonitro compounds and facilitating isolation of target products 2. However, the refined protocol does not solve the major problem of extending the scope of the method and offers little concern regarding sluggish rate limiting step.

To address the latter issue we first analyzed the influence of the halogen atom on the energy surface of [3+2] cycloaddition event. For this purpose we calculated the free energy of activation for the cycloaddition of ethylene to model silyl nitronates in the gas phase (Table 2).4 It can be concluded from these data that the rate of cycloaddition increases in the order I < Cl ~ Br << F. Accordingly, to accelerate the step 3 (see Scheme 1) it is necessary to employ poorly studied and difficult-to-prepare α-fluoronitro compounds.5 For their synthesis we used the fluorination of nitro compounds with Selectfluor.6 1-Nitroheptane (1a, R = n-C6H13) and phenylnitro-

Table 1 Synthesis of Isoxazoline N-Oxides from Bromonitro Compounds

<table>
<thead>
<tr>
<th>Nitro Compound</th>
<th>Alkene</th>
<th>Product</th>
<th>2 Yield of 2 (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO2Br</td>
<td>OMe</td>
<td>MeO2C</td>
<td>2a 62</td>
</tr>
<tr>
<td>NO2Br</td>
<td>Ph</td>
<td>Ph</td>
<td>2b 65</td>
</tr>
<tr>
<td>NO2Br</td>
<td>Ph</td>
<td>Ph</td>
<td>2c 60</td>
</tr>
<tr>
<td>NO2Br</td>
<td>Ph</td>
<td>Ph</td>
<td>2d 50</td>
</tr>
</tbody>
</table>

a Reactions performed in CH2Cl2 for 3–7 days at r.t.
b Isolated yield.
ethane (1b) were selected as model substrates, which were fluorinated to afford \( \alpha \)-fluoronitro alkanes 3a, b.

Initial experiments on silylation of 3a, b provided unexpected results. Thus, in contrast to stable and distillable 1-bromosilyl nitronates, fluorosilyl nitronates 4a, b were found to be very unstable. Even in dilute solutions they can be stored for only few hours at room temperature, whereas upon concentration the rate of decomposition significantly increases, and the process becomes autocatalytic leading to intractable mixtures. Nevertheless, silyl nitronates 4a, b were characterized by NMR spectroscopy (Equation 1).

Rewardingly, the cycloaddition of silyl nitronates 4a, b to styrene proceeded within 2 hours at ambient temperature, which is about two orders of magnitude faster than for analogous bromosilyl nitonate,\(^3\) thereby corroborating computational results. Thus, the employment of \( \alpha \)-fluoronitro compounds dramatically reduces the time of cycloaddition step. However, two other problems emerge. First is the instability of fluorosilyl nitronates mentioned above, while the second problem is the enhanced stability of 3-fluoro-\(N\)-silyloxyisoxazolidines. The latter fact was somewhat surprising, given that analogous 3-bromo-\(N\)-silyloxyisoxazolidines cannot even be observed by NMR spectroscopy owing to rapid elimination of bromosilane.\(^3\) In other words; the elimination of fluorosilane (step 4) becomes the rate limiting step.\(^7\)

To cope with the instability of fluorosilyl nitronates 4a, b we used the procedure allowing to maintain their stationary concentration at low level during the cycloaddition process. This can be achieved by performing the silylation in a solvent of low polarity. In particular, silylation of nitronate 3a in pentane in the presence of excess olefin (10 equiv) during seven days furnished cycloadduct 5a in 75% yield determined by NMR spectroscopy of reaction mixture (Equation 2). It should be pointed out that in dichloromethane under otherwise identical conditions no product 5a could be isolated.

The elimination of fluorosilane from 3-fluoro-\(N\)-silyloxyisoxazolidines 5 proved to be more challenging. Compounds 5b and 5b’ were produced from 3b and styrene as diastereomeric mixtures (ca. 1:1) and were characterized by NMR analysis. Attempted chromatographic purification was thwarted because of their noticeable decomposition\(^8\) (Equation 3).

**Table 2** Calculated Activation Energies (in kcal/mol, at 298.15 K) and Relative Rate Constants\(^a\)

<table>
<thead>
<tr>
<th>X</th>
<th>(\Delta H^\circ)</th>
<th>(\Delta G^\circ)</th>
<th>(\Delta G_{X}^E-\Delta G_{H}^E)</th>
<th>(k(X)/k(H))</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>15.5</td>
<td>27.5</td>
<td>0.0</td>
<td>1</td>
</tr>
<tr>
<td>F</td>
<td>11.1</td>
<td>23.0</td>
<td>-4.5</td>
<td>2051</td>
</tr>
<tr>
<td>Cl</td>
<td>14.0</td>
<td>26.0</td>
<td>-1.6</td>
<td>14</td>
</tr>
<tr>
<td>Br</td>
<td>13.4</td>
<td>25.1</td>
<td>-2.4</td>
<td>57</td>
</tr>
<tr>
<td>I(^b)</td>
<td>15.2</td>
<td>27.1</td>
<td>-0.4</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\)Calculated at the level B3LYP/6-31G(d) unless otherwise mentioned.

\(^b\)Combined basis set was used: LanL2DZ for iodine, 6-31G(d) for all other atoms.
Screening of conditions for the elimination of fluorosilane was carried out with compound 5b. No elimination could be effected by means of Lewis acids [10 mol% BF₃·OEt₂, LiClO₄, Zn(OTf)₂] nor in the presence of silicon-specific Lewis bases (10 mol% KF/18-crown-6 or Bu₄NOAc). However, heating solutions of 5b to 80 °C effected the desired transformation with the rate increasing in the order of solvents benzene < dichloroethane < acetonitrile. In more polar media (DMF, DMSO) the decomposition of 5b was observed. The optimal conditions involved refluxing of 3-fluoro-N-silyloxyisoxazolidines in acetonitrile for one hour (Equation 4).

Equation 4

As follows from the data discussed above, the proposed scheme for the synthesis of five-membered nitronates 2 from α-fluoronitro compounds includes two steps: 1) silylation in non-polar solvent in the presence of alkene, and 2) elimination of fluorosilane in refluxing acetonitrile. Taking into account high reactivity of 1-fluorosilyl nitronates in cycloaddition, we studied their reactions with internal olefins, which were inert with 1-bromosilyl nitronates (Table 3). The desired products 2d-i were obtained in acceptable yields using cyclopentene, norbornene, indene, and methyl crotonate as alkenes. At the same time, less reactive dipolarophiles, such as cyclohexene could not be involved in this process.

Despite efficiency of utilization α-fluoronitro compounds, these derivatives appear to be quite expensive substances and use of α-bromonitro compounds is recommended for the preparation of isoxazoline N-oxides from terminal olefins.

In summary, in this work and in previous report we studied in detail and optimized a method for the synthesis of five-membered cyclic nitronates from aliphatic nitro compounds and olefins. The presented approach renders these derivatives readily available, thereby paving the way for development of their chemistry.

### Table 3 Synthesis of Isoxazoline N-Oxides from Fluoronitro Compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitro Compound</th>
<th>Alkene</th>
<th>Product</th>
<th>2</th>
<th>Yield of 2 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhNO₂ F</td>
<td>Ph</td>
<td>2d</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>n-C₅H₁₁ NO₂ F</td>
<td></td>
<td>2e</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>PhNO₂ F</td>
<td></td>
<td>2f</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>n-C₅H₁₁ NO₂ F</td>
<td></td>
<td>2g</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>n-C₅H₁₁ NO₂ F</td>
<td></td>
<td>2h</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>n-C₅H₁₁ NO₂ F</td>
<td></td>
<td>2i</td>
<td>51c</td>
<td></td>
</tr>
</tbody>
</table>

a Isolated yield.
b Cyclopentene was used as solvent, reaction time 2 d.
c The diminished yield is due to partial decomposition at the step of fluorosilane elimination.
All reactions were performed under argon. CHCl₃, MeCN, and pentane were distilled from CaH₂. Petroleum ether used had a bp of 60–70 °C. Column chromatography was carried out employing Merck silica gel (Kieselgel 60, 230–400 mesh). Precoated silica gel plates F 254 were used for TLC visualizing with UV and methanolic anisaldehyde/H₂SO₄ solution.

**Isoxazoline N-Oxides 2a–d from α-Bromonitro Compounds; General Procedure (Table 1)**

Et₃N (2.09 mL, 15 mmol) was added to a solution of α-bromonitro compound (10 mmol) and Me₃SiCl (1.52 mL, 12 mmol) in CH₂Cl₂ (20 mL) at 0 °C, and the mixture was stirred for 1 h. Alkene (15 mmol) was added, the mixture was kept for a certain time (3 d for 2a, 7 d for 2b–d), and Et₃N (2.80 mL, 20 mmol) and H₂O (50 mL) were added at 0 °C. After stirring for additional 15 min, the organic phase was separated, the aqueous phase was washed with CH₂Cl₂ and pentane were distilled from CaH₂. Petroleum ether used had a bp of 60–70 °C. Column chromatography was carried out employing silica gel (Table 1).

**Synthesis 2006, No. 13, 2265–2270 © Thieme Stuttgart · New York**

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**5-Methoxy carbonyl-3-methylisoxazoline**

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Benzyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 51–53 °C; yield: 50%.

3-Ethyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 52–55 °C; yield: 60%.

5-Methoxycarbonyl-3-methylisoxazoline

Recrystallization from Et₂O; mp 52–53 °C; yield: 62%.

3-Methyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Ethyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 52–55 °C; yield: 60%.

3-Benzyl-3-fluoro-5-phenyl-2-trimethylsilyloxyisoxazolidine

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Phenyl-3-fluoro-5-phenyl-2-trimethylsilyloxyisoxazolidine

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

5-Methoxycarbonyl-3-methylisoxazoline

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Methyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Ethyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 52–55 °C; yield: 60%.

3-Benzyl-3-fluoro-5-phenyl-2-trimethylsilyloxyisoxazolidine

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Phenyl-3-fluoro-5-phenyl-2-trimethylsilyloxyisoxazolidine

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

5-Methoxycarbonyl-3-methylisoxazoline

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Methyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Ethyl-5-phenylisoxazoline

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Benzyl-3-fluoro-5-phenyl-2-trimethylsilyloxyisoxazolidine

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

3-Phenyl-3-fluoro-5-phenyl-2-trimethylsilyloxyisoxazolidine

Recrystallization from Et₂O; mp 77–78 °C; yield: 65%.

-Fluoronitro Compounds 3a,b

A solution of α-fluoronitro compound 4a or 4b (113 mg, 0.69 mmol) was slowly added to a solution of DBU (120 mL, 0.80 mmol) and Me₃SiCl (for 4a) or t-BuMe₂SiCl (for 4b) (0.76 mmol) in CCl₄ (2 mL) at −20 °C. After stirring at −20 °C for 10 min, the cooling bath was removed, and the mixture was allowed to warm to r.t. The precipitate of DBU·HCl was removed by filtration under argon and the filtrate was charged directly into NMR tube. The yield was determined relative to internal standard (methyl benzoate).

**Trimethylsilyl 1-Fluoroheptanenitronate (4a)**

1H NMR (200 MHz, CDCl₃): δ 0.41 [s, 9 H, Si(CH₃)₃], 1.01 (t, 3JH,F = 6.8 Hz, 3 H, CH₃), 1.28–1.61 (m, 6 H, 3 CH₃), 1.64–1.88 (m, 2 H, CH₂(CH₂)₂CH₂CF), 2.73 (td, 3JH,F = 15.1 Hz, 1H, CH₃(CH₂)₂CH₂CF). 29.7 (JH,F = 139.3 Hz, 2-CH₂).

**Trimethylsilyl 1-Fluoroheptanenitronate (4b)**

1H NMR (200 MHz, CDCl₃): δ 0.26 [s, 9 H, Si(CH₃)₃], 3.82 (d, 2JH,F = 16.2 Hz, 3 CH₃), 6.96–7.32 (m, 5 H, CH₃).

**Isoxazoline N-Oxides 2d-i and 3-Fluoro-silylosioxazolidines 5b, b’ from α-Fluoronitro Compounds; General Procedure (Equation 3 and Table 3)**

Me₃SiCl (165 µL, 1.3 mmol) and Et₃N (210 µL, 1.5 mmol) were added to a mixture of fluoronitro compound 3 (1 mmol), appropriate alkené (1.5 mmol) and pentane (0.25 mL) at 0 °C, and the mixture was kept with occasional stirring for 7 d [reaction conditions for 5b, b’: CH₂Cl₂ (2 mL), 1 d, r.t.]. The solvent was removed in vacuum. To remove traces of Me₃SiCl and Et₃N, benzene (3 mL) was added and then evaporated in vacuum. The residue was again diluted with benzene (10 mL), filtered through Celite, and concentrated to afford a viscous oil, which consists of 3-fluoro-silylosioxazolidine 5 along with traces of isoxazoline N-oxide. The crude 5 (see Table 3) was refluxed in a solution of MeCN (7 mL) for 1 h (the progress of the reaction can be monitored by TLC), concentrated, and the residue purified by flash chromatography on silica gel eluting with hexanes–EtOAc.

**3-Benzyl-3-fluoro-5-phenyl-2-trimethylsilyloysoxazolidine (5b)**

1H NMR (300 MHz, CDCl₃): δ = 0.31 [s, 9 H, Si(CH₃)₃] of both isomers, 2.06 (ddd, 1 H, J = 5.2, 14.0, 20.6 Hz, CH of isomer A), 2.43–2.72 [m, 2 H, CH₂ of isomer B], 2.96 (ddd, 1 H, J = 9.6, 14.0, 37.5 Hz, CH of isomer A), 3.22–3.42 (m, 2 H, CH₂Ph of both isomers), 5.34 (dd, 1 JH,F = 7.4, 9.6 Hz, CHO of isomer B), 5.53
3-Benzyl-2-tert-butylidimethyl-3-fluoro-5-phenylisoxazoline (5b) (Two Isomers 1:1)

\[ \delta = 2.36–2.75 \text{ (m, 2 H, CH}_2\text{ of isomer B)}, 2.97 \text{ (ddd, 1 H, C}_4\text{H}_9\text{)}, 2.05 \text{ (ddd, 1 H, J = 5.1, 13.8, 20.6 Hz, CH of isomer A)}, 2.36–2.54 \text{ (m, 1 H, CH A)}.

Isomer A of 5b

\[ \delta = 0.30 \text{ (s, 3 H, SiCH}_3\text{)}, 0.35 \text{ (s, 3 H, CH}_3\text{)}, 1.06 \text{ (s, 9 H, C}_9\text{H}_3\text{)}, 2.07 \text{ (ddd, 1 H, J = 5.1, 13.8, 20.6 Hz, CH)}, 2.99 \text{ (ddd, 1 H, J = 9.6, 13.8, 37.1 Hz, CH of isomer A)}, 3.24–3.40 \text{ (m, 2 H, CH}_2\text{Ph of both isomers)}, 5.34 \text{ (dd, J = 7.4, 9.6 Hz, CHO of isomer A)}, 7.16–7.55 \text{ (m, 10 H, C}_6\text{H}_5\text{ of both isomers)}.

Chromatography in toluene–hexanes (from 1:5 to 1:1) \( R_f 0.44 \) (toluene–hexanes 1:3) afforded the isomer A.

Isomer B of 5b

\[ \delta = 1.03–1.81 \text{ (m, 14 H, CH}_2\text{)}, 2.11–2.29 \text{ (m, 1 H, C}_6\text{H}_5\text{CH}_2\text{CN and 2 CH}_2\text{)}, 3.10 \text{ (d, J = 8.1 Hz, 1 H, CHCN)}, 4.42 \text{ (d, J = 8.1 Hz, 1 H, CHO)}.

Chromatography: hexanes–EtOAc (10:1 to 1:1); \( R_f 0.56 \) (hexanes–EtOAc, 1:1).

3-Hexyl-6,7-benzo-1-oxa-2-azabicyclo[3.3.0]oct-2,3-ene N-Oxide (2h)

Chromatography: hexanes–EtOAc (5:1 to 1:1).

3-Hexyl-1-oxa-2-azabicyclo[3.3.0]oct-2,3-ene N-Oxide (2e)

Chromatography: hexanes–EtOAc (1:1); \( R_f 0.40 \) (hexanes–EtOAc, 1:1).

3-Benzyl-1-oxa-2-azabicyclo[3.3.0]oct-2,3-ene N-Oxide (2f)

Chromatography: hexanes–EtOAc (5:1 to 1:1); \( R_f 0.38 \) (hexanes–EtOAc, 1:1).

3-Hexyl-1-oxa-2-azatricyclo[3.3.1.5]dec-2,3-ene N-Oxide (2g)

Chromatography: hexanes–EtOAc (10:1 to 1:1); \( R_f 0.50 \) (hexanes–EtOAc, 1:1).

References


In a preliminary experiment we observed that the cycloaddition of a 1-chlorosilyl nitronate proceeded slightly faster than that of analogous bromo derivative.

When this work was in progress, the fluorination of nitro compounds with Selectfluor was reported: Peng, W.; Shreeve, J. M. *Tetrahedron Lett.* 2005, 46, 4905.

The rate of elimination of halosilane from 3-halo-N-silyloxyisoxazolidines depends on many factors such as nature of the halogen and structural features of the heterocyclic ring. For instance, reaction of tert-butyl(dimethyl)silyl nitronate from 1-bromonitroethane with di(methoxyacarbonyl)acetylene affords cycloadduct, which does not eliminate bromosilane at room temperature. The mechanism of halosilane elimination is currently under investigation.

Upon chromatography adduct 5b decomposed completely, whereas for 5b' one diastereomer could be isolated.

