Chemistry of Polyhalogenated Nitrobutadienes, Part 7: A Novel Synthetic Access to Chlorinated Nitrile Oxides

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Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday

Abstract: Reaction of gem-dichloronitroalkenes with base leads to the formation of chlorinated nitrile oxides, probably via a cyclic intermediate. The 1,3-dipoles can be trapped with alkenes to give dihydroisoxazoles with a chlorinated side chain in 3-position. This novel synthetic method is fairly general.

Key words: nitro compounds, halides, nitrile oxides, heterocycles, isoxazoles, 1,3-dipolar cycloaddition, nitrones

Due to its stepped reactivity, 2-nitroperchlorobuta-1,3-diene (1) has proved a valuable synthetic building block for heterocycles via SNVin reactions.1–4 Substitution with two equivalents of primary N-nucleophiles such as aniline and its electron-rich derivatives 2 (ERG = electron-releasing group) leads to the formation of ketene aminals 3, probably via the corresponding amidines.5 On the contrary, during reaction with electron deficient anilines 4 (EWG = electron-withdrawing group) such as 4-nitroaniline a different reaction channel is opened instead after the first N-substitution, leading to allylidene arylhydrazines 5 (Scheme 1).6

The assumed mechanism of this unexpected reaction of 1 can be rationalized by a competitive situation: after mono-substitution by 4 giving 6 and subsequent tautomerization to the imide chloride 7, an intramolecular nitronic acid oxygen is now apparently more nucleophilic than the amino group of a second molecule of the deactivated aniline 4, thus forming a cyclic nitrene 8. Upon addition of HCl – extruded before – and a subsequent cycloreversion two intermediates are formed: isocyanate 9 and nitroso compound 10. Subsequent coupling of 10 with the second equivalent of aniline 4 leads to the Z-isomer of allylidene arylhydrazines 5 (Scheme 2) after an additional isomerization step.

Scheme 1

Parallel to the HCl addition, direct cycloreversion of the proposed heterocycle 8 could also simultaneously lead to two reactive molecules: isocyanate 9 and a chlorinated nitrile oxide 11. Trapping of 11 with an alkene in a 1,3-dipolar cycloaddition should then result in the formation of a dihydroisoxazole such as 13 (Scheme 3).7–9 The second reaction option for 11 is the addition of hydrochloric acid to form hydroximoyl chloride 14 as a reactive intermediate, which tautomerizes easily to the nitroso compound 10. This reaction path of nitrile oxides was already reported by Ponzio et al.10 To test this hypothesis, 1.5 equivalents of norbornene (12) were added to the reaction mixture of 1 and 4-nitroaniline (1.8 equiv) in anhyd THF. Indeed, the expected dihydroisoxazole 13 could be obtained in low yield (6%), a proof for the intermediate formation of the nitrile oxide 11.

Both, nitrile oxides as well as their cycloadducts are valuable building blocks in organic synthesis.8,11–13 A number of synthetic methods for nitrile oxides are known, for example, the dehydrohalogenation of hydroxamic acid chlorides.14 Primary nitroalkanes serve as starting materials in
the Mukaiyama reaction,\textsuperscript{15} and furoxanes in cycloreversion reactions.\textsuperscript{16} Less general synthetic methods are, for example, the addition of nitric acid to alkynes in the presence of a gold catalyst,\textsuperscript{17} or the photolysis of 1,2-diaryl-substituted nitroethylenes.\textsuperscript{18}

The regioselectivity of 1,3-dipolar cycloaddition reactions with nitrile oxides has been investigated, both by experiment and calculation.\textsuperscript{7,19–22} Because of steric reasons the 5-isomer is usually the favored product. Using \(\beta\)-cyclodextrin as a molecular scaffold it is feasible though to reverse the usual regioselectivity.\textsuperscript{19} In the case of dihydroisoxazoles \(28, 29, 31, 33,\) and \(34\) we observed formation of the 5-isomer, exclusively. NMR analysis of \(30\) also showed traces of the 4-isomer (4\%, GC-MS).

Cycloaddition reactions of nitrile oxides to norbornene derivatives proceed diastereoselectively.\textsuperscript{21,22} In the case of the dihydroisoxazoles \(13\) and \(15\) (vide infra) attack of the \(exo\)-face was observed and the structure proved by 2-dimensional NMR techniques and NOE experiments. The \(H,H\)-COSY spectrum shows the \(W\)-coupling between 10\(-\)H and 2-H and 6-H. The NOE-experiment shows the \(endo\)-\(endo\) coupling between 2-H and 9\(\text{endo}\)\(-\)H as well as in the case of 6-H and 8\(\text{endo}\)\(-\)H. The expected missing of the coupling between 2-H and 9\(\text{endo}\)\(-\)H as well as between 6-H and 8\(\text{endo}\)\(-\)H presents additional proof of the \(exo\)-configuration (Figure 1).

Figure 1 Structure of 15 showing the \(exo\) and \(endo\) hydrogens

Up to now, \(\alpha\)-halovinyl nitrile oxides are unknown. Therefore, we first tried to optimize the reaction conditions in the case of 1 to obtain the 3-trichlorovinylidihydroisoxazoles as the main products. Starting from 1 without any amine, but using solid sodium hydroxide instead as base to trap HCl immediately after its formation, and performing the reaction in toluene in the presence of a phase-transfer catalyst, the desired dihydroisoxazole 13 was isolated in a maximum yield of 63\%. It also proved feasible to use a monophasic system by changing the solvent to diglyme; the same yield of 13 was obtained.

The proposed mechanism of this reaction is given in Scheme 4. A \(\text{SN}_{2}\)\(\text{Vin}\) reaction of 1 with a hydroxide anion leads in the first step to the formation of an enol 16, followed by two tautomerization reactions so that both, a nitronic acid and an acid chloride are formed. Subsequently, the nitronate attacks the acid chloride intramolecularly to form an oxazetinone-\(N\)-oxide 18 under loss of HCl. This very strained molecule undergoes cycloreversion to form nitrile oxide 11 and carbon dioxide (Scheme 4).

Scheme 3

Scheme 4

Scheme 5

It is remarkable that only dihydroisoxazoles 31 and 33 are known so far.\textsuperscript{25} This important class of heterocycles can be easily converted into isoxazoles, which also show synthetic potential due to their weak nitrogen–oxygen bond.\textsuperscript{8} Additionally, these five-membered heterocycles are often structural units in biologically active compounds, for example, the antitumor antibiotic Acivicin (AT-125) or the cholinergic channel activator ABT-418.\textsuperscript{8,26}
All synthesized dihydroisoxazoles 13, 15, and 28–34 carry functional side chains, which can be easily used to construct more complex molecules. The proposed method is a fairly general way to obtain dihydroisoxazoles with a chlorinated substituent in 3-position. Side chains in 4- and 5-positions are also tolerated.

In conclusion, we have found a new, unusual one-pot way to generate chlorinated nitrile oxides and their cycloaddition products dihydroisoxazoles starting from structurally different types of gem-dichloronitroalkenes and structurally different dipolarophiles. Most of the synthesized nitrile oxides as well as the corresponding dihydroisoxazoles were unknown, and due to their interesting substitution pattern are valuable building blocks for even complex molecules.

Table 1  Preparation of Dihydroisoxazoles

<table>
<thead>
<tr>
<th>Chloronitroalkene</th>
<th>Nitrile oxide</th>
<th>Alkene</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image12" alt="Structure 12" /></td>
<td><img src="product13" alt="Product 13" /></td>
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<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image11" alt="Structure 11" /></td>
<td><img src="structure25" alt="Structure 25" /></td>
<td><img src="product28" alt="Product 28" /></td>
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<tr>
<td><img src="image1" alt="Structure 1" /></td>
<td><img src="image11" alt="Structure 11" /></td>
<td><img src="structure26" alt="Structure 26" /></td>
<td><img src="product29" alt="Product 29" /></td>
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<tr>
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<td><img src="image11" alt="Structure 11" /></td>
<td><img src="structure27" alt="Structure 27" /></td>
<td><img src="product30" alt="Product 30" /></td>
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<tr>
<td><img src="image19" alt="Structure 19" /></td>
<td><img src="structure22" alt="Structure 22" /></td>
<td><img src="structure12" alt="Structure 12" /></td>
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<td><img src="structure27" alt="Structure 27" /></td>
<td><img src="product33" alt="Product 33" /></td>
</tr>
</tbody>
</table>
were washed with brine (70 mL), dried (Na₂SO₄), and purified by flash chromatography (60 g SiO₂, PE–EtOAc, 10:1).

Subsequently, activated molecular sieves 4 Å (250 mg) and finally powdered NaOH (3.3 mol equiv) were added to the reaction mixture, which was stirred at 60 °C until TLC showed the absence of starting material. Petroleum ether (PE) used refers to the fraction boiling at 60–70 °C. All chemicals were obtained from commercial suppliers and used without further purification. ¹H and ¹H decoupled ¹³C NMR spectra were measured on a Bruker Avance 400 (400 MHz) or Bruker DPX 200 (200 MHz) spectrometer. NMR spectra were referenced to the residual solvent peak of CDCl₃, δ = 7.26 (H) and δ = 77.0 (C). Multiplicities of ¹³C NMR signals were detected by the DEPT-135 method: + for CH or CH₃, – for CH₂, and o for C. IR spectral data were measured with a Bruker APEX IV 7 Tesla FT ion cyclotron resonance mass spectrometer. TLC was performed on Merck TLC plates (aluminum-backed) silica gel 60 F 254. Flash chromatography was carried out on silica gel 60 (Merck).

Table 1 Preparation of Dihydroisoxazoles (continued)

<table>
<thead>
<tr>
<th>Chloronitroalkene</th>
<th>Nitrile oxide</th>
<th>Alkene</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClO₂N Cl₂O₂N Cl₂</td>
<td>O₂Bu N₂</td>
<td>O₂Bu</td>
<td>34</td>
</tr>
<tr>
<td>20</td>
<td>23</td>
<td>27</td>
<td>0%¹</td>
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<tr>
<td>ClO₂N Cl₂O₂N Cl₂</td>
<td>O₂Bu N₂</td>
<td>O₂Bu</td>
<td>35</td>
</tr>
<tr>
<td>21</td>
<td>24</td>
<td>27</td>
<td>29%²</td>
</tr>
</tbody>
</table>

² Aqueous workup.

Dihydroisoxazoles 13, 15, 28–34

General Procedure I: The alkene (20 mmol) was added to a solution of the chloronitroalkene (2 mmol) in anhyd diglyme (15 mL). Subsequently, 18-crown-6 (66 mg, 0.25 mmol), activated molecular sieves 4 Å (250 mg), and finally powdered NaOH (3.3 mol equiv) were added to the reaction mixture, which was stirred at 60 °C until TLC showed the absence of starting material.

General Procedure II: The alkene (20 mmol) was added to a solution of the chloronitroalkene (2 mmol) in anhyd diglyme (15 mL). Subsequently, activated molecular sieves 4 Å (250 mg) and powdered NaOH (3.3 mol equiv) were added to the reaction mixture, which was stirred at 60 °C until TLC showed the absence of starting material.

Workup Procedure a: After cooling to r.t., the mixture was poured into sat. aq NH₄Cl (50 mL) at 0 °C. The resulting mixture was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (70 mL), dried (Na₂SO₄), and purified by flash chromatography (60 g SiO₂, PE–EtOAc, 10:1).

Workup Procedure b: The reaction mixture was placed on top of a silica gel column (50 g) and after absorption eluted with PE (300 mL, to remove the toluene), PE–EtOAc (10:1, 600 mL), and PE–EtOAc (2:1, 440 mL). The product fraction was identified by GC-MS analysis.

5-Trichlorovinyl-3-oxa-4-azatricyclo[5.2.1.0²,6]dec-4-ene (13)

Reaction of 1 and 12 for 3 d, following the general reaction procedure I or II, workup procedure a; yield: 334 mg (63%); yellow oil. IR (film): 2965, 2877, 1576, 1527, 1476, 1317, 1257, 1205, 1025, 976, 923, 911, 846, 817, 752, 721 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 1.60–1.67 (m, 2 H, 8-Hendo), 2.87 (t, J = 7.5 Hz, 2 H, 3-Hendo, 5-Hendo), 4.63 (d, J = 8.6 Hz, 1 H, 1-Hendo).

MS analysis.

HRMS (ESI): m/z (%) = 265 (M⁺, 73), 197 (38), 171 (M⁺ – nitrobororne, 20), 129 (trichlorovinyl, 11), 91 (24), 67 (100), 53 (22), 48 (12).

11C NMR (100 MHz, CDCl₃): δ = 22.6 (–, C-9), 26.9 (–, C-8), 32.3 (–, C-10), 39.2 (+, C-7), 42.8 (+, C-1), 57.8 (+, C-6), 89.2 (+, C-2), 120.7 (o, CCl), 124.0 (o, =CCl2), 153.4 (o, C-5).

GC-MS (EI): m/z (%) = 265 (M⁺, 73), 197 (38), 171 (M⁺ – nitroborane, 20), 129 (trichlorovinyl, 11), 91 (24), 67 (100), 53 (22), 48 (12).

5-Phenyl-3-(trichlorovinyl)-4,5-dihydroisoxazole (28)

Reaction of 1 and 25 for 2 d, following the general reaction procedure I or II, workup procedure a; yield: 288 mg (53%); yellow viscous oil.

IR (film): 3063, 3029, 2926, 2853, 1881, 1723, 1680, 1601, 1576, 1536, 1494, 1454, 1343, 1365, 1319, 1289, 1230, 1206, 1181, 1157, 1078, 972, 924, 884, 843, 757, 700, 604 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 3.32 (dd, J = 8.6, 17.2 Hz, 1 H, 4-H), 3.77 (dd, J = 11.2, 17.2 Hz, 1 H, 4-H), 5.76 (dd, J = 8.6, 11.2 Hz, 1 H, 5-H), 7.32–7.41 (m, 5 H, C₆H₅).
3-Chloro-5-phenyl-4,5-dihydroisoxazole (31)\textsuperscript{25}

Reaction of 19 (10 mmol) and 25 for 27 h, following the general reaction procedure I, workup procedure a: yield: 22%; b: yield: 556 mg (31%); yellow oil.

IR (film): 3065, 3033, 2928, 2738, 2217, 1958, 1886, 1783, 1701, 1634, 1587, 1552, 1520, 1494, 1456, 1366, 1343 1291, 1240, 1155, 1126, 1078, 1028, 1001, 967, 839, 757, 699 cm\textsuperscript{-1}.

1H NMR (200 MHz, CDCl\textsubscript{3}): \( \delta = 3.19 \text{ (dd, } J = 9.1, 1.7 \text{ Hz, 1 H, } 6-H\), 1.11 (m, 1 H, cyclopentane-7-H).

GC-MS (MS): \( m/z \) (%) = 146 (M\textsuperscript{+} + H\textsuperscript{+}, 100).

HRMS (ESI): \( m/z \) calcld for C\textsubscript{10}H\textsubscript{9}Cl\textsubscript{3}NO [M+H\textsuperscript{+}]: 269.0372; found: 270.0367; C\textsubscript{10}H\textsubscript{9}Cl\textsubscript{3}NO + Na [M+Na\textsuperscript{+}] + 194.0343; found 194.0344.

Butyl-3-(Trichlorovinyl)-4,5-dihydroisoxazole-5-carboxylate (32)

Reaction of 19 (10 mmol) and 26 for 1 d, following the general reaction procedure I, workup procedure a: yield: 10%; b: yield: 320 mg (22%); yellow oil.

IR (film): 3147, 2963, 2873, 2491, 2229, 1809, 1632, 1584, 1511, 1462, 1450, 1434, 1330, 1286, 1249, 1200, 1165, 1137, 1122, 1076, 1032, 1008, 954, 913, 867, 823 800 cm\textsuperscript{-1}.

1H NMR (200 MHz, CDCl\textsubscript{3}): \( \delta = 1.39–1.52 \text{ (m, 1 H, cyclopentane-H), 1.56–1.83 \text{ (m, 3 H, cyclopentane-H), 2.00–2.17 \text{ (m, 2 H, cyclopentane-H), 3.61–3.71 \text{ (m, 1 H, 3a-H), 5.18–5.24 \text{ (m, 1 H, 6a-H).}}}

GC-MS (MS): \( m/z \) (%) = 144 (M\textsuperscript{+} + H\textsuperscript{+}, 100).

HRMS (ESI): \( m/z \) calcld for C\textsubscript{13}H\textsubscript{14}Cl\textsubscript{2}NO [M+H\textsuperscript{+}]: 246.0367; found: 246.0368.

Butyl-3-Chloro-4,5-dihydroisoxazole-5-carboxylate (33)

Reaction of 19 (10 mmol) and 27 for 1 d, following the general reaction procedure I, workup procedure a: yield: 25%; b: yield: 473 mg (23%); yellow oil.

IR (film): 2962, 2875, 1742, 1592, 1561, 1466, 1433, 1396, 1352, 1297, 1158, 1129, 1062, 1021, 934, 894, 861, 754 cm\textsuperscript{-1}.

1H NMR (200 MHz, CDCl\textsubscript{3}): \( \delta = 0.92 \text{ (t, } J = 7.3 \text{ Hz, 3 H, } 4\text{-butyl-H}_3\), 1.37 (tq, \( J = 7.3, 7.4 \text{ Hz, 2 H, } 3\text{-butyl-H}_2\), 1.65 (tt, \( J = 6.7, 7.4 \text{ Hz, 2 H, } 2\text{-butyl-H}_2\)), 3.43 (d, \( J = 9.3 \text{ Hz, 2 H, } 4\text{-butyl-H}_2\)), 4.20 (t, \( J = 6.7 \text{ Hz, 2 H, } 1\text{-butyl-H}_2\)), 5.14 (t, \( J = 9.3 \text{ Hz, 1 H, 5-H).}

GC-MS (MS): \( m/z \) (%) = 205 (M\textsuperscript{+} + H\textsuperscript{+}, 96), 159 (26), 150 (28), 104 (100), 57 (44).
HRMS (EI): \( m/z \) calc'd for \( \text{C}_{10}\text{H}_{13}\text{ClNO}_{3} + \text{Na} \ [\text{M}^+ + \text{Na}] \): 228.0398; found: 228.0399.

**Butyl 3-[(Z)-2-Chloro-2-nitrovinyl]-4,5-dihydroisoxazole-5-carboxylate (34)**

Reaction of 20 (1 mmol) and 27 for 20 h, following the general reaction procedure I, workup procedure a; yield: 79 mg (29%); yellow oil.

IR (film): 3063, 2963, 2875, 1743, 1651, 1621, 1552, 1465, 1435, 1317, 1234, 1208, 1062, 941, 843, 729, 693 cm\(^{-1}\).

HRMS (EI): \( m/z \) calc'd for \( \text{C}_{10}\text{H}_{13}\text{ClNO}_{3} + \text{Na} \ [\text{M}^+ + \text{Na}] \): 228.0398; found: 228.0399.

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**References**


