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

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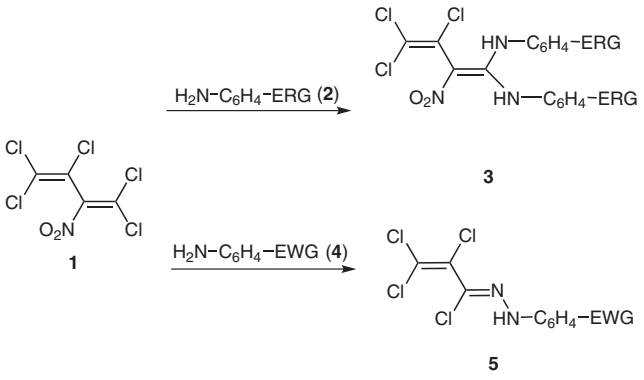
Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday

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.

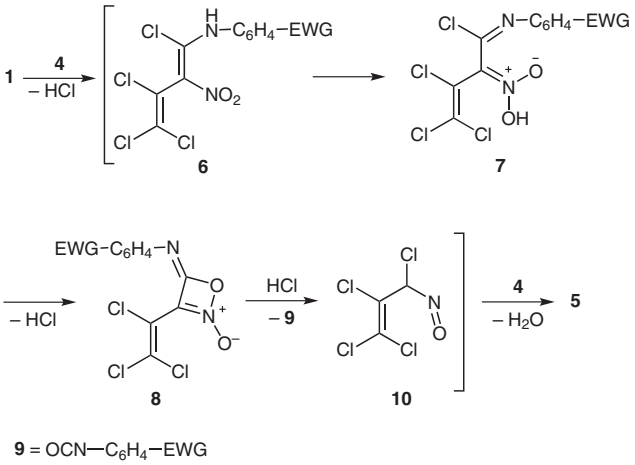
Key words: nitro compounds, halides, nitrile oxides, heterocycles, isoxazoles, 1,3-dipolar cycloaddition, nitrones

Due to its stepped reactivity, 2-nitroperchlorobuta-1,3-diene (**1**) has proved a valuable synthetic building block for heterocycles via S_NVin 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]



Scheme 1

The assumed mechanism of this unexpected reaction of **1** can be rationalized by a competitive situation: after monosubstitution 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 nitrone **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 2

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

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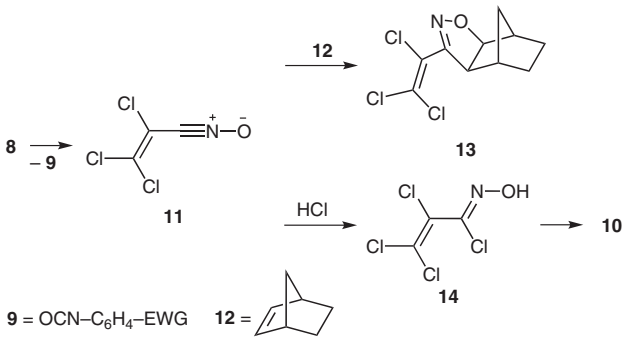
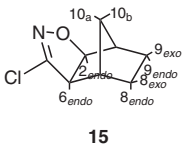


Scheme 3

the Mukaiyama reaction,[15] and furoxanes in cycloreversion reactions.[16] Less general synthetic methods are, for example, the addition of nitric acid to alkynes in the presence of a gold catalyst,[17] or the photolysis of 1,2-diarylsubstituted nitroethylenes.[18]

The regioselectivity of 1,3-dipolar cycloaddition reactions with nitrile oxides has been investigated, both by experiment and calculation.[7,19–22] Because of steric reasons the 5-isomer is usually the favored product. Using β-cyclodextrin as a molecular scaffold it is feasible though to reverse the usual regioselectivity.[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.[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_b-H and 2-H and 6-H. The NOE-experiment shows the *endo-endo* coupling between 2-H and 9_{endo}-H as well as in the case of 6-H and 8_{endo}-H. The expected missing of the coupling between 2-H and 9_{exo}-H as well as between 6-H and 8_{exo}-H presents additional proof of the *exo*-configuration (Figure 1).

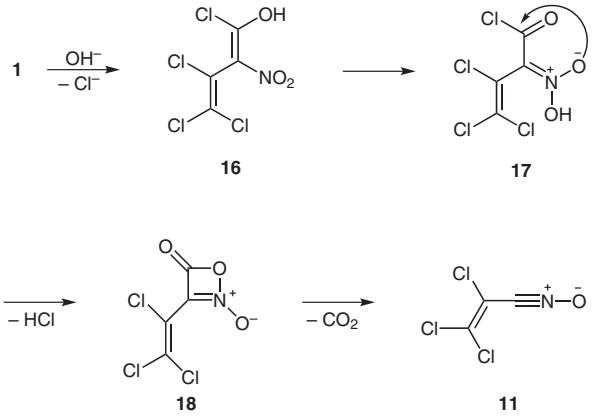


15

Figure 1 Structure of **15** showing the *exo* and *endo* hydrogens

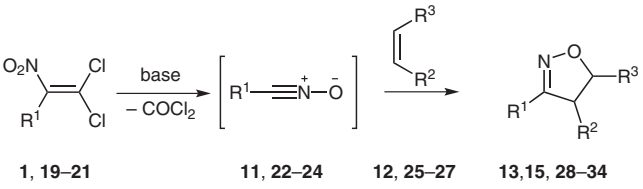
Up to now, α-halovinylic nitrile oxides are unknown. Therefore, we first tried to optimize the reaction conditions in the case of **1** to obtain the 3-trichlorovinyldihydroisoxazoles as the main products. Starting from **1** without any amine, but using solid sodium hydroxide instead as base to trap 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 S_NVin 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 4

Variation of the alkene cyclophiles **12** and **25**–**27** led to a number of unknown dihydroisoxazoles **13**, **28**–**30** with a synthetically interesting trichlorovinyl moiety in 3-position. Modification of the *gem*-dichloronitroalkenes **1** to **19**–**21** proved as well feasible. Therefore, this reaction can also be applied to more complex structures. Even another nitro group in the side chain such as in **20**[23] was tolerated. Only the bicyclic starting material **21**[24] did not react, possibly due to sterical hindrance at the *exo-gem*-dichloronitrovinyl group. The introduced dipolarophiles cover an important spectrum of structurally different alkenes; their cycloadducts are all of synthetic interest (Scheme 5, Table 1).



Scheme 5

It is remarkable that only dihydroisoxazoles **31** and **33** are known so far.[25] This important class of heterocycles can be easily converted into isoxazoles, which also show synthetic potential due to their weak nitrogen–oxygen bond.[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.[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

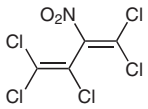
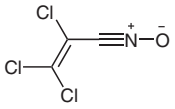
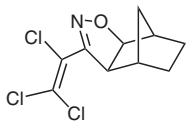
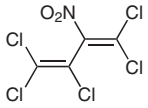
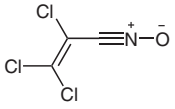
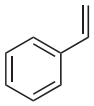
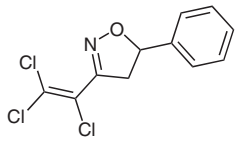
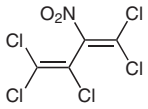
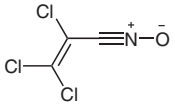
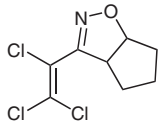
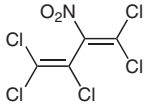
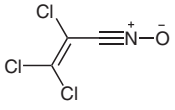
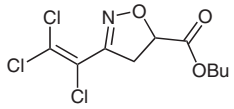
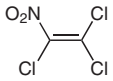
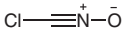
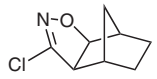
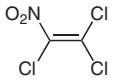
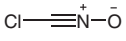
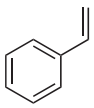
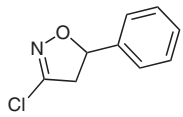
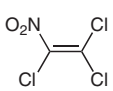
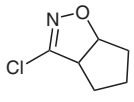
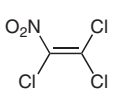
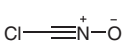
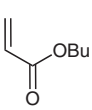
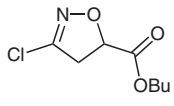
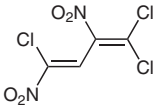
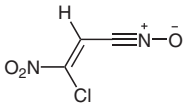
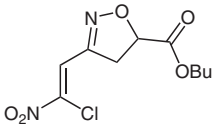
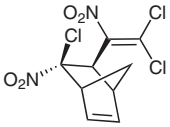
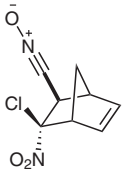
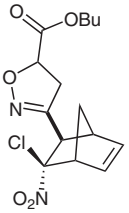
Chloronitroalkene	Nitrile oxide	Alkene	Product
 **1**	 **11**	 **12**	 **13** 63%[a]
 **1**	 **11**	 **25**	 **28** 53%[a]
 **1**	 **11**	 **26**	 **29** 29%[a]
 **1**	 **11**	 **27**	 **30** 43%[a]
 **19**	 **22**	 **12**	 **15** 32%,[a] 22%[b]
 **19**	 **22**	 **25**	 **31** 22%,[a] 31%[b]
 **19**	 **22**	 **26**	 **32** 10%,[a] 22%[b]
 **19**	 **22**	 **27**	 **33** 25%,[a] 23%[b]

Table 1 Preparation of Dihydroisoxazoles (continued)

Chloronitroalkene	Nitrile oxide	Alkene	Product
 **20**	 **23**	 **27**	 **34** 29%[a]
 **21**	 **24**	 **27**	 **35** 0%[a]

[a] Aqueous workup.
[b] Direct chromatographic workup.

All chemicals were obtained from commercial suppliers and used without further purification. ^{1}H and ^{1}H decoupled ^{13}C 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 $CDCl_3$, δ = 7.26 (^{1}H) and δ = 77.0 (^{13}C). Multiplicities of ^{13}C NMR signals were detected by the DEPT-135 method: + for CH or CH_3, – for CH_2, and o for C. IR spectral data were obtained on a Bruker Vector 22 FT-IR spectrometer. Mass spectra (GC-MS) were recorded on a Varian Saturn 2100T spectrometer, usually in direct mode with electron impact (70 eV). In the case of chlorinated compounds, all peak values of molecular ions as well as fragments *m/z* refer to the isotope ^{35}Cl. High-resolution ESI mass spectra 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).

The chloronitroalkenes trichloronitroethene (**19**),[27] 2-nitroperchlorobuta-1,3-diene (**1**),[28] and 1,1,4-trichloro-2,4-dinitrobuta-1,3-diene (**20**)[23] were prepared by nitration of the corresponding precursors. Petroleum ether (PE) used refers to the fraction boiling at 60–70 °C.

Dihydroisoxazoles 13, 15, 28–34

General Procedure I: The alkene (20 mmol) was added to a solution of the chloronitroalkene (2 mmol) in anhyd toluene (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 NH_4Cl (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 (Na_2SO_4), and purified by flash chromatography (60 g SiO_2, 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[5.2.1.0^{2,6}]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, 1474, 1456, 1317, 1257, 1205, 1129, 1025, 976, 950, 923, 911, 846, 817, 752, 721 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09–1.15 (m, 1 H, 9-H$_{endo}$), 1.22–1.27 (m, 2 H, 8-H$_{endo}$, 10-H$_b$), 1.47–1.53 (m, 1 H, 10-H$_a$), 1.53–1.60 (m, 2 H, 8-H$_{exo}$, 9-H$_{exo}$), 2.43 (d, *J* = 1.6 Hz, 1 H, 7-H), 2.60, (d, *J* = 2.3 Hz, 1 H, 1-H), 3.44 (d, *J* = 8.6 Hz, 1 H, 6-H$_{endo}$), 4.63 (d, *J* = 8.6 Hz, 1 H, 2-H$_{endo}$).

^{13}C NMR (100 MHz, $CDCl_3$): 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, =CCl_2), 153.4 (o, C-5).

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

HRMS (ESI): *m/z* calcd for $C_{10}H_{11}Cl_3NO$ [M^+ + H]: 265.9901; found: 265.9903; *m/z* calcd for $C_{10}H_{10}Cl_3NO$ + Na [M^+ + Na]: 287.9720; found: 287.9722.

Anal. Calcd for $C_{10}H_{10}Cl_3NO$ (266.55): C, 45.06; H, 3.78; N, 5.25; Cl, 39.90. Found: C, 45.04; H, 3.82; N, 5.07; Cl, 40.59.

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, 1953, 1881, 1723, 1680, 1601, 1576, 1536, 1494, 1454, 1433, 1365, 1319, 1289, 1230, 1206, 1181, 1157, 1078, 1028, 973, 924, 884, 843, 757, 700, 604 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 (dd, *J* = 8.6, 17.2 Hz, 1 H, 4-H$_1$), 3.77 (dd, *J* = 11.2, 17.2 Hz, 1 H, 4-H$_2$), 5.76 (dd, *J* = 8.6, 11.2 Hz, 1 H, 5-H), 7.32–7.41 (m, 5 H, C_6H_5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.5 (–, C-4), 84.4 (+, C-5), 121.3 (o, CCl), 124.7 (o, $=CCl_2$), 125.8 (+, 2 C, Ph-C_2, Ph-C_6), 128.6 (+, Ph-C_4), 128.9 (+, 2 C, Ph-C_3, Ph-C_5), 139.6 (o, Ph-C_1), 152.5 (o, C-3).

GC-EIMS: *m*/*z* (%) = 275 (M^+, 62), 209 (45), 162 (26), 104 (styrene$^+$, 100), 91 (12), 63 (9).

HRMS (ESI): *m*/*z* calcd for $C_{11}H_9Cl_3NO$ [M^+ + H]: 275.9744; found: 275.9746; [M^+ + Na]: 297.9564; found: 297.9565.

3-(Trichlorovinyl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole (29)

Reaction of **1** and **26** for 3 d, following the general reaction procedure I, workup procedure a; yield: 139 mg, (29%); yellow waxy solid.

IR (film): 2952, 2867, 2495, 1834, 1739, 1594, 1578, 1530, 1465, 1446, 1314, 1279, 1248, 1230, 1191, 1166, 1130, 1084, 1038, 1016, 998, 975, 952, 917, 900, 853, 825, 804, 770, 743, 652 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.42–1.61 (m, 1 H, cyclopentane-H) 1.63–1.96 (m, 4 H, cyclopentane-H), 2.11–2.21 (m, 1 H, cyclopentane-H), 3.97–4.06 (m, 1 H, 6a-H), 5.18–5.25 (m, 1 H, 3a-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.2 (–, C-5), 31.2 (–, C-4), 35.6 (–, C-6), 53.1 (+, C-3a), 88.9 (+, C-6a), 120.8 (o, CCl), 124.3 (o, $=CCl_2$), 154.6 (o, C-3).

GC-MS (EI): *m*/*z* (%) = 239 (M^+, 100), 171 ($M^+ - C_5H_8$, 22), 137 (10), 102 (10).

HRMS (ESI): *m*/*z* calcd for $C_8H_9Cl_3NO$ [M^+ + H]: 239.9744; found: 239.9745; $C_8H_8Cl_3NO$ + Na [M^+ + Na]: 261.9564; found: 261.9565.

Butyl 3-(Trichlorovinyl)-4,5-dihydroisoxazole-5-carboxylate (30)

Reaction of **1** and **27** for 1 d, following the general reaction procedure I, workup procedure a; yield: 259 mg (43%); yellow oil; contains 4% of the 4-isomer (GC-MS).

IR (film): 3443, 2961, 2935, 2874, 1735, 1577, 1541, 1465, 1395, 1322, 1205, 1167, 1119, 1064, 1020, 973, 940, 891, 851, 755 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.2 Hz, 3 H, 4_{butyl}-H_3), 1.38 (tq, *J* = 7.2, 7.4 Hz, 2 H, 3_{butyl}-H_2), 1.66 (tt, *J* = 6.7, 7.4 Hz, 2 H, 2_{butyl}-H_2), 3.62 (d, *J* = 10.3 Hz, 1 H, 4-H), 3.63 (d, *J* = 8.3 Hz, 1 H, 4-H), 4.22 (t, *J* = 6.7 Hz, 2 H, 1_{butyl}-H_2), 5.18 (dd, *J* = 8.3, 10.3 Hz, 1 H, 5-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.6 (+, C-4_{butyl}), 18.9 (–, C-3_{butyl}), 30.4 (–, C-2_{butyl}), 40.2 (–, C-4), 66.0 (–, C-1_{butyl}), 79.5 (+, C-5), 120.4 (o, CCl), 125.6 (o, $=CCl_2$), 152.5 (o, C-3), 169.1 (o, $C_{carboxyl}$).

GC-EIMS: *m*/*z* (%) = 300 (M^+ + H, 100), 282 (19), 254 (9), 198 (5), 170 (M^+ – trichlorovinyl, 6), 135 (19), 101 (4).

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{13}Cl_3NO$ [M^+ + H]: 299.9956; found: 299.9956; $C_{10}H_{12}Cl_3NO$ + Na [M^+ + Na]: 321.9775; found: 321.9775.

5-Chloro-3-oxa-4-azatricyclo[5.2.1.0^{2,6}]dec-4-ene (15)

Reaction of **19** (10 mmol) and **12** for 2 d, following the general reaction procedure I, workup procedure a; yield: 32%; b: yield: 385 mg (22%); yellow oil; mixture of *exo*- and *endo*-isomers (0.93:0.07).

IR (film): 3143, 2967, 2878, 2481, 2228, 1723 1623, 1582, 1545, 1475, 1456, 1355, 1319, 1300, 1276, 1220, 1193, 1162, 1132, 1046, 1003, 991, 950, 927, 919, 896, 849, 826, 812, 791, 762, 689, 667, 617 cm^{-1}.

***exo*-15**

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06–1.13 (m, 1 H, 9-H_{endo}), 1.15–1.33 (m, 2 H, 8-H_{endo}, 10-H_b), 1.50–1.55 (m, 1 H, 10-H_a), 1.56–1.63 (m, 2 H, 8-H_{exo}, 9-H_{exo}), 2.53 (d, *J* = 3.1 Hz, 1 H, 7-H), 2.59 (d, *J* = 3.9 Hz, 1 H, 1-H), 3.12 (d, *J* = 8.2 Hz, 1 H, 6-H_{endo}), 4.64 (d, *J* = 8.2 Hz, 1 H, 2-H_{endo}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4 (–, C-9), 26.6 (–, C-8), 32.2 (–, C-10), 38.3 (+, C-7), 43.0 (+, C-1), 59.4 (+, C-6), 88.7 (+, C-2), 150.2 (o, C-5).

GC-EIMS: *m*/*z* = 171 (M^+, 41), 118 (11), 104 (13), 91 (15), 77 (22), 67 (100), 51 (13).

HRMS (ESI): *m*/*z* calcd for $C_8H_{11}ClNO$ [M^+ + H]: 172.0524; found: 172.0524; $C_8H_{10}ClNO$ + Na [M^+ + Na]: 194.0343; found 194.0344.

3-Chloro-5-phenyl-4,5-dihydroisoxazole (31)[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, 1204, 1155, 1126, 1078, 1028, 1001, 967, 902, 839, 757, 699 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.17 (dd, *J* = 9.1, 17.2 Hz, 1 H, 4-H_1), 3.57 (dd, *J* = 10.9, 17.2 Hz, 1 H, 4-H_2), 5.75 (dd, *J* = 9.1, 10.9 Hz, 1 H, 5-H), 7.36–7.40 (m, 5 H, C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 46.2 (–, C-4), 83.8 (+, C-5), 125.9 (+, 2 C, Ph-C_2, Ph-C_6), 128.7 (+, Ph-C_4), 128.9 (+, 2 C, Ph-C_3, Ph-C_5), 139.2 (o, Ph-C_1), 148.4 (o, C-3).

GC-MS: *m*/*z* (%) = 182 (M^+ + H, 100), 115 (23), 105 (38).

HRMS (ESI): *m*/*z* calcd for C_9H_9ClNO [M^+ + H]: 182.0367; found: 182.0367; C_9H_8ClNO + Na [M^+ + Na]: 204.0187; found: 1204.0187.

3-Chloro-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole (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^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39–1.52 (m, 1 H, cyclopentane-H), 1.56–1.83 (m, 3 H, cyclopentane-H), 2.00–2.17 (m, 2 H, cyclopentane-H), 3.61–3.71 (m, 1 H, 3a-H), 5.18–5.24 (m, 1 H, 6a-H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.9 (–, 1 C, C-5), 30.2 (–, 1 C, C-4), 36.1 (–, 1 C, C-6), 55.0 (+, 1 C, C-3a), 88.2 (+, 1 C, C-6a), 150.8 (o, 1 C, C-3).

GC-EIMS: *m*/*z* (%) = 146 (M^+ + H, 100).

HRMS (ESI): *m*/*z* calcd for C_6H_9ClNO [M^+ + H]: 146.0367; found: 146.0368.

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, 1296, 1207, 1158, 1129, 1062, 1021, 934, 894, 861, 754 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.3 Hz, 3 H, 4_{butyl}-H_3), 1.37 (tq, *J* = 7.3, 7.4 Hz, 2 H, 3_{butyl}-H_2), 1.65 (tt, *J* = 6.7, 7.4 Hz, 2 H, 2_{butyl}-H_2), 3.43 (d, *J* = 9.3 Hz, 2 H, 4-H_2), 4.20 (t, *J* = 6.7 Hz, 2 H, 1_{butyl}-H_2), 5.14 (t, *J* = 9.3 Hz, 1 H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (+, C-4_{butyl}), 18.9 (–, C-3_{butyl}), 30.3 (–, C-2_{butyl}), 41.7 (–, C-4), 66.1 (–, C-1_{butyl}), 78.9 (+, C-5), 148.6 (o, C-3), 168.8 (o, $C_{carboxyl}$).

GC-EIMS: *m*/*z* (%) = 205 (M^+ + H, 96), 159 (26), 150 (28), 104 (100), 57 (44).

HRMS (EI): *m/z* calcd for $C_8H_{12}ClNO_3$ + Na [M^+ + 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, 1287, 1234, 1208, 1062, 1020, 941, 843, 729, 693 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.1 Hz, 3 H, 4_{butyl}-H_3), 1.40 (tq, *J* = 7.1, 7.5 Hz, 2 H, 3_{butyl}-H_2), 1.68 (tt, *J* = 6.8, 7.5 Hz, 2 H, 2_{butyl}-H_2), 3.67 (dd, *J* = 0.8, 11.3 Hz, 1 H, 4-H), 3.70 (dd, *J* = 0.8, 7.8 Hz, 1 H, 4-H), 4.23 (t, *J* = 6.8 Hz, 2 H, 1_{butyl}-H_2), 5.26 (dd, *J* = 7.8, 11.3 Hz, 1 H, 5-H), 8.21 (s, 1 H, 1′-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6 (+, C-4_{butyl}), 19.0 (–, C-3_{butyl}), 30.4 (–, C-2_{butyl}), 37.5 (–, C-4), 66.3 (–, C-1_{butyl}), 80.4 (+, C-5), 121.5 (+, C-1′), 152.4 (o, C-3), 168.8 (o, $C_{carboxyl}$). $CClNO_2$ was undetectable due to its high NOE effect.

GC-EIMS: *m/z* (%) = 277 (M^+ + H, 29), 221 (100), 175 (42), 148 (34), 129 (33), 101 (46), 66 (35), 57 (56), 41 (73).

HRMS (ESI): *m/z* calcd for $C_{10}H_{13}ClN_2O_5$ + Na [M^+ + Na]: 299.0406; found: 299.0405.

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References

(1) Kaberdin, R. V.; Potkin, V. I.; Zapol'skii, V. A. *Russ. Chem. Rev.* **1997**, *10*, 827.
(2) Zapol'skii, V. A.; Namyslo, J. C.; Adam, A. E. W.; Kaufmann, D. E. *Heterocycles* **2004**, *63*, 1281.
(3) Zapol'skii, V. A.; Namyslo, J. C.; Gjikaj, M.; Kaufmann, D. E. *Synlett* **2007**, 1507.
(4) Vashkevich, E. V.; Potkin, V. I.; Kozlov, N. G. *Russ. J. Org. Chem.* **2005**, *41*, 739.
(5) Ol'dekop, Y. S.; Kaberdin, R. V.; Potkin, V. I.; Shingel, I. A. *J. Org. Chem. USSR (Engl. Transl.)* **1979**, *15*, 39.
(6) Zapol'skii, V. A.; Nutz, E.; Namyslo, J. C.; Adam, A. E. W.; Kaufmann, D. E. *Synthesis* **2006**, 2927.
(7) Litvinovskaya, R. P.; Khripach, V. A. *Russ. Chem. Rev.* **2001**, *70*, 405.
(8) Melo, T. *Curr. Org. Chem.* **2005**, *9*, 925.
(9) Caldirola, P.; Ciancaglione, M.; De Amici, M.; De Micheli, C. *Tetrahedron Lett.* **1986**, *27*, 4647.
(10) (a) Ponzio, G. *Gazz. Chim. Ital.* **1936**, *66*, 115. (b) Ponzio, G. *Gazz. Chim. Ital.* **1941**, *71*, 693.
(11) Torssel, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, **1988**.
(12) (a) Jäger, V.; Colinas, P. A. In *The Chemistry of Heterocyclic Compounds*, Vol. 59; Padwa, A.; Pearson, W. H., Eds.; Wiley: New York, **2002**, 361. (b) Kislyi, V. P.; Laikhter, A. L.; Ugrak, B. I.; Semenov, V. V. *Russ. Chem. Bull.* **1994**, *43*, 98. (c) Barrett, D.; Bentley, P. D.; Perrior, T. R. *Synth. Commun.* **1996**, *26*, 3401.
(13) (a) Kanemasa, S. In *Science of Synthesis*, Vol. 19; Murahashi, S.-I., Ed.; Thieme: Stuttgart, **2004**, 17. (b) Belen'kii, L. I. *Nitrile Oxides,* In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*, 2nd ed.; Feuer, H., Ed.; Wiley: Hoboken, **2008**, 1.
(14) Huisgen, R.; Mack, W.; Anneser, E. *Angew. Chem.* **1961**, *73*, 656.
(15) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.
(16) Curran, D. P.; Fenck, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 6023.
(17) Gasparrini, F.; Giovannoli, M.; Misiti, D.; Natile, G.; Palmieri, G.; Maresca, L. *J. Am. Chem. Soc.* **1993**, *115*, 4401.
(18) Grant, R. D.; Pinhey, J. T. *Aust. J. Chem.* **1984**, *37*, 1231.
(19) (a) Barr, L.; Lincoln, S. F.; Easton, C. J. *Chem. Eur. J.* **2006**, *12*, 8571. (b) Meyer, A. G.; Easton, C. J.; Lincoln, S. F.; Simpson, G. W. *J. Org. Chem.* **1998**, *63*, 9069.
(20) (a) Kanemasa, S.; Okuda, K.; Yamamoto, H.; Kaga, S. *Tetrahedron Lett.* **1997**, *38*, 4095. (b) Alguacil, R.; Fariña, F.; Martín, M. V. *Tetrahedron* **1996**, *52*, 3457.
(21) Bagatti, M.; Rastelli, A.; Burdisso, M.; Gandolfi, R. *J. Phys. Org. Chem.* **1992**, *5*, 819.
(22) Namboothiri, I. N. N.; Rastogi, N.; Ganguly, B.; Mobin, S. M.; Cojocaru, M. *Tetrahedron* **2004**, *60*, 1453.
(23) Preparation: Zapol'skii, V. A.; Potkin, V. I.; Kaberdin, R. V. *Russ. J. Org. Chem.* **1994**, *30*, 1435.
(24) Preparation: Zapol'skii, V. A.; Namyslo, J. C.; Blaschkowski, B.; Kaufmann, D. E. *Synlett* **2006**, 3464.
(25) Halling, K.; Thomsen, I.; Torssell, K. B. G. *Liebigs Ann. Chem.* **1989**, 985.
(26) Stevens, R. V.; Polniaszek, R. P. *Tetrahedron* **1983**, *39*, 743.
(27) Preparation: Meyer, C. h. r.; Zapol'skii, V. A.; Adam, A. E. W.; Kaufmann, D. E. *Synthesis* **2008**, 2575.
(28) Preparation:Ol'dekop, Y. A.; Kaberdin, R. V. *J. Org. Chem. USSR (Engl. Transl.)* **1976**, *12*, 1986.