Cycloadditions with Alkoxynitrile Oxides, RO–C≡N⁺–O⁻, (Alkyl Cyanate N-Oxides)

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Alkyl forming imates have been synthesized by reacting alkyl orthoesters with hydrogen sulfide followed by treatment of the alkyl thioformate formed with hydroxylamine. Chlorination of alkyl forming imates with N-chlorosuccinimide gives alkyl chloroforming imates and dehydrochlorination with base generated alkoxynitrile oxides (alkyl cyanate N-oxides), which efficiently undergo cycloaddition to olefins or acetylenes to give 3-alkoxyisoxazolines or 3-alkoxyisoxazoles, respectively. These compounds are masked β-hydroxy- and β-keto-esters. Reductive cleavage of the ring was performed by hydrogenation over Raney-Ni or with Ti⁴⁺ salts. The reaction thus constitutes a novel hydroxy-carboxylation. dl-N-Boc-γ-amino-β-hydroxybutyrates (Gabob), malonic acid, citromalic acid, malic acid derivatives and N-methyl-N-hydroxythioformamide (thioformin) have been synthesized. N,N-Dimethyl-N'-hydroxychloroformamide (N,N-dimethylaminochloroform oxide) was not formed by chlorination of N,N-dimethyl-N'-hydroxyformamidine. The nitrile oxide cycloaddition to cyclohexatriene was investigated. The [6 + 4] cycloaddition mode was not observed but three isomeric [4 + 2] cycloaddition products were isolated and structurally determined.

Alkoxynitrile oxides 1¹ (alkyl cyanate N-oxides) have not been described previously in the literature. We expected that they should be short lived, reactive intermediates prone to undergo cycloadditions with dipolarophiles. They could conceivably be prepared by halogenation of alkyl forming imates 2 to give alkyl chloroforming imates 3 followed by dehydrohalogenation with base, [eqn. (1)], in analogy to the generation of nitrile oxides from aldehyde oximes. Support for our assumption was found in an early observation by Houben² who reported that chlorination of ethyl forming imate with Cl₂ gave an evanescent bluish green colour indicating an intermediate nitroso compound. Our starting material 2 belonged to a little-studied group of carboxylic acid derivatives. The alkyl forming imates 2a–e have previously been prepared by Houben² in poor to modest yields as unstable compounds from dry hydrocyanic acid, the corresponding alcohol and hydroxylamine. This procedure was somewhat complicated and not without safety risks. The synthesis of the ethyl derivative 2b was reproduced in a poor yield. Preliminary chlorination tests with N-chlorosuccinimide, NCS, indicated formation of 3b as judged from the appearance of a greenish blue colour in the reaction mixture, which faded after a short time. Treatment of the product with base in the presence of ethyl acrylate afforded 3-ethoxyisoxazoline 4h according to the ¹H NMR spectrum of the crude product [eqn. (2)]. Evidently the alkoxynitrile oxides 1 behaved

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as do other reactive nitrile oxides. 3-Alkoxysoxazolines 4, which are masked β-hydroxy esters, are available by cycladdition of dibalcoholdehyde oxide to alkenes and subsequent dehaloalkylation at C-3 \[ \text{eqn. (3)} \]. It is thus possible to shorten the routes to 4 and 5 by one step. The exchange of Cl for OR at C-3 in the aromatic isoxazoles required drastic conditions with use of strong bases.

Results and discussion

**Alkyl formhydroximates.** A simplified procedure for the preparation of alkyl formhydroximates was required. It has been reported that treatment of thioesters with hydroxylamine give alkyl hydroximates in good yields.\(^5\) However, it was also reported that some aromatic thioesters give thioglycolic acids. \(^6\) We found that the thioureas, obtained by acid \(^7\) or FeCl\(_3\) catalyzed thionation of orthoesters \(^8\) with hydrogen sulfide, reacted with hydroxylamine to give 2a,b,d,e in modest to good yields \[ \text{eqn. (4)} \]. The reaction conditions are critical for the outcome of the reaction. Compounds 2a–d are crystalline solids, which decompose and liquify within a few days at 25°C but are stable for several months in the freezer. Then benzyl derivative 2e is stable at room temperature. We were not successful in transforming triphenyl orthoformate into 2f.

**Attempted preparation of C-alkoxynitrones and dimethylamino nitride oxide.** Preparation of thioformin, \(^6\) the reaction of thioureas with N-substituted hydroxylamines took a different course. The corresponding N-hydroxythioformamides \(^9\) were obtained. The desired nitrene 7 was not observed, \[ \text{eqn. (5)} \]. Compound 6 was isolated as a crystalline solid in the absence of a substrate. The isoxazolines 4 or isoxazoles 5 were obtained most conveniently in a one-pot reaction where 2, NCS, potassium hydrogen carbonate and the olefin or acetylene were mixed in ethyl acetate as the solvent and reacted at ca. 48°C for 24 h. Table I. Monosubstituted olefins and acetylenes gave practically only the 5-substituted

\[ \text{eqn. (5)} \]

\[ \text{eqn. (6)} \]

\[ \text{eqn. (7)} \]

\[ \text{eqn. (8)} \]

\[ \text{eqn. (9)} \]
Table 1. Synthesis of 3-alkoxyisoxazolines and 3-alkoxyisoxazoles.

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Ratio oxime: alkene or alkyne</th>
<th>Base, Temp., Reaction time</th>
<th>Yield (%)</th>
<th>M.p./°C (b.p./mmHg)</th>
<th>Eluent TLC, silica</th>
<th>Alkene or alkyne</th>
<th>Selected ¹H, ¹³C NMR, δ (CDCl₃); IR νmax/cm⁻¹; UV λmax/nm; MS, m/z data</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>1 : 0.6</td>
<td>KHCO₃, 25°C, 70 h</td>
<td>85</td>
<td>Oil CHCl₃–CH₂OH</td>
<td>N-Boc-allyl-amine</td>
<td>¹H: 1.27 (6 H, d, J = 6 Hz), 1.39 (9 H, s), 2.67 (1 H, dd, J = 8.5 and 17.5 Hz), 2.91 (1 H, dd, J = 10.0 and 17.5 Hz), 3.3 (2 H, m), 4.60 (1 H, m), 4.73 (1 H, septet, J = 6 Hz), 4.93 (1 H, br s), ¹³C: 21.9, 28.5, 36.0, 43.6, 74.1, 79.7, 79.9, 156.7, 166.8. IR (film): 1720, 1628. MS: 258 (M⁺), 203, 185, 160, 143, 128, 110.</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>1 : 1.2</td>
<td>KHCO₃, 25°C, 48 h</td>
<td>51</td>
<td>Oil CHCl₃</td>
<td>Ethyl acrylate</td>
<td>¹H: 1.27 (3 H, t, J = 7.0 Hz), 3.23 (2 H, m), 4.22 (2 H, q, J = 7.0 Hz), 5.0 (1 H, dd, J = 9 and 10 Hz), 5.12 (2 H, s), 7.34 (5 H, s). ¹³C: 14.3, 36.4, 62.2, 72.8, 78.7, 128.7, 128.9, 129.1, 135.8, 166.8, 170.6. IR (film): 1760, 1640. MS: 249 (M⁺), 176, 146, 91.</td>
<td></td>
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<tr>
<td>4c</td>
<td>1 : 0.9</td>
<td>KHCO₃, 48°C, 34 h</td>
<td>78</td>
<td>Oil CH₂Cl₂–Et₂O</td>
<td>Styrene</td>
<td>¹H: 3.05 (1 H, dd, J = 9.0 and 16.5 Hz), 3.35 (1 H, dd, J = 10.5 and 16.5 Hz), 5.22 (2 H, s), 5.66 (1 H, dd, J = 9.0 and 10.5 Hz), 7.4 (5 H, m), ¹³C: 40.9, 72.4, 83.1, 167.3. MS: 254 (M⁺ + 1), 91.</td>
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<tr>
<td>4d</td>
<td>1 : 1.2</td>
<td>KHCO₃, 25°C, 48 h</td>
<td>82</td>
<td>Oil CHCl₃–CH₂OH</td>
<td>Ethyl acrylate</td>
<td>¹H: 1.20 (3 H, t, J = 7.0 Hz), 1.23 (6 H, d, J = 6.5 Hz), 3.08 (1 H, dd, J = 7.5 and 16.5 Hz), 3.16 (1 H, dd, J = 10.5 and 16.5 Hz), 4.13 (2 H, q, J = 7.0 Hz), 4.70 (1 H, septet, J = 6.5 Hz), 4.87 (1 H, dd, J = 7.5 and 10.5 Hz), ¹³C: 14.2, 21.8, 36.9, 62.0, 74.6, 77.9, 165.9, 170.8. IR (film): 1745, 1630. MS: 201 (M⁺), 186, 160, 159, 128, 127.</td>
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<tr>
<td>4e</td>
<td>1 : 1.25</td>
<td>KHCO₃, 48°C, 34 h</td>
<td>54</td>
<td>Oil CHCl₃–CH₂OH</td>
<td>1-Butene</td>
<td>¹H: 0.88 (3 H, t, J = 6 Hz), 1.28 (6 H, d, J = 6 Hz), 1.2–1.8 (6 H, m), 2.57 (1 H, dd, J = 9 and 16.5 Hz), 2.88 (1 H, dd, J = 9 and 16.5 Hz), 4.51 (1 H, m), 4.78 (1 H, septet, J = 6 Hz), ¹³C: 14.1, 22.0, 22.7, 27.8, 34.8, 38.8, 73.7, 81.3, 166.8. IR (film): 1625. MS: 185 (M⁺), 170, 143, 111, 86.</td>
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<tr>
<td>4f</td>
<td>1 : 1.25</td>
<td>Et₃N, 48°C, 1 h</td>
<td>55</td>
<td>Oil CH₂Cl₂–CH₂OH</td>
<td>Acrolein diethylacetal ¹³C: 15.4, 21.8, 34.3, 63.6, 64.6, 73.8, 80.9, 102.7, 166.6. IR (film): 1630. MS: 186 (M⁺ – OEt), 140, 116, 103.</td>
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<tr>
<td>4g</td>
<td>1 : 0.6</td>
<td>KHCO₃, 25°C, 72 h</td>
<td>65</td>
<td>Oil CH₂Cl₂</td>
<td>N-Boc-allylamine</td>
<td>¹H: 1.40 (9 H, s), 2.75 (1 H, dd, J = 8.5 and 16.5 Hz), 2.93 (1 H, dd, J = 9.5 and 16.5 Hz), 3.3 (2 H, m), 4.64 (1 H, m), 5.15 (1 H, br s), 7.3 (5 H, m). MS: 306 (M⁺).</td>
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<tr>
<td></td>
<td>1 : 1.1</td>
<td>( \text{KHCO}_3 ), 47°C, 48 h</td>
<td>83</td>
<td>Oil</td>
<td>( \text{CH}_2\text{Cl}_2 )-EtOAc</td>
<td>Ethyl acrylate</td>
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<tr>
<td>4h</td>
<td>1 : 1.25</td>
<td>( \text{KHCO}_3 ), 47°C, 45 h</td>
<td>55</td>
<td>Oil (130/0.2)</td>
<td>1-Hexene</td>
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<td></td>
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<tr>
<td>4i</td>
<td>1 : 1.5</td>
<td>( \text{KHCO}_3 ), 25°C, 72 h</td>
<td>82</td>
<td>Oil</td>
<td>Diethyl ether-ethyl acetate</td>
<td>Methyl vinyl ketone</td>
<td></td>
</tr>
<tr>
<td>4j</td>
<td>1 : 1</td>
<td>( \text{KHCO}_3 ), 25°C, 72 h</td>
<td>77</td>
<td>71</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>Phenyl vinyl ketone</td>
<td></td>
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<tr>
<td>4k</td>
<td>1 : 0.75</td>
<td>( \text{KHCO}_3 ), 48°C, 36 h</td>
<td>33</td>
<td>86-87</td>
<td>Heptane-Et(_2)O</td>
<td>Diphenylacetylene</td>
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<tr>
<td>5b</td>
<td>1 : 0.8</td>
<td>( \text{KHCO}_3 ), 48°C, 40 h</td>
<td>65</td>
<td>Oil</td>
<td>( \text{CH}_2\text{Cl}_2 )</td>
<td>Phenylacetylene</td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td>1 : 0.6</td>
<td>( \text{KHCO}_3 ), 48°C, 40 h</td>
<td>78</td>
<td>Oil</td>
<td>( \text{CH}_2\text{Cl}_2 ) on basic alumina</td>
<td>Ethynyltributyltin</td>
<td></td>
</tr>
<tr>
<td>5d*</td>
<td>1 : 1</td>
<td>( \text{KHCO}_3 ), 48°C, 48 h</td>
<td>90</td>
<td>65</td>
<td>( \text{CH}_2\text{Cl}_2 )-Et(_2)O</td>
<td>Phenylacetylene</td>
<td></td>
</tr>
<tr>
<td>5e</td>
<td>1 : 1</td>
<td>( \text{KHCO}_3 ), 48°C, 48 h</td>
<td>56</td>
<td>(55/2)</td>
<td>39-40</td>
<td>Ethynyltrimethylsilane</td>
<td></td>
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<tr>
<td>5f</td>
<td>1 : 1.1</td>
<td>( \text{KHCO}_3 ), 47°C, 45 h</td>
<td>21</td>
<td>Oil</td>
<td>( \text{CHCl}_3 )</td>
<td>Phenylacetylene</td>
<td></td>
</tr>
</tbody>
</table>

**Table continued**
<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Ratio oxime: alkene or alkyne</th>
<th>Base, Temp., Reaction time</th>
<th>Yield (%)</th>
<th>M.p./°C or (b.p./mmHg)</th>
<th>Eluent TLC silica</th>
<th>Alkene or alkyne</th>
<th>Selected ¹H, ¹³C NMR, δ (CDCl₃); IR νmax/cm⁻¹; UV, λmax/nm; MS, m/z data.</th>
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<tbody>
<tr>
<td>5h⁺</td>
<td>1 : 0.6</td>
<td>KHCO₃, 48°C, 38 h</td>
<td>89</td>
<td>Oil</td>
<td>Ethyl O-heptane, 3 : 2, on basic alumina</td>
<td>Ethynylbutylin</td>
<td>¹H: 0.8–1.8 (Sn–Bu, m), 5.27 (2 H, s), 6.01 (1 H, s), 7.4 (5 H, m)</td>
</tr>
<tr>
<td>10</td>
<td>—</td>
<td>KHCO₃, 48°C, 24 h</td>
<td>16</td>
<td>180–190 (decomp.)</td>
<td>Heptane–Et₂O, 3 : 2</td>
<td>—</td>
<td>¹H: 1.35 (6 H, d, J = 6 Hz), 1.45 (6 H, d, J = 6 Hz), 4.83 (1 H, septet, J = 6 Hz), 5.05 (1 H, septet, J = 6 Hz), 1.3C: 21.7, 22.0, 75.1, 79.9, 157.0, 178.8</td>
</tr>
<tr>
<td>11a, b</td>
<td>1 : 1</td>
<td>KHCO₃, 25°C, 72 h</td>
<td>30</td>
<td>Oils</td>
<td>Crotonaldehyde diethylacetal</td>
<td>¹H (11a): 3.04 (H⁺, dd, J = 5 and 8 Hz), ¹H (11b): 3.21 (H⁺, d, J = 7 Hz).</td>
<td></td>
</tr>
<tr>
<td>11c, d</td>
<td>1 : 1</td>
<td>KHCO₃, 48°C, 48 h</td>
<td>83</td>
<td>Oil</td>
<td>ChCl₂–CH₃OH, 99 : 1</td>
<td>Ethyl crotonate</td>
<td>¹H (11c): 1.25 (3 H, d, J = 6.5 Hz), 3.47 (H⁺, d, J = 9.5 Hz), 4.67 (H⁺, dq, J = 9.5 and 6.5 Hz). ¹H (11d): 3.19 (H⁺, quintet, J = 7 Hz), 4.37 (H⁺, d, J = 7.5 Hz).</td>
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<tr>
<td>12a–c</td>
<td>1 : 1.4</td>
<td>KHCO₃, 25°C, 68 h</td>
<td>28</td>
<td>12a*</td>
<td>Ch₂Cl₂–CH₃OH, 99.5 : 0.5</td>
<td>Cycloheptatriene</td>
<td>¹H (12a): 2.89 (1 H, ddd, J = 2.7, 8.5 and 12.0 Hz), 4.91 (1 H, dd, J = 2.7 and 8.4 Hz), ¹H (12b): 3.92 (1 H, ddd, J = 2.1, 3.6 and 10.1 Hz), 4.73 (1 H, ddd, J = 4.7, 9.9 and 9.9 Hz). ¹H (12c): 2.78 (2 H, t, J = 6.0 Hz), 3.88 (1 H, ddd, J = 4.8 and 8.7 Hz), 5.12 (1 H, ddd, J = 4.4 and 8.7 Hz).</td>
</tr>
<tr>
<td>16</td>
<td>1 : 1.2</td>
<td>KHCO₃, 48°C, 38 h</td>
<td>85</td>
<td>Oil</td>
<td>CHCl₂–CH₃OH, 95 : 5</td>
<td>Isopentenyl alcohol</td>
<td>¹H: 1.21 (6 H, d, J = 6 Hz), 1.32 (3 H, s), 1.83 (2 H, m), 2.58 (1 H, dd, J = 16 Hz), 2.80 (1 H, d, J = 16 Hz), 2.9 (1 H, br d), 3.68 (2 H, m), 4.68 (1 H, septet, J = 6 Hz). ¹C: 21.9, 25.6, 41.7, 44.2, 59.0, 73.6, 86.2, 166.7. MS: 187 (M⁺). 145, 115, 113, 100, 95. IR: 3500, 1620.</td>
</tr>
<tr>
<td>17</td>
<td>1 : 1.1</td>
<td>KHCO₃, 47°C, 48 h</td>
<td>83</td>
<td>Oil (120/0.08)</td>
<td>CH₂Cl₂–EtOAc, 1 : 1</td>
<td>Ethyl methylacrylate</td>
<td>¹H: 1.25 (6 H, m), 1.58 (3 H, s), 2.80 (1 H, d, J = 16.5 Hz), 3.38 (1 H, d, J = 16 Hz), 4.15 (4 H, m). ¹C: 14.1, 14.4, 23.4, 42.1, 62.1, 66.3, 85.9, 166.6, 172.6. IR (film): 1740, 1625.</td>
</tr>
</tbody>
</table>

*Decomp. on silica. Contaminated by 3-alkoxyisoxazole formed by metallation. *¹¹a: ¹Ib ~ 1 : 1. *¹¹c: ¹Id ~ 1 : 1. *¹²a: ¹Ib ~ 1 : 1. *¹²c: ¹Ic ~ 6 : 2.5 : 1. *The isomers were separated by HPLC, SiO₂, normal phase, diethyl ether–heptane, 1 : 5. *The corresponding 3-isopropoxy derivatives were obtained in a total yield of 65% and in approx. the same ratio.
derivatives. Disubstituted olefins gave mixtures of regioisomers with low regioselectivity. The relative stereostructure at C-4,5 depends on the cis- or trans-structure of the starting olefins (cf. compounds 11a-d and 12a-c). An excess of nitrile oxide was used for less active olefins or acetylenes in order to increase the yield of the isoxazole derivatives.

Lower temperature required longer reaction times. Triethylamine liberates the nitrile oxides very fast and the reaction is over within a few minutes. For less reactive olefins, the formation of furoxans from two moles of nitrile oxide was observed. The alkoxynitrile oxides reacted more efficiently with olefins and acetylenes than did the halonitrile oxides, i.e., the carboxy-hydroxylation reaction via the alkoxynitrile oxide route was preferred; it reduced the number of steps by one, gave higher yields and avoided the use of toxic haloform oximes.

Cycloaddition to cycloheptatriene gave three products 12a-c with the isomer 12a as the major product as predicted by MO theory. The isomer 12d, formed by a [6 + 4] cycloaddition, was not observed. The structures 12a-c were proved by two-dimensional H,H correlation spectra.

Reduction. Synthesis of γ-amino-β-hydroxybutyric acid (Gabob), mevalonic acid, malic acid and citramalic acid derivatives. Catalytic reduction over Raney-Ni was the method of choice when other reducible groups, e.g., nitro, epoxy, acetylenic or olefinic groups were absent. Reduction by TiCl₄ supplemented the catalytic reduction well. The usefulness of the reaction described here is demonstrated for the synthesis of a D,L-amino acid derivative 13, (a Gabob derivative) from Boc-allylamine via 4a or 4g, isopropyl mevalonate 14 from 3-methyl-3-butenol via 16, the diethyl ester of citramalic acid 15 from ethyl methacrylate via 17 and dialkyl malates 19a,b from ethyl acrylate via 4d,b. Citramalic acid has been synthesized previously via another isoxazole route. Reduction of 12a (R¹ = C₆H₅) with titanious ions gave 18 in a yield of ca. 30%.

Attempted preparation of tetrionic acids. Vinyl ketones gave 4j,k in high yields and reductive ring opening of 4j,k gave 20a,b. Attempted acid-catalysed enol rearrangement of 20a,b under various conditions combined with lactonization did not lead to the desired γ-methyl- and γ-phenyl-tetronic acids 21a,b, [eqn. (7)].

\[
\begin{align*}
4j,k & \rightarrow 20a,b \\
\text{(7)}
\end{align*}
\]

Experimental

The ¹H and ¹³C NMR spectra were obtained with a Varian Gemini 200 spectrometer. Me₆Si was used as an internal standard. IR spectra were recorded with a Nicolet MX-S, UV spectra with a Unikon 860 and mass spectra with a Micromass 7070 F. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. Preparative TLC was performed on silica gel 60, PF₂₅₄ + SiO₂ layers on glass plates (0.2 x 20 x 20 cm). Column chromatography on Kieselgel 60 (0.063-0.20 mm) Merck.

Trisopropyl orthoformate was prepared by acid-catalysed transesterification of trimethyl orthoformate with 4 mol of isopropyl alcohol at reflux temperature for ca. 6 h.⁷⁶ The acid was neutralized with metallic sodium and the product was distilled over an efficient fractionating column. The yield was ca. 79%, b.p. 66°C/18 mmHg. ¹H NMR (CDCl₃): δ 5.22 (1 H, s, C–H). Fractions containing mixed methyl–isopropyl orthoformates were reused for further transesterifications.

Trisethyl orthoformate was prepared according to the method of Alexander and Busch.⁷³ The crude product was heated to 130°C/0.2 mmHg to remove by-products. The residue in the flask consisted of nearly pure tribenzyl orthoformate, which was used directly for further reactions. ¹H NMR (CDCl₃): δ 5.62 (1 H, s, C–H).

Methyl formhydroximinate, 2a. Trimethyl orthoformate (5.3 g, 0.05 mol) and 0.35 g of 70% perchloric acid were reacted with H₂S in a tube-shaped reaction flask fitted with a sintered inlet tube and an outlet connected to H₂S traps containing conc. NaOH. The space above the orthoformate was first flushed with H₂S and then the inlet tube was lowered into the orthoformate. H₂S was introduced in a rapid stream at room temperature. After ca. 5–10 min the solution was poured into
a stirred aqueous solution of hydroxylamine (0.05 mol) at 0°C. The hydroxylamine solution was prepared from hydroxylammonium hydrochloride (3.5 g, 0.05 mol), sodium hydroxide (2.0 g, 0.05 mol) and potassium carbonate (2.8 g, 0.02 mol) in water (5 ml). The evolution of H₂S and CO₂ stopped after ca. 0.5 min. A 1:1 mixture of MgSO₄-K₂CO₃ (20 g) and dichloromethane (50 ml) were added with vigorous stirring at 0°C. The solid was filtered off and carefully washed with dichloromethane (100 ml). Evaporation of the solvent yielded methyl formhydroximate, 2a, 1.3 g, 35%, white crystals, m.p. 75–77°C. Recrystallization from carbon tetrachloride raised the m.p. to 85–86°C (lit.² 90°C). ¹H NMR (CDCl₃): δ 3.87 (3 H, s), 6.55 (1 H, s), 6.55 (1 H, s). The product contained some methyl formate. Methyl formhydroximate 2a was unstable at room temperature and liquefied after a few days. It could be stored in the freezer for a number of months.

Ethyl formhydroximate, 2b, was obtained in a yield of ca. 65% from triethyl orthoformate by applying the procedure described for 2a. Compound 2b melted at 81–83°C (from CCCL₃), white needles. (lit.² 80°C). ¹H NMR (CDCl₃): δ 1.36 (3 H, t, J = 7.5 Hz), 4.11 (2 H, q, J = 7.5 Hz), 6.62 (1 H, s). The compound decomposed overnight at 25°C, but could be stored in the freezer.

Isopropyl formhydroximate, 2d, was prepared as described for 2a, yield 78%, m.p. 85–86°C from carbon tetrachloride. ¹H NMR (CDCl₃): δ 1.33 (6 H, d, J = 6.5 Hz), 4.28 (1 H, septet, J = 6.5 Hz), 6.66 (1 H, s). MS: m/z = 103 (M⁺); IR (KBr): 1680 cm⁻¹ (C = N). The compound was stored in the freezer.

Benzyl formhydroximate, 2e. Tribenzyl orthoformate (16.7 g, 0.05 mol) was reacted with H₂S at 25°C in the presence of ZnCl₂ (0.3 g). The procedure described for 2a was then followed but the work-up was changed. The slurry obtained from the oxidation was poured onto the top of a silica (65 g) chromatography column (ϕ = 45 mm). Benzyl alcohol was first eluted with diethyl ether–heptane (1:4, 500 ml) and 2e with diethyl ether–dichloromethane (1:1, 500 ml). Evaporation of the solvent in vacuo gave 2e (5.1 g, 68%), white crystals, m.p. 129–130°C. Crystallization from carbon tetrachloride gave white needles, m.p. 130–132°C, ¹H NMR (CDCl₃): δ 5.09 (2 H, s), 6.70 (1 H, s), 7.37 (5 H, s). MS: m/z = 151 (M⁺); IR (KBr): 1680 cm⁻¹ (C = N). The compound was stable for several weeks at 25°C.

General procedure for the preparation of 3-alkoxyisoxazolines and 3-alkoxyisoxazoles, 4,5. Method A. NCS (N-chlorosuccinimide, 0.02 mol) was reacted with the alkyl formhydroximate (0.02 mol) at 25°C in chloroform (20 ml) with a few drops of pyridine as a catalyst. The chlorination was complete after ca. 15 min as observed by the disappearance of suspended NCS and of the blue–green colour indicating rearrangement of the intermediate chloro-nitroso compound into the chloro-oxime. For larger batches it is advisable to cool the reaction flask with tap water. The alkene or alkyne (0.02 mol) was added and finally triethylamine (0.021 mol in 3 ml of CHCl₃) was added dropwise at 48°C. The ratio dipolarophile : nitrite oxide could be adjusted according to the reactivity, availability, price, etc. of the dipolarophile. The reaction was complete after ca. 30 min. The suspension was filtered, the filtrate was evaporated and carbon tetrachloride (50 ml) was added. The succinimide was filtered off and evaporation of the solution gave the crude 3-alkylisoxazole derivative, which was purified by TLC, column chromatography on silica or basic alumina or distillation at low pressure (<1 mmHg).

Method B. NCS (0.021 mol), alkyl formhydroximate (0.02 mol), alkene or alkyne (0.02 mol), potassium hydrogen carbonate (10 g) and a few drops of water were stirred in ethyl acetate at 48°C for 1–2 days or at 25°C for 2–3 days. The reaction mixture was filtered, evaporated and suspended in carbon tetrachloride (50 ml). Filtration and evaporation of the solution gave the crude isoxazole derivatives. The yields were modest to good. Method B gave somewhat better yields but took longer to perform.

Catalytic reduction of the 3-alkylisoxazolines was carried out in aqueous methanol in the presence of boric acid using Raney-Ni as the catalyst. The reduction was complete within ca. 1–2 h. The solution was filtered through a thin layer of Celite, evaporated in vacuo to a small volume and extracted with chloroform. Drying (MgSO₄) and evaporation of the solvent gave the crude product, which was purified chromatographically on silica.

Thioformin, 6. To ethyl thioformate, prepared from triethyl orthoformate (3.7 g) according to the method described above, were added methythiohydroxylamine (from CH₃NH₂-HCl) (1.74 g), NaOH (1.0 g) and K₂CO₃ (1.5 g) in water (5 ml) at 0°C and the mixture was stirred for 3 min. Dichloromethane (40 ml), K₂CO₃ (10 g) and MgSO₄ (16 g) were added with stirring and the suspension was filtered and evaporated in vacuo. 6, 1.54 g, 69%, was obtained. ¹H NMR (CDCl₃): δ 3.57 (3 H, s), 8.57 (1 H, s), ¹³C NMR (CDCl₃): δ 42.6, 167.9. MS (m/z) 91 (M⁺). UV (λmax): 270 nm in agreement with data reported.⁸

Furoxan 10 was isolated as a crystalline solid when 1d was generated according to method B in the absence of a substrate. The crude oily product was purified by preparative TLC (SiO₂, heptane–Et₂O, 3:2) to give 10 as a solid in a yield of 16%. It decomposed at ca. 180–190°C.

Compound 13a was obtained as an oil in a yield of 79% by catalytic reduction over Raney-Ni. The crude product was purified by preparative TLC (SiO₂, CH₂Cl₂–Et₂O, 98:2). ¹³C NMR (CDCl₃): δ 22.0, 28.6, 39.1, 45.7, 68.8, 79.9, 157.1, 172.7. MS (m/z): 261 (M⁺).
13b, yield 71%, TLC (SiO₂, CH₂Cl₂-Et₂O, 9 : 1). ¹H NMR (CDCl₃): δ 1.40 (9 H, s), 2.51 (2 H, m), 3.10 (1 H, ddd, J = 14.7, 6.5 and 6.5 Hz), 3.3 (1 H, m), 4.11 (1 H, m), 4.96 (1 H, br s), 5.13 (2 H, s), 7.32 (5 H, br s). MS (m/z): 309 (M⁺).  

14, crude yield 78%, TLC (SiO₂, CH₂Cl₂). ¹H NMR (CDCl₃): δ 1.26 (6 H, d, J = 6.5 Hz), 1.30 (3 H, s), 1.75 (2 H, m), 2.40 (1 H, d, J = 15 Hz), 2.57 (1 H, d, J = 15 Hz), 3.83 (2 H, m), 5.06 (1 H, sept, J = 6.5 Hz). 

DI-Diethyl citramalate, 15, was obtained by catalytic reduction of 17 in a crude yield of 82%. It was practically pure. ¹³C NMR (CDCl₃): δ 14.3, 26.5, 44.5, 61.1, 62.3, 72.8, 71.6, 176.2. 

18. The isoxazoline 12a (60 mg) in ethanol (1.5 ml) was reduced with aqueous titanium trichloride (1.5 M solution, 150% excess) for 3 days under N₂ with stirring. Powdered Zn was added to maximize the full reducing power of the solution and it was neutralized to pH ca. 3 with sodium carbonate. The solution slowly became colourless. Water (3 ml) was added and the solution was extracted with chloroform. The organic phase was dried over MgSO₄ and evaporated. The oily residue consisted mainly of 18, 30%, contaminated by a small amount of 12a. ¹H NMR (CDCl₃): δ 1.25 (3 H, t, J = 7.3 Hz), 2.5–2.9 (3 H, m), 4.15 (2 H, q, J = 7.3 Hz), 4.62 (1 H, br s), 5.75–6.1 (4 H, m). ¹³C NMR (CDCl₃): δ 14.3, 27.4, 48.8, 61.2, 70.3, 125.5, 125.8, 133.3, 133.2, 174.9. 

19a, yield, 86%, TLC (SiO₂, CHCl₃), oil. ¹H NMR (CDCl₃): δ 1.10 (6 H, d, J = 6.5 Hz), 1.17 (3 H, q, J = 7 Hz), 2.65 (2 H, m), 3.45 (1 H, br s), 4.12 (2 H, q, J = 7 Hz), 4.35 (1 H, t, J = 5.5 Hz), 4.91 (1 H, sept, J = 6.5 Hz). 

19b, yield, 74%, TLC (SiO₂, CHCl₃), oil. ¹H NMR (CDCl₃): δ 1.16 (3 H, t, J = 7.5 Hz), 2.80 (2 H, m), 4.15 (2 H, q, J = 7.5 Hz), 4.48 (1 H, t, J = 6 Hz), 5.10 (2 H, s), 7.30 (5 H, s). 

20a. The reduction was carried out in aqueous ethanol as the solvent and was stopped when one equivalent of hydrogen had been absorbed. The pH was adjusted to ca. 4 with 2 M HCl. The solution was evaporated to a small volume and extracted several times with ethyl acetate. The organic phase was dried over Na₂SO₄, filtered and evaporated in vacuo. The crude yield of 20a was ca. 90%. The compound was unstable and could not be purified on TLC. ¹H NMR (CDCl₃): δ 1.25 (3 H, t, J = 7.5 Hz), 2.28 (3 H, s), 2.72 (1 H, dd, J = 1.35 and 6.0 Hz), 2.86 (1 H, dd, J = 1.35 and 4.4 Hz), 4.14 (2 H, q, J = 7.5 Hz), 4.36 (1 H, dd, J = 6.0 and 4.4 Hz). 

20b, yield, 63%, TLC (SiO₂, CH₂Cl₂-EtOAc, 1 : 1). The reduction was stopped when one equivalent of hydrogen had been absorbed. ¹H NMR (CDCl₃): δ 1.20 (3 H, t, J = 7.5 Hz), 2.57 (1 H, dd, J = 16.1 and 7.6 Hz), 2.83 (1 H, dd, J = 16.1 and 3.5 Hz), 4.11 (2 H, q, J = 7.5 Hz), 5.37 (1 H, dd, J = 7.6 and 3.5 Hz), 7.3–8.0 (5 H, m). 

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References
1. In the sequel this name is used in accordance with the naming of other nitrile oxides, e.g., halonitrile oxides.