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

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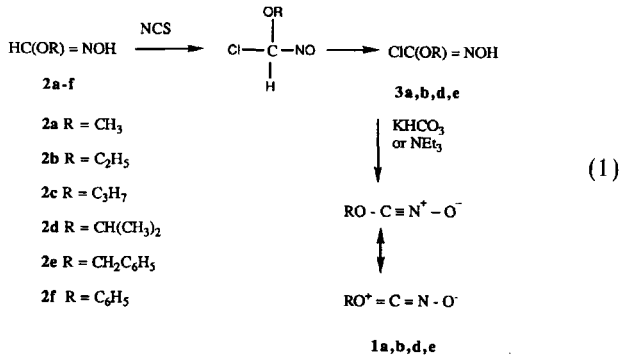
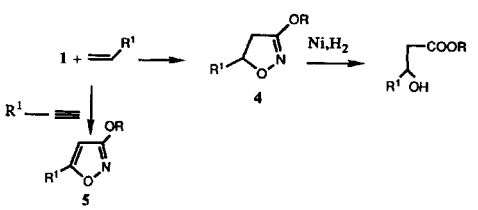
Alkyl formhydroximates have been synthesized by reacting alkyl orthoesters with hydrogen sulfide followed by treatment of the alkyl thioformate formed with hydroxylamine. Chlorination of alkyl formhydroximates with *N*-chlorosuccinimide gives alkyl chloroformhydroximates and dehydrochlorination with 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 Ti^{3+} salts. The reaction thus constitutes a novel hydroxycarboxylation. DL-*N*-Boc-γ-amino-β-hydroxybutyrates (Gabob), mevalonic acid, citromalic acid, malic acid derivatives and *N*-methyl-*N*-hydroxythioformamide (thioformin) have been synthesized. *N,N*-Dimethyl-*N'*-hydroxychloroformamidine (*N,N*-dimethylaminochloroform oxime) was not formed by chlorination of *N,N*-dimethyl-*N'*-hydroxyformamidine. The nitrile oxide cycloaddition to cycloheptatriene was investigated. The [6 + 4] cycloaddition mode was not observed but three isomeric [4 + 2] cycloaddition products were isolated and structurally determined.

Alkoxynitrile oxides **1**[1] (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 formhydroximates **2** to give alkyl chloroformhydroximates **3** followed by dehydrohalogenation with base, [eqn. (1)], in analogy to the generation of nitrile oxides from aldehyde oximes. Support for our assumption



(1)

was found in an early observation by Houben[2] who reported that chlorination of ethyl formhydroximate with Cl_2 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 formhydroximates **2a–c** have previously been prepared by Houben[2] 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 ^{1}H NMR spectrum of the crude product [eqn. (2)]. Evidently the alkoxynitrile oxides **1** behaved



(2)

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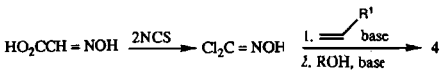
as do other reactive nitrile oxides. 3-Alkoxyisoxazolines **4**, which are masked β-hydroxy esters, are available by cycloaddition of dihaloformaldehyde oxime to alkenes and subsequent dehaloalkoxylation at C-3[3] [eqn. (3)]. It is thus possible to shorten the routes to **4** and **5** by one

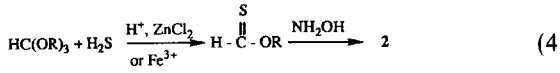


(3)

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.[4a] However, it was also reported that some aromatic thioesters give thiohydroxamic acids.[4b] We found that the thioformates, obtained by acid[5] or $FeCl_3$[6] catalyzed thionation of orthoesters[7] with hydrogen sulfide, reacted with hydroxylamine to give **2a,b,d,e** in modest to good yields [eqn. (4)]. The reaction conditions are critical



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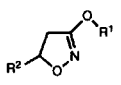
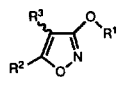


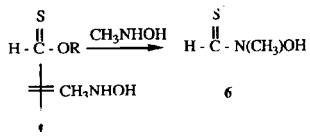


4a R^1 = i - Pr; R^2 = CH_2NHCOO-t-Bu
4b R^1 = $CH_2C_6H_5$; R^2 = $COOC_2H_5$
4c R^1 = $CH_2C_6H_5$; R^2 = C_6H_5
4d R^1 = i - Pr; R^2 = $COOC_2H_5$
4e R^1 = i - Pr; R^2 = n-Bu
4f R^1 = i - Pr; R^2 = $CH(OC_2H_5)_2$
4g R^1 = $CH_2C_6H_5$; R^2 = CH_2NHCOO-t-Bu
4h R^1 = C_2H_5; R^2 = $COOC_2H_5$
4i R^1 = C_2H_5; R^2 = Bu
4j R^1 = C_2H_5; R^2 = $COCH_3$
4k R^1 = C_2H_5; R^2 = COC_6H_5

5a R^1 = i - Pr; R^2 = R^3 = $COOCH_3$
5b R^1 = i - Pr; R^2 = R^3 = C_6H_5
5c R^1 = i - Pr; R^2 = C_6H_5; R^3 = H
5d R^1 = i - Pr; R^2 = Bu_3Sn; R^3 = H
5e R^1 = $CH_2C_6H_5$; R^2 = C_6H_5; R^3 = H
5f R^1 = i - Pr; R^2 = $(CH_3)_3Si$; R^3 = H
5g R^1 = C_2H_5; R^2 = C_6H_5; R^3 = H
5h R^1 = $CH_2C_6H_5$; R^2 = Bu_3Sn; R^3 = H

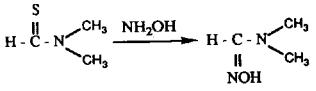
for the outcome of the reaction. Compounds **2a–d** are crystalline solids, which decompose and liquify within a few days at 25°C but are stable for several months in the freezer. Then benzyl derivative **2e** is stable at room temperature. We were not successful in transforming triphenyl orthoformate[7] into **2f**.

Attempted preparation of C-alkoxynitrones and dimethylaminonitrile oxide. Preparation of thioformin, **6**.[8] The reaction of thioformates with *N*-substituted hydroxylamines took a different course. The corresponding *N*-hydroxythioformamides[9] were obtained. The desired nitrone **7** was not observed, [eqn. (5)]. Compound **6**



(5)

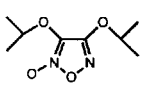
is a naturally occurring antibiotic.[8] Commercially available dimethylaminothioformamide was heated under reflux with hydroxylamine in aqueous ethanol to give *N,N*-dimethylamino-*N*-hydroxyformamidine (dimethylaminoformamide oxime), **8**.[10] Chlorination of **8** with NCS and subsequent dehydrochlorination in the presence of ethyl acrylate did not give the desired isoxazoline **9**, [eqn. (6)]. No further reactions were performed with **8**.



(6)

8

3-Alkoxyisoxazolines **4** *and 3-alkoxyisoxazoles* **5**. The chlorination of alkyl formhydroximates **2b,d,e** was conveniently carried out with NCS. Use of *tert*-butyl hypochlorite did not offer any advantages. The intermediate blue–green nitroso compounds rearranged to the oximes and the end of the chlorination was determined by the disappearance of the blue–green colour. Potassium hydrogen carbonate was the most suitable base for the dehydrochlorination of **3**. It slowly released the nitrile oxides, preventing their dimerization to furoxans and improved the yield of the cyclization products **4**. Occasionally triethylamine was used as base. The furoxan **10**



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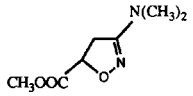

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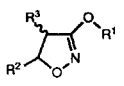
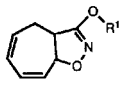




11a R^1 = C_2H_5; R^2 = CH_3; R^3 = $CH(OC_2H_5)_2$ **12a**
11b R^1 = C_2H_5; R^2 = $CH(OC_2H_5)_2$; R^3 = CH_3
11c R^1 = i - Pr; R^2 = CH_3; R^3 = $COOCH_3$
11d R^1 = i - Pr; R^2 = $COOCH_3$; R^3 = CH_3

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 1. Monosubstituted olefins and acetylenes gave practically only the 5-substituted

Table 1. Synthesis of 3-alkoxyisoxazolines and 3-alkoxyisoxazoles.

Compound No.	Ratio oxime: alkene or alkyne	Base, Temp., Reaction time	Yield (%)	M.p./°C or (b.p./mmHg)	Eluent TLC, silica	Alkene or alkyne	Selected ^{1}H, ^{13}C NMR, δ ($CDCl_3$); IR ν_{max}/cm^{-1}; UV, λ_{max}/nm; MS, *m/z* data.
4a	1 : 0.6	$KHCO_3$, 25°C, 70 h	85	Oil	$CHCl_3$–CH_3OH 93 : 7	*N*-Boc-allyl-amine	^{1}H: 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). ^{13}C: 2.19, 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.
4b	1 : 1.2	$KHCO_3$, 25°C, 48 h $KHCO_3$, 48°C, 38 h Et_3N, 48°C, 1 h	51 64 49	Oil	$CHCl_3$	Ethyl acrylate	^{1}H: 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). ^{13}C: 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.
4c	1 : 0.9	$KHCO_3$, 48°C, 34 h	78	Oil	CH_2Cl_2–Et_2O 9 : 1	Styrene	^{1}H: 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). ^{13}C: 40.9, 72.4, 83.1, 167.3. MS: 254 ($M^+ + 1$), 91.
4d	1 : 1.2	$KHCO_3$, 25°C, 48 h $KHCO_3$, 48°C, 34 h Et_3N, 48°C, 1 h	82 91 92	Oil	$CHCl_3$–CH_3OH 99 : 1	Ethyl acrylate	^{1}H: 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). ^{13}C: 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.
4e	1 : 1.25	$KHCO_3$, 48°C, 34 h Et_3N, 48°C, 1 h	54 44	Oil	$CHCl_3$–CH_3OH 99 : 1	1-Butene	^{1}H: 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). ^{13}C: 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.
4f	1 : 1.25	Et_3N, 48°C, 1 h	55	Oil	CH_2Cl_2–CH_3OH 98 : 2	Acrolein diethylacetal	^{13}C: 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.
4g	1 : 0.6	$KHCO_3$, 25°C, 72 h	65	Oil	CH_2Cl_2	*N*-Boc-allylamine	^{1}H: 1.40 (9 H, s), 2.75 (1 H, dd, *J* = 8.5 and 16.5 Hz), 2.96 (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^+).

4h	1 : 1.1	$KHCO_3$, 47°C, 48 h	83	Oil	CH_2Cl_2–EtOAc 1 : 1	Ethyl acrylate	^1H: 1.26 (3 H, t, $J = 7.5$ Hz), 1.30 (3 H, t, $J = 7.5$ Hz), 3.17 (1 H, dd, $J = 7.5$ and 16.5 Hz), 3.21 (1 H, dd, $J = 10$ and 16.5 Hz), 4.16 (2 H, q, $J = 7.5$ Hz), 4.21 (2 H, q, $J = 7.5$ Hz), 4.97 (1 H, dd, $J = 7.5$ and 10 Hz). ^{13}C: 14.2, 14.5, 36.4, 62.1, 66.8, 78.2, 166.8, 170.7. IR (film): 1735, 1630. MS: 187 (M^+).
4i	1 : 1.25	$KHCO_3$, 47°C, 45 h	55	Oil (130/0.2)		1-Hexene	^1H: 0.88 (3 H, t, $J = 7$ Hz), 1.28 (3 H, t, $J = 7$ Hz), 1.4–1.8 (6 H, m), 2.58 (1 H, dd, $J = 9$ and 16 Hz), 2.90 (1 H, dd, $J = 9$ and 16 Hz), 4.13 (2 H, q, $J = 7.0$ Hz), 4.52 (1 H, m). IR (film): 1625. MS: 171 (M^+).
4j	1 : 1.5	$KHCO_3$, 25°C, 72 h	82	Oil	Diethyl ether–ethyl acetate 1 : 9	Methyl vinyl ketone	^1H: 1.30 (3 H, t, $J = 6.9$ Hz), 2.29 (3 H, s), 3.09 (1 H, dd, $J = 10.3$ and 16.6 Hz), 3.17 (1 H, dd, $J = 6.9$ and 16.6 Hz), 4.14 (2 H, q, $J = 6.9$ Hz), 4.81 (1 H, dd, $J = 6.9$ and 10.3 Hz). ^{13}C: 14.5, 26.4, 34.7, 66.8, 84.5, 167.4, 208.5. MS: 157 (M^+), 130, 114. IR: 1720, 1625.
4k	1 : 1	$KHCO_3$, 25°C, 72 h	77	71	CH_2Cl_2	Phenyl vinyl ketone	^{13}C: 14.5, 33.7, 66.8, 81.4, 129.2, 130.1, 134.4, 134.8, 167.6, 194.4. IR: 1690, 1625. MS: 219 (M^+), 190, 114, 105, 77.
5a	1 : 1	$KHCO_3$, 40 h	35	Oil	CH_2Cl_2–Et_2O 4 : 1	Dimethyl acetylenedicarboxylate	^1H: 1.37 (6 H, d, $J = 6.3$ Hz), 3.84 (3 H, s), 3.93 (3 H, s), 4.95 (1 H, septet, $J = 6.3$ Hz). ^{13}C: 21.7, 52.7, 53.4, 75.5, 107.6, 157.1, 160.4, 160.8, 168.5. IR (film): 1735, 1625. MS: 201 ($M^+ - C_3H_6$), 170, 169, 111. UV (EtOH): 222.
5b	1 : 0.75	$KHCO_3$, 48°C, 36 h	33	86–87	Heptane–Et_2O 4 : 1	Diphenylacetylene	^1H: 1.40 (6 H, d, $J = 6.3$ Hz), 5.03 (1 H, septet, $J = 6.3$ Hz), 7.3–7.6 (10 H, m). IR (KBr): 1640, 1505. UV (EtOH): 223, 270. MS: 279 (M^+), 237, 209, 208.
5c	1 : 0.8	$KHCO_3$, 48°C, 40 h	65	Oil	CH_2Cl_2	Phenylacetylene	^1H: 1.40 (6 H, d, $J = 6.3$ Hz), 4.92 (1 H, septet, $J = 6.3$ Hz), 6.08 (1 H, s), 7.4 (3 H, m), 7.7 (2 H, m). IR (film): 1620, 1505. UV (EtOH): 258. MS: 203 (M^+), 161, 105.
5d[a]	1 : 0.6	$KHCO_3$, 48°C, 40 h	78	Oil	CH_2Cl_2 on basic alumina	Ethynyltributyltin	^1H: 0.8–1.7 (Sn–Bu, m), 1.33 (6 H, d, $J = 6$ Hz), 4.82 (1 H, septet, $J = 6$ Hz), 5.87 (1 H, s).
5e	1 : 1	$KHCO_3$, 48°C, 48 h	90	65	CH_2Cl_2–Et_2O 4 : 1	Phenylacetylene	^1H: 5.37 (2 H, s), 6.20 (1 H, s), 7.4 and 7.75 (10 H, m). MS: 251 (M^+).
5f	1 : 1	$KHCO_3$, 48°C, 34 h	56	(55/2) 39–40		Ethynyltrimethylsilane	^1H: 0.27 (9 H, s), 1.33 (6 H, d, $J = 6$ Hz), 4.82 (1 H, septet, $J = 6$ Hz), 5.94 (1 H, s). ^{13}C: −2.1, 22.0, 73.9, 104.9, 171.6, 180.4
5g	1 : 1.1	$KHCO_3$, 47°C, 45 h	21	Oil	$CHCl_3$	Phenylacetylene	^1H: 1.40 (3 H, t, $J = 6.5$ Hz), 4.33 (2 H, q, $J = 6.5$ Hz), 6.09 (1 H, s), 7.3–7.7 (5 H, m). MS: 189 (M^+).

Table continued

Table 1. Continued

Compound No.	Ratio oxime: alkene or alkyne	Base, Temp., Reaction time	Yield (%)	M.p./°C or (b.p./mmHg)	Eluent TLC, silica	Alkene or alkyne	Selected ^1H, ^{13}C NMR, δ ($CDCl_3$); IR ν_{max}/cm^{-1}; UV, λ_{max}/nm; MS, *m/z* data.
5h[a]	1 : 0.6	$KHCO_3$, 48°C, 38 h	89 (crude)	Oil	Et_2O–heptane 3 : 2, on basic alumina	Ethynyltributyltin	^1H: 0.8–1.8 (Sn–Bu, m), 5.27 (2 H, s), 6.01 (1 H, s), 7.4 (5 H, m).
10	—	$KHCO_3$, 48°C, 24 h	16	180–190 (decomp.)	Heptane–Et_2O 3 : 2	—	^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). ^{13}C: 21.7, 22.0, 75.1, 79.9, 157.0, 178.8. IR: 1610. MS: 202, 186, 145.
11a,b[b]	1 : 1	$KHCO_3$, 25°C, 72 h	30	Oils		Crotonaldehyde diethylacetal	^1H (**11a**): 3.04 (H^4, dd, $J = 5$ and 8 Hz). ^1H (**11b**): 3.21 (H^4, q, $J = 7$ Hz).
11c,d[c]	1 : 1	$KHCO_3$, 48°C, 48 h	83 (crude)	Oil	$CHCl_3$–CH_3OH 99 : 1	Ethyl crotonate	^1H (**11c**): 1.25 (3 H, d, $J = 6.5$ Hz), 3.47 (H^4, d, $J = 9.5$ Hz), 4.67 (H^5, dq, $J = 9.5$ and 6.5 Hz), ^1H (**11d**): 3.19 (H^4, quintet, $J = 7$ Hz), 4.37 (H^5, d, $J = 7.5$ Hz).
12a–c[d]	1 : 1.4	$KHCO_3$, 25°C, 68 h	28[f]	**12a**[e] 41–43 **12b,c** oils	CH_2Cl_2–CH_3OH 99.5 : 0.5	Cycloheptatriene	^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, dd, $J = 4.8$ and 8.7 Hz), 5.12 (1 H, dd, $J = 4.4$ and 8.7 Hz).
16	1 : 1.2	$KHCO_3$, 48°C, 38 h	85	Oil	$CHCl_3$–CH_3OH 95 : 5	Isopentenyl alcohol	^1H: 1.21 (6 H, d, $J = 6$ Hz), 1.32 (3 H, s), 1.83 (2 H, m), 2.58 (1 H, d, $J = 16$ 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). ^{13}C: 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.
17	1 : 1.1	$KHCO_3$, 47°C, 48 h	83	Oil (120/0.08)	CH_2Cl_2–EtOAc 1 : 1	Ethyl methacrylate	^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). ^{13}C: 14.1, 14.4, 23.4, 42.1, 62.1, 66.3, 85.9, 166.6, 172.6. IR (film): 1740, 1625.

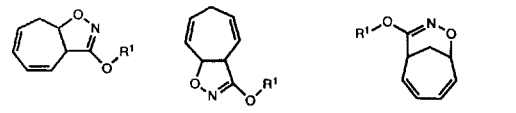
[a] Decomp. on silica. Contaminated by 3-alkoxyisoxazole formed by metallation. [b] **11a** : **11b** ~ 1 : 1. [c] **11c** : **11d** ~ 1 : 1. [d] **12a** : **12b** : **12c** ~ 6 : 2.5 : 1. [e] The isomers were separated by HPLC, SiO_2, normal phase, diethyl ether–heptane, 1 : 5. [f] The corresponding 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.

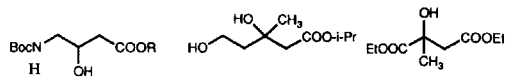
Lower temperature required longer reaction times. Triethylamine liberates the nitrile oxides very fast and the reaction is over within a few minutes. For less reactive olefins, the formation of furoxans from two moles of nitrile oxide was observed. The alkoxynitrile oxides reacted more efficiently with 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 used 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.

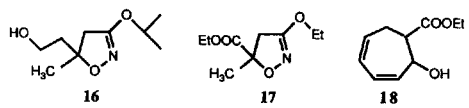
Reduction. Synthesis of γ-amino-β-hydroxybutyric acid (Gabob), mevalonic acid, malic acid and citramalic acid derivatives. Catalytic reduction over Raney-Ni was the method of choice when other reducible groups, e.g., nitro, epoxy, acetylenic or olefinic groups were absent. Reduction by Ti^{3+}[11] supplemented the catalytic reduction well. The usefulness of the reaction described here is demonstrated for the synthesis of a DL-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 isoxazoline route.[12] Reduction of **12a** ($R^1 = C_2H_5$) with titanous ions gave **18** in a yield of ca. 30%.



12b **12c** **12d**



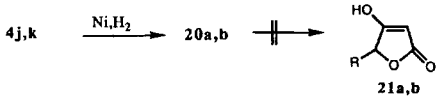
13a R = i-Pr **14** **15**
13b R = $CH_2C_6H_5$



16 **17** **18**

19a R = i-Pr **20a** R = CH_3
19b R = $CH_2C_6H_5$ **20b** R = C_6H_5

Attempted preparation of tetronic 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)].



4j,k $\xrightarrow{Ni,H_2}$ **20a,b** ⇸ **21a,b** (7)

Experimental

The ^1H and ^{13}C NMR spectra were obtained with a Varian Gemini 200 spectrometer. Me_4Si 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, $PF_{254+360}$, layers on glass plates (0.2 × 20 × 20 cm). Column chromatography on Kieselgel 60 (0.063–0.20 mm) Merck.

Triisopropyl orthoformate was prepared by acid-catalysed transesterification of trimethyl orthoformate with 4 mol of isopropyl alcohol at reflux temperature for ca. 6 h.[7a] 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 ($CDCl_3$): δ 5.22 (1 H, s, C–H). Fractions containing mixed methyl–isopropyl orthoformates were reused for further transesterifications.

Tribenzyl orthoformate was prepared according to the method of Alexander and Busch.[7b] 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 ($CDCl_3$): δ 5.62 (1 H, s, C–H).

Methyl formhydroximate, **2a**. Trimethyl orthoformate (5.3 g, 0.05 mol) and 0.35 g of 70% perchloric acid were reacted with H_2S in a tube-shaped reaction flask fitted with a sintered inlet tube and an outlet connected to H_2S traps containing conc. NaOH. The space above the orthoformate was first flushed with H_2S and then the inlet tube was lowered into the orthoformate. H_2S 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 hydroxylamime 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 H_2S and CO_2 stopped after ca. 0.5 min. A 1 : 1 mixture of $MgSO_4$–K_2CO_3 (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). ^{1}H NMR ($CDCl_3$): 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 liquified 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 CCl_4), white needles, (lit.[2] 80°C). ^{1}H NMR ($CDCl_3$): 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. ^{1}H NMR ($CDCl_3$): 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 H_2S at 25°C in the presence of $ZnCl_2$ (0.3 g). The procedure described for **2a** was then followed but the work-up was changed. The slurry obtained from the oximation was poured onto the top of a silica (65 g) chromatography column ($\phi = 45$ 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, ^{1}H NMR ($CDCl_3$): 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 $CHCl_3$) was added dropwise at 48°C. The ratio dipolarophile : nitrile 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-alkoxyisoxazolines 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 ($MgSO_4$) 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 methylhydroxylamine (from $CH_3NHOH \cdot HCl$) (1.74 g), NaOH (1.0 g) and K_2CO_3 (1.5 g) in water (5 ml) at 0°C and the mixture was stirred for 3 min. Dichloromethane (40 ml), K_2CO_3 (10 g) and $MgSO_4$ (16 g) were added with stirring and the suspension was filtered and evaporated *in vacuo*. **6**, 1.54 g, 69%, was obtained. ^{1}H NMR ($CDCl_3$): δ 3.57 (3 H, s), 8.57 (1 H, s). ^{13}C NMR ($CDCl_3$): δ 42.6, 167.9. MS (*m/z*) 91 (M^+). UV (λ_{max}): 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 (SiO_2, heptane–Et_2O, 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 (SiO_2, CH_2Cl_2–Et_2O, 98 : 2). ^{13}C NMR ($CDCl_3$): 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 (SiO_2, CH_2Cl_2–Et_2O, 9 : 1). ^1H NMR ($CDCl_3$): 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 (SiO_2, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 1.24 (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, septet, J = 6.5 Hz).

DL-Diethyl citramalate, **15**, was obtained by catalytic reduction of **17** in a crude yield of 82%. It was practically pure. ^{13}C NMR ($CDCl_3$): δ 14.3, 26.5, 44.5, 61.1, 62.3, 72.8, 171.6, 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 N_2 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 $MgSO_4$ and evaporated. The oily residue consisted mainly of **18**, 30%, contaminated by a small amount of **12a**. ^1H NMR ($CDCl_3$): 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). ^{13}C NMR ($CDCl_3$): δ 14.3, 27.4, 48.8, 61.2, 70.3, 125.5, 125.8, 133.3, 133.7, 174.9.

19a, yield, 86%, TLC (SiO_2, $CHCl_3$), oil. ^1H NMR ($CDCl_3$): 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, septet, J = 6.5 Hz).

19b, yield, 74%, TLC, (SiO_2, $CHCl_3$), oil. ^1H NMR ($CDCl_3$): 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 Na_2SO_4, 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 ($CDCl_3$): 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 = 13.5 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 (SiO_2, CH_2Cl_2–EtOAc, 1 : 1). The reduction was stopped when one equivalent of hydrogen had been absorbed. ^1H NMR ($CDCl_3$): 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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