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2-ISOXAZOLINES WITH AN ELECTRON-ACCEPTOR SUBSTITUENT AT $C_{(5)}$ IN REACTIONS WITH NUCLEOPHILIC REAGENTS

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Depending on the substituent at position 5 of the heterocycle, reaction of 2-isoxazolines with K-selectride, molybdenum hexacarbonyl, dimsyl sodium, and butyl lithium gave 1,3-cyclo-decomposition, aromatization of the isoxazoline ring, or reduction of the functional groups in the substituted isoxazolines.

Keywords: derivatives of 2-isoxazoline, dimsyl sodium, molybdenum hexacarbonyl, K-selectride, cyclodecomposition.

We described previously the reaction of 3-R-5-(4-pyridyl)-2-isoxazols with K-selectride ($KBH(s\text{-}Bu)_3$) and other organometallic reagents (butyl lithium, dimsyl sodium, and molybdenum hexacarbonyl) which occurred by decomposition of the isoxazoline ring at the N–O and $C_{(3)}$–$C_{(4)}$ bonds to give nitriles and 4-vinylpyridine [1-4]. However, 2-isoxazolines with phenyl, 2-pyridyl, or 2-oxo-1-pyrrolidyl substituents at $C_{(5)}$ did not give products of cyclodecomposition in such reactions [2, 5].

Similar 1,3-cyclodecomposition under the influence of bases was known for a series of 5-acylisoxazolines and 5-nitroisoxazolines [6, 7]. Only products of 1,4-cyclodecomposition were isolated from reactions of 2-isoxazolines with metal polycarbonyls [8, 9].

The decomposition of the heterocycle of 2-isoxazolines at two bonds is formally the reverse of the synthesis of the heterocycle and not infrequently complicates the typical decomposition of the ring of 2-isoxazolines, which normally occurs at one of the bonds of the N–O–C unit. It is generally considered that 1,3-cyclodecomposition under the influence of bases goes *via* the generation of an anion at the $C_{(5)}$ atom of the ring [6,7, 10]. However, the most acidic hydrogens are at $C_{(3)}$ in 3-substituted 2-isoxazolines and at $C_{(4)}$ in 3-unsubstituted isoxazolines [11, 12]. 5-*endo*-Deprotonation is generally uncharacteristic but may occur when there are an electron-acceptor substituents at $C_{(5)}$, capable of creating a considerable increase in the acidity of the H-5 proton and facilitating the stabilization of the anion formed.

To determine the limit of the applicability of the 1,3-cyclodecomposition reaction it was expedient to compare the reactions of 2-isoxazolines, having electron-acceptor substituents at $C_{(5)}$, with typical bases, on the one hand, and with nucleophilic organometallic reagents, on the other hand. The cryptobasic reducing agent K-selectride has a nucleophilic character. Molybdenum hexacarbonyl reacts with 2-isoxazolines with the intermediate formation of a vinyl-nitrene complex with delocalization of the π-*d* electrons from the metal into the C=N–O π-orbital of the heterocycle, which makes easy rupture of the N–O bond possible [10, 13].

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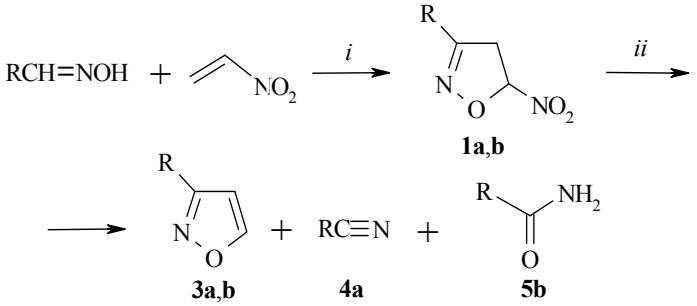
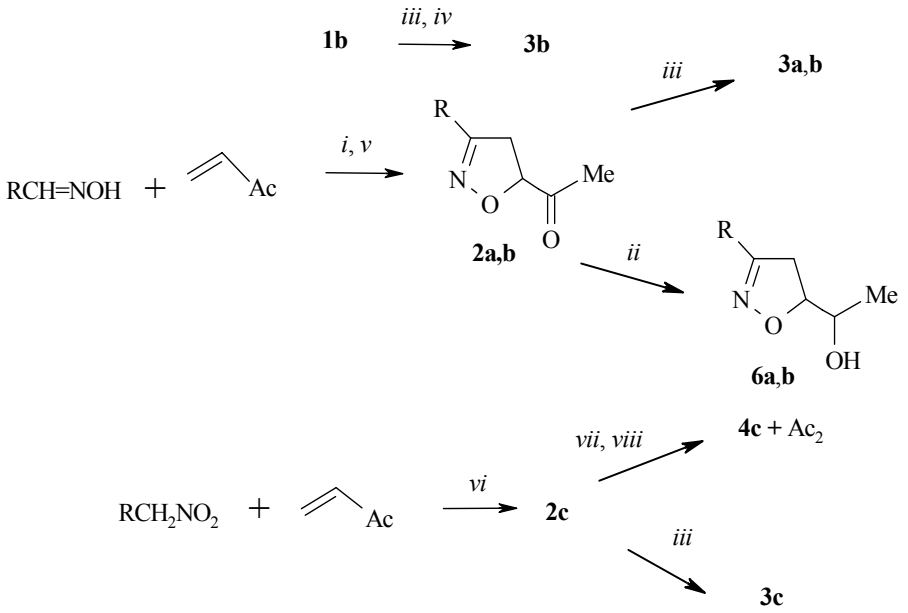
3-Aryl-5-nitro- and 5-acetyl-3-aryl-2-isoxazolines **1a,b, 2a,b** were prepared from arylhydroxamic acid chlorides and nitroethylene or methyl vinyl ketone under 1,3-dipolar cycloaddition reaction conditions. 5-Acetyl-3-(3-ethoxycarbonyl-1-propyl)-2-isoxazoline (**2c**) was obtained by 1,3-cycloaddition to methyl vinyl ketone of the nitroxide dipole *in situ*, generated by the reaction of phenyl isocyanate from ethyl ester of 4-nitrovalerianic acid. The small yield of the cycloadducts may be explained by polymerization of the alkene starting materials under conditions of the cycloaddition reaction.

On reaction of the 3-aryl-5-nitroisoxazolines **1a,b** with K-selectride the isoxazols **3a,b**, products of the aromatization of the heterocycle, were the principal products isolated. We had previously observed this with 5-imidazolyl-2-isoxazoline [14]. In the reaction of isoxazoline **1a** with K-selectride, in addition to 3-veratrylisoxazol **3a** the nitrile **4a** was isolated in 20% yield. In the reaction products from the reaction of isoxazoline **1b** with K-selectride benzamide **5b** was isolated with 3-phenylisoxazol **3b.** The former was probably the product of hydrolysis of benzonitrile **4b**, formed initially by 1,3-cyclodecomposition of the isoxazoline **1b**. The analogous amides **5a,c** were not observed. Aromatization of 5-nitro-3-phenyl-2-isoxazoline **1b** to give the isoxazol **3b** also occurred on reaction with sodium methoxide at -30°C.





1–6 a R = 3,4-$(MeO)_2C_6H_3$, **b** R = Ph, **c** R = $EtO_2C(CH_2)_3$

i Cl_2, Et_3N, $CHCl_3$, -10 °C – room temp.; *ii* KBH(*s*-Bu)$_3$, –45 °C; *iii* $Mo(CO)_6$, AcCN, 70 °C; *iv* MeONa, THF, -30 °C; *v* NCS, $CHCl_3$, Py, 20 °C; *vi* PhNCO, petroleum ether, 40-50 °C; *vii* $NaCH_2SOMe$, THF, 20 °C; *viii* *n*-BuLi, –45 °C – +15 °C

In the reaction of 5-acetyl-3-aryl-2-isoxazolines **2a,b** with K-selectride quantitative reduction of the carbonyl group with formation of 5-(1-hydroxyethyl)-2-isoxazolines **6a,b** was observed.

When the 2-isoxazolines **1b, 2a-c** were treated with dimsyl sodium in DMSO under standard conditions the reaction mixture underwent resinification. The reaction of 5-acetyl-3-(3-ethoxycarbonylpropyl)-2-isoxazoline (**2c**) with dimsyl sodium was carried out successfully in a heterogeneous medium: the isoxazoline was stirred with a suspension of dimsyl sodium in THF. The product of cyclodecomposition, ethyl 4-cyanobutanoate **4c,** was isolated. The nitrile **4c** was also isolated from the reaction of the same isoxazoline **2c** with butyl lithium. The product from the second fragment of decomposition of the isoxazoline ring was not isolated. It should be noted that reaction of 5-alkyl-, 5-penyl-, 5-(pyridyl-2)- and 5-(2-oxopyrrolidin-1-yl)-2-isoxazolines with dimsyl sodium gave 1,5-decomposition of the heterocycle to give the corresponding enoximes [2, 3].

The reaction of 5-nitro-3-phenylisoxazoline **1b** with molybdenum hexacarbonyl at the temperature of the boiling solvent – acetonitrile (70°C) gave the isoxazol **3b** (90% yield) with the evolution of nitrogen dioxide. Under these conditions 5-acetyl-2-isoxazolines **2a-c** gave the corresponding isoxazols **3a-c** as the basic product but with strong resinification of the reaction mixture.

It is known that the mobility of proton H-4 in the isoxazol ring is greater than that of proton H-5. As a result of the *–I-* and *–M*-effects of the nitro group the acidity of the $H–C_{(5)}$ of the heterocycle in the isoxazoline is increased and deprotonation occurs effectively at both positions 5 and 4. When the 5-R-substituent possesses *–I-* and *–M*-effects, removal of proton H-4 occurs and if the 5-R-substituent is a good leaving group, then aromatization occurs. So if the 5-R-substituent is a nitro, imidazolyl, or carboxyl group, then in the reactions of 5-nitroisoxazolines **1a,b** with nucleophilic reagents aromatization of the heterocycle occurs.

In the case of 5-pyridylisoxazolines, the pyridyl substituent, which possesses a negative inductive effect, facilitates the formation of an anion at $C_{(5)}$ atom, but the *+M*-effect of the substituent possibly predetermines the subsequent decomposition of the ring because of the impossibility of stabilizing the negative charge on $C_{(5)}$. From this point of view cyclodecomposition should be observed with isoxazolines containing heteroaromatic substituents – pyridine, thiophene, pyrrole. The bases should be sufficiently strong to allow deprotonation of isoxazoline ring. It should be noted that the number of the bases capable to deprotonate atom $C_{(5)}$ of the isoxazoline cycle is limited for the substituents of the type OMe, OH, NR^1, NR^2 where *–I*-effect < *+M*-effect. However, in such cases deprotonation of the $H–C_{(5)}$ may occur effectively under the influence of organometallic compounds with nucleophilic character in the intermediate complex.

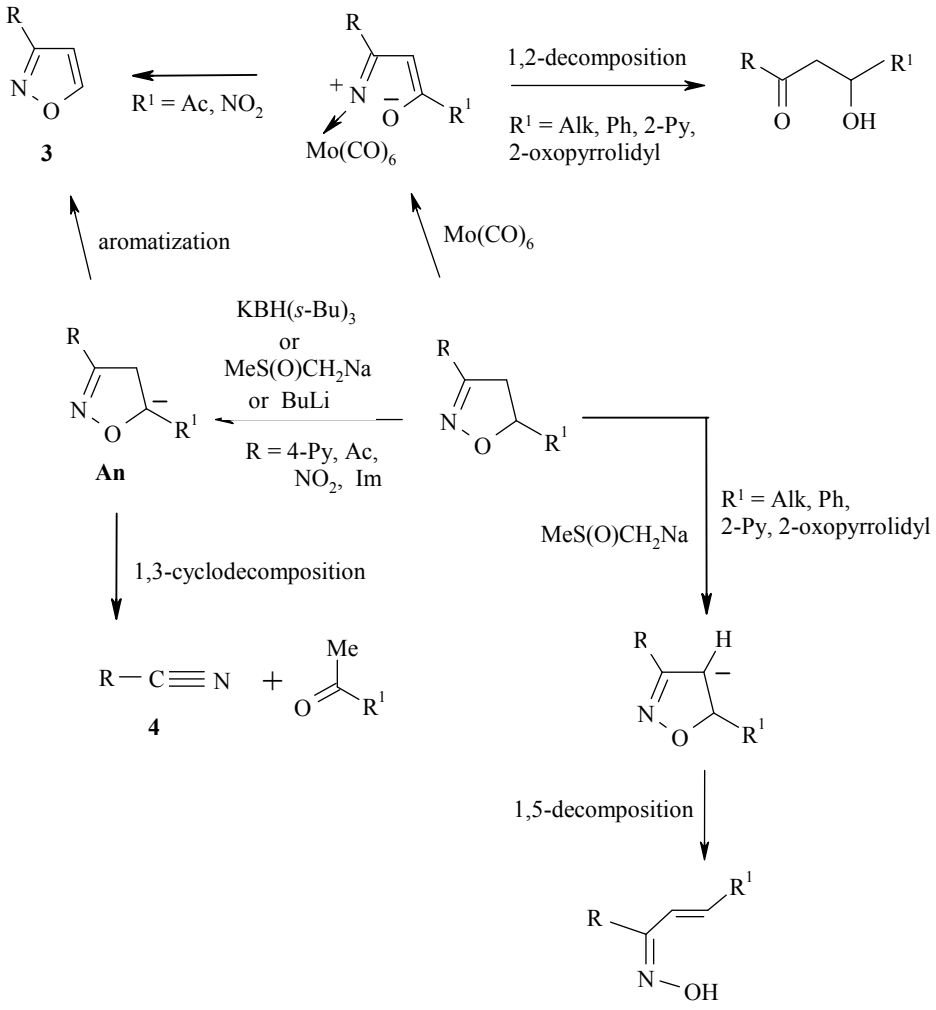
So in reaction of 2-isoxazolines with nucleophilic reagents four reaction pathways are possible for conversion of the isoxazoline ring – 1,2-cleavage, 1,5-cleavage, 1,3-cyclodecomposition, and aromatization.

The structure of the substituent at $C_{(5)}$ of the isoxazoline ring determines the results of its reaction with a nucleophilic reagent. Electron-acceptor substituents facilitate the formation of the $C_{(5)}$-anion **An**, the driving force of the subsequent ketonitrile cyclodecomposition is the formation of the stable nitrile **4**. The second direction for the stabilization of the $C_{(5)}$ is achieved when the substituent at $C_{(5)}$ is an excellent leaving group: its removal with the formation of H-(5-R) leads to the corresponding isoxazole. An exclusion is evidently the reaction with metal polycarbonyls, since in the intermediate state a complex is formed as a result of coordination *via* the unshared electron pair of the nitrogen atom of the isoxazoline. Subsequent decomposition of this complex occurs with cleavage at the N–O bond. Since in the reaction of isoxazolines **1** and **2** with molybdenum hexacarbonyl we isolated only the products of aromatization, it may be suggested that the complex formed is stabilized only by loss of the $C_{(5)}$-substituent with formation of the isoxazol **3.**

However in a case we described [4], the 1,3-cyclodecomposition of 2-isoxazolines with $Mo(CO)_6$ evidently occurred *via* formation of a complex of the polycarbonyl with the nitrogen atom of the pyridyl substituent at $C_{(5)}$.

2-Isoxazolines are very weak bases, the basicity of which correlates of the electron-acceptor properties of the substituent. Because of the conjugation of the isoxazol and benzene rings, phenyl-substituted isoxazoles and isoxazolines are an order less basic than those with alkyl substituents [15]. Therefore the presence of acceptor substituents on 2-isoxazolines determines their high reactivity in reactions with nucleophiles.

It should be noted that ^{1}H NMR data confirm the presence of conjugation of the substituent at $C_{(5)}$ with the isoxazoline ring. For example, the equivalence of the H-4 protons in the spectrum of 5-nitro-3-phenyl-isoxazoline **1b** indicates that the heterocycle and the nitro group are in the same plane. The convergence of the chemical shifts of the H-4 protons which is observed in the ^{1}H NMR spectra of the 5-acetyl-substituted **2a-c** and also 5-(2-pyridyl)- [5] and 5-imidazolyl-2-isoxazolines [14] reflects the tendency to flattening of the molecule. The possibility of the charge redistribution due to the conjugation effect with substituent arises in the flater system. The neighboring reaction center of the heteroatom of the substituent with an unshared pair of electrons also affects the charge on $C_{(5)}$ in the nitroisoxazolines **1a,b** and 5-(2-pyridyl)- and 5-imidazolyl-2-isoxazolines.



EXPERIMENTAL

^{1}H NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded with a Bruker AC-200 (200 MHz) spectrometer. IR spectra of thin films or KBr disks were recorded with UR-20 instrument. Mass spectra were recorded with a Varian MAT-311 instrument with an ionizing energy of 70 eV. The course of reactions and the purity of the products synthesized were monitored by TLC on Silufol UV-254 (Serva) and Kieselgel 60 F_{254} (Merck) plates with 1:1 hexane-ether eluent. Development was carried out with UV light, iodine, and anisic developer (90% ethanol, 5% H_2SO_4, 5% anisaldehyde). Column chromatography was carried out on 40-100μ silica gel (Czechoslovakia) or Kieselgel 60 (Merck).

Oximes of the corresponding aromatic aldehydes were obtained by known methods and their physicochemical characteristics coincided with those cited in the literature.

3-(3,4-Dimethoxyphenyl)-5-nitro-2-isoxazoline (1a). Veratraldoxime (5.2 mmol) was added to a solution of N-chlorosuccinimide (5.2 mmol) in chloroform (30 ml) and pyridine (0.01 ml). After the precipitate had dissolved completely nitroethylene (2.6 mmol) in chloroform (10 ml) was added to the reaction mixture and then over several minutes triethylamine in chloroform (5.2 mmol) was added slowly during 3 h. The reaction mixture was stirred for 48 h, evaporated, water was added to the residue, and the product was extracted with ether or chloroform. The required product **1a** was separated by chromatography as an amorphous solid mass. Yield 45%. IR spectrum, ν, cm^{-1}: 700, 765, 1365, 1565, 1600. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.86 (3H, s, OCH_3); 3.87 (3H, s, CH_3); 4.12 (2H, d, $J_{4,5}$ = 5.5, CH_2 isox); 6.20 (1H, t, $J_{5,4}$ = 5.5, CH isox); 6.48 (1H, d, $J_{2',6'}$ = 1.7, H-2'); 6.56 (1H, dd, $J_{6',5'}$ = 10.0, $J_{6',2'}$ = 1.7, H-6'); 7.58 (1H, d, $J_{5',6'}$ = 10.0, H-5'). Mass spectrum, *m/z* (I_{rel}, %): 252 $[M]^+$ (20), 206 $[M–NO_2]^+$ (65), 115 $[M–(MeO)_2C_6H_3]^+$ (35), 46 $[NO_2]^+$ (100), Found, %: C 52.36; H 4.91; N 11.13. $C_{11}H_{12}N_2O_5$. Calculated, %: C 52.38; H 4.80; N 11.11.

5-Nitro-3-phenyl-2-isoxazoline (1b). Chlorine was passed through a solution of benzaldoxime (12 mmol) in dry chloroform at -15°C until the reaction mixture became an intense green color. The excess chlorine and hydrogen chloride were removed in vacuum. The reaction mixture was warmed to room temperature and nitroethylene (13 mmol) was added. Triethylamine (2ml) in dry chloroform (10 ml) was added slowly dropwise with stirring until the solution was weakly basic, after which the mixture was stirred for 2-3 h. After removal of the chloroform, dry ether was added and the precipitate of $Et_3N·HCl$ was filtered off. The ether was evaporated off, and the product was separated by column chromatography on silica gel followed by recrystallization from ether–hexane to give isoxazoline **1b** (4.2 mmol) as colorless crystals, stable below 0°C, decomposing very slowly at room temperature and rapidly at temperatures above 50°C. Yield 35%. IR spectrum, ν, cm^{-1}: 700, 765, 850, 1370, 1575, 1590. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 4.00 (2H, d, $J_{4,5}$ = 5.5, CH_2 isox); 6.26 (1H, t, $J_{5,4}$ = 5.5, CH isox); 7.37-7.71 (5H, m, C_6H_5). Mass spectrum, *m/z* ($I_{rel,}$ %): 192 $[M]^+$ (20), 146 $[M–NO_2]^+$ (52), 116 $[M–C_6H_5]^+$ (25), 77 $[C_6H_5]^+$ (45), 46 $[NO_2]^+$ (100). Found, %: C 56.30; H 4.25; N 14,63. $C_9H_8N_2O_3$. Calculated, %: C 56.25; H 4.20; N 14.58.

5-Acetyl-3-(3,4-dimethoxyphenyl)-2-isoxazoline (2a) and **5-acetyl-3-phenyl-2-isoxazoline (2b)** were obtained analogously from veratraldoxime and benzaldoxime, respectively, with an excess of vinyl methyl ketone (15 mmol). Triethylamine in dry chloroform (2 ml in 10 ml chloroform) was added to remove the excess of hydrogen chloride only after the reaction was completed. The products were isolated by column chromatography.

Isoxazoline 2a. Yield 40%. IR spectrum, ν, cm^{-1}: 710, 760, 1365, 1575, 1600, 1735. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 2.30 (3H, s, CH_3CO); 3.5-3.65 (2H, m, CH_2 isox); 5.25 (1H, dd, $J_{5,4}$ = 10, *J* = 6.5, CH isox); 3.84 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 6.52 (1H, d, $J_{2',6'}$ = 2.0, H-2'); 6.56 (1H, dd, $J_{6',5'}$ = 10.0, $J_{6',2'}$ = 2.0, H-6'); 7.60 (1H, d, $J_{5',6'}$ = 10.0, H-5'). Mass spectrum, *m/z* (I_{rel}, %): 249 $[M]^+$ (30), 206 $[M–Ac]^+$ (60), 43 $[Ac]^+$ (100). Found, %: C 62.61; H 6.11; N 5.66. $C_{13}H_{15}NO_4$. Calculated, %: C 62.64; H 6.07; N 5.62.

Isoxazoline 2b. Mp 62-64°C. Yield 45%. IR spectrum, ν, cm^{-1}: 1365, 1580, 1610, 1736. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 3.47 (1H, dd, J_{gem} = 17.0, $J_{4,5}$ = 11.7, H-4 isox); 3.65 (1H, dd, J_{gem} = 17.0, $J_{4,5}$ = 6.5, H-4 isox), 5.01 (1H, dd, $J_{5,4}$ = 11.7, $J_{5,4}$ = 6.5, H-5 isox); 7.42 (3H, m, C_6H_5); 7.65 (2H, m, C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 189 $[M]^+$ (20), 146 $[M–Ac]^+$ (60), 112 $[M–C_6H_5]^+$ (25), 77 $[C_6H_5]^+$ (45), 43 $[Ac]^+$ (100). Found, %: C 69.91; H 5.81; N 7.46. $C_{11}H_{11}NO_2$. Calculated, %: C 69.83; H 5.86; N 7.40.

5-Acetyl-3-(3-ethoxycarbonylpropyl)-2-isoxazoline (2c). A small excess of methyl vinyl ketone (14 mmol) and phenyl isocyanate (30 mmol) was added to a solution of ethyl ω-nitrovalerate (12 mmol) in dry petroleum ether (15 ml). Triethylamine (12 mmol) was added rapidly and the reaction mixture was stirred free from moisture on a water bath at 40-50°C for 1 h. The precipitate of diphenylurea was filtered off, washed with chloroform and methanol, and the combined filtrates were evaporated on a rotary evaporator. The required product was isolated by column chromatography on silica gel with gradient elution with an ether–hexane

mixture to give compound **2c** (4.8 mmol, 40%) as an oil. IR spectrum, ν, cm^{-1}: 1610, 1735. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, t, *J* = 7.0, CH_3); 1.90 (2H, m, CH_2); 2.28 (3H, s, $CH_3C{=}O$); 2.36 (4H, m, $2CH_2$), 3.13 (2H, m, CH_2 isox); 4.52 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 4.82 (1H, dd, $J_{5,4}$ = 11.0, *J* = 6.8, CH isox). Mass spectrum, *m/z* (I_{rel}, %): 195 $[M]^+$ (25), 152 $[M–Ac]^+$ (60), 43 $[Ac]^+$ (100). Found, %: 61.93 H 8.95 N 6.53. $C_{11}H_{17}NO_2$. Calculated, %: C 61.95; H 8.98; N 6.57.

Reactions of 3-Aryl-5-nitro- (1a,b) and 5-Acetyl-3-aryl-2-isoxazolines (2a,b) with K-selectride. An isoxazoline (0.5 mmol) in THF (7 ml, freshly distilled over $LiAlH_4$) was placed in a flask flushed with argon and cooled to -45°C, and a solution of K-selectride (Aldrich) (2 ml, 1M) was added to the stirred solution with a syringe. The mixture was stirred at -45°C for 3 h, then 30% H_2O_2 (2 ml) and potassium hydroxide (1 ml, 5M) were added at -10°C with stirring for 10 min at 0 to +5°C, diluted with water (2 ml), and the reaction mixture was then evaporated. The aqueous suspension was extracted with ether, the extract was washed with water, and dried over $MgSO_4$. The products were isolated by column chromatography as crystals or oils.

3-(3,4-Dimethoxyphenyl)isoxazole (3a). Yield 35%. IR spectrum, ν, cm^{-1}: 700, 770, 880, 960, 1610. ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.85 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 6.53 (1H, d, $J_{2',6'}$ = 2.0, H-2'); 6.58 (1H, dd, $J_{6',5'}$ = 10.0, $J_{6',2'}$ = 2.0, H-6'); 6.70 (1H, d, $J_{4,5}$ = 1.9, H-4 isox); 7.62 (1H, d, $J_{5',6'}$ = 10.0, H-5'); 8.54 (1H, d, $J_{5,4}$ = 1.9, H-5 isox). Mass spectrum, *m/z* (I_{rel}, %): 205 $[M]^+$ (80), 137 $[(MeO)_2C_6H_3)]^+$ (45), 120 (45). Found, %: C 64.42; H 5.51; N 6.86. $C_{11}H_{11}NO_3$. Calculated, %: C 64.38; N 5.40; N 6.83.

3,4-Dimethoxybenzonitrile (4a). Yield 20%. Mp 67-68°C [16]. IR spectrum, ν, cm^{-1}: 810, 1030, 1580, 1610, 2220. ^1H NMR spectrum, δ, ppm: 3.85 (3H, s, OCH_3); 3.90 (3H, s, OCH_3); 6.46 (1H, d, $J_{2',6'}$ = 1.7, H-2' arom); 6.50 (1H, dd, $J_{6',5'}$ = 10.0, $J_{6',2'}$ = 1.7, H-6' arom); 7.46 (1H, d, $J_{5',6'}$ = 10.0, H-5' arom). Mass spectrum, *m/z* (I_{rel}, %): 163 $[M]^+$ (100), 120 (45), 77 $[C_6H_5]^+$ (35).

3-Phenylisoxazole (3b). Yield 40°C. Mp 143-145°C [17]. IR spectrum, ν, cm^{-1}: 700, 770, 880, 960, 1610. ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.64 (1H, d, $J_{4,5}$ = 1.9, H-4 isox); 7.45 (3H, dd, *J* = 5.0, *J* = 2.4, C_6H_5); 7.81 (2H, dd, *J* = 5.0, *J* = 2.4, C_6H_5); 8.44 (1H, d, $J_{5,4}$ = 1.9, H-5 isox). Mass spectrum, *m/z* (I_{rel}, %): 145 $[M]^+$ (80), 103, 77 $[C_6H_5]^+$ (45).

Benzamide (5b). Yield 20%. Mp 125-127°C. IR spectrum, ν, cm^{-1}: 700, 760, 860, 1670. ^1H NMR spectrum, δ, ppm (*J*, Hz): 5.70 (br. s, NH_2); 7.5-7.8 (5H, m, C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 121 $[M]^+$ (65), 105 $[M–NH_2]^+$ (90), 77 $[C_6H_5]^+$ (100).

5-(1-Hydroxyethyl)-3-(3,4-dimethoxyphenyl)-2-isoxazoline (6a) was obtained analogously from isoxazol **2a** as a mixture of stereoisomers in 98% yield. Oil. IR spectrum, ν, cm^{-1}: 605, 1610, 3420. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, d, *J* = 7, CH_3); 2.60 (1H, br. s, OH); 3.32 (1H, dd, J_{gem} = 16.0, $J_{4,5}$ = 8.0, H-4 isox); 3.48 (1H, dd, J_{gem} = 16.0, $J_{4,5}$ = 11, H-4 isox); 3.75 (1H, m, C<u>H</u>–OH); 3.94 (3H, s, CH_3); 3.95 (3H, s, CH_3); 4.70 (1H, ddd, $J_{5,4}$ = 8.0, $J_{5,4}$ = 11.0, $J_{5,1'}$ = 5.5, H-5 isox); 6.86 (1H, d, $J_{2',6'}$ = 2.0, H-2'); 7.06 (1H, dd, $J_{6',5'}$ = 10.0, $J_{6',2'}$ = 2.0, H-6'); 7.3 (1H, d, $J_{5',6'}$ = 10.0, H-5'). Mass spectrum, *m/z* (I_{rel}, %): 251 $[M]^+$ (80), 206 (45), 120 (50), 45 $[C(OH)Me]^+$ (100). Found, %: C 62.10; H 6.91; N 5.68. $C_{13}H_{17}NO_4$. Calculated, %: C 62.14; H 6.82; N 5.57.

5-(1-Hydroxyethyl)-3-phenyl-2-isoxazoline (6b) was obtained analogously from compound **2b** as a mixture of stereoisomers in 98% yield. Oil. IR spectrum, ν, cm^{-1}: 1610, 3420. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.26 and 1.16 (3H, d, *J* = 6.8, CH_3); 2.62 (1H, br. s, OH); 3.16 (1H, dd, J_{gem} = 17.0, $J_{4,5}$ = 8.0, H-4 isox); 3.36 (1H, dd, J_{gem} = 17.0, $J_{4,5}$ = 10.5, H-4 isox); 3.75 (1H, m, C<u>H</u>-OH); 4.56 (1H, ddd, $J_{5,4}$ = 8.0, $J_{5,4}$ = 10.5, $J_{5,1'}$ = 5.5, H-5 isox); 7.37 (3H, m, C_6H_5); 7.62 (2H, m, C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 191 $[M]^+$, 146 (75), 77 $[C_6H_5]^+$ (45), 45 $[C(OH)Me]^+$ (100). Found: C 69.10; H 6.91; N 7.28. $C_{11}H_{13}NO_2$. Calculated, %: C 69.09; H 6.85; N 7.32.

Reactions of Isoxazolines 1b, 2a-c with Molybdenum Hexacarbonyl. Water (1 mmol) and molybdenum hexacarbonyl (0.5 mmol) were added to a solution of an isoxazoline (1.0 mmol) in absolute acetonitrile (20 ml). The mixture was heated to the boiling point of the solvent (at which point vigorous evolution of nitrogen dioxide was observed), boiling was continued for 20 min, monitored by TLC. The reaction

mass was diluted with a 1:1 mixture of hexane and ether, filtered through celite 545, and the filtrate was evaporated. The residue was diluted with water and extracted with 1:1 hexane–ether. The solvent was removed in vacuum to give the corresponding isoxazols **3a-c** in yields of up to 90%.

3-(3-Ethoxycarbonylpropyl)isoxazole (3c). Yield 65%. IR spectrum, ν, cm^{-1}: 1615, 1730. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, t, *J* = 7.0, CH_3); 1.70 (2H, m, CH_2); 2.40 (4H, m, $C\underline{H}_2C{=}N$, $C\underline{H}_2COO$); 4.51 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.6 (1H, d, $J_{4,5}$ = 2, H-4 isox); 8.3 (1H, d, $J_{5,4}$ = 2, H-5 isox). Mass spectrum, *m/z* (I_{rel} , %): 183 $[M]^+$ (70), 110 $[M–EtO_2C]^+$ (100). Found, %: C 59.01; H 7.24; N 7.60. $C_9H_{13}NO_3$. Calculated, %: C 59.00; H 7.15; N 7.65.

Reaction of 5-Nitro-3-phenyl-2-isoxazoline (1b) with Sodium Methoxide. A suspension of sodium methoxide, prepared from sodium (90 mg) and methanol (0.15 ml), in THF (10 ml) was added to a solution of isoxazoline **1b** (0.2 g, 1.04 mmol) in dry THF (10 ml) at -35°C. After the sodium methoxide had been added the mixture was stirred for 15 min more. Then a solution of hydrochloric acid (0.5 ml) in THF (2 ml) was added and the reaction mixture was warmed to room temperature, and the precipitate was filtered off. The THF was evaporated, the residue was dissolved in chloroform and dried over $MgSO_4$. **3-Phenylisoxazole (3b)** (0.14 g, 0.94 mmol) in 90% yield was obtained after removal of the chloroform.

Reaction of 5-Acetyl-3-(3-ethoxycarbonylpropyl)-2-isoxazoline (2c) with Dimsyl Sodium. NaH (0.070 g, 3.2 mmol) was added to a solution of dry DMSO (0.220 mg, 3.2 mmol) in dry THF (5 ml) in a stream of argon, the mixture was heated to 70°C and stirred for 20 min until evolution of hydrogen ceased. A solution of the isoxazoline (0.20 g, 3.2 mmol) in dry THF (10 ml) was added to the suspension of dimsyl sodium in THF, the mixture was stirred for 1 h and then neutralized with HCl (0.3 ml, 37%). The residue was filtered off, washed with THF, and the solvent was evaporated.

Ethyl 4-cyanobutyrate 4c was isolated from the hexane extract as an oil [19]. Yield 45%. IR spectrum, ν, cm^{-1}: 1730, 2257. ^1H NMR spectrum, δ, ppm *(J*, Hz): 1.33 (3H, t, *J* = 7.0, CH_3); 1.86-2.06 (2H, m); 2.40-2.56 (4H, m, CH_2COO, CH_2CN); 4.50 (2H, q, $C\underline{H}_2CH_3$). Mass spectrum, *m/z*: 141 $[M]^+$.

Reaction of Compound 2c with Butyl Lithium. A solution of *n*-butyl lithium (1.5 mmol in hexane) was added to a solution of the isoxazoline (0.5 mmol) in dry THF (15 ml) at -45°C in an atmosphere of argon and stirring was continued for 2 h at the same temperature. The mixture was then allowed to warm to room temperature, diluted with water, the THF was evaporated off, and the aqueous phase was extracted with ether. The extract was dried with Na_2SO_4, and the solvent evaporated to give **ethyl 4-cyanobutyrate (4c)** in a yield of 25%.

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