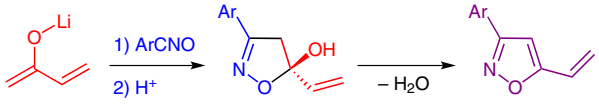
Synthesis A. Salomone et al. Paper

3-Aryl-5-vinyl-2-isoxazolines and 3-Aryl-5-vinylisoxazoles from Aryl Nitrile Oxides and Methyl Vinyl Ketone Lithium Enolate: Reaction Limits and Synthetic Utility Exploitation

Antonio Salomone[a,b]
Antonio Scilimati[a]
Paola Vitale*[a]

[a] Dipartimento di Farmacia-Scienze del Farmaco Università degli Studi di Bari 'A. Moro', Via E. Orabona 4, 70125 Bari, Italy
paola.vitale@uniba.it
[b] Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi (CINMPIS) Università degli Studi di Bari 'A. Moro', Via E. Orabona 4, 70125 Bari, Italy

Dedicated to Claudio Salomone, born November 24, 2014



Received: 22.09.2014
Accepted after revision: 17.11.2014
Published online: 18.12.2014
DOI: 10.1055/s-0034-1379640; Art ID: ss-2014-z0580-op

Abstract 3-Aryl-5-hydroxy-5-vinyl-2-isoxazolines were synthesized by reacting aryl nitrile oxides with the lithium enolate of methyl vinyl ketone (MVK) at –78 °C. Fair to good yields are obtained in the case of aryl nitrile oxides bearing electron-withdrawing groups on the aryl moiety or less bulky groups. Conversely, lower yields or no reaction was observed in the presence of hindered aryl nitrile oxides. Such a behavior was confirmed by ab initio calculations of the activation energies for three reactions. A number of 3-aryl-5-vinylisoxazoles were quantitatively obtained by dehydration/aromatization of the corresponding 5-hydroxy-2-isoxazolines under acidic conditions. The side-chain elaboration is reported as a synthetic utility of some vinylisoxazoles and vinylisoxazolines.

Key words 5-vinylisoxazolines, 5-vinylisoxazoles, aryl nitrile oxides, ketone lithium enolates, DFT/B3LYP ab initio calculations

Isoxazoles are useful and versatile building blocks in organic synthesis.[1] They are widely used for the construction of biological active compounds,[2] materials,[3] or more complex heteroaromatic rings.[4] In the presence of reducing agents[5] or bases,[6] they react to afford bifunctional compounds such as hydroxy ketones, enamino ketones,[6,7] unsaturated oximes, and bis-β-lactams.[8] Among the major versatile isoxazoles syntheses,[1] the ring construction can be achieved by reaction of nitrile oxides with alkenes, alkynes, or enolates.[9]

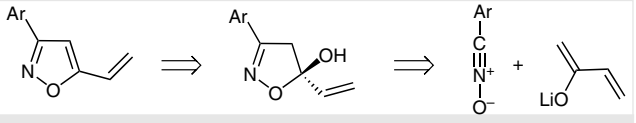
In the last decade, several substituted aryl-2-isoxazolines and arylisoxazoles have been prepared by the reaction of substituted enolates of different carbonyl compounds with functionalized nitrile oxides. Such a method could be suitable to build libraries of compounds, which could be prepared simply by varying the reacting ketone enolate and the nitrile oxides.

This two-step approach was successfully used for the synthesis of 3-arylisoxazoles, 5-alkyl-3-arylisoxazoles,[2c,f] 5-alkyl-3,4-diarylisoxazoles, and also for the synthesis of 3-phenyl-5-vinylisoxazole and 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline from the reaction of benzonitrile oxide with the lithium enolate of methyl vinyl ketone (MVK).[10]

Some synthetic approaches toward substituted vinylisoxazoles have been reported so far.[11] However, only in few cases they are related to the preparation of 3-substituted 5-vinylisoxazoles[12] and isoxazolines,[11b,13] despite their high synthetic versatility and utility in polymer syntheses.[12d,14]

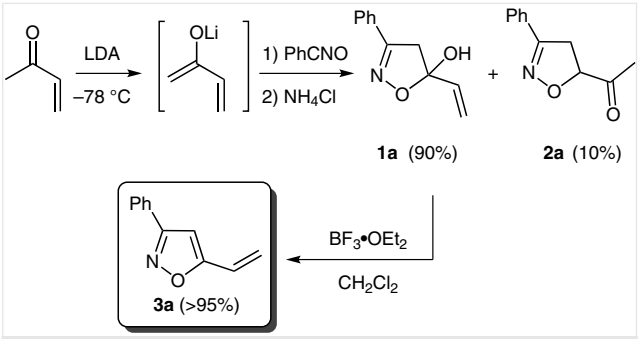
Herein, we applied our approach to the synthesis of different 5-vinylisoxazoles, to obtain more functionalized analogues and also to explore the limits of this method. Moreover, some synthetic potential of the vinyl function was exploited, as it is well known that it might be easily elaborated at both carbons,[12b,15] for the construction of additional heterocycles.

The addition of lithium enolates to aryl nitrile oxides to obtain a number of 3-aryl-5-vinylisoxazoles was studied. As for the synthesis of other substituted isoxazoles,[2c,f,8] 'the key step' of the procedure should be the formation of 3-aryl-5-hydroxy-5-vinyl-2-isoxazolines by the reaction of different aryl nitrile oxides and the lithium enolate of methyl vinyl ketone, at low temperature (–78 °C); then, the corresponding arylvinylisoxazoles might be easily prepared from the isoxazolines by a dehydration/aromatization reaction (Scheme 1).



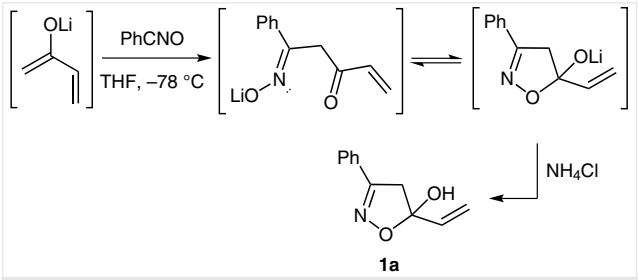
Scheme 1 Retrosynthetic analysis for the synthesis of 3-aryl-5-vinylisoxazoles and 3-aryl-5-hydroxy-5-vinyl-2-isoxazolines

We have previously reported the synthesis of 3-phenyl-5-vinylisoxazole (**3a**) and its precursor, the 5-hydroxy-3-phenyl-5-vinyl-2-isoxazoline (**1a**) (Scheme 2).[10] 5-Hydroxy-2-isoxazoline **1a** was obtained in optimal yields by reacting benzonitrile oxide and the lithium enolate of MVK, quantitatively generated at –78 °C in the presence of an excess of LDA as base, and by using a low ketone concentration to minimize a competitive reaction between aryl nitrile oxide and the vinyl moiety of neutral MVK, that gives the undesired 5-acetyl-2-isoxazoline **2a**.



Scheme 2 Synthesis of 3-phenyl-5-vinylisoxazole (**3a**)

The proposed mechanisms for the formation of **1a** likely involve two different stages (Scheme 3): the formation of the C–C bond by nucleophilic addition of the enolate to the electrophilic carbon of nitrile oxide, followed by the nucleophilic addition of the oxygen to the carbonyl intermediate, with the ring-closing to isoxazoline alcoholate.

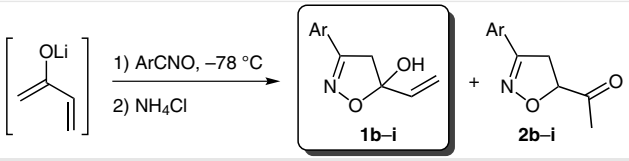


Scheme 3 Proposed reaction mechanism for the formation of **1a**

Despite the concerted mechanism of cycloaddition of nitrile oxides to a simple double bond that affords 5-acetyl derivatives **2**, such a different route should be differently influenced by electronic effects of the aryl substituents on the electrophilic carbon of the nitrile oxide. Indeed, to deepen the mechanism of the reaction and to explore the limits and potential of such a method, we studied the reaction of a variety of aryl nitrile oxides, bearing different groups with different electronic and steric effects and/or attached at different positions on the aryl moiety.

Moreover, since recent investigations allowed us to clarify that isoxazole core ring and the presence of furyl group are crucial determinants to obtain highly selective cyclooxygenase-1 (COX-1) inhibitors,[2c,f,16] the reaction of 5-chlorofuran-2-carbonitrile oxide was also investigated, toward the preparation of target pharmacologically active isoxazoles.

The aryl nitrile oxides were prepared according to previously reported procedures (see experimental section), and then reacted with the lithium enolate of MVK, obtained in the presence of LDA, at –78 °C. As expected, low yields of 5-acetyl-3-aryl-2-isoxazolines **2** were observed in all cases due to the low temperature and the excess of LDA used during the enolate formation, thus affording valuable percentages of 3-aryl-5-hydroxy-5-vinyl-2-isoxazolines **1b–i** depending on the features and the position of the aryl substituent (Scheme 4, Table 1).



Scheme 4 Synthesis of 3-aryl-5-hydroxy-5-vinyl-2-isoxazolines **1b–i**

Table 1 Synthesis of 3-Aryl-5-hydroxy-5-vinyl-2-isoxazolines **1b–i**[a]

Entry	Ar	Time(h)	Yield (%) **1**
1	Ph	1	**1a** (90)[b]
2	4-$O_2NC_6H_4$	1	**1b** (89)
3	3-$O_2NC_6H_4$	1	**1c** (84)
4	4-ClC_6H_4	1	**1d** (75)[c]
5	3-ClC_6H_4	1	**1e** (93)
6	2-ClC_6H_4	1	**1f** (44)[d]
7	5-chloro-2-furyl	2	**1g** (90)
8	2,4,6-$(MeO)_3C_6H_2$	3	**1h** (14)
9	3-chloro-2,4,6-trimethoxyphenyl	3	**1i** (9)
10	2,4,6-$Me_3C_6H_2$	3	**1j** (–)

[a] Unless otherwise indicated, only traces (<5%) of the acetyl derivatives **2** were detected by GC-MS of the reaction crude.
[b] Compound **2a** 10% was detected in the reaction crude by ^{1}H NMR analysis.
[c] Compound **2d** 20% was detected in the reaction crude by ^{1}H NMR analysis.
[d] Compound **2f** 12% was detected in the reaction crude by ^{1}H NMR analysis, together with 32% of 3,4-bis(2-chlorophenyl)-1,2,5-oxadiazole 2-oxide.

However, despite what we have previously observed for the reactions of substituted aromatic nitrile oxides with other enolates of ketones,[2c,f,8,17] in this case the reaction outcome seems to depend on the electronic effects of the substituents on the aryl group of the nitrile oxide. This is because the reaction proceeds smoothly and in high yields

in the presence of more reactive dipoles, in which the aryl was substituted with electron-withdrawing groups (EWGs) (Table 1, entries 1–6).

However, if the electronic effects were more important, the different behavior of 2,4,6-trimethoxybenzonitrile oxide (entry 8) and mesityl nitrile oxide (entry 10) in the reaction with the enolate of MVK could not be explained unless prevailing steric effects were considered. In fact, just comparing the known values of electronic effects (σ_o) for the methyl and methoxy group [$\sigma_{o(OMe)} = -0.39$; $\sigma_{o(Me)} = -0.17$],[18] the higher electron-donating effect of OMe should be more detrimental for the isoxazoline formation, with respect to the mesityl effect. No reaction was observed, indeed, by reacting the mesityl nitrile oxide with the lithium enolate of MVK (entry 10) at –78 °C, while isoxazolines **1h**,**i** were isolated in the same experimental conditions, although in very low yields (entries 8, 9). Hence, these results suggest a dependence of the reaction also on the steric effects of the substituent, as could be hypothesized by comparing the steric parameters (Es) for the two groups [$Es_{(Me)} = -1.24$; $Es_{(OMe)} = -0.55$ (for comparison, $Es_{(H)} = 0$)].[18]

A comparison of the behavior of the different chlorobenzonitrile oxides (entries 4, 5, and 6) could offer a clear further confirmation of such a hypothesis, since in the presence of similar electronic effects [see the corresponding Hammett σ(Cl) values: $\sigma_p = +0.24$; $\sigma_m = +0.37$; $\sigma_o = +0.20$],[18] high yields of 3-chlorophenyl-5-hydroxy-2-isoxazolines **1d**,**e** were obtained, while a lower yield of isoxazoline **1f** was observed from the reaction of the *ortho*-substituted nitrile oxide with the lithium enolate of MVK (Table 1).

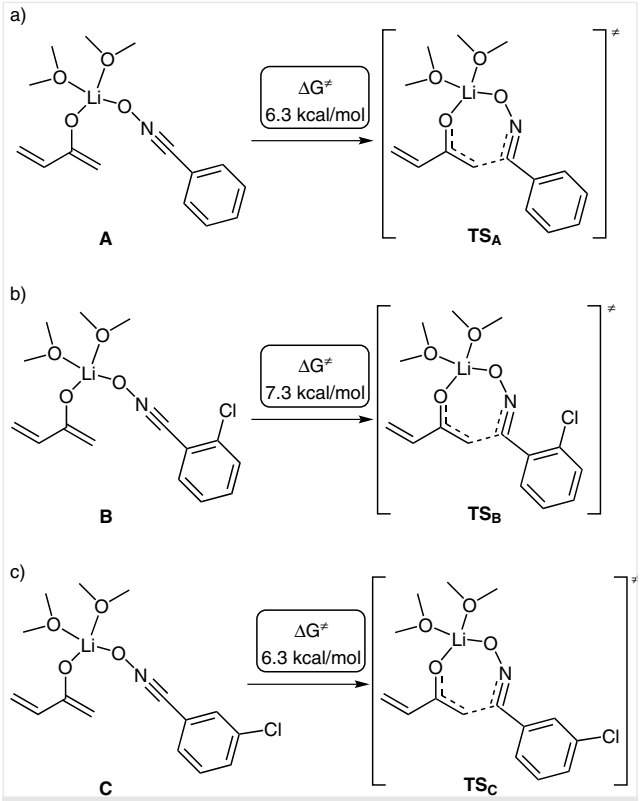
This hypothesis was also confirmed by ab initio calculations performed at DFT/B3LYP level of theory using the 6-31+G(d) basis set; in particular, the reactions of MVK lithium enolate with benzonitrile oxide, *o*-chlorobenzonitrile oxide, and *m*-chlorobenzonitrile oxide, at 195 K were modeled (Scheme 5, Table 2).

Table 2 Energies for Optimized Reactants and Transition States (TS) and Activation Free Energies at 195K (Scheme 5)

Reaction	Molecule	$E+G_{corr}$ (Hartree)[a]	Imaginary frequencies	$\Delta G^{\neq}$ (Kcal/mol)
a	**A**	–947, 681851	0	6.3
	$\mathbf{TS_A}$	–947, 671791	1	
b	**B**	–1407.285650	0	7.3
	$\mathbf{TS_B}$	–1407.273994	1	
c	**C**	–1407.287587	0	6.3
	$\mathbf{TS_C}$	–1407.277489	1	

[a] Sum of electronic and Gibbs free energy, including Zero-Point Energy correction.
[b] Activation free energy was calculated at 195 K.

Preliminary computational studies were carried out in order to investigate the possibility that a concerted cycloaddition between MVK enolate and aryl nitrile oxides could occur. Any attempt to locate a transition state (TS), on the reaction coordinate of a supposed cycloaddition, failed. We propose that the high bond polarization of both reactant should promote, through electrostatic forces, a preliminary formation of a di-solvated lithium complex (**A**, **B** and **C** in Scheme 5). Such a complex should not have the correct orbital orientation for a concerted cycloaddition, but, instead, for a stepwise ionic addition.[17] The fitting between the calculated activation barriers and experimental data strongly suggest, for the reaction of Li-MVK and aryl nitrile oxides, a two-step ionic mechanism rather than a concerted cycloaddition.

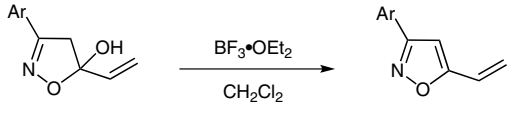


Scheme 5 Computed free energies for the ionic addition reactions of MVK enolate to aryl nitrile oxides at 195 K

The activation barriers,[19] calculated ab initio for each reaction, showed that the transition states energy is strongly affected by steric effects: in the presence of a chlorine on the *ortho*-position of the aryl nitrile oxide, the barrier height rises by 1.0 kcal/mol, at 195 K, with respect to the unsubstituted benzonitrile oxide (Table 2). Conversely, no difference in activation energy was found for the reaction of *m*-chlorobenzonitrile oxide, thus confirming the observed experimental results (Scheme 4, Table 1, entries 1, 5, 6).

The synthesis of 3-aryl-5-vinylisoxazoles **3b**–**g** was then accomplished in quantitative yields by performing the dehydration step under acidic conditions ($Et_2O{\cdot}BF_3/CH_2Cl_2$,

Scheme 6), because nucleophilic addition reactions to the vinyl group were observed if the dehydration reaction was performed in the presence of Na_2CO_3/ROH or RLi as the base.[10]

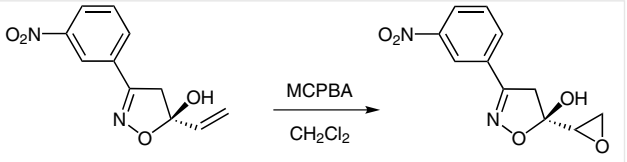


1b–g **3b–g** (44–93%)

Scheme 6 Synthesis of 3-aryl-5-vinylisoxazoles **3b–g** by aromatization of corresponding 2-isoxazolines **1b–g**

The reactivity of the vinyl moiety can be useful, for the preparation of differently functionalized isoxazolines and isoxazoles, toward the synthesis of new pharmacologically active compounds, for example, by the reaction of 5-vinyl-isoxazoles with oxidizing reagents (MCPBA) or other 1,3-dipoles.

To study the dependence of the reactivity of vinyl compounds on the aryl substituent features, if any, some reactions of the synthesized vinylisoxazoles and 5-vinyl-2-isoxazolines were investigated, aimed also at preparing more complex heterocycles to be used as intermediates or precursors of pharmacologically active compounds. Thus, the oxidation of the double bond with MCPBA was successfully carried out starting from isoxazoline **1c**, giving the corresponding diastereoisomeric epoxides **4** in good yields (Scheme 7), as already observed for unsubstituted derivatives **1a** and **3a**.

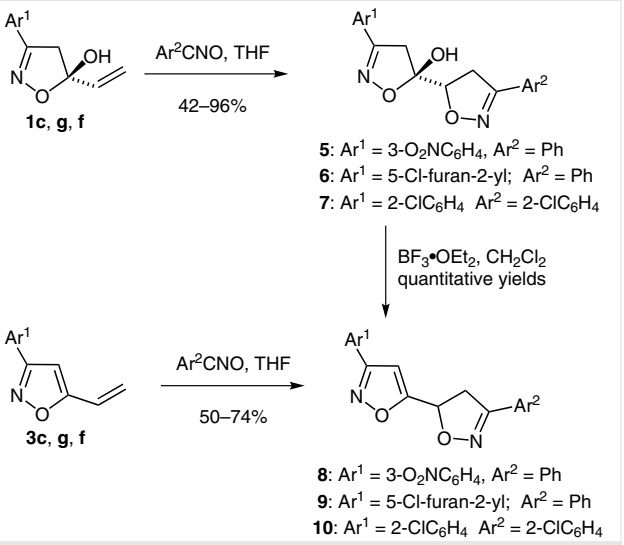


(±)-**1c** (±)-**4**
(60%, dr = 65:35)

Scheme 7 Epoxidation reaction of (±)-**1c** to 3-aryl-5-hydroxy-5-oxiranyl-2-isoxazoline (±)-**4**

Then, the 1,3-dipolar cycloaddition of some different nitrile oxides to the carbon–carbon double bond was exploited starting from isoxazolines **1c**, **1e**, and **1f**, and from the corresponding isoxazoles. Quantitative transformations were observed in both cases, as expected for a concerted mechanism, demonstrating the versatility of those molecules to be further transformed (Scheme 8). The results revealed also that the substituent features on aryl moiety are irrelevant for a further elaboration of the side chain.

In conclusion, a number of 3-aryl-5-hydroxy-5-vinyl-2-isoxazolines **1b–i** have been prepared in fair to good yields by reacting aryl nitrile oxides with lithium enolate of methyl vinyl ketone at –78 °C, followed by aromatization/dehydration to 3-aryl-5-vinylisoxazoles. Some limits of applicability of such synthetic method have been highlighted, because not hindered aryl nitrile oxides are required in order that the cycloaddition takes place, as observed by comparing the reactions of aryl nitrile oxides bearing different groups with different electronic effects and/or attached at different positions of the aryl moiety.



1c, g, f **3c, g, f**

Scheme 8 1,3-Dipolar cycloaddition between 5-vinyl-2-isoxazolines or 5-vinylisoxazoles and aryl nitrile oxides

Although a higher number of examples need to be explored, the trend observed at –78 °C seems to depend rather on the steric effects of the substituents, because high yields of 5-vinyl-2-isoxazolines were obtained in the presence of nitrile oxides bearing electron-withdrawing groups and from 5-chlorofurancarbonitrile oxide, while lower amounts of isoxazolines **1f**, **1h**,**i** were isolated from reaction of hindered aryl nitrile oxides (aryl = 2,4,6-trimethoxyphenyl, 2,4,6-trimethylphenyl, 3-chloro-2,4,6-trimethoxyphenyl, 2-chlorophenyl).

DFT calculations on the MVK enolate addition to aryl nitrile oxides (three examples), indicate that the transition state energy is strongly affected by steric effects and suggest that a stepwise ionic addition should be operative instead of a concerted cycloaddition: such a hypothesis is supported by the good fitting between calculated free energies and the product yields observed in the experiments.

Conversely, the substituent features on aryl moiety were demonstrated to be irrelevant for the reactivity of some substituted 5-vinyl-2-isoxazoline and 5-vinylisoxazoles towards further elaboration of the side chain.

The synthesis of epoxides or isoxazoline derivatives was performed through the vinyl group modification, toward novel building blocks or useful starting materials and/or intermediates in the synthesis of libraries of promising compounds as pharmacological tools for in vitro/ex vivo/in vivo

assays and in pre-clinical studies (i.e., gastrointestinal toxicity, neuroinflammation, pre-clinical in vivo diagnosis of human ovarian cancer by PET-CT imaging technique).[2b,e,20]

Melting points taken on Electrothermal apparatus are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ or acetone-d_6 at 25 °C on a Varian-Mercury 300 MHz spectrometer and chemical shifts are reported in parts per million (δ). Absolute values of the coupling constant are reported. IR spectra were recorded on a PerkinElmer 681 spectrometer. GC analyses were performed by using a HP1 column (methyl siloxane; 30 m × 0.32 mm × 0.25 µm film thickness) on a HP 6890 model, Series II. TLC was performed on silica gel sheets with fluorescent indicator, the spots on the TLC were observed under ultraviolet light or were visualized by I_2 vapour. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 µm and 230–400 ASTM. GC-MS analyses were performed on an HP 5995C model and microanalyses on a Elemental Analyzer 1106 Carlo Erba instrument. MS-ESI analyses were performed on Agilent 1100 LC/MSD trap system VL spectrometer.

Petroleum ether (PE) refres to the fraction boiling at 40–60 °C. THF from commercial source was purified by distillation (twice) from Na wire under N_2. Standardized (2.5 M) *n*-BuLi in hexane was purchased from Aldrich Chemical Co. and titrated against *N*-pivaloyl-*o*-toluidine.[21] Methyl vinyl ketone was purified over molecular sieves (4 Å). Aryl nitrile oxides[22] were prepared from aldehydes through their conversion into the corresponding oximes and then into benzohydroximinoyl chlorides.[2f,8,17,23] After purification, these were finally converted into the nitrile oxides by treatment with Et_3N at 0 °C, followed by rapid vacuum filtration of $Et_3N{\cdot}HCl$ from the solution, that have to be used immediately to avoid the formation of nitrile oxides dimers.[22] All other chemicals and solvents were commercial grade further purified by distillation or crystallization prior to use.

Computational Methods

All geometry optimizations, transition structure searches, and frequency calculations were performed at DFT/B3LYP level of theory with the 6-31+G(d) basis set by using Firefly QC package,[24] which is partially based on the GAMESS (US)[25] source code. The reactants were taken as an optimized precomplex of the monomeric disolvated lithium enolate with a O-coordinated nitrile oxide molecule (Scheme 5). The solvent effect was taken in account by means of the microsolvation approach; in particular two molecules of Me_2O (as THF surrogate) were added to the coordination sphere of lithium of all reactants and transition states structures. Activation energies for the addition of MVK lithium enolate to benzonitrile oxide, *o*-chlorobenzonitrile oxide, and *m*-chlorobenzonitrile oxide (Scheme 5, Table 2), were calculated at DFT/B3LYP/6-31+G(d) level of theory (see Supporting Information).

3-Aryl-5-hydroxy-5-vinyl-2-isoxazolines 1b–i; General Procedure

A 2.25 M solution of *n*-BuLi in hexane (15.8 mL, 35.48 mmol) was dropwise added to *i*-Pr_2NH (5 mL, 35.48 mmol) in THF (30 mL) kept at 0 °C under N_2 atmosphere, using a N_2-flushed, three-necked flask equipped with a magnetic stirrer, N_2 inlet, and two dropping funnels. After stirring the mixture for 15 min, methyl vinyl ketone (0.3 mL, 3.548 mmol) in THF (8 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 1 h, then a solution of the aryl nitrile oxide (3.225 mmol) in THF (8 mL) was added. The mixture was stirred at –78 °C for the time indicated in Table 1 and then quenched by adding aq NH_4Cl (20 mL). The product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and then evaporated under vacuum. Column chromatography (silica gel, PE–EtOAc, 8:2) of the residue afforded the 3-aryl-5-hydroxy-5-vinyl-2-isoxazolines **1b–i** in 9–93% yields (Table 1). Partial dehydration/aromatization of isoxazolines **1b**, **1d**, **1f**, was observed during chromatography over silica gel, or in solution during longer NMR experiment acquisitions.

The experimental conditions were optimized to minimize the competitive reaction between aryl nitrile oxides and the vinyl moiety of neutral MVK, that gives the undesired 5-acetyl-2-isoxazolines **2**. In the reactions where low yields of isoxazolines were isolated (Table 1, entries 8, 9, 10), the unreacted stable nitrile oxides were recovered from the reaction crude together with MVK after quenching with aq NH_4Cl solution, while in the reaction of 2-chlorobenzonitrile oxide (entry 6), 32% of 3,4-bis(2-chlorophenyl)-1,2,5-oxadiazole 2-oxide[22] was isolated from the reaction crude, together with isoxazolines **1f** and **2f** (Table 1).

3-(4-Nitrophenyl)-5-vinyl-4,5-dihydroisoxazol-5-ol (1b)

Yield: 0.526 g (89%, 2.25 mmol); yellow solid; mp 136 °C (dec. 92 °C).

FT-IR (KBr): 3420, 2925, 1604, 1563, 1513, 1340, 1108, 849, 788, 752, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10–3.13 (br s, 1 H, OH, D_2O exch.), 3.17 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 3.33 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 5.19 (dd, $^2J_{H,H}$ = 1.1 Hz, $^3J_{H,H}$ = 10.7 Hz, 1 H, =CH_2), 5.46 (dd, $^2J_{H,H}$ = 1.1 Hz, $^3J_{H,H}$ = 17.3 Hz, 1 H, =CH_2), 6.00 (dd, $^3J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 17.3 Hz, 1 H, =CH), 7.73 (d, $^3J_{H,H}$ = 9.08 Hz, 2 H_{arom}), 8.10 (d, $^3J_{H,H}$ = 9.08 Hz, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.6, 106.1, 114.8, 122.3, 126.0, 134.6, 135.2, 147.2, 154.6.

GC-MS (70 eV): *m*/*z* (%) = 234 (M^+, 5), 217 (12), 216 (10), 189 (9), 162 (6), 143 (3), 131 (2), 115 (4), 102 (5), 89 (4), 76 (8), 55 (100).

Partial characterization of isoxazoline **1b** was due to the spontaneous dehydration/aromatization observed in solution or during its purification.

3-(3-Nitrophenyl)-5-vinyl-4,5-dihydroisoxazol-5-ol (1c)

Yield: 0.633 g (84%, 2.705 mmol); yellow solid; mp 94–96 °C (hexane).

FT-IR (KBr): 3318, 3093, 1595, 1513, 1349, 1237, 1127, 1106, 989, 948, 915, 875, 731 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.37 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 3.44 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 3.48–3.70 (br s, 1 H, OH, D_2O exch.), 5.42 (dd, $^2J_{H,H}$ = 0.6 Hz, $^3J_{H,H}$ = 10.7 Hz, 1 H, =CH_2), 5.69 (dd, $^2J_{H,H}$ = 0.6 Hz, $^3J_{H,H}$ = 17.3 Hz, 1 H, =CH_2), 6.17 (dd, $^3J_{H,H}$ = 10.7 Hz, $^3J_{H,H}$ = 17.3 Hz, 1 H, =CH), 7.57–7.63 (m, 1 H_{arom}), 8.02–8.07 (m, 1 H_{arom}), 8.23–8.27 (m, 1 H_{arom}), 8.40–8.42 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.9, 107.3, 118.5, 121.9, 125.1, 130.2, 131.3, 132.5, 136.0, 148.6, 156.1.

GC-MS (70 eV): *m*/*z* (%) = 234 (M^+, 9), 217 (24), 216 (24), 189 (18), 162 (13), 102 (9), 76 (12), 55 (100).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.46; H, 4.31; N, 11.97. Found: C, 56.66; H, 4.48; N, 11.82.

3-(4-Chlorophenyl)-5-hydroxy-5-vinyl-2-isoxazoline (1d)

Yield: 0.175 g (75%, 0.784 mmol); yellow solid; mp 77–79 °C (hexane).

FT-IR (KBr): 3372, 2927, 1598, 1496, 1416, 1405, 1357, 1239, 1093, 1014, 986, 941, 906, 853, 829 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29 (d, $^2J_{H,H}$ = 17.3 Hz, 1 H, CH_2), 3.36 (d, $^2J_{H,H}$ = 17.3 Hz, 1 H, CH_2), 3.45–3.55 (br s, 1 H, OH, D_2O exch.), 5.38 (dd, $^2J_{H,H}$ = 0.7 Hz, $^3J_{H,H}$ = 10.6 Hz, 1 H, =CH_2), 5.67 (dd, $^2J_{H,H}$ = 0.7 Hz, $^3J_{H,H}$ = 17.2 Hz, 1 H, =CH_2), 6.15 (dd, $^3J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 17.2 Hz, 1 H, =CH_2), 7.33–7.39 (m, 2 H_{arom}), 7.53–7.60 (m, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.2, 99.6, 106.8, 118.0, 121.3, 122.4, 128.2, 129.2, 136.2, 136.5, 156.9.

GC-MS (70 eV): *m*/*z* (%) = 223 (M^+, 41), 222 (28), 208 (18), 207 (24), 206 (50), 205 (48), 195 (10), 180 (23), 179 (13), 178 (50), 177 (13), 153 (34), 152 (13), 151 (74), 150 (16), 139 (12), 138 (10), 137 (10), 125 (10), 111 (30), 102 (17), 75 (29), 55 (100).

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 59.09; H, 5.02; N, 6.27.

3-(3-Chlorophenyl)-5-hydroxy-5-vinyl-2-isoxazoline (1e)

Yield: 0.550 g (93%, 2.47 mmol); white crystals; mp 73–74 °C (hexane).

FT-IR (KBr): 3375, 2927, 1596, 1562, 1430, 1360, 1343, 1238, 1105, 985, 910, 861, 787, 752, 684, 484 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 3.35 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 3.70–3.95 (br s, 1 H, OH, D_2O exch.), 5.37 (dd, $^2J_{H,H}$ = 0.8 Hz, $^3J_{H,H}$ = 10.6 Hz, 1 H, =CH_2), 5.66 (dd, $^2J_{H,H}$ = 0.8 Hz, $^3J_{H,H}$ = 17.2 Hz, 1 H, =CH_2), 6.14 (dd, $^3J_{H,H}$ = 17.2 Hz, $^3J_{H,H}$ = 10.6 Hz, 1 H, =CH), 7.30–7.40 (m, 2 H_{arom}), 7.49–7.53 (m, 1 H_{arom}), 7.60–7.62 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.2, 106.7, 118.2, 125.1, 127.0, 130.3, 130.6, 131.2, 135.0, 136.2, 156.7.

GC-MS (70 eV): *m*/*z* (%) = 223 (M^+, 22), 208 (12), 207 (19), 206 (33), 205 (40), 180 (18), 179 (11), 178 (44), 177 (16), 153 (15), 152 (7), 151 (35), 150 (8), 137 (11), 113 (10), 111 (26), 102 (11), 75 (24), 55 (100).

Anal. Calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.76; H, 4.55; N, 6.11.

3-(2-Chlorophenyl)-5-hydroxy-5-vinyl-2-isoxazoline (1f)

Partial characterization of isoxazoline **1f** was due to the spontaneous dehydration/aromatization observed in solution or during its purification; yield: 80 mg (44%, 0.359 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.00–3.10 (br s, 1 H, OH, D_2O exch.), 3.49 (d, $^2J_{H,H}$ = 17.7 Hz, 1 H, CH_2), 3.59 (d, $^2J_{H,H}$ = 17.7 Hz, 1 H, CH_2), 5.41 (d, $^3J_{H,H}$ = 10.6 Hz, 1 H, =CH_2), 5.70 (d, $^3J_{H,H}$ = 17.2 Hz, 1 H, =CH), 6.20 (dd, $^3J_{H,H}$ = 17.2 Hz, $^3J_{H,H}$ = 10.6 Hz, 1 H, =CH), 7.29–7.43 (m, 3 H_{arom}), 7.70–7.72 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.8, 106.9, 118.0, 127.3, 129.5, 129.9, 130.8, 130.9, 131.3, 136.4, 157.5.

GC-MS (70 eV): *m*/*z* (%) = 223 (M^+, 5), 222 (5), 208 (6), 207 (10), 206 (16), 205 (26), 188 (60), 180 (19), 178 (39), 177 (14), 170 (11), 153 (19), 152 (12), 151 (36), 150 (13), 139 (10), 138 (9), 137 (17), 123 (7), 111 (18), 102 (16), 90 (9), 75 (29), 55 (100).

3-(5-Chlorofuran-2-yl)-5-hydroxy-5-vinyl-2-isoxazoline (1g)

Yield: 0.215 g (90%, 1.009 mmol); yellow solid; mp 86–88 °C (EtOAc–hexane).

FT-IR (KBr): 3423, 3151, 3116, 3096, 1619, 1495, 1412, 1381, 1246, 1110, 1019, 987, 942, 883, 841, 790 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29 (s, 2 H), 3.35 (s, 1 H, OH, D_2O exch.), 5.39 (d, $^3J_{H,H}$ = 10.6 Hz, 1 H, CH_2), 5.67 (d, $^3J_{H,H}$ = 17.1 Hz, 1 H, CH_2), 6.13 (dd, $^3J_{H,H}$ = 17.1 Hz, $^3J_{H,H}$ = 10.6 Hz, 1 H, =CH), 6.27 (d, $^3J_{H,H}$ = 3.3 Hz, 1 H_{furyl}), 6.73 (d, $^3J_{H,H}$ = 3.3 Hz, 1 H_{furyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.9, 106.4, 108.9, 114.3, 118.4, 135.9, 139.4, 144.1, 149.2.

GC-MS (70 eV): *m*/*z* (%) = 213 (M^+, 22), 197 (12), 196 (14), 195 (23), 162 (11), 143 (6), 127 (10), 104 (11), 73 (11), 55 (100).

Anal. Calcd for $C_9H_8ClNO_3$: C, 50.60; H, 3.71; N, 6.56. Found: C, 50.91; H, 4.04; N, 6.57.

3-(2,4,6-Trimethoxyphenyl)-5-hydroxy-5-vinyl-2-isoxazoline (1h)

Yield: 24 mg (14%, 0.086 mmol); white solid; mp 103–105 °C (EtOAc–hexane).

FT-IR (KBr): 3189, 3014, 2941, 2839, 1730, 1607, 1497, 1454, 1329, 1234, 1206, 1157, 1123, 1063, 1036, 991, 944, 905, 845, 807 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.20 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 3.37 (d, $^2J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 3.70–3.90 (br s, 1 H, OH, D_2O exch.), 3.80 (s, 6 H), 3.82 (s, 3 H), 5.35 (dd, $^2J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 10.6 Hz, 1 H, CH_2), 5.67 (dd, $^2J_{H,H}$ = 1.0 Hz, $^3J_{H,H}$ = 17.2 Hz, 1 H, CH_2), 6.13 (s, 2 H), 6.17 (dd, $^3J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 17.2 Hz, 1 H, CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.9, 55.6, 56.2, 91.0, 100.4, 105.5, 117.5, 136.7, 153.9, 159.8, 162.7.

LC-MS (ESI+): *m*/*z* = 302 (100, $[M + Na]^+$).

GC-MS (70 eV): *m*/*z* (%) = 279 (M^+, 23), 261 (100), 248 (48), 232 (86), 218 (36), 206 (83), 193 (66), 176 (22), 168 (87), 149 (18), 136 (18), 121 (23), 109 (14), 69 (46), 55 (82).

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.12; H, 6.34; N, 5. 20.

3-(3-Chloro-2,4,6-trimethoxyphenyl)-5-hydroxy-5-vinyl-2-isoxazoline (1i)

Yield: 15 mg (9%, 0.048 mmol); white solid; mp 101 °C (dec.).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.10–3.40 (s, 1 H, OH, D_2O exch.), 3.23 (d, *J* = 17.6 Hz, 1 H), 3.34 (d, *J* = 17.6 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 3.93 (s, 3 H), 5.37 (d, $^3J_{H,H}$ = 10.6 Hz, 1 H, CH_2), 5.67 (d, $^3J_{H,H}$ = 17.2 Hz, 1 H, CH_2), 6.18 (dd, $^3J_{H,H}$ = 10.6 Hz, $^3J_{H,H}$ = 17.2 Hz, 1 H, CH), 6.34 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.6, 56.6, 60.6, 62.5, 92.8, 105.9, 107.2, 117.6, 136.6, 153.3, 156.4, 157.7, 157.8.

GC-MS (70 eV): *m*/*z* (%) = 313 (M^+, 18), 295 (75), 282 (84), 266 (76), 252 (27), 240 (58), 227 (61), 202 (72), 55 (100).

LC-MS (ESI+): *m*/*z* = 336 (100, $[M + Na]^+$).

Anal. Calcd for $C_{14}H_{16}ClNO_5$: C, 53.60; H, 5.14; N, 4.46; Found: C, 53.62; H, 5.24; N, 4.46.

3-Aryl-5-vinylisoxazoles 3b–g; General Procedure

To a solution of isoxazoline **1b**–**g** (3.862 g, 20.43 mmol) in anhydrous CH_2Cl_2 (100 mL) at r.t. was added $Et_2O{\cdot}BF_3$ (2.6 mL, 20.43 mmol). The reaction mixture was stirred for 1 h and then quenched with H_2O (15 mL). The products were extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and then evaporated under vacuum. The reaction afforded crude isoxazoles **3b**–**g** in quantitative yields. The products were isolated by silica gel column and then purified by crystallization in 44–93% yields as reported in Scheme 6.

3-(4-Nitrophenyl)-5-vinylisoxazole (3b)

Yield: 0.252 g (52%, 1.17 mmol); yellow solid; mp 137–139 °C (MeOH).

FT-IR (KBr): 3090, 2922, 1605, 1563, 1526, 1435, 1351, 1110, 990, 932, 861, 852, 807, 758, 697 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 5.64 (d, $^3J_{H,H}$ = 11.4 Hz, 1 H, CH_2), 6.09 (d, $^3J_{H,H}$ = 17.8 Hz, 1 H, CH_2), 6.58 (s, 1 H), 6.67 (dd, $^3J_{H,H}$ = 11.4, 17.8 Hz, 1 H, CH), 7.90–8.00 (m, 2 H_{arom}), 8.25–8.33 (m, 2 H_{arom}).

^{13}C NMR (75 MHz, acetone-d_6): δ = 99.6, 121.8, 122.2, 124.4, 127.8, 135.3, 148.9, 161.0, 170.0.

GC-MS (70 eV): *m*/*z* (%) = 216 (M^+, 100), 189 (71), 188 (41), 170 (8), 162 (9), 143 (26), 142 (13), 115 (20), 89 (8), 76 (12), 75 (9), 55 (40), 50 (7).

Anal. Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.15; H, 3.87; N, 12.62.

3-(3-Nitrophenyl)-5-vinylisoxazole (3c)

Yield: 0.303 g (52%, 1.403 mmol); yellow solid; mp 125–127 °C (MeOH).

FT-IR (KBr): 3126, 3101, 2920, 2846, 1622, 1595, 1532, 1497, 1463, 1349, 1075, 975, 930, 906, 804, 744, 686 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 5.69 ($^3J_{H,H}$ = 11.3 Hz, 1 H, CH_2), 6.12 (d, $^3J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 6.83 (dd, $^3J_{H,H}$ = 11.3, 17.6 Hz, 1 H, CH), 7.17 (s, 1 H), 7.80–7.85 (m, 1 H_{arom}), 8.29–8.37 (m, 2 H_{arom}), 8.66–8.67 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, acetone-d_6): δ = 100.1, 121.0, 121.4, 122.7, 124.8, 130.8, 131.0, 132.8, 149.0, 161.2, 169.9.

GC-MS (70 eV): *m*/*z* (%) = 216 (M^+, 100), 189 (71), 188 (37), 143 (20), 115 (22), 89 (7), 88 (7), 76 (18), 75 (10), 55 (79), 50 (11).

Anal. Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.35; H, 4.11; N, 12.95.

3-(4-Chlorophenyl)-5-vinylisoxazole (3d)

Yield: 0.119 g (74%, 0.580 mmol); yellow solid; mp 66–67 °C (MeOH).

FT-IR (KBr): 3099, 2925, 2853, 1603, 1557, 1507, 1454, 1429, 1385, 1277, 1109, 1096, 977, 927, 817, 511 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60 (dd, $^2J_{H,H}$ = 0.7 Hz, $^3J_{H,H}$ = 11.3 Hz, 1 H, CH_2), 6.07 (d, $^3J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 6.48 (s, 1 H), 6.65 (dd, $^3J_{H,H}$ = 11.3, 17.6 Hz, 1 H, CH), 7.40–7.44 (m, 2 H_{arom}), 7.71–7.76 (m, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 99.5, 121.2, 122.5, 127.7, 128.2, 129.4, 136.2, 161.9, 169.2.

GC-MS (70 eV): *m*/*z* (%) = 205 (M^+, 100), 180 (34), 179 (23), 178 (93), 177 (40), 170 (17), 153 (14), 152 (16), 151 (37), 150 (32), 137 (11), 123 (14), 115 (11), 113 (11), 111 (19), 102 (11), 75 (27), 55 (46), 50 (9).

Anal. Calcd for $C_{11}H_8ClNO$: C, 64.25; H, 3.92; N, 6.81. Found: C, 64.35; H, 4.10; N, 6.85.

3-(3-Chlorophenyl)-5-vinylisoxazole (3e)

Yield: 0.471 g (93%, 2.30 mmol); yellow solid; mp 57–58 °C (hexane).

FT-IR (KBr): 3128, 3102, 2924, 2852, 1578, 1560, 1458, 1378, 1281, 1085, 982, 925, 813, 785, 768, 698, 674 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.61 (dd, $^2J_{H,H}$ = 0.7 Hz, $^3J_{H,H}$ = 11.3 Hz, 1 H, CH_2), 6.07 (d, $^3J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 6.49 (s, 1 H), 6.65 (dd, $^3J_{H,H}$ = 11.3, 17.6 Hz, 1 H, CH), 7.35–7.44 (m, 2 H_{arom}), 7.64–7.70 (m, 1 H_{arom}), 7.78–7.81 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 99.6, 121.3, 122.5, 125.1, 127.1, 130.2, 130.4, 131.0, 135.1, 161.7, 169.3.

GC-MS (70 eV): *m*/*z* (%) = 205 (M^+, 97), 180 (32), 179 (22), 178 (100), 177 (40), 170 (15), 153 (10), 152 (8), 151 (30), 150 (17), 139 (7), 123 (11), 115 (9), 113 (10), 111 (23), 102 (6), 75 (22), 55 (40), 50 (7).

Anal. Calcd for $C_{11}H_8ClNO$: C, 64.25; H, 3.92; N, 6.81. Found: C, 64.51; H, 4.44; N, 6.42.

3-(2-Chlorophenyl)-5-vinylisoxazole (3f)

Yield: 0.073 g (44%, 0.358 mmol); yellow solid; mp 55 °C (dec.).

FT-IR (KBr): 3100, 2925, 2852, 1557, 1560, 1456, 1380, 1279, 1090, 980, 925, 814 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60 (d, $^3J_{H,H}$ = 11.4 Hz, 1 H, CH_2), 6.08 (d, $^3J_{H,H}$ = 17.6 Hz, 1 H, CH_2), 6.67 (s, 1 H), 6.67 (dd, $^3J_{H,H}$ = 11.4, 17.6 Hz, 1 H, CH), 7.32–7.54 (m, 3 H_{arom}), 7.72–7.75 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 103.1, 120.9, 122.6, 127.3, 128.5, 130.6, 131.1, 131.2, 133.1, 161.5, 168.3.

GC-MS (70 eV): *m*/*z* (%) = 205 (M^+, 84), 180 (38), 179 (26), 178 (100), 177 (43), 170 (28), 164 (6), 153 (15), 152 (16), 151 (39), 150 (31), 139 (9), 137 (12), 123 (19), 115 (17), 114 (10), 113 (7), 111 (16), 102 (10), 99 (6), 76 (10), 75 (30), 63 (12), 55 (43), 50 (10).

Anal. Calcd for $C_{11}H_8ClNO$: C, 64.25; H, 3.92; N, 6.81. Found: C, 64.18; H, 3.77; N, 6.40.

3-(5-Chlorofuran-2-yl)-5-vinylisoxazole (3g)

Yield: 0.159 g (81%, 0.817 mmol); yellow solid; mp 134 °C (dec.) (MeOH–hexane).

FT-IR (KBr): 3129, 2929, 1622, 1587, 1519, 1439, 1392, 1208, 1148, 1065, 1015, 981, 940, 893, 790 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.62 (d, $^3J_{H,H}$ = 11.3 Hz, 1 H, CH_2), 6.35 (d, $^3J_{H,H}$ = 17.8 Hz, 1 H, CH_2), 6.32 (d, $^3J_{H,H}$ = 3.3 Hz, 1 H_{furyl}), 6.45 (s, 1 H), 6.64 (dd, $^3J_{H,H}$ = 11.3, 17.8 Hz, 1 H, CH), 6.89 (d, $^3J_{H,H}$ = 3.3 Hz, 1 H_{furyl}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.6, 108.5, 112.0, 121.3, 122.0, 128.8, 154.2, 167.7, 168.7.

GC-MS (70 eV): *m*/*z* (%) = 195 (M^+, 100), 167 (7), 143 (10), 140 (8), 112 (12), 105 (11), 104 (40), 89 (12), 77 (19), 76 (12), 75 (12), 73 (11), 55 (86), 52 (11).

Anal. Calcd for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16. Found: C, 54.91; H, 3.04; N, 6.97.

5-Hydroxy-5-(oxiran-2-yl)-3-(3-nitrophenyl)-2-isoxazoline (4)

MCPBA (70%, 0.221 g, 0.872 mmol) was added to a solution of 3-(3-nitrophenyl)-5-vinyl-4,5-dihydroisoxazol-5-ol (**1c**; 102 mg, 0.453 mmol) in anhydrous CH_2Cl_2 (6 mL) contained in a round-bottom flask equipped with a magnetic stirrer. The reaction mixture was stirred overnight at r.t. before adding 10% aq K_2CO_3 (10 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and then the solvent was evaporated under reduced pressure. Column chromatography (silica gel, PE–EtOAc, 6:4) of the residue afforded **4** in 60% yield after crystallization (CH_2Cl_2–hexane); yield: 0.068 g (60%, 0.272 mmol). Two diastereoisomers: dr = 65:35 A/B (determined by HPLC); white crystals; mp 142 °C (dec. 120 °C) (CH_2Cl_2/hexane).

FT-IR (KBr): 3420, 3085, 2967, 2934, 1695, 1532, 1432, 1350, 1321, 1279, 1266, 1200, 1072, 937, 895, 810, 799, 753, 735, 678 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.84–2.98 (m, 2 H, A + B), 3.24–3.54 (m, 3 H, A + B), 4.17–4.81 (br s, 1 H, OH, D_2O exch.), 7.33–7.42 (m, 1 H, A or B), 7.53–7.63 (m, 1 H_{arom}, A + B), 7.92–8.06 (m, 1 H_{arom}, A + B), 8.21–8.27 (m, 1 H_{arom}, A + B), 8.32–8.39 (m, 1 H_{arom}, A + B).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.2 (A or B), 43.3 (A or B), 44.3 (A or B), 45.2 (A or B), 52.7 (A + B), 105.6 (A or B), 107.6 (A or B), 121.9, 125.0, 130.2, 131.0, 132.5, 148.6, 155.4 (A or B), 156.0 (A or B).

LC-MS (ESI–): m/z = 249 (100, [M – H]$^-$).

Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H,4.03; N, 11.20. Found: C, 52.60; H, 4.04; N, 11.42.

Reaction of 3-Aryl-5-hydroxy-5-vinyl-2-isoxazolines (or Their Corresponding Isoxazoles) with Aryl Nitrile Oxides; General Procedure

A solution of appropriate nitrile oxide (0.25 mmol) in anhydrous THF (1.5 mL) was added dropwise to a solution of 3-aryl 5-hydroxy-5-vinyl-2-isoxazoline **1** (58 mg, 0.25 mmol) (or isoxazoles **3**) in anhydrous THF (2 mL) contained in a round-bottomed flask equipped with a magnetic stirrer. The reaction mixture was stirred at r.t. overnight before adding sat. aq NH_4Cl (5 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and then the solvent was evaporated under reduced pressure. Column chromatography (silica gel, PE–EtOAc, 6:4) of the residue afforded the products **5**–**7** (or **8**–**10**) in good yields.

5-Hydroxy-3-(3-nitrophenyl)-5-(3-phenyl-2-isoxazolin-5-yl)-2-isoxazoline (5)

Mixture of two diastereoisomers; yield: 84 mg (96%; 0.238 mmol); yellow crystals; mp 110–160 °C (dec. 75 °C) (EtOAc–hexane).

FT-IR (KBr): 3365, 3084, 2930, 1600, 1531, 1447, 1350, 1251, 1101, 911, 762, 737, 692, 675 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.33–3.64 (m, 4 H, v), 4.6–5.0 (br s, 1 H, OH, D_2O exch.), 5.01–5.09 (m, 1 H, A + B), 7.32–7.46 (m, 3 H_{arom}), 7.50–7.66 (m, 3 H_{arom}), 7.95–7.99 (m, 1 H_{arom}), 8.17–8.21 (m, 1 H_{arom}), 8.32–8.33 (s, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.4 (A + B), 42.4 (A or B), 42.8 (A or B), 81.8 (A + B), 108.5 (A or B), 108.7 (A or B), 121.9, 125.2, 127.1, 128.7, 129.1, 130.1, 130.3, 131.0, 132.5, 148.6, 155.8, 157.1 (A or B), 157.4 (A or B).

LC-MS (ESI+): m/z = 376 (100, [M + Na]$^+$).

LC-MS (ESI–): m/z = 352 (100, [M – H]$^-$).

Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4,28; N, 11.89. Found: C, 61.52; H, 4.32; N, 11.63.

5-Hydroxy-3-(5-chlorofuran-2-yl)-5-(3-phenyl-2-isoxazolin-5-yl)-2-isoxazoline (6)

Yield: 68 mg (82%, 0.205 mmol); yellow crystals; mp 172–175 °C (CH_2Cl_2–hexane).

FT-IR (KBr): 3366, 3120, 3051, 2951, 1617, 1496, 1446, 1421, 1382, 1357, 1255, 1232, 1208, 1155, 1107, 1017, 941, 923, 888, 792, 759, 691 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.97–3.29 (m, 1 H, A + B), 3.40–3.72 (m, 3 H, A + B), 5.01–5.08 (m, 1 H, A + B), 6.40–6.60 (br s, 1 H, OH, D_2O exch., A + B), 6.48–6.54 (m, 1 H_{furyl}, A + B), 6.89–6.92 (m, 1 H_{furyl}, A + B), 7.42–7.48 (m, 3 H_{arom}, A + B), 7.70–7.76 (m, 2 H_{arom}, A + B).

^{13}C NMR (75 MHz, acetone-d_6): δ = 36.4 (A or B), 37.2 (A or B), 41.1 (A or B), 42.1 (A or B), 81.8 (A or B), 82.1 (A or B), 108.1 (A or B), 108.7 (A or B), 109.0, 114.7, 126.9, 128.9 (A or B), 129.8 (A or B), 129.9, 130.2, 138.2, 145.0, 148.1 (A or B), 148.3 (A or B), 156.6 (A or B), 157.0 (A or B).

LC-MS (ESI+): m/z = 355 (100, [M + Na]$^+$), 333 (27, [M + H]$^+$).

Anal. Calcd for $C_{16}H_{13}ClN_2O_4$: C, 57.75; H, 3.94; N, 8.42. Found: C, 57.34; H, 3.88; N, 8.52.

5-Hydroxy-3-(2-chlorophenyl)-5-[3-(2-chlorophenyl)isoxazolin-5-yl)-2-isoxazoline (7)

Mixture of diastereoisomers (A + B); yield: 0.063 g (42%, 0.169 mmol); yellow semi-solid.

FT-IR (KBr): 3348, 3065, 2929, 1609, 1592, 1522, 1477, 1434, 1350, 1265, 1212, 1129, 1081, 1039, 896, 855, 757, 723, 511 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.41–3.80 (m, 4 H, A + B), 4.77–4.96 (br s, 1 H, OH, D_2O exch., A + B), 5.00–5.10 (m, 1 H, A + B), 7.19–7.39 (m, 6 H_{arom}, A + B), 7.52–7.64 (m, 2 H_{arom}, A + B).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 39.6 (A or B), 39.7 (A or B), 45.1 (A or B), 45.4 (A or B), 82.3 (A or B), 82.5 (A or B), 108.1 (A or B), 108.3 (A or B), 130.7, 130.8, 130.9$_0$, 130.9$_3$, 130.9$_8$, 131.0$_6$, 131.3$_2$, 131.3$_6$, 131.4$_1$, 131.4$_3$, 132.9$_6$, 133.0$_1$, 133.0$_4$, 133.0$_6$, 157.0 (A or B); 157.1$_9$ (A or B), 157.2$_7$ (A or B), 157.3$_3$ (A or B).

LC-MS (ESI+): m/z = 399 (100, [M + Na]$^+$).

Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_3$: C, 57.31; H, 3.74; N, 7.43. Found: C, 57.34; H, 3.69; N, 7.37.

3-(5-Chlorofuran-2-yl)-5-(3-phenyl-2-isoxazolin-5-yl)isoxazole (8)

Yield: 0.189 g (74%, 0.604 mmol); yellow crystals; mp 127–129 °C (EtOH).

FT-IR (KBr): 3131, 3113, 2977, 2923, 1624, 1590, 1522, 1441, 1420, 1357, 1321 1211, 1150, 1078, 1018, 1022, 980, 937, 882, 793, 760, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (dd, $^3J_{H,H}$ = 6.7 Hz, $^2J_{H,H}$ = 16.7 Hz, 1 H, CH_2), 3.80 (dd, $^3J_{H,H}$ = 11.1 Hz, $^2J_{H,H}$ = 16.7 Hz, 1 H, CH_2), 5.86 (dd, $^3J_{H,H}$ = 11.1 Hz, $^3J_{H,H}$ = 6.7 Hz, 1 H, CH), 6.29 (d, $^3J_{H,H}$ = 3.6 Hz, 1 H_{furyl}), 6.60 (s, 1 H), 6.87 (d, $^3J_{H,H}$ = 3.6 Hz, 1 H_{furyl}), 7.37–7.47 (m, 3 H_{arom}), 7.65–7.71 (m, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.5, 74.3, 100.0, 108.8, 112.8, 127.2, 128.7, 129.1, 130.9, 138.9, 143.5, 154.3, 156.5, 170.9.

GC-MS (70 eV): m/z (%) = 314 (M$^+$, 100), 220 (4), 197 (20), 195 (54), 169 (10), 141 (19), 140 (13), 118 (6), 115 (8), 104 (15), 89 (10), 77 (28), 73 (8), 55 (23), 51 (10).

Anal. Calcd for $C_{16}H_{11}ClN_2O_3$: C, 61.06; H, 3.52; N, 8.9. Found: C, 61.47; H, 3.84; N, 8.92.

3-(3-Nitrophenyl)-5-(3-phenyl-2-isoxazolin-5-yl)isoxazole (9)

Yield: 0.260 g (56%, 0.778 mmol); yellow crystals; mp 110–112 °C (EtOH).

FT-IR (KBr): 3065, 2924, 2854, 1601, 1546, 1532, 1498, 1447, 1463, 1398, 1347, 1268, 1104, 1073, 919, 893, 867, 850, 801, 761, 742, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.69 (dd, $^3J_{H,H}$ = 6.6 Hz, $^2J_{H,H}$ = 16.8 Hz, 1 H, CH_2), 3.86 (dd, $^3J_{H,H}$ = 11.0 Hz, $^2J_{H,H}$ = 16.8 Hz, 1 H, CH_2), 5.93 (dd, $^3J_{H,H}$ = 11.0 Hz, $^3J_{H,H}$ = 6.6 Hz, 1 H, CH), 6.77 (s, 1 H), 7.40–7.49 (m, 3 H_{arom}), 7.63–7.74 (m, 3 H_{arom}), 8.13–8.17 (m, 1 H_{arom}), 8.28–8.33 (m, 1 H_{arom}), 8.61–8.63 (m, 1 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.6, 74.4, 100.6, 122.1, 125.0, 127.2, 128.6, 129.2, 130.4, 130.6, 131.0, 132.8, 148.8, 156.6, 161.0, 172.1.

GC-MS (70 eV): m/z (%) = 335 (M$^+$, 100), 305 (25), 259 (10), 258 (12), 230 (10), 189 (20), 143 (12), 119 (60), 115 (15), 103 (11), 91 (15), 77 (33), 76 (19), 55 (21), 51 (11).

Anal. Calcd for $C_{18}H_{13}N_3O_4$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.69; H, 4.20; N, 12.40.

3-(2-Chlorophenyl)-5-[3-(2-chlorophenyl)-4,5-dihydroisoxazol-5-yl]isoxazole (10)

Yield: 0.064 g (50%, 0.179 mmol); white powder; mp 51–52 °C (hexane–EtOAc).

FT-IR (KBr): 3173, 2941, 1943, 1822, 1637, 1600, 1578, 1566, 1474, 1455, 1430, 1400, 1348, 1332, 1251, 1235, 1176, 1150, 1073, 1044, 1019, 963, 948, 926, 898, 863, 809, 765, 729 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.30 (dd, $^3J_{H,H}$ = 6.9 Hz, $^2J_{H,H}$ = 17.2 Hz, 1 H, CH_2), 3.44 (dd, $^3J_{H,H}$ = 10.9 Hz, $^2J_{H,H}$ = 17.2 Hz, 1 H, CH_2), 5.39 (dd, $^3J_{H,H}$ = 10.9 Hz, $^3J_{H,H}$ = 6.9 Hz, 1 H, C*H*), 6.32 (s, 1 H), 6.76–6.95 (m, 6 H_{arom}), 7.12–7.19 (m, 2 H_{arom}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.6, 74.9, 104.1, 127.4, 128.1, 128.3, 130.7, 130.9, 131.0, 131.2, 131.3, 131.6, 133.2, 156.5, 161.4, 169.7.

GC-MS (70 eV): *m*/*z* (%) = 358 (M^+, 94), 330 (22), 328 (34), 293 (9), 265 (10), 207 (17), 205 (36), 180 (40), 179 (24), 178 (100), 177 (32), 170 (23), 153 (17), 153 (17), 152 (20), 151 (22), 150 (27), 139 (11), 137 (17), 128 (11), 127 (11), 125 (12), 123 (16), 115 (13), 113 (14), 111 (31), 102 (14), 90 (10), 89 (10), 75 (33), 55 (18).

Anal. Calcd for $C_{18}H_{11}Cl_2N_2O_2$: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.24; H, 3.44; N, 7.75.

Acknowledgment

This work was financially supported by the Università degli Studi di Bari 'A. Moro' (Italy). Thanks are due to Istituto di Chimica dei Composti OrganoMetallici (ICCOM-CNR, Bari) for NMR facilities. The authors would like to acknowledge Prof. Leonardo Di Nunno for his highly qualified outstanding contribution to develop novel synthetic strategy of isoxazoles. Thanks are due also to Dr. Elena Passafiume for her contribution to the synthesis of some novel compounds.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379640.

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