REGIO- AND DIASTEREOSELECTIVE 1,3-DIPOLAR CYCLOADDITION OF IMIDAZOLINE 3-OXIDES TO STYRENE

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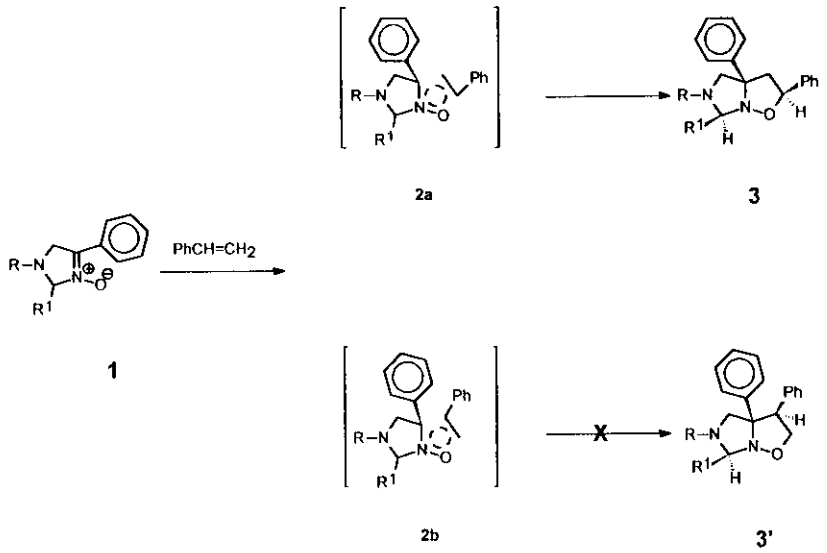
Abstract - Δ^3-Imidazoline 3-oxides (**1**) underwent regio- and diastereoselective cycloaddition with styrene to give perhydroimidazo[1,5-*b*]isoxazoles (**3**). Thermally induced retro cycloaddition of compounds (**3**) was demonstrated.

Diazoalkanes, alkyl and allyl azides, nitrile imines, nitrile ylids and nitrones are the commonly used 1,3-dipoles for the construction of a variety of five-membered heterocycles.[1]

Nitrones occupy a special place among the 1,3-dipoles because of their easy accessibility and the facility with which their adducts can be converted to other useful compounds.[2-4] A number of intramolecular 1,3-dipolar cycloadditions of alkenylnitrones were exploited in the synthesis of isoxazolidine incorporating structures some of which were converted to natural compounds.[5,6] Isoxazolidine-5-spiro derivatives obtained by the reaction of C,C-disubstituted nitrones and 3,4-dihydro-5-methyl-2*H*-pyrrole 1-oxide with methylenecyclopropanes were thermally rearranged to valuable perhydropyridone, indolizinone, and pyrrolo[1,2-*b*]quinolinone derivatives.[7] The synthesis of the potent antiviral agent carbovir was achieved by using as a key step the reaction of an oxazoline *N*-oxide derivative with cyclopentadiene.[8] Transition-metal catalysed asymmetric 1,3-dipolar cycloaddition reactions between alkenes and acyclic nitrones were reported.[9] Stereochemical aspects of 1,3-dipolar cycloaddition of cyclic[10] nitrones with 1,2-disubstituted alkenes and *C*-phenyl-*N*-methylnitrone with substituted styrenes were reported.[11]

Recently we have reported the results of the regio- and diastereoselective cycloaddition of imidazoline *N*-oxides with aryl isocyanates.[12-13] The fact that no examples of cycloaddition of imidazoline 3-oxides with alkenes have been reported encouraged us to check whether the factors controlling the stereochemistry in the reaction of imidazoline 3-oxides with aryl isocyanates will be important in the reaction of the same 3-oxides with styrene. We herein report the regio- and diastereoselective synthesis of a new class of perhydroimidazo[1,5-*b*]isoxazoles by cycloaddition of Δ^3-imidazoline 3-oxides with styrene and thermally induced retro cycloaddition reaction of compounds (**3**).



Scheme

Table1. Perhydroimidazo[1,5-*b*]isoxazoles (**3**).

entry	yield of **3** (%)	R	R^1	mp (°C) (solvent)
(**3a**)	49	4-$CH_3C_6H_4$	H	95-96.2[a]
(**3b**)	50	Ph	Ph	146[a]
(**3c**)	49	4-$CH_3C_6H_4$	Ph	156[b]
(**3d**)	40	Ph	3,4(OCH_2O)C_6H_3	138[b]
(**3e**)	50	4-BrC_6H_4	Ph	186-186.5[b]

[a]=hexane; [b]=ethanol

Attempts to react cyclic nitrones (**1**), readily prepared by methods which we have already reported,[14-16] with styrene as a solvent failed. Heating of styrene in the presence of nitrones (**1**) led to polymerization; thus it was impossible to isolate the product of cycloaddition. However, the reaction of nitrones (**1**) with styrene in refluxing toluene gave the corresponding imidazoisoxazoles (**3**) as the sole regioisomer. The

concurrent polymerization is one of the reasons for the low yields. Detailed analysis of the reaction mixture obtained from nitrone (**1c**) and styrene in a ratio indicated in the general procedure showed that there is some amount of a byproduct which is formed as a result of nitrone-oxaziridine isomerization. The structure of this product was proven to be the corresponding oxaziridinoimidazole by spectral means as well as converting it to nitrone (**1c**) by heating under vacuum.

The regiochemistry of the adduct was readily deduced to be those formed *via* transition state (**2a**) (Scheme) from the ^{1}H NMR spectra of the compounds.[17] In each case, there was a proton doublet of doublets approximately at δ 5.45 which corresponded to the C-2 in **3**. The alternative regioisomer is not expected to show a signal at this chemical-shift value.

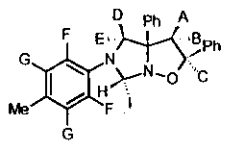


Figure. Configurational assignment of compound (**3a**).

Table 2. ^{1}H NMR Coupling Constants of the ABX System of Compounds (**3**).

δ ppm	C-2, C			C-3, A			C-3, B			C-4		C-6	
Hz	J_{BC}		J_{AC}	J_{AB}		J_{AC}	J_{AB}		J_{BC}				
		5.51			3.12			2.65		3.42	4.05	4.39	4.94
(3a)	10.00		6.00	12.00		6.00	12.00		10.00				
		5.46			3.14			2.65		4.20		6.00	
(3b)	8.84		6.85	12.60		7.00	12.52		8.95				
		5.45			3.14			2.63		4.16		5.93	
(3c)	8.96		6.62	12.50		6.59	12.55		9.26				
		5.43			3.12			2.65		4.21		5.85	
(3d)	9.00		6.83	12.59		6.82	12.50		8.82				
		5.45			3.16			2.64		4.15		5.94	
(3e)	8.71		6.75	12.68		6.84	12.59		8.84				

The stereochemical assignment for **3a** as the cis diastereomer was performed on the basis of ^{1}H NMR spectral data. The spectrum of the compound showed two doublet of doublets for the methylene protons at C-3 centered at 2.65 and 3.12 ppm.[11] The downfield resonance corresponds to the C-3H_A proton in a *cis* position with respect to phenyl substituents at C-2 and C-3a, because of the additive deshilding effects of two aromatic substituents on the same side of the isoxazolidine ring.[11] Furthermore C-2H_C proton

resonates as a doublet of doublets at δ 5.51 and the coupling constants are J_{AC} = 6 and J_{BC} = 10 Hz respectively. This is in good agreement with the fact that the dihedral angle C/B is close to zero (calculated by means of molecular models). We have also assumed that the downfield parts of the AB systems at C-4 and C-6 correspond to the protons *cis* to the phenyl at C-3a and nitrogens' lone pairs[7,11] indicated as D and H in the Figure. On the other hand if we assume that the ring fusion in compounds (**3**) is *trans* rather than *cis* the ^{1}H NMR signal corresponding to the AB part of the ABX system would appear as a complex multiplet instead of clearly defined two sets of doublet of doublets. In this case the chemical shifts of the protons at C-3 should be too close because each of them would be equally deshilded by the phenyls adjacent to them.

Irradiation of the downfield part of the AB system at C-3 (the proton at δ 3.12 ppm, indicated as A in the Figure) led to positive NOE for the protons B, C, D and negative NOE for proton E while irradiation of proton B led to positive NOE for A, C, E and I. This is clearly indicative that proton A is in *cis* relationship with D while B is in *cis* relationship with C and E . Furthermore, the irradiation of proton I led to positive NOE for protons H, F, E and Me and negative NOE for proton D. The irradiation of proton D led to positive NOE for A, E, H, F, G and Me and negative for I. When E was irradiated positive NOE for D, C and B and negative for A was observed. The NOE experiments permit a tentative *cis* configurational assignment for compound (**3a**).

The preferential formation of *cis* cycloadducts in the reaction of *C*-phenyl-*N*-methylnitrone with styrenes was reported.[11] Although, in this work the adduct was assumed to be the product of *endo* attack of the dipolarophile to the minor *cis*- isomer of the nitrone, in our case there is not a possibility for such an isomerization consequently the *cis* **3a** should be the result of an *exo* approach of the styrene. It was reported that in the reaction of cyclic nitrones with styrene the influence of steric factors dominates the stereochemichal results of the cycloaddition process and that *endo* transition state suffers from steric compressions associated with the interaction of the phenyl group in the incoming dipolarophile and the corresponding ring hydrogens of the nitrone.[11]

The steric hindrance of the aryl group at C-2 on the nitrone (**1**) seems to be responsible for the approach of the 2π fragment from the opposite side. Analogous effect of the aryl groups in the reaction of cyclic nitrones (**1**) with isocyanates gives rise to the formation of the *cis* adducts.[12-13] The analysis of chemical shifts and the coupling constants of the ABX patterns of compounds (**3b-e**) showed an resemblance with **3a**. Thus we assume that the orientation of the phenyl groups at C-2 and C-3a in compounds (**3b-e**) is the same as in **3a**. If the mentioned compounds are formed as a result of an *exo* attack of the dipolarophile from the side opposite of the aryl at C-2 the phenyls in the imidazoisoxazole system must be all *cis* oriented. NOE experiments performed for **3c** confirmed this assumption. The irradiation of the

resonance of C-6 proton results in a positive enhancement of the signals for C-2 proton and ortho protons of the aryl on C-5. Likewise, when C-2 proton was irradiated, the signal for C-6 was enhanced, together with the signals of C-3H_A and C-3H_B. This results support the assigned all *cis* phenyl oriented imidazoisoxazoles (**3b-e**).

Furthermore we achieved retro cycloaddition reactions by heating **3** in the condensed phase under vacuum (see Table 3). Thermal treatment of compounds (**3a-e**) led exclusively to the formation of compounds (**1**).

Table 3. Retro Cycloaddition of Compounds (**3**).

Starting material	React. temp.[a]	React. time[b]	Product[c]	Yield (%)	Starting material	React. temp.	React. time	Product (%)	Yield
(**3a**)	165	15	(**1a**)	85	(**3d**)	160	15	(**1d**)	68
(**3b**)	165	20	(**1b**)	72	(**3e**)	160	15	(**1e**)	67
(**3c**)	160	15	(**1c**)	91					

[a] Reaction temperatures are in °C; [b]Reaction time in min; [c]Compounds (**3a-e**) were thermolized at $1.3x10^{-3}$ mm Hg.

EXPERIMENTAL

Melting points were taken on a Electrothermal Digital melting point apparatus an are uncorrected. IR spectra were recorded on a Mattson 1000 FTIR. ^{1}H NMR spectra were recorded on a Varian 200 MHz spectrometer. Chemical shifts are reported in δ units, using TMS as an internal standart. All spectra were taken in deuteriochloroform. MS spectra were routinely recorded at 70 eV by electron impact on a Hewlett Packard GC-MS. Elemental analyses were performed in the laboratories of TUBITAK. Analytical TLC was done on Kiselgel 60 F_{254} (E. Merck). Visualisation was effected with UV light. Freshly prepared imidazoline 3-oxides were used after recrystallization from either ethanol or acetone.

Preparation of perhydroimidazo[1,5-*b*]isoxazoles (3). General Procedure;- To a solution of imidazoline 3-oxide (**1**) (4 mmol) in toluene (20 mL) styrene (5 mL, 44 mmol) was added. The mixture was refluxed at stirring for 72 h. The solvent and the excess of styrene were removed under vacuum. The residue was washed twice with warm petroleum ether or hexane (2 x 15 mL) and dissolved

at heating under condenser in hexane (25 mL) or ethanol (25 mL). The solution was left to cool at rt and after 3-4 h the formed white solid was filtered. TLC controls showed the presence of **3** and unreacted nitrone. Further purification was performed by recrystallization from solvents such as ethanol or hexane.

2,3a-Diphenyl-5-(p-tolyl)-perhydroimidazo[1,5-*b*]isoxazole (3a). The compound was obtained according to the general procedure in a 49% yield and recrystallized from hexane. mp 95-96.2°C. IR (KBr); the absorption at 1585 cm^{-1} corresponding to $\nu_{C=N}$ is absent. ^1H NMR ($CDCl_3$) δ 2.26(3H, s), 2.65(1H, dd, J=12.00, 10.00 Hz), 3.12(1H, dd, J=12.00, 6.00 Hz), 3.42(1H, d, J=9.00 Hz), 4.05(1H, d, J=9.00 Hz), 4.39(1H, d, J=10.00 Hz), 4.94(1H, d, J=10.00 Hz), 5.51(1H, dd, J=10.00, 6.00 Hz), 6.59(2H, d, J=8.50 Hz), 7.07(2H, d, J=8.50 Hz), 7.20-7.80(10H, m); MS m/z 236 (M^+-$PhCHCH_2O$). Anal. Calcd for $C_{24}H_{24}N_2O$: C, 80.87; H, 6.79; N, 7.86. Found: C, 80.50; H, 6.60; N, 7.70

Imidazoisoxazole (3b). Yield 50%. Recrystallized from hexane ; mp 146°C. IR (KBr); the absorption at 1585 cm^{-1} corresponding to $\nu_{C=N}$ is absent. ^1H NMR ($CDCl_3$) δ 2.65(1H, dd, J=12.52, 8.95 Hz), 3.14(1H, dd, J=12.60, 7.00 Hz), 4.20(2H, s), 5.46(1H, dd, J=8.84, 6.85 Hz), 6.00(1H, s), 6.54-6.79(5H, m), 7.15-7.60(15H, m); MS m/z 296 (M^+ of the corresponding 1,2,4-triarylimidazole). Anal. Calcd for $C_{29}H_{26}N_2O$: C, 83.22; H, 6.26; N, 6.69. Found: C, 82.86; H, 6.64; N, 6.50.

Oxaziridino[2,3-*c*]imidazole related to nitrone (1c) and Imidazoisoxazole (3c). To a solution of nitrone (**1c**) (1.2 g, 3.65 mmol) in toluene (20 mL) styrene (5 mL, 44 mmol) was added and the reaction mixture stirred at reflux for 72 h. The solvent and the excess of styrene were removed under vacuum. The residue was extracted with warm hexane (2 x 15 mL). The combined extracts were concentrated and left to crystallize. The solid obtained (120 mg, yield 10%) melts at 137°C. The IR (KBr) shows that the absorption at 1585 due to $\nu_{C=N}$ is absent. ^1H NMR ($CDCl_3$) δ 2.30(3H, s), 4.11(2H, AB system, J_{AB}=18.39 Hz), 6.44(1H, s), 7.10-7.70(14H, m). MS m/z 328 (M^+). 30 mg of the compound was heated in a sample vial at 137°C for 30 min in a vacuum oven under $1.3x10^{-3}$ mm Hg. After cooling the compound was triturated with ethanol. The compound was filtered and dried on air to give almost quantitatively nitrone (**1c**). The compound was identical in all respects with nitrone (**1c**). The other part of the residue was dissolved in hexane at heating and filtered. The white solid formed (1.22 g) was refluxed in hexane (100 mL) under condenser and filtered. The insoluble part (0.305 g, 25%) was nitrone (**1c**). The filtrate was concentrated and left to crystallize. The compound (**3c**) was collected by filtration. Yield 0.77 g, 49%. Mp of the needle shaped crystals is 156°C (from ethanol). IR (KBr); the absorption at 1585 cm^{-1} corresponding to $\nu_{C=N}$ is absent. ^1H NMR ($CDCl_3$) δ 2.23(3H, s), 2.63(1H, dd, J=12.55, 9.26 Hz), 3.14(1H, dd, J=12.50, 6.59 Hz), 4.16(2H, AB system, J_{AB}=10.00 Hz), 5.45(1H, dd, J=8.96, 6.62 Hz), 5.93(1H, s), 6.72(2H, d, J=8.37 Hz), 7.09(2H, d, J=8.30 Hz), 7.15-7.60(15H, m); MS

m/z 328 (M^+ of the corresponding 1,2,4-triarylimidazoline 3-oxide). Anal. Calcd for $C_{30}H_{28}N_2O$: C, 83.30; H, 6.52; N, 6.47. Found: C, 83.10; H, 6.84; N, 6.16.

Imidazoisoxazole (3d). Yield 40%. Recrystallized from ethanol; mp 138°C. IR (KBr); the absorption at 1585 cm^{-1} corresponding to $\nu_{C=N}$ is absent. ^1H NMR ($CDCl_3$) δ 2.65(1H, dd, J=12.50, 8.82 Hz), 3.12(1H, dd, J=12.59, 6.82 Hz), 4.21(2H, s), 5.43(1H, dd, J=9.00, 6.83 Hz), 5.85(1H, s), 5.88(2H, s), 6.60-6.80(6H, m), 7.20-7.60(15H, m); MS m/z 340 (M^+ of the corresponding 1,2,4-triarylimidazole). Anal. Calcd for $C_{30}H_{26}N_2O_3$: C, 77.90; H, 5.67; N, 6.05. Found: C, 77.60; H, 5.90; N, 5.90.

Imidazoisoxazole (3e). Yield 50%. Recrystallized from ethanol; mp 186-186.5°C. IR (KBr); the absorption at 1585 cm^{-1} corresponding to $\nu_{C=N}$ is absent. ^1H NMR ($CDCl_3$) δ 2.64(1H, dd, J=12.59, 8.84 Hz), 3.16(1H, dd, J=12.68, 6.84 Hz), 4.15(2H, AB system, J_{AB}=10.00 Hz), 5.45(1H, dd, J=8.71, 6.75 Hz), 5.94(1H, s), 6.47(2H, d, J=8.82 Hz), 7.10-7.40(17H, m); MS m/z 374 (M^+ of the corresponding 1,2,4-triarylimidazole). Anal. Calcd for $C_{29}H_{25}N_2OBr$: C, 70.02; H, 5.07; N, 5.63. Found: C, 69.70; H, 5.49; N, 5.50.

Retro cycloaddition of compounds (3). General Procedure;- Compound (3) (0.1 mmol) was placed in a glass sample vial and heated in a vacuum oven at 160°C for 20 min under $1.3x10^{-3}$ mm Hg, and left to cool at rt. The obtained **1** solidified. The compound was triturated with 0.5 mL of ethanol and collected by filtration. The identity of the obtained compounds with the authentic samples was determined comparing their mp as well as their IR spectra (see Table 2 for experimental details).

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