Tetrahedron Vol. 47, No. 24, pp. 4121-4132, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

AN EFFICIENT C_2-HOMOLOGATION OF AROMATIC ALDEHYDES VIA 5-HYDROXYISOXAZOLIDINES

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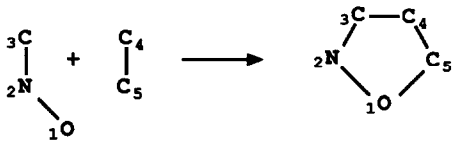
(*Received in UK* 4 *February* 1991)

Abstract. The reaction of lithium enolate of acetaldehyde (generated by the known cycloreversion of THF in the presence of *n*-BuLi) with a number of aryl N-phenylnitrones affords 2-phenyl-3-aryl-5-hydroxyisoxazolidines (trans + cis) in high yields. A low conversion or no reaction at all were instead observed with some N-alkylnitrones (methyl and *t*-butyl, respectively). Base (or acid) induced decomposition of 5-hydroxyisoxazolidines allows cinnamaldehydes to be obtained in high yields. Thus the combination of the synthesis and decomposition of 5-hydroxyisoxazolidines provides a new efficient way for the C_2-homologation of aromatic aldehydes.

Isoxazolidines, apart from some physiological activity, are interesting compounds from a synthetic point of view as they can behave as precursors of other functionalities and/or compounds by a number of ring cleavage reactions,[1] some of which are also common to the related isoxazolines (e.g., hydrogenolysis to γ-aminoalcohols).[2]

Isoxazolidines can be synthesized by a variety of different approaches,[1a] among which those involving both C_3-C_4 and C_5-O bond formation are most common (FIGURE 1). One such approach is the reaction of a nitrone and a vinyl derivative (3+2 cycloaddition). The regio- and stereo-chemical implications of this reaction have been the object of numerous studies.[1]

FIGURE 1



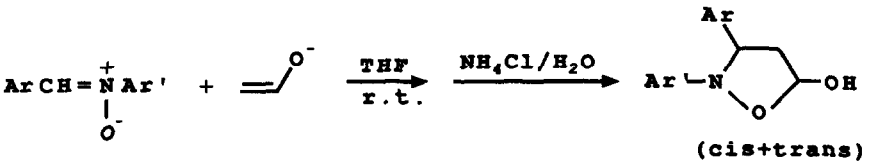
Since the closure of other pentatomic heterocycles (triazolines, isoxazolines) has already been accomplished with satisfactory results by us[3] using the appropriate 1,3-dipoles (azides and nitrile oxides, respectively) with the lithium enolate of acetaldehyde (quantitatively generated by the known cycloreversion of THF in the presence of *n*-BuLi)[4] instead of the usual vinyl derivatives, it seemed interesting to apply the same approach to the synthesis of isoxazolidines. Moreover this would offer the opportunity of testing the behavior of the cited enolate ion also towards nitrones (class II 1,3-dipoles)[5] rather than the previously studied azides and nitrile oxides (both of class I, in the same classification). Thus we synthesized a number of nitrones from arylaldehydes by the known reaction[6] with hydroxylamines (phenylhydroxylamine or, in one case, methylhydroxylamine) and subjected them to a reaction in THF with the lithium enolate of acetaldehyde. In addition to the above nitrones, two further commercially available nitrones (phenyl N-*t*-butyl and p-nitrophenyl N-*t*-butylnitrone) were also tested.

The reactions were performed in all cases at room temperature and quenched (NH_4Cl/H_2O) shortly after the complete disappearance of the nitrone (TLC), giving, except for N-alkylnitrones that are recovered largely (N-CH_3) or completely(N-*t*-Bu) unchanged, good yields of 5-hydroxyisoxazolidines (TABLE 1).

In all cases both stereoisomers (trans and cis) were obtained, the former being preferred in accordance with their presumably greater thermodynamic stability. This is at variance, however, with the stereochemical result observed, e.g., in the synthesis of the related 5-O-acetyl-2,3-diphenylisoxazolidine carried out by [3+2] cycloaddition of diphenylnitrone to vinylacetate.[7] In this case only the cis isomer was isolated, and this result has been reproduced in our laboratory. On the other hand, cis 5-O-acetyl-2,3-diphenylisoxazolidine obtained as above, subjected to hydrolysis with K_2CO_3/MeOH, gave 5-hydroxy-2,3-diphenylisoxazolidine, as a mixture of trans- and cis-isomers, apparently in the same ratio as from the reaction of nitrone with the enolate ion of acetaldehyde. Further, such a mixture, when re-acetylated(Ac_2O/Py), gave again the 5-O-acetylisoxazolidine, in this case as a mixture of both cis- and trans-isomers in a ratio apparently unchanged with respect to the starting 5-hydroxyisoxazolidine. These facts strongly suggest that, unlike 5-O-acetylderivatives, cis and trans 5-hydroxyisoxazolidines easily interconvert, presumably through the open form (ring-chain tautomerism). Such a possibility is not new. In fact a similar equilibrium has been demonstrated in the case of the related 5-hydroxyisoxazolines[8] and also indicated in the case of 5-hydroxyisoxazolidines themselves,[9] as well as in other similar cases,[10] and reasonably arises from the hemiacetalic nature of such compounds.

TABLE 1

Yields of 5-hydroxyisoxazolidines isolated from the reaction of nitrones and the lithium enolate of acetaldehyde in THF at room temperature.



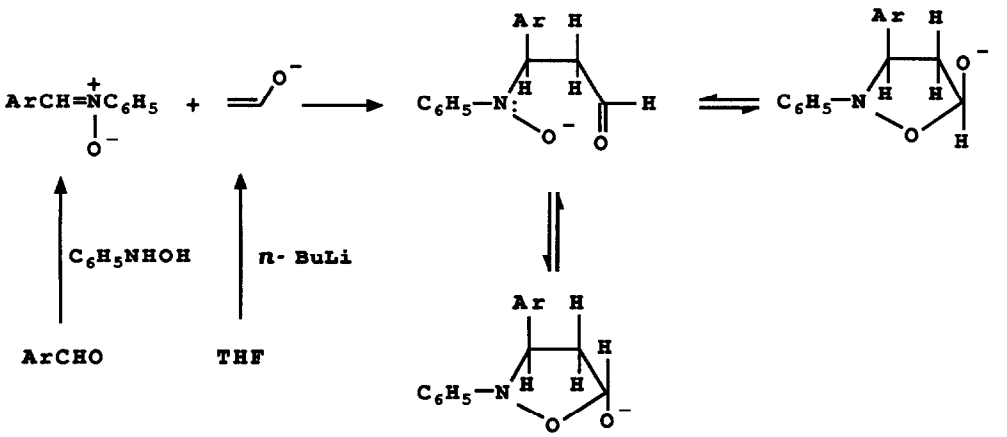
Ar(or R)	Ar'(or R')	Reaction Time (h)	Yields[a] %	[b] [trans]/[cis]
C_6H_5	C_6H_5	0.75	89	70/30
p-ClC_6H_4	C_6H_5	0.50	quantitative	60/40
p-$NO_2C_6H_4$	C_6H_5	1.0	86	65/35
p-$MeOC_6H_4$	C_6H_5	"	75	70/30
$C_6H_5CH=CH$	C_6H_5	"	70	60/40
C_6H_5	CH_3	18	<5	60/40
C_6H_5	t-C_4H_9	72	N.R.	—
p-$NO_2C_6H_4$	t-C_4H_9	72	N.R.	—

[a] The yields refer to mixtures of cis- + trans-isomers isolated by column flash chromatography. No decomposition occurred on either silica gel or alumina oxide when the 5-hydroxyisoxazolidines were chromatographed; in contrast, the 5-O-acetyl-isoxazolidines were completely decomposed on chromatography.

[b] The trans/cis ratio has been evaluated by ^1H NMR, by using the signals of the 5-hydroxyisoxazolidines in the range 3.5-5.0 ppm (two one-proton doublets of doublets(dd)), and by considering that the upfield and the downfield dd can be assigned to the C_3 proton which is trans or cis, respectively, to the C_5 OH group.

Thus we suggest a stepwise rather than a concerted [3+2] cycloaddition mechanism for the reaction, by analogy with the similar case of 5-hydroxyisoxazolines[3b] (SCHEME 1).

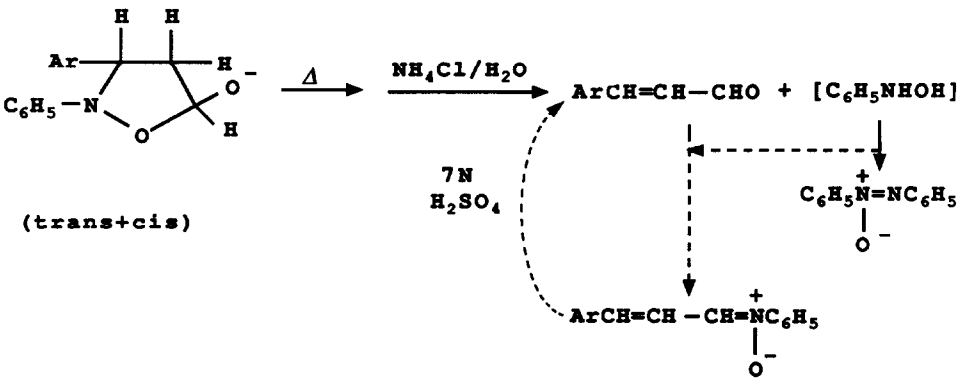
SCHEME 1



In the light of Scheme 1 the low (or the absence of) reactivity observed for N-methyl and N-*t*-butylnitrones, respectively, could be explained by considering that both groups, unlike the phenyl group in N-phenylnitrones (in which a -M effect can operate) are not capable of exerting an electron-attracting effect enhancing the positive charge on the C=N carbon and so favouring the attack of the enolate ion, but, on the contrary, are electron-donating. Steric hindrance is possibly also operating in the case of N-*t*-butylnitrones.

If the reaction mixture of 2-phenyl-3-aryl-5-hydroxyisoxazolidines is not quenched shortly after the nitrone has disappeared, but allowed to stand (one hour more under reflux), decomposition of hydroxyisoxazolidines to cinnamaldehydes (with seemingly exclusive E configuration: ^{1}H NMR analysis) and regeneration of phenylhydroxylamine (actually isolated as azoxybenzene)[11] are observed (SCHEME 2). Small quantities (ca. 10%) of the cinnamal nitrones generated from cinnamaldehydes and phenylhydroxylamine are also recovered when the reaction mixture is quenched with NH_4Cl/H_2O. These, however, by treatment with 7N H_2SO_4, completely reverse to cinnamaldehydes. By quenching the reaction mixture directly with 7N H_2SO_4, the above nitrones are no longer observed. Moreover, the cinnamal nitrone behaves just like all the other N-phenylnitrones when treated with the enolate ion of acetaldehyde, affording in good yields first the corresponding 5-hydroxyisoxazolidine and then, by decomposition, the 5-phenyl-2,4-pentadienal.

SCHEME 2



The above decomposition is formally the reverse of the reaction between alkenals and hydroxylamines reported for the synthesis of some 5-hydroxyisoxazolidines.[12] It can be accomplished with comparable results (TABLE 2) also by isolating the 5-hydroxyisoxazolidines and subjecting them to a new independent treatment with the lithium enolate of acetaldehyde in THF (or with different bases in different solvents) at the reflux temperature, while no decomposition is observed in the control reaction, i.e. by simple heating in the same solvents in the absence of base.

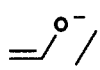
Presumably the aforesaid reversion is also due to the disappearance of the by-product phenylhydroxylamine (converted under the reaction conditions to azoxybenzene), forcing the reaction towards the alkenal.

In any case, the combination of the synthesis of 5-hydroxyisoxazolidines from nitrones and the enolate ion of acetaldehyde and the subsequent decomposition constitutes a new efficient way for the C_2-homologation of aromatic aldehydes. The overall reaction corresponds, in fact, to an indirect crossed aldol condensation between the aromatic aldehydes precursors of nitrones and the lithium enolate of acetaldehyde. This methodology is comparable, as far as yields and simplicity, with the best procedures so far reported for the above-said homologation[13-14] and much more efficient than the direct aldol reaction[15](e.g., cinnamaldehyde is synthesized in only 15% yields by direct crossed aldol condensation,[15] while 80% overall yields can be evaluated for the hydroxyisoxazolidine route).

It must be pointed out that the behaviour of 5-hydroxyisoxazolidines with bases is completely different from that previously observed for the related 5-hydroxyisoxazolines. Actually, the 5-hydroxyisoxazolines easily dehydrate to isoxazoles by the same treatment,[3b] presumably because the aromatization of the ring might be the driving force. Moreover, the decomposition of 5-hydroxyisoxazolidines is somewhat different also from that reported for other isoxazolidine derivatives, though in those cases α,β-unsaturated ketones or aldehydes are again obtained.[14,16] In fact a different by-product is generated (an

TABLE 2

Yields of cinnamaldehydes (ArCH=CHCHO) isolated (a) from 5-hydroxy-3-aryl-2-phenylisoxazolidines, and (b) starting directely from aryl N-phenylnitrones without isolating 5-hydroxyisoxazolidines intermediates.

Ar	$B:^-$ /Solv.	Yield[a] %	Yield[b] %
C_6H_5	 THF	83	90
	K_2CO_3/MeOH	85	–
	MeO^- /MeOH	80	–
p-ClC_6H_4	 THF	70	81
	K_2CO_3/MeOH	75	–
p-$MeOC_6H_4$	 THF	71	83
	K_2CO_3/MeOH	71	–
p-$O_2NC_6H_4$	 THF	70	77
	K_2CO_3/MeOH	79	–
$C_6H_5CH=CH$	 THF	76	85
	K_2CO_3/MeOH	82	–

[a]Reactions quenched with NH_4Cl/H_2O. Together with cinnamaldehydes, small quantities (ca. 10%) of the corresponding cinnamal N-phenylnitrones are isolated, for reactions performed in MeOH under air.

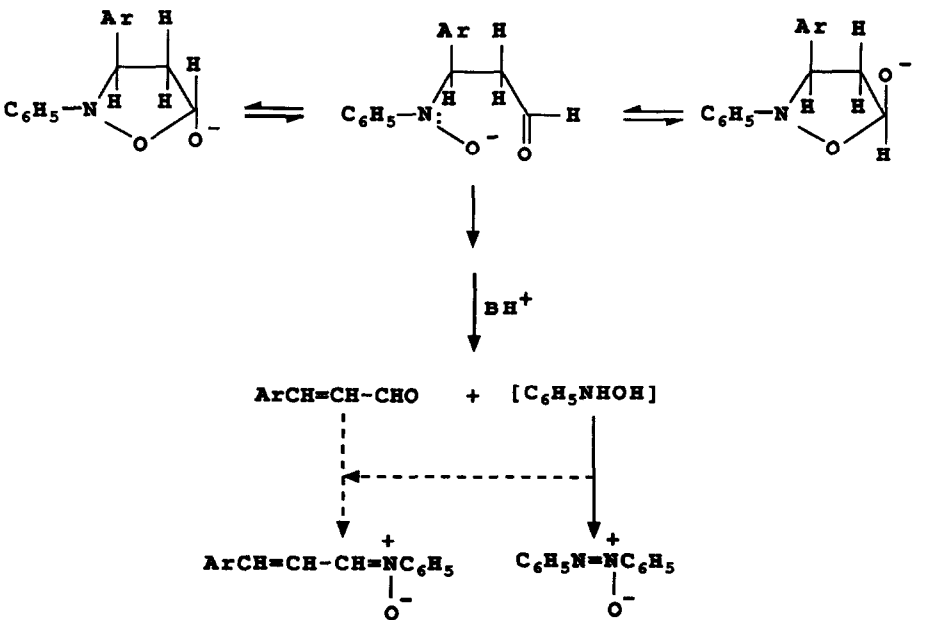
[b]Reactions quenched with 7N H_2SO_4. Under these conditions only cinnamaldehydes are isolated (see text).

amine instead of an hydroxylamino compound) and a different procedure is required, i.e. the alkylation to quaternary ammonium cation[14] in order to obtain, by a Hofmann-like degradation, the open form believed the precursor of the α,β-enones. Similarly, treatment with HF is required in the case of 5-trimethylsilylisoxazolidines.[16]

The fact that no similar treatments are needed for 5-hydroxyisoxazolidines suggests that the open form is already present in this case. This supports the above hypothesis concerning the ring-chain tautomerism (SCHEME 1).

On the other hand, there should be no doubt that the open form is really involved even in the decomposition of 5-hydroxyisoxazolidines. In fact, by subjecting 5-methoxy-2,3-diphenylisoxazolidine[9] to the same basic treatment (e.g. K_2CO_3/MeOH) causing the decomposition of the corresponding 5-hydroxy derivative, presumably because of the lack of ring opening under basic conditions due to its acetalic character, no decomposition is observed. A further indication is given by some experiments carried out in the presence of acids. In fact, by treating the 5-hydroxy-2,3-diphenylisoxazolidine with 7N H_2SO_4 (ca 1h at r.t.), decomposition to the cinnamaldehyde is once again observed and, as expected, also 5-methoxy-2,3-diphenylisoxazolidine behaves similarly under these conditions.
Thus we suggest the following mechanism of reaction for the decomposition of 5-hydroxyisoxazolidines in the presence of bases (SCHEME 3).

SCHEME 3



In the scheme the formation of cinnamaldehydes is envisaged as due to a β-elimination from the open form. Such an elimination could in turn involve the external base or, perhaps, occur internally (by a Cope-like reaction).
However, apart from the mechanistic aspects, the synthetic utility of the described reactions must be pointed out. In fact, the conversion of aromatic aldehydes to nitrones followed by reaction with the enolate ion of acetaldehyde constitutes not only a useful tool for the synthesis of a number of unknown 5-hydroxyisoxazolidines, but also a new efficient procedure for the C_2-homologation of the same aldehydes.
Moreover, it has been shown that the cinnamaldehydes so obtained can in turn be further homologated by the same way, thus suggesting the possibility of obtaining more compex polyunsaturated aldehydes by an iterative procedure.
Finally, it must also be emphasized that the isolation of 5-hydroxyisoxazolidines is not necessary, the conversion of nitrones to homologated aldehydes being feasible also by a one flask-process.
This is at variance with the other above-mentioned procedures involving isoxazolidines and should make our methodology still more interesting.

EXPERIMENTAL

MPS taken on a Electrothermal apparatus were uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 or XL 200 spectrometer and chemical shifts are reported in parts per million (δ) from internal Me_4Si. Absolute values of the coupling constant are reported. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator (stratocrom SIF, Carlo Erba), the spots on the TLC were observed under ultraviolet light or were visualized with iodine vapour. Flash chromatography was conducted by using silica gel with an average particle size of 60 μm, 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 mod. 1106, Carlo Erba-instrument.

Materials. Tetrahydrofuran (THF) from commercial source (RS, Carlo Erba) was purified by distillation (twice) from sodium wire in a N_2 atmosphere. Standardized (2.4N) *n*-butyllithium in hexane was from Aldrich Chemical Co. .

All other chemicals were commercial grade further purified by distillation or crystallization prior to use.

Nitrones. The following arylnitrones were prepared by mixing equimolar solutions of the appropriate benzaldehyde and phenylhydroxylamine dissolved in the minimum quantity of ethanol, and allowing the mixtures to stand at room temperature overnight in the dark. The reaction mixtures were then cooled in an ice-bath and filtered. The collected solids were recrystallized from ethanol (yields 70-90%) and characterized by their m.p.'s, ^{1}H NMR and IR spectra(not yet reported)

as follows:

Phenyl N-phenylnitrone , m.p.115 (lit[17] 116°C); IR(CCl_4):1190 cm^{-1}; ^1H NMR ($CDCl_3$, δ): 8.35(m, 2H); 7.90(s, 1H); 7.75(m, 2H); 7.48(m, 6H).

p-Chlorophenyl N-phenylnitrone, m.p. 155-156°C (lit[6] 152°C); IR($CHCl_3$): 1180 cm^{-1}; ^1H NMR($CDCl_3$, δ): 8.32(d, 8Hz, 2H); 7.86 (s, 1H); 7.65(m, 2H); 7.50(m, 5H).

p-Methoxyphenyl N-phenylnitrone, m.p. 116-118°C(lit[18] 118°C); IR(KBr):1160 cm^{-1}; ^1H NMR($CDCl_3$,δ): 8.40(d, J=12Hz, 2H); 7.82(s, 1H); 7.75(m, 2H); 7.44(m,3H); 6.98(d, J=12Hz, 2H); 3.88(s, 3H).

p-Nitrophenyl N-phenylnitrone, m.p. 186-188°C(lit[18] 190°C); IR(KBr):1190 cm^{-1}; ^1H NMR($CDCl_3$, δ): 8.56(d, J=9Hz, 2H); 8.28(d, J=9Hz, 2H); 8.07(s, 1H);7.75 (m, 2H); 7.50(m, 3H).

Cinnamal N-phenylnitrone, m.p. 150-151°C (lit[19] 150-151°C); IR(KBr):1190 cm^{-1}; ^1H NMR($CDCl_3$, δ): 7.81(s, 1H); 7.40(m, 12H).

Phenyl N-methylnitrone.[20] A mixture of 6.1g CH_3NO_2, 6.3g $(CO_2H)_2$, 0.6g 5% Pd-C and 100 ml H_2O, was hydrogenated (ca. 4 liters of H_2 were consumed) at 1 atm of hydrogen pressure. After the reaction mixture was filtered. The so obtained clear solution was treated with 4ml 50% NaOH, 8.5g of PhCHO and stirred for 10 minutes. Then the mixture was extracted with $CHCl_3$. The combined extracts were dried and evaporated under vacuo to dryness. The crude nitrone was recrystallized, m.p. 82-83°C (hexane) (lit[21] 84°C); IR(KBr): 1170cm^{-1}; ^1H NMR($CDCl_3$, δ):8.05(m, 2H); 7.22(m, 4H); 3.75(s, 3H) or (DMSO-d_6, δ): 8.21 (m,2H); 7.82(s, 1H); 7.40(m, 3H); 3.80(s, 3H).

Phenyl N-*t*-butylnitrone and p-Nitrophenyl N-*t*-butylnitrone were from Aldrich Chemical Co..

Phenylhydroxylamine.[22] It was prepared by zinc dust and ammonium chloride reduction of the nitrobenzene and had m.p. 80-81°(lit.[23] 80.5-81°C); IR(neat): 3500-3040, 1570, 1555, 1450 cm^{-1}; ^1H NMR (CCl_4, δ): 6.70(m, 5H); 5.45(bs, NH: exchange with D_2O); 4.20(bs, OH: exchange with D_2O).

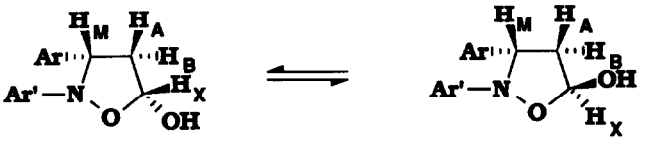
Reaction of nitrones with the enolate ion of acetaldehyde: general procedure.

A mixture containing lithium enolate of the acetaldehyde (6.5 mmole) in anhydrous THF (10 ml), prepared by allowing to stand THF in the presence of *n*-butyllithium for ca. 16h as previously reported,[4] is added dropwise and at ca. 20°C to a solution of nitrone (5 mmole) in 20 ml of THF, using a nitrogen-flushed, three necked flask equipped with a magnetic stirrer, a nitrogen inlet and a dropping funnel. After the reaction was completed, the reaction mixture was quenched by adding aqueous NH_4Cl, the organic layer separated and the aqueous layer extracted with ethyl ether. The combined extracts were dried over Na_2SO_4 and evaporated under pressure, affording the crude 5-hydroxyisoxazolidines which after purification by column flash chromatography were recrystallizated from ethyl ether-hexane.

Products

As already described the 5-hydroxyisoxazolidines in solution are present as a trans/cis mixture ranging from 7/3 to 6/4. So the experimental ^1H NMR spectra of the 5-hydroxyisoxazolidines result in several partially overlapped signals due to the presence, of the cis and trans stereoisomers. Complete assignment of the chemical shifts and coupling costants for protons of both the cis and trans isomer was achieved by spectral analysis,[24] according to the ABMX spin system[25] (SCHEME 4), as reported for the only case of 2,3-diphenyl-5-hydroxyisoxazolidine.

SCHEME 4



cis **trans**

2,3- Diphenyl -5- hydroxyisoxazolidine, m.p. 85-87°C; IR($CHCl_3$): 3590, 3500-3200, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, δ):7.20(m, aromatic protons); 5.75(d, J_{AX}=4.3 Hz, H_X, trans); 5.73(d, J_{BX}=1.9 Hz, H_X, cis); 4.85(dd, J_{AM}=10.1Hz, J_{BM}=7.0Hz, H_M, trans); 4.42(dd, J_{AM}=9.1 Hz, J_{BM}=6.2 Hz, H_M, cis); 3.25(bs, OH: exchange with D_2O); 3.05-2.45(m, H_A+H_B, cis+trans). (Found: C, 74.65; H, 6.18; N, 5.75. Calc. for $C_{15}H_{15}NO_2$: C, 74.69; H, 6.22; N, 5.81).

The following pmr data of the cis and trans 2,3-diphenyl-5-hydroxyisoxazolidines in the range of δ 6.0-2.0 ppm are obtained by spectral analysis using the program LAOCN-5:[24]

cis 2,3-diphenyl-5-hydroxyisoxazolidine: 5.73(dd,J_{AX}=6.0Hz, J_{BX}=1.9Hz, H_X); 4.42(dd, J_{AM}=9.2Hz, J_{BM}=6.2Hz, H_M); 3.03(qd, J_{AB}=13.4Hz, J_{AX}=6.0Hz, J_{AM}=9.2Hz, H_A); 2.41(qd, J_{AB}=13.4Hz, J_{BX}=1.9Hz, J_{BM}=6.2Hz, H_B).

Trans 2,3-diphenyl-5-hydroxyisoxazolidine: 5.75(d, J_{AX}=4.3Hz, J_{BX}=0.0Hz, H_X); 4.84(dd, J_{AM}=10.1Hz, J_{BM}=7.0Hz, H_M); 2.81(dd, J_{AB}=12.4Hz, J_{BM}=7.0Hz, H_B); 2.46(qd, J_{AB}=12.4Hz, J_{AM}=10.1Hz, J_{AX}=4.3Hz, H_A).

2-Phenyl-3-(4-chlorophenyl)-5-hydroxyisoxazolidine, m.p. 119-120°C; IR($CHCl_3$): 3670, 3600-3200, 1600, 1400 cm^{-1} or (KBr): 3640-3120, 1600, 1390 cm^{-1}; ^1H NMR($CDCl_3$,δ): 7.20(m, aromatic protons); 5.77(d, J_{AX}=4.3Hz, H_X, trans); 5.73(d, J_{BX}=1.7Hz, H_X, cis); 4.81 (dd, J_{AM}=10.0Hz, J_{BM}=6.1Hz,H_M, trans); 4.39(dd, J_{AM}=9.2Hz, J_{BM}=5.9Hz,H_M, cis); 2.75(bs, OH: exchange with D_2O); 3.10-2.30(m, H_A+H_B, cis+trans).

(Found: C, 65.41; H,5.10; N,5.04. Calc. for $C_{15}H_{14}ClNO_2$: C, 65.45; H, 5.09; N, 5.09).

2-Phenyl-3-(4-methoxyphenyl)-5-hydroxyisoxazolidine, m.p. 70-71°C; IR(CCl_4):

3610, 3442-3100, 1600, 1490, 1248 cm^{-1}; ^1H NMR($CDCl_3$, δ): 7.25(m, aromatic protons); 5.71(d, J_{AX}=4.2Hz, H_X, trans); 5.68(s, H_X, cis); 4.82(dd, J_{AM}=9.9Hz, J_{BM}=6.9Hz, H_M, trans); 4.32(dd, J_{AM}=7.1Hz, J_{BM}=5.9Hz, H_M, cis); 4.40-4.10(bs, OH: exchange with D_2O); 3.07-2.32(m, H_A+H_B, cis + trans). (Found: C, 70.90; H, 6.26; N, 5.15. Calc. for $C_{16}H_{17}NO_3$: C, 70.85; H, 6.27; N, 5.17).

2-Phenyl-3-(4-nitrophenyl)-5-hydroxyisoxazolidine, m.p. 114-115°C; IR(KBr): 3700-3150, 1600, 1520, 1350 cm^{-1}; ^1H NMR($CDCl_3$, δ): 7.50(m, aromatic protons); 5.82(d, J_{AX}=4.2Hz, H_X, trans; this H_X signal covers up the correspondent less intense isochronous H_X signal belonging to the cis isomer); 4.96(dd, J_{AM}=9.8Hz, J_{BM}=7.1Hz, H_M, trans); 4.53(dd, J_{AM}=9.8Hz, J_{BM}=4.9Hz, H_M, cis); 3.10-2.30(m, H_A+H_B, cis+trans); 2.80(bs, OH: exchange with D_2O). (Found: C, 62.93; H, 4.90; N, 9.74. Calc. for $C_{15}H_{14}N_2O_4$: C, 62.94; H, 4.89; N, 9.79).

2-Phenyl-3-cinnamal-5-hyroxyisoxazolidine, m.p. 72-73°C; IR($CHCl_3$): 3600, 3540-3200, 1600, 1490, 1200 cm^{-1}; ^1H NMR($CDCl_3$, δ): 7.50-6.20(m, aromatic and vinylic protons); 5.72(d, J_{AX}=5.1Hz, H_X, trans; this H_X signal covers up the correspondent less intense isochronous H_X signal belonging to the cis isomer); 4.50(dd, J_{AM}=7.1Hz, J_{BM}=6.3Hz, H_M, trans); 4.40(m, H_M, cis); 4.00-3.50(bs, OH: exchange with D_2O); 2.90-2.25(m, H_A+H_B, cis+trans).(Found: C, 76.40; H, 6.35; N, 5.20. Calc. for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.37; N, 5.24).

2-Methyl-3-phenyl-5-hydroxyisoxazolidine, oil; IR($CHCl_3$): 3690, 3596-3384, 3029, 3018, 1345, 1236 cm^{-1}; ^1H NMR($CDCl_3$, δ): 7.35(m, aromatic protons); 5.60(m, H_X, cis+trans); 4.00(dd,J_{AM}=9.8Hz, J_{BM}=7.0Hz, H_M, trans); 3.90-3.60(bs, OH: exchange with D_2O); 3.50(dd, J_{AM}=9.8Hz, J_{BM}=5.0Hz, H_M, cis); 2.80(s, methylic protons, trans); 2.60(s, methylic protons, cis); 3.10-2.10(m, H_A+H_B, cis+trans). (Found: C, 66.68; H, 6.70; N, 7.79. Calc for $C_{10}H_{12}NO_2$: C, 66.70; H, 6.70; N, 7.80).

Reactions of 5-hydroxyisoxazolidines with bases.

A THF solution of the lithium enolate of acetaldehyde (12 mmole) was added to a solution of hydroxyisoxazolidine (10 mmole) in 10 ml THF, using a nitrogen-flushed, 100 ml three necked flask, equipped with a nitrogen inlet, a dropping funnel, and a reflux condenser.

The reaction mixture was heated under reflux for about 1h, then was quenched with aqueous NH_4Cl or 7N H_2SO_4 and stirred for 10 min. at room temperature. The organic layer was then separated and aqueous layer extracted with ethyl ether. The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure affording a mixture of azoxybenzene and the homologized aldehyde, which were separated by flash cromatography (silica gel; eluent: 20% ethyl ether in petrol ether).

Reactions with sodium methoxide (10 mmole) in methanol or potassium carbonate (10 mmole) in 95% methanol were performed under air at 60 °C.

All the products isolated from the aforementioned reactions are known compounds and their GC-MS analyses, ^1H NMR and IR spectra are compatible with the given structures.[26]

Acknowledgements: We thank CNR and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Rome) for financial support of this research.

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