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SYNTHESIS OF ^2H LABELLED DIASTEROMERIC ISOXAZOLIDINES BY 1,3-DIPOLAR CYCLOADDITIONS OF NITRONES TO ALKENES.

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SUMMARY

Specifically labelled ^2H isoxazolidine epimers have been synthesized from suitably labelled nitrones and styrenes by 1,3-dipolar cycloaddition.

Discussion

Isoxazolidines (1) are the products of 1,3-dipolar cycloaddition of nitrones to alkenes (2) which can be readily transformed into chiral intermediates by methylation of the ring nitrogen atom (3). A wide variety of ring transformations of this five-membered heterocyclic systems have been so far reported (4-7) showing that the chirality of the nuclear carbons can be preserved in the reaction products thus formed (8-10). The chemistry of ionized isoxazolidines in the gas phase is characterized also by rearrangements which lead to open chain ions (11).

The involvement of the hydrogen atoms either in the condensed or in the gas-phase rearrangement processes could be eventually detected from the transformations undergone by specifically labelled substrates having the correct configuration at the chiral centers. The latter have been obtained by 1,3-dipolar cycloadditions of properly labelled nitrones and alkenes.

A number of synthesis have been reported for the preparation of ^2H labelled styrenes (12-19), however, large scale preparations of [1-^2H] (**1**), [2,2-$^2H_2$] (**2**) and [1,2,2- $^2H_3$] (**3**) styrenes, in satisfactory yields and good isotopic purity, have been achieved from acetophenone or methyl phenylacetate by simple procedures. The olefines thus obtained have been employed, after distillation or flash chromatographic purification, in the synthesis of the labelled isoxazolidines **8-25** (table).

N-benzylidene methylamine-N-oxide (**4**) and N-benzylidene aniline-N-oxide (**5**) have been prepared by following literature procedures (20-21), while the corresponding labelled dipoles **6** and **7** have been obtained from the bisulfide adduct of 1-^2H-benzaldehyde (22) and the appropriate hydroxylamines.

The cycloaddition processes afforded the isoxazolidines **8-13** and **20-25** (table) as a mixture of epimers with similar but distinct Rf on SiO_2 tlc plates. A proper choice of chromatographic conditions allowed the separation of the diasteroisomers (table) in gram quantities, by flash chromatography (23); 6 to 12% of epimeric mixtures have been obtained from the mixed fractions. The preferred formation of *exo* adducts in the reaction of N-benzylidene aniline-N-oxide with styrene (24) afforded high yield of the labelled isoxazolidines

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14-19.

The configurations of the chiral centers of the pure epimers have been assigned by ^1H n.m.r. spectroscopy with reference to the known spectroscopic properties of the unlabelled species (4), while the isotopic distribution was assessed by electron ionization mass spectrometry, by correcting the relative intensities of the molecular ion clusters for the ^{13}C contribution.

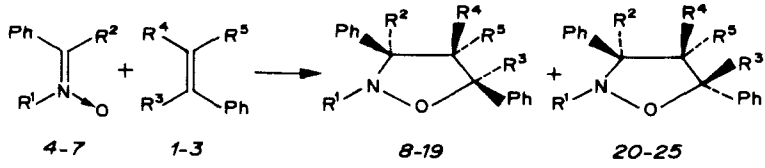

Table. ^2H labelled isoxazolidines.

	R^1	R^2	R^3	R^4	R^5	%	d_0	d_1	d_2	d_3
8	Me	D	H	H	H	54	7.2	92.8	-	-
9	Me	H	H	D	D	52	-	2.2	97.8	-
10	Me	H	D	H	H	47	3.5	96.5	-	-
11	Me	D	H	D	D	46	-	1.0	10.2	88.8
12	Me	H	D	D	D	50	-	-	1.2	98.8
13	Me	D	D	H	H	49	-	12.4	87.6	-
14	Ph	D	H	H	H	78	2.0	98.0	-	-
15	Ph	H	H	D	D	82	-	2.0	96.8	-
16	Ph	H	D	H	H	81	6.0	94.0	-	-
17	Ph	D	H	D	D	78	-	1.5	4.2	94.3
18	Ph	H	D	D	D	77	-	-	7.0	93.0
19	Ph	D	D	H	H	83	-	5.9	94.1	-
20	Me	D	H	H	H	21	7.2	92.8	-	-
21	Me	H	H	D	D	22	-	2.2	97.8	-
22	Me	H	D	H	H	19	3.5	96.5	-	-
23	Me	D	H	D	D	20	-	1.0	10.2	88.8
24	Me	H	D	D	D	18	-	-	1.2	98.8
25	Me	D	D	H	H	21	-	12.4	87.6	-

Conclusions

A straighforward procedure have been presented for the obtainment of specifically deuterated isoxazolidines of given configuration.

The peculiarity of the present approach relies in the fact that the labelled dipolarophiles have been synthetized by simple procedures from commercially available substrates and that the labelled dipoles have been generated *in situ* from the bisulfide adduct of [1-^2H]-benzaldehyde. The isomers **8-25** thus obtained can be employed in the detailed analysis of the reaction paths which characterize the chemistry of the isoxazolidine nucleus either in the content or in the gas phase.

Experimental

Merck Kieselgel 60 H without gypsum was used for short- column chromatography. ^1H n.m.r. spectra were measured at 100 MHz with Varian XL-100 spectrometer; tetramethylsilane was used as internal standard and deuterochloroform as solvent. Electron ionization mass

spectra were obtained on a Vacuum Generators (VG) ZAB-2F instrument operated at 8 KeV and 70 eV.

[2,2-$^2H_2$]-Styrene (2): To a slurry of 2.80 g (66 mmol) of lithium aluminum deuteride (LAD) in dry dioxane (150 ml) was slowly added a solution of 10 g (66 mmol) of methyl phenylacetate in dry dioxane (50 ml). After 4 hrs. under reflux with stirring, 80 ml of 2N NaOH aqueous solution was added and the mixture extracted with ether (3x30 ml). The combined extracts, dried and evaporated to dryness, yielded 6.95 g (85%) of [1,1-$^2H_2$]-phenylethanol; δ_H (100 MHz) 2.07 (1H,s,OH), 2.88 (2H,s,2-H_2), 7.20-7.44 (5H,m,Ar).

A mixture of 5.60 g (45 mmol) of [1,1-$^2H_2$]- phenylethanol, 17 g (88.2 mmol) of p-toluensulfonyl chloride, 7.2 g (180 mmol) of ground NaOH pellets in 100 ml of dry ether was stirred overnight at room temperature. The reaction mixture was partitioned between water (50 ml) and ether (4x20 ml). The organic layers were dried and evaporated to dryness to yield 11.3 g (90%) of [1,1-$^2H_2$] phenylethanol-p- toluensulfonate; δ_H (100 MHz) 2.46 (3H,s,C_6H_4-CH_3), 7.06-7.80 (9H,m, Ar).

The latter (11 g, 40 mmol) and ground KOH pellets (6.9 g, 120 mmol) were placed in a vacuum distillation apparatus. 3.5 g (81%) of [2,2-$^2H_2$]-styrene were distilled into a dry- ice cooled flask at 108°C and 3 torr. δ_H (100 MHz) 6.7 (1H,s,vinyl-H) 7.17-7.52 (5H, m, Ar).

[1,2,2-$^2H_3$]-Styrene (3): To a slurry of 1.34 g (32 mmol) of LAD in dry tetrahydrofuran (THF, 100 ml) was slowly added with stirring a solution of 4.0 g (32 mmol) of trideuteromethyl phenyl ketone (prepared from acetophenone repeatedly exchanged with D_2O in the presence of anhydrous K_2CO_3) in dry THF (25 ml). After the usual work up 3.62 g (90%) of [1,2,2,2-$^2H_4$]-1-phenylethanol were obtained. δ_H (100 MHz): 3.21 (1H,s,OH), 7.20-7.42 (5H,m,Ar). 3.30 g (26 mmol) of the latter afforded 4.20 g (86%) of [1,2,2,2-$^2H_4$]-1- phenyl-1-bromo-ethane, after overnight treatment with phosphorous tribromide (2.5 ml) in n-pentane (80 ml) and usual work-up.

To a solution of 4.97 g (44 mmol) of potassium *tert-* butoxyde in dry THF (100 ml) was added dropwise, with stirring a solution of 4.20 g (22 mmol) of [1,2,2,2-$^2H_4$]-1- phenyl-1-bromethane in dry THF (30 ml). The mixture was refluxed for 4 hrs, water (50 ml) was added followed by extraction with ether (3x20 ml) and the organic layers were dried and evaporated to dryness. Flash chromatography (23) with ether-light petroleum [(b.p. 40-70°C), (1:99)] yielded [1,2,2-$^2H_3$]-styrene (1.85 g, 79%). δ_H (100 MHz) 7.20-7.45 (m, Ar); m/z 107 (M^+, 100%, b. peak) [d_3=98.6%, d_2=1.4%].

[1-^{2}H]-Styrene (1): Compound 1 was obtained from acetophenone following the same procedure above reported for the preparation of 3. Flash chromatography with ether-light petroleum [(b.p. 40-70%), (1:99)] afforded [1-^{2}H]-styrene in 65% overall yield based on the starting ketone. δ_H (100 MHz) 5.25 (1H,d,2-H), 5.75 (1H,d,2-H), 7.22-7.45 (5H,m,Ar).

N-[^{2}H]-benzylidene methylamine-N-oxide (6): To a solution of 7.0 g (30 mmol) of the bisulfide adduct of [1- ^{2}H]-benzaldehyde[22] in 2N aqueous NaOH (50 ml) was added, with stirring, a solution of 2.5 g (30 mmol) of N- methylhydroxylamine hydrochloride in water (20 ml). The reaction mixture was stirred for 15 min at room temperature and extracted with chloroform (5x30 ml). The organic layers were dried over anhydrous sodium sulfate, evaporated to dryness and the residue crystallized from benzene-light petroleum (b.p. 40-70°C) to yield 3.81 g (94%) of **6**, m.p. 82.83°C; δ_H (100 MHz) 3.86 (3H,s,N-CH_3), 7.40-8.28

(5H,m,Ar); m/z 136 (M^+, 81%), m/z 134 [$(M-D)^+$, 100%], [d_1=93.8%, d_0=6.2%].

N-[^{2}H]-benzylidene aniline-N-oxide (7): To a solution of 7.08 (30 mmol) of the bisulfide adduct of [1-^{2}H] benzaldehyde in 2N ethanolic NaOH (50 ml) was added with stirring a solution of 3.27 g (30 mmol) of phenylhydroxylamine in ethanol (20 ml). After 50 min a colourless precipitate was formed which was filtered and crystallized from benzene to give 5.35 g (91%) of **7**, m.p. 113-114°C; δ_H (100 MHz) 7.3-8.5 (m,Ar); m/z (M^+, 18%), m/z 196 [$(M-D)^+$, 20%], m/z 91 (100%, b. peak), [d_1=98.9, d_0=1.1%].

Synthesis of isoxazolidines 8-13 and 20-25: 7.3 mmol of both nitrones **4** (or **6**) and the appropriate styrene were allowed to react in 5 ml of toluene in a screw capped vial at 120°C for 60 hrs. Flash chromatography (23) with ether-light petroleum [(b.p. 40-70°C), (4:96)] as eluent afforded the pure epimers whose yields and isotopic distribution are reported in the table.

(±)-(3R,5S)-[3-^{2}H]-2-methyl-3,5-diphenylisoxazolidine (8):
oil; δ_H (100 MHz) 2.42 (1H,q,$J_{4,4}$=11.5Hz,4-H), 2.70 (3H,s,N- CH_3), 3.08 (1H,q,4-H), 5.25 (1H,t,$J_{4,5}$cis=7.5Hz,$J_{4,5}$trans= 7.5Hz,5-H), 7.20-7.57 (10H,m,Ar); m/z 240 (M^+, 22%), m/z 135 (100%, b. peak).

(±)-(3R,5R)-[3-^{2}H]-2-methyl-3,5-diphenylisoxazolidine (20):
oil; δ_H (100 MHz) 2.53-2.95 (2H,m,$J_{4,4}$=12.5Hz,4-H_2), 2.74 (3H,s,N-CH_3), 5.34 (1H,t,$J_{4,5}$cis=7.5Hz,$J_{4,5}$trans=7.5Hz,5-H), 7.25-7.62 (10H,m,Ar); m/z 240 (M^+, 26%), m/z 135 (100%, b. peak).

(±)-(3R,5S)-[4-$^2H_2$]-2-methyl-3,5-diphenylisoxazolidine (9):
oil; δ_H (100 MHz), 2.64 (3H,s,N-CH_3), 3.91 (1H,s,3-H), 5.35 (1H,s,5-H), 7.28-7.62 (10H,m,Ar); m/z 241 (M^+, 25%), m/z 134 (100%, b. peak).

(±)-(3R,5R)-[4-$^2H_2$]-2-methyl-3,5-diphenylisoxazolidine(21):
oil; δ_H (100 MHz) 2.72 (3H,s,N-CH_3), 3.83 (1H,s,3-H), 5.35 (1H,s,5-H), 7.28-7.62 (10H,m,Ar); m/z 241 (M^+, 25%), m/z 134 (100%, b. peak).

(±)-(3R,5S)-[5-^{2}H]-2-methyl-3,5-diphenylisoxazolidine (10):
oil; δ_H (100 MHz) 2.40 (1H,q,$J_{4,4}$=11.5Hz,4-H), 2.68 (3H,s,N- CH_3), 3.06 (1H,q,4-H), 3.78 (1H,t,$J_{3,4}$cis=9.1Hz,$J_{3,4}$trans= 7.2Hz,3-H), 7.21-7.52 (10H,m,Ar); m/z 240 (M^+, 30%), m/z 134 (100%, b. peak).

(±)-(3R,5R)-[5-^{2}H]-2-methyl-3,5-diphenylisoxazolidine (22):
oil; δ_H (100 MHz) 2.54-2.96 (2H,m,$J_{4,4}$=12.5Hz,4-H_2), 2.73 (3H,s,N-CH_3), 3.78 (1H,t,$J_{3,4}$cis=8.5Hz,$J_{3,4}$trans=8.5Hz,3-H), 7.26-7.58 (10H,m, Ar); m/z 240 (M^+, 25%), m/z 134 (100%, b. peak).

(±)-(3R,5S)-[3,4,4-$^2H_3$]-2-methyl-3,5-diphenylisoxazolidine (11):
oil; δ_H (100 MHz) 2.72 (3H,s,N-CH_3), 5.28 (1H,s,5-H), 7.20-7.54 (10H,m,Ar); m/z 242 (M^+, 25%), m/z 135 (100%, b. peak).

(±)-(3R,5R)-[3,4,4-$^2H_3$]-2-methyl-3,5-diphenylisoxazolidine (23):
oil; δ_H (100 MHz) 2.54-2.96 (2H,m,4-H_2), 2.73 (3H,s,N- CH_3), 3.78 (1H,s,3-H), 7.26-7.58 (10H,m,Ar); m/z 240 (M^+, 27%), m/z 134 (100%, b. peak).

(±)-(3R,5S)-[4,4,5-$^2H_3$]-2-methyl-3,5-diphenylisoxazolidine (12):
oil; δ_H (100 MHz) 2.64 (3H,s,N-CH_3), 3.72 (1H,s,3-H), 7.18-7.48 (10H,m,Ar); m/z 242 (M^+, 30%), m/z 134 (100%, b. peak).

(±)-(3R,5R)-[4,4,5-$^2H_3$]-2-methyl-3,5-diphenylisoxazolidine (24):
oil; δ_H (100 MHz) 2.70 (3H,s,N-CH_3), 3.78 (1H,s,3-H), 7.25-7.61 (10H,m,Ar); m/z 242 (M^+, 27%), m/z 134 (100%, b. peak).

(±)-(3R,5S)-[3,5-$^2H_2$]-2-methyl-3,5-diphenylisoxazolidine (13):
oil; δ_H (100 MHz) 2.42 (1H,d,4-H), 2.69 (3H,s,N-CH_3), 3.08 (1H,d,$J_{4,4}$=11.5Hz,4-H), 7.20-7.55 (10H,m,Ar); m/z 241 (M^+, 23%), m/z 135 (100%, b. peak).

(±)-(3R,5R)-[3,5-$^2H_2$]-2-methyl-3,5-diphenylisoxazolidine (25):
oil; δ_H (100 MHz) 2.81 (2H,m,$J_{4,4}$=12.5Hz,4-H), 2.74 (3H,s,N-CH_3), 7.28-7.62 (10H,m,Ar); m/z 241 (M^+, 25%), m/z 135 (100%, b. peak).

Synthesis of isoxazolidines 14-19: 5 mmol of both nitrones **5** (or **7**) and the appropriate styrene were allowed to react in 5 ml of benzene in a screw capped vial at 80°C for 48 hrs. Crystallization from benzene of the residue afforded the pure epimers, whose yields and isotopic distribution are reported in the table.

(±)-(3R,5S)-[3-^2H]-2,3,5-triphenylisoxazolidine (14):
m.p. 101-102°C; δ_H (100 MHz) 2.48 (1H,t,$J_{4,4}$=12.5Hz,4-H), 3.18 (1H,q,4-H), 5.17 (1H,q,$J_{4,5}$cis=10.0Hz,$J_{4,5}$trans=5.5Hz,5-H), 6.87-7.60 (15H,m,Ar); m/z 302 (M^+, 25%), m/z 77 (100%, b. peak).

(±)-(3R,5S)-[4,4-$^2H_2$]-2,3,5-triphenylisoxazolidine (15):
m.p. 100-102°C; δ_H (100 MHz) 4.93 (1H,s,3-H), 5.17 (1H,s,5-H), 6.90-7.62 (15H,m,Ar); m/z 304 (M^+, 16%), m/z 77 (100%, b. peak).

(±)-(3R,5S)-[5-^2H]-2,3,5-triphenylisoxazolidine (16):
m.p. 101-102°C; δ_H (100 MHz) 2.48 (1H,q,$J_{4,4}$=12.5Hz,4-H), 3.18 (1H,q,4-H), 4.93 (1H,t,$J_{3,4}$cis=7.6Hz,$J_{3,4}$trans=7.6Hz,3-H), 6.92-7.60 (15H,m,Ar); m/z 302 (M^+, 32%), m/z 77 (100%, b. peak).

(±)-(3R,5S)-[3,4,4-$^2H_3$]-2,3,5-triphenylisoxazolidine (17):
m.p. 100-102°C; δ_H (100 MHz) 5.18 (1H,s,5-H), 6.92-7.60 (15H,m,Ar); m/z 304 (M^+, 38%), m/z 77 (100%, b. peak).

(±)-(3R,5S)-[4,4,5-$^2H_3$]-2,3,5-triphenylisoxazolidine (18):
m.p. 101-102°C; δ_H (100 MHz) 4.90 (1H,s,3-H), 6.91-7.65 (15H,m,Ar); m/z 304 (M^+, 35%), m/z 77 (100%, b. peak).

(±)-(3R,5S)-[3,5-$^2H_2$]-2,3,5-triphenylisoxazolidine (19):
m.p. 100-102°C; δ_H (100 MHz) 2.45 (1H,d,4-H), 3.18 (1H,d,$J_{4,4}$= 12.5Hz,4-H), 6.90-7.62 (15H,m,Ar); m/z 303 (M^+, 34%), m/z 77 (100%, b. peak).

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