^{17}O NMR SPECTROSCOPY OF HETEROCYCLES: SUBSTITUENT EFFECTS IN 3,5-DIARYL-ISOXAZOLES AND 3,5-DIARYLISOXAZOLINES

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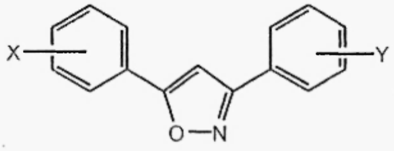
Abstract: The natural abundance ^{17}O NMR chemical shift data for 3,5-diarylisoxazoles (**1a-k**) and 3,5-diarylisoxazolines (**2a-j**) in acetonitrile at 75°C are reported. The ^{17}O NMR signals for the isoxazole oxygen of the 3-aryl-5-phenylisoxazoles showed a good correlation vs □ constants (rho = 6.3) while those for the isoxazoline oxygen of the 3-aryl-5-phenylisoxazolines showed an excellent correlation vs □ constants (rho = 13.4). The ^{17}O NMR data for the ring oxygen of 3-phenyl-5-arylisoxazoles and the 3-phenyl-5-arylisoxazolines, respectively, showed little or no sensitivity to substituent effects.

Introduction

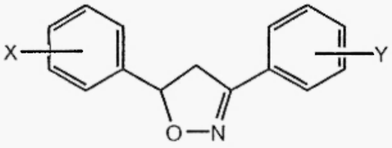
^{17}O NMR spectroscopy has been shown[1] to have applications in organic chemistry. ^{17}O NMR data can provide useful information regarding the electronic and/or geometrical structure for a variety of oxygen-containing organic compounds. Extensive reviews of organic ^{17}O NMR data are available,[1] organized by functional group type. For heterocyclic systems containing oxygen bound to nitrogen, there are only isolated reports of ^{17}O NMR data, especially for isoxazoles and isoxazolines (4,5-dihydroisoxazoles).[2,3] Furthermore, there is little or no information on aryl substituent effects on the ^{17}O chemical shift signal of the heterocyclic oxygen for these two heterocyclic ring systems. We report here the effect of aryl substitution on the ^{17}O NMR data for two series of heterocycles: 3,5-diarylisoxazoles and 3,5-diarylisoxazolines.

Results and Discussions

The natural abundance ^{17}O chemical shift data for the ring oxygen atom of eleven 3,5-diarylisoxazoles (**1a-k**) and ten 3,5-diarylisoxazolines (**2a-j**) were obtained in acetonitrile at 75 °C . The ^{17}O NMR signals for the 3-aryl-5-phenylisoxazoles showed a good correlation (r = 0.98) vs □ constants with a rho value of 6.3. The 3-phenyl-5-arylisoxazole ^{17}O NMR data results showed little or no sensitivity to substituent effects. The chemical shift data for these compounds are, essentially, within experimental error, identical (±1 ppm) to that observed (δ=331.5 ppm) for the parent 3,5-diphenylisoxazole. The data for the isoxazoles are summarized in Table 1. The ^{17}O NMR data for the 3-aryl-5-phenylisoxazolines exhibited a larger substituent chemical shift variation and showed an excellent correlation (r = 0.99) vs □ constants (rho = 13.4). The ^{17}O NMR signals for the 3-phenyl-5-arylisoxazolines showed little or no sensitivity to substituent effects; the chemical shift data were essentially within experimental error (±1 ppm) of that (δ=228 ppm) for 3,5-diphenylisoxazoline (**2h**). The data for the isoxazolines are summarized in Table 2.



1a-k



2a-j

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Table-1: ^{17}O Chemical Shift Data for 3,5-Diarylisoxazoles in Acetonitrile at 75 °C.

Compd.	X	Y	δ^a for O-N^b	δ^a for X or Y
1a	CF_3	H	331.0	--
1b	H	H	331.5	--
1c	4-F	H	331.5	--
1d	4-Me	H	331.0	--
1e	4-MeO	H	331.5	55 (630)^c
1f	H	4-CN	335.0	--
1g	H	3-Cl	333.0	--
1h	H	4-F	332.0	--
1i	H	4-Me	330.0	--
1j	H	4-MeO	329.0	56 (950)^c
1k	H	4-EtO	329.0	81 (600)^c

a) ±1 ppm; b) ν ½ = 750 ±100 Hz; c) ν ½ in Hz.

Table-2: ^{17}O Chemical Shift Data for 3,5-Diarylisoxazolines in Acetonitrile at 75 °C.

Compd.	X	Y	$\delta^{a,b}$ for O-N	$\delta^{a,b}$ for X or Y
2a	3-Br	H	227	--
2b	4-Cl	H	228	--
2c	4-F	H	229	--
2d	4-Me	H	229	--
2e	4-EtO	H	228	81
2f	H	3-Cl	233	--
2g	4-MeO	4-Cl	232	51
2h	H	H	228	--
2i	H	4-Me	226	--
2j	H	4-MeO	225	56

^{a} ±1 ppm; ^{b} ν ½ = 950 ± 100 Hz.

The chemical shift data observed for the 3,5-diarylisoxazoles (329-335 ppm) are generally upfield from those reported for alkyl substituted isoxazoles (336-356 ppm);[3c] the only aromatic substituted isoxazole listed in the literature (3-phenyl-5-trifluoromethyl) has a chemical shift of 330 ppm.[3c] The linewidths observed for the 3,5-diarylisoxazoles (750 ± 100 Hz) are much broader than those observed for alkylisoxazoles (90-160 Hz); they are closer in magnitude to those of isoxazoles with either nitro, tricholoromethyl or phenyl groups (400-600 Hz). The chemical shift data obtained for the 3,5-diarylisoxazolines appear about 20 ppm upfield to those for the only reported examples (alkyl-substituted or unsubstituted 5-hydroxyl-5-trichloromethylisoxazoline) which show in the range of 245-255 ppm;[3c] the linewidths for these other isoxazolines were not reported.

The present study appears to be the first to investigate aryl substituent effects on the ^{17}O chemical shift signal for the heterocyclic oxygen of these two heterocyclic ring systems. The 5-aryl groups of the isoxazoles and isoxazolines were expected to exhibit an inverse substituent effect for the heterocyclic oxygen signal similar to that observed in 4-substituted benzyl alcohols and esters.[4] The chemical shifts for 4-substituted benzyl alcohols had been shown to be very susceptible to the electronic effects of the substituents resulting in an inverse relationship due to the lack of conjugation of the oxygen with the aromatic ring.[4] This effect was not observed for either the 3-phenyl-5-aryl-isoxazolines or for the 3-phenyl-5-arylisoxazoles. All the chemical shift data were within experimental error of the parent for each series. On the other hand, the effect of the 3-aryl groups on the ^{17}O NMR data for the isoxazoles and isoxazolines show a trend similar to that observed for the oximes of 4-substituted benzaldehydes.[5] The chemical shift data for these oximes showed a poor correlation versus either σ or σ^+ constants attributed to a lack of conjugation between the oxygen atom and the aromatic ring.[5] In the present case, both series showed strong correlation with σ constants although the range of substituents investigated was limited due to low solubility of many of the compounds.

In conclusion, the correlation of the ^{17}O data with 3-aryl substituents for both series suggests strong conjugation between the rings. On the other hand, the lack of sensitivity of the ^{17}O data with 5-aryl substituents will require further investigation.

Experimental

The 3,5-diarylisoxazoles and 3,5-diarylisoxazolines were prepared by literature methods [**1a, 1d, 1f, 1i, 1k**;[6] **1b, 1c, 1e, 1h, 1j**;[7] **1g**;[8] **2b**;[9] **2d**;[10] **2f**;[11] **2g**;[12] **2h**;[13] **2i-j**[14]]. The melting points and the ^1H and ^{13}C chemical shift data for these compounds were in agreement with published results. Isoxazolines **2a, 2c** and **2e** are new compounds (see below). The ^{17}O NMR spectra were recorded on a Varian Inova 500 MHz NMR spectrometer, equipped with a 10 mm broad band probe under the following conditions: 48.3 kHz spectral width, 3K data points, 90^0 pulse angle, 0.075 ms acquisition delay and 30 ms acquisition time. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 100 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ± 0.2 ppm by zero filling to 8K data points. The NMR spectra were acquired at natural abundance on 0.3-0.5 M solutions, depending on the solubility, in anhydrous acetonitrile (Aldrich) at 75°C. The chemical shift data were referenced to the ^{17}O carbonyl signal of an internal standard: 1% 2-butanone (558.8 ± 0.1 ppm).

5-(3-Bromophenyl)-3-phenyl-4,5-dihydroisoxazole (2a). White crystals, m.p. 97-98 °C; MS: 301 (base 180); ^{13}C NMR (300 MHz, $CDCl_3$) δ 43.2, 81.5, 122.8, 124.4, 126.7, 128.7, 128.8, 129.1, 130.2, 130.3, 131.2, 143.3, 156. Anal. Calc. For $C_{15}H_{12}BrNO$: C, 59.62; H, 4.00; N, 4.64; found: C, 59.59; H, 3.94; N, 4.58.

5-(4-Fluorophenyl)-3-phenyl-4,5-dihydroisoxazole (2c). White crystals, m.p. 90-91.5 °C; MS: 241 (base 122); ^{13}C NMR (300 MHz, $CDCl_3$) δ 43.2, 81.9, 115.5, 115.8, 126.7, 127.6, 127.7, 128.7, 129.3, 130.2, 136.6, 136.7, 156.1, 160.9, 164.2. Anal. Calc. For $C_{15}H_{12}FNO$: C, 74.67; H, 5.01; N, 5.81; found: C, 74.57; H, 4.84; N, 6.12.

5-(4-Ethoxyphenyl)-3-phenyl-4,5-dihydroisoxazole (2e). White crystals, m.p. 96-97 °C; MS: 264 (base 148); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.7, 42.8, 63.4, 82.5, 114.6, 126.6, 127.3, 129.5, 130.0, 132.5, 156.2, 158.9. Anal. Calc. For $C_{17}H_{17}NO$: C, 76.38; H, 6.41; N, 5.24; found: C, 76.47; H, 6.51; N, 5.07.

Acknowledgments

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