Alfons L. Baumstark, Douglas R. Chrisope, Rebecca A. Keel and David W. Boykin*

Department of Chemistry, Laboratory for Microbial and Biochemical Sciences,
Georgia State University, Atlanta, Georgia 30303

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The assignment of the carbon-13 nmr resonances of 3-(aryl)-5-phenylisoxazoles (I) and 3-phenyl-5-(aryl)-isoxazoles (II) in dimethylsulfoxide-d_6 has been made. The assignments were made by using model compounds, chemical shift arguments, coupling with fluorine substituents, and shifts resulting from quaternization of the isoxazole ring. A carbon-13 nmr method for distinguishing between I and II which can be produced simultaneously by certain synthetic methods is presented.

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As a part of another investigation, it was necessary to prepare, rigorously characterize, and make carbon-13 nmr assignments for 3-(aryl)-5-phenylisoxazoles (I) and 3-phenyl-5-arylisoxazoles (II). Review of the literature reveals some confusion and uncertainty about the assignment of the structure to type I and II when isoxazoles are prepared by the reaction of hydroxylamine with 1,3-diaryl-

I II

1,3-diketones or chalcone dibromides (1,2). The latter approach is convenient because of the ready availability of the starting materials (3,4). However, the reaction of 4-substituted chalcone dibromides with hydroxylamine has been reported to form both structures I and II (5).

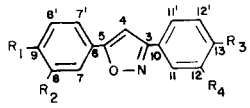
To employ the more convenient synthetic approach, it is essential to be able to distinguish between the isomeric products possible in those reactions. We report here a method to readily identify the 3,5-diarylisoxazole structure based on carbon-13 nmr spectroscopy as well as the assignment of the carbon-13 chemical shifts for several isoxazoles.

Carbon-13 nmr spectra were taken for a series of 3,5-diarylisoxazoles including the parent molecule, 3,5-diphenylisoxazole. In order to take advantage of fluorine coupling as an assignment tool, a number of fluoro-substituted compounds were also studied. The carbon-13 nmr spectra of the 3,5-diarylisoxazoles showed a number of similar features. The signal for carbon-4 always appeared upfield from the other aromatic signals and could be used to identify a compound as a 3,5-diarylisoxazole. The assignment of the upfield signal to carbon-4 is in accord with the previously reported assignments for a number of isoxazoles (6), the upfield position of the 4-proton (pmr) in these systems (7) and with its sensitivity to substituent effects (8). The signals for carbons-3 and -4 always appeared downfield from the other aromatic signals. The assignments and the chemical shift values for all carbon signals as well as fluorine-carbon coupling constants are listed in Table I.

The assignments of isoxazole structure as either I or II can be based on the changes observed in the chemical shift for carbon-4 relative to that of C-4 in the parent compound (**1**). Isoxazoles **2** and **3** have been previously prepared *via* an unambiguous route. The carbon-13 nmr

Table I

Assignment of Carbon-13 Nmr Chemical Shifts for 3,5-Diarylisoxazoles



Compound No.	R_1	R_2	R_3	R_4	3	4	5	6	7	7′	8	8′	9	10	11	11′	12	12′	13
1	H	H	H	H	162.2	98.3	169.3	126.5	125.2	125.2	128.9	128.9	130.0	128.2	126.2	126.2	128.7	128.7	129.8
2	MeO (a)	H	H	H	162.0	96.8	169.3	119.3	126.9	126.9	114.4	114.4	160.5	128.4	126.2	126.2	126.2	128.7	129.7
3	H	H	MeO (b)	H	161.8	98.0	169.0	126.6	125.2	125.2	128.8	128.8	129.9	120.6	127.7	127.7	114.2	114.2	160.3
4	AcNH (c)	H	H	H	162.1	97.2	169.3	121.2	126.0	126.0	118.9	118.9	140.9	128.4	126.2	126.2	128.7	128.7	129.8
5	H	H	AcNH (d)	H	161.8	98.1	169.1	126.7	125.2	125.2	128.9	128.9	130.0	122.7	126.8	126.8	118.9	118.9	140.8
6 (e)	F	H	H	H	162.2	98.2	168.3	123.2	127.7	127.7	116.0	116.0	157.7	128.2	126.2	126.2	128.7	128.7	129.8
7 (f)	H	F	H	H	162.2	99.3	168.0	128.5	112.1	121.3	162.0	131.1	116.9	128.0	126.1	126.1	128.7	128.7	129.9
7′ (f)	H	F	H	H	162.3	99.5	168.0	128.6	112.2	121.4	161.5	131.2	117.0	128.1	126.3	126.3	128.9	128.9	130.0
8 (g)	H	H	F	H	161.3	98.3	169.4	126.5	125.2	125.2	128.9	128.9	130.2	124.6	128.6	128.6	115.9	115.9	162.8
9 (h)	H	H	H	F	161.3	98.6	169.7	126.5	125.3	125.3	129.0	129.0	130.3	131.0	113.1	122.4	126.1	131.0	116.8

(a) CH_3 at 55.2. (b) CH_3 at 55.1. (c) C=O at 168.2; CH_3 at 24.0. (d) C=O at 168.1; CH_3 at 24.0. (e) $J_{1,9}$ (CF) = 249, $J_{2,8}$ (CF) = $J_{2,8}'$ = 22, $J_{3,7}$ (CF) = $J_{3,7}'$ (CF) = 9, $J_{4,6}$ = 3. (f) $J_{1,8}$ (CF) = 244, $J_{2,7}$ (CF) = 24, $J_{2,9}$ (CF) = 21, $J_{3,6}$ (CF) = 8, $J_{3,8}'$ (CF) = 9, $J_{4,5}$ (CF) = 3, $J_{4,7}'$ (CF) = 3. 7′ is 3-^{13}C-3-phenyl-5-(3′-fluorophenyl)isoxazole. (g) $J_{1,13}$ (CF) = 248, $J_{2,12}$ (CF) = $J_{2,12}'$ (CF) = 22, $J_{3,11}$ (CF) = $J_{3,11}'$ (CF) = 9, $J_{4,10}$ (CF) = 4. (h) $J_{1,12}$ (CF) = 244, $J_{2,11}$ (CF) = 23, $J_{2,13}$ (CF) = 20, $J_{3,10}$ (CF) = 9, $J_{3,12}$ (CF) = 9, $J_{4,5}$ (CF) = 3, $J_{4,11}$ (CF) = 3. For e-f: coupling constants are given in hertz, subscripts correspond to number of bonds of coupling and carbon number.

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Table II

Physical Data for 3,5-Diarylisoxazoles

Compound No.	M.p.	Formula	Analysis Calcd.	Analysis Found	^{1}H NMR for 4-H (δ) (b)
1	140-141° [lit. 141-143°] (a)	$C_{15}H_{11}NO$			6.8
2	125-126° [lit. 128-129°] (a)	$C_{16}H_{13}NO_2$			6.7
3	115-117° [lit. 115-117°] (a)	$C_{16}H_{13}NO_2$			6.8
4	185.5-186°	$C_{17}H_{14}N_2O_2$	C 73.36	73.13	6.7
			H 5.08	5.12	
5	200-202°	$C_{17}H_{14}N_2O_2$	C 73.36	73.14	6.8
			H 5.08	5.11	
6	165-166°	$C_{15}H_{10}FNO$	C 75.29	75.19	6.8
			H 4.22	4.25	
7	142-143°	$C_{15}H_{10}FNO$	C 75.29	75.33	6.8
			H 4.22	4.27	
8	166-167°	$C_{15}H_{10}FNO$	C 75.29	75.20	6.8
			H 4.22	4.25	
9	140-141°	$C_{15}H_{10}FNO$	C 75.29	75.20	6.8
			H 4.22	4.25	
10	160-162°	$C_{16}H_{13}FINO$	C 50.42	50.37	---
			H 3.44	3.46	

(a) Reference 7. (b) $CDCl_3$.

showed that when the anisyl group was in the 5-position the chemical shift of the carbon-4 signal was significantly affected. However, when the anisyl group was in the 3-position the chemical shift of the carbon-4 signal was relatively unchanged. Furthermore, the change in chemical shift of carbon-4 on variation of the para-substituent for compounds of type II is correlated reasonably well by σ^+ constants (8). Isoxazoles **4** and **5** were assigned using this criterion and illustrate the use of the method.

The assignments of the carbon-13 nmr spectra of the isoxazoles were achieved by employing chemical shift arguments (9) and fluorine coupling results (9b,10). The assignment of the furthermost downfield signals to the heterocyclic ring carbons-3 and -5 is consistent with electronegativity arguments, the assignments made for 3,5-dimethyisoxazole and related isoxazoles (6b,c), as well as other related 5-membered ring heterocyclics (9a), but differs with the reported assignments for 3-phenyl-5-methylisoxazole (6a). A tentative assignment of the signal of 169.3 ppm to carbon-5 in compound **1** is consistent with electronegativity arguments. The other downfield signal, 162.2 ppm, is only 7 ppm removed from C-5 and consequently to be confident that the assignments are rigorously correct, it was essential to confirm the designation by alternative means.

In order to achieve direct assignment, fluoro-substituted compounds **5-9** as well as a quaternary salt (**10**) were prepared. Since fluorine coupling beyond 4-carbon bonds is rare, to assign the chemical shifts of carbons-3 and -5 in these isoxazoles using fluorine coupling as an assignment aid, it was necessary to examine the *m*-fluoro-substituted compounds. In order to be sure of the identity of carbons experiencing fluorine coupling, a compound possessing two internal probes was necessary. To achieve this end, a 3,5-diarylisoxazole was synthesized containing one ^{13}C enriched carbon atom and a fluoro-substituent starting from 1-^{13}-C-1-phenyl-3(3'-fluorophenyl)-propenone. The downfield signal for this compound **7'** at 168.0 ppm appeared as a doublet $J_{4,5}$ (CF) = 3 Hz which was consistent with four bond fluorine coupling and the signal at 162.3 ppm is an intensified singlet consistent with the presence of the ^{13}C enrichment. This result confirmed the assignment based upon fluorine coupling. The effect of quaternization of **7** (**10**) on the carbon chemical shifts provides additional data in support of the assignment of the signals for carbons-3 and -5. The final ^{13}C nmr assignment of carbons-3, and -5 was made employing the quaternary salt of compound **7**. Similar to the reported changes in chemical shift on quaternization of pyridine (12), the signal at C-3 changed from 162.2 to 159.2. The signal at C-5 was relatively unaffected. In addition to allowing assignment of carbons-3 and -5, this approach also confirmed the structural assignment of compounds **7**, and **9**.

The assignments for the remaining carbons, those of the two aryl rings, were based upon chemical shift arguments, intensities of the signals, and particularly upon fluorine-

carbon coupling constants.

The carbon-13 nmr spectra of 3,5-diarylisoxazoles are definitive. Due to the resolution of C-13 nmr instruments, it is relatively straight forward to assign a compound to type I or II provided the value of σ^+ for the substituent is sufficiently large.

EXPERIMENTAL

Melting points were determined with a Thomas Hoover Uni-Melt apparatus in open capillary tubes and are uncorrected. Microanalyses were performed by Atlantic Microlabs, Atlanta Georgia. Infrared spectra were recorded with a Perkin-Elmer Model 710B spectrophotometer. ^1H nmr spectra were determined in deuteriochloroform using tetramethylsilane as an internal standard on a Varian EM360L spectrometer. ^{13}C nmr were obtained from a JEOL FX-60Q Fourier transform spectrometer operating at 15.04 MHz. Data were accumulated on a Texas Instrument 980B computer using 8192 data points over a 4 KHz spectra width to yield a data point resolution of 0.06 ppm. Noise-decoupled spectra were obtained by irradiation with a pulse width corresponding to 45° and a 5 second pulse repetition time. The ^{13}C nmr samples were prepared by weight as 0.2*M* solutions in commercial grade DMSO-d_6. The signals were referenced to tetramethylsilane by giving the most intense DMSO-d_6 signal the value of 39.6 ppm.

The procedure outlined below was employed to prepare all the isoxazoles reported in Table II. 1-^{13}-C-1-phenyl-3(3'-fluorophenyl)propenone was prepared from acetophenone 90% enriched at the carbonyl carbon (Merck Sharp and Dome Canada, Ltd.) which was diluted ten fold with unlabeled acetophenone. The location of the ^{13}C label was verified by examination of the ^{13}C nmr of the 1-^{13}C-1-phenyl-3(3'-fluorophenyl)-propenone.

3,5-Diarylisoxazoles.

A solution of 2.5 g. (0.02 mole) of acetophenone, 2.58 g. (0.02 mole) *m*-fluorobenzaldehyde, 1.1 g. sodium hydroxide in 16 ml. of 35% ethanol was stirred at room temperature for approximately 4 hours. The solid was filtered, washed with water, dried, and recrystallization from ethanol, yield 3.2 g. (68%), m.p. 51-52° [lit. m.p. (3) 51-52°].

The chalcone was dissolved in approximately 100 ml. of ether and bromine was added dropwise to the stirred solution until the bromine color persisted. The ether was allowed to partially evaporate and the resulting light yellow crystals were filtered and dried (4.3 g., 54%).

The dibromide (4.3 g., 0.011 mole) was used directly by suspending it in 80 ml. of ethanol to which 1.6 g. (0.022 mole) of hydroxylamine hydrochloride dissolved in 3 ml. of water was added. The solution was heated at reflux for 20 minutes. To the hot solution, potassium hydroxide (3.8 g., 0.067 mole) dissolved in 5 ml. of water was added dropwise during which time crystals started to appear. The reaction mixture was allowed to cool and filtered. The solid was washed with water and recrystallized from ethanol, yield 1.4 g. (30%) m.p. 142-143°.

Methyl-3-phenyl-5-(3'-fluorophenyl)isoxazolium Iodide (**10**).

A mixture of 0.5 g. (0.002 mole) of 3-phenyl-5-(3'-fluorophenyl)isoxazole and 2.0 g. (0.016 mole) of dimethyl sulfate were heated on a steam bath for 4 hours (13). The reaction mixture was allowed to cool and 5 ml. of 24% hydroiodic acid was added. The solution which deposited the yellow crystals of **10** was allowed to stand for 1 hour; the solid was filtered, washed with water and dried (yield 0.42 g., 53%, m.p. 160-162°); ^{13}C nmr (DMSO-d_6): C3 159.2, C4 105.9, C5 167.4, $J_{4,5}$ (CF) = 3 Hz, C6 124.7 $J_{3,6}$ (CF) = 9 Hz, C7 113.6 $J_{2,7}$ (CF) = 24 Hz, C7' 123.0, $J_{4,7'}$ (CF) = 3 Hz, C8 161.9 $J_{1,8}$ (CF) = 245 Hz, C8' 132.0, $J_{3,8}$ (CF) = 9, C9 120.3 $J_{2,9}$ (CF) = 21 Hz, C10 122.0, C11 129.4, C11' 129.4, C12 129.4, C12' 129.4, C13 133.3.

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