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Substituent effects on ^{15}N and ^{13}C NMR chemical shifts of 3-phenylisoxazoles: a theoretical and spectroscopic study

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The synthesis and assignment of ^{15}N and ^{13}C NMR signals of the isoxazole ring in a series of *para*-substituted 3-phenyl derivatives are reported. DFT calculations of ^{15}N and ^{13}C chemical shifts are presented and compared to observed values. Substituent effects are interpreted in terms of the Hammett correlation and calculated bond orders. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: ^{13}C NMR; ^{15}N NMR; chemical shifts; HMBC; DFT calculations; natural resonance theory; electronic effects; Hammett correlation; 3-phenylisoxazoles

INTRODUCTION

The 3-phenylisoxazole (1,2-oxazole) unit constitutes an important pharmacophore in a wide range of biologically and agriculturally active compounds.[1] Most of the reports assessed the impact of a series of substituents on the desired activity. Although substituent effects on ^{13}C NMR spectral assignments for 3-phenylisoxazoles (**1**) are unknown, such correlations have been reported for related heterocycles: 3,5-diphenylisoxazoles,[2] 2-phenyl-1,3,4-oxadiazoles,[3] 3-phenyl-1,2,4-oxadiazoles,[4] and 3-phenyl-1,2,5-oxadiazoles.[5] In particular, the extensive studies of Baumstark and coworkers on 3,5-diphenylisoxazoles established that *para* substituents on the 5-phenyl ring (**2a**) significantly affected the chemical shifts of isoxazole C-4 and C-5, while the same substituents on the 3-phenyl ring (**2b**) exerted minimal effect on either of these isoxazole ring carbons.[2] Those studies did note, however, that C-3 of **2b** was shielded by electron-withdrawing substituents. The same effect was observed for C-2 of oxadiazole **3** (see Fig. 1).[3]

In the NMR studies of the various oxazoles cited above, only for **3** were ^{15}N spectral assignments made.[3] Those data established a significant correlation for N-3 with electron-releasing substituents. Given the comparable electronic relationship between Y and N-2 and N-3 in **1** and **3**, respectively, and between X and C-4 in **2a**, an NMR study of a series of *para*-substituted 3-phenylisoxazoles (**1a**–**1i**) was undertaken to probe the transmission of substituent effects. To compare theory with experiment, density functional methods using the B3LYP functional and 6–311++G(2d,2p) basis set, which have been shown to be effective for the prediction of ^{13}C and ^{15}N chemical shifts,[6] were also employed. The theoretical component of this analysis also permitted commentary on bond orders of the isoxazole ring, a topic related to prior reports of electron densities of isoxazoles.[7]

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RESULTS AND DISCUSSION

Syntheses

Conversion of *para*-substituted benzaldehyde oximes (**4a**–**4i**) to 3-phenylisoxazoles (**1a**–**1i**) was carried out by a one-pot procedure (Scheme 1). The 1,3-dipolar cycloaddition of benzonitrile N-oxides (**5**) to alkynes or to substituted alkenes (as alkyne equivalents) is well documented.[8] The present method used phenyl vinyl sulfoxide and a solvent at the boiling point of which intramolecular elimination of phenylsulfenic acid occurred.[9] This sequence constituted a concise route to 3-phenylisoxazoles. The efficiency of measuring ^{15}N chemical shifts was increased by enhancing the ^{15}N content of **1a**–**1i** to *ca* 20%.

^{15}N NMR chemical shift analysis

The calculated and experimentally determined ^{15}N chemical shifts for our series of compounds, **1a**–**1i**, are listed in Table 1, arranged according to σ_p values.[10] As shown, the chemical shifts span a fairly narrow range (calculated: 11.0 ppm; experimental: 13.3 ppm), with a trend in shifts that is consistent with the electron-releasing or electron-withdrawing ability of the phenyl *para* substituent. As expected, electron-withdrawing groups cause a downfield shift (i.e., to less negative values, since CH_3NO_2 is the chemical shift reference) while electron-releasing groups lead to an upfield

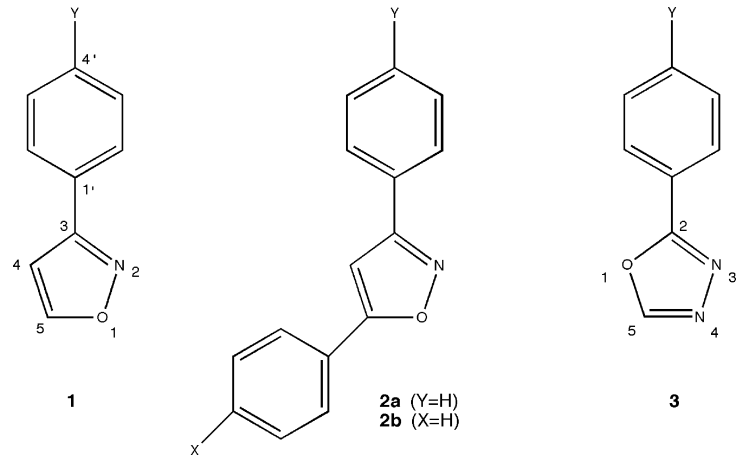
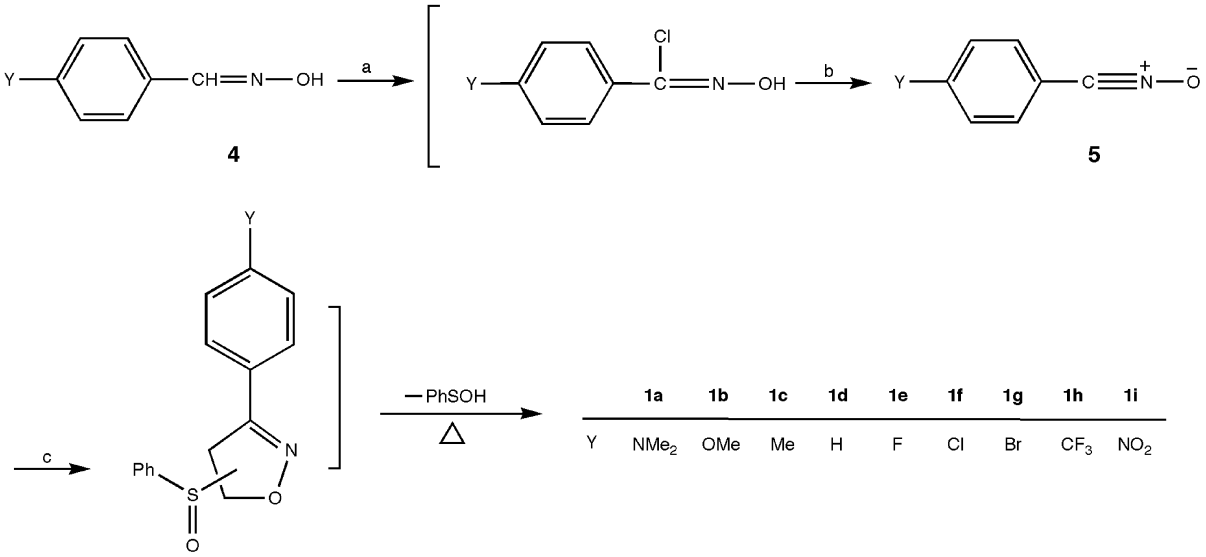


Figure 1. Phenylisoxazoles (**1**, **2**) and 2-phenyl-1,3,4-oxadiazole.



Scheme 1. Synthesis of 3-phenylisoxazoles (**1a–1i**). Reagents: (a) *N*-chlorosuccinimide, pyridine, 1,1,2-trichloroethane (TCE); (b) Et_3N, TCE; (c) Ph–SO–CH=CH_2, TCE.

shift. Similar effects have been observed for both N-3 and N-4 in 2-phenyl-1,3,4-oxadiazoles.[3] Although the calculated chemical shifts are consistently higher than the experimental values ($\Delta\delta_{ave}$ = 13.6), their variation ($\Delta\delta_{st.dev.}$ = 1.3 ppm) is small. This small systematic deviation, which is related to the calculated chemical shift of the reference compound (CH_3NO_2), is in agreement with the study by Cheeseman *et al.*[6] and does not compromise the excellent correlation between theory and experiment. Moreover, the calculated natural charge of the isoxazole ring nitrogen (N-2) is entirely consistent with the increasing electron donating ability of the phenyl ring substituent. Thus, the calculated charge on N-2 mirrors the observed (and calculated) chemical shifts nicely.

The data in Table 1 also display the expected response of the ^{15}N chemical shifts to σ_p Hammett values. Graphical analysis of the experimental shifts gave a trend line with a positive slope (ρ = 9.18) and excellent linear correlation (r^2 = 0.9853). The strongly positive ρ value is entirely consistent with our observation that ^{15}N chemical shifts are highly sensitive to the electronic nature of the phenyl *para* substituent and they were congruent with analogous measurements reported for **3**.[3]

Table 1. Experimental and calculated ^{15}N NMR chemical shift data (δ, relative to CH_3NO_2 = 0.00 ppm) Hammett substituent constants and natural atomic charges of N-2 for isoxazoles **1a–1i**

Compd.	Y	σ_p[a]	Calcd.	Expt.	Natural charge
1a	NMe_2	−0.83	0.43	−14.50	−0.164
1b	OMe	−0.27	2.74	−10.28	−0.161
1c	Me	−0.17	5.52	−10.05	−0.154
1d	H	0.00	6.50	−9.07	−0.147
1e	F	0.06	4.86	−7.79	−0.150
1f	Cl	0.23	6.47	−6.68	−0.146
1g	Br	0.23	6.54	−6.54	−0.146
1h	CF_3	0.54	9.21	−3.05	−0.144
1i	NO_2	0.78	11.47	−1.24	−0.134

[a] Ref. 10.

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Table 2. Experimental and calculated ^{13}C NMR chemical shift data (δ, relative to $CDCl_3 = 77.00$ ppm) and Hammett substituent constants of C-3, C-4, and C-5

			C-3		C-4		C-5	
Compd.	Y	σ_p[a]	Calcd.	Expt.	Calcd.	Expt.	Calcd.	Expt.
1a	NMe_2	−0.83	168.03	161.46	103.94	101.93	164.18	158.19
1b	OMe	−0.27	167.81	161.09	104.28	102.18	164.84	158.62
1c	Me	−0.17	168.15	161.42	104.49	102.33	164.89	158.68
1d	H	0.00	168.56	161.48	104.87	102.42	165.08	158.85
1e	F	0.06	167.42	163.82	104.52	102.32	165.35	159.02
1f	Cl	0.23	167.35	160.45	104.58	102.26	165.51	159.07
1g	Br	0.23	167.33	160.63	104.56	102.31	165.54	159.17
1h	CF_3	0.54	167.39	160.39	104.98	102.5	165.95	159.43
1i	NO_2	0.78	166.93	159.82	105.18	102.66	166.36	159.77

[a] Ref. 10.

^{13}C NMR chemical shift analysis

The corresponding ^{13}C chemical shifts for compounds **1a**–**1i** are presented in Table 2. We found that the calculated and experimental ranges of chemical shifts agreed closely. However, the correlations with Hammett σ_p constants for phenyl *para* substituents were weak (r^2: C-3, 0.1883; C-4, 0.8432; C-5, 0.7194), which we attribute to the fact that the narrow range of ^{13}C chemical shifts observed is similar to the variance in the calculations. At first glance, it may seem unusual that the ^{15}N chemical shift is sensitive to the phenyl *para* substituent, while the ^{13}C chemical shifts, particularly at C-3, are not. In an effort to understand the chemical shift data, the Wiberg bond indices for the isoxazole ring were calculated (Table 3).

For the series of compounds examined, the O-1/N-2 bond order increases with the electron-withdrawing ability of the phenyl *para* substituent. This trend is in agreement with the resonance model shown in Fig. 2, in which excess electron density provided by electron-releasing groups is localized on the isoxazole N-2 atom (structure I), whereas electron density removed by electron-withdrawing groups is offset by the O-1 lone pair (structure III). Consistent with this model, the calculated natural charge of the isoxazole N-2 atom decreases with increasing electron release of the phenyl *para* substituent (Table 1). Furthermore, this model also anticipates the results of the Wiberg bond index calculations. As shown in Table 3, the C-3/C-1′ bond order increases for phenyl ring substituents that are either strongly releasing or withdrawing (e.g. NMe_2, NO_2), but the bond order decreases for less-polarizing substituents (e.g. H). Consistent with this model, the N-2/C-3 bond order follows a different trajectory with the lowest bond order observed for the most polarizing phenyl substituent (**1a**). Finally, the O-1/N-2 bond order increases monotonically with the electron-withdrawing ability of the phenyl substituent. In other words, the isoxazole ring has the capacity to attenuate strongly polarizing substituents bound at the isoxazole C-3 position. On the basis of these results, the isoxazole C-3 atom should be (and is) relatively insensitive to the nature of the phenyl *para* substituent, while the isoxazole N-2 atom should be (and is) sensitive to the nature of the phenyl substituent.

EXPERIMENTAL

Melting points were determined on a MelTemp apparatus and were uncorrected. Extracts were dried over Na_2SO_4, and solvents were removed by rotary evaporation at reduced pressure. Silica gel 60 (230–400 mesh) was used for flash liquid chromatography; solvent systems for elution were hexane-ethyl acetate (9:1 to 4:1 v/v). Product purities were determined by gas chromatography-mass spectrometry analysis on a Hewlett-Packard HP 6890 system equipped with a HP-5MS cross-linked diphenyl (5%) dimethyl (95%) polysiloxane capillary column (30 m × 0.25 mm × 0.25 μm

Table 3. Calculated Wiberg bond orders of isoxazoles **1a**–**1i**

Compd.	Y	σ_p[a]	O-1/N-2	N-2/C-3	C-3/C-4	C-4/C-5	C-5/O-1	C-3/C-1′
1a	NMe_2	−0.83	1.043	1.569	1.207	1.639	1.104	1.064
1b	OMe	−0.27	1.048	1.572	1.212	1.636	1.105	1.059
1c	Me	−0.17	1.052	1.575	1.213	1.636	1.104	1.056
1d	H	0.00	1.054	1.581	1.217	1.635	1.104	1.054
1e	F	0.06	1.054	1.579	1.217	1.634	1.105	1.056
1f	Cl	0.23	1.056	1.579	1.218	1.634	1.104	1.056
1g	Br	0.23	1.057	1.578	1.218	1.634	1.104	1.056
1h	CF_3	0.54	1.061	1.573	1.218	1.633	1.104	1.053
1i	NO_2	0.78	1.067	1.574	1.221	1.632	1.103	1.057

[a] Ref. 10.

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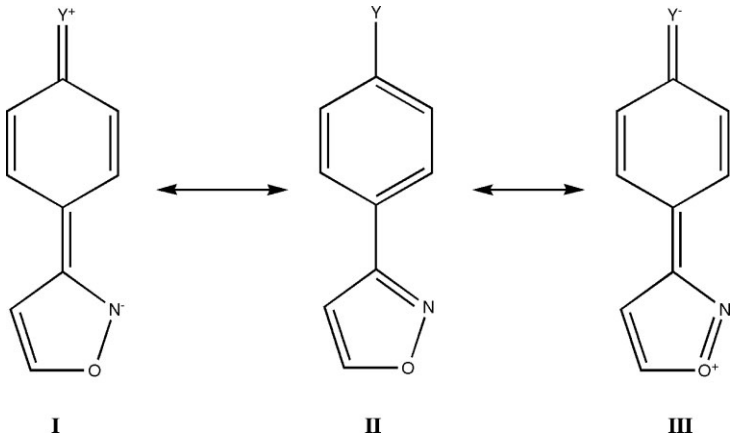

Figure 2. Resonance effects in 3-phenylisoxazoles.

film), a 5973 mass selective detector, and a HP Kayak XA computer. HRMS analyses were performed by the Nebraska Center for Mass Spectrometry at the University of Nebraska-Lincoln.

Compounds

*Preparation of oximes (**4a–4i**)*

Oximes were prepared by a standard procedure employing condensation of a *para*-substituted benzaldehyde with hydroxylamine hydrochloride (**6**).[11] Oximes **4a–4i** have been reported previously; their physical constants and spectral data matched literature values.[12–17]

*Preparation of 3-phenylisoxazoles (**1a–1i**). General procedure*

To a solution of *N*-chlorosuccinimide (0.267 g, 2.00 mmol) and pyridine (0.010 ml, 0.124 mmol) in TCE (2.1 ml) was added **4** (2.00 mmol) and the solution was stirred at 50 °C for 30 min. A solution of phenyl vinyl sulfoxide (0.335 g, 2.20 mmol) and triethylamine (0.29 ml, 2.01 mmol) in TCE (0.35 ml) was added dropwise via Pasteur pipet over 3 min, and the solution was stirred at reflux for 30 min. The reaction mixture was evaporated to dryness and the residue was treated with 2M NaOH (10 ml). The mixture was stirred at reflux for 30 min, neutralized with saturated NH_4Cl solution, and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to give crude product. Purification by flash liquid chromatography removed Ph_2S_2 (**7**) coproduct and afforded **1** in >99% purity. Isoxazoles **1b–1g, 1i** have been reported previously; their physical constants and spectral data matched literature values.[18–25]

*3-(4-Dimethylaminophenyl)isoxazole (**1a**).* m.p. 120.5–121.5 °C. HRMS for $C_{11}H_{12}N_2O$ $[M]^+$ requires 188.0950. Found: 188.0944.

*3-(4-Trifluoromethylphenyl)isoxazole (**1h**).* m.p. 98.0–98.55 °C. HRMS for $C_{10}H_6F_3NO$ $[M+H]^+$ requires 214.0480. Found: 214.0474.

For the preparation of ^{15}N-enriched **1**, natural-abundance **6** was mixed (4 : 1 w/w) with ^{15}N-enriched **6** (Cambridge Isotope Laboratories, Inc.; 98.6% ^{15}N) to give *ca* 20% ^{15}N enrichment. To maximize the efficiency of obtaining ^{15}N chemical shifts, some spectra were measured prior to the chromatographic removal of **7**.

NMR spectroscopy

NMR spectra were measured at 298 K with a Bruker Avance DRX 500 MHz NMR spectrometer operating at frequencies of 500.630 (^1H), 125.884 (^{13}C), and 50.748 (^{15}N) using a 5-mm inverse gradient (TXI) probehead (90° pulse widths: ^1H, 7.4 μs; ^{13}C, 12.5 μs; and ^{15}N, 40.0 μs).

Chemical shifts for ^1H and ^{13}C (ppm) were measured relative to internal Me_4Si; ^{15}N chemical shifts were measured relative to an external solution of $CH_3NO_2/CDCl_3$ (1 : 2, v : v) in a 1-mm diameter coaxial insert tube. Samples for measurement of ^1H and ^{13}C chemical shifts were prepared in $CDCl_3$; ^{15}N NMR samples, which were *ca* 20% enriched in ^{15}N, were prepared with concentrations ranging from 12 to 64 mg per 400 μl of $CDCl_3$ as solvent.

Two-dimensional $^1H,^{15}N$ gradient selected (heteronuclear multiple-bond coherence) HMBC experiments were performed to observe ^{15}N chemical shifts using a standard pulse sequence (hmbcgpndqf) from the Bruker pulse sequence library. The $^1H,^{15}N$ correlation observed ($^3J(^1H,^{15}N)$) was that between the isoxazole N-2 and the ^1H at C-4 (chemical shift δ 6.6–6.8). For optimal simultaneous observation of both the $^2J(^1H,^{15}N)$ correlations in CH_3NO_2, and the $^3J(^1H,^{15}N)$ correlations in our analytes, a value of 8 Hz was used for the parameter CNST13, which sets the pulse sequence delay for evolution of multiple-bond couplings. Spectral windows were set at 6 ppm in ^1H and 100 ppm in ^{15}N. A total of 16 scans of 1024 data points were collected along the t_2-axis and then zero-filled to 2048 points prior to Fourier transformation (FT). In the indirect (t_1) dimension, 128 time increments were collected and zero-filled to 1024 prior to FT. Total acquisition time per sample was *ca* 1 h. Chemical shift measurement accuracy was estimated to be better than ±0.1 ppm.

Computational methods

All computations were carried out using Gaussian 03 program[26] and employed the B3LYP functional.[27] Substituted 3-phenylisoxazoles were optimized using the very tight convergence criteria in the gas phase (the 6–311++g(2d,2p)

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basis set was used for all models) and frequency calculations were performed to demonstrate that each structure represented the minimum energy. No imaginary frequencies were observed. Performing the same calculations using an ultrafine integration grid gave similar results. ^{15}N and ^{13}C chemical shifts were calculated using the GIAO method[28–31] and were referenced to the calculated chemical shift of CH_3NO_2 and $CDCl_3$, respectively, optimized at the same level of theory. Wiberg bond indices[32] and natural population analysis charges[33] were calculated using NBO 3.1.[34]

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