Synthesis and Spectroscopic Properties of ^{15}N-Labelled 1,2,4-Thiadiazoles

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5-Phenyl-1,2,4-thiadiazole-4-^{15}N and 3-methyl-5-phenyl-1,2,4-thiadiazole-4-^{15}N were synthesized from commercially available benazmide-^{15}N. The mass spectra and the ^{1}H, ^{13}C, and ^{15}N-nmr spectra of these compounds, which show various long-range heteronuclear coupling with the ^{15}N-nucleus, are discussed.

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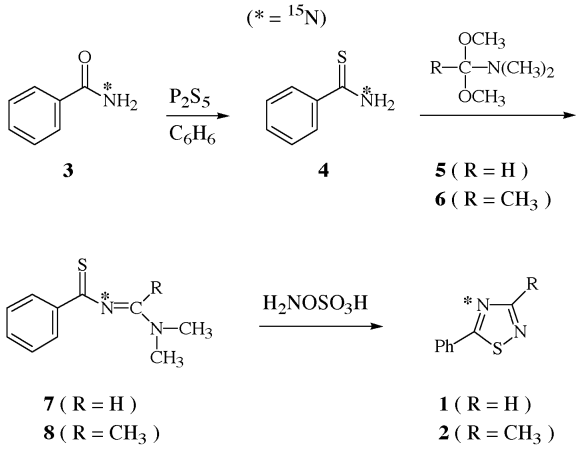
As part of our interest in the chemistry of phenyl substituted 1,2,4-thiadiazoles, we found it necessary to distinguish between the two nitrogen atoms in the 1,2,4-thiadiazole ring. To accomplish this we have synthesized 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**1**) and 3-methyl-5-phenyl-1,2,4-thiadiazole-4-^{15}N (**2**). In this paper we report the syntheses of these compounds and their spectroscopic properties.

Results and Discussion.

^{15}N-labelled thiadiazoles **1** and **2** were synthesized from commercially available benzamide-^{15}N (**3**) [1] according to the procedure shown in Scheme 1 developed by Lin and colleagues for the synthesis of unlabelled thiadiazole **1** [2].

Scheme 1

(* = ^{15}N)



3 **4** **5** (R = H) **6** (R = CH_3) **7** (R = H) **8** (R = CH_3) **1** (R = H) **2** (R = CH_3)

This sequence began with the reaction of benzamide-^{15}N (**3**) with P_2S_5 in benzene to provide thiobenzamide-^{15}N (**4**) in 60% yield [3]. The mass spectrum of **4** exhibited a molecular ion as the base peak at m/z 138 which corresponds to the molecular weight of **4**. The spectrum also exhibited a peak at m/z 137 with an intensity of 18% of the peak at m/z 138. This peak at m/z 137 could be due to an M-1 peak resulting from loss of hydrogen from the molecular ion or from the presence of thiobenzamide-^{14}N in the sample. The mass spectrum of thiobenzamide-^{14}N also exhibited a molecular ion at m/z 137 and an M-1 peak at m/z 136 with an intensity of 18% of the molecular ion. This confirms that loss of hydrogen is a normal fragmentation pathway for thiobenzamide-^{14}N and therefore will also be a normal fragmentation pathway for thiobenzamide-^{15}N (**4**). The peak at m/z 137 in the mass spectrum of thiobenzamide-^{15}N (**4**) is therefore not due to the presence of thiobenzamide-^{14}N in the sample.

The ^{1}H-nmr spectrum of thiobenzamide-^{15}N (**4**) is more complicated than the ^{1}H-nmr spectrum of unlabelled thiobenzamide [4] due to the heteronuclear coupling between the ^{1}H and ^{15}N nuclei. As a result of this coupling the two non-equivalent amide protons appear as double doublets at δ 7.24 and 7.82 ($J_{^1H - ^{15}N}$ = 89.5 Hz, $J_{^1H - ^1H}$ = 4.2 Hz). As a result of this ^{1}H-^{15}N coupling, the ^{15}N nucleus of **4** appeared in the ^{15}N-nmr spectrum at δ 134.8 as a triplet (J = 91.2 Hz), which is within experimental error of the coupling constant observed in the ^{1}H-nmr spectrum [5]. The ^{13}C-nmr spectrum of **4** exhibited signals for the thiocarbonyl carbon at δ 203.3 and for the carbons of the phenyl ring at δ 127.3, 128.9, 132.5, and 139.5. The absence of the latter signal in the DEPT-135 spectrum confirmed that this signal is due to C-1 of the phenyl ring. Interestingly, although all of these signals appear as sharp singlets in the proton decoupled spectrum of unlabelled **4**, the signals due to the thiocarbonyl carbon at δ 203.3 and the C-1 carbon of the phenyl ring at δ 139.5 of labelled **4** appeared as doublets with J = 13.3 and 3.1 Hz respectively due to their coupling with the ^{15}N nucleus.

N-[(Dimethylamino)methylene]thiobenzamide-^{15}N (**7**) or *N*-[(Dimethylamino)ethylidene]thiobenzamide-^{15}N (**8**), the precursors of **1** or **2**, were synthesized in 60% or 82% respectively by the condensation of thiobenzamide-^{15}N (**4**) with *N*,*N*-dimethylformamide dimethyl acetal (**5**) or *N*,*N*-dimethylacetamide dimethyl acetal (**6**) at room temperature.

The ^{1}H-nmr spectrum of **7** exhibited a singlet a δ 8.78 due to the imine proton. Although no coupling of this proton with the ^{15}N nucleus was observed in the ^{1}H-nmr spectrum, coupling was observed in the ^{15}N-nmr spectrum

which exhibited a doublet (J = 2.0 Hz) at δ 268.7 due to coupling of the ^{15}N-nucleus with the imine proton. The ^{1}H-nmr spectrum of **7** also exhibited two 3H singlets at δ 3.24 and 3.25 which correlated with signals in the ^{13}C-nmr spectrum at δ 36.4 and 41.9. The phenyl protons of **7** appeared as a 3H multiplet in the ^{1}H-nmr spectrum at δ 7.29-7.52 due to the *meta* and *para* protons, which correlated with signals in the ^{13}C-nmr spectrum at δ 127.7 and 131.9, and a 2H multiplet at δ 8.36-8.41 due to the *ortho* protons, which correlated with a doublet (J = 2.6 Hz) in the ^{13}C-nmr spectrum at δ 128.8 due to the *ortho* ring carbons. This is presumably due to the long-range coupling of the *ortho* carbons with the ^{15}N nucleus since no analogous coupling was observed in the unlabelled compound. The ^{13}C-nmr spectrum of **7** also shows that although the imine carbon of **7** appears as a doublet (J = 9.6 Hz) at δ 159.0 due to its coupling with the ^{15}N nucleus, the thiocarbonyl carbon appears as a sharp singlet at δ 216.1. Lack of coupling of this carbon with the ^{15}N nucleus is surprising since coupling between the ^{15}N nucleus and the carbonyl carbon was observed in benzamide-^{15}N (**3**) and thiobenzamide-^{15}N (**4**).

The ^{1}H-nmr spectrum of **8** exhibited 3H singlets at δ 3.91, 3.21, and 2.47 due to the two non-equivalent *N*-methyl groups and the allyl methyl group, respectively, which correlated with signals in the ^{13}C-nmr spectrum at δ 39.6, 39.7, and 18.4 respectively. The phenyl protons appeared in the ^{1}H-nmr as a 3H multiplet due to the meta and para hydrogens at δ 7.29-7.42, which correlated with singlets in the ^{13}C nmr spectrum at δ 128.0 and 131.3 due to the *meta* and *para* carbons respectively, whereas the *ortho* hydrogens appeared as a 2H multiplet at δ 8.22-8.24, which correlated with a doublet in the ^{13}C-nmr spectrum at δ 128.8 (J = 2.1 Hz) due to long-range coupling with the ^{15}N nucleus. The C-1 carbon of the phenyl ring, the imine carbon, and the thiocarbonyl carbon also exhibited coupling with the ^{15}N nucleus and appeared as doublets in the ^{13}C-nmr spectrum at δ 142.9 (J = 8.2 Hz), 168.3 (J = 12.3 Hz), and 202.7 (J = 6.8 Hz) respectively. The ^{15}N nucleus appeared as a sharp singlet at δ 291.4 in the ^{15}N-nmr spectrum.

5-Phenyl-1,2,4-thiadiazole-4-^{15}N (**1**) or 3-methyl-5-phenyl-1,2,4-thiadiazole (**2**) were each prepared in 80% yield by reaction of **7** or **8** with hydroxylamine-*O*-sulfonic acid at room temperature.

The mass spectrum of 5-phenyl-1,2,4-thiadiazole-4-^{15}N (**1**) exhibited a molecular ion at m/z 163 with no signal at m/z 162 indicating the absence of unlabelled **1** in the sample. The spectrum also exhibited a base peak at m/z 136 and an intense peak (92% of the base peak) at m/z 105 and a smaller peak (27% of 105 peak) at m/z 104. The signal at m/z 136 was assigned to the $[PhC^{15}NS]^{+\bullet}$ fragment formed by elimination of H-C≡^{14}N from the molecular ion. No signal was observed at m/z 135 showing that only H-C≡^{14}N was eliminated indicating that the two ring nitrogens do not interchange during fragmentation. The signal at m/z 105 was assigned to the [Ph-C≡^{15}N-H]$^{+\bullet}$ fragment formed by elimination of CNS from the molecular ion while the peak at m/z 104 was assigned to the [Ph-C≡^{15}N]$^{+\bullet}$ fragment formed by the elimination of HC^{14}NS. No signal was observed at m/z 103 which would be expected if nitrogen interchange led to the formation of [Ph-C≡^{14}N]$^{+\bullet}$. The mass spectrum of unlabelled **1** showed an analogous fragmentation pattern. Thus, in addition to an intense peak at m/z 135 due to the $[PhC^{14}NS]^{+\bullet}$ fragment formed by elimination of H-C≡^{14}N, the spectrum also had signals at m/z 104 due to the [Ph-C≡^{14}N-H]$^{+\bullet}$ fragment and a smaller signal at m/z 103 (26% of 104 peak) due to [Ph-C≡^{14}N]$^{+\bullet}$. The spectra of **1** and unlabelled **1** both exhibited intense peaks at m/z 77 (58% of base peak) due to $[C_6H_5]^{+\bullet}$ and at m/z 59 (57% of base peak) due to the formation of $[HCNS]^{+\bullet}$.

As expected, the mass spectrum of 3-methyl-5-phenyl-1,2,4-thiadiazole-4-^{15}N (**2**) exhibited a molecular ion at m/z 177 and a base peak at m/z 136 again assigned to the [Ph-C^{15}NS]$^{+\bullet}$ fragment formed in this case by elimination of $CH_3C{\equiv}^{14}N$. Again, no signal at m/z 135 was observed showing that only CH_3-C≡^{14}N was eliminated confirming that nitrogen scrambling does not occur during the fragmentation process. The spectrum also showed an intense signal at m/z 73 (77% of base) assigned to the $(CH_3\text{-}C^{14}NS)^{+\bullet}$ fragment formed by elimination of Ph-C≡^{15}N and a small peak at m/z 104 (12% of base) due to the formation of a small amount of [Ph-C≡^{15}N]$^{+\bullet}$.

The ^{1}H-nmr spectrum of **1** exhibited a doublet (J = 13.9 Hz) at δ 8.84 due to the proton at position 3 of the thiadiazole ring coupling with the ^{15}N nucleus at ring position 4. Furthermore, the ^{15}N-nmr spectrum showed a doublet (J = 13.9 Hz) at δ 304.2 confirming this coupling. This doublet in the ^{1}H-nmr spectrum correlated with a doublet at δ 164.6 (J = 3.8 Hz) in the ^{13}C-nmr spectrum that was therefore assigned to the carbon at ring position 3 which is also coupled to the ^{15}N nucleus of **1**. In contrast, both of these signals appeared as singlets in the ^{1}H and ^{13}C-spectra of unlabelled **1**. Interestingly, the C-5 carbon of the thiadiazole ring exhibited no coupling with the ^{15}N nucleus but appeared as a sharp singlet in the ^{13}C-nmr spectrum at δ 188.9.

In addition, the ^{1}H-nmr spectrum of **1** exhibited a 3H multiplet at δ 7.59-7.61 due to the *para* and *meta* phenyl protons, which correlated with signals in the ^{13}C-nmr spectrum at δ 130.3 and 133.0 assigned to the *meta* and *para* carbons respectively, and a 2H multiplet at δ 8.05-8.08 due to the *ortho* phenyl protons, which correlated with the signal in the ^{13}C-nmr spectrum at δ 128.2 assigned to the two equivalent *ortho* phenyl ring carbons. Furthermore, the doublet (J = 6.3 Hz) in the ^{13}C-nmr spectrum at δ 131.1 was assigned to the quaternary C-1 carbon of the phenyl ring since this signal was not observed in the ^{1}H-^{13}C correlation or DEPT-135 spectra. The signal again shows long-range coupling between the C-1 phenyl carbon and the ^{15}N nucleus.

In the ^{1}H-nmr spectrum of **2** the signal due to the C-3 ring proton was replaced by a 3H doublet at δ 2.71 (J = 2.3 Hz) showing long range coupling of the methyl protons with the ^{15}N nucleus. As expected by this coupling, the ^{15}N nucleus appeared as a quartet (J = 2.7 Hz) at δ 303.6 in the ^{15}N-nmr spectrum. The ^{1}H-nmr spectrum of **2** also exhibited 3H and 2H multiplets at δ 7.46-7.50 and at δ 7.90-7.92 due to the *para-meta* and *ortho* phenyl ring protons respectively. The ^{1}H-^{13}C correlation and DEPT-135 spectra allowed the signals in the ^{13}C-NMR spectrum at δ 127.8 (d, J = 1.9 Hz), 129.7, 130.9 (d, J = 6.1 Hz), and 132.3 to be assigned to the *ortho*, *meta*, C-1, and *para* carbons, respectively. Thus, both the C-1 and *ortho* ring carbons exhibit long-range coupling with the ^{15}N nucleus. As in the case of **1**, the C-3 and C-5 carbons of the thiadiazole ring were observed in the ^{13}C-nmr spectrum as a doublet (J = 2.3 Hz) at δ 174.5 and as a singlet at δ 188.5. Thus, as was observed in the spectrum of **1**, coupling was observed between the ^{15}N nucleus and the carbon at ring position 3 but not with the carbon at ring position 5 of the thiadiazole ring.

EXPERIMENTAL

^{1}H, and ^{13}C spectra were recorded at 400.1 and 100.6, MHz in deuteriochloroform on a Bruker FT-NMR system. ^{1}H and ^{13}C chemical shifts were measured relative to internal tetramethylsilane and chloroform, respectively. ^{1}H-^{13}C correlation spectra were recorded using the HETCOR (HCCOSW) experiment in the Bruker system. ^{15}N-nmr spectra were recorded at 40.5 Mhz in acetone-d_6. The ^{15}N chemical shifts are reported in ppm downfield from $NH_{3(l)}$ ($\delta NH_{3(l)}$ = 0.0) and were measured relative to aqueous $Na^{15}NO_3$ which was used as an external standard and taken to absorb at 378.4 ppm downfield from $NH_{3(l)}$ [6]. Mass spectra were recorded with an HP 5970B mass selective detector interfaced to an HP 588 capillary gas chromatograph.

Throbenzamide-^{15}N (**4**).

A solution of 1.0 g (8.2 mmoles) of benzamide-^{15}N (**3**) and 0.36 g of phosphorous pentasulfide (1.6 mmoles) in 6 ml of benzene was magnetically stirred and heated at reflux for 50 minutes. The hot yellow benzene solution was decanted and the residual red solid was extracted with four 3 ml portions of hot benzene. The combined benzene solution was concentrated and allowed to cool to yield a yellow crystalline solid which was purified on a silica gel column (3.5 x 22 cm), prepacked in dichloromethane. Elution of the column with dichloromethane gave a homogeneous yellow solid, which was recrystallized from chloroform:hexane to yield 0.6 g (60%), mp 113-115°.

N-[(Dimethylamino)methylene]thiobenzamide-^{15}N (**7**) and *N*-[(Dimethylamino)ethylidene]thiobenzamide-^{15}N (**8**).

A mixture of **4** (0.50 g, 2.60 mmoles) and *N*,*N*-dimethylformamide dimethyl acetal (**5**) (0.50 g, 4.2 mmoles) or *N*,*N*-dimethylacetamide dimethyl acetal (**6**) (0.44 g, 3.3 mmoles) was stirred in an argon atmosphere while several addition drops of **5** or **6** was added to completely dissolve any remaining **4**. The resulting red mixture was allowed to stir at room temperature under argon for 30 minutes. Removal of volatile materials *in vacuo* gave a red-orange or orange solid that was recrystallized from ethanol to give orange crystals of **7** (0.61 g, 60%), mp 52-54° or orange crystals of **8** (0.70 g, 82%), mp 110-113°.

5-Phenyl-1,2,4-thiadiazole-4-^{15}N (**1**) or 3-Methyl-5-phenyl-1,2,4-thiadiazole-4^{15}N (**2**).

A solution of hydroxylamine-*O*-sulfonic acid (0.34 g, 3.0 mmoles) in absolute methanol (10 ml) was added to a solution of **7** (0.48 g, 2.50 mmoles) in absolute ethanol (10 ml) containing pyridine (0.50 ml, 6.2 mmoles) in an argon atmosphere or to a solution of **8** (0.52 g, 2.50 mmoles) in absolute ethanol (15 ml) containing pyridine (0.50 ml, 6.2 mmoles) in an argon atmosphere. The reaction mixture was stirred at room temperature for 1 hour. Evaporation *in vacuo* gave a yellow viscous residue that was dissolved in dichloromethane (50 ml), washed with water (15 ml), 0.1 *N* aqueous sodium hydroxide (15 ml), and water (15 ml) and then dried over anhydrous sodium sulfate. Evaporation gave **1** as a yellow oil (0.48 g) which was purified by distillation (Kugelrohr, oven temperature 40-50°, 0.4 Torr) to give **1** as a colorless oil (0.34 g, 84%) or **2** as a light yellow solid (0.42 g) that was recrystallized from hexane to give a yellow solid which was sublimed (60°, 20 Torr) to give **2** (0.35 g, 80%) as white crystals, mp 50-52°.

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