

James W. Pavlik [a], Chutchawin Changtong [a] and Supawan Tantayanon [b]

[a] Department of Chemistry and Biochemistry, Worcester Polytechnic Institute, Worcester, MA 01609

[b] Department of Chemistry, Chulalongkorn University, Bangkok, 10330, Thailand

Received July 24, 2001

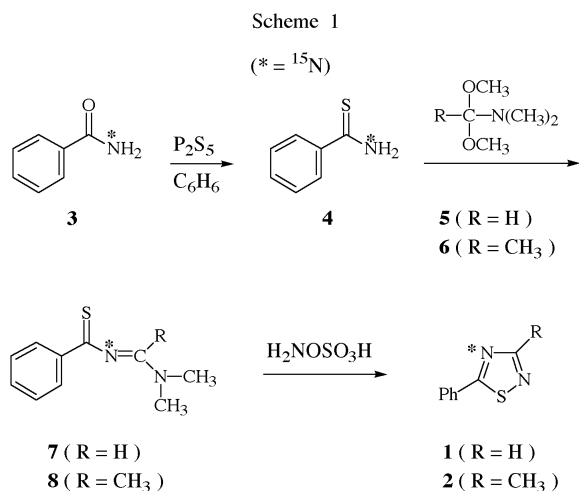
5-Phenyl-1,2,4-thiadiazole-4-<sup>15</sup>N and 3-methyl-5-phenyl-1,2,4-thiadiazole-4-<sup>15</sup>N were synthesized from commercially available benzamide-<sup>15</sup>N. The mass spectra and the <sup>1</sup>H, <sup>13</sup>C, and <sup>15</sup>N-nmr spectra of these compounds, which show various long-range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

*J. Heterocyclic Chem.*, **39**, 237 (2002).

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-<sup>15</sup>N (**1**) and 3-methyl-5-phenyl-1,2,4-thiadiazole-4-<sup>15</sup>N (**2**). In this paper we report the syntheses of these compounds and their spectroscopic properties.

#### Results and Discussion.

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



This sequence began with the reaction of benzamide-<sup>15</sup>N (**3**) with P<sub>2</sub>S<sub>5</sub> in benzene to provide thiobenzamide-<sup>15</sup>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-<sup>14</sup>N in the sample. The mass spectrum of thiobenzamide-<sup>14</sup>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-<sup>14</sup>N and therefore will also be a normal fragmentation pathway for thiobenzamide-<sup>15</sup>N (**4**). The peak at m/z 137 in the mass spectrum of thiobenzamide-<sup>15</sup>N (**4**) is therefore not due to the presence of thiobenzamide-<sup>14</sup>N in the sample.

The <sup>1</sup>H-nmr spectrum of thiobenzamide-<sup>15</sup>N (**4**) is more complicated than the <sup>1</sup>H-nmr spectrum of unlabelled thiobenzamide [4] due to the heteronuclear coupling between the <sup>1</sup>H and <sup>15</sup>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<sub>1H-15N</sub> = 89.5 Hz, J<sub>1H-1H</sub> = 4.2 Hz). As a result of this <sup>1</sup>H-<sup>15</sup>N coupling, the <sup>15</sup>N nucleus of **4** appeared in the <sup>15</sup>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 <sup>1</sup>H-nmr spectrum [5]. The <sup>13</sup>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 <sup>15</sup>N nucleus.

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

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

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

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

5-Phenyl-1,2,4-thiadiazole-4- $^{15}\text{N}$  (**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- $^{15}\text{N}$  (**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  $[\text{PhC}^{15}\text{NS}]^{+\bullet}$  fragment formed by elimination of  $\text{H-C}\equiv^{14}\text{N}$  from the molecular ion. No signal was observed at  $m/z$  135 showing that only  $\text{H-C}\equiv^{14}\text{N}$  was eliminated indicating that the two ring nitrogens do not

interchange during fragmentation. The signal at  $m/z$  105 was assigned to the  $[\text{Ph-C}\equiv^{15}\text{N-H}]^{+\bullet}$  fragment formed by elimination of CNS from the molecular ion while the peak at  $m/z$  104 was assigned to the  $[\text{Ph-C}\equiv^{15}\text{N}]^{+\bullet}$  fragment formed by the elimination of  $\text{HC}^{14}\text{NS}$ . No signal was observed at  $m/z$  103 which would be expected if nitrogen interchange led to the formation of  $[\text{Ph-C}\equiv^{14}\text{N}]^{+\bullet}$ . 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  $[\text{PhC}^{14}\text{NS}]^{+\bullet}$  fragment formed by elimination of  $\text{H-C}\equiv^{14}\text{N}$ , the spectrum also had signals at  $m/z$  104 due to the  $[\text{Ph-C}\equiv^{14}\text{N-H}]^{+\bullet}$  fragment and a smaller signal at  $m/z$  103 (26% of 104 peak) due to  $[\text{Ph-C}\equiv^{14}\text{N}]^{+\bullet}$ . The spectra of **1** and unlabelled **1** both exhibited intense peaks at  $m/z$  77 (58% of base peak) due to  $[\text{C}_6\text{H}_5]^{+\bullet}$  and at  $m/z$  59 (57% of base peak) due to the formation of  $[\text{HCNS}]^{+\bullet}$ .

As expected, the mass spectrum of 3-methyl-5-phenyl-1,2,4-thiadiazole-4- $^{15}\text{N}$  (**2**) exhibited a molecular ion at  $m/z$  177 and a base peak at  $m/z$  136 again assigned to the  $[\text{Ph-C}^{15}\text{NS}]^{+\bullet}$  fragment formed in this case by elimination of  $\text{CH}_3\text{C}\equiv^{14}\text{N}$ . Again, no signal at  $m/z$  135 was observed showing that only  $\text{CH}_3\text{-C}\equiv^{14}\text{N}$  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  $\text{CH}_3\text{-C}^{14}\text{NS}^{+\bullet}$  fragment formed by elimination of  $\text{Ph-C}\equiv^{15}\text{N}$  and a small peak at  $m/z$  104 (12% of base) due to the formation of a small amount of  $[\text{Ph-C}\equiv^{15}\text{N}]^{+\bullet}$ .

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

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

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

#### EXPERIMENTAL

$^1\text{H}$ , and  $^{13}\text{C}$  spectra were recorded at 400.1 and 100.6, MHz in deuteriochloroform on a Bruker FT-NMR system.  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts were measured relative to internal tetramethylsilane and chloroform, respectively.  $^1\text{H}$ - $^{13}\text{C}$  correlation spectra were recorded using the HETCOR (HCCOSW) experiment in the Bruker system.  $^{15}\text{N}$ -nmr spectra were recorded at 40.5 Mhz in acetone- $d_6$ . The  $^{15}\text{N}$  chemical shifts are reported in ppm downfield from  $\text{NH}_3(l)$  ( $\delta\text{NH}_3(l) = 0.0$ ) and were measured relative to aqueous  $\text{Na}^{15}\text{NO}_3$  which was used as an external standard and taken to absorb at 378.4 ppm downfield from  $\text{NH}_3(l)$  [6]. Mass spectra were recorded with an HP 5970B mass selective detector interfaced to an HP 588 capillary gas chromatograph.

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

A solution of 1.0 g (8.2 mmoles) of benzamide- $^{15}\text{N}$  (**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- $^{15}\text{N}$  (**7**) or *N*-[(Dimethylamino)ethylidene]thiobenzamide- $^{15}\text{N}$  (**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- $^{15}\text{N}$  (**1**) or 3-Methyl-5-phenyl-1,2,4-thiadiazole-4- $^{15}\text{N}$  (**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°.

#### REFERENCES AND NOTES

- [1] Cambridge Isotope laboratories, Inc.
- [2] Y. Lin, S. A. Lang, Jr., S. R. Petty, *J. Org. Chem.*, **45**, 3750 (1980).
- [3] L. C. King and F. M. Miller, *J. Am. Chem. Soc.*, **71**, 367 (1949).
- [4] P. Lin, W. Ku, M. Shiao, *Synthesis*, **1219** (1992).
- [5] R. T. C. Brownlee and M. Sadek, *Mag. Reson. Chem.*, **24**, 821 (1986).
- [6] M. Witanowski, L. Stefaniak, and G. A. Webb, in *Annual Reports on NMR Spectroscopy*, Vol **11B**, G. A. Webb, ed, Academic Press, New York, 1981, pp 2 - 494.