Long-Range Fluorine-Proton Coupling in 1,2,4-Triazole Derivatives

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Several 1,2,4-triazole derivatives containing a 2-fluorophenyl substituent at either the 3- or 5-position and a methyl group at the 4-position were synthesized. These derivatives exhibit long-range ^{19}F-^{1}H and ^{19}F-^{13}C through-space coupling in their ^{1}H and ^{13}C nmr spectra between the fluorine and the 4-methyl group. The close spatial proximity of these nuclei was confirmed by X-ray analysis and by fluorine irradiated proton observe ($\{^{19}F\}$-^{1}H) NOE difference spectroscopy.

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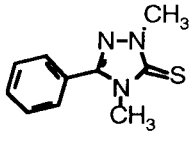
Several years ago, we discovered an unusual cleavage reaction of 2,5-difluorobenzophenone which resulted in the formation of 2,4-dihydro-2,4-dimethyl-5-phenyl-3*H*-1,2,4-triazole-3-thione (**1**) [1]. 2,4-Dimethyl-5-(2,5-difluorophenyl)-5-phenyl-1,2,4-triazolidine-3-thione (**2**), a presumed intermediate in this transformation, was also isolated from this reaction. Pharmacological evaluation of **1** revealed that it might be useful as an antidepressant. A series of 3*H*-1,2,4-triazole-3-thiones was subsequently investigated for antidepressant-like activity [2]. More recent studies have indicated that selected 3*H*-1,2,4-triazole-3-thiones might also enhance cognitive function [3-6]. These results prompted us to investigate the pharmacology of other 1,2,4-triazole derivatives. This led to the discovery that selected 2,4-dihydro-3*H*-1,2,4-triazol-3-ones possessed anticonvulsant activity [7] while selected 4*H*-1,2,4-triazoles were active as antispasticity agents [8].



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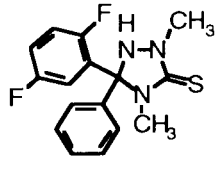
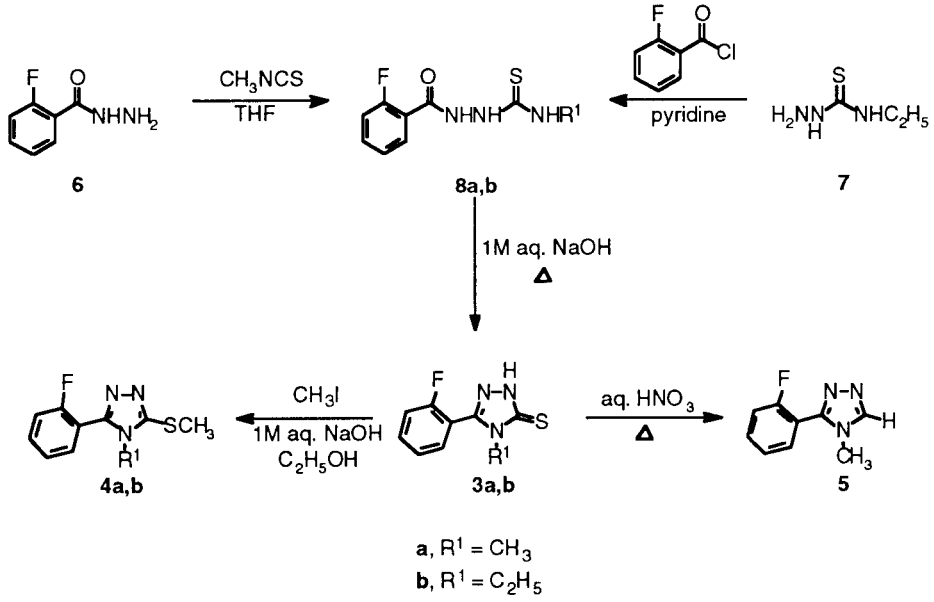


2

In our initial publication [1], we noted that, in the nmr spectrum of **2**, the protons of the methyl group at the 4-position of the triazolidine nucleus appeared as a doublet. During the course of our pharmacological investigations, we have prepared a number of 2-fluorophenyl-1,2,4-triazoles. We now wish to report that long range ^{19}F-^{1}H coupling between the fluorine atom on the aryl substituents located at the 3- or 5-position of the 1,2,4-triazole nucleus and the protons of methyl groups located at the 4-position appears to be a general phenomenon. The close spatial proximity of these nuclei, separated by six bonds, has been demonstrated by fluorine irradiated proton observe ($\{^{19}F\}$-^{1}H) NOE difference spectroscopy and by single crystal X-ray analysis, thus supporting a through-space mechanism for this coupling. By contrast, no ^{19}F-^{1}H coupling is observed when the methyl group at



6 **8a,b** **7**

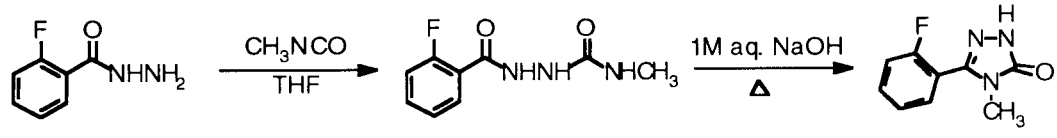
4a,b **3a,b** **5**

a, $R^1 = CH_3$
b, $R^1 = C_2H_5$

the 4-position is replaced with an ethyl group. This is presumably due to an increased inter-nuclear distance between the fluorine and the bulkier ethyl group. For both the methyl and ethyl analogs ^{19}F-^{13}C coupling is also observed. The fluorine to methyl carbon coupling constants are *ca.* twice those for the ethyl analogs consistent with the proton observations.

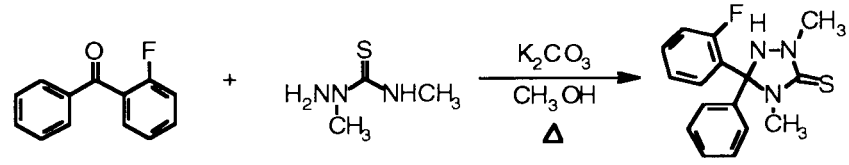
The syntheses of 5-(2-fluorophenyl)-3*H*-1,2,4-triazole-3 thiones **3** [2,8], 3-alkylthio-5-(2-fluorophenyl)-4*H*-1,2,4-triazoles **4** [8], and 3-(2-fluorophenyl)-4*H*-1,2,4-triazole **5** [9] are depicted above. Thus, reaction of either 2-fluorobenzoic acid hydrazide (**6**) and methyl isothiocyanate or 4-ethylthiosemicarbazides **7** and 2-fluorobenzoyl chloride afforded 4-alkyl-1-(2-fluorobenzoyl)thiosemicarbazides **8**. Alkaline ring closure of **8** gave **3** which could be either *S*-alkylated to yield **4** or desulfurized to yield **5**.

5-(2-Fluorophenyl)-4-methyl-3*H*-1,2,4-triazol-3-one (**9**) was prepared by known procedures [7]. More specifically, reaction of 2-fluorobenzoic acid hydrazide (**6**) and methyl isocyanate gave 1-(2-fluorobenzoyl)-4-methylsemicarbazide (**10**) which was subsequently cyclized to **9** by heating in 1 molar aqueous sodium hydroxide.



6 **10** **9**

Finally, 2,4-dimethyl-5-(2-fluorophenyl)-5-phenyl-1,2,4-triazolidine-3-thione (**11**) was prepared by the same method we used to prepare **2** [1]. Thus, heating a methanolic solution of 2-fluorobenzophenone (**12**) and 2,4-dimethylthiosemicarbazide (**13**) in the presence of potassium carbonate afforded a low yield of triazolidine **11**.



12 **13** **11**

In all compounds with a 4-methyl substituent on the triazole nucleus (compounds **3a**, **4a**, **5**, **9**, and **11**) coupling is observed between the *ortho* aromatic fluorine and the 4-methyl protons as their signals appear as doublets (J = *ca.* 2 Hz). Interestingly, in the two analogs with a 4-ethyl instead of a 4-methyl substituent (**3b** and **4b**) no coupling is observed between the methylene of the ethyl group and the fluorine. Comparison with literature examples suggests a through-space mechanism rather than through-bond interactions for these observations [10-13]. Many examples have been reported for couplings between nuclei separated by 5-, 6-, or even 7-bonds [14] which have been assigned as through-space based on inter-nuclear proximity arguments. That is, coupling is only observed if the inter-nuclear distance between the interacting nuclei is short. Myhre *et al.* [11] studied a series of trialkylfluorobenzenes and presented a plot of observed ^{19}F-^{1}H coupling constants for protons on proximate methyl carbons as a function of the calculated inter-nuclear separation of the fluorine and methyl carbon. The fluorine-carbon inter-nuclear distance was used instead of the distance between the fluorine and the individual protons because the internal rotation of a methyl group is typically very fast on the nmr time scale and any coupling observed is the average of the individual couplings. The data reported for the alkylfluorobenzene systems indicates that no coupling is observed when the methyl carbon is more than 3.3 Å from the fluorine. Below 3.3 Å a strong dependence between inter-nuclear separation and the magnitude of the coupling constant is observed.

In an attempt to correlate this information with our observations single crystal X-ray analyses of **3a** and **3b** were undertaken [15]. A methyl carbon-fluorine inter-nuclear distance of 3.07 Å was measured for **3a** while a 3.28 Å methylene carbon-fluorine distance was measured in **3b**. While these solid state measurements can not be directly extrapolated to nmr solution observations, it is plausible that the inter-nuclear distance from the fluorine to the bulkier ethyl group is sufficiently long so that through-space coupling is not observed. The 2.2 Hz coupling observed for **3a** is in general agreement with Myhre's correlation curve which predicts *ca.* 1 Hz coupling for an inter-nuclear distance of 3.07 Å. The magnitude of the coupling is also consistent with the through-space coupling reported for compounds such as *o*-fluoro-*N*,*N*-dimethylbenzamide [10]. A 1.2 Hz coupling is reported between the fluorine and the spatially proximate

syn-methyl protons but no coupling is observed to the *anti*-methyl protons.

The close spatial proximity between the fluorine and methyls in our compounds is also supported by $\{^{19}F\}$-^{1}H NOE difference spectroscopy. The $\{^{19}F\}$-^{1}H NOE difference spectrum for **4a**, shown in Figure 1, shows a large NOE between the fluorine and 4-methyl protons as well as the fluorine and the *ortho*-aromatic proton. Similar experiments with **3a**, **3b**, and **4b** showed similar results.

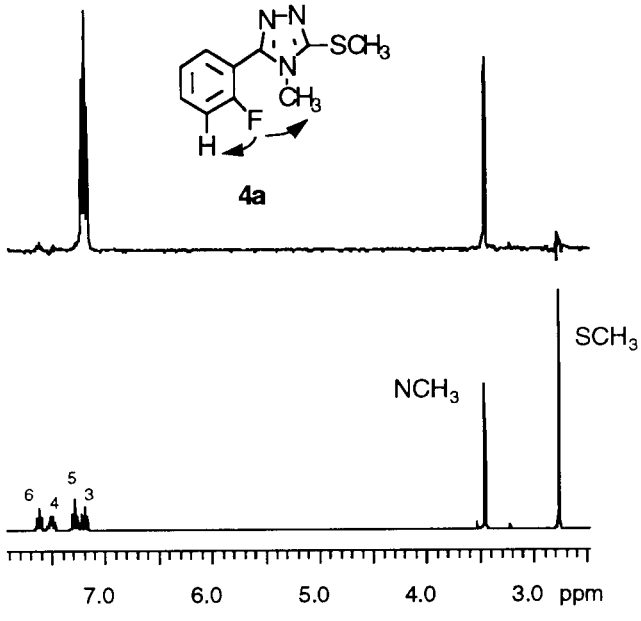


Figure 1. $\{^{19}F\}$-^{1}H NOE difference spectrum (top) and reference ^{1}H spectrum (bottom) of **4a**. Arrows indicate NOE's observed.

These experiments thus qualitatively demonstrate the short inter-nuclear distances in these compounds but are not sufficiently quantitative to differentiate between the subtle differences in distance between these methyl- and ethyl-analogs.

The ^{13}C nmr spectra of these compounds were also examined. In all compounds the methyl and ethyl carbons were observed as doublets due to ^{19}F-^{13}C coupling. For the methyl analogs **3a** and **4a** coupling constants of 5.3 and 6.1 Hz were observed whereas coupling constants to the more distant methylene carbons of **3b** and **4b** were 2.8 and 3.6 Hz, respectively. These values are qualitatively consistent with the findings of Sardella [16] who studied through-space ^{19}F-^{13}C couplings in a series of polycyclic aromatics and correlated increasing inter-nuclear distances with decreasing coupling constants.

EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas Hoover apparatus and are uncorrected. The nmr spectra were recorded at 25° on Varian VXR-300 and Unity-300 spectrometers. The chemical shifts are reported in parts per million versus internal tetramethylsilane for ^{1}H, external tetramethylsilane for ^{13}C, and external fluorotrichloromethane for ^{19}F. The $\{^{19}F\}$-^{1}H NOE difference spectra were obtained using a standard steady-state NOE difference pulse sequence (D1 = 5 to 8 sec, not optimized). Because our spectrometer is a single broadbanded system it was necessary to run these experiments in the "reverse" mode. That is, the ^{1}H decoupler was used as the observe transmitter and the broadband transmitter as the ^{19}F decoupler transmitter. Also, the experiment requires a probe which is capable of being tuned to both ^{1}H and ^{19}F simultaneously. We used a Varian 4-nucleus probe which has a double tuned circuit for ^{1}H and ^{19}F for this experiment. X-ray analysis was performed at Indiana University Department of Chemistry by Dr. J. C. Huffman [15].

1-(2-Fluorobenzoyl)-4-methylthiosemicarbazide (**8a**).

To a stirred, room temperature, solution of methyl isothiocyanate (1.72 g, 23.5 mmoles) and dry tetrahydrofuran (50 ml) was added, in one portion, a solution of 2-fluorobenzoic acid hydrazide (3.80 g, 24.6 mmoles) and dry tetrahydrofuran (70 ml). The reaction was heated to reflux. After being refluxed for 1.5 hours, the reaction was allowed to cool to room temperature where it was stirred overnight. The reaction was placed in the freezer for several hours and the precipitate was subsequently collected by filtration. Crystallization from ethanol/water afforded 4.21 g (79%) of **8a** as colorless needles, mp 214-216° dec; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.89 (d, 3H, J = 4.3 Hz), 7.35-7.27 (m, 2H), 7.59 (m, 1H), 7.82 (td, 1H, J = 7.4 and 1.7 Hz), 7.96 (bq, 1H, 4.3 Hz), 9.43 (s, 1H), 10.12 (s, 1H); ^{19}F nmr (dimethyl sulfoxide-d_6): δ -112.0 (m).

Anal. Calcd. for $C_9H_{10}FN_3OS$: C, 47.56; H, 4.44; N, 18.49. Found: C, 47.55; H, 4.19; N, 18.37.

4-Ethyl-1-(2-fluorobenzoyl)thiosemicarbazide (**8b**).

To a stirred, room temperature, solution of 4-ethylthiosemicarbazide (4.03 g, 33.9 mmoles) and dry pyridine (50 ml) was added dropwise 2-fluorobenzoyl chloride (4.2 ml, 35 mmoles). After being stirred for 17 hours, the pyridine was evaporated under reduced pressure. The concentrate was washed with water and that which did not dissolve was collected by filtration. Crystallization from ethanol gave 3.97 g (48%) of **8b** as colorless crystals, mp 171-174°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.08 (t, 3H, J = 7.3 Hz), 3.48 (m, 2H), 7.35-7.27 (m, 2H), 7.58 (m, 1H), 7.81 (td, 1H, J = 7.5 and 1.8 Hz), 7.96 (bm, 1H), 9.37 (s, 1H), 10.11 (s, 1H); ^{19}F nmr (dimethyl sulfoxide-d_6): δ -112.0 (bm).

Anal. Calcd. for $C_{10}H_{12}FN_3OS$: C, 49.78; H, 5.01; N, 17.42. Found: C, 49.95; H, 4.89; N, 17.39.

2,4-Dihydro-5-(2-fluorophenyl)-4-methyl-3*H*-1,2,4-triazole-3-thione (**3a**).

1-(2-Fluorobenzoyl)-4-methylthiosemicarbazide (11.0 g, 48.4 mmoles) and 1 molar aqueous sodium bicarbonate (485 ml, 0.485 mole) were stirred and heated to reflux. After being refluxed overnight, the reaction was allowed to cool to room temperature at which time it was carefully acidified by the dropwise addition of concentrated hydrochloric acid (44.0 ml, 0.528 mole). The resulting precipitate was collected by filtration, washed with water, and dried by suction. Crystallization from

ethyl acetate/ hexane gave 4.1 g (40%) of **3a** as colorless needles, mp 137-139°; ^{1}H nmr (deuteriochloroform): δ 3.54 (d, 3H, J = 2.2 Hz), 7.26 (ddd, 1H, J = 10.0, 7.3, and 1.0 Hz), 7.33 (td, 1H, J = 7.6 and 1.1 Hz), 7.64-7.52 (m, 2H), 12.39 (bs, 1H); ^{19}F nmr (deuteriochloroform): δ -112.4 (m); ^{13}C nmr (deuteriochloroform): δ 31.8 (d, J = 5.3 Hz), 113.8 (d, J = 14.1 Hz), 116.4 (d, J = 20.7 Hz), 125.1 (d, J = 3.6 Hz), 131.7 (d, J = 1.9 Hz), 133.6 (d, J = 8.4 Hz), 148.4, 160.1 (d, J = 251.0 Hz), 168.0.

Anal. Calcd. for $C_9H_8FN_3S$: C, 51.66; H, 3.85; N, 20.08. Found: C, 51.48; H, 3.96; N, 20.34.

2,4-Dihydro-4-ethyl-5-(2-fluorophenyl)-3*H*-1,2,4-triazole-3-thione (**3b**).

4-Ethyl-1-(2-fluorobenzoyl)thiosemicarbazide (6.03 g, 25.0 mmoles) and 1 molar aqueous sodium bicarbonate (250 ml, 0.25 mole) were stirred and heated to reflux. After being refluxed for 17 hours, the reaction was filtered. The filtrate was cooled to 0° before being carefully acidified by the dropwise addition of concentrated hydrochloric acid (21.0 ml, 0.25 mole). The resulting solid was collected by filtration, washed with water, and dried by suction. Purification by flash chromatography [17] (5% ethyl acetate/dichloromethane) and subsequent crystallization from ethyl acetate/hexane gave 2.7 g (48%) of **3b** as colorless needles, mp 138-140°; ^{1}H nmr (deuteriochloroform): δ 1.26 (t, 3H, J = 7.2 Hz), 4.05 (q, 2H, J = 7.2 Hz), 7.26 (ddd, 1H, J = 9.7, 8.4 and 1.1 Hz), 7.33 (td, 1H, J = 7.5 and 1.1 Hz), 7.48 (ddd, 1H, J = 7.5, 7.1, and 1.8 Hz), 7.60 (m, 1H), 12.38 (bs, 1H); ^{19}F nmr (deuteriochloroform): δ -112.3 (m); ^{13}C nmr (deuteriochloroform): δ 13.4 (d, J = 1.4 Hz), 40.2 (d, J = 2.8 Hz), 114.1 (d, J = 15.1 Hz), 116.5 (d, J = 20.8 Hz), 125.0 (d, J = 3.7 Hz), 131.8 (J = 1.8 Hz), 133.5 (d, J = 8.4 Hz), 147.6, 160.4 (d, J = 251.0 Hz), 167.4.

Anal. Calcd. for $C_{10}H_{10}FN_3S$: C, 53.80; H, 4.51; N, 18.82. Found: C, 53.60; H,4.44; N, 18.91.

5-(2-Fluorophenyl)-4-methyl-3-methylthio-4*H*-1,2,4-triazole (**4a**).

A stirred mixture of 2,4-dihydro-5-(2-fluorophenyl)-4-methyl-3*H*-1,2,4-triazole-3-thione (4.56 g, 21.8 mmoles), potassium carbonate (3.01 g, 21.8 mmoles), iodomethane (1.5 ml, 24 mmoles), and acetone (65 ml) was heated to reflux. After being refluxed for 17 hours, the reaction mixture was allowed to cool to room temperature. The precipitate was removed by filtration and the filtrate was evaporated at reduced pressure. The concentrate was treated with water and this mixture was extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure leaving an oil. Flash chromatography (70% ethyl acetate/ dichloromethane) and kugelrohr distillation (195°/ 0.3 mm) afforded 3.55 g (73%) of **4a** as a viscous pale yellow oil; ^{1}H nmr (deuteriochloroform): δ 2.79 (s, 3H), 3.48 (d, 3 H, J = 2.4 Hz), 7.21 (ddd, 1H, J = 10.0, 7.5, and 1.0 Hz), 7.30 (td, 1 H, J = 7.5 and 1.0 Hz), 7.51 (m, 1H), 7.64 (td, 1 H, J = 7.5 and 1.8 Hz); ^{19}F nmr (deuteriochloroform): δ -113.4 (m); ^{13}C nmr (deuteriochloroform): δ 15.0, 30.9 (d, J = 6.1 Hz), 115.2 (d, J = 14.7 Hz), 116.0 (d, J = 21.1 Hz), 124.9 (d, J = 3.6 Hz), 132.2 (d, J = 2.5 Hz), 132.5 (d, J = 8.4 Hz), 152.0, 153.0, 159.8 (d, J = 249.9 Hz).

Anal. Calcd. for $C_{10}H_{10}FN_3S$: C, 53.80; H, 4.51; N, 18.82. Found: C, 54.00; H, 4.51; N, 18.54.

4-Ethyl-5-(2-fluorophenyl)-3-methylthio-4*H*-1,2,4-triazole (**4b**).

To a solution of 2,4-dihydro-4-ethyl-5-(2-fluorophenyl)-3*H*-1,2,4-triazole-3-thione (8.3 g, 37 mmoles) and 1 molar aqueous sodium hydroxide (84 ml) was added a solution of iodomethane (3.7 ml, 59 mmoles) and ethanol (18 ml). After being stirred for 17 hours the reaction was transfered to a separatory funnel where it was extracted three times with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrated was evaporated at reduced pressure leaving an oil. Purification by flash chromatography (35% acetone/hexane) and subsequent kugelrohr distillation (230°/0.35 mm) gave 6.5 g (74%) of **4b** as a pale yellow oil; ^{1}H nmr deuteriochloroform): δ 1.25 (t, 3H, J = 7.3 Hz), 2.80 (s, 3H), 3.87 (q, 2H, J = 7.3 Hz), 7.33-7.17 (m, 2H), 7.60-7.48 (m, 2H); ^{19}F nmr (deuteriochloroform): δ -113.2 (m); ^{13}C nmr (deuteriochloroform): δ 14.7 (d, J = 2.0 Hz), 15.1, 39.7 (d, J = 3.6 Hz), 115.5 (d, J = 14.8 Hz), 116.0 (d, J = 21.2 Hz), 124.8 (d, J = 3.7 Hz), 132.3 (d, J = 2.1 Hz), 132.5 (d, J = 8.5 Hz), 151.1, 152.3, 159.9 (d, J = 252.8 Hz).

Anal. Calcd. for $C_{11}H_{12}FN_3S$: C, 55.68; H, 5.10; N, 17.71. Found: C, 55.83; H, 5.37; N, 17.64.

3-(2-Fluorophenyl)-4-methyl-4*H*-1,2,4-triazole (**5**).

2,4-Dihydro-5-(2-fluorophenyl)-4-methyl-3*H*-1,2,4-triazole-3-thione (4.07 g, 21.4 mmoles) was suspended in a solution of nitric acid prepared from concentrated nitric acid (62 ml) and water (200 ml). The reaction was warmed and, after a short induction period, evolution of nitrogen dioxide was observed. The reaction was refluxed for 20 minutes before being allowed to cool to room temperature. The reaction was then basified by the addition of a solution of potassium hydroxide (70.0 g, 1.25 mole) and water (100 ml). The reaction was transfered to a separatory funnel where it was extracted three times with dichloromethane. The extracts were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure leaving an oil. Kugelrohr distillation (205°/0.3 mm) afforded 3.01 g (86%) of **5** as an oil which solidified to a colorless solid, mp 88-90°; ^{1}H nmr (deuteriochloroform): δ 3.67 (d, 3H, J = 2.2 Hz), 7.23 (ddm, 1H, J = 10.0 and 8.4 Hz), 7.32 (td, 1H, J = 7.5 and 1.0 Hz), 7.54 (m, 1H), 7.67 (td, J = 7.5 and 6.7 Hz); ^{19}F nmr (deuteriochloroform): δ -113.5 (m); ^{13}C nmr (deuteriochloroform): δ 31.5 (d, J = 6.8 Hz), 114.8 (d, J = 14.7 Hz), 116.0 (d, J = 21.6 Hz), 124.9 (d, J = 3.2 Hz), 132.3 (d, J = 2.6 Hz), 132.6 (d, J = 7.8 Hz), 145.1, 150.6, 159.8 (d, J = 248.4 Hz).

Anal. Calcd. for $C_9H_8FN_3$: C, 61.01; H, 4.55; N, 23.72. Found: C, 61.11; H, 4.54; N, 23.58.

1-(2-Fluorobenzoyl)-4-methylsemicarbazide (**10**).

To a stirred, room temperature, solution of 2-fluorobenzoic acid hydrazide (5.00 g, 32.4 mmoles) and dry tetrahydrofuran (100 ml) was added methyl isocyanate (2.01 g, 35.7 mmoles). After being stirred for 17 hours, the reaction was diluted with diethyl ether (125 ml). The mixture was placed in the freezer and after 24 hours the precipitate was collected by filtration. Crystallization from isopropanol (charcoal) gave 2.87 g (42%) of **10** as colorless crystals, mp 122-124°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 2.59 (d, 3H, J = 4.5 Hz), 6.33 (bq, 1H, J = 4.5 Hz),

7.34-7.26 (m, 2H), 7.57 (m, 1H), 7.71 (td, 1H, J = 7.2 and 1.7 Hz), 8.03 (s, 1H), 9.91 (s, 1H); ^{19}F nmr (dimethyl sulfoxide-d_6): δ -112.90 (m); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 26.3, 116.2 (d, J = 21.8 Hz), 122.4 (d, J = 14.0 Hz), 124.4 (d, J = 3.3 Hz), 130.4 (d, J = 3.0 Hz), 132.9 (d, J = 8.5 Hz), 158.5, 159.4 (d, J = 251.01), 164.1 (d, J = 1.8 Hz).

Anal. Calcd. for $C_9H_{10}FN_3O_2$: C, 51.18; H, 4.77; N, 19.90. Found: C, 50.92; H, 4.74; N, 19.85.

2,4-Dihydro-5-(2-fluorophenyl)-4-methyl-3*H*-1,2,4-triazol-3-one (**9**).

1-(2-Fluorobenzoyl)-4-methylsemicarbazide (25.1 g, 0.119 mole) and 1 molar aqueous sodium hydroxide (143 ml, 0.143 mole) were stirred and heated to reflux. After being refluxed for 48 hours, the reaction was allowed to cool to room temperature at which time it was carefully acidified by the addition of 1 molar aqueous hydrochloric acid (157 ml, 0.157 mole). The reaction mixture was placed in the refrigerator for several hours and then the precipitate was collected by filtration. The resulting solid was dissolved in dichloromethane and this solution was transfered to a separatory funnel where it was washed four times with 1 molar aqueous hydrochloric acid and one time with saturated aqueous sodium chloride. After being dried over anhydrous sodium sulfate, the solvent was evaporated at reduced pressure. Crystallization of the resulting solid from 2-butanone gave 12.4 g (54%) of **9** as colorless crystals, mp 189-191°; ^{1}H nmr (deuteriochloroform): δ 3.26 (d, 3H, J = 2.2 Hz), 7.19-7.33 (m, 2H), 7.50-7.59 (m, 2H), 10.66 (bs, 1H); ^{19}F nmr (deuteriochloroform): δ -113.07 (m); ^{13}C nmr (deuteriochloroform): δ 28.3 (d, J = 5.9 Hz), 115.2 (d, J = 14.6 Hz), 116.2 (d, J = 21.7 Hz), 124.9 (d, J = 3.6 Hz), 131.5 (d, J = 2.5 Hz), 132.9 (d, J = 8.4 Hz), 144.2, 156.1, 160.1 (d, J = 252.4 Hz).

Anal. Calcd. for $C_9H_8FN_3O$: C, 55.96; H, 4.17; N, 21.75. Found: C, 56.05; H, 4.24; N, 21.83.

2,4-Dimethyl-5-(2-fluorophenyl)-5-phenyl-1,2,4-triazolidine-3-thione (**11**).

2-Fluorobenzophenone (10.0 g, 49.9 mmoles), 2,4-dimethylthiosemicarbazide [18] (5.96 g, 50.0 mmoles), and potassium carbonate (6.91 g, 50.0 mmoles) were stirred and warmed to reflux in methanol (250 ml). After being refluxed for 8 days, the solvent was evaporated at reduced pressure. The concentrate was slurried with water and the resulting mixture was transferred to a separatory funnel where it was extracted four times with ethyl acetate. The ethyl acetate extracts were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The drying agent was removed by filtration and the filtrate was evaporated at reduced pressure yielding an oil which slowly deposited a crystalline material. Trituration with diethyl ether and filtration afforded a solid. Purification of this material by flash chromatography (17% ethyl acetate/ hexane) and crystallization from ethyl acetate/ hexane gave 1.78 g (12%) of **11** as pale yellow flakes, mp 176-178°; ^{1}H nmr (deuteriochloroform): δ 3.06 (d, 3H, J = 2 Hz), 3.36 (s, 3H), 4.57 (s, 1H), 7.7-6.8 (m, 9H); ^{13}C nmr (deuteriochloroform): δ 31.9 (d, J = 6 Hz), 35.5, 84.5 (d, J = 1.3 Hz), 116.4 (d, J = 23 Hz), 124.3 (d, 4 Hz), 126.4, 128.6, 129.1, 129.4 (d, J = 3 Hz), 131.0 (d, J = 9 Hz), 137.8 (d, 1 Hz), 159.3 (d, J = 249 Hz), 179.4.

Anal. Calcd. for $C_{16}H_{16}FN_3S$: C, 63.76; H, 5.35; N, 13.94. Found: C, 63.86; H, 5.30; N, 14.03.

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