The Preparation of Aryl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfides and Sulfones

Roger A. Egolf*‡† and Donna M. Bilder‡

Department of Chemistry, The Pennsylvania State University, Allentown Campus, Fogelsville, PA 18051,
and Department of Chemistry, Lehigh Universtiy, Belthlehem, PA 18015

Received October 26, 1993

A series of aryl 1-(2,6-dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl sulfides was prepared by displacement of fluoride from the 5-position of 1-(2,6-dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-fluoroimidazole by substituted thiophenols and by benzyl mercaptan. This displacement reaction occurs much more slowly than the corresponding previously described reactions of 4-trifluoromethyl-5-fluorothiazoles and -oxazoles. Several solvent-base pairs were examined; the reaction was found to work best when dimethyl sulfoxide was used as the solvent and diazabicycloundecene as the base. The sulfides were oxidized to sulfones by treatment with hydrogen peroxide in acetic acid.

J. Heterocyclic Chem., **31**, 541 (1994).

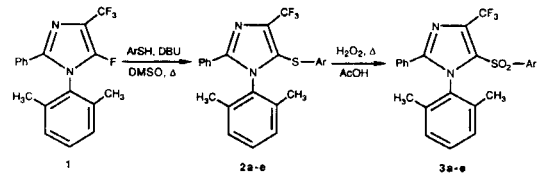
It is known that the principal determinant of the radiosensitizing efficiency of a compound is its electron affinity [1-3]. In the early 1980's it was found that 4-nitroimidazoles substituted at the 5 position with sulfonamide, sulfur ether or sulfonyl groups were extremely effective radiation sensitizers of hypoxic carcinoma cells *in vitro* [4-7]. Unfortunately the medicinal utility is limited due to high cytotoxicity, probably due to metabolic reduction of the nitro group to an amino group *in vivo* [8].

We postulated that compounds containing a sulfur group at the 5-position might function as less cytotoxic radiation sensitizers if a different, yet comparably electron affinic group such as a trifluoromethyl moiety was placed in the 4-position. The electron withdrawing power of a trifluoromethyl in aromatic systems is comparable to that of a nitro group; imidazoles that bear it in the 4-position may have radiation sensitizing ability comparable to the analogous nitro-substituted compounds. Furthermore, since the trifluoromethyl functionality cannot be reduced *in vivo*, radiation sensitizers containing it should not be neurotoxic. This paper describes the synthesis and characterization of aryl 1-(2,6-dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl sulfones as potential radiation sensitizers.

A convenient route for the preparation of these highly electrophilic sulfones is through oxidation of the corresponding sulfides, however the preparation of 4-trifluoromethyl-5-imidazolyl sulfides has never been reported. The preparation of a variety 4-trifluoromethyl-5-fluorooxazoles, -thiazoles, and -imidazoles by reductive cyclization reactions of hexafluoroacetone imines has been reported by Burger *et al.* [9]. He has also reported nucleophilic displacement of fluorine from the 5-position of the oxazoles and thiazoles using a variety of nucleophiles, including mercaptans [10], however he stated that fluorine at the 5-position of a 4-trifluoromethylimidazole is much more difficult to displace. We decided that the feasibility of displacement reactions on 4-trifluoromethyl-5-fluoroimidazoles by sulfur nucleophiles should be investigated.

The reaction of 1-(2,6-dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-fluoroimidazole (**1**) [9] with thiophenol in refluxing acetonitrile using triethylamine to deprotonate the sulfur was attempted, however, the reaction showed no progress by thin layer chromatography (tlc) and the starting fluoroimidazole was recovered quantitatively from the reaction mixture. The corresponding reaction with 4-trifluoromethyl-5-fluorooxazoles and -thiazoles typically takes 2 to 32 hours [10]. Absolute ethanol was also tried as a solvent, using either triethylamine or anhydrous ammonia as the base. These conditions are known to be useful for the displacement of chloride from 4-nitro-5-chloroimidazoles [11-15]. Again, tlc showed no indication of product. As ammonia is a strong enough base to deprotonate the thiol, the problem was thought to be solvent-related. In order to increase the effective nucleophilicity of the thiolate, **1** and thiophenol were heated in dimethylformamide (DMF) using diazabicycloundecene (DBU) as the base. Analysis (tlc) showed that the reaction was proceeding slowly. After five days, no increase in the product spot was seen and a second product was forming which was identified as the disulfide of thiophenol. When the reaction was carried out in dimethyl sulfoxide (DMSO) using DBU as

Scheme



1 2a-e 3a-e

Sulfide	Sulfone	-Ar Group
2a	3a	4-Methylphenyl
2b	3b	3-Methylphenyl
2c	3c	Phenyl
2d	3d	4-Chloromethyl
2e	3e	Benzyl

the base, the reaction proceeded faster, producing more of the desired sulfide and less of the disulfide side product. As DBU in DMSO gave the best results, this base/solvent combination was used in the syntheses reported herein. Sulfides were prepared as shown in the Scheme by heating **1** with the appropriate thiophenol with an equivalent of DBU using DMSO as the solvent. The progress of each reaction was monitored using tlc.

The reaction of **1** with benzyl mercaptan was carried out to test the effect of using a stronger sulfur nucleophile than a thiophenol. As was expected, the reaction proceeded much faster and was observed to be nearly quantitative by tlc in eight hours at 50°. The low reported yield for this product was due to a problem in its isolation. The sulfides were very soluble in all organic solvents tested, but could be recrystallized from small volumes of hexane at −10°.

The sulfides were oxidized to sulfones with hydrogen peroxide in glacial acetic acid [11]. This method affords high yields of easily isolated pure product. The reactions typically took no more than two hours, with analytically pure product precipitating out of the reaction mixture upon cooling to ambient temperatue.

EXPERIMENTAL

General.

The ^{1}H-nmr and ^{13}C-nmr were performed on a Bruker AM 500 spectrometer operating at 500 MHz and 125 MHz respectively in deuteriochloroform using tetramethylsilane (TMS) as an internal standard. Analyses (tlc) were run on silica gel plates using hexane/toluene (1:1) as the developing solvent. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Quantitative Technologies Inc., Salem Industrial Park, New Jersey. All reagents and starting materials were purchased from the Aldrich Chemical Company and were used without further purification.

General Procedure for the Preparation of Sulfides by Reaction of 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-fluoroimidazole (**1**) with Thiophenols or Benzyl Mercaptan.

A solution of 1-(2,6-dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-fluoroimidazole (**1**) [9] (0.504 g, 1.51 mmoles), DBU 0.250 g (1.64 mmoles), and the appropriate thiophenol (1.64 mmoles) in 15.0 ml of DMSO was stirred under nitrogen at 50° for 6 days. The reaction mixture was diluted with 50 ml of diethyl ether, extracted twice with equal portions of water, twice with 10% sodium hydroxide, then three times with water. The ether layer was dried over anhydrous magnesium sulfate, evaporated to near-dryness, then dissolved in 4 ml of hexanes. The solution was refrigerated overnight at −10°, causing the precipitation of the product as white crystals which were collected by vacuum filtration and dried *in vacuo*.

4-Methylphenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfide (**2a**).

This compound was obtained as a white solid; 54% yield, mp 114-118°; ^{1}H-nmr: δ 1.59-1.62 (s, 6H), 2.25 (s, 3H), 6.85-7.35 (m, 12H); ^{13}C-nmr: δ 17.9, 22.0, 77.5, 77.9, 78.3, 128.8, 129.0, 129.2, 130.1, 133.2, 134.5, 137.9, 139.7, 143.0.

Anal. Calcd. for $C_{25}H_{21}F_3N_2S$: C, 68.49; H, 4.83; N, 6.39. Found: C, 68.16; H, 4.71; N, 6.36.

3-Methylphenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfide (**2b**).

This compound was obtained as a white solid, 42% yield, mp 105-107°; ^{1}H-nmr: δ 1.5-1.6 (s, 6H), 2.1-2.2 (s, 3H), 6.6-7.4 (m, 12H); ^{13}C-nmr: δ 17.9, 21.5, 77.2, 77.6, 78.3, 120.3, 122.6, 126.8, 129.0, 129.6, 130.2, 133.5, 135.4, 138.5, 140.6, 141.0, 142.9.

Anal. Calcd. for $C_{25}H_{21}F_3N_2S$: C, 68.49; H, 4.83; N, 6.39. Found: C, 68.26; H, 4.71; N, 6.31.

Phenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfide (**2c**).

This compound was obtained as a white solid, 41% yield mp 145-149°; ^{1}H-nmr: δ 1.59 (s, 6H), 6.98-7.36 (m, 13H); ^{13}C-nmr: δ 17.8, 77.3, 77.9, 78.2, 127.5, 128.1, 128.5, 128.8, 128.9, 129.2, 129.5, 129.7, 132.1, 132.5, 134.2, 136.6, 148.5.

Anal. Calcd. for $C_{24}H_{19}F_3N_2S$: C, 68.08; H, 4.25; N, 6.62. Found: C, 67.70; H, 4.40; N, 6.38.

4-Chlorophenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfide (**2d**).

This compound was obtained as a white solid 48% yield, mp 132-134°; ^{1}H-nmr: δ 1.62 (s, 6H), 6.90-7.36 (m, 12H); ^{13}C-nmr: δ 17.8, 76.9, 77.1, 77.4, 128.1, 128.4, 128.8, 129.8, 130.2, 130.6, 131.0, 133.8, 134.5, 135.0, 137.0, 138.5, 149.4.

Anal. Calcd. for $C_{24}H_{18}ClF_3N_2S$: C, 62.80; H, 3.95; N, 6.10. Found: C, 62.83; H, 3.89; N, 5.99.

Benzyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfide (**2e**).

This compound was obtained as a orange solid, 34% yield, mp 84-86°; ^{1}H-nmr: δ 1.87 (s, 6H), 3.73 (s, 2H), 7.18-1.39 (m, 13H); ^{13}C-nmr: δ 17.9, 42.1, 77.2, 77.5, 77.9, 127.9, 128.1, 128.9, 129.1, 129.3, 129.5, 130.2, 134.5, 136.2, 136.9, 148.9.

Anal. Calcd. for $C_{25}H_{21}F_3N_2S$: C, 68.49; H, 4.83; N, 6.39. Found: C, 68.44; H, 4.77; N, 6.37.

General Procedure for the Oxidation of Benzyl and Aryl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfides (**2a-e**) to Sulfones **3a-e**.

Hydrogen peroxide (30%, 5.0 ml) was added dropwise to a stirring solution of 0.200 g (0.457 mmole) of **2a-e** in 11.0 ml of glacial acetic acid at 90°. The solution was stirred at this temperature for 1 to 8 hours, and was then allowed to stand overnight without heating. The white crystals that precipitated were collected by vacuum-filtration and dried *in vacuo*.

4-Methylphenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfone (**3a**).

This compound was obtained as white solid, 81% yield, mp 145-148°; ^{1}H-nmr: δ 1.58 (s, 6H), 2.40 (s, 3H), 7.05-7.35 (m, 12H); ^{13}C-nmr: δ 17.8, 22.0, 77.2, 77.5, 77.7, 122.0, 128.5, 129.0, 129.1, 129.3, 129.8, 130.2, 130.6, 133.4, 137.5, 138.1, 141.2, 146.0.

Anal. Calcd. for $C_{25}H_{21}F_3N_2O_2S$: C, 63.83; H, 4.51; N, 5.97. Found: C, 63.54; H, 4.38; N, 5.92.

3-Methylphenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfone (**3b**).

This compound was obtained as a white solid, 64% yield, mp 161-163°; ^{1}H-nmr: δ 1.58-1.64 (s, 6H), 2.27-2.30 (s, 3H), 7.05-7.38 (m, 12H); ^{13}C-nmr: δ 17.8, 21.5, 77.0, 77.6, 78.0, 120.0, 122.3, 126.5, 129.0, 129.8, 130.1, 133.5, 135.8, 136.5, 138.5, 140.0, 140.2, 142.0, 149.1.

Anal. Calcd. for $C_{25}H_{21}F_3N_2O_2S$: C, 63.82; H, 4.51; N, 5.97. Found: C, 63.43; H, 4.35; N, 5.86.

Phenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfone (**3c**).

This compound was obtained as a white solid, 55% yield, mp 223°; ^{1}H-nmr: δ 1.57 (s, 6H), 7.05-7.44 (m, 13H); ^{13}C-nmr: δ 17.8, 77.5, 78.0, 78.3, 127.8, 128.5, 128.8, 128.9, 129.0, 130.8, 131.0, 134.2, 137.7, 140.0.

Anal. Calcd. for $C_{24}H_{19}F_3N_2O_2S$: C, 63.15; H, 4.19; N, 6.14. Found: C, 63.30; H, 4.12; N, 6.08.

4-Chlorophenyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfone (**3d**).

This compound was obtained as a white solid, 72% yield, mp 174-178°; ^{1}H-nmr: δ 1.62 (s, 6H), 7.08-7.38 (m, 12H); ^{13}C-nmr: δ 17.8, 76.9, 77.1, 77.4, 127.6, 127.8, 128.7, 128.9, 130.1, 130.4, 130.9, 132.9, 137.2, 138.2, 140.9, 149.0.

Anal. Calcd. for $C_{24}H_{18}ClF_3N_2O_2S$: C, 58.71; H, 3.69; N, 5.71. Found: C, 58.39; H, 3.60; N, 5.61.

Benzyl 1-(2,6-Dimethylphenyl)-2-phenyl-4-trifluoromethyl-5-imidazolyl Sulfone (**3e**).

This compound was obtained as a white solid, 69% yield, mp 116-120°; ^{1}H-nmr: δ 1.87 (s, 6H), 4.34 (s, 3H), 7.13-7.36 (m, 13H); ^{13}C-nmr: δ 18.0, 63.9, 77.0, 77.4, 77.6, 126.3, 128.3, 128.7, 129.0, 129.5, 129.8, 131.1, 131.8, 134.0, 136.9, 149.8.

Anal. Calcd. for $C_{25}H_{21}F_3N_2O_2S$: C, 63.68; H, 4.50; N, 5.95. Found: C, 63.68; H, 4.33; N, 5.92.

Acknowledgment.

We thank Professor Ned D. Heindel and Lehigh University, Bethlehem, PA for laboratory space and a Visiting Research Scientist appointment for R. E. Support for this work was provided by a Research Development Grant from The Pennsylvania State University. Partial support in the form of a summer stipend for D. B. was provided from a Research Experience for Undergraduates Grant to Lehigh University by the National Science Foundation.

REFERENCES AND NOTES

* To whom correspondence should be addressed.

‡ The Pennsylvania State University, Allentown Campus.

† Lehigh University.

[1] G. E. Adams and M. S. Cooke, *Int. J. Radiat. Biol.*, **15**, 457 (1969).

[2] J. D. Chapman, J. A. Raleigh, J. Borsa, R. G. Webb and R. Whitehouse, *Int. J. Radiat. Biol.*, **21**, 475 (1972).

[3] G. E. Adams, E. D. Clarke, I. R. Flockhart, R. S. Jacobs, D. S. Sehmi, I. J. Stratford, P. Wardman, M. E. Watts, J. Parrick, R. G. Wallace and C. E. Smithen, *Int. J. Radiat. Biol.*, **35**, 133 (1979).

[4] G. E. Adams, I. Ahmed, E. M. Fielden, P. O'Neill and I. J. Stratford, *Cancer Clin. Trials*, **3**, 37 (1980).

[5] G. E. Adams, E. M. Fielden, C. Hardy, B. C. Millar, I. J. Stratford and C. Williamson, *Int. J. Radiat. Biol.*, **40**, 153 (1981).

[6] I. J. Stratford, S. Hoe, G. E. Adams, C. Hardy and C. Williamson, *Int. J. Radiat. Biol.*, **43**, 31-43 (1983).

[7] D. A. Fitzpatrick, N. D. Heindel, R. A. Egolf and H. Walton, *Radiat. Res.*, **117**, 47-58 (1989).

[8] P. J. Eifel, D. M. Brown, W. W. Lee and J. M. Brown, *Abstr. Radiat. Res. Soc.*, (1982).

[9] R. Ottlinger, K. Burger and H. Goth, *Tetrahedron Letters*, 5003 (1978).

[10] K. Burger, K. Geith and D. Hübl, *Synthesis*, 189 (1988).

[11] L. L. Bennett Jr. and H. T. Baker, *J. Am. Chem. Soc.*, **79**, 2188 (1957).

[12] N. D. Heindel, C. J. Lacey, R. Egolf, B. N. Mease and K. J. Schray, *J. Heterocyclic Chem.*, **18**, 1087 (1986).

[13] N. D. Heindel, C. J. Lacey, B. A. Mease and D. V. Woo, *O.P.P.I. Briefs*, **23**, 275 (1986).

[14] N. D. Heindel, R. A. Egolf and J. S. Stefely, *J. Pharm. Sci.*, **79**, 862 (1990).

[15] R. A. Egolf and N. D. Heindel, *J. Heterocyclic Chem.*, **28**, 577 (1991).