

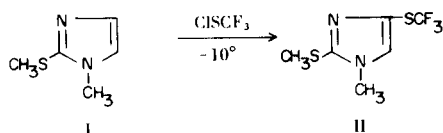
Novel Electrophilic Substitution of the Imidazole Nucleus

Dennis M. Mulvey and Howard Jones

Merck, Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065

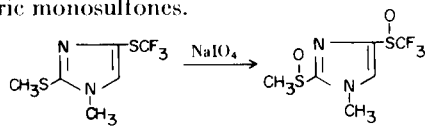
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We wish to report a novel electrophilic aromatic substitution of the imidazole nucleus. Treatment of 1-methyl-2-methylthioimidazole (I) with trifluoromethylsulfenyl chloride (2) at -10° in tetrahydrofuran afforded good yields of 1-methyl-2-methylthio-4-trifluoromethylthioimidazole (II).



Of interest is the observation that the only biproduct noted was the hydrochloride of imidazole I. Attempts to employ alternative organic bases (*i.e.* triethylamine) to effect a sparing action on I gave gross mixtures of products. These mixtures included: II, a monochloro derivative of I, and mono- and di-trifluoromethylthio derivatives of triethylamine. A control reaction in which air was passed continually through the reaction mixture (initial conditions) did not alter the reaction course, suggesting that free radical chain processes are not important.

The structure of I was established by spectroscopic and analytical means. Imidazole II was also readily converted to the corresponding disulfoxide III with excess sodium periodate. The disulfoxide structure is clearly indicated by the mass spectrum of III and thus eliminates the possible isomeric monosulfones.



The assignment of position 4 as the site of binding of the trifluoromethylthio functionality is based upon nmr studies (3) of a variety of 4 and 5 substituted imidazoles in deuterated dimethylsulfoxide. From these studies it has been noted that protons at C-4 absorbs very near 8.06 ppm whereas corresponding protons at C-5 fall at 7.76 ppm. In both II and III, the aromatic proton resonance occurs at 7.76 ppm.

Further investigation of the scope and limitations of

this reaction is in progress.

EXPERIMENTAL

1-Methyl-2-methylthio-4-trifluoromethylthioimidazole Hydrochloride (II).

A solution of 6.4 g. (0.05 mole) of 1-methyl-2-methylthioimidazole (I) in 50 ml. of anhydrous tetrahydrofuran was cooled to -10° . The 7.0 g. (0.05 mole) trifluoromethylsulfenyl chloride was introduced sub-surface by distillation. The reaction mixture was aged at -10° for 45 minutes. The resulting crystalline precipitate was isolated, washed with 10 ml. precooled tetrahydrofuran and dried *in vacuo* to afford 3.9 g. (47.5%) of 1-methyl-2-methylthioimidazole hydrochloride. The combined filtrates were concentrated *in vacuo* to afford a yellow oil. This was dissolved in 30 ml. of anhydrous tetrahydrofuran, cooled to 0° , and was saturated with dry hydrogen chloride. The resulting crystalline precipitate was isolated, washed with 15 ml. of precooled tetrahydrofuran and dried *in vacuo* yielding 5.6 g. (42.5%) of 1-methyl-2-methylthio-4-trifluoromethylthioimidazole hydrochloride, m.p. 166-167°. Spectral data were in accord with the assigned structure.

Anal. Calcd. for $\text{C}_6\text{H}_8\text{N}_2\text{S}_2\text{ClF}_3$: C, 27.22; H, 3.05; N, 10.58. Found: C, 27.07; H, 3.06; N, 10.41.

1-Methyl-2-methylsulfinyl-4-trifluoromethylsulfinylimidazole (III).

A solution of 1.5 g. (0.0057 mole) of 1-methyl-2-methylthio-4-trifluoromethylthioimidazole hydrochloride in 20 ml. of distilled water was treated with a solution of 12.19 g. (0.057 mole) sodium periodate in 70 ml. of distilled water and heated at $50-60^\circ$ for 1.5 hours. The reaction mixture was quenched on 100 ml. of saturated aqueous sodium bicarbonate and resulting solids separated by filtration. Extraction of the filtrate with ethyl acetate (3 x 100 ml.) was followed by drying of the organic layer over magnesium sulfate. After concentration *in vacuo*, a colorless solid was obtained, 1.25 g. (73%), m.p. $84-86^\circ$. Mass spectrometry indicated a disulfoxide structure, and other spectral data were in accord.

Anal. Calcd. for $\text{C}_6\text{H}_7\text{N}_2\text{S}_2\text{O}_2\text{F}_3$: C, 27.69; H, 2.71; N, 10.76. Found: C, 27.59; H, 2.55; N, 10.52.

REFERENCES

- (1) Private communication from Mr. Charles N. Habecker, Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania.
- (2) Available from Peninsular Chemresearch, P. O. Box 1466, Gainesville, Florida, 32601.
- (3) The authors wish to acknowledge the valuable assistance of Mr. Byron Arison, these laboratories, for the nmr structural studies herein mentioned.