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THE MILD OXIDATION OF SOME ALPHA-DIFLUORO SULFIDES TO SULFONES WITH SODIUM PERBORATE

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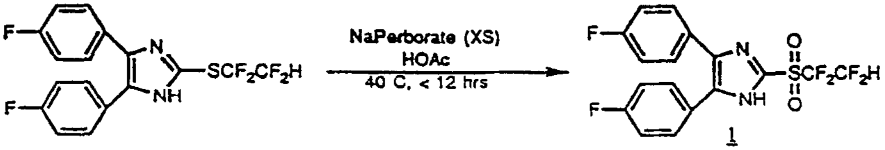
Abstract - Sodium perborate in acetic acid is an effective reagent for the mild oxidation of some electron-deficient sulfides to sulfones.

While searching for a more advantageous process for the oxidation of the pharmaceutical intermediate 4,5 bis(4-fluorophenyl)-2-[(1,1,2,2-tetrafluoroethyl)-thio]-1H-imidazole[1] to its corresponding sulfone 1, the sodium perborate procedure of A. McKillop and J. A. Tarbin[2,3] was tested. Despite the strong electron-withdrawing effect of the two alpha fluorine atoms and an oxidation potential probably comparable to hydrogen peroxide's -0.68, the oxidation proceeded extremely well under conditions thought to be far too mild to succeed.



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Substituents on sulfur affect the ease with which its oxidation occurs. Specifically, electron-withdrawing or electron-deficient groups are known to decrease sulfur's oxidizability.[4] Alkyl sulfides are much more easily oxidized than aryl sulfides. Similarly, fluorine atoms on the alkyl group decrease the oxidizability of the sulfide. A measure of the electron-withdrawing effect of a substituent is the parameter σ_p. While a simple alkyl group is slightly electron-donating (σ_p CH_3 = -0.17 to -0.23), polyfluorinated alkyl groups are very electron-withdrawing (σ_p CF_3 = 0.49 to 0.65).[5] Traditionally, the oxidation of aryl or heteroaryl polyfluoroalkyl sulfides to the corresponding sulfones has required rather harsh conditions and long reaction times, often proceeding in modest yield.[6]

The above explains the pleasant surprise which accompanied the success of the McKillop procedure. Also, the sulfide-to-sulfone examples in his sodium perborate papers[2,3,7] give no indication that the procedure would be efficacious in the presence of strong electron-withdrawing groups. The last paper[7], containing also the conversion of a variety of sulfur heterocycles to the corresponding S,S-dioxides, adds that "electron-withdrawing substituents completely inhibit the reaction".

The original oxidant used to prepare our desired sulfone was metachloroperbenzoic acid. Peracids, with oxidation potentials of approximately -1.0, are generally considered the method of choice for the oxidation of alpha-halo sulfides to sulfones.[8] Problems, however, were reagent cost, elaborate workup, impure product, low yield and the possibility of PCB formation. Oxone has also been described as an excellent reagent for the oxidation of sulfides to sulfones.[9] Its oxidation potential of -1.44 makes it seem ideal for the oxidation of electron-deficient sulfides, but when tested on our compound it gave mostly unreacted sulfide, some sulfoxide and trace sulfone. Hydrogen peroxide, at 30 and 70% concentrations, with and without catalytic traces of sulfuric acid, also gave substantial unreacted sulfide and sulfoxide.

The sodium perborate oxidation followed the straight-forward procedure given by McKillop. Sulfide was stirred overnight in acetic acid under nitrogen with an excess of sodium perborate at only 40 degrees C. Insolubles were removed by filtration. Aqueous drowning of the filtrate gave crude product which was purified by base/acid conversions to the sodium salt and back to the pure sulfone (76%). The method was also tested successfully on 4-(3,4-dichlorophenyl)-5-phenyl-2-[(1,1,2,2-tetrafluoroethyl) sulfonyl]-1H-imidazole. TLC of the crude product showed nearly pure sulfone (87%); after the base-acid purification, TLC showed only pure sulfone (72%). A quick test with 1,1,2,2-tetrafluoroethyl phenyl sulfide also gave similar satisfactory results; TLC showed only sulfone and a faint trace of sulfoxide (80%). The corresponding compound to 1 containing CF_3 in place of the tetrafluoroethyl group, however, interestingly failed to react, perhaps due to the additional electron-deficiency finally overcoming the reagent's oxidative capability. But varying the conditions might make it react also; the project was stopped due to non-chemical reasons and the work discontinued.

McKillop clearly states the strong advantages of this useful procedure, but they cannot be overemphasized for large-scale work. Primarily, the reagent is very cheap, allowing even large excesses to be used if desired. It is also safe and environmentally friendly, used considerably in detergents.

In conclusion, even certain electron-deficient sulfides can be easily oxidized to sulfones. McKillop's sodium perborate oxidation procedure is thus even more attractive.

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