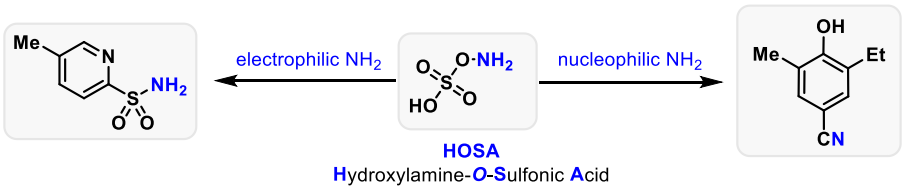
OLDIE BUT GOLDIE: THE USE OF HOSA IN ACCESSING CLASSICAL FUNCTIONAL GROUPS ON SCALE IN AN INNOVATIVE WAY

Schäfer, G.
Hembrunnstrasse 17, 5605 Dottikon
Dottikon Exclusive Synthesis AG
Switzerland
gabriel.schaefer@dottikon.com

Hydroxylamine-*O*-sulfonic acid, or short HOSA, is an easily handled, stable solid, which is produced on ton-scale by reaction of hydroxylamine with oleum/sulfuric acid or chlorosulfonic acid/sulfuric acid. Despite being a bulk chemical, HOSA has not been extensively used in the manufacturing of pharmaceuticals, which is surprising given the great versatility of this reagent to act as an electrophilic or nucleophilic source of nitrogen.



We have disclosed two new manufacturing routes, for which HOSA was used on scale and took advantage of its modular reactivity. In the first example, a novel route to 5-methyl-2-pyridinesulfonamide was developed. The new route relied on the selective oxidization of the thiophenol starting material to the sulfinate salt, followed by amination of the nucleophilic sulfinate sulfur-atom with HOSA acting as an electrophilic amine source. This oxidation/electrophilic amination sequence worked well as a "one-pot" procedure by simply adding HOSA to the reaction mixture after completed oxidation of the thiophenol. The new process was performed on 22 kg scale, delivering the desired product in 69% overall yield and excellent purity.[1]

In the second example, a new manufacturing route for 3-ethyl-4-hydroxy-5-methylbenzonitrile was urgently needed. Therefore, a conceptually novel route to the nitrile with HOSA, this time reacting as a nucleophilic amine source, was developed. The idea was to convert the corresponding aldehyde into the HOSA-derived oxime, followed by elimination of sulfuric acid to form nitrile. This reaction sequence worked well on scale and provided the product in 89% yield and high purity.[2]

1. Schäfer, G.; Fleischer, T.; Kastner, M.; Karge, R.; Huang, Q.; Libang Wu, B.; Tang, J.; Aiglstorfer, I. *Org. Process Res. Dev.* **2023**, *27*, 1377-1383.

2. Schäfer, G.; Fleischer, T. *Helv. Chim. Acta* **2023**, *e202300167*..