SYNLETT Spotlight 197

Hydroxylamine Hydrochloride

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

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Introduction

Hydroxylamine hydrochloride is a hygroscopic white crystalline powder (mp 151–152 °C). Explosion of the reagent may occur if it is heated above 115 °C. Hydroxylamine hydrochloride is harmful if inhaled or swallowed and it is irritating to eyes, skin, and respiratory tract.¹ The reagent decomposes slowly on contact with moisture and should not be stored above 65 °C. Hydroxylamine as a free base is available in the form of large white flakes or needles; however, due to its instability, commercially available hydroxylamine hydrochloride is used as a stable source of hydroxylamine.² This versatile reagent can be prepared by treatment of sulfur dioxide with a cold

solution of potassium nitrate and potassium acetate under controlled reaction conditions below 0 °C.

For over a century, hydroxylamine hydrochloride has found wide application in organic synthesis including electrophilic substitution reactions,¹ oximation,³ the synthesis of pyrazoles,⁴ nitriles,⁵ isoxazoles,⁶ pyridines,⁷ nitrones,⁸ etc. It is also used as reducing agent⁹ and its importance in areas like bioorganic and medicinal chemistry is also vivid. For example, this reagent greatly facilitates the synthesis of a new class of glycosylated β -amino acids, which exhibit good activity against human anti-malarial parasite *Plasmodium falciparum*.¹⁰

Abstracts

(1) A novel one-pot synthesis of pyrazoles has been accomplished by the reaction of β -formyl enamides with hydroxylamine hydrochloride catalysed by potassium dihydrogenphosphate in acidic medium.⁴ The reaction has been successfully extended to steroidal, aliphatic, cyclic, and aromatic β -formyl enamides.

(2) A one-pot transformation of aliphatic and aromatic aldehydes to the corresponding nitriles can be easily performed by the reaction of an aldehyde with a slight excess of hydroxylamine hydrochloride in refluxing acetonitrile and in the presence of 0.5 equivalent of sodium iodide as catalyst.⁵

(3) 3,5-Disubstituted isoxazoles are obtained in good yields by a convenient one-pot, three-step procedure utilizing a regioselective copper(I)-catalysed cycloaddition reaction between in situ generated nitrile oxides and terminal acetylenes.^{6a} This corresponding nitrile oxide can be obtained by reacting hydroxylamine hydrochloride in the presence of NaOH and TsN(Cl)Na·3H₂O with the unsaturated aldehyde.

(4) A one-pot synthesis of enantiopure five-membered cyclic nitrones has been accomplished via condensation of hydroxylamine with readily available lactols and subsequent esterification with methanesulfonylchloride. These cyclic nitrones have been employed for the preparation of pyrrolizidines.⁸

(5) Glycosylated β -amino acids afforded glycosyl β -aminohydroxamates in fair yields on reaction with $\text{NH}_2\text{OH}\cdot\text{HCl}$ in the presence of DIC/DCC. These compounds were screened against human malarial parasite.¹⁰

(6) Reaction of hydroxylamine hydrochloride with aryltrifluoromethyl- β -diketones affords 5-hydroxy-5-trifluoromethyl- Δ^2 -isoxazoles which, upon dehydration, yield 5-trifluoromethylisoxazoles.¹¹

(7) A short synthesis of pyrrolo-2-aminoimidazoles such as oroidin and its derivatives via N -acyl-1,2-dihydropyridine intermediate¹² is reported. The key step of the strategy is a one-pot oxidative bromine-mediated addition of protected guanidine to N -acyl-1,2-dihydropyridine in the presence of NH_2OH .

(8) Synthesis of 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]quinoxalines has been reported starting from 2-acetyl quinoxaline via dehydrogenative cyclisation with hydroxylamine hydrochloride in acidic medium.¹³

References

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