Copper Sulfate ($CuSO_4$): An Efficient Reagent in Organic Synthesis

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Copper sulfate ($CuSO_4$) occurs in nature as anhydrous form (hydrocyanite) and as mono- and pentahydrate. It is a simple, inexpensive, and commercially available salt synthesized by the treatment of cupric oxide with sulfuric acid.[1]

As monohydrate, also known as dried cupric sulfate, is hydroscopic, off-white powder, soluble in water, and practically insoluble in alcohol (MeOH, EtOH). As pentahydrate, also known as blue vitriol, Salzburg vitriol among others is a large, blue or ultramarine, triclinic crystals or blue granules or light-blue powder. It can be obtained from the anhydrous form by dissolving in deionized water and allowing the solvent to evaporate at room temperature, forming blue crystals in approximately one week.[2] Loses 2 H_2O at 30 °C becomes anhydrous by 250 °C. It is very soluble in water, soluble in methanol, glycerol, and slightly soluble in ethanol and shows acid characteristic with pH 0.2 molar.[1]

The anhydrous salt is used for detecting and removing trace amount of water from alcohols and other organic compounds. It is also used in agricultural as fungicide, algicide, bactericide, herbicide, and fertilizer additive.[1]

Besides, copper pentahydrate is an eye irritant but not a skin irritant, it may induce allergic dermatitis in sensitive people.[3] Copper is also an essential trace element and an important catalyst for heme synthesis and iron absorption on biological organisms. His dysregulation has been studied with a focus on neurodegenerative diseases, such as Wilson's, Alzheimer, and Parkinson disease.[4]

In chemistry, this compound is normally used as a catalyst for reactions, due to its low cost, possibility of use at low temperatures and ecological advantages.[5] Several reactions have been reported using this compound since 1944 when Hann and Hudson[6] reported the activity of $CuSO_4$ as a catalyst in triazole formation reactions. Copper sulfate stands out for its application in catalysis reactions, for example, in the synthesis of aryl/vinyl halides and azides of vinyl/aryl boronate esters/boronic acids.[7] Table 1 presents a series of recent applications of this reagent.

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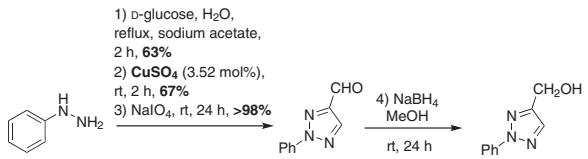
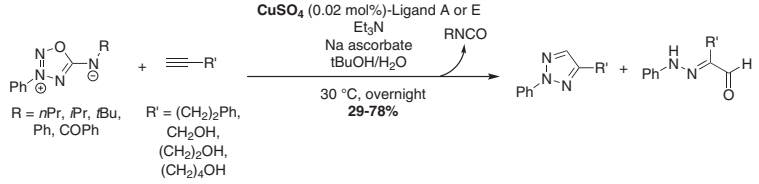
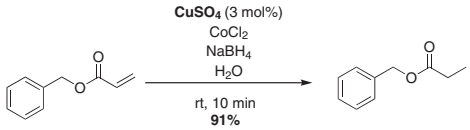
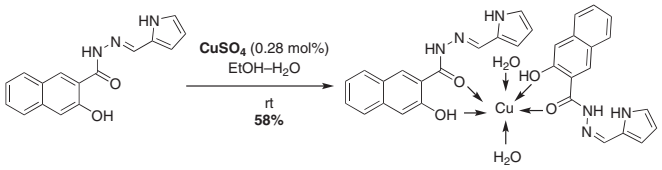
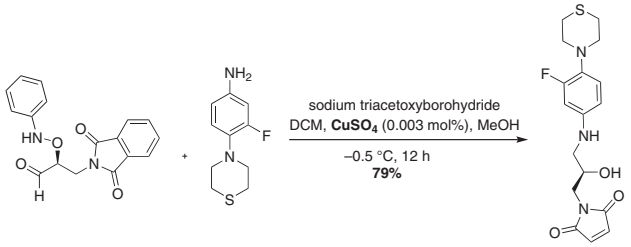
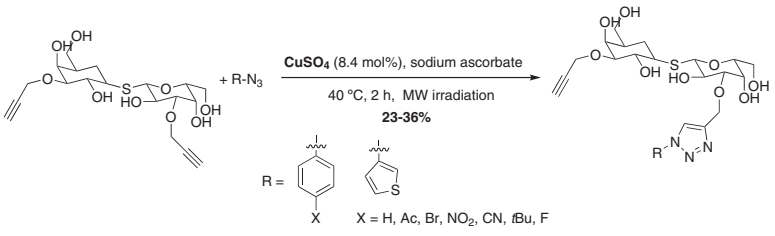
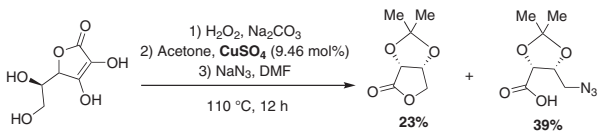
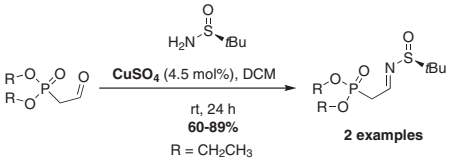
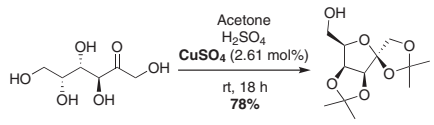
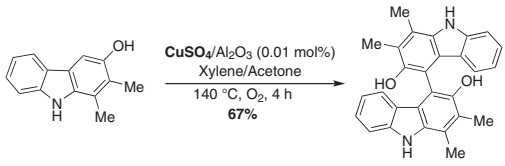
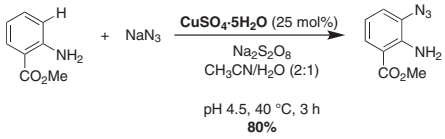
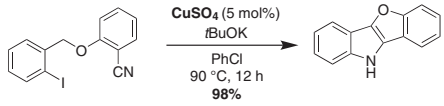
Table 1 Recent Applications of Cupric Sulfate ($CuSO_4$)

(A) Daniel Gonzaga *et al.* synthesized 2-phenyl-triazole-carbaldehyde using a three-step sequence for obtaining the Fisher osazone (D-glucose adduct with substituted phenylhydrazines) followed by oxidative cyclization by Hudson's method (refluxed in aqueous solution of $CuSO_4$), generating the derivate phenyl-D-glucosotriazol, followed by the oxidative cleavage of the glycotriazole in aqueous $NaIO_4$ to obtain the carboxaldehyde.[8]	
(B) Elodie Decuypere *et al.* synthesized a series of 1,2,3-triazoles using the $CuSO_4$ as a copper salt catalyst in the copper-catalyzed aza-iminosydnione-alkyne cycloaddition reactions. It is added to the reaction mixture along with sodium ascorbate and one of the selected ligands to form the copper complex used in the reaction.[9]	
(C) Mario Ficker *et al.* prepared an ester by reduction of alkene using a copper–cobalt catalytic system, resulting in a good product yield.[10]	
(D) Salhah D. Al-Qahtani *et al.* synthesized metallic complexes using EtOH/H_2O mixtures with a concentration of 0.001 mol dm^{-3} of copper sulfate for the preparation of the metallic binding solution with the proposed naphthohydrazide.[11]	
(E) Pankaj R Chaudhari *et al.* published a six-step synthesis for the preparation of a sutezolid compound where one of the intermediates is synthesized by the reaction involving copper sulfate catalysis for 12 h in ethanol over −0,5 °C in 79% yield.[12]	
(F) David Vrbata *et al.* performed a coupling of reaction with azide precursor under microwave irradiation at 40 °C for 1 h with a binary mixture of *t*-BuOH/H_2O (proportions related to the polarity of the azide) involving copper sulfate and sodium ascorbate.[13]	
(G) Huafang Fan *et al.* synthesized vinyl lactams using a tree-steps reaction involving oxidative cleavage of D-isoascorbic acid, followed by acetonide formation of the resulting D-erythronolactone catalyzed by copper sulfate and, per last, ring opening of the lactone with sodium azide in 39% yield.[14]	
(H) Jeffrey R. Groch, Nicholas R. Lauta, and Jon T. Njardarson synthesized two chiral sulfonimines using the copper sulfate to drive imine formation in the final product with varying yields of 60–89%.[15]	

(I) Alex A. Hunt-Painter *et al.* proposed a synthetic route for the synthesis of an iminosugar using a method of protection of isopropylidene groups using acetone, sulfuric acid, and copper sulfate for a subsequent iodination with 78% yield over two steps.[16]	
(J) Ankush Banerjee, Shuvendu Saha, and Modhu Sudan Maji proposed an economical approach to the use of biologically active marine alkaloids, where hyellazole and 6-chlorohyellazole were first synthesized and were subjected to a dimerization reaction in the presence of $CuSO_4/Al_2O_3$ under an O_2 atmosphere at 140 °C to produce the dimer known as sorazolon E2 in 67% yield.[17]	
(K) Seki and Takahashi reported a catalytic system with copper sulfate for regioselective C–H azidation of methyl anthranilate. This reaction is performed using NaN_3 and $Na_2S_2O_8$ to provide the corresponding α-azidated product in 80% yield.[18]	
(L) Shan and co-workers published the synthesis of indole-fused tetracyclic heteroacene via $CuSO_4$-catalyzed carbanion radical redox relay, yielding benzofuro[3,2-*b*]indole in 98%.[19]	

In summary, copper sulfate enables a variety of diverse reactions and functionalizations that include: triazole formation, reduction of alkenes and alkynes, complexes formation, and catalysis among others. The support reagent offers advantages for the reactions, and in the most it is used as catalyst due to all advantages such increase reagent stability, ease of workup, low cost, and ecological advantages.

Conflict of Interest

The authors declare no conflict of interest.

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