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Sodium Persulfate ($Na_2S_2O_8$)

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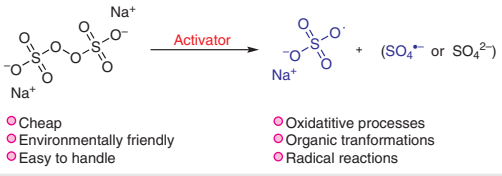
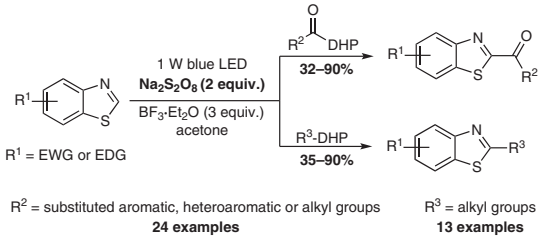
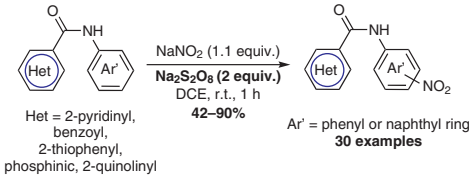
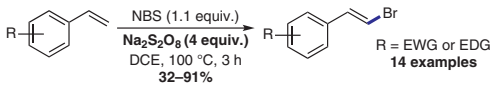
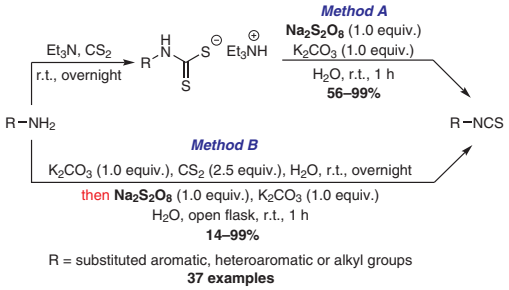
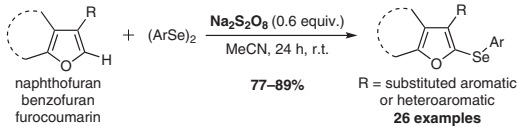
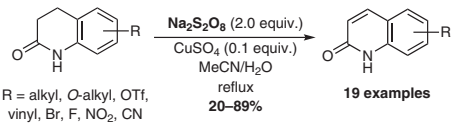
Sodium persulfate, or sodium peroxodisulfate, is an environmentally friendly inorganic compound commonly used as an oxidizing agent in chemistry. This reagent undergoes homolytic cleavage in solutions, affording sulfate radical anions that can present several applications (Scheme 1). Recently, $SO_4^{\bullet-}$ has been applied in diverse processes, such as the degradation of antibiotics and dyes in wastewater treatment.[1] In organic synthesis, sodium persulfate can be used as an oxidant in transition-metal-catalyzed reactions or as an oxidative species in crucial steps in metal-free reactions.[2,3] $Na_2S_2O_8$ is an inexpensive oxidant that is stable and easy to handle, making it a good reagent choice for several strategic synthetic transformations.[4] It is synthesized industrially through an electrolytic oxidation process from sodium hydrogen sulfate,[5] and recent applications for this compound are presented herein (Table 1).

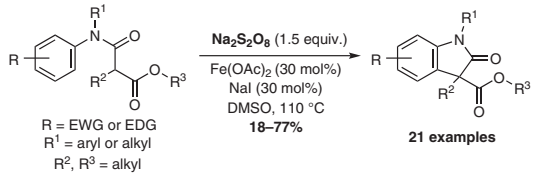
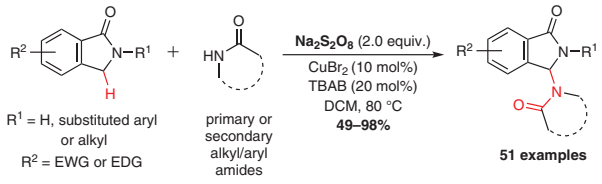
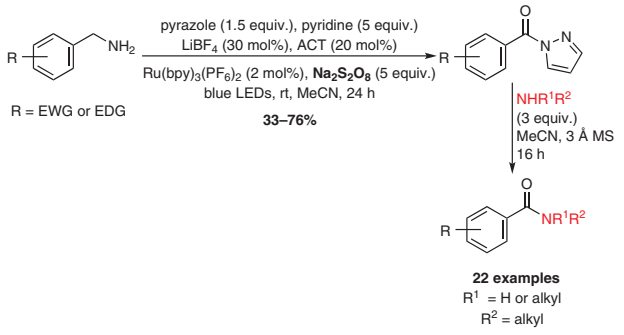
Tereza Cristina Santos Evangelista received her MSc in chemistry from the Federal University of Rio de Janeiro in 2018. Currently, she is a PhD student at the same institution under the supervision of Prof. Sabrina B. Ferreira and Prof. Carlos R. Kaiser. Her work involves the synthesis and biological evaluation of novel nitrogenated heterocycles.
Sabrina Baptista Ferreira received her PhD from the Federal University of Rio de Janeiro (UFRJ) in 2008 under the supervision of Prof. Carlos R. Kaiser and Prof. Vitor F. Ferreira. After the postdoctoral experience held at Fluminense Federal University (UFF) with Prof. Vitor F. Ferreira, she became a professor at UFRJ in 2010 where she is the head of the Laboratory of Organic Synthesis and Biological Prospecting. Her research efforts focus on the organic synthesis, acting on the following subjects: heterocycles, carbohydrates, nucleosides and naphthoquinones, search for biologically active compounds.



Scheme 1 Homolytic cleavage of sodium persulfate

Table 1 Recent Applications of Sodium Persulfate ($Na_2S_2O_8$)

(A) 2-Substituted benzothiazoles present several biological activities, attracting great interest in medicinal chemistry. For this reason, the development of C–H activation methods could represent a valuable synthetic strategy for obtaining new 2-substituted benzothiazole derivatives. Du and collaborators reported a visible-light-mediated method to provide 2-substituted acylated and alkylated benzotriazoles via Hantzsch esters in the presence of the Lewis acid $BF_3{\cdot}Et_2O$ and $Na_2S_2O_8$ as the oxidant. The reaction follows a radical pathway with a blue LED as the light source, affording compounds in yields up to 90%.[2]	
(B) Xie and co-workers synthesized nitroarylamines from protected arylamines via a sodium persulfate promoted nitration applying the mild nitrating agent sodium nitrite. The reaction occurs quickly and at room temperature, affording the products with moderate to very good yields without the addition of transition metals. Furthermore, the reaction is site selective, affording nitration at C-2 for anilines and at C-4 for 2-naphthylamines. The reaction proceeds via a free-radical mechanism, an observation that is supported by the suppression of product formation when the radical scavenger TEMPO was added to the reaction mixture. The nitroarylamines can undergo deprotection upon treatment with NaOH in ethanol at 90 °C, affording the deprotected products in high yields. Thus, this nitration method offers mild conditions and an efficient way of synthesizing strategic nitroarylamine derivatives.[6]	
(C) Halostyrene compounds are versatile building blocks for different transition-metal-catalyzed cross-coupling reactions. However, their preparation from styrenes usually involves the use of expensive Ru complexes to catalyze the reaction. As a new alternative for those methods, Ma and collaborators performed a direct bromination of styrenes using *N*-bromosuccinimide (NBS) as the halogen source and $Na_2S_2O_8$ as the final oxidant. The reaction is performed in a sealed tube, affording β-bromostyrenes in moderate to excellent yield with an *E*/*Z* ratio up to 20:1. This practical transformation proceeds via a radical mechanism, and it is suitable for gram-scale synthesis with no reduction in yield.[7]	
(D) Xu and collaborators described two novel and greener methods for preparing isothiocyanates from amines and carbon disulfide. The reactions undergo the essential desulfurization step with sodium persulfate as the oxidant. Both procedures use water as the solvent, and method B is a one-pot method, affording the isothiocyanates in good to excellent yields. These mild and efficient procedures present high tolerance for a broad substrate scope, including access to chiral isothiocyanates when chiral amines are employed. Furthermore, when performing the reaction on a gram scale, the products are easily purified by crystallization techniques, avoiding column chromatography.[8]	
(E) Hajra and co-workers reported the first metal-free procedure for the direct selenylation of various arenofurans in 2017. This novel method involves the reaction of arenofurans with diphenyl diselenide and sodium persulfate at room temperature, affording diarylselenides in very good yields. Furthermore, the reaction presents compatibility with a broad substrate scope, including benzofuran, naphthofuran, and furocoumarin derivatives. Unfortunately, naphthofuran bearing alkyl substituents failed to give the desired products. Control experiments revealed that this protocol is not affected by radical scavengers, suggesting an electrophilic substitution pathway.[9]	
(F) Quinolin-2(1*H*)-one derivatives possess a broad spectrum of biological activities, being the core structure of some drugs, such as brexpiprazole and indacaterol. Their synthesis usually involves an oxidative aromatization reaction of 3,4-dihydroquinolin-2(1*H*)-one derivatives using the potentially genotoxic DDQ as the oxidant. To develop an alternative method for this aromatization step, Aisa et al. applied a stoichiometric amount of sodium persulfate combined with a catalytic portion of copper in an acetonitrile/water system at reflux. The scope of the aromatization was investigated, and the reaction proved to be suitable for a broad range of substituents, with quinolin-2(1*H*)-one derivatives possessing electron-donating groups being easier to synthesize. Products were formed in good yields, and a 100 g scale synthesis of the 7-(4-chlorobutoxy)quinolin-2(1*H*)-one, the precursor of brexpriprazole, was performed, affording the key drug intermediate with 80% yield. The proposed mechanism for this transformation involves a transition-metal activation of persulfate salts in a single-electron-transfer (SET) pathway.[3]	

(G) To expand the scope of application for the oxidative system $Fe(OAc)_2$/NaI/$Na_2S_2O_8$, Zhou and co-workers carried out an intramolecular dehydrogenative coupling reaction to afford pharmacologically relevant oxindazole derivatives from a variety of anilides. For the reaction optimization, different oxidants were tested, including $K_2S_2O_8$, $(NH_4)_2S_2O_8$, and $Na_2S_2O_8$, where the latter gave the best results. The scope and feasibility of the proposed method were screened by reacting a series of anilide derivatives. The reaction presented broad substrate scope, and electron-rich aromatic derivatives gave the best product yields. The reaction scalability was investigated and proved to be suitable for gram-scale applications without a drop in yield.[10]	
(H) The amide functional group has a central importance in biologically active compounds. For this reason, straightforward methods to prepare this functionality are very desirable. Inspired by the cross-dehydrogenative-coupling (CDC) strategy, Zha and collaborators described the direct amidation of isoindolinone derivatives using sodium persulfate as the oxidant. The reaction optimization was performed using methylisoindolin-1-one and pyrrolidin-2-one as model substrates. To improve the formation of $SO_4^{\bullet -}$ species, catalytic amounts of transition metals were applied, including $CuBr_2$, $Pd(OAc)_2$, $AgNO_3$, and $FeCl_2$, where $CuBr_2$ gave the best results. The optimized procedure was applied to the synthesis of a variety of amide derivatives, possessing a broad substrate scope and great selectivity towards obtaining the amide functionality primarily at the C3 position of the isoindolinone motifs. The application of the method was extended to the functionalization of indobufen with different amides, which can be applied in structure–activity studies in drug design and to late-stage drug functionalization. Furthermore, control experiments suggested that the transformation involves a radical and electrophilic pathway.[11]	
(I) In connection with photoamidation strategies, Leadbeater and co-workers reported for the first time the use of a tandem oxidative pathway for the conversion of amines into amides. The proposed process occurs via a visible-light-promoted reaction with the dual catalyst $Ru(bpy)_3(PF_6)_2$ and 4-AcNH-TEMPO in the presence of the terminal oxidant sodium persulfate. This process was investigated for the synthesis of *N*-acylpyrazoles, applying a blue LED as the light source. Control experiments were performed, proving that the photocatalyst, the light source, and catalyst system are vital for the product formation. Furthermore, absence of $Na_2S_2O_8$ led to the formation of the homocoupled imine. The authors also investigated the reaction scope for the tandem process followed by a transamination reaction. The two-step method occurs with no need for purification of the *N*-acyl pyrazole intermediate. This protocol, followed by the transamination reaction also proved to be broad in substrate scope, affording a variety of amines with moderate to good yields.[12]	

Conflict of Interest

The authors declare no conflict of interest.

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