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Decarboxylative sulfation by persulfates†

Zhen Xia,[ab] Ting Deng,[a] Chunlan Song [a] and Jiakun Li *[a]

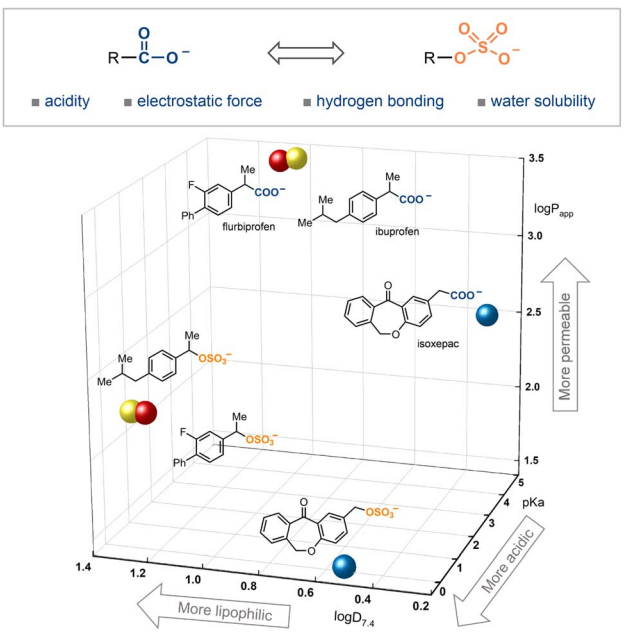
Direct decarboxylative sulfation *via* C–O bond formation is an unexplored disconnection strategy for the synthesis of organosulfates, with the potential to overcome the significant limitations of *O*-sulfonation, which is restricted to hydroxyl-containing compounds. Reported here is a radical process for direct decarboxylative sulfation by persulfates. In this reaction, persulfates serve a dual role: acting as a versatile oxidant to generate carbon-centered radicals in decarboxylation, and providing an O–O source to facilitate the synthesis of organosulfates *via* C–OSO_3^- bond formation. This method enables the replacement of diverse carboxylic acids with ionizable organosulfate groups, which could be potential isosteres to improve molecules' metabolic profiles.

Introduction

Carboxylic acids are prevalent motifs in natural products and pharmacologically active molecules. The acidity of this functional group, along with its ability to form strong electrostatic interactions and hydrogen bonds, makes it highly versatile.[1] Consequently, the carboxylic acid group often plays a crucial role in drug–target interactions. Additionally, these characteristics suggest that carboxylic acid groups can impart relatively high water solubility, a critical attribute for a drug-like molecule. On occasion, the presence of this functional group in a drug or a drug candidate may result in adverse effects, such as metabolic instability, potential idiosyncratic toxicities and limited permeability across biological membranes.[2] To mitigate one or more of these issues, medicinal chemists often resort to isosteric replacement or ester-prodrug strategies.[3]

Organosulfates (–OSO_3^-), possessing similar physicochemical properties to carboxylic acids, may serve as potential isosteres (Scheme 1). They are also prevalent in various biological compounds, ranging from exogenous metabolites to post-translationally modified endogenous bioactive molecules.[4] The incorporation of polar sulfate groups into target molecules can dramatically alter their solubility, acidity, electrostatic forces, and hydrogen bonding interactions. This modification has been implicated in the regulation of various biological and disease processes, including cell-signaling, molecular recognition, neurobiology, inflammation and cancer metastasis.[5] The intrinsically anionic character of sulfates enhances their excretion properties and reduces potential toxicity.[6] Considering the unique physicochemical properties between organosulfates and carboxylic acids, it is highly desirable to develop a method for the replacement of carboxylic acids with organosulfates to create improved drug derivatives, particularly in terms of pK_a values, lipophilicity (*i.e.*, log $D_{7.4}$), and permeability coefficients (P_{app}).[7]

In contrast to the successful development of various decarboxylative functionalizations,[8,9] the synthesis of organosulfates from carboxylic acids has not been reported. The primary



Scheme 1 Unique physicochemical properties between carboxylic acids and organosulfates.

[a]*State Key Laboratory of Chemo and Biosensing, College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China. E-mail: jkli@hnu.edu.cn*

[b]*Hunan Provincial Engineering Technology Research Center for Polyvinyl Alcohol Based New Functional Materials, College of Chemistry and Materials Engineering, Huaihua University, Huaihua 418000, China*

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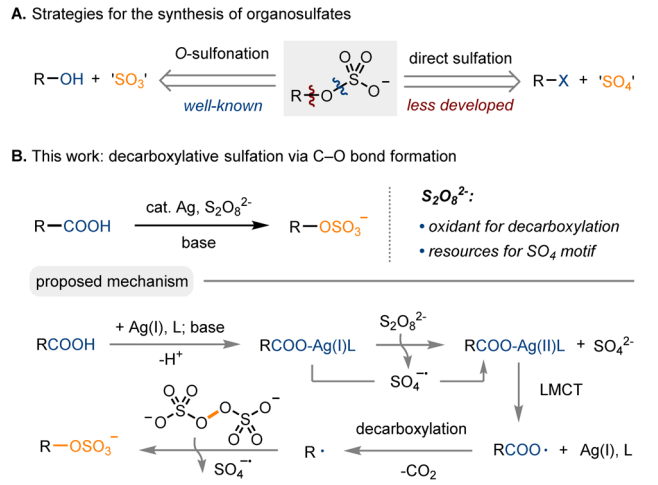
challenge in this approach is the formation of the C–OSO_3^- bond. The weak nucleophilicity of the sulfate anion (SO_4^{2-}) restricts C–OSO_3^- bond formation *via* a nucleophilic substitution pathway.[10] Furthermore, the electron-withdrawing nature of the sulfate anion contributes substantially to the ionic character of the metal–sulfate bond, which increases the energy barrier for C–OSO_3^- reductive elimination in transition-metal-catalyzed cross-coupling reactions.[11] A radical approach was alternatively employed to construct challenging C–O bonds.[12] As a persistent radical trapping reagent, tetramethylpiperidine-1-oxyl (TEMPO$^\bullet$) can form C–O bonds with carbon-centered radicals.[13] This stable aminoxyl radical was recently investigated in frustrated Lewis pairs (FLPs) and applied to regioselective C–H oxygenation by Lin and co-workers.[14] In 2020, Gooßen and co-workers reported an electrodecarboxylative etherification through a radical C–O coupling strategy; the success of this reaction is attributed to the facile oxidation of 1-hydroxybenzotriazole (HOBt) to form an O-centered radical ($^\bullet$OBt).[15]

In addition, the formation of C–O bonds through the reaction of a carbon radical with an oxygenating reagent would be a more versatile synthetic method, as it allows for the use of a wide range of radical precursors.[16] Malonoyl peroxide was utilized for aromatic C–H oxygenation by Tomkinson *et al.*,[17] while bis(methanesulfonyl) peroxide has been reported by Ritter for late-stage C–O bond formation in arenes and benzylic C–H compounds.[18] In 2024, our group reported benzylic C–H sulfation with persulfates, a classic oxidant that has been rarely employed for sulfate-transfer functions.[19,20] This radical C–O bond formation exhibits distinct reactivity compared to previous *O*-sulfonation methods, which are a common way to access organosulfates *via* an O–S bond, and therein limited to hydroxyl substrates (Scheme 2A).[21]

In this study, our objective was to establish an efficient protocol for decarboxylative sulfation *via* a radical C–OSO_3^- bond, using persulfates as both oxidants and sulfating reagents (Scheme 2B). Persulfates initially act as the oxidant to generate carbon-centered radicals from decarboxylation, and then supply an O–O source to afford the organosulfates *via* C–OSO_3^- bond formation. Notably, the oxidative properties of persulfates and their roles as sulfate sources can be modulated by their positively charged counterions.[19]

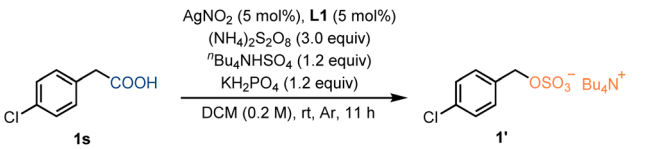


Scheme 2 Strategies for the synthesis of organosulfates.

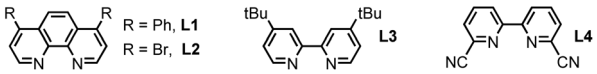
Results and discussion

We initiated our investigation into the decarboxylative sulfation of 4-chlorophenylacetic acid (**1s**) with $AgNO_2$ as the catalyst, 4,7-diphenyl-1,1-phenanthroline (**L1**) as the ligand, KH_2PO_4 as the base, and $(NH_4)_2S_2O_8$ serving as both the oxidant and sulfating agent. The desired sulfate **1** was obtained in a 69% isolated yield with $^nBu_4NHSO_4$ as an additive (Table 1, entry 1). Substitution of the phenanthroline ligand with another variant still led to the desired product, albeit in a reduced yield (Table 1, entry 2). Use of bipyridine type ligands had a deleterious effect (Table 1, entries 3 and 4). The choice of ligand influenced the oxidation potential of the *in situ* conversion of the silver(I) carboxylate complex to a silver(II) carboxylate complex, which is crucial for the subsequent decarboxylation.[22] Changing the reaction solvent from DCM to 1,2-dichloroethane resulted in a slight decrease in yield (Table 1, entry 5). In contrast, polar solvents led to either slower or no reaction (Table 1, entries 6–8). Persulfate salts $K_2S_2O_8$ and $Na_2S_2O_8$ were less productive (Table 1,

Table 1 Investigation of the reaction conditions[a]



Entry	Variation from standard conditions	Yield of **1′**
1	None	75% (69%)[b]
2	**L2** as ligand	49%
3	**L3** as ligand	Trace
4	**L4** as ligand	6%
5	DCE as solvent	64%
6	MeCN as solvent	9%
7	1,4-Dioxane as solvent	Trace
8	DMSO as solvent	Trace
9	$K_2S_2O_8$ instead of $(NH_4)_2S_2O_8$	59%
10	$Na_2S_2O_8$ instead of $(NH_4)_2S_2O_8$	47%
11	Et_4NHSO_4 instead of $^nBu_4NHSO_4$	16%
12	$^nBu_4NOAc$ instead of $^nBu_4NHSO_4$	26%
13	Without $AgNO_2$	Trace
14	Without ligand	Trace
15	Without $^nBu_4NHSO_4$	Trace
16	$(^nBu_4N)_2S_2O_8$ instead of $(NH_4)_2S_2O_4$, $^nBu_4NHSO_4$	28%

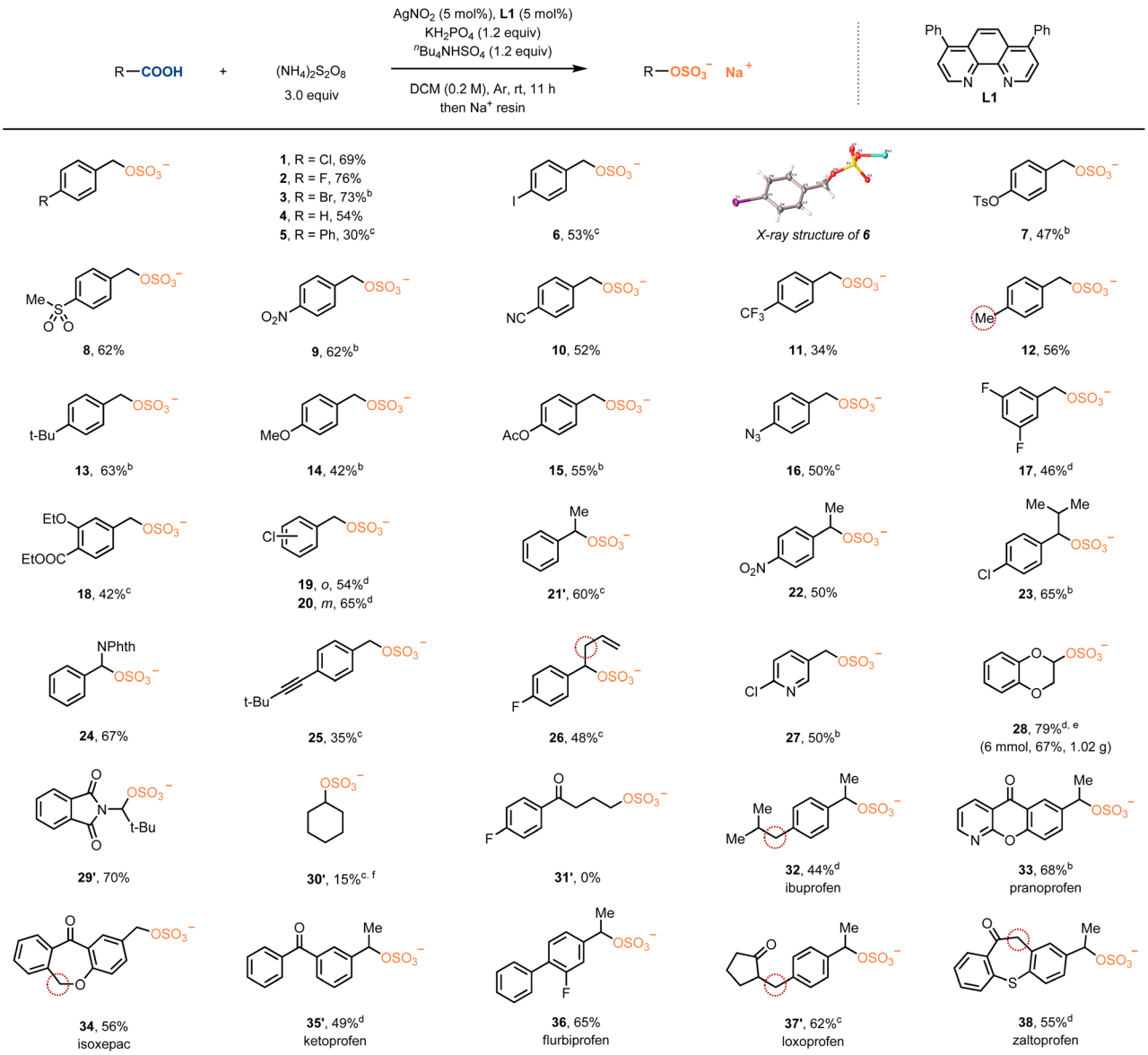


[a] Standard reaction conditions: substrate (0.2 mmol), $(NH_4)_2S_2O_8$ (3.0 equiv.), $AgNO_2$ (5 mol%), **L1** = 4,7-diphenyl-1,1-phenanthroline (5 mol%), KH_2PO_4 (1.2 equiv.), $^nBu_4NHSO_4$ (1.2 equiv.), DCM (0.2 M), Ar, rt, 11 h. Yields were determined by integration of the ^1H NMR spectrum using dibromomethane as an internal standard. [b] Isolated yield.

entries 9 and 10). Moreover, when the additive $^{n}Bu_4NHSO_4$ was replaced with other ammonium salts in the reaction, a noticeable decrease in yield was observed (Table 1, entries 11 and 12). Control experiments confirmed the requirement of a silver catalyst, ligand, and ammonium salt additive in this decarboxylative sulfation protocol (Table 1, entries 13–16).

The optimized reaction conditions were then used to explore the substrate scope. As shown in Table 2, a diverse range of primary and secondary carboxylic acids, spanning from electron-withdrawing to electron-donating substituents on the arenes, were well-tolerated to give organosulfates in moderate to good isolated yields. Compatible functional groups include halide (**2–3**), tosyl (**7**), sulfonyl (**8**), nitro (**9**), nitrile (**10**), trifluoromethyl (**11**), alkoxyl (**14**), azide (**16**), ester (**15**) and aromatic heterocycle (**27**) groups. Oxidatively labile functional groups, such as alkyne (**25**) and alkene (**26**), are viable with this method. Substrates with two substituents (**17**, **18**), or substitution at different positions on the aromatic ring (**1**, **19**, **20**) also performed smoothly. The sulfation occurred selectively at the carboxylic acid site in the presence of benzylic (**12**, **32**, **34**, **37′**, **38**) and allylic (**26**) C–H bonds, both of which can easily undergo hydrogen atom abstraction (HAA) and form corresponding sulfate products. Tertiary carboxylic acids failed due to their inherent lability and sluggish reactivity.[23] In addition, this

Table 2 Substrate scope of the decarboxylative sulfation[a]



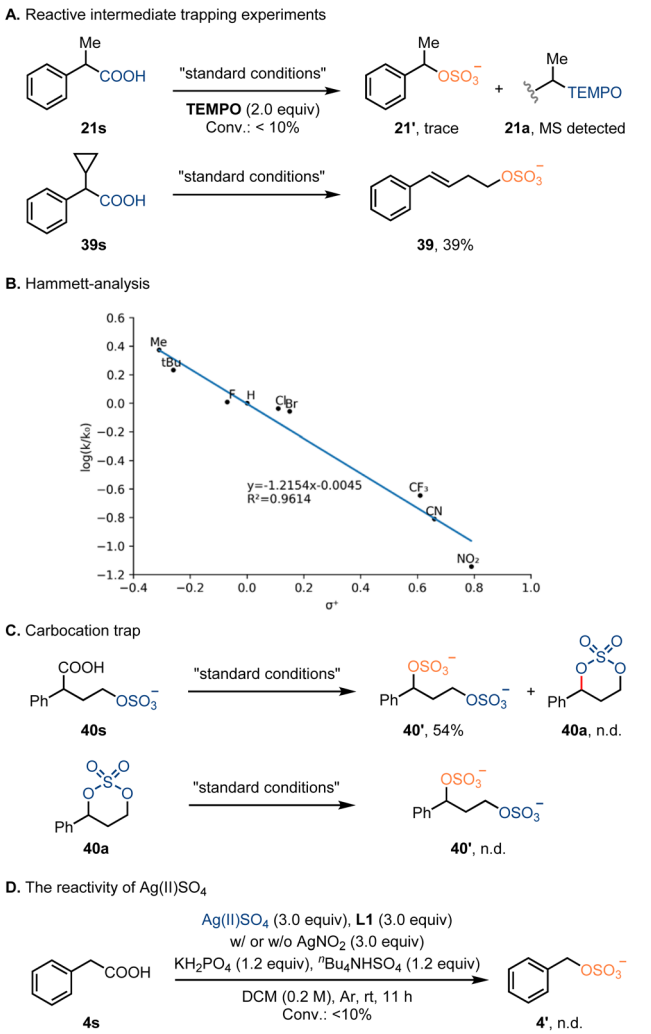
[a] Carboxylic acid (0.2 mmol), $(NH_4)_2S_2O_8$ (3.0 equiv.), $AgNO_2$ (5 mol%), **L1** = 4,7-diphenyl-1,1-phenanthroline (5 mol%), KH_2PO_4 (1.2 equiv.), $^{n}Bu_4NHSO_4$ (1.2 equiv.), DCM (0.2 M), Ar, rt, 11 h, isolated yield. [b] K_2HPO_4 as the base. [c] Et_3N (1.5 equiv.) instead of KH_2PO_4, $^{n}Bu_4NHSO_4$. [d] K_2CO_3 as the base. [e] H_2O (5.0 equiv.) was added. [f] 3,8-Dibromo-1,10-phenanthroline instead of **L1**. **29**: Na as cation; **29′**: $^{n}Bu_4N$ as cation. (′) indicates the countercation is $^{n}Bu_4N$ for other compounds as well.

method is currently restricted to arylacetic acids that form a stabilized radical. To our delight, the substrate scope can be extended to carboxylic acid fragments adjacent to oxygen (**28**) and nitrogen (**29′**) atoms. A non-activated aliphatic acid could afford the sulfated product (**30′**) in 15% yield, though broader substrate generality remains constrained (**31′**). The identity of the target sulfate group was unambiguously confirmed by the X-ray crystal structure of **6**. The generality and mild reaction conditions of this method make it suitable for late-stage sulfation of drugs, including ibuprofen (**32**), pranoprofen (**33**), isoxepac (**34**), ketoprofen (**35′**), flurbiprofen (**36**), loxoprofen (**37′**) and zaltoprofen (**38**). Meanwhile, the synthetic robustness was further demonstrated on a gram scale to give the product **28** without obviously detrimental effect on reaction efficiency.

To gain insight into the mechanism of the decarboxylative sulfation, a few experiments were conducted. The addition of the radical scavenger TEMPO to the standard reaction conditions effectively inhibited the sulfation process, resulting in a low conversion of **21s** (Scheme 3A, top). Meanwhile, the reaction of cyclopropylacetic acid **39s** afforded the ring-opened product **39** in a 39% yield (Scheme 3A, bottom). These results suggest the involvement of a benzyl radical intermediate in the silver-catalyzed decarboxylative sulfation. Subsequently, a Hammett analysis of the relative rate of decarboxylative sulfation across a series of *para*-substituted arylacetic acids was performed. The measured Hammett slope of −1.2 is consistent with ρ values indicative of benzyl radical formation as the rate-determining step in most processes (Scheme 3B).[24]

Aside from the radical pathway of C–OSO_3^- bond formation outlined in our initial mechanistic hypothesis (Scheme 2B), a nucleophilic attack by SO_4^{2-} toward a benzylic carbocation—which could be generated from further oxidation of a benzylic radical—is an alternative process to form the C–OSO_3^- bond. To validate this, substrate **40s**, containing a pendent sulfate group, was subjected to the standard conditions, leading to the exclusive formation of bisulfated product **40′**, with no detectable cyclized product **40a** (Scheme 3C, top). Furthermore, the bisulfated product **40′** was not generated from nucleophilic substitution of SO_4^{2-} on sulfate diester **40a** (Scheme 3C, bottom). These findings indicate that the decarboxylation sulfation proceeds *via* a radical pathway rather than a nucleophilic attack process. Notably, treatment of **4s** with a stoichiometric silver(II)–sulfate complex did not yield any sulfate product,[25] suggesting that high-valent Ag(II)SO_4 may not engage in C–OSO_3^- bond formation; moreover, the Ag(III) sulfate complex was not detected in the reaction mixture (see Fig. S5†).[26]

Based on the above results and pertinent literature,[22,27] a mechanism is proposed (Scheme 2B). Initially, a silver(I)–carboxylate complex was formed in the presence of the base and catalyst system. The Ag(I) complex was then oxidized to Ag(II) by either persulfate or a sulfate radical. The resulting silver(II) complex underwent a ligand-to-metal charge transfer (LMCT) with the carboxylate to produce a benzylic radical followed by decarboxylation. Finally, the benzylic radical participated in a bimolecular homolytic substitution (S_H2) reaction with persulfate,[19a] leading to the desired sulfated product *via* C–O bond formation.



Scheme 3 Mechanistic investigations.

Conclusions

In summary, we have developed a method for decarboxylative sulfation by persulfates. Persulfates serve as both versatile oxidant and sulfating agents to facilitate the challenging C–OSO_3^- bond formation. The mild reaction conditions and operational simplicity of this method allow for a broad substrate scope and high functional-group tolerance. The improved synthetic utility is demonstrated by the late-stage modification of drugs, as a potential isosteric replacement for carboxylic acids to modify their metabolic profiles.

Data availability

Detailed synthetic procedures and complete characterization data for all new compounds can be found in the ESI.†

Author contributions

J. L. conceived the idea, directed the project, and wrote the paper. Z. X. and T. D. performed the experiments. Z. X. and C. S.

analyzed the results and participated in the preparation of the manuscript.

Conflicts of interest

A patent application (No. 202310019868.5, China), dealing with the use of persulfates for sulfation, has been filed, and J. L. may benefit from royalty payments.

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