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Humic acid as a natural catalyst for C–S bond construction: decarbonylative and decarboxylative thioether synthesis

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In this study, humic acid is introduced as a sustainable and green catalyst for C–S bond formation. Thioethers were synthesized *via* the reaction of thiols with aldehydes and carboxylic acids in dimethylformamide (DMF), where humic acid effectively facilitated the generation of stable thiyil and alkyl radicals. This method offers a mild, efficient, and environmentally friendly approach with broad functional group tolerance, highlighting the potential of humic acid as a practical catalyst in green organic synthesis.

1 Introduction

Humic acid (HA) is a high-molecular-weight, naturally derived biopolymer formed through the biodegradation of organic matter in soil, coal, peat, and aquatic systems. Its structure contains various functional groups, including carboxylic acids ($-\text{COOH}$), phenolic hydroxyls ($-\text{OH}$), and quinones, which contribute to both its acidity and catalytic activity (Fig. 1).¹ Typically, humic acid is extracted using alkaline solutions such as NaOH or KOH, followed by purification steps to eliminate mineral impurities. These features make HA an eco-friendly, sustainable, and reusable catalyst, aligning well with the principles of green chemistry.²

Humic acid exhibits notable versatility in promoting a wide range of organic transformations.² It activates carbonyl groups through protonation, thereby increasing their electrophilicity and facilitating reactions under mild conditions. For instance, HA efficiently catalyzes condensation reactions such as aldol and Knoevenagel condensations, leading to the formation of β -hydroxycarbonyl and α,β -unsaturated carbonyl compounds.³ Additionally, it promotes Michael additions, enabling nucleophiles like enolates to add to α,β -unsaturated systems, thus expanding molecular complexity.⁴ HA has also proven effective in the Strecker synthesis, offering a green, metal-free route to α -aminonitriles *via* the reaction of aldehydes, amines, and cyanide sources.⁵ In multicomponent reactions, it facilitates the synthesis of 5-substituted tetrazoles through [3 + 2] cycloaddition involving aldehydes, hydroxylamine, and sodium azide in aqueous media—demonstrating its potential in heterocycle construction.⁶ Furthermore, HA supports Hantzsch⁷ and pyran syntheses,⁸ enabling the formation of dihydropyridines and functionalized substituted pyrans.

Humic acid is also valuable in cross-coupling reactions such as the Heck⁹ and Suzuki¹⁰ reactions, and has been employed in the hydroxylation of arylboronic acids to phenols using hydrogen peroxide, demonstrating its utility in oxidation processes.¹¹ In addition to its catalytic capabilities, humic acid offers excellent recyclability and reusability,¹² often maintaining consistent performance over multiple cycles. This not only enhances its environmental compatibility but also reduces costs in industrial applications. Moreover, its broad substrate scope, functional group tolerance, ability to operate in aqueous media, and wide applicability in sustainable synthesis make humic acid a unique and powerful tool in modern organic chemistry (Scheme 1).

Sulfide-containing compounds have garnered considerable attention due to their broad applications in agriculture, industry, medicine, and heterocyclic chemistry. Thioethers,

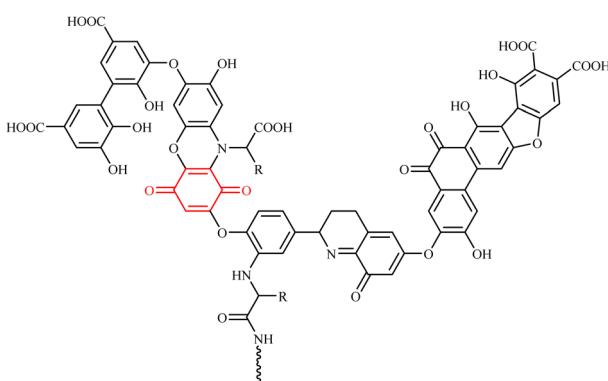
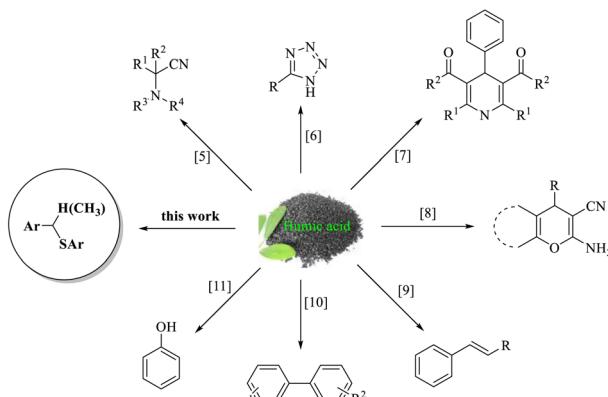


Fig. 1 Structure of humic acid.¹





Scheme 1 Summary of several reactions facilitated by humic acid as catalyst.

characterized by a carbon–sulfur (C–S) bond, play a vital role in both biological and chemical systems and serve as essential synthetic intermediates in living cells.¹³ These compounds are also valued in the pharmaceutical and agricultural sectors for their antifungal and anticancer properties and are employed as vulcanizing agents in the production of rubbers and elastomers. Given their biological and industrial significance, the development of efficient and mild methods for C–S bond formation is of great importance. Traditional methods, including reductive couplings, often depend on highly reactive, toxic, or expensive electrophiles, which restrict their practical utility.^{14–16} In this context, carbonyl-derived electrophiles—such as aldehydes and carboxylic acids—have emerged as promising alternatives in decarbonylative or decarboxylative coupling strategies.^{17–19} These approaches enable cleavage of the C–C bond in carboxylate or carbonyl functionalities and replace volatile byproducts like carbon dioxide or carbon monoxide with new C–heteroatom bonds, offering an efficient and sustainable route for constructing C–S bonds.

As summarized in Table 1, previously reported Pd- and Ni-catalyzed strategies have mainly focused on benzoic acid derivatives and rely on costly transition-metal catalysts and ligands.^{20,21} In contrast, a few metal-free approaches have been developed for aliphatic carboxylic acids. For example, the use of Cs_2CO_3 under an oxygen atmosphere in NMP enables the reaction within 6 h,²² while another method employs DMSO as both solvent and oxidant under an argon atmosphere, requiring up to 24 h.²³ These reports demonstrate that although metal-free protocols for aliphatic acids are feasible, they often demand extended reaction times or special conditions.

Building on our previous work on C–S bond formation under various conditions,^{24–27} we now aim to explore humic acid as a catalyst for synthesizing thioethers. By leveraging its sustainable and efficient catalytic properties, this study seeks to address current challenges, including selectivity, functional group tolerance, and environmental compatibility, while advancing the development of green and practical synthetic methods.

2 Results and discussion

As a model reaction, the coupling of 2-phenylpropanal (0.5 mmol) and thiophenol (1.0 mmol) was performed in the presence of humic acid (20 mg) and potassium carbonate (0.5 mmol) in DMF at 120 °C for 24 hours. Under these conditions, the reaction proceeded smoothly to afford the corresponding thioether in 92% yield (Table 2, entry 1). To examine the role of humic acid, the same reaction was carried out in its absence.

Table 2 Effect of different reaction parameters on the synthesis of thioethers in the presence of humic acid

Entry	ArSH	$\xrightarrow[\text{Humic acid (20 mg)}]{\text{PhCH}(\text{CH}_3)\text{CHO (0.5 mmol)}}$		Time (h)	Yield ^a (%)
		1.0 mmol	Base (mmol)		
1	K_2CO_3 (0.5)	DMF	120	24	92
2 ^b	K_2CO_3 (0.5)	DMF	120	24	—
3	K_2CO_3 (0.5)	EtOH	Reflux	24	38
4	K_2CO_3 (0.5)	H_2O	Reflux	24	30
5	K_2CO_3 (0.5)	CH_3CN	Reflux	24	45
6	K_2CO_3 (0.5)	Toluene	Reflux	24	52
8	K_2CO_3 (0.5)	DMSO	120	24	78
9	Na_2CO_3 (0.5)	DMF	120	24	71
10	K_3PO_4 (0.5)	DMF	120	24	48
11	Et_3N (0.5)	DMF	120	24	23
12	K_2CO_3 (0.4)	DMF	120	24	79
13	K_2CO_3 (1.0)	DMF	120	24	91
14	—	DMF	120	24	15
15 ^c	K_2CO_3 (0.5)	DMF	120	24	71
16 ^d	K_2CO_3 (0.5)	DMF	120	24	92
17 ^e	—	DMF	120	24	—
18	K_2CO_3 (0.5)	DMF	110	24	58

^a Isolated yield. ^b The reaction proceeded in the absence of humic acid.

^c The reaction proceeded in the presence of 15 mg of humic acid. ^d The reaction proceeded in the presence of 25 mg of humic acid. ^e The reaction proceeded in the absence of both the base and humic acid.

Table 1 Comparison of reported methods for thioether synthesis from carboxylic acids and thiols

Entry	Substrate type	Metal catalyst	Additive/conditions
1	Benzoic acid derivatives ²⁰	$\text{Pd}(\text{OAc})_2$, $\text{CuCO}_3 \cdot \text{Cu}(\text{OH})_2$	KF, NMP, 160 °C, 24 h
2	Benzoic acid derivatives ²¹	$\text{Ni}(\text{dppp})\text{Cl}_2$	DMAP, Piv_2O , dioxane, 160 °C, 15 h
3	Aliphatic carboxylic acids ²²	—	Cs_2CO_3 , O_2 , NMP, 120 °C, 6 h
4	Aliphatic carboxylic acids ²³	—	DMSO, 80 or 150 °C, under Ar atmosphere, 24 h
This work	Aliphatic carboxylic acids	—	Humic acid, K_2CO_3, DMF, 120 °C, 1–6 h



However, no product formation was observed, highlighting the crucial role of humic acid in promoting the reaction (Table 2, entry 2). To optimize the reaction conditions, various solvents including EtOH, H₂O, CH₃CN, DMSO, and toluene were tested. These solvents led to low yields of the sulfide product, while DMF was identified as the most effective medium, enabling efficient synthesis of the target compound (Table 2, entries 3–8). Next, the effect of different bases was evaluated. Although K₃PO₄ and Et₃N showed poor effectiveness, Na₂CO₃ performed better (Table 2, entries 9–11). However, the highest yield was achieved using 0.5 mmol of K₂CO₃ (Table 2, entry 1). Reducing K₂CO₃ to 0.4 mmol decreased the yield, whereas increasing it to 1.0 mmol did not significantly improve the result (Table 2, entries 12, 13). The removal of the base from the reaction system resulted in a lower yield of the product (Table 2, entry 14). The amount of humic acid was also examined. Reducing the amount to 15 mg decreased the yield to 71%, while 25 mg provided an optimal and consistent yield similar to the previous result (Table 2, entries 15, 16). As expected, in the absence of both the base and humic acid, no product was formed (Table 2, entry 17). Finally, temperature effects were studied. Reduced activity was observed at 110 °C; however, a significant formation of the thioether occurred at 120 °C, highlighting the importance of temperature in facilitating the coupling reaction (Table 2, entry 16).

Under the optimized reaction conditions, various thiols were reacted with aldehydes and carboxylic acids. The results are summarized in Table 3.

Aromatic thiols bearing substituents such as methyl, methoxy, chloro, bromo, and cyano were well tolerated, yielding sulfides in high yields when coupled with 2-phenylpropanal. This suggests that the reaction mechanism is not strongly dependent on electronic activation/deactivation of the thiol, likely due to radical stabilization in the reaction pathway. Notably, *ortho*-substituted thiophenols, such as *ortho*-methyl and *ortho*-chloro derivatives, exhibited excellent reactivity with 2-phenylpropanal, despite potential steric hindrance at the reactive center (Table 3, **4c** and **4e**). This indicates that steric effects did not significantly hinder the reaction. In contrast, aliphatic thiols like benzyl mercaptan and 2-furyl thiol were unreactive under the optimized conditions, failing to produce the desired sulfides. This lack of reactivity is likely due to the lower stability of radicals generated from aliphatic thiols compared to their aromatic counterparts. In addition, other aliphatic aldehydes such as 3-phenylpropanal and 2-phenyl-acetaldehyde did not undergo coupling with thiols under the same conditions. This failure is presumably due to the reduced stability of the intermediate radicals derived from these aldehydes relative to that of 2-phenylpropanal.

Based on the results obtained with aldehyde substrates, we hypothesized that aliphatic carboxylic acids capable of generating stabilized benzyl-type radicals would be suitable for the humic acid-catalyzed system. Accordingly, a series of carboxylic acids were examined as coupling partners in a sequential thioarylation–decarboxylation process with various thiols, using the same optimized conditions as for 2-phenylpropanal. As shown in Table 3, 2-phenylpropanoic acid (**5a–c**), phenylacetic

acid (**5d–g**), 1-naphthylacetic acid (**5h–k**), and 2-furoylacetic acid (**5l**) all successfully afforded the corresponding thioethers in the presence of humic acid. The reactions proceeded efficiently regardless of the electronic or steric nature of the thiols, consistently providing the desired products in good to excellent yields. As anticipated, hexanoic acid, which cannot form a stabilized radical, did not undergo the reaction under the same conditions.

Importantly, the applicability of this protocol was further demonstrated by its successful extension to structurally complex, biologically active compounds. For instance, carboxylic acid-containing anti-inflammatory drugs such as indomethacin (Table 3, **5m**) and ibuprofen (Table 3, **5n**) were subjected to the optimized reaction conditions, leading to the formation of the corresponding thioether derivatives in moderate to good yields. This highlights the method's potential for late-stage functionalization of drug-like molecules without compromising sensitive functional groups.

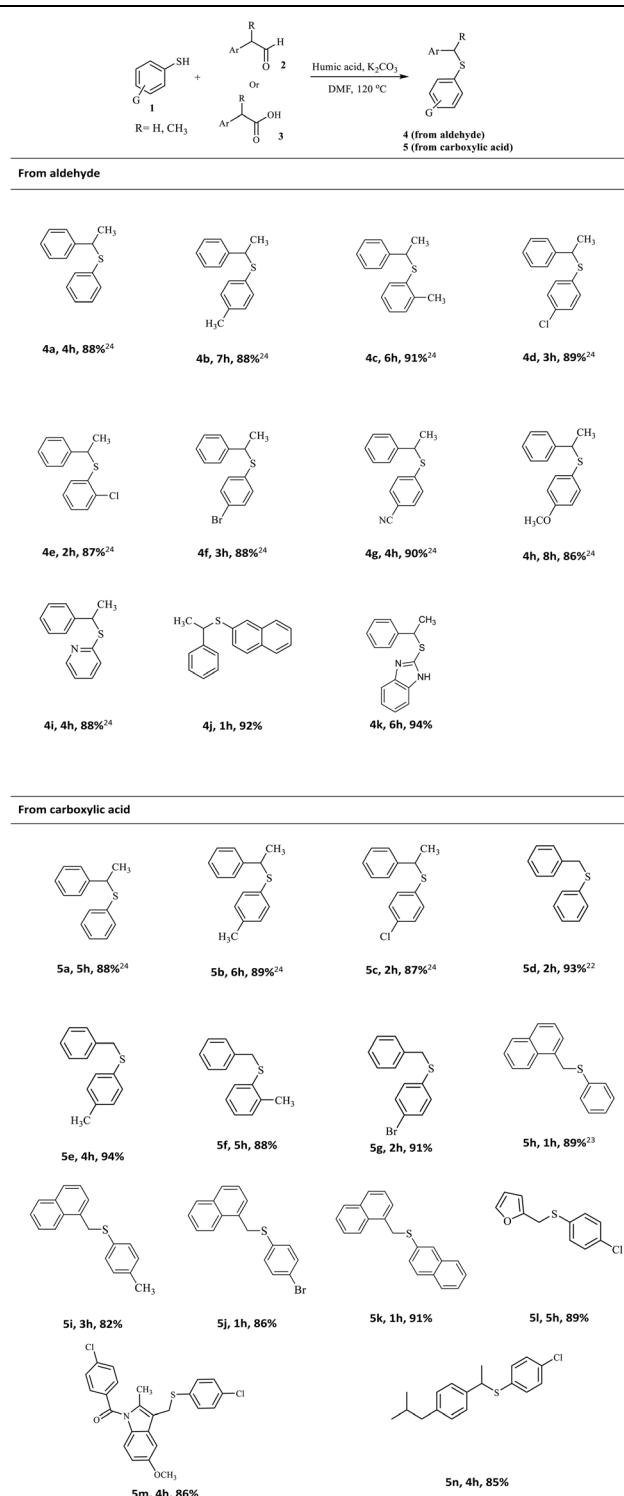
Since the reaction involves the release of carbonyl and carboxyl groups, it is likely to proceed *via* a radical pathway. To investigate this possibility and gain further insights into the reaction mechanism, radical scavenging experiments were performed using butylated hydroxytoluene (BHT) under optimized conditions with both 2-phenylpropanal and 2-phenylpropanoic acid as substrates. Under these conditions, the formation of the desired sulfide products was completely suppressed in both cases (Scheme 2). This result suggests that the reaction mechanism is most likely radical in nature. According to these results, the proposed reaction pathway is illustrated in Scheme 3.

Initially, the quinone moiety present in the structure of humic acid reacts with the thiol through a radical pathway. In this process, the thiol undergoes homolytic cleavage, generating a thiyl radical. Simultaneously, the quinone system of humic acid undergoes aromatization, in which one of the oxygen atoms is converted into a hydroxyl group (OH), while the other remains as an oxygen-centered radical (O[·]). This reactive intermediate then reacts with an aldehyde, abstracting a hydrogen radical from it. As a result, the hydroquinone form of humic acid is regenerated. Upon exposure to molecular oxygen, the hydroquinone is oxidized back to the quinone form, allowing humic acid to remain catalytically active through a redox cycle. Meanwhile, the aldehyde that has been converted into a carbon-centered radical undergoes decarbonylation, releasing a molecule of carbon monoxide. The resulting carbon radical subsequently couples with the thiyl radical, yielding the sulfide product through C–S bond formation.

Under a similar mechanism, carboxylic acids undergo decarboxylation to generate alkyl radicals by releasing a molecule of carbon dioxide. These alkyl radicals then couple with thiyl radicals in the final step to form the corresponding thioethers.

To support the proposed reaction mechanism and to confirm the involvement of the quinone moiety of humic acid in the coupling reaction, the model reaction (coupling of 2-phenylpropanal and thiophenol) was carried out using benzoquinone as the catalyst in place of humic acid. To prevent



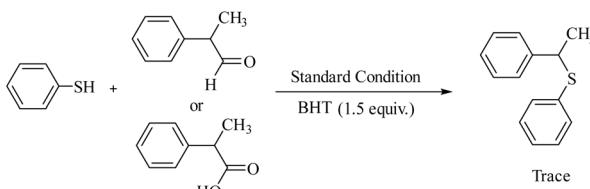
Table 3 Synthesis of thioethers from the reaction of thiols with aldehydes and carboxylic acids in the presence of humic acid^{a,b}

^a Reaction conditions: thiol (1.0 mmol), aldehyde or carboxylic acid (0.5 mmol), humic acid (20 mg), K₂CO₃ (0.5 mmol), DMF (1.0 mL), 120 °C. ^b The yields refer to the isolated pure products.

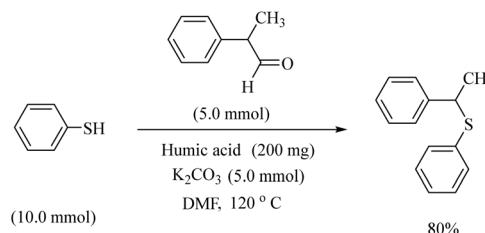
the reoxidation of the formed hydroquinone back to benzoquinone by atmospheric oxygen, a stoichiometric amount of benzoquinone was employed, and the reaction was

conducted under an argon atmosphere. This approach allowed for the isolation of hydroquinone, which was subsequently characterized and confirmed by NMR spectroscopy, providing

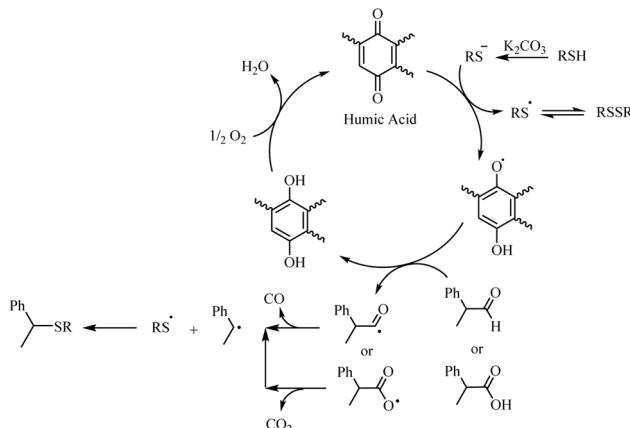




Scheme 2 Control experiments.



Scheme 5 Large scale synthesis of thioethers.



Scheme 3 Proposed mechanism for the synthesis of thioethers in the presence of humic acid.

direct evidence for the key role of the quinone moiety in the catalytic process (Scheme 4).

This radical-driven transformation highlights the role of humic acid as a redox-active mediator, facilitating thiol activation and enabling sulfide bond formation through a redox-catalytic cycle. The process efficiently couples thiols with aldehydes *via* a non-metal, radical-mediated pathway, providing a sustainable and green approach for C–S bond formation.

Organosulfur compounds have numerous applications in various fields, including industry and medicine. Therefore, performing the reaction on a large scale is of significant importance. Our investigations demonstrated that this reaction is scalable. To evaluate its scalability, the reaction of 2-phenylpropanal (5.0 mmol) with thiophenol (10 mmol) was carried out under optimized conditions, as illustrated in Scheme 5. In this case, the desired product, phenyl(1-phenylethyl) sulfane, was successfully isolated in 80% yield.

On the other hand, catalyst recyclability is a key factor in evaluating the practical efficiency and industrial relevance of

catalytic systems. Humic acid, due to its heterogeneous nature, can be easily separated and recovered. To assess this property, its recyclability was examined in the coupling of 2-phenylpropanal with thiophenol. As shown in Table 4, the product yield gradually decreased from 88% in the first cycle to 51% in the fourth cycle. This decline in efficiency is primarily attributed to the partial solubility of humic acid in water, which leads to a small loss of catalyst during the washing step of each cycle. Nevertheless, since humic acid is naturally abundant and inexpensive, it can serve as a practical and cost-effective catalyst even without recovery.

3 Experimental

Chemicals were purchased from Merck and Aldrich chemical companies. The products were characterized by comparison of their spectral and physical data with those reported in the literature. For the recorded ¹H NMR and ¹³C NMR spectra we used Bruker (300 and 400 MHz) Avance Ultrashield in pure deuterated CDCl₃ solvents with tetramethylsilane (TMS) as internal standards. The reaction monitoring was accomplished by TLC on silica gel PolyGram SILG/UV254 plates. Column chromatography was carried out on columns of silica gel 60 (70–230 mesh).

3.1 General procedure for preparation of thioethers in the presence of humic acid

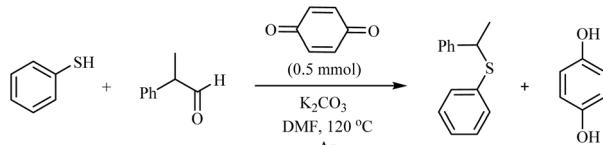
In a test tube equipped with a magnetic stir bar, aldehyde or carboxylic acid (0.5 mmol), thiophenol (1.0 mmol), humic acid (20 mg), K₂CO₃ (0.5 mmol), and DMF were added. The reaction mixture was stirred at 120 °C in an oil bath. Upon completion of the reaction, as monitored by thin-layer chromatography (TLC), the mixture was cooled to room temperature and diluted with

Table 4 Coupling of 2-phenylpropanal with thiophenol in the presence of recycled humic acid^a

Cycle	Time (h)	Yield ^b %
1	4	88
2	6	75
3	9	63
4	14	51

^a Reaction conditions: thiophenol (1.0 mmol), 2-phenylpropanal (0.5 mmol), humic acid (20 mg), K₂CO₃ (0.5 mmol), DMF (1.0 mL), 120 °C.

^b Isolated yield.

Scheme 4 Confirming the catalytic role of the quinone moiety in humic acid *via* benzoquinone-mediated coupling.

H_2O (1 mL). The crude product was then extracted using ethyl acetate (4×1 mL). Next, the solvent was evaporated and the residue was purified by column chromatography on silica-gel using *n*-hexane as eluent to provide with the desired thioether product.

4 Conclusions

The sequential thioarylation and decarbonylation/decarboxylation reactions of aldehydes or carboxylic acids with sulfur sources represent a powerful and versatile strategy for C–S bond formation, widely applicable in organic synthesis. In this study, humic acid has been successfully demonstrated as an eco-friendly and efficient catalyst for the synthesis of thioethers *via* the formation of carbon–sulfur bonds, using aldehydes and carboxylic acids in reaction with thiols. A radical pathway for the reaction was proposed and confirmed by the use of a radical scavenger. Moreover, scalability tests showed that this reaction can be performed on a larger scale with high yield, which highlights its potential for practical industrial applications. Humic acid, as a sustainable and recyclable alternative to traditional catalysts, presents itself as a promising tool for green synthesis in organic chemistry, with potential applications in pharmaceuticals, agriculture, and materials science. Furthermore, the protocol was successfully applied to structurally complex bioactive molecules, including anti-inflammatory drugs like indomethacin and ibuprofen, yielding the corresponding thioethers with good efficiency. This underscores the method's potential for late-stage functionalization of pharmaceuticals without affecting sensitive groups.

Author contributions

Maral Salehi: investigation, data curation, writing – original draft. Najmeh Nowrouzi: conceptualization, supervision, writing – review & editing. Mohammad Abbasi: conceptualization, supervision, project administration.

Conflicts of interest

The authors declare that they have no known financial or personal relationships that could be perceived as influencing the work reported in this paper.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: <https://doi.org/10.1039/d5ra05889a>.

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