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Sustainable synthesis of sulfonamides *via* oxidative chlorination in alternative solvents: a general, mild, and eco-friendly strategy

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A general, mild, and environmentally friendly method for synthesizing sulfonamides in sustainable solvents was developed. Sodium dichloroisocyanurate dihydrate (NaDCC·2H₂O) served as an efficient oxidant for converting thiols to sulfonyl chlorides, which then reacted *in situ* with various amines to afford sulfonamides in good to excellent yields in water, EtOH, glycerol and the DES ChCl/glycerol: 1/2. The process features simple conditions and a solvent-free workup involving only filtration, highlighting its potential as a green and practical approach to sulfonamide synthesis.

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Introduction

Sulfonamides were the first synthetic compounds implemented as effective antibacterial drugs.¹ Discovered in the 1930s, these compounds marked a significant breakthrough in medical science, paving the way for the development of modern antibiotics.² Sulfonamides work by inhibiting bacterial growth through the interference with folic acid synthesis, a vital nutrient for bacteria. They are particularly effective against a range of Gram-positive and Gram-negative bacteria,³ though their use has diminished due to the rise of resistance^{4,5} and the advent of newer antibiotics. Despite this, sulfonamides remain an important part of medical history and continue to be used in certain situations, particularly in the treatment of urinary tract infections.⁶ Their development not only revolutionized the treatment of bacterial infections but also laid the groundwork for the future of antimicrobial therapy including their re-evaluation for their priority in clinical practice.^{7,8}

Sulfonamides are synthesized through a variety of chemical methods, each allowing for different modifications to the sulfonamide structure.^{9,10} Among these, the most used involve S–N bond formation, typically through the reaction of amino compounds with sulfonyl chlorides in the presence of a base in organic solvents.¹¹ With the aim of improving the sustainability

of this methodology,¹² a series of greener procedures have been developed, including the use of alternative solvents like water,^{13,14} aqueous mixtures,¹⁵ PEG-400,¹⁶ ionic liquids,¹⁷ Deep Eutectic Solvents (DES),^{18,19} the use of neat conditions,^{20–22} the employment of reusable supported catalysts,^{23,24} and photocatalytic methods.²⁵

The use of sulfonyl chlorides poses significant challenges. These electrophiles are highly reactive and can be corrosive, posing risks during handling, storage, and transport. They can also release toxic gases, such as hydrogen chloride, upon decomposition. These compounds are sensitive to moisture and can degrade over time, making them difficult to store for extended periods without special precautions. Moreover, very often undesirable disulfonamides are obtained when primary amines are used, reducing the efficiency and selectivity of the process. As a result, significant recent efforts have focused on developing mild methods for synthesizing sulfonamides from *in situ* generated sulfonyl chlorides, with many of these methods utilizing oxidative chlorination of thiols and disulfides with different oxidants such as sodium hypochlorite/HCl,²⁶ ammonium nitrate/HCl,²⁷ 1,3-dichloro-5,5-dimethylhydantoin (DCH)/BnMe₃NCl,²⁸ trichloroisocyanuric acid (TCCA)/BnMe₃NCl,²⁹ TMSCl/H₂O₂,³⁰ generally using volatile organic compounds (VOC) or organic co-solvents as reaction media. Regarding alternative solvents, *N*-aryl and *N*-alkyl sulfonamides have been synthesized from thiols and disulfides using TCCA as oxidative chlorinating reagent in water and large excess of reagents.³¹

As can be demonstrated, to date there is no general method for the synthesis of sulfonamides from thiols *via* oxidative chlorination that can be employed with equal efficiency across different sustainable media. In this work, we present our studies on the synthesis of sulfonamides by reaction of amines

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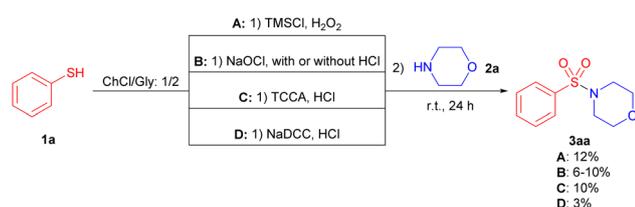


with *in situ* generated sulfonyl chlorides by oxidative chlorination of thiols in alternative solvents such as water, alcohols, and DES.

Results and discussion

The investigation began with the study of the reaction between thiophenol (**1a**) and morpholine (**2a**) by testing different conditions for the oxidative chlorination, using the DES choline chloride/glycerol (ChCl/Gly): 1/2 as the reaction medium at rt. As depicted in Scheme 1, various oxidants were tested: TMSCl/H₂O₂, NaOCl/with or without HCl, TCCA (trichloroisocyanuric acid)/HCl, and NaDCC (sodium dichloroisocyanurate)/HCl. Yields for sulfonamide formation ranged from 3% to 12%, with the TMSCl/H₂O₂ system being the most effective. Overall, the results were poor across all tested oxidants, due to the instability of the *in situ* generated sulfonyl chloride and the DES which is not able to maintain its nature under the used aqueous conditions.^{32,33}

To reduce or eliminate water content in the amide formation process from thiols, a critical factor for stability and scalability, we initially performed an optimization of the reaction conditions using the NaOCl/HCl mixture as the oxidative chlorinating agent. Notably, previous literature reports have made limited efforts to minimize the presence of water and organic cosolvents in this process. As observed in entry 1 of Table 1, when using the previously reported conditions²⁵ [**1a** (1 mmol), HCl (5 mL of a 1 M aqueous soln., 5 mmol, 5 equiv.), aqueous soln. of NaOCl (3.6 mmol, 3.6 equiv.), **2a** (6 mmol, 6 equiv.) but in the absence of the organic cosolvent (CH₂Cl₂)], a 70% isolated yield of sulfonamide **3aa** was obtained. Halving the amount of NaOCl resulted in a significant decrease in yield (entry 2), whereas reducing HCl to 2 equiv. had minimal impact in the yield, unless running the reaction at 5 °C which afforded **3aa** in an 84% isolated yield (entry 3). Upon scaling the reaction to 10 mmol of **1a**, a marked decrease in yield was observed, reaching only 30%. The detection of the sulfonyl chloride intermediate in the crude mixture suggests that extended reaction times may be required to achieve complete conversion under higher scale conditions. Further reduction of the HCl led to a lower 46% yield while in its absence, only the corresponding disulfide was obtained (Table 1, entry 5). Finally, no product formation was observed with concentrated 12 M HCl (entry 6), while the use of 6 M HCl allowed, after further optimization, to use only 1.2 equiv. of acid with a twentyfold reduction in volume, affording a 65% isolated yield of **3aa** at rt and 70% at 5 °C (Table 1, entry 7).



Scheme 1 Synthesis of sulfonamide **3aa** in ChCl/Gly: 1/2.

Table 1 Reaction conditions optimization for the synthesis of **3aa** using NaOCl/HCl as the oxidative chlorinating agent^a

| Entry | HCl ([], equiv.) | NaOCl (equiv.) | 2a (equiv.) | 3aa yield ^b (%) |
|-------|-------------------|----------------|--------------------|--|
| 1 | 1 M, 5 | 3.6 | 6 | 70 |
| 2 | 1 M, 5 | 1.8 | 6 | 5 |
| 3 | 1 M, 2 | 3.6 | 6 | 68 (84) ^c (30) ^d |
| 4 | 1 M, 0.5 | 3.6 | 6 | 46 |
| 5 | — | 3.6 | 6 | <5 ^e |
| 6 | 12 M, 2.5 | 3.6 | 6 | <5 |
| 7 | 6 M, 1.2 | 3.6 | 6 | 65 (70) ^f |
| 8 | 1 M, 2 | 2 | 6 | 20 |
| 9 | 1 M, 2 | 3 | 6 | 62 |
| 10 | 1 M, 2 | 4 | 6 | 72 |
| 11 | 1 M, 2 | 4.5 | 6 | 59 |
| 12 | 1 M, 2 | 4 | 1 | 33 |
| 13 | 1 M, 2 | 4 | 1.5 | 63 |
| 14 | 1 M, 2 | 4 | 2 | 73 |
| 15 | 1 M, 2 | 4 | 3 | 71 |
| 16 | 1 M, 2 | 4 | 4 ^g | 73 |
| 17 | 1 M, 2 | 4 | 4 | 6 ^g |

^a Reaction conditions: thiophenol (1 mmol), HCl (1–12 M, 0.5–5 equiv.), 15% aq. NaOCl (1.8–4.5 equiv.), morpholine (1.5–6 equiv.). ^b Isolated yield after precipitation from the crude reaction mixture. ^c Reaction performed at 5 °C starting from 2 mmols of **1a**. ^d Reaction performed at 5 °C starting from 10 mmols of **1a**. ^e Only disulfide was observed by ¹HNMR analysis of the crude reaction mixture. ^f Similar yields were always obtained when using 4, 5, 6 or 7 equiv. of amine. ^g Reaction performed in ChCl/glycerol: 1/2 as solvent.

These initial experiments demonstrated that no organic solvent was required, as the reaction proceeds efficiently in aqueous HCl/NaOCl through an exothermic formation of HOCl, which oxidizes the thiol firstly to the disulfide (the initial formation of white solids corresponding to this intermediate is observed) to *in situ* sulfonyl chloride, which appears as an immiscible liquid ranging from colourless to slightly yellow. Subsequent addition of morpholine yields sulfonamide **3aa** as a white solid, isolated by filtration. Reaction efficiency is highly dependent on the order and rate of reagent addition; optimal results were obtained by premixing PhSH and HCl, followed by dropwise addition of NaOCl in two portions with a 10 minute interval to control exothermicity, adding the amine 10 minutes after the NaOCl addition.

Optimization of NaOCl (15% soln.) was next continued using the 1 M HCl soln. As depicted in Table 1 (entries 3 and 8–11) the highest isolated yield for **3aa** (72%) was obtained using 4 equivalents of NaOCl (entry 10). Next, the amount of amine was also optimized (Table 1, entries 12–16), with 2 equivalents of base being established as optimal. Finally, under the optimized reaction conditions [**1a** (1 mmol), 1 M HCl (2 mmol), 15% NaOCl (4 mmol), **2a** (2 mmol)], an additional test was conducted



using ChCl/glycerol: 1/2 as the reaction medium at rt (Table 1, entry 17) affording a 6% yield for **3aa**.

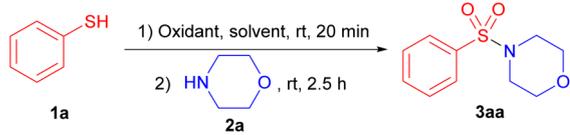
Although the synthesis of sulfonamides from thiols using the NaOCl/HCl mixture had been optimized, the conditions proved still inadequate for application in other alternative solvents such as DES. Then, we subsequently explored other oxidants such as trichloroisocyanuric acid (TCCA; H₂O solubility 10 g l⁻¹ at 25 °C), sodium dichloroisocyanurate (NaDCC; H₂O solubility 236.8 g l⁻¹ at 25 °C), and sodium dichloroisocyanurate dihydrate (NaDCC·2H₂O; H₂O solubility 236.8 g l⁻¹ at 25 °C) (Fig. 1), as HOCl precursors for using in alternative solvents.

The study began by applying the previously optimized reaction conditions (Table 1, entry 14), substituting the HOCl/HCl mixture with the corresponding TCCA derivatives. As shown in Table 2, when the reactions were performed in the presence of 1 M aqueous HCl as solvent resulted in moderate yields (20–56%) of sulfonamide **3aa**. Replacing the acidic medium with water alone led to a significant decrease in yields across all three oxidants tested (Table 2, entries 4–6). Subsequently, a study of the reaction was conducted in the DES ChCl/glycerol: 1/2 as the solvent. As shown in Table 2 (entries 7–9), the highest yield (65%) was achieved using NaDCC·2H₂O as the oxidant. Utilizing this reagent, a broad range of DESs were evaluated in the model reaction (see Table 1 in the SI for the complete dataset), all of which resulted in lower yields, except for ChCl/*d*-sorbitol: 1/1, which afforded compound **3aa** in a 58% isolated yield (Table 2, entries 11–15). Finally, some other sustainable solvents such as, 2-MeTHF, H₂O, and different alcohols were also studied as reaction media (Table 2, entries 16–23) affording **3aa** in an 81% isolated yield when using EtOH.

With the best conditions established and the most effective sustainable solvents selected, the methodology was evaluated across a broad substrate scope, including aromatic and aliphatic thiols, as well as primary, secondary, and aromatic amines (Table 3). As depicted, similar results were obtained with all the solvents studied (H₂O, EtOH, glycerol, and ChCl/Gly: 1/2) none of them outperforming significantly among the others. Nevertheless, the best results overall for products **3** were obtained in ethanol, standing out products obtained from aromatic thiophenols with yields up to 93% for sulfonamide **3da** in EtOH (Table 3, entry 29).

While solvent effects showed no clear trend, more discernible correlations emerged with the nature of thiols **1** and amines **2**. The lowest yields are observed when using benzylic thiol **1b**, obtaining from 15 to 24% yields (Table 3, entries 2, 9, 16, and 23). Aliphatic cyclohexanethiol (**1c**) was well tolerated, with the highest yield of sulfonamide **3ca** (60%) obtained using ChCl/Gly: 1/2 as reaction solvent (Table 3, entry 24). The nature of

Table 2 Reaction conditions optimization for the synthesis of **3aa** using TCCA and derivatives as oxidation agents^a



| Entry | Oxidant (equiv.) | Solvent ^b | Yield ^c (%) |
|-------|-------------------------------|-------------------------------|------------------------|
| 1 | TCCA (2) | 1 M HCl | 20 |
| 2 | NaDCC (2) | 1 M HCl | 56 |
| 3 | NaDCC·2H ₂ O (2) | 1 M HCl | 46 ^d |
| 4 | TCCA (2) | H ₂ O | 15 |
| 5 | NaDCC (2) | H ₂ O | 40 |
| 6 | NaDCC·2H ₂ O (2) | H ₂ O | 45 |
| 7 | TCCA (2.3) | ChCl/Gly: 1/2 | 58 |
| 8 | NaDCC (2.3) | ChCl/Gly: 1/2 | 31 |
| 9 | NaDCC·2H ₂ O (2.3) | ChCl/Gly: 1/2 | 65 ^e |
| 10 | NaDCC·2H ₂ O (2.3) | ChCl/urea: 1/2 | 5 |
| 11 | NaDCC·2H ₂ O (2.3) | ChCl/EG: 1/2 | 8 |
| 12 | NaDCC·2H ₂ O (2.3) | ChCl/AcOH: 1/1 | 16 |
| 13 | NaDCC·2H ₂ O (2.3) | ChCl/GA: 1/1 | 12 |
| 14 | NaDCC·2H ₂ O (2.3) | GA/H ₂ O: 1/4 | 23 |
| 15 | NaDCC·2H ₂ O (2.3) | ChCl/ <i>d</i> -sorbitol: 1/1 | 58 |
| 16 | NaDCC·2H ₂ O (2.3) | 2-MeTHF | 34 |
| 17 | NaDCC·2H ₂ O (2.3) | H ₂ O | 70 |
| 18 | NaDCC·2H ₂ O (2.3) | Glycerol | 70 |
| 19 | NaDCC·2H ₂ O (2.3) | EG | 62 |
| 20 | NaDCC·2H ₂ O (2.3) | MeOH | 63 |
| 21 | NaDCC·2H ₂ O (2.3) | EtOH | 81 |
| 22 | NaDCC·2H ₂ O (2.3) | Inositol ^f | 67 |
| 23 | NaDCC·2H ₂ O (2.3) | Erythritol ^f | 70 |

^a Reaction conditions: **1a** (0.5 mmol), solvent (1 mL) oxidant, morpholine (2 equiv.). ^b ChCl: choline chloride; Gly: glycerol; EG: ethylene glycol; GA: glycolic acid. ^c Isolated yield after column chromatography (silica, hexane/EtOAc). ^d A 25% of the sulfonyl chloride was also detected by ¹HNMR in the crude reaction mixture. ^e A similar yield (60%) was obtained when using 81% technical grade NaDCC·2H₂O. ^f A saturated aqueous soln. of the polyol was used as reaction medium.

the amine had a lesser impact on reaction efficiency compared to the thiol, as similar yields were observed when using primary cyclohexylamine, secondaries morpholine and piperidine or aniline. Nevertheless, reactions with thiophenol generally gave good yields with morpholine (57–82%; Table 3, entries 1, 8, 15, and 22), piperidine (18–92%; Table 3, entries 6, 13, 20, and 27), and cyclohexylamine (49–89%; entries 4, 11, 18 and 25). In the case of morpholine a good 60% yield was obtained when scaling the reaction to 10 mmols of starting **1a** (Table 3, entry 6). Due to its steric hindrance, *tert*-butylamine provided low yields in the reaction with thiophenol. Among the solvents tested, EtOH proved to be the most effective, affording sulfonamide **3ae** in an isolated yield of 52% (Table 3, entry 14).

Good to excellent yields were achieved for sulfonamides **3da** and **3ea** using substituted thiophenols and morpholine in EtOH, Gly, and ChCl/Gly: 1/2 (Table 3, entries 29–34). 4-Methoxythiophenol afforded **3da** in 58–93% yield, with EtOH providing the highest. In contrast, 3-chlorothiophenol afforded the best result in Gly, yielding **3ea** in 83% isolated yield (Table 3,

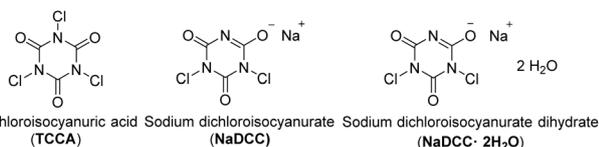


Fig. 1 TCCA and salts used as alternative oxidants.



Table 3 Sulfonamide synthesis through oxidative chlorination of thiols **1a–e** and subsequent reaction with amines **2a–c** in sustainable solvents^a

| Entry | Solvent ^b | R ¹ (1a–e) | R ² , R ³ (2a–c) | Product 3 | Yield ^c (%) |
|-------|----------------------|--|---|------------------|------------------------|
| 1 | H ₂ O | Ph (1a) | (CH ₂ CH ₂) ₂ O (2a) | 3aa | 68 |
| 2 | H ₂ O | Bn (1b) | (CH ₂ CH ₂) ₂ O (2a) | 3ba | 22 |
| 3 | H ₂ O | Cy (1c) | (CH ₂ CH ₂) ₂ O (2a) | 3ca | 30 |
| 4 | H ₂ O | Ph (1a) | H, Cy (2b) | 3ab | 54 |
| 5 | H ₂ O | Ph (1a) | H, Ph (2c) | 3ac | 76 |
| 6 | H ₂ O | Ph (1a) | (CH ₂) ₅ (2d) | 3ad | 80 (60) ^d |
| 7 | H ₂ O | Ph (1a) | H, Bu ^t (2e) | 3ae | 11 |
| 8 | EtOH | Ph (1a) | (CH ₂ CH ₂) ₂ O (2a) | 3aa | 82 |
| 9 | EtOH | Bn (1b) | (CH ₂ CH ₂) ₂ O (2a) | 3ba | 24 |
| 10 | EtOH | Cy (1c) | (CH ₂ CH ₂) ₂ O (2a) | 3ca | 45 |
| 11 | EtOH | Ph (1a) | H, Cy (2b) | 3ab | 89 |
| 12 | EtOH | Ph (1a) | H, Ph (2c) | 3ac | 66 |
| 13 | EtOH | Ph (1a) | (CH ₂) ₅ (2d) | 3ad | 92 |
| 14 | EtOH | Ph (1a) | H, Bu ^t (2e) | 3ae | 52 |
| 15 | Gly | Ph (1a) | (CH ₂ CH ₂) ₂ O (2a) | 3aa | 69 |
| 16 | Gly | Bn (1b) | (CH ₂ CH ₂) ₂ O (2a) | 3ba | 15 |
| 17 | Gly | Cy (1c) | (CH ₂ CH ₂) ₂ O (2a) | 3ca | 45 |
| 18 | Gly | Ph (1a) | H, Cy (2b) | 3ab | 49 |
| 19 | Gly | Ph (1a) | H, Ph (2c) | 3ac | 66 |
| 20 | Gly | Ph (1a) | (CH ₂) ₅ (2d) | 3ad | 49 |
| 21 | Gly | Ph (1a) | H, Bu ^t (2e) | 3ae | 36 |
| 22 | ChCl/Gly: 1/2 | Ph (1a) | (CH ₂ CH ₂) ₂ O (2a) | 3aa | 57 |
| 23 | ChCl/Gly: 1/2 | Bn (1b) | (CH ₂ CH ₂) ₂ O (2a) | 3ba | 15 |
| 24 | ChCl/Gly: 1/2 | Cy (1c) | (CH ₂ CH ₂) ₂ O (2a) | 3ca | 60 |
| 25 | ChCl/Gly: 1/2 | Ph (1a) | H, Cy (2b) | 3ab | 52 |
| 26 | ChCl/Gly: 1/2 | Ph (1a) | H, Ph (2c) | 3ac | 41 |
| 27 | ChCl/Gly: 1/2 | Ph (1a) | (CH ₂) ₅ (2d) | 3ad | 18 |
| 28 | ChCl/Gly: 1/2 | Ph (1a) | H, Bu ^t (2e) | 3ae | 25 |
| 29 | EtOH | 4-MeOC ₆ H ₄ (1d) | (CH ₂ CH ₂) ₂ O (2a) | 3da | 93 |
| 30 | Gly | 4-MeOC ₆ H ₄ (1d) | (CH ₂ CH ₂) ₂ O (2a) | 3da | 73 |
| 31 | ChCl/Gly: 1/2 | 4-MeOC ₆ H ₄ (1d) | (CH ₂ CH ₂) ₂ O (2a) | 3da | 58 |
| 32 | EtOH | 3-ClC ₆ H ₄ (1e) | (CH ₂ CH ₂) ₂ O (2a) | 3ea | 76 |
| 33 | Gly | 3-ClC ₆ H ₄ (1e) | (CH ₂ CH ₂) ₂ O (2a) | 3ea | 83 |
| 34 | ChCl/Gly: 1/2 | 3-ClC ₆ H ₄ (1e) | (CH ₂ CH ₂) ₂ O (2a) | 3ea | 60 |
| 35 | EtOH | 1-Methyl-1 <i>H</i> -imidazol-2-yl (1f) | (CH ₂ CH ₂) ₂ O (2a) | 3ef | 21 ^e |
| 36 | Gly | 1-Methyl-1 <i>H</i> -imidazol-2-yl (1f) | (CH ₂ CH ₂) ₂ O (2a) | 3ef | <5 |
| 37 | ChCl/Gly: 1/2 | 1-Methyl-1 <i>H</i> -imidazol-2-yl (1f) | (CH ₂ CH ₂) ₂ O (2a) | 3ef | <5 |

^a Reaction conditions: **1** (0.5 mmol), NaDCC·2H₂O (1.15 mmol), **2** (2 mmol), solvent (1 mL). ^b ChCl: choline chloride; Gly: glycerol. ^c Isolated yield after after column chromatography (silica, hexane/EtOAc). ^d The reaction was scaled up to 10 mmols of **1a**. ^e A 10% yield of 4-[(4-chloro-1-methyl-1*H*-imidazol-2-yl)sulfonyl]morpholine was also obtained.

entry 33). Finally, the reaction of the heterocyclic thiol 1-methyl-1*H*-imidazole-2-thiol with morpholine proceeded effectively only in ethanol, affording the sulfonamide derivative **3ef** in 21% yield, along with the corresponding chlorinated analogue, 4-[(4-chloro-1-methyl-1*H*-imidazol-2-yl)sulfonyl]morpholine, in 10% yield (Table 3, entry 37).

Regarding the reaction mechanism, sulfonamides are formed *via* the reaction of the corresponding amine with an *in situ* generated sulfonyl chloride. Based on previous studies involving TCCA-derived oxidants,^{31,34} and supported by the observation of disulfide formation in our system, the sulfonyl chloride intermediate arises from the thiol through sequential

chlorination, formation of sulfenic acid, dimerization to the symmetric disulfide, and subsequent oxidation *via* a thiosulfonate intermediate. The reaction proceeds heterogeneously in all tested solvents following the addition of the oxidant; however, the specific role of each solvent, particularly DES, requires further consideration. Previous studies¹⁸ have indicated that certain DES can slow the hydrolysis of sulfonyl chloride intermediates, while additional effects, such as reaction acceleration through intermediate stabilization and subtle catalytic contributions, may also be involved. The exact influence of the solvent remains complex and is currently under investigation by our research group.



Conclusions

An environmentally benign method has been developed for the direct synthesis of sulfonamides from thiols and amines. This one-pot protocol employs sodium dichloroisocyanurate dihydrate (NaDCC·2H₂O) as an oxidative chlorination agent, demonstrating broad applicability across different sustainable solvents in short reaction times. Overall, the method aligns with several principles of green chemistry and offers a practical approach for the synthesis of sulfonamides in good to excellent yields.

Author contributions

All the authors equally contributed to this work. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

SI is available, containing the general procedures for sulfonamide synthesis, complete characterization data for the isolated products, and the ¹H and ¹³CNMR spectra for all synthesized compounds. See DOI: <https://doi.org/10.1039/d5su00405e>.

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