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Switchable Deep Eutectic Solvents for Sustainable Sulfonamide Synthesis

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A sustainable and scalable protocol for synthesizing variously functionalized sulfonamides, from amines and sulfonyl chlorides, has been developed using environmentally responsible and reusable choline chloride (ChCl)-based deep eutectic solvents (DESs). In ChCl/glycerol (1 : 2 mol mol^{-1}) and ChCl/urea (1 : 2 mol mol^{-1}), these reactions yield up to 97% under aerobic conditions at ambient temperature within 2–12 h. The practicality of the method is exemplified by the sustainable synthesis of an FFA4 agonist and a key building block *en route* to anti-Alzheimer drug BMS-299897. A subtle interplay of electronic effects and the solubility characteristics of the starting materials in the aforementioned DESs seem to be responsible for driving the reaction successfully over the hydrolysis of sulfonyl chlorides. The procedure's eco-friendliness is validated by quantitative metrics like the *E*-factor and the EcoScale, with products isolated by extraction or filtration after decantation.

Introduction

The sulfonamide group is a pivotal structural feature present in a variety of pharmacologically active compounds. It is found in synthetic antimicrobials, adrenoceptor agonists, anti-inflammatory and anticancer agents, diuretics, antiviral inhibitors, and some derivatives have shown promise in the treatment of Alzheimer's disease.[1] Furthermore, sulfonamides can serve as protecting group for OH or NH functionalities, providing an easily removable option when necessary,[2] and as *N*-centered radical precursors for C–N coupling reactions to produce amidines.[3] Given their wide-ranging applications and significance in the pharmaceutical industry,[4] scientists have been actively pursuing new, sustainable, yet simple methods for synthesizing these scaffolds, under mild conditions, since the turn of the century.

Among the widely used methods for synthesizing sulfonamides is the reaction of amino compounds with sulfonyl chlorides. This reaction has traditionally been conducted using hazardous and environmentally harmful petroleum-based volatile organic compounds (VOCs) such as dichloromethane, dioxane, and acetonitrile, often in conjunction with metal catalysis.[1h] Furthermore, an organic base is commonly used, sometimes serving dual roles as a base and a solvent, like Et_3N or pyridine, to scavenge the generated HCl (Scheme 1a).[5] The bis-sulfonylation reaction, however, continues to be a significant drawback, when working with primary amines.[6] An alternative approach involves Schotten-Baumann conditions, which operate within a biphasic system comprising organic solvents and basic aqueous media.

Previous work:

Pawar et al. (2019):

(a) $Ar^1NH_2 + Ar^2SO_2Cl$ — pyridine, CH_2Cl_2; 0 °C to RT, 12 h → 79–89% yield

Deng et al. (2006):

(b) $Ar^1NH_2 + Ar^2SO_2Cl$ — H_2O, RT; Na_2CO_3, pH = 8 → 55–98% yield

This work:

(c) $R^1NHR^2 + R^3SO_2Cl$ — DES; RT, air, 2-4 h → up to 97% yield

Scheme 1. Sulfonamide synthesis (a) in CH_2Cl_2 in the presence of pyridine; (b) in water with dynamic pH control using Na_2CO_3; and (c) in DES, under air at RT (RT = room temperature, 25 °C).

Over the past decades, several environmentally responsible procedures have emerged.[7] In 2006, Deng and Mani introduced a benign sulfonamide synthesis by directly mixing equimolar amounts of sulfonyl chlorides and amines in water, thereby eliminating the need for organic bases.[8] However, the successful outcome of the reaction relied on dynamic pH control using Na_2CO_3, with the optimal pH range being between 8.0 and 9.0. Lower pH values resulted in decreased yields, while pH values above 10 favored the hydrolysis of sulfonyl chlorides to the corresponding sulfonates (Scheme 1b). Limitations include the partial solubility of the starting amine compound in water. Gioiello and co-workers minimized the hydrolysis of sulfonyl chlorides by employing polyethylene

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glycol 400 (PEG 400) in an acetone-water mixture with a basic ($NaHCO_3$) solution within a flow meso-reactor.[9]

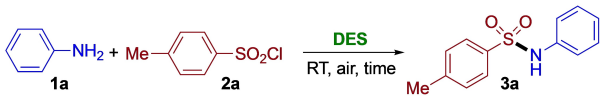
Other sustainable reactions involving sulfonyl chlorides as key partners of amines worth mentioning include: (i) processes catalyzed by β-cyclodextrin;[10] (ii) catalyst-free methodologies carried out in water or EtOH employing a two-fold excess of amines at room temperature;[11] (iii) a solvent-free method utilizing anhydrous K_2CO_3 or $NaHCO_3$ to prevent the formation of bis-sulfonated byproducts;[12] (iv) the *in situ* generation of sulfonyl chlorides either through the use of trichloroisocyanuric acid for the oxidative chlorination of thiols and disulfides,[13] or via a solvent-free mechanochemical approach involving a tandem oxidation-chlorination reaction on disulfides mediated by solid sodium hypochlorite ($NaOCl \cdot 5H_2O$);[14] and (v) a visible-light-triggered synthesis via an electron-donor-acceptor complex in 2-methyltetrahydrofuran.[15] Regarding the use of non-conventional solvents for sulfonamide preparation (i) an ionic liquid-supported synthesis;[16] and (ii) a multicomponent synthesis from triarylbismuthines, nitro compounds and sodium metabisulfite in deep eutectic solvents (DESs) as green reaction media,[17] are also noteworthy.

We recently reported on a sustainable protocol for utilizing secondary alcohols as selective monoalkylating reagents for both amides and sulfonamides in iron-based DESs.[18] Considering the tunable physical-chemical properties of DESs,[19] we explored whether they could also serve as the solvents of choice for the straightforward synthesis of sulfonamides. Advancing our research on the use of nonconventional, environmentally friendly media such as DESs for the formation of C–C, C–O and C–N bonds,[20] we herein report an efficient and sustainable metal-free synthetic methodology for the preparation of sulfonamides in DESs directly from sulfonyl chlorides and amines. Within suitable eutectic mixtures, this reaction proceeds smoothly under aerobic conditions, exhibits a broad scope and is scalable, with an *E*-factor as low as 13.48, an EcoScale value of 84.5, and with DES being reusable (Scheme 1c). All adducts were isolated by extraction or filtration after decantation.

Results and Discussion

We initiated our investigation by reacting aniline (**1a**) (0.9 mmol) with tosyl chloride (**2a**) (0.63 mmol) in DES (1.8 g), aimed at preparing *N*-phenyl-4-methylbenzenesulfonamide (**3a**), without the addition of any base (Table 1). Since the optimal pH range for controlling the hydrolysis of sulfonyl chloride to sulfonic acid was found to be between 8.0 and 9.0 in aqueous conditions,[8] we selected two prototypical DESs: one formed by choline chloride (ChCl)/glycerol (Gly) (1:2 mol mol^{-1}) and another by ChCl/urea (1:2 mol mol^{-1}) whose pH values were recently determined using a glass electrode to be 7.50 and 8.91, respectively.[21] Upon adding **1a** to **2a**, and working at RT under air in the aforementioned freshly prepared DESs, adduct **3a** could be isolated in 76% yield in ChCl/urea (unreacted **2a**: 7%) and in 66% yield in ChCl/Gly (unreacted **2a**: 15%) after 2 h (Table 1, entries 1,2). Adduct **3a** was collected by filtration after being precipitated from the reaction mixture by the dropwise addition of an aqueous HCl solution (2.0 M) until reaching a pH of 2. By comparison, **3a** formed in a 46–50% yield after 2 h when the reaction was conducted in acidic DESs such as ChCl/malonic acid (1:1 mol mol^{-1}) with a pH of 2.39,[21] resulting in 7% unreacted **2a**, or ChCl–L-lactic acid (1:2 mol mol^{-1}), which left 40% unreacted **2a** (Table 1, entries 3,4). Thus, the formation of sulfonamide **3a** likely occurs more rapidly in ChCl/urea and ChCl/Gly, while the hydrolysis of **2a** is also slowed down. After 4 h, **2a** reacted completely in ChCl/urea and in ChCl/Gly, with the yield of **3a** increasing up to 87% and 75%, respectively (Table 1, entries 5,6). The use of other ChCl-based eutectic mixtures, such as ChCl/H_2O (1:2 mol mol^{-1}) and ChCl/ethylene glycol (EG) (1:2 mol mol^{-1}) resulted in the formation of **3a** with yields of up to 60% after 2 h, with 10–40% of **2a** remaining unreacted (Table 1, entries 7,8). When the ammonium salt was changed from ChCl to choline acetate (ChOAc), the formation of **3a** in the corresponding ChOAc/urea (1:2 mol mol^{-1}) eutectic mixture significantly slowed, resulting in a 41% yield with 28% of **2a** remaining unreacted after 2 h (Table 1, entry 9). Conversely, **2a** reacted completely in ChOAc/Gly (1:2 mol mol^{-1}) providing **3a** in up to 74% yield after 2 h (Table 1, entry 10). Moreover, reacting **1a** with **2a** in a hydrophobic eutectic mixture, such as L-menthol/decanoic acid (1:1 mol mol^{-1}), yielded less than 5% of **3a**, with over 90% of **2a** remaining unreacted (^{1}H NMR analysis) (Table 1, entry 11). Attempts to

Table 1. Optimization of synthesis of sulfonamide **3a** from aniline (**1a**) and *p*-toluenesulfonyl chloride (**2a**) in DESs.[a]



Entry	DES[b]	time (h)	3a yield (%)[c]
1	ChCl/urea	2	76[d]
2	ChCl/Gly	2	66[e]
3	ChCl/malonic acid	2	46[d]
4	ChCl/L-lactic acid	2	50[f]
5	ChCl/urea	4	87
6	ChCl/Gly	4	75
7	ChCl/H2O	2	37[f]
8	ChCl/EG	2	60[g]
9	ChOAc/urea	2	41[h]
10	ChOAc/Gly	2	74
11	L-menthol/decanoic acid	2	<5[i]

[a] Reaction conditions: 1.8 g DES per 0.9 mmol **1a** and 0.63 mmol **2a** [b] DES: ChCl/urea (1:2 mol mol^{-1}); ChCl/Gly (1:2 mol mol^{-1}); ChCl/malonic acid (1:1 mol mol^{-1}); ChCl/H_2O (1:2 mol mol^{-1}); ChCl/EG (1:2 mol mol^{-1}); ChCl/L-lactic acid (1:2 mol mol^{-1}); ChOAc/urea (1:2 mol mol^{-1}); ChOAc/Gly (1:2 mol mol^{-1}); L-menthol/decanoic acid (1:1 mol mol^{-1}) [c] Isolated yield [d] Unreacted **2a**: 7% [e] Unreacted **2a**: 15% [f] Unreacted **2a**: 40% [g] Unreacted **2a**: 10% [h] Unreacted **2a**: 28% [i] Unreacted **2a**: >90%. Calculated by ^{1}H NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: CH_2Br_2).

synthesize sulfonamides from the corresponding sulfonic acids using an acidic DES were unsuccessful. For instance, when **1a** (0.9 mmol) was reacted with *p*-toluenesulfonic acid monohydrate (0.63 mmol) in ChCl/L-lactic acid (1:2 mol mol^{-1}) (1.8 g), the yield of sulfonamide **3a** was only 9% (^{1}H NMR analysis).

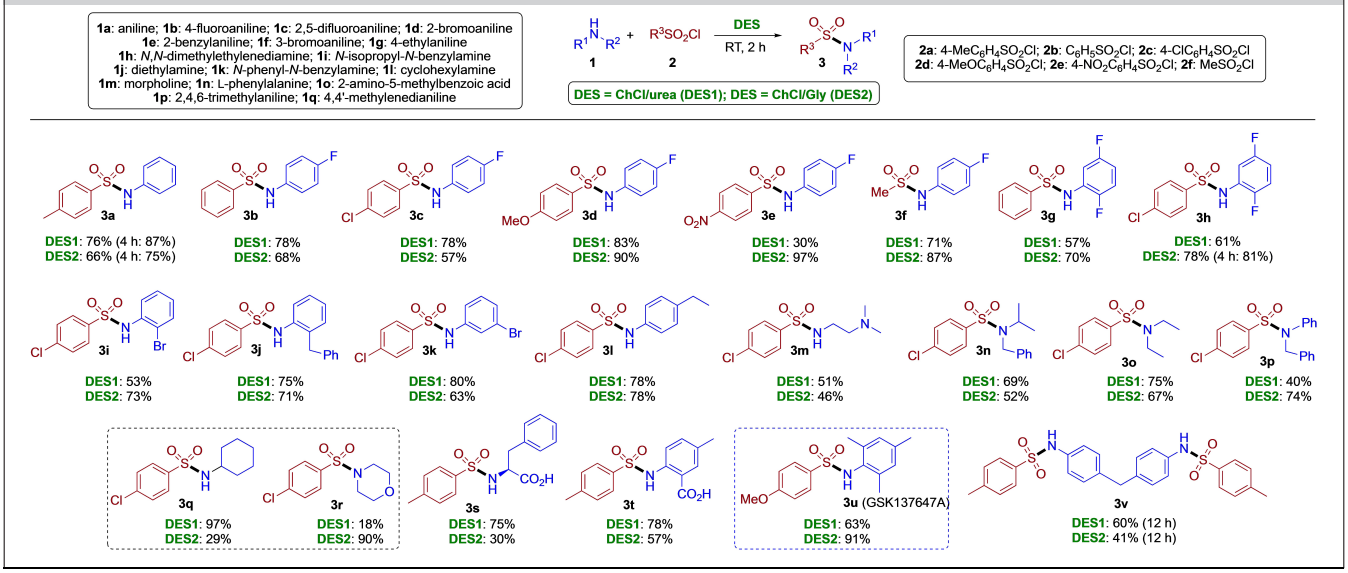
We sought to capitalize on this process by exploring the scope of the reaction in the two selected DESs, ChCl/urea and ChCl/Gly, using a variety of aromatic and aliphatic amines and sulfonyl chlorides, while synthesizing several examples of halogenated sulfonamides due to the importance of halogens in several classes of pharmaceuticals.[22] With regard to primary aromatic amines, 4-fluoroaniline (**1b**) reacted smoothly with benzenesulfonyl chloride (**2b**) providing adduct **3b** in good yield in both DESs: 78% in ChCl/urea and 68% in ChCl/Gly after 2 h (Table 2). The difference in the two values reflects the full conversion achieved shortly after 2 h in ChCl/urea, while some unreacted **2b** (25%) was still detected in ChCl/Gly after this time. Benzenesulfonyl chlorides with an electron-withdrawing (Cl) (**2c**) or an electron-donating (MeO) (**2d**) group at the *para* position also participated in the reaction, affording sulfonamides **3c** and **3d**, respectively. The highest yield, with complete consumption of **2c**, was obtained after 2 h in ChCl/urea for **3c** (78%) (ChCl/Gly: 57% with 39% unreacted **2c**), whereas reactions in both these DESs provided **3d** in similar high yields (83–90%). The reaction between **1b** and *p*-nitrophenylsulfonyl chloride (**2e**) furnished an almost quantitative yield (97%) of the desired product **3e** in ChCl/Gly. However, the yield decreased to 30% in ChCl/urea with 37% of **2e** remaining unreacted. The methodology is also applicable to aliphatic sulfonyl chlorides. The reaction between **1b** and methanesulfonyl chloride (**2f**) yielded adduct **3f** in 71% in ChCl/urea and 87% in ChCl/Gly, achieving complete conversion of **2f** after 2 h.

The dihalogenated coupling module 2,5-difluoroaniline (**1c**) efficiently reacted with both **2b** and **2c** in ChCl/Gly, affording fluorinated adducts **3g,h** in 70–78% yield after 2 h. The yield of **3h** increased in ChCl/Gly up to 81% after 4 h. In ChCl/urea, the yields were 57–61% after complete consumption of **2b,c** (2 h). An electron-poor benzenesulfonyl chloride such as **2c** proved to be a suitable substrate for the sulfonamidation of aniline derivatives bearing a bromo or a benzyl group at the *ortho*-position (**1d,e**) as well as a bromo or an ethyl group at the *meta*- and *para*-position (**1f,g**). After 2 h and complete conversion, the highest yields achieved were 73% for adduct **3i** in ChCl/Gly and 75–80% for adducts **3j–l** in ChCl/urea.

The reaction of **2c** with an aliphatic diamine such as *N*,*N*-dimethylethylenediamine (**1h**) proceeded with moderate yields in both ChCl/Gly and ChCl/urea, furnishing adduct **3m** in 46–51%. Assorted secondary aromatic and aliphatic amines, such as *N*-isopropyl-*N*-benzylamine (**1i**), diethylamine (**1j**), and *N*-phenyl-*N*-benzylaniline (**1k**), also demonstrated their effectiveness as nucleophilic partners. Their reactions delivered tertiary sulfonamides **3n,o** in 69–75% yield in ChCl/urea and **3p** in 74% yield in ChCl/Gly, after a complete reaction with **2c** within 2 h.

A quite striking result was observed in the reaction of **2c** with cyclohexylamine (**1l**) and morpholine (**1m**) for the formation of secondary and tertiary sulfonamides **3q** and **3r**, respectively. Adduct **3q** was obtained almost quantitatively (97% yield) in ChCl/urea, while in only 29% yield in ChCl/Gly, along with 36% of **2c** unreacted. Conversely, sulfonamide **3r** was isolated in 90% yield from a ChCl/Gly eutectic mixture, but only in 18% yield from ChCl/urea, with 41% of **2c** remaining unreacted. Therefore, the formation of sulfonamide proceeds more slowly, but the hydrolysis of sulfonyl chlorides occurs faster, in ChCl/Gly for **3q** and in ChCl/urea for **3r**. Some considerations are in order. All the reactions reported in Table 2 occurred under heterogeneous conditions, with at least one component, the amine or the sulfonyl chloride, being insoluble in both the investigated DESs. The differences in yields

Table 2. Synthesis of sulfonamide derivatives 3 from amines 1 and sulfonyl chlorides 2 in ChCl/urea (1:2 mol mol^{-1}) or ChCl/Gly (1.2 mol mol^{-1}) eutectic mixtures, at room temperature (RT) and under aerobic conditions. Reaction conditions: 1.8 g DES per 0.9 mmol 1 and 0.63 mmol 2. For the synthesis of 3 s, 2 equiv. of Et_3N were used (see Experimental). Isolated yields.



observed for each reaction essentially reflect the competition between the rate of product formation and the hydrolysis of the sulfonyl chloride in each DES, the last reaction being generally slower in ChCh/Gly. Regarding the reaction between **2c** (solid) and **1l** (liquid) to yield sulfonamide **3q**, we observed that *both components were insoluble in ChCl/urea*. Conversely, in the formation of sulfonamide **3r**, *both amine **1m** (liquid) and sulfonyl chloride **2c** (solid) resulted insoluble in ChCl/Gly*. Thus, a significant rate acceleration was observed in that mixture where the two insoluble reactants were vigorously stirred at the interface of the bulk DES. This situation mirrors that observed for reactions of polar organometallic compounds of s-block elements with electrophiles, which were found to take place rapidly and efficiently across the oil-water/DES interface.[23] Therefore, the formation of adducts **3q,r** serves as a notable example of accelerated processes when working "on DES". These findings deserve further investigation.

The reaction of an α-amino acid, such as L-phenylalanine (**1n**), with **2a** furnished the desired *N*-tosyl-L-phenylalanine (**3s**) only in trace amounts in the two DESs (<5% yield in both ChCl/Gly and ChCl/urea, as detected by ^{1}H NMR and GC-MS analysis). By improving the nitrogen nucleophilicity with 2 equiv. of Et_3N, adduct **3s** could be isolated in a 75% yield in ChCl/urea with complete consumption of **2a**. In contrast, in ChCl/Gly, **3s** was obtained in only a 30% yield, with 20% of **2a** remaining unreacted. The product was precipitated from the reaction mixture by the dropwise addition of an aqueous HCl solution. On the other hand, a β-amino acid, such as 2-amino-5-methylbenzoic acid (**1o**), reacted smoothly with **2a**, furnishing the expected coupling product **3t** in a 78% yield in ChCl/urea with complete consumption of **2a** after 2 h (ChCh/Gly: 57% yield, along with 40% of unreacted **2a**). By replacing the Me group of **1o** with another electron-withdrawing-group, such as NO_2, significantly reduced the nucleophilicity of the corresponding aniline derivative (2-amino-5-nitrobenzoic acid), thereby hindering the coupling reaction. This modification resulted in a complete loss of yield in both DESs.

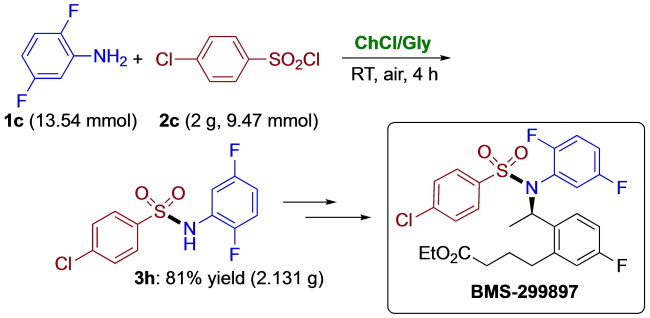
Then, we targeted the sustainable preparation of diaryl sulfonamide **3u**, which is a selective agonist (GSK137647 A) of the free fatty acid receptor 4 (FFA4), and thus potentially useful for treating individuals with type 2 diabetes.[5a] The sterically hindered and electron-rich amine 2,4,6-trimethylaniline (**1p**) reacted readily and smoothly with the electron-rich sulfonyl chloride **2d**, to afford the desired adduct **3u** in an almost quantitative yield of 91% in ChCl/Gly after 2 h (ChCl/urea: 63%, with complete consumption of the sulfonyl chloride).

Finally, we investigated the synthesis of bis-sulfonamide derivatives from diamines. The reaction between 4,4′-methylenedianiline (**1q**) (0.5 mmol) with **2a** (1.0 mmol) proceeded more slowly in both DESs compared to mono-amines, yielding the bis-tosyl derivative **3v** in only 31% in ChCl/Gly (with 68% unreacted **2a**), and 40% in ChCl/urea (with 60% unreacted **2a**) after 2 h. However, the yield in **3v** could be increased up to 60% in ChCl/urea, with complete consumption of **2a**, after 12 h (ChCl/Gly: 41% yield of **3v** after 12 h, with 25% unreacted **2a**) (Table 2).

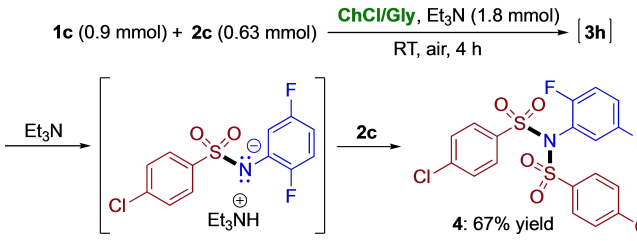
The practicality and robustness of the aforementioned methodology was also assessed by performing the synthesis of fluorinated sulfonamide **3h** on a 2 g-scale. This compound serves as a key building block for the preparation of BMS-299897, a potent γ-secretase inhibitor aimed at halting high glucose-mediated amyloid β-peptide (Aβ) secretion, with potential implications for the treatment of Alzheimer's disease[24] (Scheme 2). Under the optimized conditions outlined in Table 2, the reaction between sulfonyl chloride **2c** (9.47 mmol, 2 g) and fluorinated aniline **1c** (13.54 mmol) led to the formation of **3h** with an 81% yield (2.131 g) after 4 h, when using ChCl/Gly (25 mL, 30 g) as the reaction medium.

It is noteworthy that when **2c** (0.63 mmol) was reacted with **1c** (0.9 mmol) in ChCl/Gly (1.8 g) in the presence of Et_3N (1.8 mmol; 2 equiv), the main isolated product, obtained in 67% yield, was the α,α-bis-sulfonamide derivative **4** (Scheme 3). Only 2% of **3h** was detected in the crude reaction mixture (^{1}H NMR analysis). In contrast to the formation of **3s**, the increased nucleophilicity of the nitrogen in the conjugated base of **3h**, facilitated by the presence of Et_3N, is detrimental in this case. Therefore, the use of an additional base like Et_3N in the formation of sulfonamides, when working in basic DESs, should be evaluated on a case-by-case basis.

Notably, under the optimized reaction conditions with amines, the reaction of **2a** (0.9 mmol) with other nucleophiles, such as benzylic alcohol, 4-methoxybenzenethiol, and 4-chlorobenzamide (0.63 mmol each) proved to be ineffective in both ChCl/Gly and ChCl/urea, resulting in the quantitative recovery of these nucleophiles after 2 h. This highlights the selectivity of DESs for amine substrates under the conditions tested.



Scheme 2. Synthesis of fluorinated sulfonamide derivative 3 h on a 2 g-scale from 1c and 2c in ChCl/Gly (1 : 2 mol mol^{-1}) eutectic mixture at room temperature (RT) and under air.



Scheme 3. Synthesis of α,α-bis-sulfonamide derivative 4 from 1c and 2c, working in ChCl/Gly (1 : 2 mol mol^{-1}) eutectic mixture, in the presence of Et_3N, at RT and under air.

The potential for reusing the eutectic mixture (ChCl/Gly) was also explored in the coupling reaction of **1 c** with **2 c**. After 4 h, the reaction crude was extracted with EtOAc, which is partially insoluble in ChCl/Gly. Subsequently, the addition of fresh reagents (**1 c** and **2 c**), enabled the reuse of the DES system for four consecutive runs without any loss of the DES mass. Upon completion of the fourth cycle, followed by work-up, compound **3 h** was isolated with a yield similar (79%) to that reported in Scheme 2 for this reaction (81%).

To better quantify the greenness of the synthetic pathway developed for the synthesis of sulfonamides, we calculated the Sheldon's environmental factor (*E*-factor: total mass of waste/mass of product)[25] and the EcoScale[26] for the synthesis of sulfonamide **3 h** on a 2 g-scale, as depicted in Scheme 2. The EcoScale calculation, in particular, is based on assigning penalty points to parameters such as yield, cost of the reaction components to obtain 10 mmol of the product, safety of the reactants, technical setup of the processes, and ease of workup/purification processes. An ideal reaction achieves an EcoScale value of 100. Working in a ChCl/Gly eutectic mixture, with **3 h** isolated by filtration, after being precipitated from the reaction mixture, resulted in: a) an *E*-factor value of 13.48, which aligns well with the values suggested for fine chemicals (between 5 and 50),[25] and b) an excellent EcoScale value of 84.5 (values >75 are considered excellent).[26] In comparison, the calculated *E*-factor and the EcoScale values for the synthesis of **3 h** using pyridine as the solvent were 20.73 and 68.5, respectively (for details, see ESI).[27]

Conclusions

In summary, we have developed a sustainable and scalable protocol for synthesizing variously functionalized secondary and tertiary sulfonamides, from primary/secondary aliphatic and aromatic amines and alkyl/aryl sulfonyl chlorides. This process operates at room temperature and under heterogeneous conditions using nontoxic, cost-effective, and biodegradable deep eutectic solvents (DESs). The competition between the rate of sulfonamide formation and the hydrolysis of sulfonyl chlorides in the two selected DESs [ChCl/Gly (pH = 7.50) and ChCl/urea (pH = 8.91)], which depends on electronic factors of the starting materials, as well as their solubility characteristics, can be controlled by simply switching the DES. In particular, we observe a considerable rate acceleration and high yield in the desired adduct when the two coupling partners are both insoluble in the DES, with the reaction likely occurring at the interface of the bulk DES. This contrasts with the reactions conducted in water under dynamic pH control, where the amino compounds "need to be at least partially soluble".[8] For example, in the absence of a phase-transfer catalyst, simple aniline yielded only 30% of the expected adduct when reacted with *p*-toluenesulfonyl chloride over 3 days.[8] The methodology has been applied to the synthesis of an FFA4 agonist (**3 u**) and a key building block (**3 h**) for the synthesis of the sulfonamide γ-secretase inhibitor BMS-299897, the latter on a 2 g-scale. Regarding the synthesis of **3 h**, the DES was successfully reused for four consecutive cycles, achieving an *E*-factor as low as 13.48, and a commendable EcoScale value of 84.5.

Overall, this methodology reshapes a cornerstone synthesis of sulfonamides – based on the coupling reaction between amines and sulfonyl chlorides – from an environmental perspective. It employs bio-based solvents, and operates under aerobic and mild conditions, with the final products isolated through simple extraction (for liquids) or filtration after decantation (for solids).

Experimental Section

Synthesis of sulfonamides 3 in deep eutectic solvents: general procedure. In a 10 mL vial at room temperature (RT), sulfonyl chloride 2 (0.63 mmol) was suspended in DES [1.8 g; ChCl/urea (1 : 2 mol/mol) or ChCl/Gly (1 : 2 mol/mol)]. Amine 1 (0.9 mmol) was then added with vigorous stirring. After the reaction was complete [2, 4 or 12 h, monitored by TLC (hexane/EtOAc; 9 : 1) and ^{1}H NMR analysis], HCl (1 mL, 2 M) was slowly added until the pH reached 2.0. The reaction mixture was allowed to stand at RT for 10 min. Solid products were filtered and washed with distilled water, while waxy solids and liquid products were extracted with EtOAc (3×1 mL) or cyclopentyl methyl ether (3×1 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Finally, the solution was filtered and the volatiles were removed under reduced pressure to yield sulfonamide 3 (>98% purity by ^{1}H NMR analysis using an internal standard technique). For the synthesis of 3 s, L-phenylalanine (1 n) (0.9 mmol) was first suspended in DES (1.8 g). Et_3N (1.8 mmol) was then added, followed by the addition of sulfonyl chloride 2a (0.63 mmol) under vigorous stirring. After 2 h stirring at RT, the reaction mixture was worked up as described above, using an aqueous HCl solution (1 mL, 10% w/w).

Scaled-up synthesis of 4-chloro-*N*-(2,5-difluorophenyl)benzenesulfonamide (3 h). In a 50 mL round-bottom flask at RT, 4-chlorobenzenesulfonyl chloride (2c, 9.5 mmol, 2 g) was suspended in 30 g of ChCl/Gly (1 : 2 mol/mol). Then, 2,5-difluoroaniline (1c, 13.57 mmol, 1.75 g) was added with vigorous stirring. After the reaction was complete [4 h, monitored by TLC (hexane/EtOAc; 9 : 1) and ^{1}H NMR analysis], HCl (15 mL, 2 M) was slowly added until the pH reached 2.0. The reaction mixture was allowed to stand at RT for 10 min. The precipitated solid product was filtered and washed with distilled water to afford 3 h in 81% yield (2.131 g; >98% purity by ^{1}H NMR analysis using an internal standard technique).

Supporting Information Summary

Additional references cited within the Supporting Information.[28–37]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Deep eutectic solvents · Amines · Sulfonyl chlorides · Sulfonamides · Sustainable chemistry

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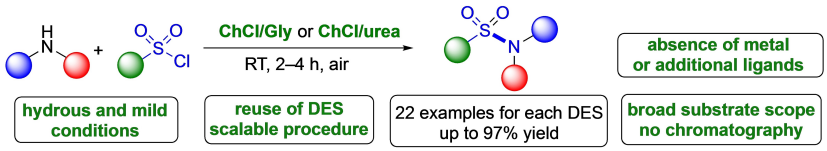

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Switchable Deep Eutectic Solvents for Sustainable Sulfonamide Synthesis

A sustainable and scalable synthesis of sulfonamides, from amines and sulfonyl chlorides, is achieved under aerobic conditions, at ambient temperature, in reusable choline chloride-based deep eutectic solvents. The interplay of electronic effects and the solubility characteristics of the starting materials in the selected DESs drives the sulfonamide synthesis over the hydrolysis of sulfonyl chlorides.

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