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Sulfonamides and sulfonate esters: Synthetic routes, proposed mechanisms, and crystallographic characterizations

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ABSTRACT

The sulfonamide and sulfonate moieties are key structural features in many pharmaceuticals, agrochemicals, and materials and have proven useful as synthetic precursors. In this review, synthetic routes for sulfonamides and sulfonate esters were examined to gain insight into the mechanism behind the sulfonylation of amines and alcohols, which remains largely unknown and highly dependent on the reaction conditions used. Furthermore, the review delves into crystallographic characterizations of previously reported sulfonamide and sulfonate ester compounds, unraveling trends associated with crucial steric and electronic factors that influence their crystallization. This exploration not only enhances our understanding of the structural nuances of these compounds, but also paves the way for informed design strategies in synthetic and medicinal chemistry. In essence, this review endeavors to provide a holistic perspective on sulfonamides and sulfonate esters, bridging the realms of synthesis, mechanism elucidation, and structural characterization.

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1. Introduction

Sulfonyl-containing compounds have proven useful as both ubiquitous building blocks in synthetic chemistry and pharmaceutical agents to improve human health [1-4]. Among the myriad of sulfonyl-containing compounds, sulfonamides and sulfonate esters stand out as particularly noteworthy classes. Similar synthetic protocols can be applied in the synthesis of both compound classes, mainly sulfonylation of alcohols/amines, the mechanistic underpinnings of which remain shrouded in ambiguity [5,6]. Beyond their utility as mere synthetic intermediates, the inherent stability of sulfonamides and sulfonate esters positions them as valuable protecting groups. Moreover, the regioselective cleavage of C-O/S-O bonds in aryl sulfonate esters introduces a compelling dimension, facilitating the targeted synthesis of either the corresponding sulfonamide or N-arylamine through nucleophilic aromatic substitution (S_NAr) [6,7]. Sulfonamides can be easily synthesized from the aforementioned cleavage of sulfonate esters or through a sulfonylation protocol similar to that used for the production of sulfonate esters. The biological significance of sulfonamides was first recognized through the discovery of sulfanilamide by Gelmo *et al.* in 1907 and continues to show promise as therapeutic agents in modern medical science [8-11].

The sulfonate ester moiety serves as an electrophilic partner and a substrate in many synthetic transformations. Sulfonate esters are also good leaving groups and have been implicated in many reactions such as elimination, reduction, substitution, and transition-metal-catalyzed reactions. Analytical methods have been developed for the determination of sulfonate esters in pharmaceuticals [12]. Kui *et al.* have reported the synthesis of sulfonates as versatile structural counterions of epoxide salts [13]. The synthesis of sulfonate esters and a study to determine their antibacterial activity have been reported [14].

Baunach *et al.* have reported a biosynthetic pathway for sulfonamides that involves enzyme-mediated sulfur dioxide capture [15]. The facile synthesis of sulfonamides from vinyl sulfones through an addition-elimination sequence has been reported [16]. Under mild reaction conditions, primary and secondary amines were reacted with *N*-bromosuccinimide (NBS) as an oxidant to form halogenated amines as electrophilic partners. The biosynthesis of natural antibiotic sulfonamide products from actinomycetes has been reported [17]. The current state of knowledge in the field of sulfonamide biosynthesis has been reviewed, with particular emphasis on the elucidation of the structure, bioactivities, and mode of action of sulfonamides.

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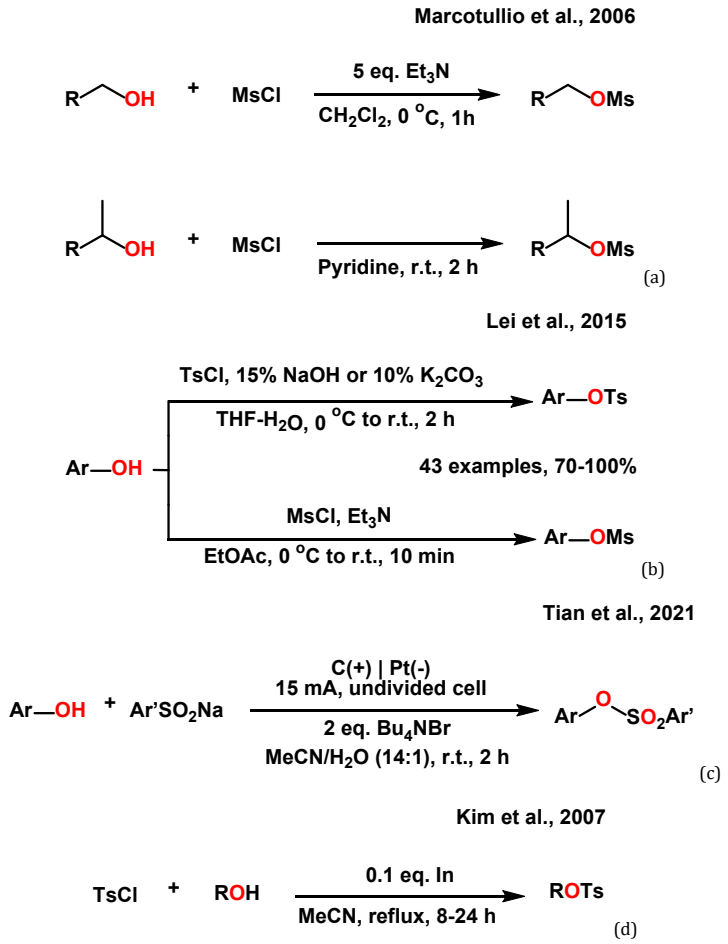


Figure 1. Previously reported methods for the synthesis of sulfonate esters, (a) Mesylation of primary and secondary alcohols in the presence on an amine base, (b) Facile and environmentally benign approach to synthesize sulfonate esters, (c) Synthesis of arylsulfonate esters via electro-oxidation, and (d) A generalizable indium-catalyzed tosylation of alcohols.

Similarly, a study of the structure, antibacterial properties, toxicity, and biophysical interactions of sulfonamide drugs has been reported [18]. Alongside findings on the biological side, the molecular mechanism of plasmid-borne resistance to sulfonamide antibiotics was put forth to aid in understanding the effectiveness of such antibiotics [19].

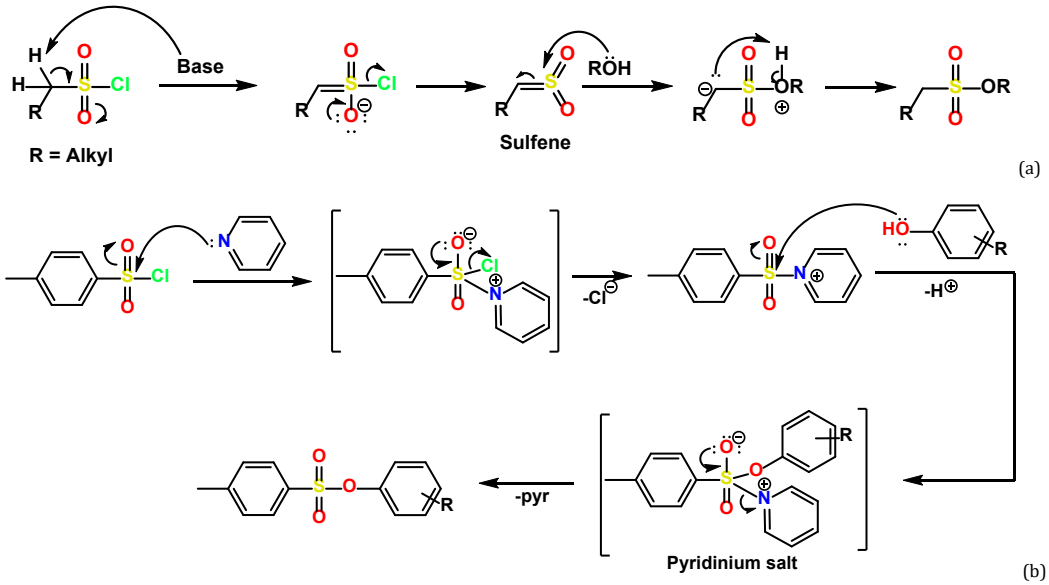
The trends elucidated through crystallographic characterization of sulfonamides and sulfonate esters offer a unique vantage point, potentially unraveling deeper insights into their biological significance. Moreover, such crystallographic studies may shed light on the intrinsic value of these compounds as synthetic precursors, particularly in the context of sulfonate esters, further advancing their utility in diverse scientific applications. Herein, we present an overview of trends in the crystallographic properties and synthetic methodologies for sulfonamides and sulfonate esters and discuss the mechanistic ambiguity for nucleophilic sulfonyl substitution.

2. Synthetic routes, proposed mechanisms, and usefulness as synthetic precursors

2.1. Sulfonate esters

Various synthetic routes exist for the synthesis of sulfonate esters. A widely used method is the treatment of alcohol with sulfonyl chloride in the presence of an amine base (Figure 1a) [20]. A similar approach developed by Lei *et al.* offers an environmentally benign approach, using aqueous bases and more environmentally friendly solvents and affording various sulfonate esters with good to excellent yield (Figure 1b) [21]. In recent years, Tian *et al.* reported the treatment of sodium arenesulfinates with phenol by electro-oxidation under mild reaction conditions, producing a wide range of aryl sulfonate esters in good to excellent yield while avoiding the use of additional oxidants (Figure 1c) [22]. Transition metal catalysis has also been utilized, an example being the facile indium-catalyzed sulfonylation of amines by Kim et al., which shows a generality for various substrates, including sterically hindered, less nucleophilic anilines (Figure 1d) [23]. Another approach of Caddic *et al.* involves the direct coupling of sulfonic acid salts with alcohols and amines in the presence of a triphenylphosphine ditriflate reagent [24].

Furthermore, delving into the intricate mechanism of substitution at the sulfonyl sulfur atom has remained a complex and debated area within the scientific community. The literature is replete with conflicting reports and diverse insights on this topic. However, a notable contribution to unraveling this mechanistic enigma comes from the work of King *et al.*, particularly in their study focused on the hydrolysis of methanesulfonyl chloride [25]. King *et al.*'s investigation underscores the pivotal role played by both the base and sulfonating agent in shaping the mechanistic pathway of sulfonylation reactions. Through kinetic isotope effect (KIE) studies, a nuanced understanding of the reaction dynamics has emerged. At pH levels below 6.7, the observed small secondary KIE implies the absence of a sulfene intermediate, aligning with an S_N2-like mechanism.



Scheme 1. Proposed mechanism for the sulfonylation of alcohols via a sulfene intermediate (a) and the tosylation of phenols in the presence of pyridine (b).

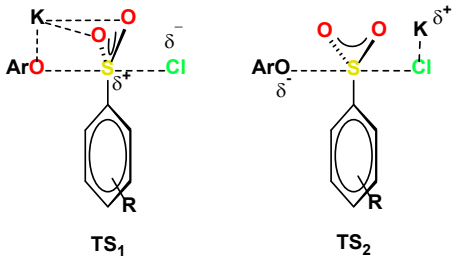


Figure 2. Proposed transition states for the sulfonylation of phenol derivates.

On the contrary, at pH levels greater than 6.7, the emergence of a significant primary KIE points to the formation of the sulfene intermediate (Scheme 1a). This revelation accentuates the impracticality of a direct attack by alcohols under basic conditions. Sulfonyl starting materials lacking an α-hydrogen, such as tosyl chloride, will not go through a sulfene intermediate.

In the case of arylsulfonyl chlorides, the proposed mechanisms differ significantly. In the presence of pyridine, treatment of tosyl chloride with phenol derivatives forms a salt, insoluble in CH_2Cl_2, which precipitates out of the reaction mixture and results in no formation of the desired product [26]. Given this insight, the mechanism in Scheme 1 was proposed [27]. Characterization shows that this species is likely the intermediate formed directly after the attack of alcohol.

Changing the conditions for the tosylation of phenol derivatives to solubilize this salt led to the formation of the desired product [26]. In parallel, for methodologies employing aqueous bases like potassium carbonate, a deeper understanding of the reaction mechanism emerges. The proposed transition states, depicted in Figure 2 indicate a reaction catalyzed by K^+ through increased electrophilicity of the reaction center (TS_1) or increased nucleofugality of the leaving group (TS_2) [6]. These proposed transition states offer a nuanced perspective on the catalytic role of counterions in sulfonylation reactions involving aqueous bases.

2.2. Sulfonamides

As with sulfonate esters, sulfonamides are also afforded using various synthetic routes. Among such strategies, one prominent approach involves the treatment of sulfonyl chlorides with amines, a method celebrated for its simplicity and widespread applicability within the synthetic chemistry realm [28,29]. This straightforward protocol exemplifies the elegance with which sulfonamides can be efficiently generated from readily available starting materials. Sulfonate esters can also be used as precursors, affording the corresponding sulfonamide via regioselective cleavage, further supporting their alleged synthetic versatility. Similarly, treatment of tosylamide with a mesylate ester under basic conditions provides secondary sulfonamide with an overall inversion of stereochemistry (Figure 3a) [20]. Regioselective S-O/C-O bond cleavage of arylsulfonate esters in the presence of amines presents yet another strategic avenue for sulfonamide formation (Figure 3b) [6,30]. This approach, governed by preferential S-O/C-O bond cleavage, allows for the selective generation of either sulfonamides or N-arylamine derivatives, adding a valuable dimension to the synthetic possibilities afforded by sulfonate esters. Similarly to the indium-catalyzed protocol previously shown for sulfonate esters, sulfonamides can be synthesized from various starting materials (Figure 3c) [23]. Methods also exist for the synthesis of primary sulfonamides, showcasing the breadth of synthetic strategies within the sulfonamide synthesis repertoire. For instance, a method utilizing *N*-sulfinyl-O-(*tert*-butyl)hydroxylamine (t-BuONSO) and organometallic reagents offers an alternative pathway to primary sulfonamides, further enriching the synthetic toolkit (Figure 3d) [31]. Along with the routes laid out in Figure 3, various other methods exist to synthesize sulfonamides, such as aromatic decarboxylative halosulfonylation of unactivated acids and amines [32] and environmentally benign convergent paired

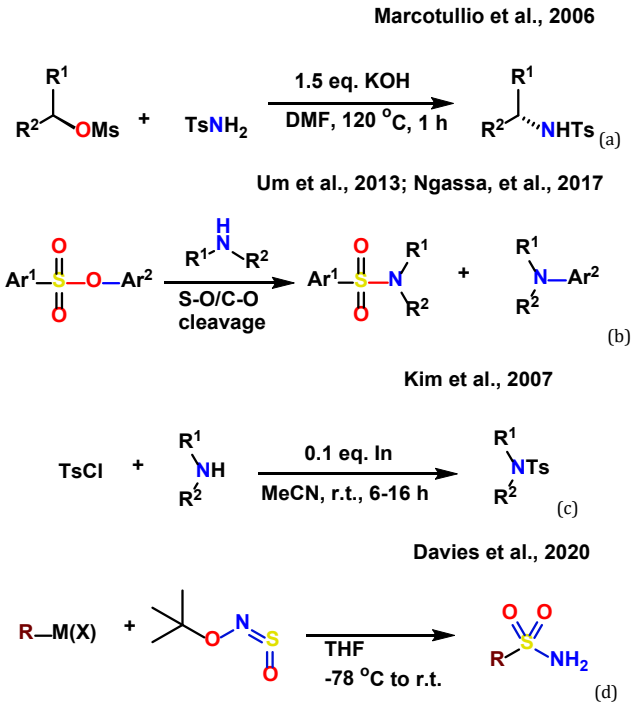


Figure 3. Previously reported methods for the synthesis of sulfonamides. (a) Synthesis of secondary sulfonamides via treatment of tosylamide with sulfonate. (b) Regioselective S-O/C-O bond cleavage of aryl sulfonate esters affording *N*-arylamines or arylsulfonamides. (c) A generalizable indium catalyzed tosylation of amines. (d) Synthesis of primary sulfonamides from *N*-sulfinyl-*O*-(*tert*-butyl)hydroxylamine (*t*-BuONSO).

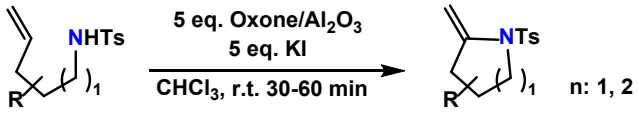


Figure 4. Synthesis of *N*-tosyl pyrrolidines and piperidines from secondary sulfonamides.

electrochemical process [33], and the reaction of amines and thiols with sulfonic esters using a H_2O_2-$POCl_3$ system [34]. This diversity of approaches not only highlights the adaptability of sulfonamide synthesis to varied synthetic needs but also underscores the continuous exploration and innovation within the field of synthetic organic chemistry.

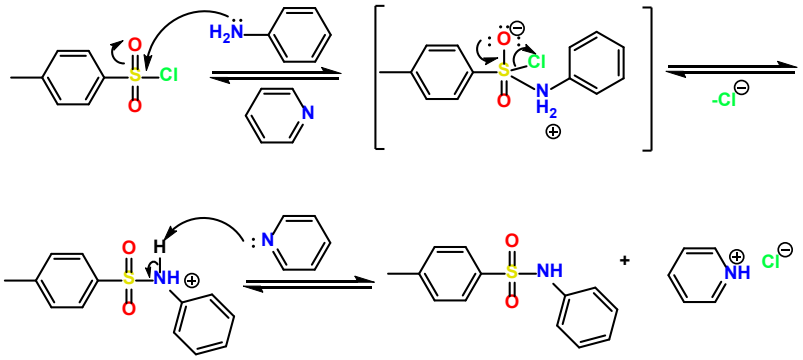
Beyond their well-established therapeutic properties, sulfonamides emerge as versatile synthetic building blocks. An illustrative example of this versatility is found in the synthesis of *N*-tosyl pyrrolidines and piperidines derived from secondary sulfonamides (Figure 4) [20]. This synthetic pathway showcases the ability of sulfonamides to serve as precursors for the construction of diverse and complex heterocyclic structures, demonstrating their utility in the creation of valuable synthetic intermediates. Expanding on this theme, previous reports detailing the functionalization of sulfonyl pyrroles further underscore the synthetic usefulness inherent in sulfonamides [35]. Such functionalization not only enhances the molecular diversity achievable with sulfonamides but also attests to their adaptability in diverse synthetic contexts. The ability to selectively modify the sulfonamide scaffold highlights its potential as a strategic starting point for the synthesis of intricate molecular architectures.

In contrast to the previously proposed mechanism for the tosylation of alcohols in the presence of pyridine, the tosylation of amines unfolds with a distinctive behavior. This dissimilarity arises from the increased nucleophilicity of the amine substrate, which is a pivotal factor in steering the reaction dynamics away from the formation of the pyridinium salt. As such, a more traditional mechanism gains credence, as schematically outlined in Scheme 2. This departure from the previously proposed mechanism emphasizes the nuanced intricacies dictated by the nature of the nucleophile. As researchers delve deeper into these mechanistic intricacies, evolving insights may enhance the precision and predictability of synthetic methodologies, fostering advancements in the field of organic chemistry.

As mentioned above, sulfonamides are often used as protected synthetic intermediates. Given that this protection is often employed in highly functionalized settings, the need for efficient and mild deprotection strategies becomes increasingly important. Furthermore, the cleavage and rearrangements of sulfonamides are complex and structure dependent, highlighting the need for chemoselective approaches [36]. Such strategies exist from mild electrochemical deprotection of *N*-phenylsulfonyl *N*-substituted amines [37] to chemoselective deprotection under acidic conditions [38].

3. Crystal structures

Numerous crystal structures exist for sulfonamides and sulfonate esters with varying functionality. Examining the crystal packing arrangements reveals the impact of hydrogen bonding, π-π stacking, and other intermolecular interactions on the stability and morphology of sulfonamide and sulfonate crystals. Insights into these interactions contribute to the design and optimization of molecular assemblies for specific applications. The incorporation of various functional groups into sulfonamides and sulfonates results in a myriad of crystal structures with diverse properties.



Scheme 2. Proposed mechanism for the tosylation of aniline in the presence of pyridine.

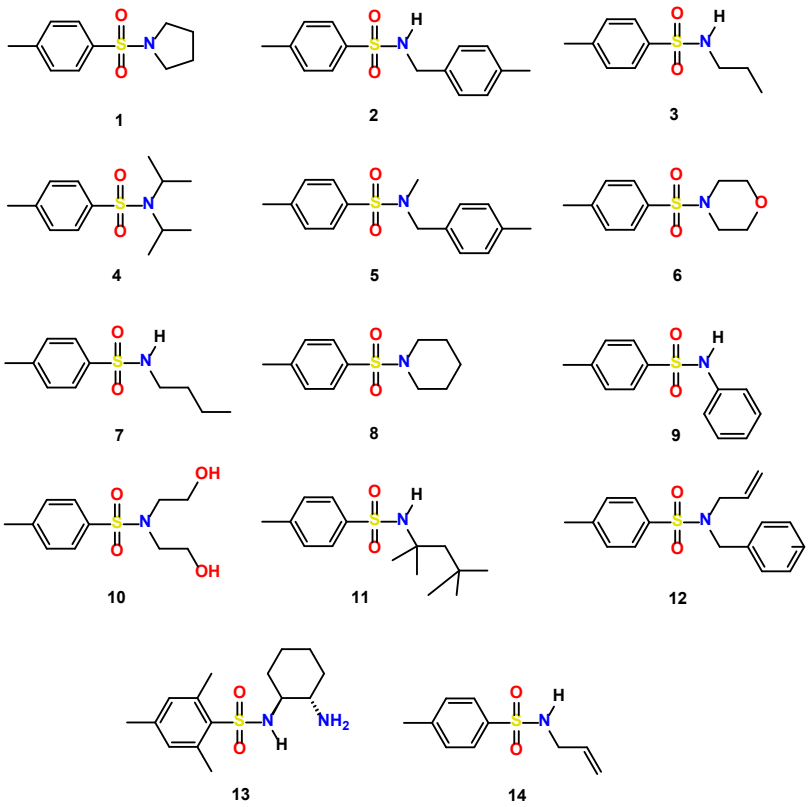


Figure 5. Arylsulfonamides **1-14**.

Single-crystal X-ray structures produced in the same lab, using the same crystallographic characterization protocol, were used for comparison purposes to ensure that any inconsistency would not result from a difference in preparation. A total of fourteen arylsulfonamides, shown in Figure 5, and seven aryl-sulfonate esters, shown in Figure 6 [26-28,39-48].

3.1. Sulfonamides

Previous reports have shown that, in the case of secondary sulfonamides, most calculated low-energy structures differ significantly from their crystallized form due to branched hydrogen bond networks [49]. These networks are also responsible for varying polymorphic forms and are observed in self-assembled organic tubular structures composed of sulfonamides [50]. Apart from compound **13**, all characterized sulfonamides were derived from the amination of tosyl chloride. This uniformity in synthetic routes underscores the reliability and applicability of this method for generating diverse sulfonamide structures within a reasonable chemical space. A comprehensive examination of the crystallographic data presented in Table 1 reveals a predominant prevalence of monoclinic and orthorhombic crystal systems, with only two exceptions: compounds **1** and **14**, which exhibit a triclinic arrangement. The N-S-C angle remains consistent with a range of 104.06(11) to 110.29(7)°. Compound **11** exhibits a slight perturbation of the N-S-C angle, most likely due to the steric bulk around the sulfonamide moiety. The smaller N-S-C angle of compound **13** is also likely due to steric effects, in this case originating from the stereochemical configuration. The decreased steric hinderance around the sulfonyl center offers a possible explanation for the observed angle. Examining the S=O bond lengths across all fourteen compounds reveals a consistent adherence to the expected values, ranging from 1.424(2) to 1.4428(11) Å. Moreover, the S-N and C-S bond lengths maintain a high degree of consistency across all characterized sulfonamides.

Table 1. Crystallographic characterization results and selected parameters for arylsulfonamides **1-14**, following the labelling in Figure 5.

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Formula	$C_{11}H_{15}NO_2S$	$C_{15}H_{17}NO_2S$	$C_{10}H_{15}NO_2S$	$C_{13}H_{21}NO_2S$	$C_{15}H_{17}NO_2S$	$C_{11}H_{15}NO_3S$	$C_{11}H_{17}NO_2S$
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P1^-$	$P2_1$	Cc	Pc	$P2_1/c$	$P2_1/c$	$P2_1/c$
C-S-N-C torsion(s) (°)	-65.62(18), 76.16(19)	57.9(2)	-54.4(2)	67.1(2), -99.0(2)	63.1(2), -71.6(2)	-65.2(2), 68.8(2)	61.1(1)
N-S-C angle (°)	107.66(9)	106.98(13)	106.86(13)	107.92(15)	106.84(8)	106.51(9)	106.66(7)
S=O bond lengths (Å)	1.4357(16)	1.429(2)	1.428(2)	1.433(3)	1.4293(16)	1.4291(16)	1.4301(11)
	1.4349(16)	1.424(2)	1.441(2)	1.439(3)	1.4312(16)	1.4267(16)	1.4428(11)
S-N bond length (Å)	1.625(2)	1.608(2)	1.618(3)	1.622(3)	1.6455(17)	1.6401(17)	1.6178(13)
C-S bond length (Å)	1.770(2)	1.764(3)	1.766(3)	1.777(3)	1.7582(18)	1.761(2)	1.7707(15)
CCDC code	1983920	1977684	2008411	2006237	2054873	2054874	2054875
Reference	[39]	[40]	[41]	[42]	[28]	[28]	[28]
Compound	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Formula	$C_{12}H_{17}NO_2S$	$C_{13}H_{13}NO_2S$	$C_{11}H_{15}NO_4S$	$C_{15}H_{25}NO_2S$	$C_{17}H_{19}NO_2S$	$C_{15}H_{24}N_2O_2S$	$C_{10}H_{13}NO_2S$
Crystal system	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic	Triclinic
Space group	$P2_12_12_1$	$P2_1/c$	$Pbca$	$P1^-$	$Pna2_1$	$P212121$	$P1^-$
C-S-N-C torsion(s) (°)	67.8(1), -70.7(1)	50.6(1)	86.4(2), -62.9(2)	78.3(2)	-66.9(2), 84.2(2)	70.4(2)	61.0(2)
N-S-C angle (°)	106.66(7)	106.57(7)	106.57(10)	110.29(7)	107.11(13)	104.06(11)	107.21(11)
S=O bond lengths (Å)	1.4315(12)	1.4263(11)	1.4332(18)	1.4400(12)	1.4290(18)	1.4330(19)	1.4282(17)
	1.4275(13)	1.4410(11)	1.4251(18)	1.4329(12)	1.4342(18)	1.4379(18)	1.4353(17)
S-N bond length (Å)	1.6371(13)	1.6395(13)	1.6296(19)	1.6079(14)	1.636(2)	1.609(2)	1.617(2)
C-S bond length (Å)	1.7657(16)	1.7589(14)	1.765(2)	1.7751(16)	1.763(2)	1.779(2)	1.760(3)
CCDC code	2054876	2054877	2081811	2081812	2022196	1437453	1856234
Reference	[28]	[28]	[28]	[28]	[43]	[44]	[45]

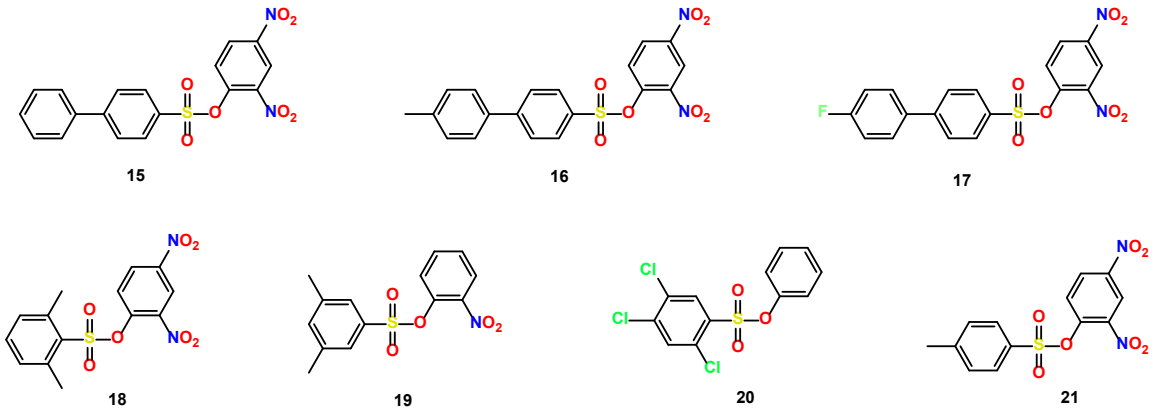


Figure 6. Aryl sulfonate esters **15-21**.

The detailed examination of the characterized sulfonamide compounds extends beyond their structural arrangement to include their coordination geometry and electronic properties. The observed fourfold coordination, denoted by the τ4 descriptors averaging at 0.94, indicates a slightly distorted tetrahedral geometry around the sulfur atom when compared to idealized geometries (0 for square planar, 0.85 for trigonal pyramidal, and 1 for tetrahedral coordination) [51]. Additionally, projections along the C-S and N-S bonds show the lone pair on nitrogen, and the *p* orbital of the aromatic carbon split the O=S=O angle in a gauche orientation, in agreement with previous reports [52]. The number of molecules in the unit cell (*Z*) for each of the aforementioned structures is as follows: *Z* = 2, compounds **1**, **2**, and **11**; *Z* = 4, compounds **4**-**9**; *Z* = 8, compounds **3** and **10**. Comparisons of this nature, involving various crystal structures of sulfonamide, have been reported by Perlovich *et al.* and offer more information on the conformational states, thermodynamic characteristics, and molecular packing of the crystal [53]. This study analyzed the structure, packing architecture, topology of hydrogen bond networks, sublimation, solubility, and solvation's characteristics of 24 sulfonamides, all of which have phenyl groups on either end of the sulfonamide moiety. A similar comparison, primarily in hydrogen bond connectivity of 39 sulfonamide crystal structures previously reported by Adsmond *et al.*, highlights the complexity of such networks, which change significantly even in the smallest of structural changes [54]. Given the complexity that exists in the characterization of these molecules, it is beneficial to cover more of the chemical space. One of such studies of sulfonamides involved the use of more than 1.4K structures from the Cambridge Structural Database (CSD) [55,56]. The correlations found in this study can be used to predict broader peculiarities of crystals; however, some details are lost due to differences in the crystallization procedure. However, the large-scale comparison revealed some interesting trends, including what the authors refer to as a special 'butterfly' packing that is topologically less dense than close packing. This could explain the ease in which such compounds crystalize.

3.2. Sulfonate esters

Analysis of crystal structure data, in the case of sulfonate esters, provides insight into the kinetic and electronic factors and how changes in functionality effect such factors. This insight is necessary not only for a better understanding of the structural effects but also could aid in understanding the adverse effects of sulfonate esters in the human body. One such study details mutagenic and therefore potentially cancer-inducing events due to a reaction with DNA, which may cause [57]. Another example that showcased the usefulness of crystallographic characterization involved a detailed study on sulfonate-based peptide coupling reagents, the products of which were evaluated against human cancer cells [58]. This study showed a moderate antiproliferative effect against the human cancer cell line SW756 for multiple sulfonate ester derivatives.

Table 2. Crystallographic characterization results and selected parameters for aryl sulfonate esters **15-21**, following the labelling in Figure 6.

Compound	15	16	17	18	19	20	21
Formula	$C_{18}H_{12}N_2O_7S$	$C_{19}H_{14}N_2O_7S$	$C_{18}H_{11}FN_2O_7S$	$C_{15}H_{14}N_2O_7S$	$C_{14}H_{13}NO_5S$	$C_{12}H_7Cl_3O_3S$	$C_{13}H_{10}N_2O_7S$
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P1^-$	$P2_1/c$	$Pna2_1$
C-S-O-C torsion (°)	131.6(1)	94.0(1)	92.7(1)	73.8(2)	84.68(11)	70.68(16)	62.0(3)
O-S-C angle (°)	120.5(1)	120.4(1)	119.2(1)	102.13(11)	104.16(6)	107.48(9)	110.64(16)
S=O bond lengths (Å)	1.420(1)	1.421(1)	1.424(1)	1.4198(19)	1.4249(12)	1.4229(15)	1.414(3)
	1.423(1)	1.417(2)	1.413(1)	1.4183(19)	1.4198(11)	1.4184(15)	1.415(3)
S-O bond length (Å)	1.626(1)	1.619(1)	1.623(1)	1.6387(18)	1.5887(11)	1.5828(15)	1.634(3)
C-O bond length (Å)	1.387(2)	1.386(2)	1.392(2)	1.390(3)	1.4268(18)	1.425(2)	1.391(4)
CCDC code	2359790	2359791	2359792	2157592	1418463	1477649	1419864
Reference	[26]	[26]	[26]	[27]	[46]	[47]	[48]

Given the common sulfonyl moiety shared between both classes of compounds, similar parameters were used for the comparison of sulfonate esters **15-21**. Table 2 summarizes some key parameters from the X-ray diffraction data. The monoclinic crystal system with a $P2_1/c$ space group was the most common, with only compounds **19** and **21** differing in this regard. Compounds **15-17** exhibit slightly higher O-S-C angles, ranging from 119.2(1) to 120.5(1)°, compared to compounds **18-21,** with a range of 102.13 (11) to 110.64 (16)°. A possible explanation may involve an increase in steric interactions or a greater extent of π-π stacking. Sulfonate esters exhibit slightly shorter S = O bond lengths than sulfonamides, ranging from 1.413(1) to 1.4249(12) Å. The S-O and C-O bond lengths are similar for all compounds. However, slight differences are seen in compounds **19** and **20**. The lower S-O bond length and the higher C-O bond length seem to be due to the absence of an electron-withdrawing *p*-NO_2 group. However, these bond lengths deviate to a greater extent in compound **19**, containing an electron-withdrawing o-NO_2 group, compared to compound **20**, suggesting that chloride groups also play a role in the observed deviation.

A notable finding from Stang *et al.* revealed that the C-S-O bond angle and the S=O and S-C bond lengths are independent of the nature of the sulfonate, where the C-O and S-O bond lengths are considerably affected, in agreement with previously shown data [59]. This same finding may be true for similar bonds in sulfonamide structures. When parallels are drawn between sulfonate esters and sulfonamides, researchers can establish a more comprehensive understanding of the inherent structural features that remain invariant despite changes in the chemical nature of the substituents. This cross-referencing of data contributes to a nuanced and unified perspective on the behavior of sulfonate-containing compounds, offering valuable insights into their structural stability and informing future investigations into their diverse applications in synthetic chemistry and pharmaceutical science.

4. Conclusions

Various aspects of sulfonamides and sulfonate esters, including synthetic routes, proposed mechanisms, and their usefulness as synthetic precursors, were reviewed. Many different methods exist for effectively synthesizing these compounds, from general processes involving a sulfonyl halide precursor to methods involving electro-oxidation, transition metal catalysis, and stereoselective approaches. The mechanism of interest, the sulfonylation of alcohols and amines, shows evidence of variable reactivity, dependent on the nature of the nucleophile and electrophile. Although previous reports offer information on the factors responsible for these changes, the true nature of this reaction remains unclear. Aside from a brief overview of past and current synthetic methodologies and mechanistic studies, this review captures two subgroups of crystal structures, sulfonamides and sulfonate esters, of which were afforded in a controlled manner (same reaction and crystallization conditions) with subtle changes in functionality. This can serve as a starting point for further investigation into the kinetic and electronic effects responsible for the observed conformation. Among the most notable trends were the consistent S=O and S-C bond lengths and the C-S-O bond angle, regardless of structural differences. In contrast, the C-N/O and S-N/O bond lengths were highly dependent on the nature of the compound and the associated steric and electronic effects. Given that crystal structures are among the most accurate molecular representations, the insights gained from this analysis can aid in the improvement of human health and the development of new mechanistic insights through computational means or intuition alone.

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Supporting information

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Disclosure statement

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CRediT authorship contribution statement

Conceptualization: Brock Anton Stenfors, Felix Nyuangem Ngassa; Methodology: Brock Anton Stenfors, Felix Nyuangem Ngassa; Software: Brock Anton Stenfors, Felix Nyuangem Ngassa; Validation: Brock Anton Stenfors, Felix Nyuangem Ngassa; Formal Analysis: Brock Anton Stenfors, Felix Nyuangem Ngassa; Investigation: Brock Anton Stenfors, Felix Nyuangem Ngassa; Resources: Brock Anton Stenfors, Felix Nyuangem Ngassa; Data Curation: Brock Anton Stenfors, Felix Nyuangem Ngassa; Writing - Original Draft: Brock Anton Stenfors, Felix Nyuangem Ngassa; Writing - Review and Editing: Brock Anton Stenfors, Felix Nyuangem Ngassa; Visualization: Brock Anton Stenfors, Felix Nyuangem Ngassa; Funding acquisition: Brock Anton Stenfors, Felix Nyuangem Ngassa; Supervision: Brock Anton Stenfors, Felix Nyuangem Ngassa; Project Administration: Brock Anton Stenfors, Felix Nyuangem Ngassa.

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