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Straightforward and sustainable synthesis of sulfonamides in water under mild conditions

Nadim Eid,[a,b] Iyad Karamé,*[b] and Bruno Andrioletti *[a]

Abstract: Ideally, a sustainable chemical synthesis should involve the uses of non-toxic solvents and reactants, easy separations and purifications with energy efficient processes. In this context, reconsidering the synthesis of widespread drugs is especially timely and should allow obtaining important benefits in terms of environmental impact. Sulfonamides are pertinent as their synthesis requires generally the use of toxic and/or hard to remove solvents such as dichloromethane, DMF and DMSO. In addition, toxic and highly reactive sulfur-containing sources such as sulfonyl chloride are often involved and coupled with amines. Moreover, the latter may exhibit some toxicity and are generally difficult to purify. Herein, we disclose the unprecedented and sustainable synthesis of sulfonamides using sodium sulfinate as a commercial and stable sulfur source and nitro- arenes as the nitrogen-containing reactant. In addition, the optimized conditions use water as the only "green" solvent and the products are collected by simple filtration.

Introduction

The unique success of the sulfonamide drug Prontosil[1] commercialized in 1935 led to intense investigations in the field. Consequently, a large number of sulfonamide bioactive molecules found applications in human[2] and veterinary medicine,[3-4] but also in agriculture[5] (Figure 1).

Several approaches describing the synthesis of the sulfonamide function from a wide variety of substrates can be found in the literature. For instance, a large number of strategies involve amines as the nitrogen source and sulfonyl chloride[6-7] or a chlorinating agent with the corresponding sulfurated starting materials in various oxidation states[8-11] to create the S-N bonds. Some non-conventional methods using transition metal[12] or Grignard reagents[13] are also effective (Scheme 1). Of note, Revankar *et al.* have prepared a purine based sulfonamide by oxidation of the sulfenamide analogue.[14]

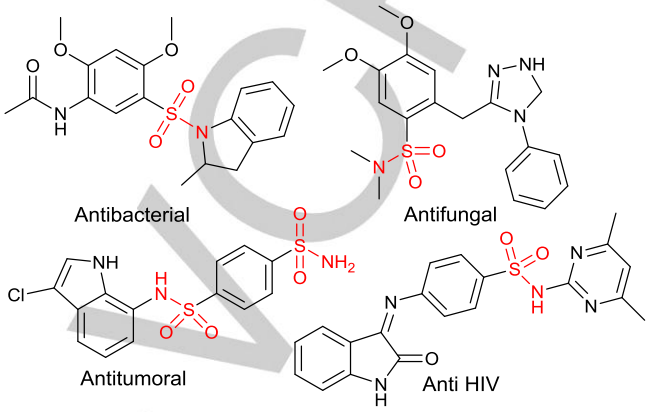
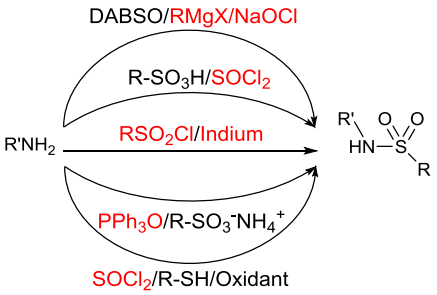


Figure 1. Different bioactive sulfonamides.

Another synthetic pathway is the functionalisation of the sulfonamides. This can be achieved by using a wide variety of reactants such as aryl nonaflate,[15] aryl halide,[16] alcohols,[17-19] aldehydes[20] or boronic acids.[21] In addition, all the methods described in the literature use organic solvents such as dichloromethane and/or toxic activating agents such as thionyl chloride for the preparation of the sulfonamides. Hence, low atom economy was achieved. Furthermore, all the reagents are prepared by multi synthetic steps and time-consuming purifications are needed generally.



Scheme 1. Synthesis of sulfonamides from different substrates.

Conversely, sodium sulfinates constitute a promising alternative to sulfonyl chloride because of their moisture tolerance and easy synthesis. Indeed, they can be prepared via addition of organometallic reagents to sulfur dioxide or DABSO.[22] For instance, sodium sulfinates were used advantageously for coupling reactions as "arene donors"[23] and for sulfonamide synthesis *via* copper catalyzed oxidative coupling with amines.[24] Recently, Yang *et al.* described another non-

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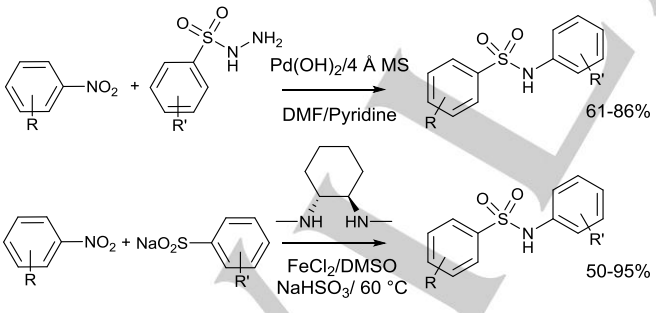
catalyzed approach to prepare sulfonamide using sodium sulfinate and an amine in the presence of iodine as oxidant in ethanol.[25-26]

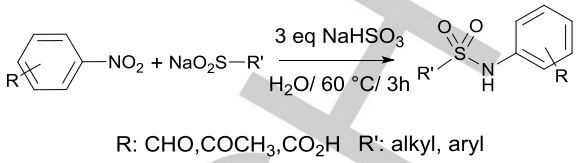
Nitrogen-containing molecules are usually prepared by reduction of imine (reductive amination),[27] azide[28] or nitro- group.[29] However, many amines are toxic[30-31] and their purification is always challenging. Hence, by-passing the amine function would afford an advantageous synthetic shortcut for the preparation of sulfonamides. The nitro- function appears as a promising alternative to amines. Indeed, nitro-containing molecules are easy available from simple nitration with nitric acid,[32] Henry reaction,[33] palladium catalyzed coupling of nitromethane,[34] or by functionalizing a nitro-containing molecule using a hypervalent iodine reagent[35]. The nitro- function is mainly used as precursor for the preparation of amines by reduction. Due to their good stability and large availability, nitro- groups constitute good nitrogen donor. Leimgruber-Batcho[36] indole synthesis is a remarkable example of the use of a nitro arene in industry at the expense of the corresponding amines for the preparation of nitrogen fused rings.

Besides, catalysts play essential roles in sulfonamide synthesis, as mentioned by Zhang *et al.*, the reaction can proceed without catalyst in DMSO but with poor yields.[37] Furthermore, metallic residues resulting from the catalytic process may not be suitable for uses in the pharmaceutical industry.[38] Zaho *et al.*[39] described a sulfonamide synthesis by coupling nitroarenes and aryl sulfonyl hydrazide in DMF using palladium acetate as the catalyst in the presence of pyridine and molecular sieves. Another catalytic system was developed by Zhang *et al.*.[37] It uses 10% of $FeCl_2$ and *trans*-*N*,*N*'-dimethylcyclohexane-1,2-diamine as the catalyst, under argon atmosphere in the presence of an excess of aryl sulfinate salts in DMSO. Using these conditions, they obtained sulfonamides in good yields (Scheme 2).



Scheme 2. Nitroaryl as nitrogen donor.

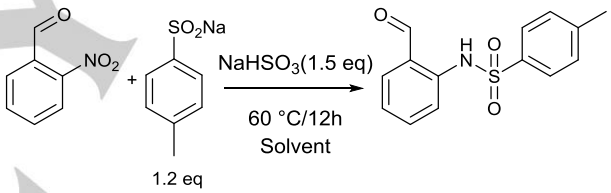
Herein, we present a simple strategy for the synthesis of sulfonamides using water as the only green solvent. This approach involves nitroarenes as nitrogen donor and sodium sulfinate salts as the sulfur source in stoichiometric amounts with 3 equivalents of sodium bisulfite as the reducing agent at 60°C (Scheme 3).



Scheme 3. Our new strategy in sulfonamide synthesis.

Results and Discussion

In a preliminary screening, we decided to react 2-nitrobenzaldehyde with sodium *p*-toluenesulfinate in different solvents. The choice of 2-nitrobenzaldehyde as a coupling partner is justified by the fact that the synthesis of sulfonamides *via* the amine route is not efficient because of the instability of 2-aminobenzaldehyde.[40] The reaction did not take place in most organic solvents (THF, 2-MeTHF, acetone, acetonitrile, ethanol, ethyl acetate and propylene carbonate, Scheme 4), probably due to the limited solubility of the sulfinate and bisulfite in these solvents.



Scheme 4. Solvent determination.

Interestingly, the reaction proceeded in DMSO or water. However, if the *N*-(2-formylphenyl)-4-methylbenzenesulfonamide (Scheme 4) is highly soluble in DMSO, it precipitates in water. Hence, the low solubility of the sulfonamide in water enables a facile separation of the product by simple filtration. Accordingly, we have selected water as solvent for this transformation.

Next, we determined the nature of the optimal reducing agent. Several sulfur-containing molecules were evaluated (Table 1). As expected, the reaction does not take place without reducing agent (Table 1, entry 1) but the screening revealed that sodium bisulfite efficiently promotes the reaction (Table 1, entries 5-9). If 3 equivalents of sodium bisulfite are used, a full conversion is observed (Table 1, entry 6).

Table 1. Optimization of the different reaction conditions.

Entry	A	eq of A	eq of B	conv (%)[a]
1	-	-	1.2	0
2	$Na_2S_2O_3$	3	1.2	0
3	Na_2SO_3	3	1.2	0

4	S_8	3	1.2	0
5	$NaHSO_3$	1.5	1.2	80
6	$NaHSO_3$	3	1.2	100
7	$NaHSO_3$	3	1	100
8[b]	$NaHSO_3$	3	1	18
9[c]	$NaHSO_3$	3	1	38

Reaction conditions: 0.375 g 2-nitrobenzaldehyde, sodium *p*-toluenesulfinate B, reducing agent A, 60 °C, 3h, [a] determined by ^{1}H NMR related to 2-nitrobenzaldehyde. [b] 25 °C. [c] 35 °C, conv: conversion.

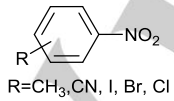
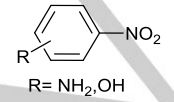
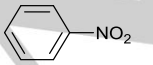
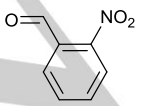
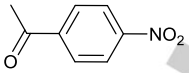
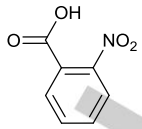
Interestingly, a complete conversion was observed within 3 hours even when a stoichiometric amount of the sulfinate salt was used (Table 1, entry 7).

The temperature appears also critical for the reaction. If the transformation proceeds at room temperature, a limited 18% conversion was determined (Table 1, entry 8). However, full consumption of the starting materials was reached when the temperature was increased from 25 °C to 60 °C (Table 1, entry 7). Consequently, 60 °C was chosen as the optimal reaction temperature.

Influence of the substitution on the nitroarenes

A variety of nitroarenes was successfully converted to the corresponding sulfonamides in good yield under the optimized conditions at the exception of water-insoluble or electron-enriched nitroarenes (Table 2, entries 1 and 2). Hence, soluble nitroarenes such as nitrobenzene (Table 2, entry 3), 2-nitrobenzaldehyde (Table 2, entry 4), 4-nitroacetophenone (Table 2, entry 5) and 2-nitrobenzoic acid (Table 2, entry 6) afforded the corresponding expected sulfonamides in good yields under the optimized reaction conditions.

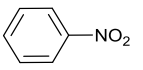
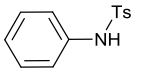
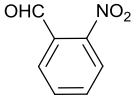
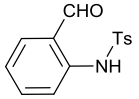
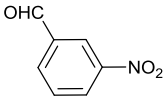
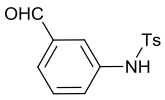
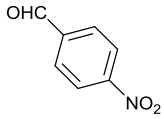
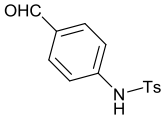
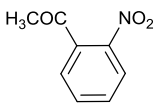
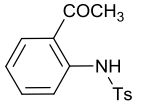
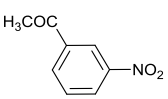
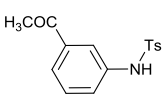
Table 2. Screening of the nitroarenes.

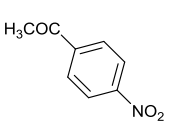
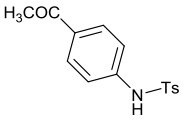
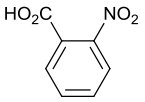
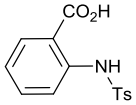
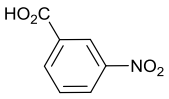
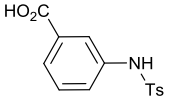
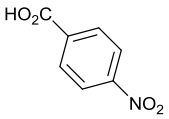
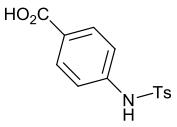
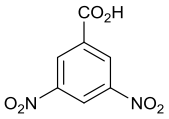
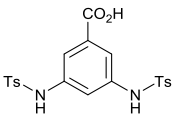
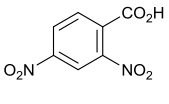
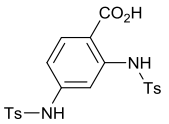
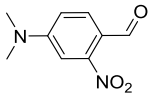
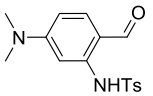
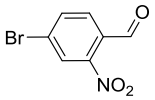
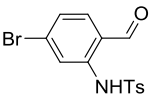
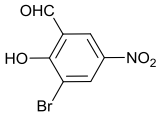
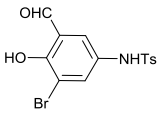
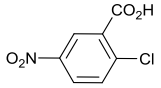
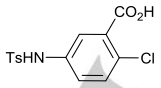
Entry	Substrate	Solubility	Y(%)
1	 R=CH_3,CN, I, Br, Cl	-	-
2	 R= NH_2,OH	+	-
3		+	33
4		+	73
5		+	60
6		+	75

Conditions: 2.5 mmol nitroarene, sodium *p*-toluenesulfinate (1 eq), sodium bisulfite (3 eq), 60 °C, 24h. +: water soluble, -: insoluble in water. Y: yield.

Next, the effect of the relative position of the substituents on the aromatic ring was investigated. As shown in Table 3, nitrobenzaldehydes, nitrobenzophenones, and nitrobenzoic acids were converted to the corresponding sulfonamides in moderated to good yield. Nitrobenzene shows a moderate reactivity and gives the corresponding sulfonamide in 33% isolated yield (Table 3, entry 1) but the formyl- or carboxylic acid *ortho*-substituted nitroarenes appeared more reactive as the expected products were isolated in 73 and 75% isolated yield, respectively (Table 3, entries 2 and 8). However, 2-nitroacetophenone did not react because of the steric strain caused by the neighboring methyl group (Table 3, entry 5). The *meta*-substituted nitroarenes (Table 3, entries 3 and 6) appeared moderately reactive (35% and 25% isolated yield, respectively) but the *para*-substituted analogues were shown more reactive (Table 3, entries 4 and 7) at the exception of 4-nitrobenzoic acid (Table 3, entry 10). Interestingly, bis-nitroarenes were also converted to sulfonamides, though in moderated yields (20-30%) (Table 3, entries 11 and 12).

Table 3. Effect of the substitution.

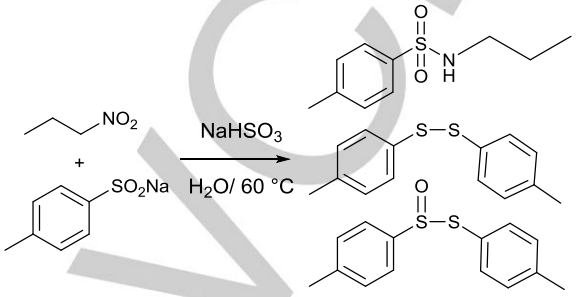
Entry	Substrate	Product	T(h)	Y(%)
1			48	33[a]
2			3	73
3			4	35
4			3	55
5			48	Nd
6			48	25[a]

7			24	60
8			4	75[b]
9			4	44[b]
10			4	23[b]
11			24	30[c]
12			24	20[c]
13			3	78[d]
14			2	38
15			4	40[d]
16			2	30

Conditions: 2.5 mmol nitroarene, sodium *p*-toluenesulfinate (1eq/ nitro fonction), sodium bisulfite (3 eq/ nitro fonction), 60 °C, [a] after column chromatography separation; [b] K_2CO_3 (1 eq), [c] $NaHSO_3$ (6 eq), sodium *p*-toluenesulfinate (2 eq), K_2CO_3 (1 eq), [d] $NaHSO_3$ (6 eq), sodium *p*-toluenesulfinate (2 eq), Nd: not determined. T: reaction time, Y: yield.

Highly functionalized sulfonamides were also prepared efficiently using our one-step methodology (Table 3, entries 13-16) For example, the 3 synthetic steps (including an oxidation and a reduction) were required for the preparation of *N*-(5-bromo-2-formylphenyl)-4-methylbenzenesulfonamide (Table 3, entry 14).[41] In our case, it could be prepared in a single step 38% isolated yield.

Nitroalkyl such as nitropropane was also converted to 4-methyl-*N*-propylbenzenesulfonamide, but the reaction was little chemoselective and afforded a variety of sulfurated by-products resulting from the homo-reaction of sodium *p*-toluenesulfinate (Scheme 5). Similar bis-sulfur products were also obtained in water using a cobalt catalyst.[42] Their presence can be explained to the slow kinetics of this transformation (low electrophilicity of the nitro group), allowing the competitive homo-reaction between sulfinates to proceed.

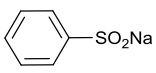
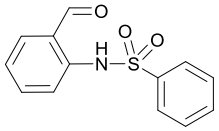
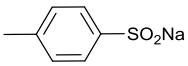
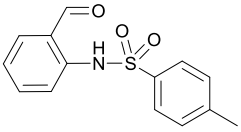
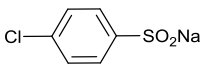
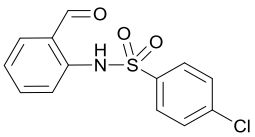


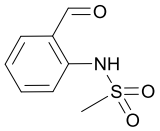
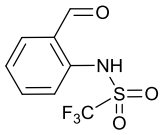
Scheme 5. Reaction of nitropropane with sodium *p*-toluenesulfinate.

Screening of sodium sulfinate salts

Several sodium sulfinates salts were evaluated. 2-Nitrobenzaldehyde was chosen as the nitrogen source (Table 4). Aromatic sodium sulfinates react with 2-nitrobenzaldehyde to afford the corresponding sulfonamide in good yield. Yet, substituted aryls with even electron withdrawing (Table 4, entry 3) or electrodonating groups (Table 4, entry 2) appear to be more reactive than sodium-benzenesulfinate (Table 4, entry 1) and afforded the expected sulfonamide in 58, 75, and 32% yield, respectively. Interestingly, the sodium methanesulfinate was transformed to the corresponding sulfonamide moiety in good yield 55% (Table 4, entry 4), and the product was crystallized from water within 48h at room temperature and collected via filtration. However, sodium triflinate (Table 4, entry 5) was not reactive under these conditions.

Table 4 Screening of sodium sulfinates.

Entry	Sulfinate salt	Product	Y(%)
1			32
2			75
3			58

4	CH_3SO_2Na		55
5	CF_3SO_2Na		0

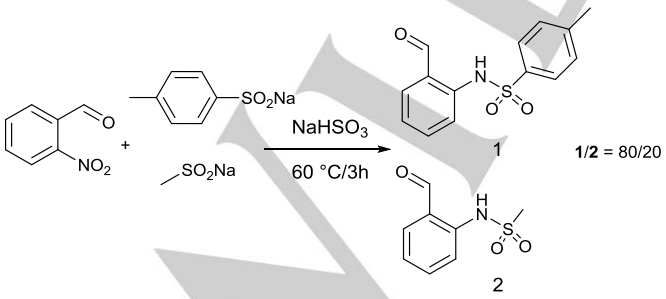
Reaction conditions: 0.375 g 2-nitrobenzaldehyde, sodium sulfinate (1 eq), $NaHSO_3$ (3 eq), 60 °C, 24h, Y: yield.

Rationalization

As mentioned above, only electron poor nitroarenes are reactive under our optimized conditions. This is in agreement with the mechanism proposed by Zhang *et al.*[42] Indeed, the key step of the reaction is the nucleophilic attack of the sulfur atom on the nitro function to create the S-N bond before the N-O is reduced by the sodium bisulfite to generate a sulfate ion and the sulfonamide function. Accordingly, electron poor nitroarenes are more reactive than the electron rich analogues.

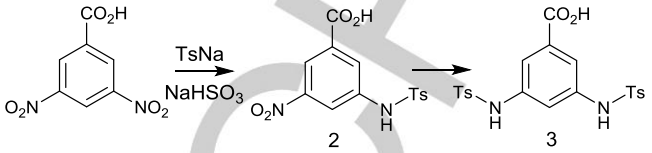
Conversely, aromatic sulfinates seem not to be affected by the electronic factors. For example, sodium *p*-toluenesulfinate (Table 4, entry 2) and sodium *p*-chlorobenzenesulfinate (Table 4, entry 3) yielded the expected sulfonamide in 75% and 58% yield, respectively. At last, electron rich aliphatic sulfonates such as sodium methanesulfinic acid (Table 4, entry 4) reacted smoothly, but the less nucleophilic sodium triflinate (Table 4, entry 5) did not react in our conditions.

This difference in reactivity was further evidenced in the competitive reaction between sodium *p*-toluenesulfinate and sodium methanesulfinic acid using 2-nitrobenzaldehyde as nitrogen source under optimized conditions. Analysis of the crude reaction mixture revealed that a 80:20 ratio between **1** and **2** (Scheme 6) was produced. Interestingly, the two products were isolated separately in pure form without any column chromatography. Indeed, **1** was isolated by a simple filtration and **2** via extraction from aqueous phase.



Scheme 6. Competitive reaction between aliphatic and aromatic sulfinates.

Next, we investigated the selectivity of the transformation using a di-nitro reactant. Unfortunately, all the attempts using 2,4-dinitrobenzoic acid or 3,5-dinitrobenzoic acid failed to afford the monosubstituted sulfonamide even when 1 equivalent of sodium *p*-toluenesulfinate per substrate was used. We believe that the monosulfonamide product **2** is more reactive than the starting 3,5-dinitrobenzoic acid leading to a mixture between mono and bis substituted aryl carboxylic acid (Scheme 7).



Scheme 7. Reaction of sodium *p*-toluenesulfinate with 3.5 dinitrobenzoic acid.

Scalability and solvent purity

In order to explore further the versatility of the transformation, a large scale reaction using 3 g of 2-nitrobenzaldehyde was carried out. Even when tap water was used as the solvent, the expected sulfonamide was collected 67% yield in pure form after precipitation. The results are comparable with the results obtained in a 0.37 g batch.

Conclusion

In summary, we have developed a sustainable sulfonamide preparation from commercially available and non-toxic starting materials under mild conditions. This method overcomes the traditional issues of sulfonamide synthesis that involve the use of toxic, unstable reagents such as thionyl and sulfonyl chloride or metal catalysis. A very high chemoselectivity was obtained as only electron poor and water soluble nitroarenes were reactive. Hence, a wide range of sodium sulfinate was transformed to the corresponding sulfonamide in good yield, in one step. In addition, no protecting groups were needed because of the high function tolerance when using nitro and sulfinate compounds. At last, the products were collected *via* simple filtration without using any organic solvent for extraction or chromatography separation ensuring a high mass efficiency.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

The authors thank the University Claude Bernard Lyon 1, the CNRS and the Lebanese University for partial financial support.

Experimental Section

1. General information

All reagents were obtained commercially and were used without further purification. ^{1}H NMR spectra were recorded on a Bruker 300 MHz spectrometer. Samples were prepared in $CDCl_3$ or DMSO-d_6 (residual solvent reference: 7.26 ppm for $CDCl_3$, 2.50 ppm for DMSO-d_6) depending on their solubility. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ or DMSO-d_6 (residual solvent reference: 77.0 ppm for $CDCl_3$ and 39.52 ppm for DMSO-d_6).

2. Synthesis of sulfonamides

A mixture of sodium sulfinates (0.5 mmol), nitroarenes (0.5 mmol), $NaHSO_3$ (1.5 mmol) in water (2 mL) were stirred at 60 °C for the appropriate reaction time (reaction was monitored by TLC (5/1 or 3/1: cyclohexane/ ethyl acetate depending on the substrate polarity)). After cooling at room temperature, water (8 mL) was added. The precipitate was collected by filtration and washed with water to afford the pure product. All sulfonamides could be crystallized from acetone/water or by slow evaporation of DCM solutions.

3. Reaction of sodium *p*-toluenesulfinate with 3.5 dinitrobenzoic acid

A mixture of sodium p-toluenesulfinate (0.5 mmol, 0.09g), 3.5-dinitrobenzoic acid (0.5 mmol, 0.107g, 1 eq), $NaHSO_3$ (1.5 mmol, 0.312g, 3 eq), K_2CO_3 (0.5 mmol, 0.07g, 1 eq) in water (2 mL) were stirred at 60 °C for 3 hours. After cooling at room temperature, water (8 mL) was added. The precipitate was collected by filtration and washed with water and analyzed by ^{1}H NMR.

4. Competition reaction between sodium *p*-toluenesulfinate and sodium methanesulfinic acid

A mixture of 0.15 g of 2-nitrobenzaldehyde, 0.1 g of sodium methanesulfinic acid (1 eq), 0.17 g of sodium *p*-toluenesulfinic acid (1 eq), and 0.312 g of $NaHSO_3$ (3 eq) in water (2 mL) were stirred at 60 °C for 3h. After cooling to room temperature, the precipitate was collected and analyzed by NMR. Next, the filtrate was extracted with 3 x 5 mL of ethyl acetate and the organic phase was separated and dried over Na_2SO_4, before the solvent was evaporated. The precipitate was mixed with the organic extract and the mix was analyzed via ^{1}H NMR.

4-methyl-*N*-phenylbenzenesulfonamide (Table 3, entry 1) ($C_{13}H_{13}NO_2S$): yellow oil, yield 33%.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.75 (d, ^3J = 8.3 Hz, 2H, ArH), 7.68 (br s, 1H, ArH), 7.22 (br d, ^3J = 7.6 Hz, 3H, ArH), 7.16 (br d, ^3J = 8.5 Hz, 2H, ArH), 7.12-7.07 (m, 1H, ArH), 2.37 (s, 3H, CH_3).^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 166.7, 143.6, 142.0, 136.4, 130.7, 129.8, 126.7, 125.5, 118, 20.9.

***N*-(2-formylphenyl)-4-methylbenzenesulfonamide (Table 3, entry 2)**($C_{14}H_{13}NO_3S$): white powder, Yield 73%.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 10.79 (s, 1H, NH), 9.83 (s, 1H, CHO), 7.77 (d, ^3J = 8.2 Hz, 2H, ArH), 7.68 (d, ^3J = 8.4 Hz, 1H, ArH), 7.59 (dd, ^3J = 7.6, ^4J = 1.5 Hz, 1H, ArH), 7.55 – 7.45 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.5 Hz 1H, ArH), 7.24 (d, ^3J = 8.2 Hz, 2H, ArH), 7.16 (ddd, ^3J = 7.5, ^3J = 7.5, ^4J = 0.9 Hz, 1H, ArH), 2.36 (s, 3H, CH_3).^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 195.1, 144.3, 140.0, 136.2, 135.9, 129.8, 127.4, 123.0, 121.9, 117.8, 21.6.

***N*-(3-formylphenyl)-4-methylbenzenesulfonamide (Table 3, entry 3)** ($C_{14}H_{13}NO_3S$): white powder, Yield 35%.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 9.91 (s, 1H, CHO), 7.70 (d, ^3J = 8.1 Hz, 2H, ArH), 7.64 – 7.54 (m, 2H, ArH), 7.42 (m, 3H, ArH), 7.24 (d, ^3J = 8.1 Hz, 2H, ArH), 2.37 (s, 3H, CH_3).^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 191.7, 144.5, 137.9, 137.4, 135.8, 130.2, 130.0, 127.3, 126.8, 126.4, 121.5, 21.6.

***N*-(4-formylphenyl)-4-methylbenzenesulfonamide (Table 3, entry 4)** ($C_{14}H_{13}NO_3S$): white powder, Yield 55%. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 10.96 (s, 1H, NH), 9.80 (s, 1H, CHO), 7.75 (br t, ^3J = 8.7 Hz, 4H, ArH), 7.37 (d, ^3J = 8.0 Hz, 2H, ArH), 7.28 (d, ^3J = 8.6 Hz, 2H, ArH), 2.32 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 191.5, 143.8, 143.5, 136.5.4, 136.2, 131.3, 131.1, 129.9, 126.7, 118.0, 20.9.

***N*-(3-acetylphenyl)-4-methylbenzenesulfonamide (Table 3, entry 6)** ($C_{15}H_{15}NO_3S$): white powder, Yield 25%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 7.67-7.61 (m, 4H, ArH), 7.41-7.31 (m, 4H, ArH), 2.49 (s, 3H, CH_3), 2.31 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 197.3, 143.4, 138.4, 137.6, 136.5, 129.7, 129.6, 126.7, 124.1, 118.4, 26.6, 20.9.

***N*-(4-acetylphenyl)-4-methylbenzenesulfonamide (Table 3, entry 7)** ($C_{15}H_{15}NO_3S$): white powder, Yield 60%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 10.80 (s, 1H, NH), 7.82 (br d, ^3J = 8.9 Hz, 2H, ArH), 7.72 (br d, ^3J = 8.3 Hz, 2H, ArH), 7.36 (br d, ^3J = 8.5 Hz, 2H, ArH), 7.20 (br d, ^3J = 8.9 Hz, 2H, ArH), 2.45 (s, 3H, CH_3), 2.32 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 196.2, 143.6, 142.3, 136.2, 131.8, 129.8, 129.7, 126.7, 117.8, 26.3, 20.9.

2-((4-methylphenyl)sulfonamido)benzoic acid (Table 3, entry 8) ($C_{14}H_{13}NO_4S$): white powder, Yield 75%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 11.16 (br s, 1H, COOH), 7.88 (br d, ^3J = 8.5 Hz, 1H, ArH), 7.70 (d, ^3J = 8.3 Hz, 2H, ArH), 7.59 – 7.47 (m, 2H, ArH), 7.35 (d, ^3J = 8.0 Hz, 2H, ArH), 7.10 (ddd, ^3J = 8.2 Hz, ^3J = 6.2 Hz, ^4J = 2.2 Hz, 1H, ArH), 2.32 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 168.8, 144.2, 139.9, 134.5, 131.5, 129.9, 126.9, 123.2, 118.2, 116.5, 20.9.

3-((4-methylphenyl)sulfonamido)benzoic acid (Table 3, entry 9) ($C_{14}H_{13}NO_4S$): white powder, Yield 44%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 12.75 (br s, 1H, COOH), 10.43 (br s, 1H, NH), 7.69 (m, 1H, ArH), 7.66-7.63 (dd, ^3J = 8.13 Hz, ^4J = 1.5 Hz, 2H, ArH), 7.58 (m, 1H, ArH), 7.34 (d, ^3J = 6.7 Hz, 4H, ArH), 2.30 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 167, 143.7, 138.4, 136.7, 132.2, 130, 126.7, 126.9, 125, 124, 120.6, 21.2.

4-((4-methylphenyl)sulfonamido)benzoic acid (Table 3, entry 10) ($C_{14}H_{13}NO_4S$): white powder, Yield 23%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 12.72 (br s, 1H, COOH), 10.74 (s, 1H, NH), 7.80 (d, ^3J = 8.7 Hz, 2H, ArH), 7.71 (d, ^3J = 8.3 Hz, 2H, ArH), 7.36 (d, ^3J = 8.0 Hz, 2H, ArH), 7.19 (d, ^3J = 8.7 Hz, 2H, ArH), 2.30 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6, 75

MHz): δ (ppm) 166.7, 143.6, 142.0, 136.4, 130.7, 129.8, 126.7, 125.5, 118.0, 20.9.

3-((4-methylphenyl)sulfonamido)-5-(phenylsulfonamido)benzoic acid (Table 3, entry 11) ($C_{21}H_{20}N_2O_6S_2$): white solid, yield 30%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 13.08 (s, 1H, COOH), 10.48 (s, 2H, NH), 7.72 (d, ^3J = 8.7 Hz, 1H, ArH), 7.69-7.40 (m, 4H, ArH), 7.44 (d, ^3J = 2 Hz, 1H, ArH), 7.51-7.40 (m, 4H, ArH), 6.74 (dd, ^3J = 8.7 Hz,^{4}J = 2.1 Hz, 1H, ArH), 2.33 (s, 6H).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 166.2, 143.4, 138.9, 136.2, 132.3, 129.7, 126.6, 115.2, 20.9.

4-((4-methylphenyl)sulfonamido)-2-(phenylsulfonamido)benzoic acid (Table 3, entry 12) ($C_{21}H_{20}N_2O_6S_2$): white solid, yield 20%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 11.58 (s, 1H, COOH), 10.90 (s, 2H, NH), 7.58 (d, ^3J = 8.1 Hz, 4H, ArH), 7.37-7.35 (m, 1H, ArH), 7.32 (d, ^3J = 8.1 Hz, 4H, ArH), 7.26 (d, ^3J = 2 Hz, 2H, ArH), 2.33 (s, 6H).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 169.4, 143.7, 143.1, 141.5, 136.2, 135.4, 132.7, 129.8, 126.9, 126.7, 112.2, 110.8, 106, 21.

***N*-(5-(dimethylamino)-2-formylphenyl)-4-methylbenzenesulfonamide (Table 3, entry 13)** ($C_{16}H_{18}N_2O_3S$): orange solid, Yield 78 %.^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 11.27 (s, 1H, NH), 9.48 (s, 1H, CHO), 7.78 (d, ^3J = 8.3 Hz, 2H, ArH), 7.29 (d, ^3J = 8.8 Hz, 1H, ArH), 7.23 (d, ^3J = 8.1 Hz, 2H, ArH), 6.82 (d, ^3J = 2.3 Hz, 1H, ArH), 6.32 (dd, ^3J = 8.8, ^4J = 2.4 Hz, 1H), 3.05 (s, 6H, CH_3N), 2.36 (s, 3H, CH_3).^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 191.7, 154.7, 143.9, 142.2, 137.9, 129.7, 127.5, 112.2, 106.4, 99.2, 40.3, 21.6.

***N*-(5-bromo-2-formylphenyl)-4-methylbenzenesulfonamide (table 3 entry 14)** ($C_{14}H_{12}BrNO_3S$): white solid, Yield 38%.^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 10.67 (s, 1H, NH), 9.94 (s, 1H, CHO), 7.74 (d, ^3J = 8.3 Hz, 1H, ArH), 7.61 (d, ^3J = 8.3 Hz, 2H, ArH), 7.55 (dd, ^3J = 8.3, ^4J = 1.8 Hz, 1H, ArH), 7.39 (d, ^3J = 8.0 Hz, 2H, ArH), 7.30 (d, ^3J = 1.8 Hz, 1H, ArH), 2.36 (s, 3H, CH_3).^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 192, 144.5, 139.9, 135.4, 133.4, 130.1, 128.6, 127, 126.5, 125.2, 21.1.

***N*-(3-bromo-5-formyl-4-hydroxyphenyl)-4 methylbenzenesulfonamide (table 3, entry 15)** ($C_{14}H_{12}BrNO_4S$): yellow solid, Yield 40%.^{1}H NMR (300 MHz, DMSO-d$_6$) δ (ppm) 10.93 (s, 1H, CHO), 10.25 (s, 1H), 10.04 (s, 1H), 7.70 (t, ^{3}J = 8.0 Hz, 1H, ArH), 7.60 (d, ^{3}J = 8.3 Hz, 2H, ArH), 7.53 (d, ^{3}J = 8.2 Hz, 1H, ArH), 7.47 (dd, ^{3}J = 14.6, ^{4}J = 2.6 Hz, 2H, ArH), 7.35 (d, ^{3}J = 8.0 Hz, 2H, ArH), 2.33 (s, 3H, CH3).^{13}C NMR (75 MHz, DMSO- d$_6$) δ (ppm) 193.2, 153.7, 143.5, 136, 131.8, 130.8, 129.8, 126.7, 123.2, 122.3, 111.8, 20.9.

2-chloro-5-((4-methylphenyl)sulfonamido)benzoic acid (table 3 entry 16) ($C_{14}H_{12}ClNO_4S$): white solid, Yield 30%.^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 13.53 (s, 1H, COOH), 10.56 (s, 1H, NH), 7.65 (d, ^3J = 8.3 Hz, 1H, ArH), 7.49 (d, ^3J = 2.7 Hz, 1H, ArH), 7.42 (s, 1H, ArH), 7.39 (d, ^3J = 4.6 Hz, 1H, ArH), 7.35 (s, 1H, Ar), 7.24 (dd, ^3J = 8.7, ^4J = 2.7 Hz, 1H, ArH), 2.34 (s, 1H, CH_3).^{13}C NMR (75 MHz, DMSO- d_6) δ (ppm) 166, 143.6, 136.8, 136.1, 131.5, 129.8, 126.5, 123.2, 121.4, 20.9

***N*-(2-formylphenyl)benzenesulfonamide (Table 4, entry 1)** ($C_{13}H_{11}NO_3S$):white solid, yield 32%.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 10.82 (s, 1H, NH), 9.83 (s, 1H, CHO), 7.89 (m, 2H, ArH), 7.70 (d, ^3J = 8.4 Hz, 1H, ArH), 7.60 (dd, ^3J = 7.6, ^4J = 1.5 Hz, 1H, ArH), 7.55 – 7.50 (m, 2H), 7.48 (m, 2H), 7.17 (td, ^3J = 7.5, ^4J = 0.9 Hz, 1H, ArH).^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 195.1, 136.2, 135.9, 133.3, 129.2, 127.3, 123.2, 117.9.

4-chloro-*N*-(2-formylphenyl)benzenesulfonamide (Table 4, entry 3) ($C_{13}H_{10}NO_3SCl$):white solid, yield 58%.^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 10.81 (s, 1H, NH), 9.83 (s, 1H, CHO), 7.86 – 7.77 (m, 2H, ArH), 7.69 (br d, ^3J = 8.4 Hz, 1H, ArH), 7.62 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, ArH), 7.55 (ddd, ^3J = 7.6 Hz, ^3J = 7.6 Hz, ^4J = 1.6 Hz, 1H, ArH), 7.46 – 7.38 (m, 2H, ArH), 7.21 (ddd, ^3J = 7.5 Hz, ^3J = 7.5 Hz, ^4J = 1.0 Hz, 1H, ArH).^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) 195.0, 136.3, 136, 129.6, 128.8, 123.4, 118.1.

N-(2-formylphenyl)methanesulfonamide (Table 4, entry 4) ($C_8H_9NO_3S$): yellow crystals, yield 55%.^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) 10.25 (s, 1H, NH), 10.07 (s, 1H, CHO), 7.90 (dd, ^3J = 7.7 Hz, ^4J = 1.5 Hz, 1H, ArH), 7.78 – 7.66 (ddd, ^3J = 7.8 Hz, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H, ArH), 7.53 (d, ^3J = 8.2 Hz, 1H, ArH), 7.38 (ddd, ^3J = 8.3 Hz, ^3J = 8.3 Hz, ^4J = 1.7 Hz, 1H, ArH), 3.16 (s, 3H, CH_3).^{13}C NMR (DMSO-d_6, 75 MHz): δ (ppm) 193.8, 139.4, 135.6, 133, 125.8, 125.6, 124.4, 120.7.

Keywords: green chemistry• synthesis on water•catalyst free• purification free•sulfonamides•Sustainable

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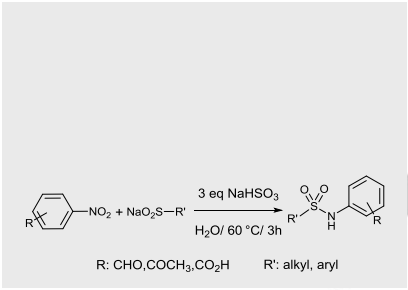
A green, sustainable and chemoselective synthesis of sulfonamides using sodium sulfinate as a commercial and stable sulfur source and nitro arenes as nitrogen-containing reactant is described. The optimized conditions use water as the solvent and the pure products are collected by simple filtration. This method is easily scalable and protecting group free because of the high functional tolerance.



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Straightforward and sustainable synthesis of sulfonamides in water under mild conditions

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