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# Hypervalent Iodine mediated sulfonamide synthesis

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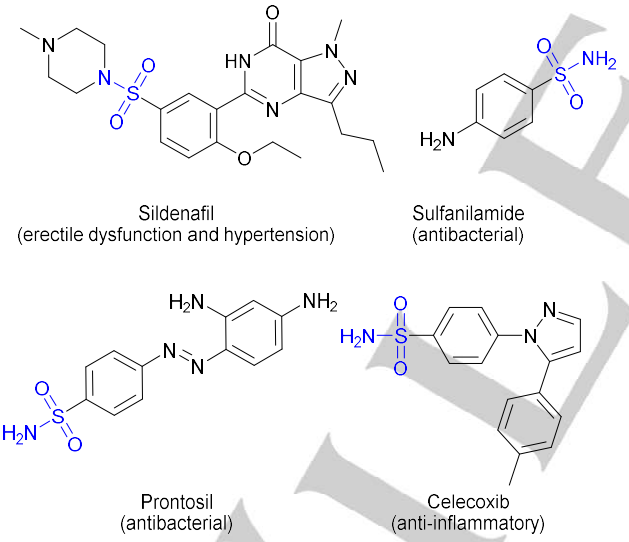
**Abstract:** A new metal-free sulfonylation reaction is described. The method takes advantage of the umpolung reactivity and group transfer properties of iodine(III) compounds, combining hypervalent iodine reagents and sulfinate salts to deliver a clean and mild transfer of sulfonyl groups to amines and anilines. A total of 25 sulfonamides were synthesised in up to 99% yield, even in a gram-scale. The reaction mechanism was investigated by ESI-MS and DFT calculations.

## Introduction

The sulfonyl group is present in many compounds, such as natural products, marketed therapeutics and materials.[1] In particular, the sulfonamide pharmacophore is present in many pharmaceutical agents, e.g. antimicrobial, anti-inflammatory, [2] or anti-hypertensive drugs. Its medicinal significance can be traced to the 30´s with the discovery of the so called "sulfa drugs" (Scheme 1).[1]




**Scheme 1** Examples of "sulfa drugs" currently in the pharmaceutical market.

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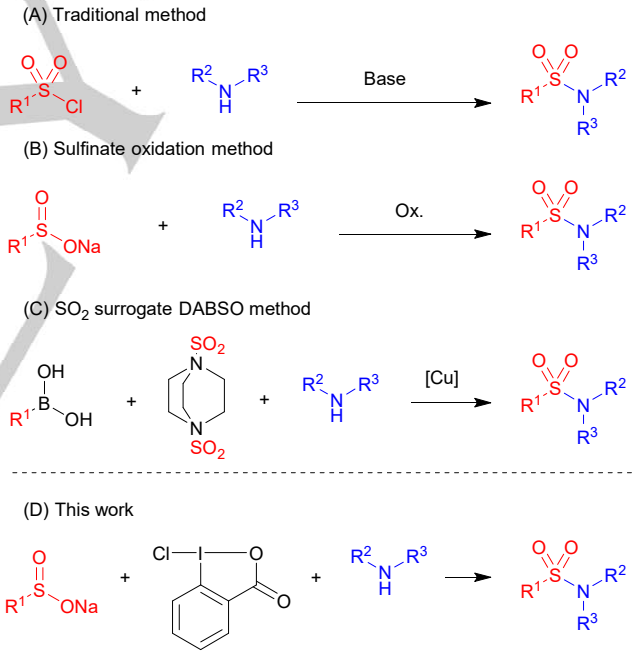
The classic method for the synthesis of sulfonamides involves the reaction between an amine and a sulfonyl chloride, in the presence of a base (Scheme 2A).[3] Other methods include metal-catalysed reactions of unsubstituted or mono-substituted sulfonamides,[4] oxidation of sulfonamides or sulfinimides,[5] oxidative coupling reactions between sulfinate salts and amines (Scheme 2B).[6-8] These methods either use harsh conditions, non-environmentally friendly reagents or are limited in scope. Recently, DABSO (a complex of 1,4-diazabicyclo[2.2.2]octane with two molecules of SO2) has been widely explored on sulfonylation reactions as a SO2 surrogate (Scheme 2C).[9] DABSO can be applied to sulfonamide synthesis from amines however, it requires the use of metal catalysts and/or organometallic reagents.[10]




**Scheme 2** Current methods for sulfonamide synthesis.

Despite the progress in this field, there is a still room for improvement in a metal-free, versatile and fast methodology towards sulfonamides compatible with the use of amines.

The exceptional properties of benziodoxolone-derived reagents have attracted the attention of the scientific community for both carbon and hetero-atom transfer reactions.[11, 12]

Benziodoxolone-derived iodine(III) compounds are characterized by the presence of an endocyclic iodine, which confers stability, while inverting the polarity of an attached moiety, proving conditions for an umpolung reaction.

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Recently, the use of these reagents on heteroatom transfer reactions became a major field of study.[12-14]

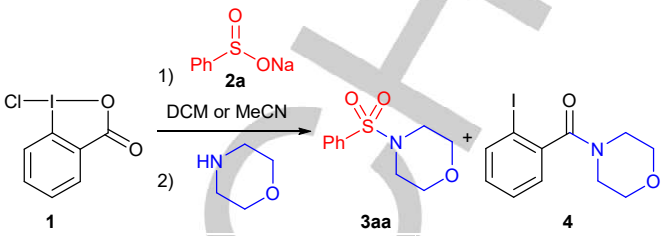
Herein, we describe a novel fundamental oxidative process for preparing sulfonamides. The method involves the sulfonyl group transfer from hypervalent iodine adducts to amines. This strategy circumvents the use of metal catalysts and sulfonyl chlorides and allows the development of an environmentally friendly alternative (Scheme 2D). In addition, similar works have been reported for the formation of sulfonates[15] and sulfones.[16]

## Results and Discussion

We initiated our studies with the synthesis of the chlorine-bearing benziodoxolone **1** in quantitative yield using Togni's protocol, where oxidation and chlorination of **2**-iodobenzoic acid is performed in one step.[13] In order to produce a sulfonyl-transfer reagent, benziodoxolone **1** was mixed with sodium phenylsulfonate **2a**. Attempts to isolate a stable product failed, however, in situ addition of morpholine to the reaction medium resulted in the formation of sulfonamide **3aa** in 40% yield (Table 1, entry 1). Benziodoxolone **1**, sodium phenylsulfonate **2** and morpholine were used as the standard reagents for the optimization of the reaction conditions (Table 1). It was shown that lowering the amount of **2a** from 1.5 to 1.0 equiv resulted in a decreased yield of the desired product **3aa** (40 vs 28%, entry 2). Due to the low reagents' solubility, 1.5 equiv of tetrabutylammonium iodide (TBAI) was added and the solvent changed to dichloromethane.[14] This resulted in an improved 61% yield of **3aa**, along with formation of an undesired amide product **4** (entry 3).

Next, the reaction time and temperature's effects were studied. The reaction time was reduced from 30 min to 15 min and 16 h to 2 h, for steps 1) and 2) respectively, with no significantly change in the yields of **3aa** and **4** (entry 4). Reduction of the reaction temperature to RT and -40 °C resulted in decreased yields of **4** (32 and 3%, respectively) while maintaining similar yields of **3aa** (entries 5 and 6). With these results in mind, lower amounts of TBAI were tested. Gratifyingly, sulfonamide **3aa** was isolated in higher yields (84 and 98% with 0.5 and 0.2 equiv of TBAI, respectively) and no trace of **4** (entries 7 and 8) was observed. Several control experiments were carried out to further understand the mechanism of the reaction. It was shown that amide **4** is only obtained in the presence of TBAI at RT (entry 9). While **4** was not observed in the absence of TBAI, either at RT or -40 °C (entries 10 and 11), yields of **3aa** decreased. These results suggest that TBAI has a role in the formation of amide **4**, while being important in the enhancement of sulfonamide **3aa** formation. Performing the reaction in MeCN with TBAI gave similar results (entries 12 and 13). Furthermore, replacing TBAI by TBAC (tetrabutylammonium chloride) gave only 55% of **3aa** (entry 14), comparable with the 59% yield of **3aa** obtained in the absence of any additive (entry 10). This suggests that the presence of TBAI is crucial for the outcome of the reaction, with the iodine anion possibly playing a role in the reaction's mechanism.

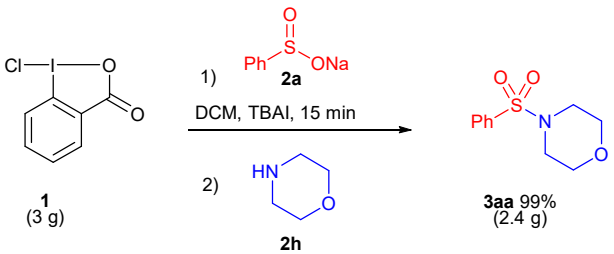
**Table 1**. Optimization of the reaction conditions.




| Entry[a] | Solvent | Additive (equiv) | T (°C) | Time[b] 1)/2) (h) | Yield[c] **3a/4** (%) |
|---|---|---|---|---|---|
| 1 | MeCN | -- | 82 | 1/16 | 40/NO |
| 2[d] | MeCN | -- | 82 | 1/16 | 28/NO |
| 3 | DCM | TBAI (1.5) | 40 | 0.5/16 | 61/38 |
| 4 | DCM | TBAI (1.5) | 40 | 0.25/2 | 53/40 |
| 5 | DCM | TBAI (1.5) | RT | 0.25/2 | 60/32 |
| 6 | DCM | TBAI (1.5) | -40 | 0.25/2 | 62/3 |
| 7 | DCM | TBAI (0.5) | -40 | 0.25/2 | 84/NO |
| **8** | **DCM** | **TBAI (0.2)** | **-40** | **0.25/2** | **98/NO** |
| 9 | DCM | TBAI (0.2) | RT | 0.25/2 | 56/43 |
| 10 | DCM | -- | -40 | 0.25/2 | 59/NO |
| 11 | DCM | -- | RT | 0.25/2 | 68/NO |
| 12 | MeCN | TBAI (0.2) | -40 | 0.25/2 | 96/NO |
| 13 | MeCN | TBAI (0.2) | RT | 0.25/2 | 54/31 |
| 14 | DCM | TBAC (0.2) | -40 | 0.25/2 | 55/NO |

[a] All experiments were carried out under the following conditions: 1) 0.18 mmol of chlorobenziodoxolone (**1**) with 0.28 mmol of sodium benzenesulfinate (**2a**, 1.5 equiv) in 1 mL of DCM or MeCN; 2) 0.28 mmol of morpholine (1.5 equiv) was added to the reaction mixture; [b] 1) refers to the time of the first step, 2) refers to the time of the second step (after the addition of morpholine); [c] Isolated yields. NO – Not Observed; [c] 0.18 mmol of **2a** (1 equiv) was used.

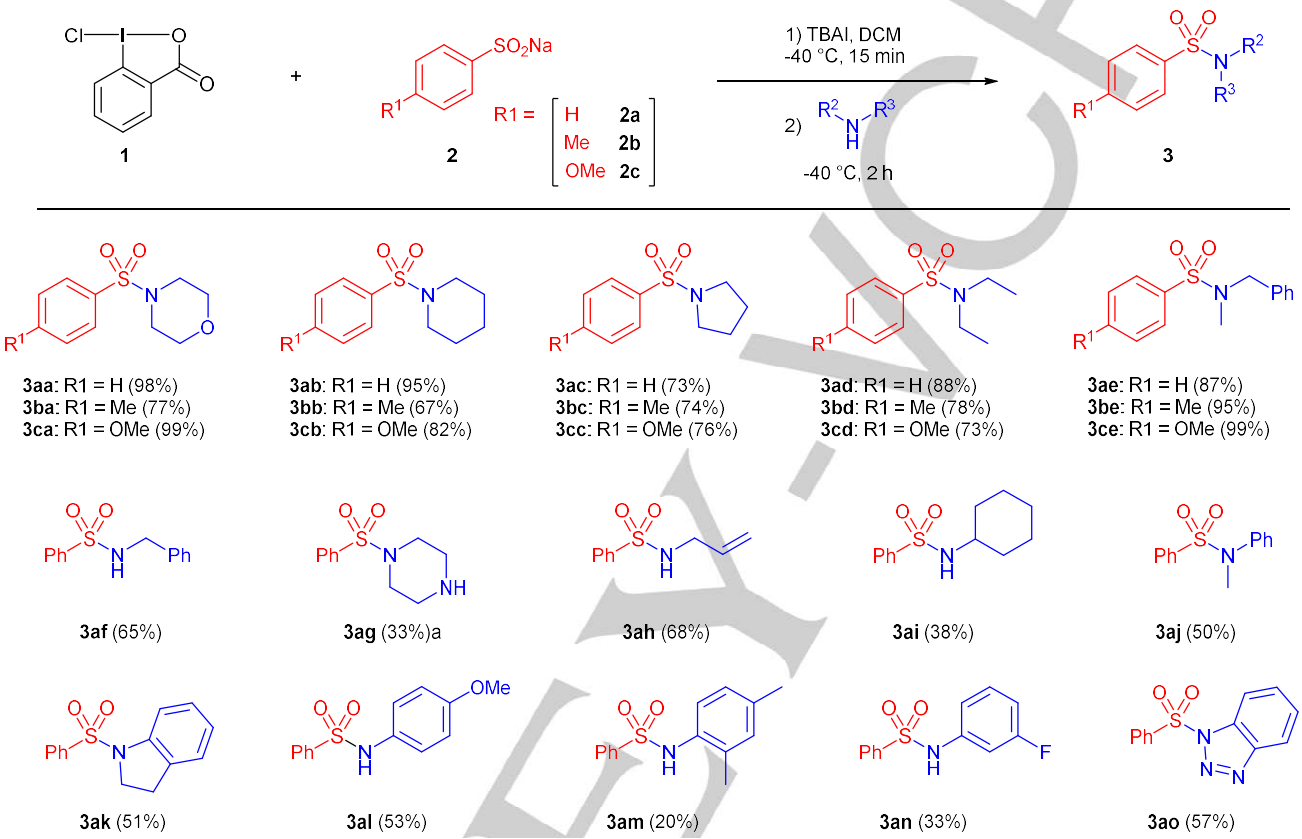
With the optimized conditions in hand, a large-scale experiment (using 10.6 mmol of **1**) was performed, resulting in a quantitative yield of **3aa** (Scheme 3).




**Scheme 3** Gram scale synthesis of **3aa**.

Further studies were performed to investigate a possible radical mechanism and the influence of the temperature in both steps (see SI). On the basis of these studies, it was concluded that the reaction does not undergo a radical mechanism, as when the reaction was carried out in the presence of TEMPO, there were no significant changes in the yields of both sulfonamide **3aa** and amide **4**.

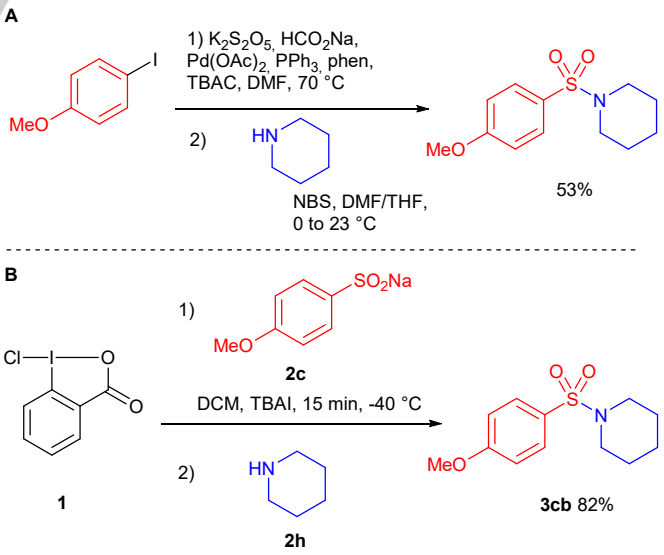
**Table 2.** Synthesis of sulfonamides from sulfinate salts and amines or anilines.




We next studied the scope of the reaction (Table 2). For the sulfinate salt **2a**, secondary aliphatic amines offered higher yields than primary amines (**3aa**, **3ab**, **3ac**, **3ad**, **3ae**, up to 98% yield vs **3af**, **3ah**, **3ai** up to 68% yield).

Distinctly, the bifunctional secondary aliphatic amine – piperazine – gave product **3ag** in 33% yield (with 1 equiv of piperazine). The use of anilines resulted in lower overall yields, e.g. sulfonamide **3aj** (50%), **3ak** (51%), **3al** (53%), **3am** (20%) and **3an** (33%). Salt **2a** was also tested with benzotriazole, and compound **3ao** was obtained in 57% yield. Comparing the three sulfinate salts **2a**, **2b** and **2c**, the corresponding sulfonamides **3aa**-**3ae**, **3ba**-**3be** and **3ac**-**3ce**, were generally obtained in higher yields when the sodium p-methoxybenzene sulfinate **2c** was used, possibly due to a p-MeO group activation.

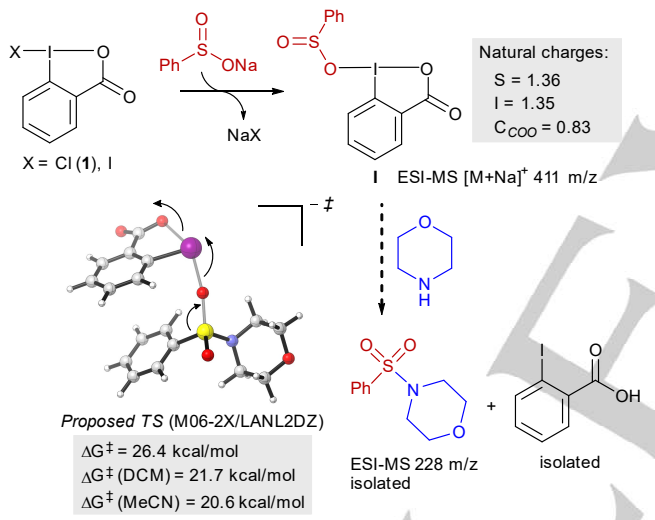
Between the sodium benzene sulfinate **2a** and the sodium p-methylbenzene sulfonate **2b**, the results are similar. In addition, sulfonamide **3cb** was prepared in 82% yield by this method. The same sulfonamide was prepared by Pfizer in 53%, using a one-pot two step procedure where an aryl halogen is




**Scheme 4** Comparison of Pfizer's method and the herein reported method for the synthesis of **3cb**.

sulfonylated using $K_2S_2O_5$ as $SO_2$ source and an amine (Scheme 4).[17]The reaction mechanism was then investigated by a combination of ESI-MS analysis and density functional theory (DFT) calculations (Scheme 5). Reaction of **1** with sodium benzenesulfinate **2a** in the absence of morpholine revealed a mass signal of 411 m/z by ESI-MS analysis. This mass was tentatively attributed to **I**, which could be a reaction intermediate formed through displacement of the halide atom of the benziodoxolone by the benzenesulfinate. In this context, the role of TBAI in the reaction could be attributed to the formation of iodine-bearing benziodoxolone via reaction of iodine atom of TBAI with **1**. DFT analysis of I suggest that sulfur is the most electrophilic center (see natural charges depicted in Scheme 5).

Thus, a possible reaction mechanism including intermediate **I** involves the addition of amine into the sulfur center. DFT calculations suggested an energy barrier of 20.6 kcal mol$^{-1}$ (via calculated proposed TS structure) for the consequent concerted sulfur oxidation/iodine reduction to yield the corresponding sulfonamide product and 2-iodobenzoic acid.




**Scheme 5** Proposed reaction mechanism.

## Conclusions

In conclusion, a new sulfonylation method was developed relying on the use of a hypervalent iodine reagent. The established protocol, a reaction between a sulfinate salt and a benziodoxolone-derived reagent, followed by in situ addition of an amine, proved to be versatile and compatible with both aliphatic and aromatic amines. The corresponding sulfonamides were obtained in moderate to excellent yields, also in a highly efficient gram scale.

A plausible mechanism for this transformation was proposed on the basis of ESI-MS data and DFT calculations. The results suggested the formation of a reactive intermediate, that delivers the final sulfonamide. The protocol herein described consists on a versatile platform for implementation of the sulfonylation method into drug optimization and drug discovery processes, avoiding harsh conditions, the use of sulfonyl chlorides and metal catalysts as used in alternative approaches.

## Experimental Section

**Synthesis of 1-chloro-1,2-benziodoxol-3-(1H)-one (1)[13]**

A round-bottom flask was charged with 2-iodobenzoic acid (500 mg, 2 mmol) and dissolved in 4 mL of acetonitrile. The mixture stirred at 82 °C until full dissolution was observed. A solution of TCICA (155 mg, 0.67 mmol) in a 1 ml of hot acetonitrile was then added to the mixture. The resulting mixture was stirred at 82 °C for 10 min and, while still hot, filtered through a hot Hirsch funnel and washed with hot acetonitrile. The resulting solution was concentrated under vacuum, affording 1-chloro-1,2-benziodoxol-3-(1H)-one (1) as a white solid in 98% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 8.26 (d, *J* = 7.4 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.99 (t, *J* = 7.2 Hz, 1H), 7.80 (t, *J* = 7.3 Hz, 1H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 167.3, 136.8, 133.6, 132.0, 128.8, 127.0, 117.2.

**General procedure for sulfinate salts synthesis**

A round-bottom flask was charged with a sulfonyl chloride (11 mmol), sodium sulfite (24 mmol), sodium hydrogencarbonate (22 mmol) and dissolved in 40 mL of water. The mixture stirred at 100 °C for 4 h. After cooled to room temperature, the water was evaporated and the mixture was extracted three times with hot ethanol. The resulting product was recrystallized from ethanol and filtered.

**Sodium 4-methylbenzenesulfinate (2b)**

Prepared according to the general procedure and obtained as a white solid in 74% yield. $^1$H NMR (400 MHz, DMSO) $\delta_H$ = 7.37 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 7.7 Hz, 2H), 2.28 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) $\delta_C$ = 156.9, 136.8, 128.2 (2C), 124.3 (2C), 20.8.

**Sodium 4-methoxybenzenesulfinate (2c)**

Prepared according to the general procedure and obtained as a white solid in 66% yield. $^1$H NMR (400 MHz, DMSO) $\delta_H$ = 7.40 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 3.74 (s, 3H). $^{13}$C NMR (101 MHz, DMSO) $\delta_C$ = 159.0, 152.1, 125.7 (2C), 112.9 (2C), 55.1.

**General procedure for sulfonamide synthesis.**

A round-bottom flask was charged with chlorobenziodoxolone (50 mg, 0.18 mmol), the sulfinate salt (0.27 mmol, 1.5 equiv.) and tetrabutylammonium iodine (41.4 µmol, 0.2 equiv.). To the solids, 1 mL of dichloromethane was added and the reaction was stirred at -40 °C for 15 min. The amine (0.28mmol, 1.5 equiv.) was then added and the reaction was stirred at -40 °C for 2 h. When completed, the reaction was allowed to warm up to room temperature, washed with water, saturated sodium hydrogencarbonate solution and brine. The resulting organic phase was dried with sodium sulfate, filtered and concentrated under vacuum. The crude was purified using preparative thin layer chromatography or flash chromatography with ethyl acetate/hexane.

**4-(phenylsulfonyl)morpholine (3aa)[18]**

Prepared according to the general procedure. Freshly distilled morpholine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a white solid in 98% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.76 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 2H), 3.74 (t, *J* = 4.6 Hz, 4H), 3.00 (t, *J* = 4.5 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 135.3, 133.2, 129.3 (2C), 128.0 (2C), 66.2 (2C), 46.1 (2C).

**4-tosylmorpholine (3ba)[8]**
Prepared according to the general procedure. Freshly distilled morpholine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a light-yellow solid in 77% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.61 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.70 (t, *J* = 4.7, 4H), 2.95 (t, *J* = 4.6, 4H), 2.41 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 144.0, 132.1, 129.8 (2C), 127.9 (2C), 66.1 (2C), 46.0 (2C), 21.6.

**4-[(4-methoxyphenyl)sulfonyl]morpholine (3ca)[8]**
Prepared according to the general procedure. Freshly distilled morpholine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (4:6) gave the title product as a light-yellow solid in 99% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.69 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H), 3.77 – 3.70 (m, 4H), 2.97 (t, *J* = 4.5 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 163.4, 130.1 (2C), 126.8, 114.4 (2C), 66.2 (2C), 55.8, 46.1 (2C).

**1-(phenylsulfonyl)piperidine (3ab)[18]**
Prepared according to the general procedure. Freshly distilled piperidine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a yellow solid in 95% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.75 (d, 2H, *J* = 7.7 Hz), 7.59 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 2H), 2.98 (t, *J* = 5.5, 4H), 1.67 – 1.60 (m, 4H), 1.45 – 1.37 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 136.4, 132.7, 129.0 (2C), 127.7 (2C), 47.0 (2C), 25.3 (2C), 23.6.

**1-tosylpiperidine (3bb)[19]**
Prepared according to the general procedure. Freshly distilled piperidine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:4) gave the title product as a light-yellow solid in 67% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.63 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.96 (t, *J* = 5.4, 4H), 2.42 (s, 3H), 1.67 – 1.58 (m, 4H), 1.45 – 1.36 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 143.4, 133.4, 129.7 (2C), 127.8 (2C), 47.1 (2C), 25.3 (2C), 23.6, 21.6.

**1-[(4-methoxyphenyl)sulfonyl]piperidine (3cb)[17]**
Prepared according to the general procedure. Freshly distilled piperidine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:8) gave the title product as a white solid in 82% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.68 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 2.95 (t, *J* = 5.4 Hz, 4H), 1.66 – 1.60 (m, 4H), 1.44 – 1.36 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 163.0, 129.9 (2C), 128.1, 114.2 (2C), 55.7, 47.1 (2C), 25.3 (2C), 23.7.

**1-[(4-methoxyphenyl)sulfonyl]pyrrolidine (3cc)[20]**
Prepared according to the general procedure. Freshly distilled pyrrolidine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a white solid in 76% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.76 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 3.87 (s, 3H), 3.21 (t, *J* = 6.6 Hz, 4H), 1.74 (t, *J* = 6.6 Hz, 4H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 163.0, 129.7 (2C), 128.7, 114.2 (2C), 55.7, 48.0 (2C), 25.3 (2C).

***N,N*-diethylbenzenesulfonamide (3ad)[18]**
Prepared according to the general procedure. Freshly distilled diethylamine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a light-yellow solid in 88% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.78 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.3 Hz, 1H), 7.47 (t, *J* = 7.3 Hz, 2H), 3.22 (q, *J* = 7.1 Hz, 4H), 1.10 (t, *J* = 7.2 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 140.5, 132.3, 129.1 (2C), 127.1 (2C), 42.1 (2C), 14.2 (2C).

***N,N*-diethyl-4-methylbenzenesulfonamide (3bd)[6]**
Prepared according to the general procedure. Freshly distilled diethylamine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a light-yellow oil in 78% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.65 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.19 (q, *J* = 7.1 Hz, 4H), 2.37 (s, 3H), 1.09 (t, *J* = 7.2 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 143.0, 137.4, 129.6 (2C), 127.0 (2C), 42.0 (2C), 21.5, 14.2 (2C).

***N,N*-diethyl-4-methoxybenzenesulfonamide (3cd)[18]**
Prepared according to the general procedure. Freshly distilled diethylamine stored under 3 Å molecular sieves was used. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a colourless oil in 73% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.72 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 3.20 (q, *J* = 7.1 Hz, 4H), 1.10 (t, *J* = 7.1 Hz, 6H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 162.7 (s), 132.2 (s), 129.1 (2C), 114.2 (2C), 55.7 (s), 42.0 (2C), 14.2 (2C).

***N*-benzyl-*N*-methylbenzenesulfonamide (3ae)[21]**
Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane (1:3) gave the title product as a white solid in 87% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.85 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 2H), 7.37 – 7.28 (m, 5H), 4.15 (s, 2H), 2.61 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 137.5, 135.7, 132.8, 129.3 (2C), 128.8 (2C), 128.5 (2C), 128.0, 127.5 (2C), 54.2, 34.4.

***N*-benzyl-*N*,4-dimethylbenzenesulfonamide (3be)[6]**
Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane (1:4) gave the title product as a white solid in 95% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.73 (d, *J* = 8.1 Hz, 2H), 7.40 – 7.26 (m, 7H), 4.12 (s, 2H), 2.58 (s, 3H), 2.46 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 143.6, 135.8, 134.5, 129.9 (2C), 128.8 (2C), 128.5 (2C), 128.0, 127.7 (2C), 54.3, 34.5, 21.7.

***N*-benzyl-4-methoxy-*N*-methylbenzenesulfonamide (3ce)[22]**
Prepared according to the general procedure. Purification by flash chromatography using ethyl acetate/hexane (1:4) gave the title product as a white solid in 99% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.78 (d, *J* = 8.8 Hz, 2H), 7.36 – 7.28 (m, 5H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.12 (s, 2H), 3.89 (s, 3H), 2.58 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 163.1, 135.8, 129.7 (2C), 129.1, 128.8 (2C), 128.5 (2C), 128.0, 114.4 (2C), 55.8, 54.3 (s), 34.5.

***N*-benzylbenzenesulfonamide (3af)[8]**
Prepared according to the general procedure. Freshly distilled benzylamine stored under 3 Å molecular sieves was used. Purification by thin layer chromatography using ethyl acetate/hexane (1:3) gave the title product as a white solid in 65% yield. 1H NMR (400 MHz, CDCl3) δH = 7.86 (d, J = 7.7 Hz, 2H), 7.58 (t, J = 7.1 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.30 – 7.13 (m, 5H), 5.02 (s, 1H), 4.14 (d, J = 6.0 Hz, 2H). 13C NMR (101 MHz, CDCl3) δC = 139.98, 136.33, 132.76, 129.20 (2C), 128.73 (2C), 127.94 (2C), 127.16 (2C), 47.30.

**1-(phenylsulfonyl)piperazine (3ag)[23]**
Prepared according to the general procedure. Purification by thin layer chromatography using ethyl acetate/hexane (1:1) gave the title product as a yellow oil in 33% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.74 (d, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.3 Hz, 2H), 3.35 – 3.15 (m, 2H), 3.11 – 2.93 (m, 7H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 135.6, 133.1, 129.3 (2C), 127.9 (2C), 46.2 (2C), 44.0 (2C).

***N*-allylbenzenesulfonamide (3ah)[24]**
Prepared according to the general procedure. Freshly distilled allylamine stored under 3 Å molecular sieves was used. Purification by thin layer chromatography using ethyl acetate/hexane (1:1) gave the title product as a white oil in 68% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.88 (d, *J* = 7.8

Hz, 2H), 7.59 (t, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 5.72 (dq, *J* = 10.7, 5.8 Hz, 1H), 5.09-5.19 (m, 2H), 4.52 (s, 1H), 3.64-3.59 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 140.1, 133.0, 132.9, 129.3 (2C), 127.2 (2C), 118.0, 45.9.

***N*-cyclohexylbenzenesulf0onamide (3ai)[25]**

Prepared according to the general procedure. Freshly distilled ciclohexilamine stored under 3 Å molecular sieves was used. Purification by thin layer chromatography using ethyl acetate/hexane (1:29) gave the title product as a yellow oil in 38% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.89 (d, *J* = 7.4 Hz, 2H), 7.59 – 7.54 (m, 1H), 7.50 (t, *J* = 7.3 Hz, 2H), 4.61 (d, *J* = 6.5 Hz, 1H), 3.21 – 3.07 (m, 1H), 1.78 – 1.70 (m, 2H), 1.66 – 1.59 (m, 2H), 1.54 – 1.47 (m, 1H), 1.24 – 1.04 (m, 5H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 141.6, 132.5, 129.2 (2C), 127.0 (2C), 52.8, 34.1 (2C), 25.3, 24.7 (2C).

***N*-methyl-N-phenylbenzenesulfonamide (3aj)[8]**

Prepared according to the general procedure. Freshly distilled *N*-methylaniline stored under 3 Å molecular sieves was used. Purification by thin layer chromatography using ethyl acetate/hexane (1:3) gave the title product as a brown solid in 50% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.62 – 7.53 (m, 3H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.33 – 7.23 (m, 3H), 7.09 (d, *J* = 6.8 Hz, 2H), 3.18 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 141.6, 136.6, 132.9, 129.0 (2C), 128.9 (2C), 128.0 (2C), 127.5, 126.8 (2C), 38.3.

**1-(phenylsulfonyl)indoline (3ak)[26]**

Prepared according to the general procedure. Indoline stored under 3 Å molecular sieves was used. Purification by thin layer chromatography using ethyl acetate/hexane (1:3) gave the title product as a light-brown solid in 51% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.79 (d, *J* = 7.7 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 3.93 (t, *J* = 8.4 Hz, 2H), 2.88 (t, *J* = 8.4 Hz, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 142.0, 137.1, 133.3, 131.9, 129.1 (2C), 127.8, 127.4 (2C), 125.3, 124.0, 115.1, 50.1, 28.0.

***N*-(4-methoxyphenyl)benzenesulfonamide (3al)[8]**

Prepared according to the general procedure. *p*-Anisidine was recrystalized before being used. Purification by thin layer chromatography using ethyl acetate/hexane (1:2) gave the title product as a black solid in 54% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.69 (d, *J* = 7.9 Hz, 2H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 158.3, 139.1, 133.0, 129.1 (2C), 128.8, 127.4 (2C), 125.9 (2C), 114.6 (2C), 55.6.

***N*-(2,4-dimethylphenyl)benzenesulfonamide (3am)[27]**

Prepared according to the general procedure. Purification by thin layer chromatography using ethyl acetate/hexane (1:3) gave the title product as a light-brown solid in 20% yield.$^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.71 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.96 – 6.89 (m, 2H), 6.18 (s, 1H), 2.26 (s, 3H), 1.93 (s, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 139.9, 136.7, 133.0, 132.3, 131.6, 129.1 (2C), 127.7, 127.3 (2C), 125.5, 21.0, 17.6.

***N*-(3-fluorophenyl)benzenesulfonamide (3an)[28]**

Prepared according to the general procedure. Purification by thin layer chromatography using ethyl acetate/hexane (1:9) gave the title product as a light-brown solid in 33% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 7.82 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.18 (dd, *J* = 14.7, 8.1 Hz, 1H), 6.96 (s, 1H), 6.90 (dt, *J* = 10.1, 1.9 Hz, 1H), 6.85 – 6.76 (m, 2H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 163.2 (d, *J* = 246.9 Hz), 138.9, 138.2 (d, *J* = 10.3 Hz), 133.5, 130.7 (d, *J* = 9.3 Hz), 129.3 (2C), 127.4 (2C), 116.6 (d, *J* = 3.1 Hz), 112.3 (d, *J* = 21.2 Hz), 108.5 (d, *J* = 25.3 Hz).

**1-(phenylsulfonyl)-1H-benzo[d][1,2,3]triazole (3ao)[29]**

Prepared according to the general procedure. Purification by thin layer chromatography using ethyl acetate/hexane (1:1) gave the title product as a light-brown solid in 57% yield. $^1$H NMR (400 MHz, $CDCl_3$) $\delta_H$ = 8.18 – 8.04 (m, 4H), 7.66 (dd, *J* = 13.9, 6.9 Hz, 2H), 7.58 – 7.43 (m, 3H). $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta_C$ = 145.5, 137.2, 135.3, 131.8, 130.5, 129.8 (2C), 128.0 (2C), 126.0, 120.7, 112.1.

**Computational methods**

DFT calculations were performed using the Gaussian 09 software package[30] and structural representations were generated with CYLview.[31] All the geometry optimizations were carried out at the M06 level of theory with the LANL2DZ basis set (Los Alamos National Laboratory 2 double ζ). All of the optimized geometries were verified by frequency computations as minima (zero imaginary frequencies) or transition states (a single imaginary frequency corresponding to the desired reaction coordinate). Single-point energy calculations on the optimized geometries were then evaluated using the functional M06-2X and the same basis set, with solvent effects (dichloromethane or acetonitrile) calculated by means of the Polarizable Continuum Model (PCM) initially devised by Tomasi and coworkers,[32] with radii and non-electrostatic terms of the SMD solvation model, developed by Truhler and co-workers.[33] The free energy values presented along the manuscript were derived from the electronic energy values obtained at the M06-2X/LANL2DZ//M06/LANL2DZ level, including solvent effects, and corrected by using the thermal and entropic corrections based on structural and vibration frequency data calculated at the M06/LANL2DZ level.

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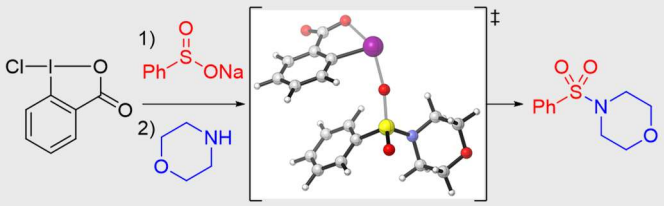
# COMMUNICATION




The method describes a clean and mild transfer of sulfonyl groups to amines and anilines, mediated by a hypervalent iodine reagent. With this reaction a total of 25 sulfonamides were synthesised in up to 99% yield, even in a gram-scale. The reaction mechanism was investigated by ESI-MS and DFT calculations.

**Sulfonamide Synthesis**

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***Page No. – Page No.***

Hypervalent Iodine mediated sulfonamide synthesis