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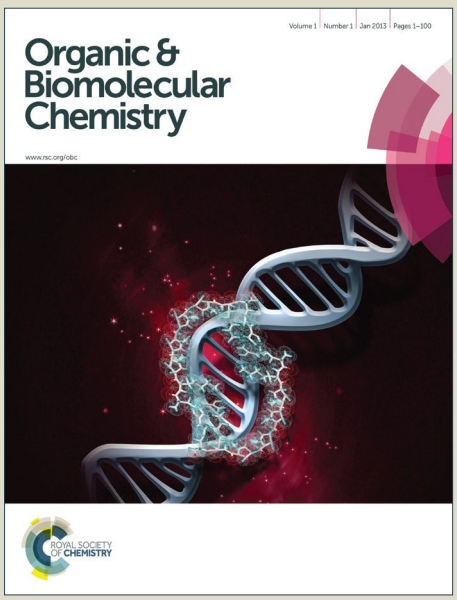

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ARTICLE

Iodine-Catalyzed Expeditious Synthesis of Sulfonamides from Sulfonyl Hydrazides and Amines

Sirilata Yotphan*, Ladawan Sumunnee, Danupat Beukeaw, Chonchanok Buathongjan and Vichai Reutrakul

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A new synthesis of sulfonamides has been developed *via* an iodine-catalyzed sulfonylation of amines with arylsulfonyl hydrazides. This metal-free strategy employs readily accessible and easy to handle starting materials, catalyst and oxidant, and can be easily conducted under mild conditions, providing a convenient access to a wide range of sulfonamides in moderate to excellent yields within a short reaction time.

Introduction

Sulfonamides are prominent structural motifs found in numerous bioactive molecules, pharmaceuticals, and natural products. They exhibit a broad spectrum of biological activities and are employed extensively in various medicinal and pharmaceutical applications, for example as antibacterials, anticonvulsants, HIV protease inhibitors, antitumor and antifungal agents.[1] Pharmaceutically important examples of sulfonamides include the analgesic celecoxib, sildenafil for erectile dysfunction and the HIV protease inhibitors darunavir and amprenavir (Fig. 1).[2] In addition, sulfonamides are important functional groups with a wide utility in herbicides, dyes and organic materials.[3] They are also used as amine protecting groups with an easy removability under mild conditions.[4]

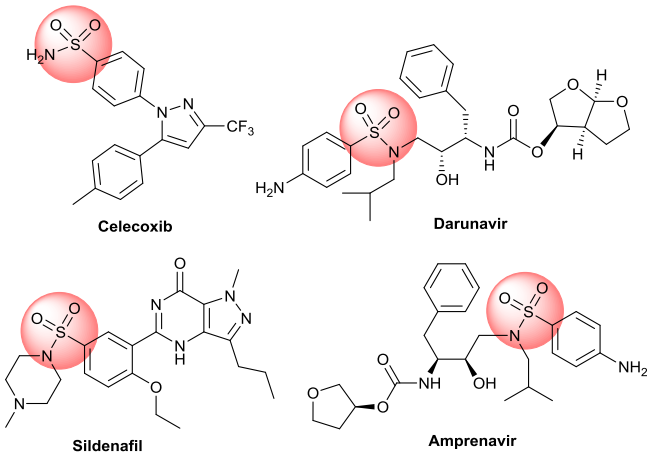
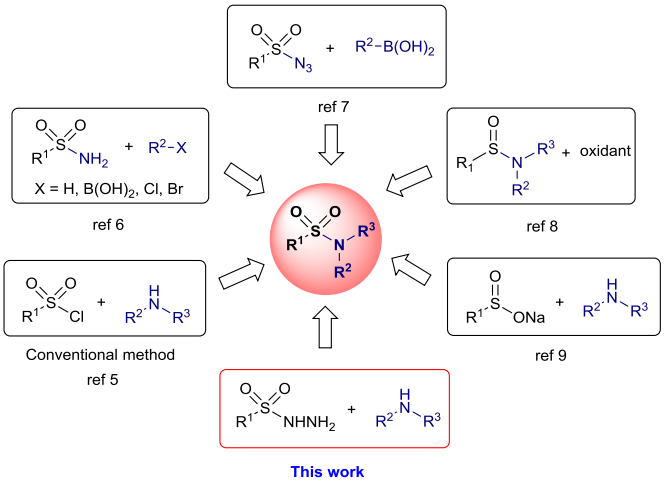


Fig.1 Examples of important sulfonamide drugs.

The traditional method for the sulfonamide formation involves a reaction of amines with sulfonyl chlorides in the presence of a base.[5] Other examples for the synthesis of sulfonamides include a transition metal-catalyzed cross-coupling of *N*-unsubstituted/*N*-monosubstituted sulfonamides with organohalides or boronic acids,[6] a copper-catalyzed Chan-Lam type coupling using sulfonyl azides and boronic acids,[7] an oxidation reaction of sulfenamides/sulfinamides,[8] and an oxidative coupling reaction of sulfinate salts with amines.[9] Although many of these available methods can form sulfonamides successfully, they are still limited by some drawbacks such as using non-stable, hazardous and mutagenic starting materials (e.g. sulfonyl chlorides and organic azides), generating a large quantity of toxic waste, difficulty in handling and storing, poor functional group tolerance, and requirement of harsh conditions and prolonged reaction time. Therefore, an alternative and facile catalytic methodology to construct sulfonamides efficiently is highly desirable for a synthetic viewpoint.



Scheme 1 Approaches for the synthesis of sulfonamides.

Center of Exellence for Innovation in Chemistry (PERCH-CIC), Department of Chemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand.
E-mail: sirilata.yot@mahidol.ac.th
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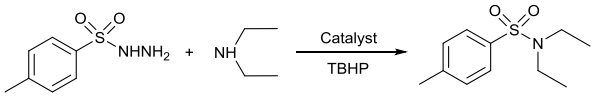
During the past few years, molecular iodine and its salts have emerged as efficient catalysts in modern synthetic chemistry because of the ease of handling, commercial availability, low toxicity, mild reactivity and versatile nature of the reagents. A number of studies have demonstrated impressive advancements of iodine- and iodide-catalyzed carbon–carbon and carbon–heteroatom bonds formation.[10] Our group are also interested in exploring a metal-free catalytic approach for the synthesis of biologically active nitrogen-containing compounds.[11] We recently reported a convenient synthesis of sulfonamides *via* an iodine-catalyzed oxidative coupling reaction of sodium sulfonates and amines.[9c] The combination of catalytic amount of iodine and *tert*-butyl hydroperoxide (TBHP) or hydrogen peroxide (H_2O_2) has provided an expedient liaison for our successful transformations.

Recently, the readily accessible sulfonyl hydrazides have received considerable attention as an excellent synthon for many organic transformations. They have been used as odourless and easy to handle sulfonyl sources,[12] sulfenylating reagents (aryl thiol surrogates),[13] and arylating precursors.[14] Depending upon the nature of the reaction conditions, sulfonyl hydrazides can act as nucleophiles or electrophiles. Comparing to other sulfur reagents, sulfonyl hydrazides are not sensitive to air and moisture, exhibit high reactivity and versatility under relatively mild conditions, and give eco-friendly byproducts (water and N_2). However, to the best of our knowledge, the formation of sulfonamides from sulfonyl hydrazides and amines has not been explored so far. With our continuing efforts towards the development of improved catalytic methods for sulfonamide preparation, herein, we wish to report a new route to synthesize sulfonamides *via* iodine-catalyzed sulfonylation of amines with arylsulfonyl hydrazides. The present method is metal-free, features simple experiment procedure, accommodates a broad scope of substrates, generates clean by-products, and can be a good synthetic tool to access a number of sulfonamide products in reasonable to excellent yields at room temperature within a short reaction time.

Results and discussion

To evaluate the feasibility of sulfonamide formation *via* a catalytic sulfonylation of amines from sulfonyl hydrazide precursors, we initiated our investigation by studying a coupling reaction between *p*-toluenesulfonyl hydrazide (**1a**) and diethylamine (**2a**) as a model reaction. After screening several combinations of catalysts (metals and non-metals) and oxidants (see Supporting Information), the reaction proceeded in high yield when 20 mol% of molecular iodine (I_2) was employed in combination with TBHP (3.0 equiv.) in 1,2-dichloroethane (DCE) solvent at room temperature. Moreover, the reaction was essentially complete after 1 hour[15] and gave the corresponding sulfonamide product **3a** in 85% yield (Table 1, entry 5). The combination of TBHP with other forms of iodine or iodide salts showed lower catalytic activities (entries 1–4). Encouraged by these results, various solvents were screened and dichloromethane (CH_2Cl_2) could also be used as a viable alternative to DCE (entry 6; 80%). Other polar or non-polar solvents were less efficient (entries 7–14). Further attempts to drive the reaction to completion by increasing the temperature were unsuccessful; there was no improvement in yield through our efforts and a slight decrease in product yield was found as temperature increased (entries 15–17).[16] Screening a range of additives (acid, base, etc) and oxidants such as H_2O_2, di-tert butyl peroxide (DTBP) revealed that other reagents were ineffective for this transformation.[16] In addition, no reaction was observed in the absence of I_2 catalyst (entry 18), and only trace amount of product was obtained when TBHP was omitted from the reaction (entry 19). These results highlighted the importance of both I_2 catalyst and TBHP for this catalytic reaction.

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

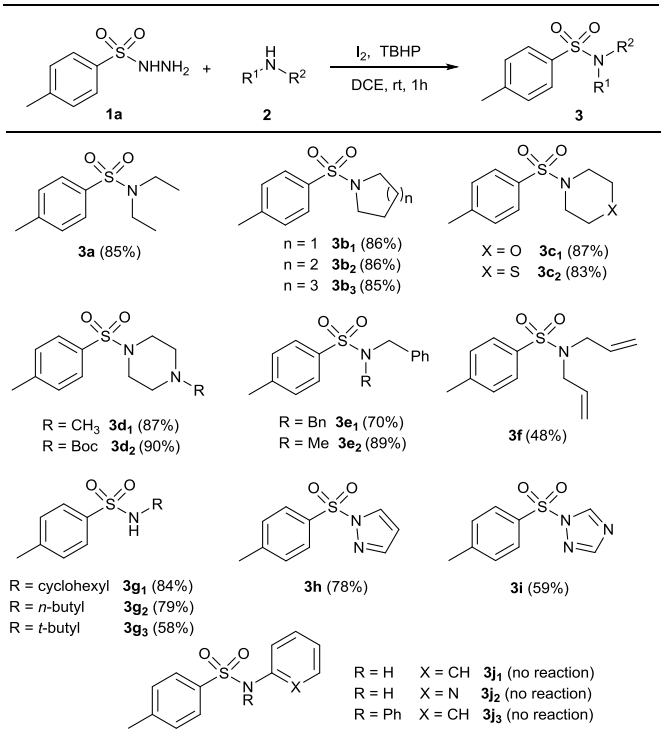
Entry	Catalyst	Solvent	T (°C)	Yield[b] (%)
1	NIS	DCE	rt	67
2	KI	DCE	rt	36
3	NH_4I	DCE	rt	64
4	TBAI	DCE	rt	45
5	**I_2**	**DCE**	**rt**	**85**
6	I_2	CH_2Cl_2	rt	80
7	I_2	Toluene	rt	49
8	I_2	MeCN	rt	46
9	I_2	MeOH	rt	20
10	I_2	H_2O	rt	trace
11	I_2	DMSO	rt	trace
12	I_2	DMF	rt	trace
13	I_2	THF	rt	73
14	I_2	1,4-Dioxane	rt	70
15	I_2	DCE	40	80
16	I_2	DCE	60	80
17	I_2	DCE	80	76
18	-	DCE	rt	0
19	I_2	DCE	rt	trace[c]

[a] Conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), TBHP in decane (1.5 mmol), catalyst (0.1 mmol; 20 mol%), solvent (4 mL), 1 h. [b] Isolated yield. [c] No TBHP added.

Overall, the optimal conditions for I_2-catalyzed sulfonylation of amines were established (Table 1, entry 5; 1 equiv. of sulfonyl hydrazide, 3 equiv. of amine, 20 mol% of I_2, 3 equiv. of TBHP, DCE, rt, 1 h). With these conditions in hand, we sought to expand the substrate scope that is applicable for the current reaction. Therefore, the sulfonylation reaction between *p*-toluenesulfonyl hydrazide (**1a**) and different types of amines were tested under the established conditions and the results were summarized in Table 2 (**3a**–**3i**). A range of secondary aliphatic amines, including acyclic and cyclic amines, were suitable for this I_2-catalyzed sulfonylation reaction and they delivered the expected products in good to excellent yields (**3a**–**3f**). Additional oxygen or sulfur heteroatom in the amine was tolerated, as shown by the successful sulfonylation reactions with morpholine or thiomorpholine in this transformation (**3c$_1$** and **3c$_2$**). Delightfully, 1-methyl piperazine and 1-boc-piperazine exhibit relatively high reactivity toward

sulfonylation reaction and the sulfonamide products **3d$_1$** and **3d$_2$** were achieved in excellent quantities (87 and 90%, respectively). Benzyl protecting groups on nitrogen were also compatible with the standard conditions, affording good to high yields of desired products **3e$_1$** and **3e$_2$**. In case of diallylamine, the sulfonamide product **3f** could be collected in moderate quantity (48 %). We next turned our attention to reactions of primary amines in which sulfonylation reactions also proceeded readily and yielded only single products under the optimal conditions (**3g$_1$**–**3g$_3$**). Moreover, modest to good amounts of sulfonamide products (**3h** and **3i**) were obtained upon examining sulfonylation reactions of heterocyclic amines (pyrazole, and triazole). On the other hand, we observed no reaction when less nucleophilic aromatic amines were employed under these conditions. These results suggested that nucleophilic character of amine could play a crucial role on a product formation.

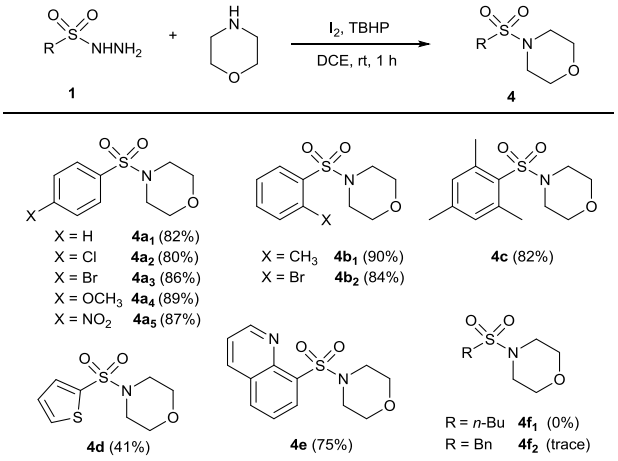
Table 2 Reaction of sulfonyl hydrazide **1a** with various amines[a]



[a] Conditions: **1a** (1.0 mmol), **2** (3.0 mmol), TBHP in decane (3.0 mmol), I_2 (0.2 mmol; 20 mol%), DCE (8 mL), rt, 1 h. Isolated yield.

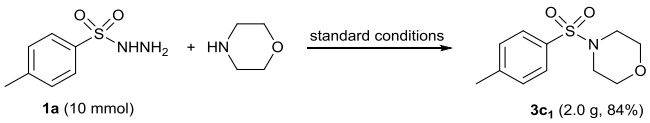
The scope of this reaction with a variety of sulfonyl hydrazides was also investigated as illustrated in Table 3. Various types of arylsulfonyl hydrazides are compatible with standard conditions, affording the desired sulfonamide products (**4a**–**4e**) in moderate to excellent quantities. Arylsulfonyl hydrazides with halogen-substituents (Cl and Br) could serve as practical substrates for the I_2-catalyzed sulfonylation reaction and the sulfonamide products **4a$_2$** and **4a$_3$** were obtained in 80% and 86% yields. The electron-rich (methoxy) and electron-deficient (nitro) substituents on the aryl ring of arylsulfonyl hydrazides also underwent a successful transformation, leading to a formation of products **4a$_4$** and **4a$_5$** in decent yields. Notably, arylsulfonyl hydrazides bearing substitutents at *ortho* position (*o*-CH_3 and *o*-Br) could be converted to their corresponding sulfonamide products **4b$_1$** and **4b$_2$** in very high yields (90 and 84%, respectively). Additionally, mesitylenesulfonyl hydrazide substrate was effective substrate for this reaction, furnishing the product **4c** in 82% yield. Remarkably, the heteroarylsulfonyl hydrazides were also tolerated under these conditions as exemplified by the successful reaction using 2-thiophene- and 8-quinolinesulfonyl hydrazide substrates (**4d** and **4e**). Nevertheless, none or trace amount of the desired product was obtained when aliphatic sulfonyl hydrazides such as butylsufonyl hydrazide and benzylsulfonyl hydrazide were employed. In this regard, it could be due to an instability of reaction intermediates generated from alkylsulfonyl hydrazide substrates.

Table 3 Substrate scope with various sulfonyl hydrazides[a]



[a] Conditions: **1** (1.0 mmol), morpholine (3.0 mmol), TBHP in decane (3.0 mmol), I_2 (0.2 mmol, 20 mol%), DCE (8 mL), rt, 1 h. Isolated yield.

It is noteworthy that the synthesis of sulfonamide *via* this iodine-catalyzed sulfonylation of amine could be effectively scaled up to the gram scale (10 mmol) with a similar efficacy (Scheme 2). As shown below, *p*-toluenesulfonyl hydrazide (**1a**) and morpholine were reacted with each other under the standard conditions and generated sulfonamide **3c$_1$** in 84% yield (2.0 gram), which might suggest a potential application in industry.



Scheme 2 Gram scale reaction

The utility of this protocol was further extended to the sulfonylation of amine hydrochloride salt. Unfortunately, trace amount of product was detected. Thus, we added a stoichiometric amount of Na_2CO_3 base for neutralization and increasing a solubility of amine salt. In the presence of added base, sulfonylation reactions of diethylamine hydrochloride and

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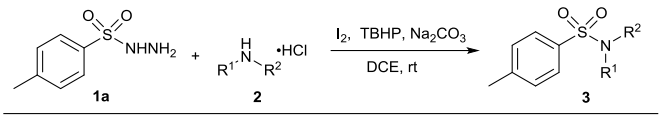
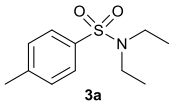
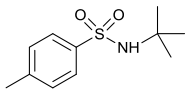
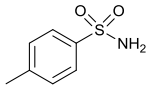
t-butylamine hydrochloride gave the sulfonamide products in comparable yields to those from the reactions of normal amine substrates (Table 4, entries 1–2). Interestingly, when ammonium chloride (NH_4Cl) was applied as an amine source, the corresponding product **3k** was produced in 66% yield.

Table 4 Sulfonylation of amine hydrochloride salts[a]



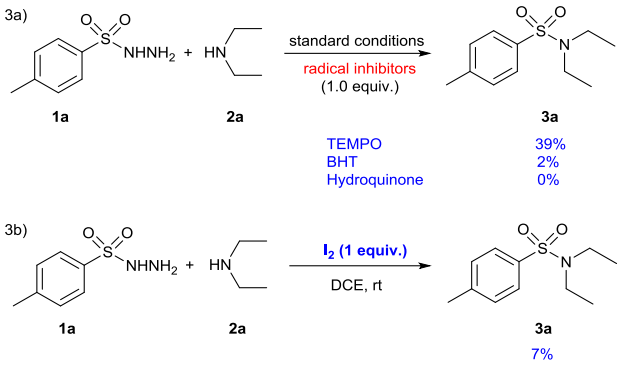
Entry	Amine hydrochloride salt	Product	Yield (%)[b]
1	Et_2NH•HCl	 **3a**	80
2	*t*-$BuNH_2$•HCl	 **3g$_3$**	54
3	NH_4Cl (NH_3•HCl)	 **3k**	66[c,d]

[a] Conditions: **1a** (1.0 mmol), **2** (3.0 mmol), Na_2CO_3 (3.0 mmol), TBHP in decane (3.0 mmol), I_2 (0.2 mmol; 20 mol%), DCE (8 mL), rt, 1 h.
[b] Isolated yield.
[c] Isolated yield after 16 h.
[d] Product **3k** was obtained in 30% yield after 1 h of reaction.

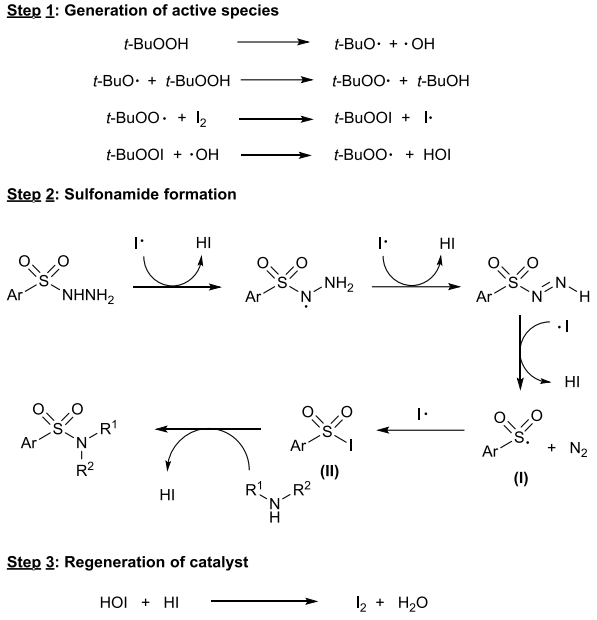
In comparison to previous approaches using other synthetic precursors (e.g. sulfonyl chloride, sulfonyl azide, sodium sulfinate), sulfonyl hydrazides have proven to be particularly useful and attractive substrates for the preparation of sulfonamides due to their commercial availability and synthetic accessibility, their stability to air and moisture at ambient temperature, their good solubility in organic solvents, and their high reactivity under I_2/TBHP-catalyzed reaction. Therefore, this method greatly enriches current N–S bond formation chemistry with several advantages including metal-free catalysis, mild conditions, simple experimental procedure, using easy to handle and readily available reagents, generating clean by-products, and can be carried out at room temperature within a short reaction time with reliable scalability as well as broad substrates scope, which make this synthetic strategy highly valuable for future applications.

To elucidate the reaction mechanism of the sulfonamide formation, several control experiments were conducted (Scheme 3).[16] A reaction of sulfonyl hydrazide **1a** and amine **2a** in the presence of radical scavenger under the standard conditions resulted in a decrease in product yield. Sulfonamide **3a** was obtained in 39%, 2% and 0% in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), BHT (2,6-di-*tert*-butyl-4-methylphenol), and hydroquinone, respectively (Scheme 3a). These results indicated that the reaction was inhibited by a radical scavenger; thus, the reaction pathway is likely to involve a radical process.

To understand the role of iodine, this reaction was carried out in the absence of TBHP. Upon subjecting 1 equivalent of I_2, small amount of product was observed at 1 h and 24 h (Scheme 3b). This outcome implies that I_2 does not react with substrates directly in this transformation. The I_2 precatalyst, therefore, is likely to be converted to another intermediate in the presence of TBHP prior to reacting with sulfonyl hydrazide or amine.



Scheme 3 Control experiments



Scheme 4 Possible mechanism

Based on the aforementioned results and relevant literature,[10,17] a plausible mechanism for the I_2-catalyzed sulfonylation of amine is proposed in Scheme 4. This transformation presumably involves an initial reaction of I_2 and TBHP to form a reactive iodine radical species through a radical process.[17c] Then, the sequential N–H abstraction by iodine radical would lead to a formation of sulfonyl radical (**I**). This resulting sulfonyl radical could subsequently combine with iodine radical and yield a sulfonyl iodide (**II**). A direct

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displacement of the sulfonyl iodide (**II**) by amine would furnish the sulfonamide product and release HI species. Further transformation of HI under standard conditions could regenerate I_2 to resume the catalytic cycle.[16,18]

Conclusions

In summary, we have developed a new protocol for the synthesis of sulfonamides *via* an iodine-catalyzed sulfonylation of amines with sulfonyl hydrazides. In this work, for the first time sulfonyl hydrazides were applied to the preparation of a variety of sulfonamides at room temperature and provided moderate to excellent yields of products within a short reaction time. This method utilizes cheap and readily available reagents, features simple experimental procedure, generates non-toxic by-products, demonstrates good functional group compatibility and proves to be versatile for a range of arylsulfonyl hydrazides and various types of amines such as primary and secondary aliphatic amines, heteroaromatic amines and amine hydrochloride salts. Further mechanistic investigation and expansion of the synthetic application of this chemistry are currently under exploration in our laboratory.

Experimental section

General Information

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All experiments were carried out under air atmosphere, and oven-dried glassware was used in all cases. Column chromatography was performed over silica gel (SiO_2; 60 Å silica gel, Merck Grade, 70–230 Mesh). GC experiments were carried out with an Agilent 6890N GC-FID on chromatograph equipped with an Agilent column (HP-1, polysiloxane, 24.5 m × 0.32 mm ID × 0.17 µm). ^1H and ^{13}C NMR spectra were recorded on Bruker-AV400 spectrometers in $CDCl_3$ solution, at 400 and 100 MHz, respectively. NMR chemical shifts are reported in ppm, and were measured relative to $CHCl_3$ (7.24 ppm for ^1H and 77.00 ppm for ^{13}C). IR spectra were recorded on Bruker FT-IR Spectrometer Model ALPHA by neat method, and only partial data are listed. Melting points were determined on Buchi Melting Point M-565 apparatus. High resolution mass spectroscopy (HRMS) data were analysed by a high-resolution micrOTOF instrument with electrospray ionization (ESI). The structures of known compounds were corroborated by comparing their ^1H NMR, ^{13}C NMR data with those of literature.

Typical procedure for the synthesis of sulfonamides 3a–3i, 3k and 4a$_1$–4e.

To a 20 ml oven-dried scintillation vial equipped with a magnetic stir bar, sulfonylhydrazide substrate (1.00 mmol, 1.00 equiv.), iodine (I_2) (51 mg, 0.20 mmol, 0.20 equiv.), 1,2-dichloroethane (DCE) (8.00 mL), amine (3.00 mmol, 3.00 equiv.), and TBHP in decane (3.00 mmol, 3.00 equiv.) were added. The reaction mixture was stirred at room temperature for 1 h. Upon completion, distilled deionized H_2O (10 mL) and saturated $Na_2S_2O_3$ (10 mL) were added, and the mixture was extracted with ethyl acetate (EtOAc) (2 × 20 mL). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography to afford a desired sulfonamide product.

***N,N*-diethyl-4-methylbenzenesulfonamide (3a).**[9c] White solid (192 mg, 85% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 3.18 (q, *J* = 7.0 Hz, 4H), 2.37 (s, 3H), 1.11 (t, *J* = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 137.3, 129.5, 126.9, 41.9, 21.4, 14.1; HRMS (ESI): calcd for $C_{11}H_{17}NO_2SNa$ $[M+Na]^+$ 250.0872, found 250.0871.

1-tosylpyrrolidine (3b$_1$).[9c] White solid (194 mg, 86% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.22–3.18 (m, 4H), 2.40 (s, 3H), 1.73–1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 133.8, 129.6, 127.5, 47.9, 25.2, 21.5; HRMS (ESI): calcd for $C_{11}H_{15}NO_2SNa$ $[M+Na]^+$ 248.0716, found 248.0729.

1-tosylpiperidine (3b$_2$).[9c] White solid (206 mg, 86% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.61–7.59 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.92 (t, *J* = 5.6 Hz, 4H), 2.39 (s, 3H), 1.62–1.57 (m, 4H), 1.40–1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 133.1, 129.5, 127.6, 46.9, 25.1, 23.4, 21.4; HRMS (ESI): calcd for $C_{12}H_{17}NO_2SNa$ $[M+Na]^+$ 262.0872, found 262.0877.

1-tosylazepane (3b$_3$).[9c] White solid (215 mg, 85% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 3.21 (t, *J* = 5.8 Hz, 4H), 2.38 (s, 3H), 1.68–1.66 (m, 4H), 1.55–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 136.5, 129.5, 126.9, 48.1, 29.0, 26.8, 21.4; HRMS (ESI): calcd for $C_{13}H_{19}NO_2SNa$ $[M+Na]^+$ 276.1029, found 276.1032.

4-tosylmorpholine (3c$_1$).[9c] White solid (211 mg, 87% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 3.70 (t, *J* = 4.8 Hz, 4H), 2.94 (t, *J* = 4.8 Hz, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 131.9, 129.7**,** 127.8**,** 66.0**,** 45.9**,** 21.5**;** HRMS (ESI): calcd for $C_{11}H_{15}NO_3SNa$ $[M+Na]^+$ 264.0665, found 264.0679.

4-tosylthiomorpholine (3c$_2$).[9c] White solid (213 mg, 83% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.28–3.26 (m, 4H), 2.67–2.64 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7**,** 133.6, 129.7, 127.3, 47.7, 27.2, 21.4; HRMS (ESI): calcd for $C_{11}H_{15}NO_2S_2Na$ $[M+Na]^+$ 280.0436, found 280.0442.

1-methyl-4-tosylpiperazine (3d$_1$).[9c] White solid (221 mg, 87% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 2.96 (br, 4H), 2.43–2.41 (m, 4H), 2.37 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 132.1, 129.5, 127.8, 53.9, 45.9, 45.6, 21.4; HRMS (ESI): calcd for $C_{12}H_{19}N_2O_2S$ $[M+H]^+$ 255.1162, found 255.1167.

***tert*-butyl 4-tosylpiperazine-1-carboxylate (3d$_2$).**[9c] White solid (307 mg, 90% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 3.46 (t, *J* = 5.0 Hz, 4H), 2.91 (t, *J* = 5.0 Hz, 4H), 2.40 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 143.9, 132.3, 129.7, 127.7, 80.3, 45.8, 43.2, 28.2, 21.5; HRMS (ESI): calcd for $C_{16}H_{24}N_2O_4SNa$ $[M+Na]^+$ 363.1349, found 363.1352.

***N,N*-dibenzyl-4-methylbenzenesulfonamide (3e$_1$).**[9c] White solid (245 mg, 70% yield); ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.22–7.18 (m, 6H), 7.05–7.02 (m, 4H), 4.29 (s, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 137.7,

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135.6, 129.7, 128.5, 128.4, 127.6, 127.2, 50.4, 21.5; HRMS (ESI): calcd for $C_{21}H_{21}NO_2SNa$ $[M+Na]^+$ 374.1185, found 374.1191.

***N*-benzyl-*N*,4-dimethylbenzenesulfonamide (3e$_2$).**[9c] White solid (246 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.35–7.25 (m, 7H), 4.10 (s, 2H), 2.56 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 135.6, 134.2, 129.7, 128.6, 128.3, 127.8, 127.4, 54.1, 34.3, 21.5; HRMS (ESI): calcd for $C_{15}H_{17}NO_2SNa$ $[M+Na]^+$ 298.0872, found 298.0878.

***N,N*-diallyl-4-methylbenzenesulfonamide (3f).**[19] Colorless oil (121 mg, 48% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 5.63–5.53 (m, 2H), 5.14–5.09 (m, 4H), 3.77 (d, *J* = 6.4 Hz, 4H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 137.3, 132.6, 129.6, 127.1, 118.9, 49.3, 21.5; HRMS (ESI): calcd for $C_{13}H_{17}NO_2SNa$ $[M+Na]^+$ 274.0872, found 274.0880.

***N*-cyclohexyl-4-methylbenzenesulfonamide (3g$_1$).**[9c] Dark yellow solid (213 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.8 Hz, 2H), 4.97–4.96 (m, 1H), 3.08–3.06 (m, 1H), 2.39 (s, 3H), 1.71–1.68 (m, 2H), 1.60–1.56 (m, 2H), 1.47–1.43 (m, 1H), 1.19–1.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0, 138.4, 129.5, 126.9, 52.5, 33.7, 25.1, 24.5, 21.4; HRMS (ESI): calcd for $C_{13}H_{19}NO_2SNa$ $[M+Na]^+$ 276.1029, found 276.1037.

***N*-butyl-4-methylbenzenesulfonamide (3g$_2$).**[9c] Colorless oil (180 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.10 (*br* s, 1H), 2.88–2.83 (m, 2H), 2.37 (s, 3H), 1.40–1.35 (m, 2H), 1.26–1.20 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 136.8, 129.5, 127.0, 42.8, 31.4, 21.4, 19.6, 13.4; HRMS (ESI): calcd for $C_{11}H_{17}NO_2SNa$ $[M+Na]^+$ 250.0878, found 250.0878.

***N*-(*tert*-butyl)-4-methylbenzenesulfonamide (3g$_3$).**[9c] White solid (131 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.02 (br, 1H), 2.38 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 140.5, 129.4, 126.9, 54.4, 30.1, 21.4; HRMS (ESI): calcd for $C_{11}H_{17}NO_2SNa$ $[M+Na]^+$ 250.0878, found 250.0894.

1-tosyl-1H-pyrazole (3h).[9c] White solid (173 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.07 (m, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.69–7.68 (m, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.36–6.35 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 145.1, 133.9, 131.0, 130.0, 128.0, 108.7, 21.6; HRMS (ESI): calcd for $C_{10}H_{10}N_2O_2SNa$ $[M+Na]^+$ 245.0355; found 245.0365.

1-tosyl-1H-1,2,4-triazole (3i).[20] White solid (131 mg, 59% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.98 (s, 1H), 7.93 (d, *J* = 8.6 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 147.2, 144.4, 132.6, 130.3, 128.6, 21.8; HRMS (ESI): calcd for $C_9H_9N_3O_2SNa$ $[M+Na]^+$ 246.0313; found 223.0323.

4-methylbenzenesulfonamide (3k).[9c] White solid (113 mg, 66% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.92 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 139.0, 129.7, 126.4, 21.5; HRMS (ESI): calcd for $C_7H_9NO_2SNa$ $[M+Na]^+$ 194.0246, found 194.0252.

4-(phenylsulfonyl)morpholine (4a$_1$).[9e] White solid (187 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.70 (m, 2H), 7.61–7.57 (m, 1H), 7.54–7.50 (m, 2H), 3.69 (t, *J* = 4.8 Hz, 4H), 2.95 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 133.0, 129.0, 127.7, 66.0, 45.9; HRMS (ESI): calcd for $C_{10}H_{13}NO_3SNa$ $[M+Na]^+$ 250.0508, found 250.0514.

4-((4-chlorophenyl)sulfonyl)morpholine (4a$_2$).[9b] White solid (210 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dt, *J* = 8.8, 2.4 Hz, 2H), 7.50 (dt, *J* = 8.8, 2.4 Hz, 2H), 3.71 (t, *J* = 4.8 Hz, 4H), 2.96 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 135.6, 129.4, 129.2, 66.0, 45.9; HRMS (ESI): calcd for $C_{10}H_{12}ClNO_3SNa$ $[M+Na]^+$ 284.0119, found 284.0125.

4-((4-bromophenyl)sulfonyl)morpholine (4a$_3$).[9e] White solid (263 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.65 (m, 2H), 7.60–7.56 (m, 2H), 3.70 (t, *J* = 4.8 Hz, 4H), 2.95 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 132.4, 129.2, 128.1, 65.9, 45.8; HRMS (ESI): calcd for $C_{10}H_{12}BrNO_3SNa$ $[M+Na]^+$ 327.9613, found 327.9617.

4-((4-methoxyphenyl)sulfonyl)morpholine (4a$_4$).[9e] White solid (229 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dt, *J* = 9.6, 2.4 Hz, 2H), 6.97 (dt, *J* = 9.6, 2.4 Hz, 2H), 3.84 (s, 3H), 3.69 (t, *J* = 4.8 Hz, 4H), 2.93 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 129.9, 126.4, 114.2, 66.0, 55.6, 45.9; HRMS (ESI): calcd for $C_{11}H_{15}NO_4SNa$ $[M+Na]^+$ 280.0614, found 280.0619.

4-((4-nitrophenyl)sulfonyl)morpholine (4a$_5$).[9e] Yellow solid (236 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (dt, *J* = 9.2, 2.0 Hz, 2H), 7.92 (d, *J* = 9.2, 2.0 Hz, 2H), 3.72 (t, *J* = 4.8 Hz, 4H), 3.02 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 141.2, 128.9, 124.4, 65.9, 45.8; HRMS (ESI): calcd for $C_{10}H_{12}N_2O_5SNa$ $[M+Na]^+$ 295.0359, found 295.0365.

4-(*o*-tolylsulfonyl)morpholine (4b$_1$). White solid (218 mg, 90% yield); m.p. 79.8 – 89.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.84 (m, 1H), 7.44 (td, *J* = 7.2, 0.8 Hz, 1H), 7.32–7.28 (m, 2H), 3.68 (t, *J* = 4.8 Hz, 4H), 3.11 (t, *J* = 4.8 Hz, 4H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 134.8, 133.0, 132.8, 130.3, 126.1, 66.2, 45.2, 20.8; IR (neat, cm^{-1}): *ν* 2860, 1447, 1337, 1261, 1158, 1114, 942, 728; HRMS (ESI): calcd for $C_{11}H_{15}NO_3SNa$ $[M+Na]^+$ 264.0665, found 264.0670.

4-((2-bromophenyl)sulfonyl)morpholine (4b$_2$). White solid (256 mg, 84% yield); m.p. 127.2 – 128.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.02 (m, 1H), 7.73 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.45–7.36 (m, 2H), 3.70–3.67 (m, 4H), 3.26–3.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 135.8, 133.8, 132.3, 127.5, 120.4, 66.3, 45.6; IR (neat, cm^{-1}): *ν* 2860, 1573, 1344, 1262, 1166, 1113, 942, 761, 532; HRMS (ESI): calcd for $C_{10}H_{12}BrNO_3SNa$ $[M+Na]^+$ 327.9613, found 327.9618.

4-(mesitylsulfonyl)morpholine (4c).[21] White solid (220 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 2H), 3.67–3.65 (m, 4H), 3.13–3.10 (m, 4H), 2.60 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 140.6, 131.9, 130.7, 66.1, 44.3, 22.9, 20.9; HRMS (ESI): calcd for $C_{13}H_{19}NO_3SNa$ $[M+Na]^+$ 292.0978, found 292.0985.

4-(thiophen-2-ylsulfonyl)morpholine (4d).[22] White solid (106 mg, 41% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 4.8, 1.2 Hz, 1H), 7.51 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.14 (dd, *J* = 4.8, 4.0 Hz, 1H), 3.74 (t, *J* = 4.8 Hz, 4H), 3.03–3.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 132.7, 132.5, 127.7, 65.9, 45.9; HRMS (ESI): calcd for $C_8H_{11}NO_3S_2Na$ $[M+Na]^+$ 256.0073, found 256.0081.

4-(quinolin-8-ylsulfonyl)morpholine (4e).[9e] White solid (208 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (dd, *J* = 4.0, 1.6 Hz, 1H), 8.44 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.22 (dd, *J* = 8.4, 1.6 Hz, 1H), 8.02 (dd, *J*

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= 8.4, 1.2 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.52–7.49 (m, 1H), 3.68 (t, *J* = 4.8 Hz, 4H), 3.41 (t, *J* = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 144.1, 136.4, 136.3, 133.6, 133.3, 128.9, 125.4, 122.0, 66.8, 46.3; HRMS (ESI): calcd for $C_{13}H_{14}N_2O_3SNa$ $[M+Na]^+$ 301.0617, found 301.0620.

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