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Reaction of Alkyl Halides with Rongalite: One-Pot and Telescoped Syntheses of Aliphatic Sulfonamides, Sulfonyl Fluorides, and Unsymmetrical Sulfones

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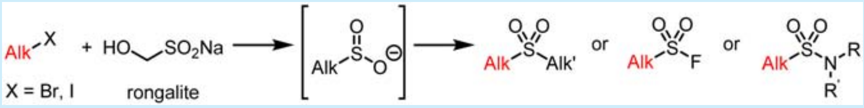
Supporting Information



ABSTRACT: An efficient methodology has been developed for the one-pot or telescoped synthesis of aliphatic sulfonamides, sulfonyl fluorides, and unsymmetrical sulfones on the basis of interrupted alkylation of sodium hydroxymethylsulfinate (rongalite) with alkyl halides. The protocols are conducted under mild conditions, use inexpensive and shelf-stable reagents, and are not sensitive to air/moisture. These conditions can be applied in rapid parallel chemical synthesis, which was demonstrated by the preparation of a small sulfonamide library based on the core structure of the anticoagulant drug Tirofiban.

The sulfone and sulfonamide motifs are found in many compounds of pharmaceutical,[1] agrochemical,[2] and material science[3] importance. In particular, a variety of *aliphatic* sulfones and sulfonamides have been developed for a broad range of therapeutic indications (Figure 1), owing to the specific three-dimensional structural features, metabolic stability, and polarity of the sulfonyl functional group.[4]

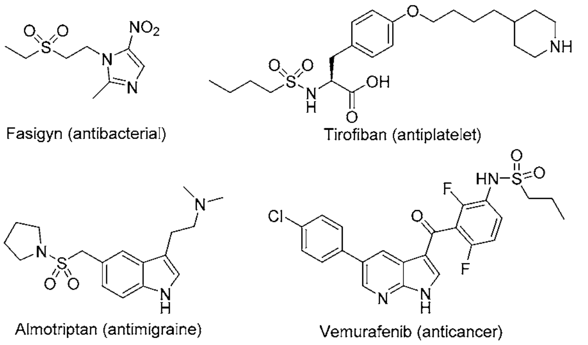


Figure 1. Commercial pharmaceuticals with aliphatic sulfone and sulfonamide fragments.

Dialkylsulfones are classically prepared by oxidation of dialkylsulfides, while sulfonamides are formed by reacting sulfonyl chlorides with amines (Scheme 1). This approach is based on multistep processes involving thiol intermediates and harsh oxidative conditions.[5] Recently, several groups reported methods where the sulfone group is incorporated with sulfur in the desired oxidation state to form alkyl sulfinate salts, which are further alkylated producing dialkyl sulfones, or chlorinated furnishing sulfonyl chlorides. These methods of sulfinate generation include reaction of SO_2 gas or DABSO with organolithium,[6a,b] -magnesium,[6a,b] and -zinc[6c] reagents. Alkyl sulfinates have also been prepared by alkylation of 2-mercaptopyridine,[7a] 2-mercaptobenzothiazole,[7b] or 2-mercaptopyrimidine,[7c] followed by sulfur oxidation and basic cleavage of the heteroaromatic sulfone. Primary sulfonamides can be obtained via direct sulfonamidation of organolithium and organomagnesium nucleophiles with Burgess-type reagents.[8] However, all the above methods include multistep syntheses, use air-sensitive, strongly basic, or oxidative conditions, and therefore lack the practicality required for high-throughput synthesis, which is an essential part of modern structure−activity relationship exploration in medicinal chemistry. Of the more streamlined procedures, alkyl sulfonamides were synthesized in a three-component reaction of *N*-tosylhydrazones, DABSO, and amines;[9] however, this method requires preparation of hydrazones from aldehydes or ketones and is not applicable to sulfone synthesis. Another promising method for sulfone group incorporation was accomplished by introduction of sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS, Scheme 1).[10] Reaction of this reactant with alkyl halides affords β-sulfonyl esters, which can be cleaved with a strong base releasing the desired sulfinate salts. The potential utility of SMOPS is limited by its relatively poor shelf stability[11a] and high price,[11b] which prevents its broader use, especially when reliability and reproducibility are of paramount importance. Moreover, the strongly basic cleavage conditions can also impede its application for sensitive molecules.

In addition to sulfones and sulfonamides, there is growing interest in aliphatic sulfonyl fluorides as tool compounds in chemical biology[12a,b] and as stable alternatives to sulfonyl chlorides in organic synthesis.[12c] They are typically synthesized by chlorine−fluorine exchange starting from alkyl sulfonyl

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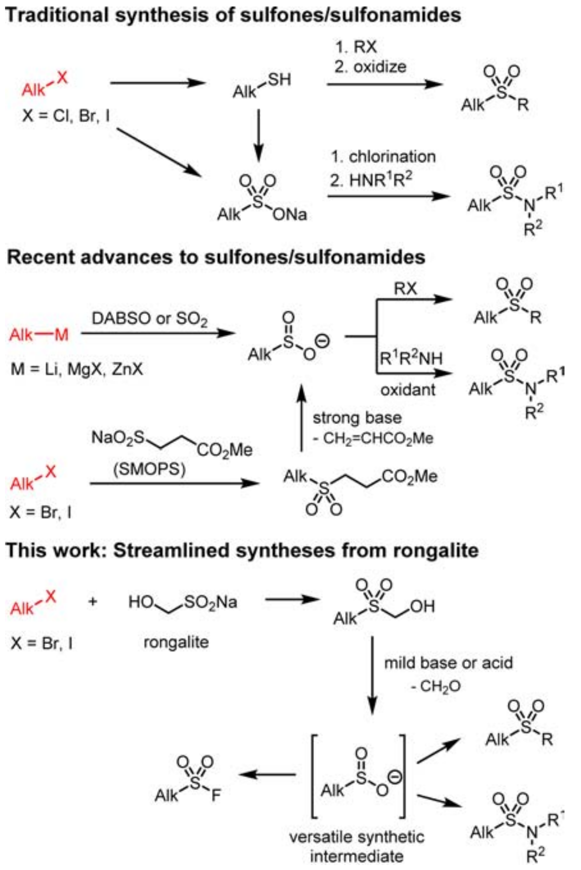
Scheme 1. Synthesis of Sulfonamides, Sulfonyl Fluorides, and Unsymmetrical Sulfones

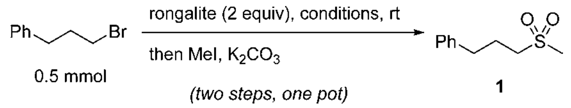


chlorides, which suffer from poor stability and limited availability. Notably, one-pot conversion to any of these three related classes of compounds (sulfones, sulfonamides, and sulfonyl fluorides) from readily available alkyl sources has not been previously demonstrated, to the best of our knowledge.

As part of our program for the development of versatile methods of aliphatic[9] and aromatic[13] sulfonylations for rapid chemical space expansion, herein we report the one-pot synthesis of aliphatic sulfones, sulfonamides, and sulfonyl fluorides from alkyl halides and sodium hydroxymethylsulfinate (rongalite). This safe,[11c] cheap, and stable commodity chemical has been known to react with activated alkyl halides at elevated temperatures yielding symmetrical sulfones.[14] However, the literature provides no evidence that this reaction can be interrupted after the first alkylation to provide an intermediate that could further lead to more diversified sulfonyl products. We envisioned that if the reaction of rongalite with alkyl halides is intercepted after the first alkylation and the intermediate hydroxymethyl sulfone is cleaved, the released alkyl sulfinate will potentially lead to sulfonamides, sulfonyl fluorides, or unsymmetrical sulfones (Scheme 1). Unlike in the SMOPS method, the sulfinate release would occur under mild basic or acidic conditions.

After screening for the desired monoalkylation in various solvents under mild conditions it was found that 3-phenylpropyl bromide reacts with rongalite in DMSO even at the ambient temperature. Subsequent treatment of the reaction mixture with potassium carbonate decomposed the presumed intermediate alkyl hydroxymethyl sulfone releasing the alkyl sulfinate, which then was quenched with methyl iodide resulting in formation of the unsymmetrical alkyl methyl sulfone in 42% yield (Table 1, entry 1). In addition, 21% of the symmetrical dialkylsulfone was isolated. While rongalite is only partially soluble in DMSO, its extremely low solubility in other solvents led to unacceptable yields (entry 2). To increase the concentration of rongalite in solution, water was added as a cosolvent, but this led to reduced yield (entry 3). However, the addition of TBAI improved it to 55% (entry 4). A slight increase in reaction temperature and application of a weaker base had negative effects (entries 5 and 6), while use of aqueous sodium hydroxide instead of solid K_2CO_3 was also found to be practical (entry 7). It is interesting that 3-fold dilution had the same or a better effect than TBAI (entry 8) and at this new concentration the additive's contribution was no longer substantial (entry 9). Finally, the best result was achieved when a mixture of rongalite and DMSO was prestirred for 30 min before addition of the alkyl bromide (entry 10). In a separate set of experiments the optimal molar ratio of rongalite to the alkyl bromide was found to be 2:1 [see Supporting Information (SI)].

Table 1. Summary of Reaction Optimization[a]



1

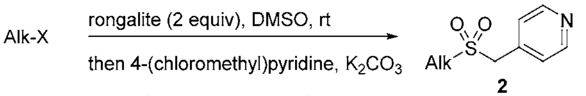
entry	conditions	yield (%)[b]
1	DMSO (1 mL)	42
2	Solvents (1 mL): DMF, NMF, MeCN, MeOH, or EtOH	<10
3	DMSO (1 mL), H_2O (0.1 mL)	34
4	DMSO (1 mL), TBAI (0.3 equiv)	55
5	DMSO (1 mL), TBAI (0.3 equiv), 45 °C	27
6	DMSO (1 mL), TBAI (0.3 equiv), Et_3N, no K_2CO_3	13
7	DMSO (1 mL), TBAI (0.3 equiv), aq NaOH, no K_2CO_3	53
8	DMSO (3 mL)	57
9	DMSO (3 mL), TBAI (0.3 equiv)	58
10	DMSO (3 mL), prestir before addition of substrate	65

[a] Reaction conditions: AlkX (0.5 mmol), rongalite (2 equiv), solvent, 18 h; then MeI (2 equiv), 3 h at 23 °C. [b] Isolated yield of sulfone **1**.

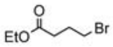
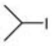
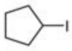
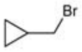
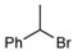
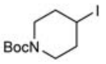
With the optimized conditions identified, the substrate scope was explored using 4-(chloromethyl)pyridine as the quenching electrophile for the second step (Table 2). Both primary (entries 1−7) and secondary halides (entries 8−11) were competent substrates in this reaction. Ester (entry 2) and carbamate groups (entries 3, 11) were tolerated. Alkyl bromides and iodides reacted smoothly, whereas alkyl tosylates gave <10% yields. Benzyl bromide gave a modest yield (entry 5) due to substantial symmetrical sulfone formation, in accordance with prior observations.[14]

Next, the types of electrophiles were examined that can be applied in a one-pot procedure following the initial monoalkylation of rongalite with 3-phenylbromopropane (Table 3). Primary (entries 1, 3) and secondary iodides (entry 5), primary bromides (entry 2), tosylates (entry 4), and activated chlorides (entry 6) were found to be suitable for the second alkylation in the synthesis of unsymmetrical dialkylsulfones. Notably, electrophilic amination of the intermediate sulfinate with hydroxylamine-*O*-sulfonic acid led to the primary sulfonamide (entry 7).[10,13a]

Table 2. Representative Set of Alkyl Halides[a]

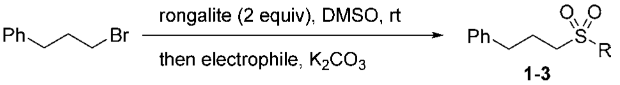


(two steps, one pot)

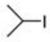
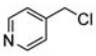
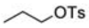
entry	Alk-X	2	yield (%)[b]	entry	Alk-X	2	yield (%)[b]
1		**2a**	59	7		**2g**	34
2		**2b**	35	8		**2h**	25
3		**2c**	38	9		**2i**	40
4		**2d**	47	10		**2j**	33[c]
5		**2e**	27	11		**2k**	17
6		**2f**	37				

[a] Reaction conditions: (1) AlkX (0.5 mmol), rongalite (2 equiv), DMSO (3 mL), 23 °C, 18 h; (2) K_2CO_3 (4 equiv), electrophile (2.0 equiv), 23 °C, 3 h. [b] Isolated yield. [c] Step 2 run at 55 °C.

Table 3. Representative Set of Electrophiles[a]



(two steps, one pot)

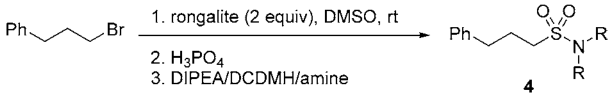
entry	electrophile	1, 3	yield (%)[b]	entry	electrophile	2, 3	yield (%)[b]
1	CH_3I	**1**	65	5		**3b**	42[d]
2		**3a**	51[c]				
3		**3a**	57[c]	6		**2a**	59
4		**3a**	39[c]	7	H_2NOSO_3H	**3c**	59[e]

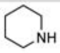
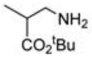
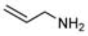
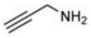
[a] Reaction conditions: see Table 2 and SI. [b] Isolated yield. [c] Step 2 run at 50 °C for 16 h. [d] Step 2 run at 23 °C for 5 h. [e] H_2NOSO_3H (4 equiv), AcONa (7 equiv).

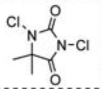
The monoalkylation of rongalite was also found to be useful for efficient telescoped synthesis of aliphatic sulfonamides. Under the optimized conditions, the intermediate sulfinic acid was released with phosphoric acid and extracted with dichloromethane−heptane (4:1). Without drying, the organic extract was basified with Hünig's base, combined with an amine, and finally treated with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as an oxidant, thus delivering an aliphatic sulfonamide in an efficient telescoped procedure (Table 4). This reagent was found to be optimal after applying several halogenating agents (see SI) in a manner analogous to previous precedents.[13a,b]

Both primary and secondary amines furnished the desired sulfonamide products. Alkene, alkyne (entries 3−4), and hydroxyl functionalities (entry 5) were well tolerated providing possibilities for subsequent synthetic elaboration or orthogonal bioconjugation of the sulfonamide products. *β*-Aminoester (entry 6) was also a competent reactant in the amination step; however, the more hindered *α*-aminoester, i.e. *O*-benzyl-L-tyrosine methyl ester [L-Tyr(Bzl)OMe] intended for Tirofiban core formation (Figure 1), was unproductive (entry 7). Therefore, a more versatile method for sulfonamide synthesis would be required for coupling of hindered amines (vide infra).

Table 4. Representative Examples of Telescoped Synthesis of Sulfonamides[a]



entry	amine	4	yield (%)[b]	entry	amine	4	yield (%)[b]
1		**4a**	50	5		**4e**	40
2	$BnNH_2$	**4b**	35	6		**4f**	39
3		**4c**	53	7	L-Tyr(Bzl)OMe (HCl salt)	-	0
4		**4d**	29				

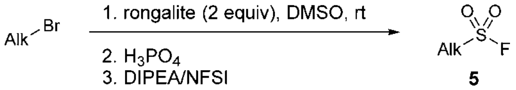
DCDMH:


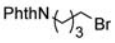
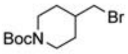
[a] Reaction conditions: (1) AlkX (0.5 mmol), rongalite (2 equiv), DMSO (3 mL), 23 °C, 18 h; (2) H_3PO_4 (2 equiv); (3) DIPEA (2.0 equiv), amine (2 equiv), DCDMH (0.3 equiv), 0 to 23 °C, 1 h. [b] Isolated yield.

Aliphatic sulfonyl fluorides have been shown to be advantageous sulfonylating reagents, especially for parallel synthesis, due to their superior stability and selectivity as compared to sulfonyl chlorides.[12c] Therefore, the compatibility of the newly developed sulfination conditions with subsequent fluorination of the released sulfinate was investigated with the aim of developing a one-pot synthesis of aliphatic sulfonyl fluorides.

Gratifyingly, the sulfinic acid produced in a manner analogous to the above-described sulfonamidation procedure readily reacted with *N*-fluorobenzenesulfonimide (NFSI) furnishing the desired sulfonyl fluoride in good yield (Table 5, entry 1). Of note, using Selectfluor for this fluorination gave a lower yield and less favorable impurity profile. Other functionalized alkyl sulfonyl fluorides were synthesized in the same manner demonstrating generality of this protocol (Table 5).

Table 5. Representative Examples of Telescoped Synthesis of Sulfonyl Fluorides[a]



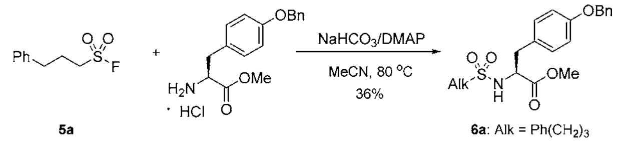
entry	Alk-Br	5	yield (%)[b]	entry	Alk-Br	5	yield (%)[b]
1		**5a**	55	3		**5c**	38
2		**5b**	31	4		**5d**	36[c]

[a] Reaction conditions: (1) AlkX (0.5 mmol), rongalite (2 equiv), DMSO (3 mL), 23 °C, 18 h; (2) H_3PO_4 (2 equiv); (3) DIPEA (2.0 equiv), NFSI (2 equiv), 0 to 23 °C, 1 h. [b] Isolated yield. [c] Step 1 run at 45 °C.

Contrary to the method involving chlorination (Table 4, entry 7), sulfonyl fluoride **5a** (1 equiv), synthesized according to Table 5 conditions and purified by chromatography, successfully reacted with HCl-Tyr(Bzl)OMe (1 equiv) in the presence of DMAP and $NaHCO_3$ to give the desired sulfonamide **6a** containing the Tirofiban core in 36% yield

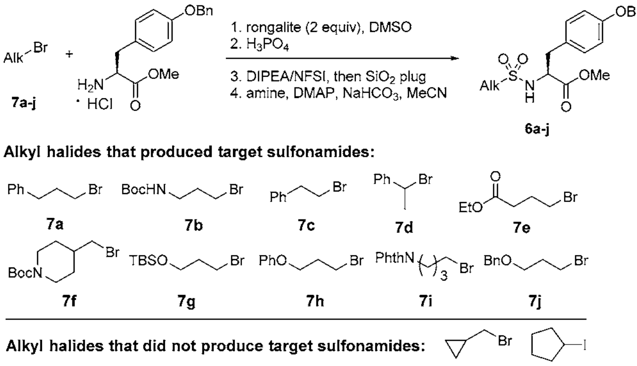
(Scheme 2). Several catalysts and bases were examined, and only the DMAP/$NaHCO_3$ combination was found to be productive. This result is significant for sulfonamide synthesis because analogous sulfonyl fluorides were reported to give typically <5% yields in reactions with hindered amines without DMAP catalysis.[12c]

Scheme 2. Optimized Conditions for Coupling of Sulfonyl Fluorides with Amines



These alternative conditions for sulfonamide synthesis were tested in a setup typical for parallel synthesis, starting directly from alkyl halides. In this case, the key sulfonyl fluoride intermediates were not purified by chromatography but rather used in crude form after a short silica gel plug. The four-step protocol conducted in a parallel chemistry manner furnished a small library of sulfonamide analogs with an 83% success rate after a single HPLC purification on a reversed-phase column (Scheme 3; see SI for details).

Scheme 3. Parallel Synthesis of Aliphatic Sulfonamides from Alkyl Halides with a Single Final Purification



In conclusion, we have developed an efficient methodology for the expeditious preparation of aliphatic sulfones, sulfonamides, and sulfonyl fluorides starting from primary and secondary alkyl halides and rongalite. These one-pot or telescoped reactions are performed under mild conditions using inexpensive and stable reagents, not sensitive to air and moisture, and can be successfully applied to parallel chemical syntheses of a variety of aliphatic sulfonyl compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02894.

Experimental procedures and characterization data of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(11) (a) According to our records, the NMR purity of purified SMOPS decreased from 87% to 70% over three weeks; the yields of SMOPS alkylation typically dropped 20−50% depending on the reagent storage time. (b) The current price of commercial SMOPS reagent is ∼ \$19,000/mol vs ∼\$10/mol for rongalite. (c) The "green" switch to low-toxic rongalite eliminates operations with highly toxic methyl vinyl ketone, which is used and then generated as waste during production of SMOPS.

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