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Alkyl Sulfinates: Formal Nucleophiles for Synthesizing TosMIC Analogs

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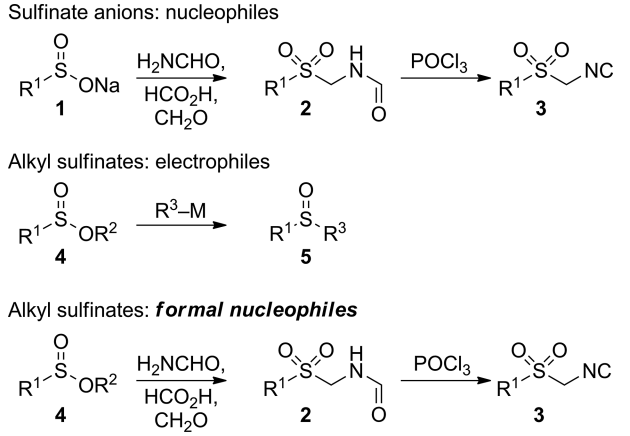
Alkyl sulfinates function as formal nucleophiles in Mannich-type reactions to give sulfonyl formamides, which are readily dehydrated to the corresponding sulfonylmethyl isonitriles. The efficient, two-step synthesis provides a general route to sulfonylmethyl isonitriles from readily available methyl sulfinates or thiols. Mechanistic analysis reveals that the unusual nucleophlicity of the alkyl sulfinates arises from the in situ release of sulfinic acids.

Introduction

Sulfonylmethyl isonitriles such as TosMIC [(tolylsulfonyl)methyl isocyanide; Scheme 1; compound **3**, R^1 = *p*Tol], are extremely valuable precursors to multifarious isonitriles,[1] heterocycles,[2] and N-heterocyclic carbene complexes.[3] Traditionally, metal sulfinates **1** have featured prominently in the stoichiometric[4] and metal-catalyzed[5] syntheses of sulfonylmethyl isonitriles and sulfones.[6] The versatility of metal sulfinates **1** stems from the potent nucleophilicity[7] of the central sulfur atom, whose reaction with electrophiles directly generates sulfones (Scheme 1; **1** → **2**). The interception of metal sulfinates with iminium ions forges aminomethyl sulfones[8] **2**, which are readily dehydrated to give versatile sulfonyl isonitriles **3**.

Esterification of metal sulfinates **1** inverts the reactivity at the central sulfur atom to create alkyl sulfinates **4**, which are potent electrophiles with reactivities comparable to those of the corresponding sulfonyl chlorides[9] (Scheme 1). Organometallic addition to alkyl sulfinates provides a valuable route to sulfoxides **5**, particularly chiral sulfoxides.[10]

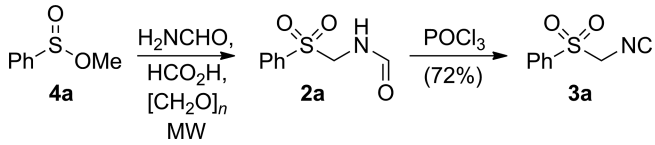
Although alkyl sulfinates are electrophilic, the presence of the two lone pairs of electrons on the adjacent oxygen atom increases the nucleophilicity of the central sulfur atom.[11] The potential nucleophilicity of alkyl sulfinates make them an attractive replacement for metal sulfinates **1**, which suffer from three significant disadvantages: few metal sulfinates are commercially available, many show modest solubility, and often metal sulfinates are not particularly stable.[12] Alkyl sulfinates, in contrast, have good stability, excellent solubility, and are rapidly synthesized from commercially available disulfides or thiols.[13] Using alkyl sulfinates as formal nucleophiles in Mannich reactions addresses the longstanding challenge of synthesizing structurally diverse sulfonylmethyl isonitriles (Scheme 1; **4** → **2** → **3**).



Scheme 1. Contrasting reactivity of sulfinate anions and esters.

Results and Discussion

In exploratory experiments, commercially sourced methyl benzenesulfinate (**4a**) was employed as a prototype in a Mannich reaction with formamide, formic acid, and paraformaldehyde (Scheme 2). In initial reaction optimization, microwave heating was used to facilitate precise tempera-



Scheme 2. Methyl sulfinate Mannich–dehydration sequence.

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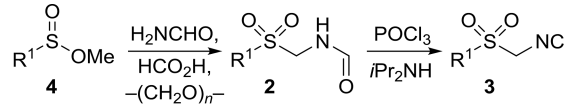
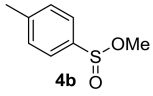
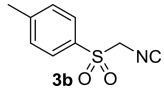
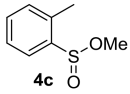
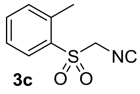
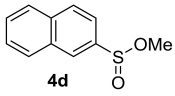
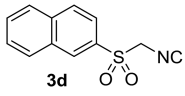
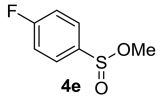
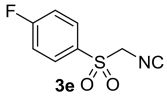
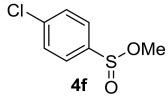
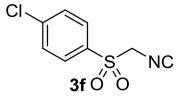
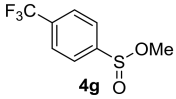
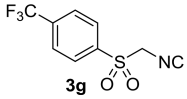
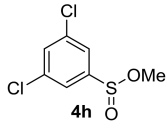
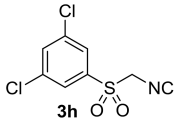
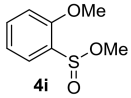
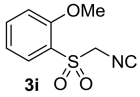
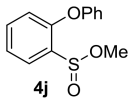
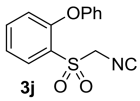
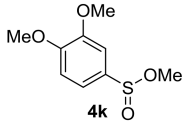
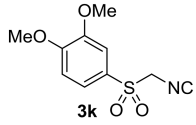
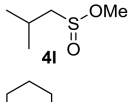
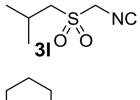
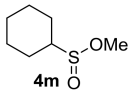
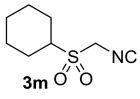
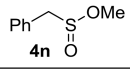
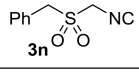
ture control, and formamide **2a** was formed at temperatures above 50 °C. Further experimentation identified 90–110 °C as optimal; at lower temperatures the reaction rate was slow, whereas higher temperatures resulted in lower yields. Solvent screening revealed an essential role for toluene,

Table 1. Conversion of methyl sulfinates to sulfonyl isonitriles.



Entry	Sulfinate	Isonitrile	Yield[d]
1	 **4b**	 **3b**	71%[b]
2	 **4c**	 **3c**	57%[b]
3	 **4d**	 **3d**	70%[a]
4	 **4e**	 **3e**	81%[b]
5	 **4f**	 **3f**	71%[b]
6	 **4g**	 **3g**	57%[a][c]
7	 **4h**	 **3h**	72%[a][c]
8	 **4i**	 **3i**	60%[b]
9	 **4j**	 **3j**	72%[a]
10	 **4k**	 **3k**	45%[a]
11	 **4l**	 **3l**	45%[b]
12	 **4m**	 **3m**	51%[a]
13	 **4n**	 **3n**	57%[a]

[a] Reaction was performed by heating with an oil bath. [b] Reaction was performed in a microwave reactor. [c] Et_3N was used instead of iPr_2NH. [d] Yield over two steps after purification.

which presumably reflects the unusual solvation; the biphasic mixture[14] formed at room temperature coalesces into a single phase on heating. After 2–3 h, formamide **2a** was obtained in high yield. The crude formamide (i.e., **2a**) was formed cleanly and efficiently, and, because of the strong absorption during silica gel chromatography,[15] was dehydrated without prior purification to directly give isocyanide **3a** (72% yield over two steps).

The generality of the two-step Mannich–dehydration sequence was ascertained by converting a series of methyl sulfinates into the corresponding sulfonylmethyl isonitriles (i.e., **3**; Table 1). Varying the electronic nature of the sulfinate had a minimal impact on the reaction efficiency (Table 1; compare Entries 1–3, 4–7, 8–10, and 11–13). The efficiency is sensitive to steric compression adjacent to the sulfinate, with *p*-tolylsulfinate **4b** reacting significantly more efficiently than *o*-tolylsulfinate **4c** (Table 1; Entries 1 and 2). Similarly, *o*-phenyoxysulfinate **4j** reacted more efficiently than *o*-methoxysulfinate **4i** (Table 1; Entries 8 and 9).[16] In general, the isolated yields of aliphatic sulfonylmethyl isonitriles **3l**–**3n** were lower, which reflects an instability of the isonitriles to purification and storage.[15] With the exception of **3l**, all the isonitriles had minimal odor.

In most instances, the reaction was equally efficient with microwave or conventional heating. Comparative microwave and conventional heating gave **4h** in yields of 89 and 87%, respectively. However, the reactions that generated **4m** and **4n** with microwave heating were sluggish, whereas conventional heating significantly improved the conversion. Although speculative, the pressure increase that accompanies microwave irradiation, and not conventional heating, may be responsible for the difference in efficiency.

Insight into the mechanism was obtained by comparing the relative conversion rates of a series of alkyl toluenesulfinates in the Mannich reaction (Figure 1). Increasing the steric demand of the alkyl substituent from methyl to ethyl and isopropyl decreased the conversion rate. A similar rate correlation occurs in the NBS-promoted racemization

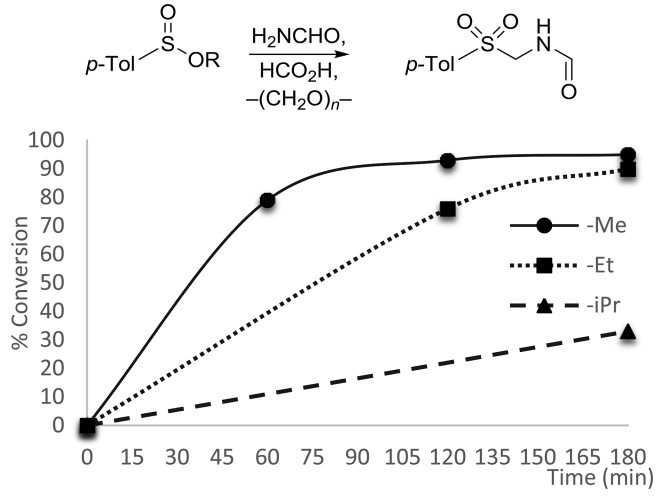
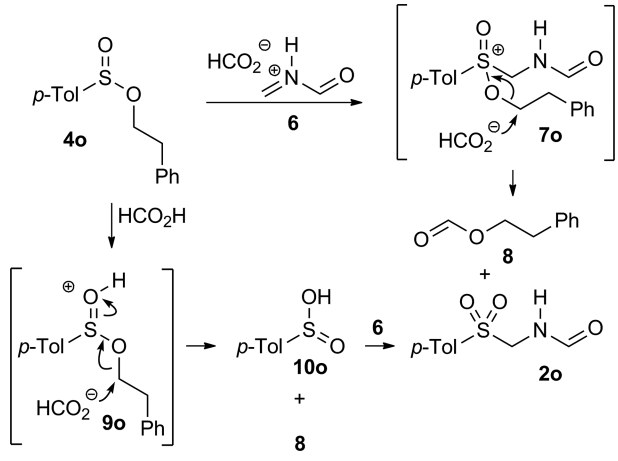


Figure 1. Influence of steric demand of the R group of pTolSO$_2$R on conversion.

of alkyl sulfinates, where methyl arylsulfinates racemize ten times faster than sterically more demanding isopropyl sulfinates.[11b]

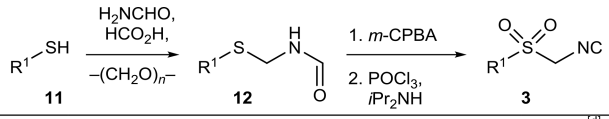
The dependence of the conversion rate on alkyl sulfinate steric demand is consistent with at least two different mechanisms: nucleophilic attack from the sulfinate followed by alkyl cleavage of a sulfurane intermediate[17] (Scheme 3; **4o** → **7o** → **2o**); or alkyl cleavage followed by nucleophilic attack from a sulfinic acid (**4o** → **9o** → **10o** → **2o**). Phenethyl sulfinate **4o**[18] was selected as a probe to differentiate between these two mechanisms, because the substantial molecular weight of the phenethyl substituent facilitates tracking the fate of the alkyl fragment. NMR spectroscopic analysis of the crude reaction mixture showed equal amounts of formate **8** and formamide **2o**,[19] which is consistent with an alkylation of formic acid by sulfonium salt **7o**, but does not distinguish between the two mechanisms. However, a control experiment in which **4o** was treated with formic acid in formamide *without* paraformaldehyde gave formate **8**, which implies that alkyl cleavage occurs before sulfinate attack. The mechanistic experiments suggest that the reaction proceeds by sulfinate protonation (**4o** → **9o**)[20] and formate alkylation by the sulfonium salt[21] to generate a sulfinic acid **10o**[22] as the true nucleophilic species, and that this then intercepts the iminium ion (i.e., **6**).[23]

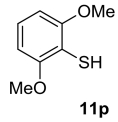
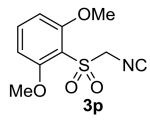
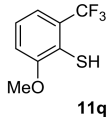
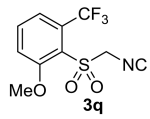
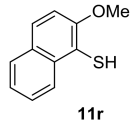
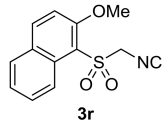
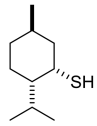
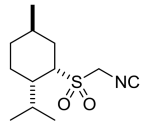
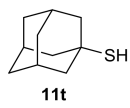
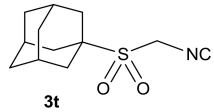


Scheme 3. Mechanistic pathways for the sulfinate Mannich reaction.

Insight into the reaction mechanism stimulated a second approach to sterically congested sulfonylmethyl isonitriles. The new strategy harnessed the greater nucleophilicity of sulfides to address the challenge of preparing isonitriles with sterically demanding alkyl substituents (Table 2).[24] Subjecting dimethoxythiophenol **11p** to the standard Mannich conditions gave the corresponding formamide (i.e., **12p**), which was sequentially oxidized with *m*CPBA (3-chloroperbenzoic acid) and dehydrated to give **3p** (Table 2; Entry 1). Analogous three-step sequences with the 2,6-disubstituted thiol **11q**, 1,2-substituted naphthalene **11r**, and even adamantane **11t** formed the corresponding isonitriles (Table 2; Entries 2 and 3). None of these isonitriles (i.e., **3p**–**3t**) were accessible by the methyl sulfinate method. Subjecting menthol-derived thiol **11s** to the Mannich–oxidation–dehydration sequence efficiently gave isocyanide **3s**, thus demonstrating the viability of preparing chiral, secondary sulfonylmethyl isonitriles (Table 2; Entry 4).

Table 2. Three-step sulfide to isonitrile synthesis.



Entry	Thiol	Isonitrile	Yield[d]
1[a]	 **11p**	 **3p**	40%
2[a,c]	 **11q**	 **3q**	46%
3[b]	 **11r**	 **3r**	56%
4[a]	 **11s**	 **3s**	55%
5[a]	 **11t**	 **3t**	32%

[a] Heating was performed with a conventional oil bath. [b] Microwave heating was used. [c] Et_3N was used instead of iPr_2NH. [d] Yields over three steps after purification.

Conclusions

A diverse array of sulfonylmethyl isonitriles were easily prepared in Mannich-type condensations with alkyl sulfinates or thiols. The strategy features a formal polarity reversal of alkyl sulfinates through in situ cleavage to nucleophilic sulfonic acids. The resulting formamides are readily dehydrated to provide an efficient synthesis of sulfonylmethyl isonitriles. This method demonstrates that alkyl sulfinates are a practical alternative to metal sulfinates in providing access to a diverse range of sulfonylmethyl isonitriles.

Experimental Section

Representative Experimental Procedure: The methyl sulfinate, paraformaldehyde (5 equiv.), formamide (6 equiv.), formic acid (5 equiv.), and toluene (5 equiv.) were added sequentially to a Biotage® microwave vial. The vial was capped and purged with N_2, and then it was irradiated at 100 °C. In cases where the internal pressure rose above 20 psi, the vial was vented after 30 min, and then the heating was continued. After 3 h, the contents were poured

onto an ice/water mixture, and the resulting mixture was extracted with EtOAc (4×). The combined organic layers were washed with brine, and dried (Na_2SO_4). Some formamides solidified upon cooling, and could be recrystallized from benzene/pentane. All formamides were sufficiently pure to be used directly in the dehydration reaction (after complete removal of volatiles).

A round-bottomed flask containing the crude formamide was purged with N_2 (3×), and then a 2:1 mixture of THF/MeCN (1.5 M) was added to dissolve the formamide. The flask was cooled to –10 °C, *i*Pr_2NH was added dropwise (9.3 equiv.), and $POCl_3$ (3.3 equiv.) was added dropwise at a sufficiently slow rate to keep the temperature below 5 °C. After 1 h, the mixture was poured onto a 50:50 mixture of ice/$NaHCO_3$ (satd. aq.). The resulting mixture was extracted with CH_2Cl_2 (4×), and the combined organic layers were washed with brine and dried (Na_2SO_4). The crude products were prepurified by passing through a short silica gel plug, eluting with hexanes/diethyl ether (70:30), and then purified by radial chromatography. Complete experimental details are provided in the Supporting Information.

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[19] Purification gave sulfone **2o** in 40% yield, and formate **8** in 22% yield. Presumably, the lower isolated yield of formate **8** is due to easy hydrolysis during silica gel chromatography.

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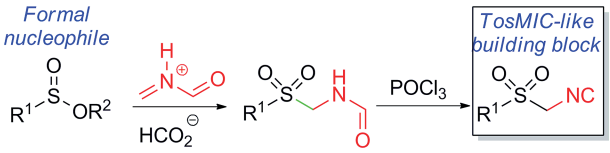

Alkyl sulfinates function as formal nucleophiles in Mannich reactions. Dehydration of the resulting *N*-(sulfonylmethyl)formamides gives TosMIC [(tolylsulfonyl)methyl isocyanide] analogs in an efficient two-step synthesis. The strategy provides a rapid, general, and efficient synthesis of sulfonylmethyl isonitriles by formally reversing the usual role of alkyl sulfinates as electrophiles.

Keywords: Sulfinates / Isonitriles / Umpolung / Isocyanides / Nucleophilic addition / Mannich reaction

