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Letter

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A General, One-Pot Method for the Synthesis of Sulfinic Acids from Methyl Sulfones

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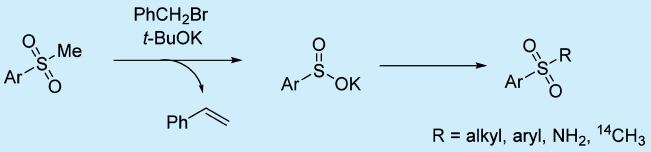
Supporting Information

ABSTRACT: A simple and efficient method for converting methyl sulfones to sulfinic acids is described. The process involves alkylation with a benzylic halide, followed by *in situ* elimination of the resulting styrene in the presence of excess base to yield a sulfinic acid in a single reaction process. The usefulness of the alkylation−elimination sequence is demonstrated by generating a variety of sulfinic acids from methyl sulfones. Late stage functionalization and ^{14}C-labeling of several biologically active methyl sulfones were accessed via sulfinate intermediates.

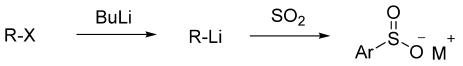


Sulfone and sulfonamide groups are an important functionality often found in biologically active molecules. Many methodologies are available to prepare sulfones, and several of these methods involve sulfinic acid precursors.[1] Sulfinic acids are also precursors toward sulfonamides;[2] however, only a few practical methods are available to prepare organo-sulfinic acids. In this letter we report a mild one-step, general method starting from methyl sulfones.[3] In this context, the methyl sulfone group may serve as a protected sulfinic acid since methyl sulfones are compatible with a wider range of chemistry and, upon conversion to the sulfinate, may allow access to more efficient strategies toward preparation of sulfone or sulfonamide targets.

Initial demonstration of the methodology was effected by development of operationally simple chemistry to convert methyl sulfones to sulfinic acids. We further demonstrated the utility of this methodology by conversion of methyl sulfone containing drug candidates to diaryl sulfones, sulfonamides, and ^{14}C-methyl sulfones via their sulfinate intermediates.

Arene sulfinic acid salts are often generated from aryl halides by reaction of arylmetal reagents with sulfur dioxide (Scheme 1).[4] However, functional group incompatibility to the strongly basic and nucleophilic conditions can often be problematic applying this methodology for late stage incorporation. A viable alternative was demonstrated using 3-methoxy-3-oxopropane-1-sulfinate (SMOPS),[5] a commercially available yet uncommon starting material, which couples with alkyl and aryl halides and, upon exposure to base, yields sulfinic acid salts.

Scheme 1. Sulfinic Acids from Halides



The methodology reported herein stems from the classic Julia olefination reaction where an arenesulfinate (typically *p*-toluenesulfinate) is the byproduct resulting from reduction of a *β*-hydroxyalkyl sulfone with a powerful single-electron reducing agent.[6] We envisioned that focusing on the elimination byproduct instead of the typically desired olefin may lead to a general approach to sulfinates, thereby making these important synthetic intermediates more attractive. Our initial strategy was to introduce a *β*-electron-withdrawing group, such as a nitrile, promoting *β*-elimination of the sulfinate upon exposure to base. Attempted alkylation of methyl phenyl sulfone with chloroacetonitrile under a variety of conditions failed to produce any products other than decomposed chloroacetonitrile and unreacted methyl phenyl sulfone. Work by Procopiou[7] and Deng[8] demonstrated that aryl methyl sulfones can be alkylated with benzylic and allylic halides and subsequently treated with a base to promote stereoselective formation of *E*-alkenes. Further examination of this chemistry in our laboratories with focus on the sulfinate product rather than the alkene revealed that a wide range of sulfinic acids could be generated.

Initial experiments revealed that the alkylation with a strong base such as potassium hexamethyldisilazane (KHMDS) was not necessary and potassium *tert*-butoxide (*t*-BuOK) is sufficient at room temperature. Attempted benzylation (1 equiv, BnCl) of methyl phenyl sulfone with KHMDS at −78 °C or *t*-BuOK at 23 °C resulted in a complex mixture of mono-, di-, and tribenzylated products along with unreacted starting material and trace amounts of benzenesulfinate and styrenes. In an effort to avoid these complex reaction outcomes, we explored a tandem alkylation/elimination sequence to generate the sulfinate. This one-pot process was made feasible by utilizing excess base whereby the monobenzylated sulfone is transient and undergoes immediate elimination (Scheme 2). In practice, dropwise addition of benzyl bromide (1.3 equiv) to a tetrahydrofuran (THF) solution of methyl phenyl sulfone and

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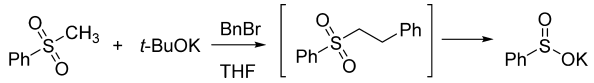
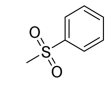
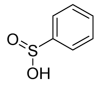
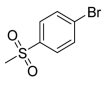
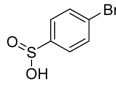
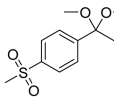
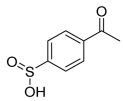
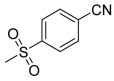
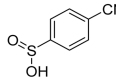
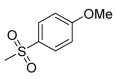
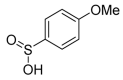
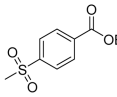
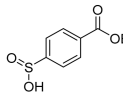
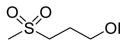
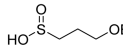
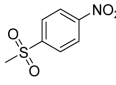
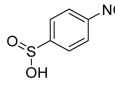
Scheme 2



t-BuOK (2.5 equiv) at room temperature provided a precipitated mixture of potassium benzenesulfinate within minutes of adding benzyl bromide. THF is a poor solvent for sulfinic acid alkylation; thus, benzylated sulfone products are not observed. In addition, the poor solubility of the sulfinate salt in THF allowed the desired sulfinate product to be filtered from the reaction mixture in 98% yield. We explored several readily available methyl sulfones using the same procedure (Table 1, method **A**). For sulfones bearing more sensitive

Table 1. Sulfinic Acids from Methyl Sulfones[a]

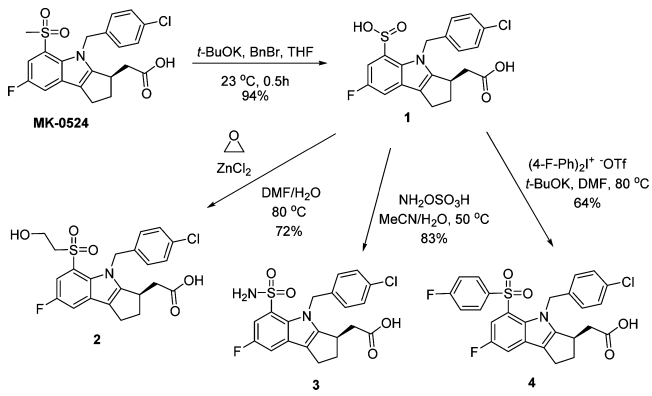
entry	methyl sulfone	sulfinic acid	method	yield (%)
1			**A**	98
2			**A**	79
3			**A**	76
4			**B**	78
5			**B**	98
6			**B**	45
7			**C**	30
8			**D**	51

[a]Conditions: (method **A**) *t*-BuOK, BnBr, THF, 23 °C, 1 h; (method **B**) *t*-BuOK, 2,4-difluorobenzyl bromide, THF, −78 °C to −10 °C; (method **C**) (i) LDA, BnBr, THF, −78 °C; (ii) *t*-BuOK, THF, 23 °C; (method **D**) *t*-BuONa, BnBr, THF, 23 °C, 1 h.

functionality such as nitriles and esters (Table 1, entries 4 and 6) we developed a modified procedure involving low temperature alkylation with 2,4-difluorobenzyl bromide. A selective alkylation was achieved on 3-benzyloxypropyl methyl sulfone (Table 1, entry 7) using LDA and benzyl bromide to provide the 3-benzyloxypropanesulfinic acid in 30% assay yield. The nitrobenzene substrate (Table 1, entry 8) did not produce any product with *t*-BuOK; however, use of *t*-BuONa provided a moderate 51% yield of sulfinic acid product.

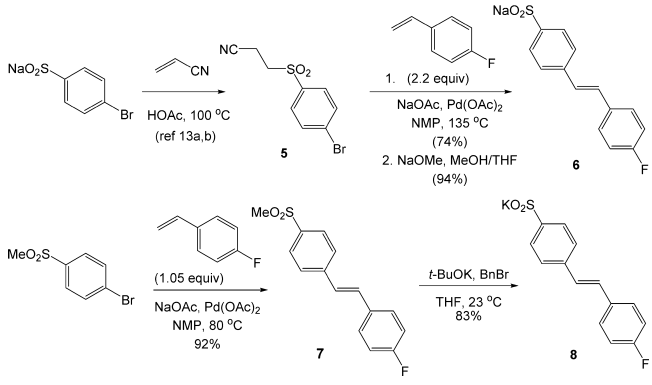
We next applied the chemistry to biologically active compounds discovered at Merck. The methyl sulfone to sulfinate transformation may prove particularly useful for structure−activity relationship (SAR) studies since a sulfinate intermediate produced late in a synthesis provides a useful point of diversity. To illustrate, Laropiprant (MK-0524), a potent and selective prostaglandin D2 (PGD2) receptor antagonist,[9] was converted to sulfinic acid **1** in 94% yield (Scheme 3). The utility of this chemical transformation is demonstrated by the preparation of β-hydroxysulfone **2**,[10] sulfonamide **3**,[11] and biarylsulfone **4**.[12]

Scheme 3



When protection of the sulfino group is required, aryl 2-cyanoethyl sulfones can be prepared from the reaction of the sulfinate salt with acrylonitrile. This strategy was recently used to prepare a series of stilbene sulfinates as $5HT_{2A}$ antagonists (Scheme 4).[13] Starting from sodium 4-bromobenzenesulfinate,

Scheme 4



the protected sulfone **5** underwent Heck coupling with excess 4-fluorostyrene to provide stilbene **6** after the base labile protecting group was removed to yield the sulfinate which provided a core structure for SAR studies. Here we demonstrate a more efficient approach by performing the Heck coupling on 4-bromophenyl methyl sulfone to provide stilbene **7** followed by conversion to sulfinate **8** via the one-step benzylation/elimination sequence. The methyl sulfone, acting as a latent sulfinate, is more tolerant to the Heck coupling conditions, and an excess of alkene was not required.[14]

Etoricoxib (MK-0663) was of particular interest due to the need to prepare a ^{14}C-labeled version of MK-0663. We envisioned conversion of MK-0663 to its sulfinate **9** followed

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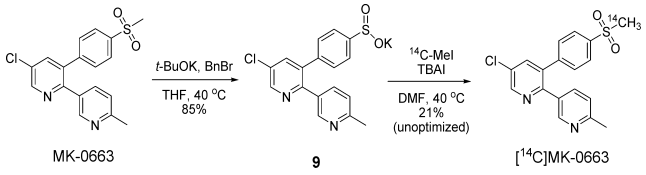
Org. Lett. XXXX, XXX, XXX−XXX

by alkylation with ^{14}C-MeI (Scheme 5). Using the standard conditions (BnBr, *t*-BuOK, 23 °C) sulfinate **9** was generated as

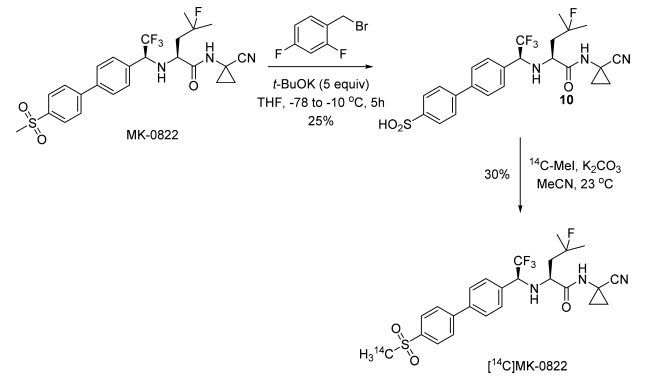
Scheme 5



a crystalline salt in 85% yield. Alkylation with MeI (1 equiv) in DMF at 23 °C led to the formation of several products due to competitive pyridine N-alkylation. The selectivity issue was addressed by the addition of a phase transfer catalyst such as tetrabutylammonium iodide (TBAI) to provide only the sulfone product. This two-step, high-yielding route demonstrates a remarkable improvement over the previously reported [^{14}C]MK-0663 synthesis.[15]

Odanacatib (MK-0822) **1**, identified as a potent and selective inhibitor of Cathepsin K,[16] is in late stage clinical trials. A ^{14}C-labeled tracer was required for environmental risk assessment.[17] Using a modified approach due to the sensitive functionality present, we successfully generated sulfinate **10** in 25% yield (Scheme 6). Although the yield of this key intermediate was

Scheme 6



modest, it provided an efficient tactical approach, considering an alternative would have required the design of a new multistep synthesis possibly involving several radioactive intermediates. Furthermore, as in the case of most clinical drug candidates, bulk quantities of odanacatib were readily available[18] and only milligram quantities of radioactive ^{14}C compounds are typically required for routine tracer studies. Subsequent alkylation of sulfinate **10** with ^{14}C-MeI in MeCN provided [^{14}C]MK-0822.

In conclusion we have developed a one-step conversion of methyl sulfones to sulfinates and have applied this chemistry to a range of substrates to demonstrate its application in synthesis. This late stage functionalization protocol affords a practical point of diversity in targets of significant complexity and provides a convenient method to incorporate ^{14}C into bioactive molecules containing a methyl sulfone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02723.

Experimental procedure and data (PDF)

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Notes

The authors declare no competing financial interest.

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