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Scalable Preparation of 4,4-Disubstituted Six-Membered Cyclic Sulfones

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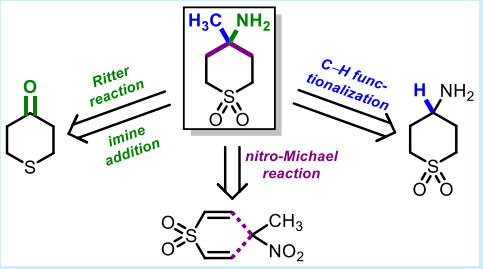
ABSTRACT: We provide an account of synthetic strategies aimed at the efficient preparation of 4-amino-4-methyltetrahydro-2*H*-thiopyran 1,1-dioxide (**3**), an important cyclic sulfone building block for medicinal chemistry. A practical and scalable protocol has been developed that readily gives access to the title compound from commercially available and inexpensive starting materials. In addition, this novel approach has enabled the synthesis of various related 4,4-disubstituted cyclic sulfone derivatives that serve as valuable structural motifs for drug discovery.



Sulfones have found extensive applications as versatile building blocks in organic synthesis[1] and in the field of medicinal chemistry.[2] Acting as ligands in a protein environment, sulfonyl groups frequently exhibit a dual character, functioning simultaneously as hydrogen bond acceptors as well as interacting with hydrophobic groups.[2b] The unique properties of these polar, metabolically stable groups thus renders their incorporation especially attractive in pharmaceuticals.[3] In some cases, conformationally restrained cyclic sulfones have been discovered to be particularly beneficial in enhancing binding to the biological targets,[4] leading to diverse drug candidates containing this substructure being reported (Figure 1).[5] In particular, six-membered aliphatic sulfones are frequently explored as bioisosteres of tetrahydropyran and piperidine derivatives due to their highly favorable pharmacokinetic profiles.[6]

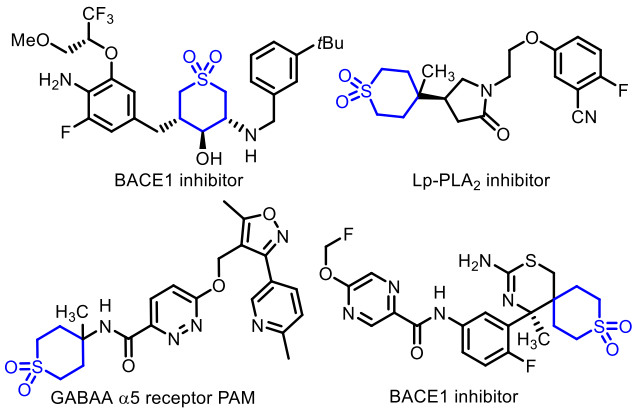


Figure 1. Importance of six-membered aliphatic sulfones in medicinal chemistry.

In an effort to enable preclinical toxicological studies in a medicinal chemistry project, we required facile and large-scale access to amides with an appended six-membered cyclic sulfone of the general structure **1** (Figure 2A). A literature survey revealed that this moiety is commonly introduced via amide formation of a carboxylic acid with amino sulfide **2**, followed by oxidation of the thioether functionality to the sulfone.[7] For our purposes, this two-step approach was deemed unsuitable due to the sulfide oxidation not being tolerated by other incorporated functional groups as well as the high cost of **2**. We instead were attracted to employ the more oxidized analogue, amino sulfone **3** (Figure 2B), in the amide-coupling step. Besides gaining access to **1** with increased synthetic efficiency, we importantly would avoid the problematic late-stage oxidation. To the best of our knowledge, no synthesis of **3** has been reported in the literature, and due to limited commercial availability (at a prohibitive cost), sufficient quantities of this key building block could not be acquired in the short term. As such, we strove to develop a practical, efficient, and scalable protocol that would readily give access to decagram quantities of **3**. Following consideration of various retrosyntheses, and assessing the availability of the respective starting materials within a short timeline, we prioritized route scouting efforts utilizing ketone **4**, amine **5**, sulfide **6**, and

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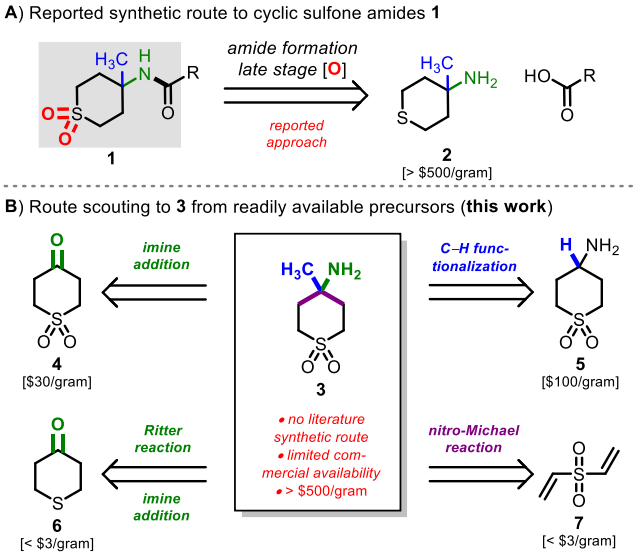
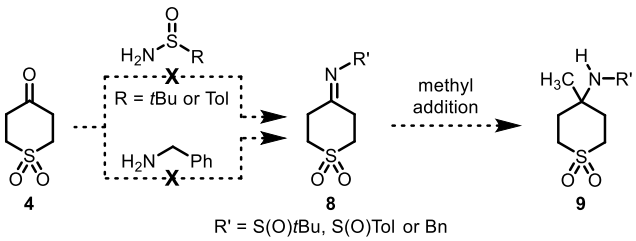


Figure 2. Retrosynthesis of amino sulfone **3**.

divinyl sulfone **7** as viable, low-cost precursors.[8] Herein, we summarize the exploration of various synthetic strategies including classical imine chemistry, α-C−H functionalization, Ritter reaction, and nitroalkane-Michael addition to ultimately establish an efficient and practical preparation of **3**.

In an early synthetic undertaking, we envisioned that the high oxidation state of readily available precursor ketone **4** could be leveraged for developing a concise route to amino sulfone **3**. Along these lines, we foresaw conversion of **4** to an imine, followed by nucleophilic 1,2-addition and deprotection of the resulting secondary amine derivative (Scheme 1). In

Scheme 1. Attempted Synthesis of Imine 8[a]

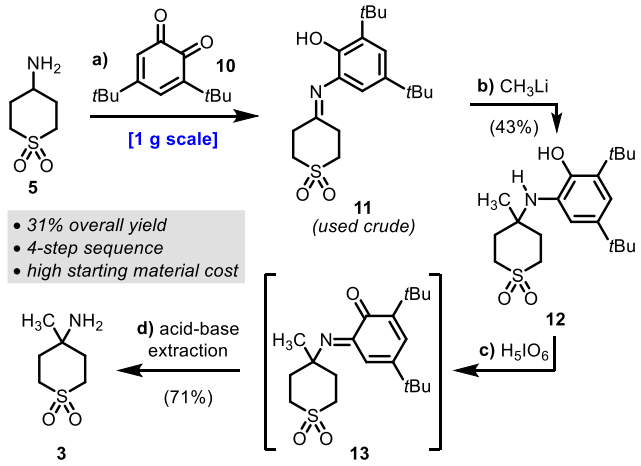


[a]Selected condensation conditions investigated: toluene, 110 °C; 4 Å molecular sieves; $Ti(OEt)_4$; $MgSO_4$.

practice, execution of this straightforward plan proved unexpectedly problematic: Condensation of ketone **4** with benzylamine[9] or classical sulfinamides[10] under a variety of thermal or Lewis acid promoted conditions failed to provide imines of type **8**, and instead, we observed formation of complex product mixtures. To avoid isolation of the supposedly unstable intermediate **8**, telescoping the reaction mixture from the imine condensation with the ensuing organometal addition (CH_3MgBr or CH_3Li) to give **9** was also investigated, yet these attempts remained equally unsuccessful.

In parallel to the attempted route outlined in Scheme 1, we were drawn to a distinct approach involving conversion of commercially available amine **5**[11] to the title α-tertiary amine **3** by introduction of the requisite methyl group via a formal α-C−H functionalization (Scheme 2). In this respect, modified

Scheme 2. α-C−H Functionalization Approach[a]



[a]Reagents and conditions: (a) **10**, 1,2-dichloroethane, 23 °C; (b) CH_3Li, *N,N,N,N*-tetramethylethyldiamine, toluene, Et_2O, −78 to 23 °C (43%, two steps); (c) H_5IO_6, CH_3CN, H_2O, 0 °C; (d) acid−base extraction (71%).

conditions of Corey's seminal and bioinspired protocol for generation of ketimines were investigated.[12] In the first step, amine **5** underwent quinone-mediated oxidation to afford intermediate ketimine **11** as a result of condensation followed by an in situ [1,5] H-shift. Subsequent addition of methyllithium then furnished amine **12**. We found orthoperiodic acid to be superior to reported oxidative hydrolytic workup conditions (I_2, aq NaOH)[12d] for detaching the hydroxyarene and, following an acid−base extraction, enabling clean isolation of amino sulfone **3**. Although this outlined synthetic route to **3** is concise, it proved problematic for scale-up due to the necessity for a large excess of methyllithium (6 equiv) in the conversion of **11** to **12** and the poor solubility of starting amine **5**. Furthermore, the high price of **5** compared less favorably to the other precursors (Figure 2B).

At this stage we returned to a strategy involving imine chemistry and it was envisioned that utilizing sulfide **6**,[8] rather than the more oxidized analogue **4** (Figure 2B), might render the corresponding imine formation feasible and obviate the putative interference of the sulfone functionality in this step (Scheme 3, left). Indeed, titanium(IV) ethoxide successfully promoted condensation of 2-methyl-2-propanesulfinamide with **6** to give imine **14**, albeit in moderate yield due to the instability of this intermediate.[13] After methylmagnesium bromide addition to **14** furnished **15**, we explored installation of the sulfone. Using *m*-CPBA or Oxone, we encountered concomitant oxidation of the sulfinamide moiety, affording the corresponding sulfone−sulfonamide product. Cleavage of the N−S bond in this sterically encumbered sulfonamide required harsh conditions (trifluoromethanesulfonic acid, 23 °C, 4 h) and resulted in a very low yield (<5%) of amino sulfone **3**. Therefore, we resorted to first convert **15** to carbamate **16**, which cleanly underwent oxidation to afford the corresponding sulfone. Finally, treatment of this intermediate with hydrochloric acid unveiled the α-tertiary amine and, after filtration, provided spectroscopically pure amino sulfone salt (**3**·**HCl**). The outlined synthetic approach proved scalable and later allowed preparation of >350 g of **3**·**HCl**. While serviceable, the instability of the intermediate imine **14** was a clear drawback in

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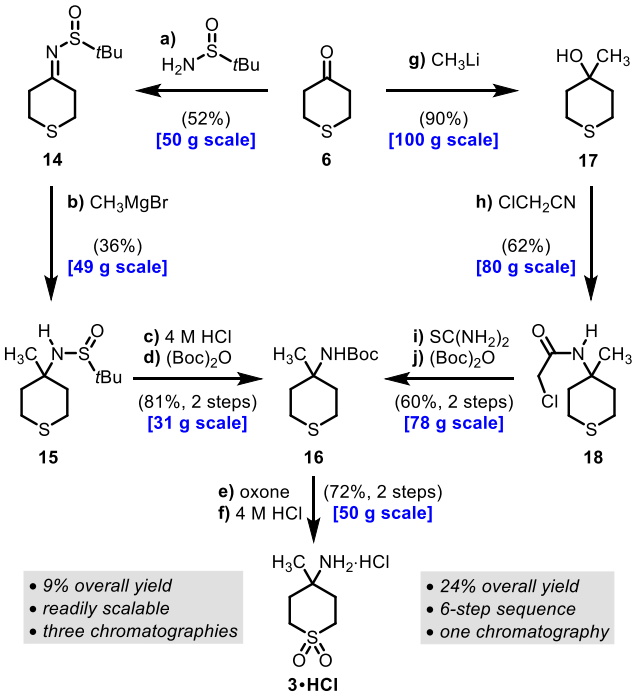
Scheme 3. Sulfinyl Imine and Ritter Reaction Route[a]



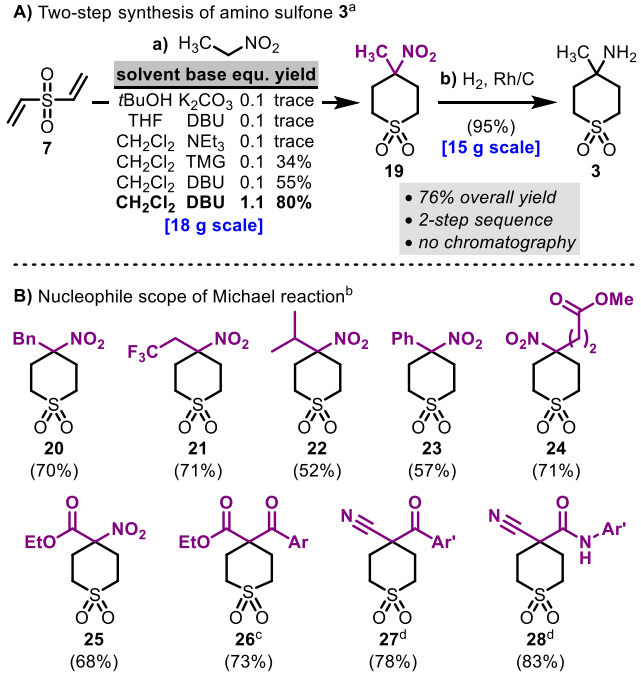
[a]Reagents and conditions: (a) *t*BuS(O)NH_2, $Ti(OEt)_4$, THF, 70 °C (52%); (b) CH_3MgBr, THF, 0 °C (36%); (c) 4 M HCl, EtOAc, 20 °C (85%); (d) $(Boc)_2O$, NEt_3, CH_2Cl_2, 50 °C (95%); (e) oxone, $NaHCO_3$, CH_3CN, H_2O, 0 to 20 °C (75%); (f) 4 M HCl, 1,4-dioxane, 0 to 20 °C (96%); (g) CH_3Li, THF, −78 °C (90%); (h) $ClCH_2CN$, H_2SO_4, AcOH, CH_2Cl_2, 0 to 20 °C (62%); (i) thiourea, AcOH, EtOH, 80 °C; (j) $(Boc)_2O$, 2 M aq NaOH, 1,4-dioxane, 0 to 20 °C (60%, two steps). THF = tetrahydrofuran, Ac = CH_3CO, Boc = C(O)O*t*Bu, DME = 1,2-dimethoxyethane.

this route and a major factor affecting the low overall yield (~9%), thus prompting us to pursue further strategies.

As an alternative to the sulfinyl imine route, we investigated installation of the amine functionality after introduction of the methyl group via formal nitrogen addition to a tertiary carbocation. Accordingly, in the first step, sulfide **6** was treated with methyllithium to furnish tertiary alcohol **17** in 90% yield on a 100 g scale (Scheme 3, right). Initially we pursued a Ritter reaction[14] of **17** with acetonitrile (not shown) to give the corresponding α-tertiary acetamide. However, under various forcing acidic, basic, or hydridic[15] conditions, the ensuing *N*-acetyl deprotection could not be smoothly accomplished; the reaction resulted in either unreacted starting material or led to nonspecific decomposition. Cognizant that haloacetyl groups can generally be cleaved under milder conditions with thiourea,[16] we thus turned to converting tertiary alcohol **17** into the related chloroacetamide **18**. Although on a small scale (<1 g) this Ritter reaction proceeded well using standard conditions,[17] formation of a thick reaction mixture complicated stirring upon scale-up, and the isolated yield of **18** dropped significantly. Careful experimentation revealed that dropwise addition of a solution of **17** and chloroacetonitrile in dichloromethane to a mixture of sulfuric and acetic acid at 0 °C circumvented these issues, and chloroacetamide **18** could be prepared in 62% yield on an 80 g scale. Next, removal of the haloacetyl group was achieved in a mixture of boiling ethanol and acetic acid in the presence of thiourea; the precipitated amine salt was directly converted to carbamate **16**, thus intercepting the sulfinyl imine route. Importantly, installation of the *tert*-butyl carbamate facilitated removal of the 2-aminothiazol-4(5*H*)-one byproduct at this stage and enabled facile liquid−liquid extraction of the product from the aqueous reaction mixture in the ensuing oxidation step. The described synthetic route proved practical and readily enabled preparation of >30 g of **3·HCl** in the largest single pass conducted (24% overall yield from **6**).

While the outlined route proved serviceable, we realized that, due to the need for chromatographic purification, further scalability would become unfavorable and time-consuming. Additionally, we were drawn to the opportunity of further simplifying the synthetic sequence and importantly gaining modular access to novel analogues of **3**. Thus, we finally turned our attention to a distinct synthetic route starting from divinyl sulfone **7**, which based on its use as a popular cross-linking agent is cheap and widely available in bulk quantities. We formally aimed to stitch together this bifunctional Michael acceptor with an ethylamine equivalent to give the desired six-membered ring heterocycle (Figure 2B). In practice, initial attempts of a base-mediated Michael reaction of nitroethane with **7** led to formation of large amounts of polymeric material and only trace amounts of nitro sulfone **19** could be detected in the reaction mixture (Scheme 4A). A survey of inorganic

Scheme 4. Nitroethane−Michael Approach[a]



[a]Reagents and conditions: (a) DBU, CH_2Cl_2, 23 °C (80%); (b) H_2 (50 psi), Rh/C (1 mol %), MeOH, 75 °C (95%). [b]Active methylene compound, divinyl sulfone, DBU, CH_2Cl_2, 23 °C. Yield of isolated products after purification by flash chromatography on silica gel. [c]Ar = *o*-F-phenyl. [d]Ar′ = *p*-Cl-phenyl. TMG = 1,1,3,3-tetramethylguanidine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

and organic bases across various solvents eventually revealed the combination of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane to be uniquely effective for this transformation. Under the optimized conditions (1.1 equiv DBU, dropwise addition of **7**), the undesired polymerization was largely suppressed, and after a simple aqueous hydrochloric

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acid wash to remove the amidine base, **19** was isolated cleanly in 80% yield (150 mmol scale). For the conversion of **19** to the corresponding amino sulfone **3**, we ultimately found hydrogenation using Rh/C (1 mol %) to be the most efficient reduction protocol on large scale,[18] furnishing **3** in 95% yield. The outlined two-step synthesis of the title compound stands most favorably compared to the other synthetic routes in terms of starting material cost, step count, and experimental practicality.

Following the successful development of a highly concise and scalable preparation of amino sulfone **3**, evaluation of a diverse set of other active methylene nucleophiles highlighted that this synthetic approach proved readily amenable to the preparation of related, valuable 4,4-disubstituted cyclic sulfones (Scheme 4B). The established conditions successfully promoted substituted alkyl nitro, benzylic nitro, and β-nitro ester derivatives to undergo the double Michael reaction with divinyl sulfone **7** and gave access to the corresponding cyclic sulfone products (**20**–**25**) in synthetically useful yields. Furthermore, we demonstrated that the scope of this transformation is not limited to nitroalkane nucleophiles, but also readily allowed preparation of functionalized sulfones starting from β-keto ester,[19] β-keto nitrile, and α-cyano amide derivatives (**26**–**28**).

In conclusion, we evaluated various synthetic strategies aimed at the preparation of amino sulfone **3** to ensure material supply of this building block for key analogue synthesis in preclinical safety studies. The development of a practical, efficient, and scalable protocol was governed by commercial availability of affordable starting materials within the necessary timeline. Following an optimized two-step sequence involving a double Michael addition of nitroethane to divinyl sulfone, the target compound **3** was readily synthesized in 76% overall yield. In addition, this novel approach has also enabled the preparation of related 4,4-disubstituted cyclic sulfones derived from a diverse set of active methylene nucleophiles. We anticipate the outlined procedures and investigated synthetic strategies will be of high value for researchers requiring not only scalable access to **3** but also to related, functionalized cyclic sulfone building blocks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04141.

Experimental details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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(8) The starting material $/gram prices stated are average values for purchase of decagram quantities from US chemical retailers available within a two-week time period (November 2020).

(9) The benzylimine derivative of **8** has been reported in the literature, yet clean isolation of this product could not be reproduced in our hands; see: Melnykov, K. P.; Artemenko, A. N.; Ivanenko, B. O.; Sokolenko, Y. M.; Nosik, P. S.; Ostapchuk, E. N.; Oleksandr, O.; Grygorenko, O. O.; Volochnyuk, D. M.; Ryabukhin, S. V. Scalable Synthesis of Biologically Relevant Spirocyclic Pyrrolidines. *ACS Omega* **2019**, *4*, 7498.

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