A Novel Route towards Bicyclo[1.1.1]pentane Sulfoxides from a Bench-Stable Starting Material

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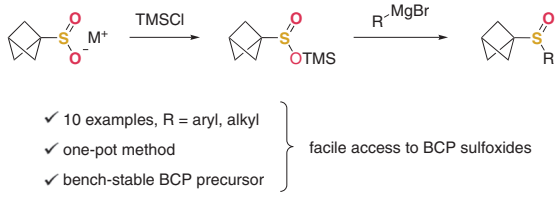
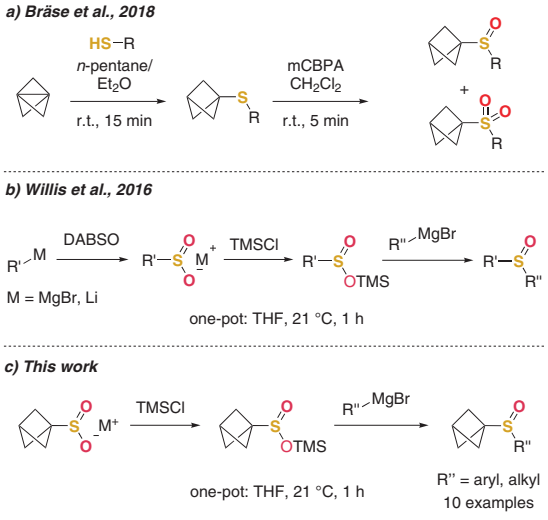


Abstract Bicyclopentanes (BCPs) are non-classical bioisosteres that have gained a lot of interest in drug discovery as non-conjugated rigid hydrocarbons. There has been substantial progress in the synthesis of carbon- and nitrogen-substituted derivatives using [1.1.1]propellane as a precursor, while sulfur-substituted BCPs are rather underdeveloped. This work investigates a new method for the synthesis of BCP-sulfoxides. Herein, a previously reported bench-stable sodium BCP-sulfinate precursor is converted, using a range of aryl and alkyl magnesium bromides, into unsymmetrical BCP-sulfoxides via a convenient one-pot procedure. Furthermore, the conversion of the obtained sulfoxides into sulfoximines is explored.

Key words bicyclo[1.1.1]pentane, sulfoxide, sulfoximine, bioisostere, one-pot, Grignard reagent

In medicinal chemistry, efforts are constantly being made to expand the available chemical space. This is not limited to modifying and substituting functional groups; new structures can swap entire basic building blocks. This concept is called bioisosterism, which means achieving a similar effect with a similar structure. One interesting three-dimensional building block that is increasingly being used as a bioisostere is bicyclopentane (BCP).[1] BCP consists of a cyclobutane that formally forms another cyclobutane via a bridging bond. The distance between the bridged carbons is 1.845 Å.[2] Due to their similar structures, BCPs are used in medicinal chemistry as bioisosteres of *para*-substituted phenyl rings or alkynes, i.e., groups forming a rigid linker of 180°.[3] Phenyl and other aryl groups are present in countless natural products and medicinal agents.[4] The substitution of aryl groups with bioisosteres (e.g., BCPs, cubanes or bicyclo[2.2.2]octanes) can alter the physical properties of a molecule, such as increasing water solubility, and improving metabolic stability as aromatic functional groups like phenols and anilines are metabolized faster than their aliphatic bioisosteres.[5] Furthermore, a change in the length of the linker can result in an increase, decrease, or even loss of the biological activity since the length of the linker is often crucial for binding at the active site of the target enzyme.[5a] Another prominent motif in medicinal chemistry is the sulfoxide group. Due to its ability to enhance the pharmacological properties of compounds like water solubility and membrane permeability, sulfoxides are often used in drugs (e.g., omeprazole and sulindac).[6] Sulfoxides can also be converted into sulfoximines, which can be further functionalized, for example, by *N*-arylation.[7] As the interest in BCPs as bioisostere motifs in medicinal chemistry is continuously growing, there is also an increasing demand for novel synthetic methodologies to modify the BCP scaffold and combine it with other pharmacophoric motifs such as sulfoxides (Scheme 1).

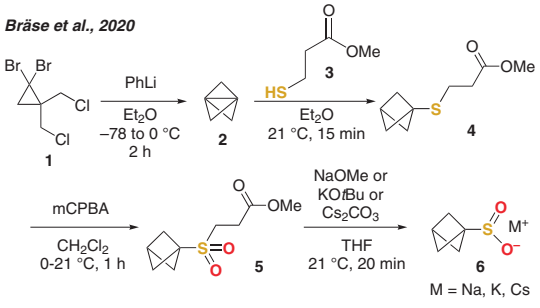


Scheme 1 Synthetic methods for unsymmetric sulfoxides

Our group previously reported the synthesis of BCP-functionalized sulfoxides by oxidation of the corresponding BCP-sulfide (Scheme 1a).[8] The BCP-sulfides are synthesized by thiol addition to [1.1.1]propellane. Thus, this route towards BCP-sulfoxides is less advantageous due to the low boiling point and elaborate preparation of [1.1.1]propellane.[9] Additionally, preparative work with thiols is challenging due to their odor, particularly in the case of small, volatile, and gaseous thiols.

In 2016, Willis et al. reported a one-pot synthesis of unsymmetrical sulfoxides using organometallic nucleophiles (Scheme 1b).[10] In this process, an organolithium or an organomagnesium species is first converted into a sulfinate silyl ester using 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO), followed by treatment with trimethylsilyl chloride (TMSCl). The resulting intermediate is subsequently converted into the target sulfoxide by the addition of a second Grignard reagent.

Based on this method, the present work aims to synthesize different BCP-sulfoxide derivatives. However, while Willis et al.[10] used an organometallic starting material which is converted into a sulfinate in situ using the sulfur dioxide surrogate DABSO, our approach utilizes a BCP-sulfinate as a convenient, bench-stable BCP precursor (Scheme 1c). In 2020, our group presented a concise and scalable protocol for the synthesis of sodium BCP-sulfinate (**6-Na**) through a thiol addition/oxidation/retro-Michael sequence (Scheme 2).[11] Since BCP-sulfinates are bench-stable solids, they enable facile access to BCP derivatives (e.g., sulfones and sulfoximines) while avoiding the volatile [1.1.1]propellane.[12]

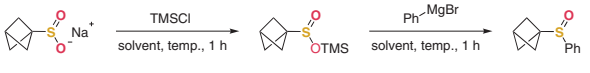


Scheme 2 Synthesis of BCP-sulfinates via a retro-Michael addition of a BCP-sulfone according to Bräse et al.

The original reaction conditions reported by Willis et al.[10] were adjusted and applied to prepare BCP-sulfinate **6**. Phenylmagnesium bromide was used as the Grignard reagent. Starting with the conditions in the literature, the reaction was optimized through variation of the solvent and the temperature (Table 1).

Under literature conditions, using THF as the solvent without any additional heating source (Table 1, entry 1), only 6% of the sulfoxide **8a** was isolated. Raising the temperature to 50 °C increased the yield by about a factor of 10 to 64% (entry 2). The product was also obtained using 1,4-dioxane at 50 °C, but the yield significantly decreased to 8%. Since the reaction was performed in closed crimp vials, the temperature was increased to 100 °C, even if the added TMS chloride had a boiling point of 57 °C. In this case, the yield decreased by about half compared to entry 3, which could be caused by evaporation of the TMSCl through the septum via cannula holes. Also, the sulfinate was not completely dissolved in THF and 1,4-dioxane, and the reaction was performed in a suspension. In 2-methyl-THF, on the other hand, BCP-sulfinate **6-Na** was completely soluble, increasing the yield to nearly 80% (entry 5).

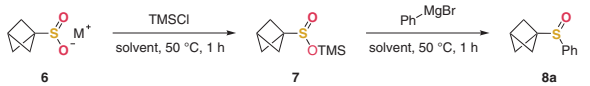
Table 1 Optimization of the Sulfoxide Synthesis According to Willis et al.



Entry	Solvent	Temp (°C)	Yield (%)
1	THF	21	6
2	THF	50	64
3	1,4-dioxane	50	8
4	1,4-dioxane	100	3
5	**2-methyl-THF**	**50**	**79**

After optimizing the reaction conditions, the influence of the counterion was investigated. Therefore, lithium, potassium, cesium, and rubidium sulfinates (**6**) were employed in the reaction under the optimized conditions. While the potassium and cesium sulfinates were synthesized according to the procedure of Bräse et al.[11] using KOt-Bu and Cs_2CO_3, the lithium and rubidium sulfinates were obtained by acidification, extraction and precipitation using the corresponding hydroxides LiOH and RbOH, since the

Table 2 Yields of Sulfoxide **8a** Depending on the Counterion of Compound **6**

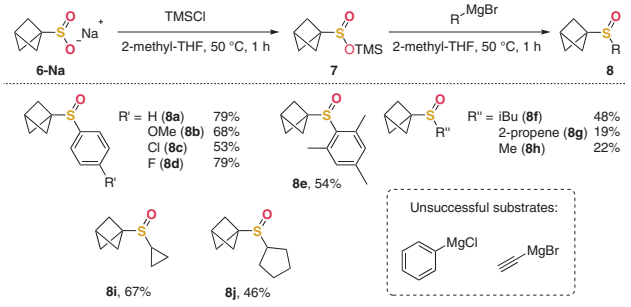


Entry	Counterion	Solvent	Yield (%)
1	Li	THF	54
2	Li	2-methyl-THF	49
3	Na	THF	64
4	**Na**	**2-methyl-THF**	**79**
5	K	THF	64
6	K	2-methyl-THF	70

synthesis according to Bräse et al. was not possible. ESI-MS successfully confirmed the formation of the potassium and lithium sulfinates. Unfortunately, the mass spectrum of the cesium and rubidium sulfinates showed only a single signal of low intensity due to the desired product, while an intense signal for the sodium sulfinate was detected. Thus, the subsequent reactions were performed with lithium, sodium, and potassium sulfinate only. In Table 2, the yields of sulfoxide **8a** are shown, using the different starting sulfinates in both THF and 2-methyl-THF.

In the reaction with lithium sulfinate, the yield in THF and 2-methyl THF was around 50% (Table 2, entries 1 and 2). The yields using sodium and potassium sulfinate were significantly higher with 64% in THF (entries 3 and 5), and 70% (entry 6) or 79% (entry 4) in 2-methyl-THF. This could be explained by the smaller size and higher electronegativity of the lithium counterion, resulting in a lower reactivity and solubility of **6**.

Using the optimized conditions and different Grignard reagents, a library of five aromatic- and five alkyl-substituted BCP-sulfoxides was synthesized from sodium sulfinate **6-Na**.[13] The reactions were performed on a 200 µmol to 1 mmol scale. The structures of the obtained sulfoxides **8a**?**j** are shown in Scheme 3.



Scheme 3 The library of sulfoxides (**8a–j**) synthesized from sulfinate **6-Na** using the optimized conditions

The alkyl-substituted sulfoxides were obtained in moderate to good yields of up to 67% (**8i**). Lower yields were observed for **8g** and **8h**, which were isolated in around 20% yield. In the case of the sulfoxide **8g** bearing a terminal alkene group, this can be explained by a Mislow–Evans rearrangement, wherein the synthesized sulfoxide rearranges to form an organic sulfonate.[14] The BCP-methyl sulfoxide **8h** could only be isolated with a reduced yield of 22% due to the slightly volatile properties of the molecule. While drying the compound under reduced pressure, the amount of **8h** decreased. No sulfoxides could be isolated from reactions with ethynylmagnesium bromide and phenylmagnesium chloride. In the reactions using aromatic magnesium bromides, the sulfoxide products were isolated in good yields ranging from 53% (**8c**) to 79% (**8a**, **8d**). No particular influence of the electron density and substitution pattern of the arylmagnesium bromides was observed. The sulfoxide **8e** with mesityl substitution was isolated in 54% yield. The ^{1}H NMR spectrum of **8e** shows signal broadening for the methyl groups at the *ortho*-positions in $CDCl_3$. Using deuterated methanol, the peak broadening is reduced (Figure 1).

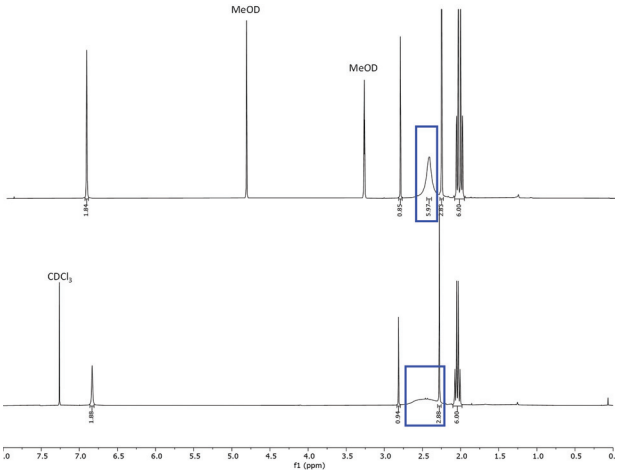
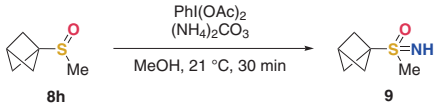


Figure 1 ^{1}H NMR spectra of the sulfoxide **8e** in MeOD (top) and $CDCl_3$ (bottom). The signal marked in blue corresponds to the two methyl groups at the *ortho*-positions. Peak broadening is evident in both spectra; however, MeOD enables better rotation of the methyl groups, resulting in a reduction of broadening. The broad signals indicate steric hindrance due to the *ortho* substitution and the sulfoxide.

This can be explained by steric congestion between the methyl groups and the oxygen on the sulfur. In earlier investigations, attempts to synthesize BCP-mesityl sulfoxides, sulfoximines, and BCP-2,6-dichloro sulfoximines were unsuccessful as the *ortho*-substituents prevented further functionalization of the corresponding BCP-sulfide.[7] In order to explore the scalability of this reaction, the synthesis of **8a** was also performed on larger scales (5 and 50 mmol, originally 1 mmol). It was observed that the yield dropped drastically on scale-up. In the case of the reaction on 5 mmol scale, even after a prolonged reaction time of 6 hours, only a 23% yield of **8a** could be isolated. In the 50 mmol reaction, only trace amounts of the product were detected. This effect can be explained by solubility issues arising on larger scales. Further optimization of the reaction conditions and solvent system would be necessary to ensure better scalability.

Since the previously reported synthetic route towards BCP-sulfoxides and sulfoximines was only suitable for liquid and solid thiol precursors, synthesizing the corresponding methyl sulfide and sulfoximines was not possible using the literature procedure.[8] This new synthetic route thus enables the synthesis of the methyl-substituted sulfoxide **8h**. Through reaction with bis(acetoxy)iodobenzene (BAIB, $PhI(OAc)_2$) and ammonium carbonate, sulfoxide **8h** could be converted into the methyl-substituted sulfoximine **9** in 80% yield (Scheme 4). This methyl-substituted sulfoximine is a

desirable compound in medicinal chemistry as BCP-sulfoximines combine two bioisosteres into one molecule and the building block itself can be incorporated easily by reaction of the free NH.[15]



Scheme 4 Synthesis of the BCP-methyl sulfoximine **9**. The synthesis of the sulfoxide **8h** and the corresponding sulfoximine **9** was previously impossible using the synthetic route in the literature,[8] since methyl thiol is gaseous.

In summary, we have established a concise method for the synthesis of a BCP-sulfoxide library using ten aromatic and aliphatic organomagnesium reagents in combination with our previously reported sodium BCP-sulfinate. The use of this BCP precursor offers several advantages over established routes towards BCP-sulfoxides, as it is bench-stable, offering convenient handling in contrast to synthetic approaches using [1.1.1]propellane. Furthermore, no repugnant volatile thiols are required to introduce the sulfur moiety. Through this approach, we successfully synthesized a methyl-substituted sulfoxide **8h**, which was previously inaccessible. Since the residues on the sulfoxides are introduced as Grignard reagents, the scope of this reaction could easily be expanded as bromide-substituted precursors are widely accessible. Additionally, further modification of the sulfur is possible, for example towards sulfoximines, another important bioisostere in medicinal chemistry.

Conflict of Interest

The authors declare no conflict of interest.

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Primary Data

The primary data can be found in the Chemotion Repository under the DOI: 10.14272/collection/LL_2023-07-25_6

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(13) **Sulfoxides 8a–j; General Procedure**
Na-6 (1.00 mmol, 1.00 equiv.) was dissolved in 2-MeTHF (2.00 mL) under argon. TMSCl (1.50 mmol, 1.50 equiv.) was added and the mixture was heated to 50 °C for 1 h. RMgBr (1.00 mmol, 1.00 equiv.) was added and the reaction was stirred for 1 h at 50 °C. The reaction was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with EtOAc (×3). The organic layers were collected and dried by the addition of Na_2SO_4. The mixture was filtered through a glass funnel and the solvent evaporated under reduced pressure. The crude residue was adsorbed on a small amount of Celite and was purified via column chromatography (cyclohexane/EtOAc, 5:1). Products **8a–j** were isolated in yields of 19–79%.
Bicyclo[1.1.1]pentyl 4-Methoxyphenyl Sulfoxide (8b)
Yield: 76.0 mg (68%); yellow oil; R_f = 0.10 (cyclohexane/EtOAc, 2:1). IR (ATR): 3452, 2969, 2915, 2880, 2840, 1594, 1493, 1460, 1407, 1302, 1248, 1203, 1130, 1085, 1026, 868, 830, 796, 773, 557, 524, 493, 463, 441, 387 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.45 (m, 2 H, $H_{aromatic}$), 7.04–7.00 (m, 2 H, $H_{aromatic}$), 3.86 (s, 3 H, OCH_3), 2.82 (s, 1 H, $C(CH_2)_3CH$), 1.89 (s, 6 H, $C(CH_2)_3CH$). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.8 (C_q, $C_{aromatic}$), 132.6 (C_q, $C_{aromatic}$), 126.0 (+, 2 C, $C_{aromatic}H$), 114.4 (+, 2 C, $C_{aromatic}H$), 55.5 (C_q, $C(CH_2)_3CH$), 55.5 (+, OCH_3), 48.7 (–, 3 C, $C(CH_2)_3CH$), 27.7 (+, $C(CH_2)_3CH$). MS (EI, 70 eV, 50 °C): *m*/*z* (%) = 222 (2) $[M]^+$, 169 (4) $[C_8H_8O_2S + H]^+$, 156 (14) $[C_7H_7O_2S + H]^+$, 155 (8) $[C_7H_7O_2S]^+$, 139

(6) $[C_7H_7OS]^+$, 108 (3) $[C_7H_7O + H]^+$, 100 (13) $[C_5H_7S]^+$, 67 (3) $[C_5H_7]^+$. HRMS (EI): m/z $[M]^+$ calcd for $C_{12}H_{14}O_2S^+$: 222.0715; found: 222.0714.

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