Synthesis of *N*-alkylsulfonamides by borane–dimethyl sulfide reduction of *N*-acylsulfonamides

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ABSTRACT

A convenient synthesis of *N*-alkylsulfonamides in good to excellent yields by reduction of *N*-acylsulfonamides using $\text{BH}_3\cdot\text{SMe}_2$ is described. This methodology presents an attractive alternative for sulfonamide formation.

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Sulfonamides have long been of significant interest to synthetic chemists, most notably due to their wide range of biological activities.^{1,2} Early sulfonamide-based drugs (sulfa drugs) were used as antibiotics, but sulfonamides are now found in a number of different drug classes.³ Sulfonamides also represent useful “protected” intermediates for the synthesis of primary and secondary amines, which can be afforded via desulfonylation under mild conditions.⁴

Sulfonamides are frequently synthesised by sulfonylation of amines with sulfonyl chlorides, in the presence of a base.^{5,6} Despite a number of other known methods,⁷⁻¹³ this remains the most common synthetic strategy. However, the use of sulfonyl chlorides can be problematic, since they are often difficult to handle and store due to their instability.¹⁴ Therefore, the development of synthetic methods that avoid the use of sulfonyl chlorides is highly desirable.

As part of a program directed towards hydrogen-bonding organocatalysts, we sought a general and convenient synthetic route to a variety of bis-*N*-alkylsulfonamides. For this work, we envisaged that the requisite sulfonamides could be obtained by the reduction of *N*-acylsulfonamides. *N*-Acylsulfonamides present attractive intermediates due to their stability, ease of synthesis and generally crystalline nature. We sought to extend the methodology of Belletire and Fry, involving the synthesis of sulfonamides from *N*-acylsulfonamides, using $\text{BH}_3\cdot\text{SMe}_2$, *en route* to primary amines.¹⁵ Since this original report, the method has not found common use, although more aggressive reagents, e.g., LiAlH_4 and $\text{BH}_3\cdot\text{THF}$ have been utilised.¹⁶⁻²⁰

We report a simple, efficient and general method for the reduction of *N*-acylsulfonamides to the corresponding sulfonamides using $\text{BH}_3\cdot\text{SMe}_2$ (Scheme 1). EDC-mediated coupling of carboxylic acids **1** with primary sulfonamides **2** provided convenient access to the substrate *N*-acylsulfonamides **3**.

Scheme 1. Formation and reduction of *N*-acylsulfonamides

Conditions for $\text{BH}_3\cdot\text{SMe}_2$ reduction of *N*-acylsulfonamides were optimised using *cis*-*N*-acylsulfonamide **3i** (Table 1). Treatment of **3i** with $\text{BH}_3\cdot\text{SMe}_2$ (4 equiv.) in THF for 72 hours at r.t., followed by heating to 55 °C for 24 hours gave sulfonamide **4i** in 29% yield. Increasing the quantity of $\text{BH}_3\cdot\text{SMe}_2$ to 8 equivalents gave **4i** in 57% yield after 18 hours at reflux. However, reducing the reaction time to 2 hours proved more convenient and provided a slightly better 64% yield of **4i**. Indeed, the reduction generally proceeds to completion within 15–120 minutes under these conditions. With these optimised conditions at hand, the scope of the transformation was further investigated (Table 2).

Table 2. Scope of the $\text{BH}_3\cdot\text{SMe}_2$ reduction of *N*-acylsulfonamides.

Entry	Substrate	Time	Product	Yield ^a %
1		15 min		87
2		15 min		67

Table 1. Optimisation of the reaction conditions.

Entry	Conditions	Yield ^a (%)
1	$\text{BH}_3\cdot\text{SMe}_2$ (4 equiv), THF, r.t., 72 h, then 55 °C, 24 h.	29
2	$\text{BH}_3\cdot\text{SMe}_2$ (8 equiv), THF, reflux, 18 h.	57
3	$\text{BH}_3\cdot\text{SMe}_2$ (8 equiv), THF, reflux, 2 h.	64

^a Yields are given for isolated products.

Treatment of *N*-acetylbenzenesulfonamide (**3a**) with $\text{BH}_3\cdot\text{SMe}_2$ provided *N*-ethylbenzenesulfonamide (**4a**) in good yield (87%) after 15 minutes. The more hindered *N*-pivaloylsulfonamide **3b** produced the corresponding sulfonamide **4b** in moderate yield (67%), whereas *N*-benzoylsulfonamide **3c** gave **4c** quantitatively (100%). Pleasingly, the more electron deficient *N*-(4-nitrobenzoyl)sulfonamide **3d**, also afforded the corresponding sulfonamide **4d** in excellent yield (94%). When 3,5-bis(trifluoromethyl)benzoyl substituted compounds, **3e** and **3f**, were used, the corresponding sulfonamides **4e** and **4f** were produced in 48% and 71% yields, respectively, while 4-(trifluoromethyl)benzoylsulfonamide **3g** provided **4g** in 67% yield. The suitability of *N*-acyltrifluoromethylsulfonamides as substrates was demonstrated by the conversion of **3h** into **4h**, albeit in modest yield (53%).

A longer reaction time of 2 hours was required for the reduction of bis-*N*-acylsulfonamides **3i–3n**. Diastereomeric *cis*- and *trans*- bis-*N*-acylsulfonamides, **3i** and **3j**, delivered the corresponding bis-*N*-alkylsulfonamides, **4i** and **4j**, in moderate to excellent yields (64% and 90%). The more electron-deficient substrate **3k** afforded sulfonamide **4k** in 78% yield. 2-Naphthylsulfonamide **4l** was produced from **3l** in excellent yield (89%). The more flexible glutaric acid derived sulfonamides **4m** and **4n** were produced in excellent (94%) and good (70%) yields, from their *N*-acyl counterparts, **3m** and **3n**, respectively. For the synthesis of bis-*N*-alkylsulfonamides, this procedure has the significant advantage of avoiding the intermediacy of highly polar, water-soluble diamines.

In conclusion, we have demonstrated a simple, efficient and general method for the formation of sulfonamides by the reduction of *N*-acylsulfonamides, using mild and convenient $\text{BH}_3\cdot\text{SMe}_2$. The method offers several advantages such as stable and crystalline intermediates,²¹ short reaction times, and the use of stable, readily available reagents.

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3		15 min		100
4		15 min		94
5		15 min		48
6		15 min		71
7		15 min		67
8		15 min		53
9		2 h		64
10		2 h		90
11		2 h		78
12		2 h		89
13		2 h		94
14		2 h		70

^aYield of isolated product.

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