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

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A convenient synthesis of N-alkylsulfonamides in good to excellent yields by reduction of N-acylsulfonamides using BH₃•SMe₂ 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. Early sulfonamide-based drugs (sulfapyridine, sulfinpyrazone, sulfasalazine) were used as antibiotics, but sulfonamides are now found in a number of different drug classes. Sulfonamides also represent useful “protected” intermediates for the synthesis of primary and secondary amines, which can be afforded via desulfonation under mild conditions.

Sulfonamides are frequently synthesised by sulfonation of amines with sulfonic chlorides in the presence of a base. Despite a number of other known methods, this remains the most common synthetic strategy. However, the use of sulfonic chlorides can be problematic, since they are often difficult to handle and store due to their instability. Therefore, the development of synthetic methods that avoid the use of sulfonic 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 Bellettre and Fry, involving the synthesis of sulfonamides from N-acylsulfonamides, using BH\textsubscript{3}·SMe\textsubscript{2}, en route to primary amines. Since this original report, the method has not found common use, although more reagents, e.g., LiAlH\textsubscript{4} and BH\textsubscript{3}·THF have been utilised.

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

Conditions for BH\textsubscript{3}·SMe\textsubscript{2} reduction of N-acylsulfonamides were optimised using cis-N-acylsulfonamide (Table 1). Treatment of 3i with BH\textsubscript{3}·SMe\textsubscript{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 BH\textsubscript{3}·SMe\textsubscript{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 1. Optimisation of the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>BH\textsubscript{3}·SMe\textsubscript{2} (4 equiv.), THF, r.t., then 55 °C, 24 h.</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>BH\textsubscript{3}·SMe\textsubscript{2} (8 equiv.), THF, reflux, 18 h.</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>BH\textsubscript{3}·SMe\textsubscript{2} (8 equiv.), THF, reflux, 2 h.</td>
<td>64</td>
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* Yields are given for isolated products.

Treatment of N-acetylbenzensulfonamide (3a) with BH\textsubscript{3}·SMe\textsubscript{2} provided N-ethylbenzenesulfonamide (4a) in good yield (87%) after 15 minutes. The more hindered N-[4-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-acetyltrifluoromethylsulfonamides 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-acetyl sulfonamides 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 substrates 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-acetyl 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 BH\textsubscript{3}·SMe\textsubscript{2}. The method offers several advantages such as stable and crystalline intermediates, short reaction times, and the use of stable, readily available reagents.

Acknowledgments

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References and notes


*Yield of isolated product.