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A Novel One-Pot Conversion of Methyl Sulfones to Sulfonamides

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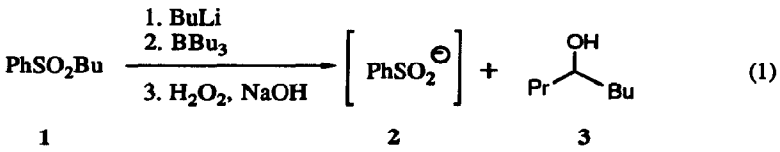
Abstract : A one-pot synthesis of sulfonamides from methyl sulfones has been developed. Treatment of methyl sulfones with base and trialkylboranes gave the corresponding rearranged sulfinic acid salts which were converted to sulfonamides during oxidative-amination workup.

Sulfonamides have been widely used for treatment of bacterial or viral infections, and are also found in drugs such as diuretics, hypoglycemic, antimalarial agents and many others.[1] The most common synthetic method[2] used to make sulfonamides usually involves the preparation of a sulfonyl chloride from a sulfonic acid and phosphorous pentachloride, followed by treatment with amines. Alternatively, aryllithiums (generated from aryl halides and butyllithium) have been reacted with sulfur dioxide to give the corresponding arylsulfinates,[3] which were subsequently treated with chloramine or hydroxylamine-O-sulfonic acid to give sulfonamides directly.[4] This process usually is tedious, inconvenient, and often incompatible with other existing functional groups, especially if one wishes to introduce the sulfonamidyl group at a later stage of a multi-step synthesis. Moreover, the versatility of this process also depends on the availability of the appropriate aryl halide. Herein, we report a novel convenient one-pot synthesis of sulfonamides from widely accessible methyl sulfones (or methyl sulfides) under very mild reaction conditions.

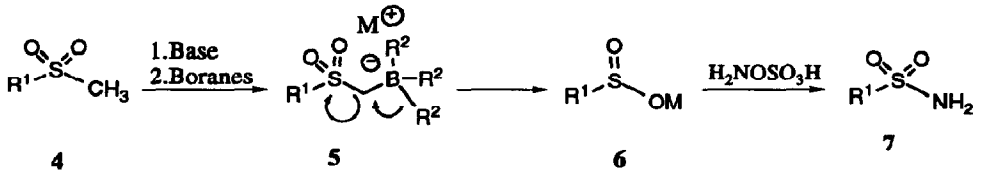
Trialkylboranes have been known to form "ate" complexes with lithiated organosulfur compounds.[5] Uguen has proposed that the anion of a phenyl alkylsulfonyl **1** and tributylborane form an anionic complex, which thermally rearranged, with the formation of phenylsulfinate anion **2** as a side-product, to a trialkylborane which was oxidized to a secondary alcohol **3** (eq 1).[6] We envisioned a one-pot synthesis of sulfonamides **7** from methyl sulfones **4** by the rearrangement of the "ate" complexes **5** to the desired sulfinic acid salts **6** and subsequent reaction with hydoxylamine-O-sulfonic acid. (Table 1).

A typical experimental procedure is exemplified for the preparation of phenylsulfonamide from phenyl methylsulfone: A solution of methylsulfone (10 mmol) in 5 mL of THF at 0 °C was treated with 4.5 mL (12.6 mmol) of methylmagnesium chloride (2.8 M in THF), and the resulting solution was stirred at room temperature for 30 min. The solution was cooled to 0 °C, treated with 15 mL (15 mmol) of tributylborane (1 M in THF), stirred at room temperature for 30 min, and then stirred at reflux for 18 hours. To the resulting mixture at 0 °C was added 5.7 g of sodium acetate, 25 mL of water, and 3.95 g of hydroxyamine-O-sulfonic

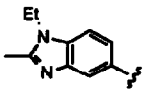


1 2 3 (1)

Table 1. Conversion of Methylsulfones to Sulfonamides



4 5 6 7

Entry	R^1	Base	Borane	4, % [a]	7, % [a]
1	Ph	MeMgCl	$B(Et)_3$	40 [50]	50 [50]
2	Ph	LDA	$B(Et)_3$	[26]	[58]
3	Ph	MeMgCl	$B(Bu)_3$	15 [2]	67 [70]
4	Ph	MeMgCl	$B(allyl)_3$	[60]	[6]
5	Ph	MeMgCl	$B(Ph)_3$	(100)	(0)
6	4-Cl-Ph (r.t.)	MeMgCl	$B(Bu)_3$	[60]	[15]
7	4-Cl-Ph	MeMgCl	$B(Bu)_3$	38 [20]	36 [61]
8	4-Br-Ph	MeMgCl	$B(Bu)_3$	20 [18]	43 [60]
9	4-MeO-Ph	MeMgCl	$B(Bu)_3$	28 [30]	66 [66]
10	$PhCH_2$	MeMgCl	$B(Bu)_3$	0	58 [61][b]
11	2-Thienyl	MeMgCl	$B(Bu)_3$	32 (27)	43 (46)
12		MeMgCl	$B(Bu)_3$	20 (23)	55 (40)
13	Methyl	MeMgCl	$B(Bu)_3$	(48)	(52)
14	Ethyl	MeMgCl	$B(Bu)_3$	(64)	(15/21)[c]
15	t-Butyl	MeMgCl	$B(Bu)_3$	(58)	(42)

[a] Isolated yields,[7] [ ] indicates HPLC ratios,[8] and ( ) indicates ^1H NMR ratios. [b] The isolated product was actually 1-phenyl-pentan-1-ol,[9] but by ^1H NMR analysis we could calculate the yield for $MeSO_2NH_2$, which was derived from the deprotonation and rearrangement of the methylene group instead of the methyl group. [c] The product ratio was for $MeSO_2NH_2$ and $EtSO_2NH_2$, respectively.

acid; the resulting mixture was stirred at room temperature for 3 hours. The organic layer was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and then brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by silica gel chromatography gave 1.06 g (67%) of phenylsulfonamide.

Methylmagnesium chloride was preferably used as the base for deprotonation (entry 1); however, if existing functional groups are incompatible with Grignard reagents, LDA may be used (entry 2). Both triethylborane and tributylborane complexes (entries 1, 3) rearranged quite readily, while the use of triallyborane and triphenylborane yielded mostly recovered starting material after the oxidative-amination work-up (entries 4, 5). The apparent lack of migratory aptitude with allylborane and phenylborane may be attributed to the stabilization of the anionic borane complex 5 by the phenyl or allyl groups. Stirring the borane complex at room temperature gave only 15% of product (entry 6), whereas 61% of product (by HPLC analysis) was formed from an identical experiment at reflux temperature (entry 7).[10]

Electron-withdrawing substituents on the phenyl ring seem to lower slightly the efficiency of this conversion (entries 7-9). The benzylmethylsulfone, which has two acidic sites next to the sulfonyl group, gave only the methylsulfonamide (entry 10) indicating that deprotonation and complex formation occurred exclusively at the thermodynamically more acidic methylene group of benzyl moiety. The scope of this conversion has been expanded to include heteroaromatic methyl sulfone (entries 11 and 12) and alkylmethylsulfones (entries 13-15).

In conclusion, a novel one-pot conversion of methyl sulfones to sulfonamides has been developed. This procedure should prove convenient and general for those compounds which have only one acidic methyl or methylene sulfonyl group. The fact that methylsulfides or methylsulfones are more accessible commercially, and can tolerate a wide variety of common chemical transformation conditions, also suggests that one may use a methylsulfide or methylsulfone as a masked sulfonamide to be carried through multi-step synthesis and demasked later at an appropriate, chosen stage. Furthermore, since it has been shown that sulfides, sulfoxides and dithioketals all form the "ate" complexes with trialkyl boranes,[5] one would expect that they also may be used as substrates for this rearrangement. Our continued research in the development of this methodology will be reported in the near future.

References and Notes

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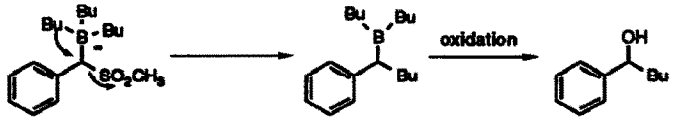
7. All new compounds were fully characterized spectrally and purity was established by combustion analysis (± 0.4%)
8. The ratio of products were analyzed by reverse phase HPLC on a C-18 column (Waters Delta Pak, 100 A, 3.9 mm x 30 cm), eluting with water and CH_3CN containing 0.05% trifluoroacetic acid, and detected by UV at 254 nm.
9. The isolated product, 1-phenyl-pentan-1-ol, was derived from the oxidation of rearranged trialkylborane.



10. Excess of base (1.5 or 2.0 eq. of MeMgCl) or stirring the borate complex at reflux for 36 hours did not improve the yield.

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