Pergamon

Tetrahedron Letters 43 (2002) 1377–1379

TETRAHEDRON LETTERS

An efficient synthesis of geminal di-sulfones

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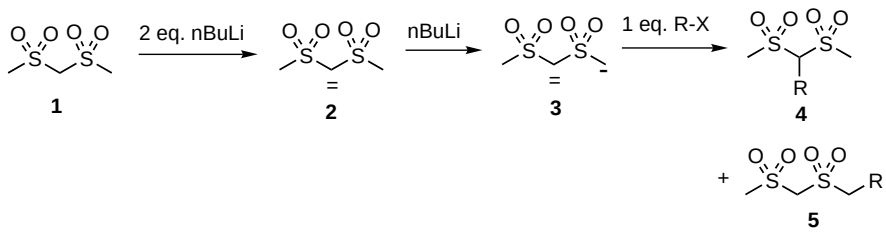
Received 28 November 2001; revised 19 December 2001; accepted 20 December 2001

Abstract—A simple and efficient method for the synthesis of *gem*-disulfones is reported. This method is based on protection of one of the central acidic hydrogens of bis(methylsulfonyl)methane as a thioether followed by formation of the dianion and selective alkylation of the methyl group. Alkylation of one of the methyl groups was demonstrated as well as alkylation of both methyl groups with the same or different alkyl groups. Removal of the thioether moiety furnished the desired substituted disulfones. © 2002 Elsevier Science Ltd. All rights reserved.

The pyrophosphate moiety is a common structural motif in many biologically important compounds including the prenyl pyrophosphates, dinucleotide coenzymes, and nucleoside diphosphate sugars. The lability of the pyrophosphate moiety to phosphatase enzymes and the inability of such ionic compounds to cross cell membranes necessitates the modification of this moiety in the design of analogs of these compounds for potential in vivo use as enzyme inhibitors and biological probes.[1] A number of surrogates of the pyrophosphate moiety have thus been prepared including various phosphonates, though these compounds maintain the ionic characteristics.[2–4] Neutral analogs include a carbonyl sulfonamide,[5] derivatives of malonic and tartaric acid, and structures based on monosaccharide moieties.[6] Sulfones[7] and sulfonate esters[8] have been proposed as neutral mimics of the phosphodiester linkage in nucleic acids and more recently the disulfone moiety has been proposed as a neutral mimic of the diphosphate functionality.[9–12] However, efforts to synthesize the appropriately substituted disulfones have had limited success.

Castro and Spencer studied the alkylation of bis-(methylsulfonyl)methane **1** as a possible route to disulfones.[9,10] They showed that reaction with 2 equiv. of base resulted in double deprotonation of the central methylene group to form the geminal dianion **2**, as demonstrated by alkylation and deuteration experiments (Scheme 1). Reaction with 3 equiv. of base formed the trianion **3**, alkylation of which formed products **4** and **5** resulting from alkylation of both the central and terminal carbons. Yields of the desired terminal alkylation products **5** were only 25–35%. This mirrored earlier results observed in alkylation of the trianion of trifluoromethylsulfonyl methyl sulfone.[13] Subsequent alkylation with a second alkyl group was not demonstrated. Gervay-Hague and co-workers recently reported a novel reagent **6** that reacts with aldehydes to form α,β-unsaturated *gem*-disulfones **7** by a Horner–Emmons–Wadsworth type reaction (Scheme 2).[11] Non-symmetrical products were obtained in good yields based on the initial aldehyde if an excess of the disulfone reagent **6** was used in the first step.



Scheme 1.

Keywords: disulfone; alkylation; pyrophosphate mimic.

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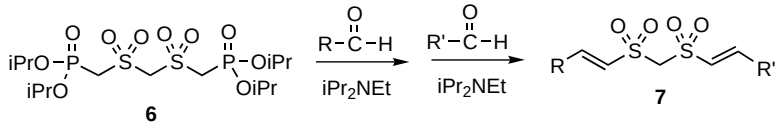
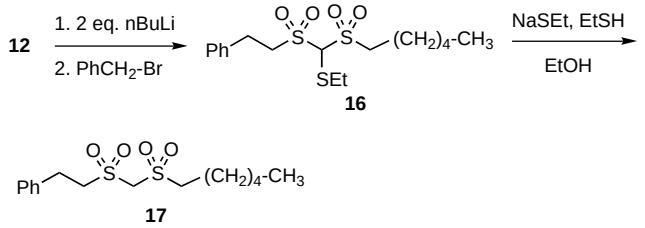
PII: S0040-4039(02)00023-0



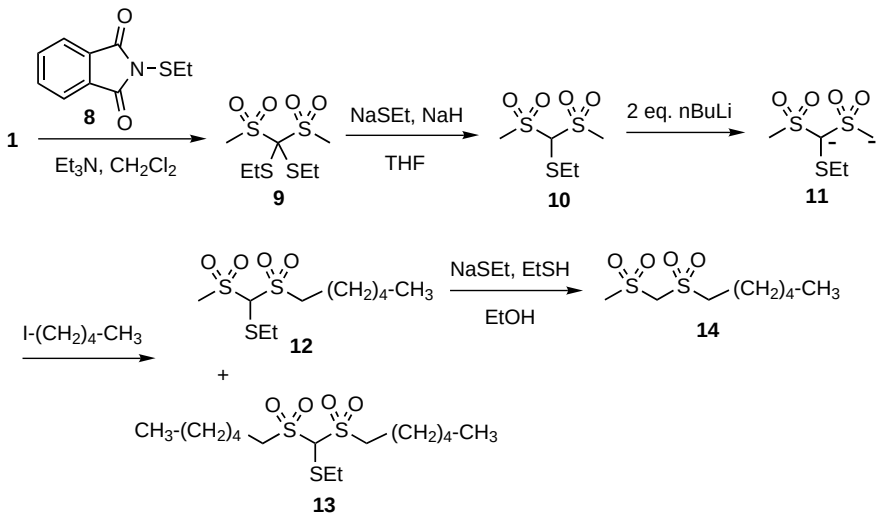
Scheme 2.

Presented here is a newly developed method for the synthesis of unsymmetrical geminal disulfones. The key feature of this method is 'protection' of one of the central methylene hydrogens of bis(methylsulfonyl)methane **1** as a thioether. Thus, initial reaction of the disulfone **1** with *N*-ethylthio phthalimide **8** under basic conditions as previously described for several active methylene compounds formed the thioketal **9** in 97% yield (Scheme 3).[14] Compound **9** was converted to the thioether **10** in 87% yield upon reaction with ethanethiolate with excess sodium hydride, again following the general method previously described (Scheme 3).[14] The thioether prevents formation of a dianion at the central carbon, thus reaction of **10** with 2 equiv. of butyllithium formed the dianion **11**. Alkylation of this dianion with iodopentane formed **12**. Using 1.67 equiv. of **11** relative to iodopentane, a 76% yield of **12** was obtained based on iodopentane along with 17% yield of the dialkylation product **13**. The formation of **13** is consistent with the expectation that proton exchange between **11** and the monoanion of **12** should be more rapid than the alkylation reaction, as has been observed in the alkylation of methyl phenyl sulfone.[15] When 3 equiv. of **11** were used, the yield of **12** was essentially unchanged, though no dialkylation product was observed. Removal of the ethylthio group from **12** was accomplished by reaction with ethanethiolate in the presence of ethanethiol in ethanol to form **14** in quantitative yield.[14]

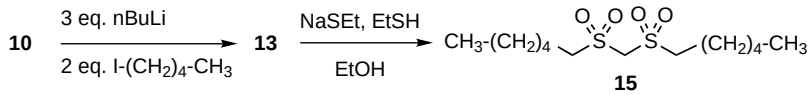
Synthesis of a symmetrically disubstituted disulfone was accomplished as shown in Scheme 4. Reaction of **10** with 3 equiv. of *n*-butyllithium followed by addition of 2 equiv. of pentyl iodide formed the disubstitution product **13** in 63% yield. Removal of the ethylthio group was accomplished as before to form **15** in quantitative yield. For synthesis of an unsymmetrically disubstituted disulfone, the monosubstituted product **12** was converted to the dianion which was reacted with benzyl bromide to form **16** in 87% yield (Scheme 5). Removal of the ethylthio group formed the unsymmetrical disulfone **17** quantitatively. Interestingly, no product from



Scheme 5.



Scheme 3.



Scheme 4.

dialkylation at the same carbon was observed in any of the reactions. This is in contrast to alkylation reactions of the anion of phenyl methyl sulfone, in which significant amounts of dialkylation products were observed, even using only 1 equiv. of base and alkylating agent.[15]

The procedures described here may provide a general method for the synthesis of the disulfone analogs of natural diphosphates. This method offers advantages and complementary features relative to previously reported methods. Most notably, the method provides direct access to unsymmetrical disulfones and gives good yields using only a modest excess of the starting disulfone in the first alkylation step. The ability to selectively activate one methyl group at a time may permit selective introduction of other functionality such as a phosphonate or silyl group, which may be useful in known reactions of phosphoryl and silyl sulfones.[11,16] Applications of the described method are currently being pursued.

Acknowledgements

This work was supported by National Institutes of Health Grant GM45831.

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