Pergamon

Tetrahedron Letters 42 (2001) 5137–5140

TETRAHEDRON LETTERS

A novel reagent for the synthesis of geminal di-sulfones

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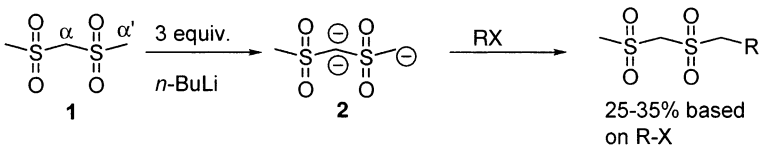
Received 6 April 2001; accepted 8 June 2001

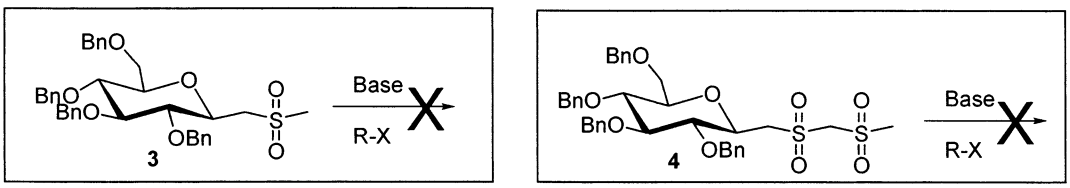
Abstract—A novel reagent (diisopropoxyphosphorylmethanesulfonylmethanesulfonylmethyl)-phosphonic acid diisopropyl ester (**8**) capable of forming symmetrical and non-symmetrical α,β unsaturated *gem*-disulfones is reported. Both aromatic and aliphatic aldehydes react in good yields to give exclusively the *trans* isomer. Selectivity for the mono-olefin can be achieved by varying the stoichiometry of reagents. © 2001 Published by Elsevier Science Ltd.

The diphosphate functionality is ubiquitous in nature where it serves several important roles. For example, diphosphates are known to chelate metalloenzymes, which can result in nucleophilic displacement of the pyrophosphate group.[1] In this capacity, diphosphates serve as nature's leaving group. A number of studies have focused on the synthesis of diphosphate mimics as potential inhibitors of important enzymatic transformations. The diphosphate has been successfully replaced with several other functionalities including methylene diphosphonates,[2] sulfonamides,[3] and monophosphates[4] to provide potent inhibitors of targeted enzymes. Diphosphate isosteric design and synthesis has also included the use of *gem*-disulfones as potential transferase inhibitors.[5]

In their syntheses of differentially functionalized *gem*-disulfones, Spencer and co-workers showed that double deprotonation of bis(methylsulfonyl)methane (**1**) occurred at the α-position forming the α,α dianion.[6] Upon reaction with a third equiv. of base, the α,α,α′ tri-anion (**2**) was generated (Scheme 1). Subsequent alkylation of the trianion with alkyl halides resulted in only moderate yields of the α′ substituted product. Similar difficulties were encountered in our attempted alkylation of *C*-glycosyl sulfones (Scheme 2).[7] Alkylation of both the mono (**3**), and *gem*-disulfones (**4**) gave complex reaction mixtures under a variety of conditions (Scheme 2). We attributed the failure of these reactions to competing formation of the methyl and methylene anions, either of which could be alkylated. Complica-



Scheme 1.



Scheme 2.

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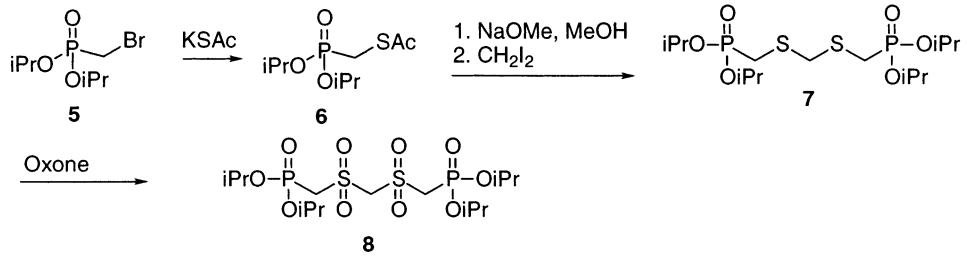
PII: S0040-4039(01)01004-8



Scheme 3.

tions arising from retro-Michael of the methylene anion also seemed plausible.

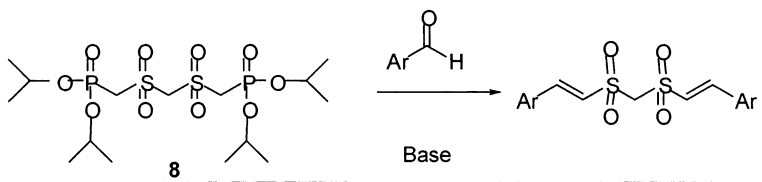
To circumvent difficulties resulting from multiple anion generation, other methods of selectively functionalizing the α′ positions of *gem*-disulfones were investigated. We reasoned that incorporation of a phosphonate functionality at both α′ positions would allow generation of stabilized anions under relatively mild conditions. The phosphonate functionality would also serve to direct the carbon–carbon bond forming reaction to the α′ position, due to the irreversibility of the Horner–Emmons–Wadsworth (HEW) reaction. Reported herein is the synthesis of a novel reagent (**8**) that provides selective and differential functionalization of geminal disulfones under mildly basic conditions.[8]

The synthesis of **8**[9] began with commercially available diisopropyl bromomethylphosphonate **5**, which was treated with potassium thioacetate to afford **6**. Deprotection of the thioester with sodium methoxide provided the thiolate, which was subsequently reacted with diiodomethane to yield the thioacetal **7**. Oxidation of **7** with oxone provided the symmetrical reagent **8** (Scheme 3). The yield of (diisopropoxyphosphorylmethanesulfonylmethanesulfonylmethyl)-phosphonic acid diisopropyl ester for the 3-step process was 64% and this reagent has been prepared on multiple gram scale. The 250 MHz NMR of compound **8** in chloroform showed as singlet at δ 5.57, a multiplet at δ 4.80, a doublet at δ 3.91 ($J=16.0$ Hz) and a doublet at δ 1.32 ($J=6.2$ Hz). Interestingly, when **8** was dissolved in deuterated methanol all of the methylene protons exchanged and only the isopropyl protons (multiplet at 4.80, doublet at 1.32) were visible in the NMR. The rapid exchange of the methylene protons suggests that they are relatively acidic.

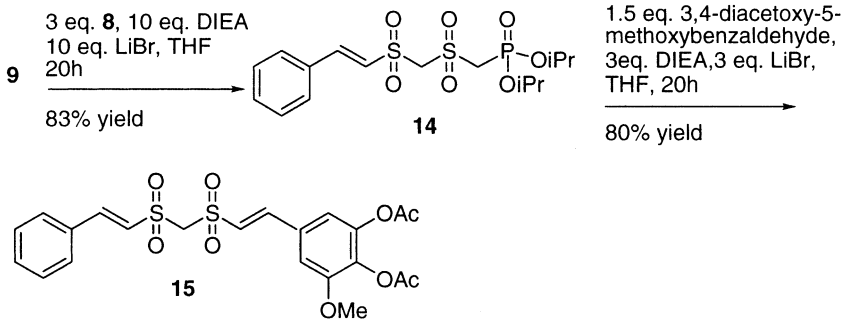
Investigations of **8** as a HEW reagent were first conducted on several aromatic aldehydes. Good yields, and high stereoselectivities (no *Z* isomers were identified) were observed. Three equiv. of benzaldehyde were reacted with 1 equiv. of **8** to give a 70% yield of the bis adduct **9** after 20 h. Three equiv. of the aldehyde were used in order to assure bis addition. Both activated and deactivated aldehydes underwent reaction with **8**, however, *p*-nitrobenzaldehyde (**10**) reacted much more rapidly and in higher yield than *p*-methoxybenzaldehyde (**11**). Reactions with phenols failed, but this limitation was easily overcome by simple acetate protection of the hydroxyl functionality (entry 4).

A typical reaction involved deprotonation of **8** with 3 molar equiv. of base (3 equiv. of base was found to be the most efficient due to the presence of three acidic methylenes) followed by addition of excess aldehyde (typically 3 equiv.). We have used a number of different bases and solvents and the yields do not vary significantly. However, the Masamune/Roush conditions for generating anions in the presence of lithium salts and an amine base are most convenient, due to the availability of pure reagents and the ease of measuring them.[10] Entry 5 in Table 1 nicely illustrates that aliphatic aldehydes undergo efficient coupling using these conditions, and there was no evidence of complications from possible aldol condensation.

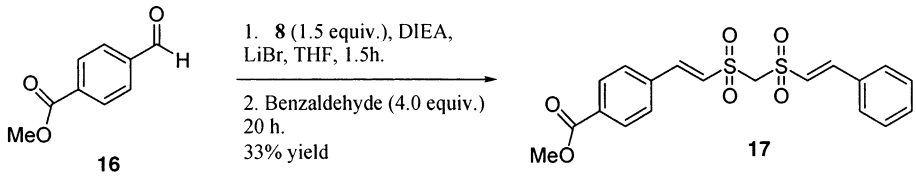
Table 1. Reaction conditions for bis-adduct formation



Entry	1	2	3	4	5
Aldehyde	**9**	**10**	**11**	**12**	*n*-Butanal **13**
Base/Solvent	NaH/*i*-prOH	*t*-BuOK/*t*-buOH	LiBr/DIEA/THF	*t*-BuOLi/THF	LiBr/DIEA/THF
Time (h)	20	2	20	0.5	1.5
Yield	70	66	45	60	93



Scheme 4.



Scheme 5.

Varying the ratio of aldehyde to **8** (1:3) was shown to enhance selectivity for the mono-olefin **14**, which could be reacted in a second step to provide the unsymmetrical geminal disulfones **15** (Scheme 4).

Unsymmetrical geminal disufones have also been generated in a one-pot procedure (Scheme 5). For example, *p*-carbomethoxy benzaldehyde (**16**) was reacted with 1.5 equiv. **8** for 1.5 h at room temperature before the addition of 4 equiv. benzaldehyde. After 20 h reaction time, the unsymmetrical *gem*-disulfone (**17**) was isolated and purified in 33% yield. Purification of the desired product can be problematic (due to similar R_f's) depending upon the aldehydes chosen in the condensation reactions. Nonetheless the feasibility of such a reaction has been demonstrated.

In summary, the synthesis and characterization of a novel reagent for the incorporation of geminal disulfones has been accomplished. One can achieve mono- or bis-addition by varying the stoichiometry of reagents. Aromatic aldehydes containing both electron withdrawing and electron donating groups undergo reaction with **8** in an efficient manner, as do aliphatic aldehydes. The extension of these studies to the synthesis of biologically relevant geminal disulphones is currently under investigation in our laboratories.

Acknowledgements

The authors thank the Arizona Disease Research Commission for partial support of this research. The financial contribution of the National Institutes of Health (GM60917) is also acknowledged. J.G.H. thanks the Alfred P. Sloan foundation and Eli Lilly for their generous support of this research.

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9. **(Diisopropoxyphosphorylmethanesulfonylmethanesulfonylmethyl)-phosphonic acid diisopropyl ester (8)**: To commercially available diisopropyl bromomethylphosphonate (Lancaster) (5.24 g, 20 mmol) in 15 mL of DMF, potassium thioacetate (3.46 g, 30 mmol) and tetrabutylamonium iodide (373 mg) were added and heated to 80°C with stirring for 2 h. The solution was cooled and partitioned between water and ethyl acetate. The ethyl acetate layer was collected and dried over sodium sulfate and then evaporated to dryness. To the crude oil was added acetonitrile (15 mL), 3 M NaOH (7.4 mL) and methanol (7.4 mL) and the solution was stirred for 30 min. The flask was cooled to 0°C and diiodomethane (797 μL, 10 mmol) was added and the reaction was warmed to room temperature and stirred overnight. The

reaction was then partitioned between water and ethyl acetate and the ethyl acetate layer collected and dried over sodium sulfate. After evaporation, the crude oil was oxidized using oxone (24.86 g, 40 mmol) in methanol/water (~100 mL 1:1) overnight to give a crude solid after ether/bicarbonate extraction. Recrystallization from ether/hexanes provided 3.15 g of **8** (64% yield). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.33 (d, 24H, $J=6.2$ Hz), 3.91 (d, 4H, $J=16.0$ Hz), 4.80 (m, 4H), 5.58 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.7, 24.1, 50.7, 51.8, 68.1, 73.2, 73.3. HRFABMS calcd for $C_{15}H_{35}O_{10}P_2S_2$ (M+H): 501.1147. Found: 501.1151 (M+H).

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