BIS-ALKYLATION OF DIMETALLATED PHENYLSULFONYLMETHYL TRIFLONE. A n+1 ANNULATION STRATEGY FOR SYNTHESIS OF CYCLIC VINYL SULFONES.¹

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Abstract: Bis-metallation of phenylsulfonylmethyl triflone **4b** produces a geminal dianion which can be dialkylated to afford α -phenylsulfonyl triflones. Treatment of these compounds with DBU affords vinyl sulfones which can be isomerized to allyl sulfones.

We recently required access to dioxygenated vinyl sulfone **1** in optically pure form. The success of 4 + 1 annulation strategies² combined with the recent synthesis of compound **2a** (R = R' = CH₂Ph) by Cunningham and Kündig³, compelled us to attempt conversion of this substrate to vinyl sulfone **1**. Following the general procedure,³ alkylation of acetonide dibromide **3** (R = CMe₂; X = Br) with bis(phenylsulfonyl)methane under mildly basic conditions (K₂CO₃, DMF, 75°C) afforded adduct **2a** (R = R' = CMe₂) in 67% isolated yield. For practical purposes, the labile acetonide bis-sulfone **2a** (R = R' = CMe₂) was directly hydrolyzed (1N HCl, THF) to the corresponding trans-diol **2a** (R = R' = H; 71% in two steps; 48% overall yield from (+)-diethyl tartarate). Monosilylation of the <u>trans</u>-diol **2a** (R = R' = TBDMS) in 56% yield along with 10% of the bis-silyl ether **2a** (R = R' = TBDMS). All attempts at elimination of both the alcohol moiety of monosilyl ether **2a** (R = H; R' = TBDMS), as well as *ortho* - metallation of the aryl sulfone of bis silylether **2a** (R = H; R' = TBDMS) in hopes of effecting a self-immolative elimination.⁴



Hendrickson⁵ has shown that the triflone functional group is both powerfully electron-withdrawing and also serves as a leaving group in 1,2-elimination reactions and intramolecular nucleophilic displacements. Therefore we turned our attention to employing phenylsulfonylmethyl triflone **4b**⁶ (pKa = 5.1) in the above strategy. This compound has been prepared previously by chromic acid oxidation of phenylthiotrifluoromethylthiomethane **5** which is made by condensation of thiophenoxide with trifluoromethyl chloromethyl sulfide **6**. Compound **6** is not readily available, and its preparation from dimethyl sulfide is quite cumbersome.^{6a} An improved synthesis of phenylsulfonyl triflone **4b** involved reaction of chloromethyl phenyl sulfide **7**⁷ with potassium triflinate (Parish Chemical Company) to afford phenylsulfenylmethyl triflone **8**. This reaction is uncomplicated but slow due to the low nucleophilicity of potassium triflinate. Peracetic acid oxidation of **8** provided **4b** in 61% overall yield.



Initial attempts at alkylation of α -triflone anion of **4b** employing simple alkylating agents using the standard hydride-base/DMF conditions gave encouraging results. For example, alkylation with methyl iodide gave the dialkylated product **10** accompanied by elimination product vinyl sulfone **11** in a ratio of 22:78 (17% and 69% isolated yields). Use of 2 equiv of <u>n</u>-BuLi failed to give substantial dialkylation in the absence of HMPA. These results are summarized in the table below.



Mel (eq)	Conditions	Product (NMR		integral	ratio)
		9	10	11	Rec.4b
2.5	n-BuLi (2 eq), THF, -78°C, add Mel, warm to 25°C, 10h	45	49	0	6
2.1	n-BuLi (2 eq), THF, -50°C, (1.5h), add Mel, warm to 25°C, 10h	41	16	0	43
2.3	<u>п</u> -BuLi (2.3eq), THF, HMPA (5%v/v), -78°С to 25°С, 10h	0	97	3	0
10	K2CO3, DMF, 105°C, 10h	0	95	5	0
10	NaH, DMF, <u>n</u> -Bu ₄ NI, 75°C, 2h	0	22	78	0

The results obtained with <u>n</u>-BuLi/THF/-78°C are quite interesting. The α -monoanion formed by the first equiv of <u>n</u>-BuLi is very stable and difficult to alkylate.⁸ With 2 equiv of <u>n</u>-BuLi the α, α -dianion is apparently formed,⁹ which undergoes rapid side reactions rather than reacting with the alkylating agent, resulting in lower yield of the dialkylated product. Addition of HMPA¹⁰ activates the dianion presumably by chelating with the lithium counterion. This suggested that a combination of <u>n</u>-BuLi/HMPA in an anhydrous non-polar solvent such as toluene would generate an activated dianion, which should be able to react with the alkylating agent with minimal side reactions. The validity of this assumption was substantiated by carrying out model [4+1] alkylations on straight chain primary diiodides. The results given in the following scheme again showed that non-polar solvents and addition of HMPA to the <u>n</u>-BuLi were essential for the dianion formation/cycloalkylation sequence.¹¹ Reaction of **13** with neat DBU for 4h gave rise to a mixture of vinyl sulfone **14** and the isomerized allyl sulfone **15** in approximately 1:1 ratio. After 2 days at 25°C, the thermodynamic product,¹² allyl sulfone **15** was isolated in quantitative yield.



Synthesis of symchiral¹³ cyclopentenyl sulfone **1** required cycloalkylation of dianion **4b-Li2** with symchiral reagents **3a-d**. In spite of the success with synthesis of model **13** we had anticipated that similar cycloalkylations on carbon centers bearing a β -oxygen functionality¹⁴ might pose serious problems because of the electron-withdrawing nature of the oxygen moiety. Kotsuki, <u>et</u> <u>al</u>.¹⁵ have explored methods for the direct nucleophilic alkylation at the carbon center bearing a β -oxygen atom by using the exceedingly reactive triflate alkylating agents.



The ditriflates $3b^{14}$ and 3d were readily prepared in quantitative yield from the corresponding alcohols by treatment with 2.5 equiv of triflic anhydride in pyridine. Subsequent cycloalkylation of the phenylsulfonyl triflone 4b with ditriflate 3b using our earlier conditions, provided an difficultly separable mixture, which after acidic work-up gave symchiral 2b in only 27% yield. On the other hand, use of dibenzyl ditriflate 3d under the same cycloalkylation conditions resulted in essentially quantitative formation of the desired adduct 2b (R=CH₂Ph). Treatment of 2b (R=H) with 2.2 equivalents of <u>n</u>-BuLi in THF (-78°C to 25°C) afforded bicyclic alcohol 17 in quantitative yield. The same material was produced upon reaction of 4b (R=TBDMS) with tetrabutylammonium fluoride. The mechanism apparently involves intramolecular triflation of the

alkoxide moiety followed by intramolecular carbon alkylation of the resulting α -sulfonyl anion [16]. Fortunately 2b (R=CH₂Ph) underwent facile 1,2-elimination of triflinic acid with DBU in CH₂Cl₂ or ether, to give the symchiral vinylsulfone 1 ([α]_D +88.5° (CDCl₃, c 1.42)) which under more forcing conditions (neat DBU, 16h) quantitatively isomerized to allylic sulfone 18.

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- Deprotonation of the α-monoanion removes the second α-hydrogen in preference to <u>ortho-</u>lithiation. This parallels the ease of abstraction of the second hydrogen from the anion of bistriflylmethane (ref 5e) and mesyl triflone (ref 5a). For other examples of β-disulfonyl dianions see: Castro, A.; Spencer, T. A. Paper # 253 199th ACS National Meeting, Boston, MA (April **1990**).
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