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Reductive Lithiation of Bis-Phenylsulfones

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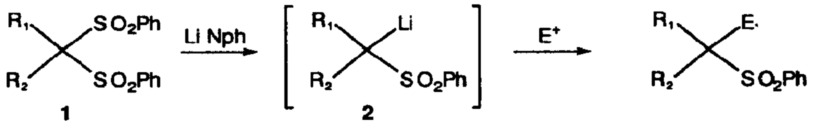
Abstract: Reductive cleavage of geminal bis-phenylsulfones using lithium naphthalenide in THF at -78°C selectively affords α-sulfonyl carbanions which participate in typical reaction with electrophiles.

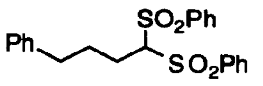
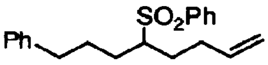
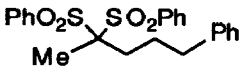
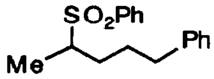
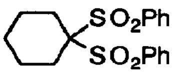
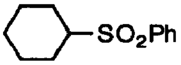
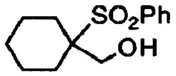
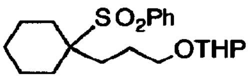
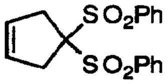
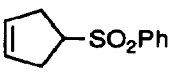
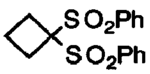
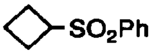
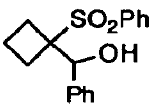
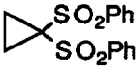
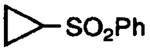
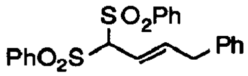
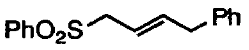
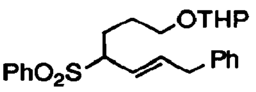
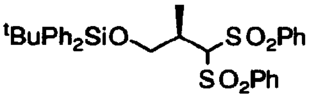
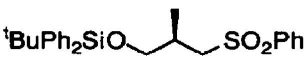
The general synthetic utility of geminal bis-sulfones[1] is limited, in part, by their relative inaccessibility as well as a lack of methods for interconversion to other functionalities and/or stepwise desulfonylation.[2] The former restriction has been addressed by new methodology developed in these laboratories for the synthesis of cyclic and acyclic geminal bis-phenylsulfones **1** under exceptionally mild conditions.[3] For the latter, we report herein the controlled reductive desulfonylation of **1** using lithium naphthalenide (Li Nph) in THF at low temperature (eq 1).[4] The resultant α-phenylsulfonyl carbanions **2** participate in typical reactions with electrophiles including alkylations and carbonyl additions.[5]



(eq 1)

The scope and limitations of the reaction were defined using representative bis-phenylsulfones and 2.2 equivalents of freshly prepared Li Nph (Table 1). Generally, mono-and di-substituted bis-sulfones (entries 1 and 2, respectively) reacted smoothly and the derived α-sulfonyl carbanions were quenched to furnish the corresponding mono-sulfones free of over-reduced products or alkylated to create a new C-C bond.[6] Cyclic bis-sulfones ranging from cyclobutyl to cyclohexyl (entries 3,4, and 5) behaved analogously and readily added to aldehydes, e.g., paraformaldehyde (entry 3) and benzaldehyde (entry 5). On the other hand, both cyclic and acyclic systems gave comparatively poor yields of adduct with ketones, a consequence of facile reversion of the intermediate β-alkoxysulfone.[7] An alternative approach to ketone adducts based on reductive cleavage of bis-phenylsulfones by SmI_2 is provided in the accompanying manuscript.[8]

Table 1. Reductive Desulfonylation and/or Alkylation of Bis-Phenylsulfones

Entry	Bis-Sulfone	Electrophile	Product	Yield[a],%
1		H_2O		85
				79
2		H_2O		94
3		H_2O		85
		$(CH_2O)_n$		84
		$Br(CH_2)_3OTHP$		87
4		H_2O		68(87)[b]
5		H_2O		97(82)[b]
		PhCHO		76
6		H_2O		0(0)
7		H_2O		85
		$Br(CH_2)_3OTHP$		86
8		H_2O		84(82)[b]

[a] Based on isolated, chromatographically homogeneous material. [b] Yield for reductive desulfonylation using SmI_2 (3 equiv) shown in parenthesis (see accompanying manuscript).

Significantly, cyclopropyl bis-phenylsulfone (entry 6) was resistant to even prolonged exposure to Li Nph and was recovered unchanged. This may reflect, to some extent, the larger pKa value[9] of α-sulfonylcyclopropane and, hence, its higher reduction potential compared to its homologs. Also of note is the reductive cleavage of the allylic bis-sulfone (entry 7) which proceeded without olefin migration or further reduction.[10] The preparation of the chiral C_4 building block (entry 8) suggests this methodology will be compatible with many common protecting groups; and, since α-sulfonyl carbanions can be converted to a variety of functional groups,[5,11] the one-pot transformation of bis-sulfones into other functional groups is also possible.[12]

General Procedure

Method A: To a -78°C solution of bis-phenylsulfone (1 mmol) in anhydrous THF (5 ml) under an argon atmosphere is added dropwise a blue, 0.6 M solution of lithium naphthalenide (3.67 ml, 2.2 mmol) in THF. After 5 min, the reaction is quenched with saturated NH_4Cl solution and the desulfonylated product isolated by extractive isolation. Alternatively, a solution of electrophile (1.1 mmol) in THF (5 ml) is added dropwise and the reaction is allowed to warm to ambient temperature over 1 h. After quenching, extractive isolation, and removal of the solvent *in vacuo*, the residue is purified by chromatography on silica gel.

Method B: For large scale preparations or when separation of the naphthalene is difficult, this procedure based on recycled naphthalene is convenient and furnishes approximately the same yields as Method A. To a -78°C suspension of naphthalene (0.1 mmol) and lithium sand (2.2-4 mmol) in THF (5 ml) under an argon atmosphere is added a solution of bis-sulfone (1 mmol) in THF (5 ml). The reaction in monitored by TLC until complete consumption of the starting material, then quenched or exposed to an electrophile as described above.

Acknowledgment: Supported financially by the USPHS NIH (GM31278) and the Robert A. Welch Foundation.

Notes and References

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6. Satisfactory spectral data (^{1}H and ^{13}C NMR, MS) were obtained for all new compounds using chromatographically homogeneous samples.
7. Kocienski, P.J. *Chem. Ind.* **1981**, 548-551.
8. Chandrasekhar, S.; Yu, J.; Falck, J.R.; Mioskowski, C., following report in this issue.
9. Bordwell, F.G.; Vanier, N.R.; Matthews, W.S.; Hendrickson, J.B.; Skipper, P.L. *J. Am. Chem. Soc.* **1975**, *97*, 7160-7162.
10. β,γ-Unsaturated sulfones are more stable than the α,β-isomer: Magnus, P.D. *Tetrahedron* **1977**, *33*, 2019-2045.
11. For example: (a) Hwu, J.R. *J. Org. Chem.* **1983**, *48*, 4433-4436. (b) Baudin, J.-B.; Julia, M.: Rolando, C. *Tetrahedron Lett.* **1985**, *26*, 2333-2334.
12. To illustrate this, the α-sulfonyl carbanion generated in entry 2 was converted in one pot to the corresponding ketone as described in ref. 11a in 84% over-all yield from bis-sulfone. Instead, quenching the anion with a convenient proton source, e.g., MeOH, followed by another 2.2 equivalents of Li Nph gave rise to the fully reduced alkane in 90% yield.

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