Stereospecific Dehydrative Alkylation of Bis-Sulfones: Synthesis of a Lesser Tea Tortrix Pheromone[1]

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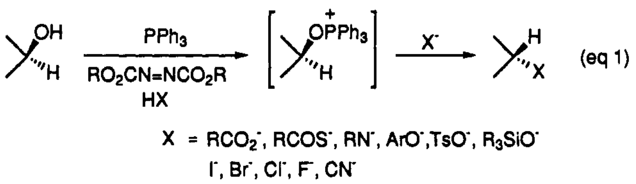
Received July 2, 1993•

Summary: The intra- and intermolecular condensation of alcohols with bis-sulfone methylenes, i.e., dehydrative alkylation, using DEAD and Ph_3P proceeds stereospecifically at room temperature under essentially neutral conditions affording good to excellent yields of alkylation/annulation products.

The classic Mitsunobu condensation[2] of an alcohol with a carboxylic acid, mediated by dialkyl azodicarboxylate/triphenylphosphine, involves the *in situ* generation of a highly reactive alkoxyphosphonium intermediate[3] which undergoes nucleophilic displacement under mild, nearly neutral conditions with virtually complete inversion of configuration at the electrophilic site (eq 1). Numerous modifications[4] of this protocol have extended its utility to other types of nucleophiles, *inter alia*, thiolacetate, halides, silanols, tosylate, phthalimide, and heterocycles. Our recent observation[5] that DEAD/Ph_3P complex converts γ-nitroalkanols to α-nitrocyclopropanes in good to excellent yields represents a rare example of participation by a carbon-centered nucleophile.[6]



(eq 1)

X = RCO_2^-, $RCOS^-$, RN^-, ArO^-, TsO^-, R_3SiO^-
I^-, Br^-, Cl^-, F^-, CN^-

However, all efforts to exploit the latter dehydrative alkylation of nitro paraffins to form larger rings or for intermolecular condensations failed and, thus, prompted us to evaluate other functionalities.[7] Herein, we report that bis-sulfones are particularly effective for a wide variety of dehydrative alkylations/annulations[8] as summarized in Table I. Cyclizations affording both small- (entries 1 and 2) and medium-sized rings (entry 3) were achieved with equal ease. Likewise, intermolecular alkylative dehydrations proceeded smoothly (entry 4) and, when applied to diols in the presence of excess reagent, provided ready access to functionalized carbocycles in good yield (cf. entries 2 and 5). In consideration of the gentle reaction conditions, the creation of carbon–carbon bonds by this technique is anticipated to be compatible with many common functionalities, e.g., acetonides (entry 6). While simple secondary alcohols are suitable substrates (entry 7), sterically congested cases are unreactive (entry 8). Backside displacement by the incoming nucleophile was confirmed in entry 9 with the stereospecific formation of a *cis*-fused decalin, an AB-ring synthon of interest in natural products synthesis. With allylic alcohols, either S_N2 or S_N2' attack is possible; entries 10 and 11, respectively, clearly demonstrate that both modes of reaction are operative depending on structural constraints.

The versatility of the sulfone[9] moiety in synthesis is noteworthy and enhances the ultimate utility of the preceding methodology. The transformations in Figure 1 illustrate, in part, the broad range of applications now available. Of particular interest are those procedures developed in these laboratories to complement the present studies: a facile and sequential sulfone reduction using lithium naphthalenide[10] (4.4 equiv) at −78 °C gives the corresponding methylene (route a); monodesulfonylation with naphthalenide and trapping of the resultant anion according to literature precedent gives rise to a carbonyl[11] (route b), tertiary sulfone[12] (route c), trisubstituted olefin[13] (route d), or α,β-unsaturated sulfone[14] (route e). Taking advantage of the acidity of the methine hydrogen, terminal bis-sulfones are converted to perdeuterated methyls upon warming (60 °C, 3 h) with excess magnesium turnings[15] in MeOH-d_1 (route f). Controlled SmI_2 cleavage[16] of the bis-sulfone in the presence of ketones furnishes good yields

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• Abstract published in *Advance ACS Abstracts,* October 1, 1993.

[1] Presented in part at the 205th ACS National meeting, Denver, CO, March 28–April 2, 1993: Org 132.

[2] Reviews: Castro, B. R. *Org. React.* **1983**, *29*, 1–162. Mitsunobu, O. *Synthesis* **1981**, 1–28.

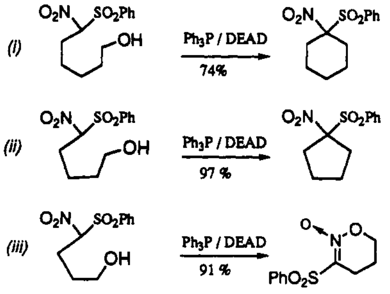
[3] Camp, D.; Jenkins, I. D. *J. Org. Chem.* **1989**, *54*, 3045–3049. Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.

[4] Thiolacetate: Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119–3122. Halides: Manna, S.; Falck, J. R.; Mioskowski, C. *Synth. Commun.* **1985**, *15*, 663–668. Silanols: Clive, D. L. J.; Kellner, D. *Tetrahedron Lett.* **1991**, *32*, 7159–7160. Tosylate: Galynker, I.; Still, W. C. *Ibid.* **1982**, *23*, 4461–4464. Phthalimide: Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220–2222. Heterocycles: Jenny, T. F.; Previsani, N.; Benner, S. A. *Tetrahedron Lett.* **1991**, *32*, 7029–7032.

[5] Yu, J.; Falck, J. R.; Mioskowski, C. *J. Org. Chem.* **1992**, *57*, 3757–3759.

[6] Other examples of carbon nucleophiles: (a) Macor, J. E.; Wehner, J. M. *Tetrahedron Lett.* **1991**, 32, 7195–7198. (b) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Ibid.* **1976**, 2455–2458. (c) Wada, M.; Mitsunobu, O. *Ibid.* **1972**, 1279–1282.

[7] With ambident active methylenes, O-alkylation is often competitive, e.g., eqs i–iii. Also see: Falck, J. R.; Yu, J. *Tetrahedron Lett.* **1992**, *33*, 6723–6726. Reference 6b,c.



[8] Satisfactory analytical and spectral data were obtained for all new compounds.

[9] Review of sulfone chemistry: Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: New York, 1993.

[10] Related cleavages of bis-sulfides: Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152–161.

[11] Hwu, J. R. *J. Org. Chem.* **1983**, *48*, 4432–4433.

[12] Reference 9, pp 111–118.

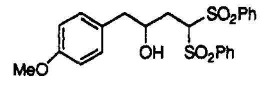
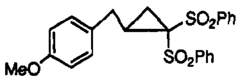
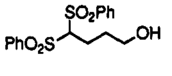
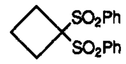
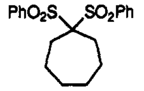
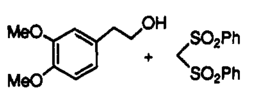
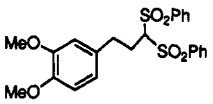
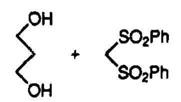
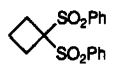
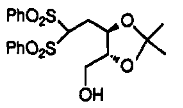
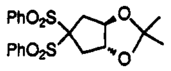
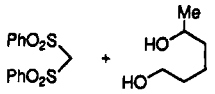
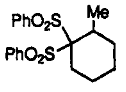
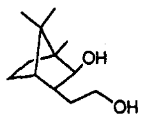
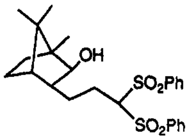
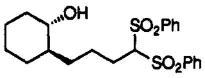
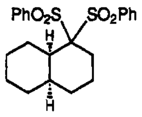
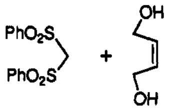
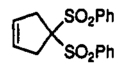
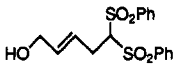
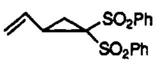
[13] Review: Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97–127.

[14] Baudin, J. B.; Julia, M.; Rolando, C.; Verpeaux, J. N. *Tetrahedron Lett.* **1984**, *25*, 3203–3204.

[15] For the prior use of Mg/MeOH to reduce sulfones see: Brown, A. C.; Carpino, L.A. *J. Org. Chem.* **1985**, *50*, 1749–1750.

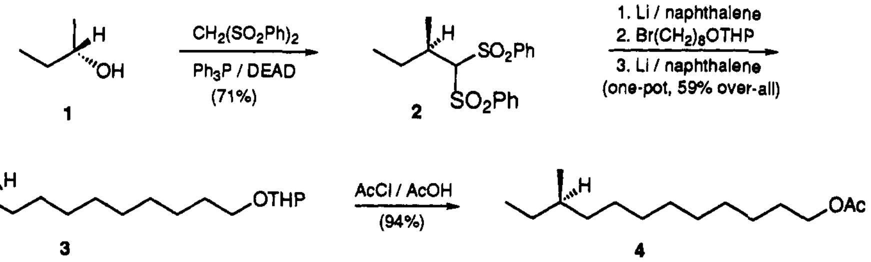
0022-3263/93/1958-5892$04.00/0

Table I. Dehydrative Alkylations/Annulations of Bis-Sulfones

entry	reactant(s)	product	condns^{a}	yield^{b} (%)
1			A	97^{c}
2			A	89^{c}
3			A	82^{c}
4			B	87^{c}
5			B	86^{d}
6			A	$75^{c,e}$
7			B	80^{d}
8			B	71^{d}
9			A	84^{c}
10			B	90^{d}
11			A	95^{c}

[a] Reaction conditions. A: reactant(s) was added dropwise to a preformed complex of DEAD/Ph_3P in benzene at ambient temperature. After 1 h, the solvent was evaporated and the residue purified by chromatography. B: DEAD was added dropwise to a benzene solution of reactant(s) and Ph_3P. After 1 h, the product was isolated as above. [b] Based on isolated, chromatographically homogeneous material. [c] 1.5 equiv each of DEAD and Ph_3P. [d] 3 equiv each of DEAD and Ph_3P. [e] Characterized as the bis-acetate after acetonide hydrolysis.

Scheme I



of adducts (route g); this contrasts sharply with alkali metal salts of sulfones which are typically unreactive towards ketones.[13]

The synergism amongst the various facets of the present investigation as well as their efficacy and operational simplicity are highlighted in a brief, asymmetric total synthesis of pheromone component 4 of the lesser tea tortrix[17] (Scheme I). Alkylation of commercial (*S*)-(+)-2-butanol (1) with inversion of configuration using bis(phenylsulfonyl)methane (1 equiv) and DEAD/Ph_3P complex in benzene evolves bis-sulfone 2. The one-pot monodesulfonylation of 2 with lithium naphthalenide (−78 °C, 5 min), *in situ* alkylation (−78° → +23 °C, 1 h), and

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(16) SmI_2 cleavage of a mono-sulfone: Kunzer, H.; Strahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 1949–1952.

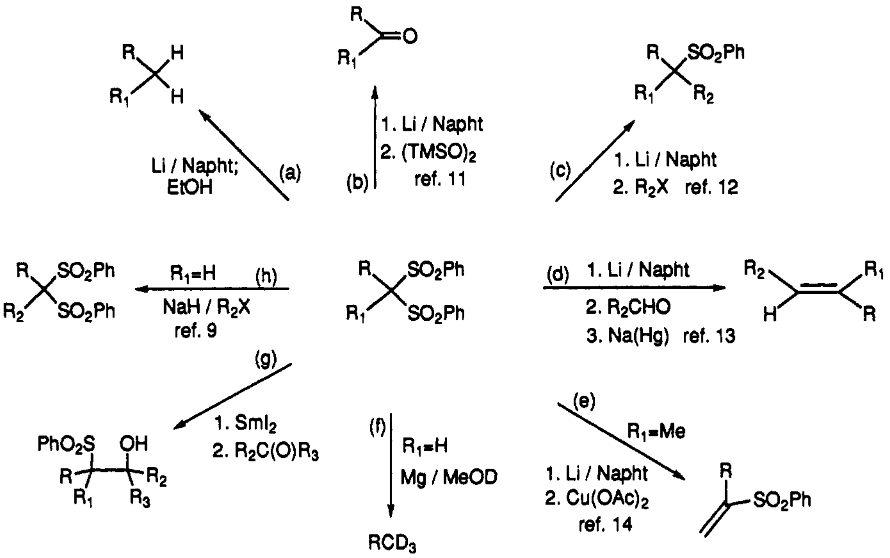

Figure 1. Transformations of bis-sulfones.

second desulfonylation (−78 °C, 5 min) leads to THP ether **3**.[17c] Direct acetylation of **3** as prescribed[18] generates **4**, $[\alpha]^{23}_D = -5.94°$ (c 10, $CHCl_3$) (lit.[17a] $[\alpha]^{23}_D = -5.93°$ (c 10, $CHCl_3$)).

Acknowledgment. Financial support provided by the Robert A. Welch Foundation (I-782) and NIH (R01 GM31278). High-resolution mass spectra were provided by the Midwest Center for Mass Spectrometry with partial support from the NSF (DIR9017262).

Supplementary Material Available: Physical data and spectra ($^1H/^{13}C$) for new compounds (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) (a) In 18 steps via chiral hydroboration: Brown, H. C.; Bakshi, R. K.; Singaram, B. *J. Am. Chem. Soc.* **1988**, *110*, 1529–1535. (b) In 16 steps by resolution: Sonnet, P.E. *J. Org. Chem.* **1982**, *47*, 3793–3796. (c) Hjalmarsson, M.; Hogberg, H.-E. *Acta Chem. Scand. B* **1985**, *39*, 793–796.

(18) Bakos, T.; Vincze, I. *Synth. Commun.* **1989**, *19*, 523–528.