

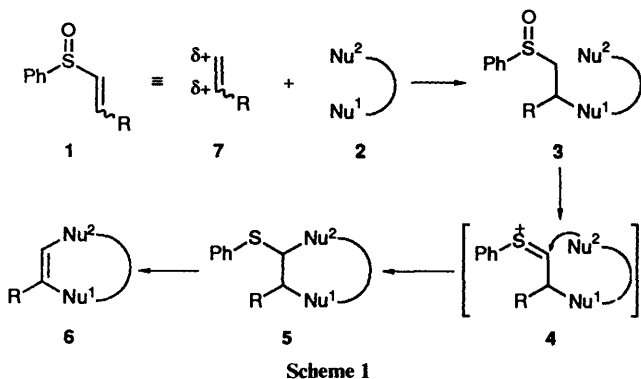
# Unsaturated Sulfoxides in Organic Synthesis: A New General Furan Synthesis

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Furans have been efficiently synthesised by a three-step reaction sequence. Michael addition of keto esters to alkenyl sulfoxides followed by Pummerer rearrangement afforded the cyclic intermediates **11** in good yield. Treatment of the latter with 2-chloroperoxybenzoic acid led by oxidation and *syn*-elimination of the corresponding sulfoxide, to substituted furans.

Efficient syntheses of furans continue to be of interest<sup>1</sup> in view of the widespread occurrence of this system in Nature.<sup>2</sup> Our interest in using unsaturated sulfoxides in organic synthesis,<sup>3a-c</sup> has led us to use them to synthesize substituted furans (see Scheme 1 for general strategy).

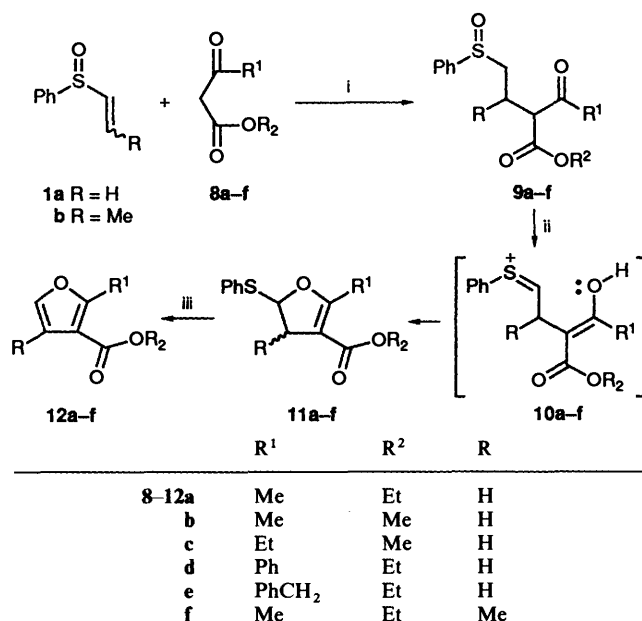


Compound **3**, prepared by Michael addition of the bi-functional nucleophile **2** to the  $\alpha,\beta$ -unsaturated sulfoxide **1**, undergoes a Pummerer rearrangement.<sup>4</sup> Intramolecular trapping of the presumed sulfenium ion intermediate **4** by the second nucleophile gives the cyclized product **5** which, upon oxidation followed by thermal elimination of the resulting sulfoxide, yields an olefinic compound **6**. In this respect, the alkenyl sulfoxide **1** can be viewed as the alkenyl 1,2-dielectrophilic synthon **7**.<sup>3c</sup>

In the furan synthesis, this strategy was effected by Michael addition of  $\beta$ -keto esters **8** to alkenyl sulfoxides **1** in the presence of sodium methoxide in methanol. The best yields of Michael adducts were obtained by using alkenyl sulfoxide, keto ester and sodium methoxide in a ratio of 1:3:2 (see Table 1). It was argued that Pummerer rearrangement of the Michael adducts would produce reactive sulfenium ion intermediates **10** susceptible to a second nucleophilic attack; intramolecular trapping by the enol oxygen would then give the cyclized products **11** (Scheme 2).<sup>5</sup> This two-step transformation was achieved directly in good yield by treatment of the Michael adduct with trichloroacetic acid-acetic anhydride in refluxing toluene. To complete the furan synthesis, two additional steps were needed: 2-chloroperoxybenzoic acid (MCPBA) oxidation of the cyclized products **11** followed by subsequent *syn*-elimination of the corresponding sulfoxides to yield furans. Thus, **11d** was oxidized with MCPBA at room temp. in  $\text{CH}_2\text{Cl}_2$  to give **12d** (78%), the sulfoxide intermediate not being isolated, presumably because of facile thermal elimination as it was formed. In the case of propenyl sulfoxide (entry 6, Table 1), Pummerer cyclization gave a mixture of two inseparable *cis/trans* stereoisomers, the *trans*-isomer appearing to predominate: *syn*-elimination of the corresponding sulfoxide afforded **12f**.<sup>6</sup>

## Experimental

*Formation of Adduct 9 by Michael Addition.*—At room temp.,



Scheme 2 Reagents and conditions: i, NaOMe-MeOH or NaOEt-EtOH; ii,  $\text{CCl}_3\text{CO}_2\text{H}$ ,  $\text{Ac}_2\text{O}$ , toluene, reflux; iii, MCPBA,  $\text{CH}_2\text{Cl}_2$

ethyl benzoylacetate (1.25 g, 6.53 mmol) in dry ethanol (4  $\text{cm}^3$ ) was slowly introduced to a solution of sodium (92 mg, 4 mmol) in dry ethanol (15  $\text{cm}^3$ ) prepared under nitrogen. A solution of the sulfoxide **1a** (1.003 g, 6.6 mmol) in dry ethanol (6  $\text{cm}^3$ ) was added dropwise to the ethoxide solution and the mixture stirred at room temp. for 20 h. It was then quenched with dil. aq. HCl and the ethanol removed under reduced pressure. The residue was extracted with dichloromethane (3  $\times$  30  $\text{cm}^3$ ) and the combined extracts were dried, filtered and evaporated to dryness. Chromatography of the organic residue (silica gel column; ethyl acetate-light petroleum, 1:1) gave **9d** as a colourless liquid (1.76 g, quantitative yield);  $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$  1680 and 1730;  $\delta_{\text{H}}(60 \text{ MHz}; \text{CDCl}_3)$  1.10 and 1.16 (total 3 H, t,  $J$  7.0), 2.20-2.67 (2 H, m), 2.67-3.07 (2 H, m), 4.05 and 4.12 (total 2 H, q,  $J$  7.0), 4.47 (1 H, t,  $J$  7.5) and 7.10-7.97 (10 H, m);  $m/z$  236 ( $\text{M}^+$ , 9.4%) and 219 ( $\text{M}^+ - \text{OH}$ , 8.2).

*Typical Procedure for the Pummerer Cyclization.*—A mixture of the Michael adduct **9d** (185 mg, 0.54 mmol), acetic anhydride (2.5  $\text{cm}^3$ ), trichloroacetic acid (286 mg, 1.75 mmol) in toluene (7  $\text{cm}^3$ ), brought to reflux within 2 to 3 min under a nitrogen atmosphere was kept at this temp. for a further 23 min. It was then allowed to cool to room temp. when it was basified with aq. saturated sodium carbonate and extracted with dichloromethane (3  $\times$  30  $\text{cm}^3$ ). The combined organic extracts were dried, filtered, and evaporated to give the crude product. Flash chromatography of this (silica gel; ethyl acetate-light

**Table 1** Furan synthesis

Entry	Alkenyl sulfoxide	Keto ester	Yield (%)		
			Michael adduct	Cyclized product	Furan
1	<b>1a</b>	<b>8a</b>	<b>9a</b> (83)	<b>11a</b> (84)	<b>a</b> (55)
2	<b>1a</b>	<b>8b</b>	<b>9b</b> (quantitative)	<b>11b</b> (53)	<b>a</b> (80)
3	<b>1a</b>	<b>8c</b>	<b>9c</b> (75)	<b>11c</b> (83)	<b>12c</b> (56) <sup>b</sup>
4	<b>1a</b>	<b>8d</b>	<b>9d</b> (quantitative)	<b>11d</b> (64)	<b>12d</b> (78)
5	<b>1a</b>	<b>8e</b>	<b>9e</b> (61)	<b>11e</b> (67)	<b>12e</b> (71) <sup>b</sup>
6	<b>1b</b>	<b>8a</b>	<b>9f</b> (68)	<b>11f</b> (56)	<b>12f</b> (58)

<sup>a</sup> Oxidation of corresponding acid of **11a** and **11b**; thus furan was identified as substituted 3-furoic acid. <sup>b</sup> The structures of new compounds were supported by satisfactory IR, NMR and MS data.

petroleum, 1:4) afforded the *product* **11d** as a yellowish liquid (113 mg, 64%);  $\nu_{\max}/\text{cm}^{-1}$  1690;  $\delta_{\text{H}}$ (60 MHz;  $\text{CDCl}_3$ ) 1.17 (3 H, t, *J* 6), 3.05 (1 H, dd, *J* 6, 16), 3.39 (1 H, dd, *J* 9.5, 16), 4.07 (2 H, q, *J* 6), 6.00 (1 H, dd, *J* 6, 9) and 7.45 (10 H, m) ( $M^+$ , 326.0969; *M*, 326.0977).

*Formation of Substituted Furans.*—To a stirred solution of furan **11d** (110 mg, 0.34 mmol) in dichloromethane (6 cm<sup>3</sup>), was added MCPBA (70 mg, 0.4 mmol). The mixture was stirred at room temp. for 2 h and then basified with aq. saturated sodium carbonate and extracted with dichloromethane (3 × 20 cm<sup>3</sup>). The combined extracts were dried, filtered and concentrated to dryness. Flash chromatography of the crude product (silica gel; ethyl acetate–light petroleum, 1:9) gave the product **12d** as a colourless liquid (57.3 mg, 78%);  $\nu_{\max}(\text{neat})/\text{cm}^{-1}$  1712;  $\delta_{\text{H}}$ (60 MHz;  $\text{CDCl}_3$ ) 1.30 (3 H, t, *J* 6.5), 4.25 (2 H, q, *J* 6.5), 6.77 (1 H, d, *J* 1.5) and 7.17–8.10 (6 H, m); *m/z* 216 ( $M^+$ , 50.1%), 187 ( $M^+$  – C<sub>2</sub>H<sub>5</sub>, 5) and 171 ( $M^+$  – OC<sub>2</sub>H<sub>5</sub>, 100).

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