A Highly Efficient Synthesis of β-Substituted Six- and Seven-Membered-Ring Enones via Carbon Alkylation of γ-Methoxy Allylsulfonyl Anions[1]

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A previous paper from these laboratories detailed the use of γ-silyloxy vinyl sulfones **2** (Scheme 1) as the focal point of a four-step synthesis of α,β-disubstituted enones **4**.[2] A serious deficiency of this strategy has been revealed by our recent need for β-substituted enones which bear a hydrogen in the α-position (**4**, $R^1 = H$).[3] This limitation has now been removed for six- and seven-membered rings by implementation of an alternative one-pot metalation/alkylation/fragmentation sequence starting from γ-methoxy vinylsulfones **5b,c**. Phase-transfer alkylation of γ-hydroxy vinyl sulfones **1a-c** (readily available on the mole scale[2]) using tetrabutylammonium bromide and excess methyl iodide in methylene chloride and 50% aqueous KOH for 1–6 hr at 25 °C affords **5a-c** in 96–99% yield.

Reaction of γ-methoxy vinyl sulfones **5b,c** with 1.05 equiv of *tert*-butyl lithium[4] in THF at −78 °C smoothly affords an orange solution of γ-methoxy allylsulfonyl anions[5] **6b,c** as assayed by isolation of γ-methoxy allylsulfones **7b,c** ($R^2 = H$) in 99% and 91% yields, respectively, after quenching of the reaction mixture with saturated sodium bicarbonate (Table 1, entries 3, 16). Unfortunately utilization of the above procedure with the five-membered ring γ-methoxy vinylsulfone **5a** is totally unrewarding. The reaction rapidly produces several polar products from competitive self-condensation of **5a** with the initially produced five-membered-ring allyl anion **6a**, thereby consuming **6a** as rapidly as it is formed.[6] Happily, the cyclohexyl and cycloheptyl systems are exceptionally well-behaved, affording β-substituted enones **4b,c** in nearly quantitative yields for the cases cited in Table 1. The reaction simply involves addition of the electrophile to the −78 °C THF solution of γ-methoxy allylsulfonyl anions **6b,c** and stirring for 15 min, followed by addition of saturated $NaHCO_3$ to the −78 °C solution and extraction with CH_2Cl_2 to afford a mixture of enol ethers **7b,c** containing variable amounts of enones **4b,c**. Completion of the process was effected by stirring the CH_2Cl_2 solution with commercial 230–400-mesh silica gel (10 g/g of substrate) for 2 h at 25 °C. Purification by flash chromatography provides the target enones in the yields described in Table 1. As can be seen from entries 14 and 15, additions of **5b** to cyclohexyl substrates fail under the standard conditions, the quenched allylic sulfone **7b** being the only product recovered in high yield.

Scheme 1

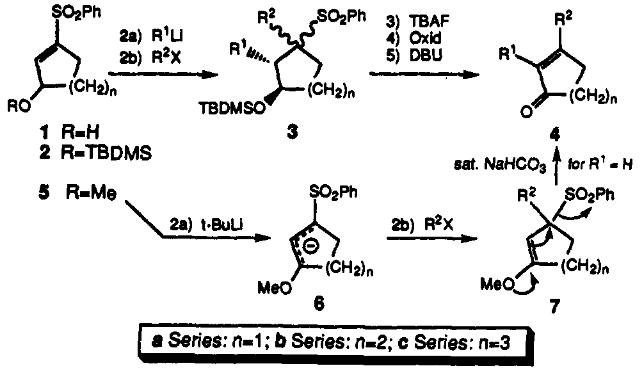
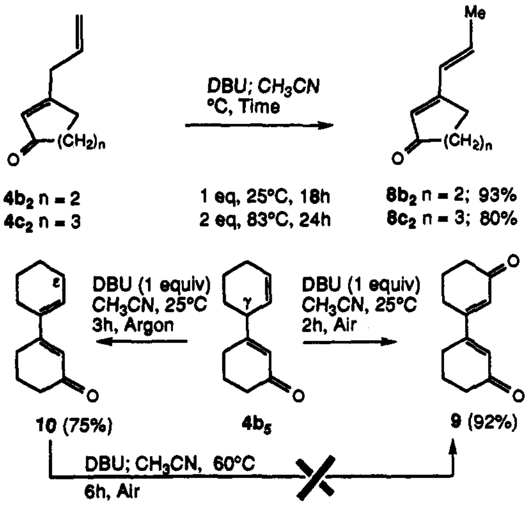


Table 1

entry	sm[a]	electrophile R^2X	product (R^2=); yield, %
1	**5a**	H_2O	**7a** ($R^2 = H$); 0
2	**5a**	$CH_2{=}CHCH_2Br$	**4a**$_2$ ($R^2 = CH_2CH{=}CH_2$); 0
3	**5b**	H_2O	**7b** ($R^2 = H$); 99
4	**5b**	$PhCH_2Br$	**4b**$_1$ ($R^2 = CH_2Ph$); 98
5	**5b**	$CH_2{=}CHCH_2Br$	**4b**$_2$ ($R^2 = CH_2CH{=}CH_2$); 96
6	**5b**	n-C_4H_9-Br[c]	**4b**$_3$ ($R^2 = n$-C_4H_9); 92
7	**5b**	*i*-Pr[c]	**4b**$_4$ ($R^2 = i$-Pr); 92
8	**5b**	3-bromocyclohexene	**4b**$_5$ ($R^2 = C_6H_9$); 98
9	**5b**	Me_3SiCl	**4b**$_6$ ($R^2 = Me_3Si$); 96
10	**5b**	$TMSCH_2CH_2SSO_2Ph$[7]	**4b**$_7$ ($R^2 = SCH_2CH_2TMS$); 99
11	**5b**	PhSeCl	**4b**$_8$ (R^2 = SePh); 86
12	**5b**	PhCOCl	**4b**$_9$ (R^2 = COPh); 94
13	**5b**	PhCHO	**4b**$_{10}$ (R^2 = CHOHPh); 99
14	**5b**	c-$C_6H_{11}Br$[d]	**4b**$_{11}$; 0
15	**5b**	cyclohexane epoxide[d]	**4b**$_{12}$; 0
16	**5c**	H_2O	**7c** ($R^2 = H$); 91[b]
17	**5c**	$CH_2{=}CHCH_2Br$	**4c**$_2$ ($R^2 = CH_2CH{=}CH_2$); 92[b]
18	**5c**	Me_3SiCl[c]	**4c**$_6$ ($R^2 = Me_3Si$); 88[b]
19	**5c**	$TMSCH_2CH_2SSO_2Ph$[7]	**4c**$_7$ ($R^2 = SCH_2CH_2TMS$); 91[b]

[a] Starting material ring size: **a** series = 5; **b** series = 6; **c** series = 7. [b] 3–5% of the *tert*-butyl conjugate addition product is also produced in this reaction. [c] Addition of TMEDA (1.0 equiv) increased the alkylation rate. [d] Addition of TMEDA did not provide the desired adduct.

Scheme 2



Allylated products **4b**$_2$ and **4c**$_2$ serve as useful progenitors for dienyl ketones **8b**$_2$ and **8c**$_2$ respectively, simply by DBU-mediated isomerization (Scheme 2). In attempting to apply this method to cyclohexenylated adduct **4b**$_5$ we were surprised to initially obtain dione **9** with no trace of the expected dienyl ketone **10**. Repeating the reaction with careful exclusion of oxygen affords the desired dienyl ketone in 75% yield (93% using CH_2Cl_2). Contrary to expectations, a control reaction demonstrates that

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(1) Syntheses via Vinyl Sulfones. 52.

(2) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 346.

(3) An alternative soution to this problem might involve conjugate addition of hydride (*cf.*: Jones, D. N.; Maybury, M. W. J.; Swallow, S.; Tomkinson, N. C. O. *Tetrahedron Lett.* **1993**, *34*, 8553–8556) to **2** followed by alkylation of the incipient α-sulfonyl anion to give **3** ($R^1 = H$). Deprotection, oxidation, and elimination then likely would generate enone **4** ($R^1 = H$). The new strategy obviates the reduction/reoxidation steps.

(4) Use of *n*-Butyllithium or *sec*-butyllithium results principally in conjugate addition to the vinyl sulfone.

(5) Craig has shown that *acyclic* γ-benzyloxy allyl sulfones undergo smooth metalation to afford acyclic γ-benzyloxy allylsulfonyl anions, which were shown to efficiently react at the α-sulfonyl position with aldehydes and alkyl halides. The resulting intermediates were converted to butenolides and furans. (See: Craig, D.; Etheridge, C. J.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 7445–7446. Craig, D.; Etheridge, C. J. *Tetrahedron Lett.* **1993**, *34*, 7487–7488.)

(6) The exceptional Michael acceptor properties of cyclopentenyl sulfones has been exploited for the synthesis of polycyclic dienyl ketones and will comprise the subject of a subsequent manuscript.

(7) Ranasinghe, M. G.; Fuchs, P. L. Synth. Commun. **1988**, *18*, 227.

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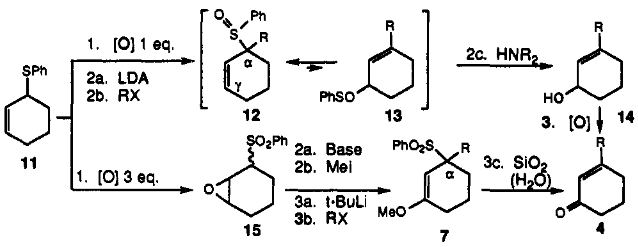
Scheme 3



treatment of **10** with DBU in the presence of air does not generate dione **9**, compound **10** being recovered in high yield. This implies that interception of the dienolate by oxygen is faster than the isomerization process and ε-deprotonation of **10** by DBU is very slow relative to γ-deprotonation of **4b**$_5$ under these conditions. It is currently postulated that the immediate progenitor of compound **9** is an allylic hydroperoxide which suffers base-catalyzed fragmentation to install the second carbonyl moiety. The detailed mechanism[8] and the generality of this reaction have yet to be established.

In summary, the β-substituted enone strategy described in this work can be seen to be complementary to a method developed in the Evans laboratories (Scheme 3).[9] In the Evans method, allyl sulfide **11** is oxidized to allylic sulfoxide **12a** (R = H), which is metalated and alkylated to provide **12b** (R = alkyl). Allyl sulfoxide **12b** is in equilibrium with allyl sulfenate **13** via 2,3 sigmatropic rearrangement. Treatment of the **12**/**13** mixture with a thiophilic reagent like a secondary amine provides allyl alcohol **14**, which can be subsequently oxidized to enone **4**. The current method also utilizes allylic sulfide **11**, but proceeds via β-epoxy sulfone **15** to the α-alkylated allylic sulfone **7** on the way to enone **4**. While both processes are of equivalent length, the Evans protocol provides lower overall yields as well as forming α/γ mixtures during addition of the allyl sulfoxide anion to carbonyl compounds,[10] while the alkylation of the allylic sulfone anion faithfully undergoes alkylation adjacent to the sulfone moiety in all cases examined.

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Supplementary Material Available: Copies of proton and carbon spectra for all new compounds are available (44 pages). This material is contained in many 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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[8] The possibility of trapping oxygen at α or γ positions of the dienolate followed by 2,3 sigmatropic rearrangements leading ultimately to the ε-hydroperoxy intermediate must be seriously entertained at this stage.

[9] Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155.

[10] (a) Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Tetrahedron Lett.* **1973**, 1385. (b) Evans, D. A.; Andrews, G. C.; Fujimoto, T. T.; Wells, D. *Ibid.* **1973**, 1389.