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SYNTHESIS OF BETA-SUBSTITUTED CYCLOPENTENONES VIA CARBON ALKYLATION OF METALATED GAMMA-METHOXYCYCLOPENTENYL PHENYLSULFONYL ANION.[1]

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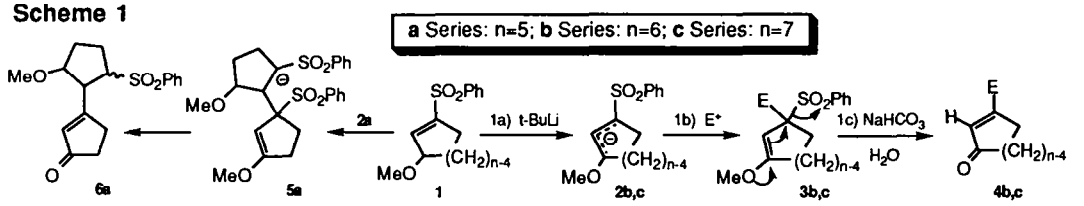
Abstract: Metalation of γ-methoxyallyl sulfone **13** provides phenylsulfonyl anion **2a** which undergoes alkylation followed by hydrolysis to afford β-substituted cyclopentenones.

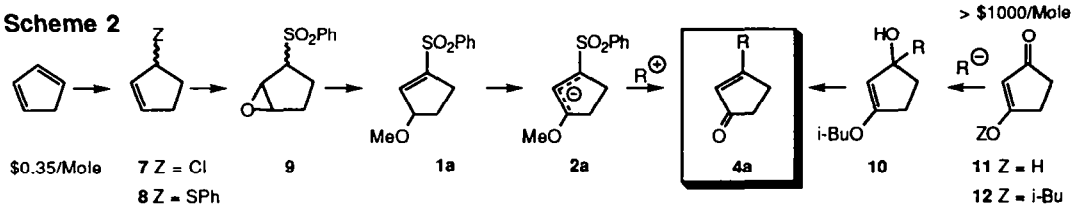
Six and seven membered γ-methoxy vinyl sulfones **1b,c** are converted to γ-methoxy allylsulfonyl anions **2b,c** upon reaction with t-BuLi. Regiospecific trapping by electrophiles provided enol ethers **3b,c** which were hydrolyzed in >90% yield to β-substituted enones **4b,c** (Scheme 1).[2] Unfortunately, attempts to extend this chemistry to the cyclopentenyl series were compromised by the propensity of γ-methoxycyclopentenyl sulfone **1a** to intercept intermediate allylsulfonyl anion **2a** via conjugate-addition, leading to the formation of δ-sulfonyl substituted enone **6a** in 88% yield.[3] While this finding was instrumental in developing a series of useful unsymmetrical cross-coupling reactions,[3] it did not provide access to the desired β-substituted cyclopentenones **4a**.

Scheme 1



Extension of the above enone synthesis to the cyclopentyl series is of considerable general significance since generic β-substituted cyclopentenones like **4a** are traditionally prepared by anionic addition to vinylogous ester **12**, acidic hydrolysis of adduct **10** serving to complete the transformation.[4] While this is appropriate on small scale, the cost of dione **11** is a considerable disadvantage relative to the complementary (charge-inverted) vinyl sulfone protocol (Scheme 2).

Scheme 2



Synthesis of key substrate **1a** is a trivial exercise on the multi-mole scale. Addition of gaseous HCl to neat cyclopentadiene results in formation of allylic chloride **7** which is directly treated with thiophenylate anion to afford allyl sulfide **8**. Oxidation with three equivalents of

peracetic acid (to **9**[5]) followed by treatment with sodium hydroxide and methyl iodide under phase-transfer conditions provides **1a** in 73% overall yield.

Since attempts at direct metalation of **1a** result in instantaneous formation of adduct **5a**, it is clear that generation of **2a** must be accomplished in the absence of the reactive Michael acceptor vinyl sulfone **1a**. Accordingly, base catalyzed isomerization of **1a** to allylic sulfone **13** was carefully investigated. While treatment of **1a** with DBU returned starting material and reaction with KOt-Bu in DMSO provided dimer **6a**, successful isomerization to **13** could be accomplished by heating **1a** in THF at 50-55°C for 65-70h in the presence of 0.2 equivalents of the Schwesinger P_2-Et phosphazene base.[6] Isolation of >90% yield of the sensitive γ-methoxyallyl sulfone **13** as an yellowish-orange oil involved rapid filtration through fluorosil/celite using 1:5 EtOAc/CH_2Cl_2. Compound **13** could be conveniently stored in the freezer as a ~0.15M THF solution over anhydrous potassium carbonate or polyvinylpyridine. Metalation/alkylation/hydrolysis as per our previous procedure[2] afforded enones **15** in the yields indicated in Table 1 below.

Scheme 3

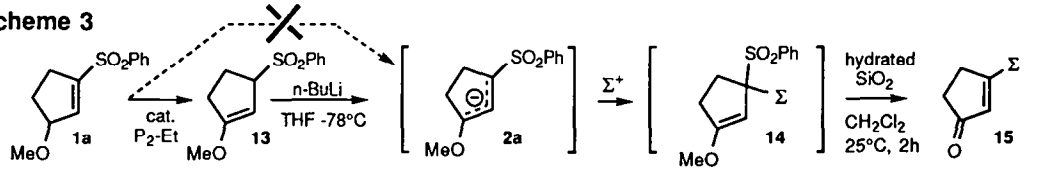


Table 1. Electrophilic functionalization of anion **2a**.

Entry	Electrophile Σ =	Product 15* ; yield
1	5.5:1 E/Z $BrCH_2CH{=}CH(CH_2)_7OTBDMS$	Σ= 5.5:1 E/Z $CH_2CH{=}CH(CH_2)_7OTBDMS$; 76%
2	PhCHO	Σ= CHOHPh; 78%
3	Bu_3SnCl	Σ= Bu_3Sn; 80%
4	$PhMe_2Si$-Cl	Σ= $PhMe_2Si$; 89%
5	Tosyl Aziridine[7]	Σ= CH_2CH_2NHTs; 85%
6	$TMSCH_2CH_2SSO_2Ph$[8]	Σ= SCH_2CH_2TMS; 87%
7	$PhCH_2Br$	Σ= CH_2Ph; 86%
8	PhSeCl (PhSeSePh)	Σ= SePh; 61% (65%)

* The initial α-functionalized γ-methoxyallylsulfone intermediate **14** was routinely hydrolyzed at 25°C in methylene chloride in the presence of hydrated silica gel for 12h to effect cleavage to enone **15**.

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References and notes

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