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A NOVEL SYNTHESIS OF α,β-UNSATURATED γ-HYDROXY CARBONYL COMPOUNDS FROM ENONES WITH CARBON HOMOLOGATION[1]

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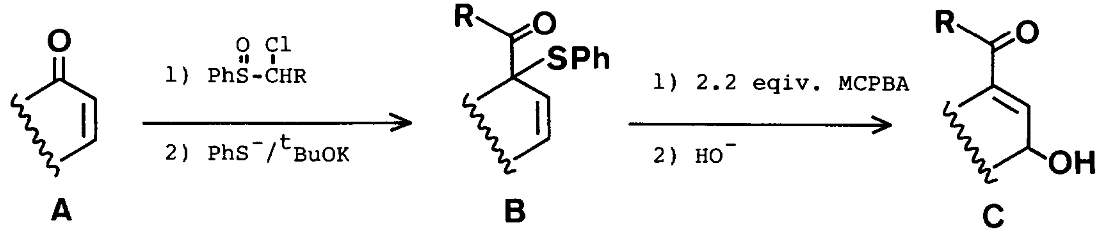
Summary The alkylation of enone with 1-chloroalkyl phenyl sulfoxide followed by treatment with thiophenolate afforded α-phenylthio-β,γ-unsaturated carbonyl compound, which was oxidized and then hydrolyzed to give α,β-unsaturated γ-hydroxy carbonyl compound in good yield.

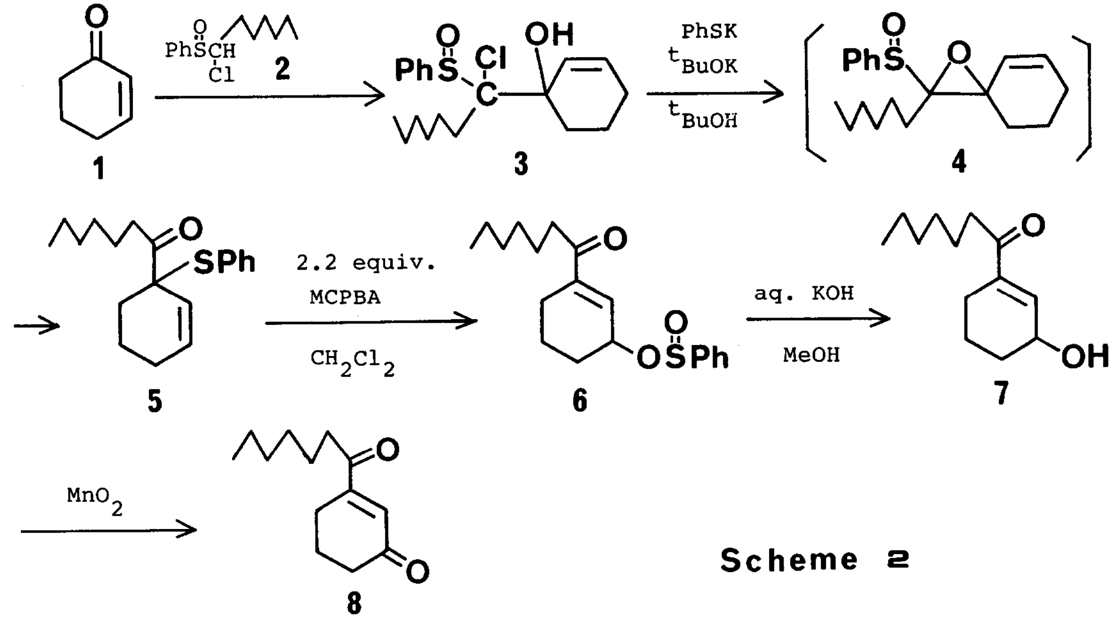
Highly oxygenated ketones and aldehydes are very useful compounds in synthetic organic chemistry. Especially enones and enals are of most important in the chemistry of carbon-carbon bond formation. They are frequently used as dienophiles in the Diels-Alder reaction[2] or as Michael acceptors[3] etc.

Recently, we reported[4] a new and versatile procedure for synthesizing α-substituted ketones and aldehydes from lower carbonyl compounds with carbon homologation.[5] In the course of studies on the homologation of carbonyl compounds through α,β-epoxy sulfoxides, a new and efficient procedure for the synthesis of α,β-unsaturated γ-hydroxy carbonyl compounds from enones was found. The procedure is given in Scheme 1.

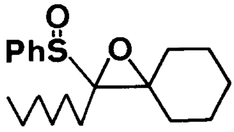


Scheme 1

The alkylation of cyclohexenone (1) with 1-chloroheptyl phenyl sulfoxide (2) by using LDA as a base gave the chlorohydrin (3) in 91% yield. Treatment of this chlorohydrin with ^{t}BuOK in ^{t}BuOH gave the α,β-epoxy-γ,δ-unsaturated sulfoxide (4) but this epoxide was found to be too unstable to be isolated. For example, on exposure with silica gel or alumina it decomposed immediately giving a complex mixture. Next, this reaction was carried out in the presence of 2.2 equivalents of thiophenol with excess of ^{t}BuOK in ^{t}BuOH at room temperature for 10 min. This reaction worked well to afford the desired α-phenylthio-β,γ-unsaturated ketone (5) in 61% yield. It is worthwhile noting that the phenylsulfenylation of the corresponding saturated α,β-epoxy



Scheme 2



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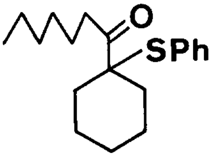

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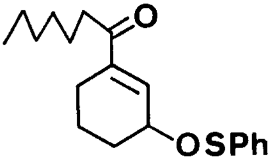


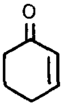
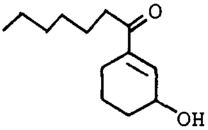
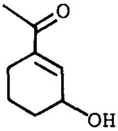
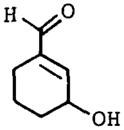
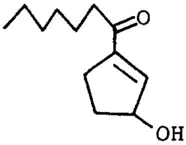
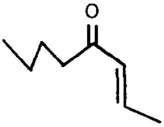
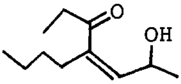
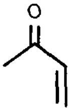
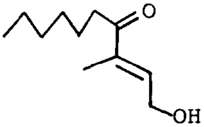
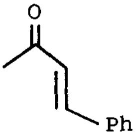
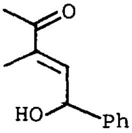
6'

sulfoxide (4'), as already reported,[4b] required excess (7 equivalents) thiophenolate and the condition of reflux in ethanol for 2.5 h (giving 5' in 96% yield). In contrast with the reported result, the present reaction required much milder condition and this result indicates that the reactivity of α,β-epoxy-γ,δ-unsaturated sulfoxides toward the nucleophiles might be much higher than that of α,β-epoxy-γ,δ-saturated sulfoxides.

Oxidation of the sulfur group of 5 with 1.1 equivalents of MCPBA in CH_2Cl_2 at -60 °C ~ -30 °C for 2 h gave the rearranged sulfinate (6) and sulfenate (6') in 26% and 36% yields, respectively, along with some amount of the starting material (5) and no sulfoxide was observed. We were somewhat surprised by this result because sulfoxide-sulfenate equilibrium is usually much in favour of the sulfoxide.[6] In order to convert all the starting material into the desired rearranged product, 5 was oxidized with 2.2 equivalents of MCPBA at 0 °C for 15 min to afford the sulfinate (6) in 89% yield along with no 5 and no sulfenate (6'). The sulfinate (6) was found to be relatively unstable compound, and it was immediately hydrolyzed with excess 10% aq. KOH in methanol at room temperature for 15 min to give 93% of α,β-unsaturated γ-hydroxy ketone (7).

Table 1.

Preparation of α,β-unsaturated γ-hydroxy carbonyl compounds from enones through α-phenylthio-β,γ-unsaturated carbonyl compounds

Entry	Enone (A)	R in $\mathrm{Ph}\overset{\underset{\|}{O}}{S}\mathrm{CH(Cl)R}$	α-Phenylthio-β,γ-unsaturated carbonyl compound (B)/ %a)	α,β-Unsaturated γ-hydroxy carbonyl compound (C)/ %b)	
1		$CH_3(CH_2)_5$	61		83
2	"	CH_3	82		69
3	"	H	62		70
4		$CH_3(CH_2)_5$	59		75
5		CH_3CH_2	43		72c)
6		$CH_3(CH_2)_5$	52		44c)
7		CH_3	89		44c)

a) Isolated and purified yields of the sulfenylation of the chlorohydrin. b) The overall yields of two steps from α-phenylthio-β,γ-unsaturated carbonyl compound (B). c) The configuration of the double bond of the product was determined from the chemical shift of the vinyl proton. See reference 7.

Though this α,β-unsaturated γ-hydroxy ketone (7) itself is quite useful in synthetic organic chemistry, as mentioned above, 7 is easily converted into another useful compound, 2,3-unsaturated 1,4-diketone (8) by oxidation with activated manganese(IV) oxide in good yield (over 85% yield). Table 1 shows the representative results of the synthesis of α,β-unsaturated γ-hydroxy carbonyl compounds from enones through the α,β-epoxy sulfoxides.

We should like to report the limitation of this reaction found at the present stage. The alkylation of 1-chloroalkyl phenyl sulfoxide having secondary alkyl group, such as isopropyl or cyclohexyl group, with enones gave low yields of the products (usually less than 50%) and the treatment of thus synthesized chlorohydrin with thiophenolate and base gave only retro-alkylation products.

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