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Synthesis of β-Hydroxysulfides from Alkenes under Supramolecular Catalysis in the Presence of β-Cyclodextrin in Water

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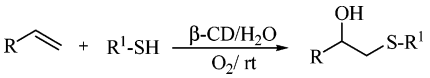
Received April 17, 2006



An environmentally benign and highly efficient procedure has been developed for the direct one-pot synthesis of β-hydroxysulfides in good yields under neutral conditions from alkenes and thiophenols in the presence of aerial oxygen using β-cyclodextrin in water. This protocol tolerates a wide variety of functional groups or substrates and does not require the use of either acid or base catalysts. β-Cyclodextrin can be recovered and reused for a number of runs without any loss of activity.

Improving the efficiency of organic synthesis, including minimizing the energy cost and chemical waste, is a major goal in synthetic chemistry. In this regard, performing multistep bond formation and/or bond cleavage in one pot is an attractive strategy.[1] Among various approaches, green chemistry with water as solvent is becoming important in the present day organic synthesis.[2] Water is a safe, economical, and environmentally benign solvent.[3] Water with a recyclable catalyst under supramolecular catalysis and without the use of any harmful organic solvents appears to be ideal. We felt the need to apply the principles of supramolecular catalysis with water as solvent for the synthesis of β-hydroxysulfides during the course of our investigations. β-Hydroxysulfides are important building blocks for the synthesis of higher functionalized organic molecules.[4] β-Hydroxysulfides are of great synthetic utility in the field of pharmaceuticals[5] and natural products,[6] particularly for the synthesis of leukotrienes such as LTC_4 and LTD_4.

One of the most straightforward synthetic procedures for the preparation of β-hydroxysulfides is the ring opening of epoxides with thiols in the presence of promoters and/or catalysts.[7] However, most of the methods reported consist of Lewis acid catalysts to perform these reactions under mild conditions, but these methods suffer with various disadvantages such as drastic reaction conditions, poor regioselectivity, lower yields, and undesirable side products by rearrangement of oxiranes and oxidation of thiols.[8]

However, another method commonly used for the straightforward synthesis of β-hydroxysulfides involves the thiol−oxygen cooxidation reactions (TOCOs) of olefins.[9] Generally, the TOCO reaction proceeds on the free-radical-chain pathway. However, these reactions usually require a base catalyst with a large excess of thiols and are initiated by UV irradiation or peroxides. This methodology also suffers with regioselectivity, lower yields (up to 50%), and undesirable side products. Thus, in principle, a direct conversion of alkenes into β-hydroxysulfides would be a useful contribution to the synthesis of this functional class. The addition of thiols and various nucleophiles onto carbon−carbon double bonds proceeds usually in a Markovnikov or anti-Markovnikov manner.[10]

In continuation of our interest in the use of cyclodextrins as mild and efficient biomimetic catalysts in promoting various transformations,[11] we have attempted the addition of thiols to alkenes in water in the presence of cyclodextrins.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host−guest complexes by noncovalent bonding as seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. We describe, herein, the remarkable catalytic activity of β-cyclodextrin in the addition

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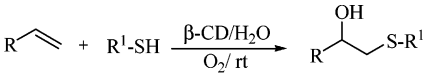
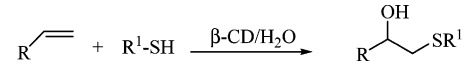
10.1021/jo060805a CCC: $33.50
Published on Web 06/27/2006

SCHEME 1



R = aryl, aryloxy-methylene,alkyl; R^1 = aryl

TABLE 1. One-Pot Synthesis of β-Hydroxysulfides from Alkenes in the Presence of β-CD in Water



Entry	R	R^1	Time(h)	Yield(%)[a,b]
1	Ph	Ph	2.0	86[c]
2	Ph	*p*-BrC_6H_4	2.0	86
3	Ph	*o*-MeC_6H_4	3.0	82
4	*p*-ClC_6H_4	Ph	2.0	85
5	*p*-ClC_6H_4	*p*-BrC_6H_4	2.0	86
6	*p*-ClC_6H_4	*o*-MeC_6H_4	3.0	80
7	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	3.5	84
8	*p*-BrC_6H_4	Ph	2.0	84
9	*p*-BrC_6H_4	*p*-BrC_6H_4	2.0	82
10	*p*-BrC_6H_4	*p*-$MeOC_6H_4$	3.5	84
11	*p*-MeC_6H_4	Ph	2.5	82
12	*p*-MeC_6H_4	*p*-BrC_6H_4	2.0	84
13	*p*-MeC_6H_4	*o*-MeC_6H_4	3.5	80
14	*p*-MeC_6H_4	*p*-$MeOC_6H_4$	4.0	82
15	*p*-$MeOC_6H_4$	Ph	3.0	84
16	*p*-$MeOC_6H_4$	*p*-BrC_6H_4	3.0	82
17	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	4.0	80
18	*p*-$AcOC_6H_4$	Ph	3.0	80
19	*p*-$AcOC_6H_4$	*p*-BrC_6H_4	3.0	80
20	$PhOCH_2$	*p*-ClC_6H_4	6.0	64
21	$PhOCH_2$	*p*-$MeOC_6H_4$	6.0	60
22	*p*-$ClPhOCH_2$	Ph	6.0	60
23	*p*-$MePhOCH_2$	Ph	6.0	62
24		Ph	6.0	70

[a] All the products were characterized by IR, ^{1}H NMR, and mass spectrometry. [b] Isolated yields. [c] The catalyst was recovered and reused for five consecutive runs in this reaction without change in the yield and purity.

of various thiols to alkenes with water as solvent for the exclusive formation of β-hydroxysulfides (Scheme 1).

This work reports the first one-pot β-hydroxysulfide synthesis with broad substrate specificity. The yields are impressive with various substituted styrenes and thiols (Table 1). The regioselectivity of entries 1−19 was a perfect single isomer. In all these cases, the single isomer was derived from the attack of thiols at the terminal carbon. *trans*-β-Hydroxysulfide could be obtained in 70% yield even from the much less-reactive cyclohexene (Table 1, entry 24), and the yields are also encouraging in the case of phenoxy methylalkenes (Table 1, entries 20−23). This is the first practically feasible anti-Markovnikov addition reaction of thiols with a variety of alkenes in water. The reaction proceeds efficiently at room temperature without the need of any acid or base catalyst. The reaction goes to completion in a short time (2−6 h). This methodology is compatible with various substituted alkenes and substituted aromatic thiols with different functionalities such as bromo, chloro, methyl, methoxy, and acetoxy under mild reaction conditions. No byproduct formation

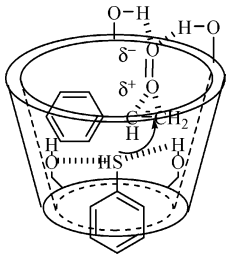


FIGURE 1. Biomimetic synthesis of β-hydroxysulfides.

was observed. These reactions are highly selective forming β-hydroxysulfide as the only product in excellent yields keeping the other functionalities intact. Though asymmetric induction was seen to some extent in these reactions, the ee's observed are not encouraging (<10%). β-Cyclodextrin can be easily recovered and reused. The compounds were characterized by spectroscopy or elemental analysis or were otherwise compared with the known compounds.[8]

The catalytic activity of cyclodextrin for this anti-Markovnikov addition is established by the fact that no reaction was observed in the absence of cyclodextrin. In the case of organic solvents such as DCM, MeOH, THF, CH_3CN, and aqueous MeOH and CH_3CN, only the formation of thioether was observed and a trace amount of β-hydroxysulfide could be seen. When the reaction was performed with β-CD in water under an argon atmosphere, the addition product thioether only was formed (∼65%). This indicates that aerial oxygen is involved in the formation of β-hydroxysulfides. The operation of a TOCO reaction can also be ruled out in this case as follows.

The fact that the olefin and thiol are taken in an equimolar ratio and the yields are always more than 50% in all the compounds studied rules out the TOCO mechanism. In the case that thiol acts as the reducing agent, the maximum possible theoretical yield of β-hydroxysulfides cannot exceed more than 50%.

The formation of β-hydroxysulfides may be explained as follows: The oxygen may be complexing with the alkene in the β-CD−alkene complex assisted by the hydrogen bonding with the CD hydroxyls, and this would be followed by the nucleophilic attack by thiophenol from the primary side of the β-CD (Figure 1). This was confirmed from the ^{1}H NMR studies of the freeze-dried reaction mixture of β-CD, the β-CD−alkene complex, and alkene−β-CD with thiophenol. It was observed that, apart from the upfield shift of H_3 (0.028 ppm) and H_5 (0.011 ppm) protons of cyclodextrin in the β-CD−alkene complex as compared to β-CD which indicates the formation of an inclusion complex of alkene from the secondary side, there is also an upfield shift of a H_6 proton, i.e., 0.013 ppm. This indicates the complexation of thiophenol from the primary side of cyclodextrin (Figure 2).[12] The starting alkene from the CD−alkene complex was isolated intact without any change indicating that no transformation takes place in the absence of the nucleophile thiophenol. It is further observed that this reaction does not take place with nucleophiles such as amines and phenols even after long reaction times (∼24 h). Thus, it could be seen that the reaction may not be going through the formation

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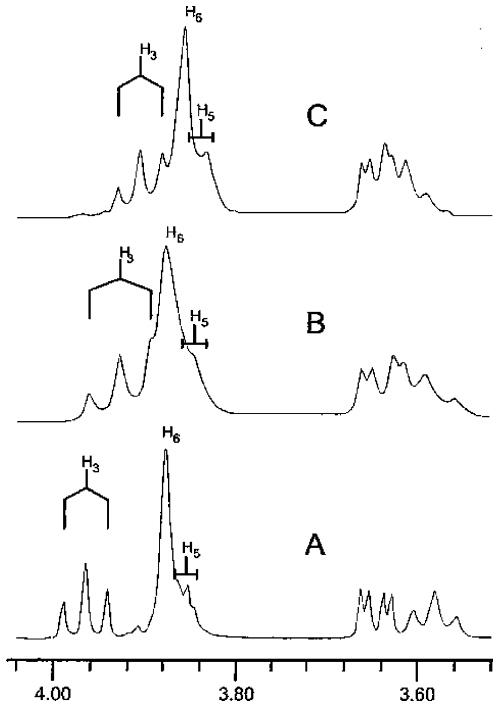

FIGURE 2. ^{1}H NMR spectra (D_2O) of (A) β-CD, (B) the β-CD−styrene complex, and (C) the freeze-dried reaction mixture of the styrene−β-CD complex with thiophenol at 1 h.

of epoxide because epoxides can be opened up with this type of nucleophile.[11b,c]

In summary, we have documented, for the first time, a cyclodextrin-catalyzed hydroxysulfide reaction as a new entry to β-hydroxysulfides directly from alkenes. These CD-mediated water solvent reactions are very useful from both economical and environmental points of view. β-Cyclodextrin, apart from being nontoxic, is also considered as metabolically safe.[13] This reaction is simple and runs under relatively mild conditions with short reaction times and higher selectivities using a recyclable catalyst. To our knowledge, this is the first example of CD-mediated activation of inert alkenes toward nucleophilic addition. This study may open a new direction for alkene functionalization.

Experimental Section

Typical Procedure for the Synthesis of 1-Phenyl-2-(phenylsulfanyl)-1-ethanol. β-CD (1 mmol) was dissolved in water (15 mL) by warming to 60 °C until a clear solution was formed, and then styrene (1 mmol) dissolved in acetone (1 mL) was added dropwise and allowed to come to room temperature. Thiophenol (1 mmol) was then added and stirred at room temperature in the presence of oxygen until the reaction was complete (Table 1). The organic material was extracted with ethyl acetate, dried, and concentrated under reduced pressure, and the resulting product, though seen as a single compound by TLC, was further purified by passing over a column of silica gel. CD was recovered by filtration and reused.

Representative example (entry 1, Table 1): pale yellow oil; IR (neat) 3420 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.69 (brs, 1H, OH), 2.91−3.0 (m, 1H), 3.21 (dd, 1H, J = 3.0, 13.5 Hz), 4.60 (dd, 1H, J = 3.7, 9.8 Hz), 7.10−7.24 (m, 8H), 7.33 (d, 2H, J = 7.5 Hz); Mass (EI) 230 *m*/*z*.

Acknowledgment. We thank the Indo-French Center for the Promotion of Advanced Research (IFCPAR) for financial support of this project.

Supporting Information Available: Experimental procedures and characterization data for all compounds including ^{1}H NMR spectra are described. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060805A

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