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SHORT COMMUNICATION

Enantioselective Cycloetherification in a Micellar Catalysis System

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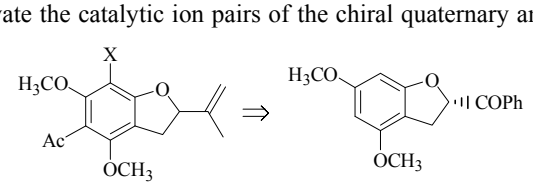
Abstract: The enantioselective cycloetherification of substituted keto phenols into their corresponding dihydrobenzofuran derivatives was carried out using hydrogen peroxide and chiral quaternary ammonium iodide in micellar media. This approach increased the conversion rate of cycloetherification and also widened the scope of this particular reaction for various substituted keto phenols with electron withdrawing as well as electron donating functionalities. The use of a surfactant in the cycloetherification reaction increased the yield of the corresponding enantioselective dihydrobenzofuran four times. The conversion rate of keto phenols into their corresponding dihydrobenzofuran derivatives was proportional to the concentration of the surfactant used in the reaction.

Key words: enantioselective cycloetherification; dihydrobenzofuran derivative; micellar catalysis

Chiral 2-substituted-2,3-hydrobenzofuran is the backbone structure for many biologically active compounds in medicinal chemistry [1–8]. As part of our ongoing research [9,10] into novel chemical entities with antitrypanosomal activities we became interested in the synthesis of (+)-remirol and (+)-remiridiol (**1**) from (*R*)-(4,6-dimethoxy-2,3- dihydrobenzofuran-2-yl) (phenyl methanone, **2**) (Scheme 1).

Although a number of methods for the synthesis of 2-substituted-2,3-hydrobenzofuran have been reported [11–18] they generally require very harsh conditions and most result in racemic mixtures of the product. One of the most important approaches in the synthesis of chiral 2-substituted-2,3- hydrobenzofuran is the use of hydrogen peroxide as an oxidant to activate the catalytic ion pairs of the chiral quaternary ammonium iodide [19]. Recently, a very useful synthesis of 2-substituted-2,3-hydrobenzofuran using N-spiro quaternary ammonium iodide has been reported [20]. In this report the cyclization was catalyzed by in situ-generated chiral quaternary ammonium (hypo)iodite salts with hydrogen peroxide as an environmentally benign oxidant. This process successfully avoids the use of rare and/or toxic metals as catalysts for the oxidative reactions of inorganic iodine derived oxoacids and, therefore, replace aryliodane or transition metal catalysts. However, this method requires a long reaction time for an improved yield. Limitations in the synthesis of dihydrobenzofuran derivatives and their important applications in various fields have led to an increase in research about new methodologies of cycloetherification for the later stages of total synthesis and with substrates containing heavy functionalities. A unique approach to overcome these limitations is the use of micelles in the reaction medium.



Remirol X = H
Remiridiol X = OH

1 **2**

Scheme 1. Retrosynthetic approach for remirol and remiridiol.

Micelles are self-assembled nanostructures of amphiphilic monomers that form a hydrophilic outer shell area and a hydrophobic core. The use of micelles as a reaction medium is widespread and has been investigated in detail for different reactions in aqueous and organic solvents [21–24]. Most aro-

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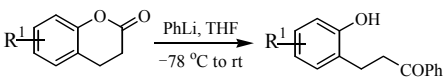
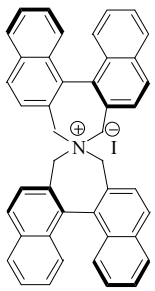


Scheme 2. Synthesis of **3-13**.

matic compounds have very low solubility in water and the presence of water adversely affects the product yield. Therefore, organic solvents (non polar media) are often used for various organic reactions. The cost effective and eco-friendly option of using micellar aggregates as microreactors enhances the scope of organic reactions. Previously, we reported on an improvement in the regioselectivity of aromatic chlorination [21] and the nitration of aromatic aldehydes [9,10] by the use of micelles. In continuation of this work we now propose a novel improvement in the enantioselective cycloetherification of substituted keto phenols into the corresponding dihydrobenzofuran derivatives.

The synthesis of 3-[2(3,5-dimethoxyphenol)-1-phenylpropane-1-one (**3**, Scheme 2) was carried out as described earlier [25]. To an agitated mixture of 5,7-dimethoxy chroman-2-one (208 mg, 1 mmol) in THF-Et_2O (1:5 (*v*/*v*), 5 ml), PhLi (0.92 ml, 1.1 mol/L, 1.0 mmol) was added slowly at –78 °C. After 7 h, the resulting mixture was poured into aqueous NH_4Cl (5 ml), extracted with EtOAc (2 × 5 ml), and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc) to afford 223 mg of **3** in 78% yield.

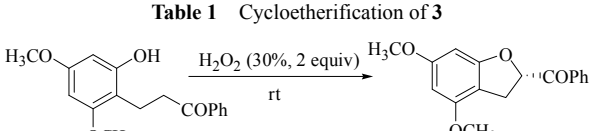
For the cycloetherification reaction, in an agitated mixture of **3** (286 mg, 1 mmol, 1 equiv), $Bu_4N^+I^-$ (36.9 mg, 0.10 mmol, 10 mol%), tetrahydrofuran (THF, 5 cm^3), and 30 wt% hydrogen peroxide (0.0021 ml, 2.0 mmol) were added. The mixture was agitated for 1 h in a 50 cm^3 baffled glass reactor equipped with a six-blade turbine agitator of 0.3 cm diameter. The speed of agitation was maintained at 1.67 Hz. Isothermal conditions were maintained at 25 °C. After 5 h, the resulting mixture was poured into water (20 ml) and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with a saturated Na_2SO_3 solution, brine, and water. The combined organic layers were dried over anhydrous Na_2SO_4 and the solvents were removed in vacuo. The crude product was purified by flash chromatography on silica gel using hexane-EtOAc = 4:1 to give product **2** as a white solid; yield: 281 mg (99% yield, racemic mixture, Table 1, entry 1). Three independent tests were done and the variation in results was ± 0.75%. When we replaced THF with diethyl ether (Et_2O)/H_2O and $Bu_4N^+I^-$ with chiral quaternary ammonium iodide (*R*,*R*-$R_4N^+I^-$, Scheme 3) the yield of the reaction decreased with an increase in enantioselectivity (Table 1, entry 2). The synthesis and characterization of the *R*,*R*-quaternary ammonium iodide ($R_4N^+I^-$) was done as described elsewhere [20]. By replacing THF/Et_2O with toluene/H_2O the yield of the cycloetherification reaction was moderate with very poor enantioselectivity (Table 1, entry 3). On the other hand, when the reaction was carried out in the micellar media by adding sodium dodecylsulphate (SDS) surfactant an increase was observed in the enantioselectivity as well as in the yield of the reaction (Table 1, entry 4). For this reaction we added 30 wt% hydrogen peroxide (0.0021 ml, 2.0 mmol) to an agitated mixture of **3** (286 mg, 1 mmol, 1 equiv) as well as chiral *R*,*R*-$R_4N^+I^-$ (11.38 mg, 0.01 mmol) in a SDS (60 mmol)-toluene (10 cm^3) solution. The mixture was agitated for 1 h in the baffled glass reactor. The speed of agitation was maintained at 1.67 Hz. Isothermal conditions were maintained at 25 °C. A cetyltrimethyl ammonium bromide (CTAB, 60 mmol) and toluene (5 cm^3) solution was added to the reaction mixture and agitated for an extra 2 min. The mixture was filtered through a plug of celite. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel using hexane/EtOAc = 4:1 to give the product **2** as a white solid; yield: 281 mg (99% yield, 90% ee).



Scheme 3. The chiral *R*,*R*-quaternary ammonium iodide used in the enantioselective cycloetherification of **3**.

All the products formed were solubilized in $CDCl_3$ and

Table 1 Cycloetherification of **3**



Entry	Reagent and condition	Reaction time (h)	Yield (%)	ee (%)
1	THF, $Bu_4N^+I^-$ (10 mol%)	5	99	Racemic mix.
2	Et_2O + H_2O (5:1, *v*/*v*), *R*,*R*-$R_4N^+I^-$ (10 mol%)	24	25	69
3	Toluene + H_2O (5:1, *v*/*v*), *R*,*R*-$R_4N^+I^-$ (10 mol%)	24	50	2
4	Toluene + H_2O (5:1, *v*/*v*), *R*,*R*-$R_4N^+I^-$ (10 mol%), SDS (60 mmol)	1	99	90

ee—enantiomeric excess.

identified satisfactorily using ^{1}H NMR (300 MHz) and ^{13}C NMR (75.46 MHz). The peak positions are given in parts per million (δ) using tetramethylsilane as an internal standard, and the coupling constant values (J) are given in Hz. Reagent conversion was analyzed using a gas chromatograph (Chemito 8610) with a flame ionization detector. A 4 m long and 0.37 cm internal diameter stainless steel column packed with 10% SE-30 on chromosorb WHP was employed for the analysis. N_2 at a flow rate of 0.5×10^{-7} m^3/s was used as the carrier gas. The ee of all the products was determined by high-performance liquid chromatography (HPLC) using hexane-*i*PrOH as the mobile phase and a 25 cm long, 4.6 mm internal diameter chiral column of Daicel CHIRALCEL OD-H.

Figure 1 shows the effect of concentration and the nature of the surfactant on the yield of product **2** in the reaction. The conversion of **2** increased with an increase in the surfactant concentration and remained constant beyond a specific surfactant concentration (60 mmol for SDS). Two types of ionic surfactants i.e. anionic (SDS and LABS), and cationic (CTAB) were used to study the effect of micellar head group charges on the rate and selectivity of the reaction. However, no difference was observed in the rate or the yield of the reaction product for these ionic surfactants indicating that the hydrophobic and hydrophilic media are the driving factors rather than the nature of the charges on the micellar head and tail groups.

The conversion (approximately 10%–15%) remained relatively unchanged at surfactant concentrations up to 30–35 mmol. This might be because of an insufficient number of micelles present in the reaction mixture. We observed that once the concentration of the surfactant exceeds the critical micellar concentration and reaches a specific concentration (25 mmol for SDS) an increase occurs in the reaction rate. This concentration is known as the effective micellar concentration and a sufficient number of micelles were present in the reaction medium to affect the reaction rate. This indicates that an increase in the conversion rate of the enantioselective cycloetherification reaction was caused by micellar phenomena.

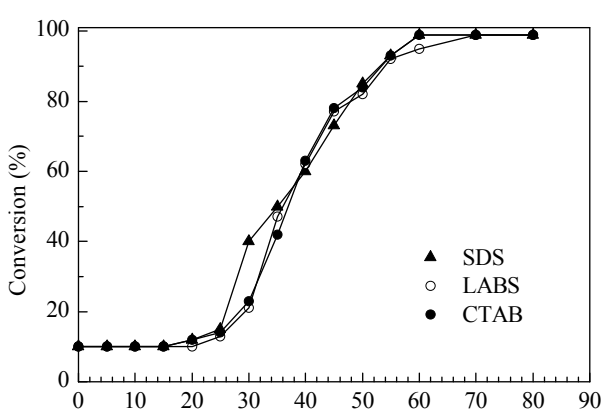


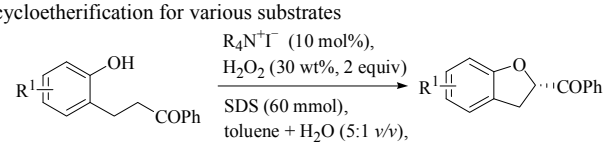
Fig. 1. The effect of surfactant concentration on the cycloetherification of **3** in the presence of 10 mol% $Bu_4N^+I^-$, 2 equiv H_2O_2 (30 wt%) and toluene + H_2O (5:1 *v/v*) at 25 °C for 1 h.

The applicability of this enantioselective cycloetherification reaction in the micellar medium to obtain various substituted 2,3-hydrobenzofurans is shown in Table 2 wherein keto phenol derivatives that have electron withdrawing as well as electron donating functionalities were converted into their corresponding dihydrobenzofuran derivatives with excellent yield and high enantioselectivity. These results demonstrate the scope of the micellar catalyzed enantioselective cycloetherification in the total synthesis of various pharmaceutically important, biologically active compounds.

To study the exact reaction mechanism of the enantioselective cycloetherification, several experiments were optimized to identify the role of micellar media in the activation of the hypervalent iodine species. $[R_4N]^+[IO]^-$ is generated as an active oxidant species in the reaction between I_2 and tetrasubstituted ammonium hydroxide ($R_4N^+OH^-$) [26]. The anisotropic interface of the micellar aggregate (located between the outer hydrophilic bulk and the inner organic core) acts as a useful site for the activation of the hypervalent iodine species. Hydrophilic hydrogen peroxide oxidizes the relatively hydrophobic $R_4N^+I^-$ at the anisotropic interface of the micellar aggregates to generate $[R_4N]^+[IO]^-$. This active oxidant species further reacts with a corresponding substrate to give dihydrobenzofuran derivatives with high yield and excellent enantioselectivity.

In conclusion, the cycloetherification of substituted keto phenols to their corresponding dihydrobenzofuran derivatives was improved using a micellar reaction medium. The anisotropic palisade layer of the ionic micelles acts as an effective reaction site for the generation of the active oxidant species $[R_4N]^+[IO]^-$. A high yield of the enantioselective dihydrobenzofuran derivative as a product was obtained using this approach. The overall scope of this cycloetherification pathway was widened to include various substrates especially in the

Table 2 Applicability of micellar catalyzed enantioselective cycloetherification for various substrates



Substrate	Reaction time (h)	Yield (%)	ee (%)
4, R^1 = H	1	99	91
5, R^1 = 5-OMe	1	99	90
6, R^1 = 5-OEt	1	99	88
7, R^1 = 5-F	1	99	92
8, R^1 = 5-Cl	1	99	94
9, R^1 = 5-Br	1	99	89
10, R^1 = 4-Me, 6-Me	1.5	99	88
11, R^1 = 3-Me, 4-Me, 5-Me, 6-Me	2	99	85
12, R^1 = 2-OMe, 3-Ac, 4-OMe	1.5	99	89
13, R^1 = 2-OMe, 3-Ac, 4-OMe, 5-OMe	2	99	87

total synthesis of biologically active compounds. The use of micellar microreactors in the cycloetherification reaction increased the yield of the corresponding dihydrobenzofuran derivatives four times with a reduction in the reaction time from 1 to 24 h. The conversion of keto phenols to their corresponding dihydrobenzofuran derivatives was directly proportional to the concentration of the surfactant used in the reaction. Ionic surfactants (anionic and cationic) with a concentration of 60 mmol and above gave a 99% yield for the reaction. We observed that the effect of hydrophobic and hydrophilic media has more influence in increasing the yield than the nature of the charges on the micellar head and tail groups. The presented data shows the applicability of micellar media in increasing the rate of a reaction for a particular product and this method can be efficiently employed for various other reactions.

Supplementary data

Supplementary data include the synthesis process, the CMC determination and characterization data (^{1}H NMR, ^{13}C NMR, elemental analysis and isolated yield) for compounds **3–13** and all the products.

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