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Short communication

Aqueous phase synthesis of *vic*-halohydrins from olefins and *N*-halosuccinimides in the presence of β-cyclodextrin

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Abstract

A series of bromo- and iodohydrins was prepared regioselectively in excellent yields in one-step procedure by treating the corresponding alkenes at room temperature with NBS and NIS respectively in the presence of β-cyclodextrin in water.

Keywords: Olefins; *N*-Halosuccinimides; β-Cyclodextrin; Bromo- and Iodohydrins; Water

1. Introduction

Vic-halohydrins are valuable synthons for transformation into epoxides [1], ketones [2] and several halogenated marine natural products [3]. These halo derivatives are also widely applicable in industrial processes for the synthesis of drugs, pharmaceuticals, agrochemicals, pigments and photographic materials [4]. Conversely, epoxides are also frequently opened to form halohydrins by the use of hydrogen halides [5], however, this methodology will not be suitable for substrates with acid sensitive functionalities apart from being toxic. These procedures are generally associated with by-products such as *vic*-dihalides and 1,2-diols [6]. Halohydrins can also be directly synthesized by a variety of methods other than forming epoxides, most often by functionalization of alkenes to *vic*-halohydrins with reagents, such as *in situ* generation of hypoiodous acid from H_5IO_6 in the presence of $NaHSO_3$ [7], but this methodology has the disadvantage of acidic reagent. Elemental halogens in water where there is no recovering of the reagent [8], has the drawbacks of toxicity and danger of handling.

In some cases the α,β-unsaturated esters could not be transformed into the desired iodohydrins with NIS, at the reaction temperature −20 °C [9].

These methods often involve the use of expensive reagents, controlled temperatures, and formation of mixtures of products resulting in low yields [8b,10]. Of recent, there is also a report of utilizing ionic liquids for halohydroxylations but even in this case, allyloxy benzene gives regio-isomers [10]. Some of these ionic liquids have serious drawbacks such as toxicity, release of hazardous HF during recycling, high cost and disposability problems [11]. In view of these shortcomings, there is need to find a reaction medium to replace polluting organic solvents which forms one of the principles of Green Chemistry [12].

Water is the cheap, non-toxic and most readily available reaction medium, making it an environmentally and economically attractive solvent [13]. However, the fundamental problem in performing reactions in water is that many organic substrates are hydrophobic and are insoluble in water. In our efforts to develop biomimetic approaches through supramolecular catalysis [14] and also to overcome some of the drawbacks in the existing methodologies for the synthesis of *vic*-halohydrins from olefins, we report herein, for the first time, the aqueous phase synthesis of halohydrins from olefins and *N*-halosuccinimides in the presence of β-cyclodextrin by encapsulating the olefin in the hydrophobic cavity of cyclodextrin (Scheme 1).

By using β-cyclodextrin the hydrophobic substrates can be solubilized promoting regio-selectivity in the products. β-Cyclodextrin can also be easily recovered and reused.

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions by supramolecular catalysis, involving the reversible formation of host–guest complexes with the substrates by non-covalent bonding as seen in enzyme

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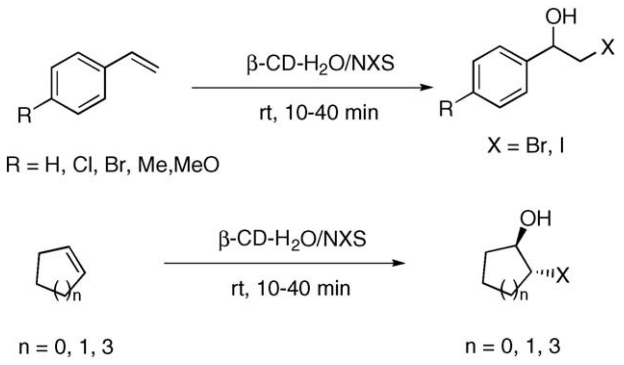


Scheme 1.

complexation processes [15]. Complexation depends on the size, shape and hydrophobicity of the guest molecule. These attractive features of cyclodextrins in the biomimetic modelling of chemical reactions prompted us to investigate a variety of hydroxyhalogenations using the substrate-β-cyclodextrin complexes with NBS/NIS in water.

2. Experimental

All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from Fluka and S.D. Fine Chemicals and used as received. The ^{1}H NMR spectra were recorded on VARIAN-200 or BRUCKER-300 MHz spectrometer. IR spectra were recorded on a NICOLET FT-IR spectrometer. Mass spectra were observed on V.G. auto spectrometer.

Table 1
Synthesis of halohydrins from olefins and *N*-halosuccinimides in the presence of β-cyclodextrin in water

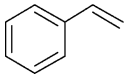
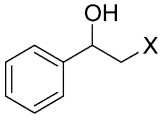
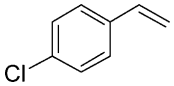
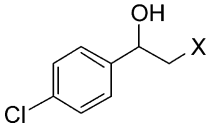
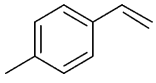
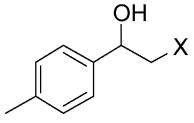
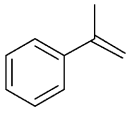
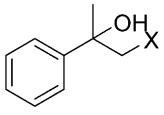
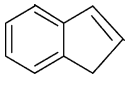
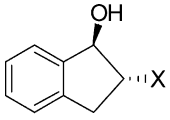
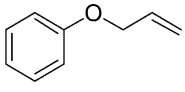
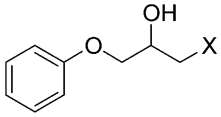
Sl. no.	Substrate	Product[a]	Time (min)	Yield[b] (%)
				
1		X = Br	10.0	92
2		X = I	10.0	90
				
3		X = Br	20.0	88
4		X = I	15.0	90
				
5		X = Br	10.0	92
6		X = I	10.0	90
				
7		X = Br	25.0	84
8		X = I	15.0	80
				
9		X = Br	15.0	89
10		X = I	10.0	93
				
11		X = Br	30.0	90
12		X = I	25.0	85

Table 1 (*Continued*)

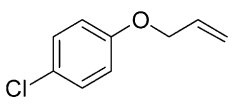
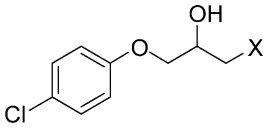
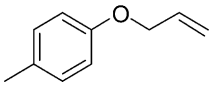
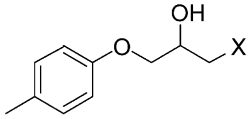
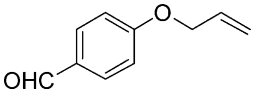
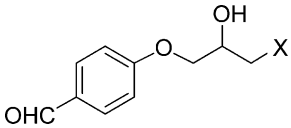
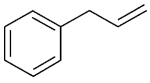
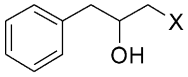
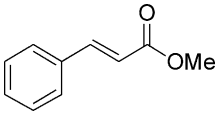
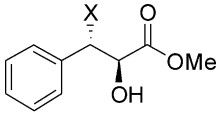
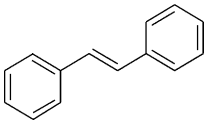
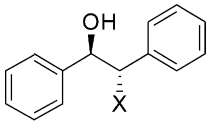
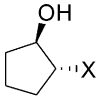
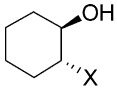
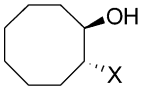
Sl. no.	Substrate	Product[a]	Time (min)	Yield[b] (%)
				
13		X = Br	40.0	86
14		X = I	30.0	82
				
15		X = Br	20.0	90
16		X = I	15.0	90
				
17		X = Br	40.0	86
18		X = I	35.0	88
				
19		X = Br	40.0	92
20		X = I	30.0	86
				
21		X = Br	15.0	92
22		X = I	10.0	87
				
23		X = Br	30.0	85
24		X = I	30.0	83
				
25		X = Br	20.0	83
26		X = I	15.0	80
				
27		X = Br	20.0	84
28		X = I	10.0	84

Table 1 (*Continued*)

Sl. no.	Substrate	Product[a]	Time (min)	Yield[b] (%)
				
29		X = Br	30.0	80
30		X = I	25.0	82

[a] All the products were characterized by ^{1}H NMR, IR spectroscopy and mass spectrometry, and reported in literature [5c,9].
[b] Isolated yield obtained after column chromatography.

2.1. General procedure for the synthesis of vic-halohydrins from olefins

β-CD (1 mmol) was dissolved in water (15 ml) by warming up to 60 °C until a clear solution was formed, then alkene (1 mmol) dissolved in acetone (1 ml) was added dropwise and allowed to come to room temperature. *N*-Halosuccinimide (1 mmol) was then added and stirred at room temperature until the reaction was complete (as monitored by TLC) (Table 1). The mixture was extracted with ethyl acetate and the extract filtered. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure and the resulting product was further purified by column chromatography.

The aqueous layer was cooled to 5 °C to recover CD by filtration. To the filtrate which contains succinimide and HBr was added $NaBrO_3$ and concentrated H_2SO_4 as already reported [16] and stirred for 30 min. Then, it was extracted with ethyl acetate and the solvent was removed under vacuum to regenerate NBS in an isolated yield of 75–80%.

3. Results and discussions

In general, the reaction was carried out by the *in situ* formation of the β-cyclodextrin complex of the substrate in water followed by the addition of NBS/NIS and stirring at room temperature to give the corresponding *vic*-halohydrins in impressive yields. Treatment of styrene and substituted styrenes (entries 1–8) with NBS/NIS in the presence of β-cyclodextrin in water medium afforded 2-bromo- or 2-iodo-1-phenyl ethanol in high yields (Table 1). In a similar manner various substituted alkenes were converted into the corresponding bromo- and iodohydrins in high yields within shorter reaction times at room temperature with high selectivity. The reactions were smooth and succinimide as by-product. The succinimide can also be recycled to NBS as described in experimental section. To study the scope of the reaction, we extended it to various substituted alkenes. Alkenes like α,β-unsaturated esters (entries 21 and 22), cyclohexene (entries 27 and 28), cyclopentene (entries 25 and 26) and cyclooctene (entries 29 and 30) form the trans products as deduced by ^{1}H NMR spectroscopy.

Here, the role of β-cyclodextrin appears to be to solubilize the reactants and promote the reaction to completion in short reaction times. In the absence of β-cyclodextrin the reaction takes longer time (6 h) and some of the substrates are insoluble in water hence no reaction was observed.

4. Conclusions

Thus, we have demonstrated, for the first time, a novel and efficient biomimetic conversion of olefins to *vic*-halohydrins with easily accessible NBS/NIS using β-cyclodextrin as a catalyst and water as the reaction medium. This novel methodology may find wide range of applications.

Acknowledgment

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