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A mild and efficient biomimetic synthesis of α-hydroxymethylarylketones from oxiranes in the presence of β-cyclodextrin and NBS in water[†]

M. Arjun Reddy, N. Bhanumathi and K. Rama Rao*

Organic Chemistry Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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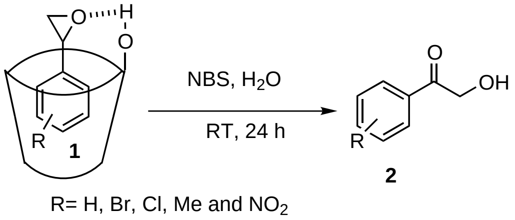
Abstract—α-Hydroxymethylarylketones can be synthesized in good yields from easily accessible epoxides in the presence of β-cyclodextrin and NBS in water. This method is a direct, one-pot, synthesis under mild conditions using water as solvent and has many advantages over existing methodologies. © 2002 Elsevier Science Ltd. All rights reserved.

α-Hydroxymethylarylketones are widely used synthetic intermediates of considerable significance in organic and medicinal chemistry.[1] In view of their importance as versatile intermediates, a number of methods such as the oxidation of enolates[2] using dioxygen ($^3O_2$), oxidation of epoxides[3] and diols,[4] synthesis from α-hydroxy ketone dimethylacetals using iodobenzene diacetate–potassium hydroxide–methanol followed by oxidation,[5] partial reduction of 1,2-diketones[6] etc. have been reported. However there are still severe limitations with these methodologies such as the use of anhydrous organic solvents, moisture sensitive and hazardous reagents, complex catalysts, low yields etc. In view of these limitations, there is still a need for a mild and widely applicable alternative approach using water as the solvent, which is environmentally benign.

In our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins (CD),[7] we were trying to synthesize optically active bromohydrins by the opening of styrene epoxide-β-cyclodextrin complexes with NBS in water. These conditions resulted in the unexpected and exclusive formation of α-hydroxyketones.

Cyclodextrins which are cyclic oligosaccharides possessing hydrophobic cavities mimic enzymes in their ability to bind substrates selectively and to catalyze chemical reactions. These reactions involve supramolecular catalysis through reversible formation of host–guest complexes with the substrates by non-covalent bonding. Complexation depends on the size, shape and hydrophobicity of the guest molecule. Thus, biochemical-like selectivity which exhibits shape and substrate selectivity with the reactions being carried out in water will be superior to chemical selectivity. These attractive features of cyclodextrins in the biomimetic modelling of chemical reactions prompted us to investigate the reaction of styrene epoxide:β-cyclodextrin complexes with NBS in water. The complexes were formed with β-cyclodextrin since it is the most accessible and least expensive of the cyclodextrins. The catalyst can also be recovered and reused.

In general these reactions were carried out as follows: the inclusion complexes were prepared by adding the epoxide (**1**, 1 mmol) in acetone (1 ml) to an aqueous solution of β-cyclodextrin (1 mmol) at 60°C and the solution was allowed to cool to room temperature (Scheme 1). Then NBS (1.5 mmol) was added and the mixture stirred at room temperature for 24 h. The



Scheme 1.

Keywords: oxiranes; NBS; β-cyclodextrin; H_2O; biomimetic; α-hydroxymethylarylketones.

* Corresponding author. E-mail: ramaraok@iict.ap.nic.in

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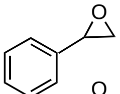
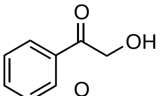
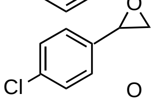
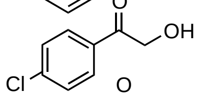
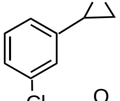
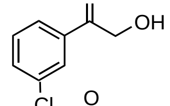
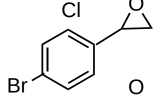
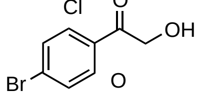
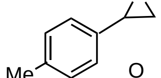
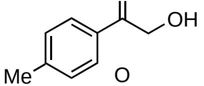
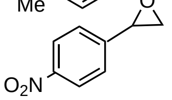
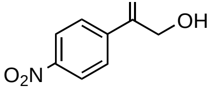
product was extracted with ethyl acetate and purified by column chromatography on silica gel. The yields obtained were good to excellent (Table 1). Higher yields were obtained when electron-donating substituents were present on the aromatic ring. All the products were fully characterized by ^{1}H NMR, IR and mass spectroscopic data and by comparison with known compounds.[8] These CD mediated water based reactions benefit from mild conditions and are also useful from the practical point of view of not having to handle flammable, anhydrous solvents and toxic reagents.

The mechanism of α-hydroxyketone formation may be postulated as follows: the fact that these reactions do not take place in the absence of cyclodextrin and that the starting epoxide is intact indicates the essential role of cyclodextrin. The cyclodextrin appears to activate not only the epoxide but also further catalyzes the reaction through the formation of cyclodextrin hypobromite (from NBS and water) as observed by Breslow in the chlorination of anisole with sodium hypochlorite.[9] The cyclodextrin hypobromite thus formed can catalyze the opening of the epoxide with water to form the 1,2-diol which is further oxidized to the ketone at the secondary alcohol position to yield the α-hydroxyketones.

Table 1. Biomimetic synthesis of α-hydroxyketones from oxiranes

Entry	Epoxide	Product [a]	Yield [b] (%)
a			86
b			96
c			92
d			94
e			91
f			67

[a] All Products were identified by IR, NMR and Mass spectroscopy

[b] Yields of products isolated after column chromatography

In conclusion, we have demonstrated for the first time that α-hydroxymethylarylketones can be synthesized in a biomimetic fashion directly from easily accessible epoxides in the presence of cyclodextrin and NBS using water as the solvent. This approach may be considered as simple with high potential for future applications.

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References

1. (a) Raduchel, B. *Synthesis* **1980**, 292; (b) Tamura, Y.; Yakura, T.; Haruta, J.-I.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 3837; (c) Tamura, Y.; Annoura, H.; Yamamoto, H.; Kondo, H.; Kita, Y.; Fujioka, H. *Tetrahedron Lett.* **1987**, *28*, 5709; (d) Murahashi, S.-I.; Naota, T.; Hanaoka, H. *Chem. Lett.* **1993**, 1767.
2. (a) Moriarty, R. M.; Prakash, O.; Duncan, M. P. *Synthesis* **1985**, 943; (b) Moriarty, R. M.; Duncan, M. P.; Prakash, O. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1781; (c) Moriarty, R. M.; Hu, H.; Gupta, S. C. *Tetrahedron Lett.* **1981**, *22*, 1283; (d) Betancor, C.; Francixco, C. G.; Freire, R.; Suarez, E. *J. Chem. Soc., Chem. Commun.* **1988**, 947.
3. (a) Santosusso, T. M.; Swern, D. *J. Org. Chem.* **1975**, *40*, 2764; (b) Trost, B. M.; Fray, M. J. *Tetrahedron Lett.* **1988**, *29*, 2163; (c) Cohen, T.; Tsuji, T. *J. Org. Chem.* **1961**, *26*, 1681; (d) Nusrat, I.; Nageswara Rao, R. *Chem. Lett.* **2000**, 844; (e) Villemin, D.; Hammadi, M. *Synth. Commun.* **1995**, *25*, 3141; (f) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819.
4. (a) Kang, S. K.; Jung, K. Y.; Park, C. H.; Namkoong, E. Y.; Kim, T. H. *Tetrahedron Lett.* **1995**, *36*, 6287; (b) Morimoto, T.; Hirano, M.; Iwasaki, K.; Ishikawa, T. *Chem. Lett.* **1994**, 53; (c) Macrouhi, F.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1997**, *38*, 7183; (d) Filler, R. *Chem. Rev.* **1963**, *63*, 21.
5. Moriarty, R. M.; Hou, K. C. *Tetrahedron Lett.* **1984**, *25*, 691.
6. Ho, T. L.; Olah, G. A. *Synthesis* **1976**, 815.
7. (a) Arjun Reddy, M.; Bhanumathi, N.; Rama Rao, K. *Chem. Commun.* **2001**, 1974; (b) Rajender Reddy, L.; Bhanumathi, N.; Rama Rao, K. *Chem. Commun.* **2000**, 2321; (c) Rajender Reddy, L.; Arjun Reddy, M.; Bhanumathi, N.; Rama Rao, K. *Synlett* **2000**, 339; (d) Arjun Reddy, M.; Rajender Reddy, L.; Bhanumathi, N.; Rama Rao, K. *New J. Chem.* **2001**, *25*, 359; (e) Arjun Reddy, M.; Rajender Reddy, L.; Bhanumathi, N.; Rama Rao, K. *Chem. Lett.* **2001**, 246.
8. Wei, Z. L.; Lin, G. Q.; Li, Z. Y. *Bioorg. Med. Chem.* **2000**, *8*, 1129.
9. Breslow, R. *Acc. Chem. Rec.* **1980**, *13*, 170.