



Pergamon

Tetrahedron: Asymmetry 9 (1998) 3967–3969

TETRAHEDRON:
ASYMMETRY

The use of sonochemistry in the asymmetric epoxidation of substituted chalcones with sodium perborate tetrahydrate

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Received 5 October 1998; accepted 6 October 1998

Abstract

The synthesis of optically pure compounds in a safe and efficient manner is an increasingly important area of organic chemistry. Enantioselectivity in the oxidation of substituted chalcones is induced by the use of a polyamino acid catalyst. By employing sodium perborate tetrahydrate as an oxidizing agent and an ultrasonic reaction vessel, reaction times and conditions are improved from those obtained conventionally. © 1998 Elsevier Science Ltd. All rights reserved.

Epoxidation of α,β -unsaturated ketones results in compounds which serve as important intermediates in the pharmaceutical industry. In particular, the enantioselective synthesis of chalcones using polyamino acids has received a great deal of attention.¹ Typically, these reactions employ hydrogen peroxide as an oxidizing agent, which poses a potential environmental and safety hazard. Sodium perborate tetrahydrate, $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$, can serve as a viable alternative to H_2O_2 and organic peroxy acids, as it is safer and results in relatively innocuous side products.² Recently, the use of ultrasonic irradiation has offered chemists a way to significantly reduce reaction times for a variety of organic reactions, including oxidations.³ This approach has been known to induce *cis-trans* isomerization of β -carotene,⁴ but to the best of our knowledge has not been used in the production of chiral compounds with a high degree of optical purity. We report here the incorporation of the aforementioned advances in reaction conditions and methodology to the asymmetric epoxidation of various substituted chalcones.

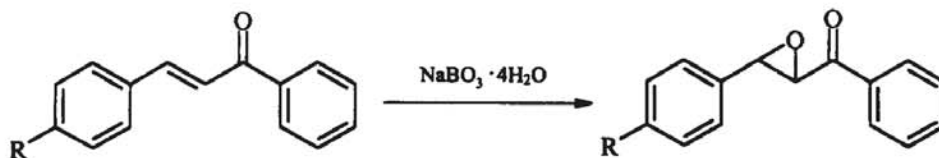
The epoxidation reaction under investigation occurs in a three-phase system composed of an alkaline water phase (in which the $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ is somewhat soluble), an organic layer, and a polyamino acid which is suspended between these two liquid layers (Scheme 1). Because of the nature of this catalyst, the use of a phase-transfer catalyst to aid the migration of perborate ions is currently under investigation. A typical reaction procedure is as follows: 1.5 mmol of the substrate⁵ is dissolved in 10 ml of toluene,

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while 1.00 g NaOH is dissolved in 25 ml of water. 160 mg of poly-L-leucine⁶ is then added, and the system is allowed to equilibrate for 16 h^{7a,b} using a magnetic stirrer. After the addition of 20 mmol of NaBO₃·4H₂O, the mixture is sonicated for 7 h in an ultrasonic bath⁸ and worked up by extracting with dichloromethane, drying with sodium sulfate, and then removing the solvent by using a rotary evaporator.



Scheme 1. General epoxidation reaction (R=H, Cl, NO₂, OH, or OCH₃)

So that an adequate length of sonication time could be determined, a series of experiments was conducted using benzyl triethyl ammonium chloride (TEBA). The results obtained through the use of this achiral quaternary ammonium salt are summarized in Table 1. Our results with an optically active catalyst such as poly-L-leucine indicate that the desired epoxyketones can be obtained in very high yield and moderate enantiomeric excess (ee) under non-optimized conditions (Table 1).⁹ Although the ees are slightly lower than those reported in the literature for similar reactions using H₂O₂ with poly-L-alanine¹⁰ or with a polymer-supported poly-L-leucine,¹¹ the yields are as good or better in almost all cases. Moreover, the reaction times utilizing sodium perborate tetrahydrate and ultrasound are roughly half of those reported above using H₂O₂ and a magnetic stirrer. Coupled with the fact that NaBO₃·4H₂O is a safer oxidizing agent than H₂O₂, we believe this reaction scheme holds considerable promise in the future synthesis of enantiomerically pure compounds.

In the course of this investigation it became apparent that there are certain limitations to this general system, regardless of the oxidizing agent and reaction type that are adopted. For example, epoxidation of mesityl oxide (**1**) afforded no detectable degree of enantioselectivity. This is consistent with the fact that no reference of the successful asymmetric epoxidation of this compound has been found. Further experimentation using related α,β -unsaturated ketones will be pursued. In order to better understand the

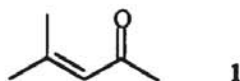
Table 1
Epoxidation of substituted chalcones using sodium perborate tetrahydrate and ultrasound

Entry	R	Catalyst	Sonication period (hr)	Yield (%) ^a	Enantiomeric Excess (%)
1	H	TEBA	1	3	0
2	H	TEBA	4.5	41	0
3	H	TEBA	7.5	58	0
4	H	poly-L-leucine	4.5	67	49
5	H	poly-L-leucine	3 + 4.5 ^b	77	39
6	H	poly-L-leucine	7	94	57
7	NO ₂	poly-L-leucine	7	85	79
8	OCH ₃	poly-L-leucine	7	88	89
9	OH	poly-L-leucine	7	99	67
10	Cl	poly-L-leucine	7	97	74

(a) Yields were found by establishing calibration curves relating the areas acquired via HPLC analysis to the concentrations of each component. For the reactions using chalcone, a relation between its concentration and that of its racemic epoxide (purchased from Lancaster Synthesis) was established. For entries 7-10, chalcone was used as an internal standard.

(b) The equilibration period (prior to addition of oxidizing agent) was also carried out inside the ultrasonic bath.

structural requirements for asymmetric epoxidation using polyamino acids, a molecular docking study in which both the substrate and the catalyst are modeled is also currently underway.



Acknowledgements

We would like to thank Mr. Timothy Sosnowski for his help with the HPLC analysis, Ms. Monica Sircar for her assistance in making the calibration curves, and Professor Robert Q. Topper for useful conversations.

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9. Analyses were performed using HPLC with both a Beckman PDA UV detector and a digital polarimeter (Jasco chiral detector OR-990) and a Daicel Chiralpak AS chiral column (0.46 cm ID×25 cm). The mobile phase consisted of a hexane:ethanol mixture (ranging from 98:2 to 7:1 by volume) at a flowrate of 1.0 ml/min. Absorbances were collected in 10 nm intervals from 190 to 320 nm, and the spectra at 250 nm were used for calculation purposes.
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