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Enantioselective tautomerization of a new metastable enol

Rüdiger Henze,[a] Lucette Duhamel [a,*] and Marie-Claire Lasne [b]

[a] Equipe associée au CNRS, Institut de Recherche en Chimie Organique Fine, Université de Rouen, 76821 Mont-Saint-Aignan, France

[b] Laboratoire de Chimie Moléculaire et Thioorganique, CNRS, ISMRA, Université de Caen, 14050 Caen Cedex, France

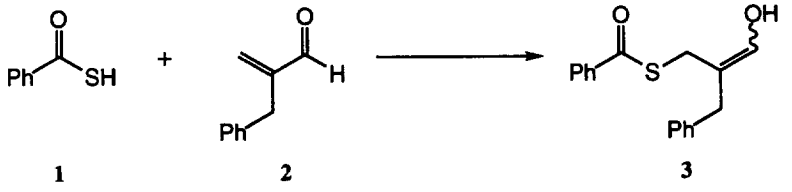
Abstract: A new metastable enol was prepared by the reaction of 2-benzyl acrolein with thiobenzoic acid in aprotic solvents. The enantioselective tautomerization of this enol was studied and enantiomeric excesses up to 71% were found. The absolute configuration of the resulting aldehyde was assigned. © 1997 Elsevier Science Ltd

Introduction

The chemistry of enols has interested many chemists during the past decade. The pioneering work in this field was done by Kohler[1] and Fuson.[2] Kohler discovered the exceptional stability of mesityl substituted enols whereas Fuson carried out a systematic study of these molecules.

The development of new and more sophisticated methods for the preparation and detection of enols in the second half of this decade has led to extensive investigations in the field of stable and metastable enols.[3]

We have found in our group that the reaction of 2-benzyl acroleine **2** with thiobenzoic acid **1** in aprotic solvents led to an enol **3** that can be characterised by spectroscopic methods without tautomerization (Scheme 1).[4] The study of the preparation of **3**, its stability and the attempts to generalize this reaction will be fully described in another publication.



1 **2** **3**

Scheme 1. Conditions: CH_2Cl_2, −18°C, 7d; **3**: Z/E>95/5.

The enantioselective protonation of prochiral species under kinetic control has been proposed and studied in our group since 1976.[5] In the meantime, many groups have worked on this kind of reaction[6] and today, a large number of chiral protonating agents (CPAs) are available. Up to now, it is hard to predict the appropriate CPA for a given substrate, but more work in this field might result in a set of guidelines for the best choice of a CPA.

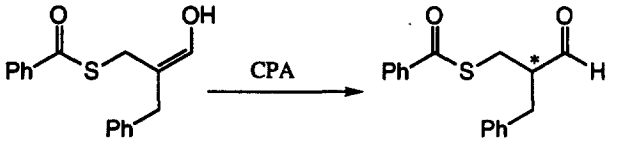
In many cases, the prochiral species is an enolate.[6] Few examples of enantioselective protonations of an enol have been reported. Pète and coworkers have described such a reaction as part of the photodeconjugation of α-unsaturated esters.[7] In our group an enediol intermediary was proposed in 1983 to explain the results of the deracemisation of benzoine.[8] Here, we present the enantioselective tautomerization of the enol **3** in presence of chiral protonating agents.

* Corresponding author. Email: lduhamel@osiriris.univ-rouen.fr

Results and discussion

Under the conditions described in Scheme 1, the enol **3** was obtained as a solution in dichloromethane containing less than 5% of the E isomer. This solution was used to examine the influence of various CPA on the stereochemical outcome of the tautomerization of **3.**

Among the tested products, chiral 1,2-amino alcohols were shown to be the most efficient. Up to 58% e.e. was obtained with (−)-N-methylephedrine. With cinchonidine, also containing a chiral 1,2-amino alcohol moiety, up to 71% e.e. was obtained (Scheme 2).

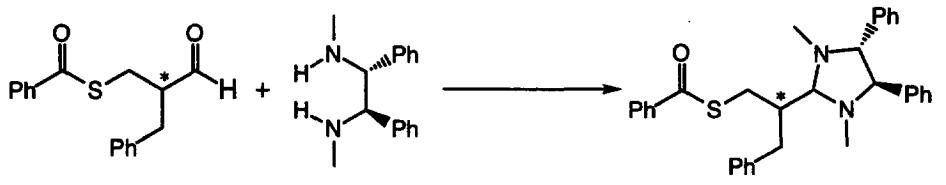


CPA	e.e.:
(-)-N-methyl ephedrine:	58% (S)
(-)-Cinchonidine:	71% (S)

3 **4**

Scheme 2. Conditions: 1 eq CPA, 48 h, −70°C.

Ideally, 1 equivalent of the CPA was added to a solution of **3** in dichloromethane at −70°C. After 48 hours, the enantiomeric excesses were determined by NMR spectroscopy of diastereomeric aminals **6** as described by Mangeney *et al.*[9] for other substrates (integration of the signals of the N-methyl groups) (Scheme 3).

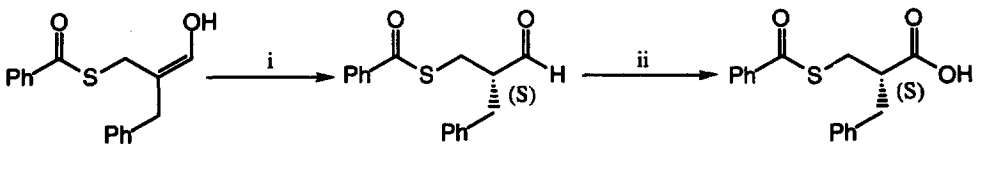


4 **5** **6**

Scheme 3. Conditions: molecular sieves, CH_2Cl_2, −70°C warming to rt.

To minimize the racemization of **4** during the work-up, a sample of the reaction mixture was added to a solution of the diamine **5** at −70°C. After warming to room temperature, the aminal **6** was isolated by flash chromatography.

The absolute configuration of the aldehyde **4** resulting from the enantioselective tautomerization was determined by the oxidation of **4** to the corresponding acid **7** by the Jones reagent.[5c] This acid is described in the literature[10] and the specific rotation sign showed that the enantioselective tautomerization of **3** with (−)-N-methylephedrine led to **4** enriched in the S isomer (Scheme 4).



3 **4** **7**

Scheme 4. Conditions: (i) (−)-N-methylephedrine, −70°C, 48 h, warm to rt, workup HCl 1 N, (ii) CrO_3, H_2SO_4, H_2O, acetone.

The same configuration was obtained using cinchonidine as the CPA. It is noteworthy that both (−)-N-methylephedrine and cinchonidine have the same configuration (1R, 2S) of the amino alcohol moiety.

We have tested a large number of other bifunctional CPAs, which will be published elsewhere as well as models which can explain the stereochemical results.

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