Chiral 4-substituted 2-oxetanones
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SUMMARY

In this thesis the catalytic stereoselective synthesis of chiral 4-substituted 2-oxetanones is described. Chiral 4-substituted 2-oxetanones are formed by a C,C-bond forming cycloaddition reaction of ketene and reactive, α-halogenated aldehydes and ketones. The cycloaddition reaction is catalyzed by tertiary amines. Use of chiral tertiary amines such as quinidine, causes the reaction to proceed stereoselectively.

The general concepts of stereoselective synthesis and some literature examples of recent achievements in the area of catalytic stereoselective C,C-bond forming reactions are described in Chapter 1.

In Chapter 2 the influence of reaction conditions and of the structure of catalysts and substrates on the course of the catalytic stereoselective cycloaddition reaction are described. The highest chemical yields and enantiomeric excesses (e.e.) are obtained when the cycloaddition is performed at temperatures ranging from -50°C to -25°C, using toluene as a solvent, in the presence of 2-4 mol % of a chiral tertiary amine as a catalyst. The cycloaddition reaction of ketene (21a) and chloral (22a), catalyzed by quinidine gives (-)-4-(trichloromethyl)-2-oxetanone and in 95% e.e., a high enantiomeric purity.

Most of the 4-substituted enantiomerically pure 2-oxetanones obtained in Chapter 2 are described. The four 2-oxetanones 23a, 23c, 23h, and 23r, obtained enantiomerically pure 2-oxetanones in Chapter 2 are described. The four 2-oxetanones 23a, 23c, 23h, and 23r, obtained enantiomerically pure 2-oxetanones in Chapter 2 are described.

In Chapter 3 the determination of absolute configuration of the salt of (R)-(−)-o-phenylacetic acid, derived from (−)-23a, has been established, an in contradiction results of a number of 2-oxetanones by CD methods. Dichloroalkyl)-2-oxetanones, first example of assignment of configuration, show a positive

\[ \text{HO} \]
\[ \text{H}_2\text{C} = \text{C} = \text{O} \]
\[ \text{Cl}_3\text{C} = \text{C} = \text{O} \]
\[ \text{H} \]

Scheme 1

21a 22a

(−)-23a, 95% e.e.
Analysis of chiral 4-substituted 2-oxetanones are versatile and reactive; the reaction is catalyzed by quinidine, causes some literature examples. The structure of these enantiomeric cycloaddition reactions can be obtained enantiomerically pure by recrystallization of the crude products. Binary melting-point phase diagrams are an important tool in obtaining enantio-merically pure compounds from enantiomerically enriched mixtures by crystallization. The enantiomer (+)-23a is obtained in 85% e.e. from reactions catalyzed by benzyloquinine.

Most of the 4-substituted 2-oxetanones described in this thesis can be obtained enantiomerically pure by recrystallization of the crude products. Binary melting-point phase diagrams are an important tool in obtaining enantiomerically pure compounds from enantiomerically enriched mixtures by crystallization. In Chapter 2 the construction of melting-point diagrams of 2-oxetanones 23a, 23c, 23h, and 23k, using Differential Scanning Calorimetry (DSC), is described. The four 2-oxetanones 23a, 23c, 23h, and 23k belong to the class of racemic compounds. Consequences of this conclusion on attempts to obtain enantiomerically pure 2-oxetanones by crystallization are discussed.

In Chapter 3 the determination of absolute configuration of 4-substituted 2-oxetanones is described. Attempts to determine the absolute configuration by chemical correlation led to contradictory results. For an unambiguous assign-ment of absolute configuration the crystal structure of the diastereomeric salt of (R)-(+)-o-phenylethylamine and (+)-4,4,4-trichloro-3-hydroxybutanoic acid, derived from (-)-23a, was determined by X-ray analysis. The absolute con-figuration of (-)-23a is shown to be R. Once the configuration of (-)-23a had been established, an inversion mechanism could be proposed to account for the contradictory results obtained by chemical correlation. The configurations of a number of 2-oxetanones has been assigned by comparison of their Circular Di-chroism (CD) spectra with CD spectra of 23a. To our knowledge this is the first example of assignment of absolute configuration of 4-substituted 2-oxetanones by CD methods. From the CD measurements it is concluded that 4-(1,1-dichloroalkyl)-2-oxetanones, such as 23a, 23c, and 23h, having the (R)-config-uration, show a positive Cotton effect in the 200-220 nm region.
Applications of enantiomerically pure 4-substituted 2-oxetanones in synthesis are described in Chapter 4. Most important applications are hydrolytic conversions of 23a and 23h to malic acid (17) and citramalic acid (40), respectively, and the hydrogenolysis of carbon-chlorine bonds of some derivatives of 4-substituted 2-oxetanones. The hydrolytic procedures to yield 17 and 40 proceed with inversion of configuration. Retention of configuration is observed in hydrogenolysis. No racemization occurs in any of the conversions. An important advantage of the use of the 2-oxetanones described in this thesis is that both enantiomers are accessible by the catalytic stereoselective cycloaddition reaction.

![Chemical structures]

The hydrolysis of the pure enantiomers of 23h constitutes a practical method for the preparation of both enantiomers of citramalic acid (40), a valuable synthon for natural products, because of its C₅-isoprenoid structure. Synthons 73 and 74 were prepared using (S)-citramalic acid, obtained via the cycloaddition reaction, as a starting material.

A proposal for a mechanism of the stereoselective cycloaddition reaction is presented in Chapter 5. The cycloaddition of ketene and chloral, catalyzed by quinidine, is used as a model system. The mechanism is speculative. The mechanism that is proposed involves the initial formation of a complex of ketene and quinidine. Reaction of chloral and the ketene-amine complex in a kinetically controlled configuration determining step produces the (R)-4-(trichloromethyl)-2-oxetanone 23a. The chiral center adjacent to the tertiary nitrogen determines the absolute configuration of the 2-oxetanone. Although the proposed mechanism cannot explain all of the observed reaction characteristics, it explains the preferred formation of the (R)-enantiomers of 2-oxetanones in the cycloaddition reactions of ketene and 2,2-dichloroaldehydes or 1,1,1-trichloroacetone, catalyzed by quinidine and the preferred formation of the (S)-enantiomers in these cycloaddition reactions, catalyzed by quinine.