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Chiral imines prepared from 1-(2-aminoalkyl)aziridines as novel chiral shifts reagents for efficient recognition of acids

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Optically pure, chiral imines synthesized from the corresponding aldehydes and 1-(2-aminoalkyl)aziridines in good chemical yields, have been assessed as an NMR chiral shift reagents for effective discrimination of the signals of some acids (mandelic acid and its derivatives and *N*-protected amino acid). The title compounds have proven to be very useful for the determination of enantiomeric purity and absolute configuration of the aforementioned acid derivatives.

1. Introduction

The synthesis of organic compounds in optically (enantiomerically and/or diastereomerically) pure state still constitutes one of the most important fields of modern synthetic chemistry. Single stereoisomers are of great importance in many industrial sectors like medicine, pharmacology and food industry. From this point of view, the quantitative determination of enantiomeric purity of chiral compounds constitutes a key aspect in the studies on the asymmetric transformations.[1] There are many methods of the enantioselective analysis of chiral compounds, like gas[2] or liquid[3] chromatography (GC or HPLC) using columns containing a chiral support, IR,[4] UV[5] or fluorescence spectroscopy,[6] mass spectrometry,[7] circular dichroism[8] and others. However, these techniques are often laborious and time-consuming.

The use of nuclear magnetic resonance (NMR) spectroscopy with various chiral auxiliaries like chiral shift reagents (chiral solvating reagents, CSA)[9,10] or chiral derivatizing agents (CDA)[11] constitute a very convenient way for determination of enantiomeric excess of scalemic mixtures of various carboxylic acids.[10] For example, enantiomeric composition of mandelic acid, its derivatives and other α-hydroxy acids was evaluated using a broad spectrum of NMR discriminating agents like salene derivatives,[10] benzyl isobornyl amines,[1] ‘calixarene-like` chiral amine systems[12,13] and other azamacrocyclic compounds,[14,15] derivatives of (*S*)-α-phenylethylamine[16] or proline,[17] pyrrolidine-functionalized BINOL,[18] chiral shift reagents derived from squaramide and indanol[19] or thiophosphoroamides built on the skeleton of (1*R*,2*R*)-1,2-diaminocyclohexane.[20] Additionally, chiral discrimination of natural isoflavanones[21] and various amines or amides[22] using (*R*)- and (*S*)-BINOL derivatives as chiral solvating agents was described.

Although variously modified amine systems constitute the vast majority of NMR discriminating agents, no contributions describing the use of chiral aziridine derivatives in evaluation of enantiomeric composition were found in literature. Taking this fact into account and basing on our experience in the field of the synthesis of chiral aziridine systems,[23–31] we decided to synthesize a series of chiral, optically pure imines prepared from 1-(2-aminoalkyl)aziridines and to check their action as chiral shift reagents towards mandelic acid derivatives and *N*-protected amino acid (*N*-benzoyl phenylglycine).

2. Results and discussion

2.1. Synthesis of the chiral shift agents

Chiral imines **3a-h** were prepared using a two-step synthetic route (Scheme 1). First, enantiomerically pure chiral aziridines **1a-d** were treated with one equivalent of $ZnBr_2$ at 80 °C without any additional solvent according to general protocol described

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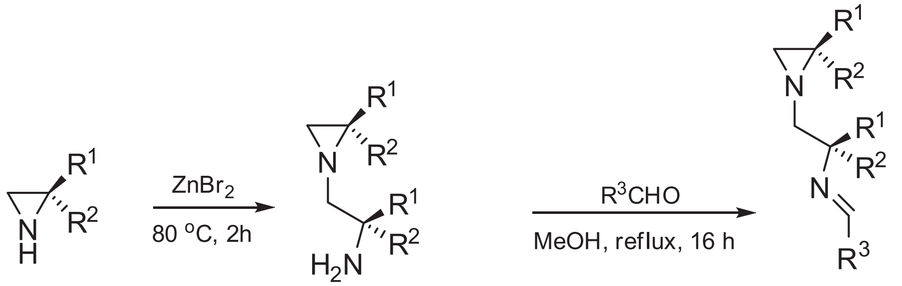

(*S*)-1a R^1 = H, R^2 = Pr^i
(*R*)-1b R^1 = Pr^i, R^2 = H
(*S*)-1c R^1 = H, R^2 = Bn
(*S*)-1d R^1 = H, R^2 = *iso*-Bu

(*S,S*)-2a R^1 = H, R^2 = Pr^i
(*R,R*)-2b R^1 = Pr^i, R^2 = H
(*S,S*)-2c R^1 = H, R^2 = Bn
(*S,S*)-2d R^1 = H, R^2 = *iso*-Bu

(*S,S*)-3a R^1 = H, R^2 = Pr^i, R^3 = Ph
(*R,R*)-3b R^1 = Pr^i, R^2 = H, R^3 = Ph
(*S,S*)-3c R^1 = H, R^2 = Bn, R^3 = *p*-$NO_2C_6H_4$
(*S,S*)-3d R^1 = H, R^2 = *iso*-Bu, R^3 = *p*-$NO_2C_6H_4$
(*S,S*)-3e R^1 = H, R^2 = Pr^i, R^3 = *p*-$NO_2C_6H_4$
(*S,S*)-3f R^1 = H, R^2 = Pr^i, R^3 = *o*-$NO_2C_6H_4$
(*S,S*)-3g R^1 = H, R^2 = Pr^i, R^3 = *o*-$OCH_3C_6H_4$
(*R,R*)-3h R^1 = Pr^i, R^2 = H, R^3 = *p*-$NO_2C_6H_4$

Scheme 1. Synthesis of chiral imines **3a-h** from 1-(2-aminoalkyl)aziridines **2a-d**.

previously.[32] The corresponding 1-(2-aminoalkyl)aziridines **2a-d** were formed as a result of nucleophilic opening of aziridine ring in good chemical yields in a diastereomerically pure state.[32] In the next step, compounds **2a-d** were subjected to the reaction with the corresponding aldehydes in boiling methanol to afford the desired imines **3a-h** in high chemical yields (Table 1).

2.2. *Studies on the application of chiral aziridine derivatives as NMR chiral shift agents*

As a preliminary studies, simple chiral aziridines **1a-d** were tested as chiral solvating agents towards mandelic acid. Thus, equimolar amounts of (*S*)-2-isopropylaziridine **1a** and racemic mandelic acid **4** were dissolved in $CDCl_3$ and subjected to ^{1}H NMR spectroscopy at 600 MHz (experiments performed with different ratio of the aziridine and mandelic acid did not change the separations of the signals). The same operation was repeated for enantiomerically pure (*S*)-mandelic acid, (*S*)-**4**, and for the scalemic mixture of enantiomers of this acid (75% of (*S*) and 25% of (*R*)). A signal at around 4.9 ppm arising from the proton of CH group was considered as diagnostic one. The fragments of all the aforementioned ^{1}H NMR spectra are presented in Fig. 1.

The preliminary results clearly evidence that (*S*)-2-isopropylaziridine **1a** can act as a chiral solvating agent towards mandelic acid. ^{1}H NMR spectrum of such aziridine with *rac*-**4** reveals two equal signals arising from both enantiomers of racemic mandelic acid.

Table 1
Synthesis of imines **3a-h**.

Entry	Substrate	Product	Yield [%]	$[\alpha]_D$[a]
1	**1a**	**2a**	50	+28.0
2	**1b**	**2b**	53	−28.0
3	**1c**	**2c**	63	+14.0
4	**1d**	**2d**	56	+20.0
1	**2a**	**3a**	85	+2.0
2	**2b**	**3b**	55	+28.0
3	**2c**	**3c**	77	−14.0
4	**2d**	**3d**	99	+2.0
5	**2a**	**3e**	85	+4.0
6	**2a**	**3f**	99	−1.0
7	**2a**	**3g**	95	−3.0
8	**2b**	**3h**	99	−5.0

[a] In chloroform (*c* 0.2).

In the light of the above results, other simple chiral aziridines, namely opposite enantiomeric (*R*)-**1b**, (*S*)-2-benzylaziridine **1c** and (*S*)-2-isobutylaziridine **1d** were screened with racemic mandelic acid. The fragments of all the corresponding ^{1}H NMR spectra are showed in Fig. 2.

On the basis of the comparison of the aforementioned ^{1}H NMR spectra, aziridines **1a-b** bearing an isopropyl substituent show moderate enantiomeric recognition for *rac*-**4**. In turn, aziridines **1c-d** bearing bulkier groups exhibit only slight baseline separation (**1d**) or show no action (**1c**), probably due to the steric hindrance around stereogenic center.

As continuation of our studies, 1-(2-aminoalkyl)aziridine (*S,S*)-**2a** was considered as a chiral shift reagent with racemic mandelic acid. In this case, the results were unsatisfactory – ^{1}H NMR of **2a** with *rac*-**4** revealed only one signal at around 4.9 ppm (Fig. 4).

Finally, chiral imine (*S,S*)-**3a** was tested as chiral solvating agent using racemic, scalemic and enantiomerically pure mandelic acid **4**. The fragments of all the appropriate ^{1}H NMR spectra are presented in Fig. 3.

Inspection of the spectra clearly shows that chiral imine (*S,S*)-**3a** constitutes an effective chiral solvating agent towards mandelic acid. In the case of *rac*-**4**, chemical shift nonequivalence exhibited a value of $\Delta\Delta\delta = 0.033$ ppm.

As a summary, the fragments of ^{1}H NMR spectra of simple chiral aziridine (*S*)-**1a**, 1-(2-aminoalkyl)aziridine (*S,S*)-**2a** and imine (*S,S*)-**3a** with racemic mandelic acid *rac*-**4** were presented in Fig. 4.

On the basis of the results collected in Fig. 5, it should be mentioned, that chiral imine **3a** constructed from the 1-(2-aminoalkyl)aziridine **2a** exhibit the best ability of recognition towards mandelic acid.

In the next step of studies, the influence of various electron-donating and electron-accepting substituents in the imine on the chiral recognition towards racemic mandelic acid was examined. Thus, chiral imines **3e**, **3f** and **3g** being methoxy- and nitro-substituted were checked in the presence of *rac*-**4**. The results are summarized in Fig. 5.

Inspection of the fragments of ^{1}H NMR spectra collected in Fig. 6 clearly evidences that the presence of electron-donating substituent (-OMe) decreases the ability of chiral recognition of imines