

Studies on the Synthesis and Dynamic NMR Properties of 2-(Benzylidene amino)-*N*-[(*R*)-2-hydroxy-2-methyl-1-phenylpropyl]acetamide

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An efficient method was employed for the preparation of 2-(benzylideneamino)-*N*-[(*R*)-2-hydroxy-2-methyl-1-phenylpropyl]acetamide utilizing optically pure (*R*)-5,5-dimethyl-4-phenyloxazolidin-2-one. This product showed interesting dynamic NMR properties for the methylene protons adjacent to the azomethine group ($\Delta G^\ddagger = 15.1 \pm 0.1$ kcal mol⁻¹).

Keywords: Chiral azomethine, Azomethine ylide, Dynamic NMR, Chiral auxiliary

INTRODUCTION

Auxiliary methodology to transfer chirality, with predictable stereochemistry in newly formed stereoisomers, proved to be an indispensable tool in asymmetric synthesis [1]. In this area, the use of enantiomerically pure oxazolidin-2-one derivatives as chiral auxiliaries in acyl group transformations, aldol reactions, conjugate addition, alkylation, azidation, hydroxylation, halogenation, amination and β -lactam synthesis has been well demonstrated [2-5]. Currently, Davies *et al.* have used SuperQuat **1** (Fig. 1) for the control of the stereoselectivity of reactions on attached acyl fragments [6]. In addition, the *gem*-dimethyl groups in the SuperQuat auxiliary affect the control of the conformation of the substituents at the C₄ position, thus enhancing the face selective shielding of the attached acyl fragments [7].

On the other hand, chiral aziridine carboxylates as useful intermediates in the synthesis of optically active compounds have attracted a lot of interest [8,9]. These valuable three-membered heterocycles are available by enzymatic separation of the racemic mixtures [9], from β -hydroxy α -amino acids

such as serine or threonine [10] or using oxiranes [11]. Furthermore, it can be obtained from α,β -unsaturated chiral imides relying on the reaction of 2,3-dihalo-carboxylic acid derivatives with primary amines or ammonia [12], or from methods using chiral 3-benzoyloxyaminoimides [8a].

In the course of our research program, which was based on the synthesis and derivatization of heterocyclic compounds [13], and in a search for a more efficient method for the synthesis of homochiral aziridine carboxylic acids, our prime objective was to use optically pure (*R*)-5,5-dimethyl-4-phenyloxazolidin-2-one (**2**) as chiral transferring auxiliary for the preparation of homochiral aziridine carboxylic acids (**8**) (Scheme 1). Interestingly, this approach led us to the preparation of the chiral azomethine **5**.

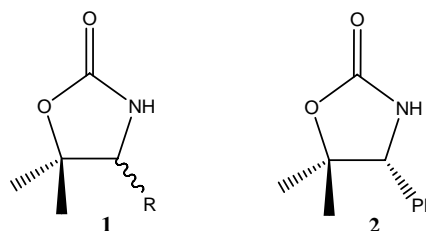
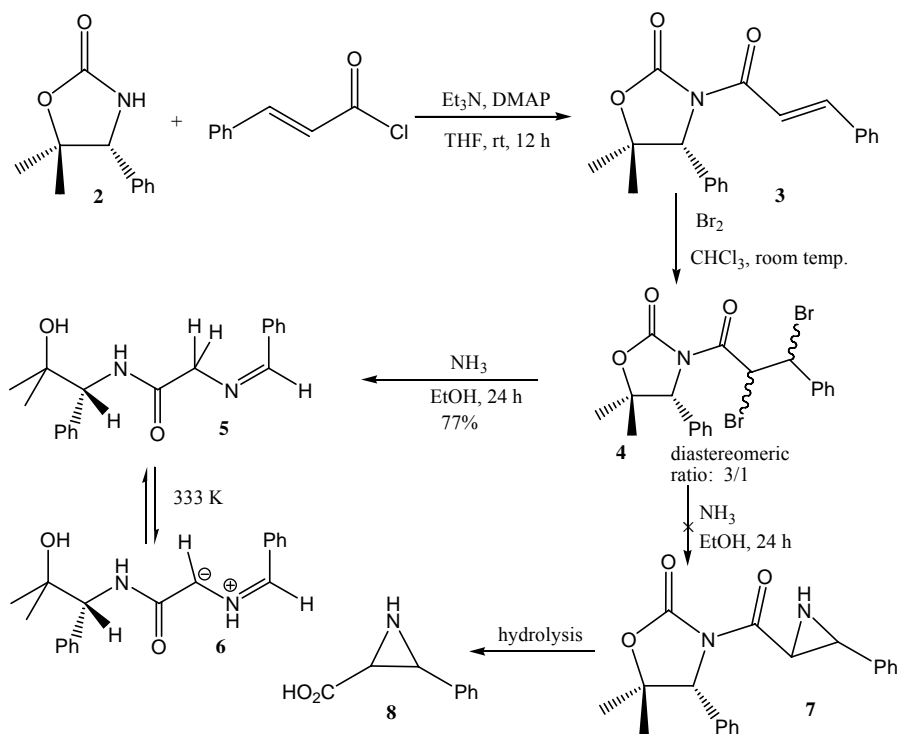


Fig. 1

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Scheme 1

EXPERIMENTAL

General

Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were determined on a Shimadzu IR-470 spectrometer. ¹H NMR spectra were recorded on a 500 MHz Bruker DRX-500 in CDCl₃ as solvent and TMS as internal standard. Mass spectra were obtained from a GC MS-QP 1100EX Shimadzu instrument. Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyzer which agreed with the calculated values. Preparative thin layer chromatography was prepared from Merck Kieselgel 60 H, F₂₅₄, Art No. 7730. For column chromatography Merck Kieselgel 60, Art No. 107733 was employed. Chemicals were purchased from Merck and Fluka. All solvents used were dried and distilled according to standard procedures.

Preparation of (R)-5,5-Dimethyl-4-phenyl-3-[(E)-3-phenylacryloyl] oxazolidin-2-one (3)

To a magnetically stirred solution of (R)-5,5-dimethyl-4-phenyloxazolidin-2-one (2) (1.0 g, 5.8 mmol) in THF (20 ml), Et₃N (1 ml), dimethylaminopyridine (DMAP) (0.2 g, 1.6

mmol) and cinnamoyl chloride (1 g, 6 mmol) were added at room temperature. The reaction mixture was stirred for 12 h and the progress of the reaction was monitored by TLC (EtOAc/hexane; 1:5). After completion of the reaction, diethylether (10 ml) and NaHCO₃ (20%) (25 ml) were added. The organic phase was separated, dried (MgSO₄) and the solvent was evaporated under vacuum. The resultant solid product was recrystallized from hot EtOH to furnish the desired product (3) (1.34 g, 4.17 mmol) as white crystals in 72% yield, m.p.: 144–145 °C, [α]_D²⁵ = +25° [c = 1, CHCl₃], IR (KBr): ν_{max} (cm⁻¹): 3060, 2930, 1771, 1682, 1615, 1450, 752, 690; ¹H NMR (500 MHz, CDCl₃, 25 °C): 1.1 (s, 3H), 1.7 (s, 3H), 5.2 (s, 1H), 7.2–7.6 (m, 8H), 7.7 (d, J = 7.2 Hz, 2H), 7.8 (d, J = 15.7 Hz, 1H), 8.1 (d, J = 15.7 Hz, 1H) ppm. Calcd. for C₂₀H₁₉NO₃ (321.37); C, 74.74; H, 5.95; N, 4.35. Found: C, 74.57; H, 6.15; N, 4.27.

Preparation of (R)-3-(2,3-Dibromo-3-phenylpropionyl)-5,5-dimethyl-4-phenyl oxazolidin-2-one (4)

To a magnetically stirred solution of (3) (0.5 g, 1.6 mmol) in chloroform (20 ml) a 30% solution of Br₂ in chloroform was added dropwise at room temperature until the bromine

color no longer discharged. The solvent was evaporated under vacuum and the residue was recrystallized from a mixture of petroleum ether/chloroform to provide a diastereomeric mixture (3/1) of (**4**) (0.67 g, 1.39 mmol) as white solid in 87%, m.p.: 152-154 °C, IR (KBr): ν_{\max} (cm⁻¹): 3050, 2950, 1778, 1512, 1615, 1450, 690, 752; ¹H NMR (500 MHz, CDCl₃, 25 °C): (major diastereomer): 1.0 (s, 3H), 1.7 (s, 3H), 5.2 (s, 1H), 5.3 (d, J = 12.9 Hz, 1H), 6.7 (d, J = 12.9 Hz, 1H), 7.4 (m, 10 H) ppm; (minor diastereomer): 1.0 (s, 3H), 1.7 (s, 3H), 5.2 (s, 1H), 5.5 (d, J = 12.5 Hz, 1H), 6.6 (d, J = 12.5 Hz, 1H), 7.4 (m, 10H) ppm; MS m/z 479, 481, 483 (M, M+2, M+4, <1%), 402 (1.8), 404 (3.57), 406 (1.78), 281 (36.2), 218 (48.1), 190 (15.1), 162 (2.5), 146 (100), 77 (12.5), 58 (16.6); Calcd. for C₂₀H₁₉Br₂NO₃ (481.17); C, 49.92; H, 3.98; N, 2.91. Found: C, 49.83; H, 3.85; N, 3.01.

Preparation of 2-(Benzylideneamino)-N-[(R)-2-hydroxy-2-methyl-1-phenylpropyl] acetamide (**5**)

Concentrated NH₃ (0.2 ml) was added dropwise to a magnetically stirred solution of (*R*)-3-(2,3-dibromo-3-phenylpropanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (0.5 g, 1 mmol) in EtOH (15 ml) at room temperature. Stirring was continued at this temperature for 24 h after which the TLC (EtOAc/hexane; 1:3) examination showed the complete consumption of the starting dibromo-compound. The solvent was removed under vacuum and the solid residue was purified by column chromatography (EtOAc/hexane; 1:5) to furnish 2-(benzylideneamino)-N-[(*R*)-2-hydroxy-2-methyl-1-phenylpropyl] acetamide (**5**) (0.24 g, 0.77 mmol) as white crystals in 77% yield, m.p.: 84-86 °C, $[\alpha]_D^{25} = -42.9^\circ$ [c = 1, CHCl₃], IR (KBr): ν_{\max} (cm⁻¹): 3400, 3100, 1740, 1710, 1660, 1400, 753, 694; ¹H NMR (500 MHz, CDCl₃, 25 °C): 0.9 (s, 3H), 1.6 (s, 3H), 1.7 (s, 1H), 4.6 (s, 1H), 5.7 (s, 1H), 6.1 (s, br, 1H), 6.7 (s, br, 1H), 7.2 (d, J = 6.5 Hz, 2H), 7.4 (m, 6H), 7.7 (dd, J = 2.2, 7.8 Hz, 2H), 8.3 (s, 1H) ppm; MS m/z 295 (23.2, M-15), 294 (100), 293 (73.9), 233 (2.5), 146 (65.2), 118 (4.0), 104 (14.0), 77 (10.1), 59 (56.1); Calcd. for C₁₉H₂₂N₂O₂ (310.39) C, 73.52; H, 7.14; N, 9.02. Found: C, 73.37; H, 7.25; N, 9.20.

RESULTS AND DISCUSSION

Optically pure (*R*)-5,5-dimethyl-4-phenyloxazolidin-2-one (**2**) was readily available from the (*R*)-phenylglycine

according to the Davies protocol [6]. *N*-Acylation of **2** was achieved *via* the reaction of *trans*-cinnamoyl chloride to afford the desired acylated auxiliary **3** at room temperature in 72% yield $\{[\alpha]_D = +25^\circ$ (c = 1, CHCl₃)}. This product was reacted with 30% solution of Br₂ in chloroform to provide a diastereomeric mixture of (*R*)-3-(2,3-dibromo-3-phenylpropanoyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (**4**) in 87% yield with diastereomeric ratio of 3:1 (determined with ¹H NMR). The diastereomeric mixture was treated with concentrated NH₃ in ethanol at room temperature in order to furnish the related aziridine products (**7**), but interestingly, this reaction gave 2-benzylideneamino-N-[(*R*)-2-hydroxy-2-methyl-1-phenylpropyl]acetamide (**5**) in 77% yield (Scheme 1). The formation of azomethine products by ring opening of aziridine rings which can produce azomethine ylides by prototropic shift, have been observed before [14].

The formation of chiral azomethine product (**5**) was visualized by the initial formation of the expected aziridine **7** which underwent in situ, aziridine ring opening and endocyclic ring cleavage of the oxazolidin-2-one moiety under the alkaline condition. The structure of the amide **5** was

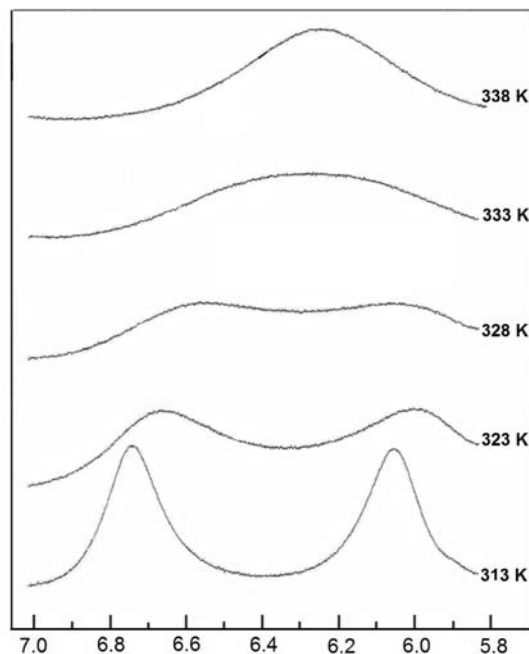


Fig. 2. Variable temperature 500 MHz ¹H NMR spectra of **5** in CDCl₃.

deduced from its elemental analysis and high-field ^1H NMR and IR spectral data.

The methylene protons in the amide **5** are diastereotopic due to the presence of a chiral center in the molecule which appear as two broad singlets at $\delta = 6.1$ and 6.7 ppm. Interestingly, these two protons showed dynamic properties and the variable temperature spectra gave the coalescence temperature 333 K (Fig. 2). The rate constant at

the coalescence temperature k_c for the dynamic process in question was calculated with the help of the Gutowsky-Holm expression [15] $k_c = \pi\Delta\nu_c/\sqrt{2}$ and the corresponding free energy of activation was obtained by the Eyring equation [16] ($\Delta G^\ddagger = 15.1 \pm 0.1\text{ kcal mol}^{-1}$).

For further refinement of the structure of the amide **5**, a series of deuterium exchange experiments were carried out in D_2O . The results of this study (Fig. 3) showed that in the

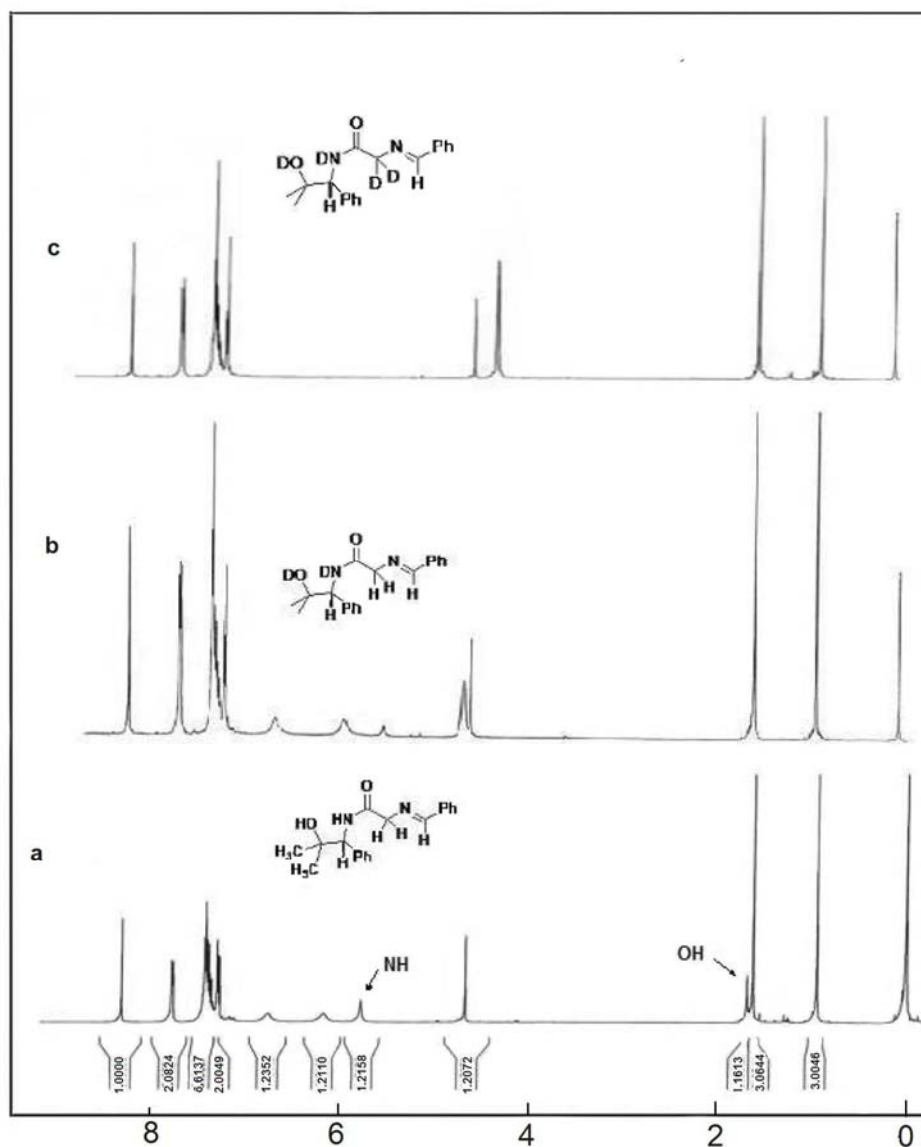


Fig. 3. Deuterium exchange experiment $500\text{ MHz } ^1\text{H}$ NMR spectra of **5** in CDCl_3 a and b at 298 K , and c at 328 K .

presence of 2 equimolars D₂O, the OH proton (δ 1.7 ppm) is completely removed from the spectra and the intensity of NH proton (δ = 5.7 ppm) is appreciably decreased (Fig. 3, b). Exchange of CH₂ protons were only observed in the presence of 4 equimolars of D₂O at 328 °K (Fig. 3, c) (signals at ~4.7 and 4.39 ppm in spectra b and c respectively, denote DOH). In conclusion, we have developed an efficient protocol for the preparation of chiral azomethine **5** which could be used as an azomethine ylide precursor for the preparation of highly substituted chiral five-membered ring nitrogen heterocycles by 1,3-dipolar cycloaddition reaction.

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