Stereoselective nucleophilic addition of chiral lithium enolates to (N-tosyl)imines: enantioselective synthesis of β-aryl-β-amino acid derivatives

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Received 7 January 2002; revised 28 February 2002; accepted 7 March 2002

Abstract—Nucleophilic addition of the chiral lithium enolates of (S)-(−)-4-benzyl-2-oxazolidinone acetamide with N-tosyl arylaldehyde imines gives β-aryl-β-amino acid derivatives in good yields and excellent diastereoselectivity. © 2002 Elsevier Science Ltd. All rights reserved.

β-Amino acids and their derivatives have attracted considerable attention in recent years due to their occurrence in biologically active natural products.1 β-Amino acids also serve as precursors in the synthesis of β-lactams,2 piperidines,3 indolizidines,4 and therapeutically enhanced peptides.5 Moreover, peptides consisting of β-amino acids, the so-called β-peptides, have been extensively studied recently.6 Given their importance in various fields, considerable efforts have been directed to the stereoselective preparation of β-amino acids and their derivatives.7

Among the various methodologies, the reactions of imines with ester enolates or ketenes are powerful approaches for the synthesis of β-amino acids and β-lactams, and they have been extensively explored in the past decades.8 N-Sulfonylimines have attracted considerable attention in recent years, since these highly electrophilic species are capable of undergoing some unique transformations, including nucleophilic additions and cycloadditions.9 They are also readily available. Evans’ chiral oxazolidinones have been widely employed in asymmetric synthesis, in particular, the aldol reactions of aldehydes with lithium or boron enolates have been found to give high diastereoselectivities in the presence of oxazolidinone as the chiral auxiliary.10 The analogous reaction of N-sulfonylimines with chiral lithium enolates would be expected to give β-amino acid derivatives with high diastereoselectivity (Scheme 1). Despite the apparent advantages of this approach, there is no report in the literature of the investigation of this reaction so far.11 In this communication, we report our study on the reactions of N-tosyl arylaldehyde imines with chiral lithium enolates derived from (S)-4-benzyl-2-oxazolidinone amides. The results indicate that the reaction is highly efficient and stereoselective, thus constituting a practical procedure for the synthesis of enantiomerically pure β-aryl β-amino acids.

Thus, the (S)-4-benzyl-2-oxazolidinone acetamide 1a was deprotonated with 1.1 equivalents of lithium diiso-

Scheme 1.

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PH: S0040-4039(02)00498-7
propylamide (LDA) at −78°C, followed by the addition of N-tosyl benzaldehyde.\textsuperscript{12} \textsuperscript{1}H NMR analysis of the crude reaction mixture indicated that the nucleophilic addition product was a single isomer. Reactions with other N-tosyl arylaldehyde imines all gave single addition products, except when the aryl group was o-methylphenyl, in which case an 89:11 mixture of two diastereoisomers was obtained (entry 6, Table 1). It is worth noting that this reaction works equally well with N-tosyl 2-furaldehyde imine, N-tosyl 5-bromo-2-thiophencarboxaldehyde imine and trans-cinnamaldehyde imine (entries 7, 8, 9). In all these cases, excellent diastereoselectivities were achieved. The stereochemistry of the newly generated chiral center was confirmed as S from the X-ray structure of the addition product 3a (Ar = o-MeC\textsubscript{6}H\textsubscript{4}) (Fig. 1).\textsuperscript{13}

Encouraged by the success of the stereocontrol in the above reaction, we proceeded to extend the investigation using the lithium enolate derived from (S)-(+)-4-benzyl-3-propionyl-2-oxazolidinone. In this case, two chiral centers will be generated in the nucleophilic addition step, thus giving four possible diastereoisomers. Under similar reaction conditions to those mentioned above, the reaction of the lithium enolate 2b with N-tosyl benzaldehyde gave a mixture of addition products in moderately high yield. Inspection of the \textsuperscript{1}H NMR spectra (400 MHz) of the crude product indicated that there were only two diastereoisomers. The diastereoselectivity of the two isomers was only moderate (dr = 77:23) (Table 2, entry 1). Addition of lithium chloride (5 equivalents) to the reaction did not improve the stereoselectivity. For two other N-tosyl imine substrates, similar results were obtained (entries 3 and 4). On the other hand, when the enolate was generated by TiCl\textsubscript{4}/Et\textsubscript{3}N,\textsuperscript{14} the nucleophilic addition gave diminished diastereoselectivity (entry 5).

The stereochemistry of the two newly generated chiral centers for the major product was established as (2’R,3’S) from the X-ray structure of 3b (Ar = C\textsubscript{6}H\textsubscript{5}) (Fig. 2).\textsuperscript{13} Although the stereochemistry of the minor isomer was not experimentally confirmed, it is postulated to be (2’R, 3’R), based on the analysis of the transition state of the reaction (vide infra).

The stereochemical outcome can be rationalized by the transition state depicted in Scheme 2.\textsuperscript{15} The absolute configuration at C-3’ is controlled by the enantiofacial selection of N-sulfonylimine, while the stereochemistry at C-2’ is due to the structure of the lithium enolate, which is predominantly the Z-enolate.

In contrast to the reaction of aldehydes with lithium or boron enolates, in which the oxygen of the aldehyde carbonyl group coordinates to the lithium or boron to form a six-membered ring transition state, the nitrogen of the N-sulfonylimine has little ability to coordinate to lithium because of the strongly electron-withdrawing

\begin{table}[h]
\centering
\caption{Reaction of chiral enolate 2a with N-tosyl imines}
\begin{tabular}{ccc}
\hline
Entry & N-Tosyl imines & Diastereoisomeric ratioa & Yield (%)b \\
\hline
1 & \(\text{C}_6\text{H}_5\) & >95:5 & 87 \\
2 & \(m\text{-CF}_3\text{C}_6\text{H}_4\) & >95:5 & 91 \\
3 & \(\rho\text{-FC}_6\text{H}_4\) & >95:5 & 81 \\
4 & \(\rho\text{-ClC}_6\text{H}_4\) & >95:5 & 92 \\
5 & \(\rho\text{-MeOC}_6\text{H}_4\) & >95:5 & 83 \\
6 & \(\rho\text{-MeC}_6\text{H}_4\) & 89:11 & 89 \\
7 & >95:5 & 78 \\
8 & \(\rho\text{-MeC}_6\text{H}_4\) & >95:5 & 77 \\
9 & trans-PhCH-CH & >95:5 & 74 \\
\hline
\end{tabular}
\textsuperscript{a} Product ratio was determined by \textsuperscript{1}H NMR (400 or 200 MHz). \\
\textsuperscript{b} Yields after chromatographic purification on silica gel.
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{ORTEP view of the addition product 3a (Ar = o-MeC\textsubscript{6}H\textsubscript{4}).}
\end{figure}

\begin{table}[h]
\centering
\caption{Reaction of chiral enolate 2b with N-tosyl imines}
\begin{tabular}{ccc}
\hline
Entry & N-Tosyl imine & Reaction conditions & Ratio\textsuperscript{a} & Yield (%)b \\
\hline
1 & \(\text{C}_6\text{H}_5\) & LDA & 77:23 & 57 \\
2 & \(\text{C}_6\text{H}_5\) & LDA + LiCl & 73:27 & 63 \\
3 & \(m\text{-CF}_3\text{C}_6\text{H}_4\) & LDA & 76:24 & 90 \\
4 & \(\rho\text{-FC}_6\text{H}_4\) & LDA & 67:33 & 78 \\
5 & \(\rho\text{-FC}_6\text{H}_4\) & TiCl\textsubscript{4}/Et\textsubscript{3}N & 54:46 & 70 \\
\hline
\end{tabular}
\textsuperscript{a} Product ratio was determined by \textsuperscript{1}H NMR (400 or 200 MHz). \\
\textsuperscript{b} Yields after chromatographic purification on silica gel.
\end{table}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{ORTEP view of the addition product 3b (Ar = C\textsubscript{6}H\textsubscript{5}).}
\end{figure}
It is interesting to note that in the aldol reaction with Evans’ oxazolidinone auxiliary, the enolate derived from acetamide gives poor selectivity at the C-3’ position, while the enolates derived from other amides in general give excellent diastereoselectivity. In the reaction with N-sulfonylimine, we have observed opposite results, the selectivity for 2a is high, while that for 2b is poor. These results can be rationally explained according to the transition state model shown in Scheme 2.

In summary, we have shown that the reaction of N-tosylimines with chiral lithium enolates derived from (S)-(-)-4-benzyl-2-oxazolidinone acetamide give high yields and excellent diastereoselectivity. The reaction is operationally simple and the N-tosylimines are readily available. Therefore, this is a highly efficient method for the synthesis of β-aryl β-amino acid derivatives, the stereoselective synthesis of which has been particularly challenging with only limited methods available.16

Acknowledgements

The project is generously supported by the Natural Science Foundation of China (Grant Nos. 29972002, 20172002) and by the Trans-Century Training Programme Foundation for the Talents by the Ministry of Education.

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3. For example, see: Jefford, C. W.; Wang, J. B. Tetrahedron Lett. 1993, 34, 2911.
12. A typical procedure. Butyllithium (1 mL, 1.1 M in hexane, 1.1 mmol) was added dropwise to diisopropylamine (1.2 mmol) in anhydrous THF (6 mL) at −78°C, under a nitrogen atmosphere. After the solution was stirred for about 15 min at the same temp., (S)-(-)-4-benzyl-2-oxazolidinone acetamide (1a, 1 mmol) in anhydrous THF (6 mL) was added dropwise. The solution was stirred for 30 min, then a solution of N-tosyl aldehydiniine (1.1 mmol) in anhydrous THF (6 mL) was slowly added at −78°C. The mixture was stirred at this temperature until TLC indicated that no starting oxazolidinone remained (about 4 h). The reaction mixture was quenched with saturated
aqueous NH₄Cl solution at the same temperature, and the mixture was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous Na₂SO₄. The usual work-up gave a crude product which was analyzed by ¹H NMR for determining the diastereoisomeric ratio. Purification by column chromatography with silica gel and recrystallization gave a pure sample for characterization. Data for (4S)-benzyl-3-[(3’S)-(N-tosyl)amino-3’-(2-methyl)phenylpropionyl]-2-oxazolidinone (3a, R=H, Ar=o-MeC₆H₄): mp 128–130°C; [α]D₂₀ +3.85 (c 0.93, CHCl₃); IR (KBr) 3245, 1786, 1682 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 2.17 (s, 3H), 2.23 (s, 3H), 2.70 (dd, J=13.6, 9.6 Hz, 1H), 3.23 (dd, J=13.6, 2.5 Hz, 1H), 3.34 (dd, J=15.4, 5.7 Hz, 1H), 3.51 (dd, J=15.5, 8.4 Hz, 1H), 4.12–4.20 (m, 2H), 4.57–4.63 (m, 1H), 5.13–5.29 (m, 1H), 5.76 (d, J=8.2 Hz, 1H), 7.01–7.53 (m, 13 H), 5.76 (d, J=8.2 Hz, 1H), 7.01–7.53 (m, 13 H); ¹³C NMR (50 MHz, CDCl₃) δ 18.94, 21.34, 37.68, 41.96, 50.86, 55.36, 66.36, 125.91, 126.35, 126.95, 127.30, 127.55, 128.93, 129.23, 129.38, 130.50, 135.11, 135.17, 137.55, 137.91, 143.03, 153.67, 170.11; EI–MS (m/z, relative intensity) 492 (M⁺, 3), 321 (12), 303 (2), 274 (8), 219 (5), 171 (34), 145 (100), 118 (70), 91 (94), 65 (60), 43 (38); Anal. Calc. for C₂₇H₂₈N₂O₅S: C, 65.84; H, 5.73; N, 5.69. Found: C, 65.79; H, 5.73; N, 5.71.

13. The crystallographic measurement was made on a Rigaku R-AXIS RAPID image plate diffractometer with graphite monochromated Mo–Kα radiation (λ=0.71073 Å). An absorption correction was applied by correction of symmetry-equivalent reflections using the ABSCOR program. The structure was solved by direct methods and successive difference maps (SHELXS 97) and refined by full-matrix least-squares on F² using all unique data (SHELXL 97). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included in their calculated positions with geometrical constraints and refined in the riding model. Lists of refined coordinates have been deposited at the Cambridge Crystallographic Data Centre (deposition number 3a, R=H, Ar=o-MeC₆H₄, CCDC 175691; 3b, R=Me, Ar=C₆H₅, CCDC 176744). Copies of the available material can be obtained free of charge on application to the CCDC, 12, Union Rd., Cambridge CB2 1EZ, UK E-mail: deposit@ccdc.cam.ac.uk.


15. This transition state model is similar to that proposed by Murahashi et al. in the addition of chiral enolates to nitrones via an N-acyloxyiminium ion, see: Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. Bull. Chem. Soc. Jpn. 2000, 79, 2423.