Crystallization Induced Dynamic Resolution and Nucleophilic Substitutions of N-((S)-(1-Phenylethyl))-α-chloro-α-phenyl Acetamide for the Preparation of N-Carboxyalkylated Flavone

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Received February 11, 2008

Key Words: Crystallization, Resolution, Asymmetric syntheses, Chiral auxiliary, Flavonoids

Chiral auxiliary mediated dynamic resolution of α-halo carboxylic acid derivatives in nucleophilic substitution has been recognized as an effective asymmetric synthetic method in recent years, and several attractive strategies have been discovered.1-3 Since α-haloacyl compounds are easily obtained in racemic form and configurational lability of them is readily induced by halide sources, base or polar solvents, dynamic resolution in nucleophilic substitutions at α-halo carbon center can allow easy access to a wide range of enantioenriched α-heteroatom substituted carboxylic acid derivatives. We previously reported a crystallization induced dynamic resolution (CIDR) method for the preparation of optically active α-chloro carbonyl functionality.2a One of two diastereomeric species of N-(S)-(1-phenylethyl)-α-chloro-α-aryl acetamides selectively crystallizes from aqueous ammonia solution controlled by the thermodynamics of phase equilibrium as shown in Scheme 1. Here we wish to report recent results on the efficient CIDR and the nucleophilic substitutions of acetamide 1. The stereospecific nucleophilic substitution with potassium thioacetate can provide a novel thiol chiral auxiliary 5 for dynamic resolution of α-bromo carboxylic acid derivatives in the nucleophilic substitution.

Initial studies to develop the CIDR process have focused on finding more effective solvent system. In order to understand the role of water in the selective crystallization, we have performed a CIDR process in the absence of water. When the solution of α-chloro-α-phenyl acetamide (αRS)-1 and NH3 in MeOH was allowed to slowly evaporate, the complete evaporation of MeOH provided 1 as a white solid with 52:48 diastereomeric ratio (dr) as shown in Scheme 1. The low selectivity indicates that water is crucial for an efficient CIDR, reducing the solubility of (αS)-1 selectively. On the basis of these observations, we set out to find appropriate water and methanol solvent system in which α-chloro acetamide (αS)-1 can be selectively precipitated while simultaneously, two epimers of 1 equilibrate in the presence of NH3 base.

We therefore investigated several CIDR protocols to establish if there was a relationship between the amount of NH4OH used and diastereomeric excess (de) of 1 as illustrated in Figure 1. We have closely monitored the progress of the reactions in terms of % de by NMR analysis of crude reaction mixture of 1 (100 mg) in 2 mL of MeOH with various amount of NH4OH. The results shown in Figure 1(a) clearly indicate that a direct relationship between the amount of NH4OH added and de of 1. As the amount of NH4OH added increases, the final de of 1 is improved. However, the addition of 8 mL of NH4OH did not provide better de of 1. Figure 1(b) presents the effect of slow addition of NH4OH on the CIDR process. Better results in de of 1 were obtained when the additional 4 mL of NH4OH was added in four equal portions every 12 h. (condition D, --●--) The CIDR system was further optimized by the use of 1 mL of MeOH, to shorten the required time for the phase equilibration. (condition E, --■--) Under this condition it is just a matter of time before thermodynamic equilibration is reached, producing (αS)-1 with 94% de. The plots show that the amount of MeOH is not crucial for final de of the product.

After a simple evaporation of NH4OH, (αS)-1 could be obtained as a white solid in quantitative yield and (αS)-1 is configurationally stable in the absence of NH4OH. As an application of the CIDR method to the asymmetric preparation of α-heteroatom substituted carboxylic acid derivatives, we have carried out substitution reactions of α-chloro acetamide (αS)-1 with various heteroatom nucleophiles as
shown in Table 1. The reactions with amine nucleophiles did not produce the substitution product in the presence of tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA). (entries 1 and 2) On the other hand, when \((\alpha S)-1\) (97:3 dr) was treated with 6-hydroxyflavone and 3,5-dimethoxyphenol in the presence of Cs\(_2\)CO\(_3\) (or NaH), the alkoxide nucleophiles provided the substituted products 2 and 3 in 66% and 57% yields, respectively. In both cases, however, the dr of products is almost 1:1. The results in entries 3 and 4 can be taken to suggest that \((\alpha S)-1\) and/or the substitution products are configurationally labile under strongly basic conditions. As shown in entry 5, treatment of \((\alpha S)-1\) (97:3 dr) with potassium thioacetate (KSAc) in MeOH at rt for 24 h gave an \(\alpha\)-acetylthio carboxylic acid derivative \((\alpha R)-4\). We were pleased to observe that no epimerization was observed during the substitution reaction as judged by \(^1\)H-NMR on the crude reaction mixture (97:3 dr). After column chromatography of crude reaction mixture, optically pure \(\alpha\)-acetylthio substituted product \((\alpha R)-4\) was obtained in 80% yield. Also, the result in entry 6 can rule out the possibility of dynamic resolution of \((\alpha R5)-1\) in nucleophilic substitution with KSAc.

Despite the significance of optically active \(\alpha\)-mercapto carboxylic acids in organic synthesis, only a few methods have been reported for asymmetric syntheses of \(\alpha\)-mercapto carboxylic acid derivatives.\(^4\) As shown in Scheme 2, we successfully accomplished the conversion of optically pure \(\alpha\)-chloro carbonyl functionality to \(\alpha\)-mercapto carbonyl functionality by the epimerization free sequences. Deacylation of \((\alpha R)-4\) with acetyl chloride in MeOH produced \((\alpha R)-5\) in 95% yield without any detectable epimerization as judged by \(^1\)H NMR. In addition, the reduction of 4 using an excess amount of BH\(_3\)-THF (5 equiv) in THF provided the expected \(\beta\)-amino thiol 6 in 58% yield.\(^5\) We then examined the capability of thiol \((\alpha R)-5\) as a chiral auxiliary in nucleophilic substitution of \(\alpha\)-bromo carboxylic acid derivatives with amine nucleophiles. The treatment of \(\alpha\)-bromo thioester 7 with dibenzylamine (1.2 equiv) in the presence of TBAI and DIEA in CH\(_2\)Cl\(_2\) at room temperature provided the substitution product in 61% yield. Subsequent reductive removal of the chiral auxiliary using LiAlH\(_4\) in THF furnished the enantioenriched \(\beta\)-amino alcohol \((R)-8\) in 55% yield with 84:16 enantiomeric ratio (er).\(^6\)

Flavones are plant products with many biological and pharmacological activities. A number of \(O\)-alkylated and \(N\)-alkylated flavones have recently been prepared to improve their biochemical and pharmacological properties of naturally occurring flavones.\(^7\) In our continuing investigation on the stereoselective preparation of alkylated flavonoids and their activity studies,\(^8\) we have attempted to prepare \(N\)-carboxyalkylated flavones by the chiral auxiliary 5 mediated dynamic resolution of \(\alpha\)-bromo thioester 7. As shown in Scheme 2, treatment of \(\alpha\)-bromo thioester 7 with 6-aminoflavone (1.2 equiv) in the presence of TBAI and DIEA for 24 h provided

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<th>Table 1. Nucleophilic substitutions of ((\alpha S)-1) with various nucleophiles</th>
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(a) Isolated yields. (b) Drs were determined by \(^1\)H-NMR.
the substitution product in 70% yield. Subsequent removal of
the chiral auxiliary with EtOH and Bu3P gave L-phenyl-
glycine-flavone conjugate (R)-9 in 66% yield with 80:20 er.

We conclude that CIDR of N-(S)-(1-phenethyl)-α-
chloro-α-phenyl acetamide 1 is effectively promoted by
addition of NH2OH. It has been found that slow addition
of NH2OH in portions gave better selectivities than the addition
at once. Stereospecific nucelophilic substitution of 1 with a
thio nucleophile (KSAc) and subsequent deacylation can
provide thiol 5, which can be used as a chiral auxiliary for
the preparation of enantioenriched β-amino alcohol 8 and N-
alkylated flavone 9 by the nucelophilic substitutions of 7.
Further studies to extend the scope of the methodology for
the preparation of various N-carboxyalkylated flavones are
underway.

Experimental

Crystallization induced dynamic resolution of N-(S)-(1-
phenethyl)-α-chloro-α-phenyl acetamides (αRS)-
I. To a solution of (αRS)-I (100 mg, 0.36 mmol) in MeOH
(1 mL) at rt was added 2 mL of NH2OH. The resulting
reaction mixture was stirred at r.t. for 2 days, adding 1 mL of
NH2OH in four equal portions every 12 hours. Simple
evaporation of reaction mixture gave (αS)-I as a white solid
in quantitative yield. The dr of 1 was determined to be 97:3
by 1H NMR using the integration of α-chloromethine protons.

1H NMR (CDCl3, 400 MHz) 7.49-7.24 (m, 10H), 6.98 (br,
J = 6.8 Hz, 3H), 5.11 (m, 1H), 1.52 (d, J = 6.8 Hz, 3H).

General procedure for the preparation of 2 and 3. To a
solution of α-chloroacetamide 1 (1.5 equiv) in CH3CN (0.1
M) at rt was added a hydroxy nucleophile (1.0 equiv) and
Cs2CO3 (1.0 equiv). After the resulting reaction mixture was
stirred at rt for 24 h, the mixture was quenched with
saturated aqueous NH4Cl solution. The resulting mixture
was extracted with EtOAc twice and the combined extracts
were washed with brine. The solvent was evaporated and
the crude material was purified by column chromatography.

N-(S)-(1-Phenylethyl)-α-(6-flavonoxy)-α-phenyl acet-
amide (2), 66% yield; 1H NMR (CDCl3, 400 MHz) 7.81-
7.18 (m, 18H), 6.68 (d, J = 5.5 Hz, 1H), 5.73, 5.69 (s, 1H,
two peaks), 5.16 (m, 1H), 1.50 (d, J = 6.9 Hz, 3H); 13C NMR
(CDCl3, 100 MHz) 178.2, 168.7, 163.8, 154.4, 152.5, 143.2,
136.4, 132.1, 129.4, 129.2, 129.1, 129.0, 127.8, 127.3,
126.7, 126.6, 126.5, 125.1, 124.0, 120.2, 110.3, 107.1, 81.2,
49.1, 22.1.

N-(S)-(1-Phenylethyl)-α-(3,5-dimethoxyphenoxy)-α-
phenyl acetamide (3), 57% yield; 1H NMR (CDCl3, 400
MHz) 7.54-7.18 (m, 10H), 6.87 (d, J = 7.5 Hz, 1H), 6.13-
6.09 (m, 3H), 5.53, 5.50 (s, 1H, two peaks), 5.10 (m, 1H),
3.75, 3.66 (s, 3H, two peaks), 1.48, 1.45 (d, J = 7.1 Hz, 3H,
two peaks); 13C NMR (CDCl3, 100 MHz) 169.3, 162.0,
159.0, 143.2, 136.8, 129.1, 129.0, 127.8, 127.0, 95.2,
95.0, 94.7, 80.9, 55.8, 49.0, 22.2.

Preparation of N-(S)-(1-phenethyl)-α-acetyltio-
phenyl acetamide (α(R)-4). To a solution of (αS)-I (139
mg, 0.51 mmol, 97:3 dr) in 3 mL of MeOH was added
potassium thioacetate (KSAc, 1.2 equiv) under a nitrogen
atmosphere. The resulting material was stirred for 24 h at r.t.
followed by regular extractive work up and column
chromatography to give α-acetyltio substituted product
(127 mg, > 99:1 dr determined by 1H NMR and HPLC) as a
colorless oil in 80% yield. 1H NMR (CDCl3, 400 MHz)
7.37-7.14 (m, 10H), 6.41 (d, J = 7.5 Hz, 1H), 5.23 (s, 1H),
5.07 (m, 1H), 2.32 (s, 3H), 1.44 (d, J = 6.9 Hz, 3H); 13C
NMR (CDCl3, 100 MHz) 195.4, 168.5, 143.1, 136.2, 129.3,
129.0, 128.9, 128.7, 127.7, 126.4, 52.6, 49.8, 30.5, 22.0.

Preparation of N-(S)-(1-phenethyl)-α-mercapto-
phenyl acetamide (α(R)-5). Deacylation of 4 (120 mg) was
carried out with acetyl chloride (1 mL) in MeOH (3 mL) at
rt. for 12 h to produce (αR)-5 in 95% yield (> 99:1 dr
determined by 1H NMR and HPLC), compared with a sample
of (αRS)-5. 1H NMR (CDCl3, 400 MHz) 7.36-7.22 (m,
10H), 6.62 (d, J = 6.4 Hz, 1H), 5.10 (m, 1H), 4.68 (d, J = 6.2
Hz, 1H), 2.57 (d, J = 6.2 Hz, 1H), 1.48 (d, J = 6.8 Hz, 3H);
13C NMR (CDCl3, 100 MHz) 169.8, 143.1, 139.4, 129.6,
129.3, 129.0, 128.6, 127.4, 126.4, 49.9, 48.4, 22.2.

Preparation of 2-(S)-(1-phenylethynylamino)-1-(S)-phenyl-
ethanethiol (6). To a solution of 4 in THF (0.5 M) was
added BH3·THF (1.0 M, 5.0 equiv), and the mixture was
refluxed for 12 h. The reaction was quenched by adding
MeOH (0.5 mL) under ice-water cooling, and the solvents
were evaporated. Aqueous 5%-HCl (2 mL) was added to the
residue, and the mixture was refluxed for 1 hour. The
reaction mixture was basified with K2CO3, saturated with
NaCl, and extracted with CHCl3 (5 mL x 3). The combined
organic extracts were dried with anhydrous MgSO4, filtered
and concentrated to provide the crude product that was
purified by column chromatography on silica gel. 58% yield;

Notes

Preparation of N-(S)-(1-phenylethyl)-α-(bromophenylacetylthio)-α-(R)-phenyl acetamide (7). Acetamide 5 (1.0 equiv), racemic α-bromo phenylacetylic acid (1.0 equiv), DCC (1.0 equiv), Et3N (2.2 equiv) and DMAP (0.2 equiv) in 70% yield. The mixture of the substituted product and Bu3P (0.1 equiv) was stirred for 3 h and then quenched with EtOAc and 0.1 M-HCl for 3 h. The precipitate was filtered off and the organic phase was washed with water. The organic phase was dried over MgSO4, filtered and concentrated to provide the crude product that was purified by column chromatography on silica gel in 75% yield. 1H NMR (CDCl3, 400 MHz) 7.34-7.18 (m, 10H), 4.03 (t, J = 6.6 Hz, 1H), 2.88 (m, 2H), 1.80 (br, 2H), 1.32 (d, J = 6.6 Hz, 3H), 1.51 (d, J = 6.6 Hz, 1H), 5.19 (d, J = 6.6 Hz, 1H), 4.20 (m, 2H), 1.24 (J = 9.6 Hz, 3H). The enantiomeric ratio of 9 was determined to be 80:20 in favor of the R enantiomer by CSP-HPLC using racemic material as a standard. (Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min): 101 min (R), 94 min (S).

Acknowledgements. This work was supported by a grant from Korea Research Foundation (KRF-2006-005-J03402).

References and Notes


5. The asymmetric reduction of acetophenone with LiAlH4 in the presence of chiral ligand 4 provided 1-phenylethanol with 65:35 α, Unpublished results.

6. The absolute configurations of (R)-8 and (R)-9 were assigned by comparison of the CSP-HPLC retention time to those of the authentic material reported previously.8
