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Practical synthesis of α-aminoalkyl-α′-chloromethylketone derivatives. Part 2: Chloromethylation of *N*-imine-protected amino acid esters

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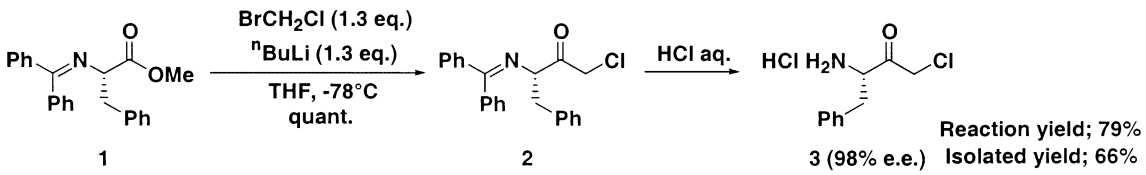
Abstract—Chloromethylation of *N*-imine-protected amino acid esters followed by acid hydrolysis gave α-aminoalkyl-α′-chloromethylketone as a HCl salt form in good yield without racemization. The amino group was conveniently protected with carbamate protecting reagents to give various useful intermediates for the protease inhibitors.

Practical syntheses of α-aminoalkyl-α′-chloromethylketone derivatives are urgently needed, and considerable effort has been directed towards the development of efficient processes.[1–4] In a previous paper,[5] we described a practical method for the synthesis of α-aminoalkyl-α′-chloromethylketone derivatives via the chloromethylation of *N*-protected 3-oxazolidin-5-ones. In this paper, we report another novel practical method using the chloromethylation of *N*-imine-protected amino acid esters as a key step.

As noted in the previous paper,[5] we had focused on the chloromethylation of several kinds of *N*-protected amino acid esters. Based on our results, we assumed that a suitable *N*-protecting group should have the following prerequisites: (1) The amino group can be protected by such an *N*-protecting group without leaving a hydrogen atom unprotected; (2) deprotection is possible while maintaining the chloromethylketone moiety intact; and (3) the protecting reagent is commercially available at a lower cost. Consistent with these hypotheses, *N*-diphenylmethylene-protected amino acid ester **1**, which can be easily prepared from amino acid esters and $Ph_2C{=}NH$,[6,7] was used as a substrate for chloromethylation. *n*-Butyllithium (1.3 equiv.) in hexane was added dropwise to a solution of ester **1** and bromochloromethane (1.3 equiv.) in anhydrous THF at −78°C to give chloromethylketone **2** in quantitative yield (Scheme 1).[8] Hydrolysis of **2** with 2 mol/l HCl afforded unprotected α-aminoalkyl-α′-chloromethylketone **3** as a HCl salt in 66% yield.[9] Its optical purity was determined by HPLC was 98% e.e.[9]

Thus, we confirmed that the ester **1** could be used for chloromethylation while retaining the *N*-diphenylmethyleneamine moiety. Next, we examined chloromethylation of the *N*-benzylidene-protected amino acid ester **4**[10] and successive hydrolysis with hydrochloric acid, in an attempt to use inexpensive benzaldehyde as a protecting reagent for the amino group. Since several nucleophilic reactions towards *N*-benzylideneamine while keeping the ester moiety intact have been reported,[11,12] it was uncertain whether such a selective reaction towards the ester moiety would proceed or not. Furthermore, *N*-benzylidene-protected



Scheme 1.

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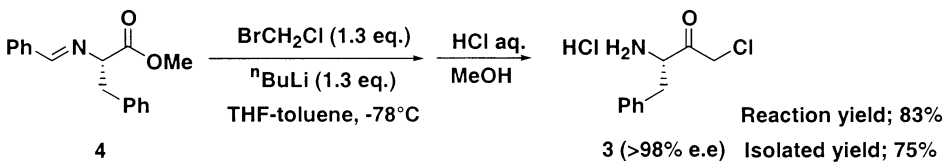
amino acid derivatives are liable to be racemized due to the high acidity of the α-proton of the ester.[13] To our surprise, however, chloromethylation and hydrolysis proceeded nicely to afford the desired α-aminoalkyl-α′-chloromethylketone HCl salt **3** in 83% yield with high optical purity (>98% e.e.) (Scheme 2). Interestingly, no side reaction towards the *N*-benzylideneamine moiety was observed. The resultant HCl salt **3** was purified and isolated in 75% yield after crystallization.[14]

The weak basicity of chloromethyllithium immediately generated in situ from $BrCH_2Cl$ and *n*-BuLi contributes to the full retention of stereochemistry.[5] An additional possible explanation is that internal chelation of lithium metal with the *N*-benzylideneamino group may prevent abstraction of the α-proton (Scheme 3).

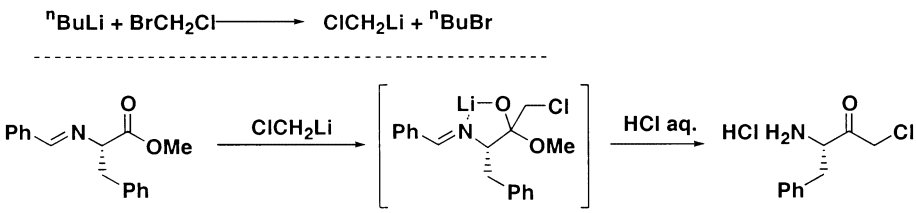
The chloromethylketone **3** is a useful intermediate for the synthesis of serine protease inhibitors, which can be obtained through the reaction of **3** with appropriate carboxylic acids.[15,16] Moreover, *N*-carbamate-protected α-aminoalkyl-α′-chloromethylketones serve as useful precursors to the hydroxyethyl isostere subunits present in many inhibitors of HIV protease.[1] To prepare them, **3** was reacted with several carbamate protecting reagents using the Schotten Baumann method[17] (Table 1; procedure A). Although *N*-Moc-protected chloromethylketone **5**[18] and *N*-Cbz-protected chloromethylketone **6**[19] could be obtained in good yield, the first attempt to protect **3** with a Boc group using Boc_2O gave the desired chloromethylketone **7** in low yield. This may be due to the lack of stability of **3** in a free base form, since Boc_2O has lower reactivity than MocCl or CbzCl. We confirmed that chloromethylketone **3** is dimerized and aromatized to form pyrazine **8** under neutral–basic conditions.[20] We eventually found that Boc-protection can be achieved in high yield by adding **3** to a mixture of Boc_2O in organic solvent and aq. Na_2CO_3 (Table 1; procedure B).[21] By using the two-layer system above, **3** immediately goes to the organic layer after neutralization and can be protected without further decomposition. The resulting chloromethylketone **7** can be converted to both *erythro* *N*-Boc-protected aminoepoxide[1] and *threo* *N*-Boc-protected aminoepoxide,[22,23] the key intermediates for various enzyme inhibitors, by diastereoselective reduction and epoxide formation.

Furthermore, chloromethylketone **3** can be reduced with $NaBH_4$ to give *erythro* aminoalcohol **9** with modest selectivity (Scheme 4).[24] The aminoalcohol **9** is also a useful compound for synthesis of the *erythro* *N*-Boc-protected aminoepoxide.[25]

In conclusion, practical syntheses of α-aminoalkyl-α′-chloromethylketone derivatives using the chloromethyl-

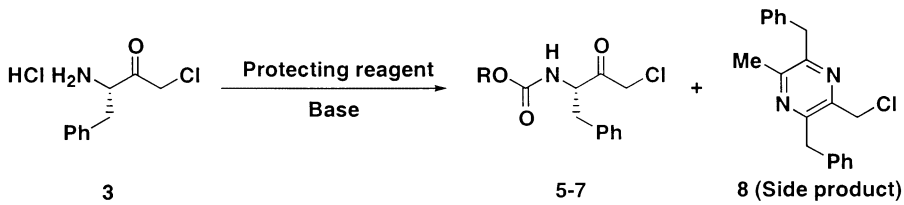


Scheme 2.

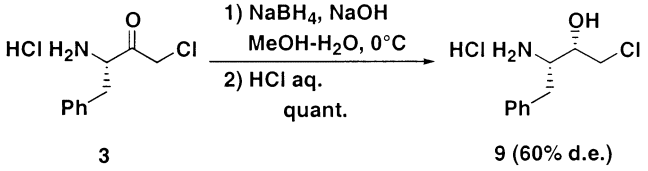


Scheme 3.

Table 1. Reaction of compound **3** with carbamate protecting reagents



Compound	R	Reagent	Base	Procedure	Conditions	Yield (%)
5	Me	$ClCO_2Me$	$NaHCO_3$	A	Toluene–H_2O, rt	78
6	Bn	$ClCO_2Bn$	$NaHCO_3$	A	Toluene–H_2O, rt	83
7	^{t}Bu	$O(CO_2{}^t Bu)_2$	Na_2CO_3	B	CH_2Cl_2–H_2O, rt–35°C	92



Scheme 4.

ation of *N*-imine-protected amino acid esters were achieved. Chloromethylation and successive acid hydrolysis afforded α-aminoalkyl-α′-chloromethylketone as a salt form in good yield without racemization. The amino group can be conveniently protected with carbamate protecting reagents to give various useful intermediates leading to the known protease inhibitors.

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8. A solution of ester **1** and bromochloromethane (1.3 equiv.) in anhydrous THF was cooled to −78°C, and *n*-butyllithium (1.3 equiv.) in hexane was added dropwise. After stirring for 30 min at −78°C, a saturated NH_4Cl aqueous solution was added. The product was extracted to give **2** as a pale yellow oil. $[\alpha]_D^{25}=+8.5$ ($c=1$, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.07 (dd, $J=8.8$, 13.8 Hz, 1H), 3.15 (dd, $J=4.2$, 13.8 Hz, 1H), 4.31 (dd, $J=4.2$, 8.8 Hz, 1H), 4.38 (d, $J=17.1$ Hz, 1H), 4.58 (d, $J=17.1$ Hz, 1H), 6.43 (d, $J=9.9$ Hz, 2H), 6.99–7.04 (m, 2H), 7.18–7.40 (m, 9H), 7.60 (d, $J=9.1$ Hz).
9. A solution of chloromethylketone **2** in THF was treated with an excess of 2 mol/l HCl at rt for 11 h. After concentration, the resultant slurry was washed with MeOH–MTBE to give **3** as a white solid. The reaction yield was determined by HPLC using an Inertsil ODS-2 column. Enantiomer purity was determined by HPLC using a Crownpak CR(+) column. $[\alpha]_D^{25}=+30.2$ ($c=0.5$, H_2O); ^{1}H NMR (DMSO-d_6) δ 3.04 (dd, $J=7.1$, 15.2 Hz, 1H), 3.22 (dd, $J=7.1$, 15.2 Hz, 1H), 4.54 (t, $J=7.1$ Hz, 1H), 4.58 (d, $J=17.3$ Hz, 1H), 4.70 (d, $J=17.3$ Hz, 1H), 7.28–7.41 (m. 5H), 8.37 (bs, 3H); ESI MASS m/z 198 (MH^+).
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18. A solution of methyl chloroformate (1.3 equiv.) in toluene was added to a solution of **3** in H_2O. An aqueous $NaHCO_3$ solution (2 equiv.) was added dropwise with good stirring. After stirring for 1 h at rt, the product was extracted and recrystallized from 2-propanol and hexane to afford **5** as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.97–3.14 (m, 2H), 3.66 (s, 3H), 3.98 (d, $J=16.0$ Hz, 1H), 4.15 (d, $J=16.0$ Hz, 1H), 4.75 (q, $J=7.2$ Hz, 1H), 5.21 (bd, 1H), 7.12–7.18 (m. 2H), 7.23–7.37 (m, 3H).
19. A solution of benzyl chloroformate (1.3 equiv.) in toluene was added to a solution of **3** in H_2O. An aqueous $NaHCO_3$ solution (2 equiv.) was added dropwise with good stirring. After stirring for 1 h at rt, the product was extracted and purified by silica gel chromatography to give **6** as a white solid. ^{1}H NMR ($CDCl_3$) δ 3.00 (dd, $J=7.0$, 13.9 Hz, 1H), 3.09 (dd, $J=6.9$, 13.9 Hz), 3.97 (d, $J=16.2$ Hz), 4.14 (d, $J=16.2$ Hz), 4.75 (bq, $J=7.0$ Hz, 1H), 5.06 (s, 2H), 5.38 (bd, $J=7.6$ Hz, 1H), 7.12–7.35 (m, 10H); ESI MASS m/z 332 (MH^+).
20. **8** (a pale orange solid); ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 4.17 (s, 2H), 4.29 (s, 2H), 4.62 (s, 2H), 7.15–7.32 (m. 10H); ESI MASS m/z 323 (MH^+).
21. A solution of di-*tert*-butyl dicarbonate (1.1 equiv.) in dichloromethane was added to an aqueous Na_2CO_3 solution (1.5 equiv.). Compound **3** was slowly added to the mixture at rt with good stirring. After stirring for 1 h at 35°C, the product was extracted and recrystallized from 2-propanol and hexane to afford **7** as a white solid. $[\alpha]_D^{25}=-55.7$ ($c=1$, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.00 (dd, $J=6.9$, 13.8 Hz), 3.08 (dd, $J=6.9$, 13.8 Hz, 1H), 3.98 (d, $J=16.2$ Hz, 1H), 4.17 (d, $J=16.2$ Hz, 1H), 4.68 (q, $J=6.9$ Hz, 1H), 5.02 (bd, $J=6.9$ Hz, 1H), 7.16 (m, 2H), 7.26–7.36 (m, 3H); ESI MASS m/z 296 ($M-H^+$).

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