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Practical synthesis of α-aminoalkyl-α′-chloromethylketone derivatives. Part 1: Chloromethylation of *N*-protected 3-oxazolidin-5-ones

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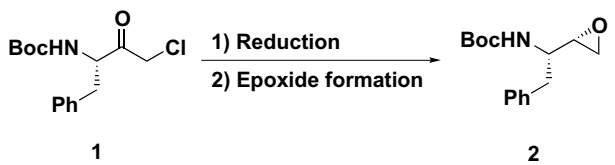
Abstract—Reaction of *N*-protected 3-oxazolidin-5-ones with in situ-generated chloromethyllithium afforded *N*-protected 5-chloromethyl-5-hydroxy-3-oxazolidines without racemization. They were easily hydrolyzed to give α-aminoalkyl-α′-chloromethylketone derivatives, which are useful intermediates for several protease inhibitors.

α-Aminoalkyl-α′-chloromethylketone derivatives serve as irreversible inhibitors of serine protease[1–3] and are useful precursors to the hydroxyethyl isostere subunits found in many inhibitors of renin[4] and HIV protease.[5] For instance, chloromethylketone **1** can be easily converted to epoxide **2**, which is the key intermediate for various enzyme inhibitors (Scheme 1).[6] The need for practical syntheses of α-aminoalkyl-α′-chloromethylketone derivatives has become of crucial importance, and considerable effort has been directed towards the development of efficient processes.[6–11] We report here a novel practical method for the synthesis of α-aminoalkyl-α′-chloromethylketone derivatives.

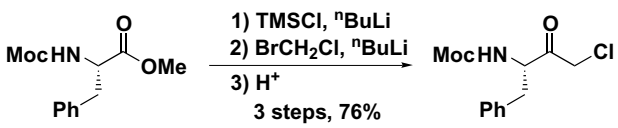
We have focused on the reaction of chloromethyllithium[12,13] with *N*-protected amino acid esters, since such a carbenoid species can be conveniently generated in situ from $BrCH_2Cl$ and *n*-BuLi, which are not unreasonably expensive. Although the chloromethylation of *N*,*N*-dibenzyl-L-phenylalanine ester has been described,[8,9] no method has been reported for deprotecting the dibenzyl group while keeping the chloromethylketone moiety intact. The Roche group reported that chloromethylation of Moc-Phe-OMe (**3**) gave chloromethylketone **4** in only modest yield (35–51%), while an improved process involving in situ protection of the carbamate group in **3** with trimethylsilyl chloride prior to the reaction with chloromethyllithium gave **4** in 76% yield after aqueous workup (Scheme 2).[10] However, to obtain unprotected α-aminoalkyl-α′-chloromethylketone, this procedure has a limitation due to lack of method to deprotect the Moc group while maintaining the chloromethylketone moiety. We attempted chloromethylation of Boc-Phe-OMe and Boc(TMS)-Phe-OMe, but did not realize good results. This prompted us to investigate the chloromethylation of 3-oxazolidin-5-one derivatives and successive deprotection.



1 **2**

Scheme 1.

First, chloromethylation of *N*-Boc-protected 3-oxazolidin-5-one **5**, which can be prepared by reacting Boc-Phe-OH and paraformaldehyde in the presence of acid catalyst,[14] was performed to obtain *N*-Boc-protected 5-chloromethyl-5-hydroxy-3-oxazolidine **6** quantitatively (Scheme 3).[15] Compound **6** was easily hydrolyzed with hydrochloric acid to give unprotected α-aminoalkyl-α′-chloromethylketone **7**[16] in 64% isolated yield without racemization.[17] This is contributed by the weak basicity of the chloromethyl-lithium which is



3 **4**

Moc; Methoxycarbonyloxy group

Scheme 2.

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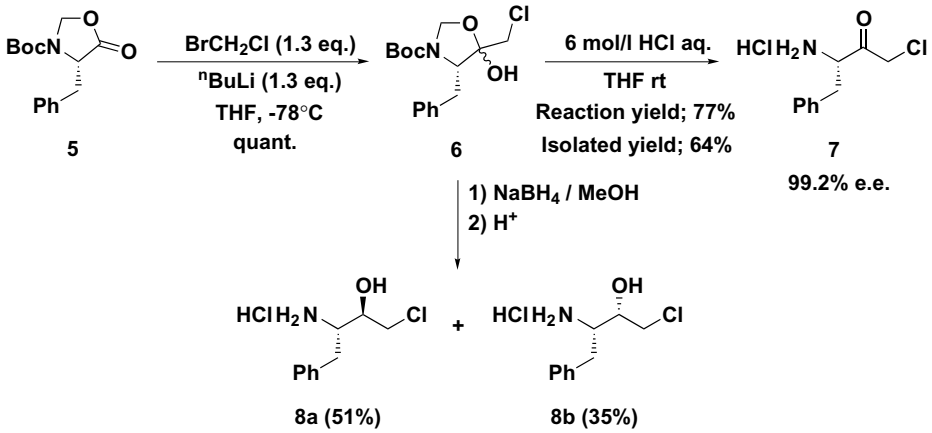
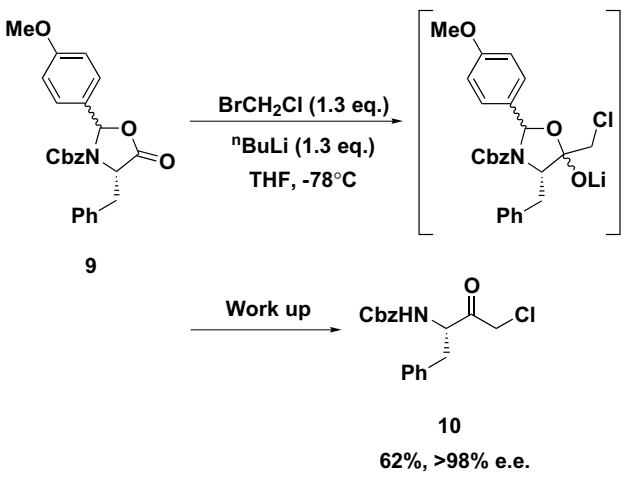


Scheme 3.

immediately generated in situ from $BrCH_2Cl$ and *n*-BuLi. $NaBH_4$ reduction of **6** and successive deprotection was also tested and gave chlorohydrin **8**[18] in good yield (86%), but with no significant diastereoselectivity.[19]

In the example above, both the *N*,*O*-acetal and Boc groups were simultaneously deprotected by acid treatment to give unprotected α-aminoalkyl-α′-chloromethylketone. To obtain *N*-protected α-aminoalkyl-α′-chloromethylketone, chloromethylation of *N*-Cbz-protected 3-oxazolidin-5-one **9**, which can be prepared by reacting the sodium salt of L-Phe and *p*-anisaldehyde followed by Cbz-protection,[20] was examined (Scheme 4). The reaction proceeded nicely to give the desired *N*-protected α-aminoalkyl-α′-chloromethylketone **10**[15] directly in 62% yield without the need for deprotection.[21]

In conclusion, practical syntheses of α-aminoalkyl-α′-chloromethylketone derivatives using the chloromethylation of *N*-protected 3-oxazolidin-5-one were achieved. This methodology is particularly useful for the synthesis of *N*-Cbz-protected α-aminoalkyl-α′-chloromethylketone since it can be prepared efficiently from amino acid in only three steps.



Scheme 4.

Acknowledgements

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15. A solution of 3-oxazolidin-5-one **5** 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 1 h at −78°C, 10%

$KHSO_4$ aq. was added. The product was extracted and purified by silica gel chromatography to give **6** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 3.02 (dd, J=10.1, 13.2 Hz, 1H), 3.24–3.34 (m, 3H), 3.80 (d, J=11.5 Hz, 1H), 3.93 (dd, J=4.5, 10.0 Hz, 1H), 4.87 (d, J=4.7 Hz, 1H), 5.17 (bs, 1H), 7.18–7.33 (m, 5H); FAB MASS m/z 328 (MH^+).

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17. A solution of 5-chloromethyl-5-hydroxy-3-oxazolidine **6** in THF was treated with an excess of 6 mol/l HCl at 50°C for 1 h. After concentration, the resultant slurry was washed with MeOH–MTBE to give **7** as a white solid. 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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21. A solution of the 3-oxazolidin-5-one **9** 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, 5% $KHSO_4$ aq. was added. The product was extracted and purified by silica gel chromatography to give **10** as a white solid. Enantiomer purity was determined by HPLC using a Chiralcel OD-H column. ^{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^+).