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Dihalomethylation of *N*-protected phenylalanine esters

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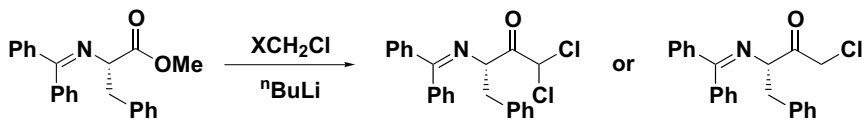
Abstract—Dihalomethylation of several *N*-protected amino acid esters gave *N*-protected α-aminoalkyl-α′-dihalomethylketones, which are useful intermediates for the synthesis of *erythro* β-amino-α-hydroxycarboxylic acids, in good yield. The dihalomethylketones were successfully converted to *N*-protected α-aminoalkyl-α′-halomethylketones by selective catalytic hydrogenation.

We previously described practical methods for the synthesis of α-aminoalkyl-α′-chloromethylketone derivatives via the chloromethylation of *N*-protected 3-oxazolidin-5-ones or *N*-imine-protected amino acid esters.[1,2] Based on our results, we concluded that during the chloromethylation, the amino group should be protected by an appropriate *N*-protecting group without leaving a hydrogen atom unprotected. As an extension of the study, we turned our attention to the reaction of *N*-protected amino acid esters with dihalomethyllithium, which can be conveniently generated in situ from dihalomethane and base.[3,4] In this paper, we report the dihalomethylation of several kinds of *N*-protected amino acid esters and its application to the synthesis of *N*-protected α-aminoalkyl-α′-halomethylketones.

First, the reaction of dichloromethyllithium[5] and *N*-diphenylmethylene-protected amino acid ester **1**,[6,7] which has been used in studies of chloromethylation, was investigated.[8,9] Due to the slower generation of dichloromethyllithium compared to that of chloromethyllithium, the addition of *n*-butyllithium in hexane to a solution of ester **1** and CH_2Cl_2 in THF did not give the desired dichloromethylketone (procedure B, Table 1). However, since dichloromethyllithium is relatively stable[10] and can be kept in ethereal solution at −78°C,[8] the addition of ester **1** to a solution of

Table 1. Comparison between dihalomethylation and chloromethylation of compound **1**



1 **2 (X=Cl)** **3 (X=Br)**

XCH_2Cl	*n*-BuLi	Procedure	Conditions	Yield (%)	
				2	**3**
CH_2Cl_2 (2.5 equiv.)	2 equiv.	A	THF–Et_2O, −78°C	96	–
CH_2Cl_2 (2.5 equiv.)	2 equiv.	B	THF–Et_2O, −78°C	Trace	–
$BrCH_2Cl$ (1.3 equiv.)	1.3 equiv.	A	THF, −78°C	–	0
$BrCH_2Cl$ (1.3 equiv.)	1.3 equiv.	B	THF, −78°C	–	Quant.

Procedure A: Ester **1** was added to a solution of dichloromethyllithium (or chloromethyllithium).
Procedure B: *n*-Butyllithium was added to a solution of ester **1** and dichloromethane (or bromochloromethane).

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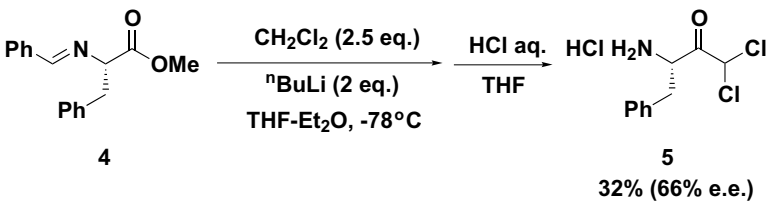
dichloromethyllithium in Et_2O–THF successfully gave the desired dichloromethylketone **2** in high yield[11] (procedure A) and with high optical purity (98% e.e. after hydrolysis).[12] This result is in contrast to the case of chloromethylation, since chloromethyllithium is quite unstable and could not be stored even at −78°C.[10]

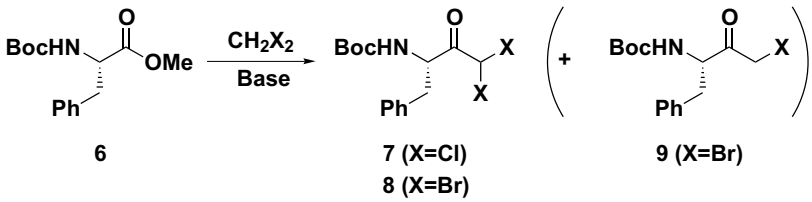
In an attempt to obtain various *N*-protected α-aminoalkyl-α′-dichloromethylketones, the dichloromethylation of *N*-benzylidene-protected amino acid ester **4**[13] followed by hydrolysis with hydrochloric acid was also examined and gave unprotected α-aminoalkyl-α′-dichloromethylketone **5** as a HCl salt in 32% yield with modest optical purity (66% e.e.) (Scheme 1).[14] The instability of compound **5** under acidic conditions may decrease the yield. Partial racemization is probably due to the abstraction of the α-proton by dichloromethyllithium, which is more basic than chloromethyllithium.

As mentioned above, compound **5** is not a stable enough intermediate for preparation of several kinds of *N*-protected α-aminoalkyl-α′-dichloromethylketones. This prompted us to examine direct dihalomethylation of *N*-carbamate-protected amino acid esters, which are not suitable substrates for the chloromethylation.[1] The results are summarized in Table 2. Using the same procedure as above, the addition of *N*-Boc-protected amino acid ester **6** to an Et_2O–THF solution of dichloromethyllithium, which was generated in situ from CH_2Cl_2 and *n*-BuLi, directly gave *N*-carbamate-protected α-aminoalkyl-α′-dichloromethylketone **7** in 54% yield without racemization (procedure A). Abstraction of the proton of NH in the carbamate contributes to the full retention of stereochemistry. The yield was nicely increased to 67% when LDA was used as a base.[15] Interestingly, in the case of *N*-carbamate-protected amino acid esters, the addition of base (*n*-BuLi or LDA) to a solution of ester and CH_2Cl_2 also gave the desired product (procedure B). Using procedure B, dichloromethylation could be performed at −20°C, which is a much higher temperature.[16] Furthermore, we examined the dibromomethylation of ester **6**. The addition of ester **6** to a THF solution of dibromomethyllithium,[17] generated in situ from CH_2Br_2 and LDA, gave the desired dibromomethylketone **8** in 46% yield.[18] Compound **8** could also be obtained using procedure B. In the case of dibromomethylation, accompanying formation of bromomethylketone **9**[19] was observed. Impurity **9** would be given by lithium–bromine exchange after the addition of dibromomethyllithium to **6**.[20,21] The



Scheme 1.

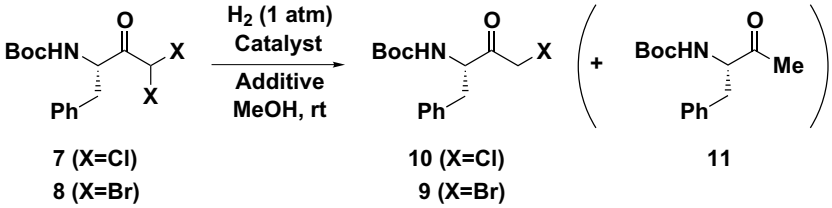
Table 2. Dihalomethylation of compound **6**



CH_2X_2	Base	Procedure	Temp. (°C)	Reaction yield (%)				Isolated yield (%)
				7	**8**	**9**	**6**	
CH_2Cl_2 (4 equiv.)	*n*-BuLi (4 equiv.)	A	−78	60	–	–	1	54
CH_2Cl_2 (2.3 equiv.)	LDA (2.3 equiv.)	A	−78	79	–	–	10	67
CH_2Cl_2 (4 equiv.)	*n*-BuLi (4 equiv.)	B	−78	62	–	–	3	52
CH_2Cl_2 (2.5 equiv.)	LDA (2.5 equiv.)	B	−20	58	–	–	24	46
CH_2Br_2 (2.5 equiv.)	LDA (2.5 equiv.)	A	−78	–	53	8	27	46
CH_2Br_2 (2.5 equiv.)	LDA (2.5 equiv.)	B	−78	–	55	12	33	31

Procedure A: Ester **6** was added to a solution of dihalomethyllithium.
Procedure B: The base was added to a solution of ester **6** and dihalomethane.

Table 3. Selective catalytic hydrogenation of dihalomethylketone



7 (X=Cl)
8 (X=Br)

10 (X=Cl)
9 (X=Br)

11

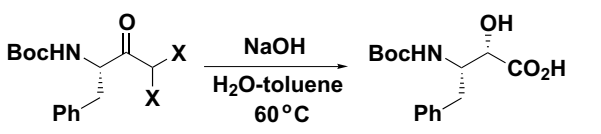
X	Catalyst	Additive	Time (h)	Yield (%)	
				Product	**11**
Cl	10% Pd/C	Nothing	1	66	4
Cl	10% Pd/C	Nothing	17	Trace	0
Cl	5% $Pd/BaSO_4$	Et_3N	3	64	6
Br	10% Pd/C	Nothing	2	40	50
Br	5% $Pd/BaSO_4$	Et_3N	2.5	71	6

Yield was determined by HPLC.

obtained dihalomethylketones **7** and **8** could be converted to *erythro* β-amino-α-hydroxycarboxylic acids by stereoselective hydrolysis, which was recently reported by the Kaneka group (Scheme 2).[22,23]

Next, to obtain *N*-protected α-aminoalkyl-α′-halomethylketones from dihalomethylketones, the selective catalytic hydrogenation of *N*-protected α-aminoalkyl-α′-dihalomethylketones was studied (Table 3). Hydrogenation of dichloromethylketone **7** using 10% Pd/C as a catalyst gave chloromethylketone **10**[2] in 66% yield. However, prolonging the reaction time caused cleavage of Boc group due to the generation of HCl. Hydrogenation of dibromomethylketone **8** only gave a mixture of bromomethylketone **9**[19] and methylketone **11**.[24] To our delight, the selective hydrogenation of compounds **7** and **8** proceeded nicely using 5% $Pd/BaSO_4$ (Lindlar catalyst) in the presence of triethylamine, which is essential for acceleration of the reaction. Under these conditions, chloromethylketone **10** and bromomethylketone **9** were obtained in respective yields of 64 and 71% with good selectivity.[25]

In conclusion, the dihalomethylation of several *N*-protected amino acid esters was investigated. In contrast to chloromethylation, direct dihalomethylation of *N*-carbamate-protected amino acid esters afforded *N*-carbamate-protected α-aminoalkyl-α′-dihalomethylketones, which are useful intermediates for the synthesis of *erythro* β-amino-α-hydroxycarboxylic acids, in good yield. The resultant dihalomethylketones could be converted to halomethylketones via selective catalytic hydrogenation using Lindlar catalyst in the presence of triethylamine.



7 (X=Cl)
8 (X=Br)

83% (68% d.e.) (X=Cl)
84% (60% d.e.) (X=Br)

Scheme 2.

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11. A solution of dichloromethane (2.5 equiv.) in anhydrous THF was added to a solution of *n*-butyllithium (2 equiv.) in hexane–Et_2O–THF at −78°C. After stirring for 10 min at −78°C, a solution of ester **1** was added dropwise. After stirring for 2 h at −78°C, saturated NH_4Cl aqueous solution was added. The product was extracted to give **2** as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 3.12 (dd, $J=4.6$, 13.2 Hz, 1H), 3.20 (dd, $J=8.4$, 13.2 Hz, 1H), 4.56 (dd, $J=4.6$, 8.4 Hz, 1H), 6.52 (d, $J=9.9$ Hz, 2H), 6.53 (s, 1H), 6.96–7.05 (m, 2H), 7.15–7.47 (m, 9H), 7.61 (d, $J=9.1$ Hz, 2H).
12. A solution of dichloromethylketone **2** in THF was treated with an excess of 2 mol/l HCl at rt for 1.5 h. Enantiomer purity was determined as 98% e.e. by HPLC using a Crownpak CR(+) column.

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14. A solution of dichloromethane (2.5 equiv.) in anhydrous THF was added to a solution of *n*-butyllithium in hexane–Et_2O–THF at −78°C. After stirring for 10 min at −78°C, a solution of ester **4** was added dropwise. After stirring for 2 h at −78°C, an excess of 2 mol/l HCl aq. was added. Yield was determined by HPLC using an Inertsil ODS-2 column. Enantiomer purity was determined by HPLC using a Crownpak CR(+) column.
15. A solution of dichloromethane (2.3 equiv.) in anhydrous THF was added to a solution of lithium diisopropylamide (2.3 equiv.) in heptane–ethylbenzene–THF at −78°C. After stirring for 10 min at −78°C, a solution of ester **6** was added dropwise (procedure A). After stirring for 1 h at −78°C, 1 mol/l HCl was added. The product was extracted and purified by crystallization from ethyl acetate to give **7** 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 Chiralcel OD-H column. $[\alpha]_D^{20}=-52.7°$ (*c* 2.25, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 3.01 (dd, $J=7.9$, 13.8 Hz, 1H), 3.22 (dd, $J=5.7$, 13.8 Hz, 1H), 4.62–5.00 (m, 2H), 6.08 (s, 1H), 7.17–7.22 (m, 2H), 7.22–7.36 (m, 3H).
16. A solution of ester **6** and dichloromethane (2.5 equiv.) in anhydrous THF was cooled to −20°C, and lithium diisopropylamide (2.5 equiv.) in heptane–ethylbenzene–THF was added dropwise (procedure B). After stirring for 1 h at −20°C, 2 mol/l HCl was added.
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18. A solution of dibromomethane (2.3 equiv.) in anhydrous THF was added to a solution of lithium diisopropylamide (2.5 equiv.) in heptane–ethylbenzene–THF at −78°C. After stirring for 10 min at −78°C, a solution of ester **6** was added dropwise. After stirring for 1 h at −78°C, 1 mol/l HCl was added. The product was extracted and purified by crystallization from ethyl acetate to give **8** as a white solid. The reaction yield was determined by HPLC using an Inertsil ODS-2 column. $[\alpha]_D^{20}=-40.6°$ (*c* 2.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.41 (s, 9H), 3.04 (dd, $J=7.3$, 13.8 Hz, 1H), 3.20 (dd, $J=6.2$, 13.8 Hz, 1H), 4.64–5.05 (m, 2H), 6.00 (s, 1H), 7.17–7.37 (m, 5H).
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25. A catalytic amount of 5% $Pd/BaSO_4$ was added to a mixture of dihalomethylketone **7** (or **8**) and triethylamine. After stirring for 3 h under a H_2 atmosphere, insoluble material was filtered off. The reaction yield was determined by HPLC using an Inertsil ODS-2 column.