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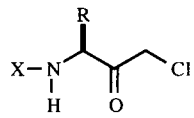
A Practical Method for the Preparation of α'-Chloroketones of N-Carbamate Protected-α-Aminoacids

Ping Chen†, Peter T. W. Cheng†, Steven H. Spergel†, Robert Zahler†,
Xuebao Wang‡, John Thottathil‡, Joel C. Barrish†*, and Richard P. Polniaszek‡*
Bristol-Myers Squibb Pharmaceutical Research Institute
†Discovery Chemistry
Princeton, New Jersey 08543-4000
‡Chemical Process Research
New Brunswick, New Jersey 08903-0191

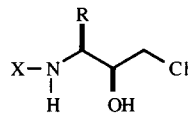
Abstract: *A practical method for the preparation of α-N-BOC-epoxides from protected amino acid esters based on the Kowalski homologation reaction is described. This procedure can be readily performed on a large scale without the use of hazardous reagents and has allowed preparation of epoxides 3 in multi-kilogram quantities.* © 1997 Elsevier Science Ltd.

α-N-acyl-α'-chloroketones **1** serve as irreversible enzyme inhibitors[1] and as precursors to the hydroxyethylamine isostere subunits present in many inhibitors of angiotensin converting enzyme,[2] renin,[3] and HIV-protease.[4] The α'-chloroketones **1** are typically converted to chlorohydrins **2**[5] and epoxides **3**[6] which are combined with a nucleophilic component in the preparation of the various enzyme inhibitors.



1

X = Boc, Cbz



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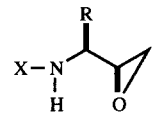
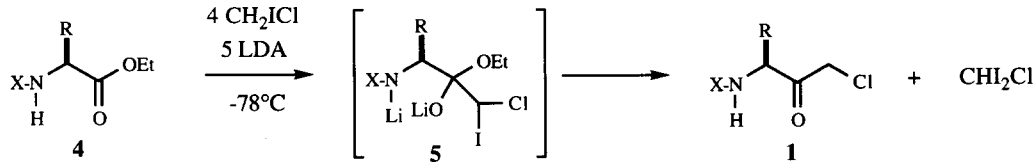


3

The classical means of preparing α-chloroketones **1** involves conversion of an N-acyl-α-amino acid to an α-diazoketone and subsequent acidolysis with HX.[7] Utilization of large quantities of diazomethane necessary for the production of **1** in bulk was prohibitive for practicality and safety reasons. In 1985[8] Kowalski described a homologation of esters to α-bromoketones with the reagent system CH_2Br_2/LDA/n-BuLi. When this reagent system was tested on BOC-Phe-OEt, a mixture of α-bromoketone, dibromoketone and starting ester was obtained. Optimization of the reaction defined the conditions shown below.



4

X = Boc, Cbz

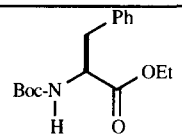
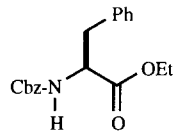
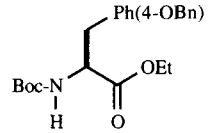
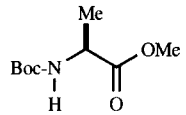
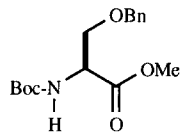
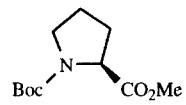
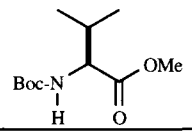
5

1

The optimum dihalomethane proved to be iodochloromethane and in this case, the n-BuLi was best replaced by

excess LDA/CH_2ICl. One equivalent of LDA was necessary to deprotonate the carbamate N-H and a total of four equivalents of CH_2ICl/LDA were necessary to carry out the addition/metalation/elimination *via* intermediate **5** and drive the reaction to completion. Deprotonation of the carbamate N-H protected the chiral center from enolization and hence, racemization.[9] Use of CH_2I_2 resulted in lower isolated yields of the iodoketone and significant amounts of a reduction product, the corresponding methyl ketone. A variety of substrates (Table) gave similar chromatographed yields of the chloroketone products. The exception was Boc-valine (**4g**) where it appears that steric hindrance prevented facile addition of the unstable chloroiodomethane lithium anion, resulting in substantial recovery of starting material.[10]

Table

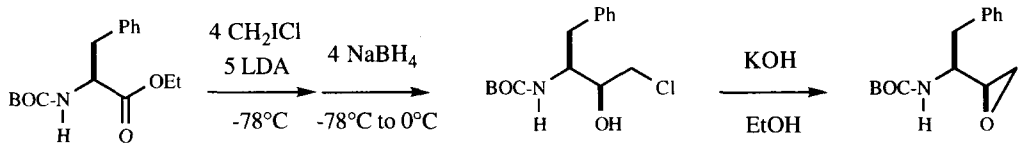
	Ester 4	1 (% Yield)[a]
4a		86
4b		77
4c		82
4d		81
4e		83
4f		79
4g		50[b]

[a] Chromatographed yield from reaction on 1 mmol scale.

[b] Recovered 37% **4g**

A drawback associated with the above method is the stoichiometric production of a high boiling, toxic byproduct CHI_2Cl, which made isolation problematical on scale-up. Since our ultimate goal was to prepare **3**, a

telescoped procedure was developed wherein the quenched chloroketone reaction mixture was reduced *in situ* with excess $NaBH_4$. The reduction step removed the CHI_2Cl and the resultant chlorohydrins were then isolated by simple precipitation. The diastereoselection[11] of the reduction was typically ~4:1, and in the case of **2a**, a single crystallization afforded the chlorohydrin with a diastereoselectivity of ~98:2 and 99% ee[11] on a 175 g scale of the starting ester. Cyclization[6] of the chlorohydrin afforded epoxide **3a** in 39% overall yield, 99.4% de, and 99.9% ee from the starting N-BOC ethyl ester **4a**.



4a **2a** **3a**

In conclusion, a practical procedure amenable to large scale has been developed for the preparation of α-N-acyl-α'-chloroketones, and their corresponding chlorohydrins and epoxides, from naturally occurring α-amino acids.[12] The method provides access to the erythro relative stereochemical series (**2a**, **3a**) present in several HIV protease inhibitors and overcomes practical limitations inherent in other published methods, i.e. avoids the use of diazomethane[1] and methyllithium[12] reagents which are not feasible for large scale processes due to safety issues. Epoxides **3a** and **3c** were prepared in multi-kilogram quantities by this approach.[13]

Representative procedures for the small scale preparation of **2c** and the large scale telescoped preparation of **3a** are described below:

a. Kowalski homologation-isolation of Chloroketone

A solution of lithium diisopropylamide, prepared from n-butyllithium in hexane (2 mL; 2.5M, 5 mmol), diisopropylamine (0.77 ml; 5.5 mmol) in THF (8.5 mL), was added dropwise over 30 min to a solution of Boc-*L*-phenylalanine ethyl ester (293 mg; 1 mmol) and chloroiodomethane (0.29 mL; 4 mmol) in THF (5.5 mL) at -78°C. The internal temperature of the reaction mixture was kept below -70°C. during the addition and the reaction mixture was stirred for 10 min at ~-75 °C. A solution of acetic acid (1.5 mL) in THF (10 mL) was added dropwise over 10 min, keeping the internal temperature below -65°C. After stirring an additional 10 min at -75°C., the reaction mixture was partitioned between ethyl acetate (75 mL) and brine (75 mL). The organic layer was washed with saturated $NaHCO_3$ solution (2 x 50 mL), 5% $NaHSO_3$ solution (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated affording a dark yellow solid. The residue was chromatographed on 2.5 x 12 cm silica gel using 7% ethyl acetate/hexane affording 256 mg, 86% of chloroketone **1a** as an off-white solid: ee 98%, $[\alpha]_D$= +20.0 (c 1.04, $CHCl_3$), mp 92-96 °C.

b. Homologation-*in situ* Reduction-conversion to Epoxide

A solution of N-BOC-Phe-OEt, **4a** (175.8 g, 0.6 mol) and iodochloromethane (180 mL, 4 equiv) in anhydrous THF (1500 mL) was cooled to -78°C and LDA (1333 mL, 5 equiv , 2.25M) was added slowly with gentle stirring at a rate which maintained the internal reaction temperature at or below -75°C. Upon completion of the addition, the solution was stirred at -78°C for an additional 15 min. An acetic acid solution (330 mL of THF and 330 mL of glacial HOAc) was added dropwise at a rate sufficient to keep the internal temperature of the reaction vessel below -68°C (1h). Upon completion of the addition, the mixture was stirred an additional 15 min at -78°C, and the flask slowly allowed to warm. Toluene (1500 mL) was added. When the internal temperature reached -20°C, ice-cold 1% aqueous HCl (1500 mL) was added, the mixture stirred vigorously to dissolve all salts, the layers separated, ice-cold 0.5M $NaHCO_3$ (1500 mL) added to the organics, the mixture stirred

vigorously for 5 min and the lower aqueous layer discarded. Anhydrous ethanol (1500 mL) was added, the flask cooled to -78°C, and ice cold ethanolic $NaBH_4$ [from $NaBH_4$ (60 g) in anhydrous ethanol (2000 mL)] was added dropwise.

The reaction vessel was stirred at -78°C for 12h, warmed to 0°C, stirred for 2h and quenched by addition of a solution of 750 mL saturated $KHSO_4$ + 750 mL of water. The mixture was stirred at 0°C for 30 min, and concentrated *in vacuo*. Water (3000 mL) was added to the solid yellow residue, and the resultant mixture stirred for 30 min. The solid was collected, rinsed with water (1000 mL), hexanes (400 mL, then 600 mL, then 400 mL), and dried overnight by suction filtration affording a yellow solid, 136.1 g (76%), which analyzed by HPLC[11] as a 9:1 mixture of diastereomers.

The solid was taken up in hot ethyl acetate (2700 mL), cooled briefly, charcoal (8.1 g, Norit, Fisher, neutral) was added, the mixture heated briefly and filtered through celite and the celite pad washed with hot ethyl acetate (200 mL, then 50 mL). The ethyl acetate filtrate was concentrated to 1700 mL *in vacuo*, the mixture heated briefly to redissolve the precipitated chlorohydrins and allowed to cool slowly to RT, then at ~5°C for 2 d. The chlorohydrin was collected as brown mossy crystals: 81.7 g, 45.5% , de 98%,[11] ee 99%.[11] The chlorohydrin **2a** was converted to epoxide **3a** with ethanolic KOH[6] and crystallized from hexane: needles, 62.1 g, 39% overall, de 99.4%,[11] ee 99.9+%,[11] mp 121.5-123.5°C, Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.32; H, 8.08; N, 5.16. Spectral data were consistent with published values.[6]

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(10) Attempts to pre-form the anion followed by reaction with **4g** gave only recovered starting material.
(11) Determined by HPLC analyses on C18 reverse phase (de) or chiral (ee) Daicel (or Chiralpak AD for **1a**) stationary phases. The enantiomeric purity of the chloromethylketone **1c** was also determined and found to be 98.4%. We thank Dr. W. Thompson, Mr. J. Venesky, and Ms. B. Beyer of our Analytical Research and Development Department for these analyses.
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