Intramolecular Alkylation of Carboxylic Acids: Application to the Synthesis of Boc-Protected Cyclic Amino Acids

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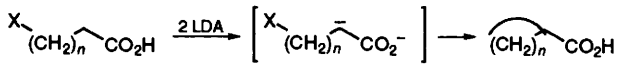
A new synthesis of Boc-protected cyclic amino acids is described as an application of an unreported method of lithium diisopropylamide-induced cyclisation of ω-chloro carboxylic acids containing a protected amine function in the chain.

Previously, we have described a new and easy preparation of Boc-protected (D,L)-amino acids by quenching the trianion of Boc-glycine with a large variety of electrophiles.[1] An intramolecular variant of this reaction, giving access to Boc-protected cyclic amino acids has been found and is discussed here.

The inter- and intra-molecular alkylations of ester enolates are well documented synthetic processes.[2,3] Dianions derived from carboxylic acids easily undergo intermolecular alkylation, an important synthetic reaction that accommodates various functionalities.[4,5] The literature provides no mention of an intramolecular version of this reaction, even for simple cases (Scheme 1). In a preliminary exploration of the feasibility of such reactions, the base-induced cyclisation of several straight chain carboxylic acids was studied with various leaving groups in the ω-position.

Unlike the case of ester analogues, where the leaving groups bromide or tosylate lead to high yields of cyclised products, the ω-chloro substituent gives the best results. The reaction gives access to cycloalkyl carboxylic acids with 3–6 members in the ring, but no cyclisation is observed for $n > 6$ (Table 1).

Application of this cyclisation method to our target molecule, *N*-(ω-chloroalkyl)-Boc-glycine **4**, was expected to give an easy access to cyclic amino acids **5**.[6] The starting material can be readily prepared by reductive amination of glyoxylic acid[7] followed by nitrogen protection in a one-pot procedure (Scheme 2). Treatment of **4** with LDA (2 equiv.) at room temp. results in the rapid formation of the expected cyclic Boc-protected (DL)-amino acids, and four-, five- and six-membered heterocycles are obtained in good yield (Table 2). Two procedures have been routinely used with similar yields: a solution of LDA in THF prepared by the conventional method[8] is added to a THF solution of ω-chloro acid, or the LDA can be formed *in situ* under sonication from metallic lithium, diisopropylamine and isoprene in the presence of the compound to be deprotonated (one-pot sequence).[9]†

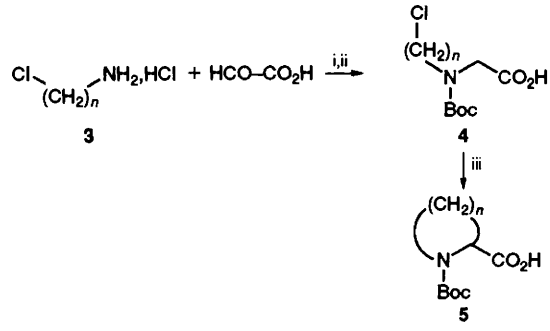


1 **2**

Scheme 1

Table 1 Cyclisation of ω-substituted carboxylic acids

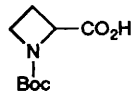
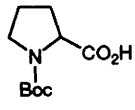
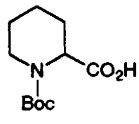
1 *n*	X	Yield of **2** (%)
4	I	3
4	Br	30
4	Cl	57
4	OTs	16
4	OMs	1
2	Cl	45
3	Cl	41
5	Cl	44
6	Cl	0
10	Cl	0

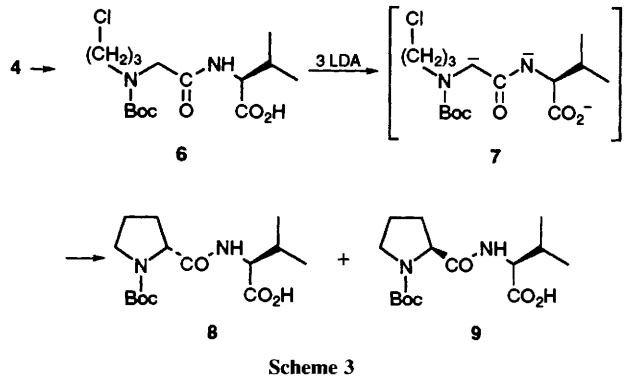


3 **4** **5**

Scheme 2 *Reagents and conditions*: i, $NaBH_3$:CN, MeOH; ii, $NaHCO_3$, Boc_2O; iii, 2 LDA

Table 2 Cyclisation of compounds **4**

Starting material **4**	Product	Yield (%)
$n = 2$		45
$n = 3$		76
$n = 4$		59



6 **7** **8** **9**

Scheme 3

Attempts were made to find an enantioselective version of this new synthesis of cyclic amino acids. Chiral lithium amides[10] gave disappointing results, yielding only racemic products. Another approach was chosen with the introduction of the inductor into the chloroalkyl glycine with a covalent bond. Thus, compound **4** was transformed to the dipeptide **6** with L-valine by known methods.[11] Deprotonation to the trianionic species **7** by sonochemically *in situ* generated LDA proved to be selective,[12] and led to the cyclisation reaction in a satisfactory 61% yield of a 1:8.5 mixture of diastereoisomers **8** and **9**, as measured by VPC analysis of the methyl esters (Scheme 3). By comparison with an authentic sample prepared from L-proline and L-valine, it appears that isomer **9**, in which the proline moiety has the 'natural' configuration, is formed in larger amounts.

This new preparation of *N*-protected cyclic amino acids should lead to further developments in the synthesis of natural or unnatural amino acids. Moreover, the new methodology based on the cyclisation of ω-chloro carboxylic acids should find many applications in other fields of synthetic chemistry.

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Footnote

† *N*-(3-Chloropropyl)-*N*-*tert*-butoxycarbonyl glycine (251.5 mg, 1 mmol), diisopropylamine (222 mg, 2.2 mmol), isoprene (75 mg, 1.1 mmol) (both freshly distilled over calcium hydride), anhydrous THF (5 ml), and lithium (14 mg, 2 mmol) are sonicated (Kerry Ultrasonics cleaning bath, 47 kHz), at 20 °C in a 10 ml round-bottom flask under an argon atmosphere until lithium disappears (15–30 min). The solution is quenched with water and worked up. 163 mg (76%) of Boc (D,L)-proline are isolated.

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12 It was observed in competitive experiments that the Boc-derivative of glycine rapidly forms the trianion, while the alanine analogue does not undergo deprotonation at the chiral centre. See also: D. Seebach, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1624.