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The synthesis of functionalised peptides using α-lithio quinuclidine *N*-oxide (Li-QNO)

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ABSTRACT

Deprotonation of protected peptides using lithiated quinuclidine *N*-oxide (Li-QNO) as a base at 0 °C, followed by addition of an alkyl halide gives C-alkylated peptide derivatives in good yield.

The C-alkylation of α-amino acid derivatives represents an attractive approach to the synthesis of higher amino acids. The use of *N*-acyl or urethane-protecting groups at the amino terminus leads to the requirement for double deprotonation in order for C-alkylation to take place (Scheme 1). Regioselective C-alkylation has been achieved through the use of an additive such as HMPA or TMEDA.[1] The acid terminus is often protected as the methyl ester derivative, although careful consideration as to the choice of base for the reaction is required, as in many cases alkyllithium bases afford substituted ketones such as **5** as the products.[2]

The reaction of methyl *N*-benzoylglycinate **1** with LDA, followed by the addition of BnBr or MeI to afford C-alkylated products **3** and **4** is described as requiring 2 equiv of LDA and HMPA at −78 °C, followed by addition of the alkyl halide at the same temperature.[2] Contrary to an earlier report[3] the use of 1 equiv of LDA results in predominantly N-alkylation. The use of HMPA leads to greater yields of products than the use of TMEDA. The role ascribed to the additives is one of deaggregating the intermediate lithium enolate **2**, (Scheme 1). The monodentate versus bidentate nature of the additives (HMPA and TMEDA, respectively) is thought to be important in controlling the coordination sphere of the metal atom and hence the reactivity of the enolate.

We have recently reported the use of α-lithio quinuclidine *N*-oxide (Li-QNO) **7** as a powerful non-nucleophilic base/HMPA mimetic.[4] It is readily prepared by oxidation of quinuclidine **6** using ozone, followed by deprotonation with *t*-BuLi at −78 °C. The low nucleophilicity of Li-QNO towards carbonyl esters suggested that it may well be a suitable base for the C-alkylation reaction.[4] Ultimately, Li-QNO was envisaged as a replacement for LDA and HMPA in the C-alkylation of amino acid derivatives.

The alkylation of methyl *N*-benzoylglycinate **1** with BnBr was used as a starting point, providing a direct comparison between the use of Li-QNO and the combination of LDA and HMPA. The N-protected compound **1** was added to a suspension of Li-QNO **7** in THF at −78 °C, and 30 minutes were allowed for lithiation to occur. Formation of an immobile yellow suspension was considered indicative of formation of the poorly soluble dianion **2**, subsequent addition of a 1 M solution of BnBr in THF led to increased solubility. After 2 h at −78 °C, the mixture was allowed to reach room temperature and quenched with aqueous NH_4Cl. Flash column chromatography of the organic extracts resulted in isolation of C-alkylated product **3** in 94% yield (Scheme 2).

We then turned to the alkylation of protected dipeptides. The necessary trianion formation often makes such alkylation reactions difficult, the trianion being poorly soluble in THF. Seebach and coworkers[5] have described the solubilisation of such intermediates through the addition of excessive amounts of inorganic salts (usually LiCl). Given the stability of Li-QNO at higher temperatures we were intrigued that if the trianion was warmed to 0 °C, then enhanced solubility may lead to higher yields of products. We were also interested in the possibility that the alkylations may show some stereoselectivity. As a starting point the alkylation of the glycine residue of *N*-benzoyl-Gly-Ala-OMe **8** was selected. The chiral substituent on the neighbouring amino acid (the alanine methyl group in this case) was expected to exert a steric effect making alkylation on one face of the carbanion more favourable than the other. The dipeptide *N*-benzoyl-Gly-Ala-OMe **8** was prepared by the DCC-mediated coupling of *N*-benzoyl glycine with alanine methyl ester hydrochloride. Treatment of dipeptide **8** with 3 equiv of LiQNO, at −78 °C followed by warming of the solution to 0 °C gave a solution of the trianion **11**. The solution was re-cooled to −78 °C, followed by addition of BnBr. Disappointingly, the reaction gave a mixture of three products, the two diasteroisomeric glycine C-alkylated dipeptides **9a/b** in a 1:1 ratio in 35% yield, and the alanine C-alkylated product **10** in 29% yield (Scheme 3).

Following this result we decided to examine the alkylation of *N*-Boc-protected amino acids using Li-QNO as a base. In order to test the viability of this approach, the benzylation of methyl *N*-Boc-glycinate **12** was first investigated. Treatment of **12** with 2 equiv of Li-

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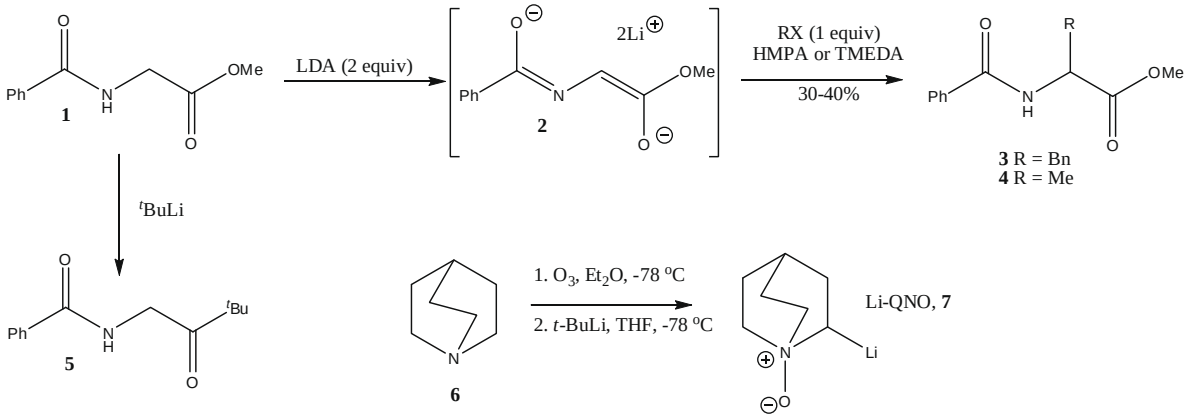
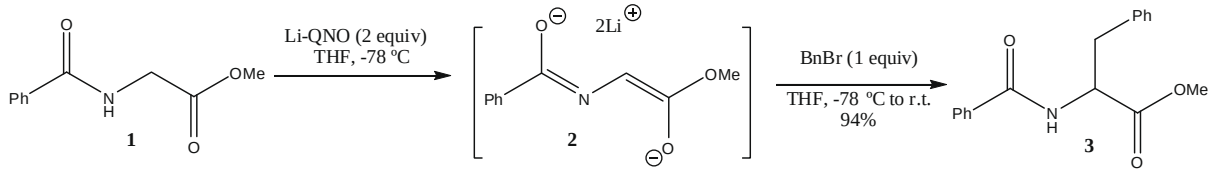
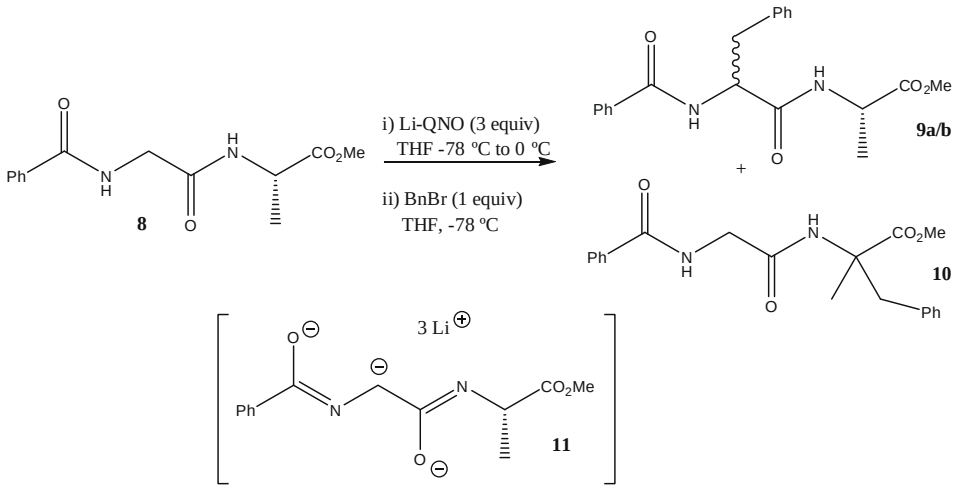


Scheme 1.



Scheme 2.



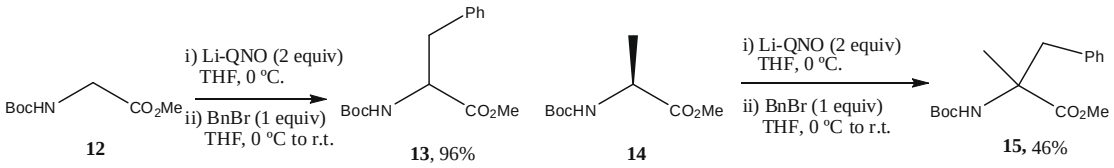
Scheme 3.

QNO at 0 °C followed by addition of BnBr at the same temperature gave an excellent 96% yield of the C-alkylated product **13**. We observed no addition of the Li-QNO into the ester. When *N*-Boc alanine methyl ester **14** was used as the substrate under identical conditions, quenching of the dianion with BnBr gave a 46% yield of the C-alkylated product **15** (Scheme 4). Unreacted starting material **14** was also recovered in 50%. Significantly, these results indicate that it is possible to C-alkylate *N*-Boc derivatives of simple amino acids without using additives such as HMPA or resorting to dianion formation at low temperatures.

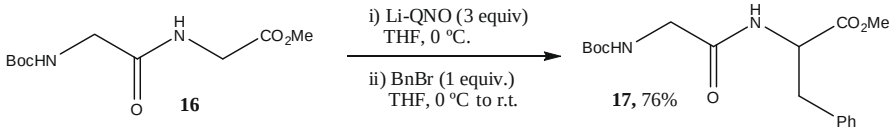
With methodology in place for the C-alkylation of dianionic Boc-protected amino acid derivatives our attention once again turned to the alkylation of dipeptide derivatives. In order to gauge whether selective C-alkylation on the amino acid residue at the *C*-terminus of the dipeptide could be achieved, *N*-Boc-Gly-Gly-OMe **16** was prepared by the DCC-mediated coupling of *N*-Boc glycine and glycine methyl ester hydrochloride.[6] Treatment of the protected dipeptide **16** with 3 equiv of Li-QNO at 0 °C, followed by addition of BnBr, again at 0 °C, gave the C-alkylated dipeptide **17** as a single regioisomer in 76% (Scheme 5).

Benzylation on the glycine residue at the *C*-terminus of the dipeptide was confirmed by ^{1}H NMR. The α-proton(s) of this glycine residue exhibited a significantly higher chemical shift than their counterparts on the residue at the N-terminus in both the starting material **16** and in the product **17**. Several more polar by-products observed by TLC remained unidentified.

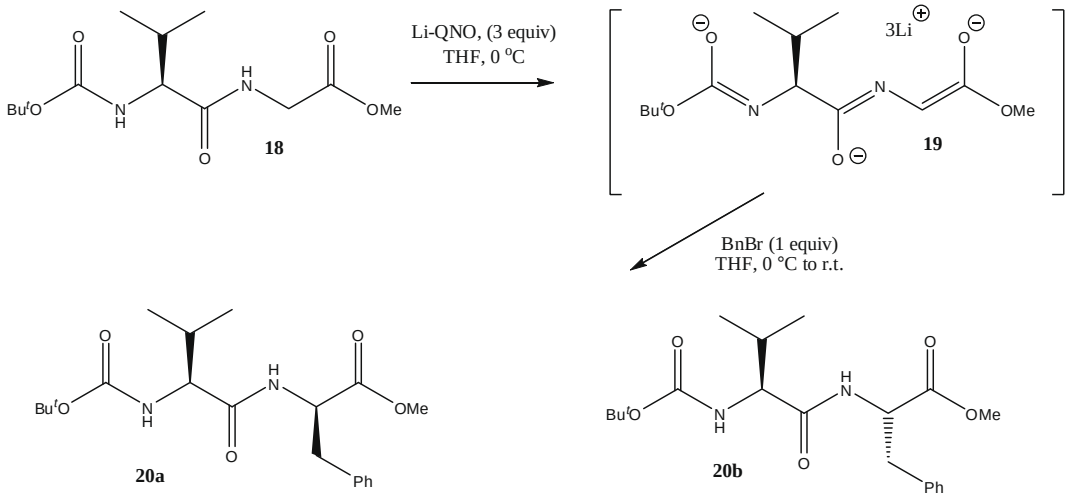
In order to study the stereoselectivity of the alkylation reaction, *N*-Boc-Val-Gly-OMe **18** was prepared. It was hoped that the isopropyl group of the valine residue would exert a large enough steric effect to influence which face of the enolate **19** would undergo alkylation (Scheme 6). The requisite dipeptide **18** was prepared by the DCC-mediated coupling of *N*-Boc valine with glycine methyl ester hydrochloride. Again, treatment of the protected dipeptide **18** with 3 equiv of Li-QNO at 0 °C, followed by addition of BnBr at 0 °C,



Scheme 4.



Scheme 5.



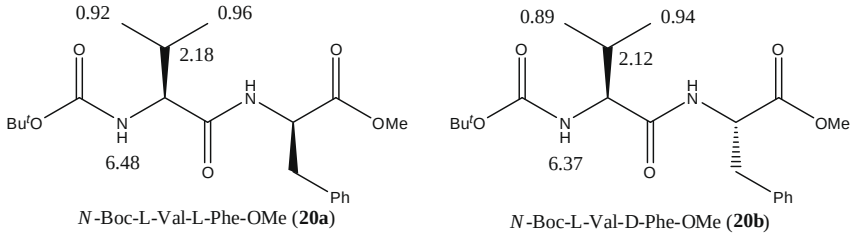
Scheme 6.

gave two diasteroisomeric C-alkylated dipeptides **20a** and **20b**, arising from benzylation at the α-carbon of the glycine residue, in a combined yield of 81%.

^{1}H NMR analysis suggested an uneven distribution of the two diastereoisomers. The methyl groups of the isopropyl side chains, the α-hydrogens and the carbamate protons (all associated with the valine residue), appeared at different chemical shifts corresponding to the two diastereoisomers. Determination of the diastereomeric ratio was possible through comparison of the relative integrations of the doublets due to the diastereotopic methyl groups in the isopropyl side chain of the valine residue. The stereochemical assignment of each diastereoisomer was achieved by comparing the observed data with those reported in the literature for the two diastereoisomers prepared via the coupling of *N*-Boc-L-valine with L-phenylalanine-OMe[7] and D-phenylalanine-OMe,[8] respectively (Fig. 1).

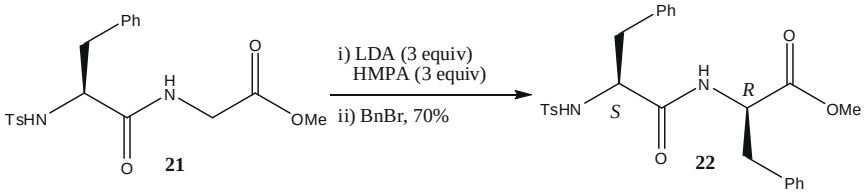
The observed data compared favourably with that reported in the literature. The diastereoisomeric ratio of **20a:20b** was 7:3, and had occurred in favour of the product incorporating unnatural D-phenylalanine.

Diastereoselectivity in such alkylations is not unfounded. Seebach[9] has reported C-alkylation of sarcosine residues affording products with *R*-configuration at the newly formed stereogenic centre. Ager and coworkers[10] have also reported products in which the newly formed stereogenic centre is of the *R*-configuration through the use of HMPA. The systems investigated by Ager appear



N-Boc-L-Val-L-Phe-OMe (**20a**) *N*-Boc-L-Val-D-Phe-OMe (**20b**)

Figure 1. Chemical shifts (δ ppm) measured in $CDCl_3$ (400 MHz).



Scheme 7.

similar to those we have investigated, Scheme 7 illustrates one such case. Benzylation of the trianion of *N*-Ts-L-Phe-Gly-OMe **21** afforded the C-benzylated product **22** in which the *R*-configuration was favoured at the new stereogenic centre, in 57% de.

Interestingly, the largely different approach of Seebach[9] (solubilisation of the anion through addition of Li salts) in comparison to the approach adopted by Ager[10] and ourselves (the use of a Li-coordinating additive) appears to afford products with the same stereochemistry at the new chiral centre. In all cases an adjacent (*S*)-amino acid generates a stereocentre with (*R*)-configuration. The difference is not as great as first appears, both approaches can be described as deaggregating the carbanionic species prior to alkylation.

In summary, Li-QNO can be used to deprotonate simple N-protected amino acid esters and protected dipeptides at 0 °C resulting in the formation of reactive di- and trianions which undergo regioselective reaction with BnBr to give the C-alkylated products in good yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.105.

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