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A Highly Efficient Azide-Based Protecting Group for Amines and Alcohols

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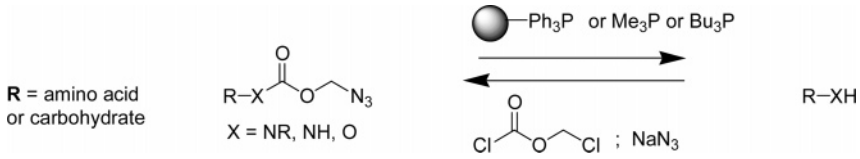
ABSTRACT

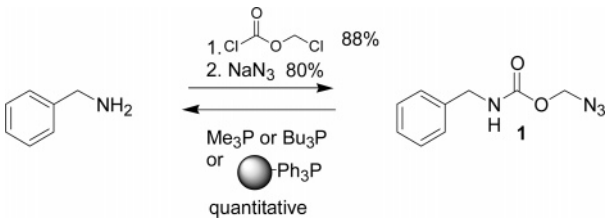


The azide-based carbamate or carbonate protecting group (Azoc) shown above can be removed in less than 2 min under neutral conditions using trimethyl or tributyl phosphine as well as polymer-bound triphenyl phosphine. It was shown to be orthogonal to Fmoc and Mtt for peptide synthesis and to afford β-glycoside with a 2-aminoglucosyl donor by virtue of the neighboring group participation.

The choice of protecting groups remains one of the crucial factors in the successful synthesis and manipulation of complex molecules. In peptide synthesis, the most frequently used strategies for the α-nitrogen are Boc and Fmoc. Carbohydrate syntheses involving 2-amino sugars have required a wider arsenal of protecting groups due to the more stringent demands of glycosylation chemistry; however, phthalamates and Cbz or Troc groups have recurrently been used to direct a β-glycosylation. In both cases, peptide[1] and oligosaccharide[2] synthesis, azides[3] have successfully been used to mask the amino group; however, this strategy has limitations. For instance, it cannot be used to mask secondary nitrogens such as in the case of proline and may lead to diketopiperazine formation in peptide synthesis. In the case of glycosylations, azide is a nonparticipating group in the reaction and thus leads predominantly to α-glycosylation.

On the basis of the success of carbamate-type protecting groups (Boc, Fmoc, Alloc, Troc, etc.), we reasoned that an azidomethyl carbamate (Azoc) may provide rapid deprotection under azide-reduction conditions while preserving the advantages of carbamate protecting groups. As shown in Scheme 1, such Azoc-protected compounds are readily prepared using commercially available chloromethyl chloroformate to obtain the chloromethyl carbamate followed by an azide displacement of the chloride.[4] The first reaction is carried out in dichloromethane (the use of DMF leads to the formation of the Vilsmeier−Haack reagent) affording a product which is stable to workup and purification. The azide

Scheme 1. Azoc Protection and Deprotection



(1) Zaloom, J.; Calandra, M.; Roberts, D. C. *J. Org. Chem.* **1985**, *50*, 2601−2603. Tornoe, C. W.; Davis, P.; Porreca, F.; Meldal, M. *J. Pept. Sci.* **2000**, 6, 594−602. Lundquist, J. T. I. V.; Pelletier, J. C. *Org. Lett.* **2001**, *3*, 781−783.

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(3) For a general review, see: Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188−5240.

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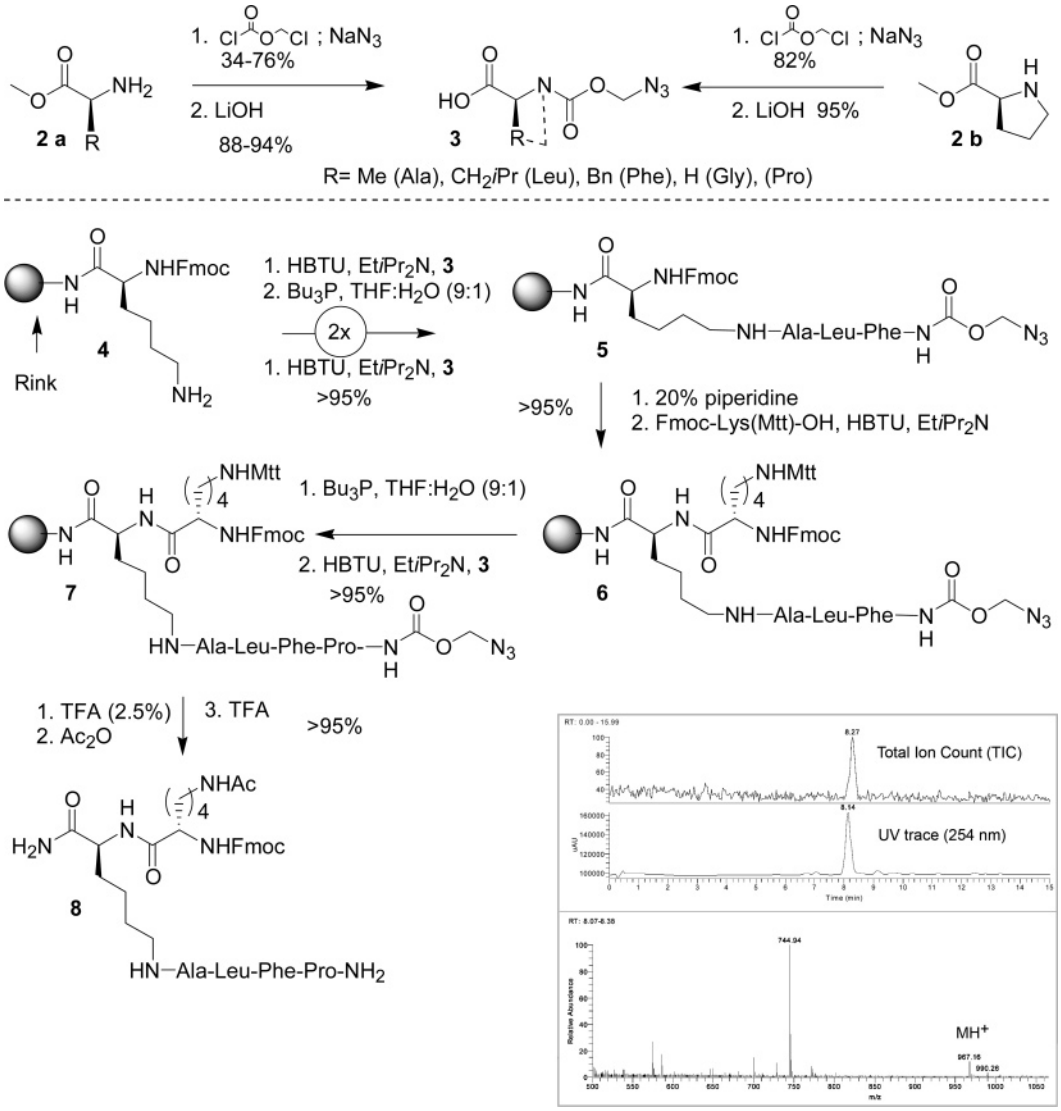
Scheme 2. Peptide Synthesis Using Azoc (Inset: LC-MS of Compound **8**)



substitution can be carried out on the purified or crude material obtained in the first steps in a variety of solvents including DMF, DMSO, or different mixtures with H_2O including MeCN−H_2O. This two-step process affords the desired azidomethyl carbamate **1** in 70% isolated yield. To our gratification, it was found that the deprotection of this compound was complete within 2 min using Me_3P or Bu_3P and quantitative in both cases as judged by LC-MS and NMR. The use of polymer-bound triphenyl phosphine was equally efficient albeit slower (30 min). The deprotection presumably proceeds through the formation of the imino-phosphorane which rapidly decomposes to afford the phosphine oxide, CO_2, and methyleneamine. The methyleneamine furthur decomposes or polymerizes to uncharacterized material. Although this protecting group is conceptually related to the previously reported 4-azidobenzyloxy-carbonyl group,[5] the deprotection of this latter group was found to be sluggish in our hands using Me_3P and required acid or base to catalyze the elimination of the 4-aminobenzyloxycarbonyl moiety.

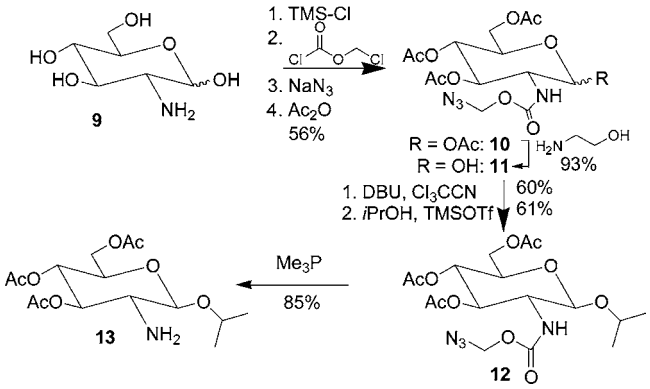
We then turned our attention to the utility of this protecting group for peptide synthesis. As shown in Scheme 2, Azoc-protected amino acids **3** were obtained from primary amino methyl esters **2a** or secondary amino methyl ester **2b** using the same general procedure as those for benzyl amine. Thus reaction with the chloromethyl chloroformate in CH_2Cl_2 for 15 min at −20 °C followed by azide displacement in MeCN−H_2O (1:1) for 8−36 h at 23 °C afforded the product in moderate to good yield (76% for Ala, 64% for Gly, 34% for Leu, 65% for Phe, and 82% for Pro). Hydrolysis of the methyl ester using LiOH in MeOH−H_2O (1:1) afforded the Azoc-protected amino acids **3** in good yields (88−95%) without detectable isomerization (see Supporting Information). It should be noted that prolonged exposure (>30 min) of **3** to LiOH led to partial Azoc hydrolysis. With these five amino acids at hand, we investigated the orthogonality of Azoc with Fmoc and Mtt. To this end, we prepared a

(5) Griffin, R. J.; Evers, E.; Davison, R.; Gibson, A. E.; Layton, D.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1205−1211.

branched hexapeptide which would require such compatibilities. Thus resin **4** was substituted on the ϵ-nitrogen of lysine with Azoc-protected Ala, and the Azoc group was removed in the presence of Fmoc. Deprotection of the Azoc using Bu_3P (1 M) in 9:1 THF−H_2O for 5 min resulted in quantitative conversion, and two more coupling cycles were used to introduce Azoc-protected Leu and Phe thus affording resin **5**. Next, the Fmoc group was removed (20% piperidine in DMF) in the presence of Azoc and HO−Lys(Mtt)−Fmoc was introduced affording resin **6**. A further cycle of Azoc deprotection and coupling yielded resin **7** from which the Mtt group was removed (2.5% TFA for 5 min), and the resulting amine was acylated with acetic anhydride. Cleavage of the final product from the resin with concomitant Azoc deprotection afforded hexapeptide **8** free of a truncated sequence or scramble sequences stemming from incompatible protecting groups as judged by LC-MS and MALDI analysis of the crude cleavage product.

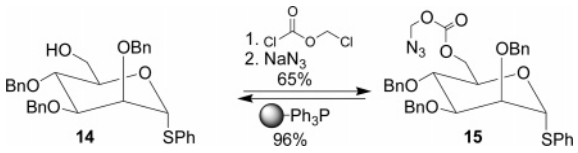
We then turned our attention to the use of Azoc for carbohydrate synthesis. As shown in Scheme 3, 2-amino

Scheme 3. Azoc Protection and Deprotection of Amino Glucose



glucose was persilylated and the amino group was protected with Azoc to obtain, after workup, the Azoc-protected aminoglucose tetrol. Peracetylation of this crude product afforded compound **10** in 56% yield for four steps as a mixture of anomers. Selective anomeric deprotection using ethanolamine gave the suitably protected lactol **11**. Activation of the anomeric position via formation of the trichloroacetimidate[6] followed by glycosylation (TMSOTf for 20 min at 23 °C) with isopropanol as a model glycosyl acceptor afforded the product **12** in 61% yield as the β-anomer exclusively. Treatment of this compound with trimethyl phosphine afforded compound **13** cleanly without any acetyl migration. To explore the suitability of the Azoc protecting group for alcohol protection, benzyl-protected thiomanoside **14** (Scheme 4) bearing a free hydroxyl group at the C6

Scheme 4. Azoc Protection and Deprotection of Glycoside **14**



position was protected with Azoc using the same general procedure as that for amines to obtain **15** in 65% yield. As for the carbamates previously investigated, this product was found to be cleanly deprotected with either Me_3P and Bu_3P in less than 2 min or polymer-bound Ph_3P in 5 min thus affording **14** in excellent yield.

In conclusion, the Azoc group adds to the repertoire of protecting groups for the nitrogen and hydroxyl groups offering very fast and mild deprotection conditions using phosphines, with the benefits of carbamate-based protecting groups. The rapidity and efficiency of deprotection rival those of Fmoc and Boc.

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Supporting Information Available: Experimental details and analytical data for compounds **1**, **3**, **8**, **10**, **12**, **13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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