Mild and Efficient Synthesis of Fmoc-Protected Amino Azides from Fmoc-Protected Amino Alcohols

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Abstract: Fmoc-protected amino azides – key intermediates for monomers of oligomeric urea and guanidine – can be efficiently prepared from the corresponding amino alcohol through iodination followed by substitution with sodium azide. This synthetic route avoids the preparation, storage, and handling of the highly toxic azidic acid that is used in an alternative method.

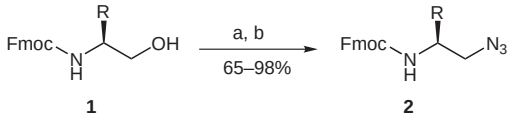
Key words: amino azides, amino alcohols, iodine

Unnatural biooligomers – peptido- or nucleotidomimetics that are built on alternative backbones – have attracted increasing attention in recent years as platforms for designing novel foldamers or biological effectors.[1–6] Among these unnatural oligomers are oligomeric ureas[7–11] and guanidines[12–20] that use monomers containing a diamine function. For peptidomimetics, these monomers should ideally be derived from α-amino acids so that mimicking of the common peptide side chains is achievable. Therefore, in solid-phase synthetic routes that utilize azide as the mask of amine,[8,10,19,20] Fmoc-protected amino azides derived from Fmoc-protected amino acids are key intermediates for the monomer synthesis.

Currently, synthesis of Fmoc-protected amino azides is commonly carried out with Fmoc-protected amino alcohols and azidic acid under Mitsunobu conditions.[10,21,22] Although this transformation is a one-step procedure, in practice, a separate step for the preparation of azidic acid[23] is required. Thus, one disadvantage of the current protocol involves the preparation, storage and handling of the highly toxic azidic acid in benzene. In addition, the reaction requires extremely dry conditions to proceed well. Here, we report an alternative synthetic strategy for the conversion of Fmoc-protected amino alcohols to the corresponding azides through an easy-to-perform, mild, and efficient two-step protocol.

General methods for the synthesis of an azide from an alcohol are mesylation or tosylation of alcohol using methanesulfonyl chloride or tosyl chloride, respectively (MsCl or TsCl, Et_3N, dry CH_2Cl_2 or THF), followed by displacement with azide (NaN_3, DMF). These systems work well with Teoc- [2-(trimethylsilyl)ethoxycarbonyl],[8] Boc-,[8] or Cbz-protected[21] amino alcohols, but not with Fmoc-protected amino alcohols because the Fmoc group is not stable in the presence of sodium azide during heating. Keeping in mind the displacement reaction with NaN_3, we sought to introduce a better leaving group instead of the mesyl and tosyl groups so that the final substitution with azide can be carried out under mild conditions to avoid the loss of the Fmoc group.

An iodine group can be an excellent candidate for this regard, not only because it can act as a good leaving group, but also because it can be easily synthesized from Fmoc-protected amino alcohols. For the formation of iodide from alcohol, we followed a very mild and efficient procedure that uses PPh_3, imidazole and iodine, which was originally developed for the iodination of carbohydrates[24] and shown to work both in solution and on solid support.[25,26] In particular, the solid-phase procedure reported by Benito and co-workers showed that the iodination reaction was compatible to amino acid side chains.[25] Although the solid-phase protocol by Benito et al. uses 10–15 equivalents of reagents to drive the reaction to completion, our solution-phase procedure suggests that the use of 3–5 equivalents of reagents can lead to excellent results. The overall conversion of amino alcohols to amino azides is shown in Scheme 1 and the yields are listed in Table 1.



1 **2**

R = amino acid side chains

Scheme 1 Synthesis of Fmoc-protected amino azides **2a**–**k**. *Reagents and conditions*: (a) PPh_3 (3 equiv), iodine (3 equiv), imidazole (5 equiv), CH_2Cl_2, r.t., 1.5–2 h; (b) NaN_3 (5 equiv), DMF, r.t., 3–5 h. Overall yields: 65–98% for the two steps from **1**.

The starting Fmoc-protected amino alcohols **1a**–**k** are commercially available or can be prepared by a one-step reduction according to Rodriguez and co-workers.[27] These alcohols were then transformed into the corresponding iodides using PPh_3 (3 equiv), iodine (3 equiv), and imidazole (5 equiv) in dry CH_2Cl_2. The reactions were allowed to proceed at room temperature for 1.5–2 hours. TLC showed that all the starting alcohols were converted to the desirable iodides during this period, except for the reaction with the proline-based system **1k** which did go to completion after overnight reaction. The reaction mixtures were then concentrated under reduced pressure and the iodides were purified by silica gel column

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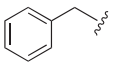
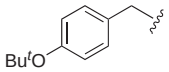
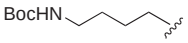
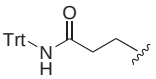
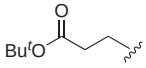
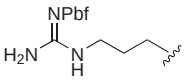
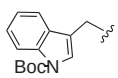
chromatography using 10–20% ethyl acetate in hexane (70% ethyl acetate in hexane for the arginine-based system). In most of the cases, the transformations from alcohols to iodides were quantitative, except a yield of 74% for the proline-based system.

The iodides were then converted into the corresponding azides **2a**–**k** by displacement reaction with azide (5 equiv NaN_3 in DMF) and stirred at room temperature for 3–5 hours (monitored by TLC). The product azides were then purified by silica gel column chromatography using 10–20% ethyl acetate (70% for the arginine-based system **2i**) in hexane in 65–98% overall yields for the two steps from alcohol **1**.[28]

Compared to the direct conversion of amino alcohols to amino azides under Mitsunobu conditions, our two-step protocol gave very similar or better overall isolated yields. For example, Fmoc-protected amino azides were reported with Val (80%), Leu (88%), Phe (80%), Tyr(O*t*-Bu) (87%), Ser(O*t*-Bu) (73%), Lys(Boc) (87%), and Pro (92%) side chains by Boeijen et al.[10] Except for the proline-based system, our protocol gave higher yields for those derivatives despite the two-step procedure (Table 1). The lower overall yield for the proline-based system **2k** is primarily due to a low conversion from the alcohol to the iodide at 74%, as the conversion from the iodide to the azide was achieved at 90%. For arginine-based system, the Meldal group reported a Arg(Pmc) derivative with 72% yield using the one-step Mitsunobu reaction,[22] while our two-step procedure gave a 65% yield for the Arg(Pbf) derivative **2i**.

Table 1 Overall Yields for Azides **2a**–**k** from Alcohols **1a**–**k**

Product number	Side chain R	Overall yields (%)
2a Val		93
2b Leu		98
2c Phe		90
2d Tyr(O*t*-Bu)		90
2e Ser(O*t*-Bu)		92
2f Lys(Boc)		90
2g Gln(Trt)		77
2h Glu(O*t*-Bu)		94
2i Arg(Pbf)		65
2j Trp(Boc)		80
2k Pro		67

In summary, we have demonstrated a mild and efficient two-step method for the synthesis of Fmoc-protected amino azides from the corresponding alcohols. These Fmoc-protected amino azides are versatile intermediates for the synthesis of monomers of oligomeric peptidomimetics. Our protocol avoids the preparation and use of azidic acid, and is a good complement to the existing synthetic strategies.

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(28) All compounds gave satisfactory analytical data. Described below are a representative procedure and spectral data for Fmoc-protected glutamate azide **2h**. Fmoc-protected glutamate alcohol **1h** (50 mg, 0.12 mmol) in dry CH_2Cl_2 was added to a pre-mixed (5 min) solution of PPh_3 (94 mg, 0.36 mmol, 3 equiv), iodine (91 mg, 0.36 mmol, 3 equiv) and imidazole (41 mg, 0.6 mmol, 5 equiv) in 1.2 mL dry CH_2Cl_2. The reaction mixture was stirred at r.t. for 1.5 h. After completion of the reaction the solvent was evaporated at reduced pressure and the corresponding iodide was purified by silica gel column chromatography (10% EtOAc in hexane). The iodide was then dissolved in 0.5 mL DMF, mixed with NaN_3 (39 mg, 0.6 mmol, 5 equiv with respect to alcohol **1h**) and stirred at r.t. for 3.5 h. After solvent removal and silica gel column chromatography (10% EtOAc in hexane), azide **2h** was obtained as a white solid in high yield. Yield 50 mg (94% overall from alcohol **1h**); mp 65–66 °C. ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9 H), 1.82–1.86 (m, 2 H), 2.29–2.36 (m, 2 H), 3.42–3.48 (m, 2 H), 3.75–3.87 (br m, 1 H), 4.23 (t, 1 H, *J* = 6.9 Hz), 4.38–4.50 (m, 2 H), 5.03 (d, 1 H, *J* = 7.7 Hz), 7.31–7.45 (m, 4 H), 7.61 (d, 2 H, *J* = 7.2 Hz), 7.79 (d, 2 H, *J* = 7.2 Hz). ESI-MS: *m/z* = 437.0 $[M + H]^+$.
Additional list of ^{1}H NMR of new compounds:
Compound **2g**: ^{1}H NMR ($CDCl_3$): δ = 1.76–1.83 (m, 2 H), 2.29–2.31 (m, 2 H), 3.31–3.37 (m, 2 H), 3.72 (br m, 1 H), 4.20 (t, 1 H, *J* = 6.5 Hz), 4.37–4.50 (m, 2 H), 5.01 (d, 1 H, *J* = 7.9 Hz), 6.75 (s, 1 H), 7.18–7.29 (m, 17 H), 7.35–7.41 (m, 2 H), 7.57 (d, 2 H, *J* = 7.4 Hz), 7.74 (d, 2 H, *J* = 7.4 Hz).
Compound **2i**: ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 6 H), 1.41–1.58 (m, 4 H), 2.06 (s, 3 H), 2.49 (s, 3 H), 2.56 (s, 3 H), 2.90 (s, 2 H), 3.16–3.31 (m, 4 H), 3.72 (br m, 1 H), 4.14 (t, 1 H, *J* = 6.5 Hz), 4.32–4.41 (m, 2 H), 5.30 (d, 1 H, *J* = 8.4 Hz), 6.34 (br s, 2 H), 7.24–7.27 (m, 2 H), 7.34–7.38 (m, 2 H), 7.54–7.55 (m, 2 H), 7.73 (d, 2 H, *J* = 7.4 Hz).
Compound **2j**: ^{1}H NMR ($CDCl_3$): δ = 1.65 (s, 9 H), 2.93–2.99 (m, 2 H), 3.45–3.49 (m, 2 H), 4.17–4.22 (m, 2 H), 4.41–4.43 (m, 2 H) 4.98 (d, 1 H, *J* = 7.8 Hz), 7.27–7.41 (m, 6 H), 7.46–7.63 (m, 4 Hz), 7.76 (d, 2 H, *J* = 7.4 Hz), 8.14 (br s, 1 H).