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CHEMISTRY

Synthesis of the Fmoc-aza-Arg(Boc)$_2$ precursor via hydrazine alkylation

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Abstract. The aza-arginine precursor Fmoc-aza-Arg(Boc)$_2$ was synthesized starting from mono-protected hydrazines via an aza-ornithine precursor. This reaction path is shorter and more efficient than the reductive alkylation reaction.

Key words: aza-arginine precursor, hydrazine derivatives, alkylation, guanylation, protecting groups.

Abbreviations
Alk – Alkyl
Aloc – allyloxycarbonyl
Boc – *tert*-butyloxycarbonyl
DCM – dichloromethane
DMF – *N*,*N*-dimethylformamide
DMSO – dimethyl sulphoxide
EA – ethyl acetate
Fmoc – 9-fluorenylmethoxycarbonyl
HRMS – high resolution mass spectra
NMP – *N*-methyl-2-pyrrolidone
NMR – nuclear magnetic resonance
PE – petroleum ether
TEA – triethylamine
Tf – trifluoromethanesulphonyl
TFA – trifluoroacetic acid
TLC – thin layer chromatography
Z – carboxybenzyl

INTRODUCTION

Substitution of DNA encoded amino acids (1) by their aza analogues (2) (Fig. 1) is a feasible structural modification of biologically active peptides for obtaining peptidomimetics with an increased effective lifetime in biological systems [1,2].

Incorporation of aza-amino acids into peptides can be done by using protected precursors, which can be presented as hydrazine derivatives (see 2 in Fig. 1). In most cases these precursors have been prepared from carbonyl compounds via reductive alkylation of protected hydrazines [3–5] (Scheme 1, **A**). However, there are other synthetic routes, mainly based on alkylation of *N*′-mono- or di-substituted hydrazine derivatives with alkyl halides [4,6–8] (Scheme 1, **B**), or introducing a protecting group into commercially available alkyl hydrazines [4,7–10] (Scheme 1, **C**).

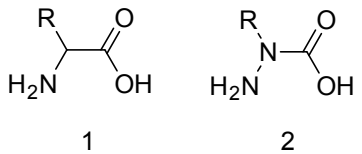

Fig. 1. α-Amino acid (1) and its unstable aza anologue (2).

However, in the case of some aza-amino acid precursors these straightforward synthetic routes cannot be used. For example, synthesis of an aza-arginine precursor is complicated by guanidyl moiety introduction and protection. Therefore guanylation of the side-chain amino group of aza-ornithine, already included into peptide sequence, was used in the first attempt to synthesize the aza-arginine containing peptidomimetics [5]. According to this methodology, ω-*N*-Aloc-protected aza-ornithine was incorporated into peptide and thereafter the Fmoc-protected resin-bound peptide was treated to remove Aloc protection followed by guanylation with *N*,*N*′-bis-Boc-1-guanylpyrazole [11]. Later, pre-

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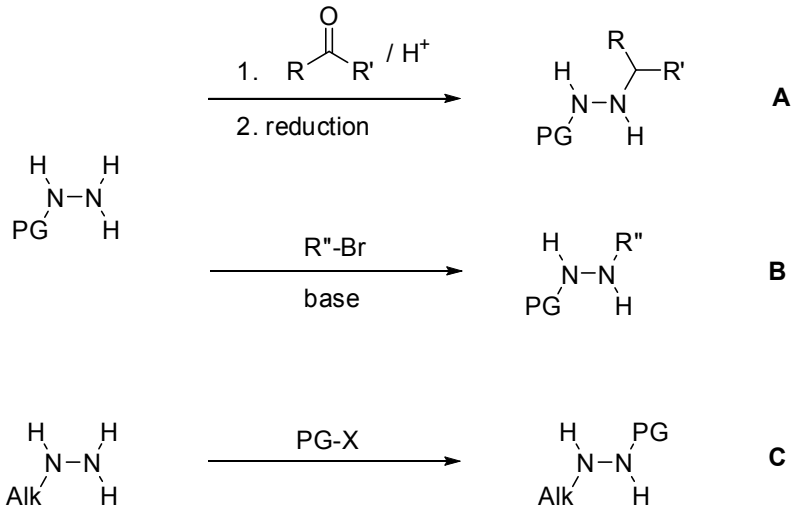
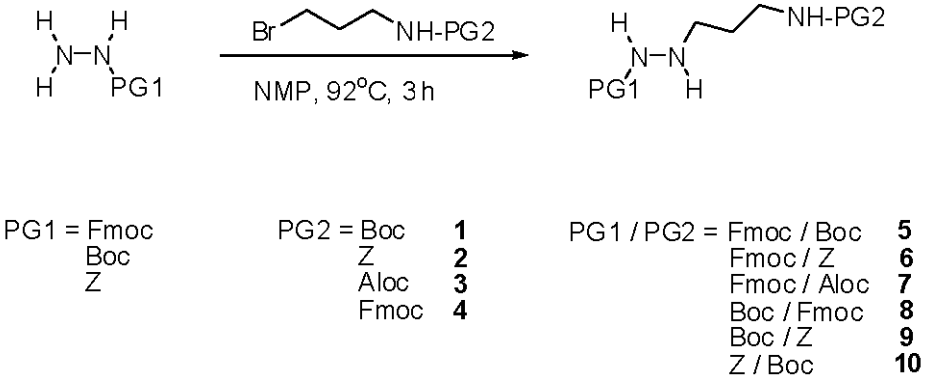
paration of the Fmoc-protected aza-arginine precursor was accomplished according to Scheme 1**A**, using reductive amination of 3-(N^{ω},N^{ω}-di-Boc-guanidyl)propanal with Fmoc hydrazine, while the required carbonyl compound was prepared by guanylation of 3-aminopropanol with *N*,*N*′-bis-Boc-*S*-methylisothiourea, followed by oxidation with the Dess–Martin reagent [12].

In this report we suggest an alternative synthesis of the aza-arginine precursor, using alkylation of *N*-protected hydrazine with *N*-protected 3-bromopropyl amine (Scheme 2), and thereafter converting the protected aza-ornithine precursor into a precursor of aza-arginine (Scheme 3). Compared with the previously published method of reductive alkylation, this synthetic pathway is shorter, allows avoiding condensation and reduction steps and does not require relatively expensive oxidizing reagents.



Scheme 1. Possible synthetic routes for the preparation of *N*′-protected *N*-alkyl hydrazine derivatives PG stands for protecting group.



Scheme 2. Alkylation of protected hydrazine derivatives with *N*-protected 3-bromopropyl amine. PG1 and PG2 are protecting goups.

Scheme 3. Preparation of the Fmoc-aza-Arg(Boc)$_2$ building block.

MATERIALS AND METHODS

Chemicals and analytical equipment

All solvents and reagents were purchased from Merck or Sigma-Aldrich and were at least ACS grade. The NMR spectra were measured on a 200 MHz spectrometer and on a 700 MHz spectrometer (Bruker, Germany) in DMSO-d6 or $CDCl_3$ as the solvent and using the internal reference. The HRMS of the products were measured on a LTQ Orbitrap (Thermo Electron) spectrometer (positive ionization, static nanospray, boron silicate emitters Proxeon, resolution 100 000 at m/z 400, external calibration), using acetonitrile as the solvent.

Syntheses

9-H-fluorenyl-9-methyl carbazate was prepared according to the method described in [5]. Fmoc-hydrazine was obtained in 95% yield. M.p. 172 °C (lit. M.p. = 171 °C [13]. NMR (200 MHz; DMSO-d_6): ^{1}H δ = 3.8 (s, 2H), 4.3 (t, J = 7 Hz, 1H), 4.5 (d, J = 6.8 Hz, 2H), 6.1 (brs, 1H), 7.3–7.9 (m, 8H). ^{13}C δ = 47.2, 66.3, 120.6, 125.7, 127.6, 128.1, 141.2, 144.4, 158.7.

Benzyl carbazate was prepared using the following procedure [14,15]: benzyl chloroformate (1 equiv.) was added dropwise to the mixture of hydrazine hydrate (11 equiv.) and diethyl ether at 0 °C and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with ethyl acetate, washed with 1 M $NaHCO_3$ solution, water, and brine. The water phase was extracted three times with ethyl acetate; combined extracts were washed with brine. Combined organic phases were dried over anhydrous sodium sulphate and concentrated in vacuum. Benzyl carbazate was obtained in 97% yield. NMR (200 MHz, $CDCl_3$): ^{1}H δ = 3.87 (brs, 2H), 5.15 (s, 2H), 6.72 (brs, 1H), 7.37 (s, 5H). ^{13}C δ = 67.2, 128.2, 128.3, 128.5, 136.2, 158.7. M.p. 60–64 °C (69–70 °C lit.) [14].

N-protected 3-aminopropyl bromides (**1**–**4**) were obtained by the modified procedure described in [15–18]. Shortly: 3-bromopropylammonium bromide (1 equiv.) was dissolved in chloroform (to give ca 0.2–0.5 M soln.), *N*,*N*-diisopropylethylamine (1.5–2.2 equiv., 1.05 equiv. in case of acylation with Boc anhydride) was added, the solution was cooled to 0 °C, and alkoxycarbonyl chloroformate (1 equiv.) or Boc anhydride (1.05 equiv.) was added slowly. The mixture was allowed to stir overnight. Then the reaction mixture was diluted with EA, washed with water and brine, dried over anhydrous magnesium sulphate, and concentrated in vacuo to obtain a crude product in nearly quantitative yield, which could be used without purification.

N-PG_1-*N*′-(3-(*N*-PG_2)aminopropyl) hydrazines were obtained by using the following procedure: alkyl carbazate (PG_1NHNH_2) (3 equiv.) and 3-(*N*-PG_2)aminopropyl bromide (1 equiv.) were stirred in NMP (~0.5 M soln.) at 92 °C. The reaction was monitored by TLC using EA–PE 1 : 2 as the eluent. After the 3-(*N*-PG_2)aminopropyl bromide was consumed (1–6 h), the reaction mixture was diluted with EA, washed with water and brine, dried over anhydrous sodium sulphate, concentrated in vacuum, and separated by column chromatography using EA–PE 1 : 2 as the eluent.

N-Fmoc-*N*′-(3-(N^{ω},N^{ω}-di-Boc-guanydil)propyl) hydrazine was prepared using the following procedure: *N*-Fmoc-*N*′-(3-(*N*-Boc)aminopropyl)hydrazine (**5**) was dissolved in DCM–TFA mixture (1 : 2) and stirred for 4 h at room temperature. The mixture was concentrated in vacuo. *N*-Fmoc-*N*′-(3-aminopropyl)hydrazine was dissolved in 1,4-dioxane (~0.2 M soln.) and stirred with $(BocNH)_2C$ = NTf (1 equiv.) and TEA (3 equiv.) for 8 h. The crude mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulphate, and concentrated in vacuo. The crude product was purified by column chromatography using PE–EA 1 : 1 as the eluent. The product was obtained in 66% yield.

Analytical data for the products

3-(*N*-Boc)aminopropyl bromide (**1**) was obtained in 94% yield. NMR (700 MHz, $CDCl_3$): ^{1}H δ = 1.45 (s, 9H), 2.05 (quint, J = 6.6 Hz, 2H), 3.30 (q, J = 6.6 Hz, 2H), 3.44 (t, J = 6.6 Hz, 2H), 4.68 (brs, 1H). ^{13}C δ = 28.4, 30.5, 39.3, 79.5, 156.6.

3-(*N*-Z)aminopropyl bromide (**2**) was obtained in 97% yield. NMR (700 MHz, $CDCl_3$): ^{1}H δ = 2.01 (quint, J = 6.6 Hz, 2H), 3.27 (q, J = 6.6 Hz, 2H), 3.38 (t, J = 6.6 Hz, 2H), 5.03 (s, 2H), 5.70 (brs, 1H, NH), 7.27 (s, 5H). ^{13}C δ = 30.5, 32.4, 39.2, 66.2, 127.6, 127.7, 128.1, 136.3, 156.3.

3-(*N*-Aloc)aminopropyl bromide (**3**) was obtained in 84% yield. NMR (700 MHz, $CDCl_3$): ^{1}H δ = 2.07 (quint, J = 6.4 Hz, 2H), 3.33 (q, J = 6.4 Hz, 2H), 3.46 (t, J = 6.4 Hz, 2H), 4.55 (d, J = 5.6 Hz, 2H), 5.19–5.30 (m, 2H), 5.73 (brs, 1H, NH), 5.89–5.93 (m, 1H). ^{13}C δ = 30.9, 32.6, 39.3, 65.4, 117.5, 132.9, 156.5.

3-(*N*-Fmoc)aminopropyl bromide (**4**) was obtained in 96% yield. NMR (700 MHz, $CDCl_3$): ^{1}H δ = 1.98 (quint, J = 6.6 Hz, 2H), 3.21–3.30 (m, 4H), 4.15 (t, J = 6.4 Hz, 1H), 4.37 (d, J = 6.4 Hz, 2H), 5.16 (brs, 1H), 7.23–7.70 (m, 8H). ^{13}C δ = 30.5, 32.5, 39.4, 47.2, 66.4, 119.9, 124.9, 127.0, 127.6, 141.2, 143.8, 156.4. HRMS: m/z for $C_{18}H_{19}BrNO_2$ calculated 360.0593, found 360.0593 $(M + H)^+$.

N-Fmoc-*N*′-(3-(*N*-Boc)aminopropyl)hydrazine [5] (**5**) was prepared according to the general hydrazine alkylation procedure described above. NMR (200 MHz, $CDCl_3$): ^{1}H δ = 1.44 (s, 9H), 1.60 (t, J =6 Hz, 2H), 2.89 (q, J = 6 Hz, 2H), 3.17 (s, 2H), 4.21 (t, J = 6.4 Hz, 1H),

4.41 (d, J = 6.4 Hz, 2H), 4.74 (brs, 1H), 4.90 (brs, 1H), 6.73 (brs, 1H), 7.25–7.77 (m, 8H). ^{13}C δ = 28.2, 28.7, 39.1, 47.6, 49.8, 67.3, 79.5, 120.3, 125.3, 127.4, 128.1, 141.7, 144.0, 156.4, 157.6, 174.6. M.p. 120.5–121 °C.

N-Fmoc-*N′*-(3-(*N*-Z)aminopropyl)hydrazine (**6**): NMR (200 MHz, $CDCl_3$): ^{1}H δ = 1.58 (quint, J = 6.8 Hz, 2H), 2.77 (s, 2H), 3.13 (q, J = 6.8 Hz, 2H), 4.23–4.38 (m, 3H), 4.61 (brs, 1H), 5.06 (s, 2H), 7.28–7.93 (m, 14H), 8.73 (brs, 1H). ^{13}C δ = 28.3, 39.0, 47.3, 49.1, 65.6, 66.0, 120.6, 125.7, 127.5, 128.1, 128.7, 137.8, 141.2, 144.3, 156.6, 157.4. HRMS: m/z for $C_{26}H_{28}N_3O_4$ $(M + H)^+$ calculated 446.2080, found 446.2074. M.p. 160–160.5 °C.

N-Fmoc-*N′*-(3-(*N*-Aloc)aminopropyl)hydrazine [5] (**7**) was prepared according to the general hydrazine alkylation procedure described above. NMR (200 MHz, $CDCl_3$): ^{1}H δ = 1.68 (s, 2H), 2.91 (s, 2H), 3.27 (d, J = 5.2 Hz, 2H), 3.95 (brs, 1H), 4.20 (t, J = 6 Hz, 1H), 4.40 (d, J = 6 Hz, 2H), 4.50 (d, J = 4.2 Hz, 2H), 5.18–5.35 (m, 2H), 5.47 (brs, 1H), 5.92 (m, 1H), 6.83 (brs, 1H), 7.29–7.80 (m, 8H). ^{13}C δ = 27.7, 39.2, 47.3, 49.5, 65.6, 67.0, 117.7, 120.1, 125.1, 127.1, 127.9, 133.2, 141.5, 143.9, 156.6, 157.5.

N-Boc-*N′*-(3-(*N*-Fmoc)aminopropyl)hydrazine (**8**): NMR (200 MHz, DMSO-d_6): ^{1}H δ = 1.51 (s, 9H), 1.70 (quint, J = 6 Hz, 2H), 2.94 (t, J = 6 Hz, 2H), 3.33 (q, J = 6 Hz, 2H), 3.90 (brs, 1H), 4.25 (t, J = 6.4 Hz, 1H), 4.42 (d, J = 6.4 Hz, 2H), 5.53 (brs, 1H), 6.28 (brs, 1H), 7.30–7.83 (m, 8H). ^{13}C δ = 27.6, 28.3, 39.3, 47.4, 49.8, 66.6, 80.7, 120.0, 125.1, 127.0, 127.7, 141.3, 144.1, 156.5, 156.9. HRMS: m/z for $C_{23}H_{30}N_3O_4$ calculated 412.2236, found 412.2230 $(M + H)^+$. M.p. 134–137 °C.

N-Boc-*N′*-(3-(*N*-Z)aminopropyl)hydrazine (**9**): NMR (200 MHz, $CDCl_3$): ^{1}H δ = 1.46 (s, 9H), 1.67 (q, J = 6.4 Hz), 2.89 (t, J = 6.4 Hz, 2H), 3.27 (q, J = 6.4 Hz, 2H), 3.92 (brs, 1H), 5.10 (s, 2H), 5.65 (s, 1H), 6.61 (s, 1H), 7.35 (s, 5H). ^{13}C δ = 28.0, 28.6, 39.5, 49.8, 66.7, 80.6, 128.1, 128.6, 137.0, 156.7, 157.0. HRMS: m/z for $C_{16}H_{25}N_3O_4$ $(M + H)^+$ calculated 324.1923, found 324.1918.

N-Z-*N′*-(3-(*N*-Boc)aminopropyl)hydrazine (**10**): NMR (200 MHz, $CDCl_3$): ^{1}H δ = 1.45 (s, 9H), 1.64 (quint, J = 6.8 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 3.19 (q, J = 6.8 Hz, 2H), 3.98 (brs, 1H), 5.00 (brs, 1H), 5.15 (s, 2H), 6.71 (brs, 1H), 7.36 (s, 5H). ^{13}C δ = 27.8, 28.4, 38.7, 49.5, 67.1, 79.1, 128.1, 128.2, 128.5, 136.1, 156.1, 157.3. HRMS: m/z for $C_{16}H_{25}N_3O_4$ $(M + H)^+$ calculated 346.1742, found 346.1737.

N-Fmoc-*N′*-(3-(*N*$^{\omega}$,*N*$^{\omega}$-di-Boc-guanydil)propyl) hydrazine (**11**) was obtained in 66% yield. NMR (200 MHz, $CDCl_3$): ^{1}H δ = 1.54 (s, 18H), 1.74 (s, 2H), 2.98 (s, 2H), 3.54 (s, 2H), 4.25 (t, J = 6.8 Hz, 1H), 4.4 (d, J = 6.8 Hz, 2H), 6.86 (brs, 1H), 7.30–7.84 (m, 8H), 8.56 (brs, 1H). ^{13}C δ = 27.0, 28.1, 28.3, 38.7, 47.3, 48.9, 66.9, 79.2, 83.2, 120.0, 125.0, 127.0, 127.7, 141.3, 143.8, 153.3, 156.1, 157.4, 163.5. HRMS: m/z for $C_{29}H_{40}N_5O_6$ $(M + H)^+$ calculated 554.2979, found 554.2973. M.p. 100–110 °C (lit. 50–55 °C) [12].

RESULTS AND DISCUSSION

As the first step of aza-arginine precursor synthesis, the double-protected aza-ornithine precursor was prepared via alkylation of protected hydrazine as shown in Scheme 2.

The reaction was performed by analogy with Boc-hydrazine alkylation in DMF, as was described by Hansen [19]; however, two modifications were introduced. Firstly, DMF was replaced by NMP to avoid formation of the formulated side product PG-NHNHCHO. Secondly, excess of the hydrazine derivative was used to minimize the formation of the di-alkylated compound PG-NHNAlk$_2$. If equivalent amounts of the alkylating reagent and Fmoc-hydrazine were used, the yield of the mono-alkylated product was around 35%. In the case of 3-fold carbazate excess, the yield was up to 70% as listed in Table 1.

Further, different combinations of protecting groups were tested in both reagents, in *N*-protected 3-bromopropyl amines and protected hydrazines, keeping in mind that these combinations may be needed for selective removal of one protecting group in the presence of another protecting group (the orthogonality requirement) in the following steps of aza-peptide synthesis. These experiments did not reveal any significant influence of the protecting group structure on the formation of the mono-alkylated product, except the reaction of Z-protected hydrazine. Therefore both ornithine precursors FmocNHNH(CH$_2$)$_3$NHBoc and BocNHNH(CH$_2$)$_3$NHFmoc can be used for the synthesis of aza-amino acid containing peptidomimetics. However, as the Fmoc strategy was selected for peptide synthesis in this project, the Fmoc-aza-Arg(Boc)$_2$ precursor was prepared, as summarized in Scheme 3.

For this step the compound FmocNHNH(CH$_2$)$_3$NHBoc (**5**) was reacted with TFA in DCM to remove the Boc protecting group, and the side-

Table 1. Alkylation of protected hydrazines with *N*-protected 3-bromopropyl amines

Alkyl carbazate	Alkyl bromide	Yield, %	Compound
FmocNHNH$_2$	Br(CH$_2$)$_3$NHBoc	62	**5**
	Br(CH$_2$)$_3$NHZ	65	**6**
	Br(CH$_2$)$_3$NHAloc	70	**7**
BocNHNH$_2$	Br(CH$_2$)$_3$NHFmoc	70	**8**
	Br(CH$_2$)$_3$NHZ	59	**9**
ZNHNH$_2$	Br(CH$_2$)$_3$NHBoc	39	**10**

chain amino group was then converted to N^{ω},N^{ω}-di-Boc-guanidyl group using *N*,*N*′-di-Boc-*N*″-Tf-guanidine as guanylating reagent in the presence of triethyl amine [20] (Scheme 3). As a result of this reaction *N*-Fmoc-*N*′-(3-(N^{ω},N^{ω}-di-Boc-guanydil)propyl)hydrazine (**11**), which is the precursor for aza-arginine introduction into peptidomimetic structure, was obtained in 66% yield.

CONCLUSIONS

Synthesis of FmocNHNH$(CH_2)_3$NHBoc, which is the precursor for aza-Arg incorporation into a peptidomimetic structure, was made by alkylating hydrazine derivatives. The alkylation reaction was performed on substrates with various combinations of protecting groups to meet different requirements of the orthogonality condition, which depends upon the applied strategy of peptide synthesis.

ACKNOWLEDGEMENTS

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Fmoc-aza-Arg(Boc)$_2$ prekursori süntees hüdrasiini alküülimise teel

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Aza-arginiini peptiidi koostisse viimiseks kasutatav reagent Fmoc-aza-Arg(Boc)$_2$ sünteesiti üle aza-ornitiini prekursori, lähtudes monokaitstud hüdrasiinidest. Selline sünteesitee oli lühem ja efektiivsem kui varem kasutuses olnud taandava alküülimise reaktsioon.