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Original and efficient synthesis of 2:1-[α/aza]-oligomer precursors

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ABSTRACT

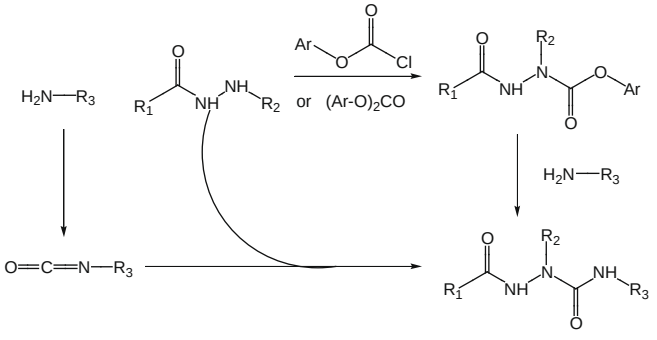
The preparation of 2:1-[α/aza]-oligomer precursors is described via Mitsunobu and exchange of protecting groups protocols in four steps in good yields starting from *N-tert*-butyloxycarbonylaminophtalimide. Conformational studies showed that these building blocks further led to β-turn-like folded 2:1-[α/aza]-trimer which suggests that they are good candidates to form foldamers.

C^{α}-modifications reported in peptide analogues are much more limited than the different types of amide surrogates[1] or the numerous possibilities of side chain modification. In addition to α,β-unsaturation,[2] α-alkylation,[3] or α-hydroxymethylation,[4] substitution of a nitrogen for the $C^{\alpha}H$ group has been also proposed as a way to preserve in the peptide analogues the side chains, which are eventually required for biological activity. The pseudopeptides are mimetics of natural peptides, however they are much more resistant to protease cleavage. In the literature, use of aza-peptides as enzyme inhibitors or receptor antagonists, such as protease papain inhibitors,[5] MHC II ligands,[6] and elastase active-site titrants[7] has been extensively studied.

Two synthetic pathways are usually followed to obtain these aza-peptides. The first pathway consists in condensing a hydrazide with an *N*-terminus isocyanate.[8] In the second pathway, the same hydrazide is first protected with aryl chloroformate or carbonate before reacting with an amine (Scheme 1).[9] An aza-aminoacid (carbazic acid) cannot be isolated in its carboxylic form, because of spontaneous decarboxylation. Employing the traditional peptide synthesis coupling methods, the introduction of an aza-residue requires a reactive 'carbonyl donor', which can be reacted either with the protected and properly substituted hydrazine or with the N-terminus of the growing chain.[9]

The key step of such chemistry is the synthesis of the substituted hydrazides. In the 70s, Dutta et al. published the synthesis of such compounds by various methods[10] and, later, Lubell et al. proposed a methodology to synthesize *N'-tert*-butyl- and *N'*-fluoren-9-methyl-carbazates,[11,12] which can be acylated. The former react with isocyanates while the latter are converted into intermediate *N'*-Fmoc-aza-amino acid chlorides.

We are currently studying a new class of foldamers based on aza/α-dipeptide oligomerization. Therefore, we need a general method to obtain these building blocks. First, we decided to use Boc chemistry because the residual by-products of Boc can be easily removed during purifications. Although the yields reported by Dutta and Lubell are from good to excellent, our first attempts to synthesize Boc-azAla-Ala-OMe[13] lead to a moderate yield. Furthermore, a major disadvantage of the methods of Dutta or Lubell for obtaining aza/α-dipeptides is that, depending on the nature of the side chain of the aza-amino acid, different acylation reactions must be used. Thus, we decided to use our experience in the synthesis of hydrazinopeptides and *N*-aminopeptides[14] to



Scheme 1. Synthesis of an aza-peptide fragment using either the isocyanate or the activated ester procedure (Ar: 4-nitro-phenyl in Ar-O-COCl or 2,4-dinitrophenyl in $(Ar\text{-}O\text{-})_2CO$)[8,9]; R_1, R_3: adequate peptide backbone; R_2: aza-residue side chain.

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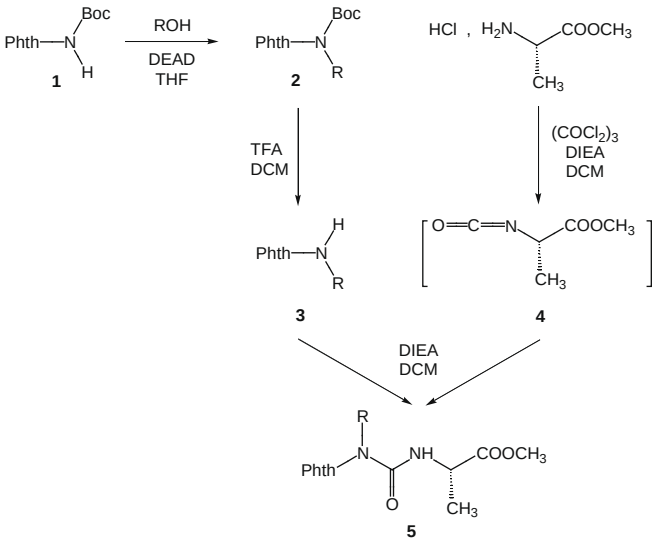


Scheme 2. Synthesis of an aza-peptide fragment using an isocyanate.

demonstrate that bis-nitrogen-containing compounds were easily synthesized *via* an original protocol involving a Mitsunobu reaction.

In this Letter, we show that the previously reported results can be extended to an easy preparation of aza/α-dipeptides, and we describe here a general method for this synthesis, which can be of interest to others. Initially, we considered the condensation of an *N*-alkyl-aminophthalimide with isocyanate derived from H-Ala-OMe (Scheme 2).

The key step in this strategy is the formation of *N*-alkyl-aminophthalimides **3** starting from *N-tert*-butyloxycarbonylaminophthalimide **1**.[14] The synthesis of **2** was easily achieved according to a protocol already described by our group.[15] A Mitsunobu reaction of **1** with an appropriate alcohol afforded the *N*-alkyl-*N-tert*-butyloxycarbonyl-aminophthalimides **2** in good yields (Table 1). The success of this reaction has been attributed to the use of an acidic partner bearing a phthalimide moiety which (i) conferred electronwithdrawing effects that are able to enhance the acidic property of the nitrogen proton and (ii) was not too hindered, allowing the S_N2 reaction. The Mitsunobu reaction is slightly sensitive to steric hindrance, thus **2c** (valine residue, Table 1, entry 3) is obtained in 75% yield. The moderate yields obtained with R = $(CH_2)_4NHZ$ (**2g**, entry 6) are due to purification problem. Indeed, in order to propose a general method, DEAD was used as Mitsunobu reagent in all cases, and the reduced product (*N*′-propionyl-hydrazinecarboxylic acid ethyl ester) had a similar R_f as **2g**. However, it is known that the yields of the Mitsunobu reaction are similar whatever the nature of R in the dialkyl azodicarboxylate is.[16] Thus, it is very likely that by choosing this reagent rationally, the yields of **2** could be optimized. After deprotection of the Boc group in **2** (quantitative), the condensation of **3** with 2-isocyanato-propionic acid methyl ester **4** is quite problematic and rather irreproducible in our hands. Thus, we decided to use the acyl chlorides methodology (Scheme 3).

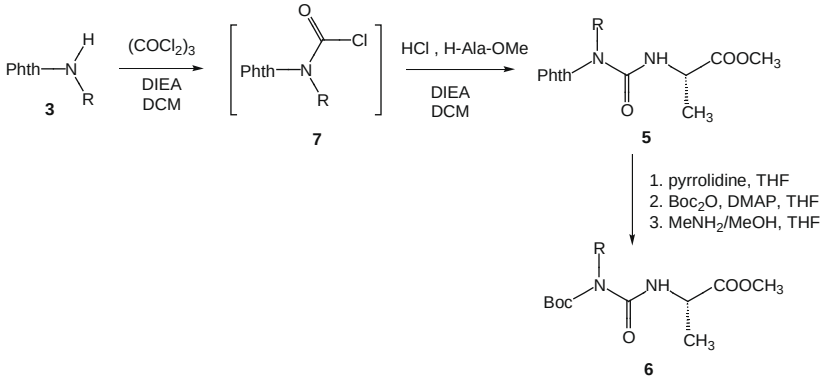
Treatment of *N*-alkyl-aminophthalimides **3** with triphosgene afforded the transient acyl chlorides **7** which were reacted with HCl, H-Ala-OMe to give the corresponding aza-dipeptides Phth-az-Xaa-Ala-OMe **5**[17] in moderate to good yields except for **5g** (Table 1, entry 7). In this special case, no reaction occurred and the starting materials remained unchanged.

Because the phthalimide group was not compatible with peptidic coupling reactions, we had to replace it with a more suitable protecting group. We used the trans-protection method developed in our laboratory for the synthesis of orthogonally protected α-hydrazinoacid derivatives.[14b,15] The conversion of compounds

Table 1
Derivatives **2**–**6** obtained via Schemes 2 and 3

Entry	R	**2** (yield%)[a] Mitsunobu reaction	**3** (yield%)[b] Boc deprotection	**5** (yield%)[c] Acid chloride method[d]	**6** (yield%)[d] Exchange of protecting group
1	CH_3	**2a** (98)	**3a** (100)	**5a** (90)	**6a** (85)
2	CH_2Ph	**2b** (81)	**3b** (100)	**5b** (86)	**6b** (97)
3	$CH(CH_3)_2$	**2c** (75)	**3c** (100)	**5c** (60)	**6c** (70)
4	$CH_2CH(CH_3)_2$	**2d** (80)	**3d** (96)	**5d** (85)	**6d** (75)
5	$(CH_2)_2SCH_3$	**2e** (98)	**3e** (91)	**5e** (50)	**6e** (73)
6	$(CH_2)_4NHZ$	**2f** (70)	**3f** (96)	**5f** (50)	**6f** (75)
7	CH_2COOCH_2Ph	**2g** (85)	**3g** (100)	**5g** (0)	—

[a] Yields in isolated compounds calculated from **1**.
[b] Yields in isolated compounds calculated from **2**.
[c] Yields in isolated compounds calculated from **3**.
[d] Yields in isolated compounds calculated from **5**.



Scheme 3. Synthesis of an aza-peptide fragment using an acyl chloride.[17]

5 into **6** can be performed in good yields by 'one-pot' reaction involving first a secondary amine (pyrrolidine) followed by *tert*-butyl-dicarbonate (Boc_2O) and, in the last step, methylamine as reactants (Scheme 3). In this way, we obtained the expected 2:1-[α/aza]-oligomer precursors.

Preliminary conformational studies by XR diffraction showed that no intramolecular hydrogen bond took place in Boc-azXaa-Ala-OMe compounds, resulting in an unfolded pseudodipeptide (not shown). In contrast, when coupled to another amino acid, the resulting pseudotripeptide Boc-Phe-azPhe-Ala-OMe **7** adopted a β-turn-folded structure (Fig. 1).

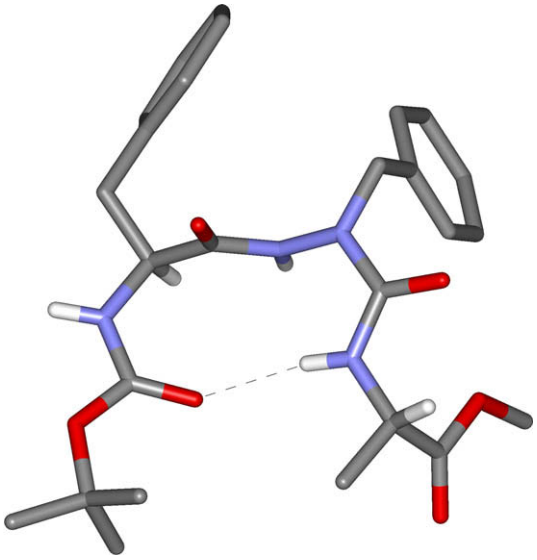


Figure 1. Crystal structure of Boc-Phe-azPhe-Ala-OMe **7**.

The crystal structure of the Boc-Phe-azPhe-Ala-OMe shows that the α-nitrogen is not planar, with a distance of 0.24(2) Å from the plane defined by the three atoms bonded to it, so that the aza-residue exhibits an R (D-like) chirality. The pseudo tripeptide is folded by a i+3→i hydrogen bond involving the (Ala)NH and (Boc)CO groups. All the amide bonds are trans-planar and the values of the torsional angles are typical of a β_{II}-turn. This fold was already observed by our group in the sequence Pro-azXaa (with Xaa = Ala or Asn).[18] The folded Boc-Phe-azPhe-Ala-OMe structure is interesting because it shows that aza-residues do not need the proline for the induction of β-folded structures. This result is in total agreement with the NMR studies and ab initio calculations described by Lee et al.[19]

In conclusion, we describe here a new general protocol for obtaining various Boc-azXaa-Xbb-OMe building blocks for introduction into biologically active peptides and oligomers. The fact that the coupling of this building block with an amino acid induces a β_{II}-turn is very promising and we expect that the iteration of this modification throughout the entire sequence will favor a highly structured pseudopeptide. We are studying extensively the oligomerization of the aza-dipeptide building block aiming to obtain new foldamers.

Acknowledgment

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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.2009.04.131.

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17. *General procedure*: *N*-alkyl-*N*-*tert*-butyloxycarbonylaminophthalimides **2**: Under N_2 to a dry THF solution of *N*-*tert*-butyloxycarbonylaminophthalimide **1** (1 equiv), PPh_3 (1.5 equiv), and alcohol (3 equiv), was added in one portion DEAD (1.5 equiv) under stirring at 0–5 °C. The resulting solution was stirred overnight (monitored by TLC until completion) and concentrated under vacuum. The residue was triturated with EtOAc, placed in the refrigerator and most of the triphenylphosphine oxide removed by filtration. The filtrate was evaporated and the residue was purified by column chromatography on silica gel affording **2**.*N*-Alkylaminophthalimides **3**: To a solution of **2** (1 equiv) in CH_2Cl_2 was added trifluoroacetic acid (10 equiv, 8% in CH_2Cl_2) at 0 °C. The mixture was stirred overnight (monitored by TLC). The solution was concentrated in vacuo. The residue was dissolved in CH_2Cl_2, neutralized with a saturated solution of $NaHCO_3$ (pH 7), and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo giving **3** as a yellow solid which was used without further purification.Phth-azXaa-Ala-OMe **5**: Triphosgene (0.37 equiv) was dissolved in dry CH_2Cl_2 under N_2. A mixture of **3** (1 equiv) and DIEA (2.2 equiv) in dry CH_2Cl_2 was added dropwise to the stirred solution of triphosgene. After a further 10 min stirring, a solution of alanine methyl ester hydrochloride (1 equiv) and DIEA (1.5 equiv) in dry CH_2Cl_2 was added in one portion. The reaction mixture was stirred overnight at rt, evaporated to dryness, dissolved in CH_2Cl_2, washed with aqueous HCl 1 N, aqueous $NaHCO_3$ 1 N and brine, dried over $MgSO_4$, and evaporated (For purification conditions see Supplementary data).Boc-azXaa-Ala-OMe **6**: To a solution of Phth-azXaa-Ala-OCH_3 **5** (1 equiv) in THF was added pyrrolidine (3 equiv) at rt. The mixture was stirred at rt until completion (overnight, monitored by TLC). The solvent and the excess of amine were removed under vacuum. The obtained yellow solid was dissolved in THF. Then Boc_2O (1.5 equiv) and a catalytic amount of DMAP (0.2 equiv) were added. The mixture was stirred at rt until completion (overnight, monitored by TLC). The solvent was removed under vacuum, the residue was dissolved in THF and a freshly prepared solution of methylamine (1.5 equiv, 2 M in MeOH) was added at rt. After a night (monitored by TLC), the solvent and the excess of amine were removed under vacuum and the residue was purified by column chromatography on silica gel.Compound **6a** (as an example): white solid, mp: 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (d, 3H, CH_3), 1.49 (s, 9H, $C(CH_3)_3$), 3.11 (s, 3H, NCH_3), 3.74 (s, 3H, $COOCH_3$), 4.48 (q, 1H, CH), 5.87 (d, 1H, NH), 6.49 (br s, 1H, NHBoc); ^{13}C NMR (300 MHz, $CDCl_3$): δ 19.4 (CH_3), 28.8 ($C(CH_3)_3$), 36.3 (NCH_3), 49.7 (CH), 52.9 ($COOCH_3$), 82.7 ($C(CH_3)_3$), 155.2 (COO^tBu), 158.1 (O=C–NH), 174.9 ($COOCH_3$). HR-MS (ESI) calculated for $C_{11}H_{22}N_3O_5$ $[M+H]^+$ *m*/*z* 276.1554, found 276.1571.
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