Pergamon

Tetrahedron Letters 43 (2002) 2009–2011

TETRAHEDRON LETTERS

Original and efficient method for the preparation of *N*-aminoamide pseudodipeptides in high optical purity

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Received 11 December 2001; revised 10 January 2002; accepted 16 January 2002

Abstract—*N*-Aminoamide pseudodipeptides ZAAΨ[CO-N(NPht)]-AAOR can be easily obtained via the Mitsunobu protocol by using α-hydroxyesters as alcohol partners and aminoacid phthaloyl hydrazide derivatives as acidic partners. The direct conversion of the phthaloyl group into *tert*-butyloxycarbonyl can be performed in a three-stage one-pot protocol.

Among the large variety of pseudopeptide structures currently investigated in organic and medicinal chemistry, little attention has been devoted to *N*-aminoamide pseudopeptides in which the nitrogen of the amide link bears an amino group (Fig. 1).

The first method of preparation was described by Niedrich in 1965 and enabled the formation of the simplest *N*-aminoamide pseudodipeptide ZGlyΨ[CO-$N(NH_2)$]-GlyOH[1] by coupling the corresponding N^{β}-protected α-hydrazinoester with a *N*-protected glycine.[2] During the past decade only a few other *N*-aminoamide pseudopeptides have been prepared because of the difficulties in obtaining the chiral α-hydrazinoester precursor in pure form and in coupling the hydrazine nitrogen regioselectively.[3] A variation of Ugi's reaction can also be used but leads to the formation of a racemic mixture.[4] However, from a structural point of view, it has been demonstrated that the amination of the amide nitrogen in a peptide chain has little influence on the local geometry but affects the hydrogen-bonding network and therefore the conformational properties of the modified peptide.[3a,5] In recent publications, we demonstrated that some *N*-acyl or *N*-alkyloxycarbonyl aminophthalimides can be efficiently used for incorporating a hydrazino group into a molecule. Because of their low steric hindrance and the presence of an acidic proton it was possible to use this kind of compound as an acidic partner in the Mitsunobu protocol, which allowed the replacement of a hydroxyl group by a protected hydrazine one.[6,7] For example, optically pure N^{α}- and/or N^{β}-protected hydrazinoester derivatives have been prepared using this method resulting in very good yields (Scheme 1).[6b] On the other hand, we showed that a large variety of substituted *N*-aminophtalimide derivatives can be obtained very easily in one-pot starting from phthalic anhydride and hydrazine derivatives. In one case, we demonstrated that this procedure can lead to the formation of an aminoacid phthaloyl hydrazide derivative (Scheme 2).[6a] We reasoned that this kind of compound bearing three electron withdrawing groups could also be used in the Mitsunobu reaction as acidic partners. Moreover, we thought that by using α-hydroxyesters as alcohol partners, this reaction pathway could prove an efficient and

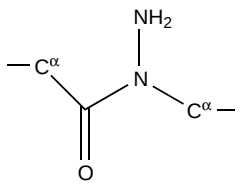
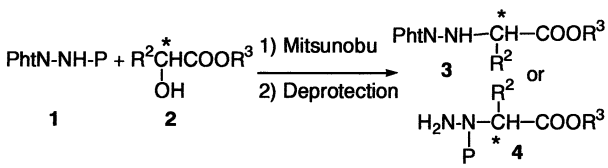


Figure 1. *N*-Amino amide.



Scheme 1. Pht = phthaloyl, P = Z or Boc, for *R* and *R'* values and conditions see Ref. 6b.

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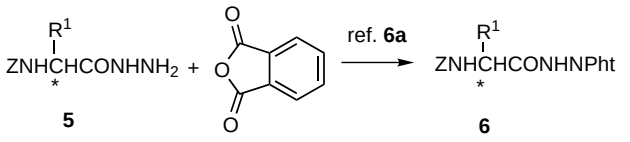
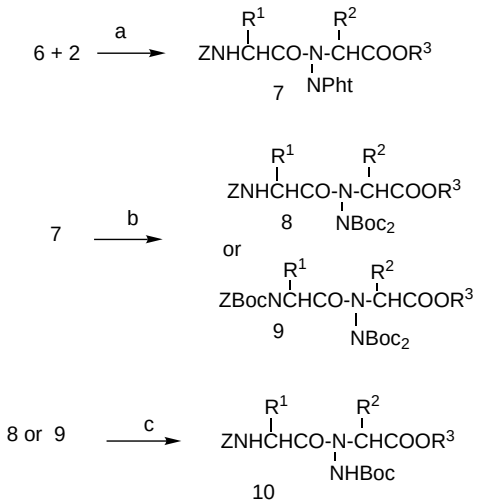
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00119-3



Scheme 2.

original method of producing *N*-aminoamide derivatives. So, in this paper, we will show that the synthesis of *N*-phthalimidoamide pseudodipeptides **7** can be performed by condensing α-hydroxyesters via the Mitsunobu protocol onto aminoacid phthaloyl hydrazide derivatives. Furthermore, we will demonstrate that compounds **7** can be efficiently converted into the corresponding *N*-(bis or *N*-(mono *tert*-butyloxycarbonylamino) amide pseudodipeptides **8**, **9** or **10**. The results are reported in Scheme 3 and Table 1.

Three *N*-protected phthaloylhydrazide aminoacids obtained by using a procedure previously described[6,7] were used as acidic partners and condensed with four optically pure (*S*)-α-hydroxyesters.[8] The combination



Scheme 3. (a) DBAD, PPh_3, THF; (b) $MeNH_2$, THF, rt, 3 h; evaporation; $(Boc)_2O$, DMAP cat., THF, rt; (b) $Mg(ClO_4)_2$ cat., CH_3CN.

of these starting materials led to the formation of seven different *N*-phthalimidoamide pseudodipeptides with very good yields. First of all, it is possible to notice that the steric hindrance due to the presence of an aminoacid side chain did not affect the yield of the reaction. Furthermore, and as expected, this Mitsunobu reaction occurred with a total inversion of configuration of the carbon bearing the hydroxyl group. This stereospecificity enabled the formation of (*L*,*D*)-diastereoisomers **7** in high optical purity starting from the corresponding (*S*)-α-hydroxyesters and (*S*)-aminoacid phthaloyl hydrazide derivatives.[9] The optical purity of the formed compounds was checked in one case by ^1H NMR (diastereoisomeric excess >95% for **7e**).[10] In comparison with the protocol previously used for the synthesis of *N*-aminoamide pseudopeptides, this reaction pathway does not require the formation and the regioselective coupling of chiral α-hydrazinoester derivatives. Furthermore, the *N*-aminoamide pseudodipeptides thus obtained can be introduced in peptide chain by using conventional peptide coupling reactions. As demonstrated previously, the presence of the phthaloyl group is essential for the success of this reaction.[6] Unfortunately, this protecting group is not suitable in peptide synthesis and furthermore it is difficult to find gentle and general methods to remove it. We recently published a very mild and efficient one-pot conversion of *N*-aminopthalimide derivatives into the corresponding *N*-amino-di-*tert*-butylimidodicarbonates.[11] Applied to compounds **7** this three-stage one-pot procedure led to the formation of the corresponding *N*-amino di-*tert*-butylimidodicarbonates **8**.[12] In the specific cases of the less hindered compounds **7a**, **7b**, **7c**, this conversion was accompanied by the fixation of a supplementary Boc group onto the nitrogen bearing the Z protection producing the corresponding compounds **9**.[13] The mechanism of this reaction has previously been described.[11] Finally, we have demonstrated that the selective removal of one Boc group from the diprotected nitrogen(s) occurred in the presence of a catalytic amount of $Mg(ClO_4)_2$, leading to the formation of orthogonally protected *N*-aminoamide pseudodipeptides **10**.[14] Structural analyses and the incorporation of these pseudodipeptide synthons in the peptide chain are under active investigation.

Table 1. Formation of *N*-aminoamide pseudodipeptide derivatives **7**, **8** and **9**

6		**7**				**8** or **9**
R^2	Yield (%)	R^1	R^2	R^3	Yield (%)[a]	Yield (%)[b]
H	87	H	H	Me	**7a**: 90	**9a**: 87
H	87	H	Me	Me	**7b**: 84	**9b**: 79
H	87	H	*i*Pr	Bn	**7c**: 79	**9c**: 74
Me	89	Me	H	Me	**7d**: 85	**8d**: 77
Me	89	Me	Me	Me	**7e**: 86	**8e**: 83
Me	89	Me	*i*Pr	Bn	**7f**: 77[c]	**8f**: 74
*i*Pr	72	*i*Pr	H	Me	**7g**: 79	**8g**: 78

[a] Yields calculated from **6**.
[b] Yields calculated from **7**.
[c] Reaction time: 4 h.

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8. General procedure: To a solution of **6** (3 mmol), PPh_3 (4.5 mmol), **2** (4.5 mmol) in dry THF (50 mL) and under nitrogen was added in one portion of DBAD (4.5 mmol) with stirring at 0–5°C. The resulting solution was stirred at room temperature for 2 h (monitored by TLC until completion) and concentrated in vacuo. The residue was evaporated and the residue was chromatographed on silica gel using a mixture hexane/EtOAc as eluent.
9. NMR spectra[15] of compound **7** $R^1=H$, $R^2=Me$, $R^3=Me$: ^1H NMR (400 MHz, $CDCl_3$): δ 7.93–7.62 m (4H); 7.37–7.17 m (5H); 5.83–5.71 m (1H); 5.24–5.10 m (3H); 3.81 d ($J=4.4$ Hz, 2H); 3.72 s (0.35H); 3.69 s (2.55H); 1.42 d ($J=6.7$ Hz, 0.35H); 1.31 d ($J=6.7$ Hz, 2.55H). ^{13}C NMR: δ 170.4; 169.7; 165.3; 164.6; 156.3; 136.6; 135.9; 135.3; 129.5; 129.4; 128.5; 124.9; 124.6; 67.4; 56.5; 55.1; 53.5; 53.1; 43.1; 42.7; 14.6; 14.3.
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12. NMR spectra[15] of compound **8** $R^1=Me$, $R^2=Me$, $R^3=Me$: ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.21 m (5H); 5.56 d ($J=8.2$ Hz, 1H); 5.17–5.00 m (2H); 4.65–4.55 m (1H); 4.48–4.55 m (1H); 3.70 s (1H); 1.54 s (9H); 1.47 s (9H); 1.39 d ($J=7.4$ Hz, 3H); 1.27 pd (3H). ^{13}C NMR: δ (ppm) 174.9; 170.6; 155.4; 150.8; 150.2; 136.8; 128.8; 128.4; 85.9; 85.7; 67.0; 58.1; 52.6; 47.4; 28.2; 27.9; 19.6; 14.4. NMR spectra[15] of compound **9** $R^1=H$, $R^2=Me$, $R^3=Me$: ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43–7.23 m (5H); 5.17 s (2H); 4.65 q ($J=7.4$ Hz, 1H); 4.39 s (2H); 3.63 s (3H); 1.50 s (9H); 1.49 s (9H); 1.40 s (9H); 1.31 d ($J=7.2$, 3H). ^{13}C NMR: δ (ppm) 170.9; 169.9; 153.9; 151.7; 150.5; 135.9; 128.7; 128.4; 85.6, 85.5; 83.5; 68.9; 56.7; 52.4; 47.8; 28.1; 28.0; 14.4; 14.0.
13. NMR spectra[15] of compound **10** $R^1=H$, $R^2=Me$, $R^3=Me$: ^1H NMR (400 MHz, $CDCl_3$): δ 7.39–7.23 m (5H); 5.71–5.61 m (1H); 5.35–5.25 m (1H); 5.15–5.05 m (3H); 4.45–3.85 m (2H); 3.69 s (3H); 1.47 s (9H); 1.40 d ($J=7.2$ Hz, 3H). ^{13}C NMR: δ 173.0; 172.9; 156.7; 155.1; 136.8; 129.0, 128.8; 128.4; 128.4; 82.6; 67.2; 54.2; 52.7; 42.8; 28.3; 14.1.
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15. The observation of two sets of resonance for some groups suggested that the compounds were present as two *Z* and *E* isomers (see Ref. 6).