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Solid phase synthesis of *N*-aminodipeptides in high optical purity

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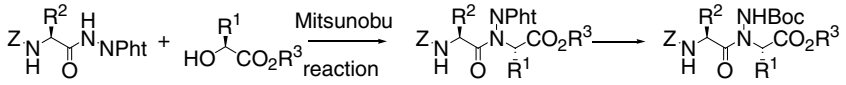
Abstract—*N*-Aminodipeptide derivatives can be easily prepared with high optical purity on solid phase via a Mitsunobu protocol between a solid supported α-hydroxyacid and a free phthaloylated α-*Z*-*N*-aminohydrazide.

Some years ago, we demonstrated that bis-nitrogen containing aminoacid analogues such as hydrazinoacid[1] and *N*-aminodipeptide[2] derivatives could be easily synthesised via an original protocol involving a Mitsunobu reaction. Using this procedure, *N*-aminodipeptide derivatives **3** were obtained from the reaction between phthaloylated α-aminohydrazide derivatives **1** and (*S*)-α-hydroxyester **2** (Scheme 1).[2]

The success of this reaction has been attributed to the use of an acidic partner bearing a phthalimide moiety, which (i) confers electronwithdrawing effects able to enhance the acidic property of the nitrogen proton and (ii) is not too hindered and then allows the S_N2 reaction. As one of the aims of the synthesis of *N*-aminodipeptides was to insert them in longer peptidic sequences via SPPS (solid phase peptides synthesis) protocol, we defined good conditions which allowed to convert the phthalimide group into the more suitable Boc group via a multi-step one-pot protocol.[3] To be more efficient and to avoid the purification steps during the synthesis, we report in this Letter conditions which allow the synthesis of these pseudodipeptides on solid support. Looking at the starting materials, it was possible to consider two possibilities depending on the nature of the reactant linked on the resin. So the reaction can be performed between: (i) supported acidic partner of the Mitsunobu reaction and free alcohol (Scheme 2) or (ii) supported alcohol and the free acidic partner (Scheme 3). Both strategies were tested.

First, as it has been demonstrated for the preparation of secondary amines derivatives on solid support,[4] we decided to synthesise the supported acidic partner from the supported trimellitic anhydride obtained via a Mitsunobu reaction between trimellitic anhydride and a Wang resin. Then, the supported phthalic anhydride **5** was able to react with α-*Z*-N-protected aminohydrazide **1** R^1 = Me to give the supported acidic partner **6**. The latter was then able to be involved in the Mitsunobu



1 **2** **3** **4**

Scheme 1. Pht = phthalimide group see Ref. 2.

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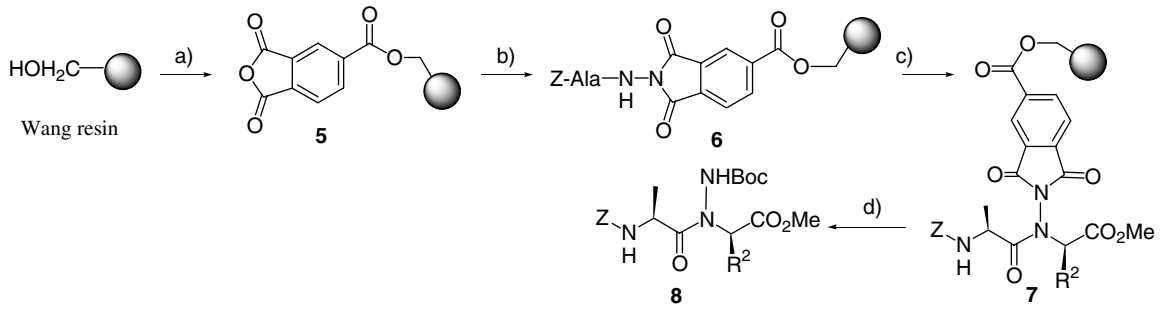
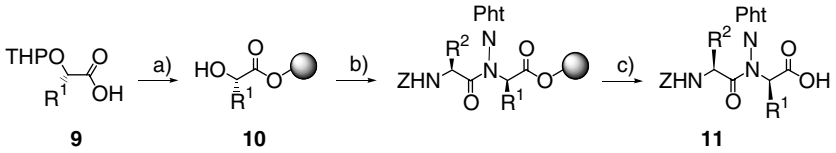


Scheme 2. Reagents: (a) trimellitic anhydride, DIAD, PPh_3, THF; (b) (1) Z-NH–CH(CH_3)-CONHNH_2 THF, (2) DCC, HOBt, THF; (c) **2** (R^3 = Me), DIAD, PPh_3, THF; (d) (1) pyrrolidine, THF, (2) Boc_2O, DMAP, THF, (3) $MeNH_2$ (2 M in MeOH, 4 equiv), THF.



Scheme 3. Reagents: (a) (1) Wang resin, DIC, DMAP, cat., THF, (2) PTSA, CH_2Cl_2/MeOH (97:3); (b) PhtNNHCOCH(R^2)NHZ (**2**), DIAD, PPh_3, THF; (c) TFA/DCM (1:1).

protocol and to react with α-hydroxyester **2** to give the supported *N*-aminophthalimide **7**. The release from the resin can be performed by using the transprotection protocol that we published previously, which allowed to directly replace the phthalimide group of a hydrazine in a Boc protection.[5] While some compounds **8** have been obtained by this way, the use of this strategy presents several drawbacks: The reaction was sometimes not reproducible and led to the formation of several byproducts, which complicated the purification process. In fact, we suspected the lability of the phthalimide group and/or of the links between the solid support and the phthalimide moiety to be responsible for all the problems met and decided to test the use of other supported systems. Several resins (aminomethyl resin, 2-chlorotrityl, BHA (Benzhydrylamine), etc.) were tested without success. Moreover, no better results were obtained when changing the trimellitic anhydride by other substituted phthalic anhydrides: 2-acid chloride or 2-isocyanate. These results let us to consider a second pathway for which the electrophilic partner is anchored onto a resin (Scheme 3).

So, the protected α-hydroxyacids **9** were linked to a Wang resin via their carboxylic group.[6] The use of PTSA allowed to remove the THP protection and then to recover the supported alcohol **10**, which can react via the Mitsunobu protocol with the free acidic partner **2**. This protocol has been successfully used for different values of R^1 and R^2 corresponding to different amino acid side chains. The results are gathered in Table 1. The main advantage of this procedure is that the α-hydroxyacid derivatives are anchored on the solid support via its carboxylic group as any first amino acids of a peptide chain constructed by SPPS. So, classical protocols can be used to release the final product from the support. Starting from a Wang resin we were able to release *N*-aminodipeptides **11** by using TFA in DCM. The overall yields of **11** calculated from the substitution level of the Wang resin (1.2 mmol/g of hydroxy groups) varied from 21% to 55% depending on the nature of the lateral chain. Taking into account the four steps of the synthesis, these results correspond to an average yield for each step varying from 68% to 86%. Moreover, they show that the Mitsunobu reaction is not affected by the steric hindrance generated by the presence of the solid support. To confirm the stereoselectivity of the reaction leading to inversion of the configuration of **10**, we converted compound **11f** into the corresponding methyl ester derivative **3f** and compared its NMR spectra with the authentic samples of **3f** and its diastereoisomer, both of which were obtained by solution phase synthesis.[2] This confirmed that the solid support protocol resulted in inversion of the stereocentre in **10**, giving *N*-aminodipeptides **11** in diastereomerically pure form (>95%).

As we started from commercially available (*S*)-α-hydroxyacids or those obtained by a nitrosation reaction[7] of the corresponding natural aminoacids, which proceed with total retention of configuration, the absolute configuration of all compounds **11** is (*S*,*R*). This

Table 1. Formation of *N*-aminodipeptides **11**

R^1	R^2	Overall yield in **11** (%)[a]
H	H	**11a** (49)
CH_3	H	**11b** (38)
CH_2–$CH(CH_3)_2$	H	**11c** (39)
CH_2–Phe	H	**11d** (48)
H	CH_3	**11e** (47)
CH_3	CH_3	**11f** (37)
CH_2–$CH(CH_3)_2$	CH_3	**11g** (44)
CH_2–Phe	CH_3	**11h** (55)
CH_2–Phe	$CH(CH_3)_2$	**11i** (21)
CH_3	$CH(CH_3)_2$	**11j** (21)

[a] Yields of pure products calculated from the substitution level of the resin (1.2 mmol/g of hydroxy groups).

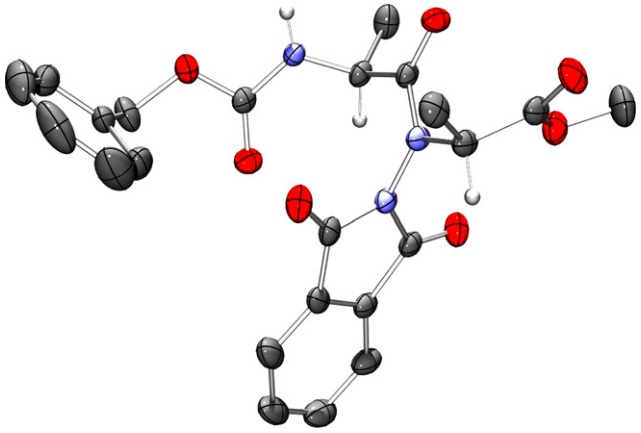


Figure 1. Ortep drawing of **3f**.

result has also been confirmed by the X-ray crystallographic analysis of **3f** (Fig. 1).[8] It is important to notice that *N*-aminodipeptides **11** obtained by this protocol are free on their *C*-terminal function and can be involved directly in a further coupling reaction. Oligomerisation of these dimers is under active investigation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.152.

References and notes

1. Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *J. Org. Chem.* **2000**, *65*, 4370–4374; Brosse, N.; Pinto, M.-F.; Bodiguel, J.; Jamart-Grégoire, B. *J. Org. Chem.* **2001**, *66*, 2869–2873.
2. Brosse, N.; Grandeury, A.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2002**, *43*, 2009–2011.
3. Brosse, N.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2002**, *43*, 249–251.
4. Glatz, H.; Bannwarth, W. *Tetrahedron Lett.* **2003**, *44*, 149–152.
5. Bouillon, I.; Brosse, N.; Vanderesse, R.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2004**, *45*, 3569–3572.
6. Typical procedure for the preparation of **11** using the procedure 2:
   Anchoring the alcohol derivative:
   Step 1: To a suspension of 0.3 g of Wang PS resin (cross linked with 1% DVB, 200–400 mesh, 1.2 mmol/g) in THF (1 mL/100 mg of resin) were added DIC (3 equiv), a catalytic amount of DMAP and THPO–hydroxy acid (3 equiv). The resulting mixture was stirred for 2 h then filtered and washed.
   Step 2: 10 mL of a solution of *p*-TsOH (5 mg/mL) in CH_2Cl_2/MeOH (97:3) was added to the resin and the resulting mixture was stirred for 1 h. The reaction was performed two times and the resin was then filtered and washed.
   Step 3: PPh_3 (3 equiv) and Z-AA-NHNPht (3 equiv) in 5 mL of anhydrous THF were added to the resin. DIAD (3 equiv) was added dropwise to the reaction and the resulting mixture was stirred for 4 h. The reaction was performed two times and the resin was filtered and washed.
   Cleavage: 10 mL of a mixture of CH_2Cl_2/TFA (1:1) was added to the resin. After 30 min, the polymer was removed by filtration and the filtrate concentrated under vacuum. Compounds **11** were purified by reverse-phase HPLC using a Waters DELTA PAK column (15 mm, 300 Å, 7.8 × 300 mm) with a linear gradient of $A = 0.1\%$ TFA in water and $B = 0.1\%$ TFA and 20% water in CH_3CN, from 95%A to 0%A over 25 min.
   *Spectroscopic data of Z-Phe*ψ*[CON(NPht)]Ala-OH* **11h**:
   ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) 7.97–7.78 (m, 4H, H arom Pht); 7.29–7.06 (m, 10H, Harom); 5.41 (d, 1H, $J = 8.6$ Hz, N*H*COOCH$_2$Ph); 5.11–4.78 (m, 3H, NHCOOC*H*$_2$Ph and C*H*CH$_3$); 4.60–4.53 (m, 1H, C*H*CH$_2$Ph); 3.17–2.83 (m, 2H, CHC*H*$_2$Ph); 1.52; 1.39 (2d, 3H, $J = 6.3$ Hz, CHC*H*$_3$). NMR splitting can be due to the classical cis/trans isomerism of the urethane or ureide CO–N amide bond.
   ^{13}C NMR ($CDCl_3$): δ (ppm) 173.6 (*C*OOH); 170.9 (*C*ON(NPht)); 166.2; 165.8 (C=O Pht); 156.2 (NH*C*OOCH$_2$Ph); 136.7; 136.3 (C arom); 136.2; 136.1 (*C*H arom pht); 130.3; 130.0 (*C*H arom Z and Phe); 129.7 (C arom); 129.1; 128.7; 128.5; 127.8; 127.6 (*C*H arom Z and Phe); 125.3 (*C*H arom Pht); 67.9; 67.7 (NHCOO*C*H$_2$Ph); 58.4 (*C*HCH$_3$); 52.9 (*C*HCH$_2$Ph); 38.6 (CH*C*H$_2$Ph); 14.3 (CH*C*H$_3$). HRMS calcd for $C_{28}H_{25}N_3O_7$ [M+Na$^+$] m/z 538.15847, found 538.15883.
7. Degerbeck, F.; Fransson, B.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 1* **1993**, 11–14.
8. Crystal data for **3f**: $C_{23}H_{23}O_7N_3$, $M_w = 453.44$, colourless prism, orthorhombic, $P2_12_12_1$ (#19), $a = 8.988(2)$ Å, $b = 13.078(3)$ Å, $c = 19.238(3)$ Å, $V = 2261.3(8)$ Å^3, $Z = 4$, $D_{calcd} = 1.332$ g/cm^3, μ(Cu Kα) = 0.837 cm^{-1}, 2409 reflections measured, 2409 unique, R_1 [$I > 2\sigma(I)$] = 0.041, wR_2 (all data) = 0.120 for 299 parameters, GooF = 1.114, residual density (max./min.) = 0. 177/−0.175 e A^{-3}. Details of the crystal structure (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 66814. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 01223 336033 or e-mail: deposit@ccdc.cam.ac.uk].