Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3569–3572
Tetrahedron Letters

Liquid and solid phase syntheses of orthogonally protected α-hydrazinoacid derivatives

Isabelle Bouillon, Nicolas Brosse,* Régis Vanderesse and Brigitte Jamart-Grégoire

Laboratoire de Chimie Physique Macromoléculaire, UMR 7568, ENSIC-INPL, BP 451, 54001 Nancy, France

Received 13 February 2004; accepted 10 March 2004

Abstract—The first solid phase synthesis of chiral α-hydrazinoacids has been developed. This synthesis was achieved by the preparation of solid supported-*N*-alkyloxycarbonyl-aminophthalimides used as acidic partners in the Mitsunobu protocol involving α-hydroxyesters. Two different final *trans*-protection steps of the phthaloyl group, developed first in liquid phase, result in efficient releases of orthogonally bis-protected or fully tris-protected hydrazine derivatives. A comparison between liquid and solid phase syntheses is outlined: even if the overall yields are sometimes rather higher by the liquid phase synthesis, the on-resin protocol is much more rapid and convenient than the liquid protocol.

1. Introduction

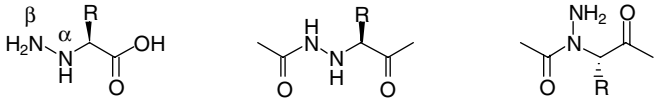
With the availability of automated techniques, the solid phase synthesis of small organic molecules is becoming a fundamental method for the rapid and easy preparation of libraries of organic compounds in order to accelerate drug discovery process.[1] This approach facilitates the rapid synthesis of a large number of compounds in a short time frame and facilitates their use in high throughput screening.

Chiral α-hydrazinoacids are a particularly attractive class of amino acid analogues since they can be incorporated in peptide syntheses by either N_α or N_β atom leading to the preparation of two families of pseudo-peptides: the hydrazino-and *N*-amino-peptides.

Nevertheless, the chemistry of chiral α-hydrazinoacid derivatives bearing an orthogonally protected hydrazino moiety (permitting selective incorporations in a peptide synthesis) has not been widely explored because of the difficulties of their preparation.[2] In the literature, four main methods are described: the catalytic hydrogenation of hydrazones,[3,4] the Schestakov rearrangement,[5] the electrophilic N-amination of α-aminoacids,[6] and the nucleophilic substitution of nosyloxy esters.[7]

We have recently shown that *N*-*tert*-butyloxycarbonyl-aminophthalimide **2a** and *N*-benzyloxycarbonylamino-phthalimide **2b** (easily obtained by the condensation of the phthalic anhydride **1** onto the corresponding carbazates[8a]) were good acidic partners in the Mitsunobu protocol;[8] optically pure N_α and/or N_β protected α-hydrazinoesters **3** have been prepared using this method involving chiral α-hydroxyesters as alcoholic partners (Scheme 1).

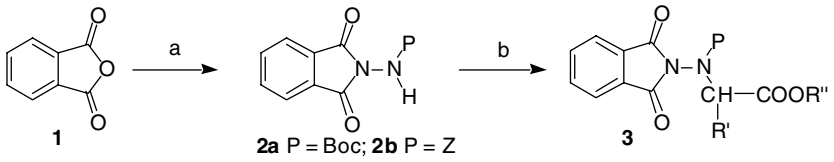
In this context, the transfer of this new liquid phase synthesis of chiral N_α, N_β orthogonally bis-protected



α-hydrazino acid hydrazinopeptide N-amino peptide

Keywords: Solid phase organic synthesis; α-Hydrazinoacid; Mitsunobu reaction; Protecting group.
* Corresponding author. Tel.: +33-(0)3-83-17-53-28; fax: +33-(0)3-83-37-99-77; e-mail: nicolas.brosse@ensic.inpl-nancy.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.063



Scheme 1. Reagents and conditions: (a) carbazate ($H_2NNHBoc$ for preparation of **2a** or H_2NNHZ for preparation of **2b**), toluene, reflux; (b) RCH(OH)COOR′, Mitsunobu conditions.

α-hydrazinoacids onto solid phase seems to be of great interest. In this paper, we report the first solid phase synthesis of chiral α-hydrazinoacid derivatives involving solid supported-*N*-alkyloxycarbonylaminophthalimides as acid partners in the Mitsunobu protocol. We also describe a *trans*-protection reaction, developed first in liquid phase, which can efficiently be used as a release step of orthogonally bis-protected α-hydrazinoacid derivatives (BocNH–NP–CHRCOOR′) from the resin. Moreover, and taking into account recent results[9] demonstrating the great interest of fully protected hydrazine moiety of hydrazinoacid derivatives, we defined a second efficient cleavage method leading to the formation of tri- protected α-hydrazinoacid derivatives.

2. *trans*-Protection reactions of phthalimide group: liquid phase reactions

We have recently described[10] a very mild and efficient conversion of *N*-aminophthalimide derivatives into the corresponding *N*-amino-di-*tert*-butylimidodicarbonates **4** (Scheme 2). We have shown that the selective removal of one of the two Boc groups was possible by using a catalytic amount of $Mg(ClO_4)_2$ and led to the formation of compounds **5**.

We were able to improve our method and avoid the use of the $Mg(ClO_4)_2$ by replacing in the first step the methyl amine by a secondary amine, the pyrrolidine. This new protocol allowed us to isolate the stable intermediates **6** and **7** and to introduce different protecting groups Σ onto the N_β nitrogen atom. So, the conversion of **3** to **5** can be performed in good yields by a 'one-pot' reaction involving first pyrrolidine, followed by Σ_2O and, in the last step methylamine as reactants (Scheme 3 and Table 1).

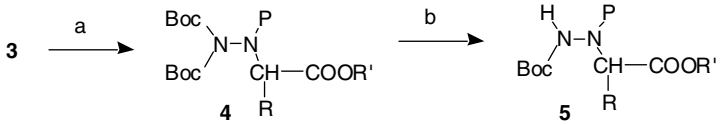
Table 1. Liquid phase preparation of protected α-hydrazinoesters **5**

Σ	P	Time[a] (h)	Yield[b] (%)
Boc	Z	4	**5a** 71
Boc	Boc	4	**5b** 75
$COCF_3$	Z	12	**5c** 71
Z	Z	12	**5d** 64

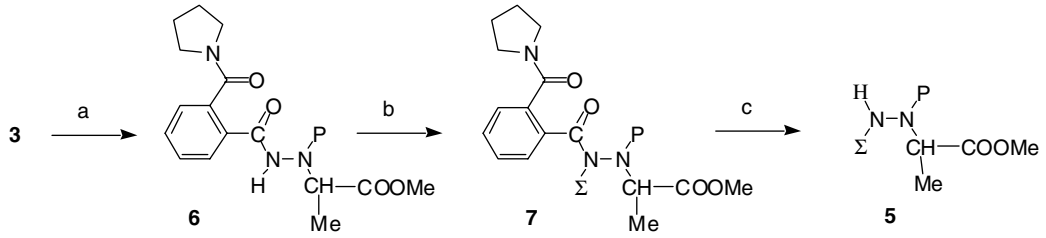
[a] For step b.
[b] Yield of isolated compound calculated from **3**.

3. Supported synthesis of α-hydrazinoesters

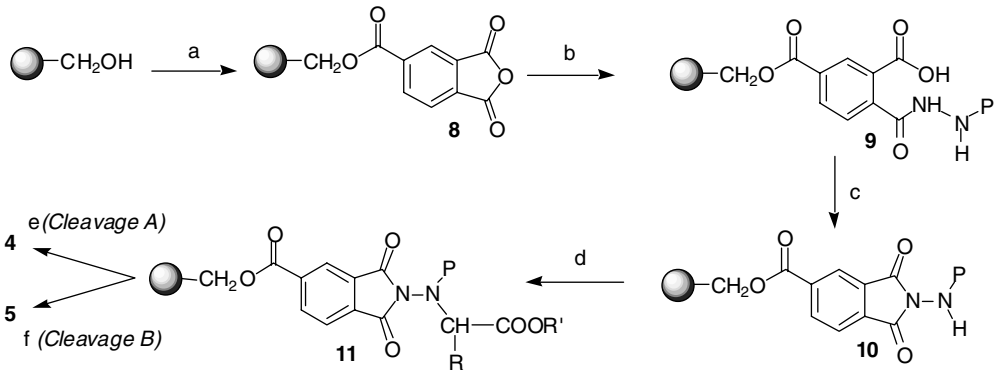
Two recent papers describe the preparation and the use of phthalimide-containing resins: in the first one, Gelb and co-workers[11] described the Gabriel reaction starting from an aminomethyl resin and in the second one Rademann and co-workers[12] (in parallel to our work) related the solid phase synthesis of labelled carbohydrates starting from a *N*-methyl-aminomethyl resin. In our study, we decided to start from a Wang resin and to synthesise the supported Mitsunobu acidic partners in three steps: (i) the formation of the trimellitic anhydride linker (TAL) resin **8** by coupling trimellitic anhydride to



Scheme 2. Reagents and conditions: (a) i. $MeNH_2$ 1.5 equiv, THF; ii. Boc_2O 3 equiv, DMAP cat.; (b) $Mg(ClO_4)_2$ cat., CH_3CN.



Scheme 3. Reagents and conditions: (a) Pyrrolidine 3 equiv, 4 h at rt, THF; (b) Σ_2O 3 equiv, DMAP cat.; (c) $MeNH_2$ 1.5 equiv, 3 h, rt, THF.



Scheme 4. Reagents and conditions: (a) trimellitic anhydride (3 equiv), PPh_3 (3 equiv), DIAD (3 equiv), THF; (b) $H_2NNHBoc$ or H_2NNHZ (3 equiv), THF; (c) DCC (4 equiv), HOBt (4 equiv), THF; (d) RCH(OH)COOR′ (3 equiv), PPh_3 (3 equiv), DIAD (3 equiv), THF; (e) *Cleavage A*. i. $MeNH_2$ (4 equiv), THF; ii. Boc_2O (4 equiv), DMAP cat.; (f) *Cleavage B*. i. pyrrolidine (4 equiv), THF; ii. Boc_2O (4 equiv), DMAP cat.; (iii) $MeNH_2$ (4 equiv), THF.

the Wang resin via the Mitsunobu reaction (ii) the transformation of the TAL resin into **9** by action of 3 equiv of the corresponding carbazate (iii) the formation of compound **10** by a cyclisation step of **9** by DCC–HOBt. The supported α-hydrazinoesters **11** were obtained using a second Mitsunobu reaction between **10** and various commercially available α-hydroxyesters (Scheme 4).

Taking into account the results described above for liquid phase *trans*-protection of the phthalimido group (pathway A Scheme 2 and pathway B Scheme 3), we have developed two solid phase cleavage protocols (*Cleavage A and B*) permitting, respectively, the preparation of compounds **4** and **5**. The fully protected hydrazinoesters **4** (*Cleavage A*) were released by treatment with $MeNH_2$ in THF (3 h) followed by action of Boc_2O/DMAP cat. After evaporation of the solvent, the excess of reagents was removed by column chromatography. For the preparation of the N_βHBoc hydrazinoesters **5** (*Cleavage B*), the solid suspension of resin-bond hydrazinoester was treated successively by pyrrolidine, Boc_2O and methylamine. The released protected hydrazinoesters **5** were isolated after removal of the solvent and the excess of amine by evaporation under vacuum.

4. Results

To demonstrate the significance of the use of our resin for the preparation of protected hydrazine derivatives, we have prepared a small collection of protected α-hydrazinoesters (Table 2). The syntheses involve three points of diversity: (i) the lateral chain of the hydrazinoester (R) (ii) the ester group (R′) (iii) the protecting group (P = Boc or Z) of the N^α nitrogen atom. The purity of the isolated compounds was checked by NMR and ccm; the overall yields (six steps for *cleavage A*, seven steps for *cleavage B*) are calculated from the resin substitution (Table 2).

For P = Z, the yields obtained are very good for multistep preparations regardless the nature of R and R′ and are quite similar to the overall yield obtained in liquid phase.[8,10] When applied to the more hindered Boc group (compounds **4d**, **5b**), the solid phase protocol leads to about 20% lower yields compared to the liquid one, suggesting that the Mitsunobu alkylation reactions using supported acidic partners could be more sensitive to steric hindrance. Nevertheless, the solid phase approach is much more rapid and convenient than the liquid phase protocol.

Table 2. Solid phase preparation of α-hydrazinoesters **4** and **5**

P	R	R′	*Cleavage*	Yield[a] (%)
Z	CH_3	CH_3	*A*	**4a** 62
Z	H	CH_3	*A*	**4b** 56
Z	H	CH_2Ph	*A*	**4c** 55
Boc	CH_3	CH_3	*A*	**4d** 35
Boc	CH_3	CH_3	*B*	**5b** 40
Z	CH_3	CH_2CH_3	*B*	**5e** 80
Z	H	CH_3	*B*	**5f** 63
Z	H	CH_2Ph	*B*	**5g** 65
Z	Ph	CH_3	*B*	**5h** 55
Z	CH_2Ph	CH_3	*B*	**5i** 58

[a] Yield of isolated compound calculated from the resin substitution.

In summary, we have developed the first solid phase synthesis of orthogonally protected chiral α-hydrazinoacid derivatives bearing three points of diversity: the lateral chain, the ester group and the protecting group of the N^α. An original *trans*-protection reaction of the phthaloyl group results in efficient releases of orthogonally bis-protected NHBoc or fully tris-protected $NBoc_2$ derivatives useful for the preparation of hydrazino- and *N*-amino-pseudopeptides.

5. Experimental

Liquid phase: General procedure for *trans*-protection reactions of phthalimide group. To a solution of compound **3** (3 mM) in THF (20 mL) was added at room temperature 3 equiv of pyrrolidine (9 mM). The mixture was stirred at room temperature until completion

(about 4 h, monitored by TLC). The solvent and the excess of amine were removed in vacuo. To the white solid those obtained dissolved in THF (20 mL) was added Σ_2O (1.5 equiv, 4.5 mmol) and a catalytic amount of DMAP. The mixture was stirred at room temperature until completion (monitored by TLC). The solvent was removed in vacuo, the residue was dissolved in THF and a solution of methylamine (4.5 mM, 2 M in MeOH) was added at room temperature. After 3 h, the solvent and the excess of amine were removed in vacuo and **5** was purified by column chromatography.

Solid phase: General procedure for supported synthesis of α-hydrazinoesters. All the reactions were performed at room temperature; the resin suspension was gently shaken by N_2 bubbling; after each step, the resin was filtrated, washed (twice with CH_2Cl_2, and twice with THF) and resuspended in THF. Step 1: to a suspension of 0.5 g of Wang PS resin (cross linked with 1% DVB, 200–400 mesh, 1.08 mM/g) in THF, was added PPh_3 (3 equiv, 1.6 mM), trimellitic anhydride (3 equiv, 1.6 mM) and then, in one portion, DIAD (3 equiv, 1.6 mM); reaction time: 4 h. Step 2: carbazate was added (3 equiv, 0.54 mM) to the mixture; reaction time: 4 h. Step 3: DCC (4 equiv, 2.2 mM) and HOBt (4 equiv, 2.2 mM) were added; reaction time: 3 h. Step 4: to the suspension was added PPh_3 (3 equiv, 1.6 mM), α-hydroxyester (RCH(OH)COOR′, 3 equiv, 1.6 mM) and then, in one portion, DIAD (3 equiv, 1.6 mM); reaction time: 4 h. *Cleavage A*. Step 5: methylamine (4 equiv, 2.2 mM, 2 M in MeOH) was added in one portion; reaction time: 3 h (without N_2 bubbling). Step 6: Boc_2O (4 equiv, 2.2 mM) and a catalytic amount of DMAP were added. After 2 h, the polymer was removed by filtration; the filtrate was evaporated and the compound **4** was chromatographed on silica gel. *Cleavage B*. Step 5: pyrrolidine (4 equiv, 2.2 mM) was added in one portion; reaction time: 3 h. Step 6: Boc_2O (4 equiv, 2.2 mM) and a catalytic amount of DMAP were added; reaction time: 3 h. Step 7: methylamine (4 equiv, 2.2 mM, 2 M in MeOH) was added in one portion; after 2 h (without N_2 bubbling), the polymer was removed by filtration; the filtrate was evaporated to yield pure compound **5**.

References and notes

1. (a) Seneci, P. Solid Phase Synthesis and Combinatorial Chemistry; Wiley Interscience: New York; (b) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: Weinheim, 2000.
2. Marraud, M.; Vanderesse, R. Peptides Containing C/N/O Amide Bond Replacements. In *Synthesis of Peptides and Peptidomimetics*; Goodman, M., Ed.; Houben-Weyl, 2003, pp 423–457.
3. Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399–4428.
4. (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395; (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397; (c) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397–6399; (d) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F., Jr. *Tetrahedron* **1988**, *44*, 5525–5540; (e) Oppolzer, W.; Moretti, R. *Tetrahedron* **1988**, *44*, 5541–5552; (f) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553–5562.
5. (a) Schestakov, P. I. *J. Soc. Phys. Chim. Russia* **1903**, *35*, 850–852; (b) Gustafsson, H.; Ragnarsson, U. *Acta Chim. Scand.* **1979**, *29B*, 93–95; (c) Viret, J.; Gabard, J.; Collet, A. *Tetrahedron* **1987**, *43*, 891–894; (d) Amour, A.; Collet, A.; Dubar, C.; Reboud-Ravaux, M. *Int. J. Pept. Protein Res.* **1994**, *43*, 297–304.
6. (a) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691–1709; (b) Guy, L.; Vidal, J.; Collet, A.; Amour, A.; Reboud-Ravaux, M. *J. Med. Chem.* **1998**, *41*, 4833–4843; (c) Niederer, D. A.; Kapron, J. T.; Vederas, J. C. *Tetrahedron Lett.* **1993**, *34*, 6859–6862.
7. Hoffman, R. V.; Kim, H. O. *Tetrahedron Lett.* **1990**, *31*, 2953–2956.
8. (a) Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *J. Org. Chem.* **2000**, *65*, 4370–4374; (b) Brosse, N.; Pinto, M.-F.; Bodiguel, J.; Jamart-Grégoire, B. *J. Org. Chem.* **2001**, *66*, 2869–2873.
9. Bonnet, D.; Grandbjean, C.; Rousselot-Pailley, P.; Joly, P.; Bourel-Bonnet, L.; Santraine, V.; Gras-Masse, H.; Melnyk, O. *J. Org. Chem.* **2003**, *68*(10), 7033–7040.
10. (a) Brosse, N.; Jamart-Grégoire, B. *Tetrahedron Lett.* **2002**, *43*, 249–251; (b) Brosse, N.; Pinto, M.-F.; Jamart-Grégoire, B. *Eur. J. Org. Chem.* **2003**(24), 4757–4764.
11. Aronov, A. M.; Gelb, M. H. *Tetrahedron Lett.* **1998**, *39*, 4947–4950.
12. Bauer, J.; Rademann, J. *Tetrahedron Lett.* **2003**, *44*, 5019–5023.