Pergamon

Tetrahedron Letters 40 (1999) 4535–4538

TETRAHEDRON
LETTERS

Solid-Phase Synthesis of α-Amino Acids by Radical Addition to a Dehydroalanine Derivative

Anne-Marie Yim*, Yves Vidal*, Philippe Viallefont, Jean Martinez

Laboratoire des Aminoacides, Peptides et Protéines, CNRS-UMR 5810, Universités Montpellier I et II,
Place E. Bataillon, 34095 Montpellier, Cedex 5- FRANCE

Received 22 March 1999; accepted 20 April 1999

Abstract: *The first synthesis of N-acetyl-α-amino acids by radical addition on solid support to commercialy available 2-acetamidoacrylic acid using the mercury method is described. The reaction proceeds in acceptable chemical efficiency (49-60%) depending on the nature of the mercury halide agent. Cleavage by mild acid treatment released the product from the solid support in excellent purity.*

Keywords: dehydroamino acids - solid phase - mercury method - radical addition - N-acetyl-α-amino acids.

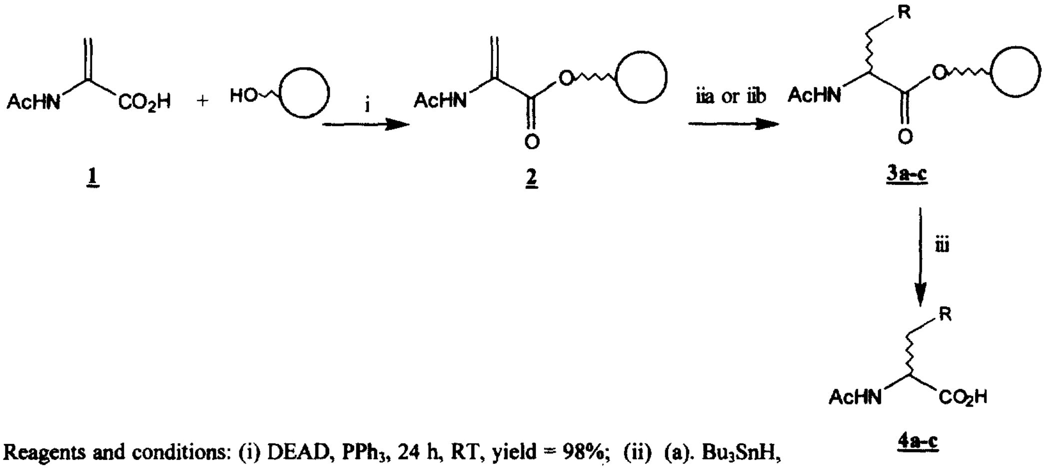
Organic synthesis of small molecules by solid-phase methods is emerging as a powerful tool for the discovery of new biologically active compounds[1] through parallel synthesis of libraries. Chemistry on solid support has been widely developed in peptide chemistry, it initiated combinatorial chemistry which stimulated development of organic chemistry on solid support. Moreover radical reactions on polymer supports remain relatively unexplored[2]. We would like to present solid phase synthesis of N-protected amino acids[3] by radical addition to a dehydroalanine derivative.

We report the first synthesis of N-acetyl-α-amino acids by the addition of radicals to polymer-supported commercialy available 2-acetamidoacrylic acid 1 using the mercury method. This type of reaction has never been performed on polymer support. The aim of this study was the preparation of N-acetyl-α-amino acids with extremely bulky side chains.

We propose a three-step strategy as depicted in Scheme 1: anchoring of 2-acetamidoacrylic acid 1 to a solid support, radical addition and subsequent cleavage from the resin by mild treatment which retains the N-protecting group. Wang resin was selected because of its easy cleavage in mild acidic conditions. Moreover this polymer matrix is inert to the radical reaction conditions[2c]. The N-acetyl protecting group was chosen to allow an eventual enzymatic resolution using an aminoacylase for obtaining optically pure α-amino acids[4].

* corresponding authors: Fax: (33) 04 67 14 48 66; e-mail: amyim@crit.univ-montp2.fr.; yvidal@crit.univ-montp2.fr.

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00799-6



Reagents and conditions: (i) DEAD, PPh_3, 24 h, RT, yield = 98%; (ii) (a). Bu_3SnH, AIBN, *tert*-BuI, C_6H_6, 2 h, RT or (b). RHgCl, $NaBH_4$, CH_2Cl_2/H_2O, 1 h 30, RT, (**3a** R = iPr, **3b** *tert*-Bu, **3c** *c*-C_6H_{11}); (iii) TFA/CH_2Cl_2 (20%), 30 min, RT.

Scheme 1

Anchoring the amino acid onto Wang resin (4-alkoxybenzyl alcohol polystyrene) through the carboxylic acid function has been accomplished by the Mitsunobu method[3b,5]. The polymer bound acrylate **2** was characterized by FTIR, which showed complete disappearance of the OH hydroxyl stretch at 3576 cm^{-1} and the appearance of the C=O carbonyl strech at 1714 cm^{-1} and the amide function: NH stretch at 3396 cm^{-1} and C=O stretch at 1700 cm^{-1}. Microanalysis of the acrylate resin **2** showed that quantitative conversion of Wang resin was achieved (%N: 1.14, calculated: 1.06). We investigated the scope of the reaction by trying to generate radicals by the action of tributylstannane on alkyl iodide, following the method described by Beckwith[6]: the dehydroamino acid **2** was heated in refluxing benzene with *tert*-butyliodide (3.0 eq.) and a solution of Bu_3SnH (1.5 eq.) and AIBN (1.0 eq.) in benzene was added. The mixture was heated under argon for 2 h. The acidic cleavage of the resin only released trace amounts (8%) of the desired product, starting material was recovered in the washings. Prolonged reaction time (24 h) resulted in degradation of the dehydroamino acid **2**. This failure may come from the reaction conditions imposed by the tributylstannane method, resulting in poor swelling of the resin in benzene[7] and in prolonged heating. In an effort to overcome these drawbacks we chose successfully the mercury method of Crich[8] to generate radicals. The synthesis of N-acetyl-d,l-leucine **4a** was performed at room temperature by dropwise addition of an excess of aqueous sodium borohydride to a mixture of compound **2** and isopropylmercury chloride (CH_2Cl_2, stirring, N_2) to give **3a**. After completion, the resin was filtered and washed (CH_2Cl_2, MeOH). Cleavage of **3a** from solid-support using TFA/CH_2Cl_2 (20%) gave the required N-acetyl-d,l-leucine **4a** in 49 % isolated yield.

Syntheses of N-acetyl-γ-methyl-d,l-leucine **4b** and N-acetyl-d,l-cyclohexylalanine **4c** were achieved under the same reaction conditions and the compounds[9] **4a** and **4c** were obtained in isolated yields of 49 and 60% (Table 1).

Entry	Organomercury chloride	Substrate	Product[a]	Yield of α-amino acid (%)[b]
1	*i*-PrHgCl	**3a**	**4a**	49
2	*tert*-Bu HgCl	**3b**	**4b**	49
3	c-C_6H_{11}HgCl	**3c**	**4c**	60

The alkylation reaction was performed with sodium borohydride (8.0 eq.) and organomercury chloride (3.0 eq.) in dichloromethane/water, RT. (a) All compouds **4a-c** were characterized by ^{1}H NMR, IR spectroscopy, mass spectrometry and gave satisfactory microanalytical and high resolution mass data. (b) Isolated yield based on the loading of the corresponding substrates **3a-c**.

Table 1: Radical alkylation using mercury method

In summary we successfully carried out a radical addition on supported dehydroamino acids with acceptable yields. The problematic removal of excess reagents from the reaction mixture was easily accomplished by simple washings of the resin. Given the wide variety of alkylmercury halides, we believe this methodology has wide potential in the synthesis of α-amino acids. Extension of enantioselective variants are under investigation and will be reported in due course.

References and notes

1. (a) Moos, W.H.; Green, J.D.; Pavia, M.R. *Annu. Rep. Med. Chem.* **1993**, *28*, 315. (b) Gallop, M.A.; Barett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gordon, E. M. *J. Med. Chem.* **1994**, *37*, 1233. (c) Gordon, E.M.; Barett, R.W.; Dower, W.J.; Fodor, S.P.A.; Gallop, M.A. *J. Med. Chem.* **1994**, *37*, 1385 and references cited.
2. (a) Routledge, A.; Abell, C.; Balasubramanian, S. *Synlett* **1997**, *1*, 61. (b) Du, X.; Armstrong, R.W. *J. Org. Chem.* **1997**, *62*, 5678. (c) Sibi, M.P.; Chandramouli, S.V. *Tetrahedron Lett.* **1997**, *38*, 8929. (d) Du, X.; Armstrong, R.W. *Tetrahedron Lett.* **1998**, *39*, 2281. (e) Berteina, S.; Mesmaeker, A. D. *Tetrahedron Lett.* **1998**, *39*, 5759. (f) Berteina, S.; Mesmaeker, A. D. *Synlett* **1998**, 1231.
3. (a) Yang, L.; Chiu, K. *Tetrahedron Lett.* **1997**, *38*, 7307. (b) Barbaste, M.; Rolland-Fulcrand, V.; Roumestant, M.L.; Viallefont, Ph.; Martinez, J. *Tetrahedron Lett.* **1997**, *39*, 6287.
4. Chenault, H.K.; Dahmer, J.; Whitesides, G.M. *J. Am. Chem. Soc.* **1989**, *111*, 6354.
5. Floyd, C.D.; Lewis, C.N.; Patel, S.R.; Whittaker, M. *Tetrahedron Lett.* **1998**, *37*, 8045.
6. Beckwith, A.L.J.; Chai, C.L. *J. Chem. Soc. Commun.* **1990**, 1087.
7. Santini, R.; Griffith, M.C.; Qi , M. *Tetrahedron Lett.* **1998**, *39*, 8951.
8. Crich, D.; Davies, J.W.; Negron, G.; Quintero, L. *J. Chem. Research (S)* **1988**,140.
9. **Typical Experimental Procedure:** *Mitsunobu reaction on Wang resin* : Wang resin (0.83 mmol/g loading), 2-acetamidoacrylic acid **1** (5.0 eq.) and triphenylphosphine (5.0 eq .) were dried *in vacuo* for 12 h and gently stirred in anhydrous freshly distilled THF (15 mL/1 g of resin) for 30 min under a blanket of argon at room temperature. DEAD (diethyl azodicarboxylate) (5.0 eq.) was added dropwise and the mixture was stirred for 24 h. The resin

was collected by filtration and then washed successively with THF (3 x 30 mL), DCM (3 x 30 mL), MeOH (3 x 30 mL), DCM (3 x 30 mL) and then dried *in vacuo*. The IR (KBr) spectrum showed the C=O ester band (1714 cm^{-1}) and the NH amide band (3396 cm^{-1}) and the C=C ethylenic band (1630 cm^{-1}) of anchored resin **2** and the absence of the OH hydroxyl band (3576 cm^{-1}) of the Wang commercial resin. Elemental analysis: %N 1.14 (1.06 calculated). *Radical addition*: loaded substrate **2** (0.05 M in CH_2Cl_2) was suspended in organomercury halide[10] dichloromethane (3.0 eq.) under a blanket of nitrogen. A solution of sodium borohydride (0.8 M, 8.0 eq.) in water was added over 20 min at room temperature and the mixture was stirred for further 90 min. The resin was washed successively with DCM (3 x 30 mL) , EtOH (3 x 30 mL) and DCM (3 x 30 mL) and then dried *in vacuo* for 24 h. *Product cleavage from resin*: The resin-bound N-acetyl amino acid (**3a**, **3b** or **3c**) was treated with a mixture of 20% TFA in DCM (30 mL/1 g of resin) for 30 min at room temperature. The resin was washed with DCM (3 x 30 mL) and MeOH (3 x 30 mL) and the solution was evaporated to yield **4a**, **4b** and **4c** which have been easily recrystallized as white solids in (1/1) AcOEt/iPr_2O system. **N-acetyl-d,l-leucine 4a**: yield (49%); mp 161-164 °C (lit[11]. mp 161 °C); MS (FAB, GT), $[M+H]^+=174$; HRMS (FAB, GT) calcd for $C_8H_{15}O_3N$ 174.1130; found 174.1060. Anal. Calcd for $C_8H_{15}O_3N$: C, 55.54; H, 8.74; N, 8.1. Found: C, 55.47; H, 8.99; N, 8.04. **N-acetyl-γ-methyl-d,l-leucine 4b:** yield (49%); mp 210-212 °C (lit[12]. mp 224-225 °C, 1 enantiomer); MS (FAB, GT), $[M+H]^+=188$; HRMS (FAB, GT) calcd for $C_9H_{17}O_3N$ 188.3112; found 188.3116. Anal. Calcd for $C_9H_{17}O_3N$: C, 57.80; H, 9.16; N, 7.49. Found: C, 57.23; H, 9.18; N, 7.30. **N-acetyl-d,l-cyclohexylalanine 4c**: yield (60%); mp 176-177 °C (lit[13]. mp 174-175 °C); MS (FAB, GT), $[M+H]^+=214$; HRMS (FAB, GT) calcd for $C_{11}H_{19}O_3N$ 214.1443; found 214.1473. Anal. Calcd for $C_{11}H_{19}O_3N$: C, 62.02; H, 9.03; N, 6.58. Found: C, 62.03; H, 9.06; N, 6.47.

10. Organomercury compounds: *iso*-propylmercury chloride, *tert*-butylmercury chloride and *cyclo*-hexylmercury chloride were prepared following the classical procedure. For rewiews see: *Organic Synthesis*, Springer-Verlag: Berlin **1985**; Houben-Weyl: *Methoden der Organischen Chemie*, Georg Thiem Verlag: Stuttgart **1974**, vol. 13/2b.
11. Fischer, E.; *Beil.* **1901**, *34*,449.
12. Prospisek, J.; Blaha, K. *Coll. Czech. Chem. Comm.* **1987**, *52*, 514.
13. Sealock, R.R.; Speeler , M.E.; Schweet, S.S. *J. Am. Chem. Soc.* **1951,** *73*, 5386.