

Nucleophilic Substitution of Protected 2-Amino-4-Butanoic Acid. An Easy Route to Exotic Amino Acids and Conformationally Constrained Peptides.

Paola Ciapetti,^a André Mann,^b Angèle Shoenfelder^b and Maurizio Taddei^{*a}

^aDipartimento di Chimica, Università di Sassari, Via Vienna 2, I-07100 Sassari, Italy, (E-mail: mtad@ssmain.uniss.it) and ^bCNRS, ERS 655, Pharmacochimie de la Communication Cellulaire, Faculté de

Pharmacie, 74, route du Rhin, BP 24, 67401 Illkirch Cedex, France

Received 30 January 1998; revised 16 March 1998; accepted 20 March 1998

Abstract: The synthesis of a series of novel α -amino acids based on the nucleophilic substitution of protected 2-amino-4-bromobutanoic acid (**1**) is described. Basic, acidic or neutral amino acids can be obtained; chimerical amino acids carrying a coenzyme type structure in the side chain, multifunctional amino acids for the synthesis of cross-linked peptides or dendrimers and conformationally constrained peptides can also be obtained. © 1998 Elsevier Science Ltd. All rights reserved.

This paper is dedicated to the memory of Antonino Fava, Professor Emeritus of the University of Bologna.

The development of synthetic methodologies for the preparation of new α -amino acids is one of the main goals of contemporary organic chemistry.¹ Even though superb asymmetric syntheses are continuously discovered,² the transformation of simple encoded amino acids into more complex compounds is still a rich source of novel structures.³

The introduction of a new function into the side chain of halogenated α -amino acid through a simple nucleophilic substitution, although conceptually trivial, has not been equally investigated.⁴ We described recently the synthesis of new chimerical amino acids carrying a nucleobase in the side chain through a nucleophilic substitution of adenine, thymine or cytosine on protected 2-amino-4-bromobutanoic acid (**1**).⁵ We decided to investigate if compound **1** could be used to prepare a larger series of nonnatural amino acids or peptides and we now report that this compound is actually a versatile tool for the synthesis of α -amino acids.

Compound **1** was prepared, as previously described,⁵ by a photochemically induced radical decarboxylation of the Barton's ester of (S)-N-Boc-glutamic acid α -*tert*-butyl ester in the presence of CBrCl₃, a single step procedure from a commercially available compound. Its use in the synthesis of new amino acids and peptides could follow two different strategies:

- i* Nucleophilic substitution in position 4 followed by deprotection of the amino acid functions, protection at the nitrogen and introduction into a peptide via liquid or solid phase protocols.
- ii* Introduction of the bromo-derivative inside an oligopeptidic structure followed by intermolecular or intramolecular nucleophilic substitution.

The first approach was really straightforward as **1** reacted with a large number of nitrogen, oxygen, sulphur and carbon nucleophiles as reported in table 1

Table 1 . Products of the reaction of **2** with different nucleophiles.

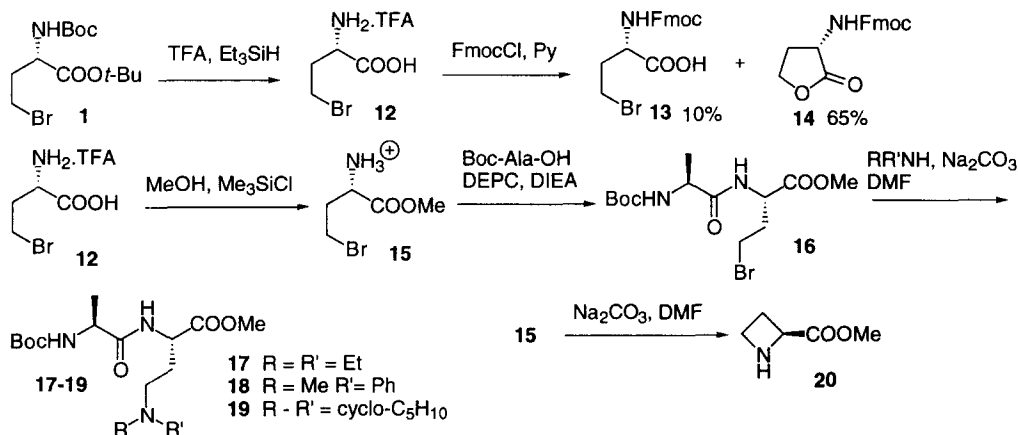
Nucleophile	Product	Nucleophile	Product
	 2 88%		 7 66%
	 3 86%		 8 65%
	 4 55%		 9 47%
Na_2S	 5 77%		 10 63%
	 6 58 %		 11 44%

The reaction conditions for the preparation of compounds **2-10** were: heating at 70°C a mixture of **1** and the appropriate electrophile in dry DMF in the presence of 4 eq. of Na_2CO_3 . As soon as tlc analysis showed the disappearance of the starting material, 2-12 h (warning: bromide **1** can be located on the plates exclusively with phosphomolybdate reagent), evaporation of the solvent and column chromatography on silica gel gave the desired compounds in the yields reported in the table. We never observed the presence of elimination,

deprotection or poly-alkylation products. The enantiomeric purity was assessed by ^1H and ^{19}F NMR of the MTPA amides, after acidic deprotection, and was always 90-95%.

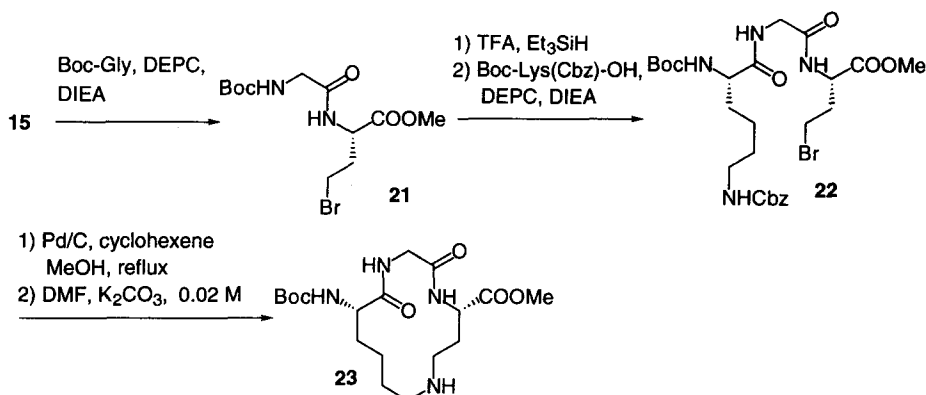
Best results were obtained with cyclic (secondary) amines which gave the heterocyclic basic amino acids **2-3** in very good yields. Phenols reacted successfully with **1** to give the substitution compounds **7-9** in acceptable yields. In fact pyridoxal gave product **7** through attack of the phenoxide ion at C-4 and concomitant formation of the hemi-acetal. Compound **7** can be considered as a chimerical amino acid with a structure related to a coenzyme.⁶ Reaction of **1** with Na_2S gave product **5** which is a doubly homologated (S,S) lanthionine derivative and reaction with pyrocatechol gave the bis-amino acid **9**. Compounds **5** and **9** might be employed for cross linking of polypeptides or as starting material for the synthesis of dendritic or multigen antigen peptides.⁷ Product **11** was obtained with a different procedure: reaction of the anion of dithiane (generated with BuLi in THF) with **1** in THF/HMPA (10:1) at room temperature, followed by hydrolysis and column chromatography.

The development of the second proposed strategy was more difficult for the intrinsic instability of N-protected 4-bromo carboxylate. In fact, after deprotection of **1** in acidic medium, the next introduction of the Fmoc group on the nitrogen gave very low yield of the desired product together with larger amounts of the N-Fmoc homoserine lactone **14** coming from an intramolecular nucleophilic substitution of the carboxylate at position 4. Thus we needed to first protect the carboxylic group in acidic medium and then use the resulting product (**15**) to prepare the brominated dipeptide **16**. This compound underwent nucleophilic substitution with secondary amines under standard conditions to give dipetide derivatives **17-19**.⁸ Moreover, if **15** is heated at 80°C in DMF in the presence of Na_2CO_3 , (S)-azetidine-2-carboxylic acid methyl ester **20** is obtained in very good yields (82%).



Scheme 1

Compound **15** was also used to prepare an oligopeptide where an intramolecular nucleophilic substitution could occur. After coupling of **15** with N-Boc-Gly-OH in the presence of diethyl cyanophosphonate (DEPC) and *i*-Pr₂NEt (DIEA), dipeptide **21** was obtained. Product **22** was finally prepared after deprotection of **21** at the nitrogen and further coupling with N-Boc-lysine-ε-N-Cbz. Selective deprotection at the nitrogen of the lysine side chain followed by heating at 70°C in DMF (0.02 M) in the presence of K_2CO_3 gave the macrocyclic peptide **23** in 50% yield. (Scheme 2)



Scheme 2

In conclusion we have demonstrated that protected 2-amino-4-bromobutanoic acid is a versatile intermediate and that the simple nucleophilic substitution of halogen in a suitable location of the side chain is a powerful tool for the synthesis of new amino acids and peptides.

Acknowledgements. This work was financially supported by MURST (Rome) in the project 40% Es.Fin. 96, Sostanze Organiche Naturali.

References and notes.

- Williams, R. M. *Organic Chemistry Series Volume 7: Synthesis of Optically Active α -Amino Acids*; Baldwin, J. E., Magnus, P. D., Eds.; Pergamon Press: Oxford, 1989. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
- Two representative examples. Petatis, N.A.; Zavialov, I.A. *J. Am. Chem. Soc.* **1997**, *119*, 445. Myers, A.G.; Gleason, J.L.; Yoon, T.; King, D.W. *J. Am. Chem. Soc.* **1997**, *119*, 656 and references therein.
- Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987. Some selected examples: Ouerfelli, O.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfuné, Y. *Synlett*, **1993**, 409. Williams, L.; Zhang, Z.; Ding, X.; Joullié, M.M. *Tetrahedron Lett.* **1995**, *36*, 7031. Shimamoto, K.; Ohfuné, Y. *J. Med. Chem.* **1996**, *39*, 407. D'Aniello, F.; Falorni, M.; Mann, A.; Taddei, M. *Tetrahedron Asymmetry* **1996**, *7*, 1217. Walker, M.A.; Kaplita, K.P.; Chen, T.; King, H.D. *Synlett* **1997**, 115. Zhang, L.; Kauffman, G.S.; Pesti, J.A.; Yin, J. *J. Org. Chem.* **1997**, *62*, 6918. Tamagnan, G.; Neumeyer, J.L.; Gao, Y.; Wang, S.; Kula, N.S.; Baldessarini, R.J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 337. Gryko, D.; Jurczak, J. *Tetrahedron Lett.* **1997**, *38*, 8275.
- Halogenated amino acids have been used for the generation of nucleophiles with the technique of Jackson: Dunn, M.J.; Jackson, R.F.W.; Pietruszka, J.; Turner, D. *J. Org. Chem.* **1995**, *60*, 2210.
- Lenzi, A.; Reginato, G.; Taddei, M. *Tetrahedron Lett.* **1995**, *36*, 1713. Ciapetti, P.; Soccolini, F.; Taddei, M. *Tetrahedron* **1997**, *53*, 1167.
- For the preparation of analogous pyridoxal-amino acid chimerae see: Imperiali, B.; Roy, R.S. *J. Org. Chem.* **1995**, *60*, 1891. Imperiali, B.; Roy, R.S. *J. Am. Chem. Soc.* **1994**, *116*, 12083.
- Tamm, J.P. in "Peptides, Synthesis, Structures and Applications," B.Gutte Ed, Academic Press, San Diego, 1995, 456.
- Compounds **17-19** could be introduced, after saponification of the carboxylate, in a polypeptidic structure using a solid phase protocol.