Pergamon

Tetrahedron Letters, Vol. 37, No. 14, pp. 2483-2486, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00299-7

A PRACTICAL SYNTHESIS OF FREE AND PROTECTED GUANIDINO ACIDS FROM AMINO ACIDS.

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***Abstract**: Synthesis of protected guanidino acids in one pot reaction is achieved . Amino acids are treated with trimethylsilyl chloride, triethylamine, dicarbobenzoxy-S-methyl isothiourea in dichloromethane followed by removal of silyl group by treatment with methanol to give the corresponding carbobenzoxy guanidino acids.* Copyright © 1996 Elsevier Science Ltd

Recently a flurry of activity has been observed for the synthesis of fibrinogen receptor antagonists, where the main basic unit for modification is a tripeptide sequence Arg-Gly-Asp. During the course of our structure activity studies on the Arg-Gly-Asp sequence, we encountered difficulty in preparing tri-Z-L-Arg. The major disadvantages associated with the earlier literature method[1] include :

i) Use of a large excess of carbobenzoxy chloride
ii) Formation of N^{α} N^{ω}-di-Z-L-Arg in significant percentage.
iii) Lengthy and time consuming purification procedure.
iv) Overall poor yield. Some recent reports[2,3] offered improved yields, but these were not achievable on large scale in our hands.

Another difficulty we observed was the coupling of protected N-terminal Arg with C- terminal component was never clean. We, therefore, decided to modify the approach by using N^{α}-Z-Orn to prepare Tri-Z-L-Arg. Alternatively the L-Orn derivative could be utilized as a latent arginine component and at a later stage of the synthesis the NH_2 group could be converted into guanidine group by a simple chemical conversion.

The literature reports which involve direct conversion of NH_2 to unprotected guanidine[4-6]were not very practical, because of the drastic reaction conditions and poor solubility of reagent and /or products. Alternatively synthesis of protected guanidines could be a better proposition. A few reported methods offer such possibilities with the use of protected S-methylisothiourea[7-9], protected 1H-pyrazole carboxamidine[10,11] or protected thiourea-mercuric chloride[12] combination. All these recent methods offer reasonably good results. But there is no general method reported in the literature, where amino acids were directly converted into protected guanidino acid except in one recent publication [3] in which synthesis of two fully protected Arg were reported.We, therefore, would like to describe in this paper a very simple highly efficient, one-pot general method for the synthesis of protected guanidino acids. To achieve our goal, we have employed the idea of *in-situ* carboxyl protection with trimethylsilyl chloride as described earlier[13]. Thus, for the synthesis of tri-Z-L-Arg, N^{α}-Z-L-Orn-HCl was treated with an equivalent amount of Et_3N and trimethylsilyl chloride

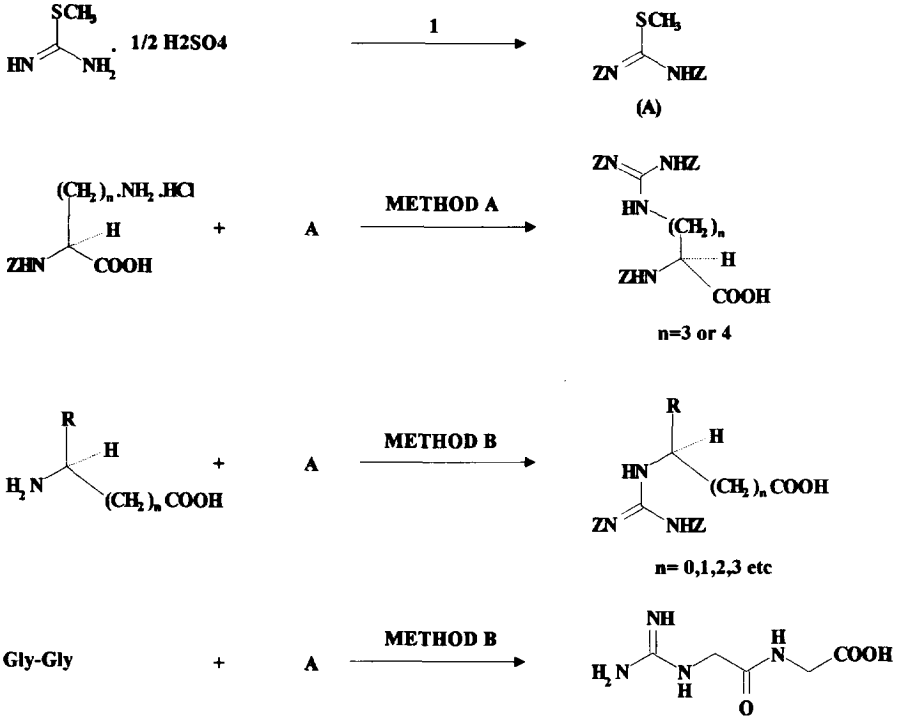
respectively to get silyl ester hydrochloride *in-situ* (method A[15]). The free base was generated by adding Et_3N which was then treated with di-carbobenzoxy-S-methyl isothiurea[14] under reflux. After the completion of the reaction, silyl deprotection was carried out by treatment with MeOH. A simple work up (see experimental[15]) leads to tri-Z-L-Arg in 87 % yield with optical purity same as reported compound.

After achieving our initial target, immediately we focused our attention to utilize this reaction as a general method . Thus, N^{α} -Z-L-Lys was converted into tri-Z-L-homo-Arg, isolated as its cyclohexylamine salt. A number of α-amino acids (by method-B) and ω-amino acids or their hydrochloride salts (by method A or B) were converted into this new class of α-guanidino and ω-guanidino acids in excellent yields. When using amino acids in zwitterionic form, initial use of Et_3N is not required. An important feature in all the examples lies in the fact that simple crystallization after work up is enough to get pure material. Further utility of the reaction, in generating protected guanidine in the later stage of the synthesis was established by converting Gly-Gly to α-dicarbobenzoxy guanidino acetyl glycine. A simple catalytic reduction of a few guanidino acid was done , gave the corresponding guanidino acid (guanidino acetic acid and arginine were compared with authentic samples). We believe that through this reaction process one can generate useful libraries for combinatorial chemistry. This approach was also subsequently utilized to generate Arg containing peptides corresponding to fibrinogen receptor antagonist, utilizing L-Ornithine as a latent Arg precursor. This part of the work will be published elsewhere.

Table-1

Entry No.	Starting Material	Method	Molar ratio SM/Reagent	Final Product	Yield
1	Nα-Z-L-Orn.HCl	A	1 : 1.25	Tri-Z-L-Arg.	87.2%
2.	Nα-Z-L-Lys.HCl	A	1 : 1.1	Tri-Z-L-homo Arg. Cyclohexylamine salt.	62%
3.	$H_2N.CH_2.COOH$	B	1.2 : 1	$ZNHC(=NZ)NHCH_2COOH$	97.5%
4.	(S) $PhCH_2CH(NH_2)COOH$	B	1.2 : 1	(S)-Z-$NHC(=NZ)NHCH(CH_2Ph)COOH$	84%
5.	$H_2N\ (CH_2)_2.COOH$	B	1.2 : 1	Z-$NHC(=NZ)NH(CH_2)_2COOH$	92%
6a.	$H_2N(CH_2)_3.COOH$	B	1.2 : 1	Z-$NHC(=NZ\ )NH(CH_2)_3\ COOH$	92%
6b.	$H_2N(CH_2)_3.COOH.\ HCl$	A	1.2 : 1	Z-$NHC(=NZ)NH(CH2)_3COOH$	92%
7.	$H_2N(CH_2)_4.COOH$	B	1.2 : 1	Z-$NHC(=NZ)NH(CH_2)_4COOH$	91%
8.	$H_2N(CH_2)_5.COOH$	B	1.2 : 1	Z-$NHC(=NZ)NH(CH_2)_5COOH$	80%
9.	HCl. p-$NH_2CH_2C_6H_4COOH$	A	1.2 : 1	p-$ZNHC(=NZ\ )NHCH_2C_6H_4COOH$	97.5%
10.	Gly-Gly	B	1.2 : 1	Z-$NHC(=NZ\ )GlyGly$	69%

SCHEME-1



1. 1 Eqv. NaOH, aq. $NaHCO_3$, Z-Cl (1.5 eqv.), CH_2Cl_2, 0°C, 3 hr. (97%).
METHOD A : 1. Et_3N, Me_3SiCl, CH_2Cl_2. 2. Et_3N, (A), CH_2Cl_2, reflux. 3. MeOH.
METHOD B : 1. Me_3SiCl, CH_2Cl_2. 2. Et_3N, (A), CH_2Cl_2, reflux. 3. MeOH.

Acknowledgments.

We gratefully acknowledge Dr.P.K.Inamdar and his group for the analytical data and Mrs.Indira Krishnasai for the manuscript.

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14. Di-carbobenzoxy -S-methyl isothiourea was prepared by modifying the reported procedure. S-methyl isothiourea sulphate was treated with one equivalent 1N NaOH, excess $NaHCO_3$, 3 equivalents Z-Cl in CH_2Cl_2 mixture with vigorous stirring for 3hr, with 97.5 % yield.

15. **Tri-Z-L-Arg. (Method A) :**

To a suspension of N^{α}-Z-L-Orn.HCl (1.21g; 4 mmol) in CH_2Cl_2 (30 ml), Et_3N (0.56 ml; 4 mmol) was added followed by trimethylsilyl chloride (TMS-Cl) (0.51 ml; 4 mmol) with vigorous stirring at 0°C. The ice bath was removed and the mixture was stirred at room temperature for 1 hr. It was again chilled to 0°C and Et_3N (1.12 ml; 8 mmol) was added followed by di-carbobenzoxy-S-methyl isothiourea[14] (1.79 g; 5 mmol). The ice bath was removed and the mixture refluxed (12 hr). The reaction mixture was brought to room temperature and MeOH ($\simeq$ 5 ml) was added, After stirring for 10-15 min, the solvent was evaporated. The residue was taken up in EtOAc and acidified. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and solvent was evaporated. The residue was dissolved in EtOAc and precipitated by adding light petroleum. The solid was filtered off and recrystallized from hot MeOH.

Yield 2.01 g (87.2%) ; $[\alpha]25$ + 16.41° (C=1. chloroform) ,(Reported + 16.8° C=1 chloroform) [16]

Di-carbobenzoxy guanidino acetic acid - 3 (Method B).

To a vigorously stirred suspension of finely powdered glycine (2.25 g ; 30 mmol) in CH_2Cl_2 (50 ml), trimethylsilyl chloride (3.81 ml ; 30 mmol) was added dropwise at room temperature over 5 min. The reaction mixture was refluxed for 1hr, and subsequently cooled to 0 °C. Et_3N (5.6 ml; 40 mmol) was added followed by dicarbobenzoxy-S-methyl isothiourea (8.95 g ; 15mmol). The reaction mixture was refluxed for 1hr, it was brought back to room temperature and stirred with MeOH (25 ml) for 10 min. The solvent was evaporated and the residue diluted with water acidified with dil.HCl to pH 2. The precipitated material was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, solvent evaporated and the product crystallized from EtOAc-light petroleum ether.Yield 9.4g (97.5 %)

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(*Received in UK* 19 *December* 1995; *revised* 9 *February* 1996; *accepted* 16 *February* 1996)