Tetrahedron Letters, Vol. 34, No. 24, pp. 3861-3862, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

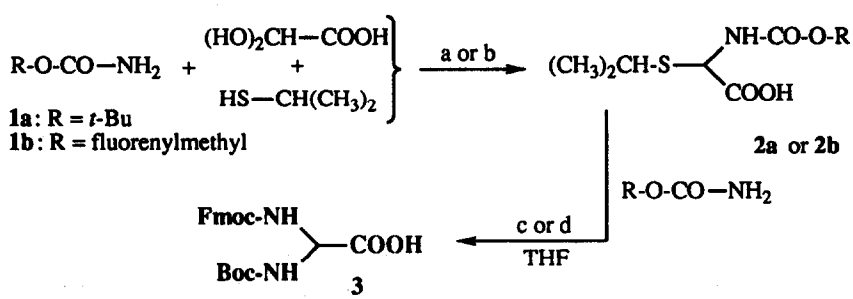
An α-Aminoglycine Derivative Suitable for Solid Phase Peptide Synthesis Using Fmoc Strategy.

Driss Qasmi, Loïc René and Bernard Badet*

Institut de Chimie des Substances Naturelles, C.N.R.S., 91198 Gif-sur-Yvette Cedex, France

Abstract: α-Boc-amino-Fmoc-glycine was prepared in two steps either from *t*-butyl carbamate or from 9-fluorenylmethylcarbamate and used in Solid Phase Peptide Synthesis to prepare α-aminoglycine-containing peptides.

A number of methods have been developed to prepare differentially protected α-aminoglycine[1] but until then none allowed to obtain Fmoc-protected α-aminoglycine. This compound would be ideally suited for Solid Phase Peptide Synthesis using Fmoc strategy leading to α–aminoglycine-containing peptides.



a) **1a**: diethylether, r.t. overnight. b) **1b**: toluene, PTSA, Dean-Stark, reflux 2h.
c) **2a**: +NBS at 0°C then reflux 2h. d) **2b**: +NBS at 0°C then 2h r.t;

Glyoxylic derivatives **2a**[2] and **2b**[3] were easily obtained by reaction of the corresponding carbamate **1a** or **1b**[4] with 2-propanethiol and glyoxylic acid hydrate. A similar compound has been already obtained from α-hydroxy-Z-glycine[5].

Treatment of compounds **2** by NBS in THF in the presence of the corresponding carbamate **1a** or **1b** afforded α-Boc-amino-Fmoc-glycine **3**[6] in 75-80% yield. α-Boc-amino-Z-glycine was previously prepared by displacement of isopropylthio group by *t*-butyl carbamate in the presence of mercury salts[5].

Using compound 3 α–aminoglycine could easily be incorporated in a peptide using Fmoc-based Solid Phase Peptide Synthesis strategy as exemplified by the synthesis of the octapeptide Ac-V-S-Q-N-F-G(NH2)-I-V-OH[7]. Since no control of the stereochemistry of the chiral center was attempted at the first step, compounds 2 and 3 as well as the α–aminoglycine-containing peptide were obtained as racemic mixtures. Applications of α–aminoglycine containing peptides will be reported elsewhere.

Acknowledgement: We thank A.N.R.S. for financial support.

References and Notes

Abbrevations : Boc: *t*-butyloxycarbonyl; Fmoc: 9-fluorenylmethyloxycarbonyl; Z: benzyloxy-carbonyl; PTSA: *para*-toluene sulfonic acid; THF: tetrahydrofuranne; NBS: N-bromo-succinimide.

1. a) Bock, M.G., DiPardo R.M., Freidinger R.M. *J. Org. Chem*, **1986**, *51*, 3718-3720
   b) Katritzky A.R., Urogdi L., Mayence A. . *J. Chem. Soc. Chem. Commun.*, **1989**, 337-338
   c) Katritzky A.R., Urogdi L., Mayence A. *J. Org. Chem*, **1990**, *55*, 2206-2214
2. Mp: 63°C. ^{1}H NMR (DMSO-d$_6$, 250 MHz): δ 1.33 (d, 3H, J=6.5); 1.36 (d,3H, J=6.5); 1.5 (s, 9H); 3.2 (m, 1H); 5.25 (d, 1H); 7.73 (d, 1H). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 22.81; 23.05; 27.35; 34.48; 54.81; 78.64; 154.41; 170.16. Mass spectrometry (chemical ionization, isobutane): *m/z* 249, M+H.
3. Mp: 152°C. ^{1}H NMR (DMSO-d$_6$, 250 MHz): δ 1.31 (d, 3H, J=6.6); 1.34 (d, 3H, J=6.6); 3.22 (m, 1H); 4.41 (m, 3H); 5.31 (d, 1H); 7.49 (m, 4H); 7.86 (d, 2H); 8.02 (d, 2H); 8.47 (d, 1H). ^{13}C NMR (DMSO-d$_6$, 62.5 MHz): δ 23.07; 23.52; 34.63; 46.57; 55.41; 65.98; 119.94; 125.25; 126.93; 127.55; 140.66; 143.54; 143.69; 155.3; 170.1. Mass spectroscopy (chemical ionization, isobutane): *m/z* 372, M+H; (FAB): *m/z* 372, M+H; 394, M+Na.
4. 9-fluorenylmethyl carbamate was easily prepared by treatment of 9-fluorenylmethyl chloroformiate with ammonia instead of using 9-fluorenylmethanol and NaOCN[8]
5. Zoller, U., Ben-Ishai, D. *Tetrahedron*, **1975**, *31*, 863-866
6. Mp: 187°C. ^{1}H NMR (DMSO-d$_6$, 200 MHz) δ 1.52 (s, 9H); 4.39 (m, 3H); 5.41 (t, 1H); 7.38 (m, 5H); 7.72 (d, 2H); 7.88 (d, 2H); 8.03 (d, 1H). ^{13}C NMR (DMSO-d$_6$, 75 MHz): 28.95; 47.39; 60.20; 66.81; 79.61; 120.94; 126.17; 127.92; 128.51; 141.54; 144.59; 155.48; 156.29; 70.79. Mass spectroscopy (chemical ionization, NH$_3$): *m/z* 413 M+H; 430 M+NH$_3$.
7. Synthesis was performed using a MilliGen 9050 PepSynthesizer™ with Fmoc-amino-acids pentafluorophenyl esters except compound 3 which was incorporated using N-N'-diisopropyl carbodiimide activation. Mass spectroscopy (FAB) *m/z*: 920 M+H; 942 M+Na. The two diastereoisomers could be resolved by C$_{18}$ Reverse-Phase HPLC (CH$_3$CN-H$_2$O, 0,05% TFA)
8. Carpino, L.A., Mansour, E.M.E., Cheng, C.H., Williams, J.R., MacDonald, R., Knapczyk, J, Carman, M., Lopusinsky, A. *J. Org. Chem.*, **1983**, *48*, 661-665

(Received in France 25 March 1993; accepted 17 April 1993)