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A Convenient, Large-Scale Preparation of a Differentially Protected α -Aminoglycine Suitable for the Synthesis of α -Aminoglycine-Containing Peptides

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**A CONVENIENT, LARGE-SCALE PREPARATION
OF A DIFFERENTIALLY PROTECTED α -AMINOGLYCINE
SUITABLE FOR THE SYNTHESIS OF
 α -AMINOGLYCINE-CONTAINING PEPTIDES**

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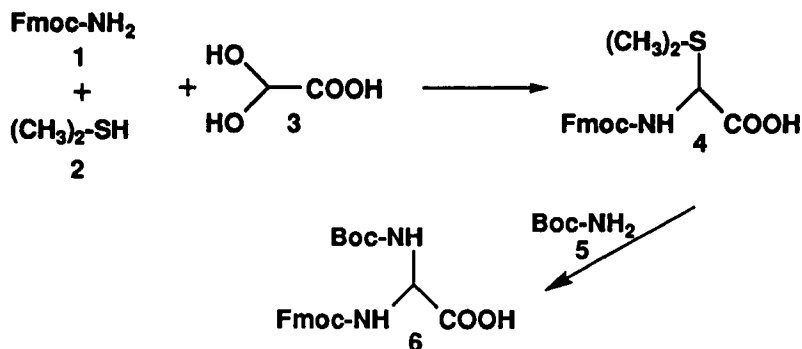
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ABSTRACT: α -Boc-amino-Fmoc-glycine **6** was prepared in two steps from 9-fluorenylmethylcarbamate **1**, glyoxylic acid **3** and *t*-butyl carbamate **5**. This compound is useful in Solid Phase Peptide Synthesis to prepare α -aminoglycine-containing peptides using Fmoc-strategy.

Thus far a limited number of natural peptides incorporating an α -aminoglycine moiety have been reported¹. Among the variety of methods which allow to obtain differentially protected α -aminoglycines²⁻⁷ we proposed one of an access⁶ to Fmoc-protected α -aminoglycine suitable for Solid Phase Peptide Synthesis.

Many inquiries about experimental details and substantial improvements in yield and work up prompt us to describe a large scale synthesis of *N*-*t*-butoxycarbonylamino-*N*-9-fluorenylmethyloxycarbonylamino-acetic acid **6** which is easily obtained in two steps (Scheme). The treatment of glyoxylic acid **3** with 9-fluorenylmethylcarbamate **1** and 2-propanethiol **2** in boiling toluene led to the

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Scheme

thioaminal: *t*-butoxycarbonylamino-isopropylthio-acetic acid **4**. Substitution of the alkylthio function by *t*-butyl carbamate **5** in the presence of *N*-bromosuccinimide afforded *N*-*t*-butoxycarbonyl-amino-*N*-9-fluorenylmethyloxy-carbonylamino-acetic acid **6** in overall yield of 50% (from *t*-butyl carbamate).

Experimental Section

9-fluorenylmethylcarbamate (1) was obtained according to three methods: from 9-fluorenylmethanol and NaOCN⁸, from 9-fluorenylmethylchloroformate or from 9-fluorenylmethyloxycarbonyloxy-succinimide. Fmoc-Cl or Fmoc-OSu (129g or 168g, 0.5 mol) was poured into a 50/50 v/v mixture (11) of dioxanne and ammonium hydroxyde (32%) cooled to 0°C. After 1h standing, most of dioxanne was evaporated under vacuum and the solid was filtered, washed with water and ether to yield up to 90% of **1**.

***t*-butyl carbamate (5)** is commercial and is also easily prepared from (Boc)₂O and ammonium hydroxyde.

***t*-butoxycarbonylamino-isopropylthio-acetic acid (4)**: A mixture of 9-fluorenyl-methylcarbamate (72g, 0.3 mol), glyoxylic acid⁹ (50% in water, 45 ml, 0.33 mol) and 2-propanethiol (50g, 60 ml, 0.66 mol) in toluene (700 ml) was refluxed with a Dean-Stark trap until distillation of water ceased. The hot solution was decanted to eliminate tar then allowed to cool to rt. The resulting solid which was filtered, washed with heptane and dried is pure enough for the next step (92g, 82%). A sample can be recrystallized from diisopropylether; mp, 152°C. ¹H NMR

(250Mz, DMSO- d_6) 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, J=9.8), 7.49 (m, 4H), 7.86 (d, 2H, J=9.2), 8.02 (d, 2H, J=9.2), 8.47 (d, 1H, J=9.8). ^{13}C (62.5 Mz, DMSO- d_6) 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).

***t*-butoxycarbonylamino-9-fluorenylmethyloxycarbonylamino-acetic acid (6):** To a solution of *t*-butoxycarbonylamino-isopropylthio-acetic acid **4** (55.65g, 0.15 mol) and *t*-butyl carbamate **5** (23.5g, 0.15 mol) in THF (300 ml) cooled to 0°C. *N*-bromosuccinimide (16g, 0.089 mol) was added in one portion. After 20min standing at this temperature the mixture was refluxed 2h. After cooling insoluble material was filtered off and THF eliminated under vacuum. After addition of ethanol (50%, 150 ml) the solid which appeared on standing was filtered, washed with ethanol (50%, 70 ml) and diethylether and finally recrystallized from ethanol to give white crystals (37g, 60%) mp, 187°C. ^1H NMR (200 MHz, DMSO- d_6) δ 1.52 (s, 9H), 4.39 (m, 3H), 5.41 (dd, 1H, J=10), 7.38 (m, 5H), 7.72 (d, 2H, J=9.2), 7.88 (d, 2H, J=9.2), 8.03 (m, 1H); ^{13}C NMR (75 MHz, DMSO- d_6): 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, 170.79. Mass spectroscopy (chemical ionization, NH_3): m/z 413 (M+H); 430 (M+ NH_3).

References and Notes

1. Yahara, S.; Shigeyama, C.; Nohara, T. *Tetrahedron Lett.*, **1989**, *30*, 6041-6042.
2. Bock, M.G.; DiPardo, R.M.; Freidinger, R.M. *J. Org. Chem.*, **1986**, *51*, 3718-3720.
3. Bock, M.G.; DiPardo, R.M.; Evans, B.E.; Rittle, K.E.; Weber, D.F.; Freidinger, R.M. *Tetrahedron Lett.*, **1987**, *28*, 939-942.
4. Katritzky, A.R.; Urogdi, L.; Mayence, A. *J. Chem. Soc. Chem. Commun.*, **1989**, 337-338.
5. Katritzky, A.R.; Urogdi, L.; Mayence, A. *J. Org. Chem.*, **1990**, *55*, 2206-2214.
6. Schmidt, U.; Stabler, F.; Lieberknecht, A. *Synthesis*, **1994**, 890-892.
7. Qasmi, D.; Rene, L.; Badet, B. *Tetrahedron Lett.*, **1993**, *34*, 3861-3862.
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.
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