A Practical Reagent for the Synthesis of Substituted Hydrazines

Leif Grehn, Barthelemy Nyasse, Ulf Ragnarsson*
Department of Biochemistry, University of Uppsala, Biomedical Center, PO Box 576, S-751 23 Uppsala, Sweden
Fax +46(18)552139; E-mail: urbki@bmc.uu.se

Received 13 June 1997

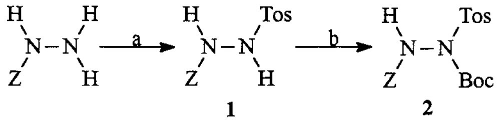
A practical, inexpensive triprotected hydrazine reagent, 2-benzyloxycarbonyl-1-*tert*-butoxycarbonyl-1-(4-methylphenylsulfonyl)-hydrazine, 1-Boc-1-Tos-2-Z-hydrazine (**2**), has been prepared on a 100 mmol scale and examined with respect to application in stepwise synthesis of unsymmetrically substituted hydrazines. The use of three protective groups excludes undesired substitution on the nitrogens even under forcing conditions. The initial alkylation which can be accomplished quantitatively is followed by the removal of the tosyl moiety. Due to the presence of a Boc group on the sulfonamide nitrogen atom, the otherwise rather stable sulfonamide function can be cleanly and efficiently cleaved reductively by magnesium in dry methanol to provide a second alkylation site. Such intermediates have recently been converted to tetrasubstituted hydrazines. With sonication this reduction is generally complete within 30 minutes. The new reagent exhibits increased stability to base in comparison with its predecessor and is more suitable and economical for work on a larger scale.

Whereas the problem connected with effecting clean monoalkylation of ammonia was, in principle, solved in the last century,[1] this was not the case for hydrazine for which direct alkylation approaches are still in use.[2] For some time it has appeared to us that standard amino-protecting groups such as those originally used in peptide synthesis should be applicable to the control of hydrazine reactivity.[3] As a first step to a practical stepwise synthesis of substituted hydrazines, we prepared and examined its Boc_3-substituted derivative,[4] which nowadays is readily prepared and, more importantly, it allowed two subsequent selective alkylations to be undertaken, one on each nitrogen. For the synthesis of unsymmetrical *N*,*N'*-dialkylated hydrazines, and symmetrically acylated derivatives thereof, this reagent would appear to be useful but increased target diversity would obviously require a combination of orthogonal amino-protecting groups.[5] More recently, we therefore developed such a novel hydrazine reagent[6] with three orthogonal protecting groups, Z, Boc and Cbs (Cbs = 4-cyanophenylsulfonyl), i.e.:

Z–NH–N(Cbs)–Boc

This hydrazine reagent also allowed for the first time four different substituents to be introduced into hydrazine. Cbs was selected because of its easy cleavage by reduction[7] which could be further enhanced after conversion to a sulfonylcarbamate. Reductive cleavage of Cbs from nitrogen could be accomplished essentially quantitatively with aluminum in moist diethyl ether, when present on the same nitrogen as Boc. This unconventional, very mild cleavage method is experimentally simple and the reagent is therefore recommended for general application in synthesis of substituted hydrazines on a small or moderate scale.

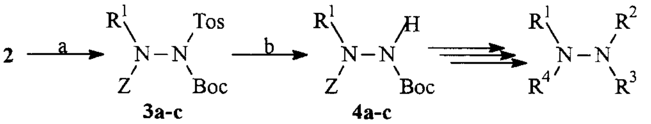
In parallel with this project, we carried out work with the analogous tosyl and other hydrazine derivatives. Although the tosyl group[8] can be cleaved by cathodic reduction and thus older, brutal, and not always selective methods can be avoided, we chose at that time to proceed with the Cbs- rather than the Tos-derivative. A new cleavage method for tosyl in this type of compound has, however, recently been identified,[9] i.e. cleavage with magnesium in methanol which, so far, appears to be both mild and fast, particularly when conducted with sonication. To this end we have now resumed our previous work and prepared the tosyl derivative on a fairly large scale. In addition, we have also verified that subsequent steps, i.e. the alkylation and the reduction with magnesium, can be scaled up without a detrimental effect on the yield.



(a) TosCl, pyridine, overnight (98 %); (b) Boc_2O, DMAP, MeCN, overnight (99 %), Boc = *tert*-butyloxycarbonyl, Tos = 4-methylphenylsulfonyl, Z = benzyloxycarbonyl.

Scheme 1

The new hydrazine reagent **2** is readily available by a convenient three-step route from hydrazine (Scheme 1). Thus $Z–NHNH_2$[10] was tosylated in pyridine to give Z–NH–NH–Tos (**1**) in essentially quantitative yield. The latter compound smoothly underwent *tert*-butoxycarbonylation with an equivalent amount of Boc_2O in acetonitrile in the presence of catalytic amounts of DMAP[11] under strictly controlled conditions providing **2** in excellent yield. This selective acylation is evidently due to the fact that the more acidic sulfonamide moiety in **1** reacted preferentially. Excess of acylating agent and higher temperature resulted in concomitant *tert*-butoxycarbonylation of the remaining urethane nitrogen.



(a) MeI or BnBr or $BrCH_2CO_2Et$, K_2CO_3, TBAHS, MeCN, 1–3 d, (essentially quantitatively); (b) Mg/MeOH, sonication (95–98 %).

Scheme 2

The pivotal trisubstituted reagent **2** carrying three orthogonal protective groups could then be alkylated with excess methyl iodide (**3a**), benzyl bromide (**3b**) or ethyl bromoacetate (**3c**) under mild phase transfer conditions in acetonitrile using K_2CO_3 as the base and tetrabutylammonium hydrogen sulfate (TBAHS) as the catalyst (Scheme 2). The yields of products **3a–c** were excellent with no detectable formation of side products. Compounds **3a–c** were then readily detosylated to **4a–c** using magnesium powder in dry methanol with sonication. The yield in this reductive cleavage was, again, almost quantitative and no significant side products were observed in the crude product. The detosylation of **3c** occurred with complete transesterification to give the corresponding methyl ester **4c**. It is also worth mentioning in this context that the quality of the solvent appears to be crucial for the outcome of the magnesium reduction.[9] We have now found that the reaction is inhibited when methanol dried over molecular sieves was employed as reaction medium, but after distillation of the dried solvent reductions are quickly initiated.

Hydrazine derivatives of the type R^1(Z)NH–NHBoc (R^1 = alkyl or aryl groups) would thus, now, be more inexpensively accessible by this approach.[6] Such compound should constitute valuable and versatile intermediates for the selective synthesis of a wide range of variously substituted hydrazines of chemical and pharmaceutical interest including tetrasubstituted hydrazines. To our knowledge no general or efficient synthetic strategy except ours exists for the preparation of such multisubstituted hydrazine derivatives. We, therefore, conclude that this improved synthesis of **4** based on the novel reagent **2** and incorporating the pivotal magnesium mediated removal of the tosyl moiety will be of considerable importance in hydrazine chemistry.

All melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. The MeOH used in the detosylation experiments was of analytical grade, containing < 0.05% water. Pyridine and MeCN were dried over molecular sieves (4A). Commercial TosCl was purified according to a standard procedure[12] and dried. All reactions were performed under argon and all reaction vessels were dried with a flame. TLC analyses were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel $60F_{254}$) with the mobile phases toluene/MeCN 2:1 (A) and CH_2Cl_2/Et_2O 19:1 (B). TLC spots were visualized under UV light or, preferentially, by alcoholic phosphomolybdic acid spray[13] and subsequent heating (blue spots). Preparative chromatography was carried out on Merck Kieselgel 60 (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded on a JEOL JMN EX 400 spectrometer in ~ 5% solution at 25 °C. All shifts are given in δ ppm using δ_H(TMS) = 0 and δ_C($CDCl_3$) = 77.02, respectively, as references. Assignments were made by comparison of chemical shifts and peak multiplicities. Elemental analyses of crystalline derivatives were carried out by Micro Kemi AB (Uppsala) and Astra Draco AB (Lund), Sweden.

1-Tos-2-Z-hydrazine (2-Benzyloxycarbonyl-1-(4-methylphenylsulfonyl)hydrazine, 1):

1-Benzyloxycarbonylhydrazine, Z-hydrazine[10] (16.6 g, 0.10 mol) was dissolved in dry pyridine (80 mL) and cooled to −30 °C under argon. Freshly purified TosCl (19.1 g, 0.10 mol) was introduced in small portions below −20 °C over 20 min with rapid stirring, whereupon the turbid yellow mixture was slowly allowed to assume r.t. The next day most of the solvent was stripped off at reduced pressure and the brownish oily residue dissolved in CH_2Cl_2 (200 mL). After distribution between EtOAc (1 L) and 1 M $KHSO_4$ (0.5 L), the extract was washed in succession with $KHSO_4$, 1 M $NaHCO_3$ and satd NaCl (3 × 250 mL each), dried (Na_2SO_4) and treated with decolorizing carbon. Removal of the solvent gave a white solid which was thoroughly triturated with cold light petroleum (50 mL). The slurry was kept at −20 °C overnight, whereupon the fine-grained white product was collected by filtration, rinsed with cold light petroleum (5 × 10 mL) and dried in high vacuo. The yield of crude product suitable for further work was 31.5 g (98%). TLC (A,B) gave one spot. An analytical specimen with mp 146–147 °C was obtained as long lustrous needles by recrystallization from EtOAc/hexane (1:2; 30 mL/g) and treatment with decolorizing carbon.

^1H NMR ($CDCl_3$/TMS): δ = 2.41 (s, 3 H, Me), 4.94 (s, 2 H, CH_2), 6.69 (br s, 1 H, Z–NH), 6.88 (br s, 1 H, Tos–NH), 7.19 (br signal) and 7.31–7.35 (complex signal, together 5 H, Ph–H), 7.22 (d, J = 8 Hz, 2 H, Tos–$H_{3,5}$), 7.76 (d, J = 8 Hz, 2 H, Tos–$H_{2,6}$).

^{13}C NMR ($CDCl_3$/TMS): δ = 21.71 (Me), 68.04 (CH_2), 128.19, 128.53, 129.62 (Ar), 133.54 (Tos–C_4), 135.10 (Z–C_1), 144.71 (Tos–C_1), 155.25 (CO).

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$ (320.4): C, 56.24; H, 5.03; N, 8.74. Found C, 56.35; H, 5.04; N, 8.88.

1-Boc-1-Tos-2-Z-hydrazine (2-Benzyloxycarbonyl-1-*tert*-butoxycarbonyl-1-(4-methylphenylsulfonyl)hydrazine, 2):

Crude **1** (33.6 g, 0.105 mol) and DMAP (641 mg, 5.25 mmol), dissolved in MeCN (525 mL), was reacted dropwise with stirring at −30 °C under argon with a solution of Boc_2O (23.6 g, 0.108 mol) in MeCN (70 mL). The resulting tan solution was left to attain r.t. (~ 3 h). The next day most of the solvent was stripped off below 30 °C to give a sirup which was distributed between Et_2O (1 L) and 0.2 M citric acid (0.5 L). The almost colorless extract was washed with in turn citric acid, 1 M $NaHCO_3$ and brine (3 × 250 mL each) and dried ($MgSO_4$, decolorizing carbon). Removal of the solvent left a colorless viscous oil which soon solidified. It was triturated with cold light petroleum (100 mL). After cooling, the white fine-grained material was collected by filtration, rinsed repeatedly with cold solvent and dried in high vacuo to give 43.2 g (99%) of **2**, suitable for further work. TLC (A,B) indicated only traces of impurities. An analytical specimen was prepared by recrystallization from Et_2O/hexane (1:3; ~ 5 mL/g; several days at −20 °C) as white, microcrystalline product with mp 103.5–104.5 °C.

^1H NMR ($CDCl_3$/TMS): main conformer; δ = 1.34 (s, 9 H, Boc–Me), 2.44 (s, 3 H, Tos–Me), 5.20 (s, 2 H, CH_2), 7.14 (br signal, ~ 1 H, NH), 7.20–7.26 (complex signal, ~ 7 H, Ph–H + Tos–$H_{3,5}$), 7.98 (d, J = 8 Hz, 2 H, Tos–$H_{2,6}$).

^{13}C NMR ($CDCl_3$/TMS): main conformer; δ = 21.71 (Tos–Me), 27.75 (Boc–Me), 68.22 (CH_2), 85.75 (Boc-C_q), 128.15, 128.47, 128.58, 129.14, 129.22, 135.30, 135.46 (Ar), 145.01 (Tos–C_1), 149.72 (Boc–CO), 154.79 (Z–CO).

Anal. Calcd for $C_{20}H_{24}N_2O_6S$ (420.5): C, 57.13; H, 5.75; N; 6.66. Found C, 57.41; H, 5.83; N, 6.53.

1-Boc-1-Tos-2-methyl-2-Z-hydrazine (2-Benzyloxycarbonyl-1-*tert*-butoxycarbonyl-2-methyl-1-(4-methylphenylsulfonyl)hydrazine, 3a):

Crude **2** (12.6 g, 30.0 mmol) was dissolved in MeCN (90 mL), finely ground, dry K_2CO_3 (16.6 g, 120 mmol) was added together with TBAHS (2.06 g, 6.0 mmol) and the resulting slurry stirred vigorously for a few min, whereafter MeI (5.60 mL, 90 mmol) was cautiously introduced with rapid stirring over 5 min under argon. The reaction was monitored by TLC (CH_2Cl_2/Et_2O 19:1). After 3 d it was generally complete, otherwise more MeI was added. Most of the solvent was stripped off at reduced pressure and the remaining semisolid material was suspended in CH_2Cl_2 (200 mL). This mixture was partitioned between Et_2O (1.0 L) and 0.2 M citric acid (0.5 L) and the extract was washed successively with citric acid, 1 M $NaHCO_3$ and brine (3 × 250 mL each) and dried ($MgSO_4$). Treatment with decolorizing carbon followed by evaporation of the solvent at reduced pressure gave a colorless viscous oil which slowly solidified on standing (13.0 g, 100%), pure by TLC and suitable for further work. An analytical sample was obtained by chromatography on silica using CH_2Cl_2/Et_2O 19:1 as eluent and crystallization from Et_2O mL/g, −20 °C) to afford white crystals with mp 112–112.5 °C.

^1H NMR ($CDCl_3$/TMS):major/minor conformer; δ = 1.32/1.34 (2 s, together 9 H, Boc–Me), 2.35/2.43 (2 s, together 3 H, Tos–Me), 3.35/3.39 (2 s, together 3 H, N–Me), 4.91, 5.15/5.19, 5.23 (2 ABq, J = 12.3 Hz, together 2 H, CH_2), 7.08–7.12 and 7.23–7.38 (complex signal, 7 H, Ph–H + Tos–$H_{3,5}$), 7.79/7.97 (2 d, J = 8.4 Hz, together 2 H, Tos–$H_{2,6}$).

^{13}C NMR ($CDCl_3$/TMS): major/minor conformer; δ = 21.60/21.68

(Tos—Me), 27.75/27.79 (Boc—Me), 38.84/39.78 (*N*—Me), 68.29/69.48 (CH_2), 85.39 (Boc—C_q), 127.86, 127.91, 128.09, 128.28, 128.53, 129.01, 129.03, 129.07, 129.30, 135.16, 135.40, 135.64, 135.68, 144.83 (ar), 149.19/149.25 (Boc—CO), 154.93/155.31 (Z—CO).

Anal. Calcd for $C_{21}H_{26}N_2O_6S$ (434.5): C, 58.05; H, 6.03; N, 6.45. Found C, 58.1; H, 6.1; N, 6.5.

1-Boc-1-Tos-2-benzyl-2-Z-hydrazine (2-Benzyl-2-benzyloxycarbonyl-1-*tert*-butoxycarbonyl-1-(4-methylphenylsulfonyl)hydrazine, 3b):
Prepared from **2** by phase transfer benzylation by analogy with **3a** using benzyl bromide (1.1 equiv) as the alkylating agent. After 3 d, the reaction was complete and the mixture was worked up as above. The yield of crude title compound containing only traces of benzyl bromide was essentially quantitative in a 30 mmol run. The analytical specimen was obtained similarly; mp 89.5–90 °C.

^{1}H NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 1.01/1.08$ (2 s, together 9 H, Boc—Me), 2.34/2.41 (2 s, together 3 H, Tos—Me), 4.59, 5.19/4.65, 5.10 (2 ABq, $J = 14.7$ Hz, together 2 H, *N*—CH_2), 5.01, 5.23/5.24, 5.33 (2 ABq, partly obscured, $J = 12.2$ Hz, together 2 H, *O*—CH_2), 7.06/~7.30 (2 d, partly obscured, $J = 8.1$ Hz, together ~2 H, Tos—$H_{3,5}$), 7.11–7.14 and 7.22–7.45 (complex signal, ~10 H, Ph—H), 7.73/7.95 (2 d, $J = 8.4$ Hz, together 2 H, Tos—$H_{2,6}$).

^{13}C NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 21.61/21.69$ (Tos—Me), 27.29/27.39 (Boc—Me), 55.20/56.56 (*N*—CH_2), 68.47/68.74 (*O*—CH_2), 84.80 (Boc—C_q), 127.99, 128.02, 128.07, 128.14, 128.30, 128.33, 128.35, 128.56, 128.90, 128.97, 129.40, 129.65, 130.09, 130.40, 134.91, 134.93, 135.14, 135.44, 135.59, 135.61, (Ar), 144.76/144.78 (Tos—C_1), 149.31/149.30 (Boc—CO), 154.90/154.84 (Z—CO).

Anal. Calcd for $C_{27}H_{30}N_2O_6S$ (510.6): C, 63.51; H, 5.92; N, 5.49. Found C, 63.49; H, 5.88; N, 5.54.

1-Boc-1-Tos-2-ethoxycarbonylmethyl-2-Z-hydrazine (2-Benzyloxycarbonyl-1-*tert*-butoxycarbonyl-2-ethoxycarbonylmethyl-1-(4-methylphenylsulfonyl)hydrazine, 3c):
Synthesized from **2** by phase transfer alkylation by analogy with **3a** and **3b** using ethyl bromoacetate (1.1 equiv) as the alkylating agent. After 1 d, the reaction was complete and the mixture was worked up as previously. The yield of crude product was quantitative in a 30 mmol run. The analytical sample was prepared as above; mp 72–72.5 °C.

^{1}H NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 1.30/1.22$ (2 t, $J = 7.2$ Hz, together 3 H, CH_3CH_2), 1.32/1.36 (2 s, together 9 H, Boc—Me), 2.35/2.43 (2 s, together 3 H, Tos—Me), 4.25/4.17 (q/dq, $J = 7.2/2.6$ Hz, together 2 H, CH_3CH_2), 4.31, 4.40/4.34, 4.38 (2 ABq, $J = 17.0/17.2$ Hz, together 2 H, *N*—CH_2), 4.87, 5.15/5.20 (ABq/s, $J = 12.3$ Hz, together 2 H, Z—CH_2), 7.06–7.14 and 7.23–7.37 (complex signal, 7 H, Ph—H + Tos—$H_{3,5}$), 7.84/7.97 (2 d, $J = 8.4$ Hz, together 2 H, Tos—$H_{2,6}$).

^{13}C NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 14.12/14.05$ (CH_3CH_2), 21.63/21.72 (Tos—Me), 27.71/27.77 (Boc—Me), 54.42/55.20 (*N*—CH_2), 61.21 (CH_3CH_2), 68.74/68.96 (Z—CH_2), 85.63/85.60 (Boc—C_q), 127.89, 127.99, 128.20, 128.28, 128.33, 128.48, 129.10, 129.14, 129.47, 134.78, 135.14, 135.24, 135.31, (Ar), 144.97/145.00 (Tos—C_1), 149.27/149.29 (Boc—CO), 154.54/154.35 (Z—CO), 167.03/167.12 (ester—CO).

Anal. Calcd for $C_{24}H_{30}N_2O_8S$ (506.6): C, 56.90; H, 5.97; N, 5.53. Found C, 56.9; H, 6.0; N, 5.5.

1-Boc-2-methyl-2-Z-hydrazine (2-Benzyloxycarbonyl-1-*tert*-butoxycarbonyl-2-methylhydrazine, 4a):
Finely ground, dry **3a** (4.35 g, 10.0 mmol) was dissolved in dry MeOH (150 mL) with gentle heating under argon and Mg powder (2.43 g, 0.10 mol; Merck 0.06–0.3 mm) was added in one portion with swirling. The slurry was subjected to sonication (35 kHz, 120–240 W, Bandelin, Berlin, type RK106), while keeping the reaction temperature at 25 °C by addition of ice to the bath. After ~5 min gentle frothing indicated initiation of the reaction and after a further 10 min, the evolution of gas had largely subsided. TLC (B) confirmed that the detosylation was complete after 30 min and most of the solvent was stripped off at reduced pressure. The semisolid residue was partitioned between Et_2O (400 mL) and 1 M $KHSO_4$ (200 mL) and the turbid aqueous phase discarded. The colorless organic extract was washed in turn with $KHSO_4$, 1 M $NaHCO_3$ and brine (3 × 100 mL each) and dried ($MgSO_4$) in the presence of decolorizing carbon. Removal of the solvent left a pale, yellow viscous oil which slowly solidified on drying under high vacuo. The yield of crude, according to TLC essentially pure product was 2.66 g (95 %). The analytical specimen was obtained by recrystallization from Et_2O/light petroleum 1 : 10 (50 mL/g) as white fluffy crystals with mp 61–61.5 °C.

^{1}H NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 1.42/1.46$ (2 s, together 9 H, Boc—Me), 3.18/3.16 (2 s, partially overlapping, together 3 H, *N*—Me), 5.15 (s, 2 H, CH_2), 6.62/6.46 (2 br s, 1 H, NH), 7.34 (br signal, 5 H, Ph—H).

^{13}C NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 28.08$ (Boc—Me), 37.91/38.34 (*N*—Me), 67.86 (CH_2), 81.49 (Boc—C_q), 127.92, 128.11, 128.41, 136.01, (Ar), 154.62/155.27 (Boc—CO), 156.32/156.70 (Z—CO).

Anal. Calcd for $C_{14}H_{20}N_2O_4$ (280.3): C, 59.99; H, 7.19; N, 9.99. Found C, 59.9; H, 7.2; N, 10.0.

1-Boc-2-benzyl-2-Z-hydrazine (2-Benzyl-2-benzyloxycarbonyl-1-*tert*-butoxycarbonylhydrazine, 4b):
Obtained by Mg mediated detosylation of **3b** according to the above procedure for **4a**. An analogous workup afforded crude, essentially pure **4b** in 98 % yield. The analytical sample was prepared similarly with mp 65–65.5 °C.

^{1}H NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 1.39/1.29$ (2 s, together 9 H, Boc—Me), 4.71 (br s, 2 H, *N*—CH_2), 5.19 (s, 2 H, *O*—CH_2), 6.32/6.09 (2 br s, together 1 H, NH), 7.25–7.34 (complex signal, 10 H, Ph—H).

^{13}C NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 28.07$ (Boc—Me), 53.40/54.08 (*N*—CH_2), 68.09/68.23 (*O*—CH_2), 81.60 (Boc—C_q), 127.71, 128.05, 128.19, 128.46, 128.57, 135.91, 136.44 (Ar), 154.45/155.01 (Boc—CO), 156.27 (Z—CO).

Anal. Calcd for $C_{20}H_{24}N_2O_4$ (356.4): C, 67.40; H, 6.78; N, 7.86. Found C, 67.4; H, 6.6; N, 7.6.

1-Boc-2-methoxycarbonylmethyl-2-Z-hydrazine (2-Benzyloxycarbonyl-1-*tert*-butoxycarbonyl-2-methoxycarbonylmethylhydrazine, 4c):
The Mg induced detosylation of **3c** occurred with concomitant transesterification[9] to give the corresponding methyl ester **4c**. The yield of crude, chromatographically pure product was 97 %. The analytical specimen was prepared by chromatography on silica using Et_2O/CH_2Cl_2 1 : 19 followed by recrystallization from Et_2O/light petroleum 1 : 8 (45 mL/g) and was obtained as white fluffy crystals; mp 113–113.5 °C.

^{1}H NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 1.40/1.47$ (2 s, together 9 H, Boc—Me), 3.75/3.69 (2 s, together 3 H, *O*—Me), 4.29/4.36 (2 s, together 2 H, *N*-CH_2), 5.17 (s, 2 H, Z—CH_2), 6.81/6.53 (2 br s, together 1 H, NH), 7.30–7.35 (complex signal, 5 H, Ph—H).

^{13}C NMR ($CDCl_3$/TMS): major/minor conformer; $\delta = 28.05/28.09$ (Boc—Me), 51.25 (*N*—CH_2), 52.27 (*O*—Me), 68.36/68.56 (Z—CH_2), 81.80/81.65 (Boc—C_q), 127.73, 128.00, 128.16, 128.32, 128.42, 128.51, 135.51, 135.62, (Ar), 154.27/154.89 (Boc—CO), 155.98/155.81 (Z—CO), 169.58/169.87 (ester—CO).

Anal. Calcd for $C_{16}H_{22}N_2O_6$ (338.4): C, 56.80; H, 6.55; N, 8.28. Found C, 56.6; H, 6.6; N, 8.2.

This work was supported by funds from the Swedish Natural Science Research Council and Astra Draco AB as well as by a scholarship (to B.N.) from the Swedish Institute.

(1) Gabriel, S. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2224.
(2) Wieland, H. *Die Hydrazine*; Enke: Stuttgart, 1913.
Westphal, O. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 759.
Sidgwick, N.V. *The Organic Chemistry of Nitrogen*, 3rd ed.; Clarendon: Oxford, 1966.

Jensen-Korte, U. In *Houben-Weyl*, 4th ed., Vol. 16a; Klamann, D., Ed.; Thieme: Stuttgart, 1990; p429.
Brown, B.R. *The Organic Chemistry of Aliphatic Nitrogen Compounds*; Clarendon: Oxford, 1994; p421.
(3) Grehn, L.; Ragnarsson, U. *Coll. Czech. Chem. Commun.* **1988**, *53*, 2778.
(4) Mäeorg, U.; Grehn, L.; Ragnarsson, U. *Angew. Chem.* **1996**, *108*, 2802; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2626.
(5) Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; Chapter 7.
(6) Grehn, L.; Lönn, H.; Ragnarsson, U. *Chem. Commun.* **1997**, 1381.
(7) Nyasse, B.; Grehn, L.; Ragnarsson, U.; Maia, H.L.S.; Monteiro, L.S.; Leito, I.; Koppel, I.; Koppel, J. *J. Chem., Soc., Perkin Trans. 1* **1995**, 2025.
(8) Rudinger, J. In *The Chemistry of Polypeptides*; Katsoyannnis, P.G., Ed.; Plenum: New York, 1973; p87.
(9) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017.
(10) Wünsch, E. *Chem. Ber.* **1965**, *98*, 797.
(11) Grehn, L.; Gunnarsson, K.; Ragnarsson, U. *Acta Chem. Scand., Ser. B* **1986**, *40*, 745.
(12) Perrin, D.D.; Armarego, W.L.F.; Perrin, D.R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, 1980, p438.
(13) Krebs, K.G.; Heusser, D.; Wimmer, H. In *Thin-Layer Chromatography*, 2nd ed.; Stahl, E., Ed.; Springer: Berlin, 1969; p887.