Rearrangement of N_α-Protected L-Asparagines with Iodosobenzene Diacetate. A Practical Route to β-Amino-L-alanine Derivatives

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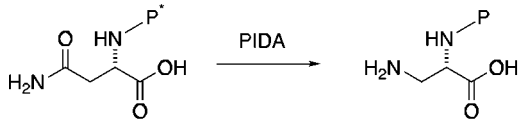
Received February 14, 1997[⊗]

A general synthetic method for the Hofmann rearrangement of protected asparagines has been developed. Reaction of asparagine derivatives with iodosobenzene diacetate (PIDA) in mixed solvents produces β-amino-L-alanines in good yield. Advantages over the commonly used reagent bis(trifluoroacetoxy)iodobenzene have been discussed.

Interest in the synthesis of β-amino-L-alanine derivatives has grown significantly in recent years.[1] Derivatives of β-amino-L-alanine exist both as free amino acids and components of peptides in nature.[2] Some of these natural products possess useful antitumor and antibiotic activities, and synthetic derivatives of β-amino-L-alanine and compounds containing them have proved to be effective enzyme inhibitors,[3] metal chelating agents,[4] and GPIIb/IIIa antagonists.[5] Several routes to β-amino-L-alanine derivatives have been reported. For example, N_α-*t*-Boc-β-amino-L-alanine was prepared by rearrangement of N_α-Boc-L-asparagine with bis(trifluoroacetoxy)iodobenzene in the presence of pyridine,[6] reaction of nitrogen nucleophiles with serine-β-lactones,[7] ring opening of serine-derived aziridines,[1f] and the Mitsunobu reaction of serine derivatives followed by reduction.[8] Preparations of N_α-CBZ or N_α-tosyl-β-amino-L-alanine from asparagine, aspartic acid, and serine are also known.[8a,9] Unfortunately, all of these methods had drawbacks for the preparation of N_α-Boc-β-amino-L-alanine due to cost, processability, and safety concerns. The present study reports a general route, amenable for large scale, to optically pure β-amino-L-alanine derivatives from N_α-protected L-asparagine through the Hofmann rearrangement with iodosobenzene diacetate.

Scheme 1



P* = Protecting groups

Considerable research on polyvalent iodoorganics has been conducted over the past 30 years.[10] Although bis(trifluoroacetoxy)iodobenzene (henceforth referred to as PIFA) has often found use in the Hofmann rearrangement,[6] surprisingly the simpler analog iodosobenzene diacetate (henceforth referred to as PIDA) is seldom used in this reaction. After examination of many oxidation reagents such as hypochlorite, hypobromite,[11] benzyltrimethylammonium tribromide,[12] *N*-bromosuccinimide, sodium dichloroisocyanuric acid,[13] PIFA, and PIDA, it became clear that PIDA provides an excellent means for inducing the Hofmann rearrangement of N_α-*n*-Boc-L-asparagine to produce N_α-*n*-Boc-β-amino-L-alanine in good yield (Scheme 1). This reagent not only supplies a useful alternative to PIFA but is also advantageous in other ways. The reaction is conducted under less acidic conditions, pyridine catalysis is unnecessary, the reaction rate is faster, the bothersome side reaction of urea formation does not occur, and the product isolated is clean.

The procedure for this rearrangement was straightforward. Reaction of the starting material with PIDA in ethyl acetate, acetonitrile, and water (39/39/22 v/v/v) with cooling led to completion in 3−5 h. The amount of water charged was critical to the impurity profile and ease of final isolation. Too much water resulted in a voluminous and gelatinous mass that was difficult to filter, while too little led to the formation of the cyclic urea that was difficult to separate from the product. The mixture was held at 20 °C until the reaction went to

[⊗] Abstract published in *Advance ACS Abstracts,* September 15, 1997.

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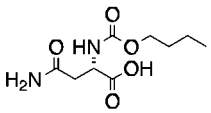
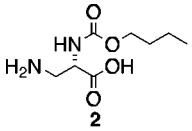
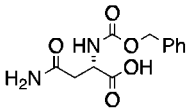
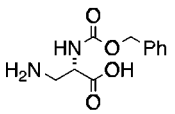
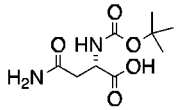
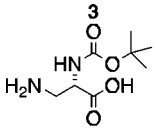
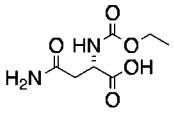
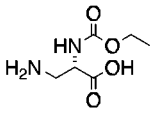
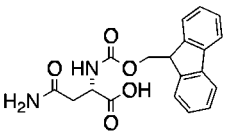
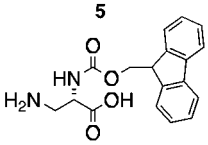
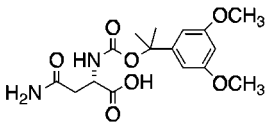
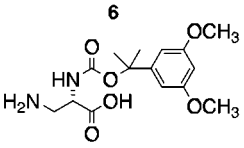
S0022-3263(97)00275-2 CCC: $14.00 © 1997 American Chemical Society

Table 1 Reaction of PIDA with N_α-Protected Asparagines

Compound	Product	Time (h)	Temp (^{0}C)	Yield (%) *
	 **2**	3	20	73
	 **3**	4	20	87
	 **4**	4	20	62
	 **5**	4	20	93
	 **6**	5	32	59
	 **7**	8	25	93

* Isolated yield.

completion and then heated to 70 °C to decompose any remaining PIDA and dissolve the solids. Upon cooling, product (**2**) precipitated slowly as large particles that filtered well. This material was of sufficient purity to carry forward in the synthesis. While this solvent system was successful for the preparation of various analogs of β-amino-L-alanine reported in Table 1, multikilo preparation of **2** was found difficulty due to foaming and inefficient stirring. In order to remedy these concerns for large scale synthesis, a second solvent system consisting of *n*-propanol, methyl acetate, and water (54/37/9 v/v/v) was developed. These improvements resolved the problems of foaming and agitation and reduced the solvent volume of the reaction.

Mechanistic aspects of the reaction[14] were elucidated by ^{1}H NMR spectroscopy. Immediately after mixing, the signals of the asparagine methylene and methine protons shifted upfield, indicating the formation of an amide−PIDA complex. Rearrangement of this complex is the rate-limiting step, which is monitored by both the disappearances of PIDA signals in the aromatic region and the progressive appearance of proton signals from iodobenzene and the product. This study of rearrangement by ^{1}H NMR allowed us to have better understanding of the reaction and provided a convenient method to follow the reaction.

The PIDA-induced Hofmann rearrangement of asparagine seems to be a general reaction. Most of the reactions of N_α-protected asparagines progressed smoothly (Table 1). The Cbz-protected analog reacted with PIDA to give an 87% isolated yield. The reaction of PIDA with sulfonyl asparagine (free acid) did not go well even when excess of PIDA was added under heating. However, Hofmann rearrangement of this protected asparagine with bromine proceeded well as reported.[9] The other examples of asparagine derivatives reacting with PIDA furnished the expected β-amino-L-alanines in good yields although the conditions were not optimized. Since the rearrangement was carried out under mild and slightly acidic conditions (pH 5−6), epimerization did not occur, which was confirmed by chiral SFC analysis.

In conclusion, iodosobenzene diacetate provides a general method to prepare optically pure β-amino-L-alanine derivatives from asparagine. As PIDA is available in bulk, and numerous substituted asparagines are readily available or prepared, this reaction provides broad applicability in both academic and industrial settings. Of particular note are the mild reaction conditions. This permits many synthetic possibilities that were unavailable through the classical Hofmann reaction since many protecting groups and chiral substrates are sensitive to base. Other advantages over bis(trifluoroacetoxy)iodobenzene include lower cost, less acidic conditions, a more stable reagent, and the fact that there is no need to use pyridine as the catalyst, which simplifies the final purification. In large scale production the byproduct iodobenzene can be recovered and reoxidized to PIDA, thus reducing the waste generated by this process. This chemistry is easy to scale-up and is suitable to produce protected β-amino-L-alanine in large quantities.

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Experimental Section

General. All melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.4 MHz, respectively, and reported in DMSO-d_6 (except where noted). The coupling constants (J) of NMR spectra are reported in hertz. Mass spectra were recorded by the analytical laboratory, Chemical Process R&D, DuPont Merck Research Laboratories. The elemental analyses were determined by Quantitative Technologies Inc., Whitehouse, NJ. Solvents, protected amino acids, and reagents were used as purchased without further purification.

***N*$_\alpha$-*n*-Boc-*β*-amino-L-alanine (2). Method A.** A solution of *N*$_\alpha$-*n*-Boc-L-asparagine (2.65 kg, 11.4 mol), ethyl acetate (12.0 L), acetonitrile (12.0 L), water (6.0 L), and PIDA (4.4 kg, 13.7 mol) was cooled and stirred at 10 °C for 30 min. The temperature was allowed to reach 20 °C, and the reaction was stirred until completion (3−4 h). The mixture was heated to 70 °C until completely dissolved and then slowly cooled to ambient temperature over a 3 h period. The solid was filtered, washed with ethyl acetate (2 L), and dried *in vacuo* at 50 °C to give **2** (1.70 kg, 73%): mp 215 °C (dec); ^{1}H NMR (DMSO/TFA) δ 7.95 (s, 3H), 7.54 (d, 1H), 4.31−4.05 (m, 1H), 3.99 (t, 2H), 3.28−3.19 (m, 1H), 3.07−2.96 (m, 1H), 1.61−1.50 (m, 2H), 1.42−1.28 (m, 2H), 0.90 (t, 3H); ^{13}C NMR (DMSO/TFA) δ 171.31, 156.83, 64.47, 52.84, 52.16, 31.03, 18.96, 13.97. Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72. Found: C, 47.28; H, 7.86; N, 13.75.

***N*$_\alpha$-*n*-Boc-*β*-amino-L-alanine (2). Method B.** A mixture of N$_\alpha$-*n*-Boc-L-asparagine (15.0 g, 64.5 mmol), methyl acetate (50 mL), *n*-propanol (50 mL), water (6.0 mL), and PIDA (27.4 g, 85.1 mmol) was stirred below 32 °C for 50 min. The mixture was warmed to 40 °C over 15 min and then cooled to 15 °C over 45 min. The solids were collected by filtration, washed with *n*-propanol, and dried *in vacuo* to give product **2** which has the same spectroscopic data as the one from method A.

***N*$_\alpha$-Cbz-*β*-amino-L-alanine (3).**[8a] A slurry of *N*$_\alpha$-Cbz-*β*-amino-L-alanine (5.0 g, 18.8 mmol), ethyl acetate (24 mL), acetonitrile (24 mL), water (12 mL), and PIDA (7.26 g, 22.5 mmol) was cooled and stirred at 16 °C for 30 min. The temperature was allowed to reach 20 °C, and the reaction was stirred until completion (4 h). The mixture was cooled to 5 °C, and the product was filtered, washed with ethyl acetate (10 mL), and dried *in vacuo* at 50 °C to give **3** (3.9 g, 87% yield): mp 210 °C (dec); ^{1}H NMR (DMSO/TFA) δ 7.99 (bs, 3H), 7.74 (d, 1H), 7.42−7.30 (m, 5H), 5.09 (s, 2H), 4.36−4.26 (m, 1H), 3.34 −3.18 (m, 1H), 3.12−2.96 (m, 1H); ^{13}C NMR δ 171.23, 156.65, 137.08, 128.76, 128.32, 128.21, 66.27, 52.27. Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.50; H, 5.92; N, 11.80. Found: C, 55.53; H, 6.04; N, 11.72.

***N*$_\alpha$-*t*-Boc-*β*-amino-L-alanine (4).**[6] A slurry of N$_\alpha$-*t*-Boc-L-asparagine (5.0 g, 21.5 mmol), ethyl acetate (24 mL), acetonitrile (24 mL), water (12 mL), and PIDA (8.32 g, 25.8 mmol) was cooled and stirred at 16 °C for 30 min. The temperature was allowed to reach 20 °C, and the reaction was stirred until completion (4 h). The mixture was cooled to 0 °C and filtered. The filter cake was washed with ethyl acetate (10 mL) and dried *in vacuo* at 65 °C to give **4** (2.73 g, 62% yield): mp 216 °C; ^{1}H NMR (DMSO/TFA) δ 7.92 (bs, 3H), 7.23 (d, 1H), 4.27−4.14 (m, 1H), 3.27−3.11 (m, 1H), 3.06 −2.89 (m, 1H), 2.52−2.46 (m, 9H). Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72. Found: C, 46.94; H, 7.87; N, 13.46.

***N*$_\alpha$-Carbethoxy-*β*-amino-L-alanine (5).** A solution of *N*$_\alpha$-carbethoxy-*n*-L-asparagine (5.0 g, 24.5 mmol), ethyl acetate (24 mL), acetonitrile (24 mL), water (6 mL), and PIDA (9.9 g, 30.6 mmol) was stirred at 15 °C for 30 min. The temperature was allowed to reach 20 °C, and the reaction was stirred until completion (4 h). Water (10 mL) was added, and the mixture was heated to 60 °C. After phase separation, the oily product was solidified by addition of ethyl acetate. Product was dried *in vacuo* at 50 °C to give **5** as off-white solids (4.0 g, 93% yield): ^{1}H NMR (DMSO/TFA) δ 8.03 (bs, 3H), 7.54 (d, 1H), 4.32−4.22 (m, 1H), 4.03 (q, 2H), 3.32−3.17 (m, 1H), 3.10−2.95 (m, 1H), 1.19 (t, 3H); ^{13}C NMR δ 171.30, 156.72, 60.75, 52.80, 52.11, 14.83; HRMS (NH_3-CI) *m*/z calcd for $C_6H_{12}N_2O_4$ (MH^+) 177.0875, found 177.0867.

***N*$_\alpha$-Fmoc-*β*-amino-L-alanine (6).** A slurry of *N*$_\alpha$-Fmoc-L-asparagine (5.0 g, 14.1 mmol), methyl acetate (50 mL), *n*-propanol (50 mL), water (5 mL), and PIDA (6.0 g, 18.6 mmol) was stirred at 25 °C for 1 h followed by 5 h at 32 °C. The mixture was filtered and the solid washed with 2-propanol (2 × 20 mL), methanol (2 × 20 mL), and methyl acetate (2 × 20 mL). The resulting white solids were dried *in vacuo* to give product **6** (2.7 g, 59% yield): mp 146 °C (decomposed); ^{1}H NMR (DMSO/TFA) δ 14.50−14.00 (m, 1H), 8.00 (s, 2H), 7.90−7.10 (m, 8H), 4.50−4.20 (m, 4H), 3.30−3.20 (m, 1H), 3.15−3.00 (m, 1H). Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 65.91; H, 5.81; N, 8.38.

***N*$_\alpha$-DDZ-*β*-amino-L-alanine (7).** A solution of N$_\alpha$-DDZ-L-asparagine (5.0 g, 14.1 mmol), acetonitrile (50 mL), water (50 mL), and PIDA (5.7 g, 17.7 mmol) was stirred from 10 to 25 °C for 8 h. The lower layer of iodobenzene was separated, and the aqueous solution was concentrated *in vacuo* to give the acetate of product **7** (5.3 g, 97% yield). An analytical sample was prepared by slurrying the product with heptane and then drying to give the acetate of **7**: mp 45 °C (dec); ^{1}H NMR (DMSO/TFA) δ 7.95 (bs, 1H), 7.56 (bs, 1H), 6.55−6.42 (m, 2H), 6.40−6.25 (m, 1H), 4.30−4.10 (m, 1H), 3.72 (br, 6H), 3.30−3.15 (m, 1H), 3.10−2.90 (m, 1H), 1.90 (s, 3H), 1.68−1.62 (br, 6H); ^{13}C NMR δ 172.1, 171.4, 160.2, 154.4, 149.4, 102.6, 98.0, 79.7, 55.1, 51.3, 29.0, 28.9, 21.2; HRMS (NH_3-CI) *m*/*z* calcd for $C_{15}H_{22}N_2O_6$ (MH^+) 327.1556, found 327.1552. Anal. Calcd for $C_{17}H_{26}N_2O_8$: C, 52.84; H, 6.78; N, 7.25. Found: C, 53.06; H, 6.52; N, 7.36.

JO9702756