Indian Journal of Chemistry
Vol. 48B, April 2009, pp. 574-579

Simple and rapid synthesis of N^{α}-urethane protected β-amino alcohols and peptide alcohols employing HATU

Vommina V Sureshbabu*, N S Sudarshan & G Chennakrishnareddy

Peptide Research Laboratory, Department of Studies in Chemistry, Central College Campus, Bangalore University,

Dr. B. R. Ambedkar Veedhi, Bangalore 560 001, India

Email: hariccb@rediffmail.com

Received 14 April 2008; accepted (revised) 21 January 2009

The activation of the N^{α}-urethane protected (Fmoc-/Boc-/Z-/Bsmoc) α-amino acids employing 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium.0hexa-flurophosphate-3-oxide (HATU) followed by reduction of the *in situ* generated –OAt ester with $NaBH_4$ results in the corresponding β-amino alcohols in good yields. This synthesis is the first demonstration of the application of the efficient coupling agent HATU for practical synthesis of β-amino alcohols. The protocol is general for all common *N*-protecting groups including the highly base sensitive Bsmoc group. The protocol has also been successfully extended for the synthesis of peptide alcohols.

Keywords: *N*-Fmoc-β-amino alcohols, Bsmoc-β-amino alcohols, HATU

Construction of the libraries of unnatural biopolymers belonging to the class of oligo carbamates[1,2] and oligo-*N*-alkylcarbamates has emerged as an effective way to design peptidomimetics based drug leads. β-Amino alcohols are the starting materials for synthesis of the reactive *N*-protected *p*-nitrophenyl carbonates[3a] and *N*-Fmoc-β-aminoalkoxy carbonyl chlorides[3b] which are the monomeric building blocks for assembling oligocarbamates. β-Amino alcohols are also extensively used in asymmetric synthesis[4], for the preparation of amino aldehydes[5] and other synthetically important compounds[6].

Soai, *et al*. [7], have developed a procedure for the chemoselective synthesis of alcohols starting from *Z*-protected amino acid esters and peptide esters. The use of UNCAs[8] as well as N^{α}-protected amino acid pentachlorophenyl esters[9] as carboxyl activated derivatives for the synthesis of β-amino alcohols have also been reported. All these methods require the synthesis of the carboxyl activated precursors. Although the *in situ* generation of carboxylic-carbonic anhydrides by employing IBC-Cl/*N*-methylmorpholine (NMM) followed by their reduction can yield β-amino alcohols[10], this method results in lesser yields of the product and also requires the use of chloroformates which are toxic phosgene derivatives.

1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-b]pyridiniumhexaflurophosphate-3-oxide (HATU), an improved version of 1-[bis(dimethylamino)-methylene]-1*H*-benzotriazoliumhexaflurophosphate-3-oxide (HBTU), was introduced by Carpino, *et al*.[11], as peptide coupling regent. HATU has several advantages such as its high reactivity and minimum induction of racemization of the products[12]. It is widely used as a coupling agent in solution phase as well as solid phase peptide synthesis. Its utility in the synthesis of cyclosporin-*O* especially for the coupling of the consecutive *N*-methyl amino acids[13] and in convergent solid phase peptide synthesis of *H*-(Val-His-Leu-Pro-Pro-Pro)$_2$-OH has been demonstrated. It has been used in the synthesis of the C1 peptides of protein kinase C isozymes[14], the total synthesis of Ser-Thr phosphatase inhibitor microcystin-LA[15], synthesis of Oscillamide Y[16], and in macrolactamization of antitumor antibiotic A83586C[17]. This communication deals with the straight forward and one-pot synthesis of Fmoc/Bsmoc/Boc/Z-β-amino alcohols employing HATU and *N*-protected α-amino acids.

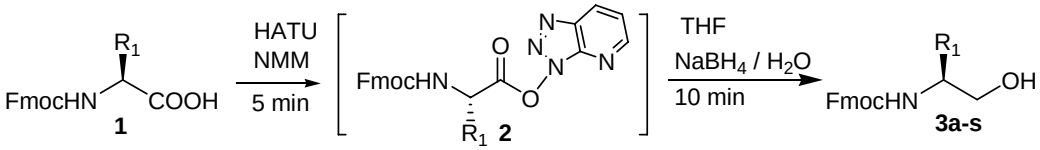
In pursuit of our work on developing useful and stable monomers for the synthesis of peptido-mimetics[18], we had focused our attention towards the synthesis of peptidylcarbamates through suitably activated monomers. For these studies, we were in regular need of Fmoc-β-amino alcohols. Our attempts to reduce the *O*-benzotriazole esters and carboxylic-carbonic anhydrides of Fmoc-amino acids were

unsatisfactory. In both these methods, the purity and the yields of the alcohols obtained were not satisfactory. Consequently, it was desired to explore the use of HATU for rapid and one-pot synthesis of *β*-amino alcohols starting from acids.

Results and Discussion

In a typical reaction, a solution of Fmoc-amino acid, HATU and NMM in THF was stirred at RT for about 5 min within which formation of –OAt ester was observed (IR peak at 1820 cm^{1}). The solution of $NaBH_4$ in water was added at the same temperature and the reaction was monitored through TLC [using (35:65) EtOAc : hexane as eluent] and the IR spectroscopy. The reaction was found to be complete within 10 min after the addition of $NaBH_4$ as evident by TLC and disappearance of –OAt peak in IR. After usual aqueous work-up, the desired product was obtained in good yield (**Scheme I**). A single recrystallization was sufficient to obtain analytically pure compounds. In the case of alcohols derived from Aib, the isolated product needed column purification. All the Fmoc-*β*-amino alcohols were obtained in good yield and were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral studies. The reduction of Fmoc-amino acid azobenzotriazole esters to the corresponding alcohols, by comparison of the experimentally determined optical rotations of *β*-amino alcohols with the literature reports, was found to be free from recemization (**Table I**).

The reaction was extended for the preparation of Bsmoc protected *β*-amino alcohols. 1,1-dioxobenzo-[*b*]thiophene-2-ylmethyloxycarbonyl (Bsmoc) amino-protecting group, introduced by Carpino *et al.* [19], has several advantages over the Fmoc group. Some of them include deprotection using very low concentration of piperidine (about 1-2%), easily removability of the side product of deprotection step by simple water wash. The present protocol was used to synthesize Bsmoc-Phe-ol, Bsmoc-Val-ol, Bsmoc-Ala-ol Bsmoc-Gly-ol and Bsmoc-Leu-ol (**Figure 1**). It was observed that the Bsmoc group was completely stable towards reduction



Scheme I — Synthesis of Fmoc-*β*-amino alcohols

Table I — Physical constants of protected *β*-amino alcohols

Compd	Fmoc *β*-amino alcohols	Yield (%)	m.p. (°C)	$[\alpha]_D^{25}$ (*c* 1.0, $CHCl_3$)	Mole. formulae	HRMS $(M+Na)^+$ Calc / Found
3a	Fmoc-Ala-ol	90	120-22	-0.58	$C_{18}H_{19}NO_3$	320.1263 / 320.1259
3b	Fmoc-Val-ol	88	107-08	-20.1	$C_{20}H_{23}NO_3$	348.1576 / 348.1570
3c	Fmoc-Ile-ol	80	114-15	-20.3	$C_{21}H_{25}NO_3$	362.1732 / 362.1725
3d	Fmoc-Met-ol	95	135-37	-17.2	$C_{20}H_{23}NO_3S$	380.1296 / 380.1290
3e	Fmoc-Leu-ol	90	112-13	-17.4	$C_{21}H_{25}NO_3$	362.1732 / 362.1726
3f	Fmoc-Gly-ol	91	128-31	-	$C_{17}H_{17}NO_3$	306.1106 / 306.1101
3g	Fmoc-Phe-ol	90	129-30	-21.6	$C_{24}H_{23}NO_3$	396.1576 / 396.1570
3h	Fmoc-L-Phg-ol	90	144-47	-9.7	$C_{23}H_{21}NO_3$	382.1419 / 382.1414
3i	Fmoc-D-Phg-ol	90	144-47	10.1	$C_{23}H_{21}NO_3$	382.1419 / 382.1413
3j	Fmoc-Glu(O^{t}Bu)-ol	80	55-57	-10.3	$C_{24}H_{29}NO_5$	434.1943 / 434.1938
3k	Fmoc-Asp(O^{t}Bu)-ol	85	96-97	-7.4	$C_{23}H_{27}NO_5$	420.1787 / 420.1780
3l	Fmoc-Trp-ol	80	86-90	-26.6	$C_{26}H_{24}N_2O_3$	449.1841 / 449.1835
3m	Fmoc-Aib-ol	70	gum	-	$C_{19}H_{21}NO_3$	334.1419 / 334.1410
3n	Fmoc-Asn-ol	60	165-67	-7.1	$C_{19}H_{20}N_2O_4$	363.1321 / 363.1328
3o	Tos-Aib-ol	65	95-97	-	$C_{11}H_{17}NO_3S$	266.0827 / 266.0820
3p	Fmoc-Tyr(O^{t}Bu)-ol	80	114-15	-18.5	$C_{28}H_{31}NO_4$	468.2151 / 468.2145
3q	Fmoc-Ser(O^{t}Bu)-ol	85	97-98	12.3	$C_{22}H_{27}NO_4$	392.1838 / 392.1830
3r	Fmoc-Lys(Boc)-ol	90	130-31	-8.2	$C_{26}H_{34}N_2O_5$	477.2365 / 477.2372
3s	Fmoc-Pro-ol	75	89-90	-30.1	$C_{20}H_{21}NO_3$	346.1419 / 346.1414

under the present reaction conditions. The yields of the Bsmoc alcohols prepared were about 65%.

The procedure was also repeated for the conversion of Boc- as well as Z-*α*-amino acids[20] to the corresponding *β*-amino alcohols and in all cases the latter was obtained in good yields. Reduction of a sterically hindered amino acid, Aib to its alcohol was also attempted. In this case, Fmoc-Aib-ol was obtained in 72% yield while the Boc-Aib-ol was obtained in 56% yield.

Finally, the protocol was extended for the synthesis of Fmoc-dipeptide alcohols. Fmoc-dipeptide acids were synthesized by reacting the Fmoc-amino acid mixed anhydrides with *N,O*-bis-trimethylsilyl amino acid. They were then converted to the corresponding *β*-amino alcohols under the similar reaction conditions described above. (**Scheme II**). All the peptide alcohols prepared were isolated as white solids in good yields.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. IR spectra were recorded on a Nicolet model impact 400D FT-IR spectrometer (KBr pellets, 3 cm^{-1} resolution). Specific rotations were recorded on a Rudolf Research Autopol IV automatic polarimeter. ^1H spectra were recorded on a Bruker AMX 400 MHz spectrometer. Mass spectra were recorded using high resolution mass spectrophotometer and the samples were dried under vacuum before analysis. The TLC analysis was carried out on precoated silica gel plates using solvent system ethyl acetate : hexane (35 : 65 v/v). All the solvents were freshly distilled prior to use.

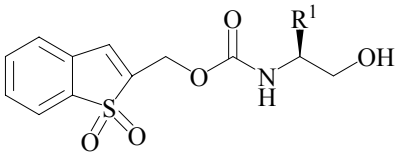


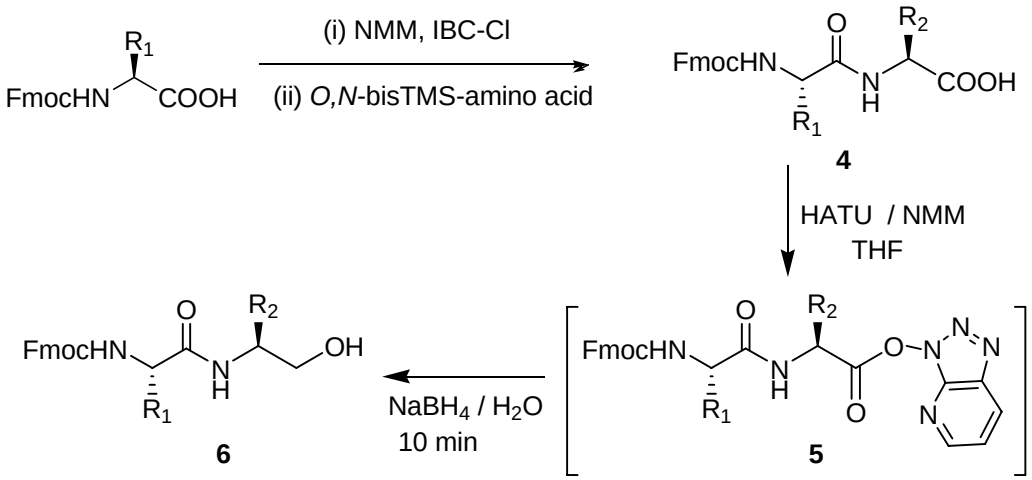
Figure 1

General procedure for the preparation of Fmoc/Bsmoc/Boc/Z- *β*-amino alcohols

To an ice cold solution of N^{α}-protected amino acid (1 mmole) and HATU (1.1 mmole) in THF, NMM (1.2 mmole) was added. After solution became clear, $NaBH_4$ (1 mmole) in water (2 mL) was added to the reaction-mixture at once and stirred at the same temperature for 10 min. Then, methanol was added to quench excess of $NaBH_4$. The reaction-mixture was concentrated to remove THF and the residue was taken into EtOAc. The organic layer was successively washed with 10% aqueous citric acid (3 × 10 mL), aqueous Na_2CO_3 (3 × 10 mL), brine (3 × 10 mL), and dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified by recrystallization or by column chromatography using EtOAc-hexane (30:70 v/v) as an eluent (only in the case of Aib) to obtain the title compound.

Bsmoc-Gly-ol. Yield: 70%; gum; ^1H NMR ($CDCl_3$) : δ 3.33 (2H, q, J = 5.8 Hz), 3.70 (2H, t, J = 7.1 Hz), 5.11 (2H, s), 5.53 (1H, s), 7.14 (1H, s), 7.34 (1H, d, J = 6.9 Hz), 7.49 (2H, m), 7.70 (1H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 47.0, 66.8, 67.9, 121.3, 125.8, 126.3, 127.7, 130.6, 134.1, 137.1, 156.8; HRMS $[M+Na]^+$: Calcd. 306.0412, Found. 306.0400.

Bsmoc-Ala-ol. Yield: 68%; gum; $[\alpha]_D$ = –5.45° (1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.25 (3H, d, J = 7.2



Scheme II — Reduction of Fmoc-dipeptide acids to peptidyl alcohols

Hz), 3.32 (1H, m), 3.71 (2H, d, *J* = 6.9 Hz), 5.10 (2H, s), 5.54 (1H, s), 7.15 (1H, s), 7.34 (1H, d, *J* = 7.0 Hz), 7.49 (2H, m), 7.71 (1H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 17.4, 47.1, 66.3, 67.2, 121.3, 125.8, 126.3, 127.8, 130.6, 134.1, 137.0, 156.9; HRMS $[M+Na]^+$: Calcd. 320.0569, Found 320.0560.

Bsmoc-Phe-ol. Yield: 72%; gum; ^{1}H NMR ($CDCl_3$): δ 2.93 (2H, d, *J* = 4.9 Hz), 3.48 (2H, d(d)), 3.87 (1H, m), 5.1 (2H, s), 7.15 (1H, s), 7.33 (1H, d, *J* = 6.9 Hz), 7.49 (2H, m), 7.71 (1H, d, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$): δ 37.9, 47.3, 52.7, 66.9, 121.3, 125.8, 126.3, 127.8, 128.5, 128.6, 129.8, 130.6, 134.1, 137.0, 139.6, 140.6, 156.9; HRMS $[M+Na]^+$: Calcd. 396.0882, Found. 396.0878.

Bsmoc-Val-ol. Yield: 65%; gum; ^{1}H NMR ($CDCl_3$): δ 0.92 (6H, d, *J* = 6.1 Hz), 1.39 (1H, m), 3.65 (2H, d, *J* = 7.1 Hz), 4.01 (1H, m), 5.10 (2H, s), 7.15 (1H, s), 7.33 (1H, d, *J* = 6.8 Hz), 7.47 (2H, m), 7.69 (1H, d, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 18.6, 29.3, 47.2, 64.5, 67.6, 121.3, 125.8, 126.3, 127.8, 130.6, 134.1, 137.0, 156.9; HRMS $[M+Na]^+$: Calcd. 348.0882, Found. 348.0891.

Bsmoc-Leu-ol. Yield: 65%; gum; ^{1}H NMR ($CDCl_3$): δ 0.94 (6H, d, *J* = 6.5 Hz), 1.40 (3H, m), 3.64 (2H, d(d)), 4.01(1H, m), 5.1 (2H, s), 5.55 (1H, s), 7.15 (1H, s), 7.35 (1H, d, *J* = 7.1 Hz), 7.51 (2H, m), 7.72 (1H, d, *J* = 7.1 Hz); ^{13} C NMR ($CDCl_3$): δ 22.3, 23.9, 40.2, 47.4, 64.5, 66.6, 121.4, 125.8, 126.9, 127.8, 130.6, 134.1, 137.2, 157.3; HRMS $[M+Na]^+$: Calcd. 362.1038, Found. 362.1031.

Boc-Phe-ol: m.p. 90-91°C; $[\alpha]_D$ –21.6° (*c*=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9H), 2.90 (d, 2H), 3.50-4.10 (m, 3H), 5.03 (s, 1H), 7.35 (s, 5H); ^{13}C NMR (δ, $CDCl_3$) : 28.0, 37.3, 54.1, 64.0, 81.3, 127.2, 128.5, 128.1, 131.9, 156.2.

Boc-Met-ol: m.p. 39-40°C; $[\alpha]_D$ –12.9° (*c*=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 9H), 1.90 (m, 2H), 2.18 (s, 3H), 2.65 (t, 2H), 3.65-4.05 (m, 3H), 5.04 (s, 1H); ^{13}C NMR (δ, $CDCl_3$): 14.9, 29.1, 29.4, 31.0, 54.1, 64.0, 81.3, 156.4.

Boc-Ser(OBzl)-ol: m.p. 56-58 °C; $[\alpha]_D$ +12.1° (*c*=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H), 3.50-3.95 (m, 5H), 4.48 (s, 2H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 28.2, 59.4, 65.4, 67.0, 73.7, 81.1, 128.1, 128.04, 128.0, 128.2, 138.0, 156.0.

Boc-Asp(OBzl)-Ala-ol: m.p. 78-80 °C; $[\alpha]_D$ –11.6° (*c*=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.21 (d, 3H) 1.45 (s, 9H), 2.75 (br, 1H), 2.85 (d, 2H, *J* = 6.0 Hz), 3.55 (br, s, 2H), 3.77-4.01 (m, 2H), 5.13 (s, 2H) 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 17.2, 28.2, 39.4, 42.7, 54.2, 63.8, 64.1, 81.2, 128.1, 128.5, 142.8, 156.4, 170.6, 171.9.

Z-Phe-ol: m.p. 87-88 °C; $[\alpha]_D$ –41.1° (*c*=2, MeOH); ^{1}H NMR ($CDCl_3$): δ 2.91 (d, 2H), 2.80 (br, H), 3.55 (m, 2H), 3.71 (br, 1H), 5.05 (s, 2H), 5.61 (s, 1H), 7.30 (s, 5H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 37.2, 54.1, 62.6, 64.0, 127.2, 127.5, 127.7, 128.10, 128.5, 136.5, 136.9, 156.6.

Z-Ala-ol: m.p. 55-56 °C; $[\alpha]_D$ –6.5° (*c*=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.15 (d, 3H, *J* = 7.9 Hz), 2.96 (s, 1H), 3.51 (m, 1H), 3.96 (m, 2H), 5.05 (s, 2H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$): δ 17.6, 51.1, 65.4, 66.2, 127.2, 127.5, 127.7, 136.5, 157.4.

Z-Glu(OMe)-ol: m.p. 64-66°C; $[\alpha]_D$ –18.2° (*c*=1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.81 (m, 2H), 2.45 (t, 2H, *J* = 10.9 Hz), 2.92 (s, 1H), 3.20 (m, 1H) 3.60 (m, 2H) 3.70 (s, 3H) 5.05 (s, 2H), 7.30 (s, 5H); ^{13}C NMR (δ, $CDCl_3$) : 26.1, 27.9, 51.2, 55.3, 65.4, 66.6, 127.2, 127.5, 127.7, 136.5, 157.7, 169.3.

Z-Phe-Ala-ol: m.p. 140.5-142.5 °C; $[\alpha]_D$ +5.9° (*c*=1, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.12 (d, 3H, *J* = 7.1 Hz), 2.90 (s, 1H), 2.94 (d, 2H, *J* = 6.0 Hz), 3.77 (d, 2H, *J* = 6.2 Hz), 4.32 (m, 1H), 5.06 (s, 2H), 5.47 (s, 1H), 5.78 (s, 1H), 7.17-7.33 (m 10H); ^{13}C NMR ($CDCl_3$): δ 17.3, 37.6, 42.7, 53.4, 65.4, 66.6, 127.2, 127.7, 128.7, 128.8, 130.4, 132.4, 136.4, 156.1, 172.4.

Synthesis of *O,N-bis*-trimethylsilyl-amino acids

To a suspension of amino acid (1 mmole) in DCM (5 mL) was added DIEA (0.35 mL, 2 mmoles) and TMS-Cl (0.15 mL, 2 mmoles) and refluxed under N_2 for 2 hr. The resulting solution was cooled to RT and used directly.

General procedure for the synthesis of N^{α}-protected peptide acids 4

To a chilled solution of Fmoc amino acid (1 mmole) and NMM (1.2 mmole) in dry THF (5 mL) was added IBC-Cl (1.1 mmole) and stirred at 0 °C for 10 min. The freshly prepared solution containing *O,N-bis*-trimethylsilyl-amino acid (1.8 mmole) was added directly in one portion. Stirring was continued for about 2 hr. The organic layer was evaporated and the resulting residue was partitioned between 10% aqueous Na_2CO_3 solution (10 mL) and washed with diethyl ether (3 × 10 mL) and acidified using 5% HCl. The precipitated solid was filtered, washed thoroughly with water and recrystallized using suitable solvent to obtain the peptide acid **4** as a crystalline solid. All the peptide acids **4a-g** made by this method have been fully characterized.

General procedure for the synthesis of Fmoc-peptidyl alcohols 6

To an ice-cold solution of N^{α}-Fmoc-peptide acid (1 mmole) and HATU (1.1 mmole) in THF, NMM (1.2 mmole) was added. After solution became clear, $NaBH_4$ (1 mmole) in water (2 mL) was added to the reaction-mixture at once and stirred at the same temperature for about 10 min. The reaction-mixture was concentrated under reduced pressure to remove THF and residue was taken in CH_2Cl_2 (15 mL). The organic layer was successively washed with 5% HCl (5 mL × 2), 10% $NaHCO_3$ (5 mL × 2) and then brine solution (5 mL × 2). It was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Addition of hexane (5 mL) resulted in precipitation of pure alcohols **6a-g**. If necessary, they were purified by recrystallization or by column chromatography using EtOAc-hexane (30:70) as an eluent to obtain alcohols **6** as white solids.

Fmoc-Phg-Phe-ol, 6a. Yield: 82%; m.p. 135-137 °C; $[\alpha]^{25}_D$ –24.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 1H), 2.87 (d, 2H, *J* = 6.4 Hz), 3.60 (m, 2H), 3.96 (m, 1H), 4.16 (t, 1H, *J* = 6.8 Hz), 4.4 (m, 3H), 5.91 (s, 1H), 7.10-7.40 (m, 14H), 7.56 (m, 2H), 7.77 (d, 2H, *J* = 7.6 Hz); ^{13} C NMR ($CDCl_3$): δ 37.3, 47.2, 54.1, 64.0, 66.7, 68.5, 120.0, 124.7, 125.0, 126.2, 126.5, 126.9, 127.0, 127.2, 128.2, 130.8, 132.7, 139.1, 141.5, 143.9, 156.4, 166.7; HRMS $[M+Na]^+$: Calcd. 529.2103, Found. 529.2109.

Fmoc-D-Phg-Phe-ol, 6b. Yield: 78%; m.p. 139-141 °C; $[\alpha]^{25}_D$ +23.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 1H), 2.79 (d, 2H, *J* = 6.8 Hz), 3.60 (m, 2H), 3.96 (m, 1H), 4.15 (t, 1H, *J* = 6.8 Hz), 4.4 (m, 3H), 5.90 (s, 1H), 7.10-7.42 (m, 14H), 7.56 (m, 2H), 7.79 (d, 2H, *J* = 7.9 Hz); ^{13} C NMR ($CDCl_3$): δ 37.0, 47.2, 54.2, 64.0, 66.7, 68.5, 120.0, 124.0, 125.0, 126.3, 126.4, 126.8, 127.1, 127.3, 128.5, 130.9, 132.6, 139.1, 141.5, 143.9, 156.4, 166.7; HRMS $[M+Na]^+$: Calcd. 529.2103, Found. 529.2109.

Fmoc-Val-Gly-ol, 6c. Yield: 80%; m.p. 180-182 °C; $[\alpha]^{25}_D$ –10.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.93 (d, 6H, *J* = 7.4 Hz), 1.84 (m, 1H), 2.37 (br, s, 1H), 3.56 (m, 2H), 3.70 (m, 2H), 3.81 (m, 1H), 4.21 (t, 1H, *J* = 6.7 Hz), 4.42 (d, 1H, *J* = 4.9 Hz), 5.03 (s, 1H), 7.26 – 7.43 (m, 4H), 7.58 (d, 2H, *J* = 6.9 Hz), 7.76 (d, 2H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$): δ 18.6, 29.1, 40.4, 47.3, 58.5, 63.6, 66.5, 119.9, 124.9, 127.0, 127.6, 141.3, 143.8, 157.1, 170.9; HRMS $[M+Na]^+$: Calcd. 405.179, Found. 405.1781.

Fmoc-Ala-Leu-ol, 6d. Yield: 82%; m.p. 150-52°C; $[\alpha]^{25}_D$ –20.6 ° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.16 (d, 6H, *J* = 5.2 Hz), 1.33 (m, 2H), 1.16 (d, 3H, *J* = 6.2 Hz), 2.81 (br, 1H), 3.55 (br, m, 2H), 3.77 (m, 1H), 4.19 (t, 1H, *J* = 6.6 Hz), 4.41 (m, 3H), 5.07 (s, 1H), 7.21 – 7.41 (m, 4H), 7.57 (d, 2H, *J* = 6.9 Hz), 7.75 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 17.2, 22.0, 23.0, 24.6, 40.3, 45.2, 47.2, 51.2, 65.5, 66.4, 119.8, 124.9, 126.9, 127.6, 141.2, 143.8, 156.7, 172.9; HRMS $[M+Na]^+$ Calcd. 433.2103, Found. 433.2112.

Fmoc-Asp(OBzl)-Ala-ol, 6e. Yield: 76%; m.p. 108-109 °C; $[\alpha]^{25}_D$ +18.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.16 (d, 3H, *J* = 6.4 Hz), 2.55 (d, 2H), 2.90 (br, s, 1H), 3.67 (d, 2H, *J* = 4.7 Hz), 4.04 (br, s, 2H), 4.20 (t, 1H, *J* = 6.6 Hz), 4.38 (d, 2H, *J* = 6.5 Hz), 5.67 (s, 1H), 7.27 – 7.41 (m, 4H), 7.58 (d, 2H, *J* = 6.0 Hz), 7.75 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$): δ 17.2, 37.2, 42.1, 47.0, 49.9, 63.8, 64.1, 66.7, 119.9, 126.2, 124.9, 126.23, 127.6, 128.1, 128.5, 141.1, 142.8, 143.7, 156.2, 170.9, 171.9; HRMS $[M+Na]^+$: Calcd. 525.2002, Found. 525.1998.

Fmoc-Ser(OBzl)-Val-ol, 6f. Yield: 74%; m.p. 135-137 °C; $[\alpha]^{25}_D$ –17.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.93 (d, 6H, *J* = 7.9 Hz), 1.40 (m, 1H), 3.65(d, 2H, *J* = 6.0 Hz), 3.75 (m, 2H, *J* = 7.1 Hz), 3.90-3.95 (m, 2H), 4.15 (t, 1H, *J* = 6.9 Hz), 4.41 (d, 2H, *J* = 7.0 Hz), 5.12 (2H, s), 5.8 (1H, br), 7.1-7.45 (m, 9H), 7.6 (d, 2H), 7.85 (d, 2H); ^{1}C NMR ($CDCl_3$): δ 18.6 29.4, 47.2, 48.3, 55.7, 64.4, 67.6, 69.7, 73.0, 120.0, 124.0, 125.1, 127.1, 27.8, 128.5, 128.6, 138.0, 141.4, 144.0, 155.4, 156.0, 172.9; HRMS $[M+Na]^+$: Calcd. 525.2365, Found. 525.2360.

Fmoc-Val-Ala-ol, 6g. Yield: 80%; m.p. 257-259°C; $[\alpha]^{25}_D$ –12.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 0.93 (d, 6H, *J* = 7.8 Hz), 1.16 (d, 3H, *J* = 6.9 Hz), 1.84 (m, 1H), 2.37 (br, s, 1H), 3.55 (br, m, 2H), 3.81 (m, 1H), 4.19 (m, 2H), 4.43 (d, 2H, *J* = 6.0 Hz), 5.03 (d, 1H, *J* = 8.0 Hz), 7.26-7.42 (m, 4H), 7.58 (d, 2H, *J* = 7.8 Hz), 7.76 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$): δ 17.2, 18.6, 29.1, 43.7, 47.3, 58.5, 63.6, 66.5, 119.9, 124.9, 127.0, 127.6, 141.3, 143.8, 157.0, 171.9; HRMS $[M+Na]^+$: Calcd. 419.1947, Found. 419.1941.

Conclusion

We have described a simple method for the preparation of *N*-protected β-amino alcohols using HATU for *in situ* activation of carboxylic acids. The present method is advantages as both the formation of –OAt ester as well as its reduction to β-amino

alcohols is rapid clean and can be executed in one-pot. The reaction is simple and free of racemization. This method can be applied for the conversion of N^{α}-Bsmoc / Boc / Z- protected amino acids and peptide acids to their respective alcohols in high yields.

Acknowledgements

The authors thank the Department of Science and Technology, Government of India for the financial assistance (Grant No. SR/S1/OC-26/2008) and Sophisticated Instruments Facility & IPC, I.I.Sc, Bangalore for NMR data.

References

1 (a) Cho C Y, Morna E J, Cherry S R, Stephans J C, Fodor S P, Adams C L, Sundaram A, Jacobs J W & Schultz P G, *Science,* 261, **1993,** 1303; (b) Moran E J, Wilson T E, Cho C Y, Cherry S R & Schultz P G, *Biopolymers (Peptide Science),* 37, **1995**, 213.

2 Cho C Y, Youngquist S R, Paikoff S J, Beresini M H, Hebert A R, Berlean L T, liu C W, Wemmer D E, Keough T & Schultz P G, *J Am Chem Soc,* 120, **1998**, 7706.

3 (a) Cho C Y, Morna E J, Cherry S R, Stephans J C, Fodor S P A, Adams C L, Sundaram A, Jacobs J W & Schultz P G, *Science,* 261, **1993,** 5126, 1303; (b) Sureshbabu V V, Sudarshan N S & Venkataramanarao R, *Int J Pept Res Ther,* 14, **2008**, 149.

4 (a) Coppola G M & Schuster H F, *Asymmetric Synthesis*, (John Wiley & Sons, New York, USA) **1987,** 85; (b) Nogradi M, *Stereoselective Synthesis*, (VCH, Weinheim. Germany) **1987,** 53**,** (c) Bolm C, *Angew Chem Int Ed Engl,* 30, **1991**, 542.

5 (a) Stanfield C F, Parker J E & Kenellis P, *J Org Chem,* 46, **1981,** 4797; (b) Hamada Y & Shioiri T, *Chem Pharm Bull,* 30, **1982,** 1921; (c) Sharma R P, Gore M G & Akthar M, *J Chem Soc Chem Commun,* **1979**, 875.

6 Wu S, Takeya R, Eto M & Tomizawa C, *J Pestic Sci,* 12, **1987**, 22.

7 Soai K, Oyamada H & Takase M, *Bull Chem Soc Japan,* 57, **1984,** 2327.

8 Fehrentz J A, Califano J C, Amblard M, Loffet A & Martinez J, *Tetrahedron Lett,* 35, **1994,** 569.

9 Nagvi T, Bhattaacharya M & Haq W, *J Chem Research (S)*, **1999**, 424.

10 Rodriguez M, Llinares M, Doulut S, Heitz A & Martinez J, *Tetrahedron Lett,* 32, **1991**, 7, 923.

11 Carpino L A, Imazumi H, E1-Faham A, Ferrer F J, Zhang C, Lee Y, Foxman B M, Henklein P, Hanay C, Mugge C, Wenschuh H, Klose J, Beyermann M & Bienert M, *Angew Chem Int Ed,* 41, **2002**, 3, 441.

12 (a) Carpino L A, *J Am Chem Soc,* 115, **1993,** 4397; (b) Ehrlich A, Rothemund S, Brydel M, Beyermann M, Carpino L A & Bienert M, *Tetrahedron Lett,* 34, **1993,** 4781; (c) Carpino L A, E1-Faham A, Minor C A & Albericio F, *J Chem Soc Chem Commun,* **1994,** 201; (d) Albericio F, Chinchilla R, Dodsworth D J & Najera C, *Org Prep Proc Int,* 33(3), **2001,** 203.

13 (a) Angell Y M, Garcia-Echuevarria C & Rich D M, *Tetrahedron Lett,* 35, **1994,** 5981; (b) Angell Y M, Thomas T L, Flentke G R & Rich D H, *J Am Chem Soc,* 117, **1995,** 7279;

14 (a) Yanai Y, Irie K, Ohigashi H & Wender P A, *Bioorg Med Chem Lett,* 7, **1997,** 117; (b) Irie K, Yanai Y, Onigashi H, Wender P A & Miller B L, *Bioorg Med Chem Lett,* 6, **1996,** 353. (c) Irie K, Oie K, Nakahara A, Yanai Y, Onigashi H, Wender P A, Fukuda H, Konishi H & Killkawa U, *J Am Chem Soc,* 120, **1998,** 9159.

15 Humphery J M, Aggen J B & Chamberlin A R, *J Am Chem Soc,* 118, **1996,** 11759.

16 Marsh I R, Bradley M & Teague S J, *J Org Chem,* 62, **1997,** 6199.

17 Hale K J & Cai J*, Chem Commun,* **1997,** 2319.

18 (a) Vasanthkumar G R, Basanagoud S P & Sureshbabu V V, *J Chem Soc Perkin Trans,* 1, **2002**, 2087; (b) Patil B S, Vasanthakumar G R & Sureshbabu V V, *J Org Chem,* 68, **2003**, 7274.

19 (a) Carpino L A, Philbin M, Ismail M, Truran G A, Mansour E M E, Shin Iguchi, Ionescu D, El-Faham A, Riemer C, Warrass R & Weiss M S, *J Am Chem Soc,* 119, **1997**, 9915; (b) Greenwald R B, Zhao H & Prasanna Reddy, *J Org Chem,* 68, **2003**, 4894.