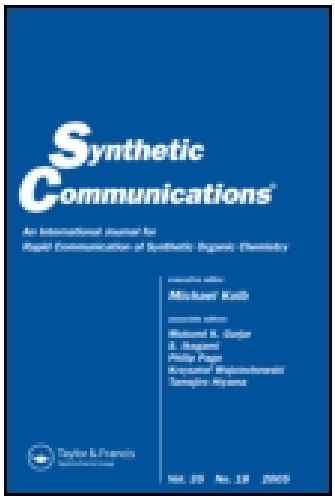

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A CONVENIENT METHOD FOR THE SYNTHESIS OF β-AMINO ACIDS VIA THE ARNDT-EISTERT APPROACH USING *p*-TOLUENESULPHONYL CHLORIDE AS A CARBOXYLIC GROUP ACTIVATING AGENT

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ABSTRACT

A simple method for the synthesis of Z-/Boc-/Fmoc-protected β-amino acids by the Arndt-Eistert approach employing *p*-toluenesulphonyl chloride for the activation of the carboxyl group of N^{α}-protected amino acid is described. The method is rapid and gave good yields with opitical purity.

β-Amino acids exhibit a wide spectrum of biological importance similar to natural α-amino acids. They serve as building blocks for the synthesis of β-peptides,[1] and β-lactam antibiotics.[2] Seebach[3] and Gellman[4,5] groups reported that β-peptides also form stable secondary structures like their

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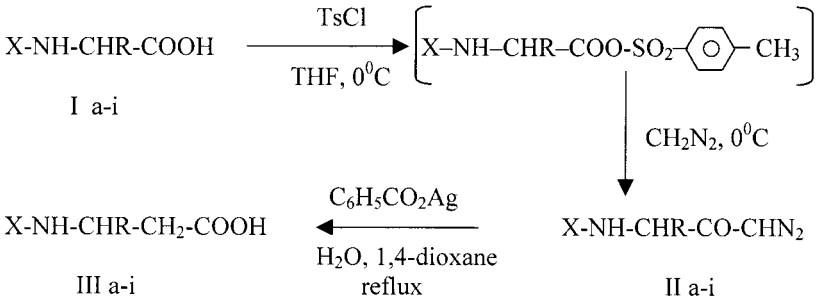
α-peptide counterpart. β-Peptides shared by proteinaceous side chains of α-amino acids have been shown to be stable to common α-peptidases for few days.[6] The Arndt-Eistert method for the homologation of α-amino acids is one of the important routes for the synthesis of β-amino acids. This route involves the synthesis of commonly used α-aminoacyldiazomethanes from the N^{α}-protected amino acids. For this, the activation of carboxylic group of α-amino acid employing the corresponding mixed anhydrides[1,3,7] (using isobutoxycarbonyl chloride or ethoxycarbonyl chloride) or acid chlorides[8] or acid fluorides[9] or activated esters[10] has been used.

The use of *p*-toluenesulphonyl chloride (TsCl) in organic synthesis is widely known. It has been used for the activation of carboxylic group in the synthesis of amides and esters of simple carboxylic acids,[11] for the synthesis of peptides,[12] β-lactams[13] etc. This paper describes the use of TsCl for the activation of carboxylic group in the synthesis of N^{α}-protected aminoacyldiazomethanes.

As shown in Scheme 1, N^{α}-protected aminoacyldiazomethane was prepared by addition of TsCl and diazomethane (CH_2N_2) in dichloromethane (CH_2Cl_2) to N^{α}-protected amino acid in THF at 0°C in presence of pyridine. The reaction proceeds through the formation of carboxylic–sulphonic mixed anhydride which was identified by IR spectra (1825–1835 cm^{-1}). The reaction was complete in about 30 min. All the resulting diazomethane derivatives were isolated as crystalline solids in good yield. They have been analysed by using IR by the presence of characteristic band at around 2105–2108 cm^{-1} (-$COCHN_2$ group) and ^{1}H NMR. They were



	X	R		X	R
a	Fmoc	$CH_2C_6H_5$	f	Boc	$CH(CH_3)_2$
b	Fmoc	$CH(CH_3)_2$	g	Z	$CH_2C_6H_5$
c/d	Fmoc	C_6H_5	h	Z	CH_3
e	Boc	CH_3	i	Z	C_6H_5

Scheme 1. Synthesis of *N*-protected-β-homoamino acids.

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then converted to their corresponding β-amino acids by the Wolff rearrangement using silver benzoate/1,4-dioxane/water by refluxing the mixture for 6 h at 70°C. All the *N*-protected β-amino acids were obtained as crystalline solids and were well characterised. The comparison of the determined optical rotations of the D- and L-isomers of Fmoc-α-Phg and that of β-Phg revealed that this method is completely free from racemisation.

Thus the present procedure is an efficient method for the synthesis of N^{α}-protected aminoacyldiazomethane using TsCl for carboxylic group activation. The advantages of this method are (a) the mild reaction conditions (b) the use of cheaper reagent (c) the general applicability (d) the selectivity, and (e) the good yields.

EXPERIMENTAL

All the amino acids used, unless otherwise specified has L-configuration only. Melting points reported are uncorrected. Thin layer chromatography (TLC) was carried out using the solvent systems: (i) ethyl acetate : hexane (35 : 65), (ii) chloroform : methanol : acetic acid (45 : 2 : 1), (iii) chloroform : methanol (9 : 1) and the R_f values are designated as R_fA, R_fB and R_fC respectively. ^{1}H NMR spectra were recorded on a Brucker AMX-400 MHz spectrometer. IR spectra were recorded on a Nicolet model impact 400 D FT-IR spectrometer. Elemental analyses were carried out by Perkin-Elmer Analyser and the samples were dried for 24 h under vacuum before analysis. Diazomethane gas was generated by heating *N*-nitroso-*N*-methyl-*p*-toluene sulphonamide with alcoholic KOH.[14]

General Procedure for Preparation of N^{α}-Protected Aminoacyldiazomethane Derivatives: TsCl (0.210 g, 1.1 mmol) and pyridine (0.08 mL, 1 mmol) were added to a solution of N^{α}-protected amino acid (1 mmol) in THF (5 mL) and stirred at 0°C for 15 min. The reaction mixture was treated with a saturated solution of CH_2N_2 in dry CH_2Cl_2 (20 mL) and stirred for 1 h at 0°C. The progress of the reaction was monitored by TLC and IR. After completion of the reaction, the excess of CH_2N_2 was decomposed by the dropwise addition of acetic acid. The mixture was washed with $NaHCO_3$ (25 mL × 3), 5% HCl (25 mL × 3) and brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The resulting residue was recrystallized using CH_2Cl_2/hexane to yield the title compound as a crystalline solid.

N^{α}-Fmoc-phenylalanyldiazomethane (IIa): Yield, 94%; m.p., 136°C; R_fA, 0.62; R_fB, 0.8; $[\alpha]_D^{25} + 16.5$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{25}H_{23}N_3O_3$: C, 72.60; H, 5.60; N, 10.16; Found: C, 72.35; H, 5.57; N,

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9.78; IR (γ_{max}): 2108 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 3.1 (2H, d), 4.2 (2H, m), 4.5 (2H, d), 5.2 (1H, s), 5.4 (1H, br) and 7.2–7.7 (13H, m).

N^{α}-Fmoc-valyldiazomethane (IIb): Yield, 85%; m.p., 124–125°C; R_fA, 0.69; R_fB, 0.81; $[\alpha]_D^{25} - 23.40$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{21}H_{21}N_3O_3$: C, 69.4; H, 5.81; N, 11.56; Found: C, 69.28; H, 5.92; N, 11.46; IR (γ_{max}): 2105 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 0.90 (6H, d), 1.75 (1H, m), 4.10 (1H, m), 4.25 (1H, m), 4.45 (2H, m), 5.30 (1H, s), 5.4 (1H, d) and 7.3–7.9 (8H, m).

N^{α}-Fmoc-phenylglycinyldiazomethane (IIc): Yield, 90%; m.p., 148–149°C; R_fA, 0.66; R_fB, 0.80; $[\alpha]_D^{25} - 32.3$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{24}H_{29}N_3O_3$: C, 72.50; H, 4.81; N, 10.57; Found: C, 72.68; H, 4.87; N, 10.6; IR (γ_{max}): 2107 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 4.25 (2H, m), 4.4 (2H, d), 5.1 (1H, s), 6.05 (1H, br) and 7.2–7.8 (13H, m).

N^{α}-Fmoc-D-phenylglycinyldiazomethane (IId): Yield, 92%; m.p., 153°C; R_fA, 0.7; R_fB, 0.83; $[\alpha]_D^{25} + 32.3$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{24}H_{29}N_3O_3$: C, 72.50; H, 4.81; N, 10.57; Found: C, 72.43; H, 4.90; N, 10.52; IR (γ_{max}): 2106 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 4.2 (2H, m), 4.5 (2H, d), 5.1 (1H, s), 6.05 (1H, br) and 7.2–7.8 (13H, m).

N^{α}-Boc-alanyldiazomethane (IIe): Yield, 93%; m.p., 82°C; R_fA, 0.72; R_fB, 0.82; $[\alpha]_D^{25} - 21.7$ ($c = 1$, $CHCl_3$); Anal. Calc. for C, 50.69; H, 7.08; N, 19.70; Found: C, 50.80; H, 7.20; N, 19.47; IR (γ_{max}): 2106 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 1.05 (3H, d), 1.32 (9H, s), 4.21 (1H, m), 5.25 (1H, s) and 5.5 (1H, br).

N^{α}-Boc-valyldiazomethane (IIf): Yield, 90%; m.p., 64°C; R_fA, 0.72; R_fB, 0.83; $[\alpha]_D^{25} - 30.4$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{11}H_{19}N_3O_3$: C, 54.75; H, 7.93; N, 17.41; Found: C, 54.62; H, 7.78; N, 17.42; IR (γ_{max}): 2107 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 0.92 (6H, d), 1.32 (9H, s), 1.75 (1H, m), 4.21 (1H, br), 5.20 (1H, s) and 5.42 (1H, br).

N^{α}-*Z*-phenylalanyldiazomethane (IIg): Yield, 92%; m.p., 82–83°C; R_fA, 0.68; R_fB, 0.78; $[\alpha]_D^{25} + 48.2$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.29; N, 12.99; Found: C, 66.72; H, 5.35; N, 12.86; IR (γ_{max}): 2107 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 2.9 (2H, d), 4.45 (1H, m), 5.0 (2H, s), 5.22 (1H, s), 5.46 (1H, br) and 7.2–7.3 (10H, m).

N^{α}-*Z*-alanyldiazomethane (IIh): Yield, 88%; m.p., 93–94°C; R_fA, 0.70; R_fB, 0.81; $[\alpha]_D^{25} - 50.3$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.29; N, 16.99; Found: C, 57.95; H, 5.13; N, 16.78; IR (γ_{max}): 2107 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 1.2 (3H, d), 4.26 (1H, m), 5.1 (2H, s), 5.25 (1H, s), 5.5 (1H, br) and 7.32 (5H, s).

N^{α}-*Z*-phenylglycyldiazomethane (IIi): Yield, 86%; m.p., 83–84°C; R_fA, 0.69; R_fB, 0.79; $[\alpha]_D^{25} - 36.4$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.88; N, 13.58; Found: C, 65.72; H, 4.76; N, 13.72; IR

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(γ_{max}): 2108 cm^{-1} (-$COCHN_2$); ^1H NMR ($CDCl_3$, δ): 4.5 (1H, br), 5.02 (2H, s), 5.22 (1H, s), 5.40 (1H, br) and 7.25 (10H, s).

General Procedure for Preparation of *N*-Protected β-Amino Acid: Silver benzoate (5.7 mg, 2.5×10^{-2} mmol) was added to a solution of N^{α}-protected aminoacyldiazomethane (1 mmol) in 1,4-dioxane (10 mL) and water (5 mL) and refluxed at 70°C for 6 h. It was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in saturated aqueous Na_2CO_3 (20 mL) and stirred for 20 min. The mixture was washed with ether (20 mL × 3). The aqueous layer was acidified to pH 2 and extracted with ethyl acetate (20 mL × 3). The extracts were pooled, washed with water (20 mL × 2), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was precipitated using CH_2Cl_2/hexane to get the title compound as a crystalline solid.

***N*-Fmoc-β-homophenylalanine (IIIa):** Yield, 85%; m.p., 110–112°C R_fB, 0.63; R_fC, 0.75; $[\alpha]_D^{25} - 26.2$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{25}H_{23}NO_4$: C, 75.05; H, 5.58; N, 3.70; Found: C, 75.21; H, 5.46; N, 3.80; IR (γ_{max}): 1703 cm^{-1} (CO of urethane); ^1H NMR ($CDCl_3$, δ): 2.43 (1H, d), 2.52 (2H, m), 2.71 (1H, d), 3.6 (1H, m), 4.1 (1H, m), 4.2 (2H, m) and 7.3–7.8 (14H, m).

***N*-Fmoc-β-homovaline (IIIb):** Yield, 80%; m.p., 153–154°C; R_fB, 0.60; R_fC, 0.78; $[\alpha]_D^{25} - 36.4$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{21}H_{23}NO_4$: C, 70.14; H, 5.89; N, 4.20; Found: C, 70.06; H, 5.67; N, 4.35; IR (γ_{max}): 1705 cm^{-1} (CO of urethane); ^1H NMR ($CDCl_3$, δ): 0.85 (6H, d), 1.75 (1H, m), 2.30 (1H, d), 2.45 (1H, d), 3.75 (1H, m), 4.30 (3H, m) and 7.3–7.8 (9H, m).

***N*-Fmoc-β-homophenylglycine (IIIc):** Yield, 82%; m.p., 96–98°C; R_fB, 0.61; R_fC, 0.78; $[\alpha]_D^{25} - 22.2$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.45; N, 3.61; Found: C, 74.26; H, 5.23; N, 3.80; IR (γ_{max}): 1705 cm^{-1} (CO of urethane); ^1H NMR ($CDCl_3$, δ): 2.5 (2H, d), 4.25 (2H, m), 4.4 (2H, d), 5.85 (1H, br) and 7.2–7.8 (13H, m).

***N*-Fmoc-β-D-homophenylglycine (IIId):** Yield, 84%; m.p., 102°C; R_fB, 0.62; R_fC, 0.79; $[\alpha]_D^{25} + 21.8$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.45; N, 3.61; Found: C, 74.34; H, 5.16; N, 3.76; IR (γ_{max}): 1705 cm^{-1} (CO of urethane); ^1H NMR ($CDCl_3$, δ): 2.4 (2H, d), 4.25 (2H, m), 4.3 (2H, d), 5.80 (1H, br), 7.2–7.8 (13H, m) and 8.3 (1H, br).

***N*-Boc-β-homoalanine (IIIe):** Yield, 88%; m.p., 98–99°C; R_fB, 0.62; R_fC, 0.72; $[\alpha]_D^{25} - 18.1$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_9H_{17}NO_4$: C, 53.45; H, 8.47; N, 6.92; Found: C, 53.28; H, 8.56; N, 6.56; IR (γ_{max}): 1690 cm^{-1} (CO of urethane); ^1H NMR ($CDCl_3$, δ): 1.2 (3H, d), 1.33 (9H, s), 2.4 (2H, d), 4.01 (1H, m), 5.25 (1H, br) and 8.4 (1H, br).

***N*-Boc-β-homovaline (IIIf):** Yield, 86%; m.p., 65–66°C; R_fB, 0.61; R_fC, 0.70; $[\alpha]_D^{25} - 20.2$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{11}H_{21}NO_4$: C, 57.37; H, 9.19; N, 6.08; Found: C, 56.90; H, 9.34; N, 5.82; IR (γ_{max}): 1690 cm^{-1}

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(CO of urethane); ^{1}H NMR ($CDCl_3$, δ): 0.94 (6H, d), 1.32 (9H, s), 1.72 (1H, m), 2.5 (2H, d), 4.20 (1H, br), 5.4 (1H, br) and 8.3 (1H, br).

***N*-*Z*-β-homophenylalanine (IIIg):** Yield, 88%; m.p., 84–85°C; R_fB, 0.60; R_fC, 0.68; $[\alpha]_D^{25} - 36.2$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{18}H_{19}NO_4$: C, 69.21; H, 6.13; N, 4.48; Found: C, 69.63; H, 6.47; N, 4.32; IR ($\gamma_{max.}$): 1698 cm^{-1} (CO of urethane): ^{1}H NMR ($CDCl_3$, δ): 2.36 (2H, d), 2.71 (2H, d), 3.8 (1H, m), 5.01 (2H, s), 5.3 (1H, m), 7.07 (5H, s), 7.28 (5H, s) and 9.4 (1H, br).

***N*-*Z*-β-homoalanine (IIIh):** Yield, 84%; m.p., 122°C; R_fB, 0.60; R_fC, 0.69; $[\alpha]_D^{25} - 19.8$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{12}H_{15}NO_4$: C, 61.00; H, 6.39; N, 5.92; Found: C, 61.27; H, 6.23; N, 5.87; IR (γ_{max}): 1700 cm^{-1} (CO of urethane); ^{1}H NMR ($CDCl_3$, δ): 1.2 (3H, d), 2.4 (2H, d), 3.6 (1H, m), 5.1 (2H, s), 5.4 (1H, br), 7.31 (5H, s) and 8.4 (1H, br).

***N*-*Z*-β-homophenylglycine (IIIi):** Yield, 82%; m.p., 86–88°C; R_fB, 0.63; R_fC, 0.74; $[\alpha]_D^{25} - 18.5$ ($c = 1$, $CHCl_3$); Anal. Calc. for $C_{17}H_{17}NO_4$: C, 68.44; H, 5.74; N, 4.95; Found: C, 68.23; H, 5.68; N, 4.67; IR (max): 1702 cm^{-1} (CO of urethane); ^{1}H NMR ($CDCl_3$, δ): 2.5 (2H, d), 4.2 (1H, m), 5.01 (2H, s), 5.46 (1H, br), 7.25 (10H, s) and 8.6 (1H, br).

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