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Facile Synthesis of Tert-Butyl Ester of N-Protected Amino Acids with Tert-Butyl Bromide

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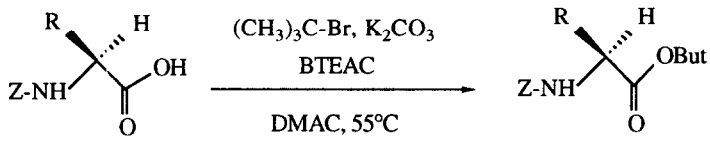
Abstract: A facile synthesis of a wide variety of N-benzyloxycarbonyl-amino acid-tert-butyl ester derivatives under mild conditions is described. N-protected amino acids were esterified with tert-butyl bromide in dimethylacetamide as solvent, in the presence of benzyltriethylammonium chloride (BTEAC)and a large excess of potassium carbonate. Many amino Z-acid-Tert-butyl esters that might be difficult to prepare by other methods have been synthesized in high yields by this procedure. The reaction is simple, unexpansive, easily scaled up, and proceeds without observable racemization.

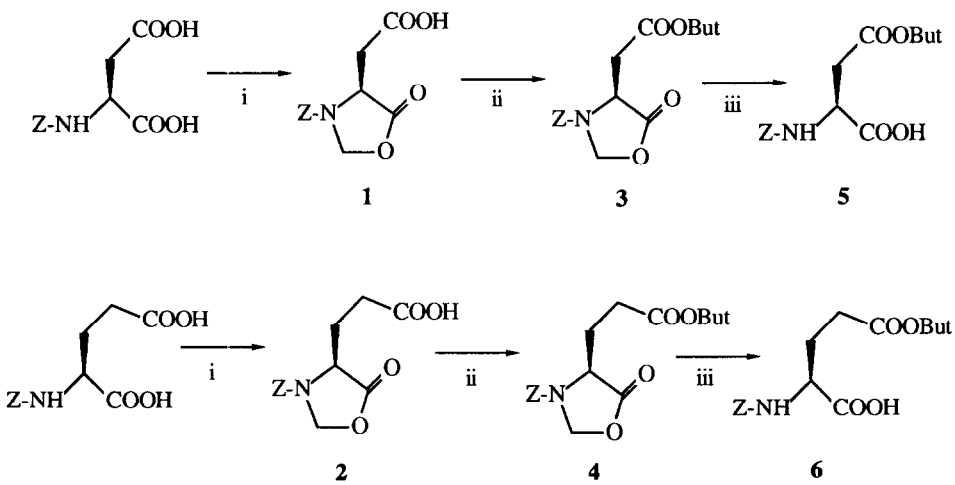
Tert-butyl esters of amino acids are key intermediates in the chemistry of amino acids and peptides. They are generally obtained by addition of the carboxyl group to isobutene[1] or transesterification of carboxylic acids with tert-butyl acetate[2], in the presence of strong acids. T-butyl esters of N-benzyloxycarbonyl-amino acids (Z-amino acids) particularly, are of great interest in peptide synthesis. They were recently synthesized by 4-dimethylaminopyridine catalyzed esterification with t-butanol of a mixed carboxylic-carbonic anhydride N-protected amino acid derivative obtained using isopropenyl chlorocarbonate[3]. A more recent report proposed the synthesis of N-benzyloxycarbonyl amino acid t-butyl esters via the tert-butyl anhydride generated *in situ* by tert-butyl fluorocarbonate (Boc-F) in the presence of t-butanol and 4-dimethylaminopyridine[4]. However, a great need still exists for a versatile and facile procedure to prepare t-butyl ester derivatives of amino acids under mild conditions. We report here on the synthesis of Z-amino acid tert-butyl esters by esterification of Z-amino acids in the presence of t-butyl bromide (Scheme 1). The usefulness of this method was demonstrated by the synthesis of a series of tert-butyl esters of benzyloxycarbonyl-amino acid, including tert-butyl esters of the hindered amino acid Z-Val-OBut, of amino acids bearing an hydroxyl side chain function, Z-Ser-OBut, Z-Thr-OBut, Z-Tyr-OBut, of the acid sensitive Z-Trp-OBut (Table 1). However, Z-Asp(OBut)-OH **7** and Z-Glu(OBut)-OH **8**, two important amino acid derivatives were synthesized by this method from regioselective β and γ tert-butylation of Z-Asp and Z-Glu through their oxazolidinone derivatives (Scheme 2). The (S)-3-benzyloxycarbonyl-5-oxo-4-oxazolidine acetic acid **1** and (S)-3-benzyloxycarbonyl-5-oxo-4-oxazolidine propionic acid **2** were prepared in about 90% yield as previously described[5]. Their esterification in the presence of tert-butyl bromide yielded the (S)-3-benzyloxycarbonyl-5-oxo-4-oxazolidine acetic acid tert-butyl ester **3** and (S)-3-benzyloxycarbonyl-5-oxo-4-oxazolidine propionic acid tert-butyl ester **4**, in respectively 82% and 91% yields. Sodium hydroxide saponification of the oxazolidinones **3** and **4** yielded Z-Asp(OBut)-OH **5** and Z-

Glu(OBut)-OH **6** in both about 80% yield. No racemization could be detected during these synthesis as indicated by comparison of their $[\alpha]_D$ with those reported in the literature.

Scheme 1. Tert-butylation of Z-amino acid residues.



Scheme 2. Synthesis of Z-Asp(OBut)-OH and ZGlu(OBut)-OH



(i) 3 eq. trioxane, cat. TsOH in refluxing toluene. (ii) Tert-butyl bromide, K_2CO_3, BTEAC, 55°C in DMAC. (iii) 1 eq. 1N NaOH in EtOH.

Table 1. Preparation of Z-Amino Acid Tert-Butyl Esters via the Tert-Butyl Bromide Method.

Amino Acid	R_f	Yield (%)	mp (°C)	mp (°C)	$[\alpha]^{20}_D$ (c, solvent)	$[\alpha]^{20}_D$lit. (c, solvent)
Z-Gly-OBut[6]	0.52 (C); 0.57 (H)	100	oil	oil		
Z-Ala-OBut	0.45 (B); 0.50 (H)	92	oil	-	- 23 (1.2 EtOH)	
Z-Val-OBut[6]	0.40 (A); 0.35 (G)	97	oil	oil	-15 (1.2 EtOH)	
Z-Pro-OBut[6]	0.49 (C); 0.38 (H)	100	oil	44-45	-51 (2, EtOH)	- 52.5 (2.2 EtOH)
Z-Phe-OBut[6]	0.28 (A); 0.30 (G)	100 (80*)	80-81	80.5-81.5	-5 (2 EtOH)	-5 (2EtOH)
Z-Ser-OBut[7]	0.61 (D); 0.66 (I)	100 (76*)	94	93-95	-16 (1.1 EtOH)	-16.3 (1.03 EtOH)
Z-Thr-OBut[7]	0.67 (D); 0.68 (I)	97 (75*)	66	-	-21 (1 EtOH)	-20.6 (1.07 EtOH)
Z-Tyr-OBut**[6]	0.40 (C); 0.69 (I)	88 (70*)	88	oil	-0.4 (1.04 EtOH)	-
Z-Trp-OBut	0.37 (D); 0.37 (H)	90	oil	-	-6 (1 EtOH)	-
Z-Gln-OBut[6, 8]	0.47 (E); 0.60 (F)	87 (70*)	82	92-93	-13 (1 EtOH)	-20.6 (1 EtOH)[8] -10.9 (5 EtOH)[6]
1[5]	0.50 (J); 0.51 (F)	91 (70*)	69 (dec)	oil	+124 (1.1 EtOH)	-
2[5]	0.69 (F); 0.53 (J)	90	oil	oil	+ 72 (1.1 EtOH)	-
3[5]	0.30 (C); 0.45 (H)	82 (70*)	74	-	+86 (1 EtOH)	-
4[5]	0.35 (C); 0.41 (H)	91	oil	oil	+ 37 (1.1 EtOH)	-
5[4]	0.37 (F); 0.54 (J)	80 (75*)	75	76-78	-11 (1pyridine) +0.8 (1, EtOH)	-12.95 (1pyridine) +0.6 (1 EtOH)***
6[4]	0.40 (F); 0.56 (J)	82 (72*)	80	79-80	-9 (1 EtOH)	-8.9 (1 EtOH)

Solvent systems : (A) Ethyl acetate/Hexane 1:9; (B) Ethyl acetate/Hexane 2:8; (C) Ethyl acetate/Hexane 3:7; (D) Ethyl acetate/Hexane 5:5; (E) Ethyl acetate; (F) Chloroform/Methanol 9:1; (G) Chloroform/Petroleum ether 1:1; (H) Chloroform; (I) Chloroform/Methanol 95:5; (J) Chloroform/Methanol/Acetic acid 180:10:5. All compounds were identified by ^{1}H NMR spectroscopy (250 MHz) and mass spectrometry. Melting points are reported uncorrected. (*) Yields of recrystallization that were performed in a mixture of Ether/Hexane. (**) In order to check racemization, Z-Tyr-OBut was hydrogenated (5% Pd/C, EtOH 95) in the presence of an equimolecular amount of diluted HCl to produce HCl.H-Tyr-OBut ($[\alpha]^{20}_D$ +25 (c 2 EtOH)); Its $[\alpha]^{20}_D$ was compared with that reported in the literature ($[\alpha]^{20}_D$lit.[9] +24.4 (c 2 EtOH)). (***) From an authentic sample obtained from Novabiochem, Switzerland.

In a typical experiment, a Z-amino acid derivative (10 mmoles) was dissolved in dimethylacetamide (75 ml) in the presence of benzyltriethylammonium chloride (BTEAC) (10 mmoles). Dried potassium carbonate (260 mmoles) was then added, followed by tert-butyl bromide (480 mmoles) and the mixture was stirred at 55°C for 24 hours. After cooling, cold water (1000 ml) was added to the reaction mixture, and the resulting solid precipitate was filtered and washed several times with water. In the case of oily compounds, the precipitate was extracted in ethyl acetate (250 ml). The organic layer was separated, washed with water (2 x 100 ml), dried over sodium sulfate and concentrated *in vacuo*. For the synthesis of the (S)-3-benzyloxycarbonyl-5-oxo-4-oxazolidine acetic acid tert-butyl ester **3** and (S)-3-benzyloxycarbonyl-5-oxo-4-oxazolidine propionic acid tert-butyl ester **4**, after 24 hours stirring, the reaction mixture was filtered, ethyl acetate (250 ml) was added, and the precipitate rinsed several times with ethyl acetate. The organic layer was washed with water (2 x 100 ml), dried over potassium sulfate and concentrated *in vacuo*.

Z-amino acid tert-butyl esters derivatives were obtained in good yields (80 to 100%) (Table 1). The reaction proceeds without observable racemization as it is indicated by their $[\alpha]_D$ compared with those reported in the literature. The ease of manipulation, mild conditions and high yields as well as the non expansive reagents that were used, are such that this method appears to be a valuable method for the tert-butyl esterification of Z-amino acids.

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