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AN IMPROVED PREPARATION OF 4-HYDROXYMETHYL-L-PHENYLALANINE

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Abstract: Palladium-catalyzed hydroformylation of methyl esters of *N*-Boc-L-tyrosine triflate (**1a**) and *N*-Boc-4-iodo-L-phenylalanine (**1b**) followed by reduction with sodium borohydride and standard deprotection procedures affords the title compound in 77 and 83% overall yield, respectively.

Tyrosine phosphorylation by protein tyrosine kinases (PTK) is of central importance in a broad range of cellular processes including cell growth, differentiation, and death.[1] Alterations in the activity of PTKs are associated with a number of human diseases like cancer, diabetes, and immune dysfunctions.[2]

In addition, the presence of a sulphated tyrosine residue is essential for the expression of the biological activity of a series of secretory and neuropeptides such as gastrin,[3] cholecystokinin,[4] fibronectin,[5] and leucosulfakinin.[6]

The preparation of amino acids mimicking tyrosine phosphate or sulphate residues for the development of PTK inhibitors or of peptide analogues is therefore of widespread interest.[7]

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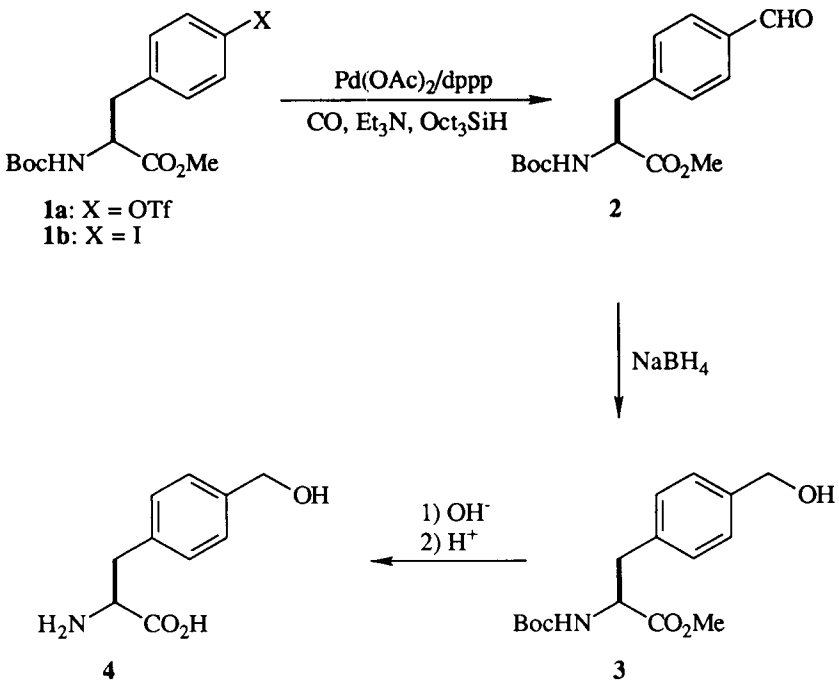
4-Hydroxymethyl-L-phenylalanine (**4**) is a versatile unnatural amino acid which has been employed to this end by different authors both in linear strategies[7b] and in divergent ones.[8] Compound **4** was also found of interest in metabolic studies.[9]

Previous reports on the synthesis of 4-hydroxymethyl-L-phenylalanine have involved the nonselective preparation of the D,L-form followed by an enzymatic resolution,[7b,9a] or have exploited the chiral phase-transfer catalysis methodology of O'Donnell.[8] The first approach appears to be inefficient and inconvenient for large scale preparations, while the latter produces a 4/1 ratio of L and D enantiomers.

As part of our interest in the palladium-catalyzed elaboration of α-amino acids,[10] we report here an alternative and convenient procedure for the preparation of **4** which utilizes as the key step a recently reported procedure for the palladium-catalyzed hydroformylation of aryl triflates (Scheme).[11]

The process starts with the tyrosine triflate or the 4-iodophenylalanine derivatives **1a,b**, both readily available from the corresponding protected tyrosine[12] or from L-phenylalanine,[13] respectively. Reaction of **1a** and **1b** with carbon monoxide and trioctylsilane in the presence of $Pd(OAc)_2$/dppp[14] as the catalyst following a procedure similar to that introduced by Kotsuki[11] afforded the aldehyde **2** in 85 and 89% yield, respectively. Faster conversion was observed with **1a**. In fact, when 3 mol% of the catalyst were employed, the reaction with **1a** went to completion in 4 h, while 12 h were required for the complete consumption of **1b**. To the best of our knowledge, this is the first application of the Kotsuki's method to an aryl iodide.

Hartman and Halczenko[15] have already reported a palladium-catalyzed carbonylative approach to *N*-Boc-4-formyl-L-phenylalanine from *N*-Boc-4-iodo-L-phenylalanine by the use of tributyltin hydride as hydrogen donor. A paper describing an application of this procedure to the preparation of the pentapeptide Ac-Ile-Phe(4-formyl)-Gly-Glu(O-tBu)-Phe-NH_2, key intermediate for divergent PTK $pp60^{c\text{-}src}$ inhibitor synthesis, has also appeared during completion of our work.[7a] The formylation of organic halides or triflates with carbon monoxide and Bu_3SnH presents however the disadvantage that it requires the slow addition of the reagent (≥ 2.5 h), in order to minimize the direct reduction of the halide or triflate.[16]



1a: X = OTf
1b: X = I

2

4

3

Scheme

Reduction of **2** with sodium borohydride at room temperature afforded the hydroxymethyl derivative **3** in 91% yield. The methyl ester function remained substantially unaffected under the conditions described in the Experimental Section. If, however, a 1.5 molar excess of the hydride was employed and the reaction time was increased to 1 h, the yield of **3** diminished to 75% and a 21% of the bis-alcohol was isolated. It is well known that the presence of suitable neighbouring groups enhances the reactivity of $NaBH_4$ toward esters.[17]

The two-step reaction sequence leading to **3** can be conveniently conducted as a one-pot operation that omits the isolation of the aldehyde. The alcohol **3** was isolated in this case in 79 and 85% yield from **1a** and **1b**, respectively.[18]

The free amino acid **4** was obtained almost quantitatively by saponification of **3** with a NaOH/MeOH/H_2O mixture at room temperature followed by removal of

the Boc protecting group using a solution of dry HCl in AcOEt. Physical data for **4**, in particular the optical rotation, were in good agreement with the values reported in literature.[9a]

EXPERIMENTAL SECTION

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured at 22 °C with a Schmidt-Haensch Polartronic D polarimeter (1 dm-cell) in 2% $CHCl_3$ (**1-3**) or H_2O (**4**) solutions. IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer as KBr disks. ^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ (**1-3**) or D_2O (**4**) as solvent and Me_4Si or 3-(trimethylsilyl)propionic acid-d_4 sodium salt as internal standard, respectively. Elemental analyses were performed by Servizio Microanalisi del C.N.R., Area della Ricerca di Roma, 00016 Monterotondo Stazione, Roma, Italy.

***N*-Boc-4-formyl-L-phenylalanine Methyl Ester (2).** A mixture of *N*-Boc-L-tyrosine triflate methyl ester (**1a**, 427 mg, 1 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), dppp (12 mg, 0.03 mmol), and Et_3N (0.35 mL, 2.5 mmol) in DMF (5 mL) was purged with carbon monoxide for 10 min. Then, trioctylsilane (0.9 mL, 2 mmol) was introduced in one portion and the mixture was stirred under a CO balloon at 70 °C for 4 h. After dilution with water, the mixture was extracted with ether. The organic phase was washed with water, saturated $NaHCO_3$, and water, dried (Na_2SO_4), and evaporated. The residue (964 mg) was chromatographed on silica gel (30 g) using hexane/AcOEt = 75/25 as eluent to give 261 mg (85%) of **2**: mp 91-92 °C (CH_2Cl_2/hexane); $[\alpha]_D$ +64°; IR 3377, 1759, 1689, 1527, 1351, 1167 cm^{-1}; ^1H NMR δ 1.41 (9H, s, *t*-Bu), 3.11 (1H, dd, J = 13.9, 6.6 Hz, CHH), 3.24 (1H, dd, J = 13.9, 5.5 Hz, CHH), 3.73 (3H, s, CO_2Me), 4.64 (1H, m, α-CH), 5.05 (1H, d, J = 7.7 Hz, NH), 7.32 (2H, d, J = 8.0 Hz, ArH), 7.82 (2H, d, J = 8.0 Hz, ArH), 9.99 (1H, s, CHO); ^{13}C δ 28.27, 38.70, 52.40, 54.20, 80.18, 129.93, 130.06, 135.34, 143.45, 169.81, 171.88, 191.83. Anal. Calcd for

$C_{16}H_{21}NO_5$ (307.4): C, 62.52; H, 6.88; N, 4.56. Found: C, 62.55; H, 7.08; N, 4.66.

The aldehyde **2** could be prepared and isolated in a similar manner using *N*-Boc-4-iodo-L-phenylalanine methyl ester (**1b**, 405 mg, 1 mmol) as the starting material. In this case, 5 mol% of $Pd(OAc)_2$ and dppp were employed. The reaction time was 4 h and the yield of **2** was 89%.

***N*-Boc-4-hydroxymethyl-L-phenylalanine Methyl Ester (3).** To a stirred solution of **2** (307 mg, 1 mmol) in CH_2Cl_2 (5 mL) $NaBH_4$ (45 mg, 1.2 mmol) was added in one portion, and MeOH (1 mL) was then added dropwise. The mixture was stirred at room temperature for 0.5 h, then treated with 10% aqueous acetic acid, and extracted with AcOEt. The organic phase was washed twice with water, dried (Na_2SO_4), and evaporated. The residue (328 mg) was chromatographed on silica gel (10 g) using hexane/AcOEt = 65/35 as eluent to give 280 mg (91%) of **3**: mp 82-83 °C (CH_2Cl_2/hexane); $[\alpha]_D$ +49°; IR 3491, 3445, 1748, 1702, 1512, 1358, 1170 cm^{-1}; ^1H NMR δ 1.42 (9H, s, *t*-Bu), 2.60 (1H, br, OH), 3.05 (1H, dd, J = 13.7, 5.9 Hz, C<u>H</u>H), 3.12 (1H, dd, J = 13.7, 5.9 Hz, CH<u>H</u>), 3.72 (3H, s, CO_2Me), 4.58 (1H, m, α-CH), 4.67 (2H, s, C<u>H</u>$_2$OH), 4.98 (1H, d, J = 7.9 Hz, NH), 7.12 (2H, d, J = 8.0 Hz, ArH), 7.30 (2H, d, J = 8.0 Hz, ArH); ^{13}C δ 28.29, 38.00, 52.24, 54.40, 65.04, 79.97, 127.24, 129.49, 135.42, 139.64, 155.08, 172.30. Anal. Calcd for $C_{16}H_{23}NO_5$ (309.4): C, 62.12; H, 7.49; N, 4.53. Found: C, 62.11; H, 7.69; N, 4.61.

One-Pot Preparation of 3. After completion of the carbonylation reaction on either **1a** or **1b**, the mixture was flushed with N_2 for 5 min and cooled at 0 °C. $NaBH_4$ (57 mg, 1.5 mmol) was added in one portion, and MeOH (1 mL) was then added dropwise. The mixture was stirred at room temperature for 1 h, then worked-up as described above to give, after chromatography, 243 mg (79%) or 262 mg (85%) of **3**, respectively.

4-Hydroxymethyl-L-phenylalanine (4). A solution of **3** (309 mg, 1 mmol) in MeOH (3 mL) and 2N NaOH (1 mL) was stirred at room temperature for 4 h, concentrated, acidified with a slight excess of 2N HCl, and extracted with AcOEt. The organic phase was washed twice with water, dried (Na_2SO_4), and

evaporated. To a solution of the residue (300 mg) in AcOEt (2 mL) was added a saturated solution of anhydrous HCl in AcOEt (4.5 mL). The solution was stirred at room temperature for 3 h and evaporated to obtain a white solid (245 mg). The crude hydrochloride was dissolved in water (20 mL) and passed through a column of the anion exchange resin Amberlite IRA-93 (6 g). The effluent was evaporated to dryness (after decolourization with activated charcoal) to give 191 mg (98%) of **4**: mp 205-207 °C ($EtOH/H_2O$); $[\alpha]_D$ -32° (lit.[9a] 213-215 °C; $[\alpha]_D$ -32.5°); IR 3291, 1601, 1485, 1402, 1325 cm^{-1}; ^1H NMR δ 3.11 (1H, dd, J = 14.4, 7.9 Hz, CHH), 3.27 (1H, dd, J = 14.4, 5.1 Hz, CHH), 3.98 (1H, m, α-CH), 4.62 (2H, s, CH_2OH), 7.31 (2H, d, J = 7.8 Hz, ArH), 7.39 (2H, d, J = 7.8 Hz, ArH); ^{13}C NMR δ 38.74, 58.66, 66.26, 130.82, 132.30, 137.21, 142.17, 176.56.

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