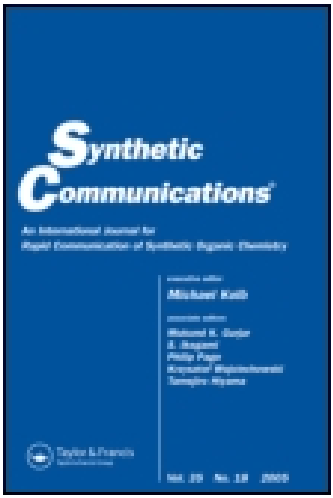

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A CONVENIENT SYNTHESIS OF 4-AMINOMETHYL-L-PHENYLALANINE

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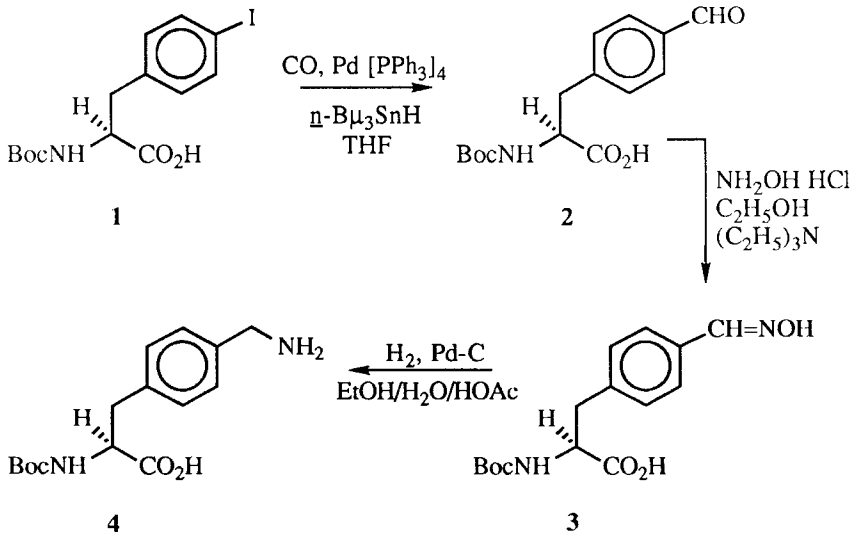
Abstract: N-Boc-4-Aminomethyl-L-phenylalanine is prepared from N-Boc-4-Iodophenylalanine in 78% yield over three steps. The method features an efficient Pd-catalyzed carbonylation, oxime formation, and subsequent catalytic reduction employing an ethanol/water/acetic acid solvent system which is crucial to successful reaction.

Scheme



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In the course of a research project directed at inhibitors of platelet aggregation,[1] significant quantities of the unnatural α-amino acid N-Boc-4-aminomethyl-L-phenylalanine (**4**) were required. In our hands the published procedure[2] for the synthesis of **4** involved several problematic steps and was not amenable to the generation of 25-50 g quantities of **4**. We wish to report an efficient three-step route for the preparation of this unnatural amino acid which features commercially available starting materials and minimal racemization at the asymmetric center.

As shown in the Scheme, commercially available N-Boc-4-Iodo-L-phenylalanine was treated with carbon monoxide at balloon pressures in the presence of tetrakistriphenylphosphine palladium and the resulting acyl palladium species was reduced in situ with tributyltin hydride to provide the aldehyde **2** in 90% yield.[3] Reproducibly high yields were only attained in this step only after the solvent had been purged with CO for > 10 minutes immediately prior to charging with **1**. The high yield further confirms the stability of the Boc group to these reaction conditions.

Oxime formation was effected in the standard manner by treatment of **2** with hydroxylamine hydrochloride in ethanol in the presence of triethylamine to give **3** in 91% yield.

Although the reduction of oximes to amines under conditions of catalytic hydrogenation is well-precedented, the conversion of **3** to **4** initially proved problematic. Treatment of **3** with hydrogen in the presence of 10% Pd/C either at atmospheric or Parr shaker pressure (50lb/in^2) in ethanol in the presence of excess HCl gas[4] or in ethanol/chloroform[5] mixtures resulted in incomplete reaction and complex mixtures. However, treatment of **3** with hydrogen (balloon pressure) in the presence of 10% Pd-C in a 4:1 mixture of ethanol/50% aqueous acetic acid[6]

afforded a clean reaction from which pure **4** was isolated without chromatography in 95% yield.

The present method constitutes a rapid and efficient method for the synthesis of 30-50 g quantities of **4**. The synthetic utility of the ethanol/water/acetic acid solvent system for catalytic reduction of an expanded range of functionalities is under study.

N-Boc-4-Formyl-L-phenylalanine (2)

A three neck flask was charged with 5.0 g (12.8 mmoles) N-Boc-4-iodo-L-phenylalanine (**1**) (Bachem) and 50 ml THF (4 Å sieve-dried). A balloon pulled over a threeway stopcock was flushed three times with CO and attached to the reaction flask. Then, 0.74 g (0.64 mmoles) tetrakistriphenylphosphine palladium was added to the reaction mixture and the clear solution was stirred for 5 minutes at room temperature. The system was flushed with a stream of carbon monoxide gas (inlet below the solvent surface) for 10 minutes and then the system was pressurized with CO via the balloon. The reaction mixture was placed in an oil bath at 50° and after stirring for 5 minutes, a solution of 4.1 g (14.1 mmoles) tri-n-butyltin hydride in 20 ml THF was added dropwise over 2.5 hours. The reaction mixture retained a clear tan color throughout.

The solvent was removed on the rotary evaporator to give an amber oil that was purified by flash chromatography on silica gel (230-400 Mesh), eluting with $CHCl_3$ (97): CH_3OH (3): HOAc(1). Under these conditions the desired product had an $R_f = 0.3$, while the starting iodo compound had $R_f = 0.4$. Solvent removal provided N-Boc-4-formyl-L-phenylalanine (**2**) (3.38 g, 90%) as a tan solid, mp. 143-145°.

^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (3H, bs); 1.41 (6H, bs); 3.15 (1H, m); 3.30 (1H, m); 4.68 (1H, m); 5.02 (1H, d), 7.38 (2H, d); 7.82 (2H, d); 9.98 (1H, s); mass spectrum, m/e $(M+1)^+$ 294.

Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found C, 61.80; H, 6.30; N, 4.77.

N-Boc-4-Oximino-L-phenylalanine (3)

To a solution of 3.14 g (10.7 mmoles) N-Boc-4-formyl-L-phenylalanine (2) in 60 ml absolute ethanol was added 3.55 g (51 mmoles) hydroxylamine hydrochloride and 6.20 g (61 mmoles) triethylamine. This solution was heated at reflux for 16 hours.

The solvent was then removed on the rotary evaporator and 50 ml of water was added. This solution was acidified with glacial acetic acid and the resulting milky suspension was extracted with 3 x 125 ml portions of ethyl acetate. The combined organic extracts were washed with water, brine and then dried over anhydrous sodium sulfate. Solvent removal provided a viscous residue that was purified by flash chromatography on silica gel (230-400 mesh) eluting with $CHCl_3$ (95): CH_3OH (3.5): HOAc(1.5). Under these conditions the desired product had an $R_f = 0.25$. The homogeneous fractions were combined and solvent removal, followed by several toluene chases to remove acetic acid, gave the desired oxime as an amorphous white solid (3.0 g, 91%). ^1H NMR (300MHz, $CDCl_3$) δ 1.44 (9H, bs), 3.15 (2H, d); 4.63 (1H, m); 5.20 (1H, d); 7.25-7.45 (4H, m); 8.14 (1H,s), mass spectrum, m/e (M+1) $^+$309.

N-Boc-4-Aminomethyl-L-phenylalanine (4)

A solution of 30.0 g (0.097 moles) oxime **3** in 500 ml of ethanol (4) / 50% aqueous acetic acid (1) was treated with 6.0 g 10% Pd-C and the resulting suspension was hydrogenated at atmospheric pressure at room temperature for 18 hours. The catalyst was then removed by filtration and the solvent removed on the rotary evaporator to give a viscous residue. This was triturated with 100 ml ether to provide 27.0 g (95%) pure **4** as a white solid.

^{1}H NMR (300MHz, $CDCl_3$) δ 1.38 (9H, s), 2.94 (1H, m), 3.18 (1H, m), 4.10 (2H, s), 4.29 (1H, m), 7.33 (2H, d), 7.41 (2H, d); mass spectrum, m/e $(M+1)^+$ 295. Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.53; N, 9.52. Found: C, 61.49; H, 7.60, N, 9.66.

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