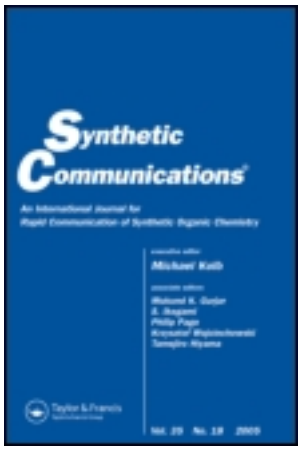

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# A Convenient Synthesis of 4-Nitrophenethylamine Hydrochloride

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# A Convenient Synthesis of 4-Nitrophenethylamine Hydrochloride

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## ABSTRACT

A short, convenient, and efficient synthesis of 4-nitrophenethylamine hydrochloride is described. The key step involved removal of water from 4-nitrophenylalanine monohydrate followed by decarboxylation.

*Key Words:* Amino acid decarboxylation.

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## INTRODUCTION

4-Nitrophenethylamine due to its bifunctionality finds wide application in the pharmaceutical industry and was needed as an intermediate in our drug discovery program.

A number of methods have been reported[1–4] in the literature which includes the nitration of phenylacetonitrile followed by reduction.[1–3] Other methods included the acetylation of phenethylamine followed by nitration, separation of isomers, and deacetylation.[4] All these methods either involve reduction or are cumbersome and give low yields.

Herein we wish to report a very simple and convenient synthesis of 4-nitrophenethylamine hydrochloride which does not involve reduction or purification methods.

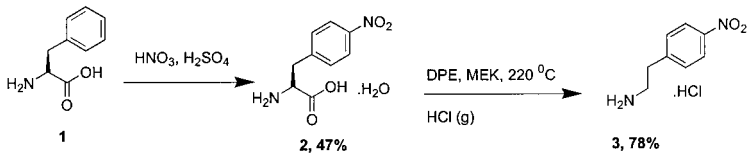
## RESULTS AND DISCUSSION

L-4-Nitrophenylalanine **2** was prepared by nitration of L-phenylalanine **1** according to the literature procedure[5,6] except that the crude product was recrystallized once from water with a yield of 47%. It was necessary to remove the water before carrying out the next step. This presumably is to facilitate imine formation with the added ketone which is essential for subsequent decarboxylation. Water was removed using Dean–Stark assembly and benzene as solvent. The amount of water was below 0.6% (by KF analysis).

Decarboxylation of **2** in diphenylether in the presence of catalytic amount of methyl ethyl ketone followed by bubbling dry HCl gas resulted in formation 4-nitrophenethylamine hydrochloride **3** with excellent yields as shown in Sch. 1.

## EXPERIMENTAL

Commercial solvents and reagents were used without further purification. $^1$H NMR spectra were recorded on a Varian 300 MHz spectrometer.




*Scheme 1.*

Melting points are uncorrected. Elemental analysis was performed on a Perkin–Elmer analyzer. The purity of the final product was checked using an Agilent 1100 HPLC system. A reverse phase C18 Hypersil BDS $250 \times 4.6$ mm 5 μ column was used. A solvent system containing 85% acetonitrile and 15% phosphate buffer with pH adjusted to 2.5 was employed at flow rate of 1.0 mL/min [$\lambda = 280$ nm].

**4-Nitrophenyl-L-alanine Monohydrate 2:** The Bergel and Stock[5] procedure was used except that the crude product obtained was recrystallized from water to give a yield of 47%.

**4-Nitrophenethylamine HCl 3:** To a suspension of **2** (5.0 g, 23.81 mM) in 50 mL of diphenylether was added methyl ethyl ketone (MEK) 0.17 g (2.37 mM). This was heated at 220°C for 3 h resulting in a clear dark red solution. This solution was diluted with 50 mL of diethyl ether and cooled in ice bath. HCl gas was bubbled through the solution to obtain a dark red precipitate which was filtered off. This residue was stirred in EtOAc and filtered to obtain the desired product **3** as a brown solid with a yield of 3.75 g (78%), m.p. 200°C decomp. IR (KBr): 2956, 2911, 1623, 1608, 1598, 1524, 1345, 1250, 1108, 856, 746 $cm^{-1}$. NMR ($d$-$_6$, DMSO): $\delta$ 3.07 (4H, br s), 7.56 (2H, d, $J = 8.4$ Hz), 8.18 (2H, d, $J = 8.4$ Hz), 8.17–8.19 (3H, embedded peaks). Anal. calcd. for $C_8H_{10}N_2O_2 \cdot HCl$: C, 47.42; H, 5.47; N, 13.82. Found: C, 47.45; H, 5.59; N, 13.48. HPLC purity > 99%.

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