Synthesis of N-Methyl a-Amino Acids via Methylation and Cleavage of 4-Nitrobenzenesulfonamide (Nbs) Derivatives

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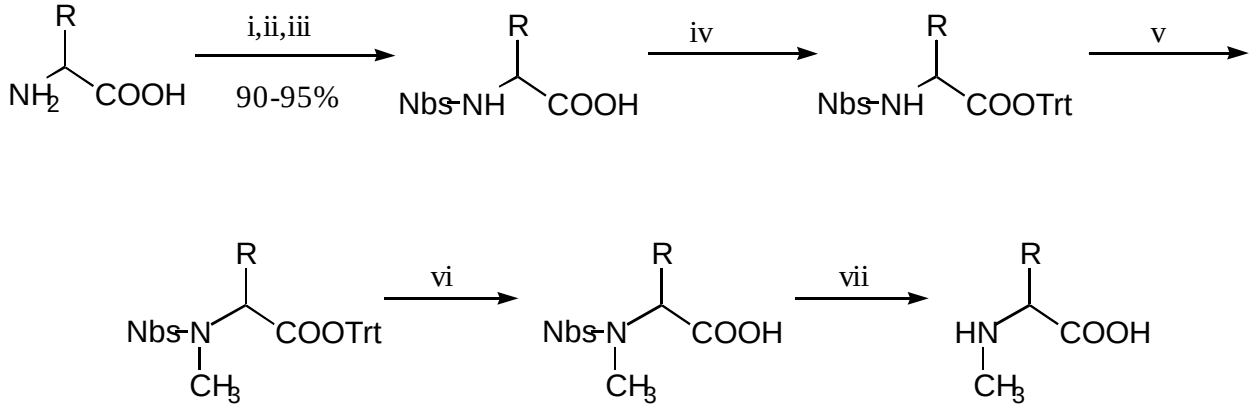
N-Methyl α-amino acids are important building elements of many naturally occurring antibiotics and find wide use for the synthesis of conformationally restricted and protease-resistant peptide analogues. Being seemingly simple, this class of compounds, nevertheless, represents quite a challenge as a synthetic target. Existing methods for the preparation of N-methyl amino acids and their N-protected derivatives include: direct alkylation of N_α-Boc or Cbz protected amino acids; reduction of N-Fmoc-oxazolidinones or methylol derivatives with triethylsilane in trifluoroacetic acid; reductive methylation of N-benzyl amino acids followed by hydrogenolysis.

We have developed a new approach to the title compounds, which is based on the ability of N-Nbs compounds to undergo facile cleavage by thiolate reagents. The direct alkylation of Nbs-amino acids (MeI/K_2CO_3 or DBU/DMF, 20°C, 3-6 h) gave corresponding N-methylated methyl esters in high yield. However, the saponification of the esters prior to the removal of N-Nbs group (NaOH/Me_2CO/H_2O) accompanied in many cases by considerable racemization at C_α-atom; the reverse order of deprotection (Nbs cleavage followed by saponification) allowed to avoid racemization, but led to poor yields of isolated N-methyl amino acids due to their high solubility in water. Our attempt to protect carboxylic group from methylation by its conversion into trimethylsilyl ester was unsuccessful, because under basic conditions required for N-methylation, TMS-group rapidly migrates from carboxyl to deprotonated nitrogen atom of sulfonamide group, thus releasing carboxylate anion for alkylation.

In order to circumvent these problems, we applied for the temporary protection of carboxylic function a trityl group. which exhibits a remarkable resistance to bases, but can be readily removed under very mild acidic conditions. The entire synthetic sequence is depicted below:



i) TMS-Cl/ TEA/ $CHCl_3$, rt, 60 min; ii) Nbs-Cl, 0-20°C, 60 min; iii) EtOAc/ H_2O; iv) Trt-Cl/ TEA/ $CHCl_3$, 0-20°C, 3 h; v) MeI/ K_2CO_3/ DMF, rt, 3-7 h; vi) EtOAc/ 1n. HCl; vii) n-BuSH/ piperidine/ DMF, rt, 6-8 h

The steps from iv) to vii) are conveniently conducted without isolation of intermediate products; the employment of a volatile reagent for the final cleavage of Nbs group allows facile isolation of target N-methyl amino acids in a pure form by precipitation with acetone or ether. Optically pure N-methyl derivatives of Val, Leu, Ile, Ala, Phe, Lys(Boc) were prepared in 45-70% yield (based on relative N-Nbs-amino acids).