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A NOVEL ASYMMETRIC SYNTHESIS OF α-AMINOACIDS FROM NITRILES EMPLOYING DIISOPINOCAMPHEYLBORANE AS A CHIRAL AGENT

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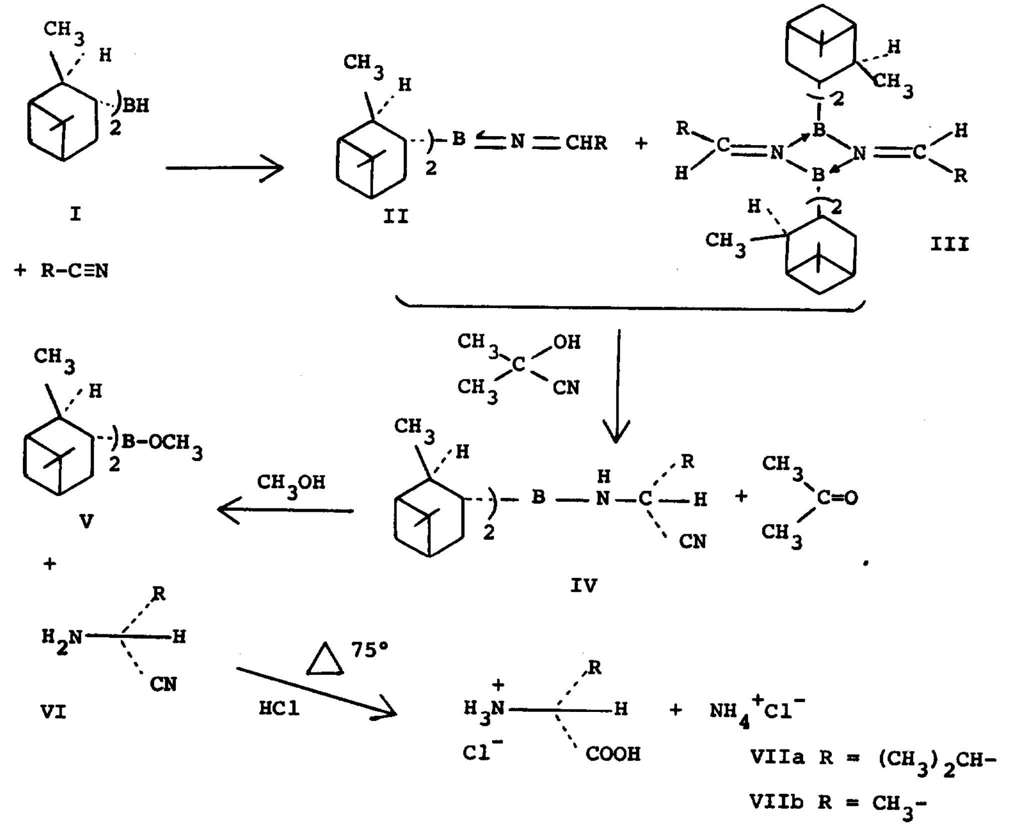
Several approaches have been adopted for a general asymmetric synthesis of α-aminoacids [1] including (a) catalytic hydrogenation of esters of α-benzoylaminocinnamates with chiral groups (-) menthyl [2] and (-) bornyl ,[3] (b) the Strecker sequence using chiral α-methylbenzylamine, an aldehyde and hydrogen cyanide [4,5], (c) the use of α-ketoacids and chiral agents (e.g. N-amino-2-hydroxymethylindolines [6] and 1-amino-(S)-2[(R)-1-hydroxyethyl]indoline [7]), (d) non-enzymatic transamination of α-ketoacids using pyridoxal [8], and (e) the hydroxyalkylation of one antipode of the complex $[Co(en)_2glycine]^{2+}$ with an aldehyde in the presence of base.[9] Many of these syntheses require lengthy initial preparations and final degradation of chiral group-containing substrates. We report a new asymmetric synthesis of α-aminoacids which makes use of readily available nitriles and employing diisopinocampheylborane [10] (I) as chiral reagent in an experimentally convenient procedure. A solution of (I) was prepared by the addition of borane in THF (50 ml, 0.05 mol, 1 molar soln, Alfa Inorganics) to a solution of (+)-2-pinene (20.4 g, 0.15 mol) in 30 ml of THF.[11] 2-Methylpropionitrile 10 g, (distilled from P_2O_5) was added, all at once, to the solution of (I) and the mixture stirred for 30 min, then concentrated in vacuo to remove excess nitrile. The ir spectrum of the product showed absorptions at 1830 and 1670 cm^{-1} characteristic of [12] and tentatively assigned to ketiminoboranes (II) and dimeric structure (III) respectively, with the 1830 cm^{-1} band being the stronger.[13]



The iminoboranes were taken up in THF and acetone cyanohydrin (4.2 g, 0.05 mole) was added.[14] Monitoring of the reaction by gas chromatography showed the addition to form (IV) to be complete within 15 min. Methanol (50 ml) was then added[15] and the solution extracted with $CHCl_3$ to remove (V). The aqueous layer was concentrated <u>in vacuo</u> the residue taken up in a small amount of water, conc. HCl (70 ml) added and the hydrolysis to (VIIa) completed by heating to 75° for 10 hr. The cooled solution was evaporated to dryness and the crude (R)(-)valine hydrochloride (VIIa) purified by ion exchange chromatography on the acidic cation exchange resin Dowex 50W-X8, eluting first with water to neutrality, then with 1N NH_4OH. The (R)(-)valine was crystallized from aqueous EtOH in 45% overall yield. Calcd. for $C_5H_{11}O_2N$: N, 11.96. Found: N, 11.50%. δ Me_4Si (D_2O): 0.95, 0.00 (2d, 6 H, $(C\underline{H}_3)_2CH$), 2.2 (m, 1H, $(CH_3)_2C\underline{H}$), 3.53 (d, 1 H, 2-proton); infrared ν_{max} ($CHCl_3$) was superimposable upon that of an authentic sample of (S)(+)-valine with the exception of small peaks at 710, 850 and 1200 cm^{-1}; t.l.c. (Kodak Chromatoscreen) $R_f = 0.60$. ($R_f = 0.60$ for authentic (S)(+)valine. $[\alpha]_D^{25}$(6NHCl) =-3.6°, (for authentic (R)(-)valine $[\alpha]_D^{25}$(6NHCl)=-29.04°,[17] representing an optical purity of 12.4 % Alanine (VIIb) was similarly prepared in 45% yield from acetonitrile.

The chirality of the potential α-aminoacid is presumably induced when the elements of HCN are added preferentially to one of the diastereotopic[16] faces of (II) or the monomer of (III). The instability of these particular iminoboranes prevented an attempted separation to clarify this point.

This convenient synthesis would appear to have wide generality. Extension employing chiral boranes derived from other optically active terpenes and reaction with a series of readily available nitriles is currently being investigated.

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13. An interesting feature of compounds containing nitrogen attached to three coordinate boron is the extent of B=N π-bonding in them. If the nitrogen is three coordinate, a structural consequence of such π-bonding is a trigonal planar arrangement of atoms about nitrogen, as in borazines. Thus dimers like (III) or the corresponding monomer would have ν(C=N) at ca. 1600-1650 cm^{-1}. If the nitrogen is two coordinate, a linear configuration may allow maximum π-bonding. This type of structure e.g. (II) gives a characteristic ν(B=N=C) at ca. 1800 - 1850 cm^{-1} comparable with the analogous band of the isoelectronic allene.

14. Initially HCN was bubbled directly into the reaction mixture using either no catalyst or a catalytic amount of KCN. Acetone cyanohydrin gives better results and is less hazardous.

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