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Hydroboration of Vinylglycine and Allylglycine as a route to Boron-derivatives of α -Amino Acids.

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Abstract: The hydroboration of protected vinylglycine and allylglycine with dicyclohexyl- or diisopinocampheylborane occurs chimio- and regioselectively with attachment of boron to the less substituted end of the carbon-carbon double bond. Homoserine or δ -hydroxynorvaline are readily obtained by H₂O₂/CH₃CO₂Na oxidation of dicyclohexylborane derivatives and 2-amino-4-boronobutanoic acid or 2-amino-5-boronopentanoic acid by reaction of diisopinocampheylborane derivatives with excess of ethanal and deprotection. Copyright © 1996 Elsevier Science Ltd

Organoboron derivatives of polyfunctional molecules are valuable synthetic intermediates ¹ and a number of them display interesting biological activities. ² Boronic analogues of α -amino acids are of particular interest : aspartic acid with boron substituted for the (γ)-carboxylic group ³ proved to be an inhibitor of dihydroorotase ⁴ and proline boronic acid dipeptides have been used as immunosuppressants. ⁵ Specific binding of boronic acids with glucids ⁶ or α -amino acids ⁷ is also noteworthy.

In the course of a work on hydroboration of unsaturated α -amino acids, ⁸ we have investigated the reactivity of protected vinylglycinate 1 and allylglycinate 2.



These two compounds are readily available as pure enantiomers or racemic modifications through known procedures. Only the racemic derivatives were used in this preliminary work. 1^9 was prepared in 37% overall yield from methionine. 2^{10} was obtained by alkylation of methyl N-(diphenylmethylene)glycinate ¹¹ with allyl bromide, ¹² mild hydrolysis and protection with acetic anhydride.



Hydroboration with dicyclohexylborane

The reagent (1.5 molar equivalents), prepared according to Brown, ¹³ was allowed to react with amino acids 1 or 2, in THF, for 12 h at room temperature. Intermediate triorganoboranes 3 and 4 were not isolated but subjected to oxidation by $H_2O_2/CH_3CO_2Na^{14}$ affording homoserine or δ -hydroxynorvaline derivatives 5 ¹⁵ or 6, ¹⁶ respectively, as the only characterized products (Scheme 1).



5 was converted to the O-benzoyl derivative 7^{17} with benzoic anhydride.

Other oxidative processes were investigated with triorganoborane 4. Pyridinium chlorochromate ¹⁸ led to unextractable mixtures and chromic acid ¹⁹ afforded pyroglutamate 8²⁰ in low yield (30%).



Hydroboration with diisopinocampheylborane

These reactions were investigated as a route to ω -boronic- α -amino acids. Diisopinocampheyltriorganoboranes are known to react readily with excess of acetaldehyde, affording α -pinene and the corresponding boronic acids ²¹ (Scheme 2).



Diisopinocampheylborane was obtained according to standard procedures ²² and hydroborations were performed with two molar equivalents of the reagent, in THF, for 24 h at room temperature.

Intermediate triorganoboranes 9, 10 are sensitive to atmospheric oxygen and were reacted *in situ* with an excess of acetaldehyde (10 equivalents) at 45°C for 17 h. ²¹ The boronic acids proved to be difficult to isolate. They are hygroscopic and give rise to anhydride formation. The best results were obtained after deprotection in boiling 6M HCl (3 h for 11, 5 h for 12), trituration of the chlorhydrates 13, ²³ 14, ²⁴ in dry CH₃CN and

elimination of the residual boric acid as the trimethylborate by repeated additions of methanol and evaporations to dryness (¹¹B NMR determinations).

4-Borono-2-aminobutanoic acid 15 25 and 5-borono-2-aminopentanoic acid 16, 26 the boronic analogues of glutamic and 2-aminoadipic acids, respectively, were then readily available through elution on a Dowex (50, H⁺) resin with 2M ammonia.

¹¹B NMR spectra are indicative of the structure. Chlorhydrates 13, 14 exhibit a broad singlet centered near 30 ppm, consistent with a trigonal, non complexed, boron atom. ²⁷ This signal is shifted to about 20 ppm for the free amino acids 15, 16, showing that some degree of association has to be taken in account.

Methyl vinylglycinate and allylglycinate are readily hydroborated with diorganoboranes in a chemo- and regioselective way. The synthetic usefulness of the intermediate triorganoboranes is evidenced through the synthesis of homoserine or δ -hydroxynorvaline and of 4-borono-2-aminobutanoic or 4-borono-2-aminopentanoic acids.

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- 10 All compounds gave satisfactory elemental analysis (An.) and/or mass spectra (MS) and were identified by NMR spectra (300 MHz for ¹H, 75 MHz for ¹³C, (CD₃)₂CO or CDCl₃/TMS int., D₂O/DSS int. ; 96 MHz for ¹¹B, THF-C₆D₆/BF₃-OEt₂ ext.; δ ppm, J Hz).

2 oil, 76% yield from Schiff base of glycinate ; An. $C_8H_{13}NO_3$; MS : m/z = 171 (M⁺). ¹H NMR [(CD₃)₂CO] δ : 1.91 (s, 3H, COCH₃) ; 2.42 (m, 1H, H³) and 2.52 (m, 1H, H³') (J_{H³H^{3'}} = 14.5, J_{H³H²} = 8, J_{H^{3'}H²} = 5.5, J_{H³H⁴} = 7.5, J_{H^{3'}H⁴} = 6.5, and 1<J<2.5 for long range coupling between H³, H^{3'} and H⁵, H^{5'}) ; 3.67 (s, 3H, OCH₃) ; 4.50 (dt, J_{H²,NH} = 8, 1H, H²) ; 5.06 (m, 1H, H⁵) and 5.12 (m, 1H, H^{5'}) (J_{H⁵H^{5'}} = 2, J_{H⁵H⁴} = 10, J_{H^{5'}H⁴} = 17) ; 5.78 (m, 1H, H⁴) ; 7.38 (br s, 1H, NH). δ and J values were determined after several selective decoupling experiments. ¹³C NMR (CDCl₃) δ : 22.9 (CO<u>C</u>H₃) ; 36.4 (C³) ; 51.7 (C²) ; 52.3 (OCH₃) ; 119.0 (C⁵) ; 132.3 (C⁴) ; 169.9 (NCO) ; 172.3 (C¹).

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- 15 5 oil, 41% yield [column chromatography on silica gel (ether)] ; FAB MS : m/z = 268 (M+H)⁺. ¹H NMR (CDCl₃) δ : 1.54-1.78 (m, 2H, 2H³) ; 2.84 (br s, 1H, OH) ; 3.54-3.68 (m, 2H, 2H⁴) ; 3.68 (s, 3H, OCH₃) ; 4.48 (m, 1H, H²) ; 5.05 (s, 2H, OCH₂Ph) ; 5.65 (d, J = 7, 1H, NH) ; 7.28 (s, 5H, C₆H₅). ¹³C NMR (CDCl₃) δ : 35.7 (C³) ; 51.2 (C²) ; 52.6 (OCH₃) ; 58.4 (C⁴) ; 67.3 (OCH₂Ph) ; 128.2, 128.3, 128.6, 136.0 (C₆H₅) ; 156.9 (NCO) ; 173.0 (C¹).
- 16 6 oil, 79% yield [column chromatography on silica gel (ether/MeOH 90/10 then 50/50)]; An. $C_8H_{15}NO_4$, 1/4 H_2O ; MS : m/z = 189 (M⁺). ¹H NMR (CDCl₃) δ : 1.55-1.64 (m, 2H, 2H³); 1.73-1.96 (m, 2H, 2H⁴); 2.03 (s, 3H, COCH₃); 3.35 (br s, 1H, OH); 3.64 (t, J_H4_H5 = 6, 2H, 2H⁵); 3.74 (s, 3H, OCH₃); 4.56 (dt, J = 5.5 and 7.5, 1H, H²); 6.98 (br s, 1H, NH). ¹³C NMR (CDCl₃) δ : 22.9 (CO<u>C</u>H₃); 28.2 and 28.9 (C³ and C⁴); 52.1 (C²); 52.4 (OCH₃); 61.6 (C⁵); 170.7 and 173.1 (NCO and C¹).
- 17 7 oil, 45% yield [column chromatography on silica gel (ether)]; An. $C_{20}H_{21}NO_{6}$, $1/2 H_{2}O$; MS : m/z = 371 (M⁺). ¹H NMR (CDCl₃) δ : 2.21-2.38 (m, 2H, 2H³) ; 3.66 (s, 3H, OCH₃) ; 4.39-4.45 (m, 2H, 2H⁴) ; 4.59 (td, J_{H2H3} = 6.5, J_{H2,NH} = 7.5, 1H, H²) ; 5.10 (s, 2H, OCH₂Ph) ; 5.63 (d, J = 7.5, 1H, NH) ; 7.34 (s, 5H, CH₂C₆H₅) ; 7.37-7.59 (m, 3H) and 7.98-8.04 (m, 2H) (COC₆H₅). ¹³C NMR (CDCl₃) δ : 31.4 (C³) ; 51.5 (C²) ; 52.6 (OCH₃) ; 60.8 (C⁴) ; 67.1 (OCH₂Ph) ; 128.1, 128.2, 128.4, 128.5, 129.8, 129.9, 133.1, 136.1 (C₆H₅) ; 155.8 (NCO) ; 166.3 and 172.3 (2CO).
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- 20 8 oil, 30% yield [column chromatography on silica gel (ether)]; An. $C_8H_{11}NO_4$, 1/4 H_2O ; MS : m/z = 185 (M⁺). ¹H NMR (CDCl₃) δ : 2.08 (m, $J_{H4H4'}$ = 13.5, $J_{H4H3'}$ = 9.5, J_{H4H3} = 3.5, J_{H4H5} = 2.5, 1H, H⁴); 2.34 (m, $J_{H4'H3'}$ = 10.5, $J_{H4'H3} \approx J_{H4'H3} \approx 9.5$, 1H, H^{4'}); 2.53 (s, 3H, COCH₃); 2.58 (ddd, $J_{H3H3'}$ = 17.5, 1H, H³); 2.73 (ddd, 1H, H^{3'}); 3.78 (s, 3H, OCH₃); 4.77 (dd, 1H, H⁵). δ and J values were determined after selective decoupling experiments. ¹³C NMR (CDCl₃) δ : 20.3 (C⁴); 23.6 (CO<u>C</u>H₃); 30.8 (C³); 51.7 and 56.7 (OCH₃ and C⁵); 170.0, 170.5 and 173.4 (C², NCO and <u>C</u>O₂CH₃).
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- 23 13 hygroscopic solid ; FAB MS : m/z = 418 [M⁺ for ester of 13 with NBA (metanitrobenzylic alcohol) matrix]. ¹H NMR (D₂O) δ : 0.82 and 0.87 (J_H4_H4⁻ = 16, J_H4_H3 = J_H4⁺H3 = 8.5, 2H, 2H⁴) ; 2.02 (dt, J_H3_H2 = 6.5, 2H, 2H³) ; 3.98 (t, 1H, H²). δ and J values were determined after selective decoupling experiments. ¹³C NMR (D₂O) δ : 12.3 (C⁴) ; 27.5 (C³) ; 57.2 (C²) ; 175.3 (C¹). ¹¹B NMR (D₂O) δ : 30.3.
- 24 **14** hygroscopic solid ; FAB MS : $m/z = 432 (M^{+} \text{ for ester of } 14 \text{ with NBA matrix})$. ¹H NMR (D₂O) δ : 0.84 (t, J_{H4H5} = 8, 2H, 2H⁵) ; 1.43-1.59 (m, 2H, 2H⁴) ; 1.83-2.04 (m, 2H, 2H³) ; 4.03 (t, J_{H2H3} = 6.5, 1H, H²). ¹³C NMR (D₂O) δ : 16.4 (C⁵) ; 21.9 (C⁴) ; 35.0 (C³) ; 55.7 (C²) ; 175.3 (C¹). ¹¹B NMR (D₂O) δ : 32.6.
- 25 **15** mp > 260°C (dec), 76% overall yield ; MS (Negative Electrospray ; $CH_3CN/H_2O : 1/1) : m/z = 146$ (M H)^{-, 1}H NMR (D₂O) $\delta : 0.70$ and 0.74 (J_H4_H4' = 15, J_H4_H3 \approx J_H4'_H3 \approx 8, 2H, 2H⁴) ; 1.90 and 1.94 (J_H3_H3' = 14, J_H3_H2 \approx J_H3'_H2 \approx 6, 2H, 2H³) ; 3.69 (t, 1H, H²). δ and J values were determined after selective decoupling experiments.¹³C NMR (D₂O) $\delta : 13.4$ (C⁴) ; 28.5 (C³) ; 58.9 (C²) ; 177.9 (C¹). ¹¹B NMR (D₂O) $\delta : 26.9$.
- 26 **16** mp > 230°C (dec), 77% overall yield ; MS (Negative Electrospray ; $CH_3CN/H_2O : 1/1) : m/z = 160$ (M H)⁻. ¹H NMR (D₂O) δ : 0.30-0.75 (m, 2H, 2H⁵) ; 1.35-1.70 (m, 2H, 2H⁴) ; 1.55-2.00 (m, 2H, 2H³) ; 3.45-3.70 (m, 1H, H²). ¹³C NMR (D₂O) δ : 17.9 (C⁵) ; 23.7 (C⁴) ; 34.5 (C³) ; 58.8 (C²) ; 179.8 (C¹). ¹¹B NMR (D₂O) δ : 18.1.
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