Tetrahedron Letters,Vol.28,No.39,pp 4499-4502,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A DIRECTED CHIRAL SYNTHESIS OF AMINO ACIDS FROM BORONIC ESTERS

Donald S. Matteson* and Ellen C. Beedle
Department of Chemistry, Washington State University
Pullman, WA 99164-4630 USA

Summary. Conversion of (s)-pinanediol (1S)-1-haloalkylboronates to (1R)-1-azido boronates, homologation with (dichloromethyl)lithium to 1-chloro-2-azido boronates, oxidation with sodium chlorite to the α-azido acids, and catalytic hydrogenation yielded L-amino acids, 92-96% enantiomeric excess.

We report an efficient chiral synthesis of L-amino acids, which starts from our previous stereoselective synthesis of (1S)-1-chloroalkylboronic esters (**2**) by chain extension of (s)-pinanediol alkyl boronic esters (**1**) with (dichloromethyl)lithium.[1] The method appears suitable for introducing isotopically labeled carbons. A novel feature is the direct oxidation of α-chloro boronic esters to carboxylic acids with sodium chlorite.

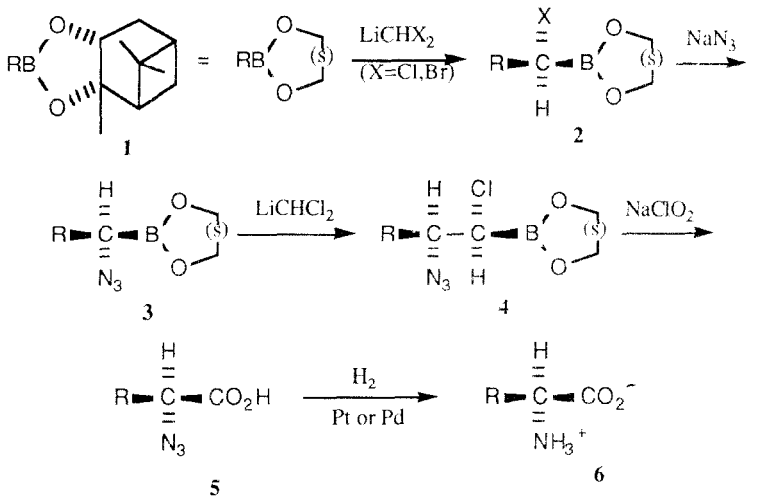
The fundamental operations on the α-chloro boronic esters involve (1) replacement of the chlorine by a nitrogen function, (2) chain extension of the *N*-substituted boronic ester, (3) oxidation of the boron-bonded carbon to a carboxyl group, and (4) conversion of the nitrogen function to the amino group.

When lithiohexamethyldisilazane was used for step (1),[2] step (2) with the 1-chloroethylboronic ester yielded highly moisture sensitive β-silylamino α-chloro boronic ester, and attempted purification failed. We then turned to the reaction of azide ion with α-chloro boronic esters, since an α-azido boronic ester (**3**, R=Bu) with (dichloromethyl)lithium had already been converted to the β-azido α-chloro boronic ester (**4**).[1]

Step (3) was originally conceived as a two-stage process, beginning with oxidation to the aldehyde by hydrogen peroxide. It has been reported that this process is not very efficient,[3] and we found out why. We did not obtain aldehyde at all from pinanediol 1-chloro-2-azido-3-phenylpropylboronate, but the aldehyde-hydrogen peroxide adduct,[4] as shown by the characteristic C*H*(OH)OO multiplet in the NMR at δ 5.0-5.2. If stored overnight, this adduct partially decomposed. Oxidation of a fresh sample with buffered potassium permanganate[5] yielded 35% 2-azido-3-phenylpropanoic acid.

Professor R. C. Ronald then called our attention to the mild oxidation of aldehydes to acids by sodium chlorite (in the presence of an alkene for suppression of radical side reactions).[6,7] We found that sodium chlorite reacts directly with β-azido α-chloro

boronic esters to provide the azido carboxylic acids (**5**). We concentrated but did not purify these potentially explosive compounds, which were hydrogenated directly to the L-amino acids (**6**).



After our procedure proved satisfactory for phenylalanine (**6a**), we synthesized valine (**6b**), serine (**6c**), and glutamic acid (**6d**). Sodium azide reacted very sluggishly with pinanediol 1-chloro-2-methylpropylboronate (**2b**, X=Cl). It is hazardous to keep sodium azide in contact with dichloromethane for several days.[8] We therefore tried the α-bromo boronic ester[9] (**2b**, X=Br) in place of the chloro compound. Epimerization of the **2b** by the bromide ion released in the reaction[1] was observed, but this was overcome by increasing the excess of sodium azide to 50:1. However, extensive epimerization occurred during conversion of **2a**, X=Br, to azide **3a**, which showed only a 7:1 diastereomer ratio. Thus, for the R groups which lead to relatively rapid nucleophilic displacements, X must be taken as Cl, and for less reactive systems, Br is the only satisfactory X.

To make serine (**6c**), we started with (s)-pinanediol benzyloxymethylboronate (**1c**).[8,10] Palladium was used as the hydrogenation catalyst for the azide, and removed the benzyloxy protecting group as well. Glutamic acid (**6d**) was reached via reaction of pinanediol iodomethylboronate[10,11] with *t*-butyl lithioacetate to form **1d**, R=*t*-$BuO_2CCH_2CH_2$. (The chloromethylboronate was unsatisfactory in this step because of competition of Claisen condensation with halide displacement.) The **1d** was converted to mono-*t*-butyl azidoglutarate (**5d**), which was cleaved with trifluoroacetic acid[12] before reduction to glutamic acid.

The enantiomeric purities of the crude amino acids were determined after converting them to the methyl esters (serine also trimethylsilylated).[13] The L/D-ratios were

estimated from the 200 MHz ^{1}H NMR spectra in the presence of the chiral shift reagent Eu(tfc)$_3$.[14] The purities of the precursor halides (**2**) and azides (**3**) were determined from the NMR spectra as previously described.[1] The yields of amino acids are for ether washed solids which generally showed some impurity near δ 1-2 in the NMR, more easily removable by recrystallization than by chromatography. Results are summarized in Table 1.

Table 1. Amino acids (**6**) from boronic esters (**1**).

Series	Initial R	Final R	X	% Yield[a] (**1** →→ **6**)	Isomer Ratios **3**	**6**
a	$C_6H_5CH_2$	$C_6H_5CH_2$	Cl	63	25:1	25:1
b	$(CH_3)_2CH$	$(CH_3)_2CH$	Br	57	≥50:1	50:1
c	$PhCH_2OCH_2$	$HOCH_2$	Br	39[b]	30:1	25:1
d	t-$BuO_2CCH_2CH_2$	$HO_2CCH_2CH_2$	Br	32[c]	--	50:1

[a] Yields are not optimized. [b] Initial yield after an ether wash was 53%. Further purification was effected by chromatography (SiO_2, 1:1 EtOH:H_2O) followed by washing with 7:3 EtOH:H_2O to give 6 (from 1) in 39% yield. [c] Initial yield after an ether wash was 43%. Further purification by an ethanol wash gave 6 (from 1) in 32% yield.

Typical experimental procedures for preparing α-chloro boronic esters have been published previously.[1,15] The new preparation of α-bromo boronic esters[9] requires *in situ* generation of (dibromomethyl)lithium[16] from dibromomethane and lithium diisopropylamide. In the present work, we neutralized the diisopropylamine with 1 mol of extra zinc chloride, which was introduced as 1 M zinc chloride in ether (from Aldrich Chemical Company) instead of the anhydrous powder.[1] This change may have caused the slightly lower stereoselectivity in the conversion of **1a** to **2a**. The reaction of the α-bromo boronic esters with sodium azide in dichloromethane/water[1] was carried out with Aliquat 336 (methyltrioctylammonium chloride) as phase transfer catalyst and a 50-fold excess of azide. Homologation of the α-azido boronic esters (**3**) was carried out as previously described.[1]

In a typical oxidation, 511 mg (1.37 mmol) of chloro azido ester **4a** in 25 mL of *t*-butyl alcohol with 7.3 mL (69 mmol) of 2-methyl-2-butene was stirred during the dropwise addition of a solution of 1.24 g (11 mmol) of 80% sodium chlorite and 1.86 g (13.7 mmol) of potassium dihydrogen phosphate in 15 mL of water at 25°C. The mixture was stirred overnight and worked up by concentration, partitioning between water and ether, extraction of the acidic product into aqueous sodium bicarbonate, and reacidification and extraction with ether to yield an oily residue of azido acid (**5a**), m/e 191.0807 (calcd 191.0693). Intermediates **3**, **4**, and **5** were, in general, characterized by 200 MHz ^{1}H NMR[17] and 22.6 MHz ^{13}C NMR spectra. Hydrogenation was carried out under 1

atmosphere of hydrogen with 12 mg of platinum (IV) oxide in 14 mL of 50% aqueous ethanol for 2 h. Filtration and evaporation of the solvent followed by washing the solid residue with ether yielded the solid amino acid (**6a**) (161 mg, 71%), [α]D -28.5° (c 1.8, H_2O) [lit.[18] [α]D -33.7 to -35.4°], confirmed by comparison with a commercial sample by 90 MHz ^1H NMR and TLC. The rotation and NMR data suggest an impurity level in the 10% range.

Acknowledgment. We thank the National Institutes of Health for support, grant number GM33801, and the Boeing Corporation for partial support of departmental purchase of the 200 MHz NMR instrument.

REFERENCES

1. Matteson, D. S.; Sadhu, K. M.; Peterson, M. L. *J. Am. Chem. Soc.*, **1986**, *108*, 810-819.
2. Matteson, D. S.; Sadhu, K. M. *Organometallics*, **1984**, *3*, 614-618.
3. Brown, H. C.; Imai, T. *J. Am. Chem. Soc.*, **1983**, *105*, 6285-6289.
4. Matteson, D. S.; Moody, R. J. *J. Org. Chem.*, **1980**, *45*, 1091-1095.
5. Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.*, **1986**, *27*, 4537-4540.
6. Hillis, L. R.; Ronald, R. C. *J. Org. Chem.*, **1985**, *50*, 470-473.
7. a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.*, **1973**, *27*, 888-890. (b) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091-2096. (c) Krause, G. A.; Roth, B. *J. Org. Chem.*, **1980**, *45*, 1175-1176.
8. a) Bretherick, L. *Chem. Eng. News* **1986**, *64*, Dec. 22, 2. (b) Hassner, A. *Angew. Chem., Internat. Ed.* **1986**, *25*, 478-479.
9. Matteson, D. S.; Peterson, M. L. *J. Org. Chem.*, in press.
10. Sadhu, K. M.; Matteson, D. S. *Organometallics*, **1985**, *4*, 1687-1689.
11. Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. *Organometallics*, **1983**, *2*, 1536-1543.
12. a) Haslam, E. "Protective Groups in Organic Chemistry," McOmie, J. F. W., Ed., Plenum Press, New York, **1973**, 205. (b) Schwyzer, R.; Kappler, H. *Helv. Chim. Acta* **1961**, *44*, 1991-2002.
13. a) Halpern, B. "Handbook of Derivatives for Chromatography," Blau, K.; King, G. S., Eds., Heyden and Son, Ltd., London, **1978**, 466-467. (b) Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109-1115.
14. Ajisaka, K.; Kamisaku, M.; Kainosho, M. *Chem. Lett. (Jpn.)* **1972**, 857-858.
15. Matteson, D. S.; Majumdar, D. *Organometallics*, **1983**, *2*, 1529-1535.
16. Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.*, **1974**, *96*, 3010-3011.
17. Partial 200 MHz ^1H NMR ($CDCl_3$), δ: **3a**, 2.87-3.10 (m, $PhCH_2$) [isomer ratio from (*R*), 3.092, 3.063 vs. (*S*), 3.101, 3.073], 3.385 (m, CHN_3) [(*S*) 3.394]; **3b**, 1.15 (d, 1, pinyl) [(*S*) 1.14, not detected], 2.97 (d, 1, CHN_3); **3c**, 1.15 (d, 1, pinyl) [(*S*) 1.13, 2%], 3.40 (m, 1, CHN_3), 3.78 (m, 2, OCH_2); **3d**, 3.16 (dd, *J* 5.7, 8.6 Hz, CHN_3) [(*S*) 3.17, not detected]; **4a**, 3.05 (m, $PhCH_2$), 3.50 (d, CHCl), 3.93 (m, CHN_3); **4b**, 3.70 (d, CHCl); **4c**, 3.59-3.83 (m, 3), 3.98 (m, 1); **4d**, 3.54 (d, CHCl); **5a**, 4.15 (dd, *J* 5.0, 8.9 Hz, CHN_3); **5b** not concentrated (may be hazardous); **5c**, 4.05 (t, *J* 4.4, CHN_3), **5d**, 4.12 (dd, *J* 5.5, 7.7 Hz, CHN_3).
18. a) Buckingham, J., Ed. "Dictionary of Organic Compounds," Chapman and Hall, New York, Vol. 5, p. 4592. (b) Aldrich Chemical Company Catalog, Milwaukee, Wisconsin, **1986**, 1061.

(Received in USA 1 June 1987)