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ASYMMETRIC SYNTHESIS OF NEW BICYCLIC PHENYLBORONIC ESTERS CONTAINING CONFIGURATIONALLY STABLE CHIRAL NITROGEN AND BORON

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Summary

The reaction between phenylboronic acid and *N*-alkyl-*N*-(ethyl-2-hydroxy)-aminoacetic acids leads stereoselectively to stable bicyclic esters containing chiral boron and nitrogen atoms.

Introduction

Our current interest in structural and dynamic effects in boron heterocycles containing intramolecular N→B coordination, in particular those derived from diethanolamine [1] and iminodiacetic acids [2] prompted us to look for bicycles **1b**–**5b** prepared from *N*-(2-hydroxyethyl)-*N*-alkyl-glycine and phenylboronic acid (Scheme 1).

The presence of carboxylic groups produces boron bicycles of great stability as has been observed in organyl boronic esters derived from iminodiacetic acids [2,3].

Two interesting features in the compounds reported here are:
(1) the carboxylic function guarantees good stability and
(2) the presence of two different groups (one alkoxide and one carboxide) originates two configurationally stable chiral centers, boron and nitrogen. There are just a few examples of molecules containing these chiral atoms in the literature [4–9].

In the following we report the synthesis, characterization and stereochemistry of bicyclic structures derived from five different ligands **1a**–**5a** [10] and phenyl boronic acids (see Scheme 1).

Formation of bicyclic structures can be easily demonstrated by spectroscopic methods since the $\delta(^{11}B)$ values (Table 1) lie in the range corresponding to N→B coordination ($\delta = +9, +12$ ppm) [1,2] while the ^1H NMR shows that diastereotopic protons in α position to carbonyl function give rise to an AB coupling pattern

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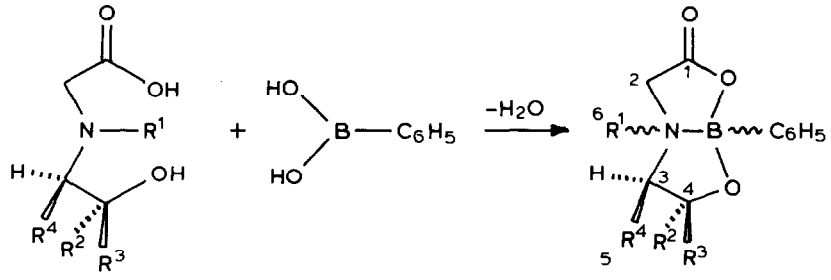


1a* (**1b** , $R^1 = CH_3$, $R^2 = R^3 = R^4 = H$;

2a* **2b-2c** , $R^1 = CH_3$, $R^2 = H$, $R^3 = C_6H_5$, $R^4 = CH_3$;

3a* **3b-3c** , $R^1 = CH_3$, $R^2 = C_6H_5$, $R^3 = H$, $R^4 = CH_3$;

4a* **4b** , $R^1 = CH(CH_3)_2$, $R^2 = H$, $R^3 = C_6H_5$, $R^4 = CH_3$;

5a* **5b** , $R^1 = CH(CH_3)_2$, $R^2 = C_6H_5$, $R^3 = H$, $R^4 = CH_3$)

* optically active

SCHEME 1

TABLE 1

^{11}B AND ^1H NMR PARAMETERS [a] FOR COMPOUNDS **1–5**

Compound	$\delta(^{11}B)$	$\delta(^1H)$					
		R^1-N	C^3H [b]	C^4H [b]	C^2H [b]	C-CH_3	C_6H_5
1b (DMSO)	+11.9	2.35(s)	3.3(m)	3.95(m)	4.10(d) *J* 16 3.86(d)		7.15–7.65(m)
2b (DMSO)	+12.2	2.30(s)	3.8(m)	5.4(d) *J* 4.5	4.50(d) *J* 18 4.00(d)	0.74(d) *J* 7.5	7.25–7.9(m)
2c (DMSO)		2.34(s)	3.8(m)	5.62(d) *J* 7.5		1.00(d) *J* 7.5	7.25–7.9(m)
3b (DMSO)	+12.0	2.35(s)	3.1(m)	4.8(d) *J* 10	4.20(d) *J* 18 3.60(d)	1.09(d) *J* 6	7.20–7.85(m)
3c (DMSO)		2.22(s)	3.1(m)	5.1(d) *J* 10.5	4.14(d) *J* 15 3.70(d)	1.14(d) *J* 6	7.20–7.85(m)
4b ($CDCl_3$)	+12.8	3.27(hep) *J* 6 0.93(d) *J* 6 1.15(d) *J* 6	3.55(m) *J* 6	5.36(d) *J* 4.5	4.03(d) *J* 18 3.73(d)	1.15(d) *J* 6	7.35–7.80(m)
5b ($CDCl_3$)	+8.9	3.1(hep) *J* 6 [c]	3.1(hep)	4.62(d) *J* 9	3.84(d) *J* 18 3.5(d)	[c]	7.36–7.76(m)

[a] $\delta(^{11}B)$ in ppm relative to $BF_3 \cdot OC_2H_5$, $\delta(^1H)$ in ppm relative to $Si(CH_3)_4$; *J* in Hz. [b] For carbons numbers see Table 2. [c] Isopropyl methyls and C-CH_3 could not be assigned, the values are: 0.9(d) *J* 6 Hz; 1.06(d) *J* 6 Hz; 1.2(d) *J* 6 Hz.

ascribed to a rigid structure (Table 1). Also the IR absorptions of the carbonyl functions are indicative of cyclic compounds ($\nu \cong 1745$ cm^{-1}) (Table 3) and mass spectra of compounds **1b**, **2b**, **3b** and **5b** shows the molecular mass M^+ m/e of high intensity (Table 4).

Stereochemistry

Although in principle two enantiomeric pairs may be expected for **1b**, due to the emergence of two chiral centers only one pair of enantiomers has been observed because of the preference for *cis*-fusion of the rings. For the four optically active ligands **2a**–**5a** four diastereomers may be expected, but, two of them are eliminated again owing to the *cis*-fusion. Thus, compounds **2a** and **3a** each afforded two isomers (**2b**, **2c** and **3b**, **3c**, respectively) and ligands **4a** and **5a** each lead preferentially to only one.

Observation in ^{1}H NMR of the reaction mixture of compounds **2a** and **3a** with phenylboronic acid showed the two expected diastereomers in a 70/30 and 75/25 ratio, respectively. Recrystallization from an acetone/hexane mixture allowed isolation of the more abundant compounds (**2b** and **3b**) as white crystalline stable solids. On the other hand, the minor isomers (**2c** and **3c**) were not isolable, but their NMR data could be easily obtained from the mixture. Reaction of compounds **4a** and **5a** with phenylboronic acid afforded only one of the two possible diastereomers; the stereoselectivity of the syntheses is probably due to the bulky substituent on nitrogen. Assignment of structures of **2b**–**3b**, **2c** and **3c** was done by analysis of the NMR spectra and NOE experiments. Assignment of configurations for **4b** and **5b** was not possible because only one isomer for each couple was available.

NMR structural analysis

It is known that ^{13}C NMR is very sensitive to steric interactions and can be used to deduce configuration [11,12]. Comparison of the ^{13}C data for each pair of diastereomers (Table 2) shows that the (C(2)) is shifted to higher magnetic field ($\Delta\delta = 7.1$ for **2** and 5.8 ppm for **3**) for one of the isomers. This can be attributed to a strong steric hindrance of a C-CH_3 group in the *endo* position of the bicyclic systems. N-CH_3 is different for each isomer ($\Delta\delta = 2.5$ and 9.7 ppm, respectively for compounds **2** and **3**).

The facts that in the isomer **2b**, the C(6) signal appears at higher field and N-CH_3 at lower field than in **2c**, and that for isomers **3b**–**3c** the reverse is true, allow us to propose structures for **2b**, **3b** and **2c**, **3c** as shown in Scheme 2.

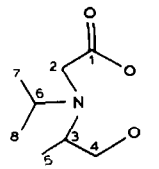
Also in ^{1}H NMR, the C(4) protons appear at lower field in isomers **2c** and **3c** ($\Delta\delta$ 0.22 and 0.3 ppm, respectively) compared to **2b** and **3b**, suggesting that this proton is deshielded by the *B*-phenyl group. In order to verify these assumptions, a nuclear Overhauser effect difference experiment was performed in compound **2b** (Fig. 1), irradiation of the C-CH_3 showed an enhancement of the N-CH_3 signal of 10% demonstrating that for this couple of isomers, the most abundant is that one which has the ring substituents in the *exo*-position. This also implies that assignment for isomers **3b**–**3c** should be correct.

Variable temperature experiments in the ^{1}H NMR of compounds **2b** and **3b** (in DMSO-d_6) did not show coalescence of the signals. However appearance of the

(*Continued on p. 196*)

TABLE 2

^{13}C NMR PARAMETERS FOR COMPOUNDS 1–5 [a]



Compound	C^1	C^2	C^3	C^4	C^5	C^6	C^7	C^8		C_i	C_o	C_m	C_p
1b (DMSO-d_6)	170.2	60.3	60.8	62.2		47.6			*B*-phenyl		132.5	127.1	127.7
2b (DMSO-d_6)	170.7	62.1	69.7	74.6	10.8	43.8			*B*-phenyl		132.6	125.6	127.0
									C-phenyl	139.2	127.1	128.0	127.8
2c (DMSO-d_6)	170.2	55.0	66.4	78.0	10.3	46.3			*B*-phenyl		133.8	125.8	127.1
									C-phenyl	139.6	127.1	127.7	127.7
3b (DMSO-d_6)	170.4	52.7	71.4	78.0	8.4	46.8			*B*-phenyl		132.7	126.7	127.8
									C-phenyl	139.2	127.1	128.2	127.9
3c (DMSO-d_6)	169.0	58.5	70.6	80.9	8.2	37.1			*B*-phenyl		132.5	126.3	127.7
									C-phenyl	140.8	127.1	128.1	127.9
4b ($CDCl_3$)	171.2	53.1	70.6	75.4	11.4	52.9	18.0	18.3	*B*-phenyl		134.1	125.1	127.1
									C-phenyl	138.3	127.4	128.4	127.6
5b ($CDCl_3$)	169.4	60.8	62.5	80.8	14.3	53.6	19.0	18.3	*B*-phenyl		132.7	126.7	127.8
									C-phenyl	140.4	127.5	128.3	128.2

[a] δ (ppm, TMS).

TABLE 3

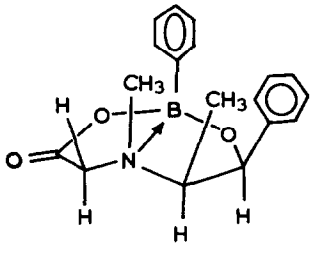
IR PARAMETERS

Compound	ν(C=O)	ν(B–O)	ν(N–B)
1b	1746	1326	1015
			985
2b	1749	1304	1102
			976
3b	1743	1299	1085
			975
4b	1745	1309	1102
			999
5b	1747	1315	1092
			968

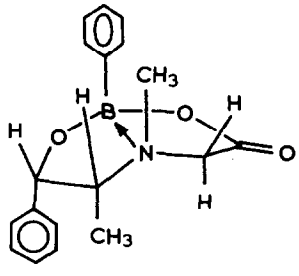
TABLE 4

MS PARAMETERS (M^+)

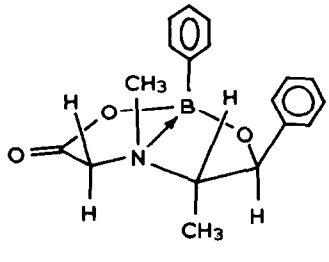
Compound M^+						
1b	219(22)	142(100)	114(89)	42(52)	104(29.4)	
2b	309(42)	70(100)	42(76)	71(76)	56(67)	91(67)
3b	309(43)	70(100)	42(96)	91(70)	56(57)	
4b		100(100)	58(39)	44(21)	41(14)	
5b	337(33)	56(100)	43(42)	337(33)	91(33)	



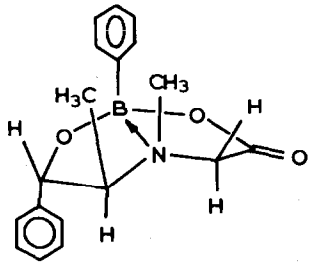
(2b)



(2c)



(3b)



(3c)

SCHEME 2

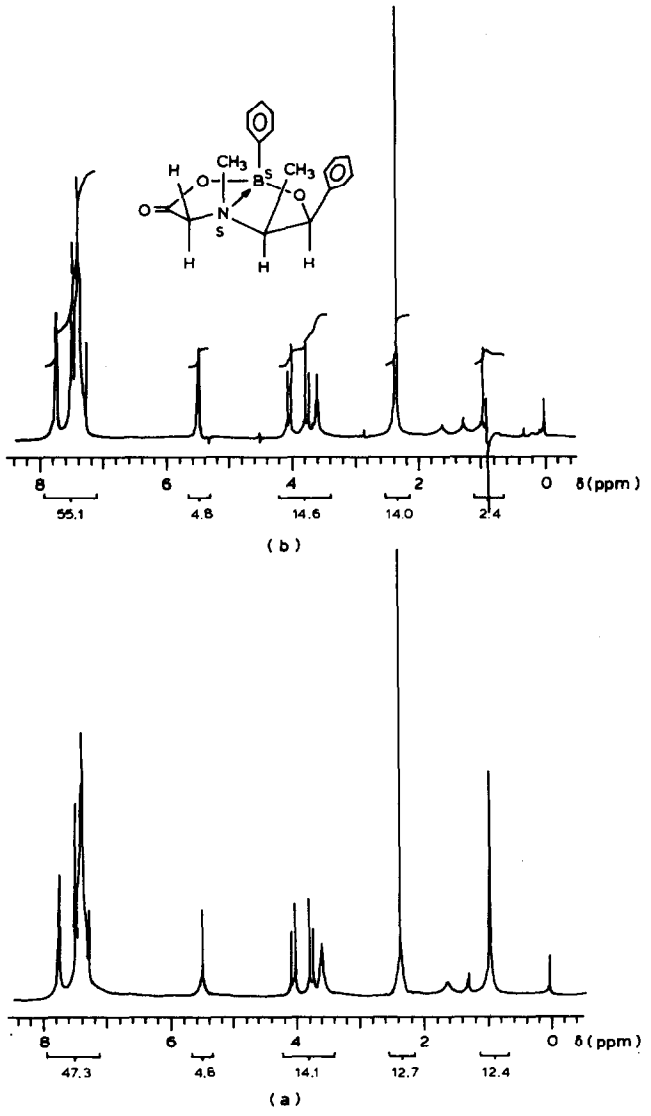


Fig. 1. (a) ^{1}H NMR (300 MHz) of isomer **2b** ($CDCl_3$) showing the AB system for the methylene protons. (b) NOE experiment of **2b**, the spectra shows by irradiation at C-CH_3 (0.95 ppm) an enhancement of the N-CH_3 signal (2.18 ppm) of 10%, the numbers below are the integration values. s indicates absolute configuration of the nitrogen and boron atoms.

minor isomer (**2c** at 90°C and **3c** at 140°C) was observed until the thermodynamic ratio of epimers was attained in the reaction mixture.

Experimental

The NMR spectra (^{1}H, ^{11}B, ^{13}C) were obtained with a JEOL FX 90Q-FT spectrometer. Mass spectra were recorded on a Hewlett Packard 5985-A spectrometer and the infrared spectra on a Nicolet MX-1FT. Starting ligands were prepared following the reported syntheses [10].

*(N–B)phenyl[N-methyl-N-(ethyl-2-hydroxy)aminoacetate-O,O'N]borane (**1b**)*

The following procedure is representative of all reactions performed in this study. A solution of *N*-methyl-*N*-(ethyl-2-hydroxy)amino acid (2.18 g, 16.4 mmol) in 50 ml of dry benzene was placed into a 100 ml flask equipped with a stirrer and a Dean-Stark trap. Phenylboronic acid (1.99 g, 16.4 mmol) was added and the mixture was kept under reflux for 8 h. After removal of the solvent in vacuo the product was recrystallized from acetone/hexane to give 3.38 g (92.5%) of compound **1**, m.p. 110–111°C. MS: M^+ *m/e* 219 (21.7%). Found: C, 59.92; H, 6.48; N, 6.36. $C_{11}H_{14}BNO_3$ calc: C, 60.03; H, 6.44; N, 6.39%.

*(N–B)phenyl[N-methyl-N-(ethyl-1-methyl-2-phenyl-2-hydroxy)aminoacetate-O, O',N]borane (**2b–2c**) (+ ephedrine derivative)*

N-methyl-*N*-(ethyl-1-methyl-2-phenyl-2-hydroxy)amino acid (0.35 g, 1.57 mmol) and phenylboronic acid (0.20 g, 1.6 mmol) gave 0.46 (91%) of a mixture of compounds **2b** and **2c**. Crystallization from acetone/hexane allows one pure isomer to be separated, compound **2b** (54.1%) m.p. 165–166°C. Found: C, 69.85; H, 6.57; N, 4.29. $C_{18}H_{20}BNO_3$ calc: C, 69.92; H, 6.52; N, 4.53%. MS: M^+ *m/e* 309 (41%).

*(N–B)phenyl[N-methyl-N(ethyl-1-methyl-2-phenyl-2-hydroxy)aminoacetate-O, O',N]borane (**3b–3c**) (–pseudoephedrine derivative)*

N-methyl-*N*-(ethyl-1-methyl-2-phenyl-2-hydroxy)amino acid (0.5 g, 2.24 mmol) and phenylboronic acid (0.27 g, 2.21 mmol) gave 0.66 g of a mixture of compounds **3b** and **3c**. Crystallization from acetone/hexane allows one pure isomer to be separated, compound **3b** (53.9%) m.p. 175°C. Found: C, 69.88; H, 6.58; N, 4.29. $C_{18}H_{20}BNO_3$ calc: C, 69.92; H, 6.52; N, 4.53%. MS: M^+ *m/e* 309 (43%).

*(N–B)phenyl[N-isopropyl-N-(ethyl-1-methyl-2-phenyl-2-hydroxy)aminoacetate-O, O',N]borane (**4b**) (+ ephedrine derivative)*

N-isopropyl-*N*-(ethyl-1-methyl-2-phenyl-2-hydroxy)amino acid (0.15 g, 0.6 mmol) and phenylboronic acid (0.07 g, 0.57 mmol) gave 0.136 g of compound **4b** (71%), m.p. 70°C. Found: C, 70.62; H, 7.19; N, 3.50. $C_{20}H_{24}BNO_3$ calc: C, 71.23; H, 7.17; N, 4.15%. MS: *m/e* 100 (100%).

*(N–B)phenyl[N-isopropyl-N-(ethyl-1-methyl-2-phenyl-2-hydroxy)aminoacetate-O,O',N] borane (**5b**) (–pseudoephedrine derivative)*

N-isopropyl-*N*-(ethyl-1-methyl-2-phenyl-2-hydroxy)amino acid (0.3 g, 1.2 mmol) and phenylboronic acid (0.14 g, 1.14 mmol) gave 0.272 g of compound **5b** (71%), m.p. 60°C (dec.). Found: C, 70.42; H, 7.64; N, 3.53. $C_{20}H_{24}BNO_3$ calc.: C, 71.23; H, 7.17; N, 4.15%. MS: M^+ *m/e* 337 (33.5%).

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