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N-ALKYLOXAZABOROLIDINES DERIVED FROM EPHEDRINES.

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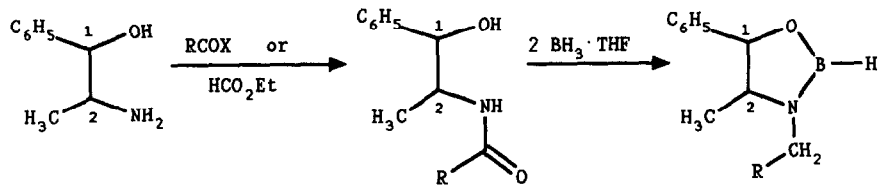
Abstract: The synthesis of oxazaborolidines from amides derived from ephedrine and pseudoephedrine by treatment with BH_3-THF is reported. The reaction affords chiral oxazaborolidines with nitrogen atom substituents of different steric requirements enlarging the potential of new oxazaborolidines prepared from readily available ephedrines. These may be useful in asymmetric synthesis.

The high enantioselectivity and broad applicability of oxazaborolidines as catalysts in reductions and other reactions have converted them into very important and valuable reagents[1-6]. For some time we have been interested in studying the behavior of borane with aminoalcohols and oxazolidines[7-11]. Recently we have found a new method, which is reported here, to prepare oxazaborolidines and due to the enormous interest[1-6] in asymmetric syntheses of this kind of heterocycle we were prompted to contribute to the knowledge of their synthesis and spectroscopy.

Herein, we report the syntheses of oxazaborolidines (**11-18**) bearing nitrogen substituents of different steric requirements. We have found that the reactions of borane-THF with amides derived from *nor*ephedrine (**3-6**) or *norpseudo*ephedrine (**7-10**) give, after ring formation and carbonyl reduction, the oxazaborolidines.



	erythro	threo		erythro	threo	
1 norephedrine (erythro)	3	7	R = H	11	15	R = H
2 norpseudoephedrine (threo)	4	8	R = CH_3	12	16	R = CH_3
	5	9	R = C_6H_5	13	17	R = C_6H_5
	6	10	R = $C(CH_3)_3$	14	18	R = $C(CH_3)_3$

The reaction of an aminoalcohol with borane using mild conditions allows the substitution of the oxygen proton by a boron atom. Under these reaction conditions

the amine proton does not react[7]; it requires heating to 120 °C[12-13]. However, in amides the more acidic amide proton readily allows formation of the B-N covalent bond. It is assumed that the ring formation precedes the amide reduction, because its proton is acidic and reacts faster than the amide carbonyl or the amine N-H[14], this assumption is supported by the ^{11}B NMR study of the reaction that shows that with one equivalent of BH_3-THF a [O, N B-H] group is formed presumably due to a boron heterocycle derived from the amide.

In conclusion, *nor*ephedrine **1** or *norpseudo*ephedrine **2** can be easily converted to the amides which may react with two equivalents of borane, to give readily oxazaborolidines. The reduction of the carbonyl led to the N-alkyl group. Hence, the reactions reported here have the advantage of nitrogen alkylation, thus allowing the size of the nitrogen substituent to be controlled. This is a useful reaction for the preparation of chiral oxazaborolidines which could be used as chiral reducing agents. The characterization of amides (**3-10**) and boron heterocycles (**11-18**) was made by spectroscopical means. Data are in tables.

TABLE. ^{1}H NMR (90 MHz) Spectral data (δ ppm, J Hz, TMS)

Compd	CH_3	C2-H	C1-H	R	-C_6H_5
1[a]	0.93 d (7.0)	3.10 m	4.48 d (5.0)		7.30 s
2[a]	0.92 d (6.0)	2.92 m	4.13 d (6.0)		7.27 s
3[a]	0.95 d (7.5)	4.25 m	4.80 dd (3.0,4.5)	8.0 s	7.30 s
4[a]	0.95 d (7.0)	4.23 m	4.85 d (3.0)	1.92 s	7.34 s
5[b]	1.09 d (7.0)	4.40 m	4.95 d (3.0)	7.2-7.7 m (Ho 7.78-8.0)	7.2-7.7m
6[a]	1.00 d (5.0)	4.30 m	4.82 d (2.0)	1.20 s	7.40 s
7[a]	1.00 d (5.0)	4.20 m	4.50 d (4.5)	8.05 s	7.35 s
8[a]	1.00 d (7.0)	4.10 m	4.49 d (5.0)	1.76 s	7.30 s
9[a]	1.20 d (7.0)	4.40 m	4.70 d (6.0)	7.2-7.5 m (Ho 7.63-7.86)	7.33 s
10[a]	1.15 d (7.0)	4.15 m	4.64 d (4.5)	1.12 s	7.35 s
11[c]	0.43 d (6.6)	3.28 m	5.41 d (8.6)	2.50 s	7.16 m
12[c]	0.44 d (6.7)	3.43 m	5.41 d (7.9)	2.66 dq, 2.96 dq(13.4) 1.00 t (6.76)	7.18 m
13[c]	0.43 d (6.5)	3.33 m	5.36 d (8.5)	4.26 d, 3.74 d (15) 7.14 m	7.14 m
14[a]	0.60 d (4.0)	3.75 m	5.53 d (5.0)	2.66 d, 2.98 d (10) 1.30 s	7.35 m
15[c]	0.88 d (5.9)	2.97 m	4.76 d (6.6)	2.32 s	7.15 m
16[c]	0.90 d (7.2)	3.17 m	4.80 d (7.2)	2.88 dq, 2.58 dq (13.5) 0.90 t (6.60)	7.20 m
17[c]	0.89 d (6.2)	3.18 m	4.90 d (7.0)	4.19 d, 3.84 d (15.1) 7.27 m	7.22 m
18[a]	1.25 d (4.0)	3.55 m	4.95 d (4.0)	2.72 d, 2.93 d (10.0) 0.90 s	7.40 m

a) $CDCl_3$, b) $CDCl_3$/DMSO-d_6, c) C_6D_6.

TABLE ^{11}B NMR (28.85 MHz) Spectral data (δ ppm, J Hz, BF_3.etherate)

11 +29 (d) J = 147; **12** +28 (d) J = 143; **13** +30 (b); **14** +29 (d) J = 149
15 +29 (d) J = 153; **16** +29 (d) J = 152; **17** +29 (d) J = 143; **18** +30 (d) J =141

TABLE. ^{13}C **NMR (22.6 MHz) Spectral data, (δ ppm, TMS)**

Compd	CH_3	C-2	C-1	C=O or CH_2 or N-CH_3	R	C_i	C_o	C_m	C_p
1[a]	18.20	52.10	77.60			142.00	126.80	128.20	127.50
2[a]	20.10	53.00	78.90			143.10	126.80	128.40	127.60
3[a]	13.42	49.35	74.90	161.54		140.67	125.90	128.04	127.20
4[a]	13.94	50.99	75.91	170.74	23.11	141.05	126.18	128.13	127.35
5[b]	13.41	51.58	75.18	166.86	d	142.37	126.13	128.18	126.86
6[a]	14.57	50.76	76.33	179.26	27.41 ,38.57	140.90	126.28	127.96	127.31
7[a]	17.35	49.96	76.18	161.89		141.30	126.24	128.08	127.49
8[a]	17.36	51.34	76.55	171.23	22.72	141.98	126.38	128.04	127.35
9[a]	17.47	51.74	77.09	168.03	e	141.65	126.34	128.29	127.70
10[a]	17.44	50.98	76.38	178.94	27.35 ,38.54	141.94	126.17	128.01	127.36
11[c]	15.42	59.62	83.58	30.25		140.02	128.13	126.59	127.32
12[c]	15.71	57.34	83.47	37.96	15.63	140.10	128.15	126.64	127.31
13[c]	15.29	56.10	83.70	47.49	f	139.83	128.17	126.57	127.38
14[a]	15.40	59.12	82.79	54.62	27.64, 32.85	139.08	127.76	125.92	126.89
15[c]	18.81	64.48	88.06	29.84		143.53	128.67	125.73	127.76
16[c]	19.20	62.30	87.86	37.65	15.37	143.62	128.67	125.71	127.78
17[c]	18.78	61.30	88.19	47.42	g	143.17	128.69	125.80	127.32
18[a]	19.61	63.27	87.49	53.95	28.06, 33.15	142.91	128.34	125.14	127.52

a) $CDCl_3$, b) $CDCl_3$/DMSO-d_6, c) C_6D_6), d) R= C_i 134.95, C_o 127.21, C_m 127.88, C_p 131.06 e)R= C_i 134.43, C_o 126.68, C_m 128.44, C_p 131.36, f) C_i 139.52, C_o 128.75, C_m 127.96, C_p 128.34, g) C_i 139.20, C_o 128.39, C_m 127.68, C_p 127.78.

General Procedures for the Synthesis of Amides:

Compounds **3** and **7** were prepared by reaction of aminoalcohols **1** and **2** with ethylformate, the following is representative for both compounds:

(1R, 2S) (-)-N-formyl-norephedrine (**3**).

(1R,2S)-(-)-norephedrine **1** (10 g, 66.1 mmol) was treated with ethylformate (25 mL, 30.71 mmol) and p-toluensulphonic acid monohydrate as catalyst. After heating to reflux temperature (52°C) with stirring, ethyl formate was removed by evaporation under reduced pressure. The residue was recrystallized from hexane/ethyl acetate to provide compound **3** (9.4 g, 80 %) mp 83°C. Compound **7** was obtained (75 %) mp 63°C.

Compounds **4-6** and **8-10** were prepared by reaction of compounds **1** or **2** with the correspondent acid chlorides in the presence of triethylamine. The following procedure is typical:

(1R,2S)-(-)-N-Acetyl-norephedrine (**4**)

(1R,2S)-(-)-norephedrine **1** (10.0 g, 66.13 mmol) in dried methylene chloride (40 mL) and triethylamine (6.69 g, 66.13 mmol) was cooled to 0° C and treated dropwise with stirring with acetyl chloride (95.19 g, 66.13 mmol) dissolved in methylene chloride (15 mL). After stirring for an additional 3 h at room temperature, water (25 mL) was added. Drying of the organic layer (Na_2SO_4) and evaporation of methylene chloride provided **4** (12.03 g, 94 %) as a white solid, mp 123°C. All the amides are white

powders, the yields and mp are the following: **5** (93 %) mp 164°C, **6** (88 %) mp 74°C, **8** (89 %), mp 75°C, **9** (83 %) mp 123°C, **10** (85 %) mp 89 °C.

General procedure for the Synthesis of Oxazaborolidines:

The procedure described below is representative for the synthesis of compounds **11-18**.

Cis-(4S,5R)-(-)-3-ethyl-4-methyl-5-phenyl-oxazaborolidine (**12**).

(1R,2S)-(-)-N-acetyl-norephedrine **4** (10.0 g, 51.75 mmol) in anhydrous THF (60 mL) was treated with 1.8 M solution of borane tetrahydrofuran complex (33.5 mL, 60.3 mmol) at -78°C. After stirring for 2.5 h at room temperature more tetrahydrofuran complex was added (33.5 mL, 60.3 mmol). After stirring for 2.5 h, THF was removed by evaporation under reduced pressure. The residue was distilled under reduced pressure (0.25 mmHg, 90°C) to obtain **12** pure (6.63 g, 67.8 %) as a colourless liquid, $[\alpha]_D^{20}$= -105.4 (c 1.453, THF).

All other oxazaborolidines were colourless liquids, their yields and specific rotations are the following: Compound **11**[12,13] (65.0 %), (4S,5R) $[\alpha]_D^{20}$= - 108.0 (c 1.0, $CHCl_3$), Compound **13** (28.5%), (4S,5R) $[\alpha]_D^{20}$= + 41.3 (c 3.63, THF), Compound **14** (49.4 %), (4S,5R) $[\alpha]_D^{20}$= - 63.23 (c 1.174, THF), Compound **15**[12,13] (63.0 %), (4S,5S) $[\alpha]_D^{20}$= + 59.0 (c 1.0, $CHCl_3$), Compound **16** (70.4 %), (4R,5R) $[\alpha]_D^{20}$= - 26.4 (c 4.93, THF), Compound **17** (28.8 %), (4R,5R) $[\alpha]_D^{20}$= + 9.66 (c 2.46, THF), Compound **18** (49.3 %), (4R,5R) $[\alpha]_D^{20}$= - 20.2 (c 2.28, THF).

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