EXCHANGE REACTIONS USING N-METHYLMORPHOLINE-BORANE DERIVATIVES

Mallaiah Mittakanti[+] and Karen W. Morse[#*]

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300, USA

Abstract:
A general procedure is described for the exchange reactions between N-methylmorpholine-borane derivatives and various organic bases involving a simple work-up to produce exchanged products. Thus, the procedure utilizes readily available, easy to handle aqueous as well as liquid amines in the exchange reactions with N-methylmorpholine-BH_2X (X = COOH, COOMe, CONHEt) giving the corresponding amine-BH_2X in good to excellent yields. The method also utilizes other organic bases such as phosphine, phosphite, and amino acid ester in the exchange reaction to obtain their borane derivatives.

Introduction:
Amine-carboxyboranes and their derivatives are an interesting class of compounds, being isosteric and isoelectronic to amino acids. These compounds have attracted considerable attention because of their various biological (antitumor, antiarthritic and hypocholesteremic) activities[1-4]. Boron analogues of amino acids and their derivatives are usually synthesized[5-15] by hydrolyzing the nitrilium salt of tertiary amine-cyanoborane adducts. Boron analogues containing a primary or secondary amine are prepared by an exchange reaction[8,9,15-17]. Typically a tertiary amine-carboxyborane or its derivative is allowed to react with an excess of primary or secondary amine to yield the corresponding boron analogues. Earlier we have reported[15] the use of borane adducts of some tertiary amines such as trimethylamine, pyridine and N-methylmorpholine in exchange reactions and found that N-methylmorpholine-borane adducts undergo an easy exchange reaction giving the desired products in high yields. This paper reports utilization of aqueous as well as liquid orgnic bases in exchange reactions with N-methylmorpholine-borane derivatives to produce products in good to excellent yields.

Materials and Methods:
The ^1H NMR spectra were recorded on a Varian XL-300 spectrometer with TMS as internal standard. The ^{11}B and ^{31}P NMR spectra were recorded on a Varian XL-300 spectrometer operating at 96.23 MHz and 121.42 MHz respectively, with the chemical shifts reported relative to $Et_2O{\cdot}BF_3$ and 85% H_3PO_4. The IR spectra were run on a Perkin-Elmer 1750 FT spectrometer with a $CDCl_3$ solution or nujol sample between NaCl plates. All melting points are uncorrected.

All starting materials (amines and phosphorus compounds) were obtained commercially. Glycine ethyl ester was generated from its hydrochloride in chloroform by adding triethylamine. Chloroform was then removed at reduced pressure and the residue was extracted with ether. The ether was removed on a rotavapor to obtain glycine ethyl ester as colorless liquid which was used without further purification. The compounds $O(CH_2CH_2)_2NCH_3\,BH_2X$ (X = COOH, COOMe, CONHEt) were prepared by previously reported methods[15,19].

The aqueous amine (expressed as % amine: NH_3-28%, $MeNH_2$-40%, Me_2NH-40%, Me_3N-25%, $EtNH_2$-70%) were used in large (40 times) excess. The liquid amines (Me_3CNH_2, C_5H_5N, $PhCH_2NH_2$ and $CH_2{=}CHCH_2NH_2$) were used in excess of 10 times. The compounds $EtO_2CCH_2NH_2$, $(EtO)_3P$ and $Ph_2(Me)P$ were used in excess of 4 times.

* Author to whom correspondence should be addressed
\+ Current Address: ILEX Oncology, Inc., 14785 Omicron Dr., San Antonio, TX 78245
\# Current Address: President's Office, Western Washington Univ., Bellingham, WA 98225

Preparation of $MeNH_2 \cdot BH_2COOMe$ (2b); Typical Procedure: A mixture of monomethylamine (9.1 ml of 40% aqueous solution, 120 mmol) and N-methylmorpholine-methoxycarbonylborane (519 mg, 3 mmol) was stirred at room temperature for 2 days. The progress of the reaction was followed by taking the ^{11}B NMR of the mixture and confirming the absence of the starting ester and the presence of product ester. Upon completion of the reaction, the excess amine was removed on a high vacuum rotavapor at room temperature. The residue was taken into dichloromethane and treated with activated charcoal. Filtration and solvent removal gave white solid which was recrystallized from dichloromethane-hexane to give 284 mg (92%) of pure monomethylamine-methoxycarbonylborane; mp 55-57 °C.

The work-up for most of the compounds was as described above and recrystallization was carried out from dichloromethane-ether or dichloromethane-hexane or ether-hexane mixture depending upon the solubility of the compounds. The oily products were obtained as pure materials after treatment with activated charcoal, filtration and solvent removal. Compounds **1a**, **1c** and **9a** were recrystallized from distilled water.

The following compounds needed special work-up as described below. Exchange reactions for these compounds were carried out under anhydrous condition in an inert atmosphere since the starting materials deteriorate upon continued exposure to air.

Compounds 8a-8c: Upon completion of the reaction, ether-hexane (1:1) was added to the reaction mixture, stirred thoroughly and cooled at -10 °C overnight to give solid products. The products were suction filtered, washed with ether-hexane (1:1) mixture for 3-4 times and recrystallized from dichloromethane-hexane to give pure products. Compound **8a** appears to be unstable upon continued exposure to air.

Compounds 11a-11c: Upon completion of the reaction, hexane was added to the reaction mixture and stirred thoroughly. Compound **11a** precipitated from the solution which was suction filtered, washed with hexane for 3-4 times and dried to give pure material. Compounds **11b** and **11c** were partially soluble in hexane. The solutions were cooled at -10 °C overnight and the hexane solution was decanted leaving oily residue at the bottom. The oily residue was washed with cold hexane for 4-5 times leaving thick oil as pure material.

Compounds 12a-12c: The excess phosphite in the reaction mixture was removed under high vacuum (~0.5-1.0 mm of Hg) at 40-45 °C. Then, the residue was subjected to column chromatography on silica gel (60 Å) by eluting first with hexane, followed by hexane-ether and ether. The middle fractions contained desired product.

Results:

The exchange reactions were carried out with stirring the reaction mixture, containing excess amine or phosphorus base and the N-methylmorpholine-borane derivative, for varying lengths of time (Table I) at room temperature or 40-45 °C. Heating of the reaction mixture containing the primary or secondary amine was avoided to prevent the decomposition of the BH_2 moiety which may occur with water and also to avoid the loss of volatile amine upon heating. However, with phosphine and phosphite, heating the reaction mixture decreased the reaction time from 5 to 2 days. The progress of the reaction was monitored by ^{11}B and ^{31}P NMR spectroscopy. Upon completion of the reaction, the excess amines were removed on rotavapor at ambient temperature and the residue was purified. In the case of phosphine, phosphite and glycine ester, the excess free base was removed by washing with hexane or ether and purifying the product. All products were obtained in pure form upon work-up and purification except ethyl glycinate-carboxyborane which contained glycine anhydride as impurity. Attempts to purify this compound were not successful.

Table I. Reaction Data for $R{\cdot}BH_2X$ as Product

Nr	compound	time (days)	% yield	mp (°C)
1a	$NH_3{\cdot}BH_2COOH$	7	75	114-116
1b	$NH_3{\cdot}BH_2COOMe$	12	86	91-93
1c	$NH_3{\cdot}BH_2CONHEt$	8	90	124-126
2a	$MeNH_2{\cdot}BH_2COOH$	3	88	108 d
2b	$MeNH_2{\cdot}BH_2COOMe$	2	92	55-57
2c	$MeNH_2{\cdot}BH_2CONHEt$	2	90	98-100
3a	$Me_2NH{\cdot}BH_2CONHEt$	2	91	103-105
3b	$Me_2NH{\cdot}BH_2COOMe$	2	80	52-54
3c	$Me_2NH{\cdot}BH_2CONHEt$	2	82	Oil
4a	$Me_3N{\cdot}BH_2COOH$	2	90	122-124 d
4b	$Me_3N{\cdot}BH_2COOMe$	2	72	89-91
4c	$Me_3N{\cdot}BH_2CONHEt$	2	80	Oil
5a	$EtNH_2{\cdot}BH_2COOH$	2	92	73-74
5b	$EtNH_2{\cdot}BH_2COOMe$	2	86	Oil
5c	$EtNH_2{\cdot}BH_2CONHEt$	2	85	92-94
6a	$Me_3CNH_2{\cdot}BH_2COOH$	2	88	108 d
6b	$Me_3CNH_2{\cdot}BH_2COOMe$	2	85	93-95
6c	$Me_3CNH_2{\cdot}BH_2CONHEt$	2	80	62-64
7a	$CH_2{=}CHCH_2NH_2\ BH_2COOH$	2	82	65-67
7b	$CH_2{=}CHCH_2NH_2{\cdot}BH_2COOMe$	2	89	63-65
7c	$CH_2{=}CHCH_2NH_2{\cdot}BH_2CONHEt$	2	86	Oil
8a	$PhCH_2NH_2{\cdot}BH_2COOH$	2	72	78-80
8b	$PhCH_2NH_2{\cdot}BH_2COOMe$	2	78	68-70
8c	$PhCH_2NH_2{\cdot}BH_2CONHEt$	2	74	116-118
9a	$C_5H_5N{\cdot}BH_2COOH$	5	90	120-122
9b	$C_5H_5N{\cdot}BH_2COOMe$	5	93	41-43
9c	$C_5H_5N{\cdot}BH_2CONHEt$	5	92	92-94
10a	$EtO_2CCH_2NH_2{\cdot}BH_2COOH$	2	(60)[a]	
10b	$EtO_2CCH_2NH_2{\cdot}BH_2COOMe$	2	52	62-63
10c	$EtO_2CCH_2NH_2{\cdot}BH_2CONHEt$	2	50	53-55
11a	$Ph_2(Me)P{\cdot}BH_2COOH$	2*	80	98-100
11b	$Ph_2(Me)P{\cdot}BH_2COOMe$	2*	90	Thick Oil
11c	$Ph_2(Me)P{\cdot}BH_2CONHEt$	2*	89	Thick Oil
12a	$(EtO)_3P{\cdot}BH_2COOH$	2*	30	Oil
12b	$(EtO)_3P{\cdot}BH_2COOMe$	2*	80	Oil
12c	$(EtO)_3P{\cdot}BH_2CONHEt$	2*	75	Oil

See Ref. 17 and 18 for original synthesis of compounds **1a-4c** and **12a-12c**, respectively. [a] % yield is from the integration of ^{11}B NMR. * at 40-45°C. d = decomposes

Discussion:

In earlier methods[8,18], the exchange reactions with volatile amines used to use a rather cumbersome and tedious process carried out in a stainless steel cylinder by condensing the anhydrous amine at low temperature and allowing the reaction to take place under pressure. Many volatile amines are available as aqueous solutions. The present method either utilizes these readily available, easy to handle aqueous amines or uses liquid amines in the exchange reactions with $O(CH_2CH_2)_2NCH_3{\cdot}BH_2X$ (X = COOH, COOMe, CONHEt) giving the corresponding amine-BH_2X in good to excellent yields. The method also utilizes other liquid organic bases such as phosphine,

phosphite, and an amino acid ester in the exchange reactions to obtain their borane derivatives (Scheme 1).

Scheme 1. Exchange reactions of N-methylmorpholine-borane derivatives with organic bases (L)

L	Nr	L	Nr
NH_3 (aq)	**1**	CH_2 =$CHCH_2$ NH_2	7
$MeNH_2$ (aq)	**2**	$PhCH_2$ NH_2	8
Me_2NH (aq)	**3**	C5H5N	9
Me_3N (aq)	**4**	EtO_2CCH_2 NH_2	**10**
$EtNH_2$ (aq)	**5**	Ph_2 (Me)P	**11**
Me_3CNH_2	**6**	$(EtO)_3P$	**12**

These compounds are characterized by IR, ^{11}B NMR and ^{31}P NMR spectroscopy. In the IR spectra (Table II), all compounds show characteristic absorptions for B-H and C=O groups. Also, compounds containing primary and secondary amines and carbamoyl group show N-H absorptions. The ^{11}B NMR spectra (Table I) of these compounds exhibit either a sharp or broad triplet. Upon proton decoupling, the triplet collapses to a singlet, indicating the presence of a single type of boron moiety. However, the proton decoupled ^{11}B NMR spectrum of the phosphine and phosphite borane adduct consists of a doublet due to coupling with phosphorus; and the proton coupled spectrum shows a quartet, a consequence of two overlapping triplets. The proton decoupled ^{31}P NMR spectra of compounds **11** and **12** (Table II) consist of either a sharp or broad quartet for each compound due to coupling with boron. The ^{1}H NMR spectrum (Table III) of each compound is consistent with the assigned structure. Because of quadrupole broadening, the BH_2 protons could not be seen clearly. The purities of the final products were confirmed by ^{1}H, ^{11}B and ^{31}P NMR spectroscopy.

Table II. IR, ^{11}B and ^{31}P NMR spectroscopic Data ($CDCl_3$) for R·BH_2X

Nr[a]	IR n(cm^{-1})	^{11}B NMR (ppm)	^{31}P NMR (ppm)
5a	3240 & 3150 (NH), 2382 (BH), 1645 (C=O)	-17.5	
5b	3238 & 3149 (NH), 2384 (BH), 1656 (C=O)	-18.2	
5c	3222 (NH), 2358 (BH), 1563 (C=O)	-16.9	
6a[n]	3261 & 3239 (NH), 2394 (BH), 1637 (C=O)	-21.9[d]	
6b	3233 & 3158 (NH), 2382 (BH), 1656 (C=O)	-20.9	
6c	3195 & 3103 (NH), 2382 (BH), 1561 (C=O)	-20.1	
7a[n]	3270 & 3236 (NH), 2422 (BH), 1636 (C=O)	-18.8	
7b	3230 & 3146 (NH), 2379 (BH), 1647 (C=O)	-17.5	
7c	3085 (NH), 2362 (BH), 1561 & 1496 (C=O)	-16.8	
8a[n]	3395 & 3239 (NH), 2390 (BH), 1636 (C=O)	-18.0[d]	
8b[n]	3439 & 3217 (NH), 2397 (BH), 1651 (C=O)	-17.2	
8c[n]	3340 & 3154 (NH), 2369 (BH), 1548 (C=O)	-16.3	
10a[n]	3260 (NH), 2380 (BH), 1740 & 1665 (C=O)	-18.4[d]	

Table II. IR, ^{11}B and ^{31}P NMR spectroscopic Data ($CDCl_3$) for $R{\cdot}BH_2X$ (contd.)

10b	3243 (NH), 2387 (BH), 1742 & 1671 (C=O)	-19.4	
10c	3243 (NH), 2370 (BH), 1742 & 1562 (C=O)	-18.4	
11a	2405 (BH), 1646 (C=O)	-30.1	4.20
11b	2399 (BH), 1665 (C=O)	-29.8	4.60
11c	2379 (BH), 1587 (C=O)	-28.0	5.86

* Spectral Data for compounds **1a-4c, 9a-9c, 12a-12c** correlate well with reported values[17,12,18]
[n] = in nujol, [d] = in D_2O

Table III. ^1H NMR ($CDCl_3$) Spectroscopic Data for $R{\cdot}BH_2X$

Nr	ppm
5a	1.31 (t, 3H), 2.90 (m, 2H), 4.34 (br s, 2H)
5b	1.30 (t, 3H), 2.88 (m, 2H), 3.58 (s, 3H), 4.33 (br s, 2H)
5c	1.12 (t, 3H), 1.28 (t, 3H), 2.82 (m, 2H), 3.28 (m, 2H), 4.62 (br s, 2H), 5.63 (br s, 1H)
6a	1.33 (s, 9H), 4.02 (br s, 2H), 4.60 (br s, 1H)
6b	1.38 (s, 9H), 3.66 (s, 3H), 4.08 (br s, 2H)
6c	1.34 (s, 9H), 3.35 (m, 2H), 4.42 (br s, 2H), 5.60 (br s, 1H)
7a	3.45 (dq, 2H), 4.22 (br s, 2H), 5.40 (m, 2H), 5.98 (m, 1H)
7b	3.42 (dq, 2H), 3.58 (s, 3H), 4.32 (br s, 2H) 5.35 (m, 2H), 5.98 (m, 1H)
7c	1.12 (t, 3H), 3.30 (m, 2H), 3.39 (dq, 2H), 4.63 (s, 2H), 5.32 (m, 2H), 5.6 (s, 1H), 5.98 (m,1H)
8a	3.92 (t, 2H), 4.45 (br s, 2H), 7.40 (m, 5H)
8b	3.58 (s, 3H), 3.94 (m, 2H), 4.39 (br s, 2H), 7.40 (m, 5H)
8c	1.10 (t, 3H), 3.25 (q, 2H), 3.85 (br t, 2H), 4.90 (br s, 2H), 5.58 (br s, 1H), 7.38 (m, 5H)
10a	1.31 (t, 3H), 3.60 (m, 2H), 4.26 (q, 2H), 5.05 (br s, 2H), 5.90 (br s, 1H)
10b	1.32 (t, 3H), 3.58 (s, 3H), 3.60 (m, 2H), 4.28 (q, 2H), 4.93 (br s, 2H)
10c	1.11 (t, 3H), 1.31 (t, 3H), 3.28 (m, 2H), 3.56 (m, 2H), 4.27 (q, 2H), 5.15 (s, 2H), 5.60 (s, 1H)
11a	2.07 (d, 3H), 7.60 (m, 10H)
11b	2.06 (d, 3H), 3.50 (s, 3H), 7.60 (m, 10H)
11c	1.01 (t, 3H), 2.10 (d, 3H), 3.21 (m, 2H), 5.72 (br s, 1H), 5.55 (m, 10H)

*Spectral Data for compounds **1a-4c, 9a-9c, 12a-12c** correlate well with reported values.[17,12,18]

In summary, a convenient method for exchange reactions to prepare various amine-boranes, phosphine-boranes, phosphite-boranes and amino acid ester-boranes is reported. The method uses easy to handle aqueous amines and other liquid organic bases and involves a simple work-up to produce exchange products in high yields.

Acknowledgments:
Financial support by the Utah Agricultural Experiment Station is gratefully acknowledged.

References:

1. I.H.Hall, C.O.Starnes, A.T. McPhail, P.Wisian-Neilson, M.K.Das, F.Harchelroad, Jr., B.F. Spielvogel, *J. Pharm. Sci.*, **69**, 1025 (1980).
2. I.H.Hall, M.K.Das, F.Harchelroad, Jr., P. Wisian-Neilson, A.T.McPhail, B.F.Spielvogel, *J. Pharm. Sci.*, **70**, 339 (1981).
3. I.H.Hall, C.J.Gilbert, A.T.McPhail, K.W.Morse, K.Hassett, B.F.Spielvogel, *J. Pharm. Sci.*, **74**, 755 (1985).

4. I.H.Hall, B.F.Spielvogel, A.Sood, F.U.Ahmed, S.Jafri, *J. Pharm. Sci.*, **76**, 359 (1987).
5. B.F.Spielvogel, L.Wojnowich, M.K.Das, A.T.McPhail, K.D.Hargrave, *J. Am. Chem. Soc.*, **98**, 5702 (1976).
6. B.F.Spielvogel, F.Harchelroad, Jr., P.Wisian-Neilson, *J. Inorg. Nucl. Chem.*, **41**, 1223 (1979).
7. B.Kemp, S.Kalbag, R.A.Geanangel, *Inorg. Chem.*, **23**, 3063 (1984).
8. B.F.Spielvogel, F.U.Ahmed, K.W.Morse, A.T.McPhail, *Inorg. Chem.*, **23**, 1776 (1984).
9. M.K.Das, P.Mukherjee, *J. Chem. Research (S)*, 66 (1985).
10. J.L. Peters, V.M.Norwood, III, K.W.Morse, *Inorg. Chem.*, **25**, 3713 (1986).
11. B.Gyori, I.Lazar, J.Emri, *J. Organomet. Chem.*, **344**, 29, (1988).
12. M.Mittakanti, K.W.Morse, *Inorg. Chem.*, **29**, 554 (1990).
13. M.Mittakanti, M.R.M.D.Charandabi, K.W.Morse, *Inorg. Chem.*, **29**, 3218 (1990).
14. W.J.Mills, C.H.Sutton, M.W.Baize, L.J.Todd, *Inorg. Chem.*, **30**, 1046 (1991).
15. M.Mittakanti, K.W.Morse, *Inorg. Chem.*, **30**, 2434 (1991).
16. B.F.Spielvogel, F.U.Ahmed, G.L.Silvery, P.Wisian-Neilson, A.T.McPhail, *Inorg. Chem.*, **23**, 4322 (1984).
17. B.F.Spielvogel, In "*Boron Chemistry-4*", IUPAC, Inorganic Chemistry Division, R.W.Parry, and G.Kodama, Pergamon Press, New York, NY, pp. 119-129 (19 80).
18. A.Sood, C.K.Sood, I.H.Hall, B.F.Spielvogel, *Tetrahedron*, **47**, 6915 (1991).
19. Mittakanti, M.; Feakes, D. A.; Morse, K. W. *Synthesis*, 380 (1992).