Selective Reduction by 2-Amino-4-methylpyridine Borane and 2-Aminopyrimidine Borane

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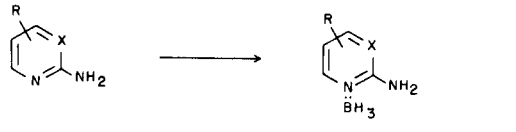
Received February 18, 1986

Stereo- and chemoselective reductions and synthetic utility of the title compounds are described.

J. Heterocyclic Chem., **23**, 1383 (1986).

In a previous communication [2], we reported a facile synthesis and several selective reductions of 2-aminopyridine borane and its analogues. The reducing agents, 2-amino-4-methylpyridine borane (**1a**) and 2-aminopyrimidine borane (**1b**), were synthesized by the reaction of the corresponding amine with sodium borohydride in the presence of cobaltous chloride in aqueous media (Scheme 1). The role of the metal ion and the coordination site of

Scheme 1



1a, R = 4-CH_3, X = C
1b, R = H, X = N

the borane have been studied, and it is clear that the borane coordinates at the endocyclic nitrogen atom of the heterocycles [2,3]. We describe here stereo- and chemoselective reductions including above selective reductions comparing with those reported by Andrews and Crawford [4,5].

Results.

As Scheme II shows, **1a** readily reacted with 4-*t*-butylcyclohexanone (**2**) to give the corresponding alcohols **3** and **4**, (96:4, respectively) almost quantitatively under the same conditions as those reported by Andrews [4]. The amine borane **1a** chemoselectively reacted with a mixture of benzaldehyde (**5**) and acetophenone (**6**) to give benzyl alcohol (**7**) and 1-phenyl-1-ethanol (**8**) (molar ratio, 93:7, respectively) in 53% conversion (**5**→**7**).

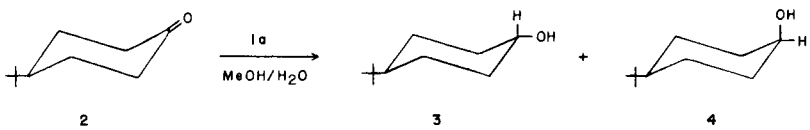
Ethyl phenyl ketone (**9**) was reduced with **1a** to 1-phenyl-1-propanol (**10**) in 75% yield in acetic acid, but not in ethanol-water (2:1). Similarly, alloxan (**18**) was reduced with **1a** to 5-alloxanol (**22**) in 58% yield in trifluoroacetic acid (TFA). Indole (**11**) was reacted with **1a** to give indoline (**12**) in 86% yield at room temperature for 7 minutes in acetic acid. Acetylation of **12** occurred when its reaction time was prolonged. Quinoxaline (**14**) was reduced with **1b** to give 1,2,3,4-tetrahydroquinoxaline (**15**) in 54% yield. *p*-Chlorobenzaldehyde (**16**) was converted with **1b** to bis(*p*-chlorobenzyl) ether (**17**) in 67% yield in acetic acid.

The amine borane **1a** was found to be effective in the synthesis of 2,4-dioxo-1,2,3,4-tetrahydro-10*H*-pyrimido-[5,4-*b*][1,4]benzothiazine (**21**) from **18** and *o*-aminothiophenol (**19**). It was worked out by one-pot reaction to obtain **21** in 35% yield.

Discussion.

The reactivity and stereoselectivity of the amine boranes are highly dependent on the nature of the amine in the amine borane complex. Andrews and Crawford reported the synthetic utility and the chemoselectivity of amine borane reagents in the reduction of aldehydes and ketones [4,5]. Their results show that primary and unhindered amine boranes afford high stereoselectivity and rapid reaction in the reduction of **2**, whereas tertiary amine boranes are unreactive. For example, ammonia borane (**23**) and *t*-butylamine borane (**24**) react with **2** to give alcohols **3** and **4**, (91:9, respectively) in above 99% conversion, whereas the tertiary amine boranes such as pyridine borane (**27**), trimethylamine borane (**28**) and *N*-phenylmorpholine borane (**29**) do not react with **2** under

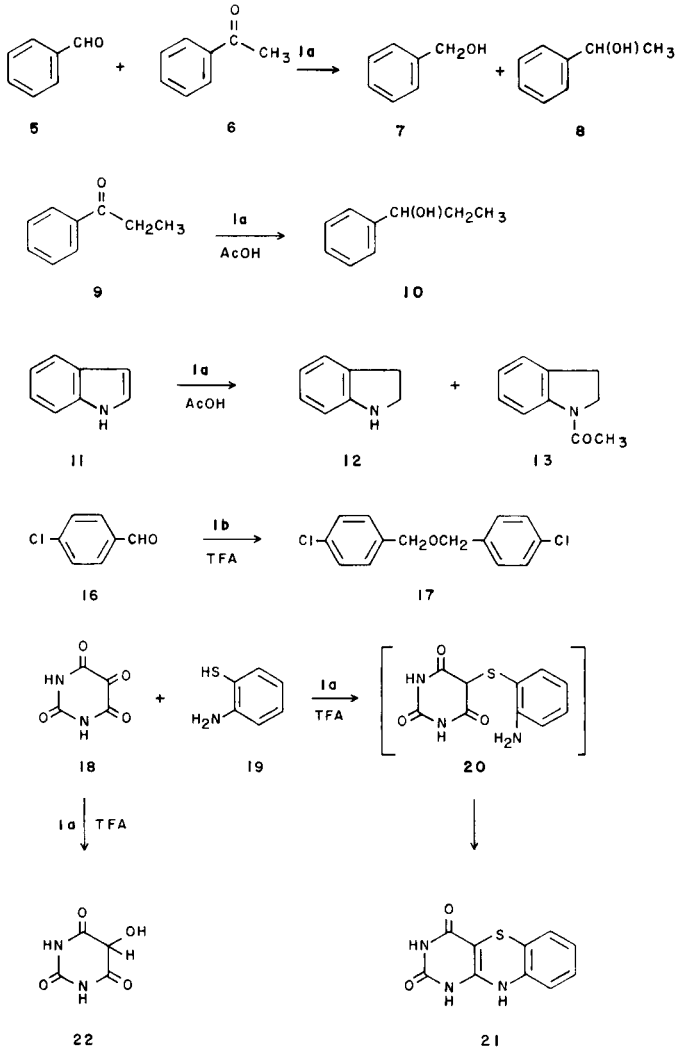
Scheme II



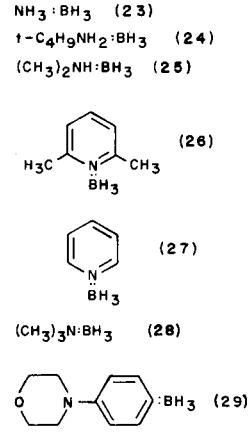
2 **3** **4**

Ratio 3:4 = 96:4
Yield (3 + 4) > 99%

Scheme III



Scheme IV



stirring at room temperature for 15 minutes, except for 2,6-lutidine borane (**26**) which reacts with **2** to give alcohols **3** and **4**, (82:18, respectively) in 33% conversion. Compound **27**, **28**, and **29** do not react with **2** although the reaction time is prolonged for 85 minutes, and even after 18 hours, **2** is converted to **3** and **4** (81:19) in only 29% conversion by **27**, 6% conversion (80:20) by **28**, and below 1% conversion by **29**. In contrast, our amine borane **1a** afforded similar results as those obtained by **23** and **24**.

It is also known that **23** and **24** are highly reactive members of the general class of amine borane reagents which exhibit chemoselective properties equal to or greater than previously reported reagents [5]. In fact, **23** and **24** chemoselectively react with a mixture of **5** and **6** to give **7** and **8** (molar ratio, 97:3, respectively) in 90% conversion (**5**→**7**) by **23**, and 81% conversion (98:2) by **24**, respectively. It should be noted that even in a protic solvent, **1a** is efficient for the chemoselective reduction, whereas **26**, **27**, and **28** are not so much effective as **1a** even in chloroform [5]. The difference of these reactivities between **1a** and **27** is mainly brought about by 2-amino group in pyridine ring. When compared with **27**, the positive charge on the ring nitrogen of **1a** is diminished both by mesomeric effect of 2-amino group and by the electron-releasing inductive effect of the 4-methyl group. This would be why the rate of the aldehyde reduction with **1a** could be accelerated. The assumption would be supported by the fact that the greatly diminished rate of carbonyl reduction by morpholine cyanoborane is attributed to destabilization of a transition state involving hydride transfer due to the electron-withdrawing inductive effect of the boron-bonded cyanide ligand [6].

Although **27** is not suitable for the reduction of **2** and **5**, the specific utility has recently been developed by Kikugawa, for example, selective reductions of **11** to **12** [7], and **14** to **15** [7], and conversion of **16** to **17** [8]. These results are similar to those described in the above section where **1a** and **1b** were used in place of **27**.

There are about seven methods on the syntheses of **21**, one of which depends on an acid-catalyzed dehydration of 5-(2-aminophenylthio)barbituric acid (**20**) [9,10]. On the other hand, **27** is known to be suitable reagent for forming thioether linkage from ketone and thiol [11]. On the basis of these data, we succeeded to synthesize **21** using **1a** without isolating the acid **20**.

In conclusion, the amine boranes **1a** and **1b** were found to have characteristic properties of both primary amine boranes and pyridine borane **27**. It should also be worth noting that these amine boranes, **1a** and **1b**, are readily synthesized in aqueous media [2].

EXPERIMENTAL

Elemental Analyses were performed on a Perkin-Elmer 240B instrument. Proton magnetic resonance (pmr) spectra (deuteriochloroform solution, tetramethylsilane as internal standard) and mass (ms) spectra were run on a Varian EM-90 and JEOL O1S spectrophotometer, respectively. All compounds obtained here were checked by comparing with thin layer chromatographic (tlc) and/or spectral data of authentic samples.

Reduction of 4-*t*-Butylcyclohexanone (**2**).

Amine borane **1a** (0.39 g, 3.2 mmoles) was added to a solution of **2** (0.5 g, 3.2 mmoles) in 50 ml of methanol-water (2:1) with stirring at room temperature. After 15 minutes, the reaction was stopped by addition of 5 ml of 36% hydrochloric acid. The solution was entirely evaporated to yield the corresponding alcohols **3** and **4**, quantitatively (checked by silica gel tlc, chloroform:methanol = 9:1). The crude compounds were washed with water to give the pure alcohols (*trans*:*cis* = 96:4 by pmr) in 62% yield; pmr: δ 0.83 (9H, s, *t*-butyl), 0.77-1.50 (5H, m, 3- and 5-CH_2, and 4-H_{ax}), 1.63-2.17 (4H, m, 2- and 6-CH_2), 2.37 (s, 1-OH_{eq}), 3.50 (m, 1-H_{ax}), 4.00 (m, 1-H_{eq}).

Reduction of Mixtures of Benzaldehyde (**5**) and Acetophenone (**6**).

Amine borane **1a** (0.41 g, 3.3 mmoles) was added to mixtures of **5** (1.2 g, 10 mmoles) and **6** (1.06 g, 10 mmoles) in 20 ml of methanol-water (1:1) with stirring at room temperature. After 15 minutes, the reaction was stopped by addition of 1 ml of 10% hydrochloric acid. The solution was extracted with chloroform (20 ml x 3). The organic layer was dried over sodium sulfate and evaporated at 40° under a reduced pressure to give oils which consisted of **5**, **6**, **7** and **8** in molar ratios as 12:33:14:1, respectively (checked by pmr analysis), with conversions of 53% (**5**→**7**) and 3% (**6**→**8**).

1-Phenyl-1-propanol (**10**) [12].

Amine borane **1a** (1.22 g, 10 mmoles) was added to a solution of 1.07 g (8 mmoles) of **9** in 20 ml of acetic acid with stirring at room temperature. After a day, a solution of 10% of sodium hydroxide (10 ml) was added to the above solution, and then the mixture was heated on a water-bath for 30 minutes. After cooling, the mixture was acidified with 10% hydrochloric acid (about *p*H 2), and extracted with chloroform (60 ml x 3). the extractant was dried over sodium sulfate, and evaporated at 40° under a reduced pressure to give oils of **10** in 75% yield.

1,2,3,4-Tetrahydroquinoxaline (**15**) [13].

Amine borane **1b** (0.43 g, 4 mmoles) was added to a solution of **14** (0.13 g, 1 mmole) in 8 ml of acetic acid with stirring at room temperature. After 1.5 hours, the solution was made alkaline with 10% sodium hydroxide solution (*p*H 11), and then extracted with benzene (30 ml x 3). The extractant was evaporated to give yellow crystals which were purified by preparative tlc (benzene:acetone = 6:1) to afford crystals of **15** in 54% yield, mp 96-97°.

Reduction of Indole (**11**).

To a solution of **11** (70 mg, 0.6 mmole) in acetic acid (8 ml) was added **1a** (300 mg, 2.5 mmoles). The mixture was stirred for 18 hours, then made alkaline (*p*H 13) by addition of 10% sodium hydroxide solution and sodium hydroxide pellets with cooling. The aqueous layer was extracted with benzene (3 x 10 ml) which was then evaporated under reduced pressure. To the residue was added 10% hydrochloric acid to decompose excess **1a**. The aqueous layer was made alkaline (*p*H 13) with 10% sodium hydroxide and sodium hydroxide pellets with cooling, and then extracted with benzene (3 x 20 ml). The extractant was washed with saturated sodium chloride solution and dried with sodium sulfate. After evaporation of benzene, the residue was submitted to preparative tlc (silica gel) using chloroform/methanol (9/1) for development to give a mixture of **12** and **13**. The mixture was acidified (*p*H 2) with 0.1 normal hydrochloric acid solution and extracted with chloroform (3 x 10 ml). The organic layer was dried with sodium sulfate and evaporated to give *N*-acetylindoline (**13**) in 28% (26.7 mg) yield, mp 102° dec [14].

The aqueous layer was made alkaline (*p*H 12) and extracted with chloroform (3 x 10 ml). The organic layer was dried with sodium sulfate and evaporated under a reduced pressure to give indoline (**12**) [7] as an oil in 47% (33.6 mg) yield.

Bis(*p*-chlorobenzyl) Ether (**17**) [8].

p-Chlorobenzaldehyde (**16**) (0.14 g, 1 mmole) was dissolved in 2 ml of TFA and the solution was stirred for 10 minutes with stirring at room temperature. The amine borane **1b** (0.27 g, 2.5 mmoles) was added to the solution with cooling and the mixture was stirred for 5 minutes. The solvent was removed, and 10% sodium hydroxide solution (15 ml) was added to the residue. After refluxing for 40 minutes, the solution was extracted with benzene (3 x 50 ml). The extractant was dried with sodium sulfate, then, evaporated to give an oily substance which was purified by preparative tlc to afford crystals of **17** in 67% (0.11 g) yield.

2,4-Dioxo-1,2,3,4-tetrahydro-10*H*-pyrimido[4,5-*b*][1,4]benzothiazine (**21**) [10].

Amine borane **1a** (0.4 g, 3.3 mmoles) was added to a solution of **18** (0.5 g, 3.1 mmoles) and **19** (0.4 g, 2.5 mmoles) in 50 ml of TFA with stirring at room temperature. After 3 hours, yellow crystals of **21** (0.11 g) were filtered off, and the filtrate was condensed at 60° to give yellow oily substance which turned to crystals when water was added. The crystals were washed with methanol to give 0.15 g of pure **21**. Total yield, 35% (0.26 g), mp >300°.

5-Alloxanol (**22**).

Amine borane **1a** (0.2 g, 1.64 mmoles) was added to a suspension of alloxan (0.2 g, 1.25 mmoles) in 30 ml of TFA with stirring at room temperature. After 3 hours, the precipitates were filtered off, and washed with chloroform to give crystals of **22** in 58% yield, mp 154-155°; ms: m/e 144 (M^+).

Anal. Calcd. for $C_4H_4N_2O_4$: C, 33.34; H, 2.80; N, 19.45. Found: C, 33.41; H, 2.91; N, 19.31.

PMR Measurement for Molar Ratio.

Compound **5** had δ 9.87 (1H, s, CHO); compound **6** had δ 2.43 (3H, s, CH_3); compound **7** had δ 4.60 (2H, s, -CH_2-); compound **8** had δ 1.43 (3H, d, J = 6 Hz, CH_3).

Acknowledgement.

We wish to thank Dr. M. Sako, Gifu College of Pharmacy, who kindly donated the authentic sample of **21** to us.

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