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A Safe and Scalable Procedure for Preparation of α-Picoline−Borane from Sodium Mono-acyloxyborohydrides and α-Picoline

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Supporting Information

ABSTRACT: Sodium monobenzoxyborohydride, which is easily prepared from sodium borohydride and benzoic acid in THF in situ, is treated with α-picoline in THF under mild conditions to give α-picoline−borane in an excellent yield. This method can be a practical preparation for α-picoline−borane.

Amine−boranes are widely used as reducing agents for electroless plating. In the area of organic synthesis, some of them are effective reducing reagents for reductive amination as well.[1] In particular, aromatic amine−boranes have some advantages for this purpose because the reaction can be achieved without preformation of imines and shows suitable reducibility. Among aromatic amine−boranes, pyridine−borane (Pyr-BH_3) is one of the most useful reagents for reductive amination.[2] The application of Pyr-BH_3 to the process chemistry, however, is limited due to its thermal instability and explosive nature.[3] As convenient alternatives, picoline−boranes (Pic-BH_3)[4] and 5-ethyl-2-methylpyridine−borane[5] have been developed, and some reports on reductive amination with these reagents were presented. For example, we have recently reported on the one-pot synthesis of alkoxyamine derivatives from carbonyl compounds via oxime ethers with α-picoline−borane (α-Pic-BH_3). We have also reported that *N*-benzyl-protected amino acid derivatives were readily prepared by α-Pic-BH_3-mediated reductive alkylation of α-amino acid esters.[6,7] α-Pic-BH_3 is regarded as a safer reducing regent than Pyr-BH_3 for the following reasons: (1) Differential scanning calorimetric data reveals that α-Pic-BH_3 has a higher onset temperature than Pyr-BH_3.[8] (2) The flash point of α-Pic-BH_3 is known to be higher than that of Pyr-BH_3 by closed-cup evaluation.[9] (3) Furthermore, we confirmed that crystalline α-Pic-BH_3 could be recovered completely after heating to 140 °C without hazardous degradation and was not decomposed under ambient conditions for over 2 years, judging from the HPLC analysis. Thus, production processes using α-Pic-BH_3 could be thought to be quite promising; however, its aggressive application to process chemistry has not been made. One of the primary reasons must be that the reagent is expensive owing to the lack of cost-effective preparations.[10]

RESULTS AND DISCUSSION

There are three known types of reactions for the preparation of amine−boranes: (1) Reaction of amines with gaseous diborane or borane−ligand complexes (BH_3−L), such as BH_3−THF and BH_3−dimethylsulfide, prepared in situ.[11,12] (2) Reaction of amine hydrochlorides and $NaBH_4$.[13,14] (3) Reaction of $NaBH_4$ with amines in the presence of cation-exchange resins.[15] Each reaction described above, however, has some problems from an industrial production viewpoint. (1) Hazardous diborane or borane complexes should be handled at special facilities. (2) Since both $NaBH_4$ and amine hydrochlorides have less solubility in general organic solvents, a large amount of solvents is required. (3) Cation-exchange resins are expensive.

In general, nonhazardous processes achieved under mild conditions using inexpensive raw materials are ideal for process chemistry. Therefore, if α-Pic-BH_3 can be prepared from $NaBH_4$ and α-picoline without using diborane or borane complexes around room temperature in a limited amount of organic solvent, it can be quite a promising process for this reagent. In this paper, we report on a safe, inexpensive, and mild procedure for the synthesis of α-Pic-BH_3.

Yamada et al. reported on the asymmetric reduction of cyclic imines through imine−borane complexes with chiral sodium triacyloxyborohydrides.[16] During their mechanistic study on the asymmetric reduction, the authors found sodium mono(trifluoroacetoxy)borohydride ($NaBH_3(OCOCF_3)$), prepared in situ from $NaBH_4$ and trifluoroacetic acid, reacted it with γ-picoline in THF to give γ-picoline−borane in moderate yield. It is unlikely that this reaction is mediated via diborane since sodium acyloxyborohydrides ($NaBH_3(OCOR)$) **2** have somewhat different reactivities from diborane.[17] Although this reaction suggests that $NaBH_3(OCOCF_3)$ may also be a useful reagent for the preparation of the target α-Pic-BH_3, the use of

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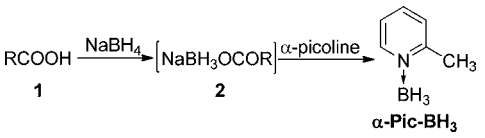
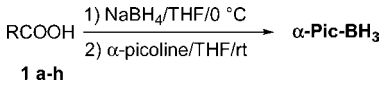
expensive trifluoroacetic acid as a reagent is unfavorable for the practical procedure in process chemistry. Therefore, to avoid the use of trifluoroacetic acid, several kinds of **2** were prepared from inexpensive carboxylic acids **1** and $NaBH_4$, and treated with α-picoline in one-pot to give α-Pic-BH_3 (Scheme 1).

Scheme 1. Practical preparation of α-Pic-BH_3



First, we explored the appropriate carboxylic acid for the one-pot synthesis of α-Pic-BH_3 as illustrated in Scheme 2. In these

Scheme 2. One-pot synthesis of α-Pic-BH_3 from carboxylic acids



experiments, $NaBH_4$ was treated with 1 equiv of carboxylic acids in THF at 0 °C for 1 h, and the resulting $NaBH_3$(OCOR) was reacted with α-picoline at room temperature for 24 h. The results are summarized in Table 1.

Table 1. Reaction of sodium acyloxyborohydrides 2 with α-picoline[a]

run	acid	R	α-Pic-BH_3 (%)[b,c]
1	**1a**	Me	45
2	**1b**	$ClCH_2$	43
3	**1c**	Cl_2CH_2	59
4	**1d**	Cl_3C	59
5	**1e**	Ph	68
6	**1f**	2-chlorophenyl	58
7	**1g**	4-nitrophenyl	61
8	**1h**	3-nitrophenyl	47

[a]All reactions were carried out in the presence of $NaBH_4$ (10 mmol), carboxylic acid (10 mmol), and α-picoline (10 mmol) in THF (10 mL). [b]Isolated yields. [c]Unreacted α-picoline was recovered.

When sodium monoacetoxyborohydride ($NaBH_3OAc$), derived from $NaBH_4$ and acetic acid, one of the most inexpensive carboxylic acids, was treated with α-picoline, the desired α-Pic-BH_3 was obtained in 49% yield along with recovered α-picoline (run 1). In order to enhance the leaving ability of the acyloxy groups from the boron atom, the reactions of the sodium chloroacetoxyborohydrides derived from the chloroacetic acids were examined. However, the expected effects were hardly observed (run 2−4). On the other hand, we found that sodium monobenzoxyborohydride ($NaBH_3OBz$), prepared from benzoic acid and $NaBH_4$ in a similar manner, reacted smoothly with α-picoline to give α-Pic-BH_3 in 68% yield (run 5). The utilization of sodium monoaryloxyborohydrides bearing electron-withdrawing substituents on the aromatic rings, which are expected to enhance the leaving ability of aryloxy groups, unfortunately lowered the yields (run 5−8). In all runs, unreacted α-picoline remained. We found that some of α-Pic-BH_3 was lost during the purification since α-Pic-BH_3 was difficult to be separated from the remaining α-picoline by column chromatography.

Although we did not make the mechanistic study on these reactions in detail, we believed on the basis of the previous study reported by Umino and co-workers[17c] that the reaction pathway through free diborane can be eliminated from the possible mechanism. The authors reported the reduction of amides to amines with $NaBH_3$(OCOR) and proved the reactive species in this reduction are not free diborane by some investigations of externally generated gases from $NaBH_3$(OCOR) and the reducibility of this reaction system.

With the above results in mind, we next investigated in detail the reaction of $NaBH_3OBz$ with α-picoline. We focused on surveying the proper reaction temperature and isolation procedure that shows a high yield without recovering starting materials. (Scheme 3). The results are summarized in Table 2.

Scheme 3. One-pot synthesis of α-Pic-BH_3 from $NaBH_3OBz$

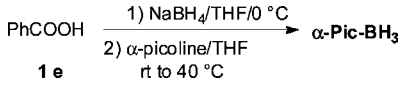


Table 2. Effects of temperature on the reaction of $NaBH_3OBz$ with α-picoline[a]

run	T (°C)	time (h)	α-Pic-BH_3 (%)[b]
1	rt	24	68
2	40	12	81
3[c]	40	5	93

[a]All reactions were carried out in the presence of $NaBH_4$ (10 mmol), benzoic acid (10 mmol), and α-picoline (10 mmol) in THF (10 mL) except run 3. [b]Isolated yields. [c]Carried out the reaction in the presence of $NaBH_4$ (10 mmol), benzoic acid (10 mmol), and α-picoline (10 mmol) in THF (15 mL).

In all runs, except run 3, $NaBH_3OBz$ was prepared at 0 °C in THF from $NaBH_4$ and benzoic acid, and then reacted with α-picoline at varying temperatures. To find mild conditions for the completion of the reaction within 24 h, the reactions around room temperature were examined. Although the unreacted α-picoline was recovered from the reaction conducted at room temperature (run 1), elevating the temperature to 40 °C gave α-Pic-BH_3 in 81% yield within 12 h accompanied by a trace amount of α-picoline (run 2). This reaction was carried out heterogeneously due to the low solubility of $NaBH_3OBz$ in THF. Therefore, we expected that the reaction would be accelerated with the complete dissolution of $NaBH_3OBz$ during the reaction. When $NaBH_4$ was reacted with benzoic acid in THF at 40 °C under a slightly diluted concentration, a clear solution of $NaBH_3OBz$ in THF was obtained. This reagent reacted with α-picoline rapidly and completely within 5 h to give α-Pic-BH_3 in an excellent yield (run 3).

The soundness of this process was demonstrated by its being scalable in large quantities up to a 10 g synthesis of α-Pic-BH_3 without purification by column chromatography as illustrated in Scheme 4. The reaction of $NaBH_3OBz$, prepared from 3.8 g of $NaBH_4$ and 12.2 g of benzoic acid at 40 °C in situ, with 9.3 g of α-picoline at 40 °C for 4.5 h, was followed by the removal of the resulting sodium benzoate by washing with water to give crude α-Pic-BH_3. The crude product was recrystallized from toluene-*n*-heptane (1:1) to give 9.5 g (89%) of α-Pic-BH_3.

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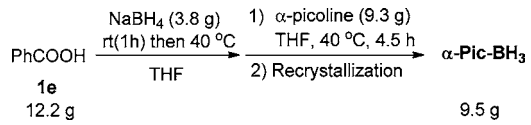
Scheme 4. Ten-gram-scale synthesis of α-Pic-BH_3 from benzoic acid, α-picoline, and $NaBH_4$



During the reaction of $NaBH_3OBz$ and α-picoline, the thermal change of the reaction was hardly observed. Furthermore, we measured differential scanning calorimetry (DSC) of resulting α-Pic-BH_3 in order to evaluate the safety of this reaction around the reaction temperature (Figure 1). As shown in Figure 1, the hazardous exothermal reaction is not observed around 40 °C. Therefore, we believe that this procedure is not only the safe process but also the scalable process to α-Pic-BH_3.

CONCLUSION

In conclusion, we present the practical synthesis of α-Pic-BH_3 from $NaBH_3OBz$, easily prepared from $NaBH_4$ and benzoic acid in situ, and α-picoline in THF under mild conditions. Because of this safe and inexpensive process, we believe that this study will contribute to the aggressive utilization of α-Pic-BH_3 in process chemistry.

EXPERIMENTAL SECTION

Characterization of α-Pic-BH_3. All α-Pic-BH_3 obtained in this study was characterized by high-resolution ^1H NMR (400 or 300 MHz, $CDCl_3$) and ^{13}C NMR (100 or 75 MHz, $CDCl_3$). ^1H and ^{13}C NMR data are consistent with those of an authentic specimen.

General Procedure for Reaction of Acyloxyborohydrides with α-Picoline for Tables 1 and 2. A typical procedure is described for preparation of α-Pic-BH_3 via $NaBH_3OBz$ (run 2, Table 2). A solution of benzoic acid (1.220 g, 10 mmol) in THF (5 mL) was added dropwise to a suspension of $NaBH_4$ (380 mg, 10 mmol) in THF (5 mL) by syringe with stirring at 0 °C under an Ar atmosphere. The reaction mixture was stirred for 1 h at 0 °C and allowed to warm to room temperature. α-Picoline (0.94 mL, 10 mmol) was added to the mixture in one portion, and then the mixture was heated to 40 °C and stirred for 12 h at 40 °C. After being stirred at room temperature, the mixture was cooled to 0 °C and treated with water for 10 min at 0 °C. The mixture was extracted with AcOEt three times, the combined extract was washed with 1 M HCl, sat. aq $NaHCO_3$ and sat. aq NaCl and dried over Na_2SO_4. After removal of Na_2SO_4 by filtration, the filtrate was concentrated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane-AcOEt 10:1−2:1) to give α-Pic-BH_3 (820 mg) as colorless crystals in 81% yield.

Optimized Procedure for Preparation of α-Pic-BH_3 from $NaBH_4$, Benzoic Acid, and α-Picoline in a Small Scale. A solution of benzoic acid (1.220 g, 10 mmol) in THF (7.5 mL) was added dropwise to a suspension of $NaBH_4$ (380 mg, 10 mmol) in THF (7.5 mL) by syringe with stirring at 0 °C under an Ar atmosphere. The reaction mixture was stirred for 1 h at 0 °C and allowed to warm to 40 °C. α-Picoline (930 mg, 10 mmol) was added to the mixture in one portion. After being stirred for 5 h at 40 °C, the mixture was poured on cold water (5 mL). The volatile component (THF) of the mixture was removed in vacuo, and the resulting mixture was extracted with AcOEt (7.5 mL × 2); the combined extracts were washed with 0.5 M aqueous citric acid (2 mL × 2) and 10% aqueous NaCl (2 mL × 2), and dried over Na_2SO_4 (1 g). After removal of Na_2SO_4 by filtration, the filtrate was concentrated in vacuo to give α-Pic-BH_3 (1.000 g) as colorless needles in 94% yield. Further purification of the material was achieved by silica gel column chromatography (SiO_2: 30 g, AcOEt) to give α-Pic-BH_3 (997 mg) as colorless needles in 93% yield.

A 10-g-Scale Synthesis of α-pic-BH_3 from $NaBH_4$, Benzoic Acid, and α-Picoline without Purification by Column Chromatography. A solution of benzoic acid (12.20 g, 0.1 mol) in 75 mL of THF was added dropwise to a suspension of $NaBH_4$ (3.8 g, 0.1 mol) in 75 mL of THF with stirring at 0 °C under a N_2 atomosphere. The reaction mixture was stirred for 1 h at 0 °C, and the resulting $NaBH_3OBz$ was dissolved by warming the mixture to 40 °C. A solution of α-

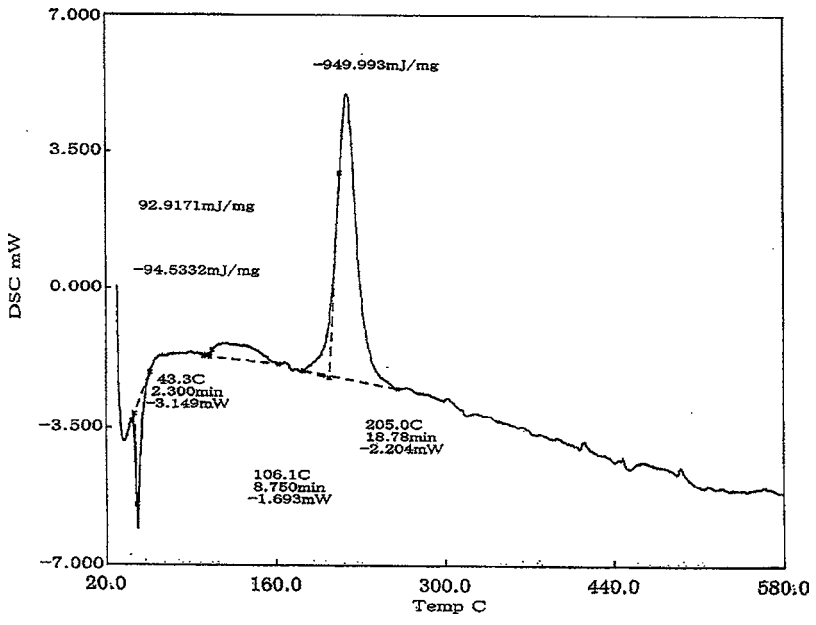


Figure 1. DSC data for α-Pic-BH_3.

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picoline (9.30 g, 0.1 mol) in THF (93 mL) was added to the reaction mixture and stirred for 4.5 h at 40 °C. Water (50 mL) was added to the reaction mixture, and the volatile component (THF) of the mixture was evaporated in vacuo. The residue was extracted with AcOEt (75 mL × 3), and the combined extract was washed with 0.5 M aqueous citric acid (15 mL × 2) and 10% aq NaCl (15 mL × 2) and then dried over $MgSO_4$ (10 g). After removal of $MgSO_4$ by filtration, the solvent was evaporated in vacuo. The residual solid was recrystallized from toluene−*n*-heptane (5 mL/25 mL) to give α-Pic-BH_3 (9.50 g) as colorless needles in 89% yield.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR charts for α-Pic-BH_3. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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