

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

Yasushi Kawase,[†] Takehiro Yamagishi,[†] Teruo Kutsuma,[†] Huo Zhibao,[‡] Yoshinori Yamamoto,[‡] Tomohiro Kimura,[§] Tadashi Nakata,[§] Tadashi Kataoka,^{||} and Tsutomu Yokomatsu^{*,†}

[†]School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

[‡]Department of Chemistry, Graduate School of Chemistry, Tohoku University, Aramaki 6-3, Aoba-ku, Sendai, Miyagi 980-8578, Japan

[§]Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

^{||}Yokohama College of Pharmacy, 601 Matano-cho, Totsuka-ku, Yokohama, Kanagawa 245-0066, Japan

Supporting Information

ABSTRACT: Sodium monobenzyloxyborohydride, 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–BH₃) is one of the most useful reagents for reductive amination.² The application of Pyr–BH₃ to the process chemistry, however, is limited due to its thermal instability and explosive nature.³ As convenient alternatives, picoline–boranes (Pic–BH₃)⁴ and 5-ethyl-2-methylpyridine–borane⁵ 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–BH₃). We have also reported that *N*-benzyl-protected amino acid derivatives were readily prepared by α -Pic–BH₃-mediated reductive alkylation of α -amino acid esters.^{6,7} α -Pic–BH₃ is regarded as a safer reducing reagent than Pyr–BH₃ for the following reasons: (1) Differential scanning calorimetric data reveals that α -Pic–BH₃ has a higher onset temperature than Pyr–BH₃.⁸ (2) The flash point of α -Pic–BH₃ is known to be higher than that of Pyr–BH₃ by closed-cup evaluation.⁹ (3) Furthermore, we confirmed that crystalline α -Pic–BH₃ 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–BH₃ 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 (BH₃–L), such as BH₃–THF and BH₃–dimethylsulfide, prepared in situ.^{11,12} (2) Reaction of amine hydrochlorides and NaBH₄.^{13,14} (3) Reaction of NaBH₄ 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 NaBH₄ and amine hydrochlorides have less solubility in general organic solvents, a large amount of solvents is required. (3) Cation-exchange resins are expensive.

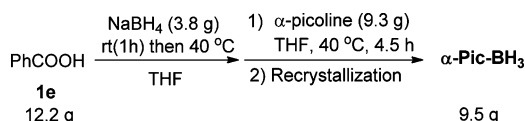
In general, nonhazardous processes achieved under mild conditions using inexpensive raw materials are ideal for process chemistry. Therefore, if α -Pic–BH₃ can be prepared from NaBH₄ and α -picoline without using diborane or borane complexes around room temperature in a limited amount of organic solvent, 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–BH₃.

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 (NaBH₃(OCOCF₃)), prepared in situ from NaBH₄ 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 (NaBH₃(OCOR)) **2** have somewhat different reactivities from diborane.¹⁷ Although this reaction suggests that NaBH₃(OCOCF₃) may also be a useful reagent for the preparation of the target α -Pic–BH₃, the use of

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Scheme 4. Ten-gram-scale synthesis of α -Pic-BH₃ from benzoic acid, α -picoline, and NaBH₄



During the reaction of NaBH₃OBz and α -picoline, the thermal change of the reaction was hardly observed. Furthermore, we measured differential scanning calorimetry (DSC) of resulting α -Pic-BH₃ 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-BH₃.

CONCLUSION

In conclusion, we present the practical synthesis of α -Pic-BH₃ from NaBH₃OBz, easily prepared from NaBH₄ 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-BH₃ in process chemistry.

EXPERIMENTAL SECTION

Characterization of α -Pic-BH₃. All α -Pic-BH₃ obtained in this study was characterized by high-resolution ¹H NMR (400 or 300 MHz, CDCl₃) and ¹³C NMR (100 or 75 MHz, CDCl₃). ¹H and ¹³C 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-BH₃ via NaBH₃OBz (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 NaBH₄ (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 NaHCO₃ and sat. aq NaCl and dried over Na₂SO₄. After removal of Na₂SO₄ 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-BH₃ (820 mg) as colorless crystals in 81% yield.

Optimized Procedure for Preparation of α -Pic-BH₃ from NaBH₄, 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 NaBH₄ (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 \times 2); the combined extracts were washed with 0.5 M aqueous citric acid (2 mL \times 2) and 10% aqueous NaCl (2 mL \times 2), and dried over Na₂SO₄ (1 g). After removal of Na₂SO₄ by filtration, the filtrate was concentrated in vacuo to give α -Pic-BH₃ (1.000 g) as colorless needles in 94% yield. Further purification of the material was achieved by silica gel column chromatography (SiO₂: 30 g, AcOEt) to give α -Pic-BH₃ (997 mg) as colorless needles in 93% yield.

A 10-g-Scale Synthesis of α -pic-BH₃ from NaBH₄, 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 NaBH₄ (3.8 g, 0.1 mol) in 75 mL of THF with stirring at 0 °C under a N₂ atmosphere. The reaction mixture was stirred for 1 h at 0 °C, and the resulting NaBH₃OBz was dissolved by warming the mixture to 40 °C. A solution of α -

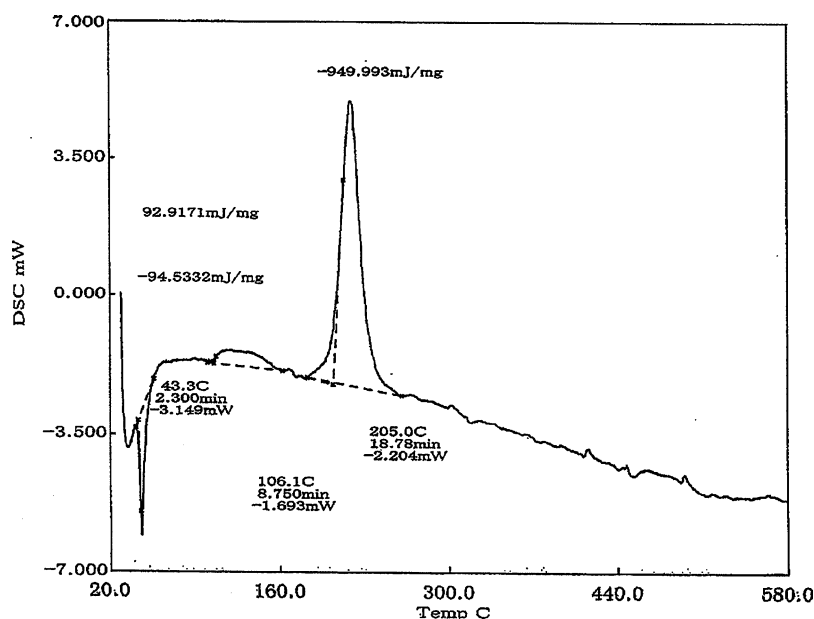


Figure 1. DSC data for α -Pic-BH₃.

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 \times 3), and the combined extract was washed with 0.5 M aqueous citric acid (15 mL \times 2) and 10% aq NaCl (15 mL \times 2) and then dried over MgSO₄ (10 g). After removal of MgSO₄ 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-BH₃ (9.50 g) as colorless needles in 89% yield.

■ ASSOCIATED CONTENT

● Supporting Information

NMR charts for α -Pic-BH₃. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

yokomatu@toyaku.ac.jp

Notes

The authors declare no competing financial interest.

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