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ONE-POT SYNTHESIS OF ALKOXYAMINE DERIVATIVES BY REDUCTIVE ALKOXYAMINATION WITH A 2-PICOLINE-BORANE COMPLEX

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Abstract – Reduction of oxime ethers with a 2-picoline-borane complex was examined to give alkoxyamine derivatives. The reduction was found to proceed in the presence of aqueous HCl in MeOH–AcOH. The method was extended to one-pot synthesis of alkoxyamine derivatives from aldehydes and ketones. The reaction of carbonyl compounds with alkoxyamines in MeOH–AcOH (10:1), followed by sequential treatment with 2-picoline-borane and 3M HCl afforded alkoxyamine derivatives in good yields. This procedure can be applied to the synthesis of various alkoxyamine derivatives from aliphatic/aromatic aldehydes and ketones.

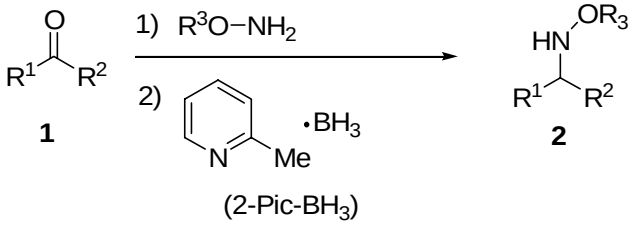
INTRODUCTION

Reductive amination is one of the most effective methods for the introduction of an amino functionality into a molecule.[1] Various kinds of reducing agents for reductive amination have been developed. For example, sodium cyanoborohydride ($NaBH_3CN$),[2] sodium triacetoxyborohydride ($NaBH(OAc)_3$),[3] $Zn(BH_4)_2$-silica gel,[4] and $NaBH_4$-Ti(O*i*-Pr)$_4$[5] are widely used for reductive amination. However, these reducing agents have some disadvantages from the viewpoint of process chemistry. The use of $NaBH_3CN$ on large scale should be achieved with great care due to its high toxicity. $NaBH(OAc)_3$ has been developed as an alternative reagent of $NaBH_3CN$. The reaction with $NaBH(OAc)_3$, however, has to

be carried out in aprotic polar solvents or halogenated hydrocarbon solvents, which have environmental problems, due to their inducing high chemo-selectivity of the reduction and the instability of the reagent in protic solvents.[3] In addition, reduction with this reagent is somewhat inefficient because it possesses only one hydrogen atom for reduction in a molecule. Some of the heterocyclic compound-borane complexes, which overcome these problems mentioned above,[6b,c] are also effective reducing agents for reductive amination. For example, successful reductive aminations with pyridine-borane (Pyr-BH_3) have been developed and applied to the organic syntheses.[6] However, it has been reported that thermally unstable Pyr-BH_3 decomposes above 54 ^oC and explodes under thermal condition.[7] Furthermore, its shelf life is relatively short (6 months). On the other hand, 2-picoline-borane (2-Pic-BH_3) had much attention paid to it as a new type of the reducing reagent for reductive amination, because it is a thermally stable crystalline powder and can be stored for a long period. Kikugawa et al. reported the reductive amination of carbonyl compounds with 2-Pic-BH_3,[8] although the scope and limitation of these reactions with this reagent have not been studied in details. Very recently, Burlhardt et al. reported the reductive amination with 5-ethyl-2-methylpyridine-borane complex as a replacement for Pyr-BH_3 or 2-Pic-BH_3.[9]

Alkoxyamine derivatives, which can be synthesized by reductive alkoxyamination of carbonyl compounds, are efficient tools for the synthesis of amine-contained compounds on solid support, because amino-functionalized materials can be readily released by cleavage of the N-O bond under mild conditions.[10c] Thus, the development of new simple methods for the synthesis of alkoxyamines is required in the field of combinatorial chemistry.

In this paper we wish to report on the reduction of oxime ethers with 2-Pic-BH_3, along with the one-pot synthesis of alkoxyamine derivatives **2** through reductive alkoxyamination from carbonyl compounds **1** with 2-Pic-BH_3 (Scheme 1).[10, 11]

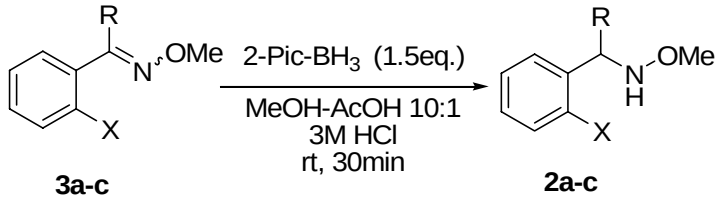


Scheme 1. Synthesis of alkoxyamines by reductive alkoxyamination via oxime ethers

RESULTS AND DISCUSSION

First, we studied the reduction of oxime ether **3a** (X=H, R=H), derived from benzaldehyde and methoxyamine, with 2-Pic-BH_3 (Table 1). Kikugawa et al. carried out the reductive amination of carbonyl compounds with 2-Pic-BH_3 in MeOH–AcOH (10:1).[8] For our preliminary study, we examined the reduction of the oxime ether under Kikugawa's conditions. However, no reduction took place on

treatment of the oxime ether with 1.5eq of 2-Pic-BH_3 even in refluxing MeOH–AcOH. We were pleased to find that the reduction began to proceed upon addition of 3M HCl (1 equiv.) to the mixture. Under the conditions, methoxyamine derivative **2a** was produced in 41% yield along with 37% yield of recovered corresponding oxime ether after 0.5 h (entry 1). This observation means that aqueous HCl is crucial to this reaction. To optimize the reaction condition, we investigated the effect of amounts of 3M-HCl on the reduction of two varieties of the substrates derived from benzaldehyde and 2-bromobenzaldehyde which differ in the electronic nature of aromatic rings. The results are summarized in Table 1.



3a-c **2a-c**

Table 1. Reduction of oxime ethers **3** to alkoxyamines **2**

Entry	X	R	3M HCl (equiv.)	Yield of **2**[a] (%)	Recovered **3**[b] (%)
1	H	H	1	**2a** (41)	37
2	H	H	2	**2a** (71)	6[c]
3	H	H	3	**2a** (76)	1
4	H	H	5	**2a** (75)	0
5	Br	H	3	**2b** (76)	15
6	Br	H	5	**2b** (85)	10
7	H	Me	5	**2c** (78)	13

[a] Isolated yields. [b] Isolated yields unless noted. [c] Determined by ^{1}H-NMR of crude product.

In the reduction of oxime ether **3a** (X=H, R=H) derived from benzaldehyde, more than 2eq of 3M HCl was required for the smooth reaction (entry 1 vs. entries 2-4) and we found that using 3–5eq of 3M HCl gave a maximum yield (entries 3 and 4). As for the reduction of oxime ether **3b** (X=Br, R=H) derived from 2-bromobenzaldehyde, 5 eq of 3M HCl obviously gave the better yield than 3eq of 3M HCl (entry 5 vs. entry 6). Therefore, we concluded that the reaction with 1.5eq of 2-Pic-BH_3 in MeOH-AcOH (10:1), followed by the addition of 5 eq of 3M HCl was the optimal condition for the reduction of general oxime ethers.[11] The reduction of oxime ether **3c** (X=H, R=Me) derived from an aromatic ketone also gave the corresponding alkoxyamine **2c** in good yield under this condition (entry 7).

Based on above results, we next studied the one-pot synthesis of alkoxyamine derivatives through 2-Pic-BH_3-mediated reductive alkoxyamination of carbonyl compounds (Table 2). Benzaldehyde (**1a**: R^1=Ph, R^2=H) was treated with methoxyamine (**4**: R^3=Me) in MeOH-AcOH (10:1) at room temperature for 2h, followed by the addition of 1.5eq of 2-Pic-BH_3 in the presence of 5eq of 3M HCl at room temperature (entry 1). After being stirred for 0.5h, methoxyamine derivative **2a** was isolated in 79% yield

without recovering the corresponding oxime ether. This method was applied to the alkoxyamination of various carbonyl compounds. Representative results are summarized in Table 2.

Table 2. 2-Picoline borane-mediated reductive alkoxyamination of carbonyl compounds **1** with alkoxyamine **4**

Entry	R^1	R^2	R^3	Product	Yield %[a]
1	C_6H_5	H	Me	**2a**	79
2	2-Br-C_6H_4	H	Me	**2b**	84 [b]
3	C_6H_5	Me	Me	**2c**	68[c]
4	3-Br-C_6H_4	H	Me	**2d**	81[d]
5	4-MeO-C_6H_4	H	Me	**2e**	92
6	cyclohexyl	H	Bn	**2f**	94
7	*n*-pentyl	H	Bn	**2g**	88
8	*n*-pentyl	Me	Bn	**2h**	90
9	*n*-Pr	*n*-Pr	Bn	**2i**	87
10	cyclohexyl	Me	Bn	**2j**	98
11	$-(CH_2)_2$-O-$(CH_2)_2-$		Bn	**2k**	93

[a] Isolated yields after purification by silica gel column chromatography. [b] The corresponding oxime ether was recovered (9%). [c] The corresponding oxime ether was recovered (13%). [d] The corresponding oxime ether was recovered (6%).

In this method, aromatic aldehydes bearing an electron-withdrawing group (entries 2 and 4) or an electron-donating group (entry 5), and aliphatic aldehydes/ketones (entries 6-11) including a cyclic ketone (entry 11) could be converted into the corresponding alkoxyamine derivatives **2b-k** in good to excellent yields. The one-pot reductive alkoxyamination of acetophenone with methoxyamine gave the corresponding alkoxyamine **2c** in 68% yield (entry 3), although the yield was somewhat lower compared with that of the direct reduction of oxime ether **3c** (see Table 1).

In conclusion, the synthesis of alkoxyamine derivatives via one-pot reductive alkoxyamination with 2-Pic-BH_3 was achieved. Because of the simplicity and good yields, the method presented in this paper is very useful for the synthesis of alkoxyamine derivatives. Further application of this method is now being investigated in our laboratories.

EXPERIMENTAL

^{1}H and ^{13}C-NMR were taken at 400 MHz and 100 MHz, respectively. The chemical shifts were reported in ppm relative to $CHCl_3$ (7.26 ppm) for ^{1}H-NMR and relative to the central resonance of $CDCl_3$ (77.00

ppm) for ^{13}C-NMR.

***N*-Benzyl-*O*-methylhydroxylamine (2a)**

Et_3N (0.26 mL,1.88 mmol) was added to a solution of methoxyamine hydrochloride (157 mg, 1.88 mmol) in 2.5 mL of MeOH at 0 °C and the mixture was stirred for 10 min at the same temperature. A solution of benzaldehyde (199.5 mg, 1.88 mmol) in 2.5 mL of MeOH and 0.5 mL of AcOH was added to the mixture at 0 °C. After stirring for 2 h at rt, 2-Pic-BH_3 (302 mg, 2.82 mmol) was added to the reaction mixture at 0 °C and the mixture was stirred for 5 min at the same temperature. After the addition of 3 M HCl (3.13 mL, 9.4mmol) at 0 °C, the mixture was stirred for 0.5 h at ambient temperature. After cooling to 0 °C, aq.Na_2CO_3 (2.5 g/10 mL) was carefully added to the mixture at 0 °C and the mixture was extracted with AcOEt(x3). The combined extracts were washed with brine and dried over $MgSO_4$. After the removal of $MgSO_4$ by filtration, the solvent was evaporated in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane:AcOEt=20:1) to give 202.9 mg of **2a** (79 % yield) as a colorless oil. IR (neat) 3258, 2937, 1494, 1454 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (5H, m), 5.71 (1H, br s), 3.99 (2H, s), 3.47 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.5, 128.6, 128.2, 127.2, 61.5, 55.9. MS (ESI) m/z: 138 $[M+H]^+$. HRMS (ESI) m/z:138.0938 $[M+H]^+$ Calcd for $C_8H_{12}NO$: 138.0919.

Alkoxyamines (2b-2k) were synthesized in a similar way as described for **2a**.

***N*-(2-Bromobenzyl)-*O*-methylhydroxylamine (2b)**

^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.7, 132.8, 131.2, 129.1, 127.4, 124.1, 61.6, 55.8. Other spectral data (^{1}H-NMR and IR) were identical with the data on this compound in reference 10c.

***O*-Methyl-*N*-(1-phenylethyl)hydroxylamine (2c)**

Colorless oil; IR (neat) 3247, 2976, 2937, 1493, 1453 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (5H, m), 4.14 (1H, q, *J*=6.7 Hz), 3.48 (3H, s), 1.37 (3H, d, *J*=6.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.8, 128.4, 127.4, 127.0, 62.4, 60.4, 19.8. MS (ESI) m/z: 152 $[M+H]^+$. HRMS (ESI) m/z:152.1082 $[M+H]^+$ Calcd for $C_9H_{14}NO$: 152.1075.

***N*-(3-Bromobenzyl)-*O*-methylhydroxylamine (2d)**

Colorless oil; IR (neat) 3257, 2937, 1471 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.53–7.18 (4H, m), 4.01 (2H, s), 3.50 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.2, 131.7, 130.4, 129.9, 127.3, 122.4, 55.5. MS (ESI) m/z: 216 $[M+H]^+$. HRMS (ESI) m/z:216.0017 $[M+H]^+$ Calcd for $C_9H_{14}NO$: 216.0024.

***N*-(4-Methoxybenzyl)-*O*-methylhydroxylamine (2e)**

Colorless oil; IR (neat) 3259, 2937, 1512, 1464 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.22 (2H, d, *J*=8.6 Hz), 6.83 (2H, d, *J*=8.6 Hz), 5.67 (1H, br s), 3.93 (2H, s), 3.60 (3H, s), 3.46 (3H, s). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 158.7, 129.8, 129.4, 113.5, 61.3, 55.2, 54.8. MS (ESI) m/z: 168 $[M+H]^+$. HRMS (ESI) m/z:168.1019 $[M+H]^+$ Calcd for $C_9H_{14}NO_2$: 168.1025.

***O*-Benzyl-*N*-cyclohexylhydroxylamine (2f)**

Colorless oil; IR (neat) 3266, 2922, 2851, 1495, 1450 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.29 (5H,m), 5.60 (1H, br s), 4.69 (2H, s), 2.77 (2H, d, *J*=6.7Hz), 1.76-1.55 (6H, m), 1.26-0.88 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.1, 128.34, 128.30, 127.7, 76.0, 58.7, 35.4, 31.4 (2 carbons), 26.6, 26.0 (2 carbons). MS (ESI) m/z: 220 $[M+H]^+$. HRMS (ESI) m/z:220.1692 $[M+H]^+$ Calcd for $C_{14}H_{22}NO$: 220.1701.

***O*-Benzyl-*N*-hexylhydroxylamine (2g)**

Colorless oil; IR (neat) 3262, 2929, 2857, 1495, 1455 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33–7.22 (5H, m), 5.49 (1H, br s), 4.67 (2H, s), 2.87 (2H, t, *J*=7.1 Hz), 1.48–1.43 (2H, m), 1.32-1.23 (6H, m), 0.88 (3H, t, *J*=6.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.0, 128.04, 128.00, 127.4, 75.9, 51.9, 31.5, 27.1, 26.6, 22.3, 13.8. MS (ESI) m/z: 208 $[M+H]^+$. HRMS (ESI) m/z:208.1697 $[M+H]^+$ Calcd for $C_{13}H_{22}NO$: 208.1701

***O*-Benzyl-*N*-(1-methylhexyl)hydroxylamine (2h)**

Colorless oil; IR (neat) 3251, 2957, 2929, 2857, 1495 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.35–7.24 (5H, m), 5.37 (1H, br s), 4.69 (2H, s), 3.02-2.98 (1H, m), 1.50–1.23 (8H, m), 1.06 (3H, d, *J*=6.3 Hz), 0.88 (3H, t, *J*=7.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.0, 128.20, 128.18, 127.5, 76.6, 56.0, 33.9, 31.9, 25.5, 22.5, 18.1, 13.9. MS (ESI) m/z: 222 $[M+H]^+$. HRMS (ESI) m/z:222.1845 [M+H]+ Calcd for $C_{14}H_{24}NO$: 222.1858.

***O*-Benzyl-*N*-(1-propylbutyl)hydroxylamine (2i)**

Colorless oil; IR (neat) 3255, 2957, 2931, 2870, 1495 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33–7.21 (5H, m), 5.42 (1H, br s), 4.67 (2H, s), 2.86–2.82 (1H, m), 1.46-1.31 (8H, m), 0.89 (6H, t, *J*=7.1Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.1, 128.12, 128.05, 127.4, 76.3, 59.9, 34.1 (2 carbons), 18.9 (2 carbons), 14.1 (2 carbons). MS (ESI) m/z: 222 $[M+H]^+$. HRMS (ESI) m/z:222.1860 $[M+H]^+$ Calcd for $C_{14}H_{24}NO$: 222.1858.

_O_-Benzyl-_N_-(1-cyclohexylethyl)hydroxylamine (2j)

Colorless oil; IR (neat) 3244, 2924, 2852, 1495, 1450 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (5H, m), 5.43 (1H, br s), 4.68 (2H, s), 2.88-2.83 (1H, m), 1.85–1.67 (5H, m), 1.46-1.43 (1H, m), 1.25–1.10(3H, m), 1.02–0.95 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.1, 128.2, 128.1, 127.5, 76.4, 50.4, 40.1, 29.8, 27.9, 26.6, 26.4, 26.3, 14.5. MS (ESI) m/z: 234 $[M+H]^+$. HRMS (ESI) m/z:234.1839 $[M+H]^+$ Calcd for $C_{15}H_{24}NO$: 234.1858.

_O_-Benzyl-_N_-tetrahydro-2_H_-pyran-4-ylhydroxylamine (2k)

Colorless oil; IR (neat) 3246, 2952, 2848, 1495, 1453 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (5H, m), 4.71 (2H, s), 3.97 (2H, ddd, *J*=3.6, 3.6, 11.2 Hz), 3.41 (2H, ddd, *J*=2.3, 11.2, 11.2 Hz), 3.15–3.09 (1H, m), 1.84–1.80 (2H, m), 1.51–1.41 (2H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.8, 128.3 (4 carbons), 127.8, 76.8, 66.3 (2 carbons), 56.4, 30.8 (2 carbons). MS (ESI) m/z: 208 $[M+H]^+$. HRMS (ESI) m/z:208.1318 $[M+H]^+$ Calcd for $C_{12}H_{18}NO_2$: 208.1338.

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11. 2-Pic-BH_3 is available from Junsei Chemical Co., Ltd. (TEL.:+81-48-986-6161; FAX.:+81-48-989-2787)