A facile N-monoalkylation of aminopyridines

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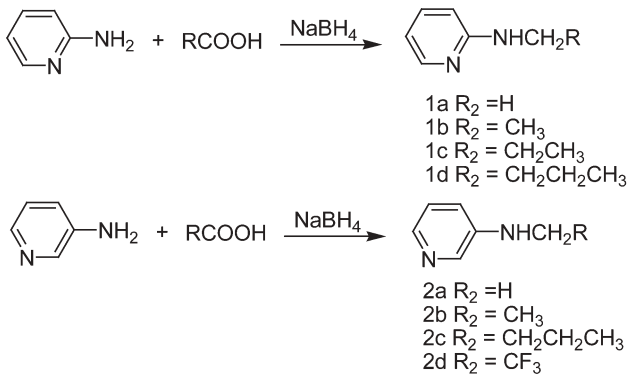
The N-monoalkylation of 2- or 3-aminopyridines by a carboxylic acid and sodium borohydride afforded the corresponding alkylaminopyridine under mild conditions in good yields. N-Alkylaminopyridines are important intermediate for preparing N-containing heterocycles, such as "flytrap" aminopyridinium-based anion hosts and pharmaceuticals.

Keywords: N-monoalkylation, aminopyridines, sodium borohydride, carboxylic acids, flytrap aminopyridinium-based anion hosts

N-Alkylaminopyridines are important intermediates for preparing N-containing heterocycles,[1] such as "flytrap" aminopyridinium-based anion hosts[2] and various pharmaceuticals.[3] However, the conventional direct method for the N-alkylation of amino-compounds using an alkyl halide is inefficient for the N-alkylation of aminopyridines and gives poor yields.[1,4,5] It has been reported that N-methyl-3-aminopyridine was prepared in only 17% yield by treating 3-aminopyridine with iodomethane in the presence of LDA, because alkylation on the nitrogen atom of pyridine was much faster than that on the amino group.[5] Recently, N-alkylaminopyridines have been synthesised in better yield with sodium borohydride ($NaBH_4$) and the appropriate aldehydes.[6–8] Although the product could be obtained by this route, some aldehydes are gases or difficult to prepare and limit the application of this method. This led us to explore an alternativee route.

We report here a facile alkylation of a variety of aminopyridines with $NaBH_4$ and carboxylic acids. The reaction proceeds smoothly under very mild conditions to afford the corresponding alkylaminopyridine in good yields. Note that this reaction is chemoselective and gives monoalkylation of primary amines.

Typically, $NaBH_4$ was added slowly to a mixture of the aminopyridine and carboxylic acid in THF (Table 1) over 0.5 h. The mixture was stirred for 0.5 to 2 h and the progress of the reaction was monitored by GC-MS. The product was obtained after the usual work-up. This alkylation procedure is simple and practical, and the utility of this reaction could be extended to 2-aminopyridine, 3-aminopyridine and with carboxylic acids such as formic, acetic, propanoic, butanoic and trifluoroacetic acid. The alkylation of 3-aminopyridine was carried out more rapidly and gave higher yields compared with that of 2-aminopyridine. For the acetic, propanoic and butanoic acid systems, the alkylaminopyridines were obtained in high yields at 40–50 °C. However, formic and trifluoroacetic acid (stronger acids) gave the alkylaminopyridines in only moderate yields at 15–20 °C due to their higher reactivity resulting in the formation of N,N-dialkylaminopyridine. In following the progress of reactions, the N,N-dialkylaminopyridine and the formation of acylamides at low temperatures could be identified by GC-MS. We assume that the mechanism was: (1) the carboxylic acid and amine reacts to give the acylamide; (2) hydride reduction of the acylamide then gives the corresponding alkylamine. At higher temperature, N,N-dialkylaminopyridines were obtained readily as a byproduct, resulting in lower yields. The structures of final products were identified by ^1H NMR and GC-MS.



Scheme 1 N-Alkylation of aminopyridine.

In conclusion, we have developed a straightforward and convenient method for the synthesis of N-monoalkylated aminopyridines under mild condition with sodium borohydride and carboxylic acid. They are easy to handle, more efficient and afford products in good yields.

Experimental

Melting points were obtained on Büchi B540 apparatus and uncorrected. ^1H NMR spectra were recorded on a Bruker AV-400 (400 MHz) spectrometer with TMS as an internal reference, and $CDCl_3$ was used as the solvent. IR spectra were measured on a Nicolet FT-IR-20SX instrument in potassium bromide (KBr) disks. GC-MS were recorded on a Micromass GCT CA055 at an ionising potential of 70 eV. All chemicals or reagents were purchased from standard commercial supplies.

N-alkylation of 2 or 3-aminopyridines with sodium borohydride - typical procedure sodium borohydride (10 mmol) was added to a stirring mixture of aminopyridine (3 mmol) and carboxylic acid (6 mmol) in THF (10 mL) within 0.5 h. On completion of the reaction (monitored by GC), 30 mL of water was added, and the pH was adjusted to 10 with sodium carbonate. The mixture was extracted with

Table 1 Reaction of aminopyridine with $NaBH_4$-RCOOH

Entry	R	Yield /%	Temp /°C	M.p. /°C Obs.	M.p. /°C Lit.	MS *m/z* (M^+)
1a	H	65	15–20	Liquid	Liquid[9]	108
1b	CH_3	89	40–50	Liquid	Liquid[9]	122
1c	CH_2CH_3	86	40–50	Liquid	Liquid[9]	136
1d	$CH_2CH_2CH_3$	85	40–50	41–43	42[10]	150
2a	H	59	15–20	Liquid	Liquid[11]	108
2b	CH_3	83	40–50	Liquid	liquid[9]	122
2c	$CH_2CH_2CH_3$	80	40–50	Liquid	Liquid[12]	150
2d	CF_3	55	15–20	71–72	73.8[13]	176

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diethyl ether, and the combined extracts were dried over $MgSO_4$, and evaporated under vacuum. The crude oil was purified by flash chromatography to give the alkylated derivatives of aminopyridines. The work-up procedures were similar to those indicated in Table 1.

2-(Methylamino)pyridine (**1a**): Colourless liquid. IR (neat): 3267, 3042, 2945, 1604, 1520, 1411, 1330, 1289 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ: 8.08 (ddd, 1H, J = 5.1, 2.0, 0.8 Hz), 7.42 (ddd, 1H, J = 8.4, 7.1, 2.0 Hz), 6.57 (ddd, 1H, J = 7.1, 5.0, 0.8 Hz), 6.37 (ddd, 1H, J = 8.4, 0.8, 0.8 Hz), 4.64 (br s, 1H), 2.91 (d, 3H, J = 5.1 Hz).

3-(Methylamino)pyridine (**2a**): A pale yellow liquid. IR (neat): 3250, 3041, 2965, 1611, 1520, 1350, 1300 cm^{-1}; ^1H NMR δ: 8.02 (1H, d, J = 2.9 Hz), 7.95 (1H,dd, J = 4.7, 1.3 Hz), 7.09 (dd, 1H, J = 8.3, 4.7 Hz), 6.86 (ddd, 1H, J = 8.2, 2.9, 1.3 Hz), 3.79 (br s, 1H), 2.85 (d, 3H, J = 5.1 Hz).

We thank the National Science Foundation China Program (grant 20902037), and the Promotive Research Fund for Excellent Young and Middle-aged Scientists of Shandong Province (grant BS2010NY001).

Received 12 September 2011; accepted 11 October 2011
Paper 1100887 doi: 10.3184/174751911X13190991845013
Published online: 22 November 2011

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