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Nucleophilic β-amination of pyridine nuclei

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Abstract—3-Bromo-4-nitropyridine *N*-oxide behaves as a useful substrate for causing nucleophilic substitution at the β-position (3-position) with amines to afford 3-aminopyridine derivatives.

The pyridine nuclei is one of the fundamental skeletons which composes a partial structure of functional materials such as medicine, agricultural chemicals and dyes. In spite of the importance, functionalized pyridines are not easily prepared compared with functionalized π-electron sufficient heterocyclic compounds. Functionalized pyridines are generally synthesized by nucleophilic[1] and electrophilic substitutions,[2] transition metal catalyzed coupling reaction,[3] construction of pyridine ring[4] and ring transformation.[5] Although numerous preparative methods for pyridine derivatives have been developed, nucleophilic functionalization at the β-position (3-position) is rarely seen in organic syntheses because of low electrophilicity at this position.[6] 2-Nitro-3-halopyridines are known to cause the nucleophilic substitution at the 3-position, however the substitution at the 2-position occurs competitively.[7] If the nucleophilic β-functionalization is easily performed, this protocol will provide a new class of pyridine derivatives. In the present Letter, we would like to demonstrate a methodology of nucleophilic β-amination of the pyridine ring.

3-Bromo-4-nitropyridine *N*-oxide (**1**) is a suitable structure for the present purpose on the basis of three structural features as shown below. (1) The 3-bromo group behaves as a good leaving group. (2) The 4-nitro group diminishes the electron density at the vicinal position. (3) The substrate **1** is easily prepared by *N*-oxidation of commercially available 3-bromopyridine followed by nitration at the 4-position. Indeed, we have reported that *N*-oxide **1** is substituted by enolates at the β-position.[8] The β-amination based on the similar concept has been reported, in which 3-fluoro-4-nitropyridine *N*-oxide[9,10] and 3-bromo-4-nitroquinoline *N*-oxide are used.[11] In the former case, starting 3-fluoropyridine is more expensive than 3-bromopyridine, which diminishes synthetic utility of this reaction. In the latter case, the regioselectivity is sometimes lost and leading to 4-aminated quinoline derivatives when sterically hindered amines were employed. From this viewpoint, we studied the β-amination of the pyridine ring by use of *N*-oxide **1**.

In the present substitution, addition of base was considered to be necessary since generated hydrogen bromide might prevent the reaction by forming ammonium salt with amine. To a solution of the substrate **1** (1 mmol) in ethanol (10 mL) in the presence of sodium carbonate (5 mmol), propylamine **2a** (2 mmol) was added, and the resultant mixture was heated at 60 °C for 1 h. After removal of the solvent, the residue was treated with column chromatography on silica gel to afford 4-nitro-3-propylaminopyridine *N*-oxide (**3a**)[12] in 32% yield (Table 1, run 1). Several solvents were examined, however all of the reaction mixtures were somewhat complicated with unidentified by-products (runs 1–5). This problem was solved when sodium carbonate was not employed (runs 6–8). THF was found to be the most suitable solvent for the present reaction because no by-product was detectable, and the yield of **3a** was improved up to 99% by prolonging the reaction time (run 9). On the other hand, only 41% of aminopyridine **3b** was obtained in the reaction of **1** with isopropylamine **2b** under the same conditions which were optimized for propylamine **2a** (run 10). Although aminopyridine **3b** was formed in higher yields in the reactions in the presence of base, the reaction mixtures were also complicated (runs 11 and 12). The use of

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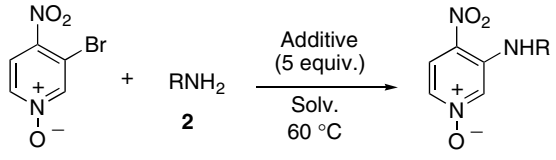
Table 1. Optimization of reaction conditions



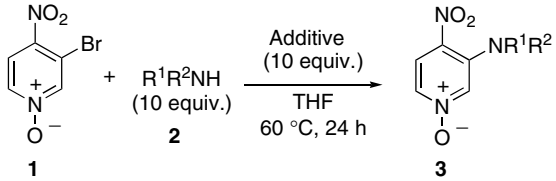
Run	R (equiv)	Solv.	Additive	Time (h)	Yield (%)
1	Pr (2)	EtOH	Na_2CO_3	1	32
2	Pr (2)	MeCN	Na_2CO_3	1	41
3	Pr (2)	Pyridine	Na_2CO_3	1	51
4	Pr (2)	AcOEt	Na_2CO_3	1	52
5	Pr (2)	THF	Na_2CO_3	1	59
6	Pr (2)	EtOH	—	1	28
7	Pr (2)	Pyridine	—	1	33
8	Pr (2)	THF	—	1	36[a]
9	Pr (2)	THF	—	24	99
10	*i*-Pr (2)	THF	—	24	41
11	*i*-Pr (2)	THF	NEt_3[b]	24	55
12	*i*-Pr (2)	THF	Na_2CO_3	24	54
13	*i*-Pr (5)	THF	—	24	62
14	*i*-Pr (10)	THF	—	24	77

[a] 62% of **1** was recovered.
[b] 1 equiv of NEt_3 was used.

larger amount of **2b** was rather effective for improving the yield of **3b** in one day (runs 13 and 14).

The present reaction was applicable to other amines **2c**–**m** to afford corresponding aminated pyridines **3c**–**m** as shown in Table 2. Sterically hindered *tert*-butylamino group was introduced under the same conditions giving **3c** in a moderate yield (run 1). Arylamination was also possible in cases of aniline **2d** and *p*-anisidine **2f** though triethylamine should be added (runs 2–4). *N*-Oxide **1** similarly reacted with secondary amines, diethylamine **2g** and pyrrolidine **2h**, to afford **3g** and **3h** in high yields (runs 5 and 6).

Table 2. Reactions of **1** with other amines **2c**–**m**



Run	R^1	R^2		Additive	Yield (%)
1	*t*-Bu	H	**c**	—	43
2	Ph	H	**d**	NEt_3	25
3	*p*-$NO_2C_6H_4$	H	**e**	NEt_3	0
4	*p*-$MeOC_6H_4$	H	**f**	NEt_3	55
5	Et	Et	**g**	—	84
6	–$(CH_2)_4$–		**h**	—	90
7	$(CH_2)_2NH_2$	H	**i**	—	89[a]
8	$(CH_2)_3NH_2$	H	**j**	—	70[a]
9	$(CH_2)_2OH$	H	**k**	—	28
10	CH_2COOEt	H	**l**	NEt_3	46
11	CH_2COOEt	H	**l**	NEt_3	57[b]
12	$CH(Pr^i)COOMe$	H	**m**	NEt_3	14[b]

[a] 1 equiv of amine was used.
[b] Reaction time 48 h.

Further functionalization could be also performed by use of amines having an additional functional group (runs 7–12). The substitution with diamines **2i** and **2j** effectively proceeded even though only equimolar diamine was employed without any modification of another amino group. A hydroxy and an ester functions were also introduced to the amino group by using amino alcohol **2k** and amino acid derivatives **2l** and **2m**, respectively.

Recently, Yao et al. carried out the reaction of 3-bromo-4-nitropyridine with piperazines.[13] They isolated three kinds of substituted pyridines, small amounts of 3-aminated 4-nitropyridine and 4-aminated 3-bromopyridine in addition to major product, 4-aminated 3-nitropyridine, whose nitro group was migrated from the vicinal position. To the contrary, *N*-oxide **1** underwent the nucleophilic β-amination regioselectively upon treatment with primary or secondary amines **2**. On the basis of these different reactivities, it is considered that the electron-donating *N*-oxide increases the electron density at the α- (2-) and the γ- (4-) positions to realize the regioselective amination at the β- (3-) position. In conclusion, *N*-oxide **1** is demonstrated to be a useful precursor for 3-aminopyridine derivatives.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.102.

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12. Spectral data for **3a**. Orange plates; mp 133–134 °C; IR (KBr) 3363, 1579, 1342, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, $J = 7.3$ Hz, 3H), 1.79 (tq, $J = 7.3$, 7.3 Hz, 2H), 3.24 (dt, $J = 7.3$, 5.4 Hz, 2H), 7.48 (dd, $J = 7.3$, 1.7 Hz, 1H), 7.88–7.95 (br, 1H), 7.99 (d, $J = 1.7$ Hz, 1H), 8.04 (d, $J = 7.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 21.9, 44.9, 122.4, 125.9, 126.0, 127.5, 142.3; MS (FAB) 198 (M^++1, 100%). Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31. Found: C, 49.13; H, 5.89; N, 21.51.
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