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Synthesis of substituted pyridines by the reactions of halopyridines with sulfur, oxygen and carbon nucleophiles under focused microwave irradiation

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Abstract—The nucleophilic substitution reactions of halopyridines with sulfur, oxygen and carbon nucleophiles under microwave irradiation was complete within several minutes with yields up to 99%. The method using microwave irradiation is superior to those conducted under conventional heating processes.

1. Introduction

Extensive efforts have been exerted on developing methodology for the synthesis of pyridine derivatives, which are often found in natural products and pharmaceuticals (such as phenoxypyridines which are anticholinergic agents).[1] For example, Hunt has reported the synthesis and the pharmacological effects of pyridine onium derivatives.[2] However, introduction of substituents to pyridine rings often requires long reaction times and vigorous conditions to achieve acceptable yields under conventional heating or photolysis conditions.[3] Along with the application of microwaves in promoting organic reactions,[4] we have found that the reaction time of nucleophilic aromatic substitution dramatically decreases by using microwave heating.[5] We report herein that microwave heating also provides a convenient and efficient way to the synthesis of substituted pyridines.

2. Results and discussion

A detailed study of the reactions of halopyridines with nucleophiles in various amounts, reaction times, temperatures and solvents was investigated in order to find the optimized conditions for the preparation of pyridine derivatives (Tables 1–3). When 2-iodopyridine was treated with the sulfur, oxygen and carbon nucleophiles (PhSNa, MeSNa, $PhCH_2OH$, PhONa and $PhCH_2CN$) under irradiation in a monomode microwave reactor, the corresponding 2-substituted pyridines were obtained in 36–99% yields (Table 1, entries 1–10). The reaction with PhSNa (2 equiv.) in either HMPA or NMP (*N*-methylpyrrolidone) at about 100°C for a short period (0.5–3 min) afforded a quantitative yield of 2-phenylthiopyridine. Although substitution with benzyl alcohol was achieved in NMP to provide an 81% of 2-benzloxypyridine, the reaction with PhONa in NMP was less efficient to give only 36% yield of 2-phenoxypyridine. The yield was improved to 77 and 84% by using DMSO and HMPA as the solvents.

The nucleophilic displacement reactions of 2-bromopyridine, 2-chloropyridine and 2-fluoropyridine were similarly carried out (Table 1, entries 11–40). Of the four halopyridines studied, the relative reactivity of 2-halopyridines toward sulfur nucleophiles (PhSNa and MeSNa) in HMPA appeared to decrease in the order of I>Br>Cl>F (compared entries 1, 11, 24 with 33, and 3, 15, 26 with 34 in Table 1). In the series of four halogens, polarizability increases steadily from fluorine to iodine. As iodide ion is the best leaving group than other halides, the trend of 2-halogenpyridines toward sulfur nucleophiles is predictable. The results suggested that the second step of the nucleophilic aromatic substitution (S_NAr) is rate-determining because fluoride is the poorest leaving group. In contrast, 2-halopyridines reacted with the oxygen nucleophile ($PhCH_2OH$) in NMP followed the reactivity of F>Cl>Br>I (compared entries 5, 17, 28 with 36 in Table 1). The rate-determining steps might vary in the S_NAr mechanism when different nucleophiles are employed. A charge-controlled reaction might occur with a charge-localized nucleophile such as $PhCH_2OH$. The fluorine atom with the highest electronegativity would induce a highly electrophilic center at C-2,[3a] and thus fluorine is displaced by $PhCH_2OH$ considerably faster than Cl, Br and I. The reactions of the four 2-halopyridines toward the carbon nucleophile ($PhCH_2CN$) showed no substantial difference in reactivity (entries 9, 21, 32 and 40 in Table 1).

Keywords: microwave irradiation; nucleophilic heteroaromatic substitution; halopyridines.

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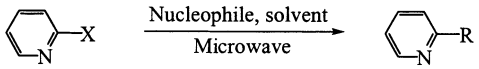
Table 1. Reactions of 2-halopyridine with nucleophiles



Entry	X	Nucleophile	Solvent	Molar proportions of nucleophile	Temp. (°C)	Time (sec)	Product, R=	Yield (%)
1	I	PhSNa	HMPA	2.0	100	30	SPh	99
2	I	PhSNa	NMP	2.0	110	180	SPh	99
3	I	MeSNa	HMPA	1.5	80	30	SMe	67
4	I	MeSNa	NMP	2.0	90	40	SMe	74
5	I	$PhCH_2OH$	NMP	2.0	100	60	OCH_2Ph	81
6	I	PhONa	NMP	3.0	110	120	OPh	36
7	I	PhONa	HMPA	3.0	110	120	OPh	84
8	I	PhONa	DMSO	4.0	120	180	OPh	77
9	I	$PhCH_2CN$	NMP	4.0	110	60	CH(CN)Ph	68
10	I	$PhCH_2CN$	HMPA	3.0	110	60	CH(CN)Ph	59
11	Br	PhSNa	HMPA	2.0	110	40	SPh	97
12	Br	PhSNa	HMPA	2.0	110	40	SPh	N.R.[a]
13	Br	PhSNa	HMPA	2.0	110	40	SPh	97[b]
14	Br	PhSNa	NMP	2.5	110	420	SPh	91
15	Br	MeSNa	HMPA	1.5	90	40	SMe	60
16	Br	MeSNa	NMP	2.0	90	45	SMe	74
17	Br	$PhCH_2OH$	NMP	2.0	100	60	OCH_2Ph	91
18	Br	PhONa	NMP	3.0	110	120	OPh	43
19	Br	PhONa	HMPA	3.0	110	120	OPh	67
20	Br	PhONa	DMSO	4.0	120	180	OPh	64
21	Br	$PhCH_2CN$	NMP	4.0	110	60	CH(CN)Ph	73
22	Br	$PhCH_2CN$	HMPA	3.0	110	60	CH(CN)Ph	70
23	Br	$PhCH_2CN$	DMSO	3.0	110	60	CH(CN)Ph	56
24	Cl	PhSNa	HMPA	2.0	110	60	SPh	91
25	Cl	PhSNa	NMP	4.0	120	600	SPh	53
26	Cl	MeSNa	HMPA	1.5	90	40	SMe	50
27	Cl	MeSNa	NMP	2.0	90	45	SMe	54
28	Cl	$PhCH_2OH$	NMP	2.0	100	60	OCH_2Ph	93
29	Cl	PhONa	NMP	3.0	110	120	OPh	4
30	Cl	PhONa	HMPA	3.0	110	120	OPh	45
31	Cl	PhONa	DMSO	3.0	120	300	OPh	38
32	Cl	$PhCH_2CN$	NMP	4.0	110	60	CH(CN)Ph	68
33	F	PhSNa	HMPA	2.0	110	90	SPh	68
34	F	MeSNa	HMPA	1.5	90	60	SMe	41
35	F	MeSNa	NMP	2.0	90	60	SMe	72
36	F	$PhCH_2OH$	NMP	2.0	100	60	OCH_2Ph	95
37	F	PhONa	NMP	3.0	110	210	OPh	56
38	F	PhONa	HMPA	2.0	110	45	OPh	74
39	F	PhONa	DMSO	3.0	110	60	OPh	72
40	F	$PhCH_2CN$	NMP	4.0	110	60	CH(CN)Ph	67

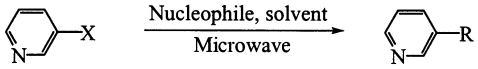
[a] Heating in an oil bath. N.R. represents no reaction.
[b] Benzoquinone (10 mol%) was added to the reaction.

In principle, these reactions might proceed with either S_NAr or $S_{RN}1$ mechanisms. In an attempted inhibition experiment using 10 mol% of benzoquinone as a radical scavenger, the yield for the substitution reaction of 2-bromopyridine with sodium thiophenoxide remained practically unchanged (entry 13, Table 1). The result indicated that the $S_{RN}1$ mechanism did not operate.

In order to compare the efficacy of microwave irradiation with conventional heating, a HMPA solution of 2-bromopyridine and PhSNa (2 equiv.) was heated at 110°C in an oil bath for 40 s. No product of 2-phenylthiopyridine was found (entry 12, Table 1). Thus, the high yields in substitution reactions of 2-bromopyridine might be attributable to the microwave effect in addition to heating efficiency.[6]

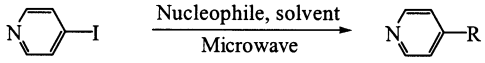
It is well known that 3-halopyridines are less reactive than 2-halopyridines in nucleophilic reactions.[7] High yields (97–99%) of 3-phenylthiopyridine were still attainable by microwave irradiation of 3-iodopyridine or 3-bromopyridine with PhSNa in HMPA for 1–2.5 min (entries 1 and 6 in Table 2). On the other hand, the reaction of 3-fluoropyridine with $PhCH_2OH$ afforded 3-benzyloxypyridine in the yield up to 88% (entries 16–18, Table 2). The dipolar solvent HMPA might facilitate the substitution reactions. The yield (0–58%) decreased dramatically by using 3-iodopyridine, 3-bromopyridine or 3-chloropyridine (entries 4, 8 and 12, Table 2). The reactivity of 3-halopyridines toward the nucleophile $PhCH_2CN$ also followed F>Cl>Br>I (compared entries 5, 9, 13 with 19 in Table 2). Upon microwave irradiation, 2-phenyl-2-(3-pyridyl)acetonitrile was prepared in 69% yield from 3-fluoropyridine and phenyl-

Table 2. Reactions of 3-halopyridine with nucleophiles



Entry	X	Nucleophile	Solvent	Molar proportions of nucleophile	Temperature (°C)	Time (min)	Product, R=	Yield (%)
1	I	PhSNa	HMPA	2.0	110	1	SPh	99
2	I	PhSNa	NMP	4.0	120	10	SPh	77
3	I	MeSNa	NMP	3.0	100	2.5	SMe	55
4	I	$PhCH_2OH$	NMP	5.0	110	10	OCH_2Ph	0
5	I	$PhCH_2CN$	NMP	5.0	110	10	CH(CN)Ph	0
6	Br	PhSNa	HMPA	2.0	110	2.5	SPh	97
7	Br	MeSNa	NMP	3.0	90	2.5	SMe	70
8	Br	$PhCH_2OH$	NMP	5.0	110	5	OCH_2Ph	17
9	Br	$PhCH_2CN$	NMP	5.0	110	10	CH(CN)Ph	6
10	Cl	PhSNa	HMPA	2.0	110	10	SPh	63
11	Cl	MeSNa	NMP	3.0	100	2.5	SMe	45
12	Cl	$PhCH_2OH$	NMP	5.0	120	3	OCH_2Ph	58
13	Cl	$PhCH_2CN$	NMP	5.0	110	1.5	CH(CN)Ph	30
14	F	PhSNa	HMPA	2.0	110	3.5	SPh	68
15	F	MeSNa	NMP	3.0	100	2.5	SMe	70
16	F	$PhCH_2OH$	NMP	5.0	110	3	OCH_2Ph	70
17	F	$PhCH_2OH$	HMPA	4.0	100	2	OCH_2Ph	88
18	F	$PhCH_2OH$	DMSO	4.0	100	2	OCH_2Ph	65
19	F	$PhCH_2CN$	NMP	5.0	100	2	CH(CN)Ph	69
20	F	$PhCH_2CN$	HMPA	5.0	100	1.5	CH(CN)Ph	48

Table 3. Reactions of 4-iodopyridine with nucleophiles



Entry	Nucleophile	Solvent	Molar proportions of nucleophile	Temperature (°C)	Time (sec)	Product, R=	Yield (%)
1	PhSNa	NMP	2.5	110	180	SPh	99
2	MeSNa	NMP	2.0	100	40	SMe	73
3	$PhCH_2OH$	NMP	3.0	110	120	OCH_2Ph	30
4	$PhCH_2OH$	HMPA	4.0	110	120	OCH_2Ph	32
5	$PhCH_2OH$	DMSO	2.0	110	120	OCH_2Ph	28
6	PhONa	NMP	5.0	120	900	OPh	42
7	PhONa	HMPA	5.0	120	360	OPh	60
8	PhONa	DMSO	5.0	120	600	OPh	57

acetonitrile in NMP (entry 19, Table 2). The substitution reactions of 3-halopyridines occurred in a regioselective manner. The reaction is not likely to proceed with pyridyne intermediates as no 2- or 4-substituted pyridine products were found.

Under microwave irradiation, 4-iodopyridine also reacted with PhSNa, MeSNa, $PhCH_2OH$, PhONa and $PhCH_2CN$ to give the corresponding 4-substituted pyridines in varied yields (28–99%, Table 3). The results indicated that the chemical behavior of 2- and 4-iodopyridines were similar.

In conclusion, efficient nucleophilic substitution reactions of 2-, 3- and 4-halopyridines are realized by using microwave irradiation. These reactions probably proceed via an S_NAr mechanism. The relative reactivity of halopyridines in substitutition reactions follows 2-halopyridine>4-halopyridine>3-halopyridine. This method is especially important for the preparation of 3-pyridyl ethers, thioethers and acetonitriles, because these substrates are not readily accessible by the conventional procedures.[8]

3. Experimental

^1H NMR spectra were measured in $CDCl_3$ solutions on a Varian Mercury 400 spectrometer using Me_4Si as the internal standard. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F-254 (0.2 mm layer thickness). Flash chromatography was carried out by utilizing silica gel 60 (70–230 mesh ASTM). The Synthewave 402™ monomode microwave reactor was purchased from Prolabo Co.

3.1. General procedure for reaction of halopyridines with nucleophile

In a quartz reaction vessel (12 mL) were placed a nucleophile and a halopyridine (0.3 mmol) in an appropriate solvent (1 mL). *t*-BuOK (1.1 equiv. vs nucleophile) could be added as the base if needed. The reaction vessel was then placed into the cavity of a focused monomode microwave reactor (Synthewave 402) and irradiated for the period listed in the tables. The reaction temperature was maintained by modulating the power level of the reactor. The crude reaction mixture was then absorbed directly onto silica gel, and purified by silica gel chromatography eluting with a mixture of hexane and ethyl acetate.

3.1.1. 2-Phenylthiopyridine.[3d] Yellow oil, ^{1}H NMR (400 MHz) δ 8.43 (d, J=4.8 Hz, 1H), 7.62–7.59 (m, 2H), 7.48–7.42 (m, 4H), 7.00 (m, 1H), 8.00 (d, J=8.0 Hz, 1H).

3.1.2. 2-Methylthiopyridine.[3d] Yellow oil, ^{1}H NMR (400 MHz) δ 8.44 (d, J=4.0 Hz, 1H), 8.49 (m, 1H), 7.19 (d, J=8.0 Hz, 1H), 6.98 (m, 1H), 2.58 (s, 3H).

3.1.3. 2-Phenoxypyridine.[3a] Colorless crystals, mp 40–41°C (lit. 42–44°C); ^{1}H NMR (400 MHz) δ 8.21 (d, J=4.8 Hz, 1H), 7.68 (m, 1H), 7.43–7.14 (m, 5H), 6.99 (m, 1H), 7.90 (d, J=8.4 Hz, 1H).

3.1.4. 2-Benzyloxypyridine.[3e] Yellow oil, ^{1}H NMR (400 MHz) δ 8.17 (dd, J=5.2, 1.4 Hz, 1H), 7.58 (m, 1H), 7.47–7.31 (m, 5H), 6.88 (m, 1H), 6.80 (d, J=8.4 Hz, 1H), 5.37 (s, 2H).

3.1.5. 2-Phenyl-2-(2-pyridyl)acetonitrile.[9] Colorless crystals, mp 85–86°C (lit. 87–88°C); ^{1}H NMR (400 MHz) δ 8.61 (d, J=4.8 Hz, 1H), 7.71 (m, 1H), 7.46–7.33 (m, 5H), 7.27–7.26 (m, 2H), 5.11 (s, 1H).

3.1.6. 3-Phenylthiopyridine.[3c] Yellow oil, ^{1}H NMR (400 MHz) δ 8.55 (d, J=1.6 Hz, 1H), 8.46 (dd, J=4.8, 1.6 Hz, 1H) 7.60 (ddd, J=8.0, 1.8, 1.6 Hz, 1H), 7.40–7.31 (m, 5H), 7.22 (dd, J=8.0, 4.8 Hz, 1H).

3.1.7. 3-Methylthiopyridine.[3d] Yellow oil, ^{1}H NMR (400 MHz) δ 8.51 (d, J=2.4 Hz, 1H), 8.38 (d, J=4.8, 1H), 7.58 (m, 1H), 7.23 (dd, J=8.0, 4.8 Hz, 1H), 2.51 (s, 3H).

3.1.8. 3-Benzyloxypyridine.[8a] Yellow oil, ^{1}H NMR (400 MHz) δ 8.39 (d, J=2.4 Hz, 1H), 8.23 (dd, J=4.4, 1.6 Hz, 1H), 7.45–7.32 (m, 5H), 7.25 (dd, J=2.4, 1.6 Hz, 1H), 7.23 (d, J=4.4 Hz, 1H), 5.11 (s, 2H).

3.1.9. 2-Phenyl-2-(3-pyridyl)acetonitrile.[10] Colorless needles, mp 60–61°C (lit. 63–65°C); ^{1}H NMR (400 MHz) δ 8.64 (s, 1H), 8.61 (d, J=4.0 Hz, 1H), 7.48 (d, J=8.4 Hz, 1H), 7.44–7.34 (m, 6H), 5.21 (s, 2H).

3.1.10. 4-Phenylthiopyridine.[3d] Yellow oil, ^{1}H NMR (400 MHz) δ 8.35 (dd, J=4.8, 1.6 Hz, 2H), 7.56 (m, 2H), 7.46 (m, 3H), 6.95 (dd, J=4.8, 1.6 Hz, 2H).

3.1.11. 4-Methylthiopyridine.[8a] Yellow oil, ^{1}H NMR (400 MHz) δ 8.39 (dd, J=4.8, 1.2 Hz, 2H), 7.10 (dd, J=4.8, 1.2 Hz, 2H), 2.49 (s, 3H).

3.1.12. 4-Phenoxypyridine.[7b] Colorless crystals, mp 42–43°C (lit. 44–45°C); ^{1}H NMR (400 MHz) δ 8.46 (d, J=5.8 Hz, 2H), 7.45–7.09 (m, 5H), 6.84 (d, J=5.8 Hz, 2H).

3.1.13. 4-Benzyloxypyridine.[11] Colorless crystals, mp 50–51°C (lit. 55–56°C); ^{1}H NMR (400 MHz) δ 8.49 (d, J=4.8 Hz, 2H), 7.41–7.36 (m, 5H), 6.92 (d, J=4.8 Hz, 2H), 5.13 (s, 2H).

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