Amination of halopyridines on KF-alumina under microwave irradiation

De-Hong Yang[a]*, Ben-Yong Yang[a], Zhen-Chu Chen[b] and Song-Ying Chen[b]

[a]*Department of Materials & Chemistry, Zhongyuan University of Technology, Zhengzhou, 450007, P. R. China*

[b]*Department of Chemistry, Zhejiang University, Hangzhou, 310028, P. R. China*

A convenient and clean synthesis of halopyridine-2-amines has been provided by amination of halopyridines on KF-alumina under microwave irradiation with good yields.

Keywords: microwave, amination, halopyridine

Pyridine-2-amine is an important class of synthetic intermediates in organic synthesis, and many compounds can be synthesised with them that display biological and pharmaceutical activities. Their derivatives are often used as ligands in coordination and organometallic chemistry, and now have found industrial applications as fluorescent dyes.[1]

The earlier preparations of aminopyridines which involve aromatic nucleophilic substitution by S_NAr, benzyne or SRN1 either have the problem of nucleophilic region control, or have the requirements of high temperature or special functional groups in heterocycle, all resulting in low yields or poor selectivity.[2] The recently developed chelating bis-phosphine-palladium catalysing cross-coupling reactions for the preparation of pyridine-2-amine suffers from the specific catalyst that is sensitive to the strong base NaOBu needed in the reaction, yet, substituting KF-alumina for NaOBu need longer reaction time, toxic solvent toluene and excessive amines.[3]

The microwave assisted organic reactions coupled with solvent-free techniques have attracted much attention due to their reaction rate enhancement, easier work-up, and in many cases, no solvents requirements.[4] Here, we report the synthesis of pyridine-2-amines by the amination of halopyridines on KF-alumina under microwave irradiation without solvent. This method is simple and fast to afford good yields.

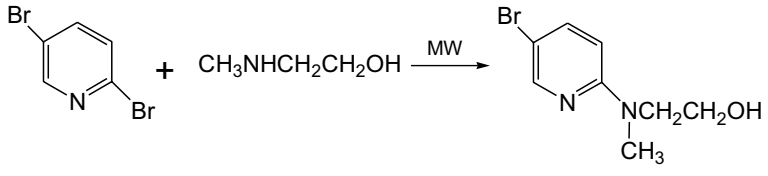
Firstly, the reaction of 2,5-dibromopyridine with 2-(methylamino)ethanol (see Scheme 1) can be chosen as a representative to investigate the effects of the power and time of microwave irradiation, the amounts of KF-alumina (KF/alumina = 2/3, g/g) and different catalysts (see Table 1).

The results summarised in Table 1 show the catalytic action of the used catalyst is relatively obvious, and among the tested catalysts, such as KF–Al_2O_3, KF, alumina, basic alumina, and KOH, the KF–Al_2O_3 combination can give the best yield. It's also shown that the optimum ratio of KF–Al_2O_3 to substrate 2,5-dibromopyridine is about 1 : 1(g/mmol), and that the seemly irradiation power and time is respectively about 350 watt and 15 min, higher irradiation power (>350W) and longer irradiation time (>15 min) all leading to lower results.

Then the scope of the amination of halopyridines with various amines was investigated (see Scheme 2) and the results are listed in Table 2.

It is found that the reactions of halopyridines with amines occurred smoothly on KF–Al_2O_3 (0.5 g) under microwave irradiation (350W, 15 min) with the yields ranging from 50 to 86%. It seemed that 2,5-dibromopyridine is more active than 2-bromopyridine is, and 2-bromopyridine is more active than 2-chloropyridine is, in as much bromine negative ion is easier to drop out than chlorine ion. The reactions are general applicable to various primary amines and secondary amines, yet $C_6H_5NH_2$, $C_6H_5NHCH_3$, piperidine and indole did not react with 2,5-dibromopyridine under the same conditions, owing to their poor nucleophilic ability. The reactions proceeded by heating with much longer time; the reaction of 2,5-dibromopyridine and 2-methylaminoethanol at 150°C gave a yield 80% of **3a** in 16 h.

In conclusion, we have provided a simple, fast and convenient method for the preparation of pyridine-2-amines from halopyridines on KF–Al_2O_3 under microwave irradiation. Additionally, the solvent-free conditions make this procedure more economic and environmentally benign.



3a

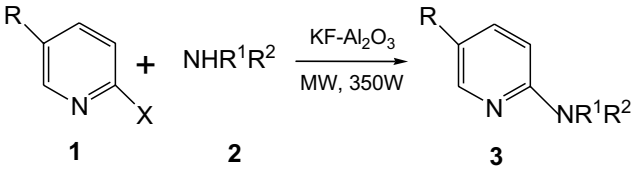
Scheme 1

Table 1 Effect of power, time, catalyst and amount of catalyst on the yield[a] of **3a**

Power[b]/W	Yield/%	Time[c]/min	Yield/%	Catalyst[d]	Yield/%	Amount[e] of KF-Al_2O_3/g	Yield/%
100	31	5	30	KF-Al_2O_3	86	0.1	50
210	64	10	52	KF	39	0.3	65
350	86	15	86	Al_2O_3	45	0.5	86
500	75	20	73	Basic Al_2O_3	57	1	80
700	40	25	47	KOH	68	1.5	71
				None	36		

[a]Yields of pure product, all reactions were run on 0.5 mmol 2,5-dibromopyridine and 1 mmol 2-methylaminoethanol; [b]KF–Al_2O_3/g, 0.5, Time/min, 15; [c]KF–Al_2O_3/g, 0.5, Power/W, 350; [d]Catalyst/g, 0.5, Power/W, 350, Time/min, 15; [e]Power/W, 350, Time/min 15.

* Correspondent. E-mail: ydh@zzti.edu.cn



Scheme 2

Experimental

Melting points were uncorrected. IR spectra were recorded as KBr pellets on VECTOR-22 IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker (400 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard. Microwave irradiation was run in a commercial microwave oven (2450 MHz, 350W) under atmospheric pressure. Elemental analysis was performed on Carlo Erba EA 1106 instrument.

General procedure for synthesis of pyridine-2-amine **(3)**

$KF–Al_2O_3$ (0.5 g) were added to the mixture of halopyridine (0.5 mmol), amine (1 mmol) and ethyl ether (2 mmol) in a flask (10 ml) at room temperature, shaking and placing for a few minutes, followed by distilling off ethyl ether. Then the mixture was subjected to microwave irradiation (350W) for 15 min. After cooling, extracted the reaction mixture with ethyl ether (10 ml × 3). The combined ether solution was evaporated under reduced pressure. The residue was further purified by preparative TLC (EtOAC: *n*-Hexane, 1: 4) to give pure product **3**.

2-[(5-Bromopyridin-2-yl)methylamino]ethanol **(3a):** M.p. 38–41°C. MS *m/z* (%), 230 (M^+ -1, 33.56), 199 (100), 156 (15.31). IR 3435, 3312, 2856, 1591, 1540, 1437, 1155. ^{1}H NMR δ 3.01 (3H, s, NCH_3), 3.54 (4H, m, NCH_2CH_2O), 4.66 (1H, bs, OH), 6.61 (1H, d, J = 9.0 Hz), 7.60 (1H, d, J = 8.6 Hz) 8.11 (1H, d, J = 3.4 Hz). Anal. Calcd. for $C_8H_{11}BrN_2O$ C% 41.56, H% 4.76, N% 12.12; Found C% 41.63, H% 4.69, N% 12.10.

2[(Methylpyridin-2-yl)amino]ethanol **(3b, 3c)**: MS *m/z* (%), 153(100), 152(M^+, 30.07), 135 (21.33), 121 (90.45). IR 3423, 1592, 1460, 1154. ^{1}H NMR δ 3.05 (3H, s, NCH_3), 3.68 (2H, t, J = 4.4 Hz), 3.81 (2H, t, J = 4.4 Hz), 4.86 (1H, b, OH), 6.56 (2H, m), 7.46 (1H, m), 8.04 (1H, m). Anal. Calcd. for $C_8H_{12}N_2O$ C% 63.13, H% 7.95, N% 18.41; Found C% 63.43, H% 7.88, N% 18.30.

2[(5-Bromopyridin-2-yl)amino]ethanol **(3d)**: MS *m/z* (%), 219 (97.72), 217(M^+, 100), 199 (8.66), 185 (7.87), 78 (5.93). IR 3309, 1598, 1446, 1148. ^{1}H NMR δ 3.43 (2H, t, J = 5.6 Hz), 3.77 (2H, t, J = 5.6 Hz), 4.80 (1H, b, OH), 5.25 (1H, bs, NH), 6.64 (1H, d, J = 8.4 Hz), 7.62 (1H, d, J = 3.6 Hz), 8.15 (1H, d, J = 3.0 Hz). Anal. Calcd. for $C_7H_9BrN_2O$ C% 38.71, H% 4.15, N% 12.90; Found C% 38.87, H% 4.11, N% 12.76.

2-(Pyridin-2-ylamino)ethanol **(3e)**: MS *m/z* (%), 138(M^+, 100), 78 (11.15). IR 3440, 3301, 1587, 1445, 1140. ^{1}H NMR δ 3.65 (4H, m), 4.85 (1H, b, OH), 5.29 (1H, bs, NH), 6.58 (2H, m), 7.51 (1H, m), 8.07 (1H, m). Anal. Calcd. for $C_7H_{10}N_2O$ C% 60.87, H% 7.25, N% 20.29; Found C% 61.11, H% 7.26, N% 19.94.

2-Benzylamino-5-bromopyridine **(3f)**: M.p. 124–125°C IR 3441, 3040, 2849, 1603, 1521, 1142. ^{1}H NMR δ 4.45 (2H, d, J = 6.0 Hz), 6.50 (1H, d, J = 9.2 Hz), 7.22 (1H, NH), 7.31 (5H, m), 7.52 (1H, d, J = 3.2 Hz), 8.02 (1H, d, J = 2.4 Hz). Anal. Calcd. for $C_{12}H_{11}BrN_2$ C% 54.77, H% 4.21, N% 10.65, Found C% 54.90, H% 4.10, N%.10.68.

2-(2-Nitrophenylamino)5-bromopyridine **(3g)**: M.p. 143–144°C MS *m/z* (%), 294(M^+, 100). IR 3309, 2924, 1618, 1580, 1498, 1138, 739. ^{1}H NMR δ 7.03 (1H, d, J = 8.8 Hz), 7.15 (1H, t, J = 7.2 Hz), 7.66 (1H, t, J = 7.2 Hz), 7.85 (1H, dd, 6.4 and 2.4 Hz), 7.99 (2H, m), 8.20 (1H, d, J = 2.4 Hz). 9.7(1H). Anal. Calcd. for $C_{11}H_8BrN_3O_2$ C% 44.90, H% 2.72, N% 14.29; Found C% 44.85, H% 2.80, N% 14.21.

2-(2-Nitrophenylamino)pyridine **(3h, 3i)**: M.p. 95–98°C IR 3307, 1618, 1495, 1140. ^{1}H NMR δ 6.93 (1H, m), 7.14 (2H, m), 7.65 (2H, m), 8.04 (1H, d), 8.19 (2H, m), 9.66 (1H, bs, NH). Anal. Calcd. for $C_{11}H_9N_3O_2$ C% 61.40, H% 4.19, N% 19.53; Found C% 61.27, H% 4.21, N% 19.68.

2-Cyclohexylamino-5-bromopyridine **(3j)**: M.p. 45–46°C IR 3267, 2931, 2852, 1593, 1446, 1394, 1092. ^{1}H NMR δ 1.45-2.05 (11H, m), 6.30 (1H, d, J = 8.8 Hz), 7.67 (1H, NH), 8.09 (1H, d, J = 1.6 Hz), 8.47 (1H, d, J = 2.4 Hz). Anal. Calcd. for $C_{11}H_{15}BrN_2$ C% 51.78, H% 5.93, N% 10.98; Found C% 52.08, H% 5.97, N% 10.66.

Table 2 Preparation of pyridine-2-amines by amination of halopyridines on $KF–Al_2O_3$ under microwave irradiation[a]

Product	R	X	NHR^1R^2 (**2**)	Yield/%
3a	Br	Br	$CH_3NHCH_2CH_2OH$	86
3b	H	Br	$CH_3NHCH_2CH_2OH$	80
3c	H	Cl	$CH_3NHCH_2CH_2OH$	73
3d	Br	Br	$NH_2CH_2CH_2OH$	85
3e	H	Br	$NH_2CH_2CH_2OH$	80
3f	Br	Br	$NH_2CH_2C_6H_5$	75
3g	Br	Br	$NH_2C_6H_4$-NO_2-2	81
3h	H	Br	$NH_2C_6H_4$-NO_2-2	70
3i	H	Cl	$NH_2C_6H_4$-NO_2-2	55
3j	Br	Br	C_6H_{12}	50

[a]Yields of pure products, all reactions were run with halopyridines (0.5 mmol), amines (1 mmol) and $KF–Al_2O_3$ (0.5 g) under microwave irradiation (350W) for 15 min.

Received 2 February 2006; accepted 10 April 2006
Paper 06/3771

References

1 (a) J.A. Montgomary and J.A. Secrist, *Comprehensive Heterocyclic Chemistry,* 1984, **5**, 607; (b) A.R. Katriky, G. Qiu, Q.H. Long, H.Y. He and P.J. Steel, *J. Org. Chem*., 2000**, 65**, 9201; (c) R. Benigni, A. Giuliani, R. Franke and A. Gruska, *Chem. Rev.,* 2002, **100**, 3697; (d) C.L.E. Broekkamp, D.B. Leysen, W.M.M. Peeters and R.M. Pinder, *J. Med. Chem.*, 1995, **38**, 4615; (e) R. Kempe and P. Arndt, *Inorg. Chem.,* 1996, **35**, 2644; (f) A. Togni and L.M. Venanzi, *Angew. Chem., Int. Ed. Engl.,* 1994, **33**, 497; (g) G. Stathyamoorthy, M.L. Soong, T.W. Ross and J.H. Boyer, *Heteroatom. Chem.*, 1993, **4**, 603; (h) K. Araki, T. Mutai, Y. Shigemitsu, M. Yamada, T. Nakajima, S. Kuroda and I. Shimao, *J. Chem. Soc., Perkin Trans*. *2*. 1996, 613.

2 M.B. Smith and J. March, *March's Advanced Organic Chemistry,* New York, 2001, 850.

3 (a) B.H. Yang and S.L. Buchwald, *J. Organomet. Chem*., 1999, **576**, 125; (b) S. Wagaw and S.L. Buchald, *J. Org. Chem*., 1996, **61**, 7240; (c) J. Wolfe and S.L. Buchwald, *J. Org. Chem*., 2000, **65**, 1144; (d) B. Jamart-Gregorie, C. Leger and P. Caubene, *Tetrahedron Lett.,* 1990**, 31**, 7599; (e) M.A. Walters and J.J. Shay, *Synth. Commun.,* 1997, **27**, 3573; (f) B. Basu, S. Jha, N.K. Mridha, Bhuiyan and M.H. Md, *Tetrahedron Lett.,* 2002**, 43**, 7967.

4 (a) S. Caddick, *Tetrahedron,* 1995, **51**, 10403; (b) R.A. Abramovitch, *Org. Prep. Proc. Int.*, 1991, **23**, 683; (c) A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacqualt and D. Mathe, *Synthesis*, 1998, 1213; (d) R.S. Varma, *Green Chem*., 1999**, 1**, 43; (e) D.M.P. Mingos and D.R. Baghurst, *Chem. Soc. Rev*., 1991, **20**, 1.