Tetrahedron Letters 51 (2010) 3886–3889

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave-assisted amination of 3-bromo-2-chloropyridine with various substituted aminoethanols

Jeong Geun Kim [a], Eun Hae Yang [b], Woo Sup Youn [b], Ji Won Choi [b], Deok-Chan Ha [a], Jae Du Ha [b,*]

[a] Department of Chemistry, Korea University, Sungbuk-gu, Seoul 136-701, Republic of Korea
[b] Bio-Organic Science Division, Korea Research Institute of Chemical Technology, Daejeon 305-600, Republic of Korea

ARTICLE INFO

Article history:
Received 26 March 2010
Revised 6 May 2010
Accepted 10 May 2010
Available online 13 May 2010

Keywords:
Microwave-assisted amination
3-Bromo-2-chloropyridine
Aminoethanol
Pyrido[1,4]oxazine

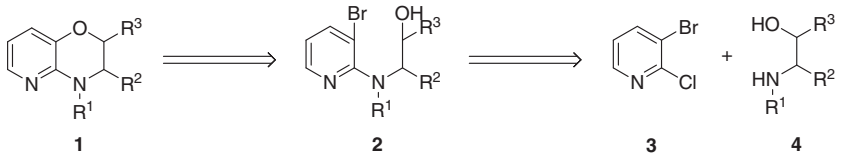
ABSTRACT

A simple method for microwave-assisted amination of 3-bromo-2-chloropyridine with various substituted aminoethanols is described. The reaction was carried out under microwave irradiation conditions (at 180 °C for 1–2 h) and the result was superior in terms of conversion and yield when compared to that of the corresponding conventional heating conditions.

3,4-Dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazines **1** have shown potential innumerous drug discovery applications. Members of this class have been appeared in antiviral agents,[1] antibacterial agents,[2] and anticancer agents.[3] Despite the biological importance of 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazines, synthetic methods for the preparation of analogs containing different substituents at C-2 and C-3 are limited.[4]

Our interest in the search for new tyrosine kinase inhibitors has been focusing on the synthesis of 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazines in which these scaffolds might be able to bind to hinge domains of various tyrosine kinase proteins.[5] In Scheme 1, we envisioned that the oxazine ring could be constructed from 2-aminoalcohol-substituted 3-bromopyridines via a Pd-catalyzed C–O bond formation. In order to prepare 2-amino-3-bromopyridines containing hydroxy moiety **2**, 3-bromo-2-chloropyridine was coupled with various aminoalcohols by heating in the presence of a base. Although these conventional methods have proven to be useful protocols, they are of limited use for producing compounds **2** with various substituents because of the requirement of high temperature (~150 °C) and long reaction time (>24 h).[6]

Although a promising substitution reaction of 2-chloropyridines with amines in the presence of transition metal catalysts such as Pd,[7] Ni,[8] and Co[9] has been reported, the adaption of these approaches to our system has been met with limited success resulting in the generation of a mixture of regioisomers[10] due to the presence of two halides in the starting material **3**. Thus, the convenient methodology to overcome this problem is required. In this Letter, we described our microwave-assisted amination reacting 3-bromo-2-chloropyridine with several amine nucleophiles to provide 2-amino-3-bromopyridines in good yields. Whereas several syntheses of 2-aminopyridines via microwave-assisted amination have been described in the literature, these reports had an amine substrate scope that was limited to cyclic secondary amines (pyrrolidines and piperidines)[11] and no synthetic study for various amine bearing hydroxy moiety has been reported.



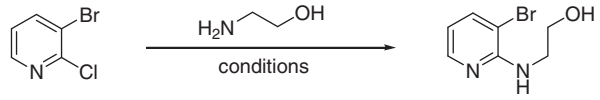
1 2 3 4

Scheme 1. Synthetic approach to 3,4-dihydro-2*H*-pyrido[3,2-*b*]-1,4-oxazines.

* Corresponding author. Tel.: +82 042 860 7072; fax: +82 042 860 7160.
E-mail address: jdha@krict.re.kr (J.D. Ha).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.021

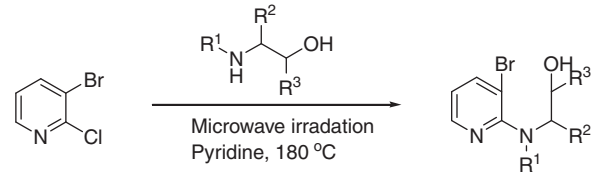
Table 1
Optimization of amination reaction



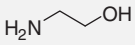
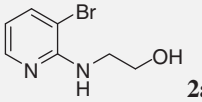
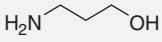
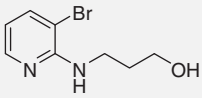
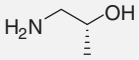
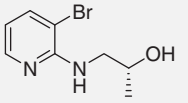
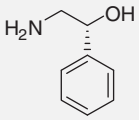
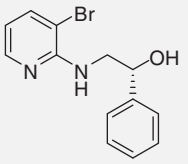
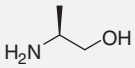
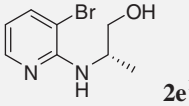
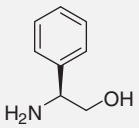
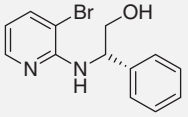
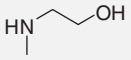
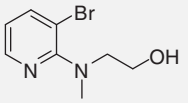
3 2

Entry	Equiv of amine (equiv)	Conditions	Temp/time	Yield (%)
1	2	Sealed tube *i*-Pr_2EtN(3 equiv)/DMSO	180 °C/24 h	65
2	2	Microwave irradiation *i*-Pr_2EtN(3 equiv)/DMSO	180 °C/1 h	82
3	1	Microwave irradiation Pyridine	180 °C/3 h	45
4	1.5	Microwave irradiation Pyridine	180 °C/2 h	66
5	2	Microwave irradiation Pyridine	180 °C/1 h	87
6	4	Microwave irradiation Pyridine	180 °C/0.5 h	92

Table 2
[13]Microwave-assisted amination of 3-bromo-2-chloropyridine with various aminoalcohols

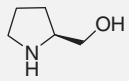
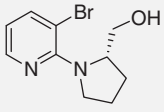
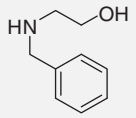
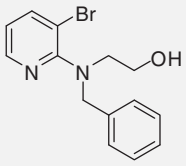
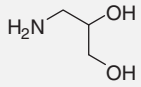
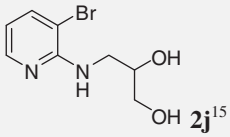
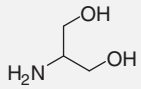
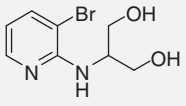
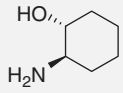
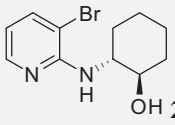


3 2

Entry	Amine (2 equiv)	Time (h)	Product	Yield[a] (%)
1		1	 **2a**	87
2		1	 **2b**	91
3		2	 **2c**[15]	80
4		2	 **2d**	79
5		1.5	 **2e**[15]	84
6		1.5	 **2f**	80
7		2	 **2g**	68

(*continued on next page*)

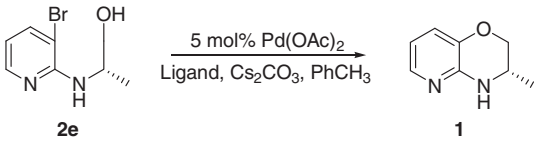
Table 2 (*continued*)

Entry	Amine (2 equiv)	Time (h)	Product	Yield[a] (%)
8		1	 **2h**	80
9		2	 **2i**	43
10		1	 **2j**[15]	81
11		1.5	 **2k**	76
12		2	 **2l**	10[b]

[a] Isolated yield.
[b] 3-Bromo-2-chloropyridine decomposed during prolonged reaction times.

The initial experiment was performed with 2-aminoethanol by using *i*-Pr_2EtN/DMSO at 180 °C for 24 h in sealed tube (Table 1, entry 1). The desired amination product **4** was isolated in moderate yield (65%). When the reaction was conducted under microwave irradiation conditions (at 180 °C for 1 h), the result was superior in terms of conversion and yield when compared to that of the corresponding reactions in sealed tube by conventional heating conditions, in which unreacted starting material remained even after prolonged reaction time. A variety of solvents (pyridine, THF, DME, and DMSO) and bases (*i*-Pr_2EtN, DBU, and pyridine) were investigated in great detail, and we found that the use of pyridine was optimal in many cases, although the reactions also proceeded well using a combination of *i*-Pr_2EtN (3 equiv) and DMSO (entry 2). Nevertheless amination under microwave irradiation conditions proved successful, completion of the reaction required the use of a large excess of aminoethanol (entry 6). Due to the expense of the chiral aminoethanol derivatives used, a ratio of 1:2 2-chloropyridine/aminoethanols was found to be optimal to provide the amination product in high yield at relatively short reaction time (entry 5).

The reaction between 3-bromo-2-chloropyridine and several aminoalcohols is shown in Table 2. The reaction with unsubstituted aminoalcohols (2-aminoethanol and 3-amino-1-propanol) gave good yields of the amination products (entries 1 and 2). Substituted aminoethanols (entries 3–6) with either R^1 or R^2 (methyl and phenyl groups) gave a slightly lower yield and also required longer reaction time (1.5–2 h) compared to the corresponding unsubstituted aminoethanol. The yield was 80% in the case of a cyclic secondary amine (pyrrolidine-2-ylmethanol; entry 8), whereas the corresponding noncyclic secondary amines (entries 7 and 9) gave a slightly lower yield (65% and 48%), suggesting that the reactivity of cyclic amine is higher than that of noncyclic amines. Aminoethanols bearing additional hydroxy moiety (entries 10 and 11) also gave high yields (81% and 76%) without decreasing the reactivity of amine. Finally, amination of 2-aminocyclohexanol (entry 12) was very sluggish and gave only 10% desired product, presumably due to strong hydrogen bonding between hydroxy and amino groups to decrease the reactivity of amine. Both prolonged reaction time (>2 h) and increased reaction temperature (210 °C) resulted in the slow decomposition of the starting material.



2e **1**

Scheme 2.

With the (*S*)-2-(3-bromopyridin-2-ylamino)propan-1-ol (**2e**) in hands, our attention was turned to a Pd-catalyzed C–O bond formation of **2e** to provide the desired (*S*)-3-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (Scheme 2). By following Buchwald's conditions [5 mol % of $Pd(OAc)_2$, 8 mol % of 2-(di-*t*-butylphosphino)biphenyl, Cs_2CO_3, PhMe, 80 °C],[12,14] cyclization of **2e** cleanly afforded the pyrido[1,4]oxazine derivative **1** in 74% yield {$[R]_D^{20}$ = 0.42 (*c* 0.86, $CHCl_3$)}. Although enantioselective syntheses of chiral pyrido[1,4]oxazine bearing C-3 substituents have been reported[4b,4d], to the best of our knowledge, there is no report for the synthesis of (*S*)-3-methyl-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine (**1**).

In conclusion, we have reported an efficient synthesis of 2-aminoalcohol-substituted pyridine derivatives via microwave-assisted amination of 3-bromo-2-pyridine. This methodology could provide a key intermediate for the synthesis of substituted pyrido[1,4]oxazine derivatives.

Acknowledgment

We are grateful to the Korea Research Institute of Chemical Technology (KRICT) for financial support.

References and notes

1. Sin, N.; Venables, B. L.; Sun, L.-Q.; Sit, S.-Y.; Chen, Y.; Scola, P. M. US2008/119461.
2. (a) Mira, M.; Hinman, M. M.; Rosenberg, T. A.; Balli, D.; Black-Schaefer, C.; Chovan, L. E.; Kalvin, D.; Merta, P. J.; Nilius, A. M.; Pratt, S. D.; Soni, N. B.; Wagenaar, F. L.; Weitzberg, M.; Wagner, R.; Beutel, B. A. *J. Med. Chem.* **2006**, *49*, 4842–4856; (b) Sargent, B. J.; Pauls, H.; Berman, J. M.; Ramnauth, J.; Sampson, P.; Toro, A.; Martin, F. J. L.; Surman, M. D.; Decornez, M. Y.; Manning, D. D. WO2007/053131.
3. (a) Leonard, K.; Pan, W.; Anaclerio, B.; Gushue, J. M.; Guo, Z.; DesJarlais, R. L.; Chaikin, M. A.; Lattanze, J.; Crysler, C.; Manthey, C. L.; Tomczuk, B. E.; Marugan, J. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2679–2684; (b) Arnould, J.-C.; Delouvrie, B.; Ducray, R.; Lambert-Van Der Brempt, C. M. P. WO2007/141473.; (c) Perron, J.; Joseph, B.; Mérour, J.-Y. *Eur. J. Org. Chem.* **2004**, 4606–4613.
4. (a) Arrault, A.; Touzeau, F.; Guillaumet, G.; Leger, J.-M.; Jarry, C.; Merour, J.-Y. *Tetrahedron* **2002**, *58*, 8145–8152; (b) Henry, N.; Guillaumet, G.; Pujol, M. D. *Tetrahedron Lett.* **2004**, *45*, 1465–1468; (c) Hartz, R. A.; Nanda, K. K.; Ingalls, C. L. *Tetrahedron Lett.* **2005**, *46*, 1683–1686; (d) Henry, N.; Sanchez, I.; Sabatie, A.; Beneteau, V.; Guillaumet, G.; Pujol, M. D. *Tetrahedron* **2006**, *62*, 2405–2412; (e) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283–3286.
5. (a) Liao, J. J.-L. *J. Med. Chem.* **2007**, *50*, 409–424; (b) Collins, I.; Workman, P. *Curr. Signal Transduct. Ther.* **2006**, *1*, 13–23.
6. Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285–294.
7. (a) Stauffer, S. P.; Stambuli, L. J. P.; Hauck, S. I.; Hartwig, J. F. *Org. Lett.* **2000**, *2*, 1423–1426; (b) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron* **2005**, *61*, 9705–9709; (c) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett.* **2003**, *5*, 1479–1482; (d) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816–3821.
8. (a) Desmarets, C.; Schneider, R.; Fort, Y. *J. Org. Chem.* **2002**, *67*, 3029–3036; (b) Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429–1434.
9. Toma, G.; Fujitta, K.-i.; Yamaguchi, R. *Eur. J. Org. Chem.* **2009**, 4586–4588.
10. For representative examples, see: Schoen, U.; Messinger, J.; Buckendahl, M.; Prabhu, M. S.; Konda, A. *Tetrahedron Lett.* **2007**, *48*, 2519–2525.
11. (a) Ognyanov, V. I.; Balan, C.; Bannon, A. W.; Bo, Y.; Dominguez, C.; Fotsch, C.; Gore, V. K.; Klionsky, L.; Ma, V. V.; Qian, Y.-X.; Tamir, R.; Wang, X.; Xi, N.; Xu, S.; Zhu, D.; Gavva, N. R.; Treanor, J. J. S.; Norman, M. H. *J. Med. Chem.* **2006**, *49*, 3719–3742; (b) Narayan, S.; Seelhammer, T.; Gawley, R. E. *Tetrahedron Lett.* **2004**, *45*, 757–759.
12. For Pd-catalyzed intramolecular cyclization of 2-(2-bromophenyamino)ethanol derivatives to benzoxazines, see: Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. T. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206.
13. Typical experimental procedure: *2-(3-Bromopyridin-2-ylamino)ethanol* (**2a**). The solution of 3-bromo-2-chloropyridine (100 mg, 0.52 mmol), ethanolamine (63 μL, 1.04 mmol) and pyridine (1 mL) in sealed vial was placed in an Emrys Optimizer microwave apparatus (300 W). The reaction was carried out at 180 °C for 1 h. Saturated $NaHCO_3$ aq. and CH_2Cl_2 were added to the reaction mixture and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure and purified by flash chromatography (1:3 EtOAc/hexane) to give **2a** (98 mg, 87%) as a colorless oil : ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, 1H, J = 1.3 and 4.9 Hz), 7.63 (dd, 1H, J = 1.4 and 7.6 Hz), 6.48 (dd, 1H, J = 4.9 and 7.6 Hz), 5.46 (br s, 1H), 4.47 (s, 1H), 3.83 (t, 2H, J = 4.6 Hz), 3.46 (t, 2H, J = 4.6 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.3, 146.1, 140.5, 114.1, 105.7, 68.9, 50.3; MS-ESI 218 (M^+, 15), 216 (16), 198 (3), 185 (100), 172 (26), 158 (22), 79 (28).
14. *(S)-3-Methyl-3,4-dihydro-2H-pyrido[3,2-b][1,4]oxazine* (**1**). A sealed tube was charged with $Pd(OAc)_2$ (5.2 mg, 0.023 mmol, 5 mol %), 2-(di-*t*-butylphosphino)biphenyl (11 mg, 0.036 mmol, 8 mol %), and Cs_2CO_3 (225 mg, 0.68 mmol). The sealed tube was evacuated and back-filled with nitrogen and fitted with a rubber septum. (*S*)-1-(3-bromopyridin-2-ylamino)propan-2-ol (**2e**) (105 mg, 0.45 mmol) and toluene (1.5 mL) were added via a syringe. The sealed tube was then sealed under nitrogen and placed in a preheated oil bath at 100 °C until the aryl halide had been consumed as judged by TLC analysis. The reaction mixture was cooled to room temperature, diluted with diethyl ether (2 mL), and filtered through a pad of Celite. The resulting solution was concentrated under reduced pressure and purified by flash chromatography on silica gel (1:1 EtOAc/hexane) to give **1** (50.2 mg, 74%) as a brown oil. $[R]_D^{20}$ = 0.42 (*c* 0.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, 1H, J = 2.3, 8.2 Hz), 6.96 (dd, 1H, J = 2.2, 12.9 Hz), 6.55 (dd, 1H, J = 8.2, 12.9 Hz), 4.96 (br s, 1H), 4.16 (dd, 1H, J = 2.4, 13.0 Hz), 3.63–3.77 (m, 2H), 1.22 (d, 3H, J = 10.2 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.5, 140.2, 139.2, 121.8, 114.2, 70.4, 45.4, 17.8; MS-ESI 150 (M^+, 100), 135 (94), 121 (47), 94 (26), 71 (19), 57 (50).
15. *Representative spectroscopic data*. *Compound* **2c**: $[R]_D^{20}$ = −23.5 (*c* 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 1.1, 4.9 Hz), 7.62 (dd, 1H, J = 1.3, 7.6 Hz), 6.48 (dd, 1H, J = 4.9, 7.6 Hz), 5.42 (br s, 1H), 4.50 (s, 1H), 3.98–4.07 (m, 1H), 3.60 (dd, 1H, J = 4.2, 13.1 Hz), 3.40 (dd, 1H, J = 6.3, 13.1 Hz), 1.12 (d, 3H, J = 6.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.4, 146.4, 140.3, 114.1, 105.8, 68.7, 50.1, 21.2; MS-ESI 232 (M^+, 9), 230 (9), 187 (100), 172 (16), 158 (30), 105 (14), 79 (22).
Compound **2e**: $[R]_D^{20}$ = −20.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (dd, 1H, J = 1.4, 4.9 Hz), 7.62 (dd, 1H, J = 1.5, 7.6 Hz), 6.48 (dd, 1H, J = 4.9, 7.6 Hz), 5.04 (br s, 1H), 4.62 (s, 1H), 4.10–4.22 (m, 1H), 3.77 (dd, 1H, J = 2.7, 10.8 Hz), 3.61 (dd, 1H, J = 7.3, 10.8 Hz), 1.29 (d, 3H, J = 6.8 Hz); ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.1, 146.3, 140.4, 114.2, 105.9, 69.2, 50.8, 18.0; MS-ESI 294 (M^+, 1), 293 (1), 185 (100), 172 (2), 158 (20), 105 (16), 79 (24).
Compound **2j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 1.1, 5.0 Hz), 7.65 (dd, 1H, J = 1.3, 7.6 Hz), 6.51 (dd, 1H, J = 5.0, 7.6 Hz), 5.39 (br s, 1H), 4.04 (br s, 1H), 3.83 (pentet, 1H, J = 4.8, 9.7 Hz), 3.73 (br s, 1H), 3.57–3.65 (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 155.4, 146.3, 140.5, 113.7, 105.8, 71.8, 63.4, 44.6; MS-ESI 248 (M^+, 10), 246 (10), 217 (25), 215 (27), 187 (100), 185 (98), 172 (22), 158 (18), 105 (9), 79 (15).