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A convenient synthesis of 4-aryl-1,8-naphthyridin-2(1*H*)-ones by the Suzuki coupling

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Abstract—4-Halo-1,8-naphthyridin-2(1*H*)-ones readily available from 2-chloronicotinic acid were subjected to the Suzuki coupling reaction with arylboronic acids to give a diversity of 4-aryl-1,8-naphthyridin-2(1*H*)-ones.

1,8-Naphthyridin-2(1*H*)-ones[1] are a group of compounds possessing antibacterial,[2] antiinflammatory,[3] antiallergic, or antisecretory activites.[4] Among them, 4-aryl-1,8-naphthyridin-2(1*H*)-ones have recently attracted considerable interests: we examined acyl-CoA: cholesterol acyltransferase (ACAT) inhibitory activity[5] and developed SL-7665; Yamanouch group developed YM-10335 possessing phosphodiesterase inhibitory activity[6] (Fig. 1).

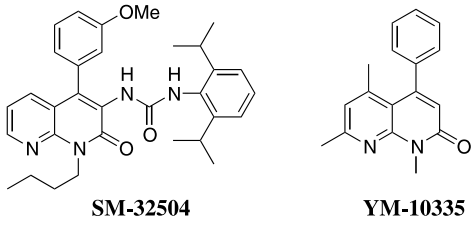
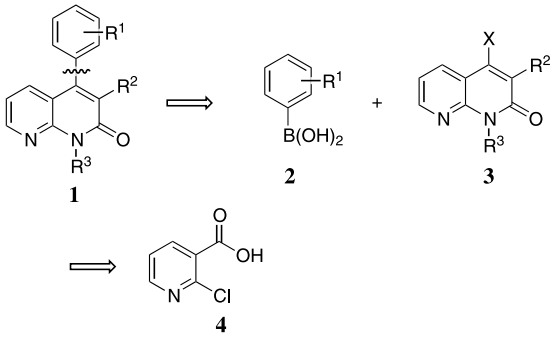


Figure 1.

As for synthesis of 1,8-naphthyridin-2(1*H*)-ones, classical Skraup reaction or the Friedländer reaction have been employed.[1] The former reaction involves the condensation of a 2-aminopyridine with a three-carbon unit such as β-ketoester. The latter is the condensation of a 2-amino-3-carbonylpyridine with a two-carbon unit typically enolizable carbonyl compound. Preparation of 4-aryl-1,8-naphtyhyridin-2(1*H*)-ones, however, is rather rare: Condensation reaction of 4-phenyl-2(1*H*)-pyridine and β-ketoesters[6,7] (Skraup reaction); condensation of 2-amino-3-benzoylpyridine and β-ketoesters[6,8] (Friedländer reaction); cyclization of 2-[(2,2-dimethyl-1-oxopropyl)amino]-β-hydroxy-β-phenyl-3-pyridinepropanoic acids.[9] These methods, however, are not effective for the synthesis of a diversity of compounds required in our bioassay study. We therefore developed an efficient method for the synthesis of 4-aryl-1,8-naphthyridin-2(1*H*)-ones. This method contains the following novel chemistry: (1) An efficient construction of 1,8-naphthyridin-2(1*H*)-one nuclei from 2-chloro-3-carboxypyridine **4** by amination and modified Friedländer reaction using acetic anhydride. Such cyclization has been known only for quinoline synthesis.[10] (2) The Suzuki coupling[11] of 4-chloro-1,8-naphthyridin-2(1*H*)-ones (Scheme 1). Only two precedents of the Suzuki coupling were reported for naphthyridines.[12,13]

Heating 2-chloronicotinic acid **4** and butylamine or benzylamine gave 2-aminonicotinic acids **5a** and **5b**,



Scheme 1.

Keywords: cyclization; Suzuki coupling; 4-aryl-1,8-naphthyridine-2-ones.

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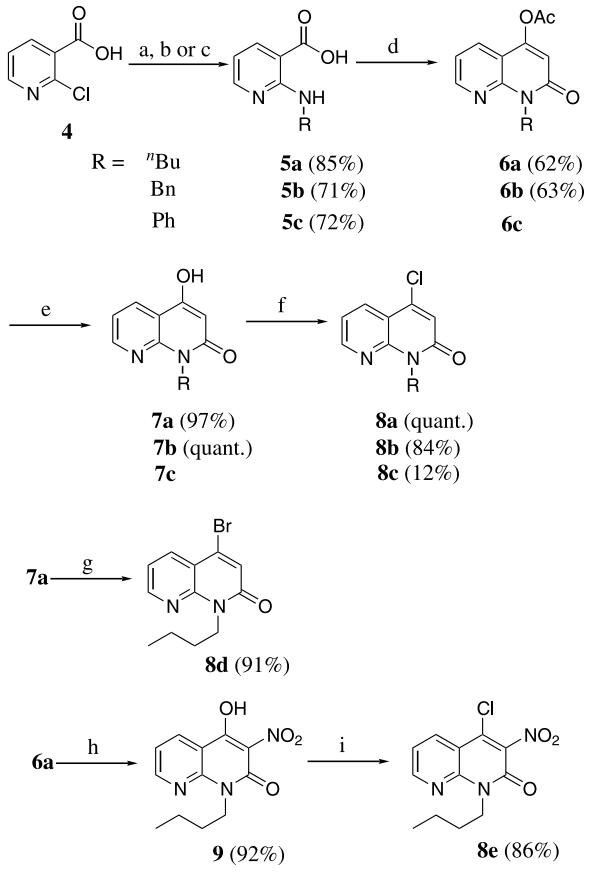


Scheme 2. *Reagents and conditions*: (a) butylamine, reflux, 2 d; (b) benzylamine, 90°C, 10 h; (c) aniline (2 equiv.), cat. Cu, cat. CuBr, K_2CO_3 (2 equiv.), DMF, 150°C, 4 h; (d) Ac_2O, AcOH, reflux, 2 h; (e) K_2CO_3, H_2O–MeOH, rt, 3 h; (f) $POCl_3$, 90°C, 0.5–2 h; (g) $POBr_3$, 100°C, 30 min; (h) conc. HNO_3, conc. H_2SO_4, rt, overnight; (i) $POCl_3$, 90°C, 45 min.

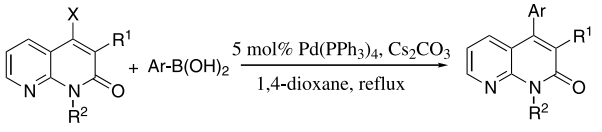
respectively.[2,14] *N*-Phenyl derivative **5c** was obtained according to the literature.[15] The reaction of **5a** or **5b** with acetic anhydride in boiling acetic acid for 2 h directly gave cyclized products 4-acetoxy-1,8-naphthyridines **6a** and **6b** in good yields. It may be likely that the intramoleculer C–C bond formation takes place via the Claisen condensation of acetamide and mixed anhydride of pyridinecarboxylate.

4-Acetoxynaphthyridines **6a** and **6b** thus obtained were converted to 4-chloronaphthyridines **8a** and **8b** by deacylation and treatment with $POCl_3$, total in four steps from a readily available starting material **4**. **5c** was converted analogously to **8c** without isolating the intermediates **6c** and **7c**. Although the yield of **8c** was low due to the formation of various by-products in the cyclizaion step, the method provided a sufficient amount of **8c** for our study. Treatment of **7a** with $POBr_3$ gave a bromide **8d**. It should be noted that these syntheses provide 1-alkyl- or 1-aryl-3-halonaphthyridin-2(1*H*)-ones without 3-substituent, which have not appeared in literature. 4-Chloro-3-nitronaphthyridine **8e**[16] was obtained from **6a** by a known method[17] with slight modification. The nitration was conducted in conc. H_2SO_4, which promoted simultaneous deacylation (Scheme 2).

The Suzuki coupling reaction of **8** with arylboronic acids (1.2 equiv.) yielded the desired 4-aryl-1,8-naphthyridin-2(1*H*)-ones in high yields under 1,4-dioxane reflux using 5 mol% $Pd(PPh_3)_4$ in the presence of cesium carbonate (1.8 equiv.) (Table 1). The coupling reaction proceeded equally well using chloride **8a** or bromide **8d** (entries 1 and 4). As indicated by the reactions of **8a**, **8b** and **8c**, 1-substituent also did not affect the yield (entries 1–3). A variety of arylboronic acids possessing either electron-donating or electron-withdrawing substituent underwent the Suzuki coupling. The reaction of 3-acetyl and 3-cyanophenylboronic acid, however, required slightly prolonged reaction time (entries 18–21). The 3-nitro group of **8e** did not interfere with the reaction (entries 5, 7, 9, 11, 13, 15, 17, 19 and 21).

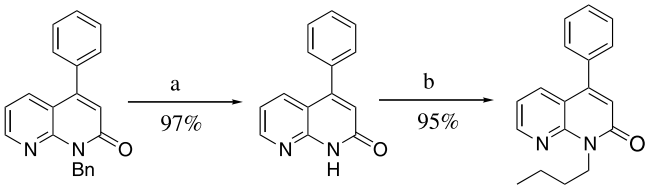
1-Benzyl-4-phenylnaphthyridin-2(1*H*)-one thus obtained was readily debenzylated with 47% aq. HBr in a high yield, and the product could be converted to a

Table 1. The Suzuki coupling reaction of 4-halonaphthyridines **8** with substituted boronic acids



8

Entry	Ar	8	Time/h	Yield/%
1		**8a**	4	90
2		**8b**	4	91
3		**8c**	4	88
4		**8d**	3	95
5		**8e**	5	82
6	4-OMe	**8a**	4	91
7	4-OMe	**8e**	5	80
8	3-OMe	**8a**	4	86
9	3-OMe	**8e**	5	83
10	2-OMe	**8a**	4	80
11	2-OMe	**8e**	5	79
12	4-CF_3	**8a**	4	92
13	4-CF_3	**8e**	5	79
14	3-CF_3	**8a**	4	98
15	3-CF_3	**8e**	5	82
16	2-F	**8a**	4	86
17	2-F	**8e**	5	73
18	4-Ac	**8a**	5	85
19	4-Ac	**8e**	7	82
20	4-CN	**8a**	10	83
21	4-CN	**8e**	12	75



Scheme 3. *Reagents and conditions*: (a) 47% aq. HBr, reflux, 2 h; (b) butyl bromide (1.2 equiv.), NaH (1.2 equiv.), DMF, rt, 5 h.

N-butylnaphthyridine (Scheme 3). Such *N*-alkylation would provide a variety of *N*-substituted 4-aryl-1,8-naphthyridin-2(1*H*)-ones.

In summary, we have developed a convenient synthesis of 4-aryl-1,8-naphthyridin-2(1*H*)-one derivatives starting from 2-chloronicotinic acid employing the Suzuki coupling reaction in the biaryl bond formation.

Cyclization procedure: 2-(Benzylamino)nicotinic acid **5b** (2.00 g, 8.76 mmol) was suspended in a mixture of acetic anhydride (25 mL) and acetic acid (17 mL) under a nitrogen atmosphere, and the mixture was stirred under reflux for 2 h. After cooled, volatile materials was evaporated, and the residue was purified by silica gel chromatography to give 1-benzyl-2-oxo-1,2-dihydro-1,8-naphthyridin-4-yl acetate **6b**[18] (1.62 g, 63%).

The Suzuki coupling: 1-Butyl-4-chloro-1,8-naphthyridin-2(1*H*)-one **8a** (100 mg, 0.384 mmol), phenylboronic acid (56.2 mg, 0.461 mmol), Cs_2CO_3 (225 mg, 0.691 mmol), and $Pd(PPh_3)_4$ (22.2 mg, 5 mol%) were suspended in 1,4-dioxane (7 mL) under a nitrogen atmosphere, and the mixture was stirred under reflux for 4 h. The reaction mixture was cooled to room temperature, and water was added. The organic materials were extracted with ethyl acetate (20 mL), washed with brine (20 mL), and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography to give 1-butyl-4-phenyl-1,8-naphthyridin-2(1*H*)-one[19] (96.4 mg, 90%).

References

1. For review of the synthesis of 1,8-naphtyridin-2(1*H*)-ones, see: (a) Paudler, W. W.; Kress, T. J. *Adv. Heterocyclic Chem.* **1970**, *11*, 123; (b) Cheng, C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37; (c) Paudler, W. W.; Sheets, R. M. *Adv. Heterocyclic Chem.* **1983**, *33*, 147.
2. Sherlock, M. H.; Kaminski, J. J.; Tom, W. C.; Lee, J. F.; Wong, S.; Kreutner, W.; Bryant, R. W.; McPhail, A. T. *J. Med. Chem.* **1988**, *31*, 2108.
3. Kuroda, T.; Suzuki, F.; Tamura, T.; Ohmori, K.; Hosoe, H. *J. Med. Chem.* **1992**, *35*, 1130.
4. Santilli, A. A.; Scotese, A. C.; Bauer, R. F.; Bell, S. C. *J. Med. Chem.* **1987**, *30*, 2270.
5. Muraoka, M.; Ioriya, K.; Ohashi, N. World Patent WO9638445A1; *Chem Abstr.* **1996**, *126*, 89279.
6. (a) Takayama, K.; Iwata, M.; Hisamichi, H.; Okamoto, Y.; Aoki, M.; Niwa, A. *Chem. Pharm. Bull.* **2002**, *50*, 1050; (b) Takayama, K.; Iwata, M.; Okamoto, Y.; Aoki, M. World Patent WO9606843A1; *Chem Abstr.* **1996**, *125*, 86620.
7. (a) El-Taweel, F. M. *J. Prakt. Chem.* **1990**, *332*, 762; (b) Kubo, K.; Ito, N.; Isomura, Y.; Sozu, I.; Homma, H.; Murakami, M. *Yakugaku Zasshi* **1979**, *99*, 788.
8. Davis, H. L.; Gedir, R. G.; Hawes, E. M. *Eur. J. Med. Chem. Chim. Ther.* **1985**, *20*, 381.
9. Turner, J. A. *J. Org. Chem.* **1990**, *55*, 4744.
10. Lutz, R. E.; Codington, J. F.; Rowlett, R. J.; Deinet, A. J.; Bailey, P. S. *J. Am. Chem. Soc.* **1946**, *68*, 1810.
11. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
12. Hersperger, R.; Bray-French, K.; Mazzoni, L.; Müller, T. *J. Med. Chem.* **2000**, *43*, 675.
13. Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024.
14. Brunel, S.; Montginoul, C.; Torreilles, E.; Giral, L. *J. Heterocyclic Chem.* **1980**, *17*, 235.
15. (a) Ullman, U. *Liebigs Ann. Chem.* **1907**, *355*, 320; (b) Nantka-Namirski, P. *Acta. Pol. Pharm.* **1967**, *24*, 113.
16. (a) Suzuki, F.; Kuroda, T.; Kawakita, T.; Manabe, H.; Kitamura, S.; Ohmori, K.; Ichimura, M.; Kase, H.; Ichikawa, S. *J. Med. Chem.* **1992**, *35*, 4866; (b) Kuroda, T.; Suzuki, F. *J. Heterocyclic Chem.* **1991**, *28*, 2029.
17. Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Spicer, B. A. *J. Med. Chem.* **1975**, *18*, 726.
18. Mp 133–134°C; IR (neat): ν 1770, 1651 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 2.44 (3H, s), 5.60 (2H, s), 6.70 (1H, s), 7.20–7.30 (5H, m), 7.37 (1H, dd, $J=4.6$, 7.9 Hz), 7.26 (1H, dd, $J=1.7$, 7.9 Hz), 8.68 (1H, dd, $J=1.7$, 4.6 Hz). Anal. calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.53; H, 4.65; N, 9.63.
19. Mp 96–97°C (lit.[6b] Mp 96–97°C); IR (neat): ν 1647 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz), δ (ppm) 0.92 (3H, t, $J=7.4$ Hz), 1.37 (2H, qt, $J=7.4$, 7.4 Hz), 1.64 (2H, tt, $J=7.4$, 7.4 Hz), 4.42 (2H, t, $J=7.4$ Hz), 6.60 (1H, s), 7.28 (1H, dd, $J=4.6$, 7.9 Hz), 7.48–7.55 (5H, m), 7.85 (1H, d, $J=7.9$ Hz), 8.68 (1H, d, $J=4.6$ Hz). Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.74; H, 6.49; N, 9.84.