A Palladium Catalyzed New Synthesis of *N,N*-Dimethyl[1,8]-naphthyridine-2-amines: Facile Incorporation of *N,N*-Dimethylamino Group From DMF in Aqueous Medium

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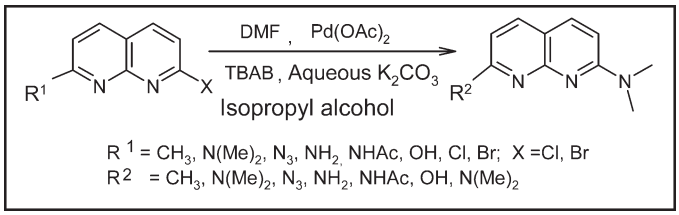

Here we report Pd catalyzed synthesis of *N,N*-dimethyl[1,8]naphthyridine-2-amines by facile incorporation of $N(Me)_2$ group from DMF in moderate to good yield.

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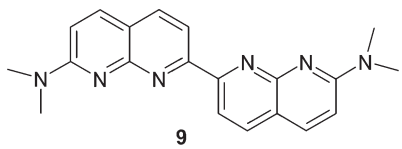
INTRODUCTION

Naphthyridine system is of great importance because of their broad applications in medicine. 1,8-Naphthyridine or naphthyridone systems are potentially useful as antihypertensives, antitumor agents, immunostimulants, and herbicide safeners. Also, *N,N*-dimethyl amino substituted 1,8-naphthyridines act as diuretic agents [1]. *N,N*-Dimethylamino group is present in methylene blue, crystal violet, 4-*N,N*-dimethylaminopyridine *etc*. (which are both biologically and chemically important compounds) [2]. In addition to palladium catalyzed C—C homo and hetero coupling reactions of aryl halides [3], it has been emerging as a powerful approach for the C—N coupling reactions [4,5]. Hawes *et al*. [1d] were able to incorporate the *N,N*-dimethylamino group in 1,8-napthyridines by treatment with gaseous dimethylamine. Palladium catalyzed aminocarbonylation using formamides as the amine source is also reported [5c]. With this information, we became interested to explore the reactions capable of introducing *N,N*-dimethylamino group in halo[1,8]naphthyridine systems.

RESULTS AND DISCUSSION

In our attempt to synthesize *N,N*-dimethylamino substituted 1,8-naphthyridines, we have carried out the reaction at room temperature with *N,N*-dimethylamine for direct replacement of halides but it does not work. Even under refluxing condition, the reaction does not proceed. The reaction is then carried out in the presence of $Pd(OAc)_2$ at room temperature and then it is also refluxed but the reaction fails. We then intended to change to *N,N*-dimethylformamide to see whether it may be a possible source of *N,N*-dimethylamino group by use of palladium catalysis. By several attempts, the reaction of one mmol of halo-napthyridine using DMF (0.95 mL), aqueous K_2CO_3 (1 mmol in 0.35 mL of water), TBAB (0.5 mmol), and $Pd(OAc)_2$ (0.05 mmol) at room temperature does not proceed but under reflux at 115°C, the reaction is successful with moderate to high yield (Table 1). The reaction rate and the yields are increased by the addition of isopropyl alcohol due to acceleration in the generation of Pd (0) [3g]. Although this method is similar to carbon-carbon homo-coupling reaction as reported by Lamaire, [3g] we are able to isolate only in one case the carbon-carbon homo-coupled yellow crystalline product *N,N,N′,N′*-tetramethyl-3,3′-bi-[1,8]-naphthyridin-7,7′-diamine **9** from (7-chloro-[1,8]-napthyridin-2-yl)-dimethylamine **2**.

Although various types of palladium catalyzed amination reactions are known [4], the incorporation of *N,N*-dimethylamino group is not hitherto reported from DMF in the [1,8]-naphthyridine system. So we report for the first time the incorporation of *N,N*-dimethylamino group from DMF under this reaction condition in the variously substituted [1,8]-napthyridines (Table 1). In the other aryl halides including pyridine halides homocoupled products result as reported in the literature [3g].



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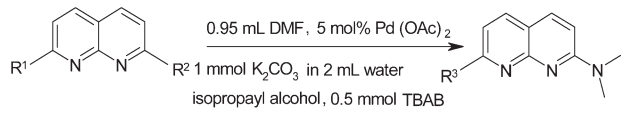
Scheme 1. Synthesis of *N,N*-dimethyl-1,8-naphthyridin-2-amines from the corresponding halo-naphythyridines by palladium catalysis.



In Table 1, entry 8, 7-bromo-1*H*-[1,8]naphthyridine-2-one **8** is represented as the enol-form for convenience but it is actually present in the lactam form.

The yield of the products increases as the number of chlorine atoms decreases from **5** to **7** which may be due to the C—Cl bond strength. In case of 2,7-dichloro-1,8-naphthyridine **5**, after 4 h reflux, mono- and disubstituted products **2** and **2a** are, respectively, formed with the same ratio but after 8 h no mono substituted product **2** is found. For mixed bromo chloro napthyridine **7**, the same result is observed where bromo group is always substituted but not chloro, which may be due to the lower bond strength of C—Br bond than C—Cl bond. The starting chloro and bromo derivatives are made according to the literature procedure [6,7].

EXPERIMENTAL

Representative experimental procedure for *N*-(7-dimethyl amino[1,8]naphthyridin-2-yl)acetamide 4a. In a round-bottomed flask, a mixture of *N*-(7-chloro-[1,8]naphthyridin-2-yl)-acetamide **4** (170 mg, 0.813 mmol), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), K_2CO_3 (112 mg, 0.813 mmol), TBAB (130.1 mg, 0.4065 mmol), water (0.8 mL), DMF (1.5 mL), and 2 mL of isopropayl alcohol is taken and refluxed for 7.5 h under nitrogen atmosphere. The whole solution is then passed through a celite bed (2 cm), washed well with isopropyl alcohol, the filtrate is then evaporated under reduced pressure and washed well with brine followed by water. The organic layer is then dried with Na_2SO_4 (anhydrous) and evaporated under reduced pressure followed by column chromatography using 2% methanol in CH_2Cl_2 offering the corresponding *N,N*-dimethylamino derivative, *N*-(7-dimethylamino-[1,8]naphthyridin-2-yl)-acetamide **4a** as yellow crystals. mp. 214–216°C; IR (KBr): 3219, 3062, 1692, 1609, 1326, 1151, 834, 796.45 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.349 (bs, 1H), 8.094 (d, 1H, J = 8.5 Hz), 7.914(d, 1H, J = 8.5 Hz), 7.786 (d, 1H, J = 9.0Hz), 6.827 (d, 1H, J = 9.0Hz), 3.266 (s, 6H), 2.215 (s, 3H); ms (ESI) *m/z* 244.97 (M^++H+Na, 100), 497.97 (2M+H+Na, 80). Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.59; H, 6.13; N, 24.33. Found: C, 62.56; H, 6.16; N, 24.37.

Methyl(7-methyl[1,8]napthyridin-2-yl)amine 1a. mp. 140–142°C; IR (KBr): 1665, 1348, 1153, 842, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.99 (d, 1H, J = 9.04 Hz), 7.98 (d, 1H, J = 7.96 Hz), 7.07 (d, 2H, J = 8.48 Hz), 3.17 (s, 6H), 2.55 (s, 3H). ms (ESI): *m/z* 188.3 (M^++ 1, 100), (M^++ 2, 10). Anal. Calcd. for $C_{11}H_{13}N_3$: C 70.56; H, 7.00; N, 22.44. Found: C 70.58; H, 7.03; N, 22.40.

***N,N,N′,N′*-Tetramethyl[1,8]naphthyridine-2,7-diamine 2a.** mp. 155–157°C; IR (KBr): 2928, 1540, 1379, 1148, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 2H, J = 8.9 Hz), 6.54 (d, 2H, J = 8.9 Hz), 3.23 (s, 12H). ms (ESI): *m/z* 217.3 (M^++ 1, 100), 218.1 (M^++ 2, 15). Anal. Calcd. for $C_{10}H_{10}N_6$: C, 66.64; H, 7.46; N, 25.90. Found: C, 66.66; H, 7.43; N, 25.94.

(7-Azido[1,8]naphthyrin-2-yl)dimethylamine 3a. mp. 135–137°C; IR (KBr): 2927, 2122, 1531, 1354, 1148, 900, 739 cm^{-1}; ^1H NMR (d_6-DMSO, 400 MHz): δ 8.15 (d, 1H, J = 8.2 Hz), 8.08 (d, 1H, J = 9.2 Hz), 7.21 (d, 1H, J = 8.3 Hz), 7.18 (d, 1H, J = 9.1 Hz), 3.29 (s, 6H). Anal. Calcd. for $C_{10}H_{10}N_6$: C, 56.07; H, 4.71; N, 39.23. Found: C, 56.05; H, 4.68; N, 39.26.

7-Dimethylamino-1*H*-[1,8]naphthyridin-2-one 5a. mp. 118–120°C; IR (KBr): 2931, 1659, 1612, 1370, 1150, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.92 (bs, 1H), 7.56 (d, 1H, J = 9 Hz), 7.51 (d, 1H, J = 9 Hz), 6.46 (d, 1H, J = 8.7 Hz), 6.32 (d, 1H, J = 9.0 Hz), 3.16 (s, 6H), ms (ESI): *m/z* 212.1 (M^++Na, 67), 401.1 ($2M^+$+Na, 100). Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.44; H, 5.91; N, 22.18.

***N,N,N′,N′*-Tetramethyl-3,3′-bi[1,8]naphthyridin-7,7′-diamine 9.** mp > 300°C, IR (KBr): 1615, 1529, 1378, 1121, 844 cm^{-1}; ^1H NMR (CDCl3, 400 MHz): δ 8.65 (d, 1H, J = 8.2 Hz), 8,05 (d, 1H, J = 8.2 Hz), 7.88 (d, 1H, J = 9.0 Hz), 6.95 (d, 1H, J = 9.0 Hz). ms (ESI): *m/z* 345.4 (M^++H, 65), 376.5 (M^++HCl, 100). 376.5 (M^++H+HCl, 70). Anal. Calcd.

Table 1

Synthesis of *N,N*-dimethyl-1,8-naphthyridines from the corresponding halo-naphthyridines by palladium catalysis.

Entry	Reactant	Product	Time (h)	Yield (%)
1	R^1 = CH_3, R^2 = Br (**1**)	R^3 = CH_3 (**1a**)	5	75
2[a,b]	R^1 = $N(Me)_2$, R^2 = Cl (**2**)	R^3 = $N(Me)_2$ (**2a**)	6	30
3	R^1 = N_3, R^2 = Cl (**3**)	R^3 = N_3 (**3a**)	5.5	70
4	R^1 = NHAc, R^2 = Cl (**4**)	R^3 = NHAc (**4a**)	7.5	55
5	R^1 = Cl, R^2 = Cl (**5**)	R^3 = $N(Me)_2$ (**2a**)	8	58
6	R^1 = Cl, R^2 = Br (**6**)	R^3 = $N(Me)_2$ (**2a**)	6.5	65
7	R^1 = Br, R^2 = Br (**7**)	R^3 = $N(Me)_2$ (**2a**)	6	70
8	R^1 = OH, R^2 = Br (**8**)	R^3 = $N(Me)_2$ (**5a**)	12	72

[a] In this case dehydro halogenated product is obtained in 20% yield. All reactions are carried out at 115°C, $Pd(OAc)_2$ (0.05 mmol), K_2CO_3 (1 mmol in 0.35 mL of water), TBAB (0.5 mmol), and 2 mL of isopropyl alcohol with respect to 1 mmol of the naphthyridine halide.
[b] Also C—C coupled product *N,N,N′,N′*-tetramethyl-3,3′-bi-[1,8]-naphthyridine-7,7′-diamine **9** is isolated in 15% yield.

for $C_{20}H_{20}N_6$: C, 69.75; H, 5.85; N, 24.40. Found: C, 69.78; H, 5.80; N, 24.44.

Preparation of 2-bromo-7-methyl[1,8]naphthyridine 1. In a round-bottomed flask, hydrobromic acid (0.624 mL 48%, 5.65 mmol) is taken. The flask is cooled to 0°C by ice-salt bath and then 7-methyl-[1,8]-napthyridin-2-yl-amine (200 mg, 1.257 mmol) is added to it over a period of 10 min. Then bromine [0.194 mL (0.464 mg), 3.77 mmol] is added dropwise carefully maintaining the temperature at 0°C. After addition of bromine, $NaNO_2$ (216.66 mg, 3.14 mmol) in water (0.31 mL) is added for a period of 1.5 h. Here, the temperature of the reaction should be maintained at 0°C to −5°C. After addition is complete, it is stirred for 30 min. The precipitate obtained is filtered and finally washed well with water to make it acid-free and the mother liquor is collected and neutralized with NaOH adding crushed ice and then it is extracted with CH_2Cl_2 (4 × 25 mL) and is dried with anhydrous Na_2SO_4. The solvent is removed by evaporation under reduced pressure. This crude product is pure enough to be crystallized to afford white microcrystals of the title compound **1**, 215 mg (77%). mp. 202–205°C, IR (KBr): 2931, 1277, 1150, 545 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, 1H, J = 9.33 Hz), 7.97 (d, 1H, J = 8.4 Hz), 7.58 (d, 1H, J = 8.1 Hz), 7.41 (d, 1H, J = 8.1 Hz), 2.80 (s, 3H), ms (ESI): m/z 244.96 (M^++Na, 100), 246.97 (M^++Na+2, 98). Anal. Calcd. for $C_{20}H_{20}N_6$: C, 48.46; H, 3.16; N, 12.56. Found: C, 48.51; H, 3.12; N, 12.58.

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