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PALLADIUM-CATALYZED SUZUKI COUPLING TOWARDS 2-AMINO-1,8-NAPHTHYRIDINES

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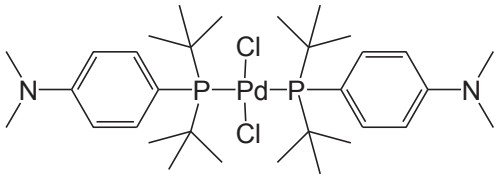
Abstract – Several 2-amino-6-aryl-1,8-naphthyridines were reported. The cyclocondensation of 2,6-diaminopyridine, 2-bromomalonaldehyde in phosphoric acid resulted in the formation of 2-amino-6-bromo-1,8-naphthyridine, which was converted into 2-amino-6-aryl-1,8-naphthyridines by palladium-catalyzed Suzuki reaction with arylboronic acid. It is shown that the Suzuki coupling with palladium catalyst (**Pd-132**) could be completed efficiently with lower catalyst loading and good to excellent yields. The title compounds were characterized by NMR spectra and mass spectra.

Organic molecules with naphthrydine skeleton have attracted numerous attention. They could be used as anti hepatitis C (HCV) agents.[1] Water soluble (η^6-arene)ruthenium(II) complexes based on pyrazolyl-naphthryridine ligands could be used as catalysts for the hydrogenation of aromatic ketones.[2] The naphthyridine-based compounds could also be utilized as probes and sensors, for example, Jachak[3a] reported that benzo[b][1,8]naphthyridienes could be as fluorescent agents with human serum albumin (HAS) and Bovine serum albumin (BSA). Some others reported ferrocene naphthyridine derivatives such as di-substituted ferrocene derived FecDN behave as a selective visual chemosensor for mercury ions with good selectivity and sensitivity.[3b] Naphthalimide-naphthyridines have also been synthesized for the detection of hydroxyl radicals, which could be used to distinguish hydroxyl radicals from other reactive oxygen species with high selectivity and short response time.[3c] A rhodamine B based chemosensor containing 2-amino-7-methyl-1,8-naphthyridine moiety was reported for colorimetric and fluorescent response on corresponding nucleoside polyphosphates through multi-hydrogen bond interaction.[3d] Lanthanide complex Gd-ANAMD with 2-amino-7-methyl-1,8-naphthyridine moiety as ligand was achieved for selective magnetic resonance imaging towards GMP over other ribonucleotide

polyphosphates.[3e] 1,8-Naphthyridine-modified rhodamine B has also been used as sensor to detect Cu^{2+} selectively with a dramatic color change.[3f] Some 1,8-naphthyridines display red-fluorescence emissions and two-photon absorption properties.[3g]

However no any information about 6-aryl-2-aminonaphthyridines has been reported up to now which might be due to the synthetic difficult of the key precursor 2-amino-6-bromonaphthyridine.[4] We have ever reported some aza-heterocycles by different synthetic approaches.[5,6] With 2-amino-6-bromo-naphthyridine as a suitable precursor, the Suzuki cross coupling reaction with different arylboronic acid could be employed to construct 2-amino-6-arylnaphthyridines for further evaluation of their properties. Considering the potential application of 2-amino-6-arylnaphthyridines, it is worthy to explore the method with palladium catalyst system.

The initial effort on the Suzuki coupling of 2-amino-6-bromo-naphthyridine and 4-methylphenylboronic acid has been performed with $Pd(PPh_3)_4$ (10% mole loading)，however only an inseparable mixture was obtained (crude yield *ca.* 13.7%). We envisage that a novel phosphine based catalyst, [(A-^{ta}Phos)$_2$PdCl$_2$] (CAS No. 887919-35-9, **Pd-132**), which is highly effective for various cross couplings such as Suzuki(or Suzuki-Miyaura), Negeshi-like, Sonogashira-like reactions with mild reaction conditions and different halide or pseudohalide substrates as early reported, might be a suitable catalyst for this coupling. [7-9]

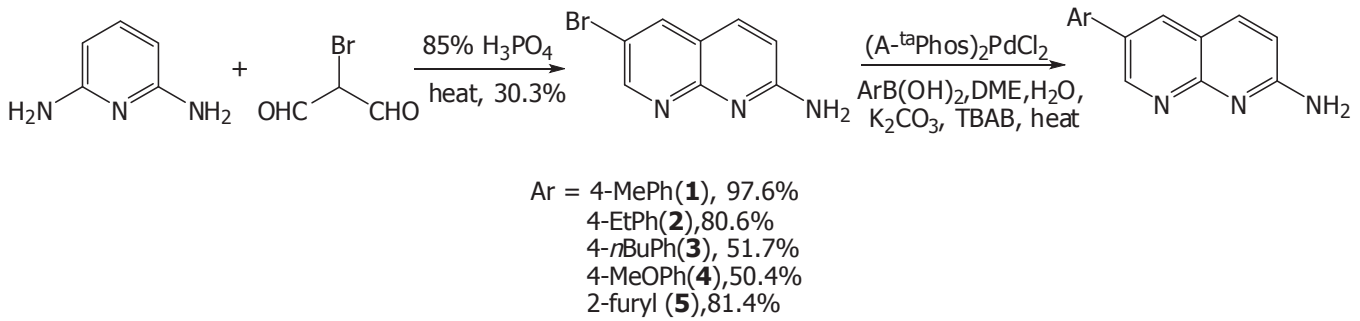


(A-^{ta}Phos)$_2$PdCl$_2$

Scheme 1. Catalyst [(A-^{ta}Phos)$_2$PdCl$_2$]

Since naphthyridine-based molecules could be potentially useful in medicinal chemistry and opt-electric areas, we are interested in 6-aryl-2-aminonaphthyridines. The precursor 2-amino-6-bromonaphthyridine is synthesized from the reaction of 2,6-diaminopyridine, 2-bromomalonaldehydre in phosphoric acid with heating as previously reported.[4] It is proved that the separation of this intermediate is quite difficult due to its low solubility. The Suzuki coupling of 2-amino-6-bromonaphthyridine with different arylboronic acids is performed in the presence of [(A-^{ta}Phos)$_2$PdCl$_2$] and it is pleased to find that all of these reactions proceed with good to excellent yields (50 % to 98 %) with a relatively low catalyst loading (*ca.* 0.8%),

while it is no need to protect amino group during the process (**Scheme 2**).



Scheme 2. Synthetic approach toward target molecules

In conclusion, we developed an easy and simple synthetic method towards 2-amino-6-naphthyridines by palladium-catalyzed Suzuki cross coupling of amino-substituted aryl bromide with different arylboronic acid with low catalyst loading and without protection of amino group. This method might be applied to the construction of other aza-heterocycles from suitable precursors with amino-substituent.

EXPERIMENTAL

All chemical are commercially available as analytic grade and used without further purification. Solvents are purified according to standard methods prior to use. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance III 500MHz spectrometer (^{1}H NMR 500 MHz, ^{13}C NMR125 MHz). Mass spectra were measured on Bruker Daltonics maXis Impact spectrometer. Melting point was measured on an X-4 micrographic melting point measuring instrument. Mass spectra were measured on micOTOF II (ESI).

Synthetic procedures

2-Amino-6-bromonaphthyridine is prepared according to literature.[4]

A mixture of 2,6-diaminopyridine (6.0 g, 55 mmol) and 2-bromo-1,3-malonaldehyde (8.0 g, 53 mmol) in 85% orthophosphorous acid (160 mL) was heated at reflux for 6 h, then it was stirred at room temperature till the reaction is completed by thin layer chromatography (TLC) monitoring. The reaction mixture was neutralized with aq. NH_4OH to afford a dark-brown solid, which was filtered and dried before dissolved in MeOH with assistance of ultrasonic instrument. The target molecule was then separated by column chromatography to afford a pale-yellow solid (3.85 g, 30.3%) R_f = 0.39 (CH_2Cl_2:MeOH = 10:1), mp 160-162 °C. (Lit.[4] mp 210-212 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.82 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H), 6.14 (s, 2H), 5.99 (d, J = 8.8 Hz, 1H).

Pd(PPh$_3$)$_4$-catalyzed the Suzuki cross coupling towards compound 1

A pressure flask was charged with 2-amino-6-bromonaphthyridine (0.56 mmol) and 4-methyl-

phenylboronic acid (1.12 mmol), K_2CO_3 (1 g, 7.24 mmol), Bu_4NBr (0.3 g, 0.93 mmol), H_2O (1.5 mL, 83.3 mmol), and DME (30 mL). Nitrogen was bubbled into the mixture for 10 min before $Pd(PPh_3)_4$ (65 mg, $5.6*10^{-2}$ mmol) was introduced and the flask was screwed up. The mixture was heated at 120 °C for 16 h. After cooling, the volatiles were removed under vaccum before the residues were subjected to column chromatography to afford compound **1** (18 mg, crude yield *ca.* 13.7%) with impurity which could not be removed (see supporting information).

General procedure for the Suzuki cross coupling reaction by Pd-132

A pressure flask was charged with 2-amino-6-bromonaphthyridine (0.56 mmol) and arylboronic acid (1.12 mmol), K_2CO_3 (1 g, 7.24 mmol), Bu_4NBr (0.3 g, 0.93 mmol), H_2O (1.5 mL, 83.3 mmol), and DME (30 mL). Nitrogen was bubbled into the mixture for 5 min before [(A-^{ta}Phos)$_2$PdCl$_2$ (5 mg, $7.06*10^{-3}$ mmol) was introduced and the flask was screwed up. The mixture was heated at 120 ºC for 16 h. After cooling, the volatiles were removed under vaccum before the residues were subjected to column chromatography to afford the target molecules.

Compound **1**, pale-yellow solid (128 mg, 97.6%), mp 161.1-161.9 ºC . R_f = 0.4 (DCM : MeOH=10:1). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ: 8.12 (d, *J* = 2.5 Hz, 1H), 7.49 (d, *J* = 2.5 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 2H), 6.43 (d, *J* = 8.0 Hz, 2H), 6.25 (s, 2H), 6.01 (d, *J* = 8.8 Hz, 1H), 1.47 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ: 149.96 (s), 138.42 (s), 134.15 (s), 133.60 (s), 129.77 (s), 129.29 (s), 126.42 (s), 114.11 (s), 13.52 (s). HR-MS (ESI) Required for $C_{15}H_{13}N_3$: 235.11, found 236.1186 ($M+H^+$).

Compound **2** brown solid (112 mg, 80.6%). mp 162-163 ºC. R_f =0.35 (DCM : MeOH=10:1). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ: 8.08 (s, 1H), 7.40 (s, 1H), 7.10 (d, *J* = 10.3 Hz, 1H), 6.77 (d, *J* = 6.4 Hz, 2H), 6.41 (d, *J* = 6.7 Hz, 2H), 6.05 (s, 2H), 5.99 (d, *J* = 8.7 Hz, 1H), 1.72 (s, 2H), 0.29 (s, 3H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ: 180.70 (s), 176.01 (s), 170.17 (s), 163.06 (s), 157.82 (s), 154.67 (s), 153.13 (s), 148.82 (s), 148.51 (s), 146.40 (s), 136.46 (s), 133.84 (s), 43.10 (s), 33.48 (s). Required for $C_{16}H_{15}N_3$ 249.13, found 250.1354 ($M+H^+$).

Compound **3**. pale-yellow solid (80 mg, 51.7%), mp 269-269.8 ºC. R_f =0.34 (DCM : MeOH=10:1). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ: 8.14 (d, *J* = 2.5 Hz, 1H), 7.57 (d, *J* = 2.3 Hz, 1H), 7.22 (d, *J* = 8.9 Hz, 1H), 6.81 (d, *J* = 8.1 Hz, 2H), 6.53 (s, 2H), 6.45 (d, *J* = 8.1 Hz, 2H), 6.06 (d, *J* = 8.9 Hz, 1H), 1.75 (t, *J* = 7.6 Hz, 2H), 0.70 (s, 2H), 0.44 (dd, *J* = 14.9, 7.4 Hz, 2H), 0.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ: 160.70 (s), 156.01 (s), 150.17 (s), 143.06 (s), 137.82 (s), 134.67 (s), 133.13 (s), 128.82 (s), 128.51 (s), 126.40 (s), 116.46 (s), 113.84 (s), 27.82 (s), 23.10 (s), 19.20 (s), 13.48 (s). HR-MS (ESI) Required for $C_{18}H_{19}N_3$: 277.16, found 277.9551.

Compound **4** brown solid (78 mg, 50.4%). mp 248-249 ºC. R_f =0.38 (DCM : MeOH=10:1). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ: 8.05 (s, 1H), 7.31 (s, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 2H), 6.11 (d,

J = 8.3 Hz, 2H), 6.01 (s, 2H), 5.94 (d, *J* = 8.7 Hz, 1H), 2.86 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 160.66 (s), 158.93 (s), 155.91 (s), 150.17 (s), 137.79 (s), 132.69 (s), 129.70 (s), 128.69 (s), 127.68 (s), 116.49 (s), 114.60 (s), 113.81 (s), 55.22 (s). Required for $C_{15}H_{13}N_3O$ 251.11, found: 252.1145 ($M+H^+$).

Compound **5** yellow solid (96 mg, 81.6%). mp 158-159 ºC. R_f =0.33 (DCM : MeOH=10:1). ^{1}H NMR (500 MHz, DMSO-*d6*) δ: 8.18 (d, *J* = 1.6 Hz, 1H), 7.41 (d, *J* = 1.8 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 1H), 6.91 (s, 1H), 6.14 (d, *J* = 3.2 Hz, 1H), 6.06 (s, 2H), 5.98 (d, *J* = 8.8 Hz, 1H), 5.75 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 160.74 (s), 148.00 (s), 143.03 (s), 137.74 (s), 129.82 (s), 120.04 (s), 116.28 (s), 114.05 (s), 112.16 (s), 105.64 (s), 39.52 (s). Required for $C_{12}H_9N_3O$: 211.07, found: 212.0828 ($M+H^+$).

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