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Synthesis of Pyrido[2,1-*b*]quinazolin-11-ones and Dipyrido[1,2-a:2′,3′-*d*]pyrimidin-5-ones by Pd/DIBPP-Catalyzed Dearomatizing Carbonylation

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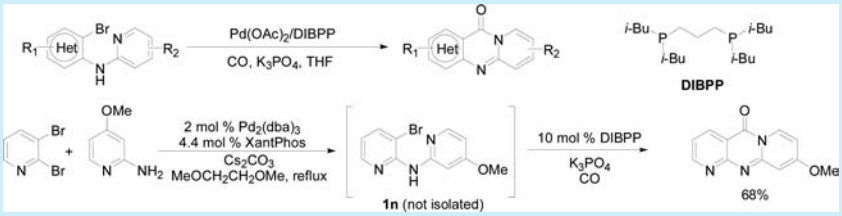
Supporting Information



ABSTRACT: N-Fused heterocycles can be easily synthesized by palladium-catalyzed dearomatizing carbonylation using 1,3-bis(diisobutylphosphino)propane (DIBPP) as the ligand. Pyrido[2,1-*b*]quinazolin-11-ones were obtained from *N*-(2-bromophenyl)pyridine-2-amines in up to quantitative yield and dipyrido[1,2-a:2′,3′-*d*]pyrimidin-5-ones from 3-bromo-*N*-(pyridine-2-yl)pyridine-2-amines in up to 84% yield. The cyclocarbonylation can be also realized without isolation of compound **1** and additional palladium catalyst.

Nitrogen-containing heterocycles are important molecular motifs in natural products, materials and bioactive molecules.[1] The development of efficient and environmental friendly methods for the synthesis of diverse heterocycles is an important challenge in synthetic chemistry.[2,3] Transition-metal-catalyzed reactions are potentially valuable for the synthesis of a wide range of heterocycles. Dearomatization has become an efficient method to prepare complex nitrogen-containing heterocycles.[4,5] For example, pyridine derivatives have been used to synthesize different kinds of N-fused heterocycles via transition-metal-catalyzed coupling, cycloisomerization, oxidation, and other reactions.[5] Carbonylation is a powerful tool to synthesize many valuable carbonyl-containing compounds from a broad scope of substrates.[6] There are a few reports using dearomatizing carbonylation to synthesize N-fused heterocyclic compounds.[7] Recently, Beller, Wu and co-workers reported the base-controlled synthesis of fused quinazolinones by a palladium-catalyzed carbonylation/nucleophilic aromatic substitution sequence.[7a] 11*H*-Pyrido[2,1-*b*]quinazolin-11-one[8] was also prepared by the palladium-catalyzed C−H carbonylation of *N*-aryl-2-aminopyridines using $K_2S_2O_8$ as the oxidant in TFA.[7b] Gevorgyan and co-workers reported a method to prepare indolizines from 2-propargylpyridines by palladium-catalyzed carbonylative cyclization/arylation.[7c] Tilley and co-workers reported a palladium-catalyzed carbonyl insertion route to pyrido[2,1-*b*]quinazoline, but with only four examples.[7d] However, the carbonylation of 3-bromo-*N*-(pyridine-2-yl)-pyridine-2-amine to form dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one[9] was not reported, where two pyridinyl moieties can retard the catalytic activities. Herein we describe the facile synthesis of both pyrido[2,1-*b*]quinazolin-11-ones and dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-ones by palladium-catalyzed dearomatizing carbonylation using 1,3-bis(diisobutylphosphino)propane (DIBPP) as the ligand.

Initially, substrate **1a** was used to optimize the reaction conditions (Table 1). Different ligands were studied when the reaction was carried out in DMA at 120 °C using DBU. Davephos (**L1**) gave 11*H*-pyrido[2,1-*b*]quinazolin-11-one **2a** in 18% isolated yield, and most of **1a** was recovered (entry 1). Product **2a** was obtained in 21−38% yield using A-^{ta}Phos (**L2**), RuPhos (**L3**), or JohnPhos (**L4**) (entries 2−4). When tri-*tert*-butylphosphine (**L5**) was used, the yield of **2a** increased to 41% (entry 5). Tricyclohexylphosphine (**L6**) afforded **2a** in 74% yield (entry 6). The yield of **2a** increased to 92% when THF was used as the solvent (entry 7). Acetonitrile and toluene gave **2a** in 45% and 89% yields, respectively (entries 8 and 9). Different bases were then studied. Inorganic bases potassium carbonate and potassium phosphate afforded **2a** in 89% and 97% yields, respectively, while the organic base triethylamine gave **2a** in 23% yield (entries 10−12). When the temperature was lowered to 100 °C, the yield of **2a** decreased to 33% or 50% using DBU or K_3PO_4 as the base (entries 13 and 14). When a phenyl-substituted phospha-adamantane ligand **L7** was used instead of **L6**, **2a** was isolated in only 15% yield (entry 15). When the bidentate phosphine ligand **L8** (1,3-bis-(diisobutylphosphino)propane, DIBPP) was used for the reaction, **2a** was obtained in excellent yield (entry 16). Another

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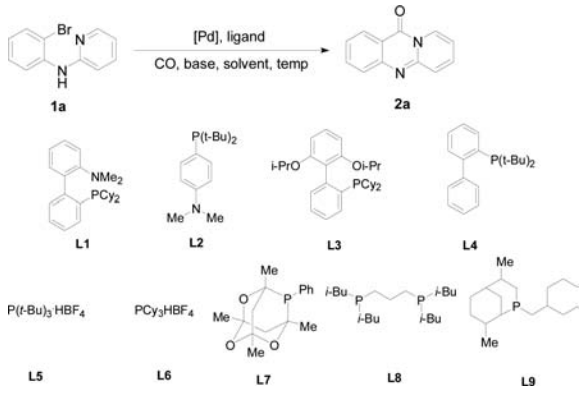
Table 1. Screening of the Reaction Conditions[a]



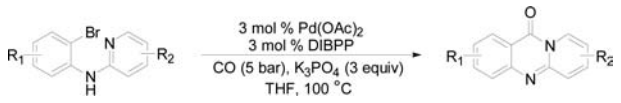
entry	ligand	base	solvent	temp (°C)	P_{CO} (bar)	yield[b] (%)
1	L1	DBU	DMA	120	20	18
2	L2	DBU	DMA	120	20	38
3	L3	DBU	DMA	120	20	35
4	L4	DBU	DMA	120	20	21
5	L5	DBU	DMA	120	20	41
6	L6	DBU	DMA	120	20	74
7	L6	DBU	THF	120	20	92
8	L6	DBU	MeCN	120	20	45
9	L6	DBU	toluene	120	20	89
10	L6	K_2CO_3	THF	120	20	89
11	L6	K_3PO_4	THF	120	20	97
12	L6	Et_3N	THF	120	20	23
13	L6	DBU	THF	100	20	33
14	L6	K_3PO_4	THF	100	20	50
15	L7	K_3PO_4	THF	120	20	15
16	L8	K_3PO_4	THF	120	20	99
17	L9	K_3PO_4	THF	120	20	65
18	L8	K_3PO_4	THF	120	10	99
19	L8	K_3PO_4	THF	100	10	99
20	L8	K_3PO_4	THF	70	10	10
21	L8	K_3PO_4	THF	100	5	99
22[c]	**L8**	**K_3PO_4**	**THF**	**100**	**5**	**99**
23[d]	L8	K_3PO_4	THF	100	5	86

[a]Conditions: 0.2 mmol **1a**, 5 mol % $Pd(OAc)_2$, Pd/P = 1/2, 0.6 mmol of base, 2 mL of solvent, 15 h. [b]Isolated yield. [c]3 mol % of $Pd(OAc)_2$. [d]2 mol % of $Pd(OAc)_2$.

trialkylphosphine **L9** afforded **2a** in 65% yield (entry 17). When the reaction temperature was lowered to 100 °C and the CO pressure to 5 bar, **2a** was obtained in nearly quantitative yield (entries 18−21). The yield did not change when the amount of catalyst was reduced to 3 mol % (entries 22 and 23).

The scope of the reaction was studied using a variety of reactants in the presence of 3 mol % of $Pd(OAc)_2$/3 mol % of DIBPP, THF as the solvent, and K_3PO_4 as the base at 100 °C and 5 bar of CO (Table 2). Electron-donating or electron-withdrawing substituents on the phenyl moiety have little effect on the reaction. Substrates with electron-donating substituents on the pyridyl moiety smoothly afford **2** (entries 1−3), but electron-withdrawing substituents on the pyridyl moiety retard the reaction. For example, when **1f** with fluoride on the pyridyl moiety was reacted, there was little conversion to **2f**. The carbonylation of **1f** needed higher temperature (120 °C) to give **2f** (entry 6), indicating that electron-withdrawing substituents on the pyridyl moiety could reduce the reactivity of the nitrogen in the pyridyl ring. When pyridine was replaced by quinoline, **2g** was obtained in 90% yield (entry 7). Then the

Table 2. Synthesis of 11*H*-Pyrido[2,1-*b*]quinazolin-11-one via Pd-Catalyzed Dearomatizing Carbonylation of *N*-(2-Bromophenyl)pyridine-2-amine Derivatives[a]



entry	substrate	product	yield (%)[b]
1	**1a**	**2a**	99
2	**1b**	**2b**	98
3	**1c**	**2c**	92
4	**1d**	**2d**	88
5	**1e**	**2e**	84
6	**1f**	**2f**	80[c]
7	**1g**	**2g**	90
8	**1h**	**2h**	99
9	**1i**	-	0
10	**1j**	-	0
11	**1k**	**2k**	31

[a]Conditions: 0.5 mmol of **1**, 3 mol % of $Pd(OAc)_2$, 3 mol % of DIBPP, 1.5 mmol of base, 5 bar CO, 5 mL of THF, 100 °C, 15 h. [b]Isolated yield. [c]120 °C, 10 bar.

reaction was applied to **1h**, affording **2h** in 99% yield (entry 8). However, when *ortho*-substituted substrates **1i** and **1j** were used, no carbonylation product **2** was isolated, while starting materials disappeared (entries 9 and 10). The product with an *o*-chlorine or methoxy substituent may not be stable. The substrate with an *o*-methyl substituent gave the desired product **2k** in 31% yield (entry 11).

Our method was also applied to bromo-substituted heteroaromatic compounds (Table 3). At 100 °C, most **1l** was not consumed in the presence of 3 mol % of $Pd(OAc)_2$. 5*H*-Dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one (**2l**) was obtained in 52% isolated yield at 120 °C under 10 bar of CO in the presence of 5 mol % of $Pd(OAc)_2$ and 5 mol % of DIBPP. Substituents can have a significant effect on the reactions.

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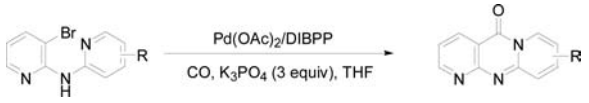
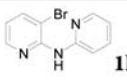
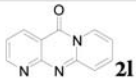
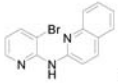
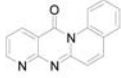
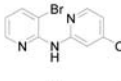
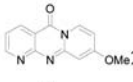
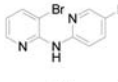
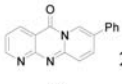
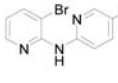
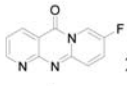
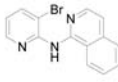
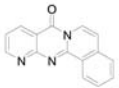
Table 3. Synthesis of 5*H*-Dipyrido[1,2-*a*:2′,3′-*d*]pyrimidin-5-one via Pd-Catalyzed Dearomatizing Carbonylation of 3-Bromo-*N*-(pyridine-2-yl)pyridine-2-amine Derivatives[a]



entry	substrate	product	yield (%)[b]
1	 **1l**	 **2l**	52
2	 **1m**	 **2m**	61
3	 **1n**	 **2n**	80
4	 **1o**	 **2o**	84
5	 **1p**	 **2p**	40[c] (51)[d]
6	 **1q**	 **2q**	65

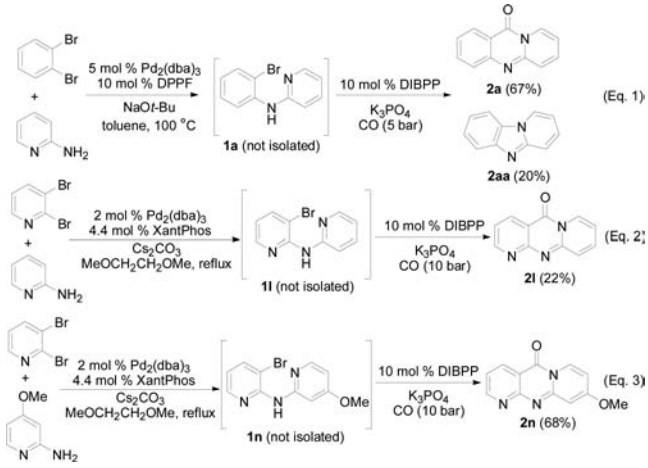
[a]Conditions: 0.5 mmol of **1**, 5 mol % of $Pd(OAc)_2$, 5 mol %of DIBPP, 1.5 mmol of base, 10 bar CO, 5 mL of THF, 120 °C, 15 h. [b]Isolated yield. [c]120 °C, 72 h. [d]135 °C, 15 h.

Reactants with an electron-donating substituent gave higher yields (61−84%, **2m−o**, entries 2−4). Substrate **1o** with electron-withdrawing substituent (F, entry 5) gave **2p** in 40% yield after 72 h at 120 °C, while the yield was 51% after 15 h at 135 °C. Substrate **1q** with an isoquinoline ring in the molecule also reacted smoothly to give the product **2q** in 65% yield.

The substrates (**1**) for the research were prepared via Pd-catalyzed coupling reactions.[10] The dearomatic cyclocarbonylation reaction was also attempted without the isolation of compound **1** (Scheme 1). Specifically, the reaction mixture of **1a** generated in situ from 1,2-dibromobenzene and 2-aminopyridine in toluene was directly transferred to an autoclave followed by addition of DIBPP and K_3PO_4 (eq 1), affording carbonylation product **2a** in 67% yield with 20% yield of the C−N coupling product **2aa**. When the process was applied to prepare **2l**, the yield was only 22% (eq 2). However, **2n** was obtained in 68% yield from 2-amino-4-methoxypyridine and 2,3-dibromopyridine (eq 3), indicating that the electron-donating substituent could promote the reactivity of nitrogen in the pyridinyl moiety.

In conclusion, the palladium-catalyzed dearomatizing carbonylation reaction to synthesize N-fused heterocycles proceeds efficiently, affording pyrido[2,1-*b*]quinazolin-11-ones and dipyrido[1,2-a:2′,3′-*d*]pyrimidin-5-ones in moderate to excellent yields.

Scheme 1. Dearomatic Cyclocarbonylation Reaction without Isolation of Intermediate 1



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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