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Synthesis of 2-Alkylaminoquinolines and 1,8-Naphthyridines by Successive Ruthenium-Catalyzed Dehydrogenative Annulation and *N*-Alkylation Processes

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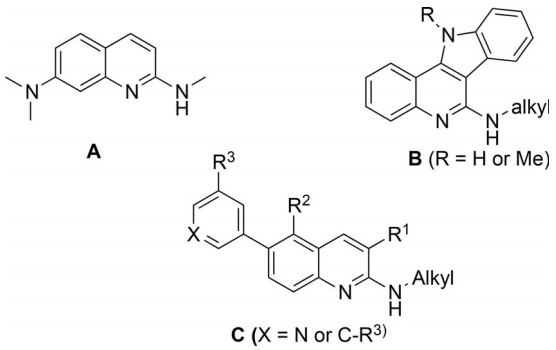
Abstract: A new one-pot synthetic protocol, enabling the facile access to 2-alkylaminoquinolines and 1,8-naphthyridines by successive ruthenium-catalyzed dehydrogenative annulation and *N*-alkylation processes, has been demonstrated. A series of 2-aminoarylmethanols were efficiently converted in combination with different types of nitriles and alcohols into various desired products in moderate to excellent yields after isolation. Advantageously, the synthesis proceeds with high atom-efficiency, broad substrate scope, operational simplicity, no need for external hydrogen sources and less environmentally benign halogenated reagents, thus offering a practical approach to access these two types of compounds that are currently difficult to prepare with the conventional methods.

Keywords: 2-alkylamino-1,8-naphthyridines; 2-alkylaminoquinolines; *N*-alkylation; dehydrogenative annulation; ruthenium catalysis

Introduction

2-Alkylaminoquinolines constitute an important class of nitrogen heteroaromatics, which are frequently found in numerous functional products possessing diverse biological and therapeutic activities. Selected examples that are employed as anti-herpes virus (structure **A**),[1a] anti-cancer[1b] and anti-malarial[1c] (structure **B**) agents as well as potent compositions (structure **C**) for the treatment of chronic infection with hepatitis virus C (HCV)[1d] are shown in Scheme 1. Moreover, 2-alkylaminoquinolines serve as interesting building blocks that have been extensively applied for various synthetic purposes.[2]

In general, 2-alkylaminoquinolines can be synthesized by the conventional Ullmann[3] or Buchwald–Hartwig[4] amination protocols. Nevertheless, these transformations are based on the use of less-environmental benign halogenated reagents. In recent years, much attention has been focused on the development of new and efficient approaches to access such compounds. For example, the strategy through palladium-catalyzed C(sp^2)–H bond activation and isocyanide insertion with *ortho*-heteroarene-substituted anilines was firstly demonstrated by the Zhu group.[5] Then, the palladium-catalyzed intermolecular aerobic oxidative cyclization of 2-ethynylanilines with isocyanides was also disclosed.[6] More recently, the Ji group presented an interesting cobalt-catalyzed isocyanide insertion with 2-arylanilines under an O_2 atmosphere *via* homolytic aromatic substitution-type C–H functionalization.[7] Despite these significant contributions, one limitation is generally associated with the preparation of isocyanides that has to date remained somewhat difficult. Hence, the search for shortcuts to



Scheme 1. Selected 2-alkylaminoquinolines possessing interesting biological and therapeutic activities.

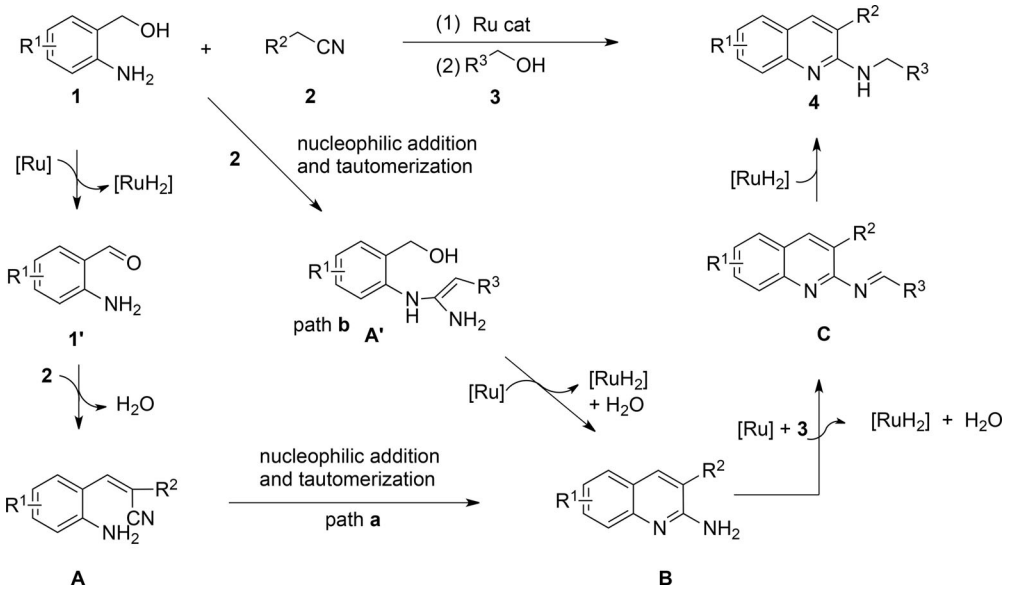
access 2-alkylaminoquinolines from easily available feedstocks still remains a demanding goal.

Although 2-aminoquinolines could be prepared *via* the cross-condensation of 2-aminobenzaldehydes with 2-arylacetonitriles,[8] there are very limited 2-aminobenzaldehydes available due to their high reactivity and the easy occurrence of homo-condensation, thus the synthetic diversity is restricted. Inspired by our recent efforts on alcohol transformations,[9,10] we believed that such an issue could be addressed by replacing 2-aminobenzaldehydes with stable and easily accessible 2-aminoaryl alcohols in the presence of a suitable ruthenium catalyst system.[9,10] Consequently, a new synthetic protocol, enabling the facile access to 2-alkylaminoquinolines *via* successive ruthenium-catalyzed dehydrogenative annulation and *N*-alkylation processes, was envisaged as shown in Scheme 2. The reaction is initiated with the ruthenium-catalyzed dehydrogenation of 2-aminobenzyl alcohol **1** and subsequent condensation with nitrile **2** at the α-site, resulting in a 2-alkenylaniline **A**. Then, the nucleophilic addition of the amino group to the cyano unit followed by a tautomerization gives 2-aminoquinoline **B** (path **a**). Alternatively, a direct amino addition of **1** to the cyano group of **2** followed by alcohol dehydrogenation, condensation and tautomerization also affords the adduct **B** (path **b**). Finally, the *N*-alkylation of **B** *via* a hydrogen-borrowing process[11] would afford the product (**4**).

Results and Discussion

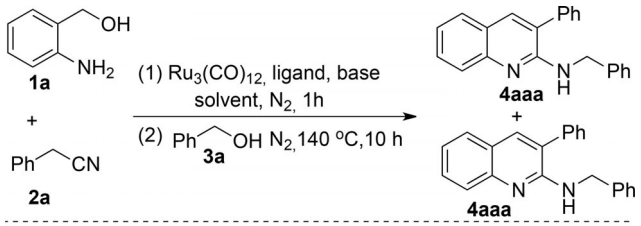
The above-described idea prompted us to start the investigation by testing the reaction of (2-aminophenyl)methanol **1a**, 2-phenylacetonitrile **2a** and benzyl alcohol **3a**. In consideration of the excellent catalytic performance of the complex $Ru_3(CO)_{12}$ in the activation of alcohols,[9] we therefore chose it as the catalyst for screening different reaction parameters. First, by using DPPB (**L1**) as the ligand and *t*-BuOK as the base, the three-component reaction in toluene was performed at 140 °C for 11 h, which gave the desired product **4aaa** in 53% GC yield along with a by-product **4aa** (36%) from the coupling of **2a** and **3a** *via* a hydrogen borrowing reaction. To avoid such a side reaction, we switched the protocol to a one-pot, two-step synthesis. Thus, under the same conditions, **1a** was initially reacted with **2a** for 1 h. Then, the reaction was continued for another 10 h by introducing alcohol **3a**. Among the four ligands tested (Table 1, see **L1–L4**), **L3** exhibited the highest activity in affording product **4aaa** (Table 1, entries 2–5). Blank experiments showed that both the catalyst and ligand are essential in affording a desirable result (entries 6 and 7). Next, we examined several conventional solvents, and the results showed that they were less effective or totally ineffective as compared to toluene (entries 8–11). Furthermore, another four inorganic bases in combination with **L3** in toluene were evaluated, but these bases were inferior to *t*-BuOK (entries 12–15). Finally, we chose **L3**/*t*-BuOK/toluene as the preferred combination. We found that either a decrease of the base loading or a change of reaction temperature led to diminished product yields (entries 16–18). Hence, the optimal conditions are as indicated in entry 3 of Table 1.

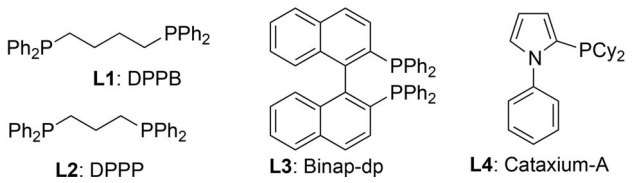
With the optimal reaction conditions in hand, we then tested the generality and the limitations of the synthetic protocol. First, the reactions of (2-amino-



Scheme 2. Possible pathways to access 2-aminoquinolines.

Table 1. Optimization of the reaction conditions[a]





Entry	Ligand	Solvent	Base	Yield [%]
1	**L1**	toluene	*t*-BuOK	53
2	**L1**	toluene	*t*-BuOK	74
3	**L2**	toluene	*t*-BuOK	76
4	**L3**	toluene	*t*-BuOK	88
5	**L4**	toluene	*t*-BuOK	68
6	**L3**	toluene	*t*-BuOK	–[c]
7	–	toluene	*t*-BuOK	<15
8	**L3**	*p*-xylene	*t*-BuOK	77
9	**L3**	DMSO	*t*-BuOK	–
10	**L3**	DMF	*t*-BuOK	–
11	**L3**	*t*-amyl alcohol	*t*-BuOK	70
12	**L3**	toluene	*t*-BuONa	56
13	**L3**	toluene	Cs_2CO_3	–
14	**L3**	toluene	K_2CO_3	–
15	**L3**	toluene	NaOH	59
16	**L3**	toluene	*t*-BuOK	–[d]
17	**L3**	toluene	*t*-BuOK	–[e]
18	**L3**	toluene	*t*-BuOK	72[f]

[a] *Reaction conditions:* unless otherwise stated, all reactions were carried out by using **1a** (0.3 mmol), **2a** (0.3 mmol), $Ru_3(CO)_{12}$ (1 mol%), ligand (3 mol%), additive (100 mol%), solvent (2.0 mL), temperature (140 °C) under a nitrogen atmosphere for 1 h. Then, **3a** (0.4 mmol) was added and the reaction mixture was stirred for another 10 h.
[b] GC yield using hexadecane as an internal standard.
[c] Without catalyst.
[d] *t*-BuOK (50 mol%).
[e] Temperature: 110°.
[f] Temperature: 130 °C.

phenyl)methanol **1a** in combination with various 2-arylacetonitriles **2** and alcohols **3** were examined (for substrate structures, see Scheme S1 of the Supporting Information). As shown in Table 2, all the reactions proceeded smoothly and gave the desired products in moderate to excellent isolated yields (entries 1–14). No homo-coupling of **1a** was observed in all the tested reactions, showing that the developed synthetic method exhibits an excellent chemoselectivity. Also, the substituents on the aryl ring of nitriles **2** have little influence on the product yields, whereas the al-

Table 2. Variation of different coupling partners[a]

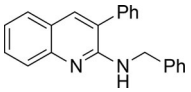
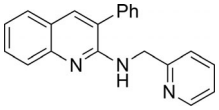
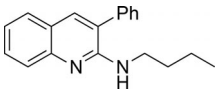
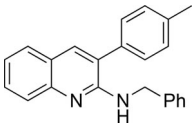
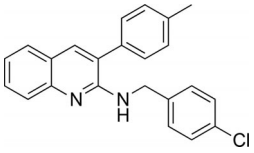
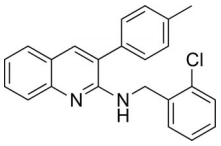
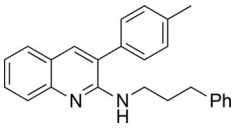
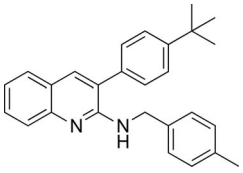
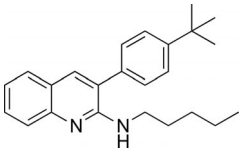
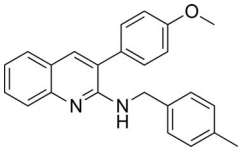
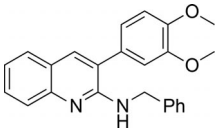
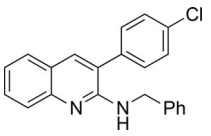
Entry	Reactants	Product	**4**, Yield [%][b]
1	**1a**, **2a**, **3a**		**4aaa**, 78
2	**1a**, **2a**, **3b**		**4aab**, 60
3	**1a**, **2a**, **3c**		**4aac**, 60
4	**1a**, **2b**, **3a**		**4aba**, 81
5	**1a**, **2b**, **3d**		**4abd**, 79
6	**1a**, **2b**, **3e**		**4abe**, 84
7	**1a**, **2b**, **3f**		**4abf**, 60
8	**1a**, **2c**, **3g**		**4acg**, 63
9	**1a**, **2c**, **3h**		**4ach**, 55
10	**1a**, **2d**, **3g**		**4adg**, 77
11	**1a**, **2e**, **3a**		**4aea**, 74
12	**1a**, **2g**, **3a**		**4aga**, 80

Table 2. (Continued)

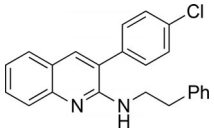
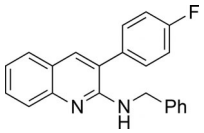
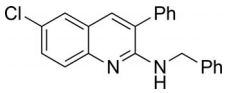
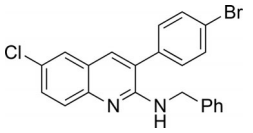
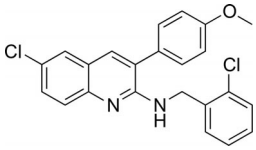
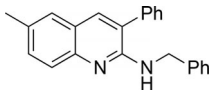
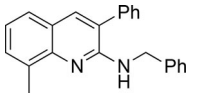
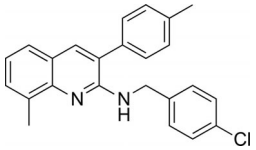
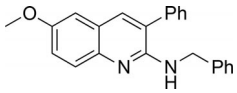
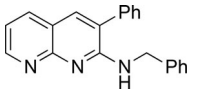
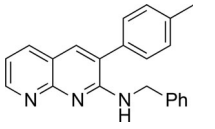
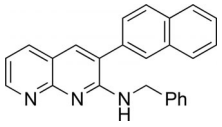
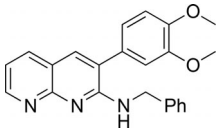
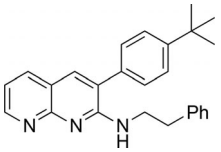
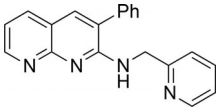
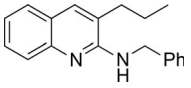
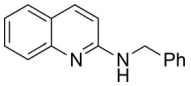
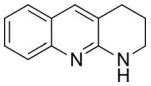
Entry	Reactants	Product	**4**, Yield [%][b]
13	**1a**, **2g**, **3i**		**4agi**, 65
14	**1a**, **2f**, **3a**		**4afa**, 58
15	**1b**, **2a**, **3a**		**4baa**, 86
16	**1b**, **2h**, **3a**		**4bha**, 63
17	**1b**, **2d**, **3e**		**4bde**, 84
18	**1c**, **2a**, **3a**		**4caa**, 76
19	**1d**, **2a**, **3a**		**4daa**, 70
20	**1d**, **2b**, **3d**		**4dbd**, 71
21	**1e**, **2a**, **3a**		**4eaa**, 78
22	**1f**, **2a**, **3a**		**4faa**, 72
23	**1f**, **2b**, **3a**		**4fba**, 74
24	**1f**, **2i**, **3a**		**4fia**, 66
25	**1f**, **2e**, **3a**		**4fea**, 69

Table 2. (Continued)

Entry	Reactants	Product	**4**, Yield [%][b]
26	**1f**, **2c**, **3i**		**4fci**, 60
27	**1f**, **2a**, **3b**		**4fab**, 60
28	**1a**, **2j**, **3a**		**4aja**, 46
29	**1a**, **2k**, **3a**		**4aka**, < 5
30	**1a**, **2l**		**4al**, –

[a] *Reaction conditions:* unless otherwise stated, all the reactions were carried out at 140 °C for 1 h under a nitrogen atmosphere using **1** (0.3 mmol), **2** (0.3 mmol), $Ru_3(CO)_{12}$ (1 mol%), **L3** (3 mol%), base (1 equiv.) in toluene (2 mL). Then, **3a** (0.4 mmol) was added and the reaction mixture was stirred for another 10 h.

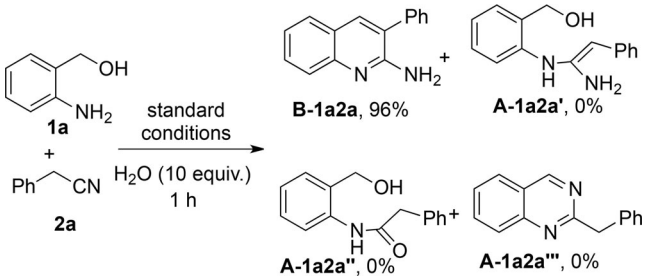
[b] Isolated yield.

cohols significantly affect the product formation. Specifically, benzylic alcohols furnished the products in much higher yields (entries 1, 2, 4–6, 8 and 10–12) than did the aliphatic ones (entries 3, 7, 9 and 13), presumably because the benzylic alcohols favor the dehydrogenation to form relatively stable arylaldehyde intermediates.

Next, we turned our attention to the variation of 2-aminoarylmethanols **1**. Substrates **1** bearing different substituents (Cl, Me, OMe) were evaluated. As shown in Table 2, entries 15–21, all the reactions proceeded efficiently to afford the desired products in high yields after isolation. Notably, the halogen-containing products could be applied for further elaboration of complex molecules *via* cross-coupling reactions. Interestingly, (2-aminopyridin-3-yl)methanol **1f** was also proven to be an effective coupling partner, which affords the 2-alkylamino-1,8-naphthyridines in good yields (entries 22–27). Contrary to our previous studies,[9a,c] the naphthyridyl unit in these cases did not undergo further transfer hydrogenation. Also, the pyridin-2-ylmethylamino product **4fab** is a potential bi- or tridentate ligand that could be applied in organometallic chemistry. Attracted by the utilization of different types of nitriles in quinoline syntheses,[12] we therefore further tested the alkyl nitrile **2j**, a more challenging coupling partner. Gratifyingly, it was also compatible with catalytic transformation, resulting in

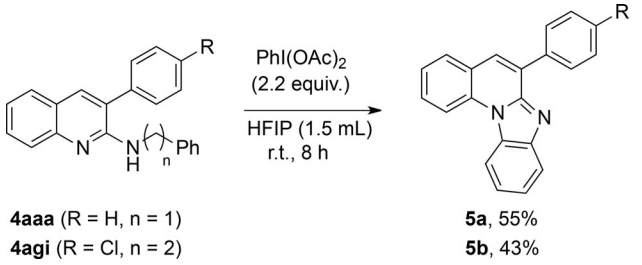
a 2-alkylamino-3-alkyl quinoline **4aja** in 46% yield (entry 28). However, the reaction of **1a**, acetonitrile (**2k**) and **3a** gave only a trace of the expected product **4aka** (entry 29, <5%). In addition, the bifunctional cyanobutanol **2l** was unable to generate the polycyclic quinoline **4al** (entry 30), which is due to the fact that **2l** tends to undergo an intramolecular coupling reaction at the alpha site *ortho* to the cyano group.

To gain insight into the reaction information, 10 equivalents of H_2O was introduced into the reaction of **1a** and **2a** to trap the possible intermediate **A-1a2a′** as proposed in Scheme 3. However, except the detection of 3-phenyl-2-aminoquinoline **B-1a2a** in 96% yield, we did not observed even trace of **A-1a2a′**, its hydrolysis form **A-1a2a″** or its further coupling product **A-1a2a‴** (Scheme 3), suggesting that the formation 2-aminoquinoline **B** through path **b** (Scheme 2) is less likely.



Scheme 3. Verification experiment.

To further demonstrate the utility of the obtained products, compounds **4aaa** and **4agi** were selected for further transformation. By employing $PhI(OAc)_2$ as an oxidant, these two compounds in hexafluoro-2-propanol (HFIP) were able to undergo dealkylative cyclization,[13] affording products **5a** and **5b** in 55% and 43% yields, respectively (Scheme 4). Noteworthy, the formed benzimidazo-fused quinoline skeleton constitutes the core structure of numerous products exhibiting interesting bioactivities including DNA-intercalation[14] and inhibition of topoisomerase II.[15]



Scheme 4. The synthetic utility of the obtained compounds.

Conclusions

In summary, we have developed a new one-pot synthetic protocol, which enables a facile access to 2-alkylaminoquinolines and 1,8-naphthyridines by successive ruthenium-catalyzed dehydrogenative annulation and *N*-alkylation processes. Advantageously, the synthesis proceeds with high atom-efficiency, broad substrate scope, no need for external hydrogen sources and less environmentally benign halogenated reagents, thus offering a practical approach to access these two types of compounds that are currently difficult to prepare with the conventional methods. Furthermore, the obtained products were applicable for further elaboration to benzimidazo-fused nitrogen heteroaromatics. Considering the importance of the obtained compounds in biological, medicinal and synthetic organic chemistry, the presented protocol should attract the attention of different scientific communities to formulate specific applications.

Experimental Section

Typical Procedure for the Synthesis of *N*-Benzyl-3-phenylquinolin-2-amine (4aaa)

Under an N_2 atmosphere, *t*-BuOK (100 mol%), Binap (3 mol%), $Ru_3(CO)_{12}$ (1 mol%), (2-aminophenyl)methanol **1a** (0.3 mmol), 2-phenylacetonitrile **2a** (0.3 mmol) and toluene (2.0 mL) were introduced in a Schlenk tube (50 mL), successively. The resulting mixture was stirred at 140 °C for 1 h. Then, benzyl alcohol **3a** (0.6 mmol) was added to the Schlenk tube and the reaction mixture was stirred for another 10 h under N_2 protection. After cooling down to room temperature, the reaction mixture was concentrated by removing the solvent under vacuum, and the residue was purified by preparative TLC on silica, eluting with petroleum ether (60–90 °C):ethyl acetate (60:1) to give *N*-benzyl-3-phenylquinolin-2-amine (**4aaa**) as a yellow gel; yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.53(t, J = 8.0 Hz, 1H), 7.43–7.46 (m, 4H), 7.34–7.40 (m, 3H), 7.29 (t, J = 8.0 Hz, 2H), 7.22 (t, J = 8.0 Hz, 2H), 5.10 (s, 1H), 4.82 (d, J = 4.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.21, 139.87, 137.43, 136.49, 129.30, 129.28, 129.10, 128.54, 128.27, 127.76, 127.41, 127.07, 126.25, 125.62, 123.70, 122.34, 45.50; IR (KBr): ν = 3421, 3028, 2922, 1565, 1512, 1410, 1344, 1267, 1025, 750, 701 cm^{-1}; HR-MS (ESI): m/z = 311.1542, calcd. for $C_{22}H_{19}N_2$ $[M+H]^+$: 311.1543.

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