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Amine-Mediated Transimination and Aromatization-Triggered Domino Reaction in the Synthesis of Polyfunctionalized 4-Aminoquinolines

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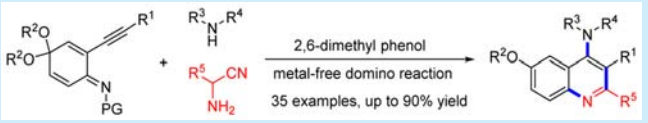
Supporting Information

ABSTRACT: Dearomatization provides numerous possibilities for the development of new transformative modes of aromatic compounds. A conceptually novel metal-free multicomponent domino reaction of the dearomatized products of 2-alkynylanilines is developed. The reaction involves the secondary amine-mediated transimination with α-amino nitriles and subsequent aromatization-triggered cascade rearrangement, nucleophilic cyclization, and retro-Strecker reaction. This process provided a new practical method for the rapid synthesis of polyfunctionalized 4-aminoquinolines from readily available starting materials.

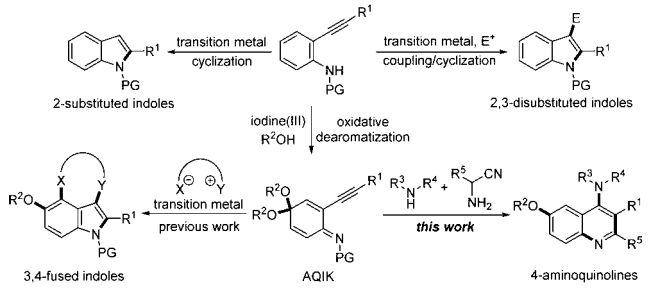


Dearomatization of aromatic compounds is emerging as a highly attractive strategy for use in complex syntheses, owing to its simple elegance and high economy.[1] Upon dearomatization, the conjugated π system of an aromatic ring is broken up, and the masked internal functionality stored in the aromatic systems can be conveniently exploited. Consequently, dearomatization offers a strategic opportunity to circumvent the inherent reactivity and selectivity of aromatic compounds and provides numerous possibilities for the development of new transformative modes of aromatic compounds.

While the oxidative dearomatization of phenols has been extensively investigated,[2] the dearomatization of anilines and their derivatives has been examined by organic chemists only in recent years.[3] Under anodic[4] or chemical oxidizing conditions, the dearomatization of anilines generates quinone imines or quinone imine ketals,[5] and these products have been used in the synthesis of highly functionalized aromatic compounds that are difficult to obtain by electrophilic substitution of anilines. The elegance and success of these new synthetic strategies led us to investigate the dearomatization of 2-alkynylanilines, which have been utilized almost exclusively in the synthesis of indoles by cyclization or coupling/cyclization reactions.[6] In this context, we developed a transition-metal-catalyzed dipolar cycloaddition of the dearomatized intermediate of 2-alkynylanilines to produce 3,4-fused indoles.[7] In connection with this study, we recently focused our attention on evaluating the versatility of the dearomatized intermediate, 2-alkynyl quinone imine ketals (AQIK), because of their multifunctional structural features. In principle, the alkynyl, allylacetal, and α,β-unsaturated imino functionalities in the skeleton of AQIKs are all potential reaction sites for nucleophilic additions.[8] This feature not only renders AQIKs attractive synthetic intermediates but also makes chemo- and regioselective control in AQIK-involved reactions a significant challenge.

Secondary amines have been widely used to activate α,β-unsaturated compounds via an iminium intermediate. Recently, this activation mode has been employed in the synthesis of aldimines by a transimination process.[9] In our previous work, we found that secondary amines could catalyze the Knoevenagel condensation reaction of cyclohexadienimines.[10] Based on these observations, we conceived a three-component domino reaction of AQIKs leading to the formation of polyfunctionalized 4-aminoquinolines (Scheme 1). New

Scheme 1. Transformation of 2-Alkynylanilines



practical methods for the rapid synthesis of 4-aminoquinolines from readily available substrates are highly desired because of their significant pharmacological and biological activities.[11]

The underlying principle of this three-component domino reaction is depicted in Scheme 2. A secondary amine-mediated imino exchange reaction between AQIK and α-aminonitriles is directly followed by a rearrangement forming intermediate **III**. The electron deficiency of the α-iminonitrile functionality in this intermediate might induce a nucleophilic *endo*-cyclization. After a retro-Strecker reaction, the skeleton of 4-aminoquinoline is constructed. In this domino process, secondary amines not only serve as a promoter mediating the transimination but

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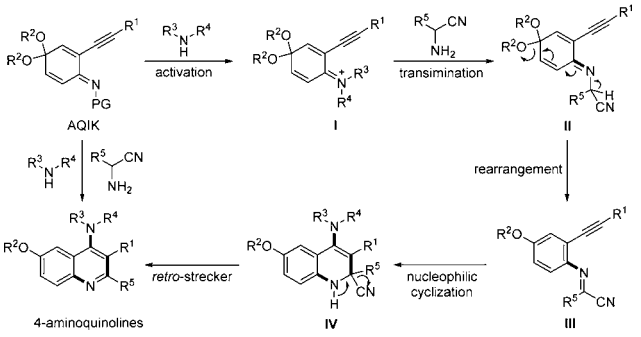
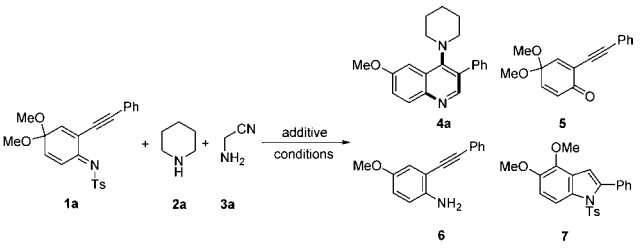
Scheme 2. AQIK-Involved Three-Component Domino Reaction for the Synthesis of 4-Aminoquinolines



also act as the nucleophilic reagent that is regioselectively introduced into the C-4 position of quinolines. Moreover, aromatization might be a significant driving force triggering both the rearrangement and the retro-Strecker reaction.

To test the feasibility of this domino process, the reaction of *N*-Ts 2-phenylethynyl quinone imine ketal **1a**, piperidine **2a**, and 2-aminoacetonitrile **3a** was first examined. The three-component reaction in 1,2-dichloroethane at room temperature for 12 h afforded the desired 4-aminoquinoline **4a** in 34% yield (Table 1, entry 1). Further optimization of the reaction

Table 1. Optimization of Reaction Conditions[a]

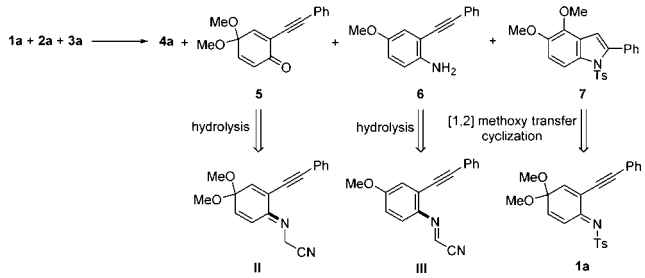


entry	additive (equiv)	solvent	temp (°C)	**4a** (%)[b]
1	none	$ClCH_2CH_2Cl$	25	34
2	none	THF	25	30
3	none	toluene	25	21
4	none	dioxane	25	23
5	none	CH_3CN	25	39
6	none	CH_3CN	reflux	43
7	none	CH_3CN	105[c]	53
8[d]	none	CH_3CN	105[c]	58[g]
9[d]	$Cu(OTf)_2$ (0.1)	CH_3CN	105[c]	16
10[d]	$Bi(OTf)_3$ (0.1)	CH_3CN	105[c]	7
11[d]	$Sc(OTf)_3$ (0.1)	CH_3CN	105[c]	<5
12[d]	AgOTf (0.1)	CH_3CN	105[c]	11
13[d]	$AgOCOCF_3$ (0.1)	CH_3CN	105[c]	15
14[d]	TfOH (1)	CH_3CN	105[c]	0
15[d]	TsOH (1)	CH_3CN	105[c]	0
16[d]	CH_3COOH (1)	CH_3CN	105[c]	53
17[d]	PhOH (1)	CH_3CN	105[c]	49
18[d]	BHT[e] (1)	CH_3CN	105[c]	63
19[d]	2,6-DMP[f] (1)	CH_3CN	105[c]	79
20[d]	2,6-DMP (1.3)	CH_3CN	105[c]	88

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.1 equiv), and **3a** (1.1 equiv) in solvent (2.0 mL), nitrogen atmosphere. [b]Isolated yield. [c]Reactions in a sealed tube. [d]**3a** (1.3 equiv). [e]BHT = 2,6-di-*tert*-butyl-4-methylphenol. [f]2,6-DMP = 2,6-dimethyl phenol. [g]Compounds **5**, **6**, and **7** were isolated in 8%, 11%, and 17% yields, respectively.

conditions by varying the solvent, temperature, and stoichiometry improved the yield of compound **4a** to 58% (Table 1, entries 2−8). To gain more insight into this reaction, a number of byproducts were isolated and identified as 4,4-dimethoxy-2-(phenylethynyl)cyclohexan-1-one **5**, 4-methoxy-2-(phenylethynyl)aniline **6**, and 4-methoxy substituted indole **7** (Scheme 3). It is speculated that compounds **5** and **6** might be formed

Scheme 3. Possible Route to the Formation of Isolated Byproducts



from the hydrolysis of the corresponding transimination and rearrangement intermediates, and compound **7** might be generated through a [1,2] methoxy group transfer and subsequent cyclization of compound **1a**. Therefore, we sought a suitable additive to promote the rearrangement and nucleophilic cyclization steps in the domino process. Some representative results are shown in Table 1. We initially examined a range of metal salts, but the presence of metal salts dramatically decreased the yield of compound **4a** and, instead, compound **7** was formed as the major product (Table 1, entries 9−13). The addition of a strong Brønsted acid such as trifluoromethanesulfonic acid or 4-methylbenzenesulfonic acid produced no reaction (Table 1, entries 14 and 15). When acetic acid or phenol was used as the additive, the yield of **4a** decreased slightly, but the 1,4-addition of compound **1a** by acetic acid or phenol was observed (Table 1, entries 16 and 17). When the sterically hindered 2,6-di-*tert*-butyl-4-methyl-phenol (BHT) was employed, the yield of **4a** improved, but only slightly (Table 1, entry 18). Screening a variety of sterically hindered Brønsted acids revealed that 2,6-dimethyl phenol was the best promoter for the formation of compound **4a** (Table 1, entry 19). Finally, a set of optimum reaction conditions were defined as **1a** (0.1 mmol, 1.0 equiv), **2a** (1.1 equiv), **3a** (1.3 equiv), 2,6-dimethyl phenol (1.3 equiv), and CH_3CN (2.0 mL), at 105 °C, in a sealed tube. The reaction under these conditions provided **4a** in 88% yield (Table 1, entry 20).

The scope of this metal-free three-component domino reaction was investigated (Scheme 4). The replacement of the tosyl group in compound **1a** by a mesyl (Ms) or benzoyl (Bz) group did not lead to a higher yield of **4a**. Not only the dimethyl or diethyl ketal but also the propylene ketal proved to be a suitable substrate, and the reaction produced the 6-(3-hydroxypropoxy)-substituted 4-aminoquinoline **4c** in 64% yield. Reaction of AQIKs bearing an aryl-subtituted alkynyl moiety proceeded smoothly, providing the corresponding products in moderate to good yield. A variety of secondary amines, including substituted piperidines, morpholine, 1-methyl-piperazine, and symmetrical or unsymmetrical dialkylamines, were suitable reaction partners in this process. For example, when piperidin-4-ol was used, the existence of the free hydroxyl group does not influence the reaction, and compound **4n** was formed in 85% yield. No desired product was obtained

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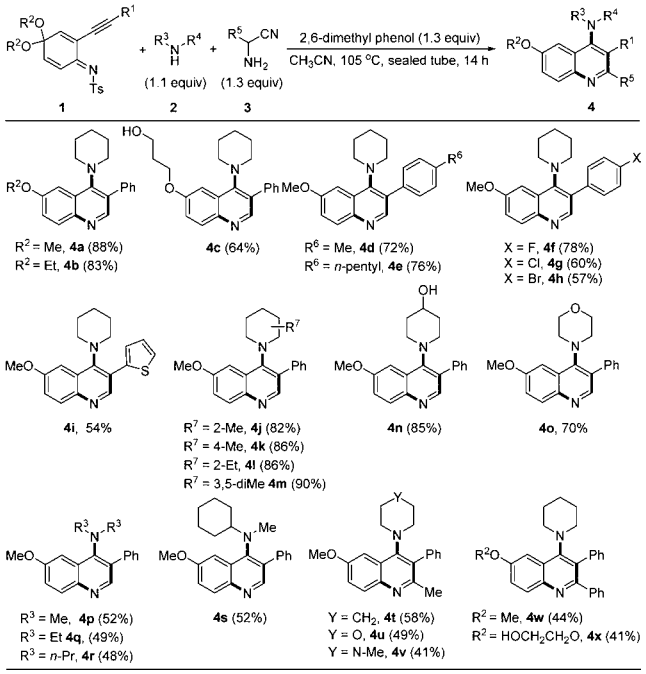
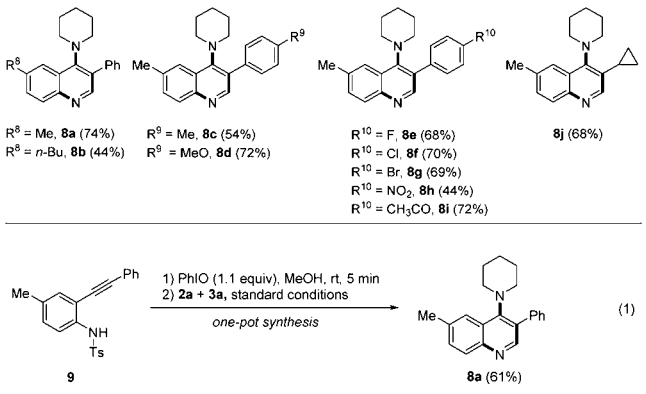
Scheme 4. Metal-Free Three-Component Domino Reaction of AQIKs



from the reaction of proline. When 2-amino propanenitrile or phenyl-acetonitrile was used, the reactions gave rise to polyfunctionalized 4-aminoquinolines in moderate yields.

We further extended the scope of reactants to 2-alkynyl cyclohexadienimines, the dearomatized product of *para*-substituted 2-alkynylanilines. As shown in Scheme 5, the

Scheme 5. Reaction of 2-Alkynyl Cyclohexadienimines



domino reactions, with a range of 2-alkynyl cyclohexadienimines, proceeded smoothly, whether the substituent at the alkynyl moiety is an electron-rich or -deficient aryl group or a cyclopropyl group (Scheme 5). The structure of compound **8a** was confirmed by its single-crystal diffraction analysis.[12] The one-pot synthesis of 4-aminoquinoline from 2-alkynylaniline was tested,[13] and when the reaction was conducted in a one-pot stepwise manner, compound **8a** was formed in 61% yield (eq 1).

In conclusion, we have developed a conceptually novel metal-free multicomponent domino reaction of the dearomatized products of 2-alkynylanilines. The reaction involves the secondary amine-mediated transimination with α-amino nitriles and subsequent aromatization-triggered cascade rearrangement, nucleophilic cyclization, and retro-Strecker reaction. This process provides a new practical method for the rapid synthesis of polyfunctionalized 4-aminoquinolines from readily available starting materials. The application of this strategy in the synthesis of other quinoline derivatives and the investigation of the biological activities of the 4-aminoquinolines synthesized in this way are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02643.

Experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR of new compounds, X-ray diffraction structure (PDF)

Crystallographic data for compound **8a** (CIF)

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Notes

The authors declare no competing financial interest.

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