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Synthesis of 2-Alkoxy(aroxy)-3-substituted Quinolines by DABCO-Promoted Cyclization of *o*-Alkynylaryl Isocyanides

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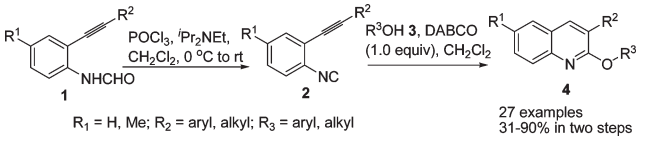

Diversified 2-alkoxy- and 2-aroxy-3-substituted quinolines were synthesized from *o*-alkynylaryl isocyanides and alcohols and phenols promoted by DABCO, respectively. The reaction was initiated by nucleophilic addition of DABCO to isocyanide and subsequent cycliztion, leading to a DABCO-quinoline-based adduct as the reactive intermediate, followed by substitution of the DABCO moiety with oxygenated nucleophiles.

2-Alkoxy(aroxy)quinolines exist as substructures in many medicinally interesting compounds exhibiting a wide spectrum of biological activities, such as antimycobacterial tuberculosis,[1] antitumor,[2] antimalarial,[3] antithrombin,[4] and many others.[5] Despite the great importance of 2-alkoxy-(aroxy)quinolines in medicinal chemistry, efficient approaches to their preparation are limited. One of the most widely used methods is probably nucleophilic substitution of 2-haloquinoline derivatives with corresponding alcohols or phenols in the presence of bases, such as K_2CO_3, *t*BuOK, or NaH, under heating (path a, Scheme 1).[6,1b,2,3] This process can also be promoted in the presence of copper catalysts.[7] The major drawback of this method is the nucleophilicity requirement of alcohols and phenols used. For less nucleophilic alcohols and phenols, the yields are extremely low.[1b,7b] The use of strong bases under elevated temperatures also limits its application. Another common approach to 2-alkoxyquinolines is alkylation of 2-quinolones (path b, Scheme 1). Unfortunately, the selectivity between *O*- and *N*-alkylation is always a problem. As a fact, the unwanted *N*-alkylation product usually predominates.[8] Copper-catalyzed coupling of 2-quinolones with aryl halides provides the C−N bond forming product exclusively.[9] Thus, an efficient synthesis of diversified 2-alkoxy and 2-aroxyquinolines, especially applicable to sterically demanding and/or electron-deficient alcohols and phenols, is highly desirable.[10] We report herein a novel metal- and strong base-free synthesis of 2-alkoxy-(aroxy)-3-aryl(alkyl)quinolines from readily accessible *o*-alkynylaryl isocyanides and various alcohols and phenols including less nucleophilic ones in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) under mild conditions (path c, Scheme 1).

In 1999,[11] Ito et al reported a new access to 2,3-disubstituted quinolines through cyclization of *o*-alkynylaryl isocyanides with MeOH, Et_2NH, and other carbanions as nucleophiles. We also developed an efficient synthesis of diversified 2-chloro-3-substituted quinolines from *o*-alkynylaryl isocyanides and tetrabutylammonium chloride under mild conditions.[12] We hypothesized that extension of Ito's strategy to other less nucleophilic oxygenated nucleophiles, such as phenols and secondary alcohols, would lead to a general approach to 2-alkoxy(aroxy)-3-aryl(alkyl)quinolines.

Having this idea in mind, we initiated the study with *o*-(phenylethynyl)phenyl isocyanide **2a** and phenol **3a** as substrates under various conditions as summarized in Table 1.

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SCHEME 1. Strategies to 2-Alkoxy(aroxy)quinolines

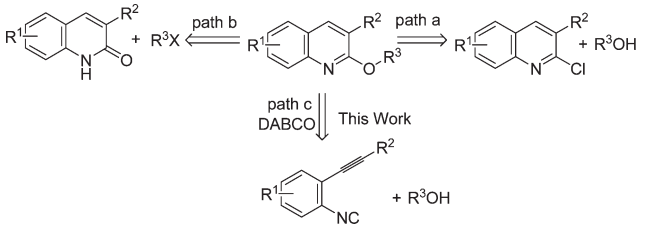
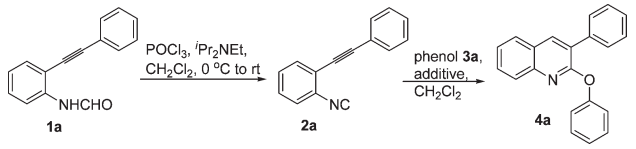


TABLE 1. Optimization of Conditions for 2-Phenoxy-3-phenylquinoline 4a[a]



entry	equiv of **3a**	additive (equiv)	temp (°C)	time (h)	yield (%)[b]
1	2	Na_2CO_3 (1.0)	25	24	0
2	2	NaH (1.0)	25	24	0
3	2	pyridine (1.0)	25	24	0
4	2	Et_3N (1.0)	25	24	0
5	2	PPh_3 (1.0)	25	24	0
6	2	DABCO (1.0)	25	24	72
7	2	DABCO (0.5)	25	24	35
8	2	DABCO (0.2)	25	24	17
9	2	DABCO (1.0)	40	14	71
10	1	DABCO (1.0)	40	14	68

[a]Reaction conditions: **1a** (0.1 mmol), $POCl_3$ (0.15 mmol), $(^iPr)_2NEt$ (0.8 mmol), CH_2Cl_2 (1.0 mL), 0 °C 30 min; after workup with $NaHCO_3$, **3a** (0.1 or 0.2 mmol), additive, CH_2Cl_2 (1.0 mL), 25 or 40 °C; [b]Isolated yield of **4a** for 2 steps.

Because *o*-alkynylaryl isocyanides are unstable especially at high concentration, they are used directly after dehydration of the corresponding *N*-formylamide and subsequent aqueous sodium bicarbonate workup.[13] No desired cyclization product was observed by screening of inorganic (Na_2CO_3, NaH) and organic bases (pyridine, Et_3N) (entries 1−4, Table 1). It seemed that the nucleophilicity of phenoxide was not strong enough to promote the cycloaddition reaction. Inspired by the dual function of DABCO in Morita−Baylis−Hillman reaction,[14] acting as both a strong nucleophile and a good leaving group, we speculated that a similar role that DABCO could play in our proposed reaction. To our delight, a stoichiometric amount of DABCO did promote the reaction in the presence of 2.0 equiv of phenol and the desired 2-phenoxy-3-phenylquinoline **4a** was formed in 72% overall yield from the corresponding *N*-formylamide **1a** at rt (entry 6, Table 1). The yield of **4a** dropped dramatically when the amount of DABCO was reduced (entries 7−8, Table 1). The reaction time was greatly shortened at slightly elevated temperature (40 °C) with equal yields (entry 9, Table 1). Triphenyl phosphane, a surrogate of DABCO in Morita−Baylis−Hillman reaction in some cases,[14] cannot promote the reaction at all (entry 5, Table 1).

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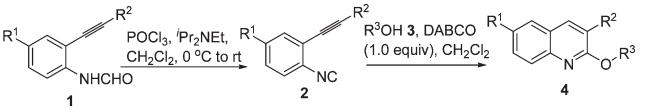
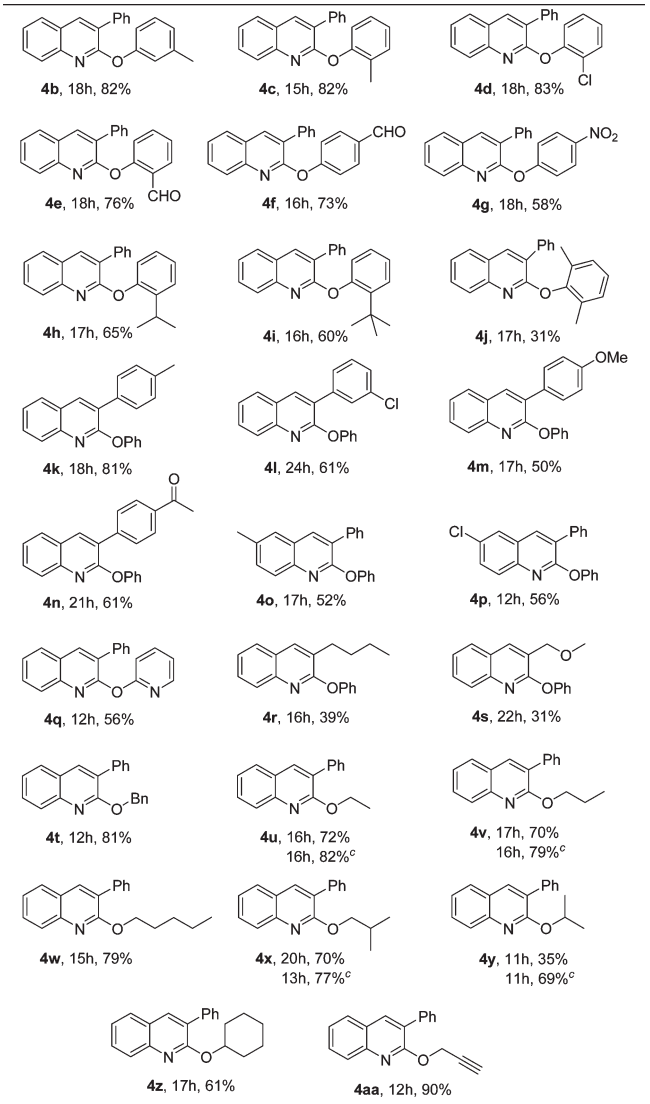
TABLE 2. Synthesis of 2-Alkoxy(aroxy)-3-substituted Quinolines 4[a]

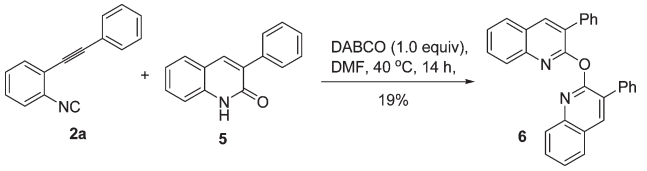




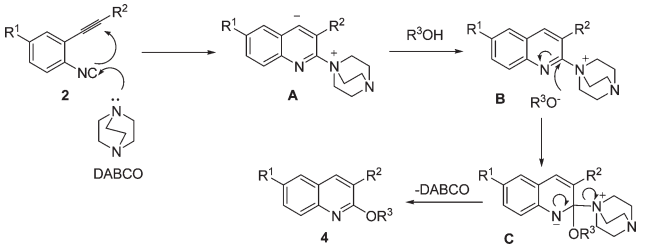
[a]Reaction conditions: **1a** (0.5 mmol), $POCl_3$ (0.75 mmol), $(^iPr)_2NEt$ (4.0 mmol), CH_2Cl_2 (5.0 mL), 0 °C 30 min; after workup with $NaHCO_3$, **3a** (1.0 mmol), DABCO (0.5 mmol), CH_2Cl_2 (5.0 mL), 40 °C; [b]Isolated yield of **4a** for two steps. [c]Additional 1.0 equiv of Na_2CO_3 was added.

The generality of the reaction in terms of oxygenated nucleophiles as well as substituents on *o*-alkynylaryl isocyanides was studied under the optimal reaction conditions identified. The results were summarized in Table 2. In general, electron-rich phenols (**4b**−**c**) gave better results than less nucleophilic electron-deficient phenols (**4d**−**g**) as expected. It is noteworthy that functionalities, such as aldehyde and nitro group, not only survive the reaction conditions but also provide handles for further diversification. Moreover, sterically hindered 2-isopropyl, 2-*tert*-butyl, and even 2,6-dimethyl phenols furnished the corresponding substituted 2-phenoxy-3-phenylquinolines (**4 h**−**j**) in moderate to acceptable yields. This methodology is efficient for the synthesis of 2-phenoxy-3-phenylquinolines with substituents (Me, Cl,

SCHEME 2. Synthesis of *O*-Tethered Dimeric Quinoline



SCHEME 3. Plausible Reaction Mechanism



OMe, Ac) on the 3-phenyl ring and the quinoline core (**4k**−**p**). 2-Hydroxypyridine is also a suitable nucleophile for the synthesis of a heterocyclic variant of 2-aryoxy-3-phenylquinoline **4q**. However, the current approach is less efficient for the synthesis of 2-phenoxy-3-alkylquinolines (**4r**−**s**). Primary and secondary alcohols can also act as nucleophiles to deliver corresponding 2-alkoxy-3-phenylquinolines in moderate to good yields (**4t**−**aa**). The presence of additional 1.0 equiv of Na_2CO_3 can improve the yield dramatically in case of using isopropanol as a nucleophile (**4y**), while the influence is less significant on the formation of **4u**−**v**, and **4x**. For other cases, either no improvement or negative effect on the yields was observed in the presence of Na_2CO_3 (see Supporting Information).

A unique *O*-tethered dimeric quinoline **6** was obtained when 3-phenyl-2-quinolone **5** was applied as the nucleophile (Scheme 2). Although the isolated yield was low due to steric hindrance, the scaffold is difficult to be accessed via existing methods.

A plausible mechanism is depicted in Scheme 3. Acting as a strong nucleophile, DABCO initiates the reaction by addition of the tertiary amine to the terminal carbon of the isocyanide moiety in **2**. Cycloaddition of the resulting carbanion to the triple bond delivers the DABCO-quinoline-based adduct **A**. The addition of oxygenated nucleophiles on the C2 of intermediate **B**, forming the adduct **C**. Subsequent elimination of the DABCO moiety furnishes the desired product **4**, with concurrent regeneration of the catalyst. Although the reaction mechanism suggests that DABCO could be regenerated, stoichiometric amount of DABCO is needed for efficient conversion of the starting *o*-alkynylaryl isocyanide **2**.

In summary, an efficient approach for the synthesis of 2-alkoxy- and 2-aroxy-3-substituted quinolines, starting from *o*-alkynylaryl isocyanides and various oxygenated nucleophiles in the presence of 1.0 equiv of DABCO, has been developed. A wide range of functionalities are well tolerated under the reaction conditions. Compared with the existing methods, the current approach features mild reaction conditions and less nucleophilic phenols and alcohols applied. A C−C bond and a C−O bond are formed sequentially from nonquinoline-based precursors which are readily available. DABCO triggers the reaction as a nucleophile and provides the product as a leaving group being replaced by oxygenated nucleophiles.

Experimental Section

General Procedure for DABCO Promoted 2-Alkoxy(aroxy)-3-substituted Quinolines. $POCl_3$ (0.75 mmol, 1.5 equiv) was added dropwise to a solution containing *o*-alkynylaryl *N*-formylamide **1** (0.5 mmol) and diisopropylethylamine (4.0 mmol, 8.0 equiv) in CH_2Cl_2 (5.0 mL) cooled in a water/ice bath under argon atmosphere. The reaction was stirred at 0 °C for 30 min. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and washed with saturated $NaHCO_3$ solution three times. The organic phase was separated and dried over Na_2SO_4. The CH_2Cl_2 solution of *o*-alkynylaryl isocyanide **2** was concentrated to about 5 mL in volume. Oxygenated nucleophile **3** (1.0 mmol) and DABCO (0.5 mmol) were added to the above solution at rt. In some cases as specified in Table 2, an additional 1.0 equiv of Na_2CO_3 was added. The mixture was stirred at 40 °C, and the reaction was monitored by TLC. When *o*-alkynylaryl isocyanide **2** had disappeared, the reaction mixture was washed with water (10 mL) and brine successively. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography using petroleum ether/dichloromethane as eluent to give the desired product **4** in 31−90% yields.

2-Phenoxy-3-phenylquinoline (4a): ^{1}H NMR (400 MHz, DMSO): δ 8.45 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 6.8 Hz, 2H), 7.62 (t, J = 8.4 Hz, 2H), 7.45−7.54 (m, 6H), 7.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 154.2, 145.7, 139.0, 136.6, 129.5, 129.2, 128.3, 127.9, 127.6, 127.3, 127.0, 126.3, 125.0, 124.3, 121.6; HRMS (ESI): Exact mass calcd for $C_{21}H_{16}NO$ $[M + H]^+$: 298.1232; Found: 298.1230.

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Supporting Information Available: General experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.