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Optimization of the Reaction Conditions for Synthesis of 3-(Aryloxy)quinoline Derivatives *via* Friedländer's Cyclization Reaction

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6,7-Dimethoxy-2-methyl-3-(4-nitrophenoxy)quinoline was synthesized by Friedländer's cyclization reaction. Different bases and solvents were tested in order to optimize the reaction conditions. The highest yields were obtained using piperidine in refluxing ethanol. Further reactions were carried out in order to prepare different diarylamide and diarylurea derivatives in moderate to high yields in order to examine their anticancer activities.

Key Words : Cyclization reaction, 2-Amino-4,5-dimethoxybenzaldehyde, Friedländer's reaction, Quinoline

Introduction

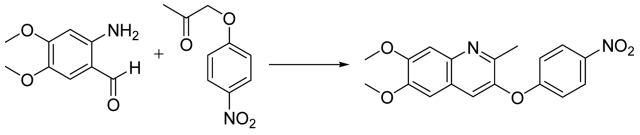
Much attention has been paid to the chemistry and applications of quinoline derivatives. Quinoline-containing compounds have been reported as antimalarial,[1] antiinflammatory,[2] *anti*-asthmatic,[3] antihypertensive,[4] antibacterial,[5] cytotoxic,[6] or antiprotozoal[7] agents. In addition, quinoline derivatives have been successfully applied in the fields of bioorganic[8] and industrial organic chemistries.[9]

Quinolines represent a major class of heterocycles, and so many preparation pathways have been known since the late 1800s. Quinolines have been generally synthesized by well-known classical methods such as Skraup, Doebner-von Miller, Friedländer's, Ptzinger, Conrad-Limpach, and Combes reactions.[10] Among them, the Friedländer's annulation[11] is still considered as one of the simplest and direct approaches for the synthesis of quinolines. The Friedländer's protocol consists typically of the reactions between aromatic *o*-amino-ketones or aldehydes and another carbonyl compound with an activated α-methylene group. The reaction can be promoted by acid or base catalysis. However, drastic reaction conditions, low yields, lengthy column purification, and numerous byproducts are common drawbacks of Friedländer's reaction. To make it more suitable and convenient, different approaches were put forward in order to get better results.[12] Herein, we optimized the optimum reaction conditions to synthesize 3-(aryloxy)quinoline derivatives in terms of higher yield and by avoiding lengthy workup and column purification. Our optimized reaction conditions can be applied to scale up to large scales with simple isolation of the pure product. In the present investigation, we report the optimized reaction conditions for preparation of 3-aryloxy-quinoline *via* Friedländer's cyclization, followed by synthesis of diarylurea and diarylamide derivatives possessing quinoline nucleus.

Results and Discussion

Herein we report an efficient method for the synthesis of novel quinoline derivatives *via* the Friedländer's reaction through condensation of dimethoxy substituted *o*-amino-benzaldehyde with a ketone, 1-(4-nitrophenoxy)propan-2-one (**2**), in the presence of different bases and solvents. Among all the bases tested, piperidine was found to be the

Table 1. Optimization of Friedländer's cyclization reaction condition using different bases and solvents



1 **2** **3**

Entry	Base	Solvent	Yield % (isomer A)
1.	NaOH	Ethanol	45
2.	KOH	Ethanol	40
3.	TEA	Ethanol	15
4.	K_2CO_3	Ethanol	40
5.	$NaOC_2H$	Ethanol	45
6.	**Piperidine**	**Ethanol**	**85**
7.	NaOH	Methanol	32
8.	KOH	Methanol	17
9.	NaOH	Isopropanol	10
10.	KOH	Isopropanol	15
11.	NaOH	*n*-Butanol	17
12.	KOH	*n*-Butanol	13
13.	Piperidine	Methanol	57
14.	Piperidine	Isopropanol	74
15.	Piperidine	*n*-Butanol	52

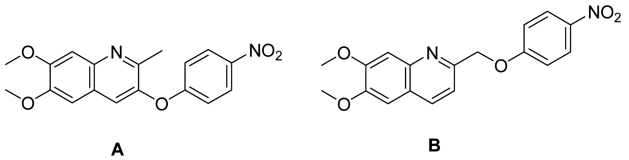


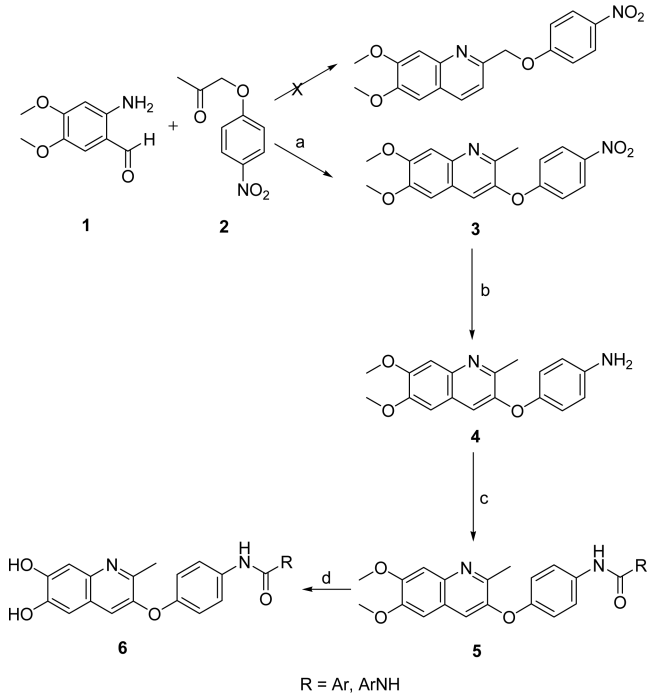
Figure 1. Graphical representation of the possible isomeric structures of product **3**. The isomeric structure A was obtained as the sole product.

most efficient base yieldwise in ethanolic solution. The use of stronger bases such as sodium ethoxide, sodium hydroxide, or potassium hydroxide might lead to formation of side products *via* Cannizzaro's reaction with the aldehyde starting material. This can rationalize the best yields obtained with piperidine. Weaker bases such as sodium carbonate or potassium carbonate gave lower yields compared with piperidine. Under typical Friedländer's reaction conditions in different solvents and different bases, the best conditions (Table 1, entry 6) gave good yield (85%). We used 1.4 equivalents of piperdine with ethanolic solution and carried out the reaction for 24 h at reflux temperature, and the product **3** was precipitated after cooling the reaction mass to 0-5 °C, the reaction mass was filtered out to get the pure product. Upon using different alcoholic solvents with piperidine, the optimum solvent was ethanol.

Normal Friedländer's reaction mechanism proceeds through the formation of imines (Schiff's bases) or α,β-unsaturated carbonyl compound which subsequently dehydrated to give quinoline moiety. Here we encountered the possibility of formation of two isomers A&B, but predominately we got the isomer A (Figure 1).

The formation of isomer B can be ruled out based on the mechanistic fact that active methylene group present between nitrophenoxy and keto groups actively attacks the aldehydic carbon atom of the substrate and subsequently leads to formation of imine intermediate which is cyclized and subsequently dehydrated to give the isomer A. ^{1}H NMR data also supported our assumption. The absence of methylene signal at about δ 5.53 ppm indicates the absence of the isomer B. And the presence of singlet equivalent to methyl group at δ 2.59 ppm for compound **3** confirms the formation of isomer A. Isomer B was not obtained upon using different solvents or bases. The probable mechanism for the cyclization to quinoline nucleus has been proposed as illustrated in Figure 2.

After preparation of the quinoline intermediate compound **3**, the target diarylamides and diarylureas **5**, **6** were synthesized by the sequence of reactions illustrated in Scheme 1. The nitro group of **3** was reduced into amino using palladium over carbon in hydrogen atmosphere. Condensation of the amino compound **4** with the appropriate benzoic acid derivatives in the presence of 1-hydroxybenzotriazole (HOBt), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), and triethylamine produced the target diarylamide products **5a-c**. Reaction of the amino group of **4** with the appropriate aryl isocyanates afforded the corresponding urea derivatives **5d-f**. Demethylation of the methoxy groups of **5c**, **5f** using boron tribromide yielded the corresponding hydroxyl



Scheme 1. Reagents and conditions: (a) piperidine, ethanol, reflux, 24 h; (b) Pd/C (10%), methanol, rt, 4 h; (c) HOBt, EDCI, TEA, DMF, 80 °C, 24 h (for amide derivatives); K_2CO_3, THF, rt, 12 h (for urea derivatives); (d) BBr_3, CH_2Cl_2, -78 °C, 1 h; rt, 4 h.

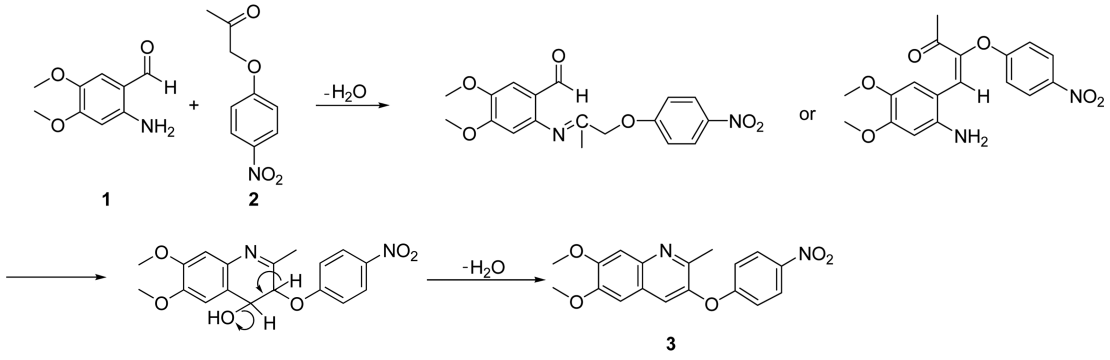
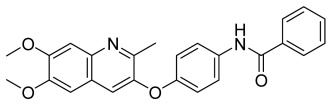
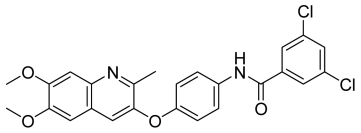
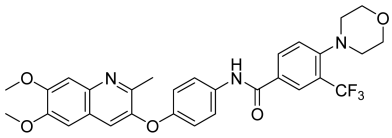
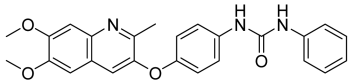
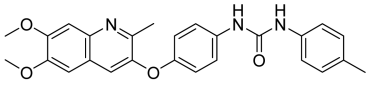
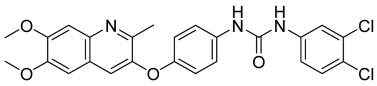
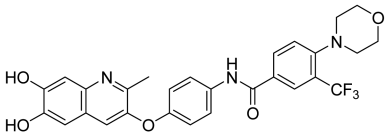
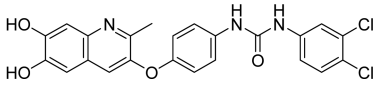


Figure 2. Mechanism of cyclization to quinoline intermediate **3**.

Table 2. Yield % of the target diarylamide and diarylurea derivatives

Comp. No.	Structure	Yield %
5a		47
5b		64
5c		80
5d		52
5e		40
5f		76
6a		43
6b		45

derivatives **6a**, **b**. The yield percentages of the final products are illustrated in Table 2.

The target quinoline compounds **5a-f** and **6a**, **b** possessing diarylamide and diarylurea scaffolds have been designed and assumed to possess anticancer activity. They have been considered for *in vitro* antiproliferative activity evaluation over a panel of 60 cancer cell lines of nine different cancer types (leukemia, non-small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer) at the National Cancer Institute (NCI, Bethesda, Maryland, USA).[13] The preliminary results showed that the urea derivatives **5f** and **6b** possess the best mean %inhibition (83.39% and 40.55%, respectively) at a single dose concentration (10 μM) over the NCI-60 cancer cell line panel. Both compounds have been selected for 5-dose testing in order to determine their IC_{50} values over each cell line of the NCI-60 panel. After receiving all the biological results, we look forward to further exploration of the SAR of this series of compounds to be reported in due course.

Conclusion

We reported an efficient method for the synthesis of novel aryloxyquinoline derivatives *via* Friedländer's reaction through the condensation reaction of dimethoxy-substituted *o*-aminobenzaldehyde with *para*-nitrophenoxyacetone. The optimum reaction conditions were the use of piperidine in refluxing ethanol. The experimental procedure was very simple with high yield. Our protocol can be applied to a wide range of substrates. These methods not only afford significant improvements in the reaction rates and yields, but also avoid lengthy work-up and purification procedure. The preliminary anticancer activities of the target diarylurea derivatives **5f** and **6b** were promising. Further biological screening of this series of compounds are currently in progress.

Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 or 300 spectrometer using tetramethylsilane as an internal standard. Solvents and liquid reagents were transferred using hypodermic syringes. Purity % of all the target compounds were determined by HPLC and found to be > 95%. All solvents and reagents were commercially available and used without further purification.

Preparation of 6,7-Dimethoxy-2-methyl-3-(4-nitrophenoxy)quinoline (3). To a solution of 2-amino-4,5-dimethoxybenzaldehyde (**1**, 0.182 g, 1.0 mmol) and 1-(4-nitrophenoxy)propan-2-one (**2**, 0.195 g, 1.0 mmol) in ethanol (10 mL), piperdine (0.119 g, 1.4 mmol) was added. The reaction mixture was refluxed for 24 h, and then cooled to 0-5 °C to get the product precipitated out. The product was filtered, washed with little ethanol, and dried. Yield: 0.29 g, 85%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.26 (d, J = 3.0 Hz, 2H), 7.64 (s, 1H), 7.45 (s, 1H), 7.30 (d, J = 3.0 Hz, 2H), 7.01 (s, 1H), 4.08 (s, 3H), 4.03 (s, 3H), 2.59 (s, 3H); LC-MS (*m/z*): 341.86 $(M + 2)^+$, 340.89 $(M + 1)^+$.

Preparation of 4-(6,7-Dimethoxy-2-methylquinolin-3-yloxy)benzenamine (4). A mixture of compound **3** (0.34 g, 1.0 mmol) and Pd/C (10%) in methanol (20 mL) was stirred in hydrogen atmosphere at room temperature for 4 h. The reaction mixture was filtered through celite, and the filtrate was evaporated to dryness under reduced pressure to get the pure title compound (0.279 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (s, 1H), 7.20 (s, 1H), 6.94-6.85 (m, 3H), 6.77-6.72 (m, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 3.52 (brs, 2H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.8, 150.6, 150.4, 149.5, 148.3, 143.0, 140.3, 123.3, 120.8, 117.8, 116.4, 107.5, 104.4, 56.0, 55.9, 20.2.

General Procedure for Synthesis of Diarylamide Derivatives 5a-c. A mixture of compound **4** (18.6 mg, 0.06 mmol), the appropriate carboxylic acid derivative (0.12 mmol), HOBt (18.1 mg, 0.13 mmol), and EDCI (29.1 mg, 0.15 mmol) in dry DMF (1.0 mL) was cooled to 0 °C under nitrogen atmosphere. To the reaction mixture, triethylamine (0.002 mL, 0.015 mmol) was added at 0 °C. The mixture was then stirred at 80 °C for 24 h. The reaction mixture was cooled and then partitioned between water (5 mL) and ethyl acetate (5 mL), and the organic layer was separated. The aqueous layer was then extracted with ethyl acetate (3 × 3 mL), and the com-

bined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by column chromatography (silica gel, using the proper ratio of hexane and ethyl acetate) to yield the target diarylamide compound.

***N*-(4-(6,7-Dimethoxy-2-methylquinolin-3-yloxy)phenyl)-benzamide (5a):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (brs, 3H), 7.66-7.64 (m, 2H), 7.59-7.49 (m, 3H), 7.38 (d, J = 8.6 Hz, 2H), 7.05-7.03 (m, 2H), 6.90 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 153.5, 151.3, 150.7, 149.7, 149.0, 134.8, 133.7, 132.0, 128.9, 127.0, 123.3, 122.3, 120.2, 119.2, 107.4, 104.5, 99.2, 56.1, 56.0, 20.1.

3,5-Dichloro-*N*-(4-(6,7-dimethoxy-2-methylquinolin-3-yloxy)phenyl)benzamide (5b): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 7.66 (brs, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 1.7 Hz, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 2.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 154.1, 151.4, 150.8, 149.7, 148.6, 141.2, 137.6, 135.6, 132.9, 131.7, 125.8, 123.3, 122.6, 120.8, 118.9, 107.3, 104.5, 56.1, 56.0, 20.1.

***N*-(4-(6,7-Dimethoxy-2-methylquinolin-3-yloxy)phenyl)-4-morpholino-3-(trifluoromethyl)benzamide (5c):** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.96 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.40-7.34 (m, 3H), 7.03 (d, J = 8.8 Hz, 2H), 6.90 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.86 (t, J = 4.1 Hz, 4H), 3.01 (t, J = 4.0 Hz, 4H), 2.66 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 154.9, 153.6, 151.3, 150.8, 149.6, 148.9, 141.1, 133.6, 131.9, 131.7, 130.6, 126.9, 123.7, 123.35, 123.2, 122.5, 120.4, 119.0, 107.4, 104.5, 67.1, 56.0, 53.6, 53.4, 20.1.

General Procedure for Synthesis of Diarylurea Derivatives 5d-f. To a solution of compound **4** (18.6 mg, 0.06 mmol) in anhydrous THF (3 mL), the appropriate aryl isocyanate (0.06 mmol) and anhydrous potassium carbonate (16.6 mg, 0.12 mmol) were added. The reaction mixture was stirred under nitrogen atmosphere at room temperature for 12 h. The inorganic material was filtered off and washed with THF, the organic solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, using the proper ratio of hexane and ethyl acetate) to obtain the target diarylurea product.

1-(4-(6,7-Dimethoxy-2-methylquinolin-3-yloxy)phenyl)-3-phenylurea (5d): ^{1}H NMR (Acetone-d_6, 400 MHz) δ 8.04 (brs, 1H), 7.98 (brs, 1H), 7.48-7.41 (m, 5H), 7.24 (s, 1H), 7.17-7.13 (m, 3H), 7.03 (s, 1H), 6.90-6.84 (m, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.45 (s, 3H).

1-(4-(6,7-Dimethoxy-2-methylquinolin-3-yloxy)phenyl)-3-*p*-tolylurea (5e): ^{1}H NMR (Acetone-d_6, 400 MHz) δ 8.05 (brs, 1H), 7.93 (brs, 1H), 7.46 (d, J = 7.1 Hz, 2H), 7.28-7.24 (m, 3H), 7.16 (s, 1H), 7.02 (s, 1H), 6.95 (d, J = 6.4 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 3.83 (s, 3H), 3.76 (s, 3H), 2.45 (s, 3H), 2.13 (s, 3H).

1-(3,4-Dichlorophenyl)-3-(4-(6,7-dimethoxy-2-methylquinolin-3-yloxy)phenyl)urea (5f): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (brs, 1H), 7.83 (brs, 1H), 7.35 (d, J = 7.0 Hz, 1H), 7.24 (s, 1H), 7.19-7.09 (m, 4H), 6.99 (d, J = 8.5 Hz, 1H), 6.83-6.76 (m, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 2.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 153.8, 153.2, 151.6, 150.4, 149.9, 148.7, 140.5, 138.0, 133.5, 132.7, 130.5, 126.5, 123.4, 122.8, 121.3, 121.0, 119.1, 106.6, 104.6, 56.1, 19.7.

General Procedure for Demethylation of the Dimethoxy Derivatives (Preparation of Dihydroxy Derivatives 6a, b). To a solution of compound **5c**, **f** (0.1 mmol) in methylene chloride (1 mL), BBr_3 (0.16 mL of a 1 M solution in methylene chloride, 2.4 mmol) was added dropwise at −78 °C under N_2. The reaction mixture was stirred at the same temperature for 1 h. The mixture was then allowed to warm to room temperature and stirred for 4 h. The mixture was quenched with saturated aqueous $NaHCO_3$. Ethyl acetate (5 mL) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layer extracts were washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the organic solvent, the residue was purified by short column chromatography (silica gel, using the proper ratio of ethyl acetate and methanol) to yield compound **6a**, **b**.

***N*-(4-(6,7-Dihydroxy-2-methylquinolin-3-yloxy)phenyl)-4-morpholino-3-(trifluoromethyl)benzamide (6a):** ^{1}H NMR (CD_3OD, 300 MHz) δ 8.10 (brs, 1H), 7.64 (s, 1H), 7.61 (brs, 1H), 7.58 (s, 1H), 7.55 (d, J = 4.4 Hz, 2H), 7.52 (s, 1H), 7.48-7.46 (m, 5H), 3.72 (t, J = 4.3 Hz, 4H), 2.92 (s, 3H), 2.87 (t, J = 4.4 Hz, 4H).

1-(3,4-Dichlorophenyl)-3-(4-(6,7-dihydroxy-2-methylquinolin-3-yloxy)phenyl)urea (6b): ^{1}H NMR (CD_3OD, 300 MHz) δ 7.71 (s, 1H), 7.37 (s, 1H), 7.34 (d, J = 5.0 Hz, 1H), 7.29 (d, J = 7.6 Hz, 2H), 7.21 (s, 1H), 7.17 (s, 1H), 7.15 (s, 1H), 6.90-6.85 (m, 4H), 2.48 (s, 3H).

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