Regioselective Synthesis of Quinazoline Containing Novel Monoaryl Ethers at Room Temperature

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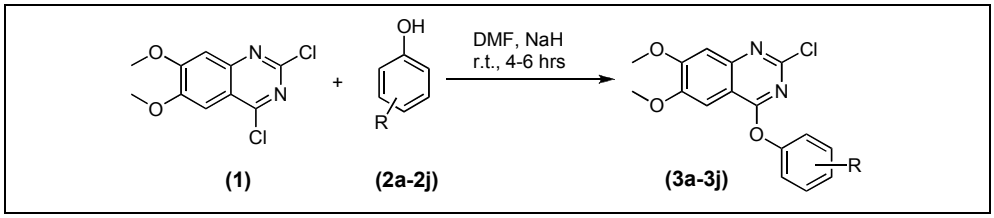

We are herein reporting the regioselective synthesis of quinazoline containing novel monoaryl ethers (quinazoline-O-Ar) (**3a-3j**) at room temperature without any catalyst. From commercially available 2,4-dichloro-6,7-dimethoxyquinazoline (**1**), 4-chloro was selectively substituted with variety of electronically rich, electronically poor and electronically neutral phenols (**2a-2j**). Reaction was carried out in DMF and NaH for 4-6 hours at room temperature in fairly good yield. The products were purified (>98% pure, hplc) by crystallization to avoid the use of column chromatography.

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INTRODUCTION

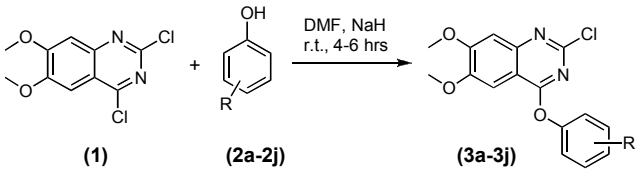
The diaryl ethers are an important class of compounds in organic synthesis [1] and are found in a large number of biologically active compounds [2,3]. Number of diaryl ethers are reported to have significant biological activity *e.g.* antibiotics vancomycin, antitumoral baubardin *etc* [4,5]. The traditional Ullmann ether syntheses [6] have been extensively used for the formation of diaryl ethers [7,8]. The Ullmann ether formation has traditionally been carried out under rather harsh conditions, usually at high temperature in pyridine solvent [3,9]. The yields are low to moderate, and it has been also reported that reaction between electron-rich aryl halide and electron-deficient phenols typically does not work well [10]. Over the past years, tremendous effort has been devoted to supplant the classical Ullmann reaction and much more new methodologies for diaryl ether formation have been developed [8]. The presence of copper catalyst has been focus of a number of recent studies because it provides a very direct access to diaryl ethers [7,11,12]. Although recent progress in palladium catalyzed ether formation reaction has solved some problems in this area [13,14] but still copper catalyst hold the advantage of low cost for large scale industrial applications. Recently, microwave heating has been extensively documented as an efficient synthetic tool and its advantages like much shorter reaction time with improved yield [15,16] have been reported. Even though these advancement have improved the synthetic scope of diaryl ethers, but still there are some limitations. For example, phenols can be converted to diaryl ethers only if they are suitably substituted or if extremely strenuous conditions (like prolonged reaction time, elevated reaction temperature) are employed.

There are several literatures documented about the formation of diaryl ethers from monocyclic substituted phenols and aryl halides; but there is still need to work on hetrocyclic-diaryl ether formation. In our earlier report we have reported the one step synthesis of 2-hydroxy diaryl ethers through microwave heating which includes few example of substituted heterobicyclic phenols and bromoarenes to get heterocyclic diaryl ethers [15]. In recent years much interest has been generated in medicinal chemistry for quinazoline derivatives with special interest to monoaryl ethers and monoaryl amines for their immerging role in anticancer drug development [17,18].

We herein report the simple and one step synthesis of quinazoline containing novel monoaryl ethers (ether bond between two aromatic ring) at room temperature without use of any catalyst. One of the rationales behind taking quinazoline was its therapeutic importance in anticancer research. The nucleophilic substitution at quinazoline ring is well known, but at the same time the selective nucleophilic substitution reaction at quinazoline to get monoaryl ether at room temperature is still a challenge. In order to get desired products, commercially available 2,4-dichloro-6,7-dimethoxyquinazoline was treated with variety of substituted phenols (electronically rich, deficient and neutral phenols **2a-2j**) in presence of DMF and NaH at room temperature, which afforded 100% regioselective 2-chloro-4-phenoxy-6,7-dimethoxyquin-

azolines (**3a-3j**; **Table-1**) in fairly good yield without the formation of any 2-substituted product. To the best of our knowledge this is the first report where any heterocyclic diaromatic ether (heterocyle-O-Ar) has been synthesize at room temperature without using any catalyst in 4-6 hours time. Surprisingly the electron deficient phenols (**2f, 2g, 2h, 2i; Table-1**) work better as compare to electron rich and electronically neutral phenols, which is against the earlier reports that electron deficient phenol typically does not work well [10].

Scheme 1

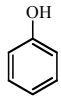
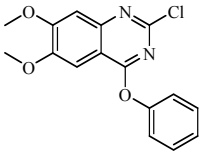
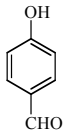
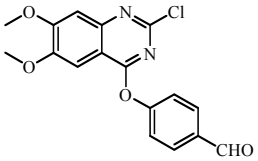
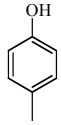
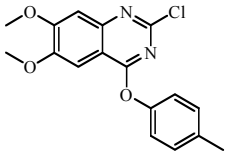
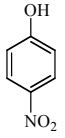
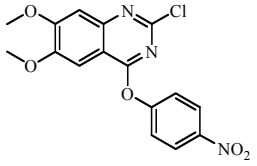
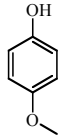
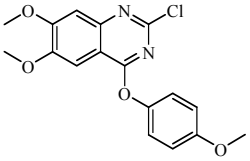
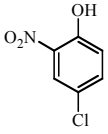
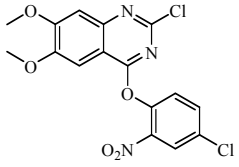
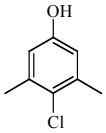
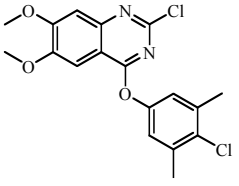
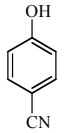
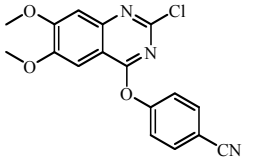
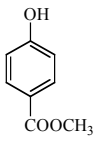
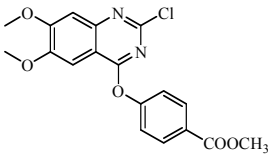
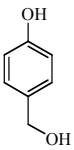
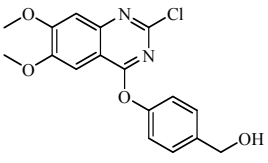


In conclusion, we present here a simple, efficient and rapid method for regioselective quinazoline containing monoaryl ether syntheses, which will open a new avenue for quinazoline containing drug discovery in medicinal chemistry. This reaction is equally good for getting quinazoline-containing monoaryl amine under similar conditions, the work is currently under progress and will be reported in due courses. This method is both time and cost efficient compared to previously described methods.

EXPERIMENTAL

2,4-Dichloro-6,7-dimethoxyquinazoline (**1**) and substituted phenols (**2a-2j**) were purchased from Sigma-Aldrich Co. USA. DMF and NaH were used without further purification. The thin layer chromatography was performed on Merck pre-coated silica gel 60 F_{254} plates, with visualization under uv light. ^{1}H nmr spectra were recorded with Bruker 300 MHz AVANCE instrument and shifts are given in ppm relative to internal

Table 1

Phenol 2	Product 3	Time (hrs)	Yield	Phenol 2	Product 3	Time (hrs)	Yield
 **2a**	 **3a**	4	70%	 **2f**	 **3f**	4	84%
 **2b**	 **3b**	4	47%	 **2g**	 **3g**	6	67%
 **2c**	 **3c**	4	56%	 **2h**	 **3h**	6	77%
 **2d**	 **3d**	4	60%	 **2i**	 **3i**	4	88%
 **2e**	 **3e**	4	75%	 **2j**	 **3j**	4	68%

tetramethylsilane. The mass spectra were measured with Thermo Finnigan-TSQ Quarter Ultra (triple Quad). Elemental analysis was performed using Thermo Finnigan-Flash EA-1112. Melting points were measured on Veego VMP-1 electrode thermal apparatus and are uncorrected. The purity of final compounds was determined by hplc (Waters 2695 Alliance) using column Kromasil C18, solvent acetonitrile and buffer (0.01 *M* ammonium acetate + 0.5% triethylamine, pH 5.0 with acetic acid).

General Procedure. 2-Chloro-6,7-dimethoxy-4-phenoxyquinazoline (3a) Phenol **2a** (1.00 mmol, 0.094 g) and 60% sodium hydride (1.2 mmol, 0.048 g) were stirred in 10 mL of *N*,*N*-dimethylformamide at room temperature for 30 minutes to get sodium phenoxide. To the reaction mixture 2,4-dichloro-6,7-dimethoxyquinazoline **1** (1.00 mmol, 0.26 g) was added. The stirring proceeded for 4 hours and the reaction was monitored by tlc using 2% methanol in chloroform as solvent. The reaction mixture was treated with 60 mL of cold water and the product was extracted with chloroform (3 X 75 mL) and washed with 50 mL of brine. The combined chloroform extract was dried over anhydrous sodium sulfate, filtered and evaporated *in vacuo*. The residue was crystallized two times with chloroform: petroleum ether (1:2 v/v, 60 mL) to produce white solid powder, 70% (0.22 g) yield, mp 200-201 °C; hplc 98.97% (RT 16.69 minutes). ^{1}H nmr, (dimethyl sufoxide-d_6): δ 7.52 (s, 1H), 7.47-7.50 (m, 2H Ar), 7.34-7.35 (m, 4H; 3H from Ar and 1H from quinazoline), 3.96 (s, 3H), 3.95 (s, 3H); ms: m/z found 317.23 (M+1) Calcd. For $C_{16}H_{13}ClN_2O_3$, 316.07. *Anal.* Calcd for $C_{16}H_{13}ClN_2O_3$: C, 60.67; H, 4.14; N, 8.84; Cl, 11.19. Found: C, 60.34; H, 4.01; N, 8.50; Cl, 11.02.

2-Chloro-6,7-dimethoxy-4-(4-tolyloxy)quinazoline (3b). The compound **3b** was prepared as outlined in **3a**, as off white powder, mp 145-146 °C; hplc: purity 99.27% (RT 18.08 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 7.52 (s, 1H), 7.34 (s, 1H), 7.27-7.30 (d, J=9.0 Hz, 2H), 7.18-7.21 (d, J=9.0 Hz, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 2.35 (s, 3H); ms: m/z found 331.19 (M+1) Calcd. For $C_{17}H_{15}ClN_2O_3$, 330.08. *Anal.* Calcd. For $C_{17}H_{15}ClN_2O_3$ x 0.1 H_2O: C, 61.40; H, 4.61; N, 8.42; Cl, 10.66. Found: C, 61.58; H, 4.49; N, 8.36; Cl, 10.28.

2-Chloro-6,7-dimethoxy-4-(4-methoxyphenoxy)quinazoline (3c) The compound **3c** was prepared as outlined in **3a**, as off white powder, mp 136 °C; hplc: purity 98.59% (RT 16.53 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 7.52 (s, 1H), 7.35 (s, 1H), 7.24-7.27 (d, J=9.0 Hz, 2H), 7.01-7.04 (d, J=9.0 Hz, 2H), 3.96 (s, 3H), 3.95 (s, 3H), 3.78 (s, 3H); ms: m/z found 347.23 (M+1) Calcd. For $C_{17}H_{15}ClN_2O_4$, 346.07. *Anal.* Calcd. For $C_{17}H_{15}ClN_2O_4$ x 0.5H_2O: C, 58.13; H, 4.45; N, 7.97; Cl, 10.09. Found: C, 57.84; H, 4.26; N, 7.96; Cl, 9.71.

2-Chloro-4-(4-chloro-3,5-dimethylphenoxy)-6,7-dimethoxyquinazoline (3d). The compound **3d** was prepared as outlined in **3a**, as brown powder, mp 192-193 °C; hplc: purity 98.69% (RT 20.95 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 7.49 (s, 1H), 7.35 (s, 1H), 7.21 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 2.35 (s, 6H); ms: m/z found 379.18 (M+1) Calcd. For $C_{18}H_{16}Cl_2N_2O_3$, 378.05. *Anal.* Calcd. For $C_{18}H_{16}Cl_2N_2O_3$: C, 57.01; H, 4.25; N, 7.39; Cl, 18.70. Found C, 57.01; H, 4.14; N, 7.30; Cl, 18.30.

Methyl-4-(2-chloro-6,7-dimethoxyquinazoline-4-yloxy)-benzoate (3e). The compound **3e** was prepared as outlined in **3a**, as white powder, mp 232-233 °C; hplc: purity 98.96% (RT 16.50 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 8.07-8.10 (d, J=9.0 Hz, 2H), 7.55 (s, 1H), 7.50-7.53 (d, J=9.0 Hz, 2H), 7.37 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H)**;** ms: m/z found 375.21 (M+1) Calcd. For $C_{18}H_{15}ClN_2O_5$, 374.07. *Anal.* Calcd. For $C_{18}H_{15}ClN_2O_5$ x 0.5 H_2O: C, 56.33; H, 4.20; N, 7.30; Cl, 9.24. Found C, 56.61; H, 3.96; N, 7.27; Cl, 9.30.

4-(2-Chloro-6,7-dimethoxyquinazoline-4-yloxy)benzaldehyde (3f). The compound **3f** was prepared as outlined in **3a**, as white powder, mp 231 °C; hplc: purity 98.32% (RT 14.91 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 10.03 (s, 1H), 8.04-8.07 (d, J= 9.0 Hz, 2H), 7.59-7.62 (d, J= 9.0 Hz, 2H), 7.56 (s, 1H), 7.38 (s, 1H), 3.98 (s, 3H), 3.96 (s, 3H); ms: m/z found 345.09 (M+1) Calcd. For $C_{17}H_{13}ClN_2O_4$, 344.06. *Anal.* Calcd. For $C_{17}H_{13}ClN_2O_4$ x 0.25 H_2O: C, 58.46; H, 3.90; N, 8.02; Cl, 10.15. Found C, 58.48; H, 3.71; N, 7.96; Cl, 9.83.

2-Chloro-6,7-dimethoxy-4-(4-nitrophenoxy)quinazoline (3g). The compound **3g** was prepared as outlined in **3a**, as off white powder, mp 239 °C; hplc: purity 99.15% (RT 16.46 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 8.36-8.39 (d, J=9.0 Hz, 2H), 7.66-7.69 (d, J=9.0 Hz, 2H), 7.56 (s, 1H), 7.39 (s, 1H), 3.97 (s, 3H), 3.96 (s, 3H); ms: m/z found 362.26 (M+1) Calcd. For $C_{16}H_{12}ClN_3O_5$, 361.05. *Anal.* Calcd. For $C_{16}H_{12}ClN_3O_5$ x 0.25 H_2O: C, 52.47; H, 3.44; N, 11.47; Cl, 9.68. Found C, 52.71; H, 3.17; N, 11.14; Cl, 9.49.

2-Chloro-4-(4-chloro-2-nitrophenoxy)-6,7-dimethoxyquinazoline (3h). The compound **3h** was prepared as outlined in **3a**, as white powder, mp 241 °C; hplc: purity 98.09% (RT 17.71 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 8.35-8.36 (d, J= 3.0 Hz, 1H), 8.00-8.04 (dd, J=3.0 and 9.0 Hz, 1H), 7.78-7.81 (d, J=9.0 Hz, 1H), 7.55 (s, 1H), 7.41 (s, 1H), 3.99 (s, 3H), 3.95 (s, 3H); ms: m/z found 396.15 (M+1) Calcd. For $C_{16}H_{11}Cl_2N_3O_5$, 395.01. *Anal.* Calcd. For $C_{16}H_{11}Cl_2N_3O_5$: C, 48.51; H, 2.80; N, 10.61; Cl, 17.90. Found C, 48.60; H, 2.74; N, 10.26; Cl, 17.63.

4-(2-Chloro-6,7-dimethoxyquinazoline-4-yloxy)benzonitrile (3i). The compound **3i** was prepared as outlined in **3a**, as white powder, mp 209 °C; hplc: purity 98.33% (RT 15.41 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ=7.99-8.02 (d, J=9.0 Hz, 2H), 7.60-7.63 (d, J=9.0 Hz, 2H), 7.54 (s, 1H), 7.37 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H); ms: m/z found 342.08 (M+1) Calcd. For $C_{17}H_{12}ClN_3O_3$, 341.06. *Anal*: Calcd. For $C_{17}H_{12}ClN_3O_3$ x 0.25 H_2O: C, 58.97; H, 3.64; N, 12.14; Cl, 10.24. Found C, 59.35; H, 3.50; N, 11.85; Cl, 10.46.

(4-(2-Chloro-6,7-dimethoxyquinazoline-4-yloxy)phenyl)-methanol (3j). The compound **3j** was prepared as outlined in **3a**, as white powder, mp 191 °C; hplc: purity 98.19% (RT 12.38 minutes). ^{1}H nmr (dimethyl sufoxide-d_6): δ 7.53 (s, 1H), 7.40-7.43 (d, J=9.0 Hz, 2H), 7.35 (s, 1H), 7.26-7.29 (d, J=9.0 Hz, 2H), 5.27-5.31(t, 1H, -OH), 4.52-4.54(d, 2H) 3.96 (s, 3H), 3.95 (s, 3H); ms: m/z found 347.18 (M+1) Calcd. For $C_{17}H_{15}ClN_2O_4$, 346.07. *Anal.* Calcd. For $C_{17}H_{15}ClN_2O_3$ x 0.5 H_2O: C, 57.39; H, 4.53; N, 7.87; Cl, 9.97. Found C, 57.63; H, 4.25; N, 7.99; Cl, 9.86.

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