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# An Efficient Microwave-assisted Suzuki Cross-coupling Reactions on Quinoline Derivatives in Water and Study the Electronic Effects Thereof

**Raghunath Toche*, Ravindra Janrao**

Organic Chemistry Research Center, P. G. Department of Chemistry, K.T.H.M. College, Nashik - 422 002, India
Fax No. 0253-2577341, E-mail: raghunath_toche@rediffmail.com

***Abstract***- Simple and rapid synthesis of various diversely functionalized unprotected 4-amino-2-chloroquinoline-3-aryl derivatives were synthesized in high yields by Suzuki cross-coupling reaction using microwave irradiation in water and in presence of tetrakis(triphenylphosphine)palladium(0). Electronic effects of *o*-substituted functional groups on the reaction were studied conclusively**.**

***Index Terms***- Microwave assisted synthesis, Suzuki Miyura cross-coupling reaction, Electronic effects.

## I. INTRODUCTION

Quinolines play a very important role in medicinal chemistry. The latest quinoline contains drug is montelukast (Singulair®), an anti-asthmatic drug. The inimitable characteristic of quinoline chemistry, stem from the sterioelectronic effects that the nitrogen atom has exerted on the quinoline molecule. Basically it is π-electron-deficient heterocycle. Due to the electronigativity of the nitrogen atom in quinoline, the α and γ position tolerate a partial positive charge, making these C (2) and C (4) position prone to nucleophilic attack. A similar trend occurs in the context of palladium chemistry. Halogen at the α and γ position of quinoline are more liable to oxidative addition to Pd(0) in comparison to simple carbocyclic aryl halides.

A few direct cross-coupling reactions on unprotected [1] and protected amines [2] on 2-chloroheteroaryl moieties have been disclosed in literature by conventional heating in organic solvents. A more challenging coupling reaction of 2-chloroheterobiaryl on unprotected amine with heteroaryl boronic acids is also reported in literature [3-4] by conventional heating method. It is common practice to protect and deprotect the functional groups such as amines, alcohols/ phenols, thiols / thiophenols and carboxylic acids [5] during coupling reaction. The Suzuki reaction on unprotected 4-amino-2-chloroquinoline was reported using expensive catalyst ($Pd(dppf)Cl_2$) at higher temperature required longer reaction time in DMF-water mixture with low yield by conventional method [6].

Meanwhile, microwave assisted organic synthesis is rapidly growing field in organic chemistry [7]. This field is suited to the increased demand in the industries because; it makes reaction time shorter and expanding the reaction range. The introduction of dedicated equipments has a large impact on the further development of this young research field [8]. On the other hand; the pharmaceutical industries require the production of higher number of novel chemical entities, which requires chemists to employ a number of resources to reduce the time for the production of compounds. Microwave radiation provides an alternate to conventional heating as utilizes the ability of liquids or solids to transform electromagnetic energy into heat.

In this paper, we first time introduce an efficient microwave assisted Suzuki cross coupling reaction on diversely functionalized unprotected *o*-amino quinolines with aryl boronic acid in water and studied the electronic effect of substituents during course of reaction under similar conditions.

## 2. Result and findings

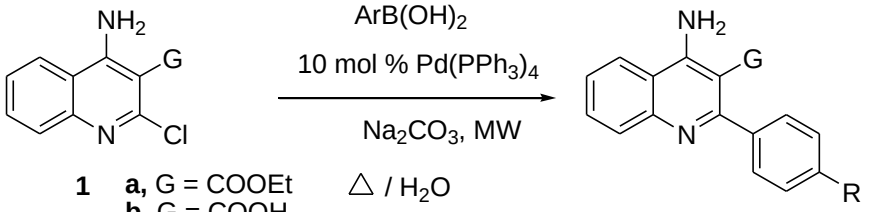
Recently we have reported the synthesis of arylbenzo[*h*][1,6]naphthyridine derivatives by Suzuki reaction only on 4-amino-2-chloroquinoline-3-carbaldehyde using conventional method and further *Friedländer* condensation [9]. The success of carbon–carbon cross coupling reaction on 4-amino-2-chloroquinoline-3-carbaldehyde by conventional method encourages us to explore microwave-assisted Suzuki reaction on diversely functionalized unmasked 4-amino-2-chloroquinoline derivatives. However, we have optimized the reaction conditions and done Suzuki reaction on unmasked *o*-amino quinolines in short reaction time with higher yields (**2a-5c**).

Based on several reports regarding the Suzuki-Miyaura reaction in aqueous media and in order to optimize the cross-coupling reactivity, we decided to use $Na_2CO_3$ as a base and $Pd(PPh_3)_4$ as a catalyst. It has been suggested that in the Suzuki reaction, the boronic acid is oxidized by the Pd(II) salt leading to formation of the Pd(0) complex and generation of a biaryl formed by concomitant homocoupling of boronic acid [10]. In light of this, we decided to use only $Pd(PPh_3)_4$ as a catalyst. We focused our research around the use of water as a solvent in conjunction with microwave heating. Water offers partial advantages over organic solvents. It is cheap,

readily available, non-toxic, nonflammable, and universally acceptable and proves to be an excellent solvent for microwave-promoted synthesis [11]. As well as being energy efficient, microwaves can also enhance rate of reaction and in many cases improve product yield. In this area the large number of papers and reviews available in the literature [12].

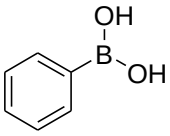
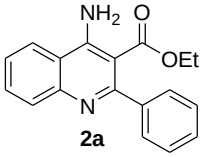
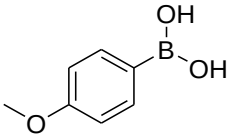
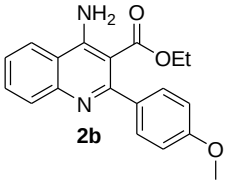
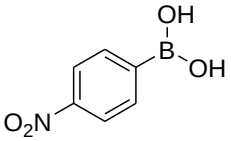
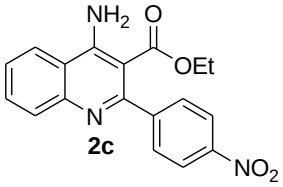
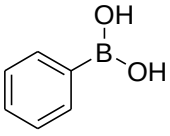
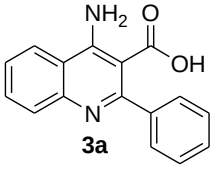
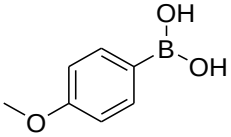
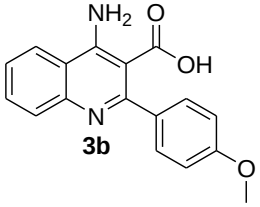
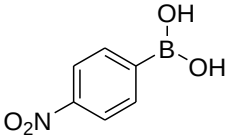
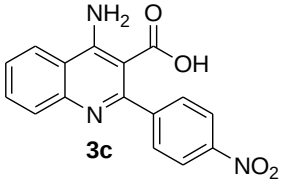
Furthermore, our attempts to use a lower catalyst loading (5 mol % $Pd(PPh_3)_4$ lead to increase the reaction time up to 1 hour (entry 12).

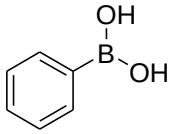
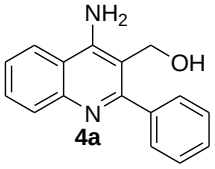
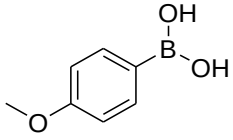
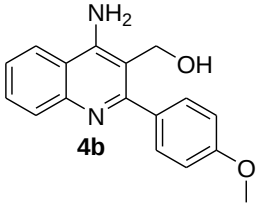
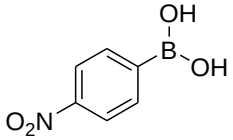
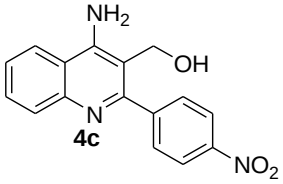
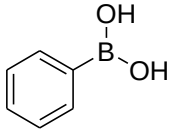
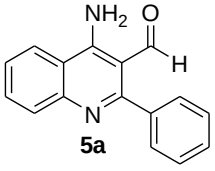
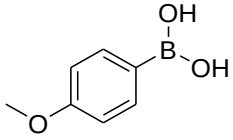
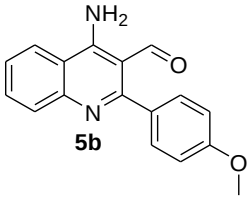
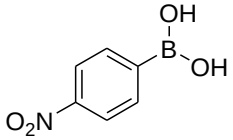
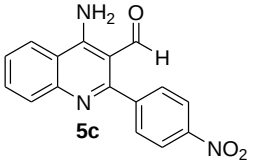
**Table 1.** Microwave-mediated Suzuki coupling reaction of 4-amino-2-chloro-3-substituted quinolines and aryl boronic acids in water using $Pd(PPh_3)_4$[a]




**1** **a,** G = COOEt
**b,** G = COOH
**c,** G = $CH_2OH$
**d,** G = CHO

**2-5** **a,** R = H
**b,** R = OMe
**c,** R = $NO_2$

| Entry | Arylboronic acid | Product | *t* (h) | Yield (%) |
|---|---|---|---|---|
| 1 |  |  **2a** | 0.66 | 87 |
| 2 |  |  **2b** | 0.33 | 88 |
| 3 |  |  **2c** | 0.88 | 81 |
| 4 |  |  **3a** | 0.66 | 79 |
| 5 |  |  **3b** | 0.55 | 75 |
| 6 |  |  **3c** | 0.75 | 83 |

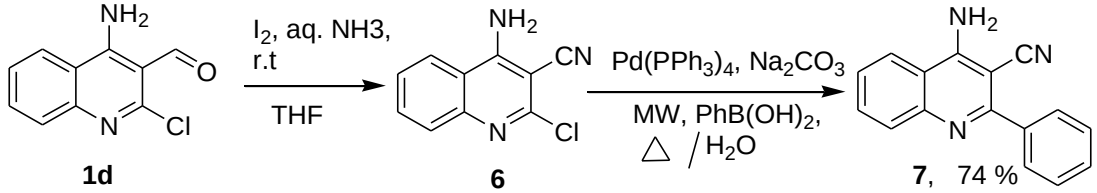
| | | | | |
|---|---|---|---|---|
| 7 |  |  **4a** | 0.66 | 70 |
| 8 |  |  **4b** | 0.33 | 68 |
| 9 |  |  **4c** | 0.88 | 71 |
| 10 |  |  **5a** | 0.66 | 89 |
| 11 |  |  **5b** | 0.33 | 91 |
| 12 |  |  **5c** | 0.88 | 95, 40[c] |

[a] Conditions: catalyst $Pd(PPh_3)_4$ 10 mol %, 4-amino-2-chloro-3-substituted quinolines (**1a-d**) (1equiv), arylboronic acid (1.3 equiv), $Na_2CO_3$ (3.0 equiv), $H_2O$. An initial microwave irradiation of 300 W was used, the temperature being ramped from rt to 105 $^oC$ where it was then held for a *t* time

[b] Microwave irradiation (500 W, 105 °C).

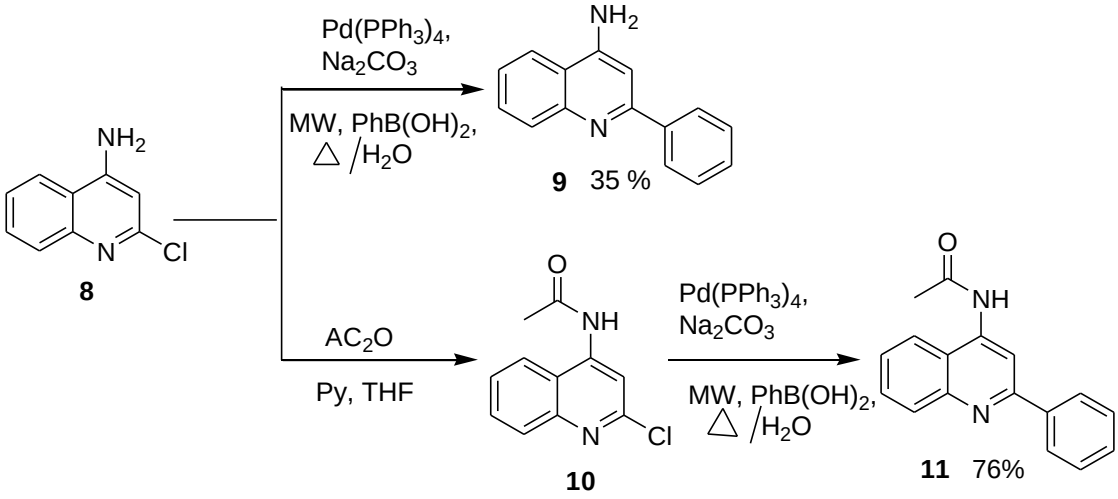
[c] Catalyst $Pd(PPh_3)_4$ 5 mol %

Initially, it was assume that due to the hydrogen-bonding between the $NH_2$ and carbonyl functionality at *ortho* position, the crowding at $C_2$ position decrease and the rate of oxidative addition on $C_2$-Cl bond increases or can also be due to the electron withdrawing effect of *ortho* substituent make $C_2$-position more prone for oxidative addition. To demonstrate the success of reaction whether due to the hydrogen-bonding or it was just electronic effect we discarded the hydrogen-bonding by introduction of nitrile at that position. Hence the 4-amino-2-chloroquinoline-3-carbonitrile **6** was obtained from 4-amino-2-chloroquinoline-3-carbaldehyde **1d** by using iodine and aqueous ammonia [13] (scheme 2). The reaction of interest compound **6** with phenylboronic acid under similar microwave conditions yield 74 % of 4-amino-2-phenylquinoline-3-carbonitrile **7**



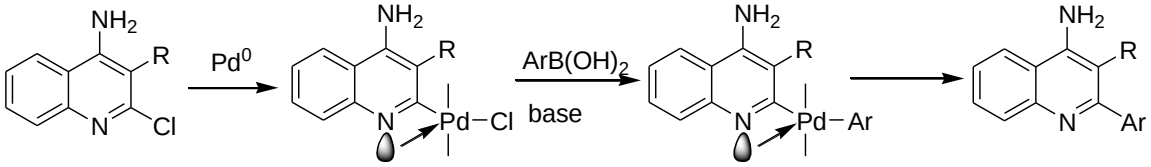

**Scheme 2**. Suzuki coupling reaction on 4-amino-2-chloroquinoline-3-carbonitrile
(To study the effect of Hydrogen bonding)

From this reaction the first assumption i.e. hydrogen-bonding was fail with conformation of only electronic effect which enhances the yields of coupling reaction. The electron withdrawing groups i.e. *o*-ester, acid, alcohol, aldehyde and nitrile at $C_3$-position of quinoline ring has inductive effect and it make $C_2$-position more deficient that favors oxidative addition on $C_2$-Cl bond.




**Scheme 3**. Suzuki coupling reaction on unprotected 9 and protected 4-amino-2-chloro quinoline without o-substituent.

Further, the reaction on unprotected amine **8** (without *ortho* substituent) yield 4-amino-2-arylquinoline **9** in 35%, while the *N*-acetyl derivative **10** yields *N*-acetyl-2-phenylquinoline **11** in 76% yield, support the effect of electron withdrawing substituents on yields of coupling reaction (scheme 3). From the above experiments we observed that due to the electronic movement of lone pair of amine with *o*-substituted groups on quinoline ring make free amine busy so it does not required any special protection to complete the reaction and also it does not effect on the yield of the reaction.




R= COOEt, COOH, CHO, CN and $CH_2OH$

**Figure 1** Plausible mechanism of Suzuki reaction on *o*-substituted unprotected 4-amino-2-chloroquinolines

The possible reaction mechanism of the present C-C bond forming reaction consisting of arylation is shown in figure 1. Due to the presence of electronegative nitrogen atom the chloro group at the azomethine carbon is more susceptible to undergo oxidative addition with Pd (0) to generated unisolated complex followed by trans-organometallation of the resultant aryl-palladium complex formed with arylboronic acids provides the desired compounds **2a-5c**.

## 3. Experimental section

### 3.1. General

All the microwave irradiation experiments were performed in a CEM Discover microwave system and reaction temperatures were monitored by an equipped IR sensor. All the 4-amino-2-chlorquinoline-3-carboxylic ethyl ester / acid / alcohol and aldehyde intermediates (**1a-d**) used in the reaction were synthesized by our literature method.[10] The detail synthetic procedures and spectroscopic data of compounds **6-11** and **3a-5c** given in the experimental section. All reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm) for detection. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker spectrometer operating at 300 and 75 MHz for $^1$H and $^{13}$C respectively using either $CDCl_3$ or DMSO-$d_6$ as the solvent. Chemical shifts, δ, are reported in parts per million (ppm) relative to solvent resonance: $CDCl_3$, δ 7.26 ($^1$H NMR), and 77.3 ($^{13}$C NMR); DMSO-$d_6$, δ 2.50 ($^1$H NMR), and 40.2 ($^{13}$C NMR). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants, *J*, are reported in Hertz. Mass spectral (MS) data were obtained on a Bruker Daltonics spectrometer using an electrospray ionizationquadrapole-time of flight (ESI-QTOF) analyzer. Infrared spectra were taken on Shimadzu IR-408, instrument in potassium bromide pellets unless otherwise stated. All melting points have been determined on a manually operated Veego (VMP-1) melting point apparatus and are uncorrected.

**Typical procedure for the coupling of ethyl-4-amino-2-chloroquinoline-3-carboxylate with phenylboronic acid in microwave condition**

A degassed mixture of ethyl-4-amino-2-chloroquinoline-3-carboxylate (**1a**, 250 mg, 1.00 mmol), phenylboronic acid (158 mg, 1.3 mmol), $Na_2CO_3$ (318 mg, 3.00 mmol), $Pd(PPh_3)_4$ (115 mg, 0.10 mmol) and water (15 mL) was introduced into CEM discover microwave reaction vessel equipped with a magnetic stirrer. The vessel was sealed and then placed into the microwave cavity. Initial microwave irradiation of 300 W was used, the temperature being ramped from room temperature to the desired 105$^o$C temperature.

Once this was reached the reaction mixture was healed at this temperature for 20 min. The reaction mixture was stirred continuously stirring during the reaction. After allowing the mixture to cool to room temperature, the contents of the reaction vessel were poured into a separatory funnel. Water (20 mL) and ethyl acetate (15 mL) were added, and the organic material was extracted and removed. After further extraction of the aqueous layer with ethyl acetate (20 mL), combining the organic washings and drying them over anhydrous MgSO4, the ethyl acetate was removed in vacuum leaving the crude product, which was purified by flash column chromatography to yield pure product (**2a)**.

**Ethyl-4-amino-2-phenylquinoline-3-carboxylate (2a)**

Yield: 254 mg (87%); White solid; mp 145-147 °C.

IR (KBr): 3410, 3280, 3182, 1679, 1620, 771 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.76 (t, 3H, *J* = 7.2 Hz, $OCH_2CH_3$), 3.95 (q, 2H, *J* = 7.2 Hz, $OCH_2CH_3$), 6.71 (br.s, 2H, $NH_2$), 7.38-7.56 (m, 4H, ArH), 7.57-7.72 (m, 5H, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.9, 60.3, 102.5, 116.7, 122.5, 125.2, 127.7, 127.7, 128.7, 128.7, 128.8, 131.3, 132.2, 142.3, 146.9, 152.3, 159.1, 168.6.

MS (EI, 70 eV): *m*/*z* (%) = 293.1 ($M^{+1}$), 294.1 ($M^{+2}$).

**Ethyl 4-amino-2-(4-methoxyphenyl)quinoline-3-carboxylate (2b)**

Yield: 283 mg (88%); White solid; mp 158-160 °C.

IR (KBr): 3475, 3365, 1680, 1252 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.81 (t, 3H, *J* = 7.0 Hz, $OCH_2CH_3$), 3.79 (s, 3H, $OCH_3$), 3.94-4.01 (q, 2H, *J* = 7.0 Hz, $OCH_2CH_3$), 6.99 (d, 2H, *J* = 8.4 Hz, ArH), 7.42-7.51 (m, 5H, $NH_2$, ArH), 7.68-7.73 (t, 1H, *J* = 8.0 Hz, ArH), 7.80 (d, 1H, *J* = 8.0 Hz, ArH), 8.35 (d, 1H, *J* = 8.4 Hz, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 13.2, 55.17, 60.1, 102.6, 113.1, 113.1, 116.8, 122.8, 124.6, 128.9, 129.3, 129.3, 130.9, 134.9, 147.3, 152.0, 158.3, 159.2, 168.8.

MS (EI, 70 eV): *m*/*z* (%) = 323.1 ($M^{+1}$), 324.1 ($M^{+2}$), 325.1 ($M^{+3}$).

**Ethyl 4-amino-2-(4-nitrophenyl)quinoline-3-carboxylate (2c)**

Yield: 272 mg (81%); White solid; mp 243-245 °C.

IR (KBr): 3470, 3370, 1680, 1537, 1358 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 0.729 (t, 3H, *J* = 7.1 Hz, $OCH_2CH_3$), 3.91-3.98 (q, 2H, *J* = 7.1 Hz, $OCH_2CH_3$), 7.56 (t, 1H, *J* = 8.0 Hz, ArH), 7.71-7.86 (m, 4H, ArH), 7.97 (br.s, 2H, $NH_2$), 8.31 (d, 2H, *J* = 8.7 Hz, ArH), 8.41 (d, 1H, *J* = 8.4 Hz, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 12.99, 60.28, 101.24, 117.2, 122.9, 122.9, 123.0, 125.6, 125.6, 128.9, 129.2, 131.6, 131.6, 146.7, 149.4, 153.4, 157.4, 167.8.

MS (EI, 70 eV): *m*/*z* (%) = 338.1 ($M^{+1}$), 336.1 ($M^{-1}$).

**4-amino-2-phenylquinoline-3-carboxylic acid (3a)**

Yield: 235 mg (79%); White solid; mp 256-258 °C.

IR (KBr): 3376, 3264, 2821, 1680.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 5.97 (br.s, 2H, $NH_2$), 7.05-7.07 (d, 2H, *J* = 8.2 Hz, ArH), 7.48-7.83 (m, 5H, ArH), 8.43-8.46 (d, 2H, *J* = 8.0 Hz, ArH) 13.43 (s, 1H, COOH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 102.5, 118.7, 122.5, 125.2, 127.7, 128.7, 128.7, 128.7, 128.8, 131.3, 132.2, 142.3, 146.9, 152.3, 159.1, 171.6.

MS (EI, 70 eV): *m*/*z* (%) = 265.1 ($M^{+1}$), 288.1 ($M^{+Na}$).

**4-amino-2-(4-methoxyphenyl)quinoline-3-carboxylic acid (3b)**

Yield: 249 mg (75%); White solid; mp 268-270 °C.

IR (KBr): 3364, 3276, 2864, 1720 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 3.83 (s, 3H, $OCH_3$), 5.29 (br.s, 2H, $NH_2$), 7.06-7.08 (d, 2H, *J* = 8.2 Hz, ArH), 7.48-7.83 (m, 5H, ArH), 8.43-8.46 (d, 2H, *J* = 8.1 Hz), 11.96 (s, 1H, COOH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 55.17, 102.6, 113.1, 113.1, 116.8, 122.8, 124.6, 128.9, 128.9, 129.3, 130.9, 134.9, 147.3, 152.0, 158.3, 159.2, 170.8.

MS (EI, 70 eV): *m*/*z* (%) = 295.1 ($M^{+1}$), 318 ($M^{+Na}$).

**4-Amino-2-(4-nitroyphenyl)quinoline-3-carboxylic acid (3c)**

Yield: 290 mg (83%); Pale yellow solid; mp 195-197 °C.

IR (KBr): 3337, 3282, 2792, 1780, 1550, 1360 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 5.55 (br.s, 2H, $NH_2$), 7.04-7.07 (d, 2H, *J* = 8.1 Hz, ArH), 7.50-7.85 (m, 5H, ArH), 8.45-8.47 (d, 1H, *J* = 8.1 Hz), 12.33 (s, 1H, COOH).

MS (EI, 70 eV): *m*/*z* (%) = 310.1 ($M^{+1}$), 333 ($M^{+Na}$).

**4-Amino-2-phenylquinolin-3-yl) methanol (4a)**

Yield: 210 mg (70%); White solid; mp 201-203 °C.

IR (KBr): = 3337, 3282, 3550 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ 4.50 (d, 2H, *J* = 4.8 Hz, $CH_2OH$), 5.07 (t, 1H, *J* = 4.8 Hz, $CH_2OH$), 6.69 (br.s, 2H, $NH_2$), 7.39-7.49 (m, 4H, ArH), 7.58-7.65 (m, 3H, ArH), 7.78 (d, 1H, *J* = 7.8 Hz, ArH), 8.27 (d, 1H, *J* = 8.1 Hz, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 57.99, 110.9, 117.6, 122.0, 123.7, 127.6, 127.6, 127.6, 128.8, 129.0, 129.1, 129.1, 141.3, 147.1, 151.0, 159.2.

MS (EI, 70 eV): *m*/*z* (%) = 251.1 ($M^{+1}$).

**4-Amino-2-(4-methoxyphenyl)quinolin-3-yl)methanol (4b)**

Yield: 228 mg (68%); White solid; mp 176-178 °C.

IR (KBr): 3592, 3475, 3364, 1251 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 3.82 (s, 3H, $OCH_3$), 4.53 (d, 2H, *J* = 4.8 Hz, $CH_2OH$), 5.10 (t, 1H, *J* = 4.8 Hz, $CH_2OH$), 6.64 (br.s, 2H, $NH_2$), 7.00 (d, 2H, *J* = 9.0 Hz, ArH), 7.36-7.63 (m, 4H, ArH), 7.71-7.77 (t, 1H, *J* = 8.4 Hz, ArH), 8.22 (d, 1H, *J* = 6.9 Hz, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 55.1, 58.1, 110.9, 113.0, 113.0, 117.5, 121.8, 122.0, 123.5, 128.7, 128.9, 130.4, 133.6, 147.1, 150.9, 158.8, 158.9.

MS (EI, 70 eV): *m*/*z* (%) = 281.1 .1 ($M^{+1}$), 279.1 ($M^{-1}$), 301.1 ($M^{+Na}$).

**4-Amino-2-(4-nitrophenyl)quinolin-3-yl)methanol (4c)**

Yield: 251 mg (71%); White solid; mp 208-210 °C.

IR (KBr): 3605, 3479, 3350, 1560, 1390 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 4.46-4.47 (d, 2H, *J* = 4.9 Hz, $CH_2OH$), 5.14-4.17 (t, 1H, *J* = 4.9 Hz, $CH_2OH$), 7.01 (br.s, 2H, $NH_2$), 7.45-7.44 (m, 5H, ArH), 8.33-8.36 (d, 2H, *J* = 8.7 Hz, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 28.9, 57.3, 110.9, 117.6, 122.3, 124.5, 128.1, 129.8, 130.4, 146.2, 147.0, 147.1, 151.8, 156.5, 163.2..

MS (EI, 70 eV): *m*/*z* (%) = 296.1 ($M^{+1}$), 297.1 ($M^{+2}$), 298.1 ($M^{+3}$), 294.1 ($M^{-1}$), 295.1 ($M^{-2}$).

**4-Amino-2-phenylquinoline-3-carbaldehyde (5a)**

Yield: 267 mg (89%); White solid; mp 192-194 °C.

IR (KBr): 3444, 3307 ($NH_2$), 2769, 1710 (CHO) $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 7.49-7.58 (m, 5H, ArH), 7.76-7.85 (m, 4H, ArH), 8.68 (br.s, 1H, $NH_2$), 9.70 (br.s, 1H, $NH_2$), 9.79 (s, 1H, CHO).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 106.8, 117.5, 123.3, 125.2, 128.0, 128.0, 128.6, 129.2, 129.8, 129.8, 132.4, 138.9, 139.8, 147.8, 154.7, 163.2, 192.3.

MS (EI, 70 eV): *m*/*z* (%) = 249.1 ($M^{+1}$), 279.1 ($M^{+2}$).

**4-Amino-2-(4-methoxyphenyl)quinoline-3-carbaldehyde (5b)**

Yield: 307 mg (91%); white solid; mp 182-184 °C.

IR (KBr): 3452 & 3310 ($NH_2$), 2780, 1715 (CHO), 1603 (aromatic) $cm^{-1}$

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 3.83 (s, 3H, $OCH_3$), 7.05 (d, 2H, *J* = 9.0 Hz, ArH), 7.51 (d, 2H, *J* = 9.0 Hz, ArH), 7.62-8.46 (m, 4H, ArH), 8.62 (br.s, 1H, $NH_2$), 9.54 (br.s, 1H, $NH_2$), 9.83 (s, 1H, CHO).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 55.2, 106.8, 113.4, 113.4, 117.4, 123.3, 124.9, 129.1, 131.1, 131.4, 131.4, 132.3, 148.0, 154.7, 159.6, 162.7, 192.5.

MS (EI, 70 eV): *m*/*z* (%) = 279.1 ($M^{+1}$), 280.1 ($M^{+2}$).

**4-Amino-2-(4-nitrophenyl) quinoline-3-carbaldehyde (5c)**

Yield: 337 mg (95%); white solid; mp 163-164 °C.

IR (KBr): 3481, 3284 ($NH_2$), 2701, 1649 (CHO), 1530, 1332 ($NO_2$) $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 7.54 (d, 2H, *J* = 8.2 Hz, ArH), 7.97 (d, 2H, *J* = 8.2 Hz, ArH), 8.34-8.48 (m, 4H, ArH), 8.52 (br.s, 1H, $NH_2$), 9.54 (br.s, 1H, $NH_2$), 9.80 (s, 1H, CHO).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 101.2, 117.2, 122.9, 122.9, 123.0, 125.6, 128.9, 129.2, 129.2, 131.6, 146.7, 149.4, 153.4, 157.4, 167.8, 192.5.

MS (EI, 70 eV): *m*/*z* (%) = 294.08 ($M^{+1}$).

**4-amino-2-chloroquinoline-3-carbonitrile (6):** Iodine (203 mg, 1.60 mmol) was added to a stirring solution of 4-amino-2-chloroquinoline-3-carbaldehyde **1d** (300 mg, 1.45 mmol) in ammonia water (10 mL of 28% solution) and THF (2.0 mL) at room temperature. The dark solution became colorless (or light gray in some cases) after stirring for 5 hr, an indication that the reaction was complete. The reaction mixture was charged with aqueous $Na_2S_2O_3$ (5.0 mL of 5 % solution), followed by extraction with ether (2 × 10 mL), to give a practically pure product.
Yield: 177 mg (60%); Reddish solid.

IR (KBr): 3477, 3366, 1638 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 7.10-7.21 (m, 2H, ArH), 7.50-7.55 (t, 1H, *J* = 7.2 Hz, ArH), 8.09-8.29 (d, 1H, *J* = 8.1 Hz, ArH), 8.29 (br.s, 2H, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 89.43, 112.1, 115.3, 120.7, 123.7, 127.1, 132.3, 139.4, 156.8, 159.8.

MS (EI, 70 eV): *m*/*z* (%) = 204.1 ($M^{+1}$), 206.1 ($M^{+2}$), 208.1 ($M^{+3}$).

**4-amino-2-phenylquinoline-3-carbonitrile (7)**

Yield: 223 mg (74%); White solid; mp 243-245 °C.

IR (KBr): 3478, 3371, 1630 $cm^{-1}$.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 7.60-7.63 (m, 4H, ArH), 7.75-7.85 (m, 2H, ArH), 8.25 (br.s, 2H, $NH_2$), 8.35-8.38 (d, 1H, J = 8.7 Hz, ArH), 8.42-8.45 (m, 2H, ArH).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 96.5, 116.0, 120.4, 123.0, 125.1, 127.7, 129.2, 129.4, 129.7, 133.0, 134.8, 136.0, 145.9, 154.1, 158.0.

MS (EI, 70 eV): *m*/*z* (%) = 246.1 ($M^{+1}$).

**2-phenylquinolin-4-amine (9)**

Yield: 108 mg (35%); White solid; mp 163-165 °C.

IR (KBr): 3478, 3358, 1633 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 6.69 (br.s, 2H, $NH_2$), 7.02 (s, 1H, ArH), 7.69-7.87 (m, 5H, ArH), 7.97-8.02 (t, J = 7.5 Hz, ArH), 8.02-8.22 (m, 3H, ArH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ = 103.8, 117.5, 123.3, 125.2, 128.0, 128.6, 129.2, 129.8, 132.4, 138.9, 139.8, 147.8, 154.7, 156.2.

MS (EI, 70 eV): *m*/*z* (%) = 221.1 ($M^{+1}$).

***N*-(2-chloroquinolin-4-yl)acetamide (10)**

Acetic anhydride (1.37 g, 0.013 mmol) and catalytic amount of pyridine was added in the mixture of 2-chloro-4-aminoquinoline (2.0 g, 0.011 mmol) in THF (15 mL) and the reaction mixture was stirred at 65°C for 3 h. (TLC monitoring, EtOAc / Pet-ether 9:1). After completion of reaction, remove THF by vacuum distillation, water (20 mL) was added and the aqueous solution was then extracted with ethyl acetate (3 x 20 mL). The ethyl acetate layer was washed with dilute citric acid to remove traces of pyridine. Combine organic layer and dried over anhydrous sodium sulphate and then evaporated under reduced pressure; the residue was chromatographed over silica gel column and eluted with chloroform-methanol (9.5: 0.5) to isolate the pure product.

Yield: 1.4 gm (60%); white solid; mp 147-149 °C.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 2.51 (s, 3H, $CH_3$), 6.88 (s, 1H, ArH), 7.48-7.91 (m, 4H, ArH), 10.08 (br.s, 1H, amide).

$^{13}$C NMR (75 MHz, DMSO-d6): δ = 25.6, 103.8, 117.2, 123.1, 125.5, 127.6, 131.7, 146.3, 147.2, 152.6, 171.7.

***N*-(2-phenylquinolin-4-yl)acetamide (11)**

Yield: 226 mg (76%); White solid; mp 141-143 °C.

$^1$H NMR (300 MHz, DMSO-$d_6$): δ = 2.17 (s, 3H), 7.50-7.57 (m, 4H, ArH), 7.56-7.59 (m, 2H, ArH), 7.76-7.85 (m, 2H, ArH), 8.45 (s, 1H, ArH), 10.45 (br.s, 1H, NH).

$^{13}$C NMR (75 MHz, DMSO-$d_6$): δ 22.15, 102.5, 116.7, 122.5, 125.2, 127.7, 128.7, 128.7, 128.7, 128.8, 131.3, 132.2, 142.3, 146.9, 152.3, 159.1, 168.6.

MS (EI, 70 eV): *m*/*z* (%) = 263.1 ($M^{+1}$), 221.1 ($M^{-41}$ *N*-deacetyl).

## II. CONCLUSION

In summary, it was proved that by using microwave promotion, commercially available, cheap base ($Na_2CO_3$) and universal water solvent, it is possible to couple a range of arylboronic acids with diversely functionalized *o*-substituted unprotected 4-amino-2-

chloroquinolines more rapidly. In addition it was studied that the electron withdrawing substituents at C3 / C4 position on quinoline ring favors most important step in Suzuki coupling reaction i.e. oxidative addition on $C_2$-Cl bond. It was also conclude that due to the continuous electronic movement of lone pair of amine with *o*-substituted groups on quinoline ring make free amine busy so it does not required any special protection to complete the reaction.

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## AUTHORS

**First Author** – Raghunath Toche, Ph.D. (Chemistry), Organic Chemistry Research Center, P. G. Department of Chemistry, K.T.H.M. College, Nashik - 422 002, India. raghunath_toche@rediffmail.com,

**Second Author** – **Ravindra Janrao**, Msc (Chemistry), Organic Chemistry Research Center, P. G. Department of Chemistry, K.T.H.M. College, Nashik - 422 002, India, ravindra.janrao@yahoo.com

**Correspondence Author** – Raghunath Toche, Ph.D. Chemistry, Organic Chemistry Research Center, P. G. Department of Chemistry, K.T.H.M. College, Nashik - 422 002, India. raghunath_toche@rediffmail.com. Mob. +919420692839