# AMINATION OF DICHLORO-6,7-QUINOLINEQUINONE WITH ELECTRON RICH AND ELECTRON DEFICIENT ANILINES: A DESCRIPTION

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**Abstract:** Palladium-catalyzed amination of 6,7-dichloro-5,8-quinolinequinone was studied using electron rich (ER) and electron deficient (ED) anilines. Selective amination with ER anilines supplied monoamine target derivatives in high yields while amination with ED anilines supplied diamine and more complex derivatives alongside target molecules.

**Keywords:** Amination, anilines, electron deficient, electron rich, quinolinediones

## Introduction

Quinolinequinone (Qq) is an important class of heterocycles known to possess antimalarial, antimicrobial, anticancer and other biological activities (Ryu & Kim, 1994; Behforouz & Merriman, 1997; Keyari *et al*., 1972 and Fryatt *et al*., 2004). The remarkable biological properties of quinolinequinone nucleus account for its exploratory functionalization with a view of discovering new chemotherapies (Egu *et al*., 2016; Egu *et al*., 2015; Surry & Buchwald, 2011; Brett *et al*., 2008 and Prate & Drake, 1960).

Ryu and Kim (1994) prepared investigated 6-(*N*-arylamino)-7-chloro-5,8-quinolinedione derivatives and found that these compounds exhibit potent antifungal and antibacterial activities (Ryu & Kim, 1994). A series of 7-amino- and 7-actamidoquinoline-5,8-diones with aryl substituents at postion-2 were synthesized and evaluated as potential NAD(P)H:quinine oxidoreductase directed antitumor agents. Amongst the synthesized compounds 7-actamido-2-(8'-quinolinyl)quinoline-5,8-dione and 7-amino-2-(2-pyridinyl)quinoline-5,8-dione showed selective cytotoxicity towards breast cancer cells (Keyari *et al*., 2013). Moreover, multistep conversion of isoquinoline and 8-hydroxyquinoline afforded variety of 7-amino-isoquinoline-5,8-dione and 6-aminoquinoline-5,8-dione derivatives that exhibited potent cytotoxic activity (Amed *et al*., 2014). Kim and his group described cytotoxicity of 6,11-Dihydro-pyrido- and 6,11-Dihydro-benzo[2,3-*b*]phenazine-6,11-dione derivatives (Hussein *et al*., 2012) while newly synthesized quinoline-5,8-dione and hydroxynaphthoquinone derivatives inhibited a chloroquine resistant plasmodium falciparum strain (Kim, *et al*., 2003).

The synthesis and biological activities of several disubstituted quinoline-5,8-diones were also reported (Ryu *et al*., 2007). The majority of these compounds were prepared by regioselective nucleophilic substitution of quinolinequinone and naphthoquinone with arylamines (Suh *et al*., 2001). Quinolinequinones are particularly important class of electrophiles for C–N cross-coupling reactions because of the appearance of heteroaryl amines in a range of valuable pharmaceutical agents (Cheng *et al*., 2008; Podeszwa *et al*., 2007). We have recently reported the synthesis of some novel derivatives of 6,7-dibromo-5,8-quinolinequinone, using a transition-metal based approach, so as to reveal easier routes by which a number of its novel derivatives can be prepared (Egu *et al*., 2015). In extension this work, we are now describing palladium catalysed amination of dichloro-6,7-quinolinequinone with electron rich and electron deficient anilines.

## Materials and Methods

***General procedures for Buchwald-Hartwig reaction***

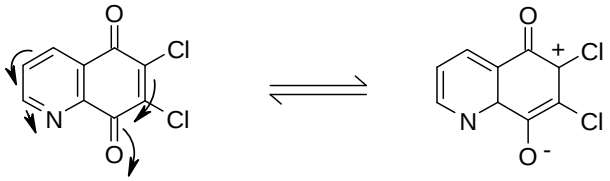
***Procedure A:*** BrettPhos (0.94 µmol, 0.5 mg, 0.15 mol%) and $Pd(OAc)_2$ (0.30 µmol, 0.1 mg, 0.05 mol%) were placed in a 25 ml three-neck round-bottom flask. After purging with nitrogen for 30 seconds, 1 ml water and 5 ml EtOH were added and the solution was heated for 60 seconds to 80ºC, the preactivation was followed by a colour change from yellow to black. Then, 6,7-dihalo-5,8-quinolinequinone, aniline derivative, base and 5 ml EtOH were added. The reaction mixture was heated at reflux with vigorous stirring for the indicated time. The completion of reaction was monitored by TLC, then cooled, filtered and recrystallized with water and acetone.

***Procedure B:*** XPhos (0.0032 mmol, 1.5 mg, 1 mol%) and $Pd(OAc)_2$ (0.0095 mmol, 2.1 mg, 3 mol%) were placed in a 25 ml three-neck round-bottom flask. After purging with nitrogen for 30 seconds, 1 ml water and 5 ml EtOH was added and the solution was heated for 60 seconds to 80 ºC, the preactivation was followed by a colour change from yellow to black. Then the 6,7-dihalogeno-5,8-quinolinequinone, aniline derivative, base and 2 ml dioxane were added. The reaction mixture was heated at reflux with vigorous stirring for the indicated time. The completion of reaction was monitored by TLC, then cooled, filtered and recrystallized with water and acetone.

Details of the preparation of the compounds are reported in our previous work (Egu *et al*., 2015, 2016).

## Results and Discussion

The results are presented in Table 1, Schemes 1 – 4 and Table 2, respectively. Qq possesses two chlorine atoms of different reactivity at positions 6 and 7. Nucleophilic substitution usually favour position **6** as a result of mesomeric effect which is aided by negative inductive involvement of nitrogen atom in 6,7-dichloroquinoline-5,8-dione ring (Prate and Drake, 1960).

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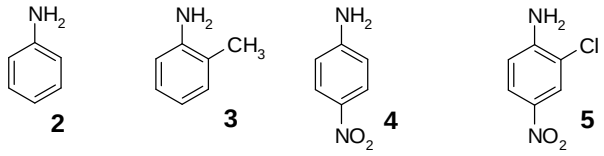
Reactions of compound 1 with both electron rich and electron poor anilines were carried out under three different conditions: $Pd(OAc)_2$ with $PPh_3$, piperazine and BrettPhos ligands, respectively. The cross-coupling reaction of dichloro-6,7-quinolinequinone with aniline under combination of $Pd(OAc)_2$ with $PPh_3$ generated weak catalyst system that gave only traces of monoamine products. However, when $Pd(OAc)_2$ was used in conjunction with piperazine and Brettphos ligands, an active catalyst was generated in situ which gave high yields of 6-substituted phenylaminoquinoline-5,8-diones (monoamines). The two

electron rich (ER) and two electron deficient (ED) anilines used in this research are aniline 2, 2-methylaniline 3, 4-nitroaniline 4 and 2-chloro-4-nitroaniline 5, respectively.

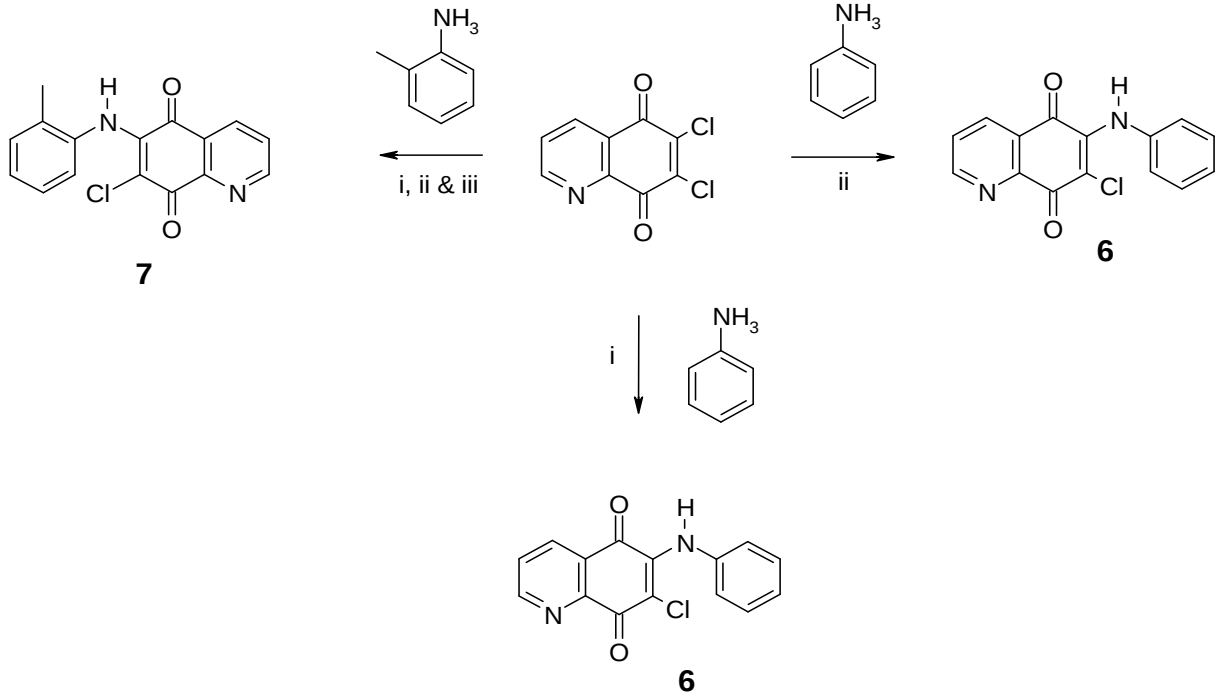


ER Anilines ED Anilines

**Table 1: Reaction of Qq with ER and ED anilines**

| Entry | Reaction Conditions | Anline | Product type/yield |
|---|---|---|---|
| 1 | $Pd(OAc)_2/PPh_3$ | ER & ED | Monoamine/traces |
| 2 | $Pd(OAc)_2$/ Piperazine | ED | Monoamines/60-70 & diamines/30-35 |
| 3 | $Pd(OAc)_2$/BrettPhos | ER | Monoanlines/80-92 |

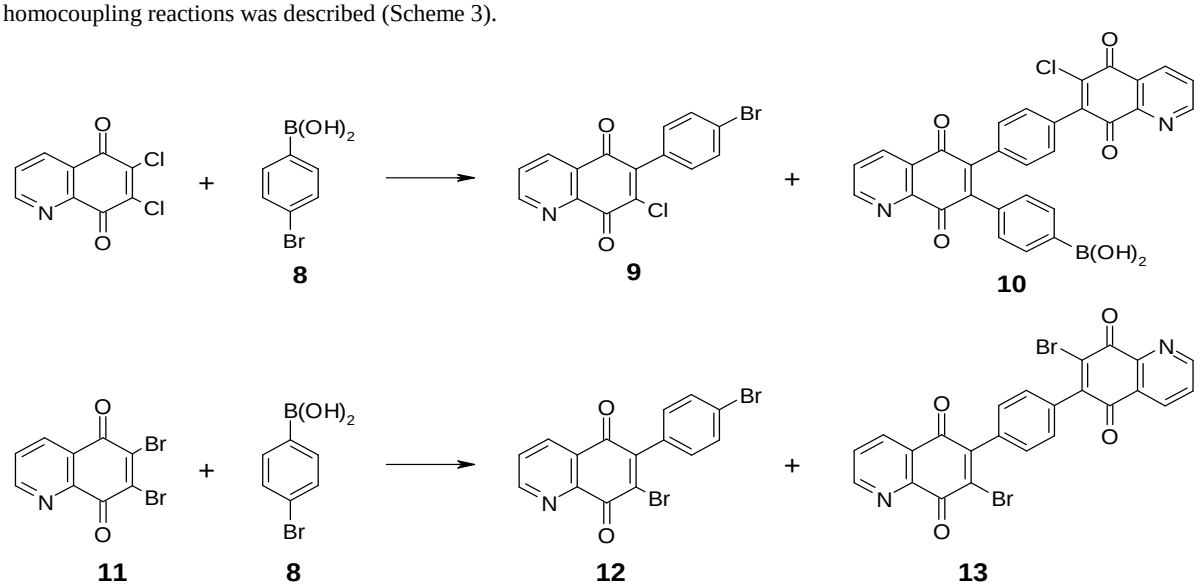
Reaction of Qq with ER anilines supplied only monoamine derivatives in high yields irrespective of the choice of ligand used except for $PPh_3$ which supplied only traces of products (Table 1) (Egu *et al*., 2015).



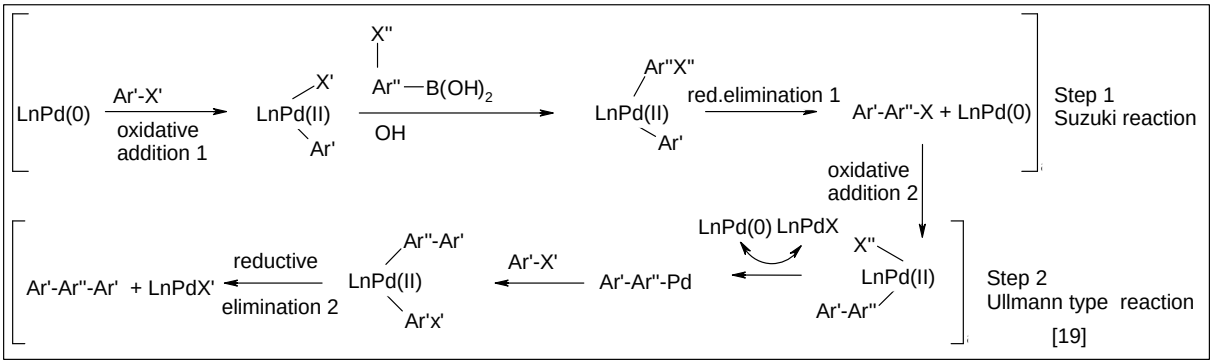
i= $Pd(OAc)_2/PPh_3$/base/solvent; ii= $Pd(OAc)_2$/BrettPhos/base/solvent; iii= $Pd(OAc)_2$/Piperazine/base/solvent

**Scheme 1: Reaction of Qq with ER anilines**

When ED anilines were used the target molecules (6-phenylamine substituted quinoline-5,8-diones) were obtained with side products. The sides product are either 6- and 7- substituted quinoline-5,8-diones and/or in some cases oligomers of complex structures (Scheme 1). In our previous paper, similar structures were obtained in the reaction of Qq with ED boronic acids using our modified Suzuki reaction protocol (Scheme 2) and the presumed mechanism for both inter- and intramolecuclar homocoupling reactions was described (Scheme 3).

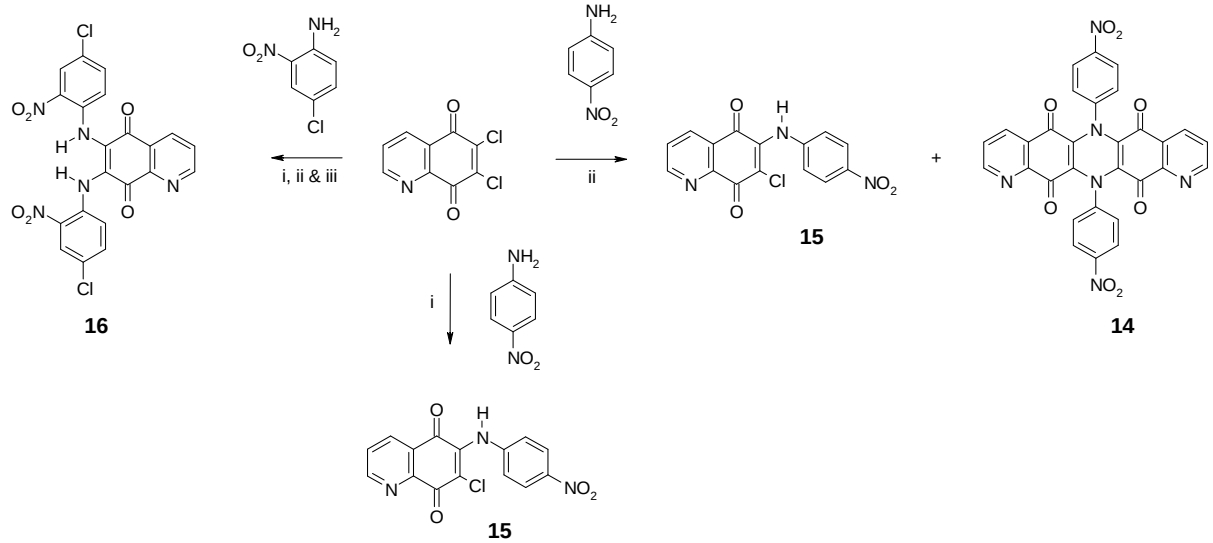


**Scheme 2: Reaction of Qq with ED boronic acid**



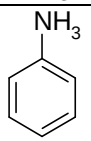
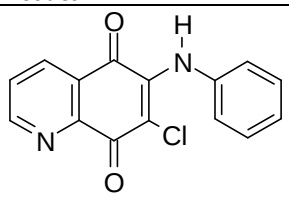
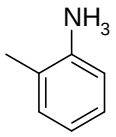
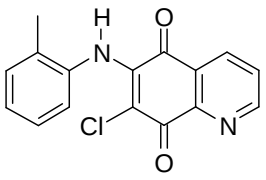
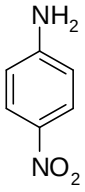
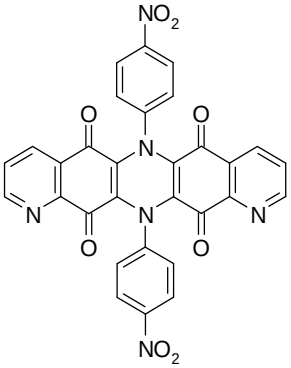

(Hennings *et al*., 1999)

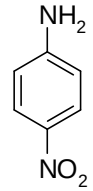
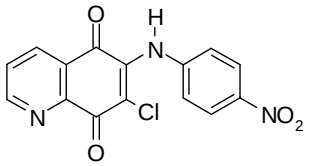
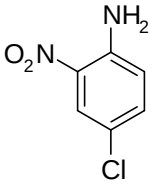
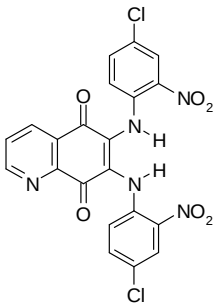
**Scheme 3: Proposed mechanism for Suzuki-Miyaura coupled and oligomeric products**




**Scheme 4: Reaction of Qq with ED anilines**

**Table 2: Products of amination of quinolinediones**

| Entry | Aniline | Product | Reaction time (s) | Yield (%)[f] |
|---|---|---|---|---|
| 1 |  2 |  6 | 120 | 50 |
| 2 |  3 |  7 | 70 | 53 |
| 3 |  4 |  | 80 | 15 |

| | | | | |
|---|---|---|---|---|
| 4 |  4 | 14  15 | 80 | 84 |
| 5 |  5 |  16 | 190 | 85 |

The products obtained from reaction of Qq with ED anilines must have followed multiple Buchwald-Hartwig reaction since only C-N bonds have formed (Scheme 4 and Table 2). The Buchwald-Hartwig amination is a known palladium-catalyzed cross-coupling reaction of an aryl halide or pseudo halide with an amine together with a strong base (Voroguslin *et al*., 2005). The Buchwald-Hartwig reaction is initiated by an oxidative addition of the aryl halide to the palladium, which is followed by coordination of the amine. The strong base then abstracts a proton from the amine, which attacks the palladium with the halide acting as a leaving group. Reductive elimination then produces the final aryl amine product and regenerates the catalyst (Paul *et al*., 1994).

The spectral and elemental analysis of the diamines and oligomers agreed with structural assignments. Moreover, their mass spectral furnished their molecular ion fragments ($M^+$, 100 %) with mass/charge ratios of 501.97 and 586.48, respectively

**Conclusion**

In conclusion, we have studied the Pd catalyzed amination reactions of Qq and ER and ED anilines and found out that ER anilines gave only target molecules and ED anilines gave both mono and diamino derivatives and in some cases oligomers especially when non phosphorous ligand was used. The findings of this study suggests that substitution at position 6 by ED anlines led to activation of substitution at position 7 of same, thereby allowing for the formation of diamino products.

**Conflict of Interest**

Authors declare that there is no conflict of interest related to this study.

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