Orbital
The electronic journal of chemistry

the electronic journal of chemistry

Full Paper | http://dx.doi.org/10.17807/orbital.v14i1.1689

Bronsted Acid Mediated Facile Greener Multicomponent Synthesis of 2,4-Diaryl-quinoline Derivatives in Water

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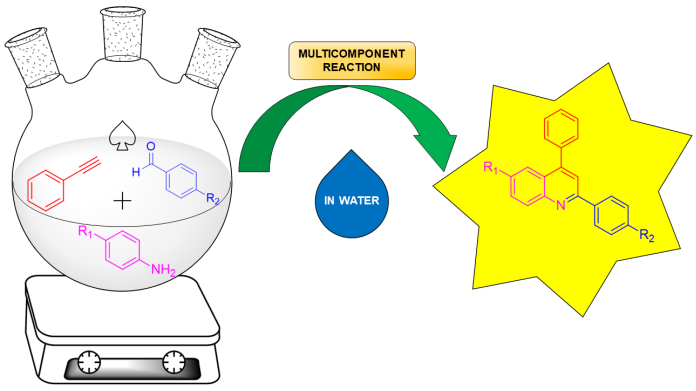
Quinolines are an important class of natural and synthetic products, with several biological activity and applications in medicine and electronics. In this work we present a greener method of synthesis of 2,4-diaryl-quinoline derivatives by an easy one-pot multicomponent reaction between aniline derivatives, aldehyde derivatives and phenylacetylene in water, with hydrochloric acid as promoter. With this method we could synthesize several compounds with good yield and reaction time, including new alkylamino-containing 2,4-diaryl-quinoline derivatives that could not be synthesized with niobium pentachloride catalyst in similar conditions.

Graphical abstract



Keywords

Acid catalyst
Green synthesis
Nitrogen heterocycles
Quinoline

Article history

Received 23 November 2021
Revised 11 January 2022
Accepted 11 January 2022
Available online 18 March 2022

Handling Editor: Jamal Rafique

1. Introduction

The quinoline nucleus (**1**) is composed of a pyridine ring fused with a benzene ring, and is a moiety present in various known drugs and other compounds with biological activity, both of natural occurrence, like quinine (**2**) and synthetic ones, such as chloroquine (**3**) (Figure 1) [1]. Its various applications include antibacterial, anticancer, antifungal, antihypertensive, anti-HIV, anti-inflammatory, antimalarial, antioxidant, antiproliferative, antiprotozoal, antitumor and antitubercular activity, among others [2-11].

In the last decades, highly conjugated quinoline derivatives has been gaining attention in the organic electronics area, appearing as dyes and phosphors in various devices, such as solar cells and OLEDs [12-17].

Quinolines can be synthesized by various routes, such as Skraup, Doebner-Miller, Gould-Jacobs, Conrad-Limpach, Friedländer and Povarov, among others [18-22]. Among the several synthetic routes for the synthesis of quinoline derivatives, some have the advantages of being environmentally-friendly, by having atom economy, reducing waste production, and using safer solvents and reagents [23]. One of these routes is a multicomponent reaction between an aniline derivative (**4**), a benzaldehyde derivative (**5**) and

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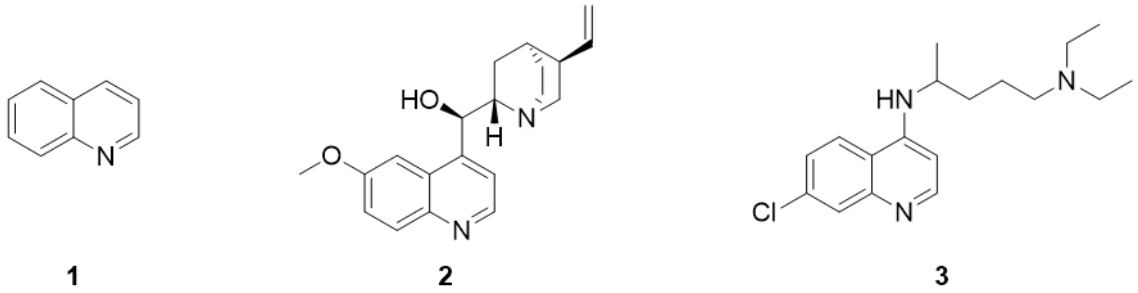
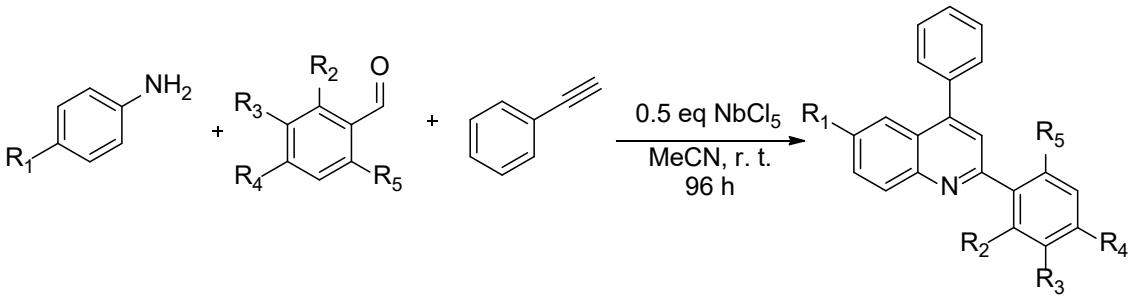
phenylacetylene (**6**), catalyzed by Niobium Pentachloride (Scheme 1) [24-26]. This reaction has some green advantages, such as being a one-step reaction with an easy purification process, by a simple recrystallization, showing atom and solvent economy.



1 **2** **3**

Figure 1. The quinoline (**1**), the naturally occurring compound quinine (**2**) and synthetic chloroquine (**3**) structures.



4 **5** **6** **7**

R_1 = H, Cl, I, Me, Et, t-But, OMe, NO_2
R_2 = H, F, Cl, Br, Me, OMe
R_3 = H, F, Cl, Br, Me, t-But, C_6H_5, OMe, SMe, NO_2, N(Me)$_2$
R_4 = H, Me
R_5

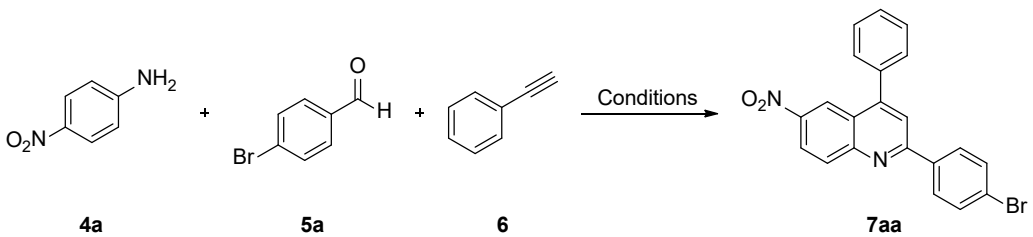
30 examples
Yield: 36-98%

Scheme 1. Niobium pentachloride catalyzed multicomponent synthesis of quinoline derivatives.

This route gives excellent results when the 4-nitroaniline is used, but for others aniline derivatives its results can vary widely, and we found it inefficient for the synthesis of 2,4-diaryl-quinolines with *N,N*-alkylaminoaniline derivatives, giving no yield. So we proposed, based on work found in the literature [27], a modification in the synthesis, using a hydrochloridric acid solution, making this route greener and effective for the *N,N*-alkylaminoaniline derivatives.

2. Results and Discussion

First optimization tests were performed to obtain the best reaction conditions. These tests were carried using the 4-nitroaniline, due to the good results obtained with niobium pentachloride catalyst for this compound. The HCl solution concentration, temperature and reaction time were varied in these tests (Scheme 2, Table 1).



4a **5a** **6** **7aa**

Scheme 2. Reaction condition tests for the synthesis of quinoline derivatives.

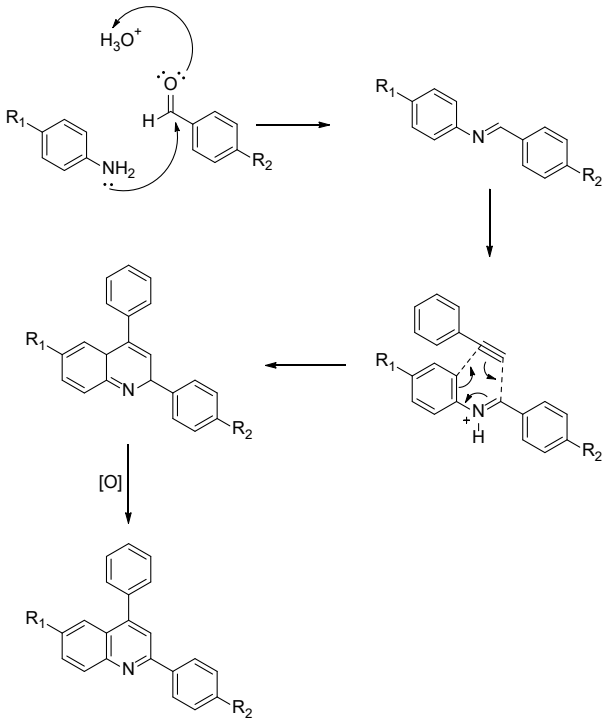
The reaction time variation tests (Table 1, entries 1 to 3) showed that the reaction reaches equilibrium after 72 hours. The room temperature test (Table 1, entry 4) and the no-catalyst test (Table 1, entry 5) did not present the aimed product formation, only the Schiff base intermediate between the 4-nitoaniline (**4a**) and the 4-bromobenzaldehyde (**5a**) reaction, even after 72 hours. The catalyst concentration variation tests (Table 1, entries 1, 6, 7 and 8) indicated that lower concentrations of HCl was more favorable, with the best results obtained with a 0.5 M HCl solution. Using the best conditions (Table 1, entry 9) it was possible to obtain the best yield for this quinoline (**7aa**).

Mechanistically, according to the literature [26] and the obtained results, the reaction starts with the benzaldehyde protonation, followed by the Schiff base formation. Then the phenylacetylene reacts with the Schiff base through a Diels-Alder reaction, a concerted cyclization that gives a dihydroquinoline. The dihydroquinoline intermediate undergoes an oxidation by the oxygen in the air, restoring the aromaticity of the ring system, yielding the desired 2,4-diaryl-quinoline derivative (Scheme 3).

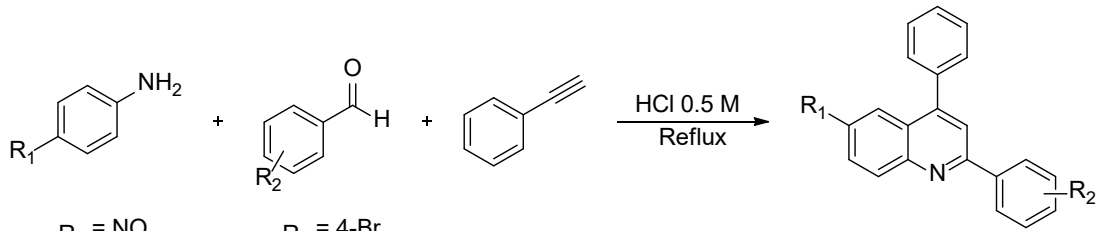
Table 1. Reaction condition tests* for the synthesis of quinoline derivatives.

Entry	HCl concentration (mol·L^{-1})	Temperature	Time (h)	Yield (%)
1	1.0	Reflux	24	15
2	1.0	Reflux	72	62
3	1.0	Reflux	96	62
4	1.0	R. T.	72	-
5	0	Reflux	72	-
6	2.0	Reflux	24	22
7	5.0	Reflux	24	16
8	0.5	Reflux	24	40
9	0.5	Reflux	72	64

*1.0 mmol of **4a**, 1.1 mmol of **5a** and 1.1 mmol of **6** were reacted in 1 mL of HCl solution.



Scheme 3. Proposed mechanism for the multicomponent synthesis of quinoline derivatives catalyzed by HCl.



4a, R^1 = NO$_2$
4b, R^1 = NMe$_2$
4c, R^1 = Me
4d, R^1 = Br
4e, R^1 = NEt$_2$

5a, R^2 = 4-Br
5b, R^2 = H
5c, R^2 = 3-Br
5d, R^2 = 4-Cl
5e, R^2 = 4-NO$_2$
5f, R^2 = 4-OH
5g, R^2 = 3-OH
5h, R^2 = 2-OH
5i, R^2 = SMe
5j, R^2 = NMe$_2$
5k, R^2 = COOH
5l, R^2 = CF$_3$

6

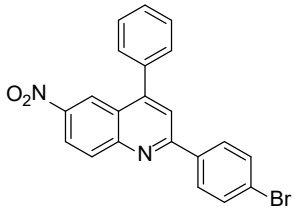
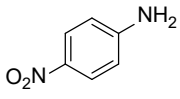
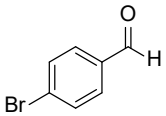
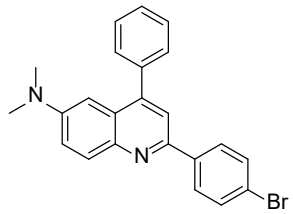
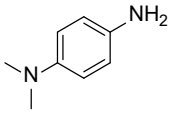
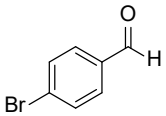
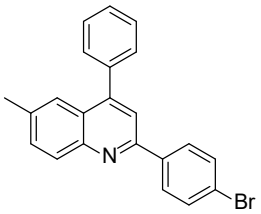
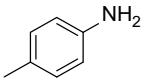
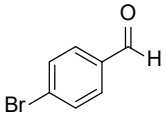
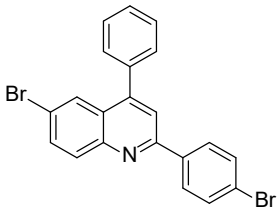
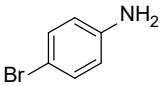
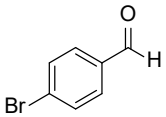
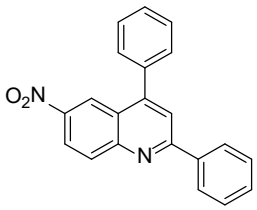
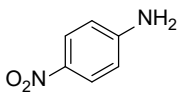
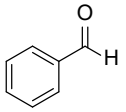
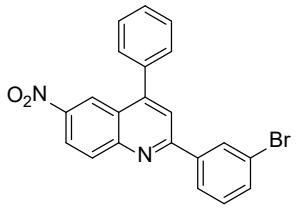
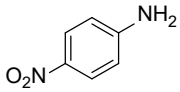
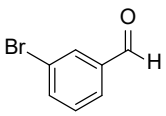
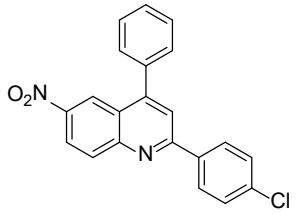
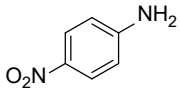
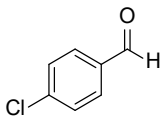
7aa
7ba
7ca
7da
7ab
7ac
7ad
7ae
7af
7ag
7ah
7ai
7aj
7ak
7bl
7el

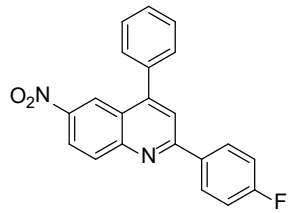
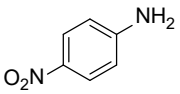
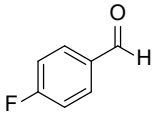
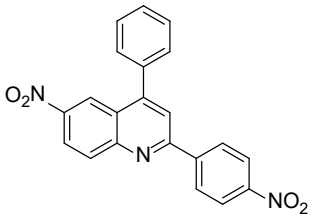
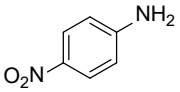
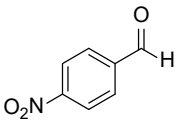
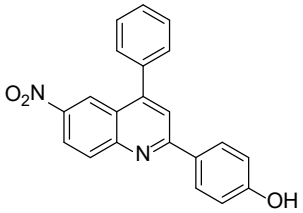
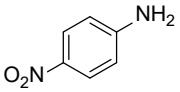
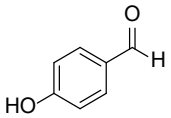
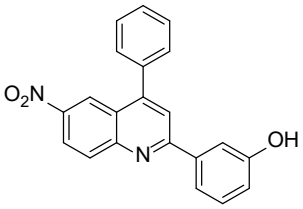
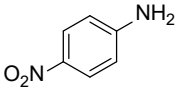
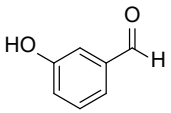
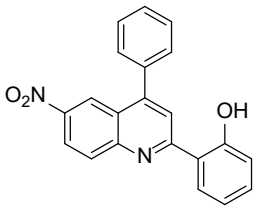
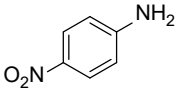
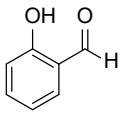
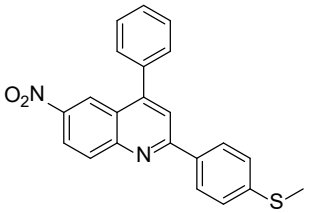
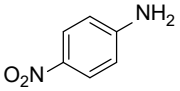
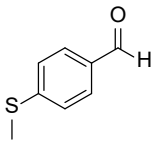
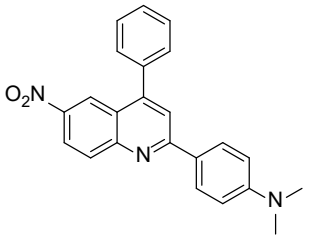
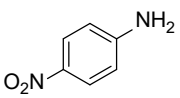
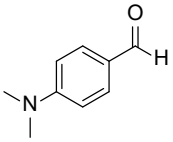
Scheme 4. Optimized conditions synthesis of quinoline derivatives.

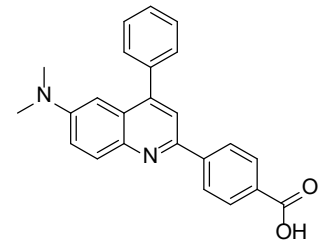
After the optimization tests, various aniline and benzaldehyde were used to synthesize quinoline derivatives in the best conditions, using 0.5 M HCl solution under reflux in 72 hours (Scheme 4, Table 2).

According to Table 2, it can be observed that the reaction occurs much more efficiently with the nitro group (**7aa**) in the aniline than with the alkylamino groups (**7ba**, **7bl** and **7el**). The alkylamino groups have a free electron pair that can act as a Lewis base, reacting with the hydrochloric acid and hindering the Schiff base formation. The nitro group does not have these free electrons, which favors the intermediate formation. Other than that, the Diels-Alder reactions occur better when the diene has electron donating groups (EDG) and the dienophile electron withdrawing groups (EWG), or in the so-called inverse electron demand, when the diene has EWG and the dienophile has EDG. Considering the electron donating effect of the phenyl group in phenylacetylene, an EWG is better in the Schiff base than an EDG.

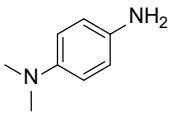
Table 2. Optimized conditions* synthesis of quinoline derivatives.

Product	Aniline derivative	Benzaldehyde derivative	Yield (%)
 **7aa**	 **4a**	 **5a**	64
 **7ba**	 **4b**	 **5a**	40
 **7ca**	 **4c**	 **5a**	40
 **7da**	 **4d**	 **5a**	50
 **7ab**	 **4a**	 **5b**	41
 **7ac**	 **4a**	 **5c**	25
 **7ad**	 **4a**	 **5d**	35

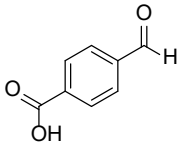
 **7ae**	 **4a**	 **5e**	21
 **7af**	 **4a**	 **5f**	14
 **7ag**	 **4a**	 **5g**	35
 **7ah**	 **4a**	 **5h**	30
 **7ai**	 **4a**	 **5i**	27
 **7aj**	 **4a**	 **5j**	36
 **7ak**	 **4a**	 **5k**	28



7bl

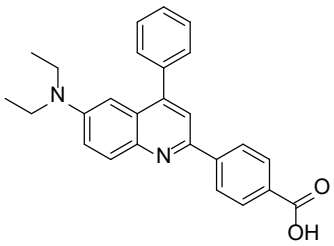


4b

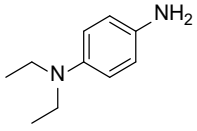


5l

33



7el



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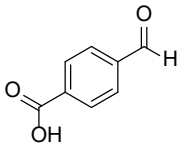

5l

52

*1.0 mmol of **4**, 1.1 mmol of **5** and 1.1 mmol of **6** were reacted in 1 mL of 0.5 M HCl solution under reflux in 72 hours.

Despite that, the HCl catalysis allowed the synthesis of these alkylamino-containing quinolines (**7ba**, **7bl** and **7el**), that cannot be obtained with the $NbCl_5$ or others catalyst described in the literature [25,28-33]. The reaction with the methyl group in the aniline (**7da**) gives similar yield to the alkylamino groups, showing that there is not much difference between the strength of EDG.

The reaction with a bromide group (**7da**) gives better yields than the EDG. When comparing these results with the nitro group (**7aa**), it can be observed that the strength of EWG in the aniline derivative makes a difference, since the bromide group is a weaker withdrawing group than the nitro group and it gives a smaller yield.

It can also be observed that between the benzaldehydes with a halide group in the *para* position, the bromide group (**7aa**) gives better yields than the other halides (**7ad** and **7ae**). Since bromine is the less electronegative of the three halides, it better stabilizes the positive charge in the benzaldehyde protonation, necessary for the Schiff base formation, which favors the formation of the intermediate. The bromide group is even better than the benzaldehyde with no substituent (**7ab**).

A similar effect can be observed when the nitro group is used in the benzaldehyde derivative (**7af**), which is a strong EWG, hindering the positive charge stabilization in the benzaldehyde protonation. The carboxylic acid group in the benzaldehyde has a similar effect (**7bl** and **7el**), but they facilitate the Diels-Alder reaction, the next step in the synthesis.

The 4-hydroxyl-containing quinoline (**7ag**), which is a strong EDG, makes the protonation of benzaldehyde more favorable, as it has several resonance structures. Despite this effect, a low yield was obtained, because this electron donating effect hinders the Diels-Alder reaction step. The *meta* and *ortho* position hydroxyl-quinolines (**7ah** and **7ai**) give lower yields than **7ag**, probably due to steric effects. The methylthio (**7aj**) and the dimethylamine (**7ak**) substituents in the benzaldehyde have similar effects to the hydroxyl (**7ag**).

Regarding the bromine group position, it was observed that the compound with *para*-bromo (**7aa**) reacted better than the *meta*-bromo (**7ac**), considering the resonance structures formed in benzaldehyde protonation, *ortho*- and *para*-bromo substituents help to stabilize the positive charge, while the *meta*-bromo does not have this influence, which explains the lower yield.

3. Material and Methods

All the reactions were performed using deionized water. The chemicals were purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA) and used without further purification.

Thin-layer chromatography was performed on 0.2 mm Merck 60 F254 silica gel aluminum sheets, which were visualized in a UV light chamber with 254 nm and 365 nm lamps. Bruker DRX 400 spectrometer was used for the NMR spectra ($CDCl_3$ and DMSO solutions) using TMS as internal reference. A Jasco FTIR model 4600 was used to record IR spectra (KBr pellets). Melting points were determined using a STUART automatic melting point SMP50, being found in good agreement with the literature [17, 25].

General procedure for the synthesis of quinoline derivatives

1.0 mL of a 0.5 M hydrochloric acid solution was added to a round-bottom flask containing a benzaldehyde derivative (1.0 mmol), an aniline derivative (1.0 mmol) and phenylacetylene (1.0 mmol). Initially a suspension occurred, but as the reaction pot was heated, the reagents solubilized. The reaction occurred under reflux and stirring for 72 hours. The completion of the reaction was verified by monitoring the consumption of the formed intermediates by thin layer chromatography (hexane:ethyl acetate 3:2). The reaction mixture was quenched with water (5.0 mL) and ethyl acetate (5.0 mL) and the pH of the solution was neutralized using a 2.0 M sodium hydroxide solution. The organic phase was extracted with ethyl acetate (3 x 10 mL) and washed with a saturated sodium chloride solution (10 mL) and dried over anhydrous magnesium sulfate. The solvent was recovered after vacuum evaporation and the organic mixture was dissolved in boiling methanol (5 to 10 mL) that, upon cooling, resulted in a yellowish solid. In some cases, the recrystallization process was repeated to yield the pure product.

2-(4-bromophenyl)-6-nitro-4-phenylquinoline (7aa): Yellowish-white solid. **mp/°C** = 182-184. **^{1}HNMR** ($CDCl_3$, 400 MHz): δ 8.86 (d, *J* = 2.5 Hz, 1H), 8.51 (dd, *J* = 9.3, 2.5 Hz, 1H),

8.33 (d, *J* = 9.3 Hz, 1H), 8.15 (AA'XX', 2H), 7.94 (s,1H), 7.70 (AA'XX', 2H), 7.65–7.55 (m, 5H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 158.7, 151.5, 150.9, 145.5, 137.3, 136.7, 132.2, 132.0, 131.7, 129.4, 129.3, 129.1, 126.3, 125.2, 124.9, 123.2, 122.9, 120.2, 111.4 ppm; **IR** (neat): ν_{max}= 696, 754, 827, 1024, 1282, 1336, 1481, 1593, 2833, 2943 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{21}H_{14}BrN_2O_2$ $[M + H]^+$: 405.0233; found 405.0232.

2-(4-bromophenyl)-N,N-dimethyl-4-phenylquinolin-6-amine (7ba): Yellow solid**, mp/°C =** 154-155. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 9.1 Hz, 1H), 8.02 (AA'XX', 2H), 7.64 (s, 1H),7.62-7.46 (m, 7H), 7.38 (dd, *J* = 9.1, 2.8 Hz, 1H), 6.90 (d, *J* = 2.8 Hz, 1H), 2.99 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 148.8, 138.9, 131.9, 130.1, 129.3, 128.8, 128.7, 128.4, 119.7, 119.4, 103.0, 40.6; **IR** (neat): ν_{max} = 591, 701, 760, 828, 958, 1007, 1069, 1176, 1219, 1320, 1358, 1498, 1616, 2849, 2916 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{23}H_{19}BrN_2$ $[M + H]^+$: 403.0804; found 403.0815.

2-(4-bromophenyl)-6-methyl-4-phenylquinoline (7ca): Yellowish-white, **mp/°C =** 143-144. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.11 (d, 8.3 Hz, 1H), 8.06 (AA'XX', 2H), 7.73 (s, 1H), 7.65-7.54 (m, 9H), 2.47 (s, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 154.7, 148.7, 147.3, 138.6, 138.5, 136.6, 132.0, 131.9, 129.8, 129.5, 129.0, 128.6, 128.4, 125.8, 124.4, 123.7, 119.0, 21.9. **IR** (neat): ν_{max} = 545, 591, 699, 762, 829, 1355, 1405, 1436, 1461, 1488, 1545, 1590, 1622, 2911, 3053 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{22}H_{16}BrN$ $[M + H]^+$: 374.0539; found 374.0531.

6-bromo-2-(4-bromophenyl)-4-phenylquinoline (7da): White solid**, mp/°C =** 190,4. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.08-8.06 (m, 3H), 8.03 (d, J = 2 Hz, 1H), 7.81-7.78 (m, 2H), 7.65 (AA'XX', 2H), 7.58-7.51 (m, 5H) ppm; **^{13}C NMR** (CDCl3, 100 MHz): δ 155.9, 148.6, 147.4, 138.0, 133.2, 132.1, 129.4, 129.1, 128.9, 127.9, 127.1, 119.6; IR (neat): vmax = 529, 587, 776, 833, 878, 1479, 1540, 1587, 1619, 1659, 2874, 3028 cm-1 **IR** (neat): ν_{max} = 529, 587, 776, 833, 878, 1479, 1540, 1587, 1619, 1659, 2874, 3028 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{21}H_{13}Br2N$ $[M + H]^+$: 439.9468; found 439.9477.

6-nitro-2,4-diphenylquinoline (7ab): Yellowish-white solid. **mp/°C** = 198-200. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.87 (d, *J*=2.4 Hz, 1H), 8.51 (dd, *J*=9.2, 2.4 Hz, 1H), 8.35 (d, *J*=9.2 Hz, 1H), 8.26-8.24 (m, 2H), 7.99 (s, 1H), 7.65-7.53 (m, 8H); **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 160.1, 151.3, 151.1, 145.4, 138.5, 136.9, 131.8, 130.5, 129.5, 129.4, 129.2, 129.1, 127.9, 124.8, 123.1, 123.0, 120.8 ppm; **IR** (neat): ν_{max}= 588, 683, 752, 883, 1078, 1228, 1335, 1439, 1485, 1593, 1618, 1740, 3055 cm^{-1}. **ESI-HRMS:** m/z calcd for $C_{21}H_{15}N_2O_2$ $[M + H]^+$: 327.1133; found 327.1129.

2-(3-bromophenyl)-6-nitro-4-phenylquinoline (7ac): Yellowish-white solid. **mp/°C** = 227-232. **^{1}HNMR** ($CDCl_3$, 400 MHz): δ = 8.87 (d, *J* = 2.5 Hz, 1H), 8.52 (dd, *J* = 9.3, 2.5 Hz, 1H), 8.43 (t, *J* = 1.7 Hz, 1H), 8.35 (d, *J* = 9.3 Hz, 1H), 8.18-8.16 (m, 1H),7.94 (s, 1H), 7.67–7.56 (m, 6H), 7.44 (t, *J* = 7.9 Hz, 1H) ppm; **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 120.4, 122.9, 123.3, 123.3, 125.0, 126.3, 129.2, 129.4, 129.4, 130.5, 130.8, 131.8, 133.3, 136.6, 140.4, 145.6, 150.9, 151.6, 158.3 ppm; **IR** (neat): ν_{max}= 696, 783, 1222, 1336, 1485, 1593, 2838, 3068 cm^{-1}. **ESI–HRMS:** m/z calcd for $C_{21}H_{14}BrN_2O_2$ $[M + H]^+$: 405.0233; found 405.0232.

2-(4-chlorophenyl)-6-nitro-4-phenylquinoline (7ad): Yellowish-white solid**. mp/°C** = 183-187. **^{1}HNMR** ($CDCl_3$, 400 MHz): δ 8.86 (d, *J* = 2.5 Hz, 1H), 8.51 (dd, *J* = 9.3, 2.5 Hz, 1H), 8.33 (d, *J* = 9.3 Hz, 1H), 8.22 (AA'XX', 2H), 7.95 (s,1H), 7.63-7.53 (m, 7H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 158.7, 151.6, 151.0, 145.5, 136.9, 136.8, 136.7, 131.8, 129.4, 129.3, 129.2, 129.1, 129.1, 128.6, 126.4, 124.9, 123.2, 123.0, 120.3, 11.4 ppm; **IR** (neat): ν_{max}= 696, 829, 1012, 1089, 1280, 1334, 1483, 15 93, 3170 cm^{-1}. **ESI–HRMS:** m/z calcd for $C_{21}H_{14}ClN_2O_2$ $[M + H]^+$: 361.0738; found 361.0723.

2-(4-fluorophenyl)-6-nitro-4-phenylquinoline (7ae): White solid. **mp/°C** = 234-235. **^{1}HNMR** ($CDCl_3$, 400 MHz): δ 8.86 (d, *J* = 2.3 Hz, 1H), 8.49 (dd, *J* = 9.0, 2.3 Hz, 1H), 8.31 (d, *J* = 9.0 Hz, 1H), 8.28-8.25 (m, 2H), 7.95 (s,1H), 7.65–7.57 (m, 5H), 7.28–7.23 (m, 2H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 164.4 (*J* = 250 Hz, 1C), 158.8, 151.4, 150.9, 145.4, 136.7, 134.6, 134.6, 131.6, 129.8, 129.8, 129.4, 128.1, 124.7, 123.2, 122.9, 120.3, 116.2, 116.0 ppm; **IR** (neat): ν_{max}= 698, 771, 835, 1027, 1081, 1220, 1328, 1483, 1589, 3103 cm^{-1}. **ESI–HRMS:** m/z calcd for $C_{21}H_{14}FN_2O_2$ $[M + H]^+$: 345.1033; found 345.1033.

2-(4-nitrophenyl)-6-nitro-4-phenylquinoline (7af): Yellowish-white solid. **mp/°C** = 235-238. **^{1}HNMR** ($CDCl_3$, 400 MHz): δ 8.90 (d, *J* = 2.5 Hz, 1H), 8.55 (dd, *J* = 9.3, 2.5 Hz, 1 H), 8.47-8.37 (m, 5H), 8.03 (s, 1H), 7.66 -7.56 (m, 5H) ppm; **^{13}C NMR** (CDCl3, 100 MHz): δ 152.1, 150.9, 146.0, 144.2, 138.6, 136.4, 132.1, 131.0, 129.6, 129.4, 129.3, 128.7, 124.1, 123.5, 122.9, 120.5 ppm; **IR** (neat): ν_{max}= 698, 754, 828, 842, 1440, 1483, 1512, 1556, 1591, 1618, 2343 cm^{-1}. **ESI–HRMS:** m/z calcd for $C_{21}H_{14}N_3O_4$ $[M + H]^+$: 372.0978; found 372.0972.

4-(6-nitro-4-phenylquinolin-2-yl)phenol (7ag): Dark yellow-orange solid, 27%, **mp/°C =** 270-273; **^{1}H NMR** (DMSO, 400 MHz): δ 10.10 (s, 1H), 8.64 (d, *J* = 2.5 Hz, 1H), 8.46 (dd, *J* = 9.3, 2.5 Hz, 1H), 8.30 (AA'XX', 2H), 8.25 (d, *J* = 9.3 Hz, 1H), 8.17 (s, 1H), 7.72-7.64 (m, 5H), 6.95 (AA'XX', 2H) ppm; **^{13}C NMR** (DMSO, 100 MHz): δ 160.2, 159.1, 150.5, 150.2, 144.4, 135.4, 131.1, 129.6, 128.9, 128.4, 123.6, 123.1, 122.3, 119.7, 115.8; **IR** (neat): ν_{max} = 536, 568, 629, 701, 751, 835, 1088, 1172, 1239, 1283, 1337, 1487, 1551, 1590, 2347, 3308, 3369, 3649 cm^{-1}. **ESI-HRMS:** m/z calcd for $C_{21}H_{14}N_2O_3$ $[M + H]^+$: 343.1077; found 343.1077.

3-(6-nitro-4-phenylquinolin-2-yl)phenol (7ah): Yellowish-white, **mp/°C =** 275-277; **^{1}H NMR** (DMSO, 400 MHz): δ 9.74 (s, 1H), 8.70 (d, *J* = 2.5 Hz, 1H), 8.51 (dd, *J* = 9.2, 2,5 Hz, 1H), 8.33 (d, *J* = 9.2 Hz, 1H), 8.19 (s, 1H), 7.85-7.81 (m, 2H), 7.76-7.66 (m, 5 H), 7.37 (t, $J_1 = J_2$ = 7.8 Hz, 1H), 6.98 (ddd, J_1 = 8, J_2 = 2.3, J_3 = 0.8 Hz, 1H) ppm; **^{13}C NMR** (DMSO, 100 MHz): δ 159.2, 158.0, 150.6, 150.3, 144.93, 139.0, 136.3, 131.5, 130.1, 129.7, 129.1, 124,2, 123.2, 122.4, 120.5, 118.8, 117.8, 114.3 ppm; **IR** (neat): ν_{max} = 523, 592, 701, 744, 813, 1081, 1227, 1322, 1440, 1550, 1591, 1686, 2346, 3295, 3401, 3629 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{21}H_{14}N_2O_3$ $[M + H]^+$: 343.1077; found 343.1104.

2-(6-nitro-4-phenylquinolin-2-yl)phenol (7ai): Soft orange solid, **mp/°C =** 259-261. **^{1}H NMR** (DMSO, 400 MHz): δ 14.03 (s, 1H), 8.69 (d, *J* = 2.5 Hz, 1H), 8.56 (dd, *J* = 9.1, 2,5 Hz, 1H), 8.48 (s, 1H), 8.41 (d, *J* = 9.1 Hz, 1H), 8.38 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.76-7.67 (m, 5H), 7.49-7.45 (m, 1H), 7.06 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.04-6.99 (m, 1H) ppm; **^{13}C NMR** (DMSO, 100 MHz): δ 160.1, 151.2, 145.1, 136.0, 129.9, 129.8, 129.5, 129.2, 129.0, 124.0, 123.8, 122.3, 120.2, 119.3,118.9, 118.0 ppm. **IR** (neat):

ν_{max} = 512, 591, 675, 701, 758, 860, 1082, 1213, 1338, 1488, 1551, 1596, 1733, 2346, 3099, 3408, 3630, 3725 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{21}H_{14}N_2O_3$ $[M + H]^+$: 343.1077; found 343.1080.

2-(4-(methyltio)phenyl)-6-nitro-4-phenylquinoline (7aj): Yellow solid. **mp/°C** = 198-200. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.83 (d, *J* = 2.5 Hz, 1H), 8.48 (dd, *J* = 9.3, 2.5 Hz, 1H), 8.33 (d, J = 9.3 Hz, 1H), 8.20 (AA'XX', 2H), 7.95 (s, 1H), 7.63-7.55 (m, 5H), 7.40 (AA'XX', 2H), 2.57 (s, 3H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 159.3, 145.3, 136.8, 131.5, 129.5, 129.4, 129.2, 128.1, 126.2, 124.8, 123.2, 123.0, 120.3, 15.2 ppm; **IR** (neat): ν_{max}= 692, 754, 810, 887, 1026, 1091, 1186, 1332, 1479, 1589, 2848, 2919 cm^{-1}. **ESI–HRMS:** m/z calcd for $C_{22}H_{17}N_2O_2S$ $[M + H]^+$: 373.1005; found 373.1005.

2-(4-(dimethylamino)phenyl)-6-nitro-4-phenylquinoline (7ak): Dark orange solid. **mp/°C** = 195-199. **^{1}H NMR** ($CDCl_3$, 400 MHz): δ 8.78 (d, *J* = 2.5 Hz, 1H), 8.44 (dd, *J* = 9.2, 2.5 Hz, 1H), 8.29 - 8.20 (m, 3H), 7.90 (s,1H), 7.63–7.55 (m, 5H), 6.83 (d, *J* = 9.2, 2H), 3.09 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 165.8, 163.4, 159.5, 144.8, 142.5, 135.3, 129.0, 123.8, 122.9, 111.5, 109.6, 106.1, 104.9, 103.0, 101.3, 101.0, 100.4, 57.5 ppm; **IR** (neat): ν_{max}= 694, 757,819, 1064, 1105, 1230, 1317, 1432, 1502, 1577, 2827, 2918 cm^{-1}. **ESI–HRMS:** m/z calcd for $C_{23}H_{19}N_3O_2$ $[M]^+$: 369,1500; found 369.1613.

4-(6-(dimethylamino)-4-phenylquinolin-2-yl)benzoic acid(7bl): Reddish brown solid. **mp/°C** = 281-282. **^{1}H NMR** ($CDCl_3$, 400 MHz): 8.40 (AA'XX', 2H), 8.07 (AA'XX', 2H), 8.02 (d, *J* = 9.3 Hz, 1H), 7.93 (s, 1H), 7.70-7.53 (m, 6H), 6.86 (d, *J* = 2.8 Hz, 1H), 2.98 (s, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 149.9, 148.7, 146.0, 142.9, 142.0, 138.2, 130.6, 129.7, 129.3, 128.7, 128.4, 126.8, 126.6, 119.7, 119.1, 101.7, 99.5, 24.9 ppm; **IR** (neat): ν_{max}= 704, 759, 820, 961, 1065, 1180, 1294, 1315, 1425, 1500, 1606, 1685, 2970 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{24}H_{20}N_2O_2$ $[M + H]^+$: 369.1598; found 369.1604.

4-(6-(diethylamino)-4-phenylquinolin-2-yl)benzoic acid (7el): Light orange solid. **mp/°C** = 237-238. **^{1}H NMR** ($CDCl_3$, 400 MHz): 8.37 (AA'XX', 2H), 8.06 (AA'XX', 2H), 7.99 (m, 2H), 7.90 (s, 1H), 7.70-7.52 (m, 5H), 6.77 (d, *J* = 2.8 Hz, 1H), 3.37 (q, J_1 = 6.9 Hz, J_2 = 13.9 Hz, 4H), 1.09 (t, J_1 = J_2 = 6.9 Hz, 6H) ppm; **^{13}C NMR** ($CDCl_3$, 100 MHz): δ 149.5, 145.9, 145.5, 141.6, 138.3, 130.9, 129.7, 129.3, 128.8, 128.6, 128.3, 127.2, 126.5, 119.2, 118.9, 100.9, 44.1, 12.4 ppm; **IR** (neat): ν_{max}= 819, 1150, 1265, 1291, 1422, 1513, 1583, 1619, 1680, 2969 cm^{-1}. **ESI–HRMS**: m/z calcd for $C_{26}H_{24}N_2O_2$ $[M + H]^+$: 397.1911; found 397.1919.

4. Conclusions

In conclusion, it was possible to develop a new greener method for the synthesis of quinoline derivatives in a one-pot multicomponent reaction between an aniline derivative, a benzaldehyde derivative and phenylacetylene using a hydrochloric acid solution, affording the desired quinolines derivatives with good yields and reaction times. It was possible to observe that this procedure gives better yields when using EWG-containing reagents, due to the inverse demand Diels-Alder reaction. This method is simple and practical and was able to produce unpublished *N,N*-alkylamino-containing 2,4-diaryl-quinolines.

Supporting Information

Supplementary data associated with this article can be found in the online version.

Acknowledgments

The authors would like to thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP 2013/07296-2, 2016/01599-1, 2018/09235-4 and 2018/14506-7), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (Proc. 302769/2018-8), Coordenadoria de Aperfeiçoamento de Pessoal do Nível Superior (CAPES), and Pró-Reitoria de Pesquisa da UNESP (PROPe-UNESP) for their financial support.

Author Contributions

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How to cite this article

Martins, L. M.; Moreno, V. F.; Rosário, I. S.; Graeff, C. F. O.; Silva Filho, L. C. *Orbital: Electron. J. Chem.* **2022**, *14*, 1. DOI: **http://dx.doi.org/10.17807/orbital.v14i1.1689**