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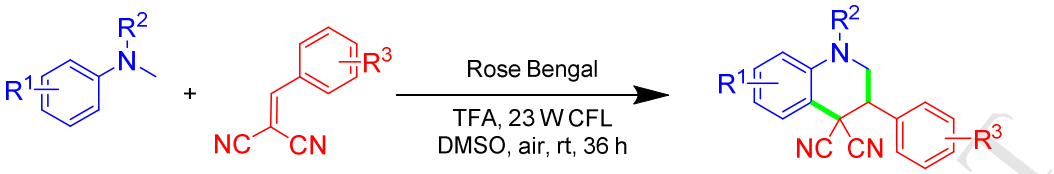
Graphical Abstract



20 examples, yields up to 74%

Metal-free Visible Light Driven Synthesis of Tetrahydroquinoline Derivatives Utilizing Rose Bengal

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Abstract: The visible-light driven reaction for the synthesis of tetrahydroquinoline derivatives via tandem radical cyclization of *N*,*N*-dimethylanilines with 2-benzylidenemalononitriles has been developed. Corresponding products were obtained with yields of up to 74% under mild conditions by using Rose Bengal as a triplet sensitizer, which is inexpensive, environmentally-friendly and easily acquired. This work demonstrates the potential benefits of Rose Bengal for the production of tetrahydroquinoline derivatives.

Key words: visible light, photoredox catalysis, Rose Bengal, tetrahydroquinoline, tandem radical cyclization

1 Introduction

Visible light is an abundant, readily available and renewable clean energy. Its application for organic synthesis has received great attention from the chemical workers.[1] However, since most of organic molecules cannot directly absorb visible light, thereby they require a medium to play this important role in the reaction system.[2] Recently, MacMillan,[3] Yoon,[4] Stephenson,[5] et al. have demonstrated that metal complexes, such as ruthenium (II) and iridium (III), have good

photocatalytic properties, which make visible light widely used in the organic synthesis. Although numerous photocatalysts based on Ru or Ir have been investigated during the past decades, these complexes are expensive and potentially toxic. Meanwhile, organic dyes possess the distinguishing qualities of high extinction coefficients in the visible-light range, long excited-state lifetimes, and low cost, which make these organic photosensitizers desirable for photoredox transformations. Therefore, more and more organic dyes have been used in photocatalytic reactions.[6] For example, the economical Rose Bengal has been employed in decarboxylative amination,[7] alkylation reaction,[8] cycloaddition reaction,[9] thiocyanation reaction[10] and formylation reaction.[11] Taking into consideration of the advantages of Rose Bengal as the photosensitizer, we decided to further explore the application of Rose Bengal in organic synthesis.

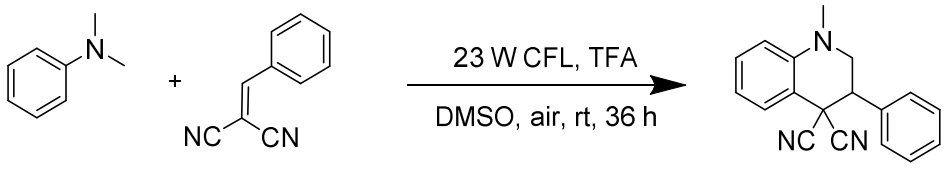
Tetrahydroquinoline derivatives are a class of very important compounds, and the fragments of tetrahydroquinoline moiety are also vital building blocks generally found in many natural products and bioactive molecules.[12] Due to their ubiquitous distribution in natural products and medicinal agents, tetrahydroquinolines have become important synthetic targets for chemists.[13] The tandem cyclization of free radical and unsaturated olefin is widely used in organic synthesis.[14] The synthesis of tetrahydroquinoline derivatives by cyclization of benzylidenemalononitriles with α-amino radical has been reported. In 2011, Miura[15] et al. used $CuCl_2/O_2$ at 60 ^oC to obtain the corresponding tetrahydroquinolines in moderate yields. In 2013, Rueping group[16] reported the photoinitiated cycloaddition reactions of *N*-methylanilines with 2-benzylidenemalononitriles for the synthesis of tetrahydroquinolines using $[Ir(ppy)_2bpy]PF_6$ under blue LED, and yields of up to 71% were obtained. In 2016, Bissember[17] et al. used $[Cu(dap)_2]Cl$ as a photosensitizer under green LED to obtain the tetrahydroquinolines in moderate yields. However, the catalysts used in these reports are metals including noble metal and costly ligands, and the photocatalytic methods used high-intensity monochromatic LEDs as light source. Taking into account the importance of tetrahydroquinolines, the exploration of more economical, environmentally-friendly and easily acquired catalysts for the synthesis of tetrahydroquinolines still has greatly practical value. Herein, we report a metal-free visible light driven synthesis of tetrahydroquinoline derivatives from 2-benzylidenemalononitriles and substituted anilines, in which Rose Bengal was used as a triplet

sensitizer and the compact fluorescent lamp (CFL) as light source. This process might provide a promising alternative protocol for the synthesis of tetrahydroquinoline derivatives.

2 Results and discussion

The tandem radical cyclization of *N*,*N*-dimethylaniline (**1a**) with 2-benzylidenemalononitrile (**2a**) under air condition was chosen as a model reaction. Firstly, fluorescence experiments with **1a, 2a** and Rose Bengal were performed. **1a** and **2a** could not absorb light in the visible light region while Rose Bengal exhibited a strong absorption in the visible light region at λ = 563 nm (ε = 122633 L $mol^{-1}cm^{-1}$) in DMSO (the spectrum shown in the Supporting Information). Then, some control experiments were conducted. As shown in **Table 1**, in the presence of Rose Bengal (3 mol%) and under irradiation of a 23 W household CFL (λ = 400-720 nm) in DMSO for 36 h,[18] the model reaction gave product (**3a**) in 55% yield (**Table 1**, entry 1). To verify both visible light and Rose Bengal are necessary in this catalytic process, control experiments were conducted. In the absence of both visible light and Rose Bengal, or either one of them, only trace amount of product (**3a**) could be observed (**Table 1**, entries 2-4). Those results indicated that both Rose Bengal and visible light are indispensable for the model reaction. When the model reaction was conducted under N_2 instead of air, the product was only obtained in 7% yield (**Table 1**, entry 5), showing that O_2 was involved in the reaction process. To get an insight into the reaction mechanism, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical scavenger, was added to the reaction system, which completely inhibited the reaction (**Table 1**, entry 6). This revealed that the reaction must proceed through a radical process. Taking into consideration of the possibility that Rose Bengal can generate singlet oxygen through energy transfer,[11,19] 1,4-diazabicyclo[2.2.2]-octane (DABCO) as a quencher of $^1O_2$ was added to the model reaction. Only trace amount of product was observed in the presence of DABCO (**Table 1**, entry 7), indicating that singlet oxygen participated in the reaction process.

Table 1. Control experiments[a]



1a **2a** **3a**

Entry	Visible light	Rose Bengal (3 mol%)	TEMPO (0.6 mmol)	DABCO (0.6 mmol)	Yield (%)[b]
1	+	+	-	-	55
2	-	-	-	-	trace
3	+	-	-	-	trace
4	-	+	-	-	trace
5[c]	+	+	-	-	7
6	+	+	+	-	trace
7	+	+	-	+	trace

[a] Reaction conditions: a mixture of **1a** (0.3 mmol), **2a** (0.2 mmol), Rose Bengal (3 mol%) and TFA (1 eq. relative to **2a**) in DMSO (1.0 mL) was irradiated using a 23 W CFL in air for 36 h.

[b] Yield of the isolated product.

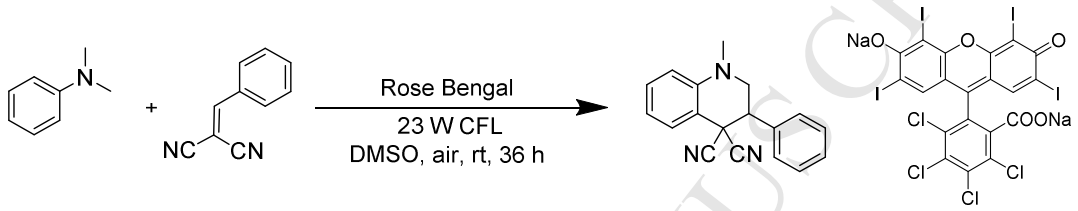
[c] Under N_2.

Next, we optimized the reaction conditions in terms of solvent, molar ratio, catalyst dosage, wattage of lamp and solvent volume. Since solvent effect also affects the rate of free radical reaction,[20] we firstly screened the solvents. DMSO was found to be the best solvent among DMSO, MeCN, MeOH, THF, toluene, $CHCl_3$, CH_2Cl_2, 1-methyl-2-pyrrolidinone and cyclohexane (**Table S1**). Then, we investigated other reaction conditions. To conclude, the optimized reaction conditions for a 0.2 mmol scale reaction were found to consist of the following: 1 mL of DMSO, a molar ratio of **1a**/**2a** = 3:2, a Rose Bengal dosage of 3 mol%, and a fluorescent lamp wattage of 23 W (For more details, please see the Supporting Information **Tables S1-S4**).

Some literatures revealed that acid additive could control formation rate of α-amino radical through affecting the balance between free amine and its corresponding (unreactive) ammonium salt.[17,21] Therefore, the species of acid additive were investigated. Among the tested acid

additives, TFA could promote the reaction significantly, giving a yield of 52% (**Table 2**, entry 2). When formic acid and *p*-toluenesulfonic acid were used, very low yields were obtained (**Table 2**, entries 3 and 4). Moreover, influence of the TFA loading was investigated. When 1 equivalent of TFA relative to **2a** (0.2 mmol) was employed, the best yield of 55% was received (**Table 2**, entry 6). Therefore, 1 equivalent of TFA relative to **2a** (0.2 mmol) was chosen as optimal conditions for the reaction.

Table 2. Influence of acids[a]



1a **2a** **3a** **Rose Bengal**

Entry	Acid	Acid equivalents (relative to **2a)**	Yield (%)[b]
1	None	-	37
2	TFA	2	52
3	HCOOH	2	34
4	TsOH • H_2O	2	22
5	TFA	0.5	47
6	TFA	1	55
7	TFA	1.5	53
8	TFA	2.5	50

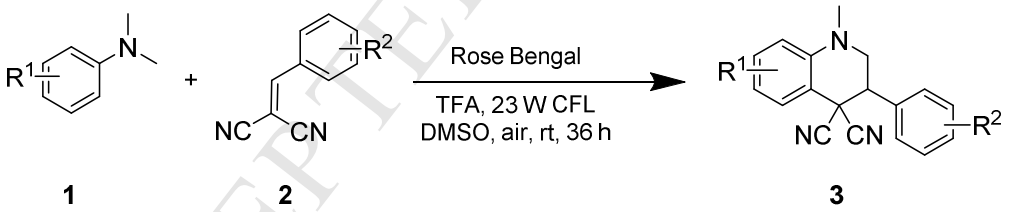
[a] Reaction conditions: a mixture of **1a** (0.3 mmol), **2a** (0.2 mmol), Rose Bengal (3 mol%) and acid in DMSO (1.0 mL) was irradiated using a 23 W CFL in air for 36 h.

[b] Yield of the isolated product.

With the optimized conditions in hand, the scope of substituted anilines **1** and benzylidenemalononitriles **2** were examined (**Table 3** and **Scheme 1**). It can be seen that *N*,*N*-dimethylanilines with an electron-donating group (4-Me) give better yields than those with an electron-withdrawing group (4-F or 4-Cl) (**Table 3,** entries 2-4). The possible reason is that the

electron-donating group is beneficial to the stability of α-amino radicals formed in the reaction process. Benzylidenemalononitriles with either an electron-withdrawing (-CF_3, -F, -Cl, -Br) or an electron-donating group (-OMe, -OEt, -Me, -Ph) could take part in the reaction smoothly (**Table 3,** entries 5-17). Generally, electron-rich benzylidenemalononitriles delivered the desired products with better yields than electron-deficient ones. Additionally, *o*-, *m*- or *p*-chloro benzylidenemalononitrile could be utilized to give the corresponding products **3** (**Table 3,** entries 12, 14 and 15). The reactions between both electron-rich *N*,*N*-dimethylanilines and benzylidenemalononitriles gave good yields (**Table 3,** entries 16 and 17). Additionally, besides *N*,*N*-dimethylanilines some other substituted anilines were also evaluated, and to our delight, N-ethyl-N-methylaniline, N-methyldiphenylamine and 4-phenylmorpholine could participate in the reaction with **2a** giving corresponding products in 34%, 55%, and 25% yields, respectively (**Scheme 1**). Eighteen new tetrahydroquinoline derivatives were obtained, and their structures were confirmed by HRMS, ^{1}H NMR, and ^{13}C NMR. (For details, please see the Supporting Information).

Table 3. Substrate scope[a].



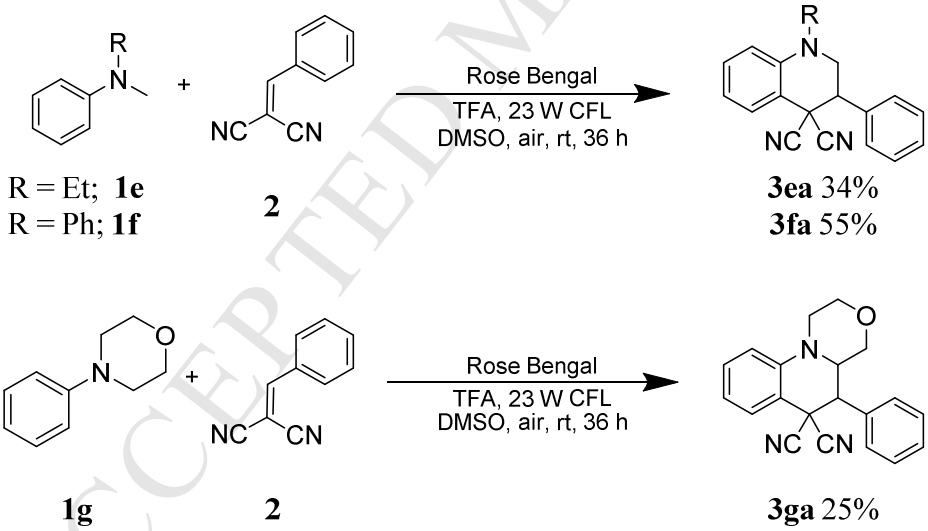
1 **2** **3**

Entry	R^1	R^2	Product	Yield (%)[b]
1	H	H	**3aa**	57
2	4-Me	H	**3ba**	67
3	4-F	H	**3ca**	52
4	4-Cl	H	**3da**	50
5	H	4-OMe	**3ab**	65
6	H	4-OEt	**3ac**	63
7	H	3-OMe	**3ad**	58

8	H	3-Me	**3ae**	58
9	H	4-Ph	**3af**	45
10	H	4-CF_3	**3ag**	38
11	H	4-F	**3ah**	55
12	H	4-Cl	**3ai**	54
13	H	4-Br	**3aj**	47
14	H	3-Cl	**3ak**	56
15	H	2-Cl	**3al**	47
16	4-Me	4-OEt	**3bb**	73
17	4-Me	4-OMe	**3bc**	74

[a] Reaction conditions: a mixture of **1** (0.3 mmol), **2** (0.2 mmol), Rose Bengal (3 mol%) and TFA (1 eq. relative to **2**) in DMSO (1.0 mL) was irradiated using a 23 W CFL in air for 36 h.

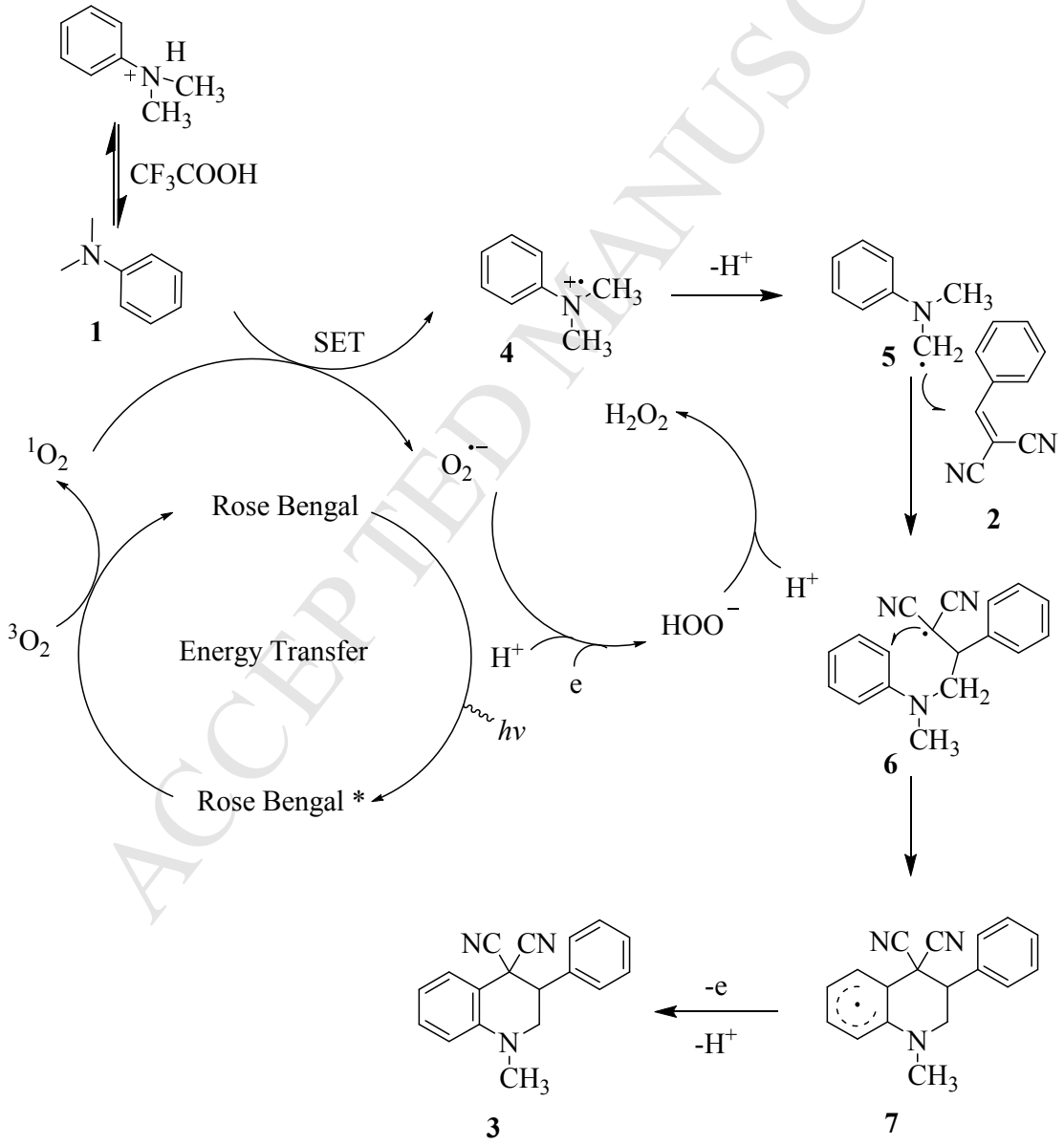
[b] Yield of the isolated product.



Scheme 1. Reactions of other substituted anilines besides *N*,*N*-dimethylanilines

On the basis of our control experiments and previous work,[6a,15-18] a plausible reaction pathway for this visible light induced cyclization reaction was proposed (**Scheme 2**). Firstly, the triplet sensitizer Rose Bengal (RB) absorbs a photon to form the excited-state RB*, which interacts with O_2 to generate $^1O_2$ via the energy transfer. Subsequently, the generated $^1O_2$ proceeds a single-electron transfer (SET) from *N*,*N*-dimethylaniline **1** to give the amine cation radical **4**.

Then **4** donates one proton to the dioxygen radical anion and results in formation of the amine radical **5**, which can easily react with 2-benzylidenepropanedinitrile **2** to produce the alkyl radical **6**. And intramolecular cyclization generates the corresponding intermediate **7**, which is then readily rearomatized by the second electron transfer/proton elimination leading to the product **3**. In this process, acid additive (TFA) maybe play a role to control the formation rate of α-amino radicals through affecting the balance between free amine and its corresponding (unreactive) ammonium salt,[17,21] which ensures a higher utilization of the radicals by avoiding the decomposition caused by free radical accumulation. On the other hand, some reports have suggested that Brønsted acids have the ability to promote radical additions.[21-22]



Scheme 2. Possible mechanism.

3 Conclusion

In summary, we have developed a metal-free visible-light driven method for the synthesis of tetrahydroquinoline derivatives. The mild conditions enable moderate yields by using cheap and commercially available Rose Bengal in place of previous transition metal photocatalysts and a household light bulb instead of a high-intensity monochromatic LED light source. The yields obtained with this method can match the previously reported yields, and eighteen new tetrahydroquinoline derivatives were obtained. This work demonstrates that there is a synergistic benefit of combining TFA with Rose Bengal and might provide a promising protocol for the synthesis of tetrahydroquinoline derivatives.

4. Experimental section

4.1. General experimental details

Rose bengal was purchased from aladdin industrial corporation Shanghai, China. R104993-1g, 95%. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) with Haiyang GF 254 silica gel plates (Qingdao Haiyang chemical industry Co Ltd, Qingdao, China) using UV light and vanillic aldehyde as visualizing agents. Flash column chromatography was performed using 200–300 mesh silica gel at increased pressure. ^{1}H NMR spectra and ^{13}C NMR spectra were respectively recorded on 600 MHz and 150 MHz NMR spectrometers. Chemical shifts (δ) were expressed in ppm with TMS as the internal standard, and coupling constants (*J*) were reported in Hz. High-resolution mass spectra were obtained by using ESI ionization sources (Varian 7.0 T FTICR-MS) and ESI-TOF. Melting points were taken on a WPX-4 apparatus and were uncorrected (Yice instrument equipment Co Ltd, Shanghai).

2.2. General procedure for the preparation of benzylidenemalononitriles (2)[23]

Malononitrile (10.0 mmol) was added to a stirred solution of aromatic aldehyde (10.0 mmol) and piperidine (1.0 mmol) in ethanol (10 mL). The reaction mixture was stirred at room temperature for 1 h. A precipitate was formed and collected by suction filtration, and then purified by recrystallization from CH_2Cl_2 and petroleum ether to afford the products **2**.

4.3. General procedure for the synthesis of tetrahydroquinoline derivatives (3)

A round-bottom flask was charged with Rose Bengal (3 mol%), substituted aniline **1** (0.3 mmol,) and 2-benzylidenemalononitrile **2** (0.2 mmol) in DMSO (1.0 ml), to which TFA (1 eq relative to **2**) was introduced. The resultant mixture was stirred at r.t. under irradiation of 23 W CFL (Philips) in air for 36 h. Then 10 mL of ethyl acetate was added to the reaction system, followed by washing with saturated salt water (3×5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography (petroleum ether/ ethyl acetate 20:1-8:1, 0.5% NEt_3 was present in the eluent) to give the products **3**.

4.3.1. *1-methyl-3-phenyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3aa)**[17]

White solid, m.p. 140-142 ^oC, ^1H NMR (600 MHz, $CDCl_3$) δ 7.51-7.53 (d, *J* = 7.2 Hz, 1H), 7.40-7.49 (m, 5H), 7.32-7.35 (m, 1H), 6.80-6.83 (m, 1H), 6.73-6.75 (m, 1H), 3.96 (t, *J* = 11.9 Hz, 1H), 3.60 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.52 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.0, 134.8, 131.7, 129.3, 129.2, 128.8, 128.5, 117.6, 115.2, 114.1, 112.9, 112.6, 51.5, 45.7, 42.4, 38.7.

4.3.2. *1,6-dimethyl-3-phenyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ba)**[16]

White solid, m.p. 192-194 ^oC, ^1H NMR (600 MHz, $CDCl_3$) δ 7.43-7.46 (m, 5H), 7.30-7.35 (m, 1H), 7.13-7.15 (m, 1H), 6.65-6.68 (m, 1H), 3.89 (t, J = 11.8 Hz, 1H), 3.60 (dd, J = 11.3, 3.6 Hz, 1H), 3.48 (dd, J = 11.3, 3.6 Hz, 1H), 2.99 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.8, 134.5, 129.5, 129.2, 128.4, 118.9, 118.8, 115.4, 114.7, 113.8, 113.6, 51.6, 45.8, 42.3, 39.1, 20.3.

4.3.3. *6-fluoro-1-methyl-3-phenyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ca)**

White solid, m.p. 207-209 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48-7.52 (m, 1H), 7.43-7.46 (m, 2H), 7.36-7.39 (m, 1H), 7.27-7.30 (m, 1H), 7.22-7.25 (m, 1H), 6.66-6.69 (m, 2H), 3.95 (t, J = 11.8 Hz, 1H), 3.57 (dd, J = 11.3, 3.5 Hz, 1H), 3.52(dd, J = 11.3, 3.5 Hz, 1H), 3.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.6, 134.3, 131.8, 129.6, 129.3, 128.4, 122.3, 115.0, 114.6, 113.7, 113.6, 51.4, 45.5, 42.1, 38.8. HRMS(ESI) m/z: calcd for $C_{18}H_{14}FN_3$ $[M+Na]^+$ 314.1064, found 314.1068.

4.3.4. *6-chloro-1-methyl-3-phenyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3da)**

White solid, m.p. 165-167 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49-7.51 (m, 2H), 7.44-7.45(m, 2H), 7.29-7.30 (m, 1H), 7.27-7.29 (m, 1H), 6.67-6.68 (m, 1H), 6.60-6.66 (m, 1H), 3.95 (t, J = 11.8 Hz, 1H), 3.57 (dd, J = 12.3, 4.0 Hz, 2H), 3.53 (dd, J = 12.4, 4.0 Hz, 2H), 3.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.6, 134.3, 131.8, 129.6, 129.3, 128.4, 122.3, 114.6, 114.0, 113.7, 113.6, 51.4, 45.5, 42.1, 38.8. HRMS(ESI) m/z: calcd for $C_{18}H_{14}ClN_3$ $[M+Na]^+$ 330.0768, found 330.0772.

4.3.5. *3-(4-methoxyphenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ab)**

Pale yellow solid, m.p. 158-160 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50-7.52 (m, 1H), 7.36-7.39 (m, 2H), 7.30-7.34 (m, 1H), 6.95-6.97 (m, 2H), 6.79-6.81 (m, 1H), 6.72-6.74 (m, 1H), 3.91 (t, *J* = 11.9 Hz, 1H), 3.83 (s, 3H), 3.56 (d, *J* = 11.3 Hz, 1H), 3.48 (d, *J* = 11.3 Hz, 1H), 3.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.4, 144.1, 131.7, 129.6, 128.8, 126.8, 117.6, 115.3, 114.6, 114.2, 112.9, 112.5, 55.3, 51.6, 45.0, 42.8, 38.7. HRMS(ESI) m/z: calcd for $C_{19}H_{17}N_3O$ $[M+H]^+$ 304.1444, found 304.1442.

4.3.6. *3-(4-ethoxyphenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ac)**

Pale yellow solid, m.p. 138-140 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50-7.52s (m, 1H), 7.36-7.38 (m, 2H), 7.30-7.34 (m, 1H), 6.94-6.96 (m, 2H), 6.79-6.82 (m, 1H), 6.72-6.74 (m, 1H), 4.06 (q, *J* = 6.8 Hz, 2H), 3.91 (t, *J* = 11.9 Hz, 1H), 3.56 (dd, *J* = 11.4, 3.5 Hz, 1H), 3.48 (dd, *J* = 11.4, 3.5 Hz, 1H), 3.02 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.8, 144.0, 133.5, 131.7, 129.6, 128.8, 126.6, 117.6, 115.6, 115.1, 114.2, 112.5, 63.6, 51.6, 45.0, 42.8, 38.7, 14.7. HRMS(ESI) m/z: calcd for $C_{20}H_{19}N_3O$ $[M+Na]^+$ 340.1420, found 340.1420.

4.3.7. *3-(3-methoxyphenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ad)**

White solid, m.p. 160-163 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52-7.54(m, 1H), 7.33-7.38 (m, 2H), 7.04-7.06 (m, 1H), 7.00-7.02(m, 1H), 6.96-6.99 (m, 1H), 6.80-6.84 (m, 1H), 6.73-6.75 (m, 1H), 3.93 (t, J = 11.9 Hz, 1H), 3.83 (s, 3H), 3.57 (dd, J = 11.2, 3.9 Hz, 1H), 3.52 (dd, J = 11.2, 3.9 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.1, 143.0, 135.3, 130.7, 129.2, 128.6, 127.8, 119.7, 116.6, 113.9, 113.2, 111.5, 54.3, 50.5, 44.7, 41.3, 37.7. HRMS(ESI) m/z: calcd for $C_{19}H_{17}N_3O$ $[M+Na]^+$ 326.1264, found 326.1268.

4.3.8. *1-methyl-3-(m-tolyl)-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ae)**

White solid, m.p. 102-104 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.53 (m, 1H), 7.42-7.43 (m, 3H), 7.32-7.34 (m, 2H), 6.79-6.82 (m, 1H), 6.73-6.74 (m, 1H), 3.95 (t, J = 11.9 Hz, 1H), 3.55 (dd, J = 11.5, 3.8 Hz, 1H), 3.49 (dd, J = 11.5, 3.8 Hz, 1H), 3.02 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.0, 144.0, 131.2, 129.5, 129.1, 127.9, 125.4, 117.6, 115.2, 114.1, 113.8, 112.5, 51.5, 45.6, 42.4, 38.7, 21.2. HRMS(ESI) m/z: calcd for $C_{19}H_{17}N_3$ $[M+Na]^+$ 310.1315, found 310.1312.

4.3.9. *3-([1,1'-biphenyl]-4-yl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3af)**

White solid, m.p. 147-149 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65-7.67 (m, 2H), 7.60-7.61 (m, 2H), 7.52-7.54 (m, 3H), 7.44-7.46 (m, 2H), 7.32–7.38 (m, 2H), 6.81-6.83 (m, 1H), 6.74-6.76 (m, 1H), 3.99 (t, J = 11.9 Hz, 1H), 3.65 (dd, J = 11.4, 3.7 Hz, 1H), 3.55 (dd, J = 11.4, 3.7 Hz, 1H), 3.04 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 144.0, 142.3, 140.2, 133.7, 131.8, 128.8, 127.8, 127.1, 117.7, 115.2, 114.1, 112.9, 112.6, 51.5, 45.4, 42.4, 38.8. HRMS(ESI) m/z: calcd for $C_{24}H_{19}N_3$ $[M+Na]^+$ 372.1471, found 372.1470.

4.3.10. *1-methyl-3-(4-(trifluoromethyl)phenyl)-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ag)**

White solid, m.p. 138-140 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71-7.73 (m, 2H), 7.59-7.60 (m, 2H), 7.52-7.53 (m, 1H), 7.34-7.37 (m, 1H), 6.83-6.86 (m, 1H), 6.76-6.77 (m, 1H), 3.95 (t, J = 11.8 Hz, 1H), 3.69 (d, J = 11.0 Hz, 1H), 3.54 (d, J = 11.0 Hz, 1H), 3.04 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9, 131.9, 129.0, 128.8, 126.2, 118.0, 114.9, 113.8, 112.7, 112.4, 51.2, 45.4, 41.9, 38.8. HRMS(ESI) m/z: calcd for $C_{19}H_{14}F_3N_3$ $[M+Na]^+$ 364.1032, found 364.1035.

4.3.11. *3-(4-fluorophenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ah)**

Pale yellow solid, m.p. 141-143 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.52 (m, 1H), 7.44-7.46 (m, 2H), 7.33-7.35 (m, 1H), 7.13-7.16(m, 2H), 6.81-6.83 (m, 1H), 6.74-6.75 (m, 1H), 3.91 (t, J = 11.8 Hz, 1H), 3.61 (dd, J = 12.3, 3.8 Hz, 1H), 3.50 (dd, J = 12.4, 3.8 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 163.3, 144.0, 131.8, 130.7, 130.2, 128.8, 117.8, 116.2, 115.1, 114.0, 112.6, 51.5, 45.0, 42.5, 38.7. HRMS(ESI) m/z: calcd for $C_{18}H_{14}FN_3$ $[M+H]^+$ 292.1245, found 292.1242.

4.3.12. *3-(4-chlorophenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ai)**

White solid, m.p. 208-210 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50-7.52 (m, 1H), 7.39-7.44 (m, 4H), 7.33 -7.36 (m, 1H), 6.81-6.84 (m, 1H), 6.74-6.75 (m, 1H), 3.90 (t, J = 11.8 Hz, 1H), 3.60 (dd, J = 11.2, 3.8 Hz, 1H), 3.51 (dd, J = 11.2, 3.8 Hz, 1H), 3.02 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9, 135.6, 133.3, 131.8, 129.8, 129.5, 128.8, 117.9, 115.0, 113.9, 112.6, 51.3, 45.1, 42.2, 38.8. HRMS(ESI) m/z: calcd for $C_{18}H_{15}ClN_3$ $[M+H]^+$ 308.0949, found 308.0947.

4.3.13. *3-(4-bromophenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3aj)**

White solid, m.p. 218-220 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58-7.59 (m, 2H), 7.50-7.52 (m, 1H), 7.33-7.36 (m, 3H), 6.81-6.84 (m, 1H), 6.74-6.75 (m, 1H), 3.90 (t, J = 11.8 Hz, 1H), 3.58 (dd, J = 12.4, 3.7 Hz, 1H), 3.50 (dd, J = 12.4, 3.7 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9, 133.8, 132.4, 131.9, 130.1, 128.8, 123.8, 117.9, 115.0, 113.9, 112.6, 51.3, 45.2, 42.1, 38.8. HRMS(ESI) m/z: calcd for $C_{18}H_{14}BrN_3$ $[M+H]^+$ 352.0444, found 352.0441.

4.3.14. *3-(3-chlorophenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ak)**

White solid, m.p. 170-172 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51-7.52 (m, 1H), 7.32–7.45(m, 5H), 6.81-6.84 (m, 1H), 6.74-6.75 (m, 1H), 3.90 (t, J = 11.8 Hz, 1H), 3.58 (d, J = 11.2 Hz, 1H), 3.51 (d, J = 11.2 Hz, 1H), 3.03 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.9, 136.8, 131.9, 130.4, 129.7, 128.8, 128.6, 126.7, 117.9, 114.9, 113.8, 112.7, 51.3, 45.3, 42.1, 38.8. HRMS(ESI) m/z: calcd for $C_{18}H_{14}ClN_3$ $[M+Na]^+$ 330.0768, found 330.0766.

4.3.15. *3-(2-chlorophenyl)-1-methyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3al)**

White solid, m.p. 128-130 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52–7.54 (m, 1H), 7.44–7.48 (m, 3H), 7.28-7.30 (m, 3H), 6.74-6.78 (m, 1H), 6.67-6.68 (m, 1H), 4.34 (dd, J = 10.7, 4.1 Hz, 1H), 3.76 (dd, J = 12.4, 4.1 Hz, 1H), 3.43 (dd, J = 12.5, 4.1 Hz, 1H), 2.95 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.9, 131.8, 130.8, 129.4, 129.2, 127.3, 127.2, 126.7, 116.7, 113.4, 113.2, 111.9, 111.5, 50.5, 39.8, 39.6, 37.6. HRMS(ESI) m/z: calcd for $C_{18}H_{14}ClN_3$ $[M+Na]^+$ 330.0768, found 330.0772.

4.3.16. *3-(4-methoxyphenyl)-1,6-dimethyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3bb)**

White solid, m.p. 192-194 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37-7.39 (m, 2H), 7.30-7.32 (m, 1H), 7.12-7.14 (m, 1H), 6.95-6.97 (m, 2H), 6.64-6.67 (d, J = 8.5 Hz, 1H), 3.83 (s, 3H), 3.56 (dd, J = 12.3, 3.6 Hz, 1H), 3.45 (dd, J = 12.3, 3.6 Hz, 1H), 2.97 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.3, 142.1, 132.4, 129.6, 129.1, 127.3, 127.0, 115.5, 114.6, 114.4, 112.8, 55.3, 51.8, 45.2, 42.76, 38.9, 20.1. HRMS(ESI) m/z: calcd for $C_{20}H_{19}N_3O$ $[M+Na]^+$ 340.1420, found 340.1423.

4.3.17. *3-(4-ethoxyphenyl)-1,6-dimethyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3bc)**

White solid, m.p. 170-172 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35-7.37 (m, 2H), 7.30-7.31 (m, 1H), 7.12-7.14 (m, 1H), 6.93-6.96 (m, 2H), 6.64-6.66 (m, 1H), 4.05 (q, J = 6.9 Hz, 2H), 3.84 (t, J = 11.8 Hz, 1H), 3.55 (dd, J = 11.3, 3.4 Hz, 1H), 3.44 (dd, J = 11.3, 3.4 Hz, 1H), 2.98 (s, 3H), 2.28 (s, 3H), 1.43 (t, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.7, 142.1, 132.4, 129.6, 129.1, 127.2, 126.8, 115.5, 115.1, 114.4, 112.9, 112.8, 63.6, 51.8, 45.3, 42.8, 38.9, 20.1, 14.8. HRMS(ESI) m/z: calcd for $C_{21}H_{21}N_3O$ $[M+Na]^+$ 354.1577, found 354.1579.

4.3.18. *1-ethyl-3-phenyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3ea)**

Pale yellow solid, m.p. 109-112 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54-7.41 (m, 6H), 7.33-7.29 (m, 1H), 6.75-6.78 (m, 2H), 3.96 (t, J = 12.0 Hz, 1H), 3.59-3.49 (m, 3H), 3.37 (dd, *J* = 15.0, 7.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.7, 134.9, 131.7, 129.4, 129.2, 129.1, 128.5, 117.15, 115.2, 114.1, 112.4, 48.9, 45.5, 45.4, 42.51, 11.09. HRMS(ESI) m/z: calcd for $C_{19}H_{17}N_3$ $[M+Na]^+$ 310.1315, found 310.1316.

4.3.19. *1,3-diphenyl-2,3-dihydroquinoline-4,4(1H)-dicarbonitrile* **(3fa)**

Pale yellow solid, m.p. 125-127 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58-7.60 (m, 1H), 7.47-7.50 (m, 2H), 7.47-7.39 (m, 5H), 7.15-7.18 (m, 1H), 6.91-6.85 (m, 1H), 6.69-6.72S (m, 1H), 4.24 (t, *J* = 11.5 Hz, 1H), 3.94 (dd, *J* = 11.4, 3.7 Hz, 1H), 3.75 (dd, *J* = 11.4, 3.7 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 145.7, 143.1, 134.6, 131.1, 130.2, 129.5, 129.2, 129.0, 128.5, 126.4, 126.2, 119.4, 116.4, 115.2, 114.1, 114.0, 51.6, 46.0, 42.5. HRMS(ESI) m/z: calcd for $C_{23}H_{13}N_3$ $[M+Na]^+$ 358.1315, found 358.1318.

4.3.20. *5-phenyl-1,2,4a,5-tetrahydro-[1,4]oxazino[4,3-a]quinoline-6,6(4H)-dicarbonitrile* **(3ga)**

White solid, m.p. 172-174 ^{o}C, ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58-7.40 (m, 6H), 7.40-7.34 (m, 1H), 6.97-6.84 (m, 2H), 4.03 (dd, *J* = 11.4, 3.4 Hz, 1H), 3.87 (m, 1H), 3.78 (d, *J* = 12.8 Hz, 1H), 3.74-3.62 (m, 2H), 3.28 (d, *J* = 10.7 Hz, 1H), 3.17 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.5, 133.2, 131.8, 129.7, 129.4, 129.1, 128.9, 119.5 , 114.6, 114.2, 113.6, 69.9, 66.5, 55.3, 49.4, 45.9. HRMS(ESI) m/z: calcd for $C_{20}H_{17}N_3$ $[M+Na]^+$ 338.1264, found 338.1265.

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