Silica Sulfuric Acid-Catalyzed One-Pot Synthesis, Mechanism, and Fluorescence Properties of 2-(2-arylquinolin-4-(1*H*)-ylidene)malononitriles

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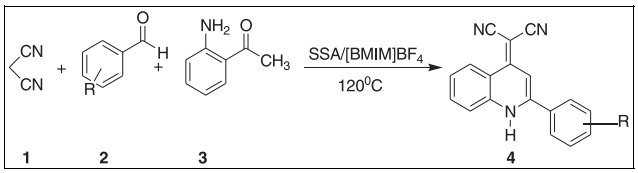

A mild, one-pot synthesis of 2-(2-arylquinolin-4-(1*H*)-ylidene)malononitriles is developed via the silica sulfuric acid-catalyzed tandem condensation of 2-aminoacetophenone with malononitrile and aromatic aldehyde in ionic liquid. It is proposed that malononitrile acted as not only a reactant but also a promoter in the interesting process. The fluorescence properties screening showed a new compound has high fluorescence quantum yield.

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INTRODUCTION

As the analogs of the plant-derived flavone, aza-flavone (2-arylquinolin-4(1*H*)-one) and its derivatives represent a major class of nitrogen-containing heterocycles frequently found in naturally occurring alkaloids and synthetic biologically active molecules [1]. They exhibit antibacterial activity and have emerged as potent antibiotics [2]. More recently, certain 2-arylquinolin-4(1*H*)-one and compounds containing these structures have been studied as potential treatments for a range of diseases [3] as they exhibit antimitotic [4], antiplatelet [3], and antiviral [3] activities and have positive cardiac effects [3]. Quinolin-4-(1*H*)-ylidene malononitriles are also versatile synthetic intermediates because of their facile derivatization [5].

May be due to the passivation between 2-OH and acetyl in it, generally, 2-aminoacetophenone could not be used as reactant to react with aromatic aldehyde to synthesize 2-arylquinolin-4(1*H*)-one via the direct cascade Knovenger condensation–intramolecular Micheal addition such as 2-hydroxyacetophenone, which has higher reactivity.

Although there are many synthesis methods of quinoline derivatives, the synthesis of 2-(2-arylquinolin-4-(1*H*)-ylidene)malononitrile derivatives has not been reported so far. Among the methods reported for the synthesis of quinoline derivatives, the most classical and common one is the condensation of aniline with Meldrum's acid (or its derivatives) and trimethyl orthoformate to afford the corresponding enamine. The enamine intermediate is then cyclized in high-boiling solvents, such as diphenyl ether at high temperature (250°C) or under microwave (300°C) conditions [6–8]. This method suffers from not only the harsh reaction conditions but also the limitation of substrate scope. Alternatively, the mild, base-promoted cyclization of *N*-(*o*-ketoaryl) amides, known as the Camps cyclization, is more attractive and has been widely employed to synthesize a variety of quinolines. However, the synthetic utility of the Camps cyclization is restricted by the limited access to *N*-(*o*-ketoaryl)amides. Some other synthesis of these compounds makes use of transition metals [9], including palladium-catalyzed carbonylation [10], titanium-mediated reductive coupling [11], and ruthenium-catalyzed reduction reactions [12]. Although the scope of copper and palladium-catalyzed amidation of aryl halides is broad in general, aryl halides bearing a ketone functional group have been reported to be incompatible because of the competitive arylation of the ketone enolate [13].

Therefore, the development of more efficient methods for preparing these kind of compounds with milder reaction conditions is desired. Herein, we will describe a new and simple approach to synthesize 2-(2-arylquinolin-4-(1*H*)-ylidene) malononitriles (**4**) via the reaction of malononitrile (**1**) with aromatic aldehydes (**2**) and 2-aminoacetophenone (**3**) in ionic liquid promoted by catalytic amount of silica sulfuric acid (SSA). (Scheme 1).

In the beginning, optimizations of the reaction conditions, including reaction solvents, temperature, and amount of SSA, were investigated using malononitrile (**1**), 3,4-dimethoxybenzaldehyde (**2d**), and 2-aminoacetophenone (**3**) as model reactants. As summarized in Table 1, the results showed that this transformation could not run smoothly except in the presence of SSA (Entries 1–4, Table 1), other acids or bases such as HCl, $NaHSO_3$, or NaOH could not be employed as promoter. The important role of SSA in this reaction may be attributed to its acidity and ability to form H-bonds. The H-bond formation between SSA and NH_2 in 2-aminoacetophenone made SSA act as a

Scheme 1

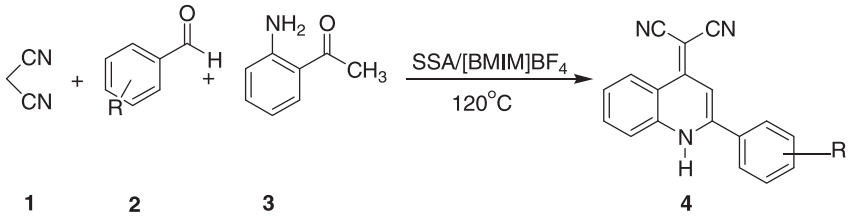


Table 1

Synthesis of **4d** under different conditions.[a]

Entry	Solvent	Catalyst (g)	Time (h)	T (°C)	Yield of **4d** (%)[b]
1	[Bmim]BF_4	HCl (0.5)	6	120	Nr[c]
2	[Bmim]BF_4	$NaHSO_3$ (0.4)	6	120	Nr[c]
3	[Bmim]BF_4	NaOH (0.2)	6	120	Nr[c]
4	[Bmim]BF_4	SSA (0.2)	6	120	69
5	H_2O	SSA (0.2)	6	120	Nr[c]
6	THF	SSA (0.2)	6	120	Nr[c]
7	alcohol	SSA (0.2)	6	120	Nr[c]
8	DMF	SSA (0.2)	6	120	Nr[c]
9	[Bmim]BF_4	SSA (0.05)	6	120	50
10	[Bmim]BF_4	SSA (0.1)	6	120	66
11	[Bmim]BF_4	SSA (0.3)	6	120	66
12	[Bmim]BF_4	SSA (0.4)	6	120	67
13	[Bmim]BF_4	SSA (0.2)	3	120	35
14	[Bmim]BF_4	SSA (0.2)	5	120	45
15	[Bmim]BF_4	SSA (0.2)	8	120	69
16	[Bmim]BF_4	SSA (0.2)	6	80	Nr[c]
17	[Bmim]BF_4	SSA (0.2)	6	100	45
18	[Bmim]BF_4	SSA (0.2)	6	140	67

[a]All reactions were carried out in the scale of 1.0 mmol of 3,4-dimethoxybenzaldehyde **2d**, 1.0 mmol of malononitrile **1**, and 1.0 mmol of 2-aminoacetophenone **3** in 2.0 mL of given solvent.
[b]Isolated yield.
[c]No reaction.

phase transformation catalyst and enhance the solubility of reactants in solvent. Water and classic organic solvents such as tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and alcohol could not be used as efficient solvents. Ionic liquids [BMIM]BF_4 could effectively promote this process (Entries 4–8, Table 1). Increasing catalytic loading of SSA from 0.05 to 0.2 g improved the yield of **4d** from 50% to 69%, which showed that the catalyst concentration plays a major role in the reaction.

However, the yield decreased unexpectedly when the amount of catalyst was over 0.2 g. A possible explanation for the decrease of yield was that the starting materials or the product had been destroyed when an excess amount of SSA was added; thus, 0.2 g of SSA was a suitable choice for optimum yield of **4d** (Entries 9–12). Finally, when the temperature was increased to 120°C with [BMIM]BF_4 as the solvent, the reaction proceeded smoothly (Entries 11 16, and 17, Table 1), However, prolonging the reaction time did not enhance the yield of the product (Entry 18, Table 1).

To apply this reaction to a library synthesis, the scope of the substrates was evaluated with a variety of substituted benzaldehydes (Table 2). It appeared that the electronic nature of substituted groups in benzene ring had not influenced on the yield. It is noteworthy that no remarkable steric hindrance on the reaction was observed; for example, the desired products were obtained in moderate to good yields when the *ortho* substitutes on the benzaldehyde were used (Entries 2 and 10, Table 2).

The fluorescence properties of products were shown in Table 3. The following are clear: (i) Compared with the fluorescence data of 9,10-diphenylanthrance, the blue-shifted $\lambda_{max(ex)}$ (224–229 nm) and red-shifted $\lambda_{max(em)}$ (464–493 nm) of all products afforded wide range of Stokes shifts (160–240 nm). It showed that all products could be excited more easily than 9,10-diphenylanthrance, and the $\lambda_{max(em)}$ of products appeared in the blue light range, which mentioned their value as luminescence or fluorescence probe. (ii) The electro and steric effects of substituted group on aromatic aldehydes have little

Table 2

Synthesis and fluorescence of 2-quinolin-4(1*H*)-ylidene malononitrile.[a]

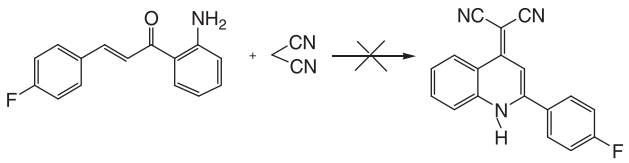
Entry	Compound	R	Yield (%)[b]	Melting point (°C)
1	**4a**	4-OH	75	281–283
2	**4b**	2-MeO	78	>300
3	**4c**	4-MeO	74	>300
4	**4d**	3,4-$(MeO)_2$	69	>300
5	**4e**	3,4,5-$(MeO)_3$	65	>300
6	**4f**	3-F	72	>300
7	**4g**	4-F	76	>300
8	**4h**	3-Br	71	>300
9	**4i**	4-Br	75	>300
10	**4j**	2,4-Cl_2	63	>300

[a]All reactions were carried out in the scale of 0.2 g of silica sulfuric acid in 2 mL ionic liquid at 120°C, and starting materials (**1**:**2**:**3** = 1.0:1.0:1.0 mmol) were completely consumed.
[b]Isolated yield.

influence on the fluorescence properties, which clearly showed that the luminescence of products came from their framework directly. (iii) Only **4h** exhibited stronger fluorescence in DMF with the bigger fluorescence quantum yield than that of 9,10-diphenylanthrance (0.660), which showed its potential application as a new fluorescent probe or luminescence material.

To verify the mechanism, we performed each step individually. First, 1-(2-aminophenyl)-3-(4-fluorophenyl) prop-2-en-1-one, the product of 4-fluorobenzaldehydes (**2g**) and 2-aminoacetophenone (**3**), reacted with malononitrile (**1**) did not give corresponding product (**4g**) (Scheme 2). This may be due to the decrease of carbonyl's reactivity caused by the strong electron-donating ability of *o*-NH_2. Second, when 2-aminoacetophenone (**3**) was treated with malononitrile (**1**) (Scheme 3), we obtain an unexpected product 2-amino-4-methylquinoline-3-carbonitrile (**5**). Its

Scheme 2



X-ray single crystal structure was shown in Figure 1. Compound (**5**) can not react with (**2g**) to afford the final product (**4g**). Finally, the reaction of the Knoevenagel condensation product, 4-fluorophenylidenemalonodinitrile (derived from 4-fluorobenzaldehydes (**2g**) and malononitrile (**1**)) with 2-aminoacetophenone (**3**), did still not give the corresponding product (**4g**) (Scheme 4). These results suggested that this interesting reaction came through an abnormal procedure.

So, we speculated that the formation of the products was via a cascade procedure (Scheme 5): the rapidly condensation of 2-aminoacetophenone with malononitrile gave intermediate **A**, then aromatic aldehyde attacked the $-NH_2$ of **A** to give **B**. Then, the high reactive $-CH_3$ in intermediate **B** caused by two –CN with strong electron-withdrawing effect added to enamine followed by tandem intramolecular cyclization to afford the final product. It also indicated the presence of mutual passivation between $-NH_2$ and carbonyl in 2-aminoacetophenone.

In conclusion, we have disclosed a simple and one-pot method to synthesize 2-(2-arylquinolin-4-(1*H*)-ylidene) malononitriles through a novel domino reaction of arylaldehyde, malononitrile, and 2-aminoacetophenone in ionic liquid by using catalyzed SSA. The mechanism research proposed that malononitrile acted as not only a reactant but also a promoter in the interesting process. The fluorescence properties screening showed one new compound has high fluorescence quantum yield.

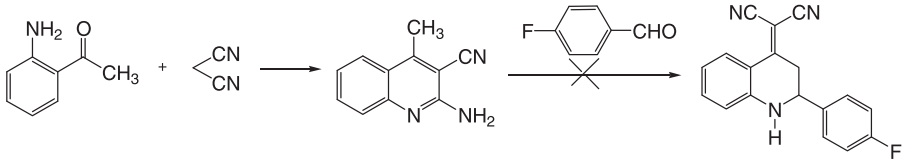
Table 3

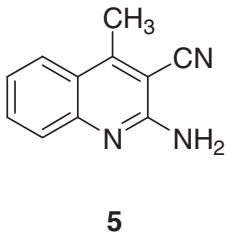
Luminescence Properties of **4**.

Compound	E_{max}(abs) ($M^{-1}.cm^{-1}$)	λ_{abs} (nm)	λ_{em} (nm)	RFI[a]	Stokes shift	Φ[b]
9,10-diphenylan thrance	2.221	261	408	9989	147	0.660
4a	2.379	227	464	123.2	160	0.010
4b	2.261	227	481	78.89	179	0.070
4c	2.017	226	448	261.1	149	0.020
4d	2.576	229	485	63.78	240	0.060
4e	2.547	229	472	56.53	174	0.060
4f	2.144	226	486	3660	177	0.275
4g	2.179	226	477	4137	168	0.344
4h	3.501	237	477	6433	149	0.670
4i	2.420	227	485	5752	172	0.531
4j	2.169	224	493	2549	177	0.211

[a]Relative fluorescence intensity.
[b]Relative fluorescence quantum yield.

Scheme 3





5

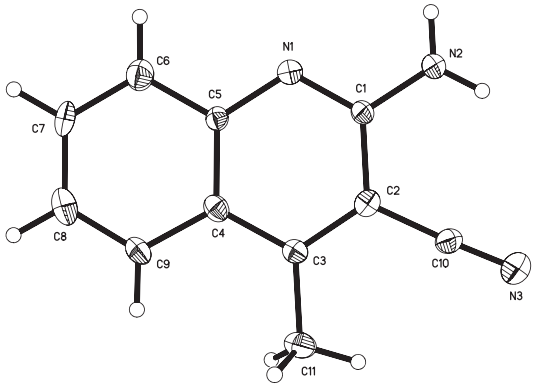
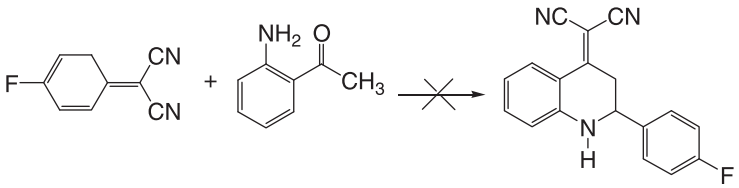
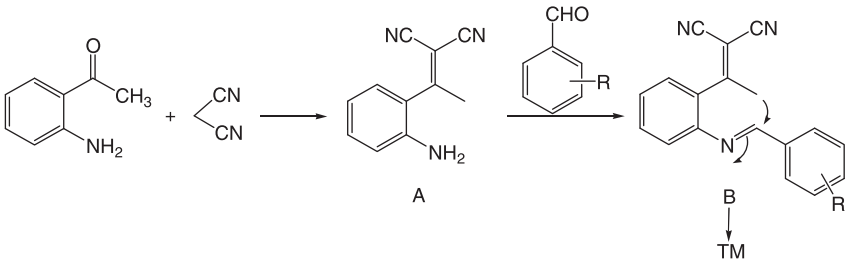


Figure 1. ORTEP diagram of **5**.

Scheme 4



Scheme 5. The possible reaction mechanism.



EXPERIMENTAL

All reagents were purchased from commercial sources and used without further purification. Melting points were determined in the open capillaries and were uncorrected. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm). NMR spectra were measured in DMSO-d_6 with Me_4Si as the internal standards on a Bruker Advance DPX-400 at room temperature. IR spectra were recorded on Bruker FTIR spectrometer; absorbance were reported in cm^{-1}. SSA was equipped with chlorosulfonic acid and silica at room temperature [14].

General procedure for the synthesis of compounds 4. A mixture of substitution-2-hydroxyacetophenone (1.0 mmol), aromatic aldehyde (1.0 mmol), malononitrile (1.0 mmol), and 0.2 g of silica sulfuric acid was stirred in ionic liquid (2 mL) at 120°C. The reaction was monitored by TLC. The crude product was precipitated by the addition of water and purified by flash column chromatography (petroleum ether : ethyl acetate = 3:1). The analytical data for represent compounds are shown below.

4a. 2-(2-(4-hydroxyphenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 10.32 (1H, s), 8.90–8.88 (1H, d, J = 8.0 Hz), 7.96 (1H, s), 7.93 (1H, s), 7.86–7.84 (1H, t), 7.76 (s, 1H), 7.73

(s, 1H), 7.57–7.53 (1H, t), 7.03 (1H, s), 7.01 (1H, s), 6.93 (1H, s). HRMS (ESI): *m/z* calcd for $C_{18}H_{11}N_3O$, 285.0902; found, 285.0874.

4b. 2-(2-(2-methoxyphenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, 281–284°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.14–13.13 (1H, m), 8.93–8.91 (1H, t), 7.86–7.85 (1H, t), 7.64–7.58 (1H, m), 7.30–7.28 (1H, d, J = 8.0 Hz), 7.20–7.16 (1H, t), 6.88 (1H, s), 3.85 (1H, s). IR (cm^{-1}): 3261, 3167, 2998, 2197, 1629, 1595, 1516, 1433, 1335, 1306, 1260, 1159, 1014. 853, 775. HRMS (ESI): *m/z* calcd for $C_{19}H_{13}N_3O$, 299.1059; found, 299.0910.

4c. 2-(2-(4-methoxyphenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.90 (1H, s), 8.89–8.87 (1H, d, J = 8.0 Hz), 7.96–7.94 (1H, d, J = 8.0 Hz), 7.87–7.83 (3H, m), 7.57–7.53 (1H, m), 7.22 (1H, s), 7.20 (1H, s), 6.94 (1H, s), 3.88 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.82, 153.29, 147.64, 138.19, 133.03, 129.51, 125.10, 124.60. 124.22, 120.13, 119.02, 114.77, 105.12, 55.59, 46.92. IR (cm^{-1}): 3263, 3162, 3002, 2197, 1597, 1517, 1441, 1343, 1281, 1186, 1156, 1027. HRMS (ESI): *m/z* calcd for $C_{19}H_{13}N_3O$, 299.1059; found, 299.1038.

4d. 2-(2-(3,4-dimethoxyphenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.87 (1H, s), 8.91–8.89 (1H, d, J = 8.4 Hz), 7.95–7.93 (1H, d, J = 8.0 Hz), 7.89–7.87 (1H, t), 7.59–7.54 (1H, m), 7.46–7.44 (2H, m), 7.24–7.21 (1H, d, J = 12.0 Hz), 6.96 (1H, s), 3.90 (3H, s), 3.87 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.23, 151.51, 148.95, 147.85, 138.09, 133.03, 125.11, 124.76, 124.21, 121.15, 120.06, 119.01, 112.06, 115.05, 105.37, 55.85, 55.78, 46.90. IR (cm^{-1}): 3258, 3210, 3161, 3140, 3002, 2950, 2839, 3193, 1631, 1603, 1583, 1516, 1449, 1023, 833, 776. HRMS (ESI): *m/z* calcd for $C_{20}H_{15}N_3O_2$, 329.1164; found, 329.1175.

4e. 2-(2-(3,4,5-trimethoxyphenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.94 (1H, s), 8.90–8.88 (1H, d, J = 8.0 Hz), 7.93–7.86 (2H, m), 7.59–7.55 (1H, m), 7.15 (2H, s), 6.95 (1H, s), 3.91 (6H, s), 3.77 (3H, s). ^{13}C NMR (100 MHz, DMSO-d_6): δ 153.32, 153.27, 148.03, 140.01, 138.02, 133.16, 128.22, 125.26, 124.25, 120.15, 119.04, 105.97, 105.73, 60.25, 55.34, 47.44. IR (cm^{-1}): 3266, 3177, 3205, 2991, 2972, 2942, 2835, 2193, 2167, 1628, 1517, 1434, 1357, 1320, 834, 774. HRMS (ESI): *m/z* calcd for $C_{21}H_{17}N_3O_3$, 359.1270; found, 359.1248.

4f. 2-(2-(3-fluorophenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (1H, s), 8.62–8.60 (1H, d, J = 8.0 Hz), 8.24–8.21 (1H, d, J = 12.0 Hz), 7.65–7.59 (2H, m), 7.53–7.51 (1H, d, J = 8.0 Hz), 7.40–7.32 (2H, m), 6.97 (2H, s). IR (cm^{-1}): 3475, 3402, 3330, 3179, 2209, 2098, 1647, 1606, 1520, 1431, 786, 761. HRMS (ESI): *m/z* calcd for $C_{18}H_{10}FN_3$, 287.0859; found, 287.0917.

4g. 2-(2-(4-fluorophenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.12(1H, s), 8.59–8.57 (1H, d, J = 8.0 Hz), 8.49–8.45 (1H, m), 8.24 (1H, s), 7.65–7.61 (1H, q), 7.53–7.51 (1H, d, J = 8.0 Hz), 7.43–7.35 (2H, q), 7.35–7.31 (1H, t), 6.92 (1H, s). IR (cm^{-1}): 3494, 3373, 3128, 3060, 2969, 2897, 2205, 1649, 1513, 1435, 1226, 829, 806, 765. HRMS (ESI): *m/z* calcd for $C_{18}H_{10}FN_3$, 287.0859; found, 287.0803.

4h. 2-(2-(3-bromophenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.68 (1H, s), 8.67 (1H, s), 8.56–8.54 (1H, d, J = 8.0 Hz), 8.52–8.50 (1H, d, J = 8.0 Hz), 8.20 (1H, s), 7.99 (1H, s), 7.81–7.78 (3H, m), 7.66–7.61 (1H, m), 7.59–7.57 (3H, m), 7.38–7.36 (1H, m). IR (cm^{-1}): 6285, 3202, 3063, 2225, 1611, 1565, 1426, 1330, 757. HRMS (ESI): *m/z* calcd for $C_{18}H_{10}BrN_3$, 347.0855; found, 347.0919.

4i. 2-(2-(4-bromophenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.16 (1H, s), 8.59–8.57 (1H, d, J = 8.0 Hz), 8.38–8.36 (1H, d, J = 8.0 Hz), 8.26 (1H, s), 7.79 (1H, s), 7.77 (1H, s), 7.65–7.61 (1H, t), 7.53–7.51 (1H, d, J = 8.0 Hz), 7.35–7.31 (1H, t), 6.96 (2H, s).IR (cm^{-1}): 3488, 3329, 3165, 3129, 3058, 2206, 1627, 1605, 1432, 823, 807, 761. HRMS (ESI): *m/z* calcd for $C_{18}H_{10}BrN_3$, 347.0855; found, 347.19104.

4j. 2-(2-(2,4-dichlorophenyl)quinolin-4(1H)-ylidene) malononitrile. Yellow crystal, >300°C, ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.22 (1H, s), 8.34 (1H, t), 7.95 (1H, s), 7.84–7.81 (1H, d, J = 12.0 Hz), 7.72–7.65 (2H, m), 7.63–7.62 (1H, d, J = 4.0 Hz), 7.62–7.60 (1H, m), 7.54–7.52 (1H, d, J = 8.0 Hz), 7.54–7.52 (1H, d, J = 8.0 Hz), 7.31–7.28 (1H, d, J = 12.0 Hz), 7.00–6.98 (2H, t) IR (cm^{-1}): 3329, 3204, 2203, 1628, 1606, 1579, 1277, 808, 760. HRMS (ESI): *m/z* calcd for $C_{18}H_9Cl_2N_3$, 337.0314; found, 337.0387.

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