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Aqueous heterogeneous synthesis of polysubstituted 2,6-dicyanoanilines via combined microwave and ultrasound-assisted multicomponent reaction

Abstract: A series of polysubstituted 3-aryl-2,6-dicyanoaniline derivatives were synthesized by one-pot multicomponent heterogeneous domino reaction of aromatic aldehyde, malononitrile and cyclic ketone under combined microwave and ultrasound irradiation in water. This facile approach reduces the reaction time and energy consumption and increases the yield and selectivity of the product.

Keywords: 2,6-dicyanoanilines; microwave; multicomponent reaction; ultrasound; water.

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1 Introduction

The development of high-throughput screening, domino processes and multicomponent reactions plays more and more important roles in modern synthetic organic chemistry for the formation of carbon-carbon and carbon-heteroatom bonds [1–7]. Such efficient and atom-economic reactions are particularly useful for constructing highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings in both solvents and reagents [8–11]. Activation of the organic reaction with microwave and ultrasound constitutes an important domain of modern organic chemistry [12–18]. This is mainly due to the fact that the power of microwave and ultrasound can reduce the reaction time, minimize energy consumption and increase the yield and selectivity of the product.

3-Aryl-2,6-dicyanoanilines with an amino group flanked by two cyano substituents not only occupy a unique place in various classes of organic compounds [19, 20] but also display interesting biological activities [21–23]. 2,6-Dicyanoanilines comprising one electron donor and two electron acceptors are typical acceptor-donor-acceptor (A-D-A) systems for the extensive study of photoinduced intramolecular electron transfer [24, 25]. The potential applications of these molecular systems, artificial photosynthetic systems [26], molecular electronic devices [27] and materials presenting semiconducting or nonlinear optical properties [28], were reported extensively. These compounds were reported to be prepared from malononitrile and α,β-unsaturated ketones, but the yields were very poor [29, 30]. The reaction between arylidenemalonodinitriles and 1-arylethylidenemalonodinitriles could also give 2,6-dicyanoanilines in the presence of base [31, 32]. Wang et al. developed the microwave-assisted one-pot synthesis of polysubstituted 3-aryl-2,6-dicyanoanilines from aldehydes, ketones and malononitrile. However, the yields of products were in the range of 50–63%, and only a few products from cycloketones have been reported [33]. In addition, most of the above-mentioned reactions were performed in organic solvent or in the presence of surfactant. Due to the environmental and economic concerns, water as a green reaction medium alternative to organic solvents has attracted more and more attention [34–36].

2 Experimental

2.1 General information

All solvents and reagents were purchased from commercial sources and were used without prior purification. All combined microwave and ultrasound irradiation (CMUI) experiments were carried out in a professional TCMC-102 microwave apparatus (Nanjing Lingjiang Technological Development Company, China) operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 500 W and an FS-250 professional ultrasound apparatus (Shanghai S. X. Ultrasonics, China) operating at a frequency of 20 KHz with controllable irradiation power from 10 to 100 W. The reactions were carried out in a 15-ml two-necked Pyrex flask, placed in the microwave cavity with the tip of the detachable horn immersed just under the liquid surface. The reaction mixture was irradiated at reflux condition using microwave (100 W) and ultrasound (50 W). Thin-layer chromatography (TLC) analysis was performed on aluminum-backed plates (SIL G/UV254). The products were purified by filtration or silica gel (200–300 mesh) column chromatography and were identified by ^{1}H nuclear magnetic resonance (NMR) ($CDCl_3$, 400 MHz) and gas chromatography-mass spectrometry (GC-MS). All the new products were identified by ^{1}H and ^{13}C NMR ($CDCl_3$, 400 MHz) and high-resolution mass spectroscopy (EI).

2.2 General procedure for preparation of 3-aryl-2,6-dicyanoanilines

A mixture of aromatic aldehyde (2.0 mmol), cyclic ketone (2.0 mmol), malononitrile (4.4 mmol), NaOH (3.0 mmol) and water (5.0 ml) was subjected to CMUI (microwave: 100 W; ultrasound: 50 W) until nearly complete conversion of aromatic aldehyde as monitored by TLC. The crude product was collected by filtration and purified by recrystallization from ethanol or column chromatography on silica gel with 1:5 ethyl acetate/petroleum (v/v). All of the products were identified by ^{1}H NMR ($CDCl_3$, 400 MHz), ^{13}C NMR, high resolution MS (HRMS) or GC-MS.

2.3 5-Amino-7-(4-fluorophenyl)-2,3-dihydro-1*H*-indene-4,6-dicarbonitrile (4b)

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.36–7.39 (m, 2H), 7.19 (t, *J*=8.6 Hz, 2H), 5.10 (s, 2H), 3.13 (t, *J*=7.6 Hz, H), 2.72 (t, *J*=7.4 Hz, 2H), 2.08–2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=164.3, 161.8, 154.9, 151.3, 145.0, 133.1, 132.5, 130.4, 116.0, 115.2, 95.3, 93.4, 34.0, 31.9, 24.7; HRMS (EI): calcd for $C_{17}H_{12}FN_3$ (M^+) 277.1015, found 277.1017.

2.4 5-Amino-7-(3-bromophenyl)-2,3-dihydro-1*H*-indene-4,6-dicarbonitrile (4c)

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.60 (d, *J*=7.6 Hz, 1H), 7.28–7.40 (m, 3H), 5.15 (s, 2H), 3.13 (t, *J*=7.6 Hz, 2H), 2.73 (t, *J*=7.4 Hz, 2H), 2.08–2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=115.0, 151.4, 144.2, 138.5, 133.0, 132.2, 131.3, 130.3, 127.1, 122.7, 95.1, 93.7, 34.0, 31.8, 24.7; HRMS (EI): calcd for $C_{17}H_{12}BrN_3$ (M^+) 337.0215, found 337.0209.

2.5 5-Amino-7-(benzo[*d*][1,3]dioxol-5-yl)-2,3-dihydro-1*H*-indene-4,6-dicarbonitrile (4g)

^{1}H NMR (400 MHz, $CDCl_3$): δ=6.84–6.97 (m, 3H), 5.09 (s, 2H), 3.12 (t, *J*=7.6 Hz, 2H), 2.76 (t, *J*=7.4 Hz, 2H), 2.07–2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.7, 151.4, 148.3, 147.8, 145.7, 133.1, 130.2, 122.6, 116.4, 108.9, 101.5, 95.4, 93.0, 34.0, 32.0, 24.7; HRMS (EI): calcd for $C_{18}H_{13}N_3O_2$ (M^+) 303.1008, found 303.1007.

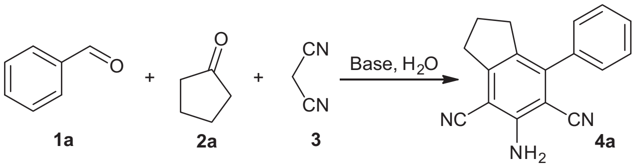
2.6 2-Amino-4-(3-bromophenyl)-5,6,7,8-tetrahydronaphthalene-1,3-dicarbonitrile (4j)

^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61 (d, *J*=7.6 Hz, 1H), 7.37–7.41 (m, 2H), 7.18 (d, *J*=7.6 Hz, 1H), 5.05 (s, 2H), 2.98 (t, *J*=7.6 Hz, 2H), 2.22–2.37 (m, 2H), 1.64–1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=149.6, 148.3, 147.3, 139.0, 132.0, 131.5, 130.5, 127.0, 122.8, 115.4, 97.2, 96.3, 29.6, 27.3, 22.4, 21.8; HRMS (EI): calcd for $C_{18}H_{14}BrN_3$ (M^+) 351.0371, found 351.0360.

3 Results and discussion

3.1 The reaction of benzaldehyde, cyclopentanone and malononitrile

Previous work from our group has demonstrated that CMUI gave significant rate enhancements and improved yields in aqueous organic reactions [37–42]. Herein, we



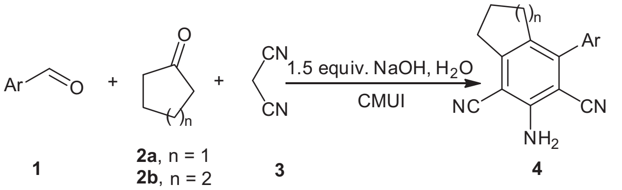
Entry	Base (equiv.)	Method	Time	Yield (%)[b]
1	K_2CO_3 (2)	CMUI (MW 100 W+US 50 W)	90 s	42
2	$NaHCO_3$ (3)	CMUI (MW 100 W+US 50 W)	90 s	37
3	K_3PO_4 (1.5)	CMUI (MW 100 W+US 50 W)	90 s	40
4	NEt_3 (3)	CMUI (MW 100 W+US 50 W)	90 s	45
5	KOH (1.5)	CMUI (MW 100 W+US 50 W)	90 s	71
6	NaOH (1.5)	CMUI (MW 100 W+US 50 W)	90 s	73
7	NaOH (1.5)	CMUI (MW 50 W+US 50 W)	90 s	47
8	NaOH (1.5)	CMUI (MW 200 W+US 50 W)	90 s	70
9	NaOH (1.5)	CMUI (MW 100 W+US 25 W)	90 s	60
10	NaOH (1.5)	CMUI (MW 100 W+US 100 W)	90 s	69
11	NaOH (1.5)	Ultrasound (50 W)+oil bath reflux	1 h	40
12	NaOH (1.5)	Microwave (100 W) under reflux	15 min	43
13[c]	NaOH (1.5)	Conventional heating under reflux	8 h	46

Table 1 Optimization of base in the synthesis of compound **4a.**[a]

[a] Reactions were performed under reflux using benzaldehyde (2.0 mmol), cyclopentanone (2.0 mmol), malononitriles (4.4 mmol), base and water (5 ml). [b] Isolated yields. [c] Solvent: CH_3CH_2OH.

report the use of this simple and facile approach for the multicomponent synthesis of polysubstituted 3-aryl-2,6-dicyanoanilines derivatives.

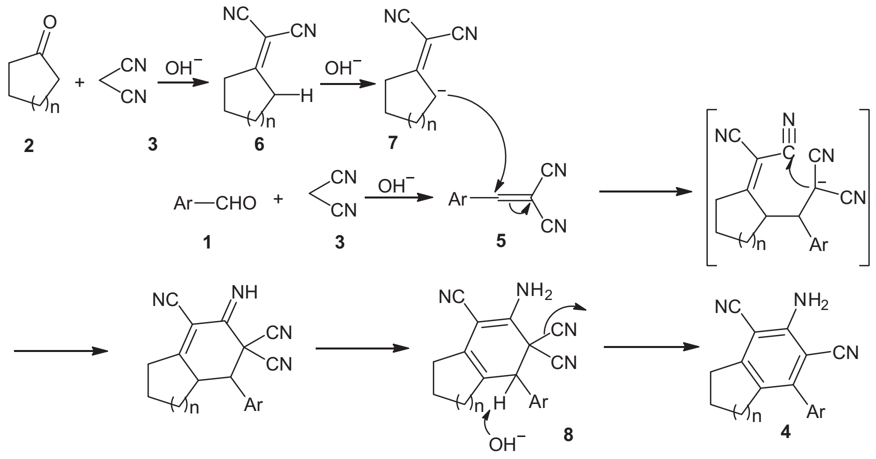
In our initial study, using a mixture of benzaldehyde **1a**, cyclopentanone **2a** (1.0 equiv.) and malononitrile (2.2 equiv.) as a model system, we focused on the evaluation of various bases under CMUI (Table 1, entries 1–6). From the result, we found that NaOH and KOH were the most effective catalysts that selectively produced the desired products in high yields (entries 5 and 6). We subsequently examined the efficiency of the power of microwave and ultrasound irradiation (entries 6–10). The results showed



Entry	Ar	Ketone	Time (s)	Product 4	Yield (%)[b]
1	C_6H_5	Cyclopentanone	90	**4a**	73
2	4-FC_6H_4	Cyclopentanone	90	**4b**	77
3	3-BrC_6H_4	Cyclopentanone	90	**4c**	74
4	2,4-diClC_6H_3	Cyclopentanone	120	**4d**	69
5	4-$CH_3C_6H_4$	Cyclopentanone	120	**4e**	67
6	4-$CH_3OC_6H_4$	Cyclopentanone	110	**4f**	73
7	3,4-$(OCH_2O)C_6H_3$	Cyclopentanone	100	**4g**	71
8	C_6H_5	Cyclohexanone	80	**4h**	76
9	4-FC_6H_4	Cyclohexanone	80	**4i**	81
10	3-BrC_6H_4	Cyclohexanone	80	**4j**	78
11	2,4-diClC_6H_3	Cyclohexanone	120	**4k**	72
12	4-$CH_3C_6H_4$	Cyclohexanone	110	**4l**	73
13	4-$CH_3OC_6H_4$	Cyclohexanone	90	**4m**	78

Table 2 Synthesis of polysubstituted 3-aryl-2,6-dicyanoanilines under CMUI.[a]

[a] A mixture of aldhyde (2.0 mmol), cyclic ketone (2.0 mmol), malononitrile (4.4 mmol), NaOH (3.0 mmol) and water (5.0 ml) was subjected to CMUI (microwave: 100 W; ultrasound: 50 W) for the indicated time (monitored by TLC) under reflux. [b] Isolated yields.



Scheme 1 Proposed reaction pathway.

that a combination of microwave irradiation at 100 W and ultrasound irradiation at 50 W gave the highest yield (entry 6). To show the usefulness of CMUI, a control experiment was carried out using the same amount of reactants (entries 11–13). The results clearly show that combined microwave and ultrasound irradiation achieved the best results in terms of both reaction time and yield. However, the conventional reaction using ethanol as the solvent went to completion with many by-products, and only 46% of desired product was obtained (entry 13). This dramatic acceleration effect of CMUI may be attributed to a combination of enforced heat transfer due to microwave irradiation and intensive mass transfer at phase interfaces caused by sonication.

3.2 The scope of the reactions

Having the optimized conditions in hand (Table 1, entry 6), we next investigated the scope and limitation of the process with variously substituted aldehydes **1** and cyclic ketones **2** (Table 2). A good yield of polysubstituted 3-aryl-2,6-dicyanoanilines were obtained, applying both electron-withdrawing (such as **1b**, **1c**, **1d**) and electron-donating (such as **1e**, **1f**, **1g**) aromatic aldehydes. Meanwhile, both cyclopentanone and cyclohexanone are well tolerated.

4 Proposed reaction pathway

According to the literature [31] and based on our experiment, the formation of 3-aryl-anthranilodinitrile derivatives could be explained by the possible reaction procedure (Scheme 1). The first step of this process involves the *in situ* condensation of an aldehyde and ketone with malononitrile resulting in the formation of the corresponding condensation products **5** and **6**. It is noteworthy that the intermediate **5** can be determined by GC-MS. Then, compound **7** undergoes Michael addition to **5** followed by cyclization to form compound **8**, which under the base condition leads to polysubstituted 3-arylanthranilodinitrile **4.**

5 Conclusions

In conclusion, a rapid and energy-efficient protocol using simultaneous microwave and ultrasound irradiation has been developed for the synthesis of polysubstituted 3-aryl-2,6-dicyanoaniline from aromatic aldehyde, malononitrile and cyclic ketone in water. This method is simple, fast and environmentally friendly. The development of this combination technique might open an extremely promising new area in the field of aqueous organic synthesis.

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