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Efficient synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by dodecylbenzenesulfonic acid in aqueous media under ultrasound irradiation

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Abstract: Synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives catalyzed by dodecylbenzenesulfonic acid was carried out in 80%-92% yields at 40-42 °C within 1-2 h in aqueous media *via* one-pot three-component condensation of isatoic anhydride, aromatic aldehyde and amine under ultrasound irradiation. Convenient work-up procedures, mild reaction conditions, avoiding the use of organic solvents, and friendly to environment are the salient features of this protocol.

Keywords: 2,3-Dihydroquinazolin-4(1*H*)-one; Catalysis; Condensation; Aqueous media; One-pot synthesis; Ultrasound irradiation

1. Introduction

2,3-Dihydroquinazolin-4(1*H*)-one derivatives are an important class of fused heterocyclic compounds and have been found to posses valuable biological and pharmacological activities [1]. They may display a wide range of medicinal properties involving antibacterial [2], anticancer [3], antifungal [4], antitumor [5], anticonvulsant [6], analgesic [7], antihypertension [8], anti-diabetes [9], and some of them have been shown to act as potent HIV-1 reverse transcriptase inhibitors [10]. In addition, quinazolinone core scaffold can also be found in some important natural alkaloids [11]. In view of their widely increased application value, investigation on the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives has attracted special attention in recent years for the organic chemists [12].

The synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives was previously carried out by multi-step reactions [13], which suffered from lengthy procedures or harsh conditions. Comparing with the traditional methods, multi-component reactions (MCRs) can produce the desired products in a single step and also the diversity could be achieved simply by varying the reacting components, which has advantages such as milder reaction conditions, lower cost, shorter reaction time, energy conservation and environment friendly [14]. In 2005, Salehi *et al* [15] reported a one-pot three-component reaction for the preparation of 2,3-dihydroquinazolin-

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4(1*H*)-ones *via* the condensation of isatoic anhydride, aromatic aldehyde and amine catalyzed by silica sulfuric acid or $KAl(SO_4)_2 \cdot 12H_2O$ in water and ethanol. Then, similar procedures for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones were presented, using various catalysts such as ethylenediamine diacetate [16], $Ga(OTf)_3$ [17], citric acid [18], silica-bonded *N*-propylsulfamic acid [19], silica-bonded *S*-sulfonic acid [20], silica sulfuric acid [21], $SrCl_2 \cdot 6H_2O$ [22], MCM-41-SO_3H [23], magnetic Fe_3O_4 nanoparticles [24], $Al(H_2PO_4)_3$ [25], montmorillonite K-10 [26], Al/Al_2O_3 nanoparticles [27], molecular iodine [28], *p*-toluenesulfonic acid [29], and ionic liquid [30], or with the aid of microwave in the presence of Amberlyst-15 [31] or Cu-CNTs [32]. However, some of these methods associated with certain drawbacks such as expensive and large amount of catalyst, using organic solvent, longer reaction time and lower yields. So, the development of a green, convenient, efficient method for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones is still in demand.

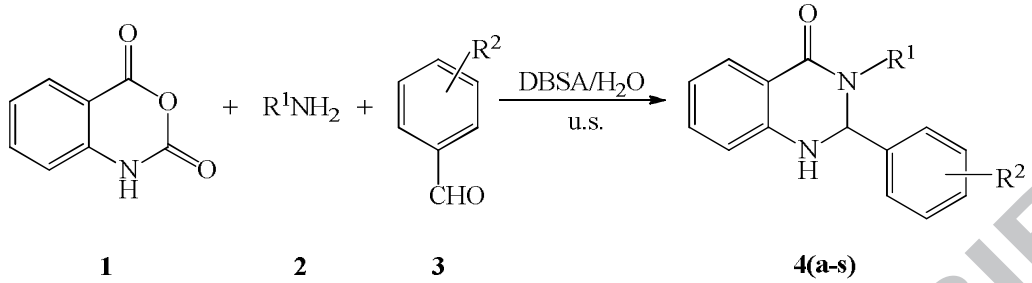
With the development of green chemistry, the use of non-toxic and environmentally friendly organic solvent is of much interest. As the most abundant, cheapest, and environmentally friendly solvent, water offers many practical and economic advantages in organic synthesis including low cost, safe handling and environmental compatibility. Moreover, water can also exhibit unique reactivity and selectivity in some organic reactions, which is different from those in conventional organic solvents [33]. Many organic reactions in aqueous media have been described in the literatures in the past few years [34].

Dodecylbenzenesulfonic acid (DBSA) is an anionic surfactant, which can act as a combined Brønsted acid surfactant-catalyst. It is both an acid catalyst to activate the substrate molecules and a surfactant to form stable colloidal dispersion with water-insoluble substrates [35]. Organic reactions catalyzed by proton acid can be carried out successfully in the presence of water using DBSA [36].

Ultrasound irradiation has been considered as a clean and useful protocol in organic synthesis. Compared with those traditional methods, ultrasound-assisted organic synthesis has the distinguishing features including short reaction times, high yields and mild conditions [37]. In recent years, the development of organic reactions catalyzed by DBSA under ultrasound irradiation in aqueous media has become an area of intense research. Our laboratory has improved some synthesis of organic compounds using DBSA as catalyst in aqueous media under ultrasound irradiation，and good results were achieved [38].

To the best of our knowledge, there are no literature examples of the synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by DBSA under ultrasound irradiation. Herein we wish to report an efficient procedure to synthesize 2,3-dihydroquinazolin-4(1*H*)-ones through a one-pot three-component condensation of isatoic anhydride, aromatic aldehyde and amine using DBSA as catalyst in aqueous media under

ultrasound irradiation (**Scheme 1**).



1 **2** **3** **4(a-s)**

Scheme 1. Synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives

2. Experimental

2.1. Apparatus, materials and analysis

All chemicals were obtained from commercial suppliers. The liquid aldehydes were distilled before using and others were used without further purification. Melting points were taken on a TECH X-4 apparatus and were uncorrected. The NMR spectra was measured on a Bruker AVANCE 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C) spectrometer using TMS as the internal standard with $CDCl_3$ or DMSO-d_6 as solvent. Mass spectrometric data were determined using a Bruker apex ultra 7.0 T spectrometer. Sonication was performed using a Shanghai Branson-BUG25-06 or BUG40-06 ultrasonic cleaner (with a frequency of 25 or 40 kHz and a nominal power 250 W), the total acoustic power injected into the sample solution was found to be 0.63 and 1.63 W respectively by calorimetry [39].

2.2. General procedure for synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1H)-ones

A 25 mL round-bottomed flask was charged with isatoic anhydride (**1**, 1 mmol), amine (**2**, 1.2 mmol), aromatic aldehyde (**3**, 1 mmol), dodecylbenzenesulfonic acid (0.2 mmol), water (5 mL), and located in the ultrasonic cleaner, where the surface of reactants was slightly lower than the level of the water in the cleaning bath. The mixture was irradiated in the water bath of the ultrasonic cleaner at 40-42 ^{o}C for the period as indicated in **Table 3**. The temperature of the water bath was controlled by addition or removal of circulated water from ultrasonic bath. The progress of the reaction was monitored by TLC (petroleum ether: ethyl acetate = 2 : 1, V/V). After completion of the reaction, the precipitation was filtered and subsequently washed with water (10 mL) and ethanol to get the crude solid products. The pure products were obtained by recrystallization from ethanol. For product **4s**, after the reaction completed, the mixture was extracted by ethyl acetate (3×3 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. Ethyl acetate was evaporated under reduced pressure to give the crude product. Pure product **4s** was obtained by recrystallization from the mixture of ethanol

and petroleum (1 : 2, V/V).

The products **4a-f, 4h-j and 4q-s** were known compounds, their authenticity was established by ^{1}H NMR, ^{13}C NMR and their melting points compared with that reported in literatures. The rest products (**4g, 4k-p**) were unknown and established by their ^{1}H NMR, ^{13}C NMR and HRMS.

*Compound **4a***

2-Phenyl-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H 6.30 (d, *J* = 2.0 Hz, 1H, CH), 6.72 (t, *J* = 7.5 Hz, 1H, Ph), 6.77 (d, *J* = 8.1 Hz, 1H, Ph), 7.19 (t, *J* = 7.2 Hz, 1H, Ph), 7.26-7.35 (m, 8H, Ph), 7.39 (d, *J* = 7.5 Hz, 2H, Ph), 7.67 (s, 1H, NH), 7.74 (d, *J* = 7.7 Hz, 1H, Ph). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C 73.1, 115.3, 115.8, 118.0, 126.5, 126.7, 127.1, 128.4, 128.8, 128.9, 129.1, 134.2, 141.2, 141.3, 147.1, 162.7.

*Compound **4b***

2-(4-Chlorphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H 6.33 (d, *J* = 2.7 Hz, 1H, CH), 6.74 (t, *J* = 7.5 Hz, 1H, Ph), 6.77 (d, *J* = 8.1 Hz, 1H, Ph), 7.21 (t, *J* = 7.4 Hz, 1H, Ph), 7.25-7.31 (m, 3H, Ph), 7.35 (t, *J* = 7.8 Hz, 2H, Ph), 7.37-7.43 (m, 4H, Ph), 7.67 (d, *J* = 2.5 Hz, 1H, Ph), 7.71-7.75 (m, 1H，NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C 72.4, 115.3, 115.8, 118.2, 126.6, 126.7, 128.5, 128.9, 129.0, 129.2, 133.4, 134.3, 140.2, 141.1, 146.9, 162.6.

*Compound **4c***

2-(4-Methylphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H 2.22 (s, 3H, CH_3), 6.24 (s, 1H, CH), 6.71 (t, *J* = 7.4 Hz, 1H, Ph), 6.76 (d, *J* = 8.1 Hz, 1H, Ph), 7.11 (d, *J* = 7.7 Hz, 2H, Ph), 7.19 (t, *J* = 7.1 Hz, 1H, Ph), 7.27 (d, *J* = 7.6 Hz, 5H, Ph), 7.33 (t, *J* = 7.6 Hz, 2H, Ph), 7.62 (s, 1H, NH), 7.73 (d, *J* = 7.6 Hz, 1H, Ph). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C 21.1, 72.9, 115.3, 115.9, 117.9, 126.4, 126.6, 127.0, 128.4, 129.1, 129.4, 134.2, 138.0, 138.3, 141.4, 147.0, 162.8.

*Compound **4d***

2-(4-Nitrolphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one, pale yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H 6.50 (s, 1H, CH), 6.76 (dd, *J* = 19.4, 7.0 Hz, 2H, Ph), 7.23 (s, 1H, Ph), 7.31 (d, *J* = 6.7 Hz, 3H, Ph), 7.36 (d, *J* = 6.7 Hz, 2H, Ph), 7.66 (d, *J* = 6.7 Hz, 2H, Ph), 7.74 (d, *J* = 6.4 Hz, 1H, Ph), 7.82 (s, 1H, NH), 8.20 (d, *J* = 7.2 Hz, 2H, Ph). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C 72.2, 115.4, 115.8, 118.5, 124.2, 126.6, 126.7, 128.4, 128.6, 129.3, 134.5, 141.0, 146.6, 147.9, 148.5, 162.4.

*Compound **4e***

2-(4-Methoxyphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H 3.69 (d, J = 1.6 Hz, 3H, OCH_3), 6.23 (s, 1H, CH), 6.72 (t, J = 6.4 Hz, 1H, Ph), 6.76 (d, J = 7.3 Hz, 1H, Ph), 6.86 (d, J = 6.7 Hz, 2H, Ph), 7.19 (d, J = 6.2 Hz, 1H, Ph), 7.23-7.38 (m, 7H, Ph), 7.57 (s, 1H, NH), 7.73 (d, J = 7.4 Hz, 1H, Ph). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C 55.5, 72.8, 114.1, 115.3, 115.8, 117.9, 126.4, 126.8, 128.4, 128.4, 129.0, 133.1, 134.2, 141.3, 147.1, 159.6, 162.8.

*Compound **4f***

2-(2-Chlorphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 5.30 (s, 1H, CH), 6.43 (s, 1H, Ph), 6.57 (d, J = 8.0 Hz, 1H, Ph), 6.86 (t, J = 7.5 Hz, 1H, Ph), 7.18-7.26 (m, 5H, Ph), 7.28 (s, 1H, Ph), 7.32 (t, J = 7.8 Hz, 2H, Ph), 7.37 (d, J = 7.6 Hz, 1H, Ph), 7.58 (d, J = 7.5 Hz, 1H, Ph), 8.03 (d, J = 7.7 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 71.1, 114.9, 116.6, 119.6, 125.8, 126.7, 127.3, 128.2, 129.0, 130.1, 130.3, 131.5, 134.1, 136.8, 140.8, 144.8, 163.3. HRMS *m/z* (ESI): calcd for $[C_{20}H_{15}ClN_2O+H]^+$: 335.0946, found 335.0943.

*Compound **4g***

2-(3,4-Methylenedioxyphenyl))-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, DMSO-d_6): δ_H 5.98 (d, J = 3.2 Hz, 2H, CH_2), 6.22 (d, J = 2.5 Hz, 1H, CH), 6.73 (t, J = 7.4 Hz, 1H, Ph), 6.78 (d, J = 8.0 Hz, 1H, Ph), 6.82 (s, 2H, Ph), 6.95 (s, 1H, Ph), 7.20 (t, J = 7.3 Hz, 1H, Ph), 7.27-7.31 (m, 3H, Ph), 7.35 (t, J = 7.8 Hz, 2H, Ph), 7.59 (d, J = 2.4 Hz, 1H, Ph), 7.74 (d, J = 7.8 Hz, 1H, NH). ^{13}C NMR (150 MHz, DMSO-d_6): δ_C 72.8, 101.7, 107.3, 108.3, 115.3, 115.8, 118.0, 120.8, 126.5, 126.7, 128.4, 129.1, 134.3, 135.1, 141.2, 147.0, 147.7, 147.8, 162.8. HRMS *m/z* (ESI): calcd for $[C_{21}H_{16}N_2O_3+H]^+$: 345.1234, found 345.1230.

*Compound **4h***

2-Phenyl-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.86 (s, 3H, CH_3), 4.69 (s, 1H, CH), 5.70 (s, 1H, Ph), 6.54 (d, J = 8.0 Hz, 1H, Ph), 6.82 (t, J = 7.5 Hz, 1H, Ph), 7.24 (t, J = 7.5 Hz, 1H, Ph), 7.36 (dd, J = 4.7, 1.3 Hz, 3H, Ph), 7.39 (dd, J = 6.5, 2.8 Hz, 2H, Ph), 7.93 (d, J = 7.8 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 32.0, 74.2, 114.1, 115.6, 119.1, 126.8, 128.5, 129.1, 129.5, 133.4, 139.5, 145.4, 163.6.

*Compound **4i***

2-(4-Chlorphenyl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.00 (d, J = 4.8 Hz, 3H, CH_3), 7.02 (d, J = 7.8 Hz, 1H, CH), 7.37 (t, J = 7.5 Hz, 1H, Ph), 7.48 (t, J = 7.7, 1H, Ph), 7.52 (d, J = 8.4 Hz, 2H, Ph), 7.82 (d, J = 8.4 Hz, 2H, Ph), 8.32 (d, J = 7.8 Hz, 1H, Ph), 8.40 (s, 1H, Ph), 8.85

(s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 26.5, 118.5, 126.9, 127.0, 129.6, 130.1, 131.3, 132.2, 133.9, 138.6, 148.9, 160.0, 166.6.

*Compound **4j***

2-(4-Methoxyphenyl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.82 (dd, *J* = 3.2, 1.3 Hz, 3H, CH_3), 3.79 (dd, *J* = 2.7, 1.0 Hz, 3H, OCH_3), 4.59-4.69 (m, 1H, CH), 5.65 (s, 1H, Ph), 6.55 (d, *J* = 7.9 Hz, 1H, Ph), 6.80-6.83 (m, 1H, Ph), 6.85-6.88 (m, 2H, Ph), 7.23-7.25 (m, 1H, Ph), 7.31-7.33 (m, 2H, Ph), 7.92 (t, *J* = 6.5 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 31.7, 55.4, 73.8, 114.1, 163.8, 114.3, 115.5, 118.9, 128.2, 128.4, 131.5, 133.4, 145.6, 160.4. HRMS *m/z* (ESI): calcd for $[C_{16}H_{16}N_2O_2+H]^+$: 269.1285, found 269.1280.

*Compound **4k***

2-(4-Methylphenyl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.34 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 4.52-4.68 (m, 1H, CH), 5.66 (s, 1H, Ph), 6.53 (d, *J* = 8.0 Hz, 1H, Ph), 6.81 (t, *J* = 7.4 Hz, 1H, Ph), 7.16 (d, *J* = 5.5 Hz, 2H, Ph), 7.22-7.25 (m, 1H, Ph), 7.28 (d, *J* = 7.8 Hz, 2H, Ph), 7.93 (d, *J* = 7.8 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 21.2, 31.9, 74.0, 114.1, 115.6, 118.9, 126.7, 128.5, 129.7, 133.4, 136.5, 139.4, 145.5, 163.7. HRMS *m/z* (ESI): calcd for $[C_{16}H_{16}N_2O+H]^+$: 253.1335, found 253.1331.

*Compound **4l***

2-(2-Chlorphenyl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.04 (s, 3H, CH_3), 5.02 (s, 1H, CH), 6.10 (d, *J* = 2.1 Hz, 1H, Ph), 6.51 (d, *J* = 8.1 Hz, 1H, Ph), 6.80 (t, *J* = 7.5 Hz, 1H, Ph), 7.18-7.27 (m, 4H, Ph), 7.41 (d, *J* = 7.8 Hz, 1H, Ph), 7.95 (d, *J* = 7.8 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 32.9, 70.2, 114.5, 115.6, 119.2, 127.2, 127.5, 128.4, 130.2, 130.3, 132.1, 133.5, 136.0, 144.6, 163.8. HRMS *m/z* (ESI): calcd for $[C_{15}H_{13}ClN_2O+H]^+$: 273.0789, found 273.0784.

*Compound **4m***

2-(4-Nitrophenyl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.01 (s, 3H, CH_3), 7.07 (d, *J* = 4.5 Hz, 1H, CH), 7.42 (s, 1H, Ph), 7.52 (s, 1H, Ph), 8.07 (d, *J* = 5.7 Hz, 2H, Ph), 8.31 (d, *J* = 4.9 Hz, 1H, NH), 8.40 (d, *J* = 5.7 Hz, 2H, Ph), 8.55 (s, 2H, Ph). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 26.6, 118.3, 124.4, 127.3, 127.8, 129.6, 131.4, 132.2, 140.5, 148.3, 149.8, 158.9, 166.4. HRMS *m/z* (ESI): calcd for $[C_{15}H_{13}N_3O_3+H]^+$: 284.1030, found 284.1025.

*Compound **4n***

2-(2-Nitrophenyl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, pale yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.02 (s, 3H, CH_3), 7.12 (s, 1H, CH), 7.41 (s, 1H, Ph), 7.51 (s, 1H, Ph), 7.72 (s, 1H, Ph), 7.82 (s, 1H, Ph), 8.10 (d, *J* = 19.0 Hz, 2H, Ph), 8.29 (s, 1H, Ph), 8.57 (s, 1H, Ph), 8.90 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 26.5, 118.7, 124.9, 127.5, 127.7, 129.6, 130.2, 131.2, 132.1, 132.2, 133.8, 148.3, 149.3, 157.3, 166.5. HRMS *m/z* (ESI): calcd for $[C_{15}H_{13}N_3O_3+H]^+$: 284.1030, found 284.1024.

*Compound **4o***

2-(2-Methoxyphenyl)-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.07 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 5.01 (s, 1H, CH), 6.00 (s, 1H, Ph), 6.47 (s, 1H, Ph), 6.75 (d, *J* = 6.2 Hz, 1H, Ph), 6.86 (d, *J* = 5.9 Hz, 1H, Ph), 6.92 (s, 1H, Ph), 7.07 (s, 1H, Ph), 7.15 (d, *J* = 5.5 Hz, 1H, Ph), 7.26 (s, 1H, Ph), 7.92 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 33.1, 55.5, 68.6, 110.7, 114.4, 115.7, 118.8, 120.8, 126.3, 126.7, 128.3, 129.8, 133.2, 145.6, 156.5, 164.1. HRMS *m/z* (ESI): calcd for $[C_{16}H_{16}N_2O_2+H]^+$: 269.1285, found 269.1280.

*Compound **4p***

2-(3,4-Methylenedioxyphenyl))-3-methyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.01 (d, *J* = 4.8 Hz, 3H, CH_3), 6.09 (s, 2H, CH_2), 6.93 (d, *J* = 8.0 Hz, 1H, CH), 7.00 (d, *J* = 8.0 Hz, 1H, Ph), 7.30 (dd, *J* = 8.0, 1.4 Hz, 1H, Ph), 7.33 (t, *J* = 7.6 Hz, 1H, Ph), 7.42 (d, *J* = 1.4 Hz, 1H, Ph), 7.46 (td, *J* = 7.7, 1.5 Hz, 1H, Ph), 8.29 (s, 1H, Ph), 8.32 (d, *J* = 7.8, 1.4 Hz, 1H, Ph), 9.02 (s, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 26.5, 102.0, 106.4, 108.6, 118.6, 126.4, 126.6, 126.8, 130.3, 131.2, 132.1, 148.9, 149.3, 151.5, 160.5, 166.7. HRMS *m/z* (ESI): calcd for $[C_{16}H_{14}N_2O_3+H]^+$: 283.1077, found 283.1072.

*Compound **4q***

2-Phenyl-3-(4-methylphenyl)-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.25 (s, 3H, CH_3), 5.04 (s, 1H, CH), 6.01 (s, 1H, Ph), 6.56 (d, *J* = 7.9 Hz, 1H, Ph), 6.82-6.84 (m, 1H, Ph), 7.04 (s, 4H, Ph), 7.23-7.25 (m, 4H, Ph), 7.32-7.33 (m, 2H, Ph), 7.97 (dd, *J* = 7.9, 1.3 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 21.1, 74.7, 114.8, 116.7, 119.3, 126.8, 128.7, 128.9, 128.9, 129.6, 133.8, 136.6, 138.0, 140.1, 145.5, 163.2.

*Compound **4r***

2-Phenyl-3-(4-methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 3.72 (s, 3H, CH_3), 4.96 (s, 1H, CH), 6.00 (d, *J* = 1.5 Hz, 1H, Ph), 6.57 (d, *J* = 8.0 Hz, 1H, Ph), 6.75-6.77 (m, 2H, Ph), 6.84 (t, *J* = 7.5 Hz, 1H, Ph), 7.03-7.06 (m, 2H, Ph), 7.25 (t, *J* = 5.0 Hz, 4H, Ph), 7.32 (dd,

J = 7.5, 1.9 Hz, 2H, Ph), 7.97 (dd, *J* = 7.8, 1.3 Hz, 1H, NH), ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 55.4, 75.0, 114.2, 114.7, 116.6, 119.3, 126.9, 128.5, 128.7, 128.9, 129.0, 133.4, 133.8, 140.0, 145.6, 158.1, 163.3.

*Compound **4s***

2-Phenyl-3-ethyl-2,3-dihydroquinazolin-4(1*H*)-one, white solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 1.12 (t, *J* = 7.0 Hz, 3H, CH_3), 2.91 (dq, *J* = 13.6, 6.7 Hz, 1H, CH_2), 3.91 (dq, *J* = 14.0, 7.0 Hz, 1H, CH_2), 4.57-4.63 (m, 1H, CH), 5.77 (s, 1H, Ph), 6.52 (d, *J* = 7.9 Hz, 1H, Ph), 6.83 (d, *J* = 6.9 Hz, 1H, Ph), 7.23 (t, *J* = 7.3 Hz, 1H, Ph), 7.35 (s, 3H, Ph), 7.40 (s, 2H, Ph), 7.95 (d, *J* = 7.3 Hz, 1H, NH). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 12.9, 39.5, 72.1, 114.2, 116.2, 119.2, 126.7, 128.4, 129.0, 129.3, 133.4, 139.9, 145.1, 163.0.

3. Results and discussion

To optimize the reaction conditions, synthesis of 2-(4-chlorphenyl)-3-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (**4b**) through the condensation of isatoic anhydride (1 mmol), aniline (1.2 mmol) and 4-chlorobenzaldehyde (1 mmol) in water (5 mL) was selected as the model reaction under ultrasound irradiation.

Table 1. The effect of various catalysts on the yield of **4b** under ultrasound irradiation[a]

Entry	Catalyst	Temperature, °C	Time, h	Isolated yield, %
1	silica sulfuric acid	23-26	3	Trace (TLC)
2	silica sulfuric acid	40-42	2	25
3	*p*-toluenesulfonic acid	23-26	3	Trace (TLC)
4	*p*-toluenesulfonic acid	40-42	2	44
5	sulfamic acid	23-26	3	Trace (TLC)
6	sulfamic acid	40-42	2	20
7	DBSA	23-26	3	Trace (TLC)
8	DBSA	40-42	2	82

[a] Isatoic anhydride (0.163 g, 1 mmol), 4-chlorobenzaldehyde (0.141 g, 1 mmol), aniline (0.111 g, 1.2 mmol), catalyst (0.3 mmol), H_2O (5 mL), irradiation frequency 25 kHz.

The effect of various catalysts on the reaction under ultrasound was observed. As shown in **Table 1**, the catalysts had a great influence on the reaction yield. No matter which catalyst was used, only trace of product **4b** was detected after 3 h by thin layer chromatography at 23-26 °C under ultrasound irradiation (**Table 1**, entries 1, 3, 5 and 7). When the reactions catalyzed by silica sulfuric acid, *p*-toluenesulfonic acid and sulfamic acid were

carried out for 2 h at 40-42 °C, the yields of **4b** were 25%, 44% and 20% respectively (**Table 1,** entries 2, 4 and 6). However, when the condensation was catalyzed by DBSA for 2 h at 40-42 °C, **4b** can be obtained in 82% yield (**Table 1,** entry 8). It is apparently that DBSA was an efficient catalyst.

To find the optimum amount of DBSA, the yields of the model reaction in water using various amount of catalyst were obtained and compared. The results are summarized in **Table 2**. From these results, it can be concluded that the optimum amount of the catalyst was 0.2 mmol, and **4b** was obtained in 85% yield (**Table 2**, entry 3). Too much DBSA can't actually improve the reaction yield (**Table 2**, entries 4 and 5). It is because high acid concentration would lead to protonation of the amine, and prevent it from acting as a nucleophile. In the absence of DBSA, no obviously reaction was taken place at all (**Table 2**, entry 1). This indicated that DBSA played an important catalytic role in the reaction under ultrasonication.

Table 2. The effect of reaction conditions on the yield of **4b** catalyzed by DBSA under ultrasound irradiation[a]

Entry	DBSA, mmol	Temperature, °C	Time, h	Isolated yield, %
1	0	40-42	2	Trace (TLC)
2	0.1	40-42	2	76
3	0.2	40-42	2	85
4	0.3	40-42	2	82
5	0.4	40-42	2	81
6	0.2	20-22	3	Trace (TLC)
7	0.2	30-32	3	54
8	0.2	50-52	2	84
9[b]	0.2	40-42	2	84

[a] Isatoic anhydride (0.163 g, 1 mmol), 4-chlorobenzaldehyde (0.141 g, 1 mmol), aniline (0.111 g, 1.2 mmol), H_2O(5 mL), irradiation frequency 25 kHz.

[b] Irradiation frequency 40 kHz.

The reaction temperature also had significant influence on the reaction yield under ultrasound irradiation. As shown in **Table 2**, when the amount of DBSA was 0.2 mmol and other conditions were identical, only trace of the product was detected by TLC at 20-22 °C for 3 h (**Table 2**, entry 6), while 85% yield of **4b** was obtained at 40-42 °C for 2 h (**Table 2**, entry 3). The results indicate that increasing the reaction temperature is favorable to the reaction. The power of sonochemistry comes from the cavitation produced by ultrasound. Increasing the

temperature would be helpful to overcome the viscosity of the reaction solution, and raise the vapor pressure of the medium, which can lead to easier cavitation and accelerate the reaction to occur [37]. However, when the reaction was carried out at 50-52 ^{o}C for 2 h, the yield of **4b** was only 84% (**Table 2**, entry 8). According to the principle of the cavitation, although increasing temperature can improve the vapor pressure of the solvent and strengthen the cavitation, meanwhile a large number of cavitation bubbles are generated at higher temperature. This will act as a barrier to sound transmission and dampen the effective ultrasonic energy from the source which enters the liquid medium, and lead to decrease in yield [37]. Therefore, the reaction temperature is an important influencing factor of this procedure under ultrasound irradiation and the proper temperature is 40-42 ^{o}C.

The same reaction was carried out with 40 kHz ultrasound irradiation and **4b** was afforded in 84% yield (**Table 2,** entry 9). The result was similar to the reaction with 25 kHz ultrasound irradiation (**Table 2,** entry 3). It seemed that the frequency of irradiation had not significant effect on the yield.

From the above results, the optimized reaction conditions were chosen for the synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one as follows: isatoic anhydride (**1**, 1 mmol), amine (**2**, 1.2 mmol), aromatic aldehyde (**3**, 1 mmol), DBSA (0.2 mmol), water (5 mL), bath temperature 40-42 ^{o}C, irradiation frequency 25 kHz.

Under this condition, a series of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives were synthesized by one-pot three-component reaction of isatoic anhydride, aromatic aldehyde and amine using DBSA as catalyst in aqueous media under ultrasound irradiation. The results are summarized in **Table 3** (Method A).

As shown in **Table 3**, the condensation of isatoic anhydride, aromatic aldehyde and amine catalyzed by DBSA was carried out in good yield under ultrasound. The dramatic improvements were the short reaction time and high yield. Comparing with the condensation catalyzed by silica sulfuric acid in refluxing ethanol reported in the literature [15a], present reaction catalyzed by DBSA in water under ultrasound irradiation was more effective and environmental friendly. For example, in the reaction catalyzed by silica sulfuric acid in refluxing ethanol, the synthesis of **4a** and **4h** needed 6.5 h and 3 h to afford 80% and 82% yield, respectively. Whereas, in the presence of DBSA and ultrasound irradiation, the same experiment can be finished at 40-42 ^{o}C within 1.5 h and 1 h with 83% and 86% yield (**Table 3**, entries a and h), respectively. It can easily be seen that the ultrasound technique represented a better procedure in terms of the higher yield and shorter reaction time compared to those conventional heating methods.

Table 3. Synthesis of target compounds catalyzed by dodecylbenzene sulfonic acid in aqueous media with and without the use of ultrasound irradiation[a]

Entry	R^1	R^2	Product	Method A[b]		Method B[b]		m.p., °C (Lit.)
				Time, h	Isolated yield, %	Time, h	Isolated yield, %	
a	C_6H_5	H	**4a**	1.5	83	3	68	212-214(209-211)[18]
b	C_6H_5	4-Cl	**4b**	2	85	5	71	219-221(217-219)[18]
c	C_6H_5	4-CH_3	**4c**	2	88	4	73	215-217(215-216)[24]
d	C_6H_5	4-NO_2	**4d**	2	84	5	67	198-200(196-199)[29]
e	C_6H_5	4-CH_3O	**4e**	1.5	90	4	68	222-224(218-220)[18]
f	C_6H_5	2-Cl	**4f**	2	80	4	63	190-192(212-214)[22]
g	C_6H_5	3,4-(OCH_2O)	**4g**	1.5	89	3	76	222-224
h	Me	H	**4h**	1	86	2	70	159-161(160-163) [15a]
i	Me	4-Cl	**4i**	1.5	88	3	72	186-188(186-188)[15a]
j	Me	4-CH_3O	**4j**	1.5	89	3	68	136-138(145-146) [15a]
k	Me	4-CH_3	**4k**	1	91	2	73	150-152
l	Me	2-Cl	**4l**	1.5	82	3	70	153-155
m	Me	4-NO_2	**4m**	1.5	85	3	67	154-156
n	Me	2-NO_2	**4n**	1.5	80	3	62	136-138
o	Me	2-CH_3O	**4o**	1.5	85	2.5	70	154-156
p	Me	3,4-(OCH_2O)	**4p**	1	92	2	75	165-167
q	4-$CH_3C_6H_4$	H	**4q**	1	91	2	73	198-200(197-198)[24]
r	4-$CH_3OC_6H_4$	H	**4r**	1	89	2	71	209-211(213-214) [24]
s	Et	H	**4s**	1	83	2	68	134-136(135-137) [24]

[a] Isatoic anhydride (**1,** 1 mmol), amine (**2,** 1.2 mmol), aromatic aldehyde (**3,** 1 mmol), DBSA (0.2 mmol), H_2O (5 mL), irradiation frequency 25 kHz, temperature 40-42 °C.

[b] Method A: ultrasound irradiation. Method B: stirred and refluxed under silent condition

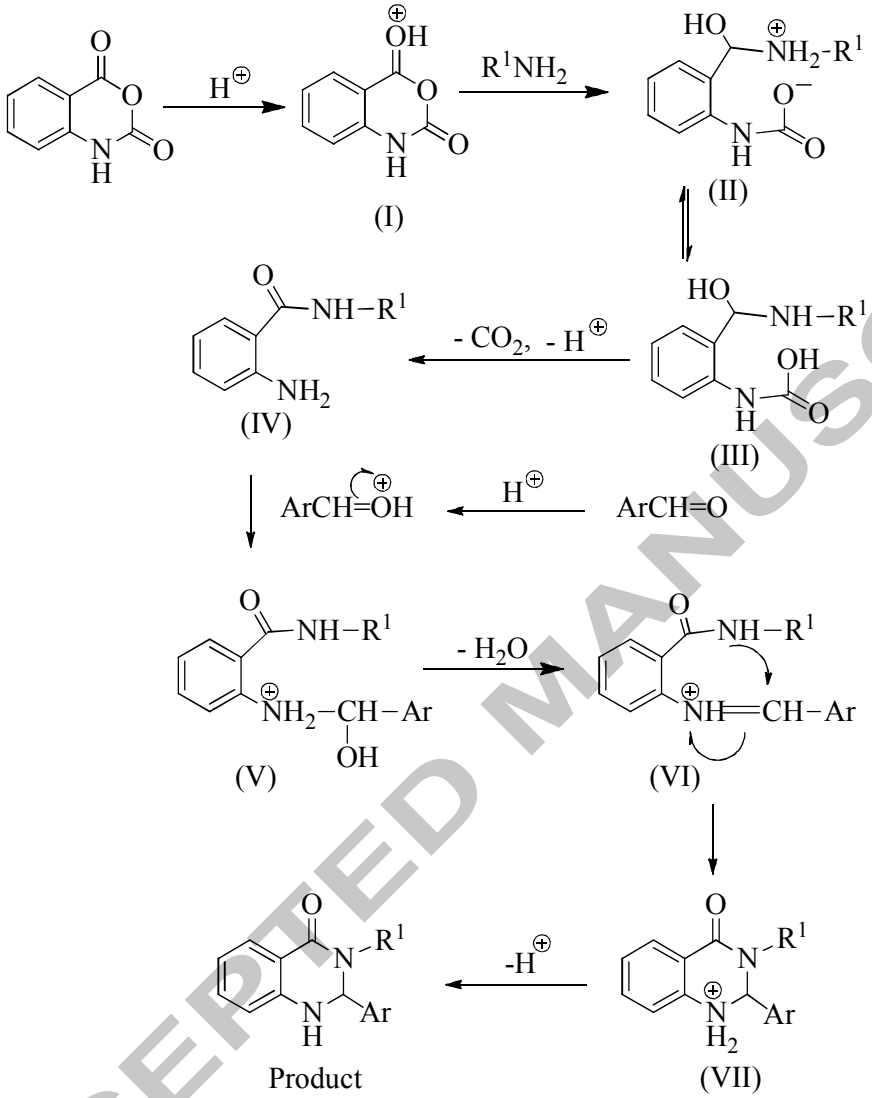
In order to verify the effect of ultrasound irradiation on this reaction, in the absence of ultrasound

irradiation, the same experiments for the preparation of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives **4**(**a-s**) were performed with stirring under refluxing conditions (**Table 3,** Method B). From the results, we can see that the reactions under refluxing needed longer reaction time (2-5 h) and the yields of the corresponding products were also lower (62-76%) than that under ultrasound. For example, the synthesis of **4a** and **4h** were carried out under refluxing for 3 h and 2 h with the yield of 68% and 70% respectively, while the same reaction under ultrasound irradiation needed only 1.5 h and 1 h with 83% and 86% yield, respectively (**Table 3**, entries a and h). It is clearly that ultrasound irradiation can accelerate the reaction and improve the results.

The reason may be the cavitation effect produced by the ultrasonication. When ultrasonic waves are irradiated into the reaction system, cavitation occurs. The violent collapse of the cavitation bubbles generates localized "hot spots" with transient high pressure and high temperature, which can provide special physical and chemical conditions for the reaction. This can induce molecular fragmentation, and highly reactive species are locally produced. In some case, sonication can probably provide more powerful stirring [37]. All these can cause the reaction to take place rapidly and efficiently.

Table 3 shows the difference in the yield and reaction time for the reactions with different amine. Aliphatic amine and aromatic amine with electron-donating substituents were more activated and the corresponding yields were higher than that of aniline (**Table 3**, entries h, s, q, r and a), while methylamine was better than ethylamine. The following sequence of reaction (**Scheme 2**) appears to afford a satisfactory explanation. As shown in **Scheme 2**, the carbonyl group of isatoic anhydride could be firstly protonated by DBSA to give intermediate **I**, which was then attacked by amine to form intermediate **II**. Easy or difficult for the amine to attack the carbonyl and the stability of intermediate **II** would directly influence the subsequent reactions. Both the methyl and ethyl are electron-donating groups, while phenyl is electron-withdrawing group and also its size is larger than methyl and ethyl. This makes methylamine and ethylamine easier attack the positively charged carbon atom of the carbonyl group than aniline. Within the same reaction time, the yield of the reaction using methylamine as substrate was higher than that using ethylamine. It is because the size of ethyl was larger than methyl, which made ethylamine more difficult attack the carbonyl group. For 4-methylaniline and 4-methoxyaniline (**Table 3,** entries q and r), in spite of the size of aryl is larger, however methyl and methoxy are electron-donating groups and can improve the stability of the intermediate **II** by their conjugation with a positively charged nitrogen, which is beneficial to the formation of the intermediate **II** and the subsequent reactions. For this reason, compared to **4a, 4q** and **4r** were obtained in higher yields within shorter reaction times (**Table 3,** entries q, r and

a).



Scheme 2. A possible mechanism of the formation of 2,3-dihydroquinazolin-4(1*H*)-one

As we can see from **Table 3**, among the condensation of isatoic anhydride and aniline with aromatic aldehydes (**Table 3**, entries a-g), 4-nitrobenzaldehyde in benzene ring with electron-withdrawing substituent reacted less rapidly than 4-methylbenzaldehyde in benzene ring with electron-donating substituent, and the yield of **4d** (84%) was lower than **4c** (88%) (**Table 3**，entries c and d). It seemed that electronic effect of the substituted groups in aromatic aldehydes had some influences on the yield of the product. As shown in **Scheme 2**, in the formation of 2,3-dihydroquinazolin-4(1*H*)-one, the protonated aromatic aldehyde firstly reacted with the

intermediate **IV** to form the intermediate **V**, followed by dehydration to produce the intermediate **VI**, which underwent intramolecular cyclization and deprotonation to afford the target compound. Methyl is an electron-donating group and can be conjugated with C=N through the benzene ring, which made the electron cloud transfer to the positively charged nitrogen atom and improved the stability of the intermediate **VI**. Nitro is an electron-withdrawing group and also can be conjugated with C=N through the benzene ring, but the electron cloud would transfer to the opposite direction and made the positive charge more concentrated, which may reduce the stability of the intermediate **VI**. In the reactions of 2-chlorobenzaldehyde or 4-chlorobenzaldehyde with isatoic anhydride and aniline, the yield of **4f** was lower than **4b** (**Table 3**, entries f and b). It seemed that the ortho steric effect of chlorine atom in 2-chlorobenzaldehyde hindered the lone electron pair in the nitrogen atom of anthranilic acid amide (**IV**) to attack the carbonyl group.

4. Conclusion

In conclusion, we have found an efficient and practical procedure for the synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives *via* the one-pot three-component condensation of isatoic anhydride, aromatic aldehyde and amine using dodecylbenzenesulfonic acid as catalyst in aqueous media at 40-42 ^{o}C under ultrasound irradiation. The advantages of this method superior to others are facile work-up procedures, mild conditions, short reaction times, high yields, avoiding the use of organic solvents, and environmental friendly.

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Table 1. The effect of various catalysts on the yield of **4b** under ultrasound irradiation[a]

Entry	Catalyst	Temperature, °C	Time, h	Isolated yield, %
1	silica sulfuric acid	23-26	3	Trace (TLC)
2	silica sulfuric acid	40-42	2	25
3	*p*-toluenesulfonic acid	23-26	3	Trace (TLC)
4	*p*-toluenesulfonic acid	40-42	2	44
5	sulfamic acid	23-26	3	Trace (TLC)
6	sulfamic acid	40-42	2	20
7	DBSA	23-26	3	Trace (TLC)
8	DBSA	40-42	2	82

[a] Isatoic anhydride (0.163 g, 1 mmol), 4-chlorobenzaldehyde (0.141 g, 1 mmol), aniline (0.111 g, 1.2 mmol), catalyst (0.3 mmol), H_2O (5 mL), irradiation frequency 25 kHz.

Table 2. The effect of reaction conditions on the yield of **4b** catalyzed by DBSA under ultrasound irradiation[a]

Entry	DBSA, mmol	Temperature, °C	Time, h	Isolated yield, %
1	0	40-42	2	Trace (TLC)
2	0.1	40-42	2	76
3	0.2	40-42	2	85
4	0.3	40-42	2	82
5	0.4	40-42	2	81
6	0.2	20-22	3	Trace (TLC)
7	0.2	30-32	3	54
8	0.2	50-52	2	84
9[b]	0.2	40-42	2	84

[a] Isatoic anhydride (0.163 g, 1 mmol), 4-chlorobenzaldehyde (0.141 g, 1 mmol), aniline (0.111 g, 1.2 mmol), H_2O(5 mL), irradiation frequency 25 kHz.

[b] Irradiation frequency 40 kHz.

Table 3. Synthesis of target compounds catalyzed by dodecylbenzene sulfonic acid in aqueous media with and without the use of ultrasound irradiation[a]

Entry	R^1	R^2	Product	Method A[b]		Method B[b]		m.p., °C (Lit.)
				Time, h	Isolated yield, %	Time, h	Isolated yield, %	
a	C_6H_5	H	**4a**	1.5	83	3	68	212-214(209-211)[18]
b	C_6H_5	4-Cl	**4b**	2	85	5	71	219-221(217-219)[18]
c	C_6H_5	4-CH_3	**4c**	2	88	4	73	215-217(215-216)[24]
d	C_6H_5	4-NO_2	**4d**	2	84	5	67	198-200(196-199)[29]
e	C_6H_5	4-CH_3O	**4e**	1.5	90	4	68	222-224(218-220)[18]
f	C_6H_5	2-Cl	**4f**	2	80	4	63	190-192(212-214)[22]
g	C_6H_5	3,4-(OCH_2O)	**4g**	1.5	89	3	76	222-224
h	Me	H	**4h**	1	86	2	70	159-161(160-163)[15a]
i	Me	4-Cl	**4i**	1.5	88	3	72	186-188(186-188)[15a]
j	Me	4-CH_3O	**4j**	1.5	89	3	68	136-138(145-146)[15a]
k	Me	4-CH_3	**4k**	1	91	2	73	150-152
l	Me	2-Cl	**4l**	1.5	82	3	70	153-155
m	Me	4-NO_2	**4m**	1.5	85	3	67	154-156
n	Me	2-NO_2	**4n**	1.5	80	3	62	136-138
o	Me	2-CH_3O	**4o**	1.5	85	2.5	70	154-156
p	Me	3,4-(OCH_2O)	**4p**	1	92	2	75	165-167
q	4-$CH_3C_6H_4$	H	**4q**	1	91	2	73	198-200(197-198)[24]
r	4-$CH_3OC_6H_4$	H	**4r**	1	89	2	71	209-211(213-214)[24]
s	Et	H	**4s**	1	83	2	68	134-136(135-137)[24]

[a] Isatoic anhydride (**1,** 1 mmol), amine (**2,** 1.2 mmol), aromatic aldehyde (**3,** 1 mmol), DBSA (0.2 mmol), H_2O (5 mL), irradiation frequency 25 kHz, temperature 40-42 °C.

[b] Method A: ultrasound irradiation. Method B: stirred and refluxed under silent condition

Highlights

- Efficient one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives.
- Reaction catalyzed by dodecylbenzenesulfonic acid under ultrasound irradiation.
- Mild conditions, short reaction times, high yields, and environmental friendly.