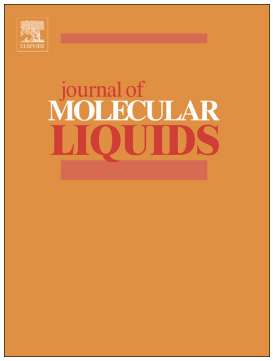

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Low melting oxalic acid/proline mixture as dual solvent/catalyst for efficient synthesis of 13-aryl-13*H*-benzo[*g*]benzothiazolo[2,3-*b*]quinazoline-5,14-diones under microwave irradiation

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ABSTRACT

Oxalic acid and proline based deep eutectic solvent (DES) has been identified as an effective catalyst and environmentally benign reaction medium for one-pot synthesis of 13-aryl-13*H*-benzo[*g*]benzothiazolo[2,3-*b*]quinazoline-5,14-diones via three-component reaction of aromatic aldehydes, 2-aminobenzothiazole and 2-hydroxy-1,4-naphthoquinone under microwave irradiation. The reported approach shows significant advantages such as easy work-up, environment-friendly process, short reaction times, excellent yields, one-pot multicomponent reaction, chromatography-free purification, the recycling and the re-use of the DES.

Keywords:

Deep eutectic solvents, Oxalic acid/proline, Multicomponent reaction, 2-Hydroxy-1,4-naphthoquinone, Aldehydes, 2-aminobenzothiazole, 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones

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1. Introduction

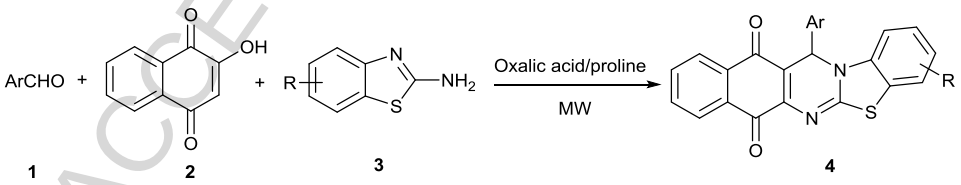
Nitrogen and sulfur containing heterocycles played a significant role in medicinal chemistry and in the development of pharmaceutically interesting drugs. Among them, pyrimidines and thiazoles have been well documented in medicinal chemistry with respect to their significant biological activities such as antimicrobial [1], antiproliferative [2], antidiabetic [3], anti-cancer [4], antimalarial [5], antiviral [6], antidiabetic [7], and antiproliferative activities [8]. Pyrimidine derivatives can also be used as acidizing corrosion inhibitors [9]. In addition, the 1,4-naphthoquinone ring is an important structural motif found in a large number of natural or synthesized bioactive compounds. These naphthoquinone-based molecules have been shown to possess various biological activities, such as antimicrobial [10], antiradical [11], antioxidant [12], antileukemic [13] and anticancer properties [14]. When two or more different heterocyclic moieties are present in a single molecule, a more pronounced effect is usually observed because it may have all the properties of the moiety and enhance the pharmacological activity. Despite the significant advancements have been made to develop atom- and step-economic strategies toward polyheterocylic compounds by combining various structurally diverse motifs [15], the development of an environmentally friendly methodology for the synthesis of a single structural framework by combining pyrimidines, thiazoles and 1,4-naphthoquinone motifs is still needed.

From the viewpoint of green chemistry, the development of a high efficiency, environmentally benign, atom- and step-economical synthesis strategy is a research priority in the field of organic chemistry. One of the most promising green synthetic strategies is the use of microwave in combination with a green solvent to develop a one-pot multicomponent reaction (MCR). In recent years, a new family of solvents, so-called low melting mixtures (LMMs) [16], low-transition-temperature mixtures [17] or deep eutectic solvents (DESs) [18-19] has introduced as a new nascent sustainable solvent. DESs have similar physical and chemical properties as ionic liquids (ILs) [20-21] such as non-flammability, low volatility and recyclability but are less toxic, better biodegradable, attractive low prices, and easier synthesis process. DESs can be simply obtained by mixing and gently warming a suitable hydrogen bond acceptor (HBA) such as choline chloride (ChCl) with hydrogen-bond donors (HBD) such as acids, alcohols, amines or carbohydrates. The melting point of DESs is much lower than that of the individual components and most DESs stay as liquids at room temperature. These inherent beneficial properties allow DESs to replace volatile organic solvents and ILs in many physical and chemical processes, especially in extraction and separation processes [22], polymerization and material sciences [23-24], biomass processing [25] as well as organic synthesis [26-43]. In addition, one-pot MCRs have become an important tool

for the development of medicinal, organic, and combinatorial chemistry and have become one of the most powerful synthetic methods for the construction of novel and structurally complex molecules in a single step without isolation of intermediates from three or more reactants [44]. MCRs offer high synthetic efficiency over conventional multistep synthesis.

Microwave assisted organic synthesis (MAOS) has recently gained popularity as a widely accepted method due to a key advantage of modern scientific microwave apparatus. In comparison with traditional heating methods, the procedure is more convenient, fast, simple and easy to manipulate. A large number of organic reactions can be carried out under microwave irradiation in higher yields, shorter reaction times, better product purity, lower costs and easier workup. The successes in MAOS may be attributed to specific microwave effects, low inertia of heating, the absence of contact between the heated body and the heater, and the possibility of selective heating of reaction mixture components. The temperature increase is likely to remain uniform throughout the sample which minimizes the formation of by-products and decomposition products [45]. Thus, the combination of MCR and DES under microwave irradiation should ensure that the reaction process is convenient, environmentally friendly and efficient to utilize all reactants in the product framework.

As part of our continuing interest in the development of efficient and environmentally benign synthetic methodologies [46-49], herein we report a novel and effective method for synthesis of 13-aryl-13*H*-benzo[*g*]benzothiazolo[2,3-*b*]quinazoline-5,14-diones via one-pot three-component reactions of aromatic aldehydes, 2-aminobenzothiazole and 2-hydroxy-1,4-naphthoquinone under the combination of DES and microwave irradiation (Scheme 1).



Scheme 1. Synthesis of 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones in oxalic acid/proline

2. Experimental section

2.1 General

All reagents were commercially available and used without further purification. Melting points were determined on an X-5 digital melting point apparatus and are uncorrected. IR spectra were determined on a Bruker Tensor 27 Fourier transform infrared spectrometer using KBr disks. NMR spectra were recorded on a Bruker

DRX-500 spectrometer (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C NMR) using $CDCl_3$ as the solvent with TMS as internal standard. High-resolution mass spectroscopy (HRMS) was recorded on Thermo Scientific LTQ FT Ultra FT-MS.

2.2. Preparation of oxalic acid and proline based deep eutectic solvent

Oxalic acid and proline based deep eutectic solvent was prepared according to reported method in literatures [40-41]. Briefly, a mixture of oxalic acid dihydrate (12.6 g, 100 mmol) and proline (11.5 g, 100 mmol) was heated at 80 ^{o}C until a yellowish viscous liquid appeared. It can be directly used without any further purification.

2.3. Typical procedure for preparation of 13-aryl-13H-benzo[g]benzothiazolo [2,3-b]quinazoline-5,14-diones

A mixture of aromatic aldehydes (1 mmol), 2-hydroxy-1,4-naphthoquinone (1 mmol) and 2-aminobenzothiazole (1 mmol) in DES (1.0 ml) was stirred under microwave irradiation at 80 °C for an appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and cold water was added to the reaction mixture. The insoluble crude product was isolated by filtration, washed with water and purified by recrystallization from ethanol.

2.4. Selected spectra data for some new compounds

13-(2-Methoxyphenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4b).

Yellow solid; IR (KBr): *v* 3069, 1639, 1645, 1558, 1515, 1448, 1401, 1322, 1235, 1174, 1078, 948, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.07-8.11 (m, 4H), 7.74 (t, *J* = 7.5 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.87 (t, *J* = 8.0 Hz, 2H), 6.33 (s, 1H), 3.76 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 184.2, 181.5, 157.4, 154.1, 135.0, 133.0, 129.5, 128.7, 128.1, 127.2, 126.6, 126.2, 122.8, 121.6, 120.3, 113.2, 110.3, 55.7 ppm; HRMS (ESI, m/z): calcd for $C_{25}H_{17}N_2O_3S$ $(M+H)^+$: 425.0960; found 425.0959.

13-(3-Methoxyphenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4c).

Brown solid; IR (KBr): *v* 3055, 1673, 1625, 1478, 1462, 1361, 1327, 1265, 1128, 1040, 958, 761 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.12-8.10 (m, 4H), 7.72 (t, *J* = 9.0, 2H), 7.68 (t, *J* = 9.0, 2H), 7.20 (d, *J* = 9.0, 1H), 6.87 (d, *J* = 9.0, 1H), 6.83 (s, 1H), 6.78-6.76 (m, 1H), 6.23 (s, 1H), 3.72 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 185.3, 181.6, 160.2, 154.1, 139.0, 136.8, 135.0, 134.8, 133.2, 129.7, 126.3, 122.4, 115.1, 113.8, 57.6 ppm; HRMS (ESI, m/z): calcd for $C_{25}H_{17}N_2O_3S$ $(M+H)^+$: 425.0960; found 425.0962.

13-(4-Methoxyphenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4d).

Yellow solid; IR (KBr): *v* 3065, 1672, 1525, 1488, 1466, 1363, 1317, 1262, 1148, 1043, 968, 781 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.09 (d, *J* = 7.5, 4H), 7.74 (t, *J* = 7.5, 2H), 7.69 (t, *J* = 7.5, 2H), 7.19 (d, *J* = 8.5, 2H),

6.81 (d, *J* = 8.5, 2H), 6.17 (s, 1H), 3.77 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 184.8, 181.3, 158.4, 154.7, 135.0, 133.2, 132.7, 129.7, 129.6, 129.2, 127.2, 126.3, 122.9, 113.8, 55.2 ppm; HRMS (ESI, m/z): calcd for $C_{25}H_{17}N_2O_3S$ $(M+H)^+$: 425.0960; found 425.0961.

13-(3,4-Dimethoxyphenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4e).

Brown solid IR (KBr): *v* 3066, 1674, 1612, 1513, 1462, 1416, 1361, 1265, 1139, 1024, 971, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.10 (t, *J* = 7.5, 4H), 7.76 (d, *J* = 7.0, 2H), 7.69 (d, *J* = 7.0, 2H), 6.84-6.80 (m, 2H), 6.76 (d, *J* = 8.5, 1H), 6.20 (s, 1H), 3.84 (s, 3H), 3.79 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 184.6, 181.7, 148.9, 147.9, 135.0, 133.1, 132.8, 129.7, 127.2, 127.1, 126.3, 122.9, 120.2, 116.2, 112.0, 110.8, 110.4, 56.0, 55.8 ppm; HRMS (ESI, m/z): calcd for $C_{26}H_{19}N_2O_4S$ $(M+H)^+$: 455.1066; found 455.1065.

13-(4-(*tert*-Butyl)phenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4h).

Brown solid; IR (KBr): *v* 2961, 1696, 1674, 1571, 1541, 1467, 1362, 1277, 1217, 1107, 829, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.11 (t, *J* = 9.0 Hz, 4H), 7.83 (d, *J* = 9.0 Hz, 2H), 7.75 (t, *J* = 7.0 Hz, 2H), 7.70 (d, *J* = 7.0 Hz, 2H), 7.19 (d, *J* = 7.5 Hz, 2H), 6.32 (s, 1H), 1.37 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 184.8, 158.5, 134.8, 133.0, 129.8, 127.4, 127.2, 126.6, 126.2, 126.0, 125.3, 123.0, 122.4, 113.3, 55.8, 31.1 ppm; HRMS (ESI, m/z): calcd for $C_{28}H_{23}N_2O_2S$ $(M+H)^+$: 451.1480; found 451.1483.

13-(2-Chlorophenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4j).

Orange solid; IR (KBr): *v* 3065, 1646, 1602, 1542, 1431, 1408, 1338, 1305, 1223, 1204, 1012, 922, 723cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.10 (t, *J* = 9.0 Hz, 4H), 7.76 (t, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 7.5 Hz, 2H), 7.57-7.53 (m, 2H), 7.22-7.17 (m, 2H), 6.36 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 183.7, 181.6, 136.7, 135.2, 134.1, 133.0, 132.9, 129.9, 129.4, 129.3, 128.1, 127.3, 126.4, 126.3, 121.6, 58.3 ppm; HRMS (ESI, m/z): calcd for $C_{24}H_{14}ClN_2O_2S$ $(M+H)^+$: 429.0465; found 429.0464.

13-(3-Chlorophenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4k).

Brown solid; IR (KBr): *v* 3066, 1656, 1662, 1523, 1473, 1448, 1368, 1355, 1233, 1224, 1052, 926, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) *δ*: 8.12 (d, *J* = 7.5 Hz, 2H), 8.06 (d, *J* = 7.5 Hz, 2H), 7.73 (t, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 2H), 7.48-7.44 (m, 2H), 7.17 (s, 1H), 6.38 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) *δ*: 184.2, 141.0, 135.0, 133.0, 132.8, 131.1, 129.7, 129.4, 128.2, 127.8, 127.2, 126.3, 125.4, 122.6, 122.1, 113.0, 55.8 ppm; HRMS (ESI, m/z): calcd for $C_{24}H_{14}ClN_2O_2S$ $(M+H)^+$: 429.0465; found 429.0466.

13-(4-Bromophenyl)-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4m).

Brown solid; IR (KBr): *v* 3161, 1662, 1644, 1588, 1715, 1484, 1467, 1362, 1279, 1253, 1071, 931, 739 cm^{-1};

^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.10 (t, J = 7.5 Hz,4H), 7.75 (t, J = 7.5 Hz, 2H), 7.69 (t, J = 7.5 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 6.21 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 184.3, 140.8, 135.5, 134.5, 133.0, 132.9, 130.0, 129.5, 129.3, 128.3, 128.0, 127.3, 127.2, 126.4, 126.3, 115.5, 63.3 ppm; HRMS (ESI, m/z): calcd for $C_{24}H_{14}BrN_2O_2S$ $(M+H)^+$: 472.9959; found 472.9959.

4-(7,12-dioxo-12,13-dihydro-7*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazolin-13-yl)benzonitrile (4o).

Brown solid; IR (KBr): ν 3068, 1671, 1605, 1574, 1543, 1469, 1366, 1278, 1218, 1159, 1019, 965, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.12 (d, J = 7.5 Hz, 2H), 8.06 (d, J = 7.5 Hz, 2H), 7.74 (t, J = 7.5 Hz, 2H), 7.68 (t, J = 7.5 Hz, 2H), 7.53 (d, J = 7.5 Hz, 2H), 7.41 (d, J = 7.5 Hz, 2H), 6.47 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 184.0, 163.5, 163.0, 135.0, 133.0, 132.9, 129.9, 129.8, 128.8, 127.2, 126.2, 121.8, 119.1, 109.9, 62.2 ppm; HRMS (ESI, m/z): calcd for $C_{25}H_{14}N_3O_2S$ $(M+H)^+$: 420.0807; found 420.0809.

1-Methyl-13-phenyl-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4r).

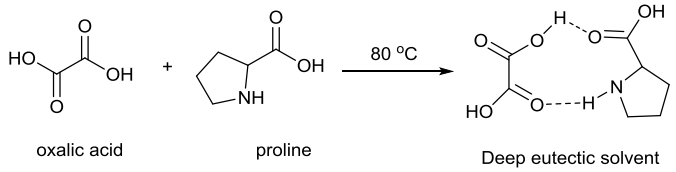
Orange solid; IR (KBr): ν 3063, 1667, 1643, 1596, 1525, 1479, 1411, 1366, 1277, 1140, 1039, 963, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.08-8.14 (m, 4H), 7.75 (t, J = 7.5 Hz, 2H), 7.69 (t, J = 7.5 Hz, 2H), 7.38 (d, J = 7.5 Hz, 1H), 7.21-7.23 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.37 (s, 1H), 2.56 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 184.5, 182.8, 138.9, 134.7, 134.5, 133.0, 132.7, 130.1, 129.8, 129.0, 128.5, 128.2, 127.8, 127.1, 126.2, 126.0, 125.5, 124.0, 123.1, 119.0, 61.8, 17.8 ppm; HRMS (ESI, m/z): calcd for $C_{25}H_{17}N_2O_2S$ $(M+H)^+$: 409.1011; found 409.1010.

3-Nitro-13-phenyl-12*H*-benzo[*g*]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (4s).

Brown solid; IR (KBr): ν 3065, 1668, 1651, 1574, 1506, 1460, 1335, 1295, 1278, 1128, 1045, 892, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.11 (t, J = 8.5 Hz, 4H), 7.76 (t, J = 7.5 Hz, 3H), 7.70 (t, J = 7.5 Hz, 3H), 7.55 (t, J = 7.5 Hz, 1H), 7.22-7.27 (m, 1H), 6.31 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 184.7, 181.7, 155.7, 138.2, 135.0, 133.1, 132.8, 129.7, 129.0, 128.3, 128.0, 127.2, 126.6, 126.3, 122.7, 117.5, 63.2 ppm; HRMS (ESI, m/z): calcd for $C_{24}H_{14}N_3O_4S$ $(M+H)^+$: 440.0705; found 440.0704.

3. Results and Discussion

The preparation of oxalic acid and proline based DES was performed by mixing oxalic acid and proline under heating at 80 ºC until a homogenous yellowish viscous liquid was formed (Scheme 2). Then, the mixture was cool to room temperature and the resulting eutectic solvent can be used directly without any further purification. This method gives DES with a 100% atomic economy because there is no by-product formation during the preparation of DES.



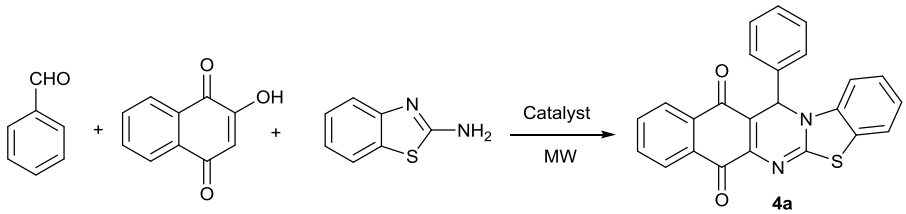
Scheme 2. Preparation of oxalic acid and proline based DES

Then, the three-component reaction of benzaldehyde, 2-hydroxynaphthalene-1,4-dione and 2-aminobenzothiazole was chosen as the model reaction for optimisation of the experimental parameters. Initially, the efficiency of different DESs was evaluated. As seen in Table 1, some DESs such as choline chloride (ChCl)/$FeCl_3$, ChCl/$ZnCl_2$, ChCl/urea, ChCl/itaconic acid, ChCl/tartaric acid, ChCl/*p*-TsOH acid, ChCl/citric acid, ChCl/oxalic acid could catalyze the reaction under microwave irradiation to furnish the expected product **4a** in 42-84% yield (Table 1, entries 2-9). To our great delight, the yield could be increased to 95% when oxalic acid/proline was used (entry 18). Based on these results, the reaction temperature was further evaluated. It was found that lower yields were obtained when the reactions were performed at lower temperature (< 80 ^{o}C, entries11-13). Therefore, 80 ^{o}C was chosen for subsequent studies. We further optimized the amount of oxalic acid/proline and found that the best amount of DES was 1.0 ml. A control experiment showed that only trace of product could be observed in the absence of DES. In addition, we also investigated the influence of not having microwave irradiation for this reaction (entry 18). It was found that the reaction under simple heating condition required longer reaction time and the expected product was obtained in relatively lower yield than under microwave irradiation. The effect of microwave power on the reaction was also examined. The results showed that 500 W was the appropriate power for this reaction. These results indicated that microwave irradiation effectively accelerated this three-component reaction.

In order to display the practical applicability, this methodology was assessed on a larger scale. Gratifyingly, the model reaction was found to proceed smoothly on a 100-mmol scale to afford the desired product in 94% yield (entry 22). On the same scale, the recovery and recyclability of deep eutectic solvent was also investigated for the selected model reaction. At the end of the reaction, the mixture was cooled to room temperature and cold water was added to the reaction mixture. The insoluble product was isolated by simple filtration and subsequent washing with water. The filtrate including DES was evaporated under reduced pressure, dried in a vacuum at 100 ^{o}C. The recycled DES was reused in the next run. The results showed that even five cycles the DES could also drive the reaction and provide the product in a fairly good yield (entry 23).

Table 1

Optimization of the reaction conditions[a]



Entry	DES	Temperature (^{o}C)	MW (W)	Time (min)	Yield (%)[b]
1	No	80	500	60	trace
2	ChCl/$FeCl_3$ (1:2)	80	500	30	42
3	ChCl/$ZnCl_2$ (1:2)	80	500	30	45
4	ChCl/urea (1:2)	80	500	30	54
5	ChCl/itaconic acid (1:1)	80	500	30	72
6	ChCl/tartaric acid (2:1)	80	500	30	76
7	ChCl/*p*-TsOH acid (1:1)	80	500	30	78
8	ChCl/citric acid (1:2)	80	500	30	81
9	ChCl/oxalic acid (1:1)	80	500	30	84
10	Oxalic acid/proline (1:1)	80	500	20	95
11	Oxalic acid/proline (1:1)	50	500	20	53
12	Oxalic acid/proline (1:1)	60	500	20	52
13	Oxalic acid/proline (1:1)	70	500	20	85
14	Oxalic acid/proline (1:1)	90	500	20	95
15[c]	Oxalic acid/proline (1:1)	80	500	20	65
16[d]	Oxalic acid/proline (1:1)	80	500	20	82
17[e]	Oxalic acid/proline (1:1)	80	500	20	95
18	Oxalic acid/proline (1:1)	80	0	120	90
19	Oxalic acid/proline (1:1)	80	300	40	88
20	Oxalic acid/proline (1:1)	80	400	30	89
21	Oxalic acid/proline (1:1)	80	600	20	95
22[f]	Oxalic acid/proline (1:1)	80	500	30	94
23[g]	Oxalic acid/proline (1:1)	80	500	20	92, 90, 89, 86, 85

[a] Reaction conditions: benzaldehyde (1 mmol), 2-hydroxynaphthalene-1,4-dione (1 mmol), 2-aminobenzothiazole (1 mmol) in solvent (1.0 ml) at 80 ^{o}C under microwave irradiation (500 W) unless otherwise specified in the table.

[b] Isolated yield.

[c] The reaction was performed in 0.50 ml oxalic acid/proline.

[d] The reaction was performed in 0.75 ml oxalic acid/proline.

[e] The reaction was performed in 1.25 ml oxalic acid/proline.

[f] The reaction was carried out in 100 mmol scale.

[g] DES was reused for 5 times.

Under the optimizing the reaction conditions, the scope and generality of this protocol were explored. As summarized in Table 2, various aromatic aldehydes bearing electron-rich (OMe, Me and ^{t}Bu) or electron-poor groups (F, Cl, Br, NO_2 and CN) reacted with 2-hydroxynaphthalene-1,4-dione and 2-aminobenzothiazole to afford the desired products in high yields. The product yields were only slightly affected by the location of the substituents (on *ortho*-, *meta*-, or *para*-positions of the benzene ring). Notably, halo-substituted aldehydes were successfully converted into target products, which allowed for easy further synthetic modifications. Furthermore, the acid-sensitive heterocyclic aldehydes such as furan-2-carbaldehyde and 2-thiophene-carbaldehyde were found to be suitable substrates for this reaction and generated the corresponding products in 85% and 89% yields, respectively (entries 16 and 17). Unfortunately, reactions with aliphatic aldehydes such as 3-methylbutyraldehyde and cyclohexanecarbaldehyde were unsuccessful. Notably, the current reaction with electronically-differentiated 2-aminobenzothiazoles also worked well to afford the corresponding products **4r** and **4s** in high yield (entries 18 and 19).

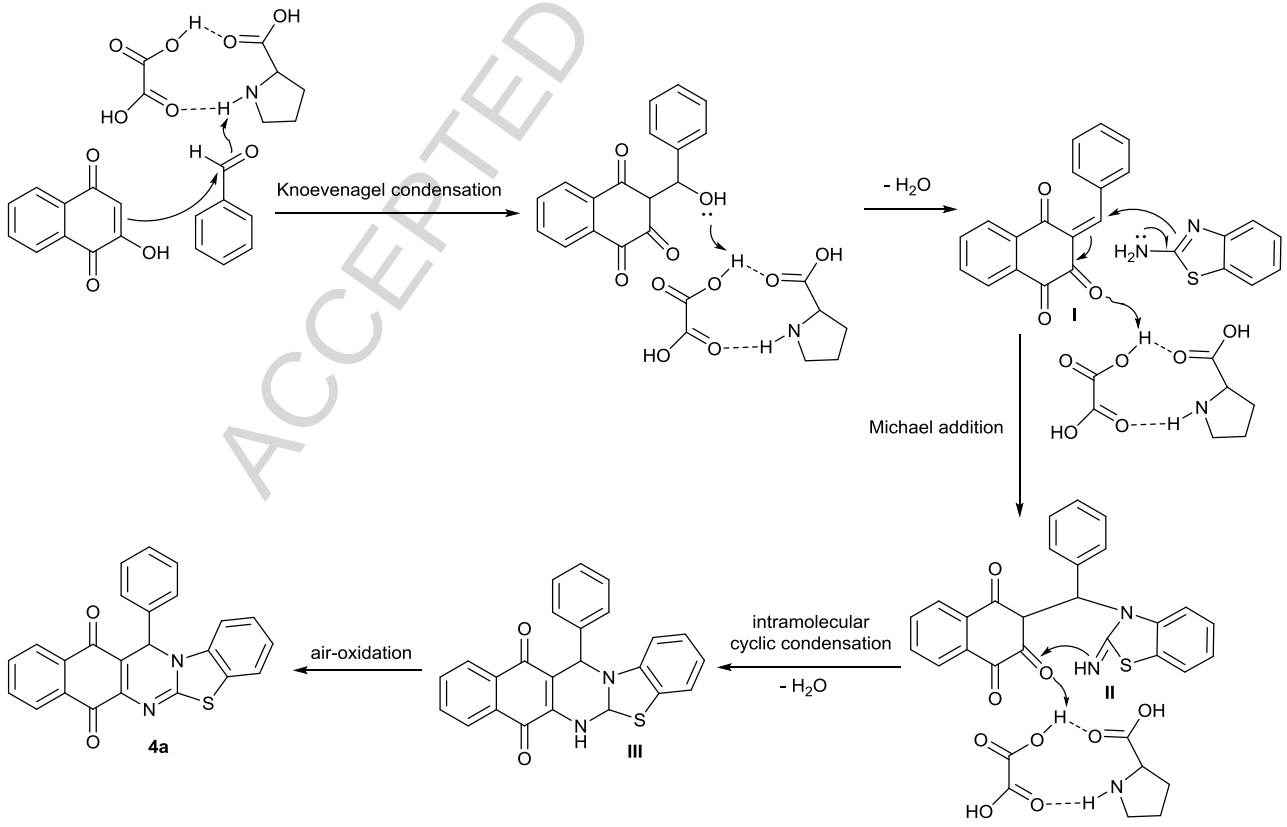
Table 2
Synthesis of 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones in oxalic acid/proline.

Entry	Ar	R^1	Product	Time/min	Yield/%[a]	m.p./^{o}C	
						Found	Reported
1	Ph	H	**4a**	10	95	262-263	261-262 [50]
2	2-$MeOC_6H_4$	H	**4b**	15	92	213-214	
3	3-$MeOC_6H_4$	H	**4c**	12	90	247-248	
4	4-$MeOC_6H_4$	H	**4d**	10	93	224-225	
5	3,4-$(MeO)_2C_6H_3$	H	**4e**	20	91	236-237	
6	3,4,5-$(MeO)_3C_6H_2$	H	**4f**	20	91	278-279	278-279 [50]
7	4-MeC_6H_4	H	**4g**	10	92	227-228	228-229 [50]
8	4-$(CH_3)_3CC_6H_4$	H	**4h**	10	91	228-229	
9	4-FC_6H_4	H	**4i**	25	88	290-292	289-290 [50]
10	2-ClC_6H_4	H	**4j**	25	92	210-211	
11	3-ClC_6H_4	H	**4k**	20	94	239-240	
12	4-ClC_6H_4	H	**4l**	20	95	271-272	272-273 [50]
13	4-BrC_6H_4	H	**4m**	20	92	216-217	
14	4-$NO_2C_6H_4$	H	**4n**	20	93	310-311	310-311 [50]
15	4-CNC_6H_4	H	**4o**	20	93	260-261	

16	2-Furanyl	H	**4p**	20	85	310-311	309-310 [50]
17	2-Thiophenyl	H	**4q**	20	89	309-310	308-309 [50]
18	Ph	4-Me	**4r**	25	85	234-235	
19	Ph	6-NO_2	**4s**	25	86	239-240	

[a] Isolated yield.

On the basis of the experimental results described above and previous literature report [50], a plausible mechanism for the synthesis of 13-phenyl-12*H*-benzo[g]benzo[4,5]thiazolo[2,3-*b*]quinazoline-7,12(13*H*)-dione (**4a**) is proposed (Scheme 3). It is assumed that DES may play dual role as solvent and catalyst in promoting Knoevenagel condensation between benzaldehyde and 2-hydroxy-1,4-naphthoquinone by activation of carbonyl carbon of benzaldehyde through hydrogen bonding to give intermediate **I**. This is followed by Michael addition of 2-aminobenzothiazole to the C=C bond of intermediate **I** and on tautomerization to generate intermediate **II**. Then, an intramolecular cyclic condensation between the amino and the carbonyl groups of the Michael adduct **II** occurred to yield intermediate III, which finally underwent dehydration and aromatization to afford the desired product **4a**. We think that the hydrogen bonding nature of DES enhances the electrophilicity of the carbonyl groups in three steps: Knoevenagel condensation, Michael addition, and intramolecular cyclization.



Scheme 3. A plausible mechanism for the synthesis of 13-phenyl-12*H*-benzo[g]benzo[4,5]thiazolo[2,3-*b*]

quinazoline-7,12(13*H*)-dione

4. Conclusion

In summary, we have successfully developed a novel process for synthesis of 13-aryl-13*H*-benzo[*g*]benzothiazolo [2,3-*b*]quinazoline-5,14-diones via one-pot three-component reactions of aromatic aldehydes, 2-aminobenzothiazole and 2-hydroxy-1,4-naphthoquinone using oxalic acid and proline based deep eutectic solvent as an effective catalyst and environmentally benign reaction medium under microwave irradiation. The current method can be readily scaled up to a preparative scale with some advantages such as cleaner reaction profile, short reaction time, high yields, simple workup procedure and avoidance of the use of toxic organic solvents and chromatographic separation.

Acknowledgments

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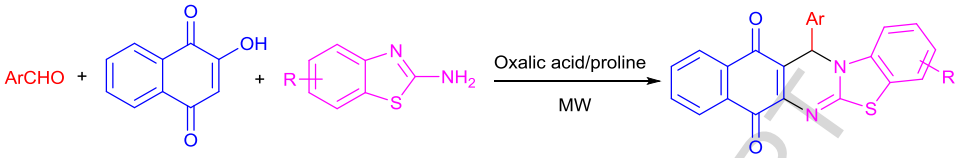
Graphical abstract

Low melting oxalic acid/proline mixture as dual solvent/catalyst for efficient synthesis of 13-aryl-13H-benzo[g]benzothiazolo[2,3-b]quinazoline-5,14-diones under microwave irradiation

Cui-Ting Ma, Peng Liu, Wei Wu, Zhan-Hui Zhang*



Highlights

- The preparation of oxalic acid and proline based deep eutectic solvent is very easy.
- The DES plays dual role as solvent and catalyst for one-pot three-component reaction.
- The separation and purfication procedure are very simple.
- The DES can be easily recovered and reused.