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ORIGINAL PAPER

One-pot solvent-free synthesis of 2, 3- disubstituted 4(3*H*)- quinazolinones catalyzed by long-chain double SO_3H-functionalized Brønsted acidic ionic liquids under microwave irradiation

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Abstract A solvent-free approach for synthesis of 2, 3-disubstituted 4(3*H*)-quinazolinones by condensation of anthranilic acid with acyl chlorides and aromatic/aliphatic amines using two long chain double SO_3H-functionalized acdic ionic liquids as catalyst under microwave irradiation was reported. Under optimized conditions, the reactions completed within 4–8 min and gave the target compounds in the yields of 76–94 %. Two ionic liquids could be recovered readily and recycled three times without any significant loss in their catalytic activity.

Keywords Brønsted acid · Ionic liquids · Multi-components · Microwave irradiation · 4(3H)-quinazolinone

Introduction

2, 3-Disubstituted 4(3*H*)-quinazolinones are an important class of fused aromatic heterocycles with a broad spectrum of biological activities [1–7]. Traditionally, these compounds were prepared by condensation of isatoic anhydride, amines and orthoesters in the presence of acid catalysts [8]; other commonly used synthetic method involves the amidation of benzoxazinones with arylamines [9]. However, these methods are limited in that only aryl groups at C-2 or N-3 position are tolerated. In order to overcome this limitation, novel synthetic approaches have been developed such as intramolecular aza-Wittig [10], Niementowski reaction [11], Appel salt transformation [12], and solid-phase synthesis using aldehydes as C2 unit [13]. However, these methods also suffered from significant limitations, which include multi-step procedure, using costly and toxic reagents, expensive catalysts and organic solvents, harsh reaction conditions, low yields, long reaction time, complex experimental processes and work-up, etc. Considering the importance of this class of molecules, finding greener alternative procedure appears highly desirable.

More recently, acidic ionic liquids as green solvent and catalysts in organic liquids transformations have attracted increasing attentions. For example, single sulfonic acid functionalized Brønsted acidic ionic liquids (SBAILs) $[(CH_2)_4SO_3HMIM][HSO_4]$ [14], $[(CH_2)_4SO_3HPy][HSO_4]$ [14], and Lewis acidic ionic liquids $Bi(TFA)_3$-[nbp]$FeCl_4$ [15], which as green solvents and catalysts had been successfully applied to the synthesis of 4(3*H*)-quinazolinones. These reports demonstrated the advantages of reactions carried out in one-pot under solvent-free conditions with high yields; the products can be isolated and purified easily and ionic liquids could be recycled. Unfortunately, these methods are only applicable for the synthesis of 3-substituted and 2-substituted 4(3*H*)-quinazolinones. Herein, we describe a practical, rapid and simple procedure for synthesis of 2, 3-disubstituted 4(3*H*)-quinazolinones via multi-component reactions of anthranilic acid, acyl chlorides and alkyl- or arylamines using two long-chain double SO_3H-functionalized **SBAILs-1** and **2** as reusable catalysts under microwave irradiation and solvent-free conditions. This synthetic strategy combines the merits of ionic liquids and microwave irradiation for the green synthesis of 2, 3-disubstituted 4(3*H*)-quinazolinones (Fig. 1).

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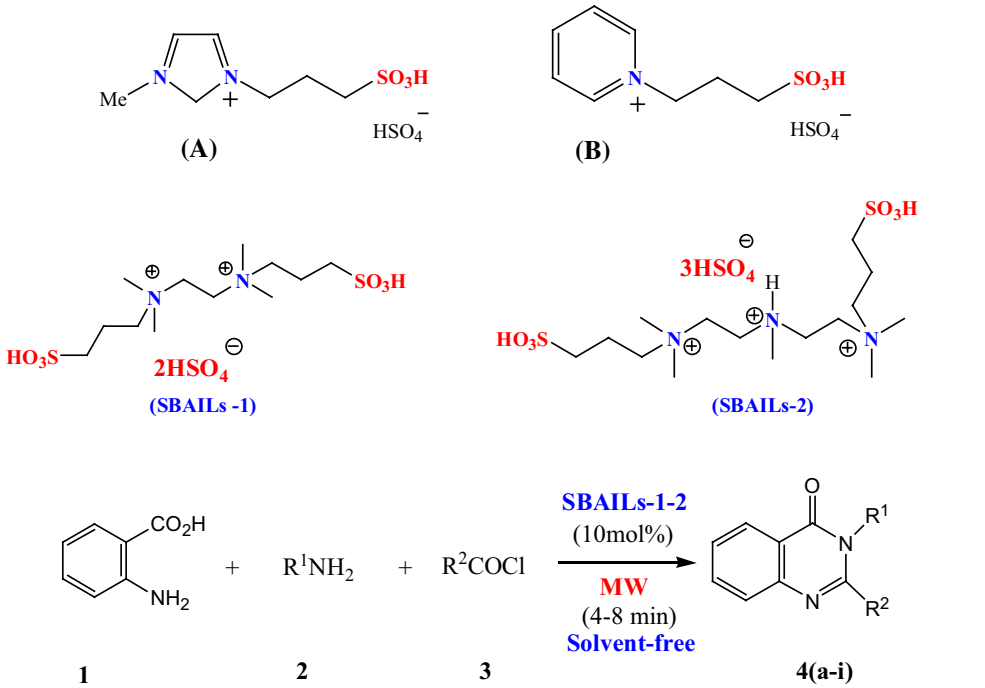

a) $R^1=R^2=C_6H_5$, b) R^1=4-MeC_6H_4, $R^2=C_6H_5$, c) R^1=4-ClC_6H_5, $R^2=C_6H_5$

d) R^1=4-$NO_2C_6H_4$, $R^2=C_6H_5$, e) R^1=4-CNC_6H_4, $R^2=C_6H_5$, f) $R^1=n$-C_4H_9, $R^2=C_6H_5$

g) $R^1=C_6H_5$, $R^2=n$-$C_{15}H_{31}$, h) R^1= 4-MeC_6H_4, $R^2=n$-$C_{15}H_{31}$, i) R^1=4-ClC_6H_4, $R^2=n$-$C_{15}H_{31}$

j) R^1=4-$NO_2C_6H_4$, $R^2=n$-$C_{15}H_{31}$, k) $R^1=n$-C_4H_9, $R^2=n$-$C_{15}H_{31}$

Fig. 1 Synthesis of 2,3-disubstituted 4(3*H*)-quinazolinones in the presence of long-chain double SO_3H-functionalized acidic ionic liquids under microwave irradiation

Results and discussion

With the aim to develop green, efficient, and generality approaches for synthesis of 2, 3-disubstituted 4(3*H*)-quinazolinones, the reaction of anthranilic acid with benzoyl chloride and aniline using **SBAILs-1** and **2** as catalyst under microwave irradiation were chosen as model reactions. Under the optimum conditions, the results of reactions are summarized in Table 1. **SBAILs-1** and **2** both exhibited high catalytic activity and led to excellent yields in 4 min after simple work-up. Based on this success, we further expanded the range of substrates, and the results are listed in Table 1. All reactions proceeded smoothly and gave the corresponding 2, 3-disubstituted 4(3*H*)-quinazolinones with good to excellent yields. These good results may be ascribed to the following facts: (1) The strong polarity of **SBAILs-1** and **2**. Which promote the intermediate benzoxazinone conversion into diamide via the ring opening reaction [9, 18]. (2) The excellent solubility of **SBAILs-1** and **2** in water. The water generated during the cyclization of diamide could enter into the ionic liquids phase easily from the organic substrates, which induced a spontaneous phase separation, this behavior drive the reaction being carried out completely. (3) The microwave irradiation effect [19]. The reaction of anthranilic acid with benzoyl chloride and aniline was carried out at 80 °C for 8 h in a oil bath was investigated, the 2, 3-diphenyl 4(3*H*)-quinazoline was obtained in the yield of 27 %. Thus, microwaves have an essential influence on the progress of the reaction.

As shown in Table 1, due to substituent effect, there are no the corresponding 4(3*H*)-quinazolines were obtained for aromatic amines with strong electron-withdrawing groups. For the purpose of comparison, the reaction of anthranilic acid with benzoyl chloride and aniline was also carried

Table 1 Synthesis of 2, 3-disubstituted 4(3*H*)-quinazolinone in **SBAILs-1** and **2** under microwave irradiation

Compound no.	R^2	R^1	Time (min)	Yield[b] SBAILs-1/SBAILs-2 (%)	M.p. (°C)	References
4a	Ph	Ph	4	89/86	156–158 (157–158)	[10]
4b	Ph	4-MeC_6H_4	4	87/91	177–179 (177–179)	[11]
4c	Ph	4-ClC_6H_4	6	83/79	188–190 (190)	[13]
4d	Ph	4-$NO_2C_6H_4$	6	0	–	
4e	Ph	4-CNC_6H_4	6	0	–	
4f	Ph	C_4H_9	4	85/82	67–70 (68–70)	[9]
4g	*n*-$C_{15}H_{31}$	Ph	4	92/89	88–90	
4h	*n*-$C_{15}H_{31}$	4-MeC_6H_4	4	94/93	95–97	
4i	*n*-$C_{15}H_{31}$	4-ClC_6H_4	8	82/76	50–53	
4j	*n*-$C_{15}H_{31}$	4-$NO_2C_6H_4$	8	0	–	
4k	*n*-$C_{15}H_{31}$	*n*-C_4H_9	8	0	–	

Reaction conditions:anthranilic acid:acyl chloride:amine:SBAILs = 1:1.2:1.2:0.1 (mol); microwave power is 300 W

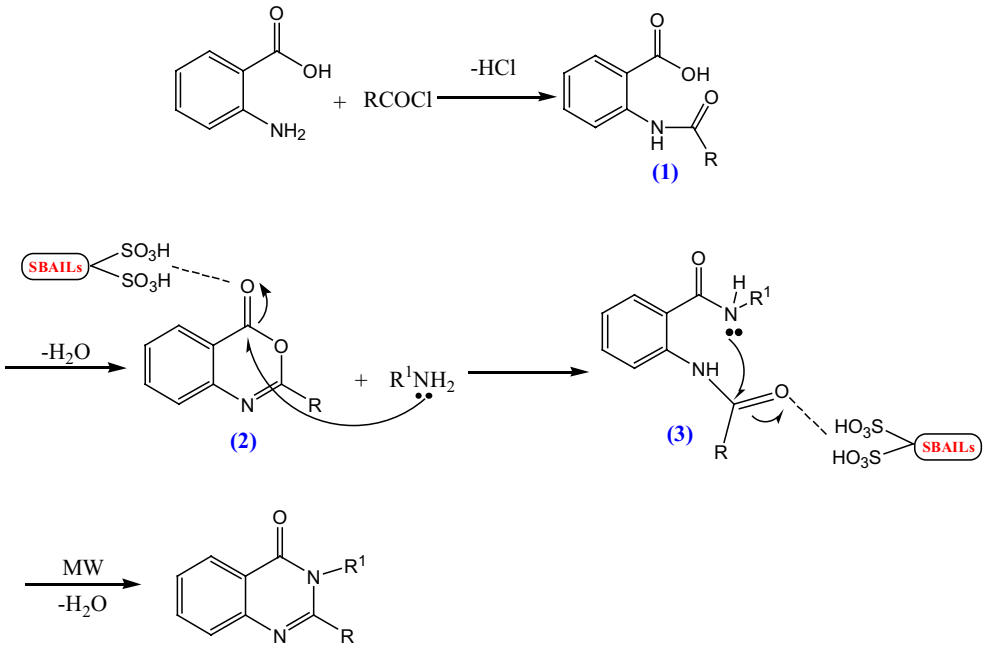

Fig. 2 The proposed mechanism of synthesis of 2, 3-disubstituted 4(3*H*)-quinazolinones catalyzed by long-chain double SO_3H-functionalized Brønsted acidic ionic liquids under microwave irradiation

out in single sulfonic acid functionalized **BAILs A** and **B** (Fig. 1). Under the same reaction conditions, the yields of 2, 3-diphenyl 4(3*H*)-quinazoline were 73 and 69 %, respectively; the reason may be ascribed to the lower acidity of **BAILs A** and **B**.

Based on current experimental results and previous reports [9,18], a plausible mechanism is proposed in Fig. 2. First, anthranilic acid reacted with active acyl chloride and gave intermediate **1**, which then converted into key intermediate **3** by intermolecular cyclization and nucleophlic attack of amines in the presence of **SBAILs-1** and **2**. Finally, the expected products were prepared by intermolecular ring-closure of intermediate **3**.

In order to investigate the recyclable of **SBAILs-1** and **2**, the reaction of anthranilic acid with benzoyl chloride and aniline was chosen as model reaction; the reaction results are listed in Table 2. There are no noticeable decreases in catalyst activity after **SBAILs-1** and **2** have been reused three times. The slight decrease in yields might be due to the slight degradation of **SBAILs-1** and **2** during their regeneration.

Table 2 Recycling of **SBAILs-1-2** in reaction of anthranilic acid with benzoyl chloride and aniline

Run	Molar ratio of acid/chloride/amine/ILs (mol)	MW power (W)	Time (min)	Yield (%) (SBAILs-1/SBAILs-2
1	1:1.2:1.2:0.1	300	4	88/85
2	1:1.2:1.2:0.1	300	4	87/84
3	1:1.2:1.2:0.1	300	4	87/84

Experimental

Materials and methods

IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR (400 MHz) spectra were recorded on Bruker spectrometer in D_2O with DSS as internal standard. The microwave devices were CEM Discover system (Model No. DUS107 manufactured by CEM Company in USA). *N*-Methylimidazole was purified by distillation before use, and the other chemicals were of commercial grade and used as received without further purification unless otherwise stated. Brønsted acidic ionic liquids **SBAILs-1** and **2** [16] and **A** and **B** [17] were synthesized according to the methods reported in the literature cited.

General procedure for the synthesis of 2, 3-disubstituted 4(*3H*)-quinazolinones(***4a-4j***)

A mixture of anthranilic acid (3.6 mmol), acyl chloride (4.3 mmol) and amine (4.3 mmol) was added **SBAILs-1** or **SBAILs-2** (0.36 mmol). After stirring at room temperature for 15 min, the mixture was subjected to microwave irradiation at 300 W for a specified time (Table 2). The progress of the reaction was monitored by TLC (silica gel 60 F 254 TLC plates, ethyl acetate: cyclohexane, 1:1 v/v). On completion, the mixture was washed with water (3 × 30 mL), saturated $NaHCO_3$ solution (3 × 30 mL) and 5 % HCl aqueous (3 × 30 mL), respectively, The rude product was collected and recrystallized in hot ethanol; the target compounds were obtained as crystalline solids.

Characterization data for target compounds

2, 3-Diphenyl 4(3H)-quinazolinone (4a)

White crystal, m.p. 156–158 °C; IR (KBr): 1,683, 1,599, 1,584, 1,555, 1,532, 1,489, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.36 (d, J = 7.2 Hz, 1H), 7.86 (m, 3H), 7.13–7.60 (m, 9H); Anal. Calcd. for $C_{20}H_{14}N_2O$: C, 80.55; H, 4.69; N, 9.39. Found: C, 80.58; H, 4.72; N, 9.41.

2-Phenyl-3-(4-methylphenyl) 4(3H)-quinazolinone (4b)

White crystal, m.p. 177–179 °C; IR (KBr): 3,033, 1,678, 1,604, 1,587, 1,562, 1,510, 808, 768 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.36 (d, J = 7.8, 1H), 7.84 (m, 2H), 7.02–7.62 (m, 10H), 2.50 (s, 3H, –CH_3); Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.78; H, 5.12; N, 8.97. Found: C, 80.75; H, 5.14; N, 9.02.

2-Phenyl-3-(4-chlorophenyl) 4(3H)-quinazolinone(4c)

White crystal, m.p. 188–190 °C;IR (KBr): 3,058, 1,655, 1,596, 1,578, 1,519, 1,491, 824, 691 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.35 (d, J = 7.8, 1H), 7.86 (m, 3H), 7.12–7.62 (m, 9H); Anal. Calcd. for $C_{20}H_{13}N_2ClO$: C, 72.18; H, 3.91; N, 8.42. Found: C, 72.13; H, 3.95; N, 8.39.

2-Phenyl-3-butyl 4(3H)-quinazolinone(4f)

White crystal, m.p. 67–70 °C; IR (KBr): 3,057, 2,957, 1,670, 1,607, 1,587, 1,567, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.34 (d, J = 7.8, 1H), 7.70–7.80 (m, 2H), 7.51–7.62 (m, 2H), 4.02 (t, N–CH_2, 2H), 1.60 (m, 2H), 1.20 (m, 2H), 0.81 (t, 3H); Anal. Calcd. for $C_{18}H_{18}N_2O$: C, 77.70; H, 6.48; N, 10.07. Found: C, 77.68; H, 6.43; N, 10.02.

2-Pentadecyl-3-phenyl 4(3H)-quinazolinone(4 g)

White crystal, m.p. 88–90 °C;IR (KBr): 3,062, 2,918, 1,684, 1,608, 1,589, 1,572, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 8.27 (d, J = 7.8, 1H), 7.78 (m, 1H), 7.12-7.64 (m, 7H), 2.52 (t, J = 7.4, N–CH_2, 2H), 1.02–1.73 (m, 26H), 0.91 (t, J = 7.2, –CH_3, 3H); Anal. Calcd. for $C_{29}H_{40}N_2O$: C, 80.57; H, 9.25; N, 6.78. Found: C, 80.55; H, 9.24; N, 6.74.

2-Pentadecyl-3-(4-methylphenyl) 4(3H)-quinazolinone(4 h)

White crystal, m.p. 95–97 °C; IR (KBr): 3,062, 2,918, 1,661, 1,595, 1,571, 1,530, 772 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm): 8.28 (d, J = 7.2, 1H), 7.78 (m, 1H), 7.50-7.70 (m, 2H), 7.12–7.40 (m, 4H), 2.50 (t, J = 7.6, N–CH_2, 2H), 1.02–1.70 (m, 26H), 0.91 (t, J = 7.2, –CH_3, 3H); Anal. Calcd. for $C_{30}H_{42}N_2O$: C, 80.73; H, 9.41; N,6.27. Found: C, 80.75; H, 9.39; N, 6.24.

2-Pentadecyl-3-(4-chlorophenyl) 4(3H)-quinazolinone(4i)

White crystal, m.p. 50–53 °C; IR (KBr): 3,063, 2,917, 1,682, 1,607, 1,589, 1,571, 1,490, 831, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ(ppm) 8.26 (d, J = 7.8, 1H), 7.78 (d, J = 7.2, 1H), 7.51–7.72 (m, 2H), 7.11–7.40 (m, 4H),

2.42 (t, $J = 7.4$, N–CH_2, 2H), 1.70 (m, 2H), 1.20–1.42 (m, 24H), 0.90 (t,–CH_3, 3H); Anal. Calcd. for $C_{29}H_{39}ClN_2O$: C, 74.62; H, 8.36; N, 6.00. Found: C, 74.64; H, 8.32; N, 5.96.

SBAILs-1 and 2 recovery and reuse

After reaction, the aqueous phase that contained the **SBAILs-1** or **SBAILs-2** was collected and washed thoroughly with ethyl ether (3 × 7.5 mL) and dried at 105 °C for 8 h under high vacuum, then reused for the next run.

Conclusions

A three-component condensation of anthranilic acid with acyl chlorides and aromatic/aliphatic amines in the presence of two long-chain double SO_3H-functionalized acidic ionic liquids was studied under solvent-free and microwave irradiation conditions. This method combines the merits of both ionic liquids and microwave irradiation and provides a rapid, simple, high efficient and eco-friendly approach for the synthesis 2,3-disubstituted 4(3*H*)-quinazolinone.

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