Ultrasound Promoted and Ionic Liquid Catalyzed Cyclocondensation Reaction for the Synthesis of 4(3*H*)-Quinazolinones

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4(3*H*)-Quinazolinones were synthesized in high yields by one-pot three-component condensation of anthranilic acid, carboxylic acid and aniline in the presence of ionic liquid such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) as catalyst under solvent free and neutral conditions.

Keywords 4(3*H*)-quinazolinone, ionic liquid, ultrasound

Introduction

Combinatorial chemistry is playing an increasingly important role as one of the tools of modern medicinal chemistry as the rapid discovery of new leads.[1] The preparation of libraries of small organic molecules is a rapidly evolving area of research.[2] Recently much attention has been devoted towards 4(3*H*)-quinazolinones derivatives due to their significant therapeutic and medicinal properties such as anti-inflammatory,[3] anti-convulsant,[4] anti-hypertensive,[5] antimalarial,[6] anti-parkinsons activities[7] and they also show blood platelet anti-aggregating activity.[8] Therefore, several methods for synthesis of substituted 4(3*H*)-quinazolinones have been reported in the literature.[9] However, some of these methods are associated with one or more disadvantages such as long reaction time, harsh reaction conditions, unsatisfactory yields, tedious work-up, use of environmentally toxic reagents or solvents and use of large amount of solid supports, which result in the generation of a large amount of toxic waste. Consequently, there is scope for further development of mild reaction conditions, better yields, free of organic solvent and easy synthetic procedure.

Ultrasound irradiation has been increasingly used in organic synthesis in last three decades, than traditional methods, which is more conveniently and easily controlled. A large number of organic reactions have been carried out in higher yields, shorter time and milder conditions under ultrasound irradiation.[10-12] Recently, significant progress has been made in the application of ionic liquids to catalytic processes.[13,14]

Ionic liquids are the salts of organic heterocyclic cations and inorganic anions. They exist in liquid state at ambient temperature; hence, reactions in the presence of ionic liquids need no additional solvent. Ionic liquids have attracted much attention due to their unique physical and chemical properties such as thermal stability, negligible vapour pressure, ability to dissolve a large range of organic and inorganic compounds, easy recyclability, milder reaction conditions, better yields and shorter reaction time.[15] Various reactions have been reported recently using ionic liquids as a catalyst,[16] reaction medium[9b,17] and rate enhancer.[9b]

Experimental

General procedure

Melting points were determined in open glass capillaries and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on a 300 MHz Varian Inova spectrometer in $CDCl_3$ using TMS as an internal standard. Sonication was performed in a Shanghai Branson-CQX ultrasonic cleaner with a frequency of 25 kHz and a nominal power 500 W. The reaction flask was located in the water bath of the ultrasonic cleaner, and the temperature of the water bath was controlled by a current of water at room temperature. Reactions were monitored by TLC on aluminum sheets precoated with silica gel $60F_{254}$. Column chromatography was performed using silica gel (60—120 mesh size). All the products are known compounds and characterized by comparing their IR, ^{1}H NMR, ^{13}C NMR and melting points with those reported in literature.

Typical procedure for the synthesis of 3-(4-chloro phenyl)-4(3*H*)-quinazolinone (4b) A mixture of anthranilic acid (0.01 mol), formic acid (0.01 mol), 4-chloroaniline (0.01 mol) and $BMImBF_4$ (0.01 mol) was irradiated at room temperature under ultrasound

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irradiation for 10 min. The reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with Et_2O (3×15 mL). The organic layer was washed with water and dried over anhydrous $MgSO_4$. Organic solvent was evaporated and residue was chromatographed on silica gel (ethyl acetate/hexane) to afford the pure product in 93% yield.

Typical procedure for the synthesis of 2-(2-hydroxyphenyl)-3-phenyl-4(3*H*)-quinazolinone (4h) A mixture of anthranilic acid (0.01 mol), 2-hydroxybenzoic acid (0.01 mol), aniline (0.01 mol) and $BMImBF_4$ (0.01 mol) was irradiated at room temperature under ultrasound irradiation for 15 min. The reaction was monitored by TLC. After completion of the reaction, the mixture was extracted with Et_2O (15 mL×3). The organic layer was washed with water and dried over anhydrous $MgSO_4$. Organic solvent was evaporated and residue was chromatographed on silica gel (ethyl acetate/hexane) to afford the pure product in 90% yield.

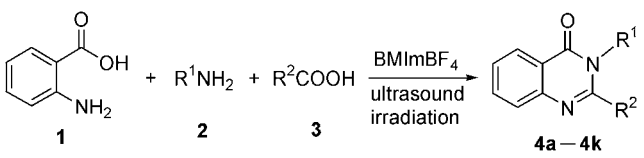
3-(4-Chlorophenyl)-4(3*H*)-quinazolinone (4b) m.p. 182 ℃; ^{1}H NMR ($CDCl_3$ 300 MHz) δ: 8.33 (d, J=7.5 Hz, 1H), 8.13 (s, 1H), 7.68—7.71 (m, 2H), 7.48 (t, J=7.3 Hz, 1H), 7.38 (d, J=7.6 Hz, 2H), 7.25 (d, J=8.6 Hz, 2H); ^{13}C NMR δ: 160.2, 148.8, 146.6, 136.1, 135.2, 134.6, 132.7, 130.5, 128.3, 127.2, 127.8, 125.1; IR ν_{max}: 1696, 1601, 1462 cm^{-1}. Anal. calcd for $C_{14}H_9ClN_2O$: C 65.51, H 3.53, N 10.91; found C 65.50, H 3.41, N 11.0.

Results and discussion

Herein, we report the synthesis of 4(3*H*)-quinazolinones promoted by the ionic liquid catalyst, 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$)[16] at room temperature under ultrasound irradiation in high yields with shorter reaction time.

In the present work, we achieved a one-pot three-component condensation of anthranilic acid (**1**), primary aromatic amine (**2**) and carboxylic acid (**3**) in the presence of ionic liquid ($BMImBF_4$) under the influence of ultrasound irradiation as a new efficient method to produce 4(3*H*)-quinazolinones **4** (Scheme 1). The reaction proceeded at room temperature within a few minutes in excellent yields. Only the reaction with 4-nitroaniline required 50 ℃ temperature and the time required was 20 min. This is due to the presence of an electron withdrawing group.

Scheme 1



Encouraged by this success, we extended the reaction of anthranilic acid and formic acid with a range of other amines under similar conditions. Inspired by high yields obtained in the presence of ionic liquid ($BMImBF_4$), a further study of 4(3*H*)-quinazolinone synthesis was carried out using different aliphatic and aromatic carboxylic acids (Scheme 1). The optimized results are summarized in Table 1.

Table 1 Synthesis of 4(3*H*)-quinazolinone derivatives using ionic liquid ($BMImBF_4$)

Compound[a]	R^1	R^2	Time/min	Yield[b]/%
4a	C_6H_5	H	7	96
4b	4-ClC_6H_4	H	10	93
4c	4-BrC_6H_4	H	12	89
4d	4-MeC_6H_4	H	12	90
4e	4-$MeOC_6H_4$	H	12	92
4f	4-$NO_2C_6H_4$	H	20	77[c]
4g	C_6H_5	C_6H_5	10	93
4h	C_6H_5	2-HOC_6H_4	15	90
4i	C_6H_5	4-MeC_6H_4	15	88
4j	C_6H_5	Methyl	12	88
4k	C_6H_5	Octanyl	12	92

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR and IR spectroscopic data and their m.p. compared with literature values.[9,18] [b] Isolated yields. In parallel non-sonicated experiments, the anthranilic acids were stirred magnetically with primary aromatic amines and carboxylic acids in the presence of $BMImBF_4$ for 30 min at room temperature; no product was detected in the absence of ultrasound. [c] Irradiation at 50 ℃.

Conclusion

In summary, we have found a practical and green synthesis procedure for preparing 4(3*H*)-quinazolinones by condensation of anthranilic acid, primary aromatic amine and carboxylic acid in the presence of ionic liquid ($BMImBF_4$) under ultrasound irradiation. The main advantages of this methodology are simple catalyst system, higher yields, free of organic solvent, and easy synthetic procedure.

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