A Carbon Material as a Strong Protonic Acid for Efficient Synthesis of 4(3*H*)-Quinazolinones

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Carbon-based solid acid catalyst has been applied to catalyzing the synthesis of 4(3*H*)-quinazolinones from the cyclization reaction of 2-aminobenzamide with aroyl chlorides. The results showed that the catalyst was very efficient with the average yield over 85%. This carbon material with strong protonic acid sites as heterogeneous catalyst has some advantages such as high activity, strikingly simple work-up procedure, non-pollution, and reusability, which will contribute to the green process greatly.

Keywords carbon-based solid acid, heterogeneous catalysis, 2-aminobenzamide, aroyl chlorides, cyclization

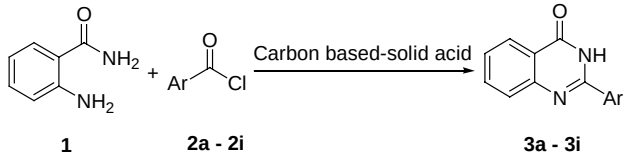
Introduction

Compounds with biological activity are often derived from heterocyclic structures. 4(3*H*)-Quinazolinones are one such class of bioactive fused heterocycles that are widely used as antimalarial,[1] antibacterial,[2] and anticancer drugs.[3] In addition, quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids, such as glycosminine,[4] deoxyvasicinone,[5] and drugs like methaqualone[6] and piriqualone.[7] There are several methods for the synthesis of 4(3*H*)-quinazolinones using I_2/KI,[8] $Yb(OTf)_3$,[9] $NaHSO_3$,[10] *P*-toluenesulfunic acid/DDQ,[11] TBAB,[12] $SnCl_4$•$4H_2O$,[13] and SiO_2•$FeCl_3$[14] as catalysts. However, most of these multi-step procedures have significant drawbacks such as long reaction times, low yields of the products, harsh reaction conditions, difficult work-up, and the use of expensive and environmentally toxic catalysts, reagents, or media. Furthermore, some of the starting materials have to be synthesized and purified first, hence these methods are time-consuming. Therefore, the development of simple and efficient methods for the synthesis of 4(3*H*)-quinazolinones is desirable.

Replacement of conventional toxic and pollutant Brønsted and Lewis acid catalysts with environmentally benign and reusable solid heterogeneous catalysts is an active area of current research. New catalysts may include acidic zeolites, sulfated zirconia and acidic groups containing resins. Using solid acid catalyst has some advantages such as low of equipments, ease of products separation, recycling of the catalyst and environmental acceptability as compared to liquid acid catalyst.[15] Moreover, ideal solid acid catalysts should have high stability and numerous strong protonic acid sites. Carbon-based solid acid catalyst with having such properties can be successfully used instead of liquid acid catalysts such as sulfuric acid.[16-18] It is also insoluble in common organic solvents, causes low corrosion, and shows environmental acceptability. Furthermore, the products could be easily separated from the reaction mixture and the catalyst is recoverable without decreasing its activity. To the best of our knowledge there are no examples on the use of carbon-based solid acids as catalyst for the synthesis of 4(3*H*)-quinazolinones.

Due to our interest in the synthesis of heterocyclic compounds,[19-23] and in continuation of our previous works on the applications of reusable acid catalysts in organic reactions,[24-31] herein we wish to report the new efficiently synthesis of 4(3*H*)-quinazolinones catalyzed by carbon-based solid acid (Scheme 1).

Scheme 1



1 **2a - 2i** **3a - 3i**

Experimental

All chemicals were available commercially and used without additional purification. The catalyst was synthesized according to the literature. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained using a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (100 & 500 MHz) spectra were recorded with a Bruker DRX500 & AC100 spectrometers.

Preparation of carbon-based solid acid

The carbon-based solid acid was prepared according to the reported procedure by Hara and co-workers.[16]

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Naphthalene (20 g) was heated in concentrated sulfuric acid (>96%, 200 mL) at 250 ℃ under a flow of N_2. After heating for 15 h, excess sulfuric acid was removed from the dark brown tar by vacuum distillation at 250 ℃ for 5 h, which resulted in a black solid. The solid was then ground to a powder and was washed repeatedly in boiling water until impurities such as sulfate ions were no longer detected in the wash water. The density of the SO_3H group was measured using NaOH (0.01 mol/L) as titrant by acid-base potentiometric titration. The amount of SO_3H attached to the polycyclic aromatic carbon was 2.84 mmol/g.

General procedure for the synthesis of 4(3*H*)-quinazolinones catalyzed by carbon-based solid acid

A mixture of 2-aminobenzamide (2 mmol), aroyl chloride (2 mmol) and carbon-based solid acid (0.12 g) as catalyst in ethanol (2 mL) was heated under reflux for the appropriate time. The reaction was monitored by TLC. After completion of the reaction, the catalyst was separated by filteration. The product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol to give compounds **3a**—**3i** in good to high yields.

Recycling and reusing of the catalyst

The catalyst is insoluble in hot ethanol and could therefore be recycled by a simple fitration. The separated catalyst was washed with ethanol, dried at 60 ℃ under vacuum for 1 h and reused in another reaction without appreciable reduction in the catalytic activity.

Results and discussion

At the outset, the synthesis of compound **3a** was selected as a model reaction to optimize the reaction conditions. Therefore, 2-aminobenzamide **1** with benzoyl chloride **2a** were reacted in ethanol in the presence of various amount of carbon based solid acid as catalyst. The efficiency of the reaction is mainly affected by the amount of the catalyst (Table 1). It showed that a trace amount of product could be detected in the absence of this catalyst in refluxing ethanol (Entry 1), which indicated that the catalyst should be necessary for this cyclocondensation reaction. When the amount of the catalyst was increased, a ramp in the yield of the product **3a** was observed. The optimal amount of the catalyst was 0.12 g (Entry 13); increasing the amount of the catalyst beyond this value did not increase the yield noticeably (Entries 14, 15).

Furthermore, the reaction was carried out in ethanol at different temperatures to assess the effect of temperature on the reaction yield. As can be seen from Table 1, the shortest time and best yield were achieved in reflux conditions.

Also, the reaction was carried out in other solvents and under solvent-free conditions. As shown in Table 2, the compound **3a** was obtained in high yield in EtOH and *n*-PrOH but in moderate yields in MeOH, CH_2Cl_2, THF, CH_3CN, H_2O and also in solvent-free conditions. In last cases, some starting materials were recycled and increasing the time of the reaction did not increase the yield of the product. Although there is no significant difference between EtOH and *n*-PrOH as solvent in the model reaction, howevere, EtOH was selected as solvent in all subsequent reactions.

Table 1 Results of the synthesis of 2-phenyl-4(3*H*)-quinazolinone **3a** under different conditions[a]

Entry	Amount of carbon-based solid acid/g	*T*/℃	Time/min	Yield[b]/%
1	None	78	60	Trace
2	0.04	r.t	60	26
3	0.04	55	60	35
4	0.04	78	60	40
5	0.08	r.t	45	49
6	0.08	55	45	62
7	0.08	78	40	66
8	0.10	r.t	40	59
9	0.10	55	40	68
10	0.10	78	30	75
11	0.12	r.t	40	67
12	0.12	55	30	77
13	0.12	78	20	88
14	0.14	78	20	88
15	0.16	78	20	89

[a] 2 mmol 2-aminobenzamide, 2 mmol benzoyl chloride in ethanol. [b] Isolated yields.

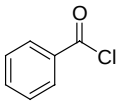
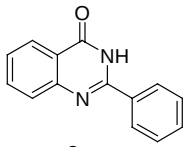
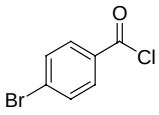
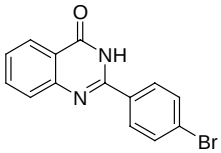
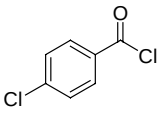
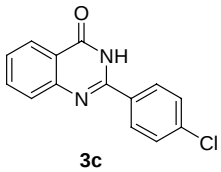
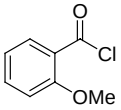
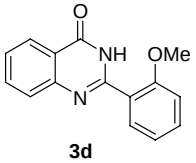
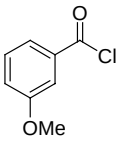
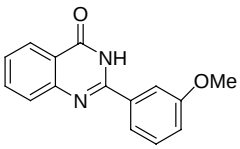
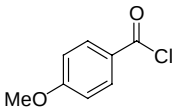
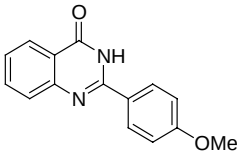
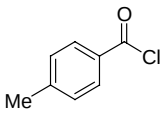
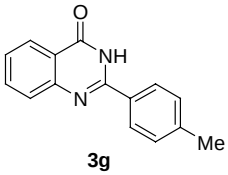
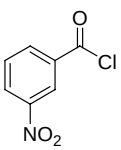
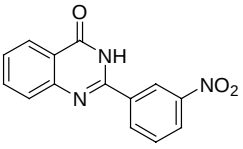
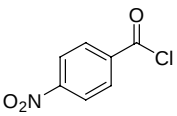
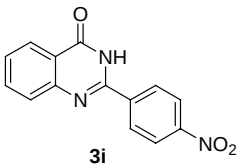
Table 2 Synthesis of 2-phenyl-4(3*H*)-quinazolinone **3a** in the presence of carbon-based solid acid (0.12 g) in different solvents at reflux temperature (for Entry 8 at 100 ℃)

Entry	Solvent	Time/min	Yield[a]/%
1	MeOH	30	63
2	EtOH	20	88
3	*n*-PrOH	20	87
4	CH_2Cl_2	60	58
5	THF	45	50
6	CH_3CN	40	56
7	H_2O	30	54
8	Solvent-free	25	52

[a] Isolated yields.

Encouraged by this success, we extended the reaction of 2-aminobenzamide with a range of other aroyl chlorides under the optimized reaction conditions. In all cases the expected products were obtained in high yields in short reaction times. The results are summarized in Table 3. As shown, aroyl chlorides with substituents carrying either electron-donating or electron-withdrawing groups reacted successfully and gave the products in high yields.

Table 3 Synthesis of 4(3*H*)-quinazolinones **3a**—**3i** in the presence of carbon-based solid acid (0.12 g) in ethanol at reflux conditions

Entry	Aroyl chloride	Product[a]	Time/min	Yield[b]/%	m.p./℃
1		 **3a**	20	88	234—236 [Lit.[8]]
2		 **3b**	15	93	317—319 [Lit.[8]]
3		 **3c**	15	92	304—307 [Lit.[8]]
4		 **3d**	20	87	210—218 [Lit.[8]]
5		 **3e**	20	86	213—215 [Lit.[8]]
6		 **3f**	18	89	248—250 [Lit.[8]]
7		 **3g**	15	91	242—243 [Lit.[8]]
8		 **3h**	13	94	352—354 [Lit.[8]]
9		 **3i**	14	92	362—365 [Lit.[8]]

[a] All the products were characterized by IR spectral data and comparision of their melting points with those of authentic samples. Also, the structures of some products were confirmed by ^{1}H NMR spectral data. [b] Isolated yields

Reusability of the catalyst was also investigated. After the completion of the reaction, the catalyst was separated by a simple filtration, dried at 60 ℃ under vacuum for 1 h, and reused for next reactions. The obtained results are summarized in Table 4. As it shown in this table, the catalyst could be used at least three times without appreciable reduction in the catalytic activity.

Table 4 The comparison of efficiency of carbon-based solid acid in the synthesis of 4(3*H*)-quinazolinones after three times

Entry	Ar	Yield[a]/%		
		First run	Second run	Third run
3a	C_6H_5	88	89	86
3g	4-$CH_3C_6H_4$	91	90	88
3h	3-$NO_2C_6H_4$	94	91	90

[a] Isolated yields.

Conclusion

In conclusion, although other procedures for the preparation of 4(3*H*)-quinazolinones have been reported, our method is more effective because of its ease, simplicity, mildness of conditions, high product yields and catalyst type. We believe this applicability of carbon based solid acid with strong acidic properties, easy work up with a gradual decline of its activity makes our method superior over other reported methods to synthesize 4(3*H*)-quinazolinones and find usefulness in organic methodologies.

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