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Highly efficient synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by using homogeneous catalysts in mixture of green solvents

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Abstract: A simple and highly efficient procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones has been developed through cyclocondensation of 2-aminobenzamide with aromatic aldehydes using homogenous catalysts such as succinic acid, 2,3-diboromosuccinic acid and tartaric acid at room temperature in water and ethanol as solvent. This method has notable advantages in terms of simple workup, short reaction time and high yields.

Keywords: 2,3-Dihydroquinazolin-4(1*H*)-ones, Succinic acid, 2,3-Diboromosuccinic acid, Tartaric acid.

Introduction

Quinazolin-4(1*H*)-ones are an important class of fused heterocycles with an array of biological activities such as inhibition of humane erythrocyte purine nucleoside phosphorylase [1] and poly(ADP-ribose) polymerase [2], antagonist [3], anti-tumor [4], anti-inflamatory [5], insecticidal and anti-microbial [6] activity. They are also important building-blocks in total synthesis of natural products [7] and are the constituents of some isolated naturally occurring alkaloids [8]. A number of synthetic methods have been reported to prepare this class of compounds in the past few years. These include the use of iridium, [9] citric acid, [10] [bmim]HSO4, [11] iodine, [12] ammonium chloride, [13] gallium trifluoro methane sulfonate, [14] ionic liquids, [15] bronsted acids, [16] phosphoric acid, [17] copper chloride, [18] tetra butyl ammonium bromide, [19] and TiCl4/Zn [20].

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However, most of the reported methods suffer from tedious procedures and often from low yields. Therefore, simpler and high yield approaches towards this valuable nucleus is much desirable.

In recent years, homogenous catalysts have been widely used in organic synthesis because of their operational simplicity, low cost, ease of preparation and handling, stability, lack of toxicity, economical and environmental consideration. Some of these homogeneous catalysts are tartaric acid succinic acid and 2,3-diboromosuccinic acid.

Tartaric acid is one of the most concentrated naturally occurring organic acids in grapes and wine and it is as a by-product of wine production that tartaric acid is prepared on an industrial scale. It is also used in the production of jams, sweets, tinned fruit and vegetables, coca powder and frozen dairy produce; mainly as an acidity adjuster but also in the form of an emulsifier. Also, tartaric acid is added to foods in order to give a sour taste too. In addition, tartaric acid also

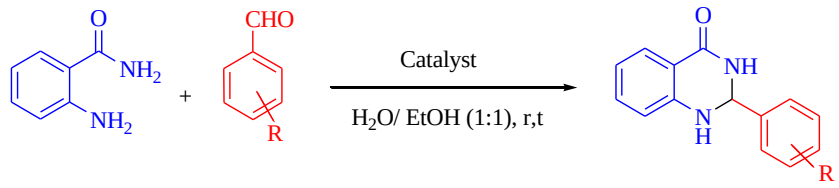
usually serves as a starting substance for numerous chemical reactions, especially for chiral synthesis [21].

Succinic acid is a dicarboxylic acid [22], and has received a great deal of attention as a green feed stock for the manufacture of synthetic resins, biodegradable polymers and chemical intermediates [23]. The production of chemicals and fuels at a low cost by fermentation makes available an alternative route of chemical feed stock [24], and the medium cost is a key aspect in the fermentative production of biochemicals and biofuels [25].

In continuation of our previous work for the synthesis of pharmaceutically compounds [26-32], herein, we report the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of some homogenous catalysts such as succinic acid, 2,3-diboromosuccinic acid and tartaric acid at room temperature and compare the results to each others.

Results and discussion

In our study a simple and highly efficient procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones has been developed through cyclocondensation of 2-aminobenzamide with aromatic aldehydes using homogenous catalysts such as tartaric acid, succinic acid and 2,3-diboromosuccinic acid at room temperature in water and ethanol as solvent (Scheme **1**).



Catalysts: Succinic acid, 2,3-Dibromosuccinic acid, Tartaric acid

Scheme 1: Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones in the presence of catalysts.

Initially, for the reaction optimization, we choose 2-aminobenzamide and benzaldehyde as model reaction to investigate several solvents in presence of homogenous catalysts. The results are shown in table **1**. As it is shown, among all solvents, water/ethanol (1:1) is the best solvent for the reaction.

Table 1: The solvent effects on time and yield of the reaction of 2-aminobezamide with benzaldehyde in the presence of catalyst (15 mol%).

Entry	solvent	Succinic acid		2,3-diboromosuccinic acid		Tartaric acid	
		Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1	H_2o	60	57	30	67	25	70
2	EtOH	50	64	25	79	20	68
3	MeOH	40	60	50	80	16	60
4	EtOAC	120	54	55	72	19	82
5	CH_3CN	90	30	15	79	17	70
6	**EtOH /H_2O (1:1)**	**35**	**83**	**7**	**90**	**10**	**94**

Continually assess of homogenous catalysts were investigated. When the reaction was carried out in the absence of any catalyst the product was not detected. In the presence of homogenous catalyst, the reaction was possible, and in order to determine the appropriate concentration of the catalyst used, we investigated the model reaction at different concentrations of catalyst. The product was formed in different yield, respectively. Use of just 2 mol % of 2,3-diboromosuccinic acid, 15 mol % of tartaric acid and 20 mol % of succinic acid and is sufficient to push the reaction forward and higher amounts of the catalyst did not improve the results to any greater extent (Table **2**).

Table 2: Optimization amount of catalysts for the reaction of 2-aminobenzamide with benzaldehyde under EtOH/H_2O (1:1) at room temperature.

Entry	Catalyst (mol%)	Succinic acid		2,3-dibromosuccinic acid		Tartaric acid	
		Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
1	2	60	43	**4**	**98**	30	76
2	5	48	56	4	98	25	82
3	10	40	75	5	93	14	92
4	15	35	83	7	90	**10**	**94**
5	20	**30**	**90**	10	85	10	94

Encouraged by this result, in order to build the generality of the reaction, our attention moved to the reactions of other aromatic aldehydes, and the results are summarized in Table **3**. As expected, this reaction proceeded smoothly and the desired products were obtained in good to excellent yields. A series of aldehydes attaching to aromatic ring were investigated. The substitution groups on the aromatic ring had no obvious effect on the yield (Table **3**).

Table 3. The synthesis of 2,3-dihydro-4(1*H*)-quinazolinone.

Entry	R	Succinic acid			2,3-dibromosuccinic acid			Tartaric acid		
		Time (min)	Yield (%)	M.p (°C)	Time (min)	Yield (%)	M.p (°C)	Time (min)	Yield (%)	M.p (°C)
1	H	30	90	220	4	98	219	10	94	220
2	2-Cl	10	99	204	10	89	202	4	97	204
3	4-Cl	10	90	199	15	86	202	8	93	200
4	4-OMe	50	94	182	6	95	180	4	98	183
5	4-Me	40	94	223	45	84	223	3	93	220
6	3,4-di-OMe	50	90	204	4	60	211	3	98	209
7	4-OH-3-OMe	45	95	222	10	91	218	13	91	217

From the data in table **2** we understand that the amount of loading catalyst from 2,3-diboromosuccinic is less than tartaric acid and succinic acid for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, and it is a good economic feature for this homogenous catalyst, but from the data in table **3** it can be concluded that tartaric acid and succinic acid have better yields and also tartaric acid's reaction time is the best. Moreover we know that tartaric acid and succinic acid are very green, available and eco-friendly catalysts than 2,3-diboromosuccinic too. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.

Conclusion

In conclusion, a highly efficient synthetic method of 2,3-dihydroquinazolin-4(1*H*)- ones has been found through cyclocondensation of 2-aminobenzamide with

aromatic aldehydes using homogenous catalysts such as tartaric acid, succinic acid and 2,3-diboromosuccinic acid at room temperature in water and ethanol as solvent . This procedure was accompanied with several advantages, such as easy workup, short reaction time, and high yields. Further investigations on the application of this kind of catalyst are underway in our laboratory.

Experimental

Melting points and IR spectra were measured on a Electrothermal 9100 apparatus and a JASCO FT/ IR-460 plus spectrometer, respectively. The ^{1}HNMR spectra were obtained on Bruker DRX- 400 Avance instruments with $CDCl_3$ as a solvent. All reagents and solvents obtained from Fluka and Merck were used without further purification.

General procedure for the synthesis of 2,3-dihydro-4(1H)-quinazolinone

2-aminobenzamide (1.0 mmol) and aldehyde (1.0 mmol) was successively added to a solution of catalyst in water and ethanol in the ratio of (1:1) at room temperature. The progress of the reaction is monitored by TLC (ethyl acetate: petroleum ether 3:1). After completion of the reaction, the reaction mixture was filtered by addition of ethanol to afford the crude product. Then the crude product was purified by recrystallization from ethanol.

2,3-dihydro-3-phenyl-2-(p-tolyl)quinazolin-4(1H)-one

^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.41 (s, 3H, CH_3), 4.38 (s, 1H, NH), 5.73 (s, 1H, NH), 5.88 (s, 1H, CH), 6.68 (d, *J*=8.0 Hz, 1H, H_{Ar}), 6.92 (t, *J*=7.2 Hz, 1H, H_{Ar}), 7.27 (d, *J*=8.0 Hz, 2H, H_{Ar}), 7.35 (td, *J*=7.2, 1.6 Hz, 1H, H_{Ar}), 7.49 (d, *J*=8.0 Hz, 2H, H_{Ar}), 7.96 (dd, *J*=8.0, 1.6 Hz, 1H, H_{Ar}).

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