Tris(hydrogensulfato)boron catalysed rapid synthesis of 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones under solvent-free conditions

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Aldehydes or ketones react readily in one-pot with isatoic anhydride and ammonium salts in the presence of tris-(hydrogensulfato)boron to produce the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones in high yields under solvent-free conditions. The use of tris(hydrogensulfato)boron makes this process quite simple, more convenient and environmentally friendly. 2,3-Dihydroquinazolin-4(1*H*)-one derivatives have interesting biological and pharmacological activities.

Keywords: dihydroquinazolinones, isatoic anhydride, tris(hydrogensulfato)boron, solvent-free conditions

Heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products. Recently, the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives have attracted great interest due to their biological and pharmacological activities.[1,2] They have been useful biological and pharmacological properties, such as anticancer,[3] anti-inflammatory,[4] and anticonvulsant[5] activities. Quinazolinones are also important building blocks in the synthesis of natural products.[6–8] Therefore, considerable efforts have been made to explore new, simple, and direct approaches towards the construction of quinazolin-4(1*H*)-one skeleton, for example, via Pd-catalysed heterocyclisation of nitroarenes[9] solid-phase synthesis of 2-arylamino-substituted quinazolinones.[10] One of the most common approaches is the cyclisation of anthranilamides with aldehyde in the presence of various catalysts.[11–15]

Recently, three-component one-pot condensation of isatoic anhydride, aldehydes and ammonium salts has been reported for the construction of 2,3-dihydroquinazolin-4(1*H*)-one derivatives under different conditions.[16–21] Although, these approaches are satisfactory for synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones, the harsh reaction conditions, expensive reagents, use of toxic organic solvents and long reaction times limit the use of these methods.

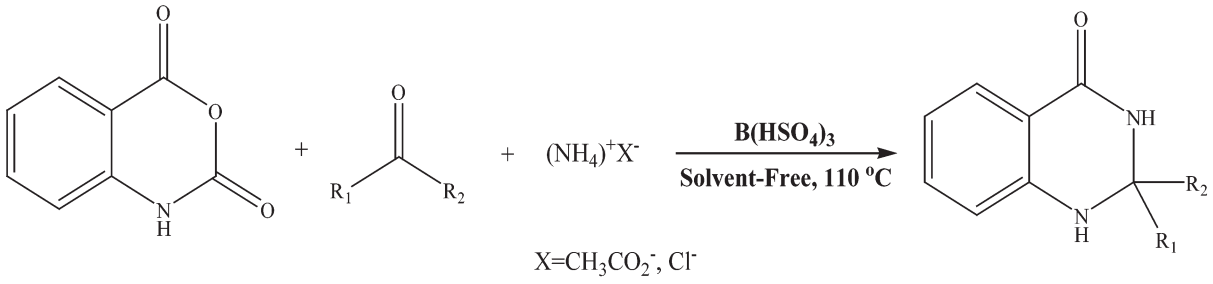
Due to our interest in the development of practical, safe, and environmentally friendly procedures for important organic transformations[22–25], we now describe a simple and efficient protocol for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones based on a three-component reaction of isatoic anhydride, aldehydes/ketones and ammonium salts using catalytic amounts of tris(hydrogensulfato)boron as a solid heterogeneous catalysts under solvent-free conditions (Scheme 1).

Tris(hydrogensulfato)boron ($B(HSO_4)_3$) was easily prepared by addition of chlorosulfonic acid to boric acid under N_2 atmosphere at room temperature. This reaction was easy and clean, because HCl gas was immediately evolved from the reaction vessel. This catalyst is safe and easy to handle (Scheme 2).[26]

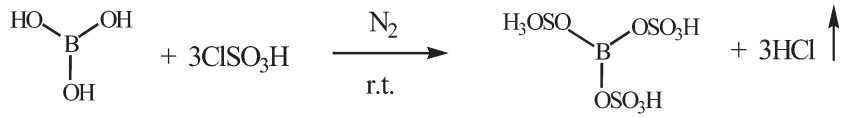
Investigations were initiated with benzaldehyde being chosen as a model compound. It was condensed with isatoic anhydride and ammonium acetate in the presence of tris(hydro gensulfato)boron under different conditions. The best yield of 80%, was obtained at 110 °C after 5 minutes using 0.036 g of tris(hydrogensulfato)boron.

Using the optimised conditions, we explored the scope of the one-pot three-component cyclocondensation reaction. As shown in Table 1, arrays of aldehydes bearing either electron-donating or electron-withdrawing groups on the aromatic ring were successfully reacted with isatoic anhydride and ammonium acetate to produce their corresponding 2,3-dihydroquinazolin-4(1*H*)-one in high yields with short reaction times. The substitution group on the phenyl ring did not make any difference to this reaction. The work-up procedure is very straightforward; that is, the products were isolated and purified by simple filtration. Our protocol avoids the use of organic solvents during the reaction process, making it superior to the previous methods.

The reaction can also proceed with ammonium chloride and provide the target products in reasonable yield (Table 1). In all



Scheme 1



Scheme 2

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Table 1 Synthesis of 2-substituted 2,3-dihydroquinazolin-4(1*H*)-one

Entry	Aldehyde/Ketone	X	Time /min	Yield/%	M.p. /°C (found)	M.p. /°C (lit.)
1	Benzaldehyde	$CH_3CO_2^-$	5	80	216–218	218–220[19]
2	4-Chlorobenzaldehyde	$CH_3CO_2^-$	5	81	204–206	205–206[16]
3	4-Methoxybenzaldehyde	$CH_3CO_2^-$	3	79	189–191	192–193[17]
4	2-Chlorobenzaldehyde	$CH_3CO_2^-$	5	80	205–207	208–210[22]
5	4-Methylbenzaldehyde	$CH_3CO_2^-$	3	86	227–230	233–234[2o]
6	3-Nitrobenzaldehyde	$CH_3CO_2^-$	8	78	216–218	216–217[17]
7	4-Nitrobenzaldehyde	$CH_3CO_2^-$	15	76	206–208	213–214[17]
8	4-Bromobenzaldehyde	$CH_3CO_2^-$	5	79	200–202	200–200[16]
9	4-Fluorobenzaldehyde	$CH_3CO_2^-$	5	82	205–206	205–206[16]
10	Cyclohexanone	$CH_3CO_2^-$	5	80	223–225	217–219[21]
11	Cyclopentanone	$CH_3CO_2^-$	5	83	250–252	257–26[21]
12	Benzaldehyde	Cl^-	5	79	216–218	218–220[19]
13	4-Chlorobenzaldehyde	Cl^-	5	76	204–206	205–206[16]
14	4-Methoxybenzaldehyde	Cl^-	5	73	189–191	192–193[17]
15	2-Chlorobenzaldehyde	Cl^-	5	78	205–207	208–210[22]
16	4-Methylbenzaldehyde	Cl^-	5	82	227–230	233–234[2o]
17	3-Nitrobenzaldehyde	Cl^-	10	70	216–218	216–217[17]
18	4-Nitrobenzaldehyde	Cl^-	5	71	206–208	213–214[17]
19	4-Bromobenzaldehyde	Cl^-	5	72	200–202	205–206[16]
20	4-Fluorobenzaldehyde	Cl^-	5	74	205–206	205–206[16]

Table 2 Comparison the results of tris(hydrogensulfato)boron with other catalysts reported in the literature

Entry	Conditions	Time /min	Yield/%	Ref.
1	$Ga(OTf)_3$ (1 mol%), EtOH, 70 °C	35–70	71–91	17
2	Copolymer-PTSA (0.3 g), EtOH, reflux	5–7 h	70–94	18
3	$[Bmim]BF_4$ (3.0 ml), H_2O, 80 °C	55–75	77–90	19
4	Montmorillonite K-10 (0.3 g), EtOH, reflux	4–7 h	70–95	20
5	$B(HSO_4)_3$ (0.036 g), solvent-free, 110 °C	3–15	70–86	This paper

these cases, the corresponding 2,3-dihydroquinazolin-4(1*H*)-ones were obtained in good yields at 110 °C under solvent-free conditions without formation of any side products. It is important to note that the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones could not be achieved in the absence of catalyst.

Moreover, the condensation of ketones with isatoic anhydride and ammonium salts was also successfully carried out under the same conditions and the corresponding 2,3-dihydro-4(1*H*)-quinazolinones were obtained in high yields and short reaction times (Table 1, entries 10–11). All products are known compounds and structures of them were confirmed by comparison with their known physical and spectral (NMR and IR) data.[16–21]

In order to compare the current protocol with previously published methods for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-one, we carried out the studies described in Table 2. These results, clearly demonstrate that tris(hydrogensulfato) boron is a good catalyst with respect to reaction times and yields of the obtained products.

In conclusion, we have described a successful strategy for the efficient and rapid synthesis of 2-substituted 2,3-dihydroquinazolinones in a one-pot, three-component cyclocondensation reaction of isatoic anhydride, aldehydes or ketones and ammonium salts using tris(hydrogensulfato)boron as catalyst at 110 °C under solvent-free conditions. The notable features of this procedure are high yields of products, operational simplicity, enhanced reaction rates, cleaner reaction profiles and ease of isolation of products, which make this process quite simple, more convenient and environmentally benign for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones.

Experimental

All chemicals were commercially available and used without further purification. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The NMR spectra were recorded on a Bruker250MHz spectrometer. Tris(hydrogensulfato) boron has been prepared according to reported method.[26]

Synthesis of 2,3-dihydroquinazolin-4(1H)-ones; general procedure

A mixture of isotoic anhydride (1 mmol), aldehyde/ketone (1 mmol), ammonium acetate or chloride (1 mmol) and tris(hydrogensulfato)boron (0.036 g) was stirred at 110 °C for the appropriate time indicated in Table 1. The progress of reactions was monitored by TLC (ethyl acetate/n-hexane). After completion of the reaction, a solid was obtained. It was washed with water and purified by recrystalisation from ethanol to afford pure products.

2-(4-Fluorophenyl)-2,3-dihydroquinazolin-4(1H)-one: IR(KBr): 3424, 3300, 3184, 2924, 1655, 1611, 1515 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 5.74 (1H, s, CH), 6.65–6.73 (2H, m, ArH), 7.08 (2H, s, NH), 7.16–7.24 (3H, m, ArH), 7.48–7.60 (3H, m, ArH), 8.27 (1H, s, N-CO).

2-(4-Nitrophenyl)-2,3-Dihydroquinazolin-4(1H)-one: IR(KBr): 3445, 3280, 2922, 2854, 1647, 1610, 1519, 1519 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ = 5.88 (1H, s, CH), 6-63–6.75 (2H, m, ArH), 7.21–7.27(1H, m, ArH), 7.33 (1H, s, NH), 7.58(1H, d, *J* = 7.75 Hz, ArH), 7.71 (2H, d, *J* = 7.5, ArH), 8.23 (2H, d, *J* = 7.5 Hz, ArH), 8.53 (1H, s, NH–CO).

2-(4-Methylphenyl)-2,3-Dihydroquinazolin-4(1H)-one: IR(KBr): 3312, 3194, 3062, 2934, 1658, 1610 cm^{-1}, ^1H NMR (250 MHz, DMSO-d_6): δ = 2.26 (3H, s, CH_3), 5.67 (1H, s, CH), 6.60–6.72 (2H, m, ArH), 7.04 (1H, s, NH), 7.14–7.23 (3H, m, ArH), 7.34 (2H, d, *J* = 7.75 Hz, ArH), 7.57 (1H, d, *J* = 7.5 Hz, ArH), 8.23 (1H, s, NH–CO).

2-(2-Chlorophenyl)-2,3-dihydroquinazolin-4(1H)-one: IR(KBr): 3361, 3194, 3064, 2922, 1646, 1615, 1503 cm^{-1}, ^1H NMR (250 MHz, DMSO-d_6): δ = 6.11 (1H, s, CH), 6.69–6.75 (2H, m, ArH), 7.0 (1H, s, NH), 7.20–7.23 (1H, m, ArH),7.36–7.40 (3H, m, ArH), 7.63 (2H, d, *J* = 6.25 Hz, ArH), 8.21 (1H, s, NH–CO).

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