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Strontium chloride-catalyzed one-pot synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones in protic media

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Abstract

A wide range of mono- and disubstituted 2, 3-dihydroquinazolin-4(1*H*)-ones were obtained in high yields by condensation of isatoic anhydride, aldehydes with ammonium salts or primary amines in the presence of strontium chloride in aqueous ethanol under reflux.

Keywords: 2, 3-Dihydroquinazolin-4(1*H*)-ones; One-pot synthesis; Strontium chloride; Isatoic anhydride

2, 3-Dihydroquinazolinones constitute an important class of heterocycles with a wide range of biological and pharmaceutical activities, such as anticancer, antibacterial, and diuretic [1–3]. Additionally, these compounds can be oxidized to their corresponding quinazolin-4(3*H*)-ones, an important biologically active compounds [4], by $KMnO_4$ in dimethylacetamide [5].

In view of these useful properties, development of a simple, environmentally benign, high-yielding, and clean method for the synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones is still in demand. Several strategies for their synthesis were already developed: (a) condensation of anthranilamide with an aldehyde or ketone using *p*-toluenesulfonic acid as a catalyst [1]; (b) desulfurization of 2-thioxo-4(3*H*)-quinazolinones [6]; (c) reaction of isatoic anhydride with Schiff-bases [7]; (d) one-step conversion of 2-nitrobenzamides to 2, 3-dihydro-4(1*H*)- quinazolinones [8]; (e) condensation of anthranilamide with benzil [9]; (f) two-step synthesis starting from isatoic anhydride and amines, then annulated with ketones [10]; (g) a one-pot three-component condensation of isatoic anhydride, aldehydes and amines [11,12]. Among above methods, strategy (g) is one of the most direct procedures for the preparation of 2, 3-dihydroquinazolin-4(1*H*)-ones and their derivatives. It is a type of multi-component reactions (MCRs), which can produce the desired products in a single step and also the diversity could be achieved simply by varying the reacting components. Recently, different acid catalysts like *p*-TsOH [13], silica sulfuric acid [14], $Zn(PFO)_2$ [15], $Ga(OTf)_3$ [16], ionic liquid [17], $Al(H_2PO_4)_3$ [18], I_2 [19], Montmorillonite K-10 [20], Amberlyst-15 [21], Al/Al_2O_3 and Fe_3O_4 nanoparticles [22,23], copolymer-PTSA [24], MCM-41-SO_3H [25], silica-bonded *N*-propylsulfamic acid [26], *etc.* have been reported to affect this MCR condensation. However, some of these methods associated with certain drawbacks such as long reaction time, low yields, expensive and large amount of catalyst, high reaction temperature,

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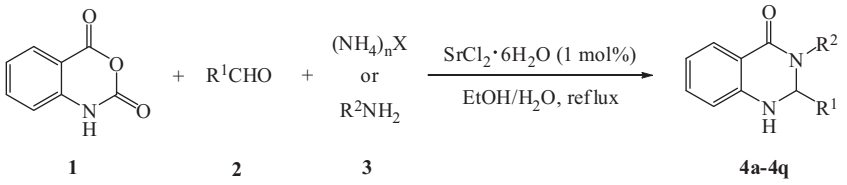


Scheme 1. One-pot three-component synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones.

and using microwave irradiation for accelerated synthesis. Thus, there is a need for a greener and milder method that might work under mild conditions.

In the course of our recent work on Lewis acid-catalyzed organic reactions, we found only 1 mol% strontium chloride ($SrCl_2{\cdot}6H_2O$) could efficiently catalyze one-pot synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones *via* three-component condensation of isatoic anhydride **1**, aldehyde **2** and ammonium salts or primary amines **3** (Scheme 1). The reaction was carried out in aqueous ethanol under reflux.

1. Experimental

Typical procedure for the synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones (**4**): a stirred mixture of isatoic anhydride (5.5 mmol), aldehyde (5 mmol), ammonium salt or primary amine (5.5 mmol) and $SrCl_2{\cdot}6H_2O$ (0.05 mmol) in 3 mL EtOH/H_2O (1/3 (v/v)) was refluxed for an appropriate time. When the reaction completed (monitored by TLC), the reaction mixture was cooled to room temperature. The corresponding pure product was obtained by gravity filtration, washed with 3 × 10 mL 50% aqueous ethanol solution (v/v) for three times, and crystallized from EtOH. The products were characterized by IR, ^{1}H NMR, LC/MS, and elemental analysis. Spectral data for new compounds:

2, 3-Dihydro-2-(2-chlorophenyl)-3-phenyl-quinazolin-4(1H)-one (**4i**): White crystal. IR (KBr, cm^{-1}): 3309, 3070, 2361, 1637, 1606, 1491, 1452, 757. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.77 (dd, 1H, J = 1.3, 6.4 Hz), 7.60–7.58 (m, 1H), 7.46 (d, 1H, J = 2.5 Hz), 7.39–7.37 (m, 1H), 7.31–7.27 (m, 5H), 7.21–7.17 (m, 3H), 6.79–6.74 (m, 2H), 6.60 (d, 1H, J = 2.7 Hz). MS (ESI) *m/z*: 335 ([M+H]$^+$, 100), 336 (23), 337 (36), 338 (8), 315 (6). Anal. Calcd. for $C_{20}H_{15}N_2OCl$: C, 71.74; H, 4.52; N, 8.37. Found: C, 71.89; H, 4.60; N, 8.43%.

2, 3-Dihydro-2-(4-nitrophenyl)-3-(4-methylphenyl)-quinazolin-4(1H)-one (**4m**): Pale blue crystal. IR (KBr, cm^{-1}): 3650, 3030, 2361, 1660, 1594, 1515, 1457, 762. ^{1}H NMR (500 MHz, DMSO-d_6,) δ: 10.41 (s, 1H), 8.82 (s, 1H), 8.37 (d, 2H, J = 8.7 Hz), 8.20 (d, 2H, J = 8.7 Hz), 7.84 (dd, 1H, J = 1.0, 6.5 Hz), 7.62–7.56 (m, 3H), 7.45 (t, 1H, J = 7.4 Hz), 7.36 (d, 1H, J = 7.8 Hz), 7.12 (d, 2H, J = 8.3 Hz), 2.25 (s, 3H). MS (ESI) *m/z*: 360 ([M+H]$^+$, 100), 361 (25), 358 (7), 227 (8). Anal. Calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.78; N, 11.69. Found: C, 70.01; H, 4.84; N, 11.77%.

2, 3-Dihydro-2-phenyl-3-n-propyl-quinazolin-4(1H)-one (**4o**): White crystal. IR (KBr, cm^{-1}): 3303, 3065, 2361, 1630, 1588, 1507, 1458, 748. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.65 (dd, 1H, J = 1.2, 6.5 Hz), 7.34–7.27 (m, 6H), 7.18 (dt, 1H, J = 1.5, 6.8 Hz), 6.66–6.62 (m, 2H), 5.83 (d, 1H, J = 2.5 Hz), 3.86–3.81 (m, 1H), 2.75–2.69 (m, 1H), 1.63–1.41 (m, 2H), 0.82 (t, 3H, J = 7.4 Hz). MS (ESI) *m/z*: 267 ([M+H]$^+$, 100), 268 (19). Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.82; N, 10.52. Found: C, 76.82; H, 6.75; N, 10.64%.

2, 3-Dihydro-2-phenyl-3-benzyl-quinazolin-4(1H)-one (**4q**): White crystal. IR (KBr, cm^{-1}): 3401, 3023, 2361, 1633, 1580, 1502, 1447, 749. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.70 (dd, 1H, J = 1.4, 6.4 Hz), 7.36–7.20 (m, 12H), 6.69–6.63 (m, 2H), 5.74 (d, 1H, J = 2.6 Hz), 5.34 (d, 1H, J = 15.4 Hz), 3.83 (d, 1H, J = 15.4 Hz). MS (ESI) *m/z*: 315 ([M+H]$^+$, 100), 316 (24). Anal. Calcd. for $C_{21}H_{18}N_2O$: C, 80.22; H, 5.78; N, 8.91. Found: C, 80.07; H, 5.84; N, 8.82%.

2. Results and discussion

To study the effect of solvent on the condensation, a one-pot reaction of isatoic anhydride (5.5 mmol), benzaldehyde (5 mmol) and ammonium acetate (5.5 mmol) was chosen as a model reaction in the presence of 1 mol% $SrCl_2{\cdot}6H_2O$ (Table 1). Because of the toxicity of organic solvents, we only consider the green media such as pure water, EtOH, and EtOH/H_2O. The results show that EtOH/H_2O (1/3 (v/v)) system was the best choice (entry 5).

We also investigated the optimal amount of solvent and catalyst. After several trials, the suitable amounts of solvent and catalyst are 3 mL and 1 mol% (based on aldehyde), respectively.

Table 1
Screening of different solvents.

Entry	Solvent	Time (h)	Isolated yield (%)
1	EtOH	2.0	73
2	H_2O	1.0	66
3	EtOH/H_2O (1/1, v/v)	1.0	81
4	EtOH/H_2O (3/1, v/v)	1.5	69
5	EtOH/H_2O (1/3, v/v)	0.7	93

Solvent is 3 mL.

Next, we study the application scope of this protocol (Table 2). As anticipated, all reactions proceeded smoothly to give the corresponding mono- or disubstituted 2, 3-dihydroquinazolin-4(1*H*)-ones. The aldehydes with either electron-withdrawing or electron-donating groups were all suitable for use. Moreover, the position of the substituents on the aromatic ring had no effects on this conversion. In addition, no desired products were isolated when aliphatic aldehydes and furfural were subjected to isatoic anhydride and ammonium salts or amines.

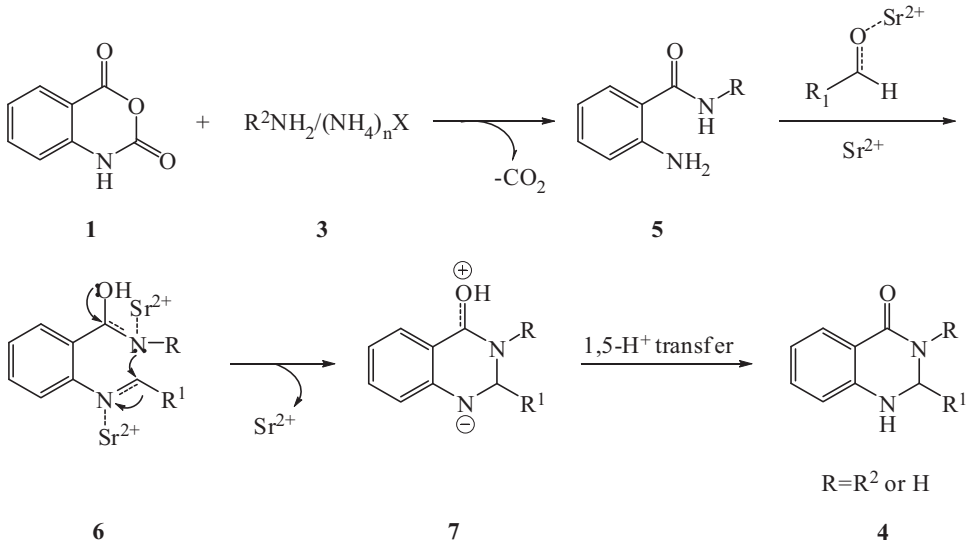
To compare the efficiency of ammonium salts, the reactions were carried out with different ammonium sources such as acetate, carbonate, and chloride under the same conditions (entries 1–9). Monosubstituted 2, 3-dihydroquinazolin-4(1*H*)-ones were produced in good yields with ammonium acetate and ammonium carbonate, however, nothing was obtained with ammonium chloride. Further, treatment of isatoic anhydride, aromatic aldehydes with primary aromatic and aliphatic amines in the presence of strontium chloride afforded disubstituted derivatives of 2, 3-dihydroquinazolin-4(1*H*)-one in good yields (entries 10–19).

We propose the following mechanism to account for the $SrCl_2$-catalyzed reaction (Scheme 2) [16]. First, isatoic anhydride **1** is activated by $SrCl_2$ followed by the *N*-nucleophilic attacks of amine on the carbonyl. After loss of carbon dioxide, 2-amino-*N*-substituted-benzamide **5** was generated. Subsequently, the activated aldehyde reacted with **5** to afford intermediate **6**, which could be converted to intermediate **7** by an intramolecular cyclization. Finally, mono- and disubstituted 2, 3-dihydroquinazolin-4(1*H*)-ones **4** could be formed by 1, 5-proton transfer of **7**.

In summary, we have introduced an efficient approach for the synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones *via* a three-component condensation of isatoic anhydride, aromatic aldehydes and ammonium salts or primary amines in the presence of $SrCl_2{\cdot}6H_2O$. The method has several advantages such as high yields of products, short reaction time,

Table 2
$SrCl_2{\cdot}6H_2O$-catalyzed one-pot reaction of isatoic anhydride, aromatic aldehydes and ammonium salts or primary amines.

Entry	R^1	$(NH_4)_nX$ or R^2	Time (h)	Product	Yield (%)	Mp (°C)
1	C_6H_5	NH_4OAc	0.7	**4a**	93	218–220 [20]
2	2-ClC_6H_4	NH_4OAc	1.5	**4b**	90	208–210 [27]
3	4-ClC_6H_4	NH_4OAc	1.0	**4c**	92	205–207 [16]
4	2, 4-$Cl_2C_6H_3$	NH_4OAc	3.0	**4d**	94	165–167 [27]
5	3-$NO_2C_6H_4$	NH_4OAc	1.5	**4e**	90	197–199 [27]
6	4-MeC_6H_4	NH_4OAc	0.5	**4f**	91	222–223 [28]
7	4-$MeOC_6H_4$	NH_4OAc	0.5	**4g**	93	181–183 [20]
8	C_6H_5	$(NH_4)_2CO_3$	0.7	**4a**	94	218–220 [20]
9	C_6H_5	NH_4Cl	6.0	**4a**	0	–
10	C_6H_5	C_6H_5	1.5	**4h**	94	215–217 [16]
11	2-ClC_6H_4	C_6H_5	2.0	**4i**	92	212–214
12	4-$CH_3OC_6H_4$	C_6H_5	1.5	**4j**	95	203–204 [15]
13	C_6H_5	4-ClC_6H_4	1.5	**4k**	90	209–211 [15]
14	C_6H_5	4-$CH_3C_6H_4$	1.2	**4l**	98	196–198 [15]
15	4-$NO_2C_6H_4$	4-$CH_3C_6H_4$	1.0	**4m**	93	212–214
16	C_6H_5	Et	6.0	**4n**	42	135–137 [20]
17	C_6H_5	*n*-Pr	6.0	**4o**	87	123–125
18	C_6H_5	*n*-Bu	6.0	**4p**	75	124–126 [15]
19	C_6H_5	$C_6H_5CH_2$	6.0	**4q**	77	160–161



Scheme 2. Proposed mechanism.

simple work-up procedures, inexpensive, nontoxic, and environmental friendly catalyst and solvent, which makes it a valuable contribution for the synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones.

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