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Strontium chloride-catalyzed one-pot synthesis of 4(3*H*)-quinazolinones under solvent-free conditions

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Abstract

Strontium chloride was used as an efficient and recyclable catalyst in one-pot condensation of anthranilic acid, ortho esters and amines leading to the formation of 4(3*H*)-quinazolinone derivatives in good yields at room temperature under solvent-free conditions.

Keywords: 4(3*H*)-Quinazolinones; One-pot synthesis; Solvent-free conditions; Strontium chloride

The synthesis of 4(3*H*)-quinazolinones and their derivatives has attracted considerable attention from organic and medicinal chemists for many years because most of them showed wide pharmacological and therapeutic properties such as antimalarial, antitumor, anticonvulsant, antiinflammatory, and antimicrobial activities [1–5]. In addition, 4(3*H*)-quinazolinones are present in several bioactive natural products [6,7]. Their properties turn them very interesting targets to organic chemists, and several strategies for their synthesis were already developed: (a) cyclocondensation of anthranilamide with aryl, alkyl or heteroaryl aldehydes in refluxing ethanol [8]; (b) poly(ethylene glycol) supported aza-Wittig reaction [9]; (c) intramolecular cyclization of fluorine-containing *S*-ethyl *N*-benzoylisothioureas [10]; (d) cyclocondensation of 2-fluorobenzoyl chlorides with 2-amino-*N*-heterocycles [11]; (e) copper-catalyzed cascade reactions of the substituted 2-halobenzoic acids with amidines [12]; (f) reaction of polymer-bound isothiourea with isatoic anhydride [13]; (g) reaction of anthranilic acids and ammonium or triethylammonium *N*-aryldithiocarbamates [14]; (h) a one-pot three-component condensation of anthranilic acid, ortho esters and amines [15–22]. Among above methods, strategy (h) is one of the most direct procedures for the preparation of 4(3*H*)-quinazolinones 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. Different acid catalysts like $NaHSO_4$, Amberlyst-15, Yb(III)-resin, $Yb(OTf)_3$, $[Bi(TFA)_3$-nbp$]FeCl_4$ ionic liquid, $La(NO_3)_3{\cdot}6H_2O$, *p*-toluenesulfonic acid, Keggin-type heteropolyacid under microwave irradiation, $SnCl_4{\cdot}4H_2O$, and SiO_2–$FeCl_3$ are known to affect this condensation [15–22]. However, some of these methods associated with certain drawbacks such as refluxed temperature (60–80 °C), long reaction time (20 h),

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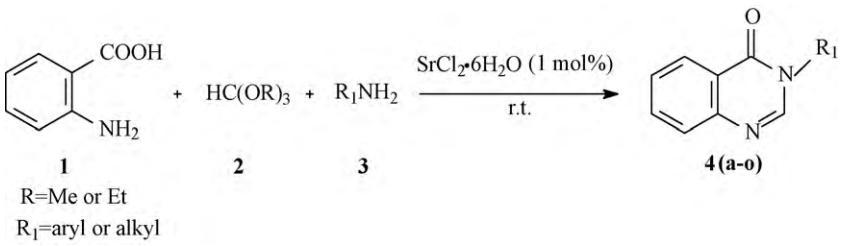

Scheme 1.

harmful organic solvent, and using microwave irradiation for accelerated synthesis. Thus, there is a need for a greener and efficient 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 4(3*H*)-quinazolinones *via* three-component condensation of anthranilic acid **1**, ortho esters **2** and amines **3** (Scheme 1). The reaction was carried out at room temperature under solvent-free conditions. The products **4** were formed within a few minutes in excellent yields.

1. Experimental

Typical procedure for the synthesis of 4(3*H*)-quinazolinones (**4**): a mixture of anthranilic acid (10 mmol) **1**, an orthoester (12 mmol) **2**, an amine (12 mmol) **3**, and $SrCl_2 \cdot 6H_2O$ (0.1 mmol) was stirred at room temperature for an appropriate time (Table 2). The reaction was monitored by TLC. After completion, 20 mL CH_2Cl_2 was added to dissolve the solid product. Then, catalyst was removed by gravity filtration and dried for its next use. The organic filtrate was evaporated to yield the crude product. The crude product was purified by recrystalization from ethanol to give the corresponding pure compound **4**. All the pure products were identified by their mp, IR, ^{1}H NMR, MS and elemental analysis. Analytical data for new compounds:

3-(2-Methylphenyl)quinazolin-4(3H)-one (**4b**). White solid. IR (KBr, cm^{-1}): 1689, 1594, 1489. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.31 (d, 1H, J = 7.2 Hz), 7.75–7.50 (m, 2H), 7.24–7.07 (m, 5H), 2.31 (s, 3H). MS (ESI) *m/z*: 237.0 $(M+H)^+$. Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 76.26; H, 5.12; O, 6.77. Found: C, 76.35; H, 5.09; O, 6.74%.

3-(2-Methoxyphenyl)quinazolin-4(3H)-one (**4e**). White solid. IR (KBr, cm^{-1}): 1682, 1595, 1455. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.21 (d, 1H, J = 7.7 Hz), 7.45 (d, 1H, J = 6.8 Hz), 7.24 (t, 1H, J = 7.0 Hz), 7.08–7.03 (m, 2H), 6.93 (t, 1H, J = 7.1 Hz), 6.78 (d, 1H, J = 8.2 Hz), 6.54 (t, 1H, J = 7.3 Hz), 3.85 (s, 3H). MS (ESI) *m/z*: 253.0 $(M+H)^+$. Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.80; O, 12.68. Found: C, 71.35; H, 4.81; O, 12.70%.

3-(4-Methoxyphenyl)quinazolin-4(3H)-one (**4f**). White solid. IR (KBr, cm^{-1}): 1715, 1591, 1453. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.05 (d, 1H, J = 7.5 Hz), 7.54–7.51 (m, 2H), 7.17 (t, 1H, J = 7.5 Hz), 6.97 (dd, 4H, J = 8.5, 9.5 Hz), 3.76 (s, 3H). MS (ESI) *m/z*: 253.0 $(M+H)^+$. Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.80; O, 12.68. Found: C, 71.30; H, 4.84; O, 12.73%.

3-(2-Chlorophenyl)quinazolin-4(3H)-one (**4g**). Yellow solid. IR (KBr, cm^{-1}): 1668, 1601, 1413. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.01 (d, 1H, J = 7.7 Hz), 7.74–7.71 (m, 2H), 7.61 (t, 1H, J = 7.6 Hz), 7.25–7.16 (m, 2H), 6.76 (d, 1H, J = 8.1 Hz), 6.52 (t, 1H, J = 7.2 Hz). MS (ESI) *m/z*: 257.0 $(M+H)^+$. Anal. Calcd. for $C_{14}H_9ON_2Cl$: C, 65.51; H, 3.53; O, 6.23; N, 10.91. Found: C, 65.42; H, 3.55; O, 6.26; N, 10.96%.

3-(4-Chlorophenyl)quinazolin-4(3H)-one (**4h**). Pale yellow solid. IR (KBr, cm^{-1}): 1671, 1616, 1484. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.52 (s, 1H), 7.71–7.68 (m, 2H), 7.24–7.20 (m, 2H), 6.75 (d, 2H, J = 7.5 Hz), 6.52 (d, 2H, J = 7.2 Hz). MS (ESI) *m/z*: 257.0 $(M+H)^+$. Anal. Calcd. for $C_{14}H_9ON_2Cl$: C, 65.51; H, 3.53; O, 6.23; N, 10.91. Found: C, 65.62; H, 3.50; O, 6.19; N, 10.85%.

3-(4-Bromophenyl)quinazolin-4(3H)-one (**4i**). White solid. IR (KBr, cm^{-1}): 1712, 1586, 1443. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.01 (d, 1H, J = 7.6 Hz), 7.60 (t, 1H, J = 7.5 Hz), 7.46–7.44 (m, 4H), 7.19 (d, 2H, J = 7.5 Hz,). MS (ESI) *m/z*: 302.0 $(M+H)^+$. Anal. Calcd. for $C_{14}H_9ON_2Br$: C, 55.84; H, 3.01; O, 5.31; N, 9.30. Found: C, 55.75; H, 3.03; O, 5.35; N, 9.24%.

3-(4-Carboxylphenyl)quinazolin-4(3H)-one (**4m**). White solid. IR (KBr, cm^{-1}): 1701, 1592, 1483. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.35 (s, 1H), 7.92–7.88 (m, 3H), 7.71 (t, 2H, J = 8.5 Hz), 7.63 (d, 1H,

Table 1
Screening of different Lewis acid catalysts[a].

Entry	Catalyst	Time (h)	Isolated yield (%)
1	None	1	5
2	$CuCl_2·2H_2O$	1	50
3	$Cu(o\text{-}CH_3C_6H_4SO_3)_2·4H_2O$	0.8	62
4	$AlCl_3·6H_2O$	0.5	67
5	$La(CH_3SO_3)_3·2H_2O$	1	84
6	I_2	1	90
7	$ZnCl_2$	0.8	92
8	$(NH_4)_2Ce(NO_3)_6$	0.6	94
9	$SrCl_2·6H_2O$	0.6	99, 97, 94, 91[b]

[a] Reaction conditions: anthranilic acid (10 mmol), triethyl orthoformate (12 mmol), aniline (12 mmol), catalyst (0.1 mmol), room temperature.
[b] Catalyst was reused four times.

J = 5.5 Hz), 7.31 (d, 1H, J = 8.5 Hz), 6.56 (d, 1H, J = 5.5 Hz). MS (ESI) m/z: 267.0 $(M+H)^+$. Anal. Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.67; H, 3.79; O, 18.03. Found: C, 67.59; H, 3.78; O, 18.06%.

3-Benzylquinazolin-4(3H)-one (**4n**). White solid. IR (KBr, cm^{-1}): 1678, 1620, 1459. ^1H NMR (500 MHz, DMSO-d_6): δ 8.52 (s, 1H), 8.00 (d, 1H, J = 7.5 Hz), 7.54–7.46 (m, 2H), 7.41–7.37 (m, 4H), 7.32 (t, 1H, J = 6.8 Hz), 7.14 (t, 1H, J = 7.0 Hz), 4.63 (s, 2H). MS (ESI) m/z: 237.0 $(M+H)^+$. Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 76.26; H, 5.12; O, 6.77. Found: C, 76.35; H, 5.09; O, 6.75%.

2. Results and discussion

First, we compared the catalytic activity of $SrCl_2·6H_2O$ with other Lewis acids in the model condensation of anthranilic acid, triethyl orthoformate and aniline (Table 1). A controlled experiment was carried out first; the results show that little product was produced after 1 h (Entry 1). Screening of different catalysts revealed that $SrCl_2·6H_2O$ was the most effective catalyst for this transformation since it resulted in the highest yield in short reaction time. Only 1 mol% $SrCl_2·6H_2O$ was enough to catalyze the transformation. The recyclability of $SrCl_2·6H_2O$ was also investigated, and it could be recycled four times without distinct loss of activity (Entry 9).

In order to explore the generality and scope of the new procedure, three-component one-pot reaction of anthranilic acid with triethyl orthoformate or trimethyl orthoformate and different substituted aryl amines or alkyl amine was tested and the results were listed in Table 2. Most reactions proceeded smoothly in the presence of 1 mol% $SrCl_2·6H_2O$

Table 2
$SrCl_2·6H_2O$-catalyzed one-pot reaction of anthranilic acid with ortho esters and amines[a].

Product (**4**)	R_1	Isolated yield (%) (time (h))		Mp (°C)	
		$HC(OEt)_3$	$HC(OMe)_3$	Found	Reported [17]
4a	Ph	99 (0.6)	58 (3)	140–142	139–140
4b	$2\text{-}MeC_6H_4$	83 (0.4)	94 (1.5)	157–159	–
4c	$3\text{-}MeC_6H_4$	74 (2.5)	55 (5.5)	138–140	136–137
4d	$4\text{-}MeC_6H_4$	83 (0.3)	85 (1)	145–148	146–147
4e	$2\text{-}MeOC_6H_4$	96 (0.6)	79 (2.5)	150–153	–
4f	$4\text{-}MeOC_6H_4$	91 (0.2)	98 (1)	133–135	–
4g	$2\text{-}ClC_6H_4$	88 (0.2)	82 (0.3)	117–119	–
4h	$4\text{-}ClC_6H_4$	69 (0.2)	74 (0.5)	122–124	–
4i	$4\text{-}BrC_6H_4$	77 (0.15)	82 (0.4)	147–149	–
4j	$2\text{-}NO_2C_6H_4$	62 (2)	62 (4.5)	155–157	156–158
4k	$3\text{-}NO_2C_6H_4$	84 (0.25)	81 (0.3)	153–156	154–156
4l	$4\text{-}NO_2C_6H_4$	94 (0.1)	90 (0.2)	165–167	165–166
4m	$4\text{-}COOHC_6H_4$	76 (0.1)	59 (0.1)	239–241	–
4n	$PhCH_2$	29 (0.03)	14 (0.35)	154–155	–
4o	$n\text{-}C_4H_9$	0 (24)	0 (24)	–	–

[a]The purity and the identity of the products were determined by mp, IR, ^1H NMR, MS and elemental analysis.

at room temperature to give the corresponding 3-substituted 4(3*H*)-quinazolinones in moderate to high yields. Triethyl orthoformate and trimethyl orthoformate are found to be equally effective for this transformation. The yields of products from trimethyl orthoformate were lower than those from triethyl orthoformate. Aryl amines carrying either electron-donating groups (–Me and –OMe) or electron-withdrawing groups (–Cl, –Br and $–NO_2$) were all suitable for use with this new procedure. Furthermore, the position of the substituents on the aromatic ring of amines has no obvious effects on this conversion. It is worth mentioning that aniline having strong electro-withdrawing substitutes, *e.g.*, Cl and NO_2, gave generally no product at room temperature in previous reports, also yielded the corresponding 4(3*H*)-quinazolinones in moderate yields when our method was used. Besides aryl amines, alkyl amines such as benzyl amine and *n*-butyl amine were also investigated. However, low and zero yields were provided (**4n**, **4o**). In conclusion, $SrCl_2{\cdot}6H_2O$ is an efficient catalyst for the preparation of 4(3*H*)-quinazolinones and their derivatives from aryl amines. The method offers several advantages including simple work-up, mild reaction conditions, commercially available and reusable catalyst, and the relatively clean procedure.

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