$SnCl_2 \cdot 2H_2O$-Catalyzed One-Pot Synthesis of 4(3*H*)-Quinazolinones from Anthranilic Acid, Ortho Esters, and Amines under Solvent Free Conditions

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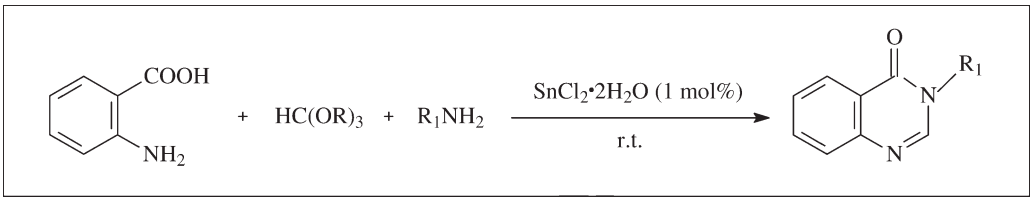

A simple, efficient, and green procedure for the one-pot synthesis of 4(3*H*)-quinazolinones by three components condensation of anthranilic acid, ortho esters, and amines in the presence of $SnCl_2 \cdot 2H_2O$ has been developed. The reaction occurred within short reaction time at room temperature under solvent-free conditions to afford the title products in excellent yields.

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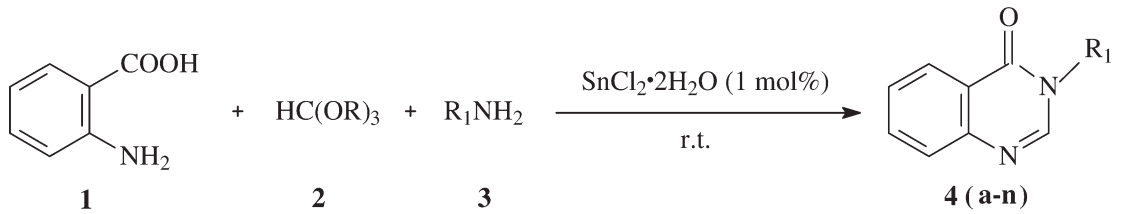
INTRODUCTION

It has been more than a century since the initial studies on 4(3*H*)-quinazolinones [1], and they are well-known as important fused heterocycles because of their pharmacological and therapeutic properties such as antimalarial, antitumor, anticonvulsant, antiinflammatory, fungicidal, and antimicrobial activities [2]. Moreover, the 4(3*H*)-quinazolinone moiety is found in several bioactive natural products [3]. Because of the importance of 4(3*H*)-quinazolinones different strategies for their synthesis have been described in the literature: (a) cyclocondensation of anthranilamide with aryl, alkyl, or heteroaryl aldehydes in refluxing ethanol [4]; (b) poly(ethylene glycol) supported by aza-Wittig reaction [5]; (c) intramolecular cyclization of fluorine-containing *S*-ethyl *N*-benzoylisothioureas [6]; (d) cyclocondensation of 2-fluorobenzoyl chlorides with 2-amino-*N*-heterocycles [7]; (e) copper-catalyzed cascade reactions of the substituted 2-halobenzoic acids with amidines [8]; (f) reaction of polymer-bound isothiourea with isatoic anhydride [9]; (g) reaction of anthranilic acids and ammonium or triethylammonium *N*-aryl-dithiocarbamates [10].

Multicomponent reactions (MCRs) are especially attractive synthesis strategies due to the fact that the products are formed in a single step and also the diversity could be achieved simply by varying the reacting components. In this type of reaction, at least three easily accessible components are reacted to form a single product, which incorporates essentially all of the atoms of the starting materials. MCRs are highly flexible, chemoselective, convergent, and atom efficient processes. Therefore, very efficient way to access heterocycles is by using MCRs in the past decade. Several groups have reported MCRs preparation methods for synthesis of 4(3*H*)-quinazolinones from anthranilic acid, orthoesters, and amines using $NaHSO_4$ or Amberlyst-15 [11], Yb(III)-resin [12], $Yb(OTf)_3$ [13], $Bi(TFA)_3$-[nbp]$FeCl_4$ ionic liquid [14], $La(NO_3)_3 \cdot 6H_2O$ or *p*-toluenesulfonic acid [15], Keggin-type heteropolyacid under microwave irradiation [16], and SiO_2—$FeCl_3$ [17] *etc*. However, some of these methods associated with certain drawbacks such as expensive catalyst, high temperature (60–80°C), long reaction time (20 h), and using harmful organic solvent. In addition, aniline having strong electron-withdrawing substitutes, *e.g*., Cl and NO_2, gave generally no products at room temperature in previous reports. Therefore, it is desirable to develop green and efficient methods for the synthesis of 4(3*H*)-quinazolinones.

During the course of our study on Lewis acid–catalyzed organic reactions, we found that stannous chloride, as an inexpensive and commercially available catalyst, can catalyze one-pot three components Mannich-type reaction efficiently [18]. As an extension of our study on efficient synthesis of 4(3*H*)-quinazolinones, we reported here a one-pot MCR of anthranilic acid **1**, orthoesters **2**, and primary amines **3** in the presence of 1 mol % $SnCl_2 \cdot 2H_2O$ at room temperature without solvent (Scheme 1). Most products were formed within several minutes in excellent yields.

Scheme 1



1 **2** **3** **4 (a-n)**

RESULTS AND DISCUSSION

First, a controlled experiment of an anthranilic acid, a triethyl orthoformate, and an aniline in the absence of catalyst was investigated. The result showed that only 5% product was obtained after 1 h. However, various 4(3*H*)-quinazolinones **4** were prepared efficiently using anthranilic acid **1**, trimethyl or triethyl orthoformate **2**, and different substituted aryl amines or alkyl amine **3** in the presence of $SnCl_2 \cdot 2H_2O$ at room temperature without solvent (Table 1). All condensations mediated by $SnCl_2 \cdot 2H_2O$ proceeded smoothly. Anilines carrying either electron-donating or electron-withdrawing groups all afford high yields. Steric hindrance seems to have no effects on the efficiency of this transformation. The reaction could tolerate different functional groups, such as alkyl, halogen, and nitro present in the anilines. The products derived from triethyl orthoformate were formed in somewhat higher yields than those from trimethyl orthoformate. Furthermore, trimethyl orthoformate required a comparatively longer reaction time. The condensation yield with primary aliphatic amines was lower than those with aniline derivatives.

A mechanism for this reaction has also been postulated as shown in Scheme 2. The first step in this reaction involves the $SnCl_2 \cdot 2H_2O$ catalyzed formation of imidic ester **5**, which stabilized by Sn^{2+}. The imidic ester **5** may be very prone to react with an aryl amine **3**,

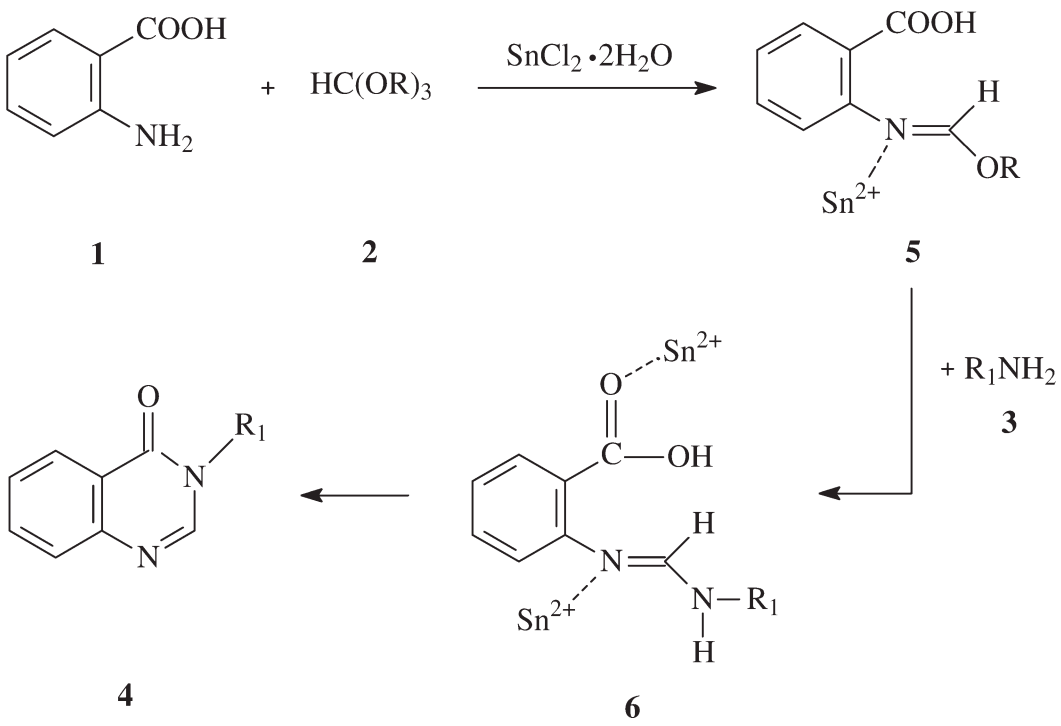
Table 1

Preparation of 4(3*H*)-quinazolinones **4**(**a**–**n**) catalyzed by $SnCl_2 \cdot 2H_2O$.[a]

Product (**4**)	R	R_1	Time (h)	Isolated yield (%)	Mp (°C) Found	Mp (°C) Reported
4a	Et	H	0.4	91	141–143	139–140 [13]
4b	Et	2-Me	1.1	93	154–156	–
4c	Et	3-Me	3	97	137–139	136–137 [13]
4d	Et	4-Me	0.2	91	150–151	146–147 [13]
4e	Et	2-MeO	0.5	97	152–154	–
4f	Et	4-MeO	0.5	96	138–140	–
4g	Et	2-Cl	0.1	81	119–120	–
4h	Et	4-Cl	0.2	84	122–124	–
4i	Et	4-Br	0.1	91	149–150	–
4j	Et	2-NO_2	0.1	61	151–153	156–158 [13]
4k	Et	3-NO_2	0.3	93	152–154	154–156 [13]
4l	Et	4-NO_2	0.2	86	167–169	165–166 [13]
4m	Et	4-COOH	0.1	64	240–242	–
4n	Et	$PhCH_2$	0.1	56	154–155	–
4a	Me	H	4	82	139–141	139–140 [13]
4b	Me	2-Me	3	96	154–156	–
4c	Me	3-Me	7	45	137–139	136–137 [13]
4d	Me	4-Me	1	87	149–150	146–147 [13]
4e	Me	2-MeO	2.2	91	152–154	–
4f	Me	4-MeO	1	94	138–140	–
4g	Me	2-Cl	0.2	80	118–120	–
4h	Me	4-Cl	0.7	51	123–125	–
4i	Me	4-Br	0.3	86	148–150	–
4j	Me	2-NO_2	7	50	152–154	156–158 [13]
4k	Me	3-NO_2	0.1	92	152–153	154–156 [13]
4l	Me	4-NO_2	0.1	80	166–168	165–166 [13]
4m	Me	4-COOH	0.1	51	240–242	–
4n	Me	$PhCH_2$	0.1	51	154–155	–

[a] The structures of the products were determined from spectral and analytical data (IR, ^1H NMR and elemental analysis).

Scheme 2



thus leading to the amidine intermediate **6**. Then, amidine intermediate **6** activated by Sn^{2+} cyclized to form the quinazolinone **4**. A similar mechanism had also been described by Wang *et al*. [13].

In conclusion, we have demonstrated a simple and efficient one-pot three components coupling condensation from an anthranilic acid, orthoesters, and primary amines in the presence of $SnCl_2 \cdot 2H_2O$ for the preparation of 4(3*H*)-quinazolinones. The mild and solvent-free conditions, short reaction time (0.1–7 h), excellent yields (45–97%), inexpensive, nontoxic, and commercially available catalysts, and simple workup make it a useful process for the synthesis of 4(3*H*)-quinazolinones.

EXPERIMENTAL

Melting points were determined using RY-1 micromelting point apparatus and were uncorrected. Infrared spectra were recorded on Scimitar 2000 series Fourier Transform instrument of VARIAN. ^{1}H NMR spectra were recorded on Bruker ARX-500 spectrometer in DMSO-d_6 using TMS as an internal standard. Elemental analyzes were performed on EA 2400II elemental analyzer (Perkin–Elmer).

General procedure for the synthesis of 4(3*H*)-quinazolinones. To a mixture of anthranilic acid (10 mmol), an orthoester (12 mmol), and an amine (12 mmol), $SnCl_2 \cdot 2H_2O$ (0.1 mmol) was added. The mixture was stirred at room temperature for an appropriate time (Table 1). The reaction was monitored by TLC. After completion, the solid obtained was crystallized in ethanol. The pure products were identified by IR, ^{1}H NMR, and elemental analysis. The spectral properties of some representative 4(3*H*)-quinazolinones are given below:

3-(2-Methylphenyl)quinazolin-4(3H)-one (4b). White solid. IR (KBr): 1687, 1594, 1489 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.56 (s, 1H), 8.31 (d, J = 7.2 Hz, 1H), 7.75–7.52 (m, 2H), 7.23–7.07 (m, 5H), 2.31 (s, 3H). Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 76.26; H, 5.12; O, 6.77. Found: C, 76.35; H, 5.10; O, 6.72.

3-(2-Methoxyphenyl)quinazolin-4(3H)-one (4e). White solid. IR (KBr): 1681, 1595, 1457 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.36 (s, 1H), 8.21 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 6.8 Hz, 1H), 7.25 (t, J = 7.0 Hz, 1H), 7.08–7.03 (m, 2H), 6.94 (t, J = 7.1 Hz, 1H), 6.78 (d, J = 8.2 Hz, 1H), 6.53 (t, J = 7.3 Hz, 1H), 3.85 (s, 3H). Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.80; O, 12.68. Found: C, 71.34; H, 4.82; O, 12.72.

3-(4-Methoxyphenyl)quinazolin-4(3H)-one (4f). White solid. IR (KBr): 1715, 1591, 1454 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.54–7.48 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 6.97 (dd, J = 8.5, 9.5 Hz, 4H), 3.76 (s, 3H). Anal. Calcd. for $C_{15}H_{12}O_2N_2$: C, 71.42; H, 4.80; O, 12.68. Found: C, 71.51; H, 4.77; O, 12.64.

3-(2-Chlorophenyl)quinazolin-4(3H)-one (4g). Yellow solid. IR (KBr): 1667, 1602, 1414 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.73–7.70 (m, 2H), 7.61 (t, J = 7.6 Hz, 1H), 7.25–7.16 (m, 2H), 6.76 (d, J = 8.0 Hz, 1H), 6.53 (t, J = 7.2 Hz, 1H). 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, 6.24; N, 10.93.

3-(4-Chlorophenyl)quinazolin-4(3H)-one (4h). Pale yellow solid. IR (KBr): 1672, 1616, 1485 cm^{-1}. ^{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, J = 7.4 Hz, 2H), 6.52 (d, J = 7.2 Hz, 2H). Anal.

Calcd. for $C_{14}H_9ON_2Cl$: C, 65.51; H, 3.53; O, 6.23; N, 10.91. Found: C, 65.43; H, 3.52; O, 6.25; N, 10.95.

3-(4-Bromophenyl)quinazolin-4(3H)-one (4i). White solid. IR (KBr): 1713, 1587, 1443 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.01 (d, J = 7.7 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.46–7.44 (m, 4H), 7.18 (d, J = 7.5 Hz, 2H). Anal. Calcd. for $C_{14}H_9ON_2Br$: C, 55.84; H, 3.01; O, 5.31; N, 9.30. Found: C, 55.77; H, 3.01; O, 5.32; N, 9.33.

3-(4-Carboxylphenyl)quinazolin-4(3H)-one (4m). White solid. IR (KBr): 1701, 1593, 1484 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 10.49 (s, 1H), 8.34 (s, 1H), 7.92–7.88 (m, 3H), 7.71 (t, J = 8.5 Hz, 2H), 7.63 (d, J = 5.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 6.56 (d, J = 5.5 Hz, 1H). Anal. Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.67; H, 3.79; O, 18.03. Found: C, 67.76; H, 3.78; O, 18.00.

3-Benzylquinazolin-4(3H)-one (4n). White solid. IR (KBr): 1678, 1621, 1459 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.52 (s, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.54–7.47 (m, 2H), 7.41–7.36 (m, 4H), 7.32 (t, J = 6.8 Hz, 1H), 7.13 (t, J = 7.0 Hz, 1H), 4.61 (s, 2H). Anal. Calcd. for $C_{15}H_{12}ON_2$: C, 76.26; H, 5.12; O, 6.77. Found: C, 76.35; H, 5.10; O, 6.74.

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