A Convenient and Efficient Synthesis of 2-Thioxoquinazolinone Derivatives via Microwave Irradiation

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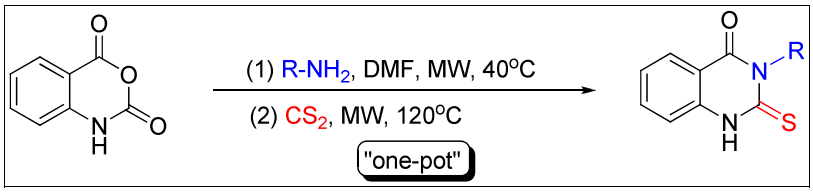

The synthesis of 2-thioxoquinazolinone derivatives was achieved by condensation of isatoic anhydride, primary amine, and carbon disulfide under microwave irradiation. This convenient and efficient method affords the desired products with good to excellent yields. Satisfactory infrared spectroscopy, ^{1}H NMR, and high-resolution mass spectrometry (electrospray ionization) spectra were obtained for all compounds described.

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INTRODUCTION

2-Thioxoquinazolinones and their derivatives are important heterocyle compounds in organic and medicinal chemistry because of their biological properties including antidiabetic agents [1], antihypertension [2], anticancer [3], anticonvulsants [4], and application for immunosuppression [5]. 2-Thioxoquinazolinones have gained wide applications as intermediates in organic synthesis [6] and preparation of many biologically active compounds, which have been extensively studied. The construction units are frequently found in many natural products as well as in pharmaceuticals, herbicides, and dyes.

As a part of our program directed at the design and synthesis of thiocarbonyl compounds [7], we studied the synthesis of the compound. Literature methods for synthesis of these molecules mainly include the reaction of isothiocyanates with substituted anthranilic acids or their functional derivatives [8a,b,c], the treatment of anilines and CS_2 with Me_2SO_4 [9], and the reaction of anthranilamides with carbonyl compounds [10a,b].

Although some of these synthesis methods are very useful [11a–e], however, most of these methods suffered from harsh reaction conditions or tedious procedures and result in very low yield. Here, we report a rapid and efficient microwave-assisted method possessed with content reaction yields, convenient product handling, and short reaction times to synthesize a new class of 2-thioxo-2,3-dihydroquinazolin-4(1H)-ones. These novel compounds contained with specific structural units were expected to exhibit biological activity in the future. The structures of products have also been fully characterized by infrared spectroscopy (IR), ^{1}H nuclear magnetic resonance (^{1}H NMR) and high-resolution mass spectrometry (HRMS).

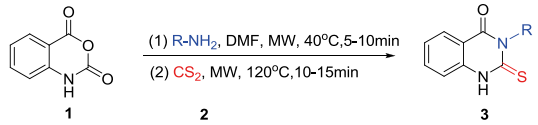
RESULTS AND DISCUSSION

Initially, on the basis of our previous experience, 2-thioxo-2,3-dihydroquinazolin-4(1H)-ones were synthesized by treatment of isatoic anhydride **1** with amines **2**, and the reaction was carried out in dimethylformamide (DMF) by using 1 : 1.2 ratio of **1** : (**2a–2m**) in an unmodified commercial microwave oven [12]. Then, the reaction mixture was allowed to cool to room temperature and was added an excess of carbon disulfide (Scheme 1). Furthermore, we found the best reaction conditions summarized in Scheme 1 and Table 1. A plausible mechanistic pathway to products **3** is illustrated in Scheme 2.

As shown in Table 1, we first examined the aliphatic amine containing aromatic and heterocyclic group and then also premeditated aromatic amines with electron-withdrawing group or electron-donating group. We chose DMF as the solvent because of its high dielectric constant as an excellent energy-transfer solvent providing a uniform heating of reaction mixture in a shorter time. The reaction time was detected by means of the thin-layer chromatography analysis of the mixture and determined by the reaction of raw materials completely.

It is found that all these anilines containing either electron-withdrawing group, or electron-donating group, or heterocycle moiety can be smoothly converted to the desired products with satisfactory yields under the analogous conditions. The reaction time is reduced from several hours

Scheme 1. Synthesis of the compounds **3a–m**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



to several minutes. It is noteworthy that the present reaction was accomplished under mild conditions and the method is operationally simple with satisfactory yields.

In summary, we report a rapid and efficient microwave-assisted method to synthesize a series of novel thioxoquinazolinones in good yields. Given the fact that many 2-thioxo-2,3-dihydroquinazolin-4(1H)-ones exhibited biological activity, we anticipate that these new compounds described in the present report would be valuable in further pharmaceutical research.

EXPERIMENTAL

Commercial solvents and reagents were used as received. Microwave irradiation was carried out with a microwave oven Emrys Creator from Personal Chemistry, (Biotage, Initiator EXPEU, Frequtncy 2450MHz, Uppsala, Sweden). Melting points are uncorrected. IR spectra were taken on an FTIR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}HNMR spectra were measured on a Bruker DPX 300-MHz spectrometer using TMS as an internal standard and dimethyl sulfoxide (DMSO)-d_6 as solvent. *J* values are in hertz. Chemical shifts are expressed in parts per million downfield from internal standard trimethylsilyl. HRMS (ESI) was determined by using a Micro TOF-QII HRMS instrument (BRUKER).

General procedure for synthesis of 2-thioxo-2,3-dihydroquinazolin-4(1H)-ones 3a–m. A solution of **1** (0.2 mmol) and different substituent amines **2** (0.24 mmol) in DMF (3 mL) was stirred in a sealed pressure-proof pipe, and the pipe was placed in the microwave oven. Then, the reaction mixture was allowed to cool to room temperature, and carbon disulfide was added to the pipe. The mixture was irradiated with power and time as indicated in Scheme 1. To control the reaction, we carried out the irradiation in two stages, with a cooling period between each irradiation. After this period, the thin-layer chromatography analysis of the mixture showed the reaction to be completed. Rinsing of the crude product with water and vacuum filtration gave the desired products. The yield of pure isolated product was based on isatoic anhydride as indicated in Table 1.

2-Amino-N-(2-hydroxyethyl)benzamide (3a). This compound was obtained as pale yellow solid with mp 236–237°C (lit. 238°C) [13]; IR (KBr) m: 3367, 3171, 2956, 2891, 1661, 1541, 1161, 760 cm^{-1}. ^{1}H NMR (DMSO-d_6): 12.91 (s, 1H, NH), 7.95 (d, 1H, *J* = 9.0 Hz, ArH), 7.73 (m, 1H, ArH), 7.45–7.22 (m, 2H, ArH), 4.84 (s, 1H, OH), 4.50 (m, 2H, CH_2), 3.65 (d, 2H, *J* = 2.7 Hz, CH_2). HRMS (ESI) [Found: *m/z* 245.0368 $(M+Na)^+$, calcd for $C_{10}H_{10}N_2O_2S$: M + Na, 245.0361].

3-(4-Hydroxyphenethyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3b). This compound was obtained as yellow solid with mp 264–265°C; IR (KBr) m: 3420, 3251, 3036, 2961, 1651, 1533, 1146, 823, 759 cm^{-1}. ^{1}HNMR (DMSO-d_6): 12.93 (s, 1H, NH), 9.20 (s, 1H, OH), 7.95 (d, *J* = 7.7 Hz, 1H, ArH), 7.72 (m, 1H, ArH), 7.44–7.24 (m, 2H, ArH), 7.07 (d, *J* = 8.3 Hz, 2H, ArH), 6.69 (d, *J* = 8.3 Hz, 2H, ArH), 4.55–4.44 (m, 2H, CH_2), 2.83 (m, 2H, CH_2). HRMS (ESI) [Found: *m/z* 321.0673 $(M+Na)^+$, calcd for $C_{16}H_{14}N_2O_2S$: M + Na, 321.0674].

3-(Furan-2-ylmethyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3c). This compound was obtained as pale yellow solid with mp 218–219°C; IR (KBr) m: 3247, 2956, 2891, 1655, 1532, 1163, 955, 759 cm^{-1}. ^{1}HNMR (DMSO-d_6): 13.01 (s, 1H, NH), 7.96 (d, 1H, *J* = 7.7 Hz, ArH), 7.74 (t, 1H, *J* = 7.6 Hz, ArH), 7.52 (s, 1H), 7.44–7.25 (m, 2H, ArH, furan-H), 6.34 (m, 2H, furanyl-H), 5.63 (s, 2H, CH_2). HRMS (ESI) [Found: *m/z*281.0392 $(M+Na)^+$, calcd for $C_{13}H_{10}N_2O_2S$: M + Na, 281.0361].

3-(2-(1H-indol-3-yl)ethyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3d). This compound was obtained as brown solid with mp 261–262°C; IR (KBr) m: 3326, 3176, 3025, 2966, 1619, 1541, 1144, 744, 692 cm^{-1}. ^{1}HNMR (DMSO-d_6): 12.97 (s, 1H, C = SNH), 10.84 (s, 1H, NH), 7.99 (d, *J* = 7.8 Hz, 1H, ArH), 7.81 (d, *J* = 7.6 Hz, 1H, ArH), 7.74 (m, 1H, ArH), 7.44–7.29 (m, 3H, ArH, indolyl-H), 7.20 (s, 1H, indolyl-H), 7.12–6.93 (m, 2H, indolyl-H), 4.70–4.58 (m, 2H, CH_2), 3.12–3.02 (m, 2H, CH_2). HRMS (ESI) [Found: *m/z* 344.0834 $(M+Na)^+$, calcd for $C_{18}H_{15}N_3OS$: M + Na, 344.0833].

3-(2-(Thiophen-2-yl)ethyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3e). This compound was obtained as white solid with mp 234–235°C; IR (KBr) mp: 3255, 2956, 2891, 1649, 1530, 1149, 824, 760, 708 cm^{-1}. ^{1}HNMR (DMSO-d_6): 12.98 (s, 1H, NH), 7.95 (d, 1H, *J* = 7.9 Hz, ArH), 7.73 (m, 1H, ArH), 7.50–7.18 (m, 3H, ArH, thiophenyl-H), 6.95 (m, 2H, thiophenyl-H), 4.81–4.41 (t, 2H, CH_2), 3.24–3.12 (t, 2H, CH_2). HRMS (ESI) [Found: *m/z* 311.0296 $(M+Na)^+$, calcd for $C_{14}H_{12}N_2OS_2$: M + Na, 311.0289].

3-(3-(1H-imidazol-1-yl)propyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3f). This compound was obtained as yellow solid with mp 216–217°C; IR (KBr) m: 3113, 2958, 1897, 1548, 1689, 1152, 926, 757 cm^{-1}. ^{1}HNMR (DMSO-d_6): 12.93 (s, 1H, NH), 7.94 (d, *J* = 6.8 Hz, 1H, ArH), 7.78–7.69 (m, 1H, ArH), 7.66 (s, 1H, imidazolyl-H), 7.42–7.27 (m, 2H, ArH), 7.19 (s, 1H, imidazolyl-H), 6.87 (s, 1H, imidazolyl-H), 4.55–4.26 (m, 2H, CH_2), 4.06 (m, 2H, CH_2), 2.24–1.87 (m, 2H, CH_2). HRMS (ESI) [Found: *m/z* 287.0988 $(M+H)^+$, calcd for $C_{14}H_{14}N_4OS$: M + H, 287.0967].

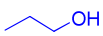
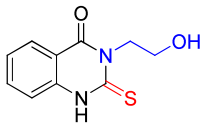
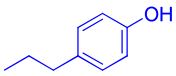
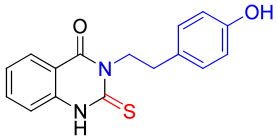
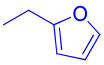
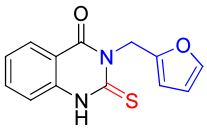
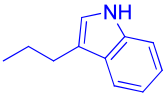
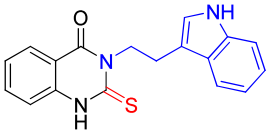
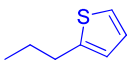
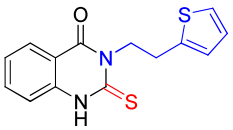
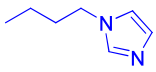
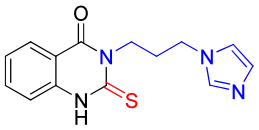
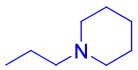
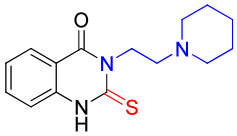
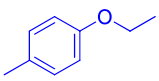
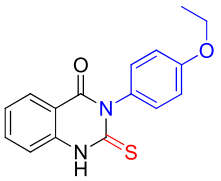
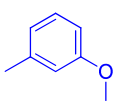
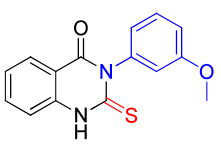
3-(2-(Piperidin-1-yl)ethyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3g). This compound was obtained as yellow solid with mp 210–211 °C(lit. 199°C) [14]; IR (KBr) m: 3248, 1648, 1119, 2928, 2850, 1532, 1335, 757 cm^{-1}. ^{1}HNMR (DMSO-d_6): 12.87 (s, 1H, NH), 7.94 (d, *J* = 7.9 Hz, 1H, ArH), 7.72 (m, 1H, ArH), 7.33 (m, 2H, ArH), 4.66–4.29 (m, 2H, piperidinyl-H), 2.59–2.53 (m, 2H, piperidinyl-H), 2.51–2.36 (m, 4H, piperidinyl-H), 1.45 (d, *J* = 4.8 Hz, 4H, CH_2), 1.35 (d, *J* = 4.7 Hz, 2H, CH_2). HRMS (ESI) [Found: *m/z* 290.1454 $(M+H)^+$, calcd for $C_{15}H_{19}N_3OS$: M + H, 290.1327].

3-(4-Ethoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3h). This compound was obtained as yellow solid with mp 296–297°C(lit. 310-312°C) [15]; IR (KBr) m: 3243, 2970, 1664, 1536, 1508, 1201, 1039, 760 cm^{-1}. ^{1}H NMR (DMSO-d_6): 12.99 (s, 1H, NH), 7.95 (d, *J* = 7.6 Hz, 1H, ArH), 7.77 (m, 1H, ArH), 7.44 (d, *J* = 8.1 Hz, 1H, ArH), 7.34 (m, 1H, ArH), 7.19 (m, 2H, ArH), 6.98 (d, *J* = 8.5 Hz, 2H, ArH), 4.07 (m, 2H, CH_2), 1.36 (m, 3H, CH_3). HRMS (ESI) [Found: *m/z* 321.0663 $(M+Na)^+$, calcd for $C_{16}H_{14}N_2O_2S$: M + Na, 321.0674].

3-(3-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3i). This compound was obtained as pale yellow solid with mp 248–249°C (lit. 255-256°C) [16]; IR (KBr) m: 3243, 2945,

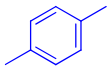
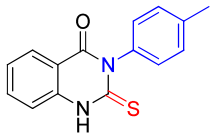
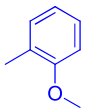
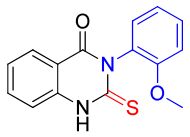
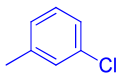
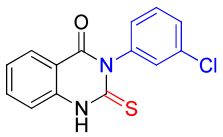
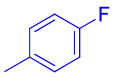
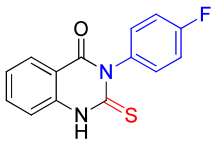
Table 1

The reaction of isatoic anhydride with amines and carbon disulfide. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

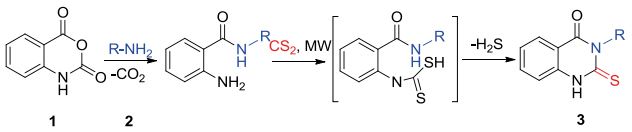
Entry		RNH_2		Product	Yield (%)
1	**2a**		**3a**		90
2	**2b**		**3b**		95
3	**2c**		**3c**		95
4	**2d**		**3d**		96
5	**2e**		**3e**		92
6	**2f**		**3f**		95
7	**2g**		**3g**		97
8	**2h**		**3h**		94
9	**2i**		**3i**		91

(*Continued*)

Table I.
(Continued)

Entry		RNH_2		Product	Yield (%)
10	**2j**		**3j**		88
11	**2k**		**3k**		93
12	**2l**		**3l**		86
13	**2m**		**3m**		88

Scheme 2. Proposed mechanism for products **3**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



1662, 1530, 1489, 1213, 1042, 757 cm^{-1}. ^{1}HNMR (DMSO-d_6): 13.01 (s, 1H, NH), 7.94 (m, 1H, ArH), 7.83 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.35 (m, 1H, ArH), 7.20 (m, 1H, ArH), 7.04 (m, 1H, ArH), 6.88 (m, 2H, ArH), 3.82–3.70 (m, 3H, OCH_3). HRMS (ESI) [Found: *m/z* 307.0512 $(M+Na)^+$, calcd for $C_{15}H_{12}N_2O_2S$: M + Na, 307.0517].

2-Thioxo-3-(p-tolyl)-2,3-dihydroquinazolin-4(1H)-one (3j). This compound was obtained as pale yellow solid with mp 294–295°C(lit. 304°C) [6]; IR (KBr) m: 3240, 2917, 1663, 1533, 1406, 1201, 761 cm^{-1}. ^{1}HNMR (DMSO-d_6): 13.00 (s, 1H, NH), 7.95 (d, J = 7.0 Hz, 1H, ArH), 7.78 (m, 1H, ArH), 7.45 (d, J = 4.7 Hz, 1H, ArH), 7.38–7.24 (m, 3H, ArH), 7.10–7.05 (m, 2H, ArH), 2.37 (s, 3H, CH_3). HRMS (ESI) [Found: *m/z* 269.0742 $(M+H)^+$, calcd for $C_{15}H_{12}N_2OS$: M + H, 269.0749].

3-(2-Methoxyphenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3k). This compound was obtained as yellow solid with mp 255–257°C(lit. 266-268°C) [17]; IR (KBr) m: 3230, 3018, 1704, 1619, 1543, 1498, 1264, 1197, 1020, 754 cm^{-1}. ^{1}HNMR (DMSO-d_6): 13.03 (s, 1H, NH), 8.04–7.86 (m, 3H, ArH), 7.46 (m, 1H, ArH), 7.21 (m, 2H, ArH), 7.15 (m, 2H, ArH), 3.79–3.71(m, 3H, OCH_3). HRMS (ESI) [Found: *m/z* 307.0512 $(M+Na)^+$, calcd for $C_{15}H_{12}N_2O_2S$: M + Na, 307.0517].

3-(3-Chlorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3l). This compound was obtained as yellow solid with mp 231–233°C(lit. 243°C) [18]; IR (KBr) m: 3227, 1663, 1637, 1524, 1482, 1201, 1023, 773 cm^{-1}. ^{1}HNMR (DMSO-d_6): 12.87 (s, 1H, NH), 7.94 (m, 1H, ArH), 7.83–7.60 (m, 2H, ArH), 7.53–7.46 (m, 2H, ArH), 7.35–7.27 (m, 2H, ArH), 7.03 (m, 1H, ArH). HRMS (ESI) [Found: *m/z* 311.0014 $(M+Na)^+$, calcd for $C_{14}H_9ClN_2OS$: M + Na, 311.0022].

3-(4-Fluorophenyl)-2-thioxo-2,3-dihydroquinazolin-4(1H)-one (3m). This compound was obtained as gray solid with mp 297–298°C; IR (KBr) m: 3274, 1666, 1619, 1553, 1536, 1201, 1020, 764 cm^{-1}. ^{1}HNMR (DMSO-d_6): 13.05 (s, 1H, NH), 7.94 (m, 1H, ArH), 7.88–7.75 (m, 1H, ArH), 7.59 (m, 1H, ArH), 7.49–7.40 (m, 2H, ArH), 7.33 (m, 2H, ArH), 7.11 (m, 1H, ArH). HRMS (ESI) [Found: *m/z* 295.1053 $(M+Na)^+$, calcd for $C_{14}H_9FN_2OS$: M + Na, 295.0317].

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