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FACILE AND SOLVENT-FREE SYNTHESIS OF QUINAZOLIN-4(3*H*)-ONES UNDER MICROWAVE CONDITION PROMOTED BY $SbCl_3$

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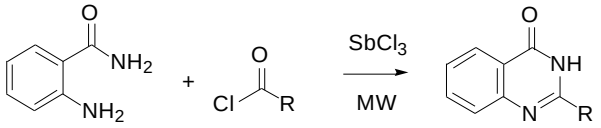
Abstract – Antimony trichloride ($SbCl_3$) was found to be an effective catalyst (1 mol%) for one-pot synthesis of quinazolin-4(3*H*)-ones in good to excellent yields using anthranilamide and acyl chlorides under microwave irradiation. This method has the advantages of simplicity, mild reaction conditions, highly tolerant to several functional groups, as well as the avoidance of hazardous solvents.

Quinazolin-4(3*H*)-ones show excellent pharmacological activities as anti-tumor,[1] anti-hypertensive,[2] anti-spasmodical[3] compounds, which have attracted great attention of scientific community to synthesize these class of compounds.[4-6] For that, all common synthetic procedures are based on the use of *o*-aminophenic acid,[7] *o*-aminophenate ester[8] and *o*-aminophenoxamide[9] as starting materials. Nevertheless, known procedures involve expensive reactants and harsh reaction conditions, for instance, thus few shortcomings[10] are needed to overcome known synthetic difficulties. Therefore, an effective method for the synthesis of quinazolinones is highly valuable for medicinal chemistry.

Within this work, basic principles of green chemistry are considered: catalytic procedures[11] rather than stoichiometric conditions, to afford the desired products almost specifically which reduce significantly the amount of waste and undesired by-products.[10] Solvent-free process under microwave heating techniques are known[12] for the efficiency and cleanliness in comparison of conventional heating techniques. Based on our previous work for synthesis of quinazolin-4(3*H*)-ones derived from acrylamides[13] or orthoformates[14] catalyzed by antimony(III) trichloride ($SbCl_3$), herein, we wish to report an efficient route for the synthesis of quinazolin-4(3*H*)-ones by condensation of anthranilamide with acyl chlorides catalyzed by inexpensive, commercial $SbCl_3$ under solvent-free microwave irradiation (Scheme 1).

Under conventional heating, the reaction is completed after 3 to 5 hours, while under microwave irradiation, it is completed within 3 to 5 minutes; efficiency is not only in terms of time, higher yields are

also obtained (Table 1). For compound **3a**, the reaction was carried out using $SbCl_3$ as catalyst in THF at reflux with an 87% yield, lower than without solvent (94%). While, only 13% of **3a** was obtained without $SbCl_3$ under microwave irradiation, which shows the importance of catalyst. The reaction times and yields are slightly different for the variation of acyl chlorides, but both aromatic and fatty acyl chlorides can obtain the title compounds from good to excellent yields (Table 1). The optimal conditions were determined as: $SbCl_3$ is 1 mol% and microwave power is 300 W without solvent at 300 °C.



1 **2** **3**

Scheme 1. $SbCl_3$-Catalyzed condensation of anthranilamide with acyl chlorides

Table 1. Condensation of anthranilamide and acyl chlorides catalyzed by $SbCl_3$

Entry	**R**	Time/MW	Time/Conventional	**3**	Yield/MW	Yield/Conventional
1	C_6H_5	3 min	180 min	**3a**	93%	74%
2	2-HOC_6H_4	4 min	270 min	**3b**	82%	68%
3	3-BrC_6H_4	5 min	300 min	**3c**	90%	76%
4	4-ClC_6H_4	4 min	240 min	**3d**	93%	85%
5	4-FC_6H_4	3 min	210 min	**3e**	96%	87%
6	C_6H_5CH=CH	4 min	180 min	**3f**	85%	76%
7	2-furyl	3 min	180 min	**3g**	88%	68%
8	Me	3 min	180 min	**3h**	86%	79%
9	Et	3 min	240 min	**3i**	89%	81%
10	*n*-Pr	3 min	180 min	**3j**	92%	80%

In conclusion, quinazolin-4(3*H*)-ones can be readily obtained by one-pot catalysis solvent free procedure with $SbCl_3$ under microwave heating in high yields. All the evidences show that $SbCl_3$ is a good catalyst for this condensation reaction and plays an important role in this methodology. The advantages of this method are the mild reaction conditions, high yield and simple operation. Since no solvent is used, this method also has some chemical and environmental advantages.

EXPERIMENTAL

Melting points were determined on a digital melting-point apparatus and are uncorrected. Infrared were recorded on a Nicolet MAGNA-IR 550 spectrometer. ^{1}H NMR were recorded on a Bruker 400 MHz

spectrometer with TMS as internal reference and DMSO-d_6 as solvent (^{13}C NMR on 100 MHz). Mass spectra were recorded on an ABI 4000 MSD spectrometer operated at an ionization potential of 70 eV. Microwave reactor (MAS-I) was purchased from Shanghai Sineo Microwave Chemistry Co.,Ltd.

General procedure: Anthranilamide (2 mmol), acyl chloride (2 mmol) were mixed in a flask, then 0.02 mmol of catalyst ($SbCl_3$) was added, the mixture was heated in a microwave reactor (300 W, 300 °C, monitored by TLC). Then it was poured into cold water and stirred for 30 min, the precipitate was filtered and washed with ice water three times, then recrystallized from EtOH to give pure products **3**.

2-Phenylquinazolin-4(3*H*)-one (3a): White powder; mp 252-254 °C (lit.[15]: 242-246 °C); IR (KBr) 3139, 3061, 1667, 1604, 1563; ^{1}H NMR: δ 7.50-7.59 (m, 4H), 7.74 (d, 1H, *J* = 8.0 Hz, ArH), 7.82-7.86 (m, 1H, ArH), 8.14-8.19 (m, 3H, ArH), 12.54 (s, 1H, NH).

2-(2-Hydroxyphenyl)quinazolin-4(3*H*)-one (3b): White powder; mp 249-250 °C (lit.[4]: 250 °C); IR (KBr) 3440, 3098, 1673, 1610, 1563, 1506 cm^{-1}; ^{1}H NMR δ 6.89-6.97 (m, 2H, ArH), 7.40 (t, 1H, *J* = 7.6 Hz, ArH), 7.50 (t, 1H, *J* = 7.4 Hz, ArH), 7.73 (d, 1H, *J* = 8.0 Hz), 7.81 (t, 1H, *J* = 7.4 Hz, ArH), 8.11 (d, 1H, *J* = 8.0 Hz, ArH), 8.18 (d, 1H, *J* = 8.0 Hz, ArH), 13.76 (s, 1H, OH) ; MS *m*/*z* 238.07 (M$^+$, 100).

2-(3-Bromophenyl)quinazolin-4(3*H*)-one (3c): White powder; mp 297-298 °C (lit.[9]: 295-296 °C); IR (KBr) 3172, 3063, 3026, 1684, 1610 cm^{-1}; ^{1}H NMR δ 7.52-7.58 (m, 2H, ArH), 7.80 (t, *J* = 8.0 Hz, 2H, ArH), 7.87 (t, *J* = 8.0 Hz, 1H, ArH), 8.19 (m, 2H, ArH), 8.4 (m, 1H, ArH), 8.23 (s, 1H, ArH). ^{13}C NMR δ 121.09, 121.86, 125.83, 126.75, 126.91, 127.58, 130.36, 130.72, 134.0, 134.66, 134.88, 148.42, 150.86, 162.05; MS *m*/*z* 299.99 (M$^+$, 100).

2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (3d): White powder; mp >300 °C (lit.[6]: >300 °C); IR (KBr) 3134, 3088, 1679, 1604 cm^{-1}; ^{1}H NMR δ 7.53-7.57 (m, 1H, ArH), 7.63 (d, *J* = 8.8 Hz, 2H, ArH), 7.75 (d, *J* = 8.4 Hz, 1H, ArH), 7.84-7.88 (m, 1H, ArH), 8.15-8.20 (m, 3H, ArH).

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (3e): White powder; mp 293-295 °C (lit.[3]: 288-289 °C); IR (KBr) 3172, 3089, 3049, 1678, 1610 cm^{-1}; ^{1}H NMR δ 7.34 (t, *J* = 8.0 Hz, 2H, ArH), 7.47 (t, *J* = 8.0 Hz, 1H, ArH), 7.67 (d, *J* = 8.0 Hz, 1H, ArH), 7.79 (t, *J* = 8.0 Hz, 1H, ArH), 8.09 (d, *J* = 8.0 Hz, 1H, ArH), 8.18-8.22 (m, 2H, ArH).

2-Styrylquinazolin-4(3*H*)-one (3f): White powder; mp 253-255 °C (lit.[5]: 249-251 °C); IR (KBr) 1669, 1608 cm^{-1}; ^{1}H NMR δ 6.95 (d, 1H, *J* = 16.0 Hz, H_{vinyl}), 7.34-7.44 (m, 4H, ArH), 7.54-7.73 (t, 3H, *J* = 7.0 Hz, ArH), 7.75 (t, 1H, *J* = 7.6 Hz, ArH), 7.90 (d, 1H, *J* = 16.4 Hz, H_{vinyl}), 8.06 (d, 1H, *J* = 8.0 Hz, ArH).

2-(2-Furyl)quinazolin-4(3*H*)-one (3g): White powder; mp 233-235 °C (lit.[5]: 219-221 °C); IR (KBr) 1663, 1602, 1553, 1457 cm^{-1}; ^{1}H NMR δ 6.69 (d, 1H, *J* = 1.6 Hz), 7.44 (t, 1H, *J* = 7.4 Hz), 7.57 (d, 1H, *J* = 3.6 Hz), 7.63 (d, 1H, *J* = 8.0 Hz), 7.75 (t, 1H, *J* = 7.8 Hz), 7.95-8.07 (m, 2H).

2-Ethylquinazolin-4(3*H*)-one (3i): White powder; mp 238-240 °C (lit.[6]: 235-236 °C); IR (KBr) 3178, 1683 cm^{-1}; ^{1}H NMR δ 1.26 (t, 3H, *J* = 8 Hz), 2.61-2.66 (m, 2H), 7.47 (t, 1H, *J* = 8.0 Hz), 7.60 (d, 1H, *J* =

7.2 Hz), 7.77 (t, 1H, *J* = 4 Hz), 8.09 (d, 1H, *J* = 8 Hz). ^{13}C NMR δ 21.22 11.25, 27.80, 120.79, 125.64, 125.87, 126.77, 134.21, 148.92, 158.27, 161.75; MS *m*/*z* 174.08 (M^+, 100).

2-Propylquinazolin-4(3*H*)-one (3j): White powder; mp 210-212 °C (lit.[2]: 208-210 °C); IR (KBr) 3182, 1961, 1679 cm^{-1}; ^{1}H NMR δ 0.92 (t, 3H, *J* = 6.4 Hz), 1.78 (m, 2H), 2.68 (t, 2H, *J* = 7.2 Hz), 7.29 (d, 1H, *J* = 6.4 Hz), 7.51 (t, 1H, *J* = 7.2 Hz), 7.70 (d, 1H, *J* = 7.2 Hz), 8.31 (t, 1H, *J* = 6.8 Hz), 11.19 (s, 1H, NH).

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