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Microwave-assisted synthesis of quinazolin-4(3*H*)-ones catalyzed by $SbCl_3$

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Abstract: Antimony(III) trichloride ($SbCl_3$) is an effective catalyst (1 mol%) for the condensation of anthranilic amide with various aldehydes or ketones to quinazolin-4(3*H*)-one derivatives in good to excellent yields under microwave irradiation. The process is carried out within several minutes under solvent-free conditions. This general methodology has the advantages of simplicity, mild reaction conditions and high yields of products.

Keywords: microwave irradiation; quinazolin-4(3*H*)-ones; $SbCl_3$; solvent-free.

Introduction

Quinoline and quinazoline derivatives have received attention due to their bioactivitives [1]. The quinazolin-4(3*H*)-ones have been found to exhibit antimalarial [1, 2], antiinflammatory [3], antibacterial [4], as well as antihypertensive activities [5]. Generally, quinazolin-4(3*H*)-ones [6, 7] can be prepared from anthranilic acids [8], anthranilamides [9], 2-halobenzamides [10], isatoic anhydrides [11] and 2-azidobenzamides [12]. Several catalytic processes have also been used [6–8, 13, 14]. However, most methods are disadvantageous with high catalyst loading, poor yields, prolonged reaction times, and the use of toxic organic reagents or solvents.

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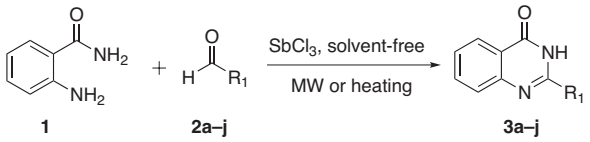
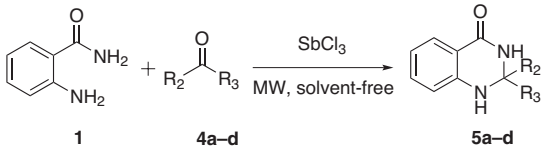
Our work has focused on using green chemistry [15–20]. In particular, we have been interested in the application of microwave irradiation and efficient catalysts in organic synthesis [21–25]. In continuation of the research on the synthesis of quinazolin-4(3*H*)-ones using antimony trichloride ($SbCl_3$) as a catalyst [25, 26] herein, we wish to report a general and highly efficient synthetic route to quinazolin-4(3*H*)-ones. The method involves condensation of anthranilic amide with aldehydes or ketones in the presence of inexpensive, commercially available $SbCl_3$ as a Lewis acid catalyst without solvent under microwave irradiation (Schemes 1 and 2).

Results and discussion

In a model study, benzaldehyde (**2**, 2 mmol) and anthranilic amide (**1**, 2 mmol) were allowed to react in the presence of $SbCl_3$ (1 mol%) under microwave irradiation (Scheme 1). The best yield of 94% of product **3a** was obtained when the reaction was conducted under solvent-free conditions. Lower yields were obtained when the reaction was carried out with $SbCl_3$ in organic solvents. For example, the reaction conducted in tetrahydrofuran (THF) furnished **3a** in 85% yield. Product **3a** was obtained in low yield (34%) using $SbCl_3$ as the catalyst at room temperature without microwave irradiation, and with yield of 72% upon heating under otherwise similar conditions. As can be seen from Table 1, all products **3a–j**, were obtained in yields of 80–98% after a microwave-assisted irradiation for 3–5 min. By contrast, the classical heating method requires heating for 3–5 h and provides smaller yields. The condensation of substrate **1** with ketones furnishes the corresponding 2,2-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones **5a–d** (Scheme 2 and Table 2). Both aromatic and aliphatic carbonyl substrates can be used in the synthesis of **3** and **5**. Optimization of the reaction conditions was studied with different amounts of the catalyst and under different microwave powers. The optimum amount of $SbCl_3$ was found to be 1 mol% in respect to anthranilic amide. The microwave power of 200 W was found to give the best results. The yields of the products decrease with the increases of microwave power.



Scheme 1 Synthesis of quinazolin-4(3*H*)-ones **3a–j**.



Scheme 2 Synthesis of quinazolin-4(3*H*)-ones **5a–d**.

Table 1 $SbCl_3$-catalyzed synthesis of quinazolin-4(3*H*)-ones by condensation of anthranilamide with aldehydes.[a]

R_1	Time (MW)/min	Time (thermal)/min	Product	Yield (%)[a]
C_6H_5	3	180	**3a**	94, 85[b], 72[c]
2-OHC_6H_4	5	240	**3b**	80, 67[c]
3,4-$(CH_3O)_2C_6H_3$	3	240	**3c**	87, 71[c]
3-BrC_6H_4	5	240	**3d**	91, 77[c]
4-ClC_6H_4	4	240	**3e**	94, 83[c]
4-FC_6H_4	3	240	**3f**	98, 86[c]
$C_6H_5CH{=}CH$	3	240	**3g**	87, 74[c]
2-Furyl	3	240	**3h**	88, 69[c]
n-C_2H_5	4	240	**3i**	84, 72[c]
n-C_3H_7	3	240	**3j**	80, 70[c]

[a]Reaction on 2 mmol scale, MW power as specified. Catalyst loading: 1 mol% of anthranilamide. [b]Reaction carried out using $SbCl_3$ as catalyst at reflux in THF. [c]Reaction carried out using $SbCl_3$ as catalyst under thermal condition.

Table 2 $SbCl_3$-catalyzed synthesis of quinazolin-4(3*H*)-ones by condensation of anthranilamide with ketones.[a]

R_2	R_3	Time (MW)/min	Time (thermal)/min	Product	Yield (%)[a]
CH_3	CH_3	3	240	**5a**	92, 85[b]
CH_3	C_2H_5	3	240	**5b**	94, 89[b]
$(CH_2)_5$		3	240	**5c**	95, 91[b]
C_6H_5	CH_3	3	240	**5d**	89, 83[b]

[a]Reaction on a 2 mmol scale, MW power and reaction time as specified. Catalyst loading: 1 mol% in respect to anthranilamide. [b]Reaction carried out using $SbCl_3$ as catalyst under thermal condition.

Conclusions

Quinazolin-4(3*H*)-ones **3a–j** are efficiently prepared by the reaction of anthranilamide (**1**) with aldehydes in the presence of a catalytic amount of $SbCl_3$ in the absence of solvent under microwave irradiation. 2,2-Disubstituted-2,3-dihydroquinazolin-4(1*H*)-ones **5a–d** are the products of the reaction of **1** with ketones under otherwise similar conditions.

Experimental

Melting points are uncorrected. Infrared spectra were recorded on a Brucker Vector 22 spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Brucker 400 MHz spectrometer with tetramethylsilane (TMS) as internal standard and DMSO-d_6 as solvent. Elemental analyses were conducted using an Elementar Vario EL instrument.

General procedure for synthesis of substituted quinazolin-4(3*H*)-ones 3a–j and 5a–d

Classical heating Anthranilamide (2 mmol) and an aldehyde or ketone (2 mmol) were mixed thoroughly with $SbCl_3$ (1 mol%) in a flask equipped with a condenser and the mixture was heated under reflux. After the reaction was completed [monitored by thin-layer chromatography (TLC)], the mixture was poured into ice-cooled water and stirred for 30 min. The resultant precipitate was filtered, washed with water and crystallized from ethanol.

Microwave irradiation Anthranilamide (2 mmol) and an aldehyde or ketone (2 mmol) were mixed thoroughly with $SbCl_3$ (1 mol%) and irradiated for 3–5 min in a microwave reactor equipped with a condenser. Work-up was conducted as described above.

2-Phenyl-quinazolin-4(3*H*)-one (3a) This compound was obtained in yields of 72% (heat) and 94% (MW); mp 252–254°C; (lit. [27] mp 242–246°C).

2-(2-Hydroxyphenyl)quinazolin-4(3*H*)-one (3b) This compound was obtained in yields of 67% (heat) and 80% (MW); mp 248–250°C (lit. [7] mp 250°C).

2-(3,4-Dimethoxyphenyl)quinazolin-4(3*H*)-one (3c) This compound was obtained in yields of 71% (heat) and 87% (MW); mp 257–259°C (lit. [28] mp 231–233°C).

2-(3-Bromophenyl)quinazolin-4(3*H*)-one (3d) This compound was obtained in yields of 77% (heat) and 91% (MW); mp 316–318°C (lit. [29] mp 295–296°C).

2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (3e) This compound was obtained in yields of 83% (heat) and 94% (MW); mp >300°C (lit. [30] mp >300°C).

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (3f) This compound was obtained in yields of 86% (heat) and 98% (MW); mp 293–295°C (lit. [31]; mp 288–289°C).

2-Styryl-quinazolin4-(3*H*)-one (3g) This compound was obtained in yields of 74% (heat) and 87% (MW); mp 253–255°C (lit. [28] mp 249–250°C).

2-(2-Furyl)quinazolin-4(3*H*)-one (3h) This compound was obtained in yields of 69% (heat) and 88% (MW); mp 233–235°C (lit. [28] mp 219–221°C).

2-Ethyl-quinazolin-4(3*H*)-one (3i) This compound was obtained in yields of 72% (heat) and 84% (MW); mp 238–240°C (lit. [32] mp 235–236°C).

2-Propyl-4(3*H*)-quinazolin-4(3*H*)-one (3j) This compound was obtained in yields of 70% (heat) and 80% (MW); mp 210–212°C (lit. [33] mp 208–210°C).

2,2-Dimethyl-2,3-dihydroquinazolin-4(1*H*)-one (5a) This compound was obtained in yields of 92% (MW); mp 178–180°C (lit. [34] mp 183–184°C).

2-Ethyl-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (5b) This compound was obtained in yields of 94% (MW); mp 178–180°C (lit. [35] mp 184–186°C).

1′*H*-spiro[cyclohexane-1,2′-quinazolin]-4′(3′*H*)-one (5c) This compound was obtained in yields of 95% (MW); mp 225–226°C (lit. [35] mp 224–225°C).

2-Methyl-2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one (5d) This compound was obtained in yields of 89% (MW); mp 226–228°C (lit. [36] mp 225–229°C).

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