Microwave-assisted synthesis of quinazolin-4(3H)-ones catalyzed by SbCl₃

Abstract: Antimony(III) trichloride (SbCl₃) is an effective catalyst (1 mol%) for the condensation of anthranilic amide with various aldehydes or ketones to quinazolin-4(3H)-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(3H)-ones; SbCl₃; solvent-free.

Introduction

Quinoline and quinazoline derivatives have received attention due to their bioactivities [1]. The quinazolin-4(3H)-ones have been found to exhibit antimalarial [1, 2], antiinflammatory [3], antibacterial [4], as well as antihypertensive activities [5]. Generally, quinazolin-4(3H)-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.

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 SbCl₃ (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 SbCl₃ 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 SbCl₃ 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(1H)-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 SbCl₃ 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.
Conclusions

Quinazolin-4(3H)-ones 3a–j are efficiently prepared by the reaction of anthranilamide (1) with aldehydes in the presence of a catalytic amount of SbCl₃ in the absence of solvent under microwave irradiation. 2,2-Disubstituted-2,3-dihydroquinazolin-4(1H)-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. ¹H NMR spectra were recorded on a Brucker 400 MHz spectrometer with tetramethylsilane (TMS) as internal standard and DMSO-d₆ as solvent. Elemental analyses were conducted using an Elementar Vario EL instrument.

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

Classical heating Anthranilamide (2 mmol) and an aldehyde or ketone (2 mmol) were mixed thoroughly with SbCl₃ (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 SbCl₃ (1 mol%) and irradiated for 3–5 min in a microwave reactor equipped with a condenser. Work-up was conducted as described above.

Table 1 SbCl₃-catalyzed synthesis of quinazolin-4(3H)-ones by condensation of anthranilamide with aldehydes.⁺

| R₁     | Time (MW)/min | Time (thermal)/min | Product | Yield (%)⁺⁺ |
|--------|---------------|--------------------|---------|-------------|
| C₆H₅   | 3             | 180                | 3a      | 94, 85⁺⁺, 72⁺⁺ |
| 2-OHC₆H₄ | 5             | 240                | 3b      | 80, 67⁺⁺     |
| 3,4-(CH₂O)₂C₆H₃ | 3         | 240                | 3c      | 87, 71⁺⁺     |
| 3-BrC₆H₄ | 5             | 240                | 3d      | 91, 77⁺⁺     |
| 4-ClC₆H₄ | 4             | 240                | 3e      | 94, 83⁺⁺     |
| 4-FC₆H₄ | 3             | 240                | 3f      | 98, 86⁺⁺     |
| C₆H₅CH=CH | 3             | 240                | 3g      | 87, 74⁺⁺     |
| 2-Furyl | 3             | 240                | 3h      | 88, 69⁺⁺     |
| n-C₃H₇ | 4             | 240                | 3i      | 84, 72⁺⁺     |
| n-C₃H₇ | 3             | 240                | 3j      | 80, 70⁺⁺     |

⁺Reaction on 2 mmol scale, MW power as specified. Catalyst loading: 1 mol% of anthranilamide. ⁺⁺Reaction carried out using SbCl₃ as catalyst at reflux in THF. ⁺Reaction carried out using SbCl₃ as catalyst under thermal condition.

Table 2 SbCl₃-catalyzed synthesis of quinazolin-4(3H)-ones by condensation of anthranilamide with ketones.⁺

| R₂ R₃ | Time (MW)/min | Time (thermal)/min | Product | Yield (%)⁺⁺ |
|-------|---------------|--------------------|---------|-------------|
| CH₃ CH₃ | 3             | 240                | 5a      | 92, 85⁺⁺     |
| CH₃ C₂H₅ | 3             | 240                | 5b      | 94, 89⁺⁺     |
| (CH₂)₅ | 3             | 240                | 5c      | 95, 91⁺⁺     |
| C₆H₅ CH₃ | 3             | 240                | 5d      | 89, 83⁺⁺     |

⁺Reaction on a 2 mmol scale, MW power and reaction time as specified. Catalyst loading: 1 mol% in respect to anthranilamide. ⁺⁺Reaction carried out using SbCl₃ as catalyst under thermal condition.

2-Phenyl-quinazolin-4(3H)-one (3a) This compound was obtained in yields of 72% (heat) and 94% (MW); mp 252–254°C (lit. [27] mp 262–264°C).

2-(2-Hydroxyphenyl)quinazolin-4(3H)-one (3b) This compound was obtained in yields of 67% (heat) and 80% (MW); mp 248–250°C (lit. [7] mp 288–289°C).

2-(3,4-Dimethoxyphenyl)quinazolin-4(3H)-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(3H)-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(3H)-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(3H)-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-quinazolin-4(3H)-one (3g) This compound was obtained in yields of 76% (heat) and 87% (MW); mp 253–255°C (lit. [28] mp 269–250°C).

2-(2-Furyl)quinazolin-4(3H)-one (3h) This compound was obtained in yields of 69% (heat) and 88% (MW); mp 233–235°C (lit. [32] mp 235–236°C).

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

2-(2-Furyl)quinazolin-4(3H)-one (3j) This compound was obtained in yields of 94% (MW); mp 178–180°C (lit. [34] mp 184–186°C).

2,2-Dimethyl-2,3-dihydroquinazolin-4(1H)-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(1H)-one (5b) This compound was obtained in yields of 96% (MW); mp 178–180°C (lit. [35] mp 226–227°C).

1H-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 226–225°C).

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

Acknowledgments: This work was financially supported by the Natural Science Foundation of Shandong Province (Funder Id: 10.13039/501100007129, No. ZR2017PB006), the Ph.D. Programs Foundation of Ludong University (No. 32840301), the National University Student Innovation and entrepreneurship training Program (No. 201710451034, 201810451326, 201810451344) and the Innovation Foundation Plan of Ludong University (No. Id171062).

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