

Full Paper

Microwave Assisted Synthesis of *N*-Arylheterocyclic Substituted-4-aminoquinazoline Derivatives

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Abstract: A simple, efficient, and general method has been developed for the synthesis of various *N*-aryl heterocyclic substituted-4-aminoquinazoline compounds from 4-chloroquinazoline and aryl heterocyclic amines under microwave irradiation using 2-propanol as solvent. The advantages of the use of microwave irradiation in relation to the classical method were demonstrated.

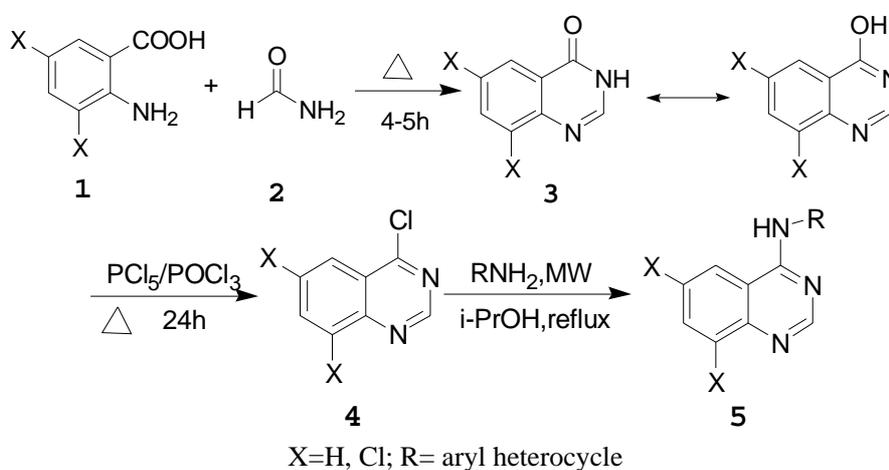
Keywords: 4-Aminoquinazoline, Heterocyclic moiety, Microwave irradiation.

Introduction

As part our ongoing research program on heterocyclic compounds which may serve as leads for designing novel antitumor agents, we were particularly interested in 4-substituted quinazolines [1-2]. We considered the well known activity of the quinazoline nucleus in chemotherapy, where many of its substituted derivatives are effective antitumor agents [3-6]. Furthermore, more recent data has reported that a broad class of quinazolines also act as potent and highly selective inhibitors of epidermal growth factor receptor (EGFR) or epidermal growth factor receptor tyrosine kinase (EGFR-TK) [7-9];

members of this class are expected to have great therapeutic potential in the treatment of malignant and nonmalignant epithelial diseases [10-11]. In view of these facts, and in order to study the influence of 4-position substituted on antitumor activity, we have now prepared a series of new 4-aryl heterocyclic aminoquinazolines containing diverse heterocyclic moieties in the hope of discovering more active ATP site inhibitors. In the classical synthesis of these compounds [12-13], a mixture of 4-chloroquinazoline and aniline are refluxed at 80°C for 12 h. in 2-propanol. This method, however, involves long reaction times and complex handling and gives low yields of products. We have recently developed a new synthesis method for the target compounds using microwave irradiation in 2-propanol (Scheme 1). The new method requires short reaction times, is very easy and mild and environmentally friendly. To the best of our knowledge, this is the first report on the synthesis of new quinazoline compounds containing heterocycle moieties using microwave irradiation.

Scheme 1. Synthesis of *N*-arylheterocyclic substituted-4-aminoquinazoline derivatives.



Results and Discussion

The reaction results with or without microwave irradiation are shown in Table 1. It can be seen that the presence of microwave irradiation both accelerated the reactions and gave higher yields. The reaction time for synthesis of compounds **5a**–**5g** was shortened from 12 h. to only 20 min. with the one-step microwave-assisted procedure.

In order to optimize the reaction parameters, we selected compound **5b** for further study under different conditions. These results are shown in Table 2. Without microwave irradiation (Table 1) compound **5b** could be obtained in 37.3% after 12 h. When the reaction was carried out under microwave irradiation at 80°C for 10 min. the yield of **5b** was increased to 91.0%, and increased further to 96.5% when the reaction time was extended to 20 min. (Table 2, entries 1 and 2). However, no further improvement of the yield was noted when the reaction time was prolonged to 30 min. (Table 2, entry 3) and the yield even decreased a little, a fact we attribute to the formation of byproducts. Consequently, we chose 20 min. as the optimum reaction time (Table 2, entry 2). As for the effect of the microwave power, it could be seen that when it was increased from 40 to 60, 80 and 100W, the yields of **5b** were 75.9%, 96.5%, 98.8%, and 97.0%, respectively (Table 2, entries 2 and 4-6). Hence, it's better for the reaction to be carried out at 60W or higher power settings than at 40W. No improvement was observed under irradiation when the microwave power varied from 80 to 100W

(Table 2, entries 5 and 6). When the reaction temperature was increased from 30°C to 50°C, 70°C or 80°C, **5b** was obtained in 79.9 %, 84.0 %, 90.0 % and 96.5 % yields respectively (Table 2, entry 2 and entries 7-9).

Table 1 Yields ^a and reaction conditions used for the microwave assisted synthesis of **5a-5g**.

Product	Microwave method ^b		Classical method ^c	
	Reaction time	Yield(%)	Reaction time	Yield(%)
5a	20 min.	84.0	12h	29.5
5b	20 min.	96.5	12h	37.3
5c	20 min.	80.1	12h	43.2
5d	20 min.	79.1	12h	38.7
5e	20 min.	83.1	12h	51.3
5f	20 min.	89.0	12h	45.9
5g	20 min.	92.5	12h	24.4

^a Yields of isolated products.

^b Reaction conditions: *i*-PrOH, reflux under MW (60W power).

^c Reaction conditions: *i*-PrOH, reflux temperature.

Table 2. Different conditions used for the microwave assisted synthesis of **5b**.

Entry	Reaction time	Power / Watt	Reaction temperature / °C	Yield ^a / %
1	10 min.	60	80	91.0
2	20 min.	60	80	96.5
3	30 min.	60	80	92.5
4	20 min.	40	80	75.9
5	20 min.	80	80	98.8
6	20 min.	100	80	97.0
7	20 min.	60	30	79.9
8	20 min.	60	50	84.0
9	20 min.	60	70	90.0

^a Yields of isolated products. Each reaction was repeated three times and the result was averaged.

Conclusions

In summary, the present new method of the formation of *N*-arylheterocyclic substituted-4-aminoquinazoline derivatives **5a-5g** under microwave irradiation offers several advantages: faster reaction rates and high yields, while the classical method of formation of *N*-arylheterocyclic substituted-4-aminoquinazoline derivatives involves long reaction times (12 h). All compounds **5a-5g** were fully characterized by spectroscopic methods.

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Experimental

General

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purification. All melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. The infrared spectra were recorded on a Bruker VECTOR22 spectrometer in KBr disks. $^1\text{H-NMR}$ (solvent DMSO- d_6) and $^{13}\text{C-NMR}$ spectra (solvent DMSO- d_6) were recorded on a Varian-Inova 400 MHz spectrometer at room temperature using TMS as internal standard. D_2O exchange was used to confirm the assignment of the signals of NH protons. The mass spectra were taken on an HP5988A spectrometer. Elemental analysis was performed by an Elementar Vario-III CHN analyzer. Microwave reactions were performed on a variable power Focused Microwave Synthesis, DiscoverTM LabMate equipped with a high sensitivity IR sensor for temperature control and measurement. The following compounds were prepared as described in the literature: 3,5-dichloro-2-aminobenzoic acid (**1b**): white needles, yield 86.4%; m.p. 231~233°C (lit. [14], m.p. 231°C); quinazolin-4-one (**3a**): white solid, yield 95.4%; m.p. 214~215°C (lit. [15], m.p. 215.5~216.5°C); 6,8-dichloroquinazoline-4-one (**3b**): grey solid, yield 77.8%; m.p. >300°C (lit. [16], m.p. >300°C); 4-chloroquinazoline (**4a**): white solid, yield 54.5%; m.p. 92~93°C (lit. [15], m.p. 96.5~97.5°C) and 4,6,8-trichloroquinazoline (**4b**): pale solid, yield 15.3%; m.p. 145.5~147.5°C (lit. [17], m.p. 139~140°C).

Synthesis of N-arylheterocyclic substituted-4-aminoquinazolines 5a-g (microwave method): A mixture of 4-chloroquinazoline (3.0 mmol) and aryl heterocyclic amine (3.0 mmol) in 2-propanol (30 mL) was stirred for three min., then the mixture was irradiated in the microwave oven at 60W for 20 min. Upon completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure and the residue was washed with water, filtered off and purified by silica gel column chromatography (petroleum ether-ethyl acetate, 5:1 v:v) to give the title compounds.

Synthesis of N-arylheterocyclic substituted-4-aminoquinazolines 5a-g (classical method): A solution of 4-chloroquinazoline (3.0 mmol) and aryl heterocyclic amine (3.0 mmol), in 2-propanol (30 mL) was stirred under reflux for 12 h. The work-up was carried out as described for the microwave method.

N-(5-methylisoxazol-3-yl)-4-aminoquinazoline (5a). Pale yellow needles, m.p. 188~190°C; IR: 3275.1, 3149.8, 2988.2, 2850, 1631.7, 1475.5, 1575.8 cm^{-1} ; $^1\text{H-NMR}$: δ 10.86 (s, 1H, NH), 8.69 (s, 1H, quinazoline H-2), 8.62 (d, 1H, $J=7.6\text{Hz}$, quinazoline H-8), 7.60-7.90 (m, 3H, quinazoline H-5,6,7), 6.99 (s, 1H, isoxazole H-4), 2.37 (s, 3H, CH_3); $^{13}\text{C-NMR}$: δ 169.1 (quinazoline C-4), 159.1 (quinazoline C-2), 157.2 (isoxazole C-5), 154.2 (quinazoline C-9), 149.9 (isoxazole C-3), 133.6 (quinazoline C-7), 127.9 (quinazoline C-8), 126.8 (quinazoline C-6), 123.3 (quinazoline C-5), 114.9 (quinazoline C-10), 98.5 (isoxazole C-4), 12.2 (CH_3); EIMS: m/z 226 (M^+ , 18.1); *Anal.* Calc. for $\text{C}_{12}\text{H}_{10}\text{N}_4$ (226.2): C, 63.87; H, 4.34; N, 24.31. Found: C, 63.71; H, 4.46; N, 24.77.

N-(2-methoxydibenzofuran-3-yl)-4-aminoquinazoline (**5b**). Pale yellow needles, m.p. 263~264°C; IR: 3421.7, 1618.3, 1469.8, 1572.0 cm⁻¹; ¹H-NMR: δ 9.23 (s, 1H, NH), 8.84 (s, 1H, quinazoline H-2), 8.51(s, 1H, dibenzofuran H-9), 7.24-7.87 (m, 9H, quinazoline H-5,6,7,8 + dibenzofuran H-4,5,6,7,8), 4.05 (s, 3H, OCH₃); ¹³C-NMR: δ 156.6 (quinazoline C-4), 156.4 (quinazoline C-2), 154.7 (dibenzofuran C-13), 150.7 (quinazoline C-9), 149.6 (dibenzofuran C-10), 145.2 (quinazoline C-7), 132.7 (dibenzofuran C-2), 128.9 (quinazoline C-8), 128.0 (dibenzofuran C-3), 126.7 (dibenzofuran C-12), 126.0 (quinazoline C-6), 124.6 (dibenzofuran C-8), 122.4 (dibenzofuran C-7), 120.1 (dibenzofuran C-6), 119.7 (quinazoline C-5), 117.7 (quinazoline C-10), 115.7 (dibenzofuran C-5), 111.5 (dibenzofuran C-9), 103.9 (dibenzofuran C-4), 100.7 (dibenzofuran C-11), 56.6 (OCH₃); EIMS: m/z 341 (M⁺, 14.8); *Anal. Calc.* for C₂₁H₁₅N₃O₂ (341.4): C, 73.93; H, 4.17; N, 12.21. Found: C, 73.89; H, 4.43; N, 12.31.

N-(6-methoxybenzothiazol-2-yl)-4-aminoquinazoline (**5c**). yellow solid, m.p. 231~233°C; IR: 3200, 2982, 2200, 1625.1, 1608.6, 1554.1, 1464.1, 1283.3, 1267.2, 1055.1 cm⁻¹; ¹H-NMR: δ 9.14 (s, 1H, NH), 8.62 (d, 1H, *J*=8.0Hz, quinazoline H-8), 7.17-8.08 (m, 6H, quinazoline H-2,5,6,7 + Ar-H), 3.85 (s, 3H, OCH₃); EIMS: m/z 308 (M⁺, 14.8); *Anal. Calc.* for C₁₆H₁₂N₄OS (308.4): C, 55.73; H, 3.80; N, 16.25. Found: C, 55.51; H, 3.93; N, 16.32.

N-(6-methoxybenzothiazol-2-yl)-4-aminoquinazoline hydrochloride (**5d**) Yellow solid, m.p. 300°C (decomposed); IR: 3100, 2981, 2300, 1645.3, 1580.3, 1453.1 cm⁻¹; ¹H-NMR: δ 9.20 (s, 1H, NH), 8.65 (d, 1H, *J*=8.0Hz, quinazoline H-8), 7.19-8.13 (m, 6H, quinazoline H-2,5,6,7 + Ar-H), 3.98 (s, 3H, OCH₃); EIMS: m/z 345 (M⁺, 11.1); *Anal. Calc.* for C₁₆H₁₃ClN₄OS (344.8): C, 55.73; H, 3.80; N, 16.25. Found: C, 55.64; H, 3.97; N, 16.03.

N-(6-methylbenzothiazol-2-yl)-4-aminoquinazoline hydrochloride (**5e**) Orange needles, m.p. 90~92°C; IR: 3093.5, 1612.5, 1556.6, 1483.3, 1323.2 cm⁻¹; ¹H-NMR: δ 14.46 (s, 1H, N-H), 8.91 (s, 1H, quinazoline H-2), 8.19 (d, 1H, *J*=8.0Hz, quinazoline H-8), 7.65-7.98 (m, 3H, quinazoline H-5,6,7), 7.14-7.48 (m, 3H, Ar-H), 2.28 (s, 3H, CH₃); EIMS: m/z 328 (M⁺, 13.0); *Anal. Calc.* for C₁₆H₁₃ClN₄S (328.8): C, 58.44; H, 3.98; N, 17.04. Found: C, 58.37; H, 3.90; N, 17.11.

6,8-dichloro-*N*-(5-methylisoxazol-3-yl)-4-aminoquinazoline (**5f**). Pale yellow crystals, m.p. 226~228°C; IR: 3259.7, 3223.1, 3030, 1627.9, 11573.9, 1450.5 cm⁻¹; ¹H-NMR: δ 11.07 (s, 1H, NH), 8.82 (s, 1H, quinazoline H-2), 8.79 (s, 1H, quinazoline H-7), 8.21 (s, 1H, quinazoline H-5), 6.98 (s, 1H, isoxazole H-4), 2.46 (s, 3H, CH₃); EIMS: m/z 295 (M⁺, 13.0); *Anal. Calc.* for C₁₂H₈Cl₂N₄O (295.1): C, 48.84; H, 2.73; N, 18.98. Found: C, 48.64; H, 2.50; N, 19.19.

6,8-dichloro-*N*-(2-methoxydibenzofuran-3-yl)-4-aminoquinazoline (**5g**). Yellow crystals, m.p. 292~294°C; IR: 3417.9, 1614.4, 1556.6, 1469.8 cm⁻¹; ¹H-NMR: δ 9.88 (s, 1H, N-H), 8.69 (d, 1H, *J*=2.0Hz, dibenzofuran H-4), 8.58 (s, 1H, quinazoline H-2), 8.19(d, 1H, *J*=2.0Hz, dibenzofuran H-5), 8.16 (d, 1H, *J*=8.0Hz, H-9 dibenzofuran), 7.99 (s, 1H, quinazoline H-7), 7.92 (s, 1H, quinazoline H-5), 7.68 (d, 1H, *J*=8.0Hz, dibenzofuran H-6), 7.52-7.39 (m, 2H, dibenzofuran H-7,8), 3.27 (s, 3H, OCH₃); ¹³C-NMR: δ 158.3 (quinazoline C-4), 156.2 (quinazoline C-2), 155.8 (dibenzofuran C-13), 150.4 (quinazoline C-9), 149.2 (dibenzofuran C-10), 145.2 (quinazoline C-7), 133.0 (dibenzofuran C-2),

129.8 (quinazoline C-8), 127.2 (dibenzofuran C-3), 126.5 (dibenzofuran C-12), 124.0 (quinazoline C-6), 123.0 (dibenzofuran C-8), 121.8 (dibenzofuran C-7), 121.5 (dibenzofuran C-6), 121.0 (quinazoline C-5,10), 116.7 (quinazoline C-10), 111.7 (dibenzofuran C-5,9), 110.5 (dibenzofuran C-4), 103.3 (dibenzofuran C-11), 56.4 (OCH₃); EIMS: m/z 410 (M⁺,14.1); Anal. Calc. for C₂₁H₁₃Cl₂N₃O₂ (410.3): C, 61.48; H, 3.19; N, 10.24. Found: C, 61.20; H, 2.99; N, 10.36.

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Sample Availability: Samples of the compounds are available from authors.