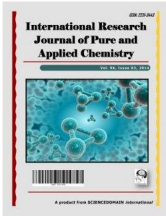

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Optimization of Synthesis Process of 4-Methylquinazoline

Juan Liu[1], Yun Yang[1] and Liangchun Li[1*]

[1]School of Life Science and Engineering, Southwest University of Science and Technology, Mianyang 621010, China.

Authors' contributions

This work was carried out in collaboration between all authors. Author LL designed the study and wrote the protocol. Author JL undertook the experimental work, preformed the statistical analysis and wrote the first draft of the manuscript with assistance from author YY. All authors read and approved the final manuscript.

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ABSTRACT

4-Methylquinazoline was synthesized with 2-aminoacetophenone and formamide as the starting materials. The reaction conditions, including catalyst, ratio of substrates, temperature and time were optimized. Results showed that the optimal condition were as follows: Catalyst BF_3-Et_2O, the molar ratio of 2-aminoacetophenone: BF_3-Et_2O = 1:0.5, the weight ratio of 2-aminoacetophenone: formamide = 1:52, temperature 150°C, and time 6 h. Under the optimal conditions, the yield of the reaction achieved the highest (86%), which are better than the past reports.

Keywords: Quinazolines; 4-methylquinazoline; synthesis; Lewis acid; reaction condition.

1. INTRODUCTION

Quinazolines are kinds of the important bioactive natural products. Quinazoline ring, as a key skeleton structure, can be combined with a variety of biological macromolecules, which leads to different biological activities [1]. Usually, the different pharmacophore can be introduced into

**Corresponding author: E-mail: kibyn@126.com;*

the quinazoline skeleton to obtain various biological activities [2], and these derivatives have been widely used in pesticide and medicine fields, such as sterilization, insecticidal, antiviral, anti-inflammatory, antitumor, antihypertensive, tuberculosis, malaria, etc [3-6]. During the last decade, the protein kinase has become an important target field of anti-tumor drug researches [7].

4-Methylquinazoline is an important synthetic intermediate, and itself also has insecticidal activity of antimicrobial. 4-methylquinazoline as promising compounds to be included in monitor and control devices currently under development for *T. infestans*, the most important vector of Chagas disease in Argentina and much of South America. And the preliminary structure–activity relationship was concluded revealing that 4-position is the key modification site for potent quinazoline immunosuppressive agent [8]. Due to people have a great interest in quinazolines, they sought to prepare quinazoline analogues via 4-methylquinazoline.

4-Methylquinazoline can be prepared by the reaction of 2-aminoacetophenone and formamide with a Lewis acid catalyst. In the literature [9], the yield of 4-methylquinazoline is about 50%-75% and few researches were reported. And previous literature the yields were reported below 75%.The possible mechanism [10] for the reaction can be proposed as Scheme 1. Firstly, with the assistance of Lewis acid formamide attacks the carbonyl carbon of 2-aminoacetophenone, then the resulting transient state possibly undergoes an intramolecular cyclization (the *N*-formyl carbonyl reacts with adjacent amine like first step), and finally after dehydration the quinazoline is produced. In this paper, we optimized the reaction conditions including Lewis acids, ratio of substrates, temperature and time. Under the optimal reaction conditions, the total yield is obtained up to 86% with the cheap Lewis acid BF_3-Et_2O. These researches offer an expanded potential to prepare for multigram quantities of 4-methylquinazoline.

2. MATERIALS AND METHODS

2.1 General Information

^{1}H NMR spectrum was recorded with a Bruker Avance 400 spectrometer in DMSO and tetramethylsilane was used as an internal standard substance. All the reagents were purchased from commercial suppliers and used without further purification.

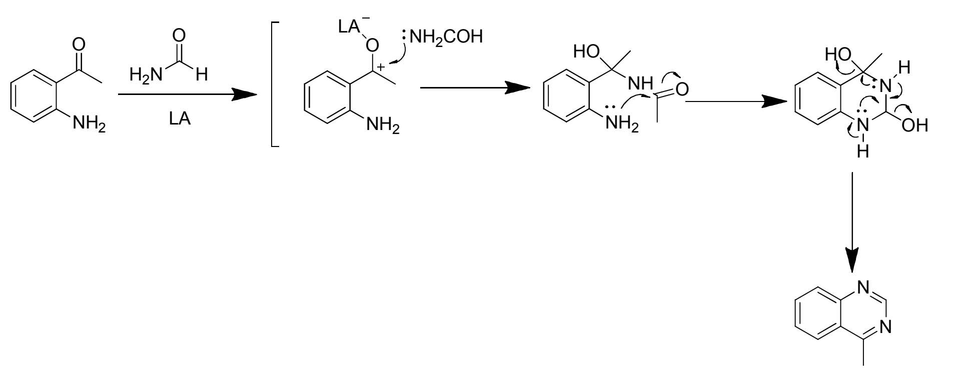
2.2 Synthesis Section

2.2.1 General method in the optimized researches

A solution of 2-aminoacetophenone in formamide containing Lewis acid was heated at pre-set temperature until the reaction is completed by TLC monitor. The reaction mixture was cooled to room temperature, then extracted with benzene. The organic layer was dried with anhydrous Na_2SO_4, filtrated, and evaporated to dryness in vacuum. The residue was purified by column chromatography on flash silica gel to give a yellow oil of 4-methylquinazoline.

2.2.2 Typical method for synthesis of 4-methylquinazoline by BF_3•Et_2O

A solution of 2-aminoacetophenone (0.5 g, 3.70 mmol) in freshly distilled formamide (10 mL) containing $BF_3 \cdot Et_2O$ (0.25 mL, 1.85 mmol) was



Scheme 1. Proposed mechanism for the formation of 4-methylquinazoline

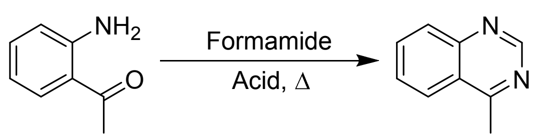
heated at 150°C for 6 h, while the complete disappearance of the starting product was followed by TLC (Ethyl acetate/Petroleum ether = 2/5, v/v). The reaction mixture was cooled to room temperature, extracted with benzene (3×75 mL), dried with anhydrous Na_2SO_4, filtrated, and evaporated to dryness in vacuum. The residue was purified by column chromatography on flash silica gel, eluting the reaction products first with dichloromethane and then with ethyl acetate/petroleum ether (1/10, v/v) to give a yellow oil of 4-methylquinazoline (0.475 g, 85.7% yield). ^1H NMR (400 MHz, DMSO): δ 9.11 (s, 1H, CH), 8.27 (dt, *J* = 8.4, 0.9 Hz, 1H, CH), 7.99 (dd, *J* = 2.3, 0.9 Hz, 1H, CH), 7.98 (d, *J* = 1.0 Hz, 1H, CH), 7.78 – 7.70 (m, 1H, CH), 3.34 (s, 1H, CH), 2.91 (s, 3H,Me); ^{13}C NMR (100 MHz, DMSO): δ 168.3, 154.5, 149.6, 133.7, 129.1, 127.6, 125.1, 124.6, 21.9; GC-MS m/z(%rel inten.) : 144(M^+,100),129(26),103(33),76(34).

3. RESULTS AND DISCUSSION

In our initial experiments, we studied the reaction in the presence of a variety of Lewis acids such as $ZnCl_2$, $AlCl_3$, $BF_3{\cdot}Et_2O$ and $B(OH)_3$ under 150°C and the results were shown in Table 1. In this study, 4-methylquinazoline was formed in 24–74% yield and $BF_3{\cdot}Et_2O$ gave the best result (Entry 4, yield in 74%) in 6 h. Considering the proton acids are usually used in the formation of imine [11], we screened acetic acid and sulfuric acid with molecular sieve (4 Å) exist, which can eliminate water produced in the reaction. We can find out that the yields are moderate as 55% (acetic acid, Entry 6) and 44% (sulfuric acid, Entry 7), respectively. Temperature of reaction was also an important condition; the experiments indicated that 150°C was the best. At 140°C (Entry 8), the yield of reaction changed a little and about 2% lower than the reaction at 150°C. When the temperature was raised up to 160 or 180°C, the reaction time were not short as usually and the yields were down to 29% and 20% (Entry 9 and 10) due to the appearances of more new impurities with particularly unpleasant smell. It also should be noticed that prolong the reaction time cannot increase the yield because of the increasing of impurities (Entry 12).

At the end, we optimized the weight ratio of 2-aminoacetophenone:formamide and the molar ratio of the $BF_3{\cdot}Et_2O$:2-aminoacetophenone (Table 2). The results showed that when the weight ratio of 2-aminoacetophenone:formamide = 1:52 and the molar ratio of the $BF_3{\cdot}Et_2O$:2-aminoacetophenone = 0.5:1, the reaction yield was the best (86%).

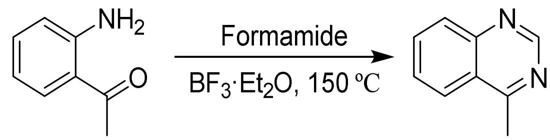
Table 1. Initial optimization of reaction conditions for the synthesis of 4-methylquinazoline[a]



Entry	Acid[b]	Temperature (°C)	Time (h)	Yield (%)
1	$ZnCl_2$	150	6	46.2
2	$FeCl_3$	150	6	32.2
3	$AlCl_3$	150	6	23.6
4	BF_3-Et_2O	150	6	74.6
5	$B(OH)_3$	150	6	42.2
6	CH_3COOH	150	6	54.9
7	H_2SO_4	150	6	44.0
8	BF_3-Et_2O	140	6	73.5
9	BF_3-Et_2O	160	6	28.6
10	BF_3-Et_2O	180	6	19.7
11	BF_3-Et_2O	150	4	63.0
12	BF_3-Et_2O	150	8	40.7

[a] The weight ratio of 2-aminoacetophenone: formamide = 1:52; [b] The molar ratio of the acid:2-aminoacetophenone = 0.36:1

Table 2. Optimization of the reaction conditions for the synthesis of 4-methylquinazoline



Entry	weight ratio of 2-aminoacetophenone:formamide	molar ratio of the $BF_3 \cdot Et_2O$:2-aminoacetophenone	Yield (%)
1	1 : 26	0.36 : 1	48.4
2	1 : 52	0.36 : 1	74.6
3	1 : 104	0.36 : 1	64.8
4	1 : 52	0.5 : 1	85.7
5	1 : 52	1 : 1	41.2

4. CONCLUSION

In conclusion, we have presented optimized procedures for the synthesis of 4-methylquinazoline by intermolecular condensation reaction of 2-aminoacetophenone and formamide with the assistant of Lewis acid. Results showed that the optimal condition were as follows: the Lewis acid is $BF_3 \cdot Et_2O$, the molar ratio of 2-aminoacetophenone:$BF_3 \cdot Et_2O$ is 1:0.5, the weight ratio of 2-aminoacetophenone:formamide is 1:52, the reaction temperature is 150°C, and time is 6 h. Under the optimal conditions, the yield of the reaction achieved the highest (86%), which are better than the past reports.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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