

Optimization of Synthesis Process of 4-Methylquinazoline

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 $\text{BF}_3\text{-Et}_2\text{O}$, the molar ratio of 2-aminoacetophenone: $\text{BF}_3\text{-Et}_2\text{O}$ = 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.

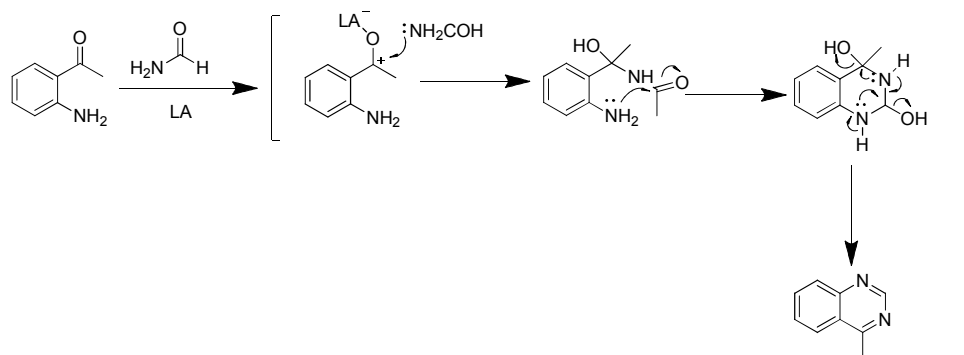
1. Introduction

Quinazolines are kinds of the important bioactive natural products. The derivatives of quinazolines originally can be extracted from plants and used as anti-malaria and anti-bacterial drugs. 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 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]. Quinazolines were also widely applied in the field of cancer drug development due to their good kinase inhibitor activity. The research of quinazoline derivatives is one of the hot medicinal chemistry field, and a variety of novel quinazoline compounds with better activities are eagerly expected to be synthesized.

4-methylquinazoline is an important synthetic intermediate, and itself also has insecticidal activity of antimicrobial. It can be prepared by the reaction of aminoacetophenone and formamide with a Lewis acid catalyst. In the literature^[8], the yield of 4-methylquinazoline is about 50%-75% and few researches were reported. The possible mechanism^[9] 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$. These researches offer an expanded potential to prepare for multigram quantities of 4-methylquinazoline.



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

2. Materials and methods

2.1 General Information

^1H 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

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-methylquinazoline⁸.

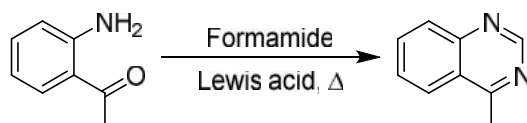
Typical method for synthesis of 4-methylquinazoline by $\text{BF}_3 \cdot \text{Et}_2\text{O}$: A solution of 2-aminoacetophenone (0.5 g, 3.70 mmol) in freshly distilled formamide (10 mL) containing $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.25 mL, 1.85 mmol) was heated at 150 °C for 6 h, while the complete 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), 8.27 (dt,

61 $J = 8.4, 0.9$ Hz, 1H), 7.99 (dd, $J = 2.3, 0.9$ Hz, 1H), 7.98 (d, $J = 1.0$ Hz, 1H), 7.78 – 7.70 (m, 1H),
 62 3.34 (s, 1H), 2.91 (s, 3H).

63 3. Results and discussion

64 In our initial experiments, we studied the reaction in the presence of a variety of Lewis acids
 65 such as ZnCl_2 , AlCl_3 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and B(OH)_3 under 150°C and the results were shown in Table 1.
 66 In this study, 4-methylquinazoline was formed in 24–74% yield and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave the best result
 67 (Entry 4, yield in 74%) in 6 h. Considering the proton acids are usually used in the formation of
 68 imine^[10], we screened acetic acid and sulfuric acid with molecular sieve (4 Å) exist, which can
 69 eliminate water produced in the reaction. We can find out that the yields are moderate as 55%
 70 (acetic acid, Entry 6) and 44% (sulfuric acid, Entry 7), respectively. Temperature of reaction was
 71 also an important condition; the experiments indicated that 150°C was the best. At 140°C (Entry
 72 8), the yield of reaction changed a little and about 2% lower than the reaction at 150°C . When the
 73 temperature was raised up to 160 or 180°C , the reaction time were not short as usually and the
 74 yields were down to 29% and 20% (Entry 9 and 10) due to the appearances of more new
 75 impurities with particularly unpleasant smell. It also should be noticed that prolong the reaction
 76 time cannot increase the yield because of the increasing of impurities (Entry 12).

77 **Table 1. Initial optimization of reaction conditions for the synthesis of 4-methylquinazoline^a**



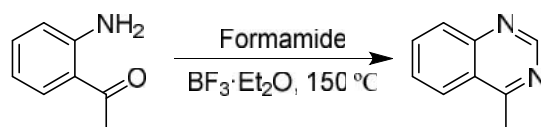
Entry	Lewis acid ^b	Temperature ($^\circ\text{C}$)	Time (h)	Yield (%)
1	ZnCl_2	150	6	46.2
2	FeCl_3	150	6	32.2
3	AlCl_3	150	6	23.6
4	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	150	6	74.6
5	B(OH)_3	150	6	42.2
6	CH_3COOH	150	6	54.9
7	H_2SO_4	150	6	44.0
8	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	140	6	73.5

9	BF ₃ ·Et ₂ O	160	6	28.6
10	BF ₃ ·Et ₂ O	180	6	19.7
11	BF ₃ ·Et ₂ O	150	4	63.0
12	BF ₃ ·Et ₂ O	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.

At the end, we optimized the weight ratio of 2-aminoacetophenone:formamide and the molar ratio of the BF₃·Et₂O:2-aminoacetophenone (Table 2). The results showed that when the weight ratio of 2-aminoacetophenone:formamide = 1:52 and the molar ratio of the BF₃·Et₂O:2-aminoacetophenone = 0.5:1, the reaction yield was the best (86%).

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 ·Et ₂ O: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	0.36 : 1	85.8
5	1 : 52	0.36 : 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 BF₃·Et₂O, the molar ratio of 2-aminoacetophenone:BF₃·Et₂O is 1:0.5, the weight ratio of 2-aminoacetophenone:formamide is 1:52, the reaction temperature is 150 °C,

95 and time is 6 h. Under the optimal conditions, the yield of the reaction achieved the highest (86%),
96 which are better than the past reports.

97 References

- 98 [1] El-Azab A S, Al-Omar M A, Alaa A M, et al. Design, synthesis and biological evaluation of
99 novel quinazoline derivatives as potential antitumor agents: molecular docking study[J]. Eur. J.
100 Med. Chem., 2010, 45(9): 4188-4198.
- 101 [2] Khan, Imtiaz, et al. "Synthetic approaches, functionalization and therapeutic potential of
102 quinazoline and quinazolinone skeletons: The advances continue." European journal of medicinal
103 chemistry 90 (2015): 124-169.
- 104 [3] L.F. Kuypers, D.P. Bacanari, M.L. Jones, R.N. Hunter, R.L. Tansik, S.S. Joyner, C. Boytos,
105 S.K. Rudolph, V. Knick, H.R. Wilson, J.M. Caddell, H.S. Friedman, J.C.W. Comley, J.N. Stables,
106 High-affinity inhibitors of dihydrofolate reductase: antimicrobial and anticancer activities of 7,8-
107 dialkyl-1,3-diaminopyrrolo[3,2-f] quinazolines with small molecular size, J. Med. Chem. 39 (1996)
108 892e903;
- 109 [4] P. Verhaeghe, N. Azas, M. Gasquet, S. Hutter, C. Ducros, M. Laget, S. Rault, P. Rathelot, P.
110 Vanelle, Synthesis and antiparasitic activity of new 4-aryl-2-trichloromethylquinazolines,
111 Bioorg. Med. Chem. Lett. 18 (2008) 396e401.
- 112 [5] V. Alagarsamy, V.R. Solomon, R.V. Sheorey, R. Jayakumar, Synthesis of 3-(3-ethylphenyl)-2-
113 substituted amino-3H-quinazolin-4-ones as novel class of analgesic and anti-inflammatory agents,
114 Chem. Biol. Drug Des. 73 (2009) 471e479;
- 115 [6] D. Giardin, D. Martarelli, G. Sagratini, P. Angeli, D. Ballinari, U. Gulini, C. Melchiorre, E.
116 Poggesi, P. Pompei, Doxazosin-related α_1 -adrenoceptor antagonists with prostate antitumor
117 activity, J. Med. Chem. 52 (2009) 4951e4954;
- 118 [7] Smaill J B, Showalter H D H, Zhou H, et al. Tyrosine kinase inhibitors. 18. 6-Substituted 4-
119 anilinoquinazolines and 4-anilinopyrido [3, 4-d] pyrimidines as soluble, irreversible inhibitors of
120 the epidermal growth factor receptor[J]. Journal of medicinal chemistry, 2001, 44(3): 429-440.
- 121 [8] Madabhushi S, Mallu K.K.R, Jillella R, et al. One-step method for synthesis of 2, 4-
122 disubstituted quinazoline 3-oxides by reaction of a 2-aminoaryl ketone with a hydroxamic acid
123 using $\text{Zn}(\text{OTf})_2$ as the catalyst[J]. Tetrahedron Letters, 2014, 55(12): 1979-1982.
- 124 [9] Alzogaray R A, Fontán A, Camps F, et al. Behavioural response of *Triatoma infestans*
125 (Klug)(Hemiptera: Reduviidae) to quinazolines[J]. Molecules, 2005, 10(9): 1190-1196.
- 126 [10] Pàmies O, Éll A H, Samec J S M, et al. An efficient and mild ruthenium-catalyzed
127 racemization of amines: application to the synthesis of enantiomerically pure amines[J].
128 Tetrahedron letters, 2002, 43(26): 4699-4702.

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