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Microwave assisted synthesis of quinazolinone using different bases

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ABSTRACT
Microwave assisted organic synthesis (MAOS) has emerged as frontier in pharmaceutical research for synthesis of newer drugs. MAOS help not only in implementing GREEN chemistry but also led to the revolution in organic synthesis. For this purpose Methyl 2-acetoamidobenzoate was synthesized using methyl Anthranilate and acetic anhydride in presence of catalytic pyridine. Methyl 2-acetoamidobenzoate treated with different bases like ammonia, hydrazine hydrate to yield 2-methyl-3(H)-quinazolinone and 2-methyl-3-amino-4-quinazolinone respectively. The microwave irradiation has resulted high product yields and reduced reaction times.

KEY WORDS: acetamide, microwave, quinazolinone

Introduction

Quinazoline-4(3*H*)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds [1,2]. Quinazolinone are excellent reservoir of bioactive substances. The stability of the Quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. Quinazoline is 1, 3-diazanaphthalene. It is also known as 5, 6-benzopyrimidine [3] and its 4-oxo derivative are called 4(3*H*)-quinazolinone [4-6]. Quinazolin-4(3H)-ones are also important building blocks in the synthesis of natural and pharmacological compounds[7]. The Quinazoline skeleton, when selectively functionalized, is a building block for the preparation of numerous alkaloids and substances with pronounced biological activities. Various approaches toward the synthesis of quinazolin-4(3H)-one derivatives have been explored during the past years. Recent progress in quinazoline alkaloids and related chemistry was focusing on developments of the synthetic methodologies and their synthetic applications. A vast number of quinazoline derivatives have been synthesized to provide synthetic drugs and to design more effective medicines.

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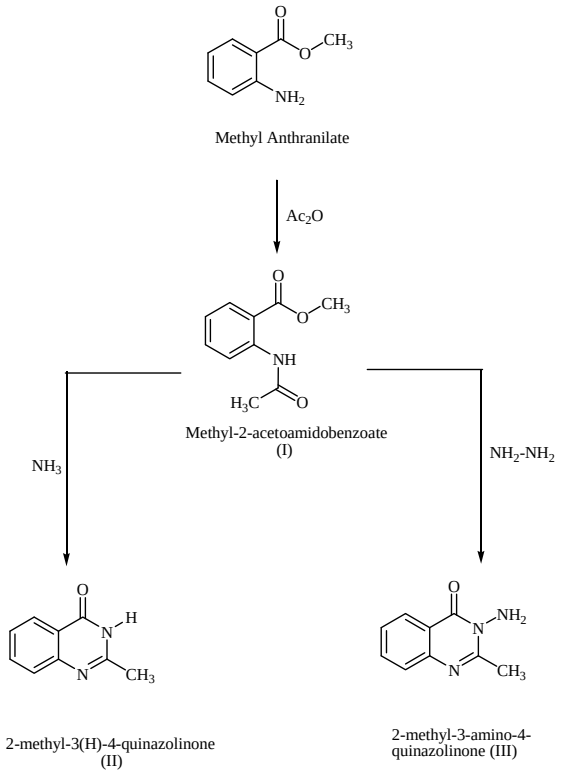
Chemistry

Methyl Anthranilate was refluxed with acetic anhydride to form Methyl 2-Acetamidobenzoate (I). Compound (I) treated with ammonia and hydrazine hydrate to form 2-methyl-3(H)-4-quinazolinone (II) and 2-methyl-3-amino-4-quinazolinone (III) respectively.



Experimental

All chemicals used were of Laboratory Reagent (LR) Grade. The synthesized derivatives were characterized by melting point, TLC, FT-IR and GC-MS. Thin Layer Chromatography was performed using Silica Gel G (Merck Index) coated on glass plates and the spots were visualized by exposure to iodine. Melting points were taken in open glass capillary tubes in liquid paraffin bath and were uncorrected. IR spectra were recorded on FTIR-8400S SHIMADZU spectrophotometer. GC-MS spectra & chromatogram were recorded on GCMS-QP 2010 SHIMADZU instrument. All microwave reactions were carried on 'Catalyst systems Scientific microwave System' with automatic power setting from 140 watt to 700 watt. The reactions were started for initial 2 min. and monitored by TLC for completion of the reaction. All required chemicals were procured from commercial sources.

Methyl 2-Acetoamidobenzoate (I)

In 100 ml RBF, heat a solution of Methyl Anthranilate (0.016 mol) in acetic anhydride (0.127 mol) under reflux for 15 minutes. Cool the solution, pour into cold water (50 ml) containing a drop of pyridine and stir until the oil solidifies. Filter the product, wash with cold water (4x50) and dry at 100^0C. Recrystallise from ethanol (6 ml/gm)
Yield 73.70%
m.p. 98-100^0C

2-methyl-3(H)-4-quinazolinone (II)

In 100 ml RBF, a solution of ammonia (10 ml) and Methyl 2-Acetamidobenzoate (2 gm) in ethanol was irradiated under microwave at 140 W for 15 min. The reaction mixture was cooled and stirred into cold water. The crude product was filtered, dried at 100^0C and finally recrystallised from ethanol.
Yield 63.41%
m.p. 84-86^0C

3-amino-2-methyl-4-quinazolinone (III)

In 100 ml RBF, a solution of hydrazine hydrate (10 ml) and 2 gm of Methyl 2-Acetoamidobenzoate (I) in ethanol was irradiated at 140 W for 3 min. The reaction mixture was cooled and stirred into cold water (50 ml). Crude product was filtered, washed with cold water and dried it at 100^0C. Crude product was recrystallised from ethanol.
Yield 77.93%
m.p. 150-152^0C

Table 1: IR and MS data of Quinazolinone

Sr No.	Compound	IR (KBr) vcm^{-1}	MS (EI, 70eV) m/z
1	Methyl 2-Acetoamidobenzoate	1784.21 (C=O in ester), 1234.48 (C-O), 1697.41 (C=O in amide), 1593.25 (N-H), 1089.82(C-N)	193 (100%).
2	2-methyl-3(H)-4-quinazolinone	1695.49 (C=O), 1595.18 (N-H), 1265.35 (C-N), 3304.17 (N-H str.)	162 (79.12%)
3	3-amino-2-methyl-4-quinazolinone	1666.91 (C=O), 1597.11 (N-H), 1257.63 (C-N), 3300.31 (N-H str.)	177 (78.80%)

Results and discussion

Our work is initiated with the reaction between Methyl Anthranilate and acetic anhydride. To optimize the reaction conditions, the irradiation power and reaction time were variably investigated. We are pleased to find that the reaction provided of 2-methyl-3(H)-4-quinazolinone (II) and 3-amino-2-methyl-quinazolin-4(3*H*)-one (III) in 63.41% and 77.93% yield after 15 min and 3 min of irradiation at 140 W respectively. Mechanistically, the reaction proceeds via a methyl 2-acetamidobenzoate (I) intermediate. Appearance of molecular ion m/z 193 (M^+) in mass spectrum confirmed the intermediate (I).

Conclusion

Considering the environmentally friendly role of neat reaction conditions under microwaves, the bio potential of quinazolinone and our ongoing endeavours towards green synthesis, we have thus developed a facile, rapid and environmentally benign microwave-assisted synthesis of quinazolinone (II and III) using different bases.

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