Sandip S Kotgire et al, /J. Pharm. Sci. & Res. Vol.2 (8), 2010, 518-520

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Synthesis of ethyl 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetate as important analog and intermediate of 2,3 disubstituted quinazolinones

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Abstract:
Microwave assisted organic synthesis (MAOS) has emerged as frontier in pharmaceutical research for synthesis of newer drugs and implementing GREEN chemistry. For this purpose 2-methylquinazolin-4(3*H*)-one was synthesized using Anthranilic acid and acetic anhydride forming 2-methyl-4*H*-benzo[1,3]oxazin-4-one as an intermediate, to this intermediate ammonium acetate was added insitu. Further step was performed using NaH and ethyl 2-chloroacetate through stirring at room temperature. This method was very efficient and easy method for synthesis of ethyl 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetate.
Key Words: *microwave, 2-methyl-4H-benzo[1,3]oxazin-4-one, quinazolinone*

Introduction:

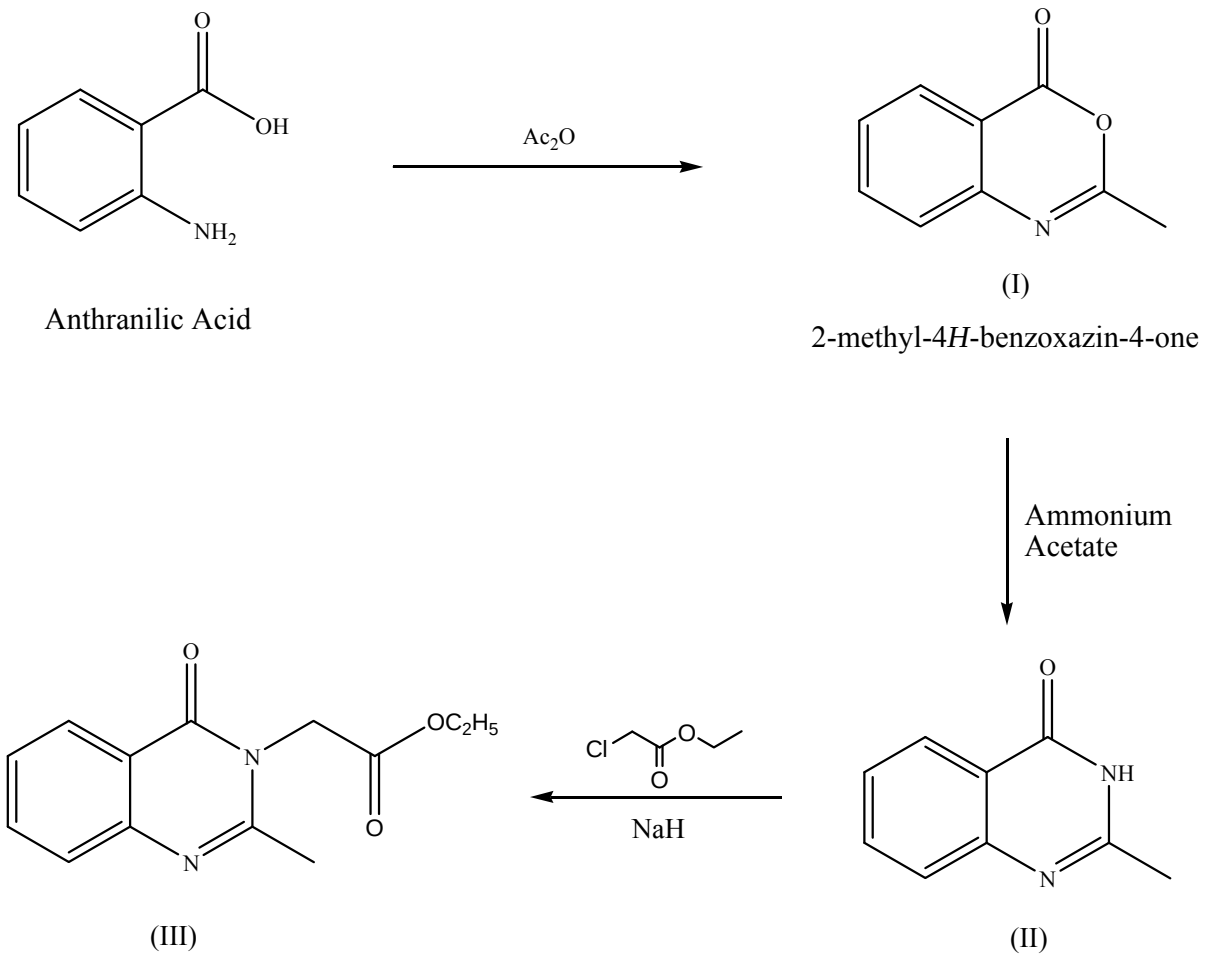
Quinazoline-4(3*H*)-ones and its derivatives are versatile nitrogen heterocyclic compounds which have long been known as a promising class of biologically active compounds [1,2]. Quinazolinone are excellent reservoir of bioactive substances. The stability of the Quinazoline nucleus has inspired medicinal 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]. 2,3 disubstituted 3(*H*)-quinazolin-4 ones are a privileged structures frequently encountered building block moiety in approx. 150 naturally occurring alkaloids and drugs with pronounced biological activities [7]. Various approaches toward the synthesis of quinazolin-4(3*H*)-one and 2,3 di-substituted quinazolin-4(3*H*)-one derivatives have been explored during the past years. Recent progress in quinazolinone alkaloids and related chemistry was focusing on developments of the synthetic methodologies and their synthetic applications. A vast number of quinazolinone derivatives have been synthesized to provide synthetic drugs and to design more effective medicines. So, this intermediate was synthesized, which can be used as starting material for synthesis and QSAR studies of acetamides and other derivatives.

Chemistry

Anthranilic acid was heated with acetic anhydride to form 2-methyl-4H-benzoxazin-4-one (I) as an intermediate. As Compound (I) moisture sensitive and could be easily hydrolyzed into the N-acylanthranilic acid, Ammonium Acetate added insitu to Compound (I) to form 2-methyl-3(*H*)-4-quinazolinone (II). This compound (II) is treated with ethylchloroacetate in the presence of sodium hydride and reaction was completed by stirring at room temperature.

Experimental:

All chemicals used were of Laboratory Reagent (LR) Grade. The synthesized compounds were characterized by melting point, TLC, FT-IR, GC-MS and NMR. 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. ^{1}H-NMR spectra were recorded on Mercury plus 300 MHz (Varian) spectrometer. Chemical shifts are shown in δ values (ppm) with tetramethylsilane (TMS) as internal standard. All solvents were distilled before use. All nonaqueous reactions were performed in dry glassware. All microwave reactions were carried on 'Catalyst systems Scientific microwave System' with automatic power setting



Anthranilic Acid

(I)

2-methyl-4*H*-benzoxazin-4-one

(III)

(II)

ethyl 2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)acetate

2-methylquinazolin-4(3*H*)-one

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.

2-methylquinazolin-4(3H)-one (II)

Heat a solution of Anthranilic acid (0.01 mol) in acetic anhydride (2.5%) under reflux for 10 minutes at 210 watt. Add ammonium acetate (5.0%) to the same insitu. Cool the solution, filter it & wash with water. Finally recrystalised from ethanol.(6 ml/gm)

Yield 62%

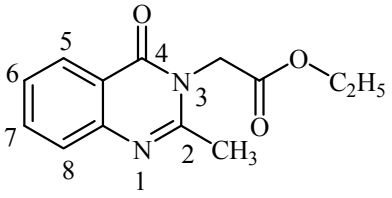
m.p. 239-241^{0}C

ethyl 2-(2-methyl-4-oxoquinazolin-3(4H)-yl) acetate (III)

To a solution of 2-methylquinazolin-4(3*H*)-one (2mmol) in DMF (10 ml), sodium hydride (60%) (2.4 mmol) was added in small portions at 0°C. After the complete addition, the temperature of the reaction slowly raise to room temp and stirred at this temp for 1hr. The reaction mixture was again cooled to 0°C and ethyl chloroacetate (2mmol) was added. The temperature of the reaction mixture was then allowed to rise to room temp and stirred at this temp for 4hrs. (Monitored by TLC). After the completion of reaction, the reaction mixture was quenched with water (50 ml). The white precipitate was obtained, washed with water and dried. The crude product was recrystalised with aq. ethanol.

Yield 59.41%; m.p. 128-130^{0}C

Analytical data:



2-methylquinazolin-4(3H)-one (II): Yield 62 %; white crystalline solid; R_f: 0.58; mp: 239-241^{0}C; FTIR (KBr) νcm^{-1}: 1647.26 cm^{-1} (C=O in amide), 1597.11 cm^{-1} (C=C stretch-Aromatic), 1247.99 cm^{-1} (C-N), 3362.04, 3379.40 cm^{-1} (N-H str.); m/z: 161 (100% [M^+ + 1]).

ethyl 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetate (III): Yield 59.41 %; white crystalline solid; R_f: 0.83; mp: 128-130^{0}C; FTIR (KBr) νcm^{-1}: 1680.05 cm^{-1} (C=O in amide), 1595.18 cm^{-1} (C=C stretch-Aromatic), 1321.28 cm^{-1} (C-N), 1230.63 cm^{-1} (C-O stretch Ester), 1718.63 cm^{-1} (C=O-Ester); ^{1}H NMR ($CDCl_3$, δ_{ppm}): (Ar-H) 7.4-8.3[d, (C5, 8.24-8.28); t, (C6, 7.72-7.78); t, (C7, 7.43-7.49); d, (C8, 7.62-7.66)], 2.59 [s, 3H, 1CH_3], 4.90 [s, 2H, (CH_2COO=2H)], 4.20-4.35 [q, 2H, (COOCH_2CH_3=2H)], 1.20-1.35 [t, 3H, (COOCH_2CH_3=3H)] **m/z**: 246 (100% [M]$^+$).

Results and discussion:

Our work is initiated with the reaction between Anthranilic acid and acetic anhydride. To optimize the reaction conditions, the irradiation power and reaction time were variably investigated starting from 140 W. We are pleased to find that the reaction provided of compound (I) after 10 min at 210 W and 2-methylquinazolin-4(3H)-one (II) with 62% yield after 10 min at 210 W. Mechanistically, the reaction proceeds via a 2-methyl-4H-benzo[*d*][1,3]oxazin-4-one (I) intermediate. Second step to form compound (III) was performed at 0^{0}c to room temperature. Appearance of molecular ion m/z 246 (M^+) in mass spectrum confirmed the product (III).

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 ethyl 2-(2-methyl-4-oxoquinazolin-3(4H)-yl)acetate (III) as a important and novel analogue of 2,3-disubstituted quinazolinones with high yields and less reaction time.

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