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Microwave Assisted Solvent Free Synthesis of Bioactive Quinazolin-4-(*3H*)-one Compounds

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ABSTRACT

Quinazolin-4-(3H)-ones and their derivatives are the important class of heterocycles that are of considerable interest due to their diverse range of biological properties. In present investigation a simple, facile, rapid and solvent free microwave enhanced synthesis of quinazolin-4-(3H)-ones in excellent yield has been developed.

Keywords: Quinazolin-4-(*3H*)-ones, Microwave, Solvent free synthesis, Bioactivity.

INTRODUCTION

Condensed heterocyclic systems with a partially or a completely reduced pyrimidine nucleus are of interest, since they display valuable pharmaceutical activities. There has been an increasing interest in the chemistry of 4-(3*H*)-quinazolinones because of their potent biological significance. Many of them show antifungal, antibacterial, anticancer, anti inflammatory, anticonvulsant, antitubercular activity and antiproliferative activities as well as inhibitory effects for thymidylate synthase and poly-(*ADP*-ribose) polymerase (*PARP*) [1,2].

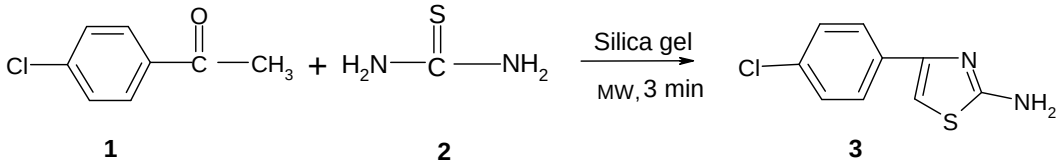
An increasing interest in the synthesis of libraries of biologically active 4-(*3H*)-quinazolinones encouraged the chemists to search for environmentally benign synthetic approaches [3,4]. In the present work, we have developed the synthesis of 4-(*3H*)-quinazolinones under microwave irradiation using solid support.

EXPERIMENTAL SECTION

All chemicals used were synthetic grade (s. d. Fine Chemicals Ltd., Mumbai, India). The anthranilic acid was prepared in laboratory from phthalimide using sodium hypobromite [5]. The

products were characterized by comparing their physical constants with authentic samples. The melting points were determined by open capillary method and are uncorrected. ^{1}H NMR spectra were recorded on Bruker FT 300 (300 MHz) using TMS as an internal standard and chemical shift are expressed in δ (ppm). IR spectra were recorded on Perkin-Elmer (Spectra One) FTIR spectrophotometer in the form of KBr pellets.

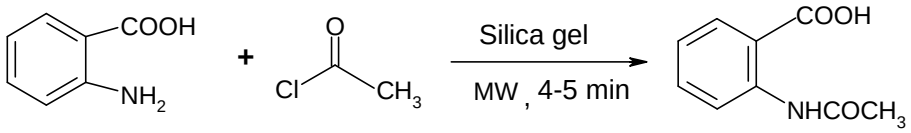
a) Synthesis of 2-amino-4-chloro phenylthiazole (3)



1 **2** **3**

A mixture of p-chloroacetophenone (**1,** 0.01 m) and thiourea (**2,** 0.02 m) was dissolved in methanol (5 ml) and this mixture was supported on silica gel (5 g) taken in 100 ml beaker. It was then irradiated under microwaves at pulse of 10 sec. for 3 min at power level 40. The progress of reaction was monitored by silica gel TLC (hexane: ethyl acetate, 9:1). Ethanol (10 ml) was then added to reaction content, stirred and filtered. The solvent was removed from filtrate to afford 2-amino-4-chlorophenylthiazole **(3),** which was recrystallized from ethanol to give colourless needles of **3,** yield 91 %, m.p.98-99^0 (lit. [1], m. p. 99 ^{0}C), IR (KBr, cm^{-1}): 3350 (NH_2), 2922, 2626 (CH of thiazole), 1461 (Ar C=C), 1190 (C-S).

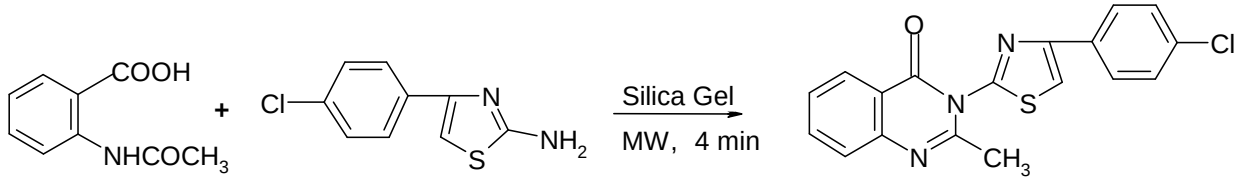
b) Synthesis of N-acetyl anthranilic acid (6)



4 **5** **6**

Anthranilic acid **(4,** 0.06 m) was dissolved in dichloromethane (5 ml) and acetyl chloride (**5,** 0.06 m) was added to it and this mixture was supported on silica gel (6 g) taken in 100 ml beaker. Then it was irradiated under microwaves for 4-5 min at power level 30. The progress of reaction was monitored by silica gel TLC (hexane: ethyl acetate, 9:1). Acetone (10 ml) was added to it, stirred and filtered. The solvent from filtrate was evaporated to afford the solid product (**6**), which was recrystallized from acetone-ethanol mixture, yield 94%, m.p. 168-169^{0}C (lit. [1], m.p.169^{0}C), IR (KBr, cm^{-1}) 3500 (OH),3300, (NH_2), 3010 (Ar C-H), 2960 (alkyl C-H), 1680(C=O), 1590(Ar C=C).

c) Synthesis of 2-methyl 3-(4-(4-chlorophenyl) thiazol-2-yl) quinazolin-4-(*3H*)-one (7)

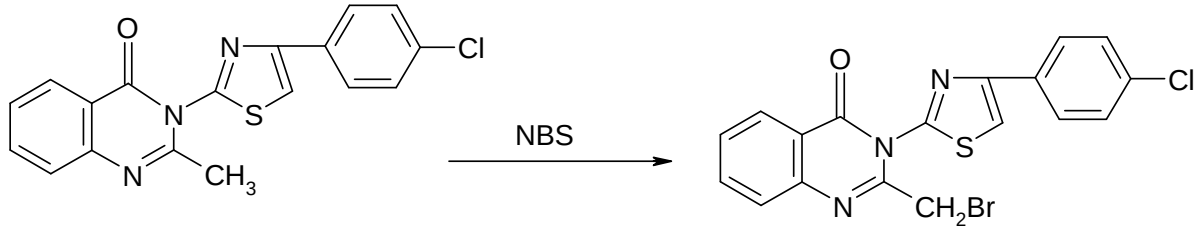


6 **3** 7

A mixture of **6** (0.01m**)** and **3** (0.01m) was dissolved in dry ethanol (5 ml) containing K_2CO_3 (1 g) and then supported on silica gel (5 g) in 100 ml beaker. It was irradiated under microwaves

for 4 min at the power level 40. The progress of reaction was monitored by silica gel TLC (hexane: ethyl acetate 9:1). Ethanol (10 ml) was added, stirred and filtered. The solvent was removed from filtrate to give crude product **7**, which was recrystallized from ethanol, yield 93%, m.p. 213-215^{0}C (lit. [1], m. p.215^{0}C), IR (KBr, cm^{-1}) 3026 (Ar C-H), 2959 (alkyl C-H), 1660(C=O), 1610 (C=N), 1525 (C-N), 1191 (C-S).

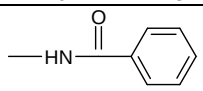
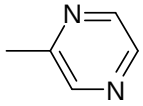
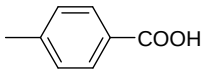
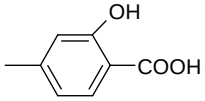
d) Synthesis of 2-bromomethyl 3-(4-(4-chlorophenyl) thiazol-2-yl)-quinazolin-4-(*3H*)-one (8) [5]



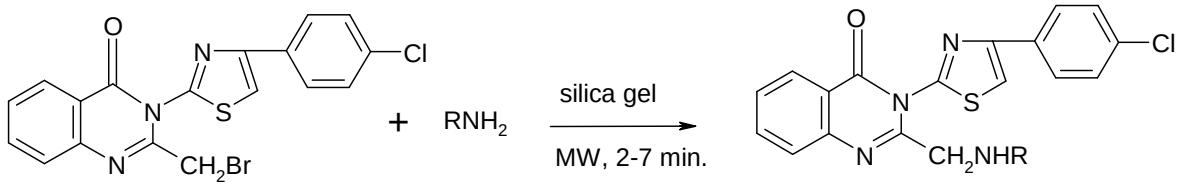
7 **8**

A mixture of **7** (0.06 m), N- bromo succinamide (0.02 m), ethanol (5 ml) and benzoyl peroxide (about 0.5 mg) was taken in 50 ml round bottom flask fitted with a reflux condenser. The reaction mixture was heated on water bath under reflux unit all NBS converted to succinamide (which floats as dispersion in solvent).The contents were cooled, filtered under suction and residue was washed with ethanol (10 ml). Removal of ethanol from filtrate afforded the product **8,** yield 94%, m. p.201-202^{0}C (lit. [1], m. p. 203^{0}C), ^{1}H NMR (DMSO-d$_6$, δ ppm): 2.61 (s, 2H, CH_2), 6.42-7.20 (m,8H, Ar H), 7.20, (m, 1H, thiazole CH), IR (KBr, cm^{-1}): 3043, 3010 (Ar C-H), 2994 (alkyl C-H), 1670(C=O), 1600 (C=N), 1525 (C-N), 1200(C-S).

Table 1: Synthesized 4-(*3H*)-quinazolinones (9 a - j)

Compound (9)	Substitute (R)	Reaction Time (min.)	Yield (%) MW assisted (Conventional)	m. p.(^{0}C) (lit [1-3]. m. p. ^{0}C)
a	-C_6H_4Cl	4	93 (52)	55 (55)
b	-$C_6H_4NO_2$	5	96 (54)	123 (123)
c	-$C_6H_4CH_3$	7	91 (52)	138 (139)
d	-$C_6H_4OCH_3$	6	93 (57)	155 (156)
e		3	94 (65)	84 (85)
f		7	90 (56)	149 (150)
g		5	93 (47)	147 (147)
h		6	90 (60)	122 (123)

e) General procedure for synthesis of 2-aminomethyl 3-(4-(4-chloro phenyl) thiazol-2-yl) quinazoline-4(*3H*) one (9)



8 **9**

A mixture of **8** (0.01 m), relevant amine (0.01 m) and pyridine (0.4 ml) was dissolved in acetic acid (5 ml). This reaction mixture was supported on silica gel (5 g) and irradiated under microwaves at power level 30 for 3 min. The progress of reaction was monitored with silica gel T. L. C. (hexane: ethyl acetate, 8:2). Ethanol (10 ml) was added, stirred and filtered. The solvent was removed from filtrate to afford crude products (**9 a – h, Table 1),** which were Recrystallized from ethanol.

9a : ^{1}H NMR (DMSO-d_6, δ ppm): 2.61 (s, 2H, CH_2), 4.80 (s, 1H, NH), 6.42-7.24 (m,12H, Ar H and 1H, thiazole CH).

9d : ^{1}H NMR (DMSO-d_6, δ ppm): 2.64, (s, 2H, CH_2), 3.66, (s, 3H, OCH_3), 4.84(s ,1H, NH), 6.44-7.62, (m, 8H, Ar H and 1H, thiazole CH).

9g: ^{1}H NMR (DMSO-d_6, δ ppm): 1.24, (s, 2H, CH_2), 3.20, (s 1H, NH), 9.01, (bs, 1H, COOH), 6.20-7.50, (m, 12H, Ar H and 1H, thiazole CH).

(9 a - h): IR (KBr, cm^{-1}): 3560-3200 (OH), 3130-3006 (Ar C-H), 2998-2959 (alkyl C-H), 1672-1660(C=O), 1610-1600 (C=N), 1525-1520 (C-N), 1200-1990(C-S).

CONCLUSION

Environmentally benign approach for solvent free synthesis of biologically active 4-(*3H*)-quinazolinone compounds has been developed using microwave and silica gel (60-120 mesh) as solid support. The yield and purity of products are excellent as compared with conventional routes. The reactions were rapid and isolation of products by simple filtration followed by evaporation of solvent is an important feature of the developed methodology. This greener methodology will be useful in synthesis of libraries of compounds having such different bioactivities as pharmaceuticals and agrochemicals.

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