International Journal of Latest Research in Science and Technology
Volume 3, Issue 6: Page No.201-204, November-December 2014
https://www.mnkpublication.com/journal/ijlrst/index.php

ISSN (Online):2278-5299

TRICHLOROTRIAZINE PROMOTED MICROWAVE INDUCED THREE-COMPONENT SYNTHESIS OF QUINAZOLINONES IN AQUEOUS MEDIA

[1]Mohammad Nikpassand, [2]Leila Zare Fekri , [3]Sara Ziafatdoust
[1]Department of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran
[2]Department of Chemistry, Payame Noor University, PO Box 19395-3697 Tehran, Iran
[1]Department of Chemistry, Rasht Branch, Islamic Azad University, Rasht, Iran
Corresponding Author E-mail: nikpassand@iaurasht.ac.ir

Abstract- A series of quinazolin-4(1H)-ones have been synthesized in excellent yields and short rection time by one-pot reaction using of isatoic anhydride, ammonium acetate and aldehydes under microwave irradiation in water. The reaction was efficiently promoted by 0.09 g trichlorotriazine (TCT).

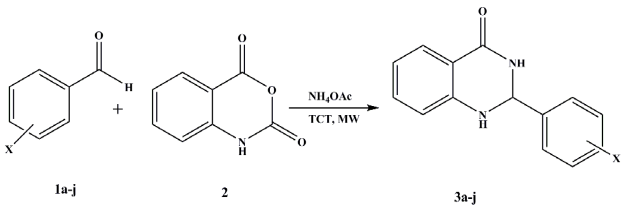
Keywords **-** quinazolinone; TCT; isatoic anhydride; microwave

I. INTRODUCTION

Dihydroquinazolinone derivatives are an important class of fused heterocyclic that display a wide range of biological, pharmacological, and medicinal properties involving anticonvulsant, sedative, tranquilizer, antimicrobial, anesthetic, antitumor, antiviral, antihypertensive, anti-inflammatory, antibiotic, antipyretic, analgesic, antihypertonic, diuretic, antihistamine, antidepressant, muscle relaxant and vasodilating activities [1, 2].

Several methods have been reported for synthesis of quinazolinone and aryl-substituted quinazolinone compounds including condensation of anthranilamide with an aldehyde or ketone using *p*-toluenesulfonic acid as a catalyst [3], desulfurization of 2-thioxo-4(3*H*)-uinazolinones [4], one-step conversion of 2-nitrobenzamides to 2, 3-dihydroquinazolin-4(1H)-ones [5], reaction of isatoic anhydride with Schiff bases [6], condensation of anthranilamide with benzyl [7], two-step synthesis starting from isatoic anhydride and amines, followed by annulation with ketones [8], reductive cyclization of o-nitrobenzamides and orthoformate, aldehydes, or ketones with the aid of a low-valent titanium reagent [9, 10] and reduction of the azide functionality [11].

In 2005, Salehi and Dabiri [12, 13] reported a more attractive and atom-efficient strategy for the preparation of 2, 3-dihydroquinazolin-4(1*H*)-ones, which involves a onepot three-component reaction of isatoic anhydride, aldehydes, and amines. Nowadays, three-component condensation of an isatoic anhydride, a primary amine, and an aromatic aldehyde for the synthesis of quinazolinones has been widely described under a variety of catalysts such as [bmim] BF_4 [14], *p*-TsOH [15], silica sulfuric acid [13], $Al(H_2PO_4)_3$ [16], $KAl(SO_4)_2$. $12H_2O$ [13], montmorillonite K-10 [17], zinc perfluorooctanoate [18], gallium triflate [19], and Amberlyst-15/microwave [20], ethylenediamine diacetate [21], I_2 [22], Al/Al_2O_3 and Fe_3O_4 nanoparticle [23, 24], *p*-toluenesulfonic acid–paraformaldehyde copolymer [25], MCM-41-SO_3H [26], silica-bonded N-propylsulfamic acid [27], and copper benzensulfonate [28]. However, these methods suffer from disadvantage, such as strongly acid conditions, long reaction time, high temperature, poor selectivity, expensive reagent, toxicity, and need for excessive amounts of reagents. To avoid using strong acids or bases and other corrosive media and replacing hazardous or expensive reactants and reagents by safer and economic ones, it is desirable to develop a green and efficient protocol for the synthesis of 2, 3-dihydroquinazolin-4(1*H*)-ones.



Scheme 1. Multicomponent synthesis of quinazolinones using TCT under MWI

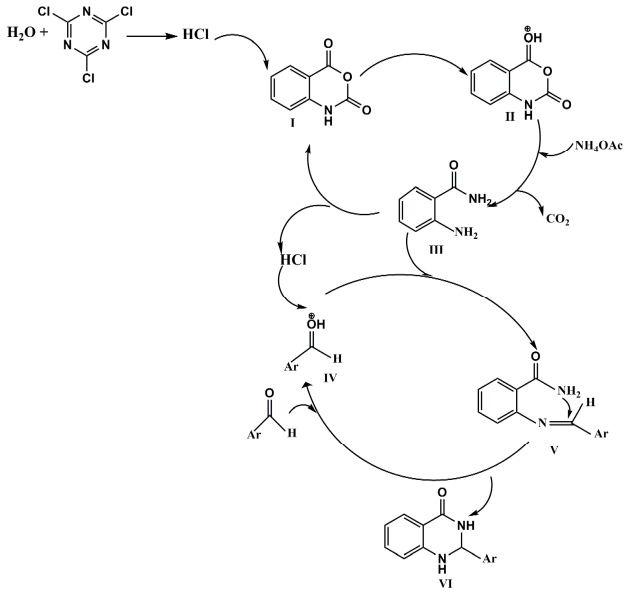
Publication History
Manuscript Received : *26 October 2014*
Manuscript Accepted : *25 November 2014*
Revision Received : *30 November 2014*
Manuscript Published : *31 December 2014*

RESULTS AND DISCUSSION

As part of our going interest for the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic and pharmaceutical compounds [29-31] we wish to report the first TCT promoted synthesis of some derivatives of quinazolinones under microwave irradiation (Scheme 1).

In an initial endeavor, **1a**, isotonic anhydride **2** and ammonium acetate were irradiated by microwave in the presence of optimized quantity of TCT (0.09 g) in10 mL H_2O. After 1 minute only 97% of product was obtained. In order to investigate the scope and generality of this promoter, various aldehydes were used in this reaction. The results are summarized in Table 1.

Initially, in the proposed mechanism for this reaction, it seems TCT act as a promoter to produce a Lewis acid activating carbonyl of ester and then ammonia can attack to intermediate II, followed by departure of CO_2, compound III was formed. Amine substituent in compound III by nucleophilic attack to active aldehyde was converted to imine intermediate V. Finally, with an intramolecular reaction, product **3** was observed.



Scheme 2. The proposed mechanism for the multicomponent synthesis of quinazolinone

EXPERIMENTAL

A mixture of aldehydes (1mmol), isotonic anhydride (1mmol) and NH_4OAc (1mmol) and 0.09g TCT in10 mL H_2O was submitted into a single mode focused microwave reactor with continuous rotation for required reaction time at 40ºC. The progress of the reaction was monitored by TLC (EtOAc: petroleum ether 1:4).

After completion of the reaction, the reaction mixture was filtered and recrystallized from EtOH. The pure products were collected in 91-99% yields.

2-(3-nitrophenyl)-2,3-dihydroquinazolin-4-(1H)-one

(3a): Yield: 97%; m.p. 213-215 °C; Anal. Calcd. For $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61; Found: C, 62.36; H, 4.19; N, 15.52; IR (KBr, cm^{-1}): 3358 (-NH stretching of secondary amine), 3192 (-NH stretching of secondary amine), 3067, 2918, 1645 (-C=O stretching of –CONH group), 1614, 1500 (-C=C stretching of aromatic ring), 1389, 1327; ^{1}HNMR (500 MHz, DMSO-d_6, δ/ ppm): 6.10 (s, 1H, C-H chiral center), 6.67 (t, 1H, *J* = 7.4 Hz, aromatic), 6.72 (d, 1H, *J* = 8.1 Hz, aromatic), 6.97 (s, 1H, -NH, D_2O exchangeable), 7.21 (d, 1H, *J* = 7.0 Hz, aromatic), 7.34-7.37 (m, 2H, aromatic), 7.43-7.46 (m, 1H, aromatic), 7.62 (d, 1H, *J* = 7.0 Hz, aromatic), 8.16 (s, 1H, -NH, D_2O exchangeable). ^{13}CNMR (125MHz, DMSO-d_6, δ/ ppm): 64.14 (carbon chiral), 115.02, 115.13, 117.92, 127.84, 127.94, 129.20, 130.04, 130.77, 132.31, 133.91, 138.31, 148.11, 164.10 (C=O).

2-(naphtyl-1-yl)-2,3-dihydroquinazolin-4-(1H)-one

(3c): Yield: 97%; m.p. 111-113 °C; Anal. Calcd. For $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21; Found: C, 78.74; H, 5.20; N, 10.14; IR (KBr, cm^{-1}): 3312 (-NH stretching of secondary amine), 3187 (-NH stretching of secondary amine), 3045, 2939, 1656 (-C=O stretching of –CONH group), 1605, 1512 (-C=C stretching of aromatic ring), 1370, 1321; ^{1}HNMR (500 MHz, DMSO-d_6, δ/ ppm): 5.89 (s,1H, C-H chiral center), 6.63 (t, 1H, *J* = 7.4 Hz, aropmatic), 6.72 (d, 1H, *J* = 8.1 Hz, aromatic), 7.13 (s,1H, -NH, D_2O exchangeable), 7.22 (t, 1H, *J* = 7.0 Hz, aromatic), 7.48 – 7.50 (m, 2H, aromatic), 7.58 (d, 1H, *J* = 7.1 Hz, aromatic), 7.64 (d, 1H, *J* = 8.6 Hz, aromatic), 7.87- 7.97 (m, 3H, aromatic), 8.30 (s, 1H, -NH, D_2O exchangeable); ^{13}CNMR (125MHz, DMSO-d_6, δ/ ppm): 63.75 (carbon chiral), 116.43, 116.94, 118.98, 123.57, 124.04, 125.05, 127.50, 129.55, 130.33, 130.65, 134.91, 135.66, 136.32, 137.01, 138.48, 146.22, 165.23 (C=O).

2-(1,4-phenylen)bis(2,3- dihydroquinazolin-4-(1H)-one

(3d): Yield: 99%; m.p. 122-113 °C; Anal. Calcd. For $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13; Found: C, 71.39; H, 4.89; N, 15.09; IR (KBr, cm^{-1}): 3747 (-NH stretching of secondary amine), 3446 (-NH stretching of secondary amine), 3068, 2926, 1653 (-C=O stretching of –CONH

Table 1. Microwave assisted TCT catalyzed synthesis of quinazolinones

Entry	aldehyde	product	Time / min	Yield / %	Mp/ °C Observed/ Reporeted	Ref.
1	3-nitrobenzaldehyde	**3a**	1	97	190-192/195-196	[17,26]
2	2-Chlorobenzaldehyde	**3b**	3	95	205-206/ 208-210	[26]
3	2-naphtylcarbaldehyde	**3c**	2	97	111-113/ -	-
4	therphthaldehyde	**3d**	3	99	122-123/ -	-
5	4-bromobenzaldehyde	**3e**	2	96	171-173/ -	-
6	4-Chlorobanzaldehyde	**3f**	1	95	200-202/ 206-207	[17, 23, 26]
7	4-methylbenzaldehyde	**3g**	5	94	217-218/224-226	[17,23,26]
8	4-methoxybenzaldehyde	**3h**	5	92	184-185/ 184-186	[17,23,26]
9	4-hydroxybenzaldehyde	**3i**	5	95	201-202/ -	-
10	N,N-dimethylaminobenzaldehyde	**3j**	4	94	209-210/ 210-212	[17,23, 26]
11	benzaldehyde	**3k**	4	91	212-214/ 217-222	[17, 23, 26]
12	furfural	**3l**	3	96	219-220/ 221-222	-
13	2-pyridincarbaldehyde	**3m**	2	98	271-272/ -	-

a. Entries 1, 2, 6-8 and 11 are known and their spectra and physical data have been reported in literature.

group), 1610, 1506 (-C=C stretching of aromatic ring), 1383; ^{1}HNMR (500 MHz, DMSO-d_6, δ /ppm): 5.69 (s, 2H, C-H chiral center), 6.60 (t, 2H, *J* = 7.4 Hz, aromatic), 6.69 (d, 2H, *J* = 8.0 Hz, aromatic), 7.08 (s, 2H, -NH, D_2O exchangeable), 7.20 (t, 2H, *J* = 7.9 Hz, aromatic), 7.43 (s, 4H, aromatic), 7.66 (d, 2H, *J* = 7.1 Hz, aromatic), 8.32 (s, 1H, -NH, D_2O exchangeable); ^{13}CNMR (125MHz, DMSO-d_6, δ / ppm): 62.76 (carbon chiral), 115.87, 117.32, 127.84, 130.65, 132.23, 133.91, 138.31, 150.90, 166.31 (C=O).

2-(4-bromo-phenyl)- 2,3- dihydroquinazolin-4-(1H)-one **(3e):** Yield: 96%; m.p. 171-173 °C; Anal. Calcd. For $C_{14}H_{11}BrN_2O$: C, 55.47; H, 3.66; N, 9.24. Found: C, 55.36; H, 3.57; N, 9.22. IR (KBr, cm^{-1}): 3301 (-NH stretching of secondary amine), 3197 (-NH stretching of secondary amine), 3067, 2912,1651 (-C=O stretching of –CONH group), 1605, 1504 (-C=C stretching of aromatic ring). ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 5.75 (s, 1H, C-H chiral center), 6.68 (t, 1H, *J* = 7.2 Hz, aromatic), 6.73 (d, 1H, *J* = 7.6 Hz, aromatic), 7.14 (s, 1H, -NH, D_2O exchangeable), 7.24 (t, 1H, *J* = 6.8 Hz, aromatic), 7.43 (d, 2H, *J* = 7.6 Hz,

aromatic), 7.58 (m, 3H, aromatic), 8.34 (s, 1H, -NH, D_2O exchangeable). ^{13}CNMR (125MHz, DMSO-d_6, δ/ ppm): 66.24 (carbon chiral), 114.92, 115.39, 117.75, 122.02, 129.53, 131.69, 133.87, 141.56, 148.07, 163.93 (C=O).

2-(4-hydroxyphenyl)- 2,3- dihydroquinazolin-4-(1H)-one **(3h)**: Yield: 95%; m.p. 201-202 °C; Anal. Calcd. For $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66; Found: C, 69.96; H, 5.11; N, 11.52; IR (KBr, cm^{-1}): 3406 (-NH stretching of secondary amine), 3191(-NH stretching of secondary amine), 3072, 1645 (-C=O stretching of –CONH group), 1514, 1458 (-C=C stretching of aromatic ring); ^{1}HNMR (500 MHz, DMSO-d_6, δ/ ppm): 6.01 (s, 1H, C-H chiral center), 6.68 (t, 1H , *J* = 7.2 Hz, aromatic), 6.79 –6.83 (m, 2H, aromatic), 6.86 (d, 1H, *J* = 8.0 Hz, aromatic), 7.14 (t, 1H, *J* = 7.2 Hz, aromatic), 7.23 (t, 1H, *J* = 7.2 Hz, , aromatic), 7.34 (d, 1H, *J* = 7.2 Hz, aromatic), 7.62 (d,1H, *J* = 7.2 Hz, aromatic), 7.96 (s, 1H, -NH, D_2O exchangeable), 9.88 (s, 1H, -NH, D_2O exchangeable); ^{13}CNMR (125MHz, DMSO-d_6, δ/ ppm): 64.32 (carbon chiral) , 115.65, 116.17, 118.65, 127.54, 127.99, 128.87, 130.41, 130.78, 132.21, 134.02, 138.55, 148.21, 166.03 (C=O).

II. CONCLUSIONS

Finally, we develop an efficient and convenient procedure for the synthesis of quinazolinones through three component synthesis of aldehydes, isotonic anhydride and ammonium acetate. This procedure offer advantages such as reduced reaction time, mild reaction condition, productivity and higher yield and ease of execution.

ACKNOWLEDGMENT

Financial support from the Payame Noor University (PNU), Roodsar, Guilan, Iran is gratefully appreciated.

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