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ORIGINAL PAPER

A simple, economical, and environmentally benign protocol for the synthesis of [1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one and hexahydro[4,5]benzimidazolo[2,1-*b*]quinazolinone derivatives

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Abstract An efficient synthesis of [1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one and hexahydro[4,5]benzimidazolo[2,1-*b*]quinazolinone derivatives with good yields is described. This method involves three-component reaction between aldehydes, dimedone, and 3-amino-1,2,4-triazole or 2-aminobenzimidazole in acetic acid as reaction medium at 60 °C. We have found that the use of acetic acid as reaction medium results in a remarkable beneficial effect on the reaction, allowing it to be performed without the need of incorporating a catalyst, which is the case in other similarly reported methodologies. The notable advantages of this protocol are excellent yields, short reaction time, mild reaction conditions, more readily available and inexpensive materials, more environmentally friendly, no need for column chromatography, and simple work-up procedure.

Keywords 3-Amino-1,2,4-triazole · 2-Aminobenzimidazole · Hexahydro[4,5]benzimidazolo[2,1-*b*]quinazolinone · 1,2,4-Triazolo[5,1-*b*]quinazolin-8(4*H*)-one · One-pot

Introduction

Five- and six-membered heterocyclic compounds are important constituents that often exist in biologically active natural products and synthetic compounds of medicinal interest [1, 2]. Among them quinazolinones and 1,2,4-triazoloquinazolinone derivatives are known for diverse pharmacological activities as anti-HIV [3], muscle relaxant [4], neuroleptic [5], hypnotic [6], antihistaminic [7–9], analgesic [10], anti-inflammatory [11], anticonvulsant [12], antifertility [13], latent leishmanicidal [14], anticancer [15], and antihypertensive [10, 16–18]. An alternative strategy for the synthesis of quinazolinones is using multicomponent reactions (MCRs). Recently, MCRs have emerged as a powerful synthetic tool in organic synthesis due to their advantages over the conventional multi-step synthesis [19–24]. In addition, MCRs are eco-friendly, highly atom economic, and they avoid costly purification processes and protection–deprotection steps with minimum synthetic effort and time [25, 26]. Therefore, MCRs satisfy some of the tenets of 'Green Chemistry'. Literature reveals only a few methods to synthesis [1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one and hexahydro[4,5]benzimidazolo[2,1-*b*]quinazolinone derivatives via MCRs using catalysts, such as $H_6P_2W_{18}O_{62}\cdot 18H_2O$ [27], refluxing in DMF [28, 29], molecular iodine (I_2) [30], microwave [31]. The aforesaid methods have some disadvantages such as use of expensive and excess amount of catalysts and failure in some of the cases to obtain the desired product. However, although the generality of the existing reports for the construction of quinazolinone derivatives are relatively good, there is a need for simple and greener methods, which are applicable to a broad range of substrates to access these compounds. In conclusion, in continuation of our study on the effective and green methodology [32], herein we wish to report the synthesis of [1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-one and hexahydro[4,5]benzimidazolo[2,1-*b*]quinazolinone derivatives by a one-pot three-component condensation reaction of dimedone, aromatic aldehydes, and 3-amino-1,2,4-triazole or 2-aminobenzimidazole using dual role of acetic acid as solvent and catalyst at 60 °C (Scheme 1).

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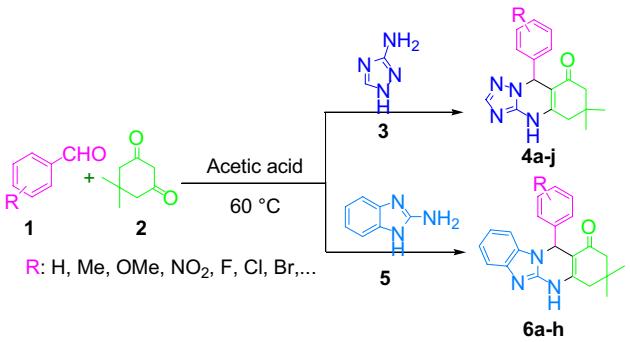


Scheme 1 Synthesis of quinazolinones in the presence of acetic acid as reaction medium

Experimental

General

Melting point and IR spectra of all compounds were obtained on an Electrothermal 9100 apparatus and a JASCO FT/IR-460 plus spectrometer, respectively. ^{1}H and ^{13}C NMR spectra of compounds were recorded on a Bruker DRX-400 Avance instrument in DMSO or $CDCl_3$ as the solvent with TMS as internal standard at 400 MHz. Elemental analyses for C, H, and N for the new compounds were performed using a Heraeus CHN-O-Rapid analyzer. The mass spectra for the new compounds were recorded on an Agilent Technology (HP) mass spectrometer, operating at an ionization potential of 70 eV. All reagents were purchased from Merck (Darmastadt, Germany), Acros (Geel, Belgium) and Fluka (Buchs, Switzerland), and used without further purification.

General procedure for the preparation of [1,2,4] triazolo[5,1-*b*]quinazolin-8(4*H*)-one and hexahydro[4,5] benzimidazolo[2,1-*b*]quinazolinone derivatives

A mixture of aromaticaldehyde (1.0 mmol) and dimedone (1.0 mmol) with 2-aminobenzimidazole or 3-amino-1,2,4-triazole (1.0 mmol) was stirred in acetic acid (5 mL) at 60 °C for the appropriate time (Tables 3, 4). The progress of the reaction was monitored by TLC. After completion of the reaction, a thick precipitate was obtained. The solid product was filtered off and washed with acetic acid (3 × 2 mL) to give the pure products **4** and **6**, and subsequently dried in air. The pure products were characterized by conventional spectroscopic methods. Physical and spectral data for the compounds, **4b**, **4c**, **4h**, **4j**, **6a**, **6c**, and **6h** are represented below:

*6,7-dihydro-6,6-dimethyl-9-p-tolyl-[1,2,4]triazolo[5,1-b] quinazolin-8(4H,5H,9H)-one (**4b**)*

White solid (95 % yield), m.p. = 262–264 °C; IR (KBr, cm^{-1}) 3421, 3036, 2964, 1649, 1578, 1364, 1259, 757; ^{1}H NMR (400 MHz, DMSO) δ = 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.07 (d, 1H, J = 16.0 Hz, H-5), 2.20 (d, 1H, J = 12.0 Hz, H'-5), 2.28 (s, 3H, CH_3), 2.48–2.59 (m, 2H, H-7), 6.16 (S, 1H, H-9), 7.07 (s, 4H, Ar–H), 7.67 (s, 1H, H-2), 11.09 (s, 1H, NH).

*6,7-dihydro-9-(2,4-dimethoxyphenyl)-6,6-dimethyl-[1,2,4] triazolo[5,1-b]quinazolin-8(4H,5H,9H)-one (**4c**)*

White solid (88 % yield); m.p. 211–212 °C; IR (KBr, cm^{-1}): 3150, 3093, 3030, 2959, 2933, 1694, 1652, 1579, 1508, 1416, 1338, 1294, 1183, 1038, 826; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.22 (d, J = 16.0 Hz, 1H, H-5), 2.29 (d, J = 16.0 Hz, 1H, H'-5), 2.48 (d, J = 16.0 Hz, 1H, H-7), 2.59 (d, J = 16.0 Hz, 1H, H'-7), 3.71 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.40 (d, J = 2.4 Hz, 1H, Ar–H), 6.47 (dd, J = 8.0, 4.0 Hz, 1H, Ar–H), 6.56 (s, 1H, H-9), 7.38 (d, J = 8.0 Hz, 1H, Ar–H), 7.64 (s, 1H, H-2), 11.76 (s, 1H, NH).

*6,7-dihydro-6,6-dimethyl-9-(naphthalen-2-yl)-[1,2,4] triazolo[5,1-b]quinazolin-8(4H,5H,9H)-one (**4h**)*

White solid (98 % yield); m.p. 266–268 °C; IR (KBr, cm^{-1}): 3416, 3246, 3091, 2963, 2927, 1652, 1574, 1469, 1410, 1364, 1335, 1251, 779; ^{1}H NMR (400 MHz, DMSO): δ 0.97 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.06 (d, J = 16.0 Hz, 1H, H-5), 2.23 (d, J = 16.0 Hz, 1H, H'-5), 2.58 (dd, J = 16.0, 24.0 Hz, 2H, H-7), 6.38 (S, 1H, H-9), 7.26 (dd, J = 4.0, 8.0 Hz, 1H, Ar–H), 7.48–7.50 (m, 2H, Ar–H), 7.69 (s, 1H, H-2), 7.80 (d, J = 4.0 Hz, 1H, Ar–H), 7.84 (d, J = 8.0 Hz, 2H, Ar–H), 7.90 (t, J = 4.0 Hz, 1H, Ar–H), 11.20 (s, 1H, NH).

*6,7-dihydro-9-(2,3-dimethoxyphenyl)-6,6-dimethyl-[1,2,4] triazolo[5,1-b]quinazolin-8(4H,5H,9H)-one (**4j**)*

White solid (98 % yield); m.p. 227–229 °C; IR (KBr, cm^{-1}): 3415, 3143, 3093, 2959, 2931, 1642, 1579, 1455, 1369, 1264, 736; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.24 (d, J = 16.0 Hz, 1H, H-5), 2.29 (d, J = 16.0 Hz, 1H, H'-5), 2.53 (d, J = 16.0 Hz, 1H, H-7), 2.60 (d, J = 16.0 Hz, 1H, H'-7), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.68 (s, 1H, H-9), 6.85 (dd, J = 8.0, 2.0 Hz, 1H, Ar–H), 6.97 (dd, J = 8.0, 2.0 Hz, 1H, Ar–H), 7.01 (t, J = 8.0 Hz, 1H, Ar–H), 7.64 (s, 1H, H-2), 11.71 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.0, 28.6, 32.8, 40.7, 50.5, 55.1, 55.7, 60.4, 107.0, 112.8, 121.2, 123.7, 133.4, 147.2, 147.4, 148.1, 149.3, 152.8, 193.8; MS (EI, 70 eV) *m/z* (%): 354 (M^+, 27), 323 (100), 296 (49), 270 (5), 239 (2), 217 (10), 185 (2), 161 (13), 138 (1), 115 (4), 84 (11), 55 (5); Anal. Calcd for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 64.50; H, 6.45; N, 15.94 %.

*3,3-dimethyl-12-phenyl-1,2,3,4,5,12-hexahydrobenzo[4,5] imidazo[2,1-b]quinazolin-1-one (**6a**)*

White solid (94 % yield), m.p. = >300 °C; IR (KBr, cm^{-1}) 3430, 3093, 2956, 1643, 1615, 1569, 1376, 1257, 750; ^{1}H NMR (400 MHz, DMSO) δ 0.92 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.05 (d, 1H, J = 16.0 Hz, H-4), 2.26 (d, 1H, J = 16.0 Hz, H'-4), 2.45 (d, 1H, J = 16.0 Hz, H-2), 2.58 (d, 1H, J = 16.0 Hz, H'-2), 6.41 (S, 1H, H-12), 6.95 (t, 1H, J = 8.0 Hz, Ar–H), 7.04 (t, 1H, J = 8.0 Hz, Ar–H), 7.15 (t, 1H, J = 8.0 Hz, Ar–H), 7.24 (t, 1H, J = 8.0 Hz, Ar–H), 7.33 (d, 3H, J = 8.0 Hz, Ar–H), 7.37 (q, 3H, J = 8.0 Hz, Ar–H), 10.18 (s, 1H, NH).

*3,3-dimethyl-12-[2,4] dichlorophenyl-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one (**6c**)*

White solid (94 % yield); m.p. >300 °C; IR (KBr, cm^{-1}): 3238, 3061, 2963, 2931, 1650, 1615, 1595, 1573, 1563, 1459, 1374, 1270, 737; ^{1}H NMR (400 MHz, DMSO): δ 0.95 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.04 (d, J = 16.0 Hz, 1H, H-4), 2.24 (d, J = 16.0 Hz, 1H, H'-4), 2.29 (d, J = 12.0 Hz, 1H, H-2), 2.33 (d, J = 16.0 Hz, 1H, H'-2), 6.65 (S, 1H, H-12), 6.96 (t, J = 8.0 Hz, 1H, Ar–H), 7.03 (s, 1H, Ar–H), 7.08–7.12 (m, 1H, Ar–H), 7.38 (s, 1H, Ar–H), 7.40 (s, 1H, Ar–H), 7.48 (d, J = 8.0 Hz, 1H, Ar–H), 11.25 (s, 1H, NH).

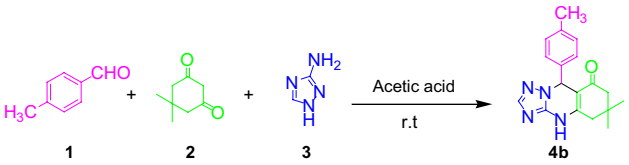
*3,3-dimethyl-12-(2-bromophenyl)-1,2,3,4,5,12-hexahydrobenzo[4,5]imidazo[2,1-b]quinazolin-1-one **(6h)***

White solid (99 % yield); m.p. >300 °C; IR (KBr, cm^{-1}): 3421, 3227, 3066, 2962, 2923, 1654, 1643, 1615, 1594, 1573, 1459, 1373, 1364, 1263, 742; ^{1}H NMR (400 MHz, DMSO): δ 0.97 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.03 (d, J = 16.0 Hz, 1H, H-4), 2.23 (d, J = 16.0 Hz, 1H, H'-4), 2.51 (d, J = 12.0 Hz, 1H, H-2), 2.63 (d, J = 16.0 Hz, 1H, H'-2), 6.64 (S, 1H, H-12), 6.95 (t, J = 8.0 Hz, 1H, Ar–H), 7.05 (t, J = 8.0 Hz, 1H, Ar–H), 7.12 (t, J = 8.0 Hz, 1H, Ar–H), 7.29 (s br s, 1H, Ar–H), 7.38 (d, J = 8.0 Hz, 1H, Ar–H), 7.52 (d, J = 8.0 Hz, 1H, Ar–H), 10.72 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): δ 27.1, 29.1, 32.8, 40.2, 50.3, 110.0, 117.5, 121.0, 122.4, 128.4, 130.1, 132.5, 132.8, 133.3, 142.2, 145.5, 151.2,193.0; MS (EI, 70 eV) *m/z* (%): 423 (M+1, 21), 422 (M^+, 8), 387 (1), 364 (1), 342 (100), 310 (1), 266 (57), 236 (1), 210 (1), 182 (9), 155 (6), 129 (4), 90 (5), 55(2); Anal. Calcd for $C_{22}H_{20}BrN_3O$: C, 62.57; H, 4.77; N, 9.95. Found: C, 62.70; H, 4.84; N, 9.98 %.

Results and discussion

In a preliminary experiment, treatment of 4-methyl benzaldehyde (**1**) with dimedone (**2**) and 3-amino-1,2,4-triazole (**3**) in 5 mL acetic acid as both solvent and catalyst at room temperature for 40 min afforded the 6,6-dimethyl-9(4-Methyl-phenyl)-5,6,7,9-tetrahydro-4*H*-1,2,4-triazolo[5,1-*b*] quinazolin-8-one **4b** in 80 % yield. Product **4b** was characterized by spectroscopic analysis. Encouraged by this result, we proceeded to study the effect of volume of solvent and reaction conditions for the synthesis of 6,6-dimethyl-9(4-Methyl-phenyl)-5,6,7,9-tetrahydro-4*H*-1,2,4-

Table 1 Condensation reaction of 3-amino-1,2,4-triazole, 4-methyl benzaldehyde and dimedone in the presence of acetic acid at ambient conditions

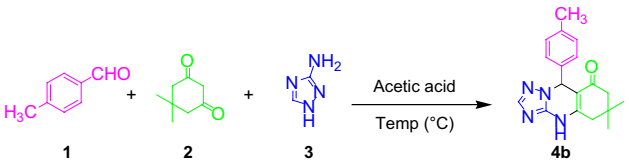


Entry	acetic acid/V (mL)	Time (min)	Yield (%)[a]
1	–	120	–
2	2	50	65
3	3	40	65
4	**5**	**40**	**80**
5	8	50	75
6	10	55	73
7	15	40	70
8	20	45	69

All the reactions were carried out using 4-methyl benzaldehyde 1 mmol, dimedone 1 mmol and 3-amino-1,2,4-triazole 1 mmol with varying volume of solvent at room temperature

[a] Yield refers to the pure isolated products

Table 2 Reaction of 3-amino-1,2,4-triazole, 4-methyl benzaldehyde and dimedone in acetic acid at different temperature



Entry	Temperature (°C)	Time (min)	Yield (%)[a]
1	25	40	80
2	40	35	89
3	50	30	92
4	**60**	**20**	**98**
5	70	25	90
6	80	20	92

All the reactions were carried out using 4-methyl benzaldehyde 1 mmol, dimedone 1 mmol and 3-amino-1,2,4-triazole 1 mmol in CH_3CO_2H (5 mL) at different temperatures

[a] Yield refers to the pure isolated products

triazolo[5,1-*b*] quinazolin-8-one (**4b**) (Table 1). As shown in Table 1, the best conversion was observed when the reaction was performed in the presence of 5 mL of acetic acid for 40 min at room temperature for 1 mmol of starting materials (entry 4, Table 1). According to the Table 1, when the reaction was carried out under solvent-free conditions and in the presence of any catalyst, no product was produced that may be due to lack of effective interaction of reactants in the absence of solvent (also in the absence of catalyst) (entry 1, Table 1).

Subsequently, the effect of temperature was studied by carrying out the model reaction at different temperatures (room temperature, 40, 50, 60, 70 and 80 °C) in 5 mL acetic acid as the most appropriate medium, and the best results were obtained at 60 °C, efficiency of 98 % was generated (entry 4, Table 2) at the higher temperature did not increase the reaction yield (entries 5 and 6, Table 2).

Therefore, in this work 5 mL of acetic acid and 60 °C were selected as standard reaction conditions. The optimized conditions were used to construct a variety of [1,2,4]triazolo[5,1-*b*]quinazolin-8(4*H*)-ones (**4a**–**j**). Various substituted aldehydes were reacted with dimedone and 3-amino-1,2,4-triazole and gave excellent yields of the desired quinazolinone products. As shown in Table 3, the electron withdrawing or donating group on the phenyl rings did not affect the reaction. The procedure is very simple: 1 equiv of aldehyde was mixed with 1 equiv of dimedone and 1 equiv of 3-amino-1,2,4-triazole in 5 mL acetic acid in a vial equipped and stirred at 60 °C for 10–35 min. After completion of the reaction, solid products were washed with acetic acid to remove organic impurities. The results are summarized in Table 3.

Under the optimized reaction conditions, we continued to demonstrate the generality and high potency of this friendly methodology, the same reaction was applied for the synthesis of hexahydro[4,5]benzimidazolo[2,1-*b*] quinazolinone derivatives including the compounds numbering **6a**–**h** by replacing 3-amino-1,2,4-triazole (**3**) with 2-aminobenzimidazole (**5**). For this, we enlarged our study using 2-aminobenzimidazole **5** as amine source, reacting with dimedone **2** and different substituted aromatic aldehydes in the presence of acetic acid as reaction medium for the synthesis of a series of benzimidazolo quinazolinones (Scheme 1; Table 4). Electron donating and electron withdrawing groups on the aldehydes show equal ease toward the product formation in good to high yields. The results are shown in Table 4. The results show that the substituent groups did not play any significant role in the reactivity of the substrate.

The notable advantages of this method are easy isolation of products by simple filtration, no need to column chromatogaphy, and no need to further purification. All known products were characterized by comparison of the melting points and the analytical data (IR, ^{1}H NMR) with those reported for authentic samples. The structure of new compounds **4j** and **6h** were deduced on the basis of IR, ^{1}H, ^{13}C

Table 3 Synthesis of 1,2,4-triazolo[5,1-*b*]quinolin-8(4*H*)-ones **4** in acetic acid as reaction medium

Entry	R	Amine	Product	Time (min)	Yield (%)[a]	M.p. (°C)	Lit. m.p. (°C) [References]
1	H	3	**4a**	25	95	247–249	248–250 [29]
2	4-Me	3	**4b**	10	98	262–264	264–269 [27]
3	2,4-$(OMe)_2$	3	**4c**	30	88	211–212	210–212 [30]
4	4-OH	3	**4d**	35	86	303–305	307–309 [27]
5	2,4-Cl_2	3	**4e**	15	98	324–326	323–325 [30]
6	4-Cl	3	**4f**	20	96	303–305	304–306 [30]
7	4-F	3	**4g**	25	92	257–259	258–260 [31]
8	2-Naphthyl-	3	**4h**	20	98	266–268	287–290 [30]
9	3-NO_2	3	**4i**	18	96	267–269	266–269 [30]
10	2,3-$(OMe)_2$	3	**4j**	20	98	227–229	New[b]

[a] Yields refer to the pure isolated products

[b] New compound synthesized

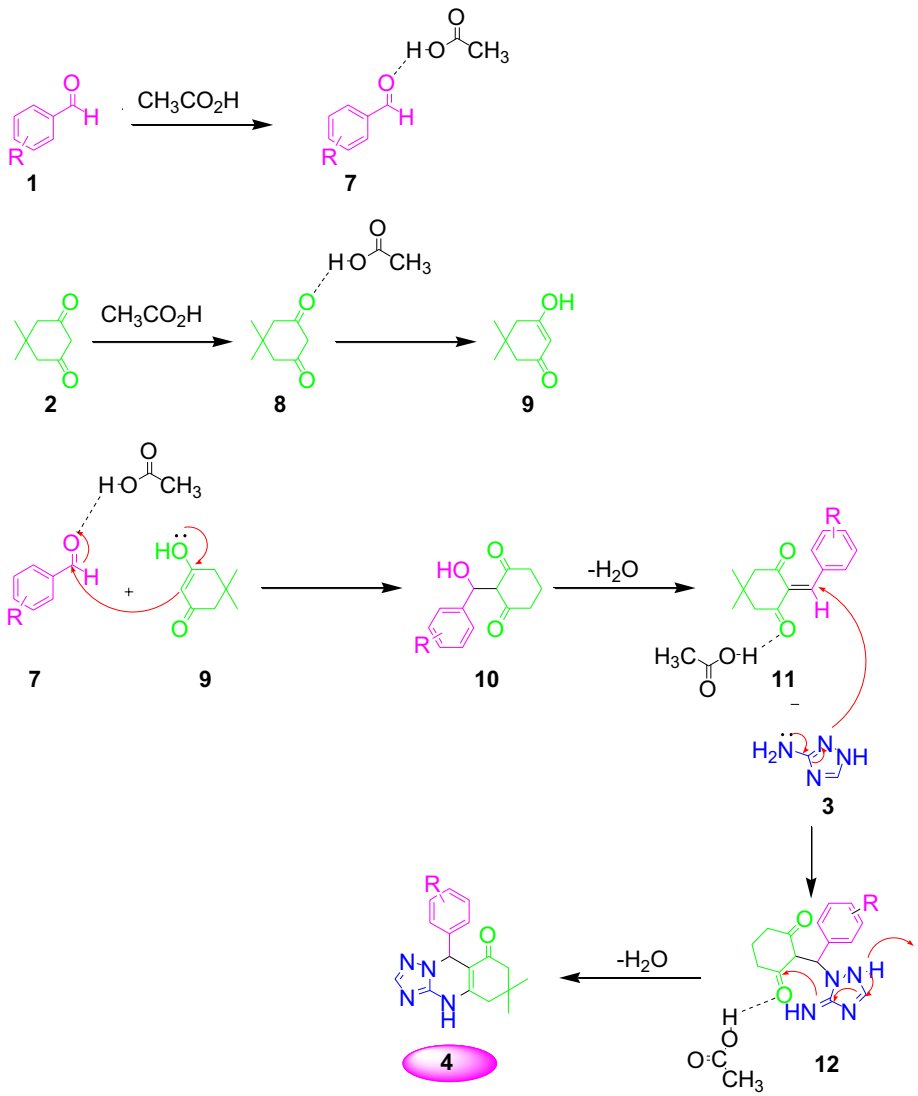
Table 4 Synthesis of hexahydro[4,5] benzimidazolo[2,1-*b*] quinazolinones **6** in acetic acid as reaction medium

Entry	R	Amine	Product	Time (min)	Yield (%)[a]	M.p. (°C)	Lit. m.p. (°C) [References]
1	H	5	**6a**	20	94	>300	>300 [27]
2	4-F	5	**6b**	25	90	>300	>300 [31]
3	2,4-Cl_2	5	**6c**	30	94	>300	>300 [30]
4	4-Cl	5	**6d**	15	93	>300	>300 [27]
5	4-OMe	5	**6e**	20	96	>300	>300 [28]
6	4-Br	5	**6f**	30	92	>300	>300 [27]
7	4-NO_2	5	**6g**	25	95	>300	>300 [28]
8	2-Br	5	**6h**	20	99	>300	New[b]

[a] Yields refer to the pure isolated products

[b] New compound synthesized

Scheme 2 Tentative mechanism for the synthesis of quinazolinone derivatives



NMR spectroscopies, mass spectrometry, and elemental analysis. For example, the mass spectrum of **4j** displayed the molecular ion peak (M^+) at $m/z = 354$, which is consistent with the proposed structure. The ^{1}H NMR spectrum of **4j** exhibited two singlet at $\delta = 1.13$ and 1.15 ppm for the geminal methyl protons. Four doublets were observed at $\delta = 2.24$ ($J = 16.0$ Hz), 2.29 ($J = 16.0$ Hz), 2.53 ($J = 16.0$ Hz) and 2.60 ($J = 16.0$ Hz) for the diastereotopic methylene protons of H-5, H'-5, H-7 and H'-7, respectively. Two singlets were monitored at $\delta = 3.81$ and 3.83 ppm for the methyl protons on aromatic ring. The methine proton of the central ring (H-9) was observed as a singlet at $\delta = 6.68$ ppm. The aromatic proton resonance was observed as mixture of doublet of doublet and triplet at $\delta = 6.84$–7.03 ppm. The proton of CH (H-2) appeared as a singlet at $\delta = 7.64$ ppm and a singlet was observed at $\delta = 11.71$ ppm for the NH group. Therefore, all of the spectral data are in agreement with the proposed structure.

Based on the observations, obtained results and according to the previous reports on the catalytic synthesis of quinazolinone derivatives we propose a tentative mechanism as depicted below (Scheme 2). This reaction may proceed via Knoevenagel condensation for the formation of α,β-unsaturated carbonyl compounds **11** upon the loss of a water molecule. In the next step, the intermediate **12** achieved via an intermolecular reaction undergoing nucleophilic attack by amine. Further intermediate **12** undergoes intra-molecular cyclization by the loss of a water molecule to yield the observed quinazolinones **4**.

In conclusion, in continuation of our study on the effective methodology [33, 34] for the synthesis of [1,2,4] triazolo[5,1-*b*]quinazolin-8(4*H*)-one and hexahydro[4,5] benzimidazolo[2,1-*b*]quinazolinone derivatives an efficient, simple, and acetic acid-promoted protocol is developed by one-pot multicomponent reaction using readily available starting materials under metal-free conditions. The

advantageous features of this procedure are mild reaction conditions, high atom economy, good yields, operational simplicity, no tedious separation procedures, inexpensive starting materials, metal-free synthesis, environmentally benign reaction, and short reaction times when compared to the reaction catalyzed by the catalyst. In this procedure, the products were collected easily by simple filtration with no need for further purification. The advantageous features of this procedure make it a useful and attractive process for the synthesis of a wide variety of biologically active compounds.

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