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Application of the Ultrasonic in the Mild Synthesis of Substituted 2,3-Dihydroquinazolin-4(1*H*)-ones Catalyzed by Heterogeneous Metal-MWCNTs

Nanocomposites

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Abstract

A practical method has been applied successfully to synthesize mono- and disubstituted dihydroquinazolinones through three-component condensation of isatoic anhydride, primary amines or ammonium salts with aromatic aldehydes in presence of some transition metals-carbon nanotubes under sonication. Also, CNT-supported metals have shown excellent catalytic performance for above-mentioned condensation. This methodology provides general, easy and versatile approach to afford the corresponding aryl substituted quinazolinone derivatives using mentioned nanocomposites as catalyst under sonication in excellent yields. The advantages of present protocol are convenient reaction and simple work-up, greenness, energy efficiency, green and reusable catalyst as well as mild reaction conditions. The employed Metal-CNTs catalyst is heterogeneous and recyclable, that makes the process more environmentally friendly.

Keywords: Ultrasound irradiation, Quinazolinone, Transition metals, Supported catalyst

1. Introduction

Multicomponent reactions (MCRs) are emerging increasingly as an attractive synthetic strategy to be developed fast in biologically active compounds and natural products with several degrees of structural diversity [1-5]. MCRs as an important subclass of tandem reactions are in agreement with Principles of Green Chemistry in chemical biology and drug discovery [6-9]. Moreover, MCRs have the significant virtues including of convergent nature, simplicity, superior atom economy, facile execution, and synthetic efficiency as well as environmentally friendlier aspects in a conventional linear-type synthesis [10]. Quinazolinone scaffold is a

privileged structure in a variety of biologically active compounds with unique position in the field of medicinal chemistry [11]. 2,3-Dihydroquinazolinones are an important class of bioactive heterocyclic compounds with a broad spectrum of pharmacological, biological and medicinal activities [12]. Additionally, the 2,3-disubstituted quinazolinones have been reported to possess antihypertensive and antiviral activities [13]. 2,3-Disubstuted-2,3dihydroquinazoline-4(1H)-one alkaloids also have a key role in various cellular processes and exhibit a variety of pharmaceutical activity [14] including of anticancer, antibacterial, antidepressant, antimicrobial, and antiinflammatory [15]. The first reported synthesis of quinazolinone occurred in 1869 which was prepared from anthranilic acid and cyanogen in ethanol in the synthesis of 2-ehoxy-4(3H)-quinazolinone [16]. The pyrimidine ring adopts a skew-boat conformation. Boat conformation of the pyrimidinone ring shows the pseudoaxial orientation of the C_4 and P_1 group and out-of plane positions of the C_4 and N_1 atoms [17]. Therefore, compounds contain a flat aromatic area of quinazoline, hydrogen bond acceptor at position 4, hydrophobic part at position 3, aromatic region at positions 1 or 2 of the quinazoline-4-one nucleus [18]. Type and position of the substituent on the C4 and C5 atoms, dihedral angle of the aryl group (on the C4 atom) relative to the heterocycle ring, orientation of the carbonyl group (on the C5 atom) relative to the C5=C6 bond of the heterocycle ring and deviation of the C4 and N1 atoms from the boat plane affect their structural factors [17]. In view of their significance, novel chemical processes or methodologies should be benefited for synthesis of substituted 2,3dihydroquinazolin-4(1H)-ones in terms of Green Chemistry in both of synthetic and medicinal chemistry. Recently, some reported synthetic routes are included isatoic anhydride, and aldehydes with ammonium acetate or primary amine in the presence of various reagents or catalysts [19-21].

Among the different types of supports used in heterogeneous catalysis, considerable interesting research was done on carbon nanotubes (CNTs) owing to the porosity and surface chemistry, inertness and lower catalystsupport interactions, and good mechanical strength [22–25]. The decoration of metal nanoparticles onto the external surfaces of carbon nanotubes (MWNTs) is effective for attractive potential applications such as catalysts in fuel cells [26–28], reversible interconnections in sensors [29], drug carrier [30], and cold electron sources in field emission displays [31–33]. The researchers suggested that the metal-nanoparticle/CNT nanocomposites increase the reactive surface area of the metal and reduce the metal size, and also intimate interphase contact between the metal nanoparticles and MWCNTs resulted other synergistic effects [34]. The synergistic or cooperative effects of CNTs and metal NPs makes CNTs/metal heterostructures possessing the unique properties of the two types of components (CNTs and metal NPs) [35]. However, the surface of pristine CNTs, which are generally produced from decomposition of hydrocarbons, is inert and hydrophobic [36–40].

Therefore, favorable interaction and uniform dispersion of metallic nanoparticles on CNTs surface is a challenge owing to their almost perfect structure. Consequently, many protocols have been established to functionalize CNTs surface such as modification of CNTs with polymers [41,42], functionalization with amine, carboxyl, and/or sulfone groups [43,44], enlargement of their surface area with KOH [45,46], and chemical treatment with agents such as oxygen, ozone, HCl, oxidizing acids (nitric acid, sulfuric acid, perchloric acid), potassium permanganate, and hydrogen peroxide (H_2O_2) [47–58]. Such surface modification introduces an opportunity for metal NPs precursors to be correlated with MWCNTs and prompts the deposition of metals on the external walls.

The use of ultrasound is well known as useful tool in the design and development of green methods and promotion of organic reactions. Sonication accelerates the reaction by providing driving energy by cavitation and the formation and collapse of bubbles (production of high pressure and high temperature) and confirms a better contact, increasing the reaction rate and selectivity. Benefits further include the simplicity of the experimental procedure, higher yields and rate, shorter reaction times and the clean nature [59]. Our efforts for development of green and new synthetic methods for various heterocyclic compounds prompted us to investigate the utility of metals supported on CNTs as heterogeneous catalyst under sonication to be afforded substituted quinazolinones. Therefore, we would like to disclose a versatile procedure for the fabrication of mono and di-substituted 2,3-dihydroquinazolin-4(1*H*)-ones selectively in the presence of metal-CNTs catalytic systems employing three-component reactions of isatoic anhydride with aldehydes and primary amines (or ammonium salts) (Scheme 1).



Scheme 1. Co-CNTs-catalyzed synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in ethanol under sonication

2. Experimental

All the commercial available reagents were obtained from Merck and Aldrich and were used as was received. MWCNTs were purchased from Nanotech Port Co. (Taiwan). These MWCNTs were produced via the chemical

vapor deposition (CVD, or sometimes was called catalytic pyrolysis) method. The outer diameter of CNT was between 10 and 20 nm. Purity of the compounds and completion of reactions was monitored by TLC, visualizing with ultraviolet light. All melting points (m.p.) were measured in an Electrothermal MK3 apparatus and were uncorrected. The Fourier transform infrared spectroscopy (FTIR) was used to detect the functional groups on the surface of CNTs. Infrared spectra were recorded on KBr pellets on a Perkin Elmer FT–IR 550 spectrophotometer at 400-4000 cm⁻¹ with 16 scan's numbers in room temperature. The ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DRX–400 spectrometer at 400 and 100 MHz in DMSO- d_6 , respectively. The chemical shifts (δ) are given in ppm using TMS as internal reference. The scanning electron micrograph (SEM) was obtained using a TESCAN model VEGA II scanning electron microscope (SEM) operated at a 15 kV accelerating voltage. The obtained nanocomposites were characterized by XRD on a on Holland Philips Xpert X-ray diffraction (XRD) diffractometer (CuK, radiation, λ = 0.154056 nm), at a scanning speed of 2°/min from 10° to 100° (20).

2.1. Ultrasound-promoted general synthesis of mono- and disubstituted quinazolinones

A stirred mixture of isatoic anhydride (1 mmol), ammonium acetate (1.1 mmol) or primary amine (1.2 mmol), benzaldehyde (1 mmol) and Co-CNTs (0.04 g) was sonicated at 35 kHz to stipulate time at 40 °C. After completion of the reaction, as indicated by TLC (ethyl acetate: petroleum ether, 1:3), the solid catalyst was separated by filtration. After that, the filtrate was poured into crushed ice with thorough stirring for several min. The precipitated solids were filtered off and finally purified by recrystallization from ethanol.

3. Results and discussion

We introduced very convenient and environmentally benign synthesis of mono- and disubstituted 2,3-dihydro-4(1H)-quinazolinones under ultrasonic irradiation. Monosubstituted 2,3-dihydro-4(1H)-quinazolinones were synthesized efficiently by the condensation of isatoic anhydride and aryl aldehydes in the presence of ammonium acetate in ethanol under heterogeneous supported catalyst (Scheme 1). Moreover, treatment of isatoic anhydride and aromatic aldehydes with primary aromatic amines in the presence of heterogeneous supported catalyst in ethanol were afforded disubstituted derivatives of 2,3-dihydro-4(1H)-quinazolinone in excellent yields (Scheme 2). Our attempt has been focused to apply novel green metals-CNTs for ultrasound-assisted synthesis of substituted quinazolinones. These Lewis acidic nanocomposites can be prepared simply according to literature procedures [60–63]. Current study investigates the catalytic activity of nanocomposites of

the formula metal-CNTs as a heterogeneous catalyst in the ultrasound sponsored modified synthesis of quinazolinone derivatives. A diversity of supported catalysts in the synthesis of this heterocyclic scaffold was investigated to compare their efficiency. Initially, the reaction was performed in the presence of several metals supported on CNTs including of Cu-CNTs, Ag-CNTs, Co-CNTs and Pt-CNTs. Catalysts screening results are listed in Table 1. It is clear that these supported heterogeneous nanocomposites promoted successfully this multi-component reaction with high yields. Among the evaluated nanocatalysts, Co-CNT nanocomposites were superior to others and produced the best yield and time in the synthesis of the target substituted 2,3-dihydro-4(1H)-quinazolinones. The more number of empty d-orbitals of metal, and more stability are the advantages of Co-CNTs with consumption of the low amount of catalyst in compared with existing ones. Additionally, the activities of these promoters were found to decrease in the following order: Co-CNTs > Pt-CNTs > Cu-CNTs > Ag-CNTs. Currently, Co-CNTs are a novel and heterogeneous promoter to facile and generally to prepare substituted-2,3-dihydro-4(1H)-quinazolinones under mild reaction conditions.

 Table 1. Comparison between the efficiency of various catalysts in the synthesis of disubstituted 2,3-dihydro-4(1*H*)-quinazolinone derivatives

Catalyst	Time (min)	Yield (%)
Cu-CNTs	25	78
	20	70
Ag-CN1s	20	70
Co CNTs	6	07
CO-CIVIS	0	91
Pt-CNTs	10	89
11 01015	10	07
	Catalyst Cu-CNTs Ag-CNTs Co-CNTs Pt-CNTs	CatalystTime (min)Cu-CNTs25Ag-CNTs20Co-CNTs6Pt-CNTs10

The catalytic efficiency of Co-CNTs also was studied for this condensation reaction. As indicated in Table 2, increase in the amount of catalyst, initially, led to improved yield at short reaction time and optimum amount of catalyst to ensure high reaction efficiency was 0.04 g. Increment in the amount of catalyst higher than 0.04 g did not show any effect on the product yield and reaction time. Only a trace amount of the corresponding product was formed in the absence of catalyst at a long time. We performed the model reaction using different quantities of reagents to determine the appropriate molar ratio of reactants. The best yield and the shortest reaction time

were obtained with a 1:1:1:1.2 ratios of isatoic anhydride, benzaldehyde, and aniline or ammonium acetate, respectively.

 Table 2. Investigation of the amounts of catalyst in the reaction of isatoic anhydride, benzaldehyde, and ammonium acetate

Nock

Entry	Catalyst (g)	Time (min)	Yield (%)
1	0	45	15
2	0.01	30	65
3	0.02	20	76
4	0.03	15	84
5	0.04	6	97
6	0.05	6	97

The ultrasound mediated reactions have widely used in various organic transformations. A variety of reactions were successfully carried out under ultrasound irradiation within short reaction time and under mild conditions in a high yielding process. We also performed all the experiments without sonication to evaluate the role of understand irradiation and results show that the reaction without ultrasound irradiation took place in very long time and the relatively low yields. Thus, it seemed that ultrasound irradiation had a main role in enhancement of the reaction rate and the combination of ultrasound and Co-CNTs was establish to be ideal for the faster synthesis in high yield. In order to investigate the effect of irradiation power, the experiments were performed in different powers of ultrasound irradiation. As shown in Table 3, 70 W was found to be the most suitable power for the model reaction. With increase in irradiation power, considerable change was not observed in the reaction time and yield.

Table 3. Optimization of the irradiation power for the synthesis 4a catalyzed by Co-CNTs

Entry	power (W)	Temperature (°C)	Time (min)	Yield (%)
Linuy	power (m)	remperature (C)	Time (iiiii)	11010 (70)

1	20	40	56	55
2	40	40	40	60
3	50	40	25	79
4	60	40	15	88
5	70	40	6	97
6	90	40	6	97

Also, this work has been extended to observe the effect of solvent on reaction in different solvents including ethanol, CH_3CN , dioxane, DCM and THF as the medium in the presence of 0.04 g of the catalyst. The results are given in Table 4. Based on reaction yield, time, and environmental acceptance, the best result was observed when the reaction was performed in ethanol. This indicates that the solvent polarity and solubility of reactants and catalyst could play an important role in this process under ultrasound irradiation.

Solvent	EtOH	CH ₃ CN	Dioxane	DCM	THF	
				-		
Time (min)	6	10	25	46	35	
Vield (%)	07	01	61	12	53	
Γ leta (\mathcal{M}))1		01	72	55	

Table 4. Effect of different solvents in the model reaction in the presence of Co-CNTs

The reusability of catalyst is one of the most important its properties from an environmental point of view and economic consideration. Upon completion, the catalyst is easily separated from the reaction medium by filtration and washing with alkaline aqua solution (PH 9). It can be seen from Fig. 1 that the recycled catalyst was active even after five successive runs without obvious loss of activity and figures within parentheses show the corresponding yield for each run.



Fig. 1. Catalytic recyclability of Co-CNT nanocomposites

From the point of view of the success of the reaction and investigation in the scope and efficiency of the process, the wide range of substituted and structurally divers aldehydes and also aniline derivatives was treated to synthesize the corresponding products in excellent yields. From Table 5, it was clear that no simple relationship was observed between the electronic nature of substituent of the aryl groups and the desired quinazolinone products. The results illustrate the high ability of this methodology for synthesis of substituted 2,3-dihydroquinazoline-4(1*H*)-ones with varied structures. The structures of the products were established by IR, ¹H NMR and ¹³C NMR spectroscopy and the purity of the compounds was determined by TLC and elemental analysis.

 Table 5. Ultrasonic synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones in the presence of

 Co-CNTs in ethanol

					M.ŗ	o (°C)	
Product	Amine	Ar'	Time (min)	Yield (%)	Found	Reported	Ref.
4a	PhNH ₂	C ₆ H ₅	6	97	214–215	214–216	[64]
4b	PhNH ₂	4-Me C_6H_5	20	85	223–225	222–224	[65]
4c	4-Me PhNH ₂	4-OMe C ₆ H ₅	15	87	241–243	244–245	[66]
4d	4-OH PhNH ₂	4-Me C_6H_5	20	89	248-250	249–252	[67]

4 e	PhNH ₂	$4\text{-Br }C_6H_5$	15	90	220–222	219–223	[68]
4 f	4-Me PhNH ₂	4-Cl C ₆ H ₅	20	87	269–272	270–274	[69]
4g	PhNH ₂	$4\text{-}FC_6H_5$	10	93	235–237	235–238	[68]
4h	PhNH ₂	4-OMe C ₆ H ₅	15	89	204–206	205–207	[70]
4i	4-Me PhNH ₂	4-F C ₆ H ₅	10	95	240–242	241–243	[71]
4j	PhNH ₂	4-Cl C ₆ H ₅	15	91	223–225	222–224	[72]
4k	4-Me PhNH ₂	4-Me C_6H_5	20	84	244–246	243–247	[68]
41	4-Cl PhNH ₂	4-OMe C ₆ H ₅	35	76	245–247	244–247	[66]
4m	5-Cl,2-OH PhNH ₂	4-Cl C ₆ H ₅	25	82	235–236	235–237	[68]
4n	NH ₄ OAc	2,3-Cl ₂ C ₆ H ₅	15	85	223–225	225–227	[73]
40	NH ₄ OAc	2-F C ₆ H ₅	10	93	265–267	266–267	[74]
4p	NH ₄ OAc	$4\text{-NO}_2 C_6 H_5$	10	93	198–200	199–201	[72]
4q	NH ₄ OAc	3-NO ₂ C ₆ H ₅	7	95	196–198	195–196	[72]
4r	NH ₄ OAc	2-Cl C ₆ H ₅	15	90	204–205	203-205	[75]
4 s	NH ₄ OAc	4-OH,3-OMe C ₆ H ₅	20	81	226–228	226–227	[76]

SEM was used to observe the surface morphology of composites. Fig. 2 displays SEM images of the metal supported on carbon nanotubes. TEM analysis was carried out in Fig. 2 to determine the dispersion of cobalt nanoparticles, which is quite uniform without any detectable local aggregation.





Fig. 2. The scanning electron microscope (SEM) micrographs of a) Co-CNTs, b) Pt-CNTs, c) Ag-CNTs and d) Cu-CNTs, Images of the TEM of Co nanoparticles supported on carbon nanotubes

According to evolution of the reaction conditions, a possible mechanism is presented to synthesize these products in Scheme 2. It is proposed that, at first, the intermediate **I** is formed through nucleophilic attack of the amino group in 2-aminobenzamide at the activated carbonyl group in aldehyde by metal as a supported catalyst. Also the part of amide in imine intermediate **II** is converted into its tautomer in the presence of catalyst. Then the Schiff base intermediate **III** is produced by intermediate **II** dehydration. Then the intramolecular nucleophilic addition reaction between the amide group nitrogen and activated Schiff base carbon gives intermediate **IV**, which was followed by a 1,5-proton transfer takes place to give the products.



Scheme 2. Possible mechanism for the synthesis of quinazolinonones

4. Conclusions

The present study highlights the identification of several novel highly reactive nanocomposites as heterogeneous catalyst to prepare mono- and disubstituted quinazolinones in a one-pot MCR protocol. Thus, the present synthesis of 2,3-dihydroquinazolin-4(1H)-one derivatives created by the reaction of a range of amines and aldehydes with isatoic anhydride under sonication, will be served as an exclusive method of preparative importance for this class of heterocyclic compounds. The Co-CNTs exhibits promising and superior catalytic activity for this transformation over other investigated transition metals supported on CNTs, which would make this process suitable and attractive for parallel synthesis in drug discovery. Noteworthy features of this process are the cleaner reaction profile, conditional generality, the easy use of accessible starting materials, atomic economy, the feasible reusability of the catalyst and environmentally benign nature, and action under mild reaction conditions, which is important from the view point of green chemistry. These features will enable this protocol to find extensive applications in the field of medicinal chemistry.

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Scheme 1. Co-CNTs-catalyzed synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones in ethanol under sonication

Table 1. Comparison between the efficiency of various catalysts in the synthesis of 4a

Table 2. Investigation of the amounts of catalyst in the reaction of isatoic anhydride, benzaldehyde, and ammonium acetate

Table 3. Optimization of the irradiation power for the synthesis 4a catalyzed by Co-CNTs

Table 4. Effect of different solvents in the model reaction in the presence of Co-CNTs

Fig. 1. Catalytic recyclability of Co-CNT nanocomposites

Table 5. Ultrasonic synthesis of mono- and disubstituted 2,3-dihydroquinazolin-4(1H)-ones in the presence of Co-CNTs in ethanol

Fig. 2. The scanning electron microscope (SEM) micrographs of a) Co-CNTs, b) Pt-CNTs, c) Ag-CNTs and d) Cu-CNTs,

Images of the TEM of Co nanoparticles supported on carbon nanotubes

Scheme 2. Possible mechanism for the synthesis of quinazolinonones

Graphical Abstract

Application of the Ultrasonic in the Mild Synthesis of Substituted 2,3-Dihydroquinazolin-4(1*H*)ones Catalyzed by Heterogeneous Metal-MWCNTs Nanocomposites



Highlight

- This methodology provides general, easy and versatile approach.
- The employed catalyst (Metal-CNTs) is heterogeneous and recyclable.
- The Co-CNTs exhibits promising and superior catalytic activity for this reaction.