Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(7):356-361

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Caesium carbonate as an efficient catalyst for the synthesis polyhydroquinolines derivatives

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ABSTRACT

A novel methodology has been developed using Caesium carbonate as an efficient and recyclable catalyst for the synthesis polyhydroquinolines derivatives of one pot four component via aromatic aldehydes, dimedone, ethylacetoacetate and ammonium acetate, this reaction was induced by the visible light and tetrabutylamonium bromide as phase transfer catalyst.

Key words: One pot four component, Caesium carbonate, tetrabutylamonium bromide and visible light .

INTRODUCTION

Polyhydroquinoline (PHQ) and 1,4-dihydropyridine (DHP) derivatives have attracted much attention of chemists due to their applications in pharmacological and medicinal fields like vasodilator, hepatoprotective, antiatherosclerotic, bronchodilator, antitumor, geroprotective, antidiabetic activity [1,2]. Recent studies showed that Compounds of quinolines including 1,4 dihydropyridine nucleus having broad spectrum of biological activities and played a unique role in the design and synthesis of important biologically active compounds serving such as antimalarial, antiinflammatory, antibacterial, tyrosine kinase inhibiting agents [3a-b], anti-asthamatic activity in the treatment of Alzheimer's disease, and as a chemo sensitizer in tumor therapy [4]. Moreover, 4- substituteted 1,4-dihydropyridines (1,4-DHPs) are well known as calcium channel blockers and have emerged as one of the most important class of drugs for the treatment of cardiovascular diseases [5]. Various clinically used cardiovascular agents such as amlodipine, nifedipine, nicardipine and other related derivatives are dihydropyridyl compounds effective in the treatment of hypertension [6,7].

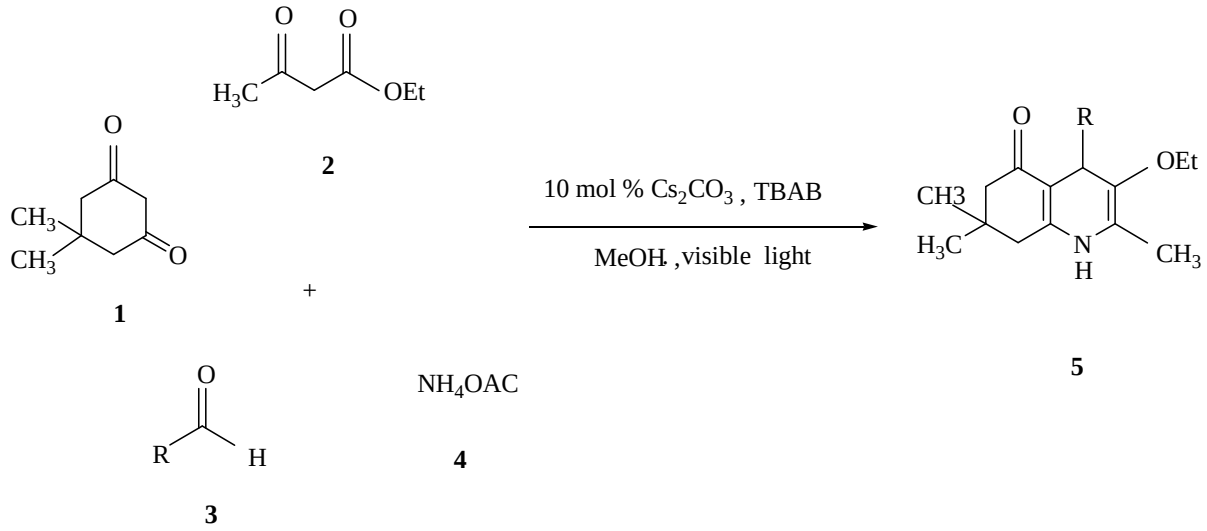
The first time of synthesis 1,4-dihydropyridines was reported in 1882 by Arthur Hantzsch using one- pot condensation of ethylacetoacetate, aromatic aldehydes and ammonia in acetic acid or at reflux in ethanol. This method, however, involves many of disadvantages such as of long reaction time, harsh reaction conditions and generally leading to low yields. For that focused many of researches of developed methods are more efficiency for synthesis 1,4 DHPs such as Sno_2 nanopracticals [8] ,CAN [9], P-TSA [10] ,Carbon –based solid acid [11] ,$Yb(oTf)_3$[12] , ZrCl4 [13] nickel nanoparticle [14], Scolecite [15],

HY-Zeolite [16], cerium(IV) ammonium nitrate [17] ionic liquid [18], Baker's yeast [19], silica sulfuric acid [20], FeF_3 [21], Iron (III)trifluoroacetate[22], L-Proline[23], $HClO_4$–SiO_2 [24], $Sc(OTf)_3$[25], TMSCl[26], Grinding[27], Microwave[28], I_2[29], Polymer [30], ZnO beta zeolite, [31].

Although that the pervious method were an efficient for synthesis polyhydroquinolines ,it is still necessary to search continuously for better method and catalyst is less consume of time and reagents (economic) able to reused the catalyst many times without loss its activity (reused ability) and more selectivity .

Herein, In continuation of our work in the development of new routes for the synthesis of heterocyclic compounds having biological activity , we reported an efficient and novel method for synthesis polyhydroquinoline derivatives (5) using cesium carbonate as hetereogenous catalyst . Caesium carbonate has vast applications in the organic synthesis such as using as catalyst in knovengeal reaction [32], catalyzed α –phenyl chalcogenation by reaction carbonyl compounds with diphenyl dichalcogenide [33], an efficient way to synthesis of 2 –amino thiophenes with Gewald reaction [34] ,dialkylation of active methylene compounds [35] and it is also used for N-alkylation of amines [36] .Caesium carbonate can be prepared by thermal decomposition of Caesium oxalate or by reacting caesium hydroxide with carbon dioxide[37].

Herein, In continuation of our work in the development of new routes for the synthesis of heterocyclic compounds having biological activity , we reported an efficient and novel method for synthesis polyhydroquinoline derivatives (5) using cesium carbonate as hetereogenous catalyst which catalyzed one pot four component of dimedone(1) ethylacetoacetate (2) ,aryl aldehyde (3) and ammonium acetate(4) irridated by visible light and TBAB as phase transfer catalyst as shown in the scheme (1) .



Scheme 1 One pot synthesis of polyhydroquinoline in the presence of Cs_2CO_3 as catalyst

EXPERIMENTAL SECTION

2.1. Materials and methods

All compounds are identified by comparison of their spectral data and physics properties with those of authentic samples .melting points were recorded on programmable melting point apparatus and are uncorrected .the complete of the reaction is mentioned by thin layer chromatography (TLC) on silica plates .IR spectra were investigated by KBr discs , 1HNMR spectra were recorded by using DMSO as solvent in 400MHz in the presence of TMS as internal reference.

2.2. General procedure of synthesis polyhydroquinoline derivatives

A mixture of arylaldehyde (2mml), dimedone (2mml), acetylacetoacetate(2.5mml) and ammonium acetate (3mml), 0.2 % of Cs_2CO_3 and TBAB (.05 gm) were dissolved by methanol (5ml) and irradiated with 200W tungsten lamp for appropriate time. upon on the complete the reaction (monitor by thin-layer chromatography TLC, the reaction mixture allowed to cooled to room temperature and poured into on ice water which filter to separate the product from the catalyst ,wash the product 2-3 times by water then dry it in the room temperature and recrystallization from hot ethanol to afford the corresponding polyhydroquinoline ,for recovered the cesium carbonate the aqueous layer was evaporated under reduced pressure to yield the catalyst which can reuse many times, all the products are characterized by IR and ^{1}HNMR and comparison the results with authentic samples.

2.3 Spectral data of selected compounds

Ethyl-1-4,7,8-tetrahydro-2,7,7,4-(phenyl)-5-(6H)-oxoquinolin-3-carboxylate (4a),

Yellow crystalline solid, yiled: 91%; mp 228-229°C; IR(KBr): 3280, 3190, 3070, 1705, 1612, 1190, 843 cm^{-1}; ^{1}H NMR (400 MHz, DMSO): 0.86(S, 3H), 1.05 (S, 3H), 1.13 (t, J=7.3Hz, 3H), 2.12-2.30(m, 4H), 2.35(S, 1H), 4.00 (q, 2H, J=7.3 Hz), 4.86 (S, 1H), 7.01 (S, 5H), 7.03-7.18 (m, 5H).

Ethyl-1-4,7,8-tetrahydro-2,7,7,4-(3-nitrophenyl)-5-(6H)-oxoquinolin-3-carboxylate (4b), Yellow crystalline solid, yield 92 %; mp 241-242°C; IR (KBr) 3278, 3193, 3076, 1705, 1605, 1211, 1166, 840 cm^{-1}; ^{1}HNMR (400 MHz, DMSO) 0.95 (S, 3H), 1.22 (t, J=7.3 Hz, 3H), 2.09-2.34(m, 4H), 2.36 (S, 3H), 4.01 (q, J=7.3 Hz, 3H), 4.99 (S, 1H), 7.40-7.49 (m, 4H), 8.02 (S, 1H).

Ethyl-1-4,7,8-tetrahydro-2,7,7,4-(4-nitrophenyl)-5-(6H)-oxoquinolin-3-carboxylate(4c), Yellow crystalline solid, yield: 93%; mp 182-184°C; IR(KBr) 3275, 3188, 3075, 1703, 1609, 1188, 831cm^{-1}; ^{1}HNMR (400 MHz, DMSO), 0.98 (S, 1H), 1.10 (S, 3H), 1.13 (t, 3H, J =7.2 Hz), 2.11(d, 2H), 2.15 (d, 2H), 2.31 (S, 1H), 3.97(q, J =7.3 Hz, 2H), 4.98 (S, 1H),7.42(d, J=9.3 Hz, 2H), 8.04 (d, J =9.4 Hz, 2H), 9.07 (S, 1H).

Ethyl-1-4,7,8-tetrahydro-2,7,7,4-(4-hydroxyphenyl)-5-(6H)-oxoquinolin-3-carboxylate (4e), White crystalline solid, m.p. 230-232°C; IR (KBr) 3285, 3188, 3070, 1712, 1609, 1213, 1027, 835 cm^{-1}; ^{1}HNMR (400 MHz, DMSO); 0.87(S, 1H), 1.01(S, 3H),1.13 (t, J=7.2Hz), 1.95-2.50 (m, 7H), 3.98 (q, J=7.3Hz, 2H), 4.74 (S, 1H), 6.52 (d, J=8.4 Hz, 2H), 6.92 (d, J=8.4 Hz, 2H), 8.98 (S, 1H).

RESULTS AND DISCUSSION

In this work, we like to report an efficient and a novel procedure for the synthesis of Polyhydroquinolines (PHQs, **5**). We first examined the catalytic role of Cs_2CO_3 in synthesis of polyhydroquinoline derivatives via multi-component condensation of aldehydes, ammonium acetate, dimedone and ethylacetoacetate in the presence of catalytic amounts of cesium carbonate under visible light condition (Scheme 1). First, to investigate the feasibility of this synthetic methodology for polyhydroquinoline derivatives, the reaction was carried out simply by mixing 4-nitrobenzaldehyde (2mmol), dimedone (**2** mmol), ethyl acetoacetate (2.5 mmol), and ammonium acetate (3 mmol) under visible light condition in the presence of 5 mol% of Cs_2CO_3. The reaction mixture was stirred for 50 min and corresponding product was obtained in 75 % yield. We have changed the amount of the catalyst the results are summarized in Table 1. An increase in the quantity of Cs_2CO_3 from 5 mol% to 10 mol% not only decreased the reaction time from 160 min to 50 min, but also increased the yield of product slightly from 75 to 92 (entry 2, 3). Although the increase of Cs_2CO_3 to 20 mol% and 30 mol% deceased the product yield from 75 to 66 respectively (entry 4, 5). Low of yield can be explained by said that the starting material or the product may have been destroyed during the reaction when excess amount (20 mol%) of Cs_2CO_3 was used in the exothermic reaction and that 10 mol% Cs_2CO_3 was sufficient to catalyze the reaction effectively. When we carried out the reaction in absence the catalyst the reaction was very sluggish and the yield of product was 25% (entry 1). For study the role which play TBAB in progress this reaction. We noticed in the absence TBAB the reaction proceed in 50 min and product was obtained in 92% yield, in the case addition 5 mol % of TBAB the time reaction decreased to 30 min and the same time the yield of product increased to 95% (entry 6).

Table-1: Study the amount of the catalyst on synthesis Ethyl-1-4,7,8-tetrahydro-2,7,7,4-(4- nitrophenyl)-5-(6H)-oxoquinolin-3-carboxylate

Entry	Amount of Cs_2CO_3 mol%	Time (min)	Yield (%)[b]
1	no catalyst	280	25
2	5	160	75
3	10	50	92
4	20	90	75
5	30	120	66
6	10 mol% Cs_2CO_3 + 5 mol % TBAB	30	95

[a] *Condition of reaction: 4-nitrobenzaldehyde (2mmol), dimedone (**2** mmol), ethyl acetoacetate (2.5 mmol), and ammonium acetate (3 mmol) (1mmol), and solvent: methanol (5ml),*
[b] *Yield of product*

Table-2: Effect of various solvents on synthesis 4b

Entry	Solvent (5ml)	Time (min)	Yield (%)[a]
1	Ethanol	70	85
2	Methanol	30	95
3	DMSO	110	70
4	THF	240	50
5	Acetone	90	75

[a] *Yield of product*

Table 3 Synthesis polyhydroquinolines by reaction aromatic aldehyde, dimedon, ethylacetocetate and ammonium acetate

Entry	R	Product	Time (min)	Yield (%)[a]	M.P°C
1	C_6H_5	5a	70	90	228-230
2	3-$NO_2C_6H_4$	5b	30	95	240-242
3	4-$NO_2C_6H_4$	5c	45	93	182-184
4	2-$NO_2C_6H_4$	5d	40	90	176-178
5	4-OHC_6H_4	5e	50	90	230-232
6	3-OHC_6H_4	5f	45	92	220-222
7	4-ClC_6H_4	5g	60	89	244-246
8	3-ClC_6H_4	5h	45	85	234-236
9	4-$CH_3C_6H_3$	5i	75	90	264-266
10	3, 4$(CH_3)_2C_6H_4$	5j	50	93	288-290
11	4-$CH_3OC_6H_4$	5k	35	88	260-262
12	4-FC_6H_4	5l	65	92	184-186
13	4-$N(CH_3)_2C_6H_4$	5m	45	90	262-264

[a] *isolated yield of product*

To investigate the role which plays solvent in the progress the reaction, the reaction carries out with varies solvent such as (methanol, ethanol, DMSO, THF and acetone). The results presented in the table 2 which indicated that methanol was the best solvent on compare it with other solvent (entry 2).

In order to show the generality of the method, this reaction was carry out with different aldehydes, The time of reaction was within 30–70min, and high yields of polyhydroquinolines were obtained the results are summarized in Table 3.

In this situation we should be mention the role which effort photochemical condition (herein our reaction progress by visible light. When we carry out this reaction at room temperature, the reaction proceed but in a long time from 2-3 hours while this reaction completed during short duration from 30-75 minutes by visible light technique which induced our reaction and save the time and can be consider and less hazardous (environmental safe).

To show the advantages of the present work in comparison with resulted which reported in the other literature, we compared the reaction of 3-NO_2benzaldehyde, dimedone, ethylacetoacetate and ammonium acetate by using Cs_2CO_3 as catalyst with another catalysts which carry out through different method such as ZnO and Scolecite in heat conditions ,L-Proline and CAN in room temperature ,all the results were summarised in the table (4) which indicated that Cs_2CO_3 is the better catalyst with respect to time of reaction and the product yield (entry 3).

Table 4 Comparison of various catalysts for synthesis polyhydroquinolines

Entry	Catalyst	Condition of reaction	Time (min)	Yield (%)	Ref
1	ZnO	Neat / 80^o C	60	92	[31]
2	Scolecite	Neat / 70 ^{o}C	60	87	[15]
3	Cs_2CO_3	Visible light	30	95	**our work**
4	CAN	R.T	50	93	[9]
5	L-proline	R.T	90	95	[23]

CONCLUSION

In summary, we have demonstrated, a simple and efficient methodology for the synthesis polyhydroquinoline by one pot four component of aldehydes, dimedone, ethylacetoacetate ,and ammonium acetate in the presence Cs_2CO_3 catalyst. In this protocol, has many of the advantages such as experiment procedure very sample, using little catalyst loading, facile catalyst separation, and reusability easily, the time of reaction was short and the yield also was very excellent .We wish that our method has applications in the synthesis of polyhydroquinoline and its derivatives.

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