Potassium Carbonate Assisted Synthesis Of α, β, γ, δ-Unsaturated Ketones

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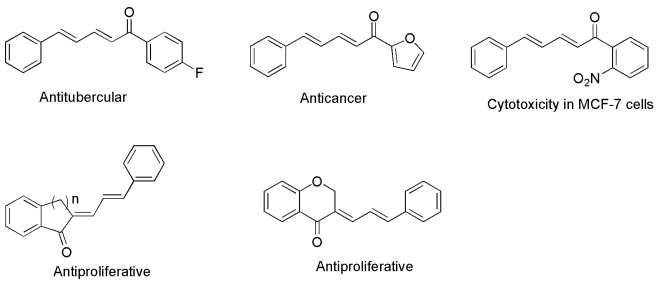
The Cinnamylideneacetophenones derivative is shows important medicinal properties and intermediate in organic synthesis. Several substituted α, β, γ, δ-Unsaturated Ketones were prepared in high yield and purity by direct reaction of substituted cinnamaldehyde and ketones in the presence of potassium carbonate as a base in ethanol at 50ºC. The merit of the method is short reaction times, high yield, easy work-up and purification process, inexpensive and easily available catalyst.

Introduction

Cinnamaldehyde is the core component in cinnamon bark oil (50-70%) and it is accountable for its spicy and sweet taste [1]. Structurally, cinnamaldehyde is a natural, simple Phenylpropanoid bearing an α, β-unsaturated aromatic aldehyde. The synthetic applications of cinnamaldehyde are vast and related to its abundance and low economic costs and have led to a collection of compounds with high chemodiversity [2]. The Cinnamylideneacetophenones derivative is α, β, γ, δ - unsaturated ketones show important bioactivities like antibacterial and antitubercular [3], antinociceptive [4], cytotoxicity in breast cancer cell [5], the antiproliferative effect [6], an antileshmanial activity [7], inhibitors of protein kinase C [8], antifungal [9], antimalarial [10] and antioxidant activity [11]. The cinnamylidene ketones have optimistic non liner optical material, in particular, in the short wavelength region [12]. Some important Cinnamylideneacetophenones is shown in **Scheme 1**.



Scheme 1. Pharmaceutical active Cinnamylideneacetophenones

The cinnamylideneacetophenones derivatives are key intermediates in organic synthesis for isoquinuclidines [13], 2, 6-diaryl-1,2-dihydropyridines [14], spiro-1-pyrazolines [15], (*E*)-3-styrylchromones [16], 2-benzoyl-1,5-diphenylpyrroles [17], 3-aryl-5-styryl-2-pyrazolines [18], pentasubstituted cyclohexanes

[19], (*E*)- and (*Z*)-2-styrylchromones [20], and 3-benzoyl-4-styryl-2-pyrazolines [21].

The Cinnamylideneacetophenones derivatives are synthesized by Claisen-Schmidt condensation reaction between acetophenone and cinnamaldehyde using sodium hydroxide as a base catalyst. However, this reported method is suffering from drawbacks such as longer reaction time, low yield, and use of a strong base. Sodium hydroxide is highly corrosive and decomposes proteins and lipids in living tissues via amide hydrolysis and ester hydrolysis which consequently cause chemical burns and may induce permanent blindness upon contact with eyes. Hence there is scope to develop a new method using a mild base that should be free from these shortcomings.

Potassium carbonate is the weakest base among are the alkali metal interest due to inexpensive and easily available, solubility in water, mild character, easy availability, eco-friendly and nontoxic nature [22]. Potassium carbonate has been widely used as a mild base catalyst in many organic reactions such as silyl ethers [23], synthesis of azoles and diazines [24], synthesis of 2*H*-chromenes [25], N-alkylation of indole and pyrrole [26], Synthesis of coumarins [27], synthesis of rhodanines derivatives [28], synthesis of thiohydantoins [29], synthesis of flavanones [30], and synthesis of 4-oxo-2-thioxohexahydropyrimidines [31], synthesis of functionalized pyrimidines [32] and synthesis of 5-aryl-2,6-dicyano-3-methylanilines [33].

Potassium carbonate has mild basic character, easy availability, eco-friendly and non-toxic nature. Thus potassium carbonate provides a mild basic medium for organic reactions to occur and get removed by easy separation by water.

Here we studied the Claisen-Schamidt condensation reaction between the aromatic ketones with cinnamaldehyde in ethanol as a solvent in the presence of potassium carbonate as a base.

Experimental part

Material and methods

All the reagents, catalysts and chemicals were obtained from the commercial sources and used without further purification. Melting points were open capillary method and are uncorrected.

^{1}HNMR and ^{13}CNMR spectra were recorded at ambient temperature on a BRUKER ADVANCE DRX-400 MHz spectrophotometer using $CDCl_3$ as the solvent and TMS as an internal standard. The purity of newly synthesized compounds and the development of reactions was monitored by TLC on Merck pre-coated silica gel 60 F 254 aluminum sheets, visualizes by UV light. All products were known and characterized by IR, ^{1}HNMR, ^{13}CNMR and HRMS.

Synthesis

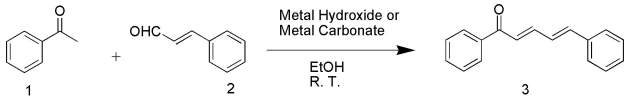
General procedure for preparation α, β, γ, δ-unsaturated carbonyl compound (1,5-diarylpenane-2,4-diene-1-one)[3a-r]:

In 50 mL RB flask 1 mmol of acetophenone and 1mmol of cinnamaldehyde was dissolved in 20 mL Ethanol and 0. 2eq. potassium carbonate was added to this. The reaction mixture was stirred at 50ºC for the respective time given in **Table 4**. The progress of the reaction was monitored by TLC. On completion, the reaction mass was diluted with cold water and acidified 2N HCl to precipitate out a solid product. The solid product was separated by filtration, washed with water and after ice-cold ethanol, dried and purified by recrystallization from ethanol to give pure products **3a-r**.

Results and discussion

The Claisen-Schamidt condensation reaction between acetophenone and cinnamaldehyde was selected as a model reaction. Initially, we have various metal hydroxides and carbonates used as a catalyst like sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide, barium carbonate, potassium carbonate, calcium carbonate, strontium carbonate, sodium carbonate, and sodium bicarbonate. The condensation was carried in a 50mL RB flask and ethanol as a solvent for the condensation reaction at room temperature and the results as summarized in **Table 1**.

The model reaction was performed in a 50 ml round bottom flask using 1 equivalent acetophenone, 1 equivalent cinnamaldehyde and 1 equivalent catalyst in 20 mL ethanol as solvent under the stirring condition at room temperature. From **Table 1** it was observed that potassium carbonate found an efficient catalyst for the synthesis of the 1,5-diarylpenane-2,4-diene-1-one as the α, β, γ , δ-unsaturated carbonyl compound with the 85% of yield [21]. We choosed the potassium carbonate as a base due (i) moderately basic nature of it as compared to sodium hydroxide, lithium hydroxide, potassium hydroxide and calcium hydroxide; (ii) less toxic as compared to sodium carbonate, sodium bicarbonate and high yield as compared to other alkali carbonate.



Scheme 2. Model reaction for catalyst screening for the synthesis of cinnamylideneacetophenone

Table 1. Screening of catalyst for the synthesis of Cinnamylideneacetophenones [a]

Entry	Catalysts	Products	Time(h)	% Yield[b]
1	NaOH	3a	12	75
2	KOH	3a	10	72
3	LiOH	3a	13	65
4	$Ca(OH)_2$	3a	24	63
5	$BaCO_3$	3a	40	60
6	$CaCO_3$	3a	42	52
7	K_2CO_3	3a	8	85
8	$SrCO_3$	3a	45	50
9	Na_2CO_3	3a	17	55
10	$NaHCO_3$	3a	50	57
11	KOAc	3a	78	20

[a] Reaction condition: 1mmol acetophenone, 1mmol cinnamaldehyde and 0.2 equivalent of catalyst in 20 mL EtOH at room temperature. [b] Isolated yield after purification.

In addition to searching for the optimal solvent, the synthesis of **3a** was accomplished by using a solvent like Ethanol, Water, DMF, DMSO, THF, Acetonitrile, Toluene and solvent-free conditions at room temperature (**Table 2**, entries 1-8). The results of solvent selection were given in **Table 2** and ethanol was found suitable solvent for this reaction. Therefore, all further reaction was carried out using 20 mol% of Potassium Carbonate in ethanol as solvent at room temperature.

Table 2. Optimization of the amount of potassium carbonate[a]

Sr. No.	Catalyst/ mol %	Product (**3**)	Time (h)	% Yield[b]
1	0	**3a**	24h	NR
2	10	**3a**	15	45
3	20	**3a**	8:45	87
4	30	**3a**	12	80
5	40	**3a**	11	75
6	50	**3a**	10:10	82

[a] Reaction condition: 1 mmol acetophenone, 1 mmol cinnamaldehyde, and 0 to 50 mol % of potassium carbonate in 20 mL EtOH at room temperature. [b] isolated yield after purification

Table 3. Selection of solvent for Calsien-Schmidt reaction[a]

Entries	Solvents	Products(**3**)	Time Hour	% Yield[b]
1	Acetonitrile	**3a**	15	74
2	DMF	**3a**	43	65
3	DMSO	**3a**	44	45
4	THF	**3a**	40	50
5	Solvent Free	**3a**	25	25
6	Water	**3a**	35	45
7	Toluene	**3a**	50	No Reaction
8	Ethanol	**3a**	8	85
9	Isopropanol	**3a**	15	46
10	Propanol	**3a**	12	30

[a] Reaction condition: 1 mmol acetophenone, 1 mmol cinnamaldehyde, and 0.2 eq. potassium carbonate in 20 mL Solvent at room temperature. [b] isolated yield after purification.

Similarly, the reaction between acetophenone and cinnamaldehyde was selected as model substrates to optimize the amount of potassium carbonate. The catalyst loading was optimized by an increasing the amount of calcium chloride from 10 mol% to 50 mol% for a 1 mmol scale reaction. When the reaction was carried in the absence of a catalyst, the product was not formed (**Table 3**, entries 1). When the reaction was carried with 10 mol%, the product formed in moderate yield and time required to form the product is long (**Table 3**, entries 2). The yield increased with the increase in the catalyst amount (**Table 3**, entries 3-6). Nevertheless, there was a very minor increase in the yield when catalyst loading has increased from 30 mol% to 50 mol%. From **Table 3** it was observed that 20 mol% of the catalyst were sufficient to obtain the best yield.

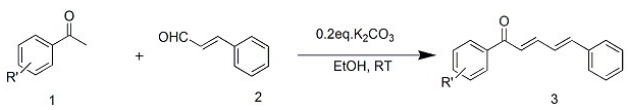
For optimization of temperature the reaction was performed at 0ºC, 25 ºC, 50 ºC and 100 ºC and the results are tabulated in **Table 4**. The reaction at 0ºC procceded very slow and afford 15% yield. Next, we performed the reaction at room temperature, the reaction was completed in 8 hrs with 85% yield. To study the effect of heat, we performed the reaction at 50 ºC and 100 ºC. The reaction performed at 50 ºC completed in 4hrs with 94% yield and at 100 ºC there was no substantial increase in yield or not reduced the reaction time. Hence, all further reaction was carried at 50 ºC.

Table 4. Optimization of the temperature of reaction[a]

Sr. No.	Temperature °C	Product	Time (h)	% Yield[b]
1	0	3a	41	15
2	30	3a	8	85
3	50	3a	4	94
4	100	3a	5	80

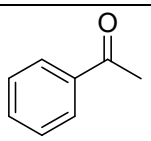
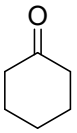
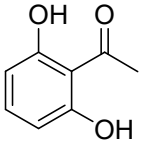
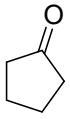
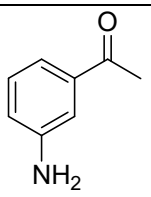
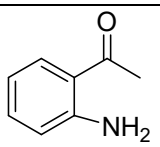
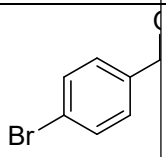
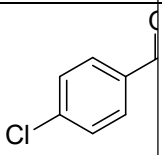
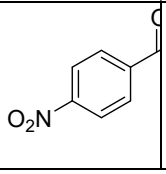
[a] Reaction condition: 1 mmol acetophenone, 1 mmol cinnamaldehyde, and 20 mol % of potassium carbonate in 20 mL EtOH at 0 -100 °C temperature. [b] isolated yield after purification

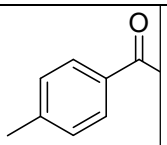
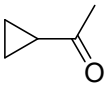
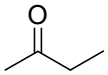
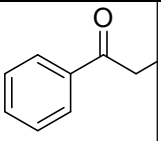
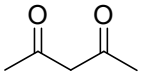
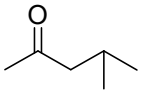
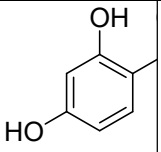
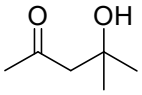
With the optimized reaction conditions in hand, the expediency of this method was evaluated using a variety of aromatic ketones and a series of compound **3** were synthesized with this simple approach (**Scheme 3**). The results are summarized in **Table 4**. The nature and position of the functional group on the phenyl ring affected the reaction time and the yield of the product. Acetophenone bearing electron donating groups like methyl, hydroxy react with the cinnamaldehyde to afford the moderate yield of product, while electron withdrawing group such as chloro, bromo, nitro, to afford the high yield in short reaction time. Acetophenone bearing electron-donating substituent gave low yields presumably due to its electron donating mesomeric and inductive which decreases the acidic character of the methyl group.



Scheme 3. Synthesis of substituted cinnamylideneacetophenone

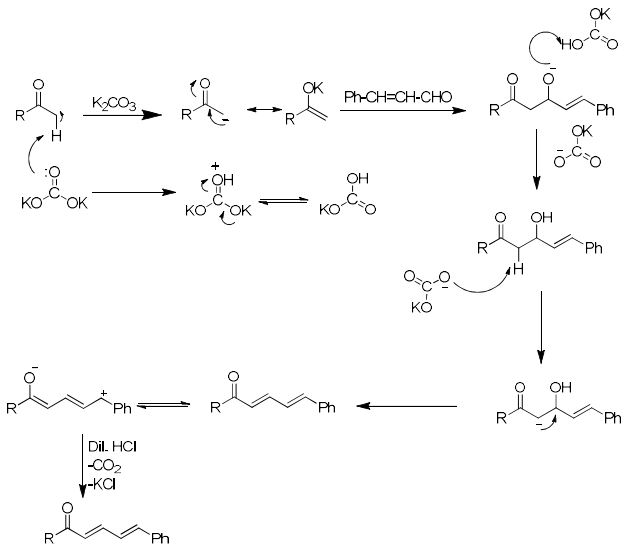
Table 5: Synthesis substituted cinnmylideneacetophenone[a]

S.N.	Ketones	Product (**3**)	Time (h)	% Yield[b]	Mp °C
1		**3a**	4:00	94	102
2		**3b**	2:30	75	140
3		**3c**	1:00	88	160
4		**3d**	6:00	93	148
5		**3e**	1:00	91	243
6		**3f**	7:00	88	96
7		**3g**	8:00	82	126
8		**3h**	1:30	89	144
9		**3i**	1:20	92	134
10		**3j**	1:00	92	170

11		**3k**	4:00	85	88
12		**3l**	6:30	86	188
13		**3m**	7:00	76	92
14		**3n**	11:00	60	158
15		**3o**	6:15	56	132
16		**3p**	7:10	65	140
17		**3q**	6:35	70	120
18		**3r**	5:30	65	116

[a] Reaction condition: 1 mmol substituted acetophenone or aliphatic ketone, 1 mmol cinnamaldehyde, 0.2 eq. potassium carbonate in 20 mL EtOH at 50°C. [b] Isolated yield after purification

The probable mechanism of the reaction is shown in Scheme 4.



Scheme 4. Mechanism of the Potassium carbonate assisted synthesis of α,β,γ,δ-unsaturaed ketone.

Conclusions

Here, we reported an efficient synthesis of 1,5-diarylpenane-2,4-diene-1-one by using solid potassium carbonate. The efficiency of the method has been demonstrated by synthesizing various substituted diaryl α, β, γ, δ-unsaturated carbonyl compound and the presence protocol offers various advantages. The advantages of the method are moderate to high yield, easily available and expensive catalyst, avoid the use of hazardous chemical, easy workup, well-tolerated with electron-donating as well as electron-withdrawing functional groups.

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