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ONE-POT SYNTHESIS OF NEW CYCLOHEXENONE DERIVATIVES CATALYZED BY POTASSIUM CARBONATE UNDER MICROWAVE IRRADIATION

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Abstract: A direct one-pot three-component reaction of 4-Acetamidocyclohexanone, aromatic aldehydes, and ethyl acetoacetate under microwave irradiation afforded a series of new cyclohexenone derivatives in the presence of potassium carbonate. One-pot reaction, high efficiency, short reaction time are some of the considerable advantages of this procedure. Microwave irradiation facilitates better thermal management of chemical reactions. The Microwave heat transfer allowed the reaction to be carried out faster and gives better yield.

Keywords: 4-Acetamidocyclohexanone, cyclohexenone, one-pot reaction, potassium carbonate.

INTRODUCTION

Microwave (MW) irradiation facilitates better thermal management of chemical reactions. The rapid MW heat transfer allows reactions to be carried out very much faster compared to conventional heating methods often resulting in increased product yield.[1-2]Furthermore, the products of temperature sensitive reactions from kinetic or thermodynamic pathways can be selectively tuned and isolated. The fundamental mechanism of microwave irradiated synthesis involves agitation of polar molecules or ions that oscillate under the effect of an oscillating electric or magnetic field. In the presence of an oscillating field, particles try to orient themselves or be in phase with the field. Only materials that absorb microwave radiation are relevant to microwave synthesis.[3]Thus this technique is simple, clean, fast, efficient and economic for synthesis of organic molecules. Therefore, this synthesis was prepared by using microwave irradiation.

Multicomponent reactions (MCRs) are one-pot procedures in which almost all atoms of three or more reagents are combined, in order to afford only one product. Nowadays, multicomponent reactions (MCRs) technique is extensively recognized for its impact on drug discovery projects and is powerfully approved by academic researchers as well as industry[4]. MCRs create a particularly attractive synthetic method since they prepare simple and quick access to wide libraries of organic compounds with different substitution groups. It has several advantages when compared to classical procedures, especially considering atom economy and purification procedures and it emerged as an efficient and powerful tool in modern synthetic organic chemistry because the synthesis of complex organic molecules from simple and readily available substrates can be achieved in a very fast and efficient manner without the isolation of any intermediate[5, 6]. Michael addition of chalcones to 1,3-dicarbonyl compounds such as acetoacetic esters leads to substituted cyclohexenones, which become attractive intermediates for the synthesis of a diversity of heterocyclic

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compounds with different biological activities.[7–9] Cyclohexenone derivatives are efficient building blocks for construction of spiranic compounds[10]. Highly substituted cyclohexenones are introduced as lead compounds for the cure of inflammation and autoimmune diseases[11].

Cyclohexenone and its derivatives were considered as one of the important synthetic chemistry methods because they are utilized as starting materials in the formation of plenty natural products as well as other interesting chemical derivatives such as antibiotics and steroids[12]. Cyclohexenone derivatives have been widely applied in biological field such as antitumor [13], anti-bacterial[14], and antimicrobial[15]. In addition, cyclohexenone compounds can be used in the synthesis of natural products with a wide spectrum of biological functions, functionalized chiral cyclohexenone has been given a lot of interest academically[16].

Due to the significance of highly substituted cyclohexenones from a pharmaceutical and biological standpoint, there is still a requirement to extend effective, mild, and ecologically benign procedures for the synthesis of these compounds. Herein, we present an efficient procedure for the one-pot synthesis of novel cyclohexenone derivatives.

RESULTS AND DISCUSSION

A new series functionalized cyclohexanones was prepared using a direct three-component reaction of 4-Acetamidocyclohexanone, aromatic aldehydes, and ethyl acetoacetate using potassium carbonate in ethanol. **(scheme 1)**

In order to optimize the reaction conditions and get the best catalytic activity, the reaction of 4-Acetamidocyclohexanone, benzaldehyde, and ethyl acetoacetate was examined as a model reaction in the several catalysts. As indicated in **Table 1**, the model reaction was carried out using Diethylamine, KOH, Triethylamine (TEA), NaOH, Sodium carbonate, Sodium bicarbonate, Potassium carbonate. In this study, it was observed that Potassium carbonate (40 mol%) in ethanol under microwave heating is more efficient with respect to reaction time and yield of the desired product **(Table 1).**

After optimizing the catalyst amount, a diversity of cyclohexenone derivatives was synthesized using potassium carbonate (40 mol%) under microwave heating **(Table 2, entries 4a–4j).** The reactions worked well with all benzaldehydes with electron-donating or electron-withdrawing substituent.

All synthesized products were characterized by FT-IR, ^{1}HNMR and ^{13}C-NMR spectra and elemental analysis.

Scheme 1. Synthesis of substituted cyclohexenones catalyzed by K_2CO_3.

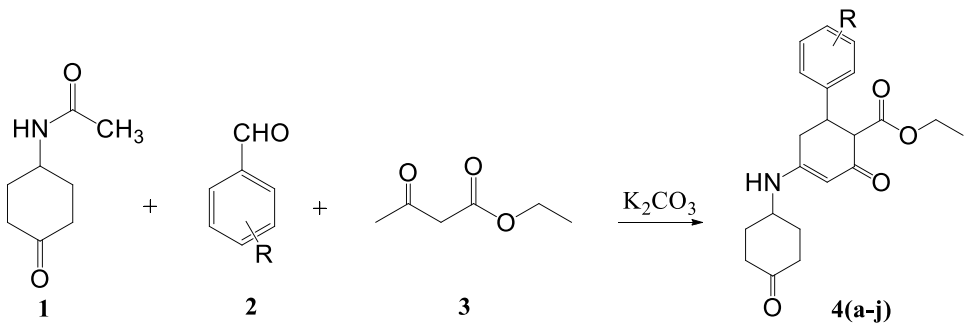

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Table 1. Synthesis of 4a by different catalysts[a]

Entry.	Catalyst (mol%)	Time(min)	Yield of product(%)[b]
1	Diethylamine	15	88
2	KOH	12	75
3	Triethylamine	13	81
4	Sodium carbonate	12	86
5	Sodium bicarbonate	13	82
6	**Potassium carbonate**	**10**	**95**
7	NaOH	12	90

[a]Reaction conditions: 4-Acetamidocyclohexanone(3mmol), benzaldehyde(3mmol) and ethyl acetoacetate , (3 mmol) in EtOH (10 mL) under microwave irradiation.

[b]Yield refers to isolated products.

Table 2. Synthesis of cyclohexenone derivatives 4(a-j) catalyzed by potassium carbonate.[a]

Compound code	R	Time (min)	Yield (%)	Melting point	Microwave (PowerWatt)
4a	H	11	95	160-168	210
4b	4-Cl	13	89	180-185	210
4c	2-Cl	12	82	176-181	210
4d	4-Br	10	90	175-180	210
4e	3-Br	14	91	172-177	210
4f	4-OCH_3	15	88	188-191	210
4g	3-NO_2	10	92	183-186	210
4h	3-Cl	12	90	170-173	210
4i	3-OCH_3	14	85	190-193	210
4j	4-OH	15	82	165-170	210

[a]Reaction and condition: 4-Acetamidocyclohexanone(3mmol), benzaldehyde(3mmol) and ethyl acetoacetate and potassium carbonate (3 mmol) in EtOH (10 mL)

[b]All yields refer to isolated products.

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CONCLUSION

1. In Summary, we have extended one-pot protocol for the synthesis of novel cyclohexenone derivatives by the three-component reaction of 4-Acetamidocyclohexanone, aromatic aldehydes, and ethyl acetoacetate in the presence of potassium carbonate as an efficient basic catalyst in ethanol under microwave.
2. The mild reaction conditions, high efficiency, and simple work-up procedure are some of the advantages of this method.

Experimental section

Unless and otherwise noted, all Chemicals used were of commercial grade and they were used without any further purification. All reactions were monitored by thin layer chromatography using aluminium sheets precoated with silica gel 60 F254 (Merck) using either UV light or iodine vapours as visualizing agents. The products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones.

General procedure for the synthesis of acrylamide derivatives **4(a-g)**

To a Mixture of 4-Acetamidocyclohexanone **(3** mmol), ethyl acetoacetate **(3 mmol)**, and substituted aldehyde **(3 mmol)** dissolves in ethanol (10 ml). To that mixture add aq. K_2CO_3**(3 mmol)** was added and the reaction mixture was irradiated in microwave for **10-15min**. The reaction was monitored on Merck pre-coated aluminum TLC plates 60F-254 and product was visualized by UV-light using n-hexane and ethyl acetate as solvent system. After completion of the reaction, the reaction mixture was poured into ice cold water the precipitate was filtered and dried.

Characterization

Melting points were measured in open capillaries and are uncorrected. IR spectra was recorded on Bruker FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker FTNMR (500MHz) spectrophotometer with DMSO-d6 as solvent and TMS as internal standard. Solvent peaks in ^{1}H-NMR and ^{13}C-NMR spectra have been removed in tracing. The chemical shifts in parts per million (δ) are reported downfield from TMS (0 ppm). The abbreviations s, d, t, q, m and dd refer to singlet, doublet, triplet, quartet, multiplet and doublet of doublet respectively.

ethyl 3-oxo-5-((4-oxocyclohexyl)amino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate **(4a):**

Molecular Formula: $C_{21}H_{25}NO_4$

Molecular Weight (gmol-1): 355.43

Melting Point (ºC): 160-168

IR (KBr, cm-1): 3242 (NH), 1658, 1660 (C=O ketone), 1740 (C=O ester).

^{1}H NMR (500 MHz, DMSO, δppm): 1.18(t, 3H, CH3), 1.8(m, 4H, CH4), 2.70(m, 4H,CH4), 3.22 (d, 2H, CH2), 3.4(d, 1H, H-2), 3.84– 3.94 (m, 1H, H-1), 4.11(tt, 1H, CH), 4.32(q, 2H, CH2), 5.0(s, 1H, H-3), 7.0-7.3 (m, 5H, Ar-H), 12.29(s, 1H,NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 14.2, 28.4, 28.5, 40.3, 40.4, 40.5, 43.7, 53.3, 58.0, 60.9, 113.0, 127.8, 127.9, 128.9, 143.4, 162.7, 168.7, 191.9, 210.8.

Ethyl 4'-chloro-3-oxo-5-((4-oxocyclohexyl)amino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate **(4b)**

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Molecular Formula: $C_{21}H_{24}ClNO_4$

Molecular Weight (gmol-1): 389.87

Melting Point (ºC): 180-185

IR (KBr, cm-1): 3247 (NH), 1660(C=O), 1665(C=O ketone) and 1745(C=O ester).

^{1}H NMR (500 MHz, DMSO, δ ppm): 1.20(t, 3H, CH3), 1.85(m, 4H, CH4), 2.80(m, 4H,CH4), 3.25 (d, 2H, CH2), 3.43(d, 1H, H-2), 3.89– 3.96 (m, 1H, H-1), 4.20 (tt, 1H, CH), 4.42(q, 2H, CH2), 5.2(s, 1H, H-3), 7.3-7.6 (m, 4H, Ar-H), 11.29(s, 1H,NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 15.2, 29.4, 29.5, 41.3, 41.4, 41.5, 42.7, 52.3, 57.0, 61.9, 112.0, 126.8, 126.9, 127.9, 142.4, 161.7, 167.7, 190.9, 211.8.

ethyl 2'-chloro-3-oxo-5-((4-oxocyclohexyl)amino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate **(4c)**

Molecular Formula: $C_{21}H_{24}ClNO_4$

Molecular Weight (gmol-1): 389.87

Melting Point (ºC): 176-181

IR (KBr, cm-1): 3319 (NH), 1661, 1664 (C=O ketone) and 1740 (C=O ester)

^{1}H NMR (500 MHz, DMSO, δ ppm): 1.15(t, 3H, CH3), 1.75(m, 4H, CH4), 2.70(m, 4H,CH4), 3.21 (d, 2H, CH2), 3.40(d, 1H, H-2), 3.87– 3.95 (m, 1H, H-1), 4.19 (tt, 1H, CH), 4.32(q, 2H, CH2), 5.1(s, 1H, H-3), 7.3-7.6 (m, 4H, Ar-H), 11.39(s, 1H,NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 15.3, 29.5, 28.6, 40.4, 40.5, 41.6, 41.8, 51.4, 56.5, 72.9, 102.2, 116.9, 135.9, 138.9, 144.4, 162.7, 167.7, 190.9, 215.8.

ethyl 4'-bromo-3-oxo-5-((4-oxocyclohexyl)amino)-1,2,3,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate **(4d)**

Molecular Formula: $C_{21}H_{24}BrNO_4$

Molecular Weight (gmol-1): 434.32

Melting Point (ºC): 175-180

IR (KBr, cm-1): 3345 (NH), 1660, 1670 (C=O ketone), 1730 (C=O ester).

^{1}H NMR (500 MHz, DMSO, δ ppm): 1.18(t, 3H, CH3), 1.85(m, 4H, CH4), 2.75(m, 4H,CH4), 3.28 (d, 2H, CH2), 3.48(d, 1H, H-2), 3.87– 3.94 (m, 1H, H-1), 4.20 (tt, 1H, CH), 4.30(q, 2H, CH2), 5.06(s, 1H, H-3), 7.4-7.8 (m, 4H, Ar-H), 12.25(s, 1H,NH).

^{13}C NMR (500 MHz, DMSO, δ ppm): 14.3, 28.5, 29.6, 41.4, 41.5, 41.6, 42.8, 52.4, 57.5, 62.9, 112.2, 126.9, 125.9, 126.9, 141.4, 160.7, 168.7, 191.9, 210.8.

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