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Regioselective Synthesis and Antibacterial Studies of α,β-Unsaturated Ketone Substituted Cyclohexanols *via* Tandem Michael Addition-Aldol Addition-Cyclization Sequence under Solvent-Free Conditions

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A simple and facile strategy was developed involving test tube with glass-rod using a base catalyst for one-pot solid-state reaction between 1,3,5-triphenyl-pentane-1,5-dione (**1**) and 1,5-diphenyl-penta-1,4-dien-3-one (**2**) to obtain novel 1-(5-benzoyl-2-hydroxy-2,4,6-triphenyl-cyclohexyl)-3-phenyl-propenone (**3**) derivatives. The reaction was accomplished in good to excellent yields and the structure of a synthesized compounds was confirmed by IR, ^{1}H NMR and ^{13}C NMR spectral data. In this one-pot transformation, the column chromatography purification was completely avoided. Besides, the method is highly environmentally benign and atom-economical, and the side product of this reaction was only the water molecule. This green process produces significant carbocycles and offers a considerable advantages such as operational simplicity, short reaction time, high yields, and absence of tedious workup. Further, synthesized derivatives was studied against Gram-positive (*Staphylococcus aureus*) and Gram-negative bacteria (*Pseudomonas aeruginosa*).

Keywords: Regioselective, Tandem Michael Addition, Aldol Addition, Cyclohexanol, Antibacterial activity.

INTRODUCTION

Cyclohexanol derivatives are the important class of carbocycles and has attracted growing interest of medicinal chemists [1-6]. An elaborative literature survey on the cyclohexanol derivatives has revealed that they displayed diverse biological activities such as acetylcholine-storage-blocking activities [7], analgesic [8], antidepressant [9], cardio-inhibitory effects [10] and also have been reported as potent microbial agents [11]. Thus, the biological significances of cyclohexanol derivatives have attracted the interest of synthetic chemists to discover an efficient methodologies for the synthesis of different cyclohexanol derivatives.

The tandem or domino reaction has recently been of interest in organic synthesis because it offers a convenient and economical ways to prepare desired organic molecules [12]. Michael addition is one of the most useful organic reactions to construct carbon skeletons. Michael addition of carbon nucleophiles to electron deficient olefins is a classical and fundamental carbon-carbon bond-forming reaction [13]. This reaction and its close variants have been extensively used in organic synthesis for the construction of heterocycles [14]. Generally, Michael additions are conducted in a suitable solvent in the presence of a strong base either at room temperature or at elevated temperatures [15]. Recently, the non-conventional procedures like conducting the reaction on the surface of a dry medium [16] or under microwave [17] irradiation were reported to facilitate the Michael reaction. For the purpose of eco-friendly "green chemistry", a reaction should ideally, be conducted under solvent free conditions with no side product formation and with maximum atom-economy [18]. There are few studies of the synthesis and characterization of pentasubstituted cyclohexanol in the literature [19].

Lu & Cai [2] reported the highly substituted cyclohexanol from the Michael addition of active methylene compounds or nitromethane to chalcones in an aqueous medium and catalyzed by tetrabutyl ammonium hydroxide (TBAOH). Hussain *et al.* [20] reported the stereostructure, antimicrobial and cytotoxic

activity of cyclohexane, cyclohexanol and pyridine derivatives synthesized from chalcones. Rong *et al*. [6] reported a facile and efficient synthesis of polysubstituted cyclohexanol derivatives under solvent-free conditions. Considering these points, the present work is planned to demonstrate a base catalyzed sequential Michael addition-aldol reaction of 1,3,5-triphenyl-pentane-1,5-dione (1,5-diketones) (**1**) and 1,5-diphenyl-penta-1,4-dien-3-one (dibenzylideneacetone) (**2**) towards the synthesis of novel 1-(5-benzoyl-2-hydroxy-2,4,6-triphenyl-cyclohexyl)-3-phenyl-propenone (**3**) derivatives.

EXPERIMENTAL

General procedure for the synthesis: To a mixture of diketones **1** (0.3 g, 0.01mmol), dibenzylidene acetone **2** (0.220 g, 0.01 mmol) and NaOEt were added. The reaction mixture was grounded at room temperature until it became incompact solid. Then, the solid was heated in water-bath for 5 min at 90 ºC. The reaction was completed as shown by TLC. Then, the solid was treated with water and the water insoluble solid was separated and recrystalised in ethanol to provide penta-substitued cyclohexanol (**3a-g**) in good yield (**Scheme-I**).

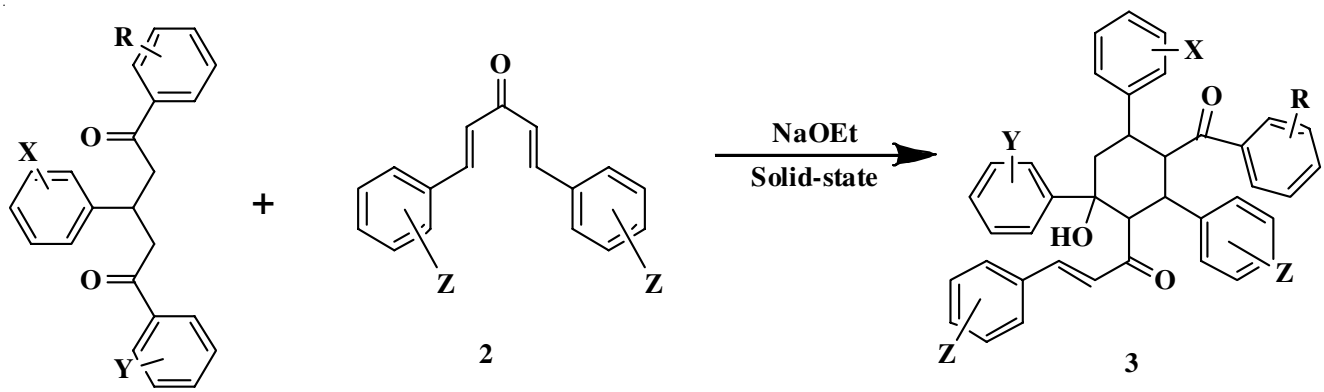
1-(5-Benzoyl-2-hydroxy-2,4,6-triphenyl-cyclohexyl)-3-phenyl-propenone (**3a**)**:** White solid, yield: 94%, 236 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.17-2.29 (t, 2H), 2.49-2.58 (t, 1H), 4.07-4.11(d, 1H, *J* = 12 Hz), 4.19-4.26 (t, 1H), 4.50-4.54 (d, 1H, *J* = 9 Hz), 5.42 (s, OH), 6.72-6.74 (d, 1H, *J* = 6 Hz), 6.82-6.84 (t, 2H), 7.04-7.10 (m, 5H), 7.11-7.19 (m, 7H), 7.24-7.30 (m, 10H), 7.55-7.58 (d, 2H, *J* = 9 Hz). ^{13}CNMR ($CDCl_3$, 75 MHz, δ ppm): 43.7, 46.2, 48.5, 50.3, 57.1, 75.7, 125.2, 126.1, 127.1, 127.3, 127.4, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.7, 129.1, 132.1, 133.0, 138.5, 139.0, 139.3, 142.4, 144.0, 146.3, 204.0, 207.5.

1-(5-Benzoyl-2-hydroxy-2,6-diphenyl-4-*p*-tolyl-cyclohexyl)-3-phenyl-propenone (**3b**)**:** White solid, yield: 94%, 240 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.12 (s, 3H), 2.17-2.25 (t, 2H), 2.45-2.53 (t, 1H), 4.02-4.05 (d, 1H, *J* = 9 Hz), 4.14-4.21 (t, 1H), 4.46-4.49 (d, 1H, *J* = 9 Hz), 5.37 (s, OH), 6.72-6.74 (d, 1H, *J* = 6 Hz), 6.82-6.84 (t, 2H), 7.04-7.10 (m, 5H), 7.11-7.19 (m, 7H), 7.24-7.30 (m, 10H), 7.55-7.58 (d, 2H, *J* = 9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 20.5, 42.7, 43.9, 45.8, 47.4, 56.7, 75.1, 124.4, 124.5, 125.2, 125.6, 126.2, 126.6, 127.0, 127.2, 127.3, 127.4, 127.5, 127.8, 128.4, 128.7, 131.3, 132.2, 135.3, 135.7, 136.0, 137.9, 138.8, 143.5, 145.7, 203.3, 207.0.

1-(5-Benzoyl-2-hydroxy-6-phenyl-2,4-di-*p*-tolyl-cyclohexyl)-3-phenyl-propenone (**3c**)**:** White solid, yield: 92%, 240 ºC; ^{1}HNMR ($CDCl_3$, 300 MHz, δ ppm): 2.12 (s, 3H), 2.19 (s, 3H), 2.39-2.47 (t, 2H), 4.00-4.14 (m, 3H), 4.41-4.45 (d, 1H, *J* = 12 Hz), 5.35-5.43 (d, OH), 6.60-6-62 (d, 2H, *J* = 6 Hz), 6.83-6.89 (t, 5H), 6.95-7.05 (m, 7H), 7.13-7.22 (m, 7H), 7.40-7.42 (d, 2H, *J* = 6 Hz), 7.52-7.54 (d, 2H, *J* = 6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 20.7, 21.2, 43.0, 46.4, 47.7, 57.0, 75.3, 117.1, 124.8, 124.9, 127.4, 127.5, 127.7, 127.8, 128.0, 128.2, 128.3, 128.6, 128.7, 128.8, 128.9, 131.4, 133.8, 136.0, 136.1, 136.2, 139.3, 141.5, 143.3, 203.7, 206.6.

1-[5-Benzoyl-4-(3-chlorophenyl)-2-hydroxy-2,6-diphenyl-cyclohexyl]-3-phenyl-propenone (**3d**)**:** White solid, yield: 95%, 245 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.22-2.26 (d, 1H, *J* = 12 Hz), 2.41-2.50 (t, 1H) 4.00-4.23 (m, 3H), 4.46-4.49 (d, 1H, *J* = 9 Hz), 5.40 (s, OH), 6.67-6-70 (d, 1H, *J* = 9Hz), 6.74-6.79 (t, 2H), 6.97-7.03(t, 3H), 7.07-7.14 (m, 6H), 7.19-7.35(m, 11H), 7.55-7.57 (d, 2H, *J* = 6 Hz), 7.94-7.96 (d, 1H, *J* = 6 Hz). ^{13}CNMR ($CDCl_3$, 75 MHz, δ ppm): 43.5, 46.2, 48.1, 56.4, 56.6, 75.6, 125.1, 127.0, 127.3, 127.6, 127.8, 128.1, 128.2, 128.3, 128.7, 129.0, 129.9, 130.1, 132.7, 133.4, 134.4, 134.6, 137.0, 138.3, 138.9, 141.1, 144.4, 145.9, 203.0, 207.0.

1-[5-Benzoyl-2-(4-chloro-phenyl)-2-hydroxy-6-phenyl-4-*p*-tolyl-cyclohexyl]-3-phenyl-propenone (**3e**)**:** White solid, yield: 96%, 230 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.15



Entry	X	Y	R	Z
a	H	H	H	H
b	*p*-CH_3	H	H	H
c	*p*-CH_3	*p*-CH_3	H	H
d	*m*-Cl	H	H	H
e	*p*-CH_3	*p*-Cl	H	H
f	*m*-Cl	H	H	*m*-Cl
g	*m*-Cl	H	H	*p*-CH_3

Scheme-I: Synthesis of 1-(5-benzoyl-2-hydroxy-2,4,6-triphenyl-cyclohexyl)-3-phenyl-propenone (**3**)

(s, 3H), 2.25-2.29 (d, 1H, *J*=12Hz), 2.36-2.45 (t, 1H), 3.99-4.24 (m, 2H), 4.35-4.45 (q, 1H), 5.35-5.41 (d, -OH), 6.64-6.69 (d, 2H, *J*=15Hz), 6.90-6.92 (d, 3H, *J*=6Hz), 7.01-7.07 (m, 6H), 7.13-7.26 (m, 9H), 7.42-7.53 (m, 4H), 7.94-7.97 (d, 1H, J=9Hz). ^{13}CNMR ($CDCl_3$, 75 MHz, δ ppm): 21.0, 42.6, 43.6, 45.3, 47.2, 56.5, 75.0, 123.3, 124.5, 125.9, 126.0, 126.5, 127.1, 127.4, 127.8, 127.9, 128.4, 128.5, 128.8, 132.3, 135.0, 136.0, 136.2, 137.6, 138.5, 138.7, 144.3, 202.0, 206.4.

1-[5-Benzoyl-4,6-*bis*-(3-chlorophenyl)-2-hydroxy-2-phenylcyclohexyl]-3-(3-chloro phenyl)propanone (3f): White solid, yield: 94%, 242 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.23-2.27 (d, 1H, *J* = 12 Hz), 2.41-2.50 (t, 1H), 4.03-4.19 (m, 3H), 4.45-4.49 (t, 1H), 5.40 (s, OH), 6.67-6-69 (d, 1H, *J* = 6 Hz), 6.73-6.78 (t, 3H), 6.97-7.02 (m, 4H), 7.07-7.11 (m, 6H), 7.20-7.34 (m, 9H), 7.54-7.56 (d, 2H, *J* = 6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 43.2, 45.9, 47.8, 56.2, 56.4, 74.5, 124.7, 126.6, 127.0, 127.1, 127.2, 127.7, 127.8, 127.9, 128.2, 128.3, 128.6, 129.4, 129.6, 132.3, 132.4, 133.0, 134.0, 134.2, 138.0, 138.6, 140.7, 144.1, 145.5. 202.5, 206.5.

1-[5-Benzoyl-4-(3-chloro-phenyl)-2-hydroxy-2-phenyl-6-p-tolyl-cyclohexyl]-3-*p*-tolyl-propenone (3g): White solid, yield: 96%, 248 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz, δ ppm): 2.18 (s, -CH_3), 2.22 (s, -CH_3), 2.26-2.27 (d, 1H, *J*=3Hz), 2.40-2.49 (t, 1H), 3.99-4.23 (m, 3H), 4.45-4.49 (d, 1H, *J* = 12 Hz), 5.39 (s, OH), 6.67-6-70 (d, 1H, *J* = 9 Hz), 6.73-6.78 (t, 2H), 6.96-7.04 (m, 5H), 7.07-7.14 (m, 8H), 7.18-7.34 (m, 6H), 7.54-7.57 (d, 2H, *J* = 9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz, δ ppm): 21.3, 22.5, 43.5, 46.2, 48.3, 56.4, 56.6, 75.6, 105.9, 121.0, 125.1, 127.0, 127.4, 127.5, 127.6, 127.8, 128.1, 128.2, 128.7, 129.9, 130.1, 132.7, 133.4, 134.4, 134.6, 138.2, 138.8, 141.0, 144.4, 145.9, 147.3, 203.0, 207.0.

RESULTS AND DISCUSSION

This work has explored the reaction of non-toxic environmentally benign reaction of 1,3,5-triphenyl-pentane-1,5-dione (**1**) and 1,5-diphenyl-penta-1,4-dien-3-one (**2**) as a starting compound. In order to achieve suitable conditions for the synthesis of compounds (**3**), the reaction was optimized with the reaction of equimolar amount of diketone **1** and dibenzylidene acetone **2** in presence of NaOEt followed by grinding at room temperature and heating for 5 min till the disappearance of substrate as monitored by TLC. The reaction mixture was then worked up with water, the insoluble solid was collected and recrystallized from ethanol to furnish a white solid of **3** good yield (**Scheme-I**). Under the optimized reaction conditions, several electron-releasing and electron-withdrawing groups substituted penta-substituted cyclohexanol **3** were synthesized with the yields ranging between 92 to 96%. All mentioned reactions proceeded smoothly to give corresponding product **3** in excellent yields and accommodated different functional groups also. It is pertinent to note that all the products **3** generated from diketone and dibenzylideneacetone had the same regiochemistry.

Further, various control experiments revealed that the basicity on the reaction medium played an important role in the formation of final products as well as yields. To examine the effects of different bases on the reaction, several bases including KOH, NaOEt, NaOMe, piperidine, diethylamine and triethylamine were applied to the reaction of diketones **1** with dibenzyliene acetone **2** under solid state condition. The observed results are outlined in Table-1. Some catalysts such as Et_3N had no effect on the reaction. However, inorganic bases such as NaOH or KOH to give good yield. The highest yield of **3** was obtained in the presence of NaOEt.

TABLE-1
SCREENING OF VARIOUS BASES FOR THE SYNTHESIS OF **3a**

Entry	Catalyst	Time (min)	Yield (%)
1	NaOH	5	78
2	KOH	5	75
3	NaOEt	3	94
4	NaOMe	4	89
5	Piperidine	10	35
6	Et_2NH	10	30
7	Et_3N	60	–

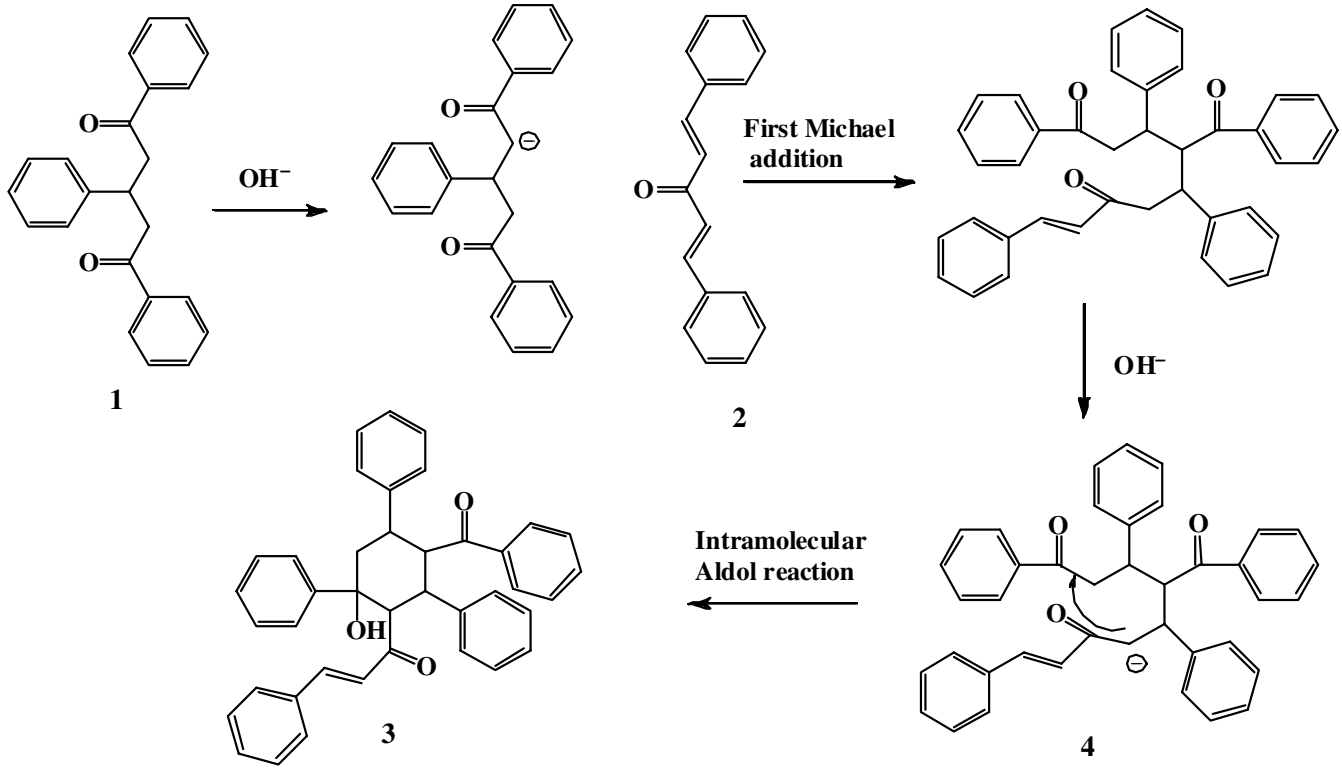
The structure of all the products **3a-g** were unambiguously determined from ^{1}H NMR and ^{13}C NMR spectral studies. In ^{1}H NMR spectrum of compound **3f**, the proton of hydroxyl gave a broad singlet at δ 5.40 ppm. Two of the doublets appear at δ 2.23-2.27 and 4.45-4.49 ppm with *J* = 12Hz is a cyclohexanol ring protons. Also, one triplet at δ 2.41-2.49 and multiplet at δ 4.03-4.19 ppm clearly explains the cyclohexanol ring protons. The five aromatic ring protons appear between δ 6.67 to 7.56 ppm. On the other hand, ^{13}C NMR spectrum of compound **3f** showed the characteristic signals at δ 202.5 and 206.5 ppm assigned for two carbonyl carbon. The cyclohexanol ring six carbons appear at δ 43.2, 45.9, 47.8, 56.2, 56.4 and 74.5 ppm. The five aromatic ring carbons appear between 124.7 to 145.5 ppm. Two of the unsaturated carbons included the aromatic regions.

The assignments of the significant IR spectral bands of product **3a-g** are presented in Table-2. The IR spectrum of compound **3a** shows a broad band at 3431.27 cm^{-1}, which are due to the stretching vibrations of the -OH group. In IR spectra, the presence of two -C=O stretching frequency around 1601 and 1665 cm^{-1} conformed the product **3a-g** contain two different environmental -C=O groups.

TABLE-2
IR SPECTRAL STUDIES OF 1-(5-BENZOYL-2-HYDROXY-2,4,6-TRIPHENYL-CYCLOHEXYL)-3-PHENYL-PROPENONE

Product	IR region (cm^{-1})	
	ν(OH)	ν(C=O)
3a	3431.27	1601.32, 1665.14
3b	3443.27	1639.83, 1667.22
3c	3447.60	1605.66, 1667.50
3d	3424.28	1643.41, 1663.13
3e	3438.58	1597.26, 1668.88

Mechanism: The proposed mechanism of the cascade reaction is depicted in **Scheme-II**. Initially, 1,5-diketone **1** undergoes an enolation and subsequent addition to dibenzylidene acetone **2** to form triketone as an intermediate. Later, this triketone intermediate transform to generate a carbanion for involving intramolecular aldol reaction to form final product **3**.



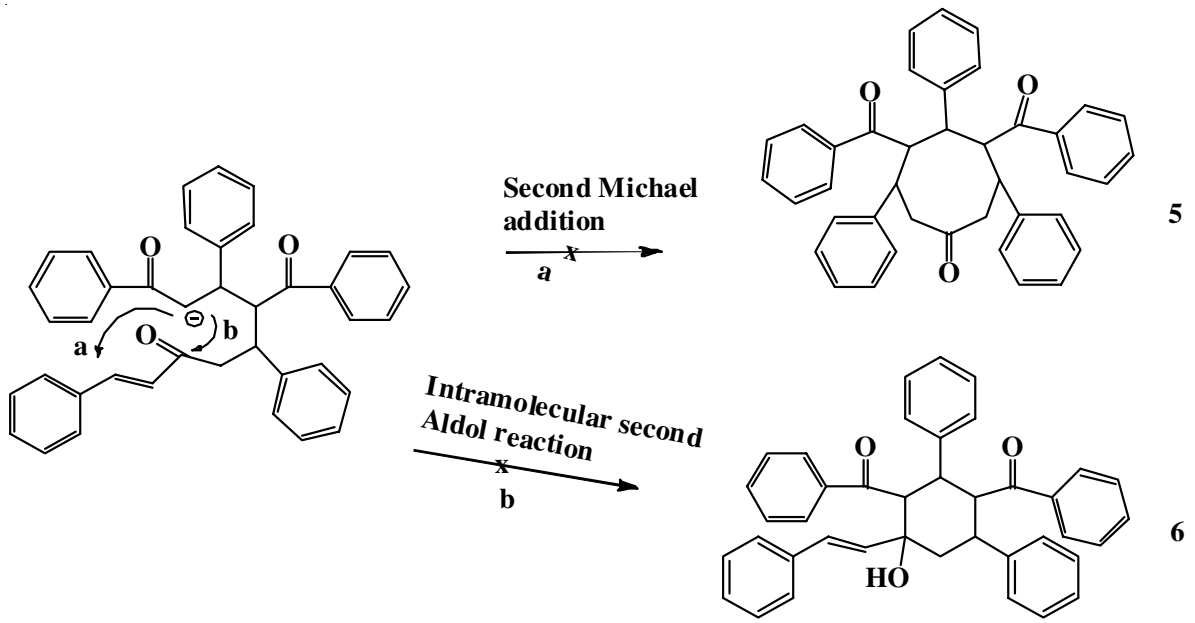
Scheme-II: A possible proposed mechanism for the formation of **3**

Regioselectivity: In above mechanism, the proposed triketone intermediate has two active methylene centres which is close to unsaturated ketone methylene to involve the intramolecular aldol reaction to form product **3**. Another methylene group two possible way to form products **5** and **6**, but do not form the products **5** and **6** as explained in **Scheme-III**.

Biological activities: The antimicrobial properties of five selective product **3** was evaluated against Gram positive and Gram negative bacterial strains. The antibacterial activity of synthesized compound **3** against bacteria is significantly rolled. The antibacterial activity of test compound are expressed as the zone of inhibition and summarized in Table-3.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.



Scheme-III: A possible route for the formation of products of **5** and **6**

TABLE-3
ANTIBACTERIAL STUDY OF COMPOUND **3**

Compound	Gram-positive bacteria (*S. aureus*)	Gram-negative bacteria (*P. aeruginosa*)
3a	11	11
3b	12	09
3c	11	08
3e	12	09
3f	09	08
Control (Amikacin)	28	22

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