International Journal of Enhanced Research in Science, Technology & Engineering
ISSN: 2319-7463, Vol. 4 Issue 9, September-2015

Synthesis of Some Novel α, β–Unsaturated Ketones and their Reactions with Some Compounds Containing Acidic Hydrogen Atom

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ABSTRACT

The present research work describes the synthesis of new heterocyclic compounds and cyclohexenone derivatives using 4-(benzylthio) acetophenone(1) and 4-(benzylsulfonyl) acetophenone(2) as a starting material. Compounds (1, 2) allowed to react with benzaldehyde to give the corresponding new chalcones (3, 4). The latter compounds reacted with guanidine hydrochloride, urea, thiourea, ethylacetoacetate, acetyl acetone and dibenzyl ketone to yield2-aminopyrimidine, pyrimidine-2-ones, pyrimidine-2-thiones and cyclohexenone derivatives (5, 6), (7, 8), (9, 10) and (11-16) respectively. The characterization of the resulting products were confirmed by UV-Visible, FTIR and ^{1}H-NMR analyses.

Keywords: New chalcones, 4-(benzylthio) acetophenone, 4-(benzylsulfonyl) acetophenone, aminopyrimidine, pyrimidine derivatives, cyclohexenone derivatives.

INTRODUCTION

Chalcones, one of the major classes of natural products with widespread occurrence in fruits, vegetables, spices and soy based foodstuff, have been reported to possess several biological activities such as anti-inflammatory[1], antibacterial [2], anti-fungal[3], and anti-tumor [4],antioxidant [5] and antimalarial activities[6].In addition of being used in pharmaceutical industries, chalcones also find wide applications in dyes [7]. Apart from being biologically important compounds, chalcone derivatives show non-linear optical (NLO) properties with excellent blue light transmittance and good crystallizability [8].An important feature of chalcones is their ability to act as an intermediate for the synthesis of biologically active heterocyclic compounds such as, pyrimidine and cyclohexenone derivatives [9]. Moreover, it has been established that introduction of thiophenyl group in strategic position of many molecules altered the biological activity considerably [10-12]. Keeping this view, it has been planned to synthesize the newpyrimidine, pyrimidine thiones and cyclohexenone containing benzyl thio phenyl or benzyl sulfone phenyl groups in position (6 or 4) and phenyl in position (4 or 6) of many molecules.

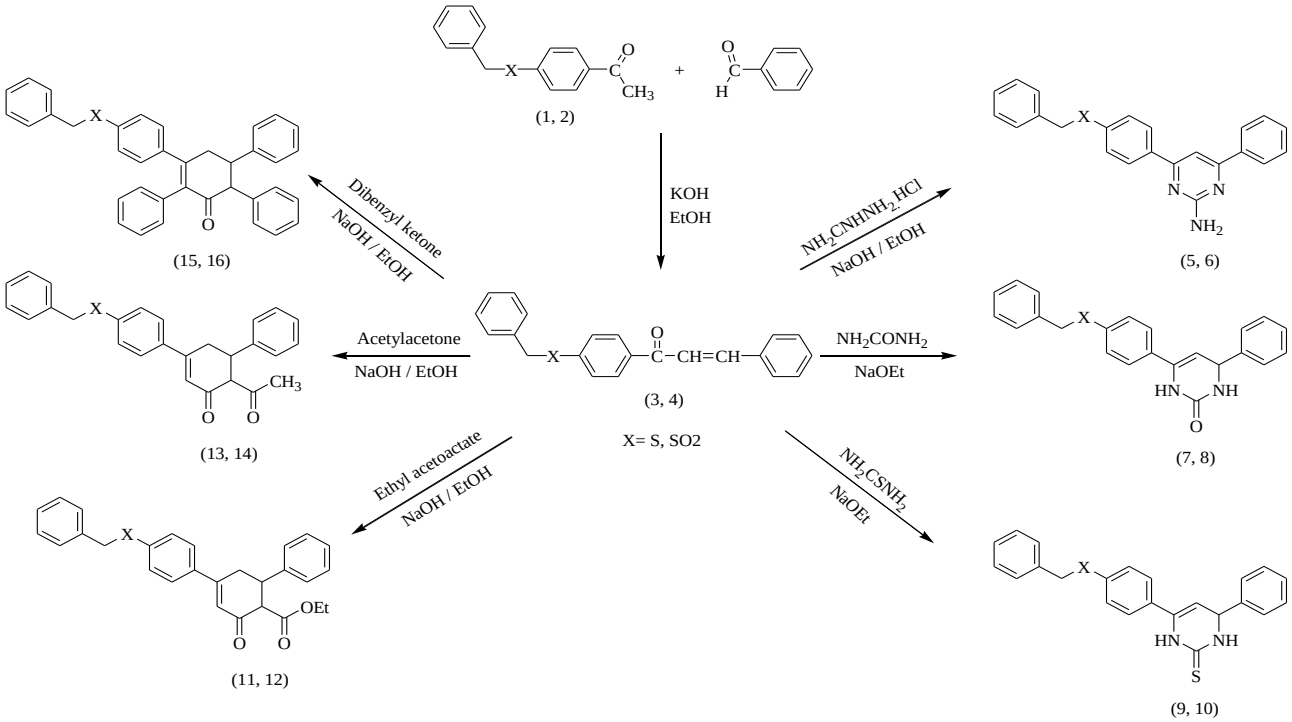
Heterocyclic ring containing nitrogen such as pyrimidine is a promising structural moiety for drug design[13] and present among the three isomeric diazines (uracil, thymine and cytosine which are the three important constituents of nucleic acids). In addition, pyrimidine ring is also found in vitamins (vitamin B, thiamine, riboflavin and folic acid) [14]. Pyrimidine derivatives form a component in a number of useful drugs and are associated with many biological and therapeutically activities [13]. Pyrimidine derivatives have been reported as antibacterial, antifungal [15], analgesic, anti-inflammatory[16], anti-HIV [17], anti-tubercular [18], anti-tumor [19], anti-neoplastic [20], anti-malarial [21],diuretic [22], activities. Pyrimidine compounds are also used as hypnotic drugs for the nervous system [23], calcium-sensing receptor antagonists [24] and also for antagonists of the human A2A adenosine receptor [25].

Michael addition of ethylacetoacetate to chalcone yields 4, 6-phenyl-2-oxo-cyclohex-3-ene-1-carboxylate derivatives. Cyclohexenone derivatives are well known lead molecules for the treatment of inflammation and autoimmune diseases [26]. Several reports have pointed out the importance of cyclohexenones for antimicrobial, antitubercular [27], antibacterial [28], anticancer activities [29]. Based on the above observation, herein I reported the synthesis of some newchalcones, aminopyrimidine, pyrimidine one, pyrimidine thione and cyclohexenone.

RESULT AND DISCUSSION

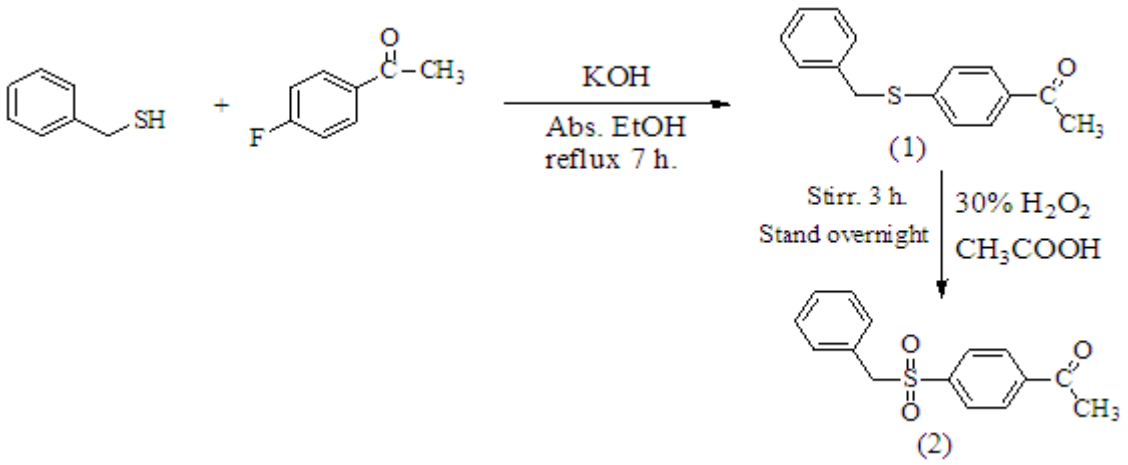
Chalcones possess high reactivity due to the presence of the carbonyl group conjugated with the double bond. This instance suggests that the nucleophiles can react with chalcones at both the carbonyl group and the double bond. The

reactions with binucleophiles leading to the broad range of cyclized compounds are of particular interest as shown in the general scheme.



General scheme

4-(benzylthio) acetophenone (1) was synthesized in 96 % yield through nucleophilic aromatic substitution reaction SNAr, (addition–elimination mechanism)according to a procedure outlined by Mulder et al.[30],as shown from the reaction of benzyl thioland 4-fluoroacetophenone in the presence of KOH. Treatment of (1) with hydrogen peroxide in acidic medium gave the desired products;4-(benzylsulfonyl) acetophenone (2) in high yields (91 %).



4-benzylsulfanyl chalcone (3) and 4-benzylsulfonyl chalcone (4)was synthesized by the base-catalyzed Claisen–Schmidtcondensation of 4-(benzylthio) acetophenone (1) or 4-(benzylsulfonyl) acetophenone(2) and benzaldehyde (general scheme).

A novelseries of compounds (3-16) were synthesized and characterized. Six membered heterocyclic ring systems represented with aminopyrimidine derivative (5 and 6) have been prepared through the reaction of 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) with guanidine hydrochloride in basic medium to give the desired compound via the formation of 1,4- addition product that followed by intermolecular cyclization affording the final product.

Also, the formation of pyrimidine ones (7 and 8) and pyrimidine thiones (9 and 10)as another six membered heterocyclic derivatives through the reaction between urea or thiourea and 4-benzylsulfanyl or 4-benzylsulfonyl

chalcone (3, 4) in basic medium. The reaction proceeded through the formation of the conjugate addition product which was cyclized to give the final compounds.

The reaction of chalcones with ethyl acetoacetate is known to lead to three structurally diverse types of compounds, depending on the experimental conditions employed. The catalyst plays a major role in directing the reaction to different end products. While 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) treated with ethyl acetoacetate in presence of basic catalyst, the intermediate Michael addition product formed which in turn converted into cyclohexenones(11 and 12) through the intermolecular cyclocondensation of the methyl group originating from ethyl acetoacetate and the ketone function of the initial chalcone [31,32]. Similarly, acetyl acetone and dibenzyl ketone reacted with 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) to afford cyclohexenone derivatives (13 and 14)and (15 and 16)respectively (general scheme). The structures of the newly synthesized compounds were confirmed by UV-Visible, I.R and NMR spectrometry. These data, detailed in ''Experimental'', are consistent with the suggested structures.

EXPERIMENTAL

GENERAL

Melting points were determined on an Electrothermal IA 9300 Digital – Series (1998) apparatus (uncorrected).I.R spectra were recorded using a Bruker, FT-IR Spectrophotometer Tensor 27, (Germany) using KBr discs. U.V spectra were recorded on a Shimadzu UV-1800, UV-Visible spectrophotometer (Japan) using chloroform as a solvent. ^{1}H-NMR spectra were recorded on a Bruker advance 300 MHz (Germany), using TMS as internal standard andDMSO-d_6 as a solvent. In that order with the use of the following abbreviations: s-singlet, d-doublet,t-triplet, q-quartet, and m-multiple. Chemical shifts are expressed in δ units.

SYNTHESIS OF 4-(BENZYLTHIO) ACETOPHENONE (1). GENERAL PROCEDURE [30]

Potassium hydroxide (2.24 g, 40mmol) was added to a solution of benzyl thiol (4.96 g, 40 mmol) in (15.0 mL) of absolute ethanol. The mixture was heated to reflux until the KOH had completely dissolved and was then cooled to room temperature. A solution of 4-fluoroacetophenone (5.52 g, 40 mmol) in (15.0 mL) of absolute ethanol was then added drop-wise and the mixture was heated to reflux for 7 h. When cooled to room temperature, the precipitate was filtered and washed with water and recrystallized from ethyl acetateto afford the desired product as white needles. Yield: 9.32 g, 96 %; m.p.112–114 ^{o}C (lit. 110–112 ^{o}C) [30]. (U.V, λ maxnm, $CHCl_3$): 242, 308. FT-IR (KBr, ν cm^{-1}): 1672 (C=O), 1578 (C ⎓ C). ^{1}H-NMR (DMSO-d_6, δ ppm): 3.26 (s, 3H), 4.32 (s, 2H,CH_2), 7.30-7.88(m, 9H).

SYNTHESIS OF 4-(BENZYLSULFONYL) ACETOPHENONE (2)

4-(benzylthio) acetophenone(1)(2.19 g, 8 mmol) was dissolved in 40 mL of acetic acid. To this solution was added (8.0 mL) of 30% aqueous hydrogen peroxide drop-wise with stirring. After (2) hours of stirring the mixture and left overnight at room temperature, a white precipitate had formed. The reaction mixture was poured into (40 mL) of ice water, then the solid was filtered and washed with water. Yield: 2.06 g, 91 %; m.p.176–178^{o}C.(U.V, λ maxnm, $CHCl_3$): 250, 284. FT-IR (KBr, ν cm^{-1}): 1678 (C=O), 1314, 1149 (-SO_2-).

SYNTHESIS OF 1-(4-BENZYLSULFANYLPHENYL)-3-PHENYL PROPENONE (3) & 1-(4-BENZYLSULFONYLPHENYL)-3-PHENYL PROPENONE (4).GENERAL PROCEDURE [33]

Equimolar amounts of 4-(benzylthio) acetophenone (1) or 4-(benzylsulfonyl) acetophenone (2) (7 mmole) and benzaldehyde (0.74 g, 7 mmole) were dissolved in(25mL) ethanol . The mixture was stirred and treated with an aqueous solution ofpotassium hydroxide (0.39 g. in 3 mL of water). Addition of the base was carried outduring (20) minutes. Stirring was continued for (3) hours. The mixture was kept overnight at room temperature. The resulting solid was filtered off and washed thoroughly with water, then dried and recrystallized from ethanol to afford the titled compounds (3) and recrystallized from ethyl acetate to afford the compound (4).

1-(4-BENZYLSULFANYLPHENYL)-3-PHENYL PROPENONE (3)

Yield: 2.15 g, 93 %; m.p.126–128^{o}C. (U.V, λ maxnm, $CHCl_3$): 242, 334. FT-IR (KBr, ν cm^{-1}): 1653 (C=O), 1585 (C=C). ^{1}H-NMR (DMSO-d_6, δ ppm): 4.35 (s, 2H,CH_2), 7.80 (d, 1H, H_α), 7.97 (d, 1H, H_β), 7.35-8.11 (m, 14H,Ar-H).

1-(4-BENZYLSULFONYLPHENYL)-3-PHENYL PROPENONE (4)

Yield: 2.33 g, 92 %; m.p. 208–210^{o}C. (U.V, λ maxnm, $CHCl_3$): 248, 318.IR (KBr, ν cm^{-1}): 1655 (C=O), 1597 (C=C), 1338, 1146 (-SO_2-).^{1}H-NMR (DMSO-d_6, δ ppm): 4.72 (s, 2H,CH_2),7.84 (d, 1H, H_α), 8.02 (d, 1H, H_β), 7.21-8.28 (m, 14H,Ar-H).

SYNTHESIS OF 2- AMINO-4-(4-BENZYLSULFANYL PHENYL)-6-PHENYL PYRIMIDINE (5) & 2-AMINO-4-(4-BENZYLSULFONYL PHENYL)-6-PHENYL PYRIMIDINE (6). GENERAL PROCEDURE [34]

In a (100 mL) two necked round bottomed flask equipped with a dropping funnel(which charged with a solution of sodium hydroxide 0.3 g. in 5 mL of water), a mixture of guanidinehydro chloride (2.4 mmole) and4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) (2.4 mmole), in (15mL) of ethanol was placed and refluxed, while the solution of sodium hydroxide was added portion wise during (2)hours. Refluxing was continued for a further (10)hours. The reaction mixture was then diluted with water and leftover rnight. The resulting product was filtered off and washed with (20 mL) of amixture of water / ethanol (1 : 1) then recrystallized from benzene to give compound (5) or the reaction mixture was cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from ethanol to give (6).

2- AMINO-4-(4-BENZYLSULFANYL PHENYL)-6-PHENYL PYRIMIDINE (5).

Yield: 20%; m.p. 155-157^{o}C. (U.V, λ maxnm, $CHCl_3$): 246, 340. FT-IR (KBr, ν cm^{-1}): 3208, 3329 (NH_2), 1638 (C=N). ^{1}H-NMR (DMSO-d_6, δ ppm): 4.31 (s, 2H,CH_2), 6.63 (s, 2H, NH_2) 7.21-8.05 (m, 15H, Ar-H).

2- AMINO-4-(4-BENZYLSULFONYL PHENYL)-6-PHENYL PYRIMIDINE (6).

Yield: 18%; m.p. >260^{o}C. (U.V, λ maxnm, $CHCl_3$): 248, 332. FT-IR (KBr, ν cm^{-1}): 3211, 3335 (NH_2), 1679 (C=N), 1149, 1314 (-SO_2-).

SYNTHESIS OF 6-(4-BENZYLSULFANYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H-PYRIMIDIN-2-ONE (7) & 6-(4-BENZYLSULFONYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H-PYRIMIDIN-2-ONE (8). GENERAL PROCEDURE [35]

A mixture of urea (2.4 mmole) and 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) (2.4 mmole) was refluxed for (10) hours in presence of sodium ethoxide solution (2.4 mmole of sodium metal in 15 mL of absolute ethanol). The reaction mixture was cooled and left to overnight. The precipitated product was filtered off andwashed with ethanol to give the titled compound without further purification.

6-(4-BENZYLSULFANYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H- PYRIMIDIN-2-ONE (7)

Yield: 19 %; m.p. 106-108^{o}C. (U.V, λ max nm, $CHCl_3$): 246, 312. FT-IR (KBr, ν cm^{-1}): 3286 (NH), 1681 (C=O), 1586 (C=C). ^{1}H-NMR (DMSO-d_6, δ ppm): 4.28 (s, 2H, CH_2), 5.07 (d, 1H, C_4-$H_{pyrimidine}$),5.28 (d, 1H, C_5-$H_{pyrimidine}$), 6.91-7.26 (m, 14H, Ar-H), 8.07 (s, 1H, NH).

6-(4-BENZYLSULFONYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H- PYRIMIDIN-2-ONE (8).

Yield: 21 %; m.p. 182-184^{o}C. (U.V, λ max nm, $CHCl_3$): 250, 308. FT-IR (KBr, ν cm^{-1}): 3268 (NH), 1674 (C=O), 1601 (C=C), 1347, 1151 (-SO_2-).

SYNTHESIS OF 6-(4-BENZYLSULFANYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H- PYRIMIDIN-2-THIONE (9)& 6-(4-BENZYLSULFONYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H- PYRIMIDIN-2-THIONE (10).GENERAL PROCEDURE [35]

A mixture of thiourea (2.4 mmole) and 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) (2.4 mmole) was refluxed for (2-4) hours in presence of sodium ethoxide solution (2.4 mmole of sodium metal in 15 mL of absolute ethanol), then left to cool. The precipitated product was filtered off andwashed with ethanol to give the titled compound without further purification.

6-(4-BENZYLSULFANYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H- PYRIMIDIN-2-THIONE (9).

Yield: 75 %; m.p. 224-226^{o}C. (U.V, λ max nm, $CHCl_3$): 244, 288. FT-IR (KBr, ν cm^{-1}): 3179 (NH), 1671 (C=C), 1568 (C=C), 1184 (C=S). ^{1}H-NMR (DMSO-d_6, δ ppm): 4.22 (s, 2H, CH_2), 5.02 (d, 1H, C_4-$H_{pyrimidine}$),5.28 (d, 1H, C_5-$H_{pyrimidine}$), 7.30-7.42 (m, 14H, Ar-H), 9.01 (s, 1H, NH).

6-(4-BENZYLSULFONYL PHENYL)-4-PHENYL-3, 4-DIHYDRO-1H- PYRIMIDIN-2-THIONE (10).

Yield: 40%; m.p. 260^{o}C decomp. (U.V, λ max nm, $CHCl_3$): 256, 322. FT-IR (KBr, ν cm^{-1}): 3238 (NH), 1678 (C=C), 1597 (C=C), 1306, 1149 (-SO_2-), 1197 (C=S).

SYNTHESIS OF ETHYL-4-(4-BENZYLSULFANYL PHENYL)-6-PHENYL-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATE (11)&ETHYL-4-(4-BENZYLSULFONYL PHENYL)-6-PHENYL-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATE (12). GENERAL PROCEDURE [36]

A mixture 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) (2.4 mmole)and ethyl acetoacetate (2.4 mmole) in (15 mL) of ethanol was refluxed for (2-4) hours in the presence of (0.4 mL) 10% NaOH. The reaction mixturewas cooled to room temperature and the solid product obtained was filtered and recrystallized from ethanol.

ETHYL-4-(4-BENZYLSULFANYLPHENYL)-6-PHENYL-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATE (11).

Yield: 77%; m.p. 136-138^{o}C. (U.V, λ max nm, $CHCl_3$): 246, 336. FT-IR (KBr, ν cm^{-1}): 1732 (C=O) ester, 1644 (C=O) cyclic, 1585 (C=C). ^{1}H-NMR (DMSO-d_6, δ ppm): 0.88 (t, 3H, CH_3), 2.46 (m, 2H, CH_2-CH-Ph),3.04 (d, 1H, COCHCO), 3.32(m, 1H, CH2-CH-ph), 3.93 (q, 2H, CH_2-CH_3),4.28 (s, 2H, -S-CH_2-ph), 6.42 (s, 1H, =CH-CO), 7.30-7.70 (m, 14H, Ar-H).

ETHYL-4-(4-BENZYLSULFONYL PHENYL)-6-PHENYL-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATE (12).

Yield: 79%; m.p. 207-209^{o}C. (U.V, λ max nm, $CHCl_3$): 244, 284. FT-IR (KBr, ν cm^{-1}): 1737 (C=O) ester, 1663(C=O) cyclic, 1595 (C=C)1315, 1149 (-SO_2-). ^{1}H-NMR (DMSO-d_6, δ ppm): 0.89 (t, 3H, CH_3), 2.46 (m, 2H, CH_2-CH-Ph),3.05-3.12 (d, 1H, COCHCO), 3.40 (m, 1H, CH2-CH-ph), 3.94 (q, 2H, CH_2-CH_3), 4.68 (s, 2H, -S-CH_2-ph), 6.61 (s, 1H, =CH-CO), 7.19-7.82 (m, 14H, Ar-H).

SYNTHESIS OF 6-ACETYL-3-(4-BENZYLSULFANYL PHENYL)-5-PHENYLCYCLOHEX-2-EN-1-ONE (13)&6-ACETYL-3-(4-BENZYLSULFONYL PHENYL)-5-PHENYL CYCLOHEX-2-EN-1-ONE (14). GENERAL PROCEDURE [36]

A mixture of 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) (2.4 mmole)and acetyl acetone (2.4 mmole) in ethanol (15 mL) wasrefluxed for (4) hours in the presence of (0.4 mL) 10% NaOH. The reaction mixture was cooled to room temperature andthe solid product obtained was filtered and recrystallized from ethanol to get yellow crystals.

6-ACETYL-3-(4-BENZYLSULFANYL PHENYL)-5-PHENYL CYCLOHEX-2-EN-1-ONE (13).

Yield: 60%; m.p. 104-106^{o}C. (U.V, λ max nm, $CHCl_3$): 244, 336. FT-IR (KBr, ν cm^{-1}): 1655 (C=O) cyclic, 1626 (C=O) ketone, 1587 (C=C). ^{1}H-NMR (DMSO-d_6, δ ppm):1.91 (s, 3H, CH_3), 2.43 (m, 2H, CH_2-CH-Ph),3.25(m, 1H,CH2-CH-ph), 4.28 (s, 2H, -S-CH_2-ph) 4.36 (d, 1H,COCHCO),6.45 (s, 1H, =CH-CO), 7.30-7.82 (m, 14H, Ar-H).

6-ACETYL-3-(4-BENZYLSULFONYL PHENYL)-5-PHENYL CYCLOHEX-2-EN-1-ONE (14).

Yield: 40%; m.p. 144-146^{o}C. (U.V, λ max nm, $CHCl_3$): 248, 284. FT-IR (KBr, ν cm^{-1}): 1664 (C=O) cyclic, 1635(C=O) ketone, 1597 (C=C), 1346, 1151 (-SO_2-). ^{1}H-NMR (DMSO-d_6, δ ppm):1.94 (s, 3H, CH_3), 2.45(m, 2H, CH_2-CH-Ph),3.27(m, 1H, CH2-CH-ph), 4.32 (s, 2H, -S-CH_2-ph) 4.67 (d, 1H,COCHCO), 6.49 (s, 1H, =CH-CO), 7.20-7.82 (m, 14H, Ar-H).

SYNTHESIS OF 3-(4-BENZYLSULFANYL PHENYL)-2,5,6-TRIPHENYL CYCLOHEX-2-EN-1-ONE (15)&3-(4-BENZYLSULFONYL PHENYL)-2,5,6-TRIPHENYL CYCLOHEX-2-EN-1-ONE (16).GENERAL PROCEDURE [36]

A mixture of 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) (2.4 mmole)and dibenzyl ketone (2.4 mmole) in ethanol (15 mL) wasrefluxed for (1) hour in the presence of (0.8 mL) 10% NaOH. The reaction mixture was cooled to room temperature and the precipitated product was filtered off andwashed with ethanol to give the titled compound without further purification.

3-(4-BENZYLSULFANYL PHENYL)-2, 5, 6-TRIPHENYL CYCLOHEX-2-EN-1-ONE (15).

Yield: 20%; m.p. 207-209^{o}C. (U.V, λ max nm, $CHCl_3$): 244, 308. FT-IR (KBr, ν cm^{-1}): 1677 (C=O), 1591(C=C). ^{1}H-NMR (DMSO-d_6, δ ppm):2.44(m, 2H, CH_2-CH-Ph),3.26(m, 1H, CH2-CH-ph), 4.21 (d, 1H,COCHph), 4.28 (s, 2H, -S-CH_2-ph), 6.77-7.56 (m, 24H, Ar-H).

3-(4-BENZYLSULFONYL PHENYL)-2, 5, 6-TRIPHENYL CYCLOHEX-2-EN-1-ONE (16).

Yield: 26%; m.p. 204-206°C. (U.V, λ max nm, $CHCl_3$): 246, 318. FT-IR (KBr, ν cm^{-1}): 1657 (C=O), 1598 (C=C), 1338, 1147 (-SO_2-). ^{1}H-NMR (DMSO-d_6, δ ppm): 2.46(m, 2H, CH_2-CH-Ph),3.27(m, 1H, CH2-CH-ph), 4.14 (d, 1H,COCHph), 4.25 (s, 2H, -S-CH_2-ph), 7.09-7.91 (m, 24H, Ar-H).

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