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Synthesis of Some Novel Heterocyclic Compounds

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ABSTRACT

In this work, synthesis of some new heterocyclic compounds (5-18), namely pyrazolines (5- 14), isoxazolines (15 and 16), oxiranes (17 and 18), derivatives by the reaction of new chalcones (3 and 4) with hydrazine hydrate, phenyl hydrazine, semicarbazide hydrochloride, thiosemicarbazide, hydroxylaminehydrochloride, and hydrogen peroxide. The structures of all synthesized compounds were confirmed by UV-Visible, I.R and ^{1}H-NMRspectra.

Keywords: Chalcones, Pyrazolines, Isoxazolines, Oxiranes, Epoxides.

INTRODUCTION

Heterocyclic compounds are very widely distributed in nature, and are essential to life in various ways. Particularly these compounds are important because of the wide variety of physiological activities associated with this class of substances. Heterocyclic rings are present in several compounds, e. g, most of the members of vitamin B complex, antibiotics, chlorophyll, haemin, other plant pigments, amino acids and proteins, drugs, dye stuffs, enzymes, the genetic material DNA etc.[1].

Pyrazolines are important five-member heterocyclic compounds containing nitrogen. Numerous pyrazoline derivatives possess importantpharmacological activities and therefore they are useful materials in drug research, which stimulated the research activity in this field. They have wide range of biological activities, such as antimicrobial [2], anti-inflammatory [3], antipyretic [4],antitumor [5], ntimyco bacterial [6],antidepressant [7], anticancer [8], antiviral [9], antitubercular [10], antihypertensive [11], activities.

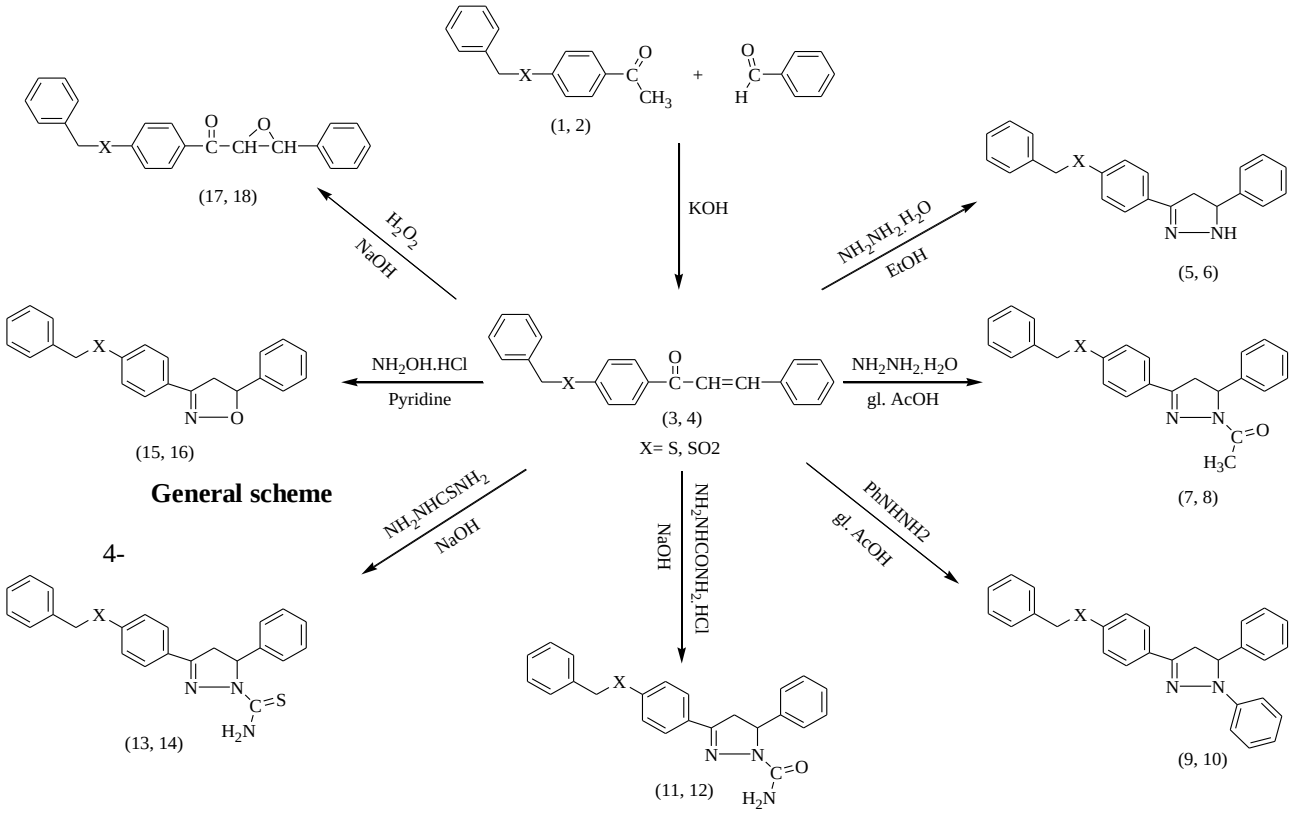
Isoxazoline derivatives are an important class of heterocyclic pharmaceuticals and bioactive natural products because of their significant and wide spectrum of biological activities such as antibacterial**,** antifungal, [12], antidepressant, antianxiety [13], antioxidant, cytotoxicity [14], anti-inflammatory and analgesic[15], antiviral [16], antitubercular [17], anticonvulsant [18], activities.

Epoxy carbonyl compounds are very important synthetic intermediates[19], and can serve as versatile precursor in synthesis of many natural products and drug molecules [20], which are usually prepared via epoxidation of □□□−unsaturated ketones [21].

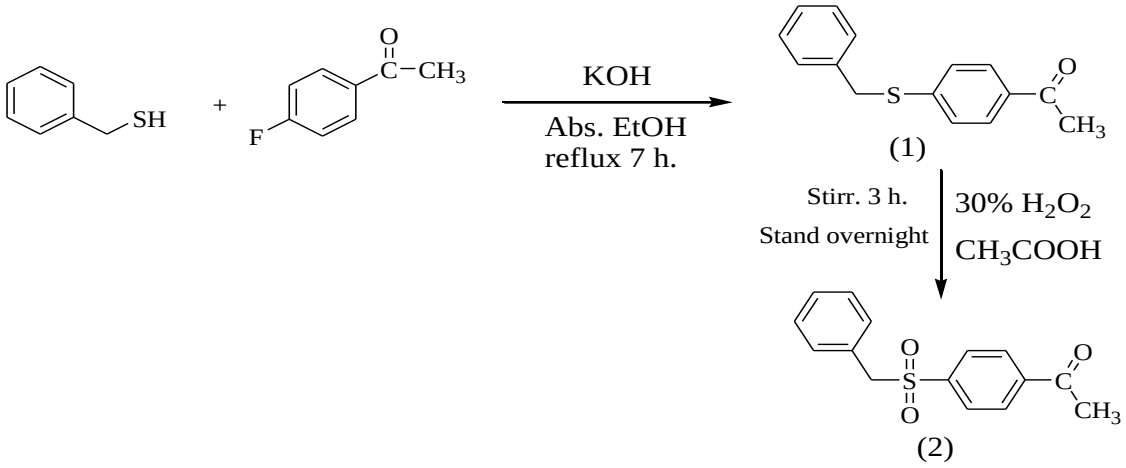
Encouraged by these observations it is worthwhile to synthesize some new α, β-unsaturated ketones and studying their reactivitytoward different nucleophiles to synthesize various heterocyclic compounds namelypyrazolines, isoxazolines and epoxidesas shown in the generalscheme.

RESULT AND DISCUSSION

In this research some heterocyclic compounds have been synthesizedvia the key intermediates 4-benzylsulfanyl chalcone (3) and 4-benzylsulfonyl chalcone (4)with different nucleophiles as shown in the general scheme.



(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.[22], 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–Schmidt condensation of 4-(benzylthio) acetophenone (1) or 4-(benzylsulfonyl) acetophenone(2) and benzaldehydein ethanol and in the presence of aqueous potassium hydroxide (general scheme).

According to the scheme the first rout involve the formation of pyrazoline derivatives (5 and 6) by reaction of chalcones (3 and 4)with hydrazine hydrateunder reflux in absolute ethanol. Whereas reaction of chalcones (3 and 4)with hydrazine hydrateunder reflux in glacial acetic acid afforded the corresponding N-acetyl pyrazoline derivatives (7 and 8).Similarly, the reaction between phenyl hydrazine and chalcone will afford pyrazoline derivatives (9 and 10).

The substituted pyrazoline-1-carboxamide derivatives(11 and 12) were synthesized from chalcones with semicarbazide hydrochloride in presence NaOH.The newly synthesized compounds pyrazoline-1-carbothioamide derivatives (13 and 14) were obtained by heating at reflux equimolar amounts of the corresponding α, β-unsaturated ketones and thiosemicarbazide in ethanolic NaOH solution.

Cyclization of chalcones with hydroxylaminehydrochloride in the presence of pyridine afforded isoxazolines derivatives (15 and 16). Epoxidation of chalcones was carried out inmoderate to good yields with aqueous hydrogen peroxide in basic medium in which thereaction proceeded via 1,4- addition to afford the final product (17 and 18). The structures of the newly synthesized compounds were confirmed by UV-Visible, I.R and NMRspectrometry. 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).Infrared spectra were recorded using a Bruker, FT-IR Spectrophotometer Tensor 27, (Germany)using KBr discs. Ultra –Violet spectra were recorded on a Shimadzu UV-1800, UV-Visiblespectrophotometer(Japan) using chloroform as a solvent. Proton 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, and m-multiple. Chemical shifts are expressed in δ units.

SYNTHESIS OF 4-(BENZYLTHIO) ACETOPHENONE (1). GENERAL PROCEDURE [22]

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 untilthe KOH had completely dissolved and was then cooled to room temperature. Asolution of 4-fluoroacetophenone (5.52 g, 40 mmol) in (15.0 mL) of absoluteethanolwas then added drop-wise and the mixture was heated to reflux for 7 h. When cooled to room temperature, theprecipitate was filtered and washed with water and recrystallized from ethyl acetateto afford the desired product, 1, as white needles. Yield: 9.32 g, 96 %; m.p.112–114 ^oC (lit. 110–112 ^oC) [22]. (U.V, λ maxnm, $CHCl_3$): 242, 308.FT-IR (KBr, νcm^{-1}): 1672 (C=O), 1578 (C ⎓ C). ^{1}H-NMR (DMSO-d_6, δ ppm): 3.26 (s, 3H, CH_3), 4.32 (s, 2H,CH_2), 7.30-7.88(m, 9H, Ar-H).

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-wisewith stirring.After (2) hours of stirring the mixtureand 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 [23]

Equimolaramounts of 4-(benzylthio)acetophenone(1) or4-(benzylsulfonyl)acetophenone (2)(7mmole) 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 keptovernight at room temperature. The resulting solid was filtered off and washed thoroughlywith water, then dried and recrystallized from ethanol to afford the titled compounds(3, 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 3-(4-BENZYLSULFANYLPHENYL)-5-PHENYL PYRAZOLINE(5) & 3-(4-BENZYLSULFONYLPHENYL)-5-PHENYL PYRAZOLINE (6). GENERAL PROCEDURE [24]

Amixture of 4-benzylsulfanyl or 4-benzylsulfonyl chalcone (3, 4) (2.0mmole) and hydrazine hydrate (6.0mmole) in ethanol (10mL) was placedand refluxed for (4) hours. The reaction mixture was cooledand left overnight at room temperature. The precipitated product was filtered off and recrystallized from ethanol to give (5 and 6).

3-(4-BENZYLSULFANYLPHENYL)-5-PHENYL PYRAZOLINE (5).

Yield: 55 %; m.p. 74-76^{o}C. (U.V, λ maxnm, $CHCl_3$): 246, 292.IR (KBr, ν cm^{-1}):3222 (NH), 1671 (C=N), 1587 (C=C).

3-(4-BENZYLSULFONYLPHENYL)-5-PHENYL PYRAZOLINE (6).

Yield: 89 %; m.p. 174-176 ^{o}C. (U.V, λ maxnm, $CHCl_3$): 244, 320.IR (KBr, ν cm^{-1}):3339 (NH), 1677 (C=N), 1596 (C=C), 1345, 1149 (-SO_2-).^{1}H-NMR (DMSO-d_6, δ ppm): [3.38 (d, 1H, C_4-H), 3.49 (d, 1H, C_4-H),4.88 (d, 1H, C_5-H), in pyrazoline ring], 4.62 (s, 2H,CH_2), 7.22-7.67 (m, 14H, Ar-H), 8.00 (s, 1H, NH).

SYNTHESIS OF 3-(4-BENZYLSULFANYLPHENYL)-5-PHENYLPYRAZOLINE-1-ETHANONE (7)&3-(4-BENZYLSULFONYLPHENYL)-5-PHENYL PYRAZOLINE-1-ETHANONE (8).GENERAL PROCEDURE [25]

A mixture of 4-benzylsulfanyl chalcone (3) or 4-benzylsulfonyl chalcone (4) (2.0mmole) and hydrazine hydrate (6.0mmole) in glacial acetic acid(10mL) was placed and refluxed for (4) hours. The reaction mixture was cooled and poured into ice-cold water (20 mL). The precipitated product was collected by filtration and purified by recrystallization from ethanol to give (7and 8).

3-(4-BENZYLSULFANYLPHENYL)-5-PHENYL PYRAZOLINE-1-ETHANONE (7).

Yield: 75 %; m.p. 125-127^{o}C. (U.V, λ maxnm, $CHCl_3$): 244, 322.IR (KBr, ν cm^{-1}): 1650 (C=O), 1589 (C=N).^{1}H-NMR (DMSO-d_6, δ ppm):2.25 (s, 3H, CH_3), [3.50 (d, 1H, C_4-H), 3.71 (d, 1H, C_4-H),5.38 (d, 1H, C_5-H), in pyrazoline ring], 4.27 (s, 2H,CH_2), 7.21-7.57 (m, 14H, Ar-H).

3-(4-BENZYLSULFONYLPHENYL)-5-PHENYL PYRAZOLINE-1-ETHANONE (8).

Yield: 74 %; m.p. >250^{o}C. (U.V, λ maxnm, $CHCl_3$): 244, 318.IR (KBr, ν cm^{-1}): 1662 (C=O), 1586 (C=N),1315, 1147 (-SO_2-).^{1}H-NMR (DMSO-d_6, δ ppm):2.29 (s, 3H,CH_3), [3.59 (d, 1H, C_4-H), 3.77 (d, 1H, C_4-H), 5.42 (d, 1H, C_5-H), in pyrazoline ring], 4.67 (s, 2H,CH_2), 7.21-7.85 (m, 14H, Ar-H).

SYNTHESIS OF 3-(4-BENZYLSULFANYLPHENYL)-1, 5-DIPHENYLPYRAZOLINE (9)&3-(4-BENZYLSULFONYLPHENYL)-1, 5-DIPHENYLPYRAZOLINE (10).GENERAL PROCEDURE [25]

A mixture of 4-benzylsulfanyl chalcone (3) or 4-benzylsulfonyl chalcone (4) (2.0mmole) and phenyl hydrazine(4.0mmole) in glacial acetic acid(10mL) was placed and refluxed for (4) hours. The reaction mixture was cooled and poured into ice-cold water (20 mL). The precipitated product was collected by filtration and purified by recrystallization from ethanol to give (9 and 10).

3-(4-BENZYLSULFANYLPHENYL)-1, 5-DIPHENYLPYRAZOLINE (9)

Yield: 90 %; m.p. 148-150^{o}C. (U.V, λ maxnm, $CHCl_3$): 252, 374.IR (KBr, ν cm^{-1}): 1595 (C=N), 1570(C=C).^{1}H-NMR (DMSO-d_6, δ ppm):[3.56 (d, 1H, C_4-H), 3.75 (d, 1H, C_4-H), 5.31(d, 1H, C_5-H), in pyrazoline ring], 4.24 (s, 2H,CH_2), 7.00-7.54 (m, 19H, Ar-H).

3-(4-BENZYLSULFONYLPHENYL)-1, 5-DIPHENYLPYRAZOLINE (10).

Yield: 92 %; m.p. 193-195^{o}C. (U.V, λ maxnm, $CHCl_3$): 254, 398.IR (KBr, ν cm^{-1}): 1591 (C=N), 1567 (C=C),1312, 1124 (-SO_2-).^{1}H-NMR (DMSO-d_6, δ ppm): [3.63 (d, 1H, C_4-H), 3.80 (d, 1H, C_4-H), 5.39(d, 1H, C_5-H), in pyrazoline ring], 4.64 (s, 2H,CH_2), 7.05-7.79 (m, 19H, Ar-H).

SYNTHESIS OF 3-(4-BENZYLSULFANYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOXAMIDE (11)&3-(4-BENZYLSULFONYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOXAMIDE (12).GENERAL PROCEDURE [26]

A mixture of 4-benzylsulfanyl chalcone (3) or 4-benzylsulfonyl chalcone (4) (2.0mmole) and semicarbazide hydrochloride (2.0mmole) in ethanol (10mL), sodium hydroxide (6.0 mmol) in (5 mL) of water was added and refluxed for (4) hours. The reaction mixture was cooled and poured into crushed ice. The precipitated product was filtered off and recrystallized from ethanol to give (11 and 12).

3-(4-BENZYLSULFANYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOXAMIDE (11).

Yield: 44 %; m.p. 192-195°C. (U.V, λ maxnm, $CHCl_3$): 242, 304.IR (KBr, ν cm^{-1}): 3457, 3271(NH_2-), 1672 (C=O), 1585 (C=N). ^{1}H-NMR (DMSO-d_6, δ ppm): [3.63 (d, 1H, C_4-H), 3.74 (d, 1H, C_4-H), 5.25 (d, 1H, C_5-H), in pyrazoline ring], 4.24 (s, 2H,CH_2), 7.27-7.72 (m, 19H, Ar-H), 10.17 (s, 2H, $CONH_2$).

3-(4-BENZYLSULFONYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOXAMIDE (12).

Yield: 26 %; m.p.126-129°C. (U.V, λ maxnm, $CHCl_3$): 250, 288.IR (KBr, ν cm^{-1}): 3461, 3278(NH_2-), 1681 (C=O), 1589 (C=N), 1313, 1147 (-SO_2-).^{1}H-NMR (DMSO-d_6, δ ppm):[4.10 (d, 1H, C_4-H),4.21 (d, 1H, C_4-H), 5.42 (d, 1H, C_5-H), in pyrazoline ring], 4.70 (s, 2H,CH_2), 7.20-8.00 (m, 19H, Ar-H), 10.24 (s, 2H, $CONH_2$).

SYNTHESIS OF 3-(4-BENZYLSULFANYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOTHIOAMIDE (13)&3-(4-BENZYLSULFONYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOTHIOAMIDE(14). GENERAL PROCEDURE [24]

A mixture of 4-benzylsulfanyl chalcone (3) or 4-benzylsulfonyl chalcone (4) (2.0mmole) and thiosemicarbazide(2.0mmole) in ethanol (10mL), sodium hydroxide(4.0 mmol) in (5 mL) of water was added and refluxed for (4) hours. The reaction mixture was cooled and poured into crushed ice. The precipitated product was filtered off and recrystallized from ethanol to give (13 and 14).

3-(4-BENZYLSULFANYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOTHIOAMIDE (13).

Yield: 74 %; m.p. 148-150°C. (U.V, λ maxnm, $CHCl_3$): 314, 346.IR (KBr, ν cm^{-1}): 3450, 3267(NH_2-), 1579 (C=N), 1186 (C=S). ^{1}H-NMR (DMSO-d_6, δ ppm): [3.49 (d, 1H, C_4-H), 3.59(d, 1H, C_4-H), 5.14 (d, 1H, C_5-H), in pyrazoline ring], 4.31 (s, 2H,CH_2), 7.29-7.87 (m, 19H, Ar-H), 8.60 (s, 2H, $CSNH_2$).

3-(4-BENZYLSULFONYLPHENYL)-5-PHENYLPYRAZOLINE-1-CARBOTHIOAMIDE (14).

Yield: 28 %; m.p. 128-130°C. (U.V, λ maxnm, $CHCl_3$): 244, 332.IR (KBr, ν cm^{-1}): 3454, 3271(NH_2-), 1584 (C=N), 1194 (C=S), 1319, 1142 (-SO_2-). ^{1}H-NMR (DMSO-d_6, δ ppm): [3.63 (d, 1H, C_4-H), 3.84(d, 1H, C_4-H), 5.42 (d, 1H, C_5-H), in pyrazoline ring], 4.67 (s, 2H,CH_2), 7.21-8.02 (m, 19H, Ar-H), 8.74 (s, 2H, $CSNH_2$).

SYNTHESIS OF 3-(4-BENZYLSULFANYLPHENYL)-5-PHENYL ISOXAZOLINE (15)&3-(4-BENZYLSULFONYLPHENYL)-5-PHENYL ISOXAZOLINE (16).GENERAL PROCEDURE [27]

Asolution of hydroxylamine hydrochloride(8.0mmole) in (2.5mL) of water was placed. The requisite 4-benzylsulfanyl chalcone (3) or 4-benzylsulfonyl chalcone (4) (2.0mmole)in (5mL) of pyridine was added. The reaction mixture wasrefluxed for (4)hours. The mixture was then acidified with dilute acetic acid, and leftovernight. The solid, thus obtained was recrystallized from ethanol to give (15 and 16).

3-(4-BENZYLSULFANYLPHENYL)-5-PHENYL ISOXAZOLINE (15).

Yield: 84 %; m.p. 162-164°C. (U.V, λ maxnm, $CHCl_3$): 290.IR (KBr, ν cm^{-1}):1591 (C=N), 1552 (C---C).^{1}H-NMR (DMSO-d_6, δ ppm): [3.96 (d, 1H, C_4-H),4.05 (d, 1H, C_4-H),5.69 (d, 1H, C_5-H), in isoxazoline ring], 4.21 (s, 2H,CH_2), 7.19-7.56 (m, 14H, Ar-H).

3-(4-BENZYLSULFONYLPHENYL)-5-PHENYL ISOXAZOLINE (16).

Yield: 58 %; m.p. 140-142°C. (U.V, λ maxnm, $CHCl_3$): 268.IR (KBr, ν cm^{-1}):1591 (C=N), 1493 (C---C), 1311, 1149 (-SO_2-).^{1}H-NMR (DMSO-d_6, δ ppm): [4.03 (d, 1H, C_4-H),4.14 (d, 1H, C_4-H), 5.79 (d, 1H, C_5-H), in isoxazoline ring], 4.56 (s, 2H,CH_2), 7.17-7.70 (m, 14H, Ar-H).

SYNTHESIS OF 2-(4-BENZYLSULFANYLBENZOYL)-3-PHENYL OXIRANE (17)& 2-(4-BENZYLSULFONYLBENZOYL)-3-PHENYL OXIRANE (18).GENERAL PROCEDURE [28]

To a solution of 4-benzylsulfanyl chalcone (3) or 4-benzylsulfonyl chalcone (4) (2.0 mmole) in (25 mL) ofmethanol was heateduntilthe chalcone had completely dissolved, was added (0.5 g.) of a 30 % hydrogen peroxide and then slowly(0.5 mL) of 16 % sodium hydroxide . After (3) hours of stirring the mixture was left overnight at room temperature. The solid was collected by filtration and washedwith cold water to give epoxide derivatives (17 and 18).

2-(4-BENZYLSULFANYLBENZOYL)-3-PHENYL OXIRANE (17).

Yield: 81 %; m.p. 106-108°C. (U.V, λ maxnm, $CHCl_3$): 246, 316.IR (KBr, ν cm^{-1}):1675 (C=O), 890 (C-O-C).^{1}H-NMR (DMSO-d_6, δ ppm): 4.05 (d, 1H, 3-CH),4.32 (s, 2H, CH_2), 4.66 (d, 1H, 2-CH), 7.37-7.87 (m, 14H, Ar-H).

2-(4-BENZYLSULFONYLBENZOYL)-3-PHENYL OXIRANE (18)

Yield: 25 %; m.p. > 330°C. (U.V, λ maxnm, $CHCl_3$): 242, 314.IR (KBr, ν cm^{-1}):1681 (C=O), 1321, 1147 (-SO_2-), 894 (C-O-C).^{1}H-NMR (DMSO-d_6, δ ppm): 4.08 (d, 1H, 3-CH),4.37(s, 2H, CH2), 4.72 (d, 1H, 2-CH), 7.34-7.89 (m, 14H, Ar-H).

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