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1,3-Bis (4-chlorophenyl)-2, 3-epoxypropanone as synthons in synthesis of some interesting potential antimicrobial agents

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ABSTRACT

This work presents a systematic and comprehensive survey on the chemical reactivity of 1,3-Bis (4-chlorophenyl)-2,3-epoxypropanone. This compound is important intermediates for the synthesis of a variety of otherwise difficult to obtain synthetically useful and novel cyclic systems **(2-12)**. The structure of the prepared products was elucidated by elemental and spectroscopic data. Moreover, the antimicrobial activity of prepared compounds has also been assessed and compound **(11)** revealed activity compared to the activity of the commonly used antimicrobial drug.

KEYWORDS

Diaryl-epoxypropanone;
2,4-Dienecarboxamide;
Oxazolidin-2-one;
1,3-Oxathiolane-2-thione;
Benzyl benzilic rearrangemen;
Pyrrolidine-2,4-dione;
Photodimerization;
Antimicrobial activity.

INTRODUCTION

The usefulness of small ring heterocyclic compound has been clearly shown in recently years[1-3]. Three-membered heterocycles are invested with a special allure that is derived from their apparent simplicity and spartan architecture. These smallest of heterocycles also exhibit a synthetically very useful balance between stability and reactivity. Thus, they are often employed as versatile and selective intermediates. With the potential to introduce two adjacent chiral centers with high atom economy, this methodology rightly deserves a place of prominence in synthetic organic chemistry[4-9].

RESULTS AND DISCUSION

The synthetic pathways depicted in Schemes 1-3 outline the chemistry of the present study. Thus, 1,3-Bis (4-chlorophenyl)-2,3-epoxypropanone **(1)** is easily prepared following the well established procedure reported in the literature[10]. Compound **(1)** was refluxed with acetoacetanilide in presence of ethanolic potassium hydroxide afforded 2,4-bis (4-chlorophenyl)-6-oxo-*N*-phenylcyclohexa-2,4-dienecarboxamide **(2)**[11] (scheme 1). The IR spectrum of latter compound displayed absorption bands at: 3299 cm^{-1} (NH); 1666, 1658 cm^{-1} (2C=O). The ^{1}H-NMR showed signals at δ 10.00 for NH Also, Mass spectrum showed the mo-

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lecular ion peak M^+ at *m/z* 433 as well as the presence of isotopic pattern of two chlorine atoms.

When compound **(2)** was reacted with hydrazine hydrate in ethanol, it produced 4,6-bis (4-chlorophenyl)-*N*-phenyl-*1H*-indazol-3-amine **(3)** (Scheme 1). The IR spectra of the latter compound revealed the absence of 2C=O signal and the ^{1}H-NMR spectrum showed signals at δ 10.02 (s, 1H, NH, D_2O exchangeable), 11.38 (s, 1H, NH indazole, D_2O exchangeable) (c.f.experimental).

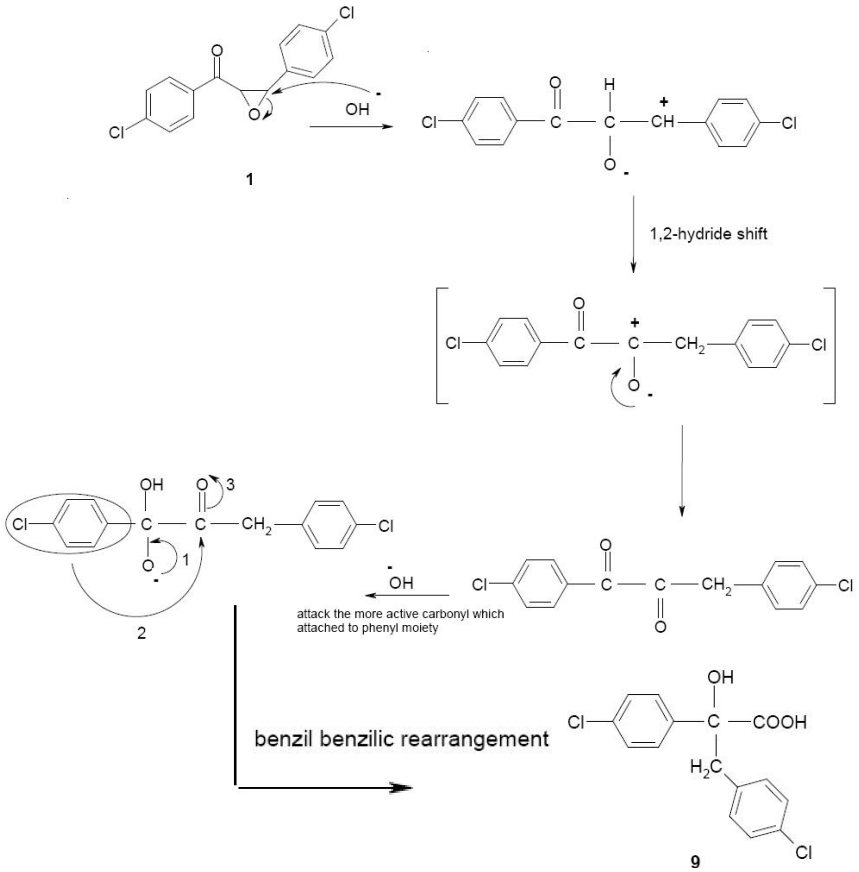
Treatment of compound **(1)** with dimethylamine in ethanol led to the formation of 1,3-bis (4-chlorophenyl)-3-(dimethylamino)prop-2-en-1-one **(4)**[12] (Scheme 1). The ^{1}H NMR spectrum for compound **(4)** indicated the presence of 2 CH_3 signals the two methyl group appear as one signal this indicate that they are magnetically equivalent due to the free of rotation around C-N bond. Also, its mass spectrum showed the molecular ion peak M^+ at *m/z* 319 as well as the presence of isotopic pattern of two chlorine atoms (c.f.experimental).

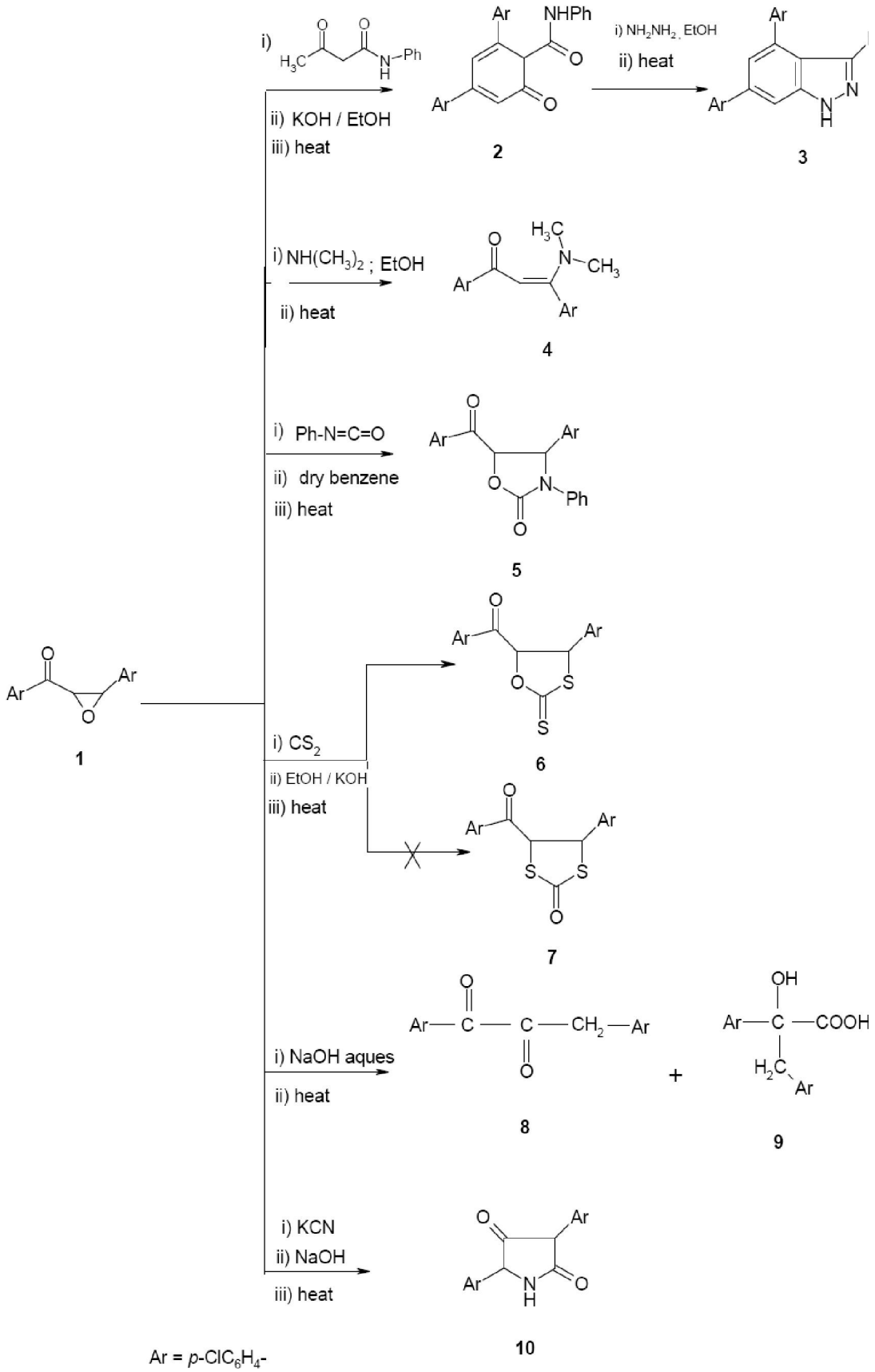
The interaction of compound **(1)** with phenylisocyanate; in dry benzene, yielded 5-(4-chlorobenzoyl)-4-(4-chlorophenyl)-3-phenyloxazolidin-2-one **(5)**(Scheme 1). The IR spectrum for compound 5 displayed absorption bands at: 1708, 1627 cm^{-1} (2C=O). Also, its mass spectrum showed the molecular ion peak M^+ at *m/z* 411 as well as the presence of isotopic pattern of two chlorine atoms (c.f.experimental).

Furthermore, when compound **(1)** was allowed to react with carbon disulphide in ethanolic potassium hydroxide, the product was identified as 5-(4-chlorobenzoyl)-4-(4-chlorophenyl)-1,3-oxa thiolane-2-thione **(6)**; not 4-(4-chlorobenzoyl)-5-(4-chlorophenyl)-1,3-dithiolane-2-one **(7)**[11, 13] (Scheme 1). The presence of signal for C=S and C=O in both of IR and ^{13}C NMR, indicated compound **(6)** not **(7)** (c.f.experimental).

Heating of compound **(1)** with aqueous solution of sodium hydroxide afforded 1,3-bis (4-Chlorophenyl)propane-1,2-dione **(8)** and 2,3-bis (4-Chlorophenyl)-2-hydroxypropanoic acid **(9)** according to benzyl benzilic rearrangement (Scheme 1; c.f.experimental).

The reaction could be represented according to the following mechanism:





Scheme 1 : Synthesis of compounds 2-10

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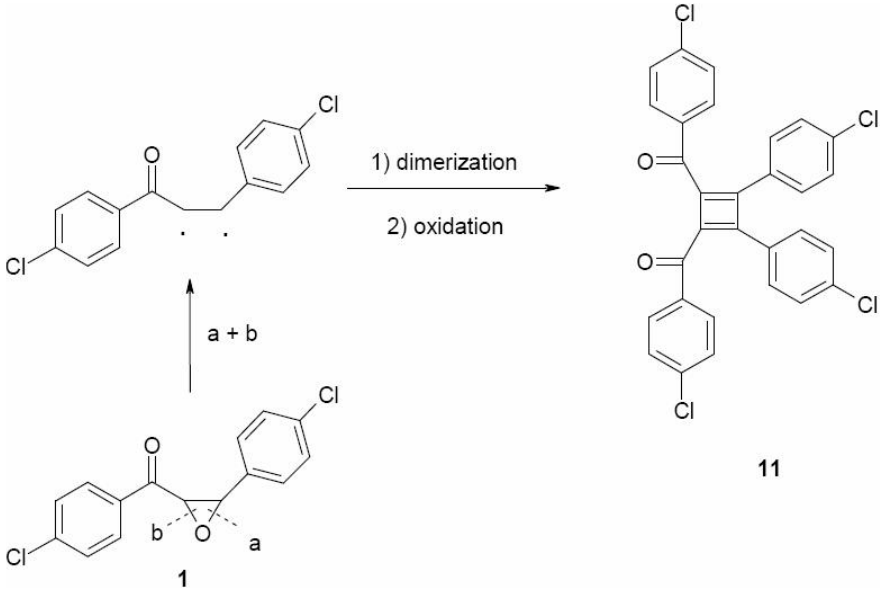
When compound **(1)** was refluxed with aqueous solution of KCN; in the presence of NaOH solution, it afforded 3,5-bis (4-chlorophenyl)pyrrolidine-2,4-dione **(10)**(Scheme 1). The IR spectrum of compound **(10)** revealed the presence of 2C=O and NH signal and the ^{1}H-NMR spectrum showed signals at δ 9.50 (s, 1H, NH, D_2O exchangeable), 11.38 (s, 1H, NH, D_2O exchangeable) (c.f.experimental).

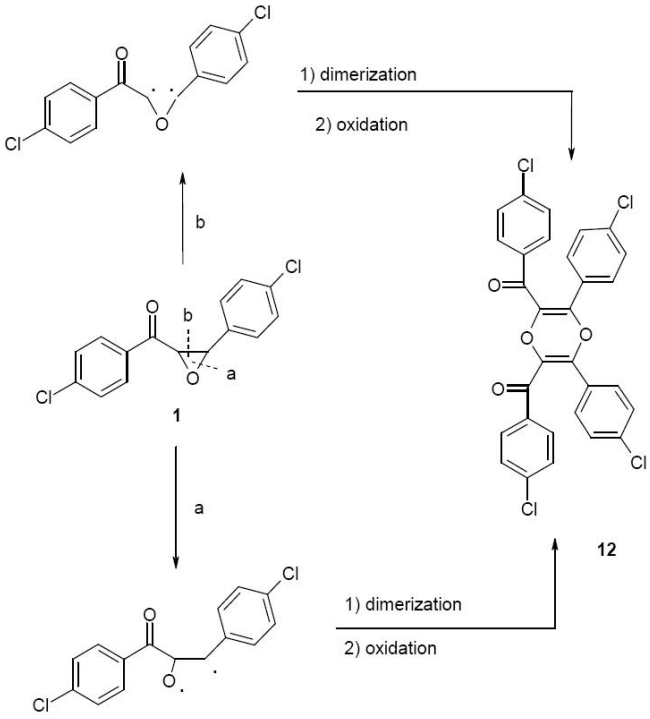


Scheme 2

The work was extended to study the Photodimerization of 1,3-Bis (4-chlorophenyl)-2,3-epoxypropanone, when compound **(1)** was dissolved in chloroform and afforded directly to sun light for long time (3 weeks), it afforded (3,4-bis (4-chlorobenzoyl))(1,2-bis (4-chlorophenyl))cyclobuta-1,3-diene **(11)** (Scheme 2); In addition to other compounds could not be separated due to the small R_f value. The IR spectrum of compound **(11)** displayed absorption bands at: 1685 cm^{-1}(2C=O). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 7.53-7.54 (m, 8H, Ar-H), 7.89-7.90 (m, 8H, Ar-H). Mass (548).

Compound **(1)** in chloroform under irradiation with 125W electric lamp for short time (6h) gave mixture of (3,4-bis (4-chlorobenzoyl))(1,2-bis (4-chlorophenyl))cyclobuta-1,3-diene **(11)** ; (3,5-bis (4-chloro benzoyl))(2,6-bis (4-chlorophenyl))-1,4dioxine **(12)** (Scheme 3); In addition to the other compounds can not be separated due to the small R_f value.

The IR spectrum of compound 12 displayed absorption bands at: 1658 cm^{-1}(2C=O). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 7.49-7.51 (d, *J* = 8.28 Hz, 4H, Ar-H), 7.61-7.62 (d, *J* = 8.28 Hz, 4H, Ar-H), 7.91-7.92(d, *J* = 10.08 Hz, 4H, Ar-H), 8.15-8.16 (d, *J* = 8.22 Hz, 4H, Ar-H). Mass (580) for $C_{30}H_{16}Cl_4O_4$.



Scheme 3

Antimicrobial assay

The antibacterial activities of the synthesized compounds were tested against *Escherichia coli* NRRL B-210 (Gram -ve bacteria), *Bacillus subtilis* NRRL

B-543 and *Staphylococcus aureus* NRRL B-313 (Gram +ve bacteria) using nutrient agar medium. The antifungal activity of these compounds was also tested against *Candida albicans* NRRL Y-477 using Sabouraud dextrose agar medium.

Agar diffusion medium

The synthesized compounds were screened in vitro for their antimicrobial activity against, by agar diffusion method[14]. 0.5 ml suspension of each of the aforementioned microorganisms was added to sterile nutrient agar media at 45°C and the mixture was transferred to sterile Petri dishes and allowed to solidify. Holes of 0.9cm in diameter were made using a cork borer. Amounts of 0.1ml of the synthesized compounds were poured inside the holes. A hole filled with DMSO was also used as control. The plates were left for 1 hour at room temperature as a period of pre-incubation diffusion to minimize the effects to variation in time between the applications of the different solutions. The diameters of the inhibition zone of were measured and compared with that of the standard and the values were tabulated. The same method was carried out using Sabouraud dextrose agar medium on using *Candida albicans* NRRL Y-477. The plates were then incubated at 30°C for 24 hours and observed for antibacterial activity.

RESULTS

The observed zone of inhibition is presented in TABLE 1.

EXPERIMENTAL

All melting points are uncorrected and measured using Electro-Thermal IA 9100 apparatus (Shimadzu, Japan). Infrared spectra were recorded as potassium bromide pellets on a Perkin-Elmer 1650 spectrophotometer, National Research Center, Cairo, Egypt. ^{1}H NMR and ^{13}C NMR spectra were determined on a Jeol-Ex-500 NMR spectrometer and chemical shifts were expressed as part per million; (δ values, ppm) against TMS as internal reference, National Research Center, Cairo, Egypt. Mass spectra were recorded on EI + Q1 MSLMR UPLR, National Research Center, Cairo, Egypt. Microanalyses were operated using Mario Elmentar apparatus, Organic Microanalysis Unit, National Research Center, Cairo, Egypt. Column Chromatography was performed on (Merck) Silica gel 60 (particle size 0.06–0.20 mm).

Compound **(1)** was identified *via* m.p.[10].

TABLE 1: In vitro antimicrobial activity by agar diffusion method of tested Compounds

Tested compounds & standards	Inhibition zone (mm)			
	Microorganism			
	Escherichia coli	Bacillus subtilis	Staphylococcus aure	Candida albeicans
Gentamycine	++++	++++	++++	-
Fluconazole	-	-	-	++++
1	-	-	-	-
2	-	-	-	-
3	-	+	-	-
4	-	-	-	-
5	-	-	-	-
6	-	-	-	-
8	-	-	-	-
9	-	+	++++	++
10	++	+++	++++	-
11	+	++	++++	++
12	-	+	-	-

++++ highly sensitive (inhibition zone = 25-21); +++ moderatly sensitive (inhibition zone = 20-16); ++ fairly sensitive (inhibition zone = 15-11); + slightly sensitive (inhibition zone = 10-6); -No sensitivity

2,4-Bis (4-chlorophenyl)-6-oxo-*N*-phenylcyclohexa-2,4-diene carboxamide (2)

A mixture of compound **(1)** (0.01 mole), acetoacetanilide (0.01 mole) in ethanolic potassium hydroxide (2g in 100 ml ethanol) was refluxed for 6 h. The solvent was evaporated and the formed precipitate was washed several time with acidified cold water filtered off and recrystallized from n-butanol to give compound **(2)**.

Yield 61 %, m.p. 237–239 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 3299 (NH); 1666, 1658 (2C=O). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.63(s, 1H, H1); 6.61-7.52(m, 15H, 13Ar-H + H3+H5), 10.00 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR spectrum (DMSO, δ ppm): 59.89 (C1); 119.59-141.58(22Ar-C); 167.54 (C=O; amide); 195.57(C=O; excocyclic). MS, *m/z* (%): (437, M^+ +4, 0.3%), (435, M^+ +2, 1.5 %), (433, M^+,

3 %). Analysis for $C_{25}H_{17}Cl_2NO_2$ (434.33): required C, 69.14; H, 3.95; Cl, 16.33; N, 3.22; found C, 68.92; H, 3.87; Cl, 16.14; N, 3.05.

4,6-Bis (4-chlorophenyl)-*N*-phenyl-*1H*-indazol-3-amine (3)

A mixture of compound **(2)** (0.01 mole) and hydrazine hydrate (0.011 mol) in methanol was refluxed for 4 h. The resulting solid was collected by filtration and recrystallized from methanol to give compounds **(3)**.

Yield 71 %, m.p.266–268 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): br 3240 (2NH). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 6.83-7.74 (m, 15H, Ar-H), 10.02 (s, 1H, NH amide, D_2O exchangeable), 11.38 (s, 1H, NH indazole, D_2O exchangeable). MS, *m/z* (%): (433, M$^+$ +4, 4%), (431, M$^+$ +2, 12%), (429, M$^+$, 24%). Analysis for $C_{25}H_{17}Cl_2N_3$ (430.34): required C, 69.78; H, 3.98; Cl, 16.48; N, 9.76; found C, 69.51; H, 3.69; Cl, 16.23; N, 9.50.

1,3-Bis (4-chlorophenyl)-3-(dimethylamino)prop-2-en-1-one (4)

A mixture of compound **(1)** (0.01 mole) and dimethylamine (0.01 mol) in 50 ml ethanol was refluxed for 24 h. The solvent was evaporated and the formed solid filtered off and recrystallized from ethanol to give compounds **(4)**.

Yield 58%; m.p.153–155 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 1656 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 2.43 (s, 6H, $2CH_3$), 7.68-8.37(m, 8 H, Ar-H), 8.48 (s, 1H, CH); MS, *m/z* (%):(323, M$^+$ +4, 4%), (321, M$^+$ +2, 19%), (319, M$^+$, 37%). Analysis for $C_{17}H_{15}Cl_2NO$ (320.22): required C, 63.77; H, 4.72; Cl, 22.14; N, 4.37; found C, 63.51; H, 4.43; Cl, 21.87; N, 4.05.

5-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-3-phenyloxazoli din-2-one (5)

A mixture of compound **(1)** (0.01 mole) and phenyl isocyanate (0.01 mole) and a catalytic amount of triethyl amine in dry benzene (20 ml) was refluxed for 12h. The reaction mixture was concentrated, and the formed precipitate was filtered off and recrystallized from dioxane to give compounds **(5)**.

Yield 74 %;m.p.169–171 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 1708, 1627 (2C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 6.54 (d, *J*= 10.08 Hz, 1H, β-CH), 6.98(d, *J*=10.08 Hz, 1H, α-CH), 7.26-7.51 (m, 8 H, Ar-H); MS, *m/z* (%):(415, M$^+$ +4, 1%), (413, M$^+$ +2, 7%), (411, M$^+$, 13 %). Analysis for $C_{22}H_{15}Cl_2NO_3$ (412.28): required C, 64.09; H, 3.67; Cl, 17.20; N, 3.40; found C, 63.78; H, 3.39; Cl, 16.92; N, 3.11.

5-(4-Chlorobenzoyl)-4-(4-chlorophenyl)-1,3-oxathiolane-2-thione (6)

To a warmed ethanolic sodium hydroxide solution [prepared by dissolving sodium hydroxide (0.01 mole) in ethanol (50ml)], compound **(1)** (0.01 mole) and carbon disulphide (10 ml) were added. The mixture was heated on water bath at 80 ^{0}C under reflux for 10h, and then it was poured into water, neutralized by diluted hydrochloric acid. The formed solid was collected and recrystallized from benzene to give **(6)**.

Yield 52%; m.p.153–155 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 1214 (C=S), 1655 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.91(d, *J*= 3.54 Hz, 1H, β-CH), 5.94 (d, *J*=3.6 Hz, 1H, α-CH), 7.16-7.91 (m, 8 H, Ar-H). ^{13}C NMR spectrum (DMSO, δ ppm): 62.99 (â-C), 102.98 (á-C), 129.38-138.70 (8Ar-C); 176.76 (C=O); 188.53 (C=S). MS, *m/z* (%): (372, M$^+$ +4, 1%), (370, M$^+$ +2, 4%), (368, M$^+$, 12%). Analysis for $C_{16}H_{10}Cl_2O_2S_2$ (369.29): required C, 52.04; H, 2.73; Cl, 19.20; S, 17.37; found C, 51.71; H, 2.45; Cl, 18.92; S, 17.05.

Synthesis of (8-9)

A mixture of compound **(1)** (0.01 mole) and aqueous solution of NaOH (0.01 mole) was refluxed for 3 h. The reaction mixture was left over night, cold water was added and extracted with ether. The ether layer was washed with water and dried over anhydrous $MgSO_4$; dried over The excess solvent was evaporated under reduced pressure the resulting solid was collected by filtration and recrystallized from ethanol to give **(8)**. The aqueous layer neutralized with HCl, the resulting solid was collected by filtration and recrystallized from dioxane to give compounds **(9)**.

1,3-Bis (4-chlorophenyl)propane-1,2-dione (8)

Yield 43%; m.p. 177–179 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 1737, 1685 (2C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 5.75(s, 2H, CH_2), 7.14-7.96(m,

8H, Ar-H); MS, *m/z* (%): (296, M^+ +4, 11%), (294, M^+ +2, 62%), (292, M^+, 100 %). Analysis for $C_{15}H_{10}Cl_2O_2$ (293.15): required C, 61.46; H, 3.44; Cl, 24.19; found C, 61.15; H, 3.16; Cl, 23.97.

2,3-Bis (4-chlorophenyl)-2-hydroxypropanoic acid (9)

Yield 63%; m.p. 267–269 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 3429 (OH), 1682 (C=O). ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.12(d, *J*= 14.7Hz, 1H, CH_2), 3.31 (d, *J*= 13.6 Hz,1H, CH_2), 5.90(bs, 1H, OH ; alcoholic ; D_2O exchangeable), 7.33-7.91 (m, 8 H, Ar-H), 9.60 (bs, 1H, OH ; acidic ; D_2O exchangeable); MS, *m/z* (%):(313, [M^+-1] +4, 13%), (311, [M^+-1] +2, 73%), (309, M^+-1, 100 %). Analysis for $C_{15}H_{12}Cl_2O_3$ (311.17): required C, 57.90; H, 3.89; Cl, 22.79; found C, 57.63; H, 3.71; Cl, 22.50.

3,5-Bis (4-chlorophenyl)pyrrolidine-2,4-dione (10)

A mixture of compound **(1)** (0.01 mole) and aqueous solution of KCN (0.01 mole), with 10% NaOH solution (10 ml) was refluxed for 3 h. The reaction mixture was left over night, acidified cold water was added and the resulting solid was collected by filtration and recrystallized from ethanol to give **(10)**.

Yield 66%; m.p.182–184 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 3220 (NH); 1737, 1689(2C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 7.53-8.19 (m, 10H, 8Ar-H+ 2CH), 9.50 (s, 1H, NH; D_2O exchangeable); MS, *m/z* (%):(323, M^+ +4, 0.2%), (321, M^+ +2, 3%), (319, M^+, 7%). Analysis for $C_{16}H_{11}Cl_2NO_2$ (320.18): required C, 60.02; H, 3.46; Cl, 22.15; N, 4.37; found C, 59.76; H, 3.14; Cl, 21.83; N, 4.09.

(3,4-Bis (4-chlorobenzoyl))(1,2-bis (4-chlorophenyl)) cyclobuta-1,3-diene (11)

Compound **(1)** (0.01 mole) in chloroform (100 ml) afforded directly to sun light for 3 weeks ;then evaporation under reduced pressure, the residues were purified on silica gel column using petroleum ether : ethyl acetate (9:1) as an eluent to give **(11)**.

Yield 48%; m.p.126–128 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 1685 (2C=O) ; ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 7.53-7.54 (m, 8H, Ar-H), 7.89-7.90 (m, 8H, Ar-H). MS (548). Analysis for $C_{30}H_{16}Cl_4O_2$ (550.27): required C, 65.48; H, 2.93; Cl, 25.77; found C, 65.20; H, 2.65; Cl, 25.49.

(3,5-Bis (4-chlorobenzoyl))(2,6-bis (4-chlorophenyl))-1,4dioxine (12)

A solution of compound **(1)** (0.01 mol) in chloroform (300 ml) in a Pyrex vessel under N_2 was irradiated with a high pressure Mercury lamp (HP, Philips, 125 W), until completion of the reaction at room temperature. The reactions were monitored by thin layer chromatography (TLC) using aluminum sheets with silica gel 60 F254 (Merck). After evaporation under reduced pressure, the residues were purified on silica gel column using petroleum ether: ethyl acetate (7:3) as an eluent to give **(11)** and **(12)**.

Yield 43%; m.p.117–119 ^{0}C. IR spectrum (KBr, ν, cm^{-1}): 1658 (2C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 7.49-7.51 (d, *J* = 8.28 Hz, 4H, Ar-H), 7.61-7.62 (d, *J* = 8.28 Hz, 4H, Ar-H), 7.91-7.92(d, *J* = 10.08 Hz, 4H, Ar-H), 8.15-8.16 (d, *J* = 8.22 Hz, 4H, Ar-H). MS (580). Analysis for $C_{30}H_{16}Cl_4O_4$ (582.27): required C, 61.88; H, 2.77; Cl, 24.35; found C, 61.63; H, 2.40; Cl, 24.09.

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