An overview of Ullmann Reaction, Its importance and applications in synthesis of Dibenzopyranones

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Abstract: 3:4-Carbocyclic and 3:4-heterocyclic fused ring systems constitute an important class of natural products with immense pharmacological properties. Recently, the dibenzopyranones nucleus have surfaced as common ring system of a group of antibiotics, antibacterials, antitumors and immunomodulators, etc. exemplified by alternariol, ravidomycin, shilajit, ellagic acid etc. Our continuing effort on the development of 2,3-diarylbenzopyrans led us to synthesize some dibenzopyranone/pyran molecules by Ullmann's reaction and reviewd its importance and applications.

1. Ullmann Reaction

1.1 Introduction

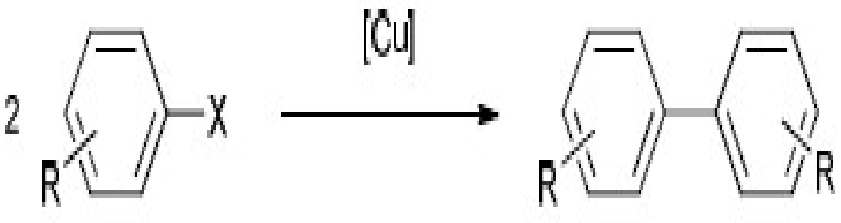
Ullmann reaction is aromatic nucleophilic substitution reaction in which copper-mediated [1-3]. Copper salts are used for this reaction in high temperature.The products are used in pharmaceutical, agrochemical, fine and polymer chemistry [4-7].Ullmann reaction shows condensation between aryl halide and amine, phenol or thiophenol to give aryl-amine, -either or –thioether.This is known as Ullmann condensation. Biaryls are formed from aryl halides through Ullmann reaction [8-11].

This coupling types reaction [12] is named by Fritz Ullmann [13]. This reaction involves Goldberg condensation [14] and Hurtley reaction [15].

1.2 Importance

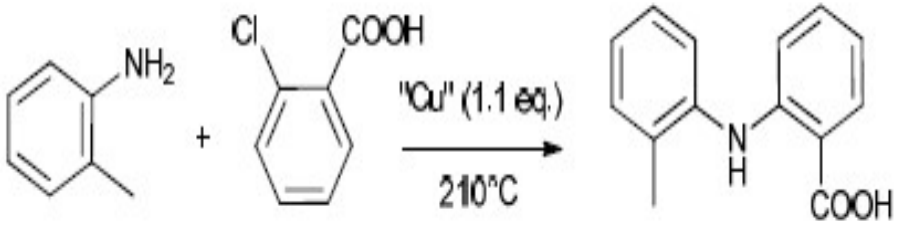
Ullmann found that biaryl moieties formed by the coupling of aryl halides in the presence of Cu catalyst in 1901. This in called classical Ullmann reaction [16]. After two years, in 1903 and 1905 same process is used between N-aryl amines and ethers [17,18]. In 1906 arylation of amines is found in the presence of Cu-catalyst. This is known as Goldberg reaction [19]. In 1929, coupling reaction is discovered between o-bromobenzoic acid and β-dicarbonyls with Cu-catalyst by Hurtley [20].

a)



Scheme 1: Ullmann reaction 1901 [16]

b)



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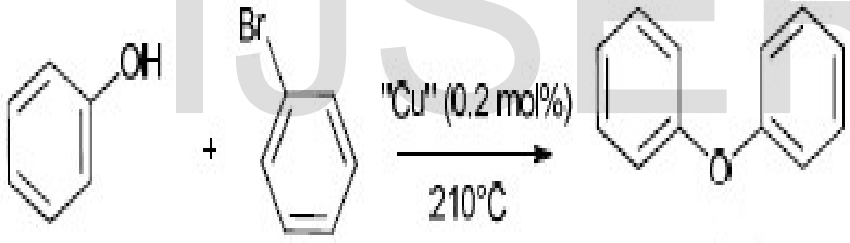
Scheme 2: Scheme 1: Ullmann reaction 1901 [17]

c)



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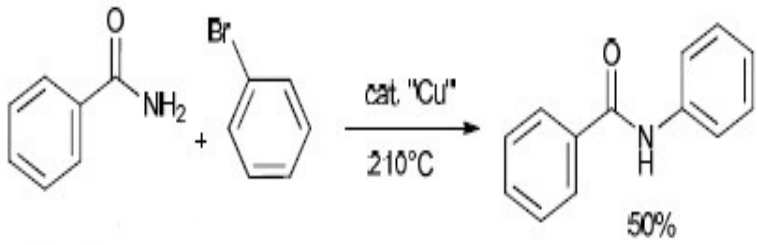
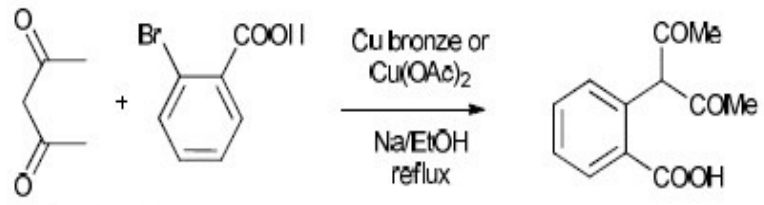
Scheme 3: Ullmann reaction 1905 [18]

d)



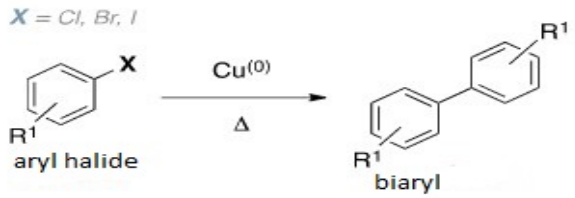
Scheme 4: Goldberg reaction [19]

e)



Scheme 5: Hurtley reaction [20]

1.3 Reaction and Mechanism

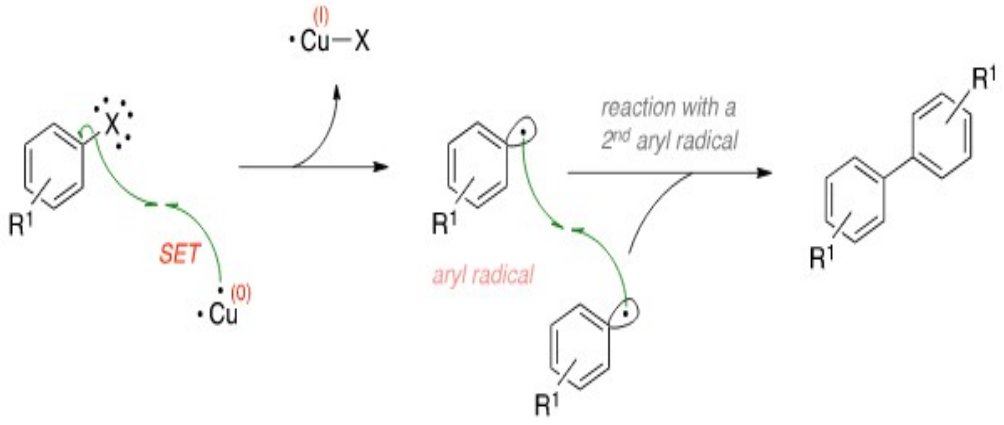


Scheme 6: Ullmann reaction [21,22]

In Ullmann reaction, biaryl is formed by coupling process between two aryl halide in the presence of copper metal. This reaction shows two types mechanism [21,22].

a) Radical mechanism

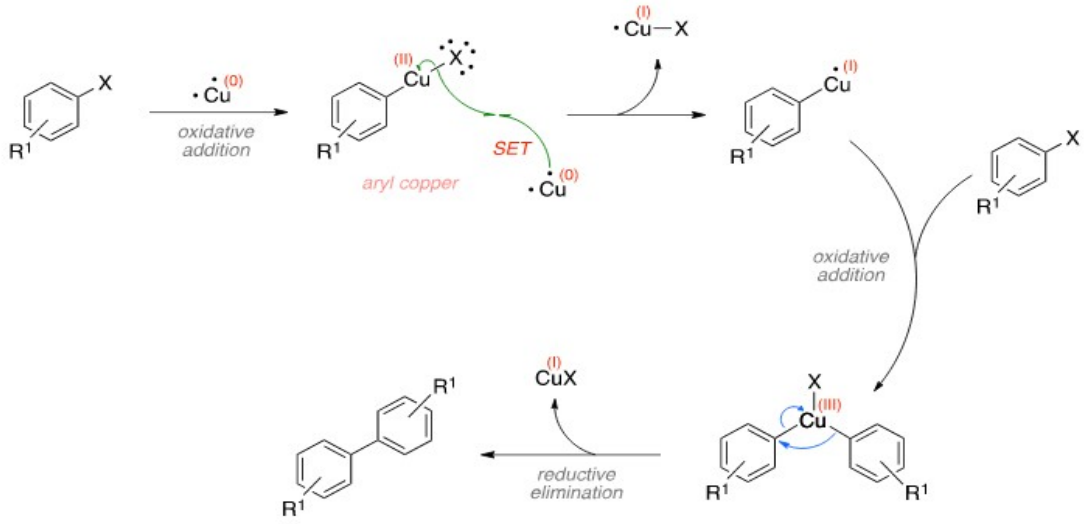
In this mechanism, firstly aryl radical is formed through single electron transfer from copper to alkyl haide. Again, two radical combine to form biaryl [21,22].



Scheme 7: Radical mechanism [21,22]

b) An aryl copper intermediate mechanism

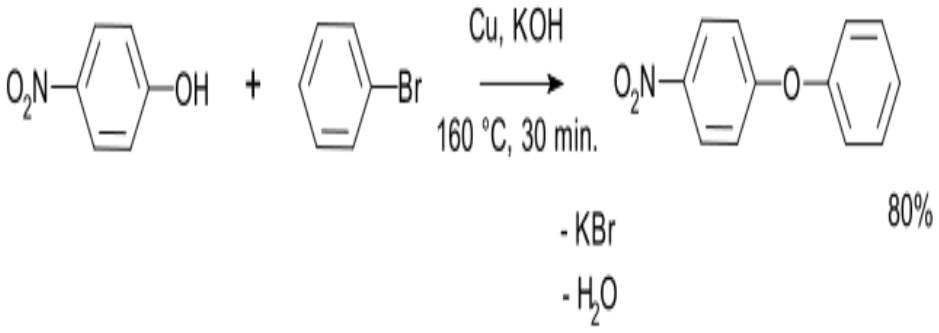
In tis mechanism, firstly organocuprate reagent is formed through single electron transfer from copper to aryl hallid. Again, organocuprate reagent shows oxidative addition with aryl halide. Finally, biaryl is formed by reductive ellimination [21,22].



Scheme 8: An aryl copper intermediate mechanism [21,22]

1.4 Ullmann condensation

The formation of diaryl ether by the coupling of phenol and aryl halide in the presence of copper metal compound. This is also known as Ullmann ether synthesiss [23]. The synthesis of p-nitrophenyl phenyl ether is Ullmann condensation reaction [24].

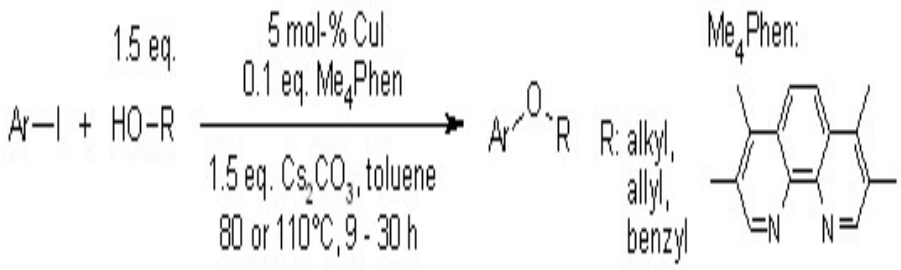


Scheme 9: Ullmann condensation [24]

Literature Review

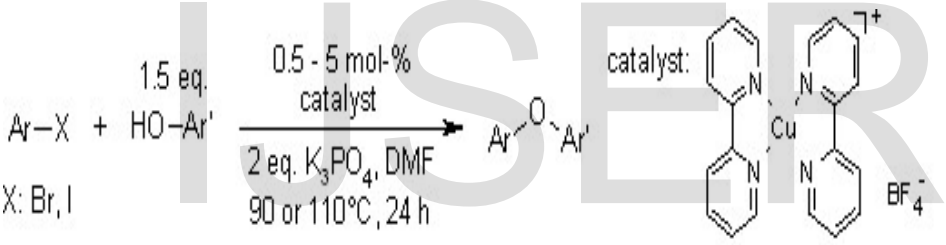
2.1 Recent literature

1. The reaction between alcohol and aryl halide was found by R. A. Altman, A. Shafir, P. A. Lichtor, S. L. Buchwald, J [25].



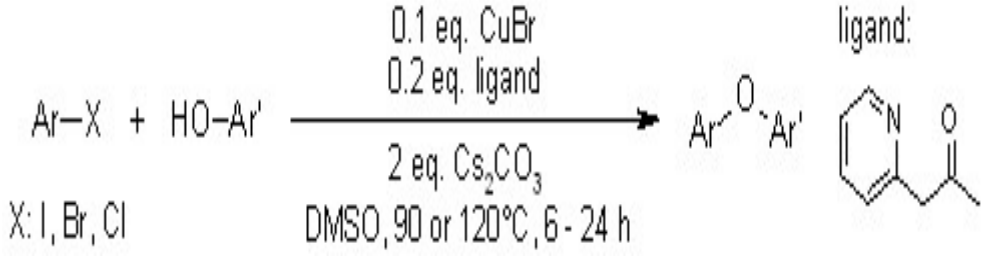
Scheme 10: Reaction between alcohol and aryl halide

2.Reaction between aliphatic alcohol, phenol and aryl halide was found by J. Niu, H. Zhou, Z. Li, J. Xu, S. Hu, J in presence of catalyst like air-stable copper(I) complex [26] .



Scheme 11: Reaction between aliphatic alcohol, phenol and aryl halide

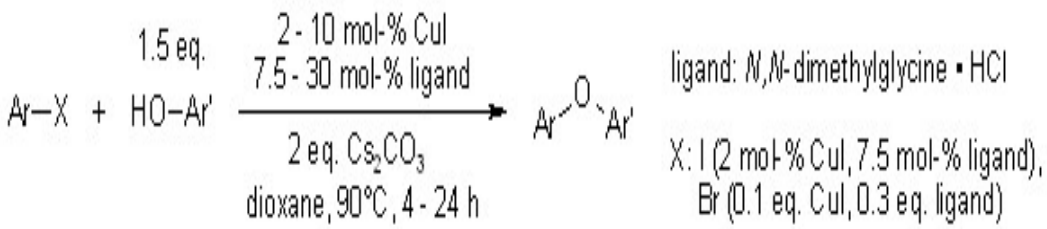
3. Reaction between aryl chlorides, aryl bromides, and aryl iodides and phenols was found by aryl chlorides, aryl bromides, and aryl iodides [27].



Scheme 12: Reaction between aryl chlorides, aryl bromides, and aryl iodides and phenol

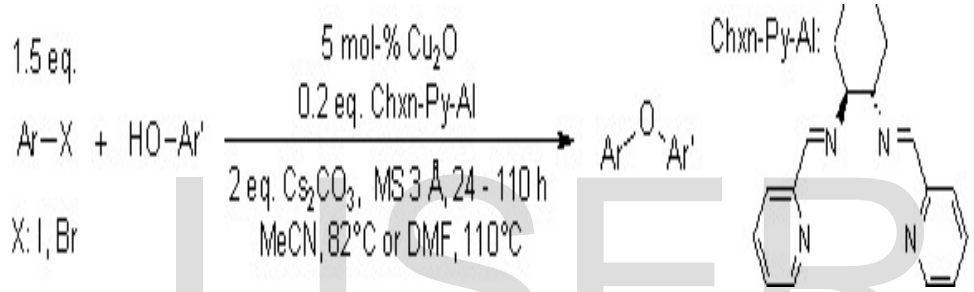
4. Diaryl ethersynthesisby the reaction between aryl halide and phenol in presence of

N,*N* Dimethyl Glycine [28].



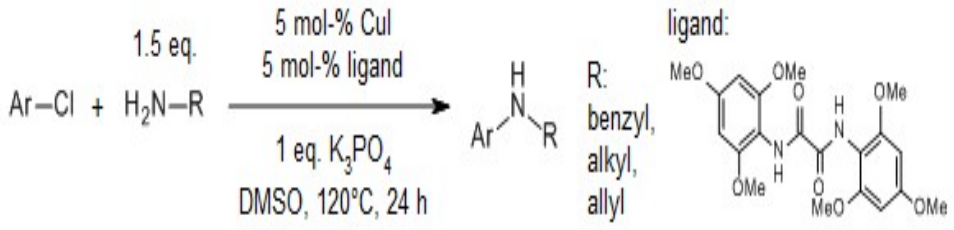
Scheme 13: Reaction between aryl halide and phenol [28]

5. Diaryl Ethers synthesis by the reaction between aryl halide and phenol in presence of Cs_2CO_3 and catalytic copper(I) oxide as catalyst [29].



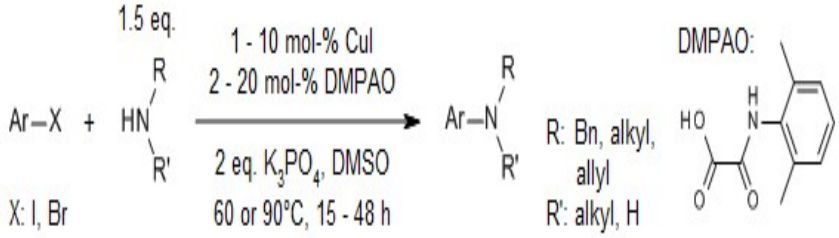
Scheme 14: Reaction between aryl halide and phenol [29]

6. The reaction between aryl Chlorides and amines was found in presence of CuI/Oxalic Diamide as catalyst [30].



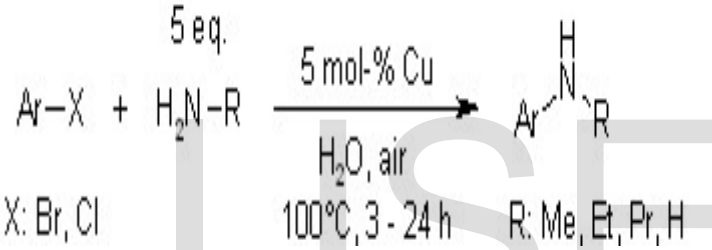
Scheme 15: Reaction between aryl Chlorides and amines [30]

7. The reaction of aryl halide with aliphatic acyclic secondary amine takes place in presence of CuI/DMPAO as catalyst [31].



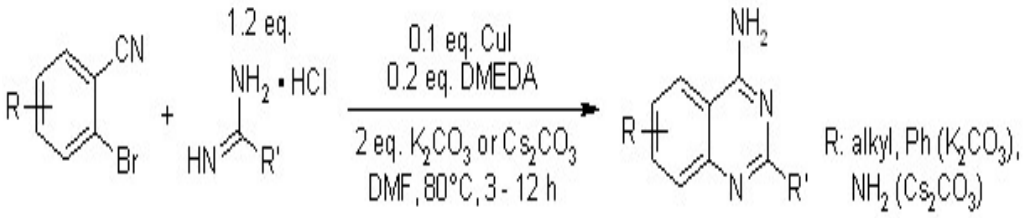
Scheme 16: Reaction betweenaryl halide and aliphatic acyclic secondary amine[31]

8.The reaction between aryl halide , aqueous methylamine aliphatic primary amines takes place in presence of organic solvent- and ligand [32].



Scheme 17: Reaction between aryl halide , aqueous methylamine aliphatic primary amines [32]

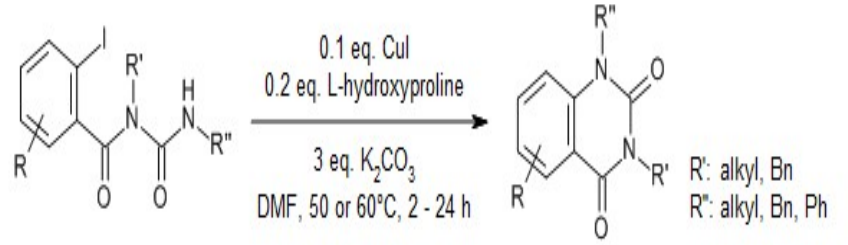
9. 4-aminoquinazoline and 2,4-diaminoquinazoline derivatives synthesise by the reaction between 2-bromo-benzonitrile and amidine or guanidine in presence of copper catalyst [33].



Scheme 18: Reaction between 2-bromo-benzonitrile and amidine or guanidine [33]

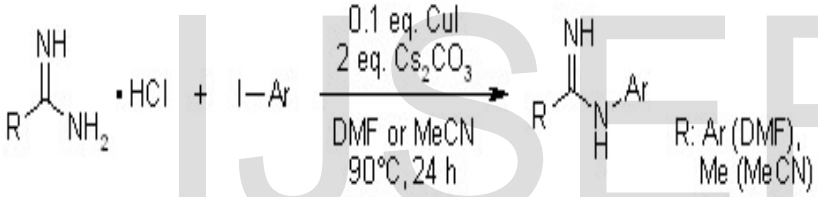
10. When Coupling of acyl area takes place in presence of copper catalyst, disubstituted

duinazolinedione with differential N-substitution formed [34].



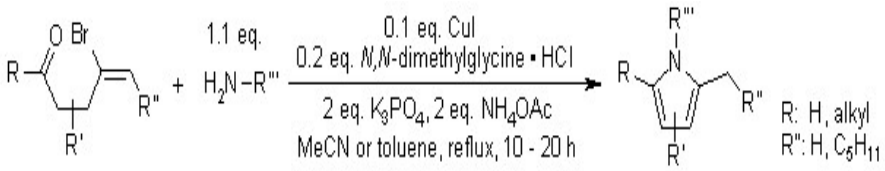
Scheme 19: Coupling of acyl area [34]

11. Monoarylatedamidine formed by the reaction between amidine salts and aryl iodide in presence of copper catalyst [35].



Scheme 20: Reaction between amidine salts and aryl [35]

12. When amines react with bromoenones in presence of copper as catalyst pyrroles was formed [36].



Scheme 21: Reaction between amines react and bromoenones [36]

Catalytic Reduction of Dibenzopyranone

3.1 Catalyst

3.1.1 Introduction

The substance which change the rate of chemical reaction without any chemical change is called catalyst. It can increase or decrease the chemical reaction rate. This process of increasing rate of chemical is called catalysis. It is used in little quantity [37].

The amount energy to form transition state is decrease in presence catalyst. As a result reaction rate increase. The equilibrium condition of reaction doesn't effected by catalyst. It can increase or decrease reaction rate.

The substance which increase chemical reaction rate is called positive catalyst. V_2O_5 acts as positive catalyst in synthesis of H_2SO_4.

The substance which increase chemical reaction rate is called positive catalyst. V_2O_5 acts as positive catalyst in synthesis of H_2SO_4.

The substance which decrease chemical reaction rate is called negative catalyst. Alcohol acts as negative catalyst in Oxidation of sodium sulphite reaction.

Enzymes also act as catalyst [38].

3.1.2 Mechanism

Reaction becomes fast in presence of catalyst because less amount of activation energy is require for catalyst. Original catalyst is from by cyclic process through temporary intermediate [39, 40].

i) $X + \mathbf{C} \rightarrow X\mathbf{C}$

ii) $Y + X\mathbf{C} \rightarrow XY\mathbf{C}$

ii) $XY\mathbf{C} \rightarrow \mathbf{C}Z$

iv)$\mathbf{C}Z \rightarrow \mathbf{C} + Z$

Scheme 22:Mechanism of catalyst [39,40]

Where,

C = catalyst, X, R = reactants

Z = product

The catalyst which doesn't represent total reaction in required for (i) is formed in (iv).

$$X + Y \rightarrow Z$$

3.1.3 Classification

On the basis of phase, catalyst areheterogeneous or homogeneous type.

a) Homogeneous catalyst

When the phases are same as reactant, the catalyst is called homogeneous catalyst.HCl is homogeneous catalyst in formation of methyl acetate from acetic acid and methanol. It is dissolved in solvents [41].

b) Heterogeneous catalyst

When the phases are different from reactant, the catalyst is called heterogeneous catalyst. They are solid which increase reaction by increasing surface area. In synthesis of ammonia, iron is heterogeneous catalyst [42].

3.2 Reduction

The process in which addition of hydrogen or removal of oxygen takes place is called reduction. In reduction, one atom gain electron to other [43]. The formation of hydrogen chloride by reaction between hydrogen and chlorine is reduction process.

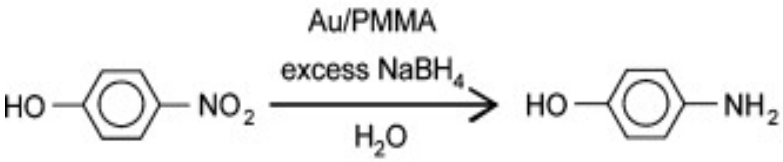
$$Cl_2 + H_2 \rightarrow HCl$$

The formation of hydrogen chloride by reaction between hydrogensulphide and chlorine is reduction process.

$$H_2S + Cl_2 \rightarrow 2HCl + S$$

3.3 Catalytic Reduction

Those reduction which occurs in presence of catalyst is called catalytic reduction. Nitro phenol reduced to amino phenol by borohydride where Au acts as catalyst and sodium borohydrideacts reducing agent is catalytic reduction[44].

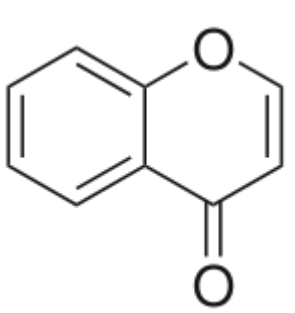


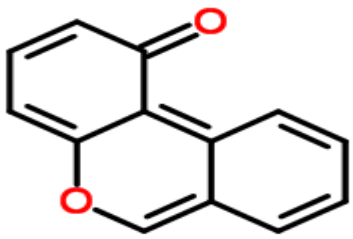
Scheme 23: Reduction of Nitro Phenol [44]

3.4 Di-benzopyranone

An additional benzene ring fused in di-benzopyranone as chromone [45].Chromene is derivative of benzopyran in which substituted keto group found on

the pyran ringUrolithin-A, urolithin-B, u-rolithin-C, urolithin-D are isomers of di-benzopyranone.

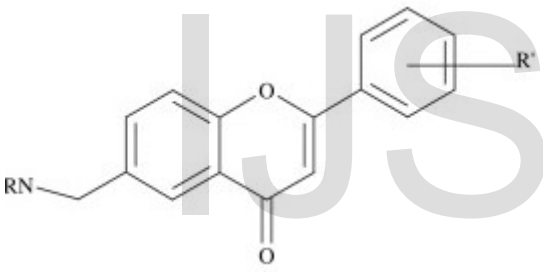




Scheme 24: Chromone [45]Scheme 25: Dibenzopyranone [45]

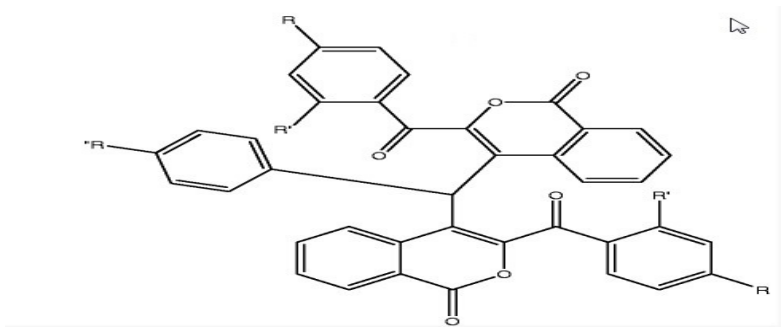
3.4.1 Substituteddibenzopyranone

In it, hydrogen on the rings of dibenzopyranone replaced. For example, 6-aminomethyl-2-aryl-1-benzopyran-4-one.



Scheme 26: 6-aminomethyl-2-aryl-1-benzopyran-4-one

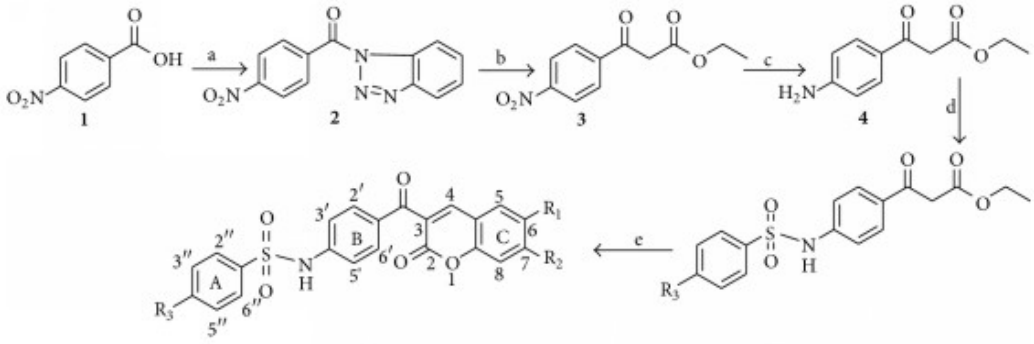
Bis-(1H-2-benzopyran-1-one) is an example of dibenzopyranone derivative.



Scheme 27: 1H-2-benzopyran-1-one

3.5 Methods of Synthesis of substituted Dibenzopyranone

1. 3-[4-(phenylsulfonamido)benzoyl]-2H-1-benzopyran-2-one is synthesis by reflux technique [46].



Scheme 28: Synthesis of Bis-(1*H*-2-benzopyran-1-one) derivatives by reflux [46]

where,

a = $SOCl_2$, 1,2,3-benzotriazole, and reflux

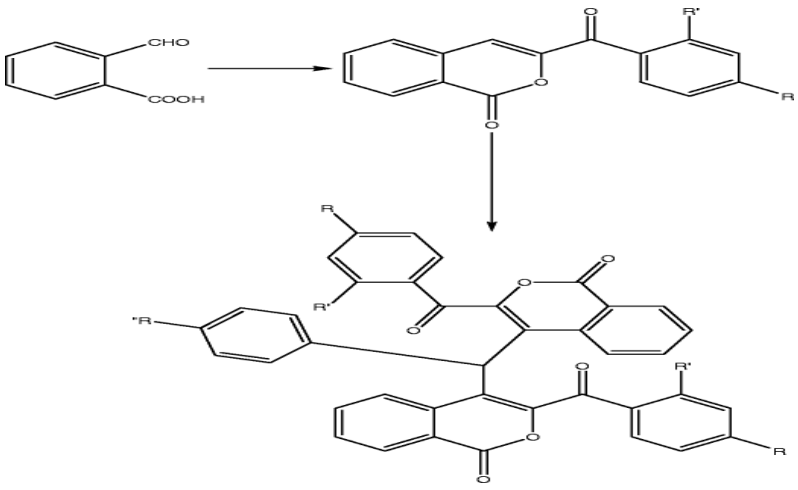
b = ethyl acetoacetate, NaH, THF, and rt

c = $SnCl_2$, ethyl acetate, and reflux

d = substitutedbenzenesulfonyl chloride, pyridine, CH_2Cl_2, −10°C, and rt

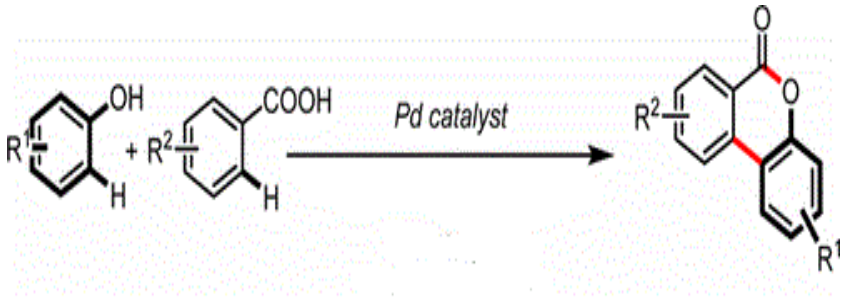
e = substitutedsalicylaldehyde, piperidine, acetic acid, EtOH, and reflux.

2. Bis-(1*H*-2-benzopyran-1-one) derivatives synthesise through condensation of 3-aroyl isocoumarins with different aromatic aldehydes [4 7].



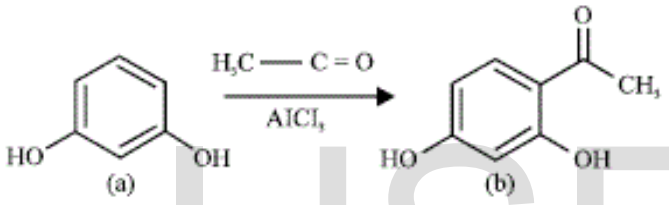
Scheme 29: Synthesis ofBis-(1H-2-benzopyran-1-one) derivatives [47]

3. Dibenzopyranone is synthesis by coupling of benzoic acid with phenol in presencve of palladium as a catalyst [48].



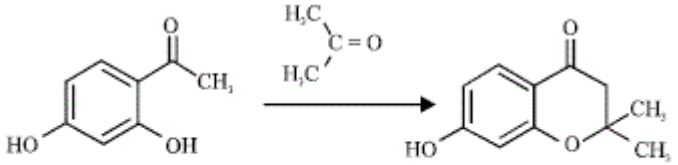
Scheme 30: Synthesis of dibenzopyronone [48]

4.2,4-Dihydroxy acetophenoneprepared from resorcinol as friedel-crafts acylation [49].



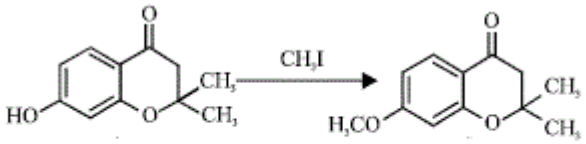
Scheme 31: Synthesis of 2,4-Dihydroxy acetophenon [49]

5. 2,2-Dimethyl-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one prepared from 2,4-dihydroxy acetophenone as aldol condensation [49].



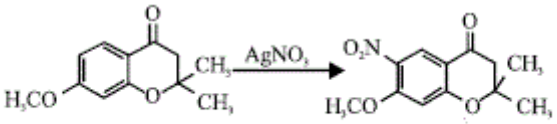
Scheme 32: Synthesis of 2, 2-Dimethyl-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one [49]

6. 2,2-Dimethyl-3,4-dihydro-7-methoxy-2H-1-benzopyran-4-one from 2,2-Dimethyl-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one as methoxylation [49].



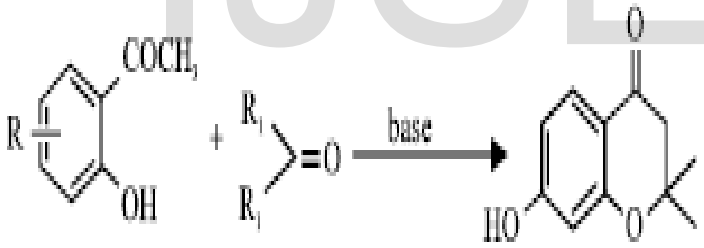
Scheme 33: Synthesis of 2,2-Dimethyl-3,4-dihydro-7-methoxy-2H-1-benzopyran-4-one [49]

7. 2,2-dimethyl-7-methoxy-3,4-dihydro-2H-1-benzopyran-4-one is prepared from 2,2-dimethyl-7-methoxy-6-nitro-3,4-dihydro-2H-1-benzopyran-4-one by reduction process [49].



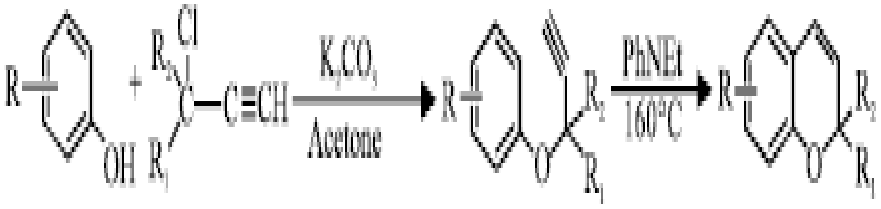
Scheme 34: Synthesis of 2,2-dimethyl-7-methoxy-3,4-dihydro-2H-1-benzopyran-4-one [49]

8.Benzopyran issynthesis by the reaction between hydroxyacetophenone and alkyl ketone or aldehyde in presence of a base [49].



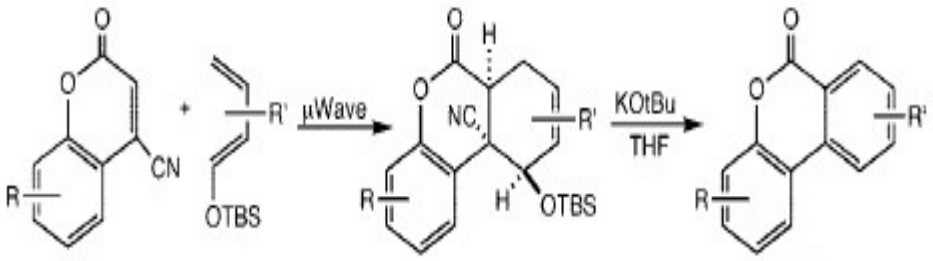
Scheme 35: Synthesis ofbenzopyran [49]

9. The pyronering is synthesis from propargyl ethers of phenol [49].



Scheme 36: Synthesis ofpyran ring [49]

10. Dibenzopyranone is synthesis by Diels-Alder cycloaddition of 4-cyanocoumarins and silyloxydienes [50].



Scheme 37: Synthesis of dibenzopyranone by Diels-Alder cycloaddition [50]

5.1 Conclusion

Dibenzopyranone were synthesis fromrefluxation of 2-bromobenzoic acid with NaOH. In this method, resorcinol condensed with 2-bromobenzoic ion and $CuSO_4$ which isused as catalyst. Naturally food sources such as citrus fruits, herbs, and vegetables used in synthesis of dibenzopyranone.Substituedproduct of dibenzopyranone were used in pharmaceuticals area as oxidant, in the prevention and treatment of emesis and nausea in mammals, antiemetic agent in chemotherapy. Some derivatives were used in DNA activation. Thesecompounds are found in many natural products such as alternariol, graphislactones, autumnariol, autumnariniol, altenuisol and biologically active compounds. Benzoyranone has antiproliferative activitiesbreast used in treatment of breast cancertumour

5.2 Future Aspects

Lactones of dibenzopyranones can be used in the synthesis of several pharmaceutically interesting compounds such as progesterone, androgen, glucocorticoid modulators, and endothelial cell proliferation inhibitors. It can be used in the treatment of anxiety, analgesia, and depression. It can be used in treatment of cancer and tumour.

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