PART -I

CHAPTER - 1

INTRODUCTION

Diketones are characterised by the presence of two oxo groups. They are classified as 1,2 or α (1); 1,3 or β(2) and 1,4 or γ (3) diketones according to position of oxo group.

R-CO-CO-R' (1)

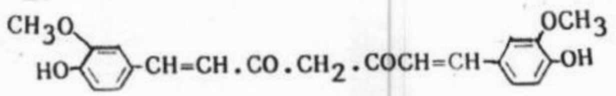
$R\text{-}CO\text{-}CH_2\text{-}CO\text{-}R'$ (2)

$R\text{-}CO\text{-}CH_2\text{-}CH_2\text{-}CO\text{-}R'$ (3)

(R or R' may be alkyl or aryl or acyclic)

1,3-or β-dicarbonyl compounds are regarded as diacylmethane derivatives. e.g. $C_6H_5\text{-}CO\text{-}CH_2\text{-}CO\text{-}C_6H_5$, 1,3-diphenylpropan-1,3,dione (IUPAC nomenclature) or dibenzoylmethane. If the two carbonyl groups are present in the ring system, they are known as cyclic diketones.

Curcumine[1], an orange red pigment belongs to this class of compounds. It occurs in the roots and shoots of curcuma tictoria and it is extracted with alcohol and precipitated as lead salt. It has been assigned the structure[2](4).



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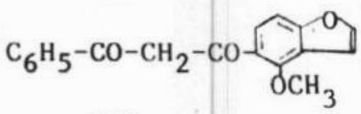
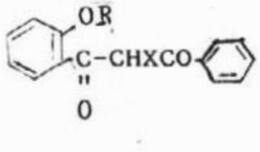


(5)

Pangamol[3] (5), the second crystalline component of seed oil of pongamia globra, is shown to be benzoyl-o-methyl-karnjoymethane[4] i.e. 5-benzoyl-acetyl-4-methoxybenzofuron. It is the first naturally occuring β-diketone related to flavone. In many naturally occuring compounds β-diketones are precursors. Despite this fact, β-diketones are not common in nature. In the early stage of biosynthesis of flavonoids e.g. karanjin, methylation occurs at hydroxyl group[5].

The biogenetic route regarding the synthesis of flavonoids (7,8 through β-diketones (6) may be schemetised as below.



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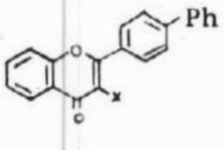

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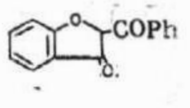

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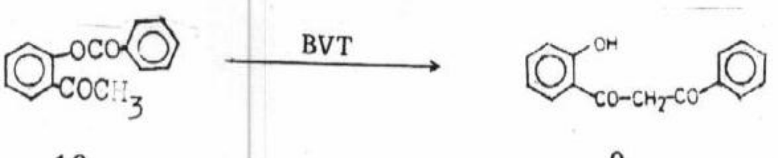
The formation of (7) and (8) depends on pH, below pH=5 compound(7) is formed, while above pH=8 Compound(8) is obtained.

Synthesis of 2-hydroxydibenzoylmethanes (9) have been carried out by Baker-Venkatraman transformation of o-aroyloxyacetophenone (10) using basic catalyst.

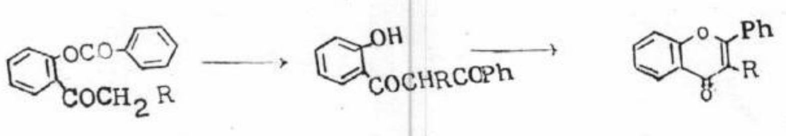


10 9

Various bases such as K_2CO_3 in benzene[8], $NaNH_2$[9], NaOEt[10], K_2CO_3/Pyridine[10], KOH/pyridine[11], potassium butyrate in dioxane[12] and sodiotriphenyl-methane[13] have been tried by various workers.

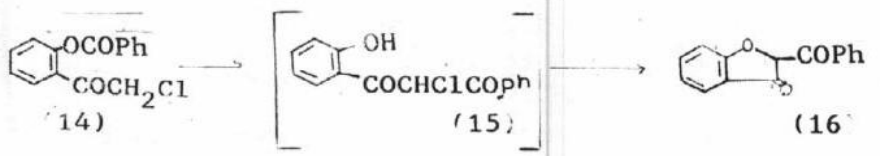
Wheeler and co-owrkers thoroughly investigated the selectivity of base and solvent for reaction medium and concluded that the best solvent was pyridine and the strongest base gave better yield. Recently, Wadodkar[14] reported the use of aprotic solvent, dimethyl formamide (DMF) and pulvarised KOH for the Baker-Venkatraman transformation. DMF proved tobe more advantageous than any other solvent.

Baker-Venkatraman transformation of w-substituted (methyl, phenyl, methoxy etc.) o-aroyloxy acetophenone has been systematically studied by Ollies and Weight[15] and they observed that w-methyl and w-phenyl derivatives (11) rearrange more easily than w-methoxy compounds giving B-diketones (12). This on subsequent cyclisation gives 3-substituted chromones (13).



(11) (12) (13)

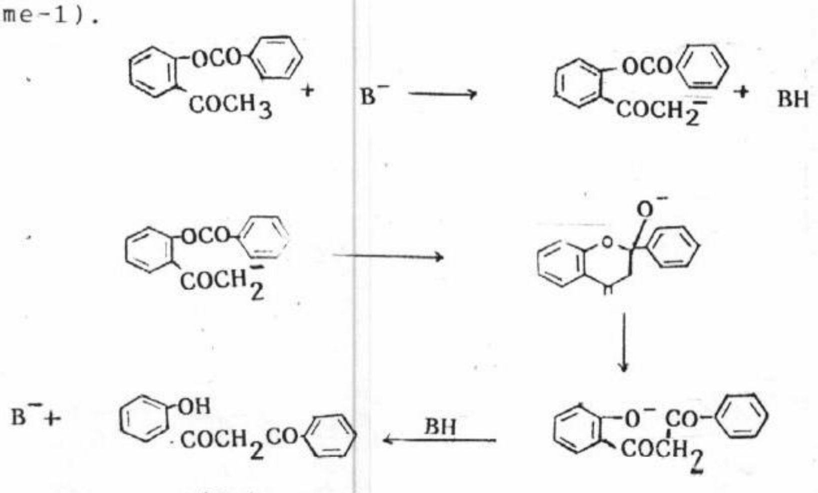
Formation of 2-aroylcoumara-3-one (16) has been reported by Wheelar and coworkers[16] using B.V. transformation of o-aroyloxy-w-chloroacetophenones (14). The transformation takes place via α-chlorodiketone (15) (not isolated).



(14) (15) (16)

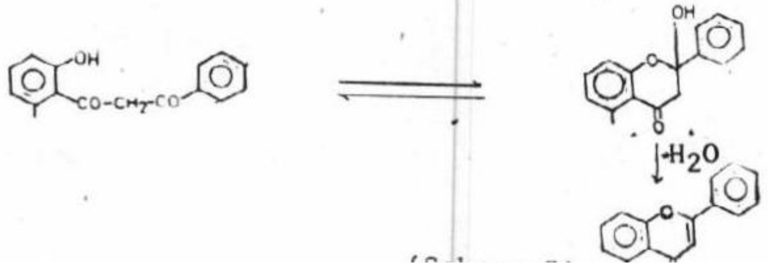
The presence of chlorine on reactive methylene group facilitates the ring closure which occurs during rearrangement[17].

The mechanism of B.V. transformation has been discussed by Wheeler and Co-workers[18,19] and concluded that it involves intramolecular claisen condensation between an ester and methyl ketone (Scheme-1).



(Scheme-1)

The presence of hydroxyl group at 6 position of o-hydroxy or o-aroyloxy-acetophenone has been shown[20] to yield directly flavone during B.V. transformation. Thus when no substituent is present at w or 6 position or when methoxy group is present at 6 position, invariably diketones are obtained. The reaction proceeds via the formation of 2-hydroxy-flavanone which eliminates water molecule to flavone or diketone depending on the nature of substituent at position 6 (Scheme-2).



(Scheme 2)

Halogenation of β-diketones and their chelates

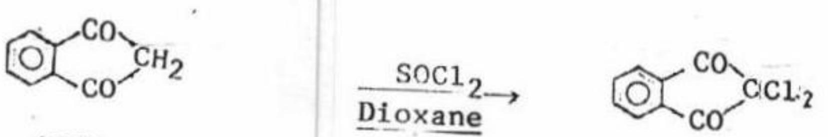
Dibenzoylmethane (17) gives α-bromo or α, α-bromo-derivative, when treated with bromine in acetic acid or in some suitable solvent[21,22]. The formation of two isomeric products (18) and (19) has been reported on bromination of acetyl acetone or 1-phenyl-1,3-butadione provided HBr is not removed from the reaction mixture. Krohnke et al.[23] showed that the compound (18) can be converted in to (19) in presence of HBr.

$$\underset{(17)}{R\text{-}CO\text{-}CH_2\text{-}CO\text{-}CH_3} \longrightarrow \underset{(18)}{R\text{-}CO\text{-}CHBr\text{-}CO\text{-}CH_3} + \underset{(19)}{R\text{-}CO\text{-}CH_2\text{-}COCH\text{-}Br}$$

In the bromination of acetylacetone or 1-3-butadione derivatives the removal of HBr is essential to obtain methylene brominated product. 1,3-Dicarbonyl compounds are known to form sodium or copper salts. Garg and Co-workers[24] obtain pure bromomethylene substituted product by brominating sodium or copper salts of the diketone. The HBr produced is immediately neutralised which otherwise could isomerise (18) to (19). The bromine atom of α-bromodiketone is reactive and labile in nature[25]. It liberates iodine from acidified KI solution regenerating the original diketone[26].

Sulphuryl chloride is an effective chlorinating agent in acetic acid medium for acetylacetone[27].

Dibenzoylmethane with sulphuryl chloride in acetic acid at 50°C gave monochlorodibenzoylmethane[28]. Indane-1,3-dione, a cyclic diketone is (20) reported to give dichloroderivative (21) when treated with sulphuryl chloride in dioxane[29].

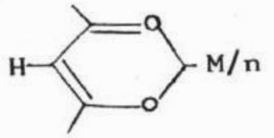


(20)

(21)

The metalchelates of 1,3-diketone have been chlorinated, brominated and iodinated to obtained corresponding halochelates. Collman and coworkers[30,31] studied the halogenation of a variety of metalchelate complexes and used bromine in acetic acid in presence of sodium acetate buffer, ICl and N-halosuccinimide as halogenating agents.

Chelate formation is an important property of β-diketone with alkalimetal ion. The β-diketones form metal enolates through enolic forms. Divalent metals (Be, Cu, Ni) and trivalent metals (Al, Cr, Fe). Chelates have been extensively studied.



M - Metal atom

n - Valency state

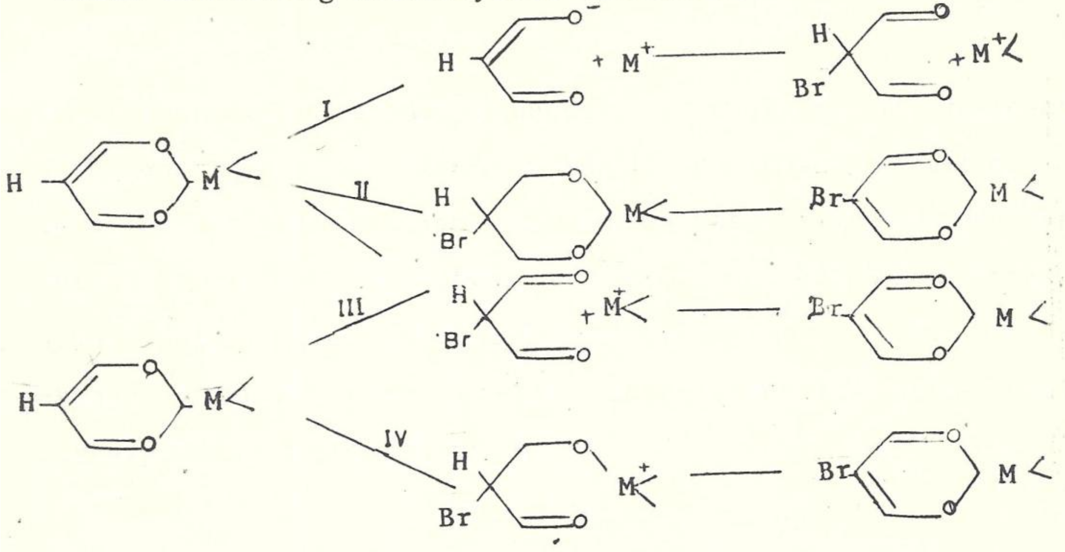
(22)

The metal β-dicarbonyl compound such as (22) with reagents like bromine, S_2Cl_2 and acid chloride lead to products of ring cleavage[32]. Thus Copper (II) complex of 3-keto aldehyde[33] has been shown to break down in presence of bromine in chloroform.

Chromium (III) acetyl acetone on bromination with bromine in chloroform is reported to give tris-(3-bromo-2,4-pentadione)-Cr (III).

Halogenated chelates containing Cr, Co, Al, Fe and Cu have been prepared by Callman and coworkers and by Kluiber by direct substitution.

The ring halogen of metal β-dicarbonyl chelate has been replaced by halogen without ring cleavage using N-halosuccinimide. Kluiber studied the bromination of metal chelate with N-bromosuccinamide (NBS) and suggested that reaction may proceed through initial ring cleavage, then halogenation and ring formation (i) or halogenation of the ring itself by partial or complete ring cleavage (iii) and (iv) or with ring remaining intact (ii). Route (ii), as suggested by Kluiber[31] seemed more probable where metal chelate acts chemically similar to metal containing heterocyclic (Scheme-3).



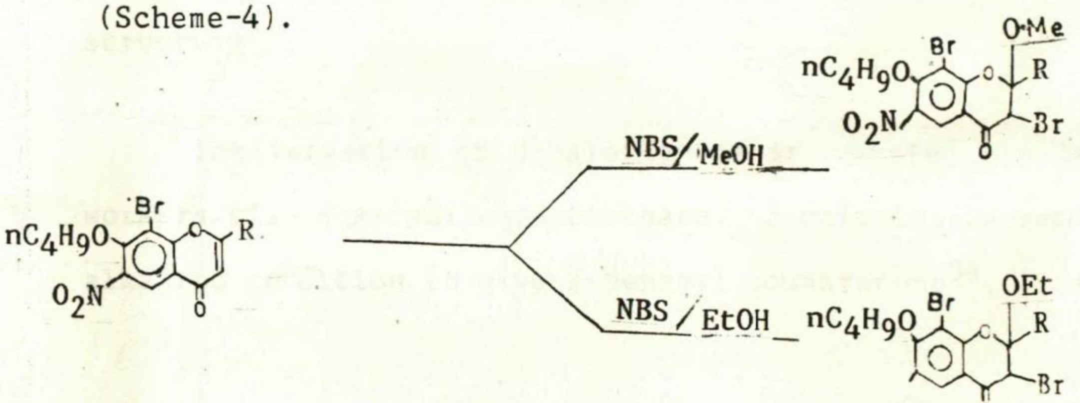
(Scheme 3)

Collman[30] studied the reaction of bromochelate of β-dicarbonyl compounds and observed that bromochelate do not form Grignard's reagent and also noted that bromine of the chelate ring can not be replaced by nucleophile.

Doifode[22] brominated 2-hydroxydibenzoylmethane by three different methods. In the first method 2-hydroxydibenzoylmethane was brominated using bromine in acetic acid and obtained nuclear brominated α-bromocompound. In the second method copper complex of 2-hydroxydibenzoylmethane is carbon tetrachloride was treated with bromine in carbontetrachloride (2 mole of bromine per mole of copper complex) and obtained nuclear brominated α-bromoproduct. In the above two cases bromine substituted simultaneously in nucleus and at reactive methylene group. α-Bromo-2-hydroxy-dibenzoylmethane was obtained exclusively when bromination was carried out in acetic acid sodium acetate buffer and on treatment with ethanolic alkali, it gave 2-benzoyl-coumara-3-one. Cyclization of α-bromo-product with acetic acid-sulphuric acid yielded corresponding 3-bromoflavone.

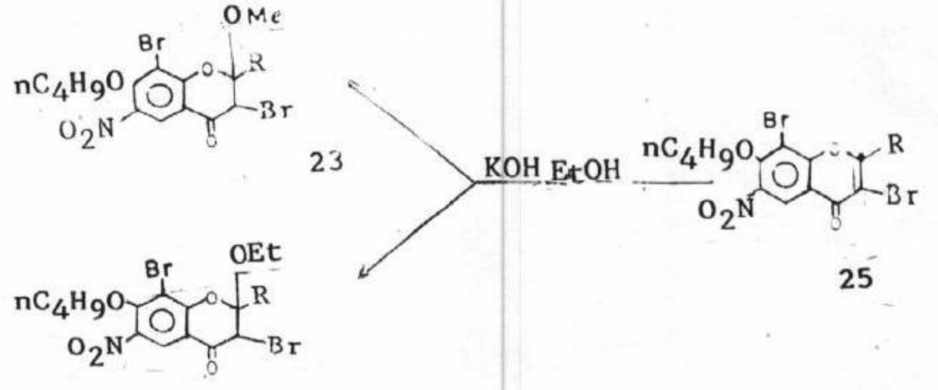
Wadodkar[14] brominated 2-hydroxydibenzoylmethane using dioxanedibromide and obtained 3-bromoflavone.

Flavones when react with N-bromosuccinimide in methanol give 2-methoxy-3-bromoflavone[34]. Flavones react with N-bromosuccinimide in ethanol to give 2-ethoxy-3-bromoflavanone (Scheme-4).



Scheme 4

These 2-methoxy-3-bromoflavanone (23) and 2-ethoxy-3-bromoflavanone[35,36] (24) on treatment with alcoholic KOH at room temperature gave 3-bromoflavone (25).



23

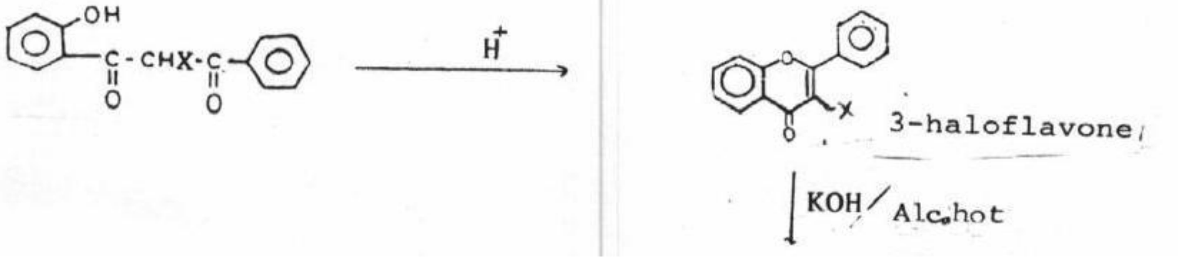
24

25

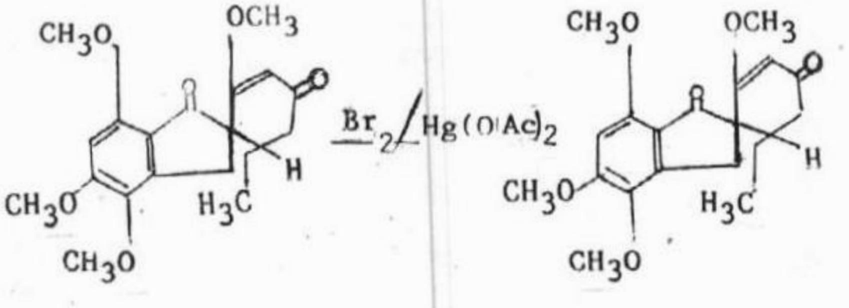
These 3-bromoflavones are physiologically active compounds[36].

Bond angles and lengths of 3-bromoflavones have been determined. The two rings of the chromone system are essentially co-planer, the 2-phenyl group is twisted by 45.9° relative to rest of the molecule, apparently the steric interaction between the bromine atom at C-3 and H-2' outweighs the resonance stabilization which would be associated with a completely planer structure[37].

The formation of 3-haloflavone is carried out by various workers via α-halodibenzoylmethane. 3-Haloflavone rearranges in alkaline condition to give 2-benzoyl coumaranone[38], (Scheme-5).

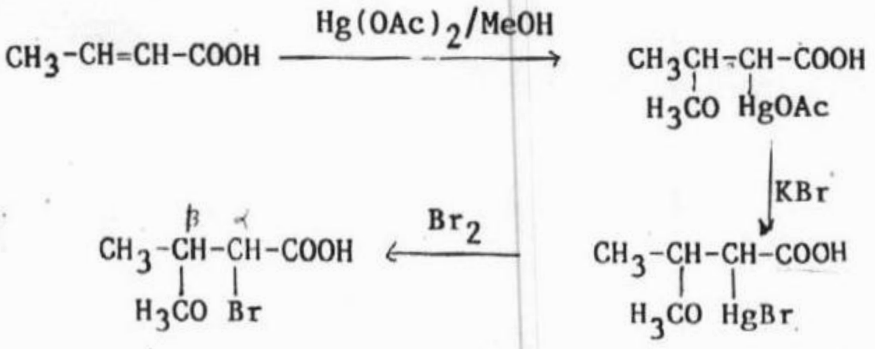


Griseofulvin (26) in acetic acid solution does not react with bromine under ordinary condition. however, while treated with bromine in presence of 0.5 mole $Hg(OAc)_2$ gives 5-bromo-derivative (27) presumable the 5-acetoxy mercuric derivative is converted to 5-bromoderivative by displacement by bromine[39].



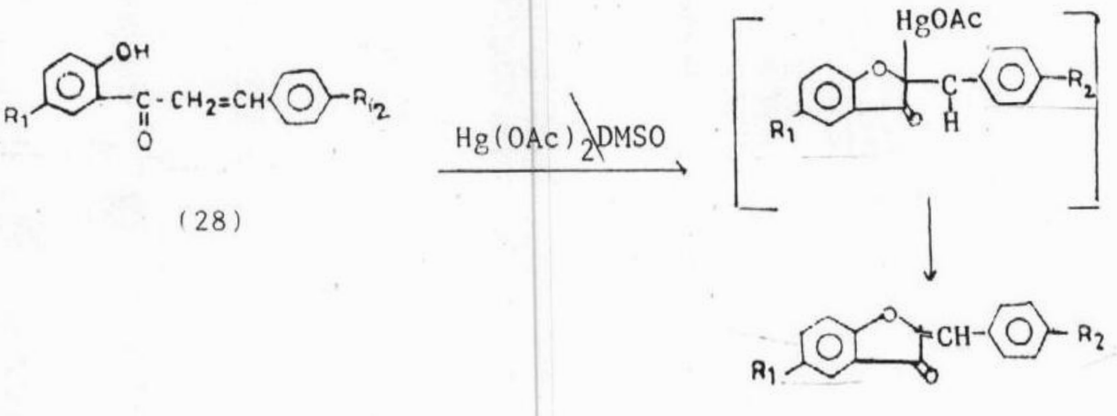
(26) (27)

α-B unsaturated acid, crotonic acid with $Hg(OAc)_2$ in methanol followed by KBr/Br_2 treatment gives α-bromo-B-MeO-n-butyric acid[40] (Scheme-6).



(Scheme-6)

2'-hydroxy-chalcone (28) with $Hg(OAc)_2$ in DMSO solvent gives aurone[41] (29).



(28)

Aurone (29)

The above surveyed literature of 3-bromoflavone was further extented for the reported work on the coupling reaction of 3-bromoflavones. Coupling of arylhalides with copper is called Ullmann reaction[42]. Picryl chloride and idobenzene gave only 2,4,6-trinitrophenyl[43]. The nitrogroup is strongly activating but only in the ortho, not in the meta and para position[44] mechanism is not known with certainty[45]. Organocopper compound have been trapped by co-ordination with organic bases[46] 2-Thiethyl copper has been independently prepared and treated with aryl iodide to give 2-arylthiopene[47]. A similar reaction has been used for ring closure[48]. Ullmann type coupling has also been carried out, with ArNa and ArCl. This proceeds by the benzene mechanism[49].

Iodochromones and Iodoflavones undergo Ullmann reaction to form bis-compounds. Some of which occure naturally or are related to such biflavonoids[50,51].

ORIGIN OF PROBLEM AND PROBLEM

The formation of 3-haloflavone[42,43] has been carried out by various workers via 2-halodibenzoylmethanes. The haloflavones rearrange in alkaline condition to give 2-benzoylcoumaranones[38].

Griseofulvin does not react with bromine in acetic acid under ordinary conditions while Griseofulvin reacts with bromine in presence of mercuric acetate to give 5-bromoderivative. The present work deals with the formation of 3-bromoflavones from flavones by reacting with bromine in acetic acid in presence of catalytic amount of mercuric acetate. Thus, in this reaction flavone converts in to 3-bromoflavone.

The 3-bromoflavone is further studied for its reaction with alcoholic potassium hydroxide or sodium hydroxide.

The 3-bromoflavone was also tried to react under the condition of Ullmann reaction.

Microbial activity of some 3-bromoflavones are considered.