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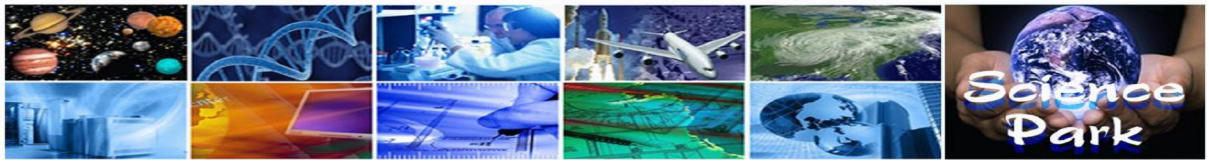
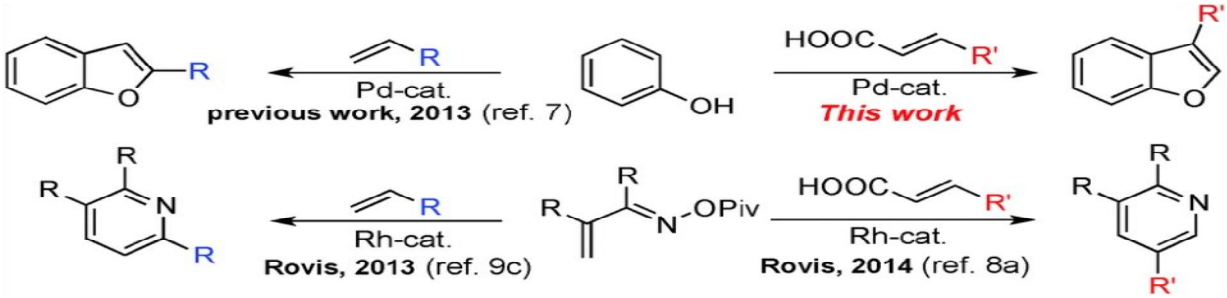
ISSN : 2321–8045
Impact Factor : 2.1005[UIF-2014]



ISSN 2321–8045 Impact Factor : 2.1005[UIF-2014] Volume - 3 | Issue - 27 | 14 th Jan - 2016



A REVIEW: AN INSIGHT ON SYNTHESIS OF BENZOFURAN

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ABSTRACT

Benzofuran are heterocyclic compounds which constitute the largest group. It is present in numerous biologically active natural products as well as synthetic material. This review presents a precise and exhaustive survey of different method of preparation of benzofurans derivatives. Benzofuran derivatives are important intermediates for the synthesis of diversity of synthetically effective and novel heterocyclic compounds.

KEYWORDS : *Benzofuran, Synthesis, Aurones*

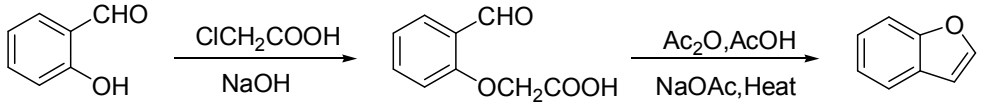
INTRODUCTION

Benzofurans have attracted a great deal of interest because of their presence in a large number of natural products, their biological activities, and their potential applications as pharmacological agents. For example, 5-benzofuranol has potent antiallergic and anti-inflammatory activities[1], Machicendiol, a benzofuran isolated from the extracts of Machilusglaucescens, a folk medicine, has been used in the treatment of asthma, rheumatism, and ulcers,[2] 2,5-disubstituted benzofurans are active in enhancing insulin sensitivity,[3] and benzofuran-fused benzocarbazoles have potential antitumor and antibiotic activities.[4] Several benzofuran ring systems bearing various substituents at the C-2 position are widely distributed in nature, for example, 2-arylbenzofuran has been isolated from a Chinese herbal plant and possesses various

biological activities.[5] Ailanthoidol, a neolignan derivative, has been reported to have antiviral, antioxidant and antifungal activities.[6] Furthermore, most of compounds prepared from 2-acetylbenzofurans have antimicrobial, antitumor, anti-inflammatory, fungicidal, and weed-killing activities and may be used for treatment of cardiac arrhythmias.[7] Benzofurans including the pyrazole nucleus are known to possess analgesic, anti-inflammatory, antipyretic, antiarrhythmic, musclerelaxant, psychoanaleptic, anticonvulsant, hypotensive, monoamine oxidase inhibitory, antidiabetic and antibacterial activities.[8,9] The pyrazole derivative celebrexis a potential anti-inflammatory drug.[10] In addition, benzofurans containing 1,3-thiazole derivatives have been reported to possess tuberculostatic, antibacterial and antifungal activities.[11]

SYNTHESIS AND REACTIONS

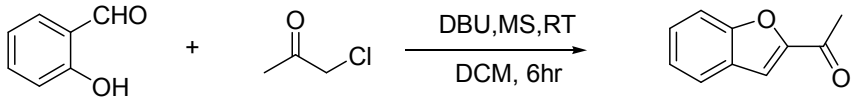
1) Reaction of salicylaldehyde1 with chloroacetic acid gives o-formylphenoxyacetic acid 2. When refluxed with acetic anhydride in glacial acetic acid, it affords the benzofuran3 (Scheme 1).[12]



1 **2** **3**

Scheme 1

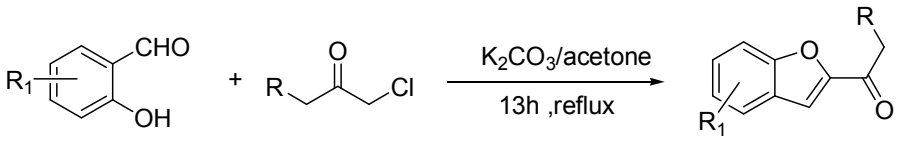
2) Treatment of salicylaldehyde1 with 1-chloro-propan-2-one 4 in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst gave 2-acetylbenzofuran 5 (Scheme 2).[13]



1 **4** **5**

Scheme 2

3) Al-kadhimi,Ahmed abdul et al. synthesized 2-acetyl benzofuran8 from salicylaldehyde6 and chlorocacetone7 by using excess amount of potassium carbonate and dry acetone in refluxing condition for 13 hours (Scheme 3).[14]

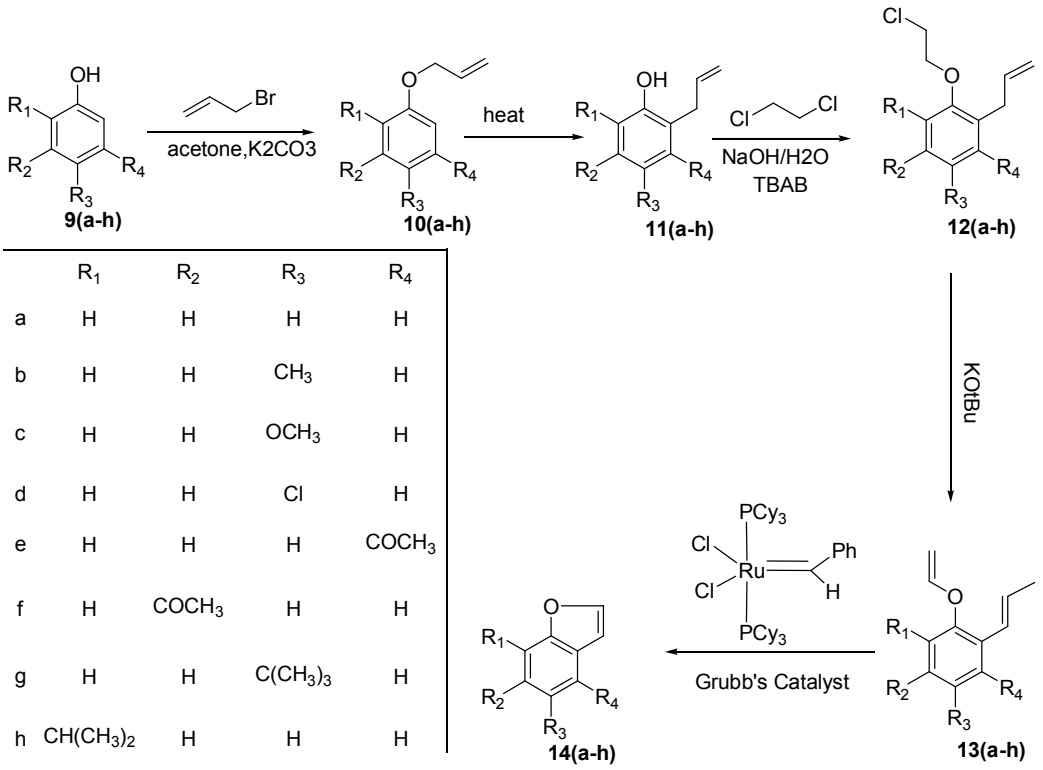


6 **7** **8**

Scheme 3

4) FROM PHENOLS:

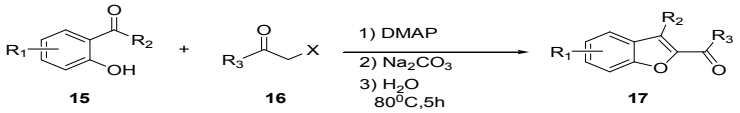
When 3-bromo propene react with substituted phenols 9(a-h) with potassium carbonate in acetone solvent to give different allyl aryl ethers 10(a-h).These allyl aryl ethers 10(a-h) further heated undergoes Claisen Rearrangement to give ortho-allyl phenols 11(a-h). Compound 12(a-h) was obtained by SN2 substitution reaction by 1,2-dichloro ethane in alkaline medium and phase transfer catalyst ,tetra butyl ammonium bromide(TBAB). Further treatment with potassium tert.butoxide in tetrahydrofuran solvent give 1,2-eliminated product with removal of HCl gas and by using Grubb's Catalyst ring closing metathesis (RCM) occur to yield 14(a-h) (Scheme 4).[15-21]



	R_1	R_2	R_3	R_4
a	H	H	H	H
b	H	H	CH_3	H
c	H	H	OCH_3	H
d	H	H	Cl	H
e	H	H	H	$COCH_3$
f	H	$COCH_3$	H	H
g	H	H	$C(CH_3)_3$	H
h	$CH(CH_3)_2$	H	H	H

Scheme 4

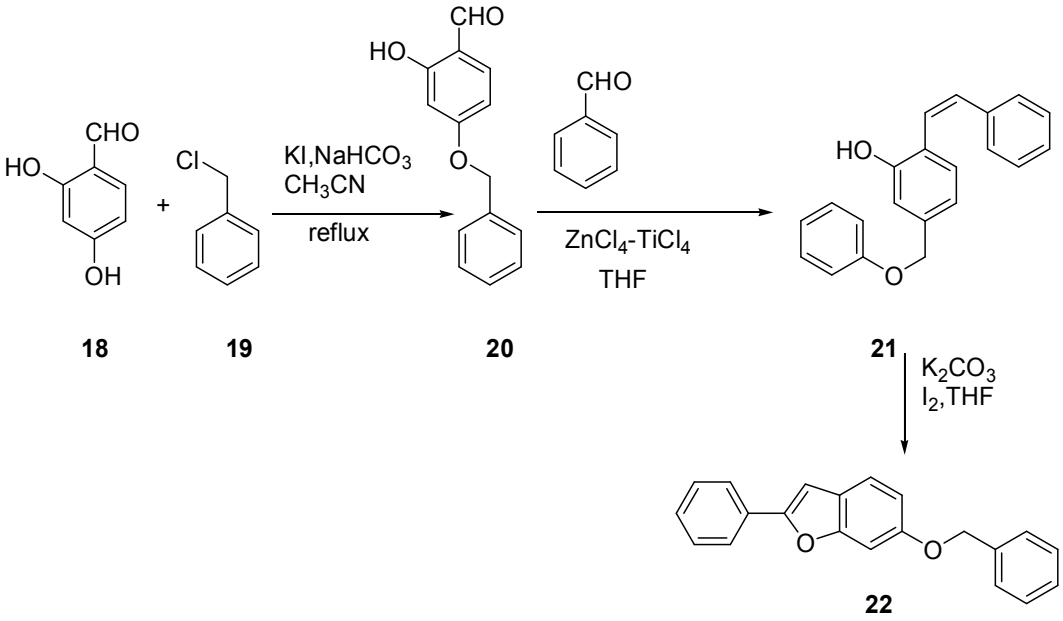
5) 4-dimethyl amino pyridine (DMAP) catalyst and halogenated ketone derivatives 16 in water at 80̊C in air environment to yield different benzofuran derivatives 17 (Scheme 5).[22]



R_1	R_2	R_3	X
3-Br	H	$CH_3C_6H_4$	Br
3-Br	H	$CH_3OC_6H_4$	Br
3-Br	H	BrC_6H_4	Br
3-Br	H	$p\text{-}NO_2C_6H_4$	Br
3-Br	H	$m\text{-}NO_2C_6H_4$	Br
3-Cl	H	C_6H_5	Br
3-Cl	H	$CH_3C_6H_4$	Br
3-Cl	H	$CH_3OC_6H_4$	Br
3-Cl	H	BrC_6H_4	Br
3-Cl	H	$p\text{-}NO_2C_6H_4$	Br
3-Cl	H	$m\text{-}NO_2C_6H_4$	Br
H	CH_3	C_6H_5	Br
H	CH_3	BrC_6H_4	Br
H	CH_3	$p\text{-}NO_2C_6H_4$	Br

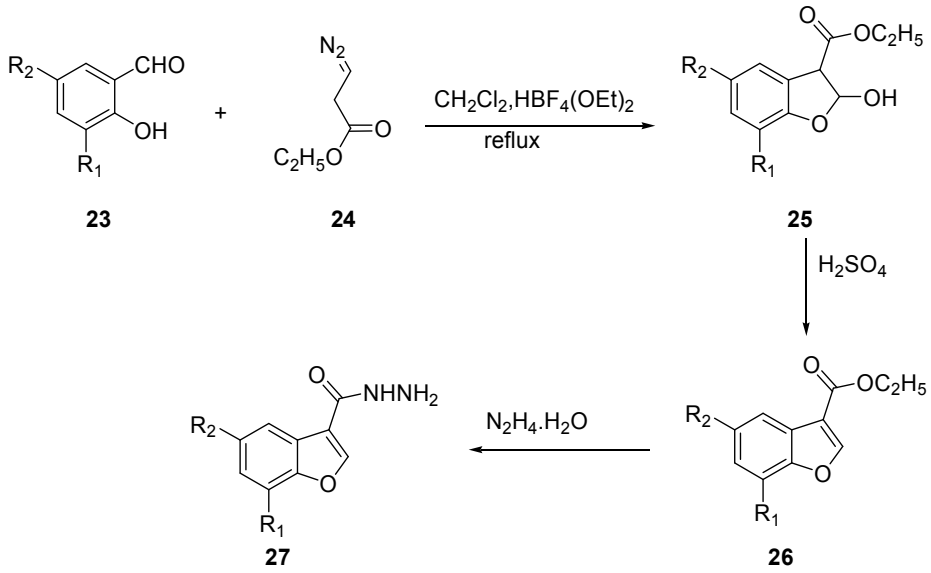
Scheme 5

6) Dihydroxy benzaldehyde 18 reacted with benzyl chloride 19 with KI produced 4-benzyloxy-2-hydroxy-benzaldehyde 20. Further reaction of 4-benzyloxy-2-hydroxy-benzaldehyde with different aldehyde gives 5-benzyloxy-2-vinyl-phenol 21 which reacted with iodine to afford 6-benzyloxy-benzofuran 22 (Scheme 6).[23]



Scheme 6

7) Reaction of 2-hydroxy-benzaldehyde derivatives 23 and 3-diazo-propionic acid ethyl ester 24 with HBF4(OEt)2 in DCM gives 25. Further reaction of 25 with sulphuric acid gives 2,3-dihydro-benzofuran-3-carboxylic acid ethyl ester derivatives 26, which then react with hydrazine hydrate afford Benzofuran-3-carbohydrazide 27 (Scheme 7).[24]

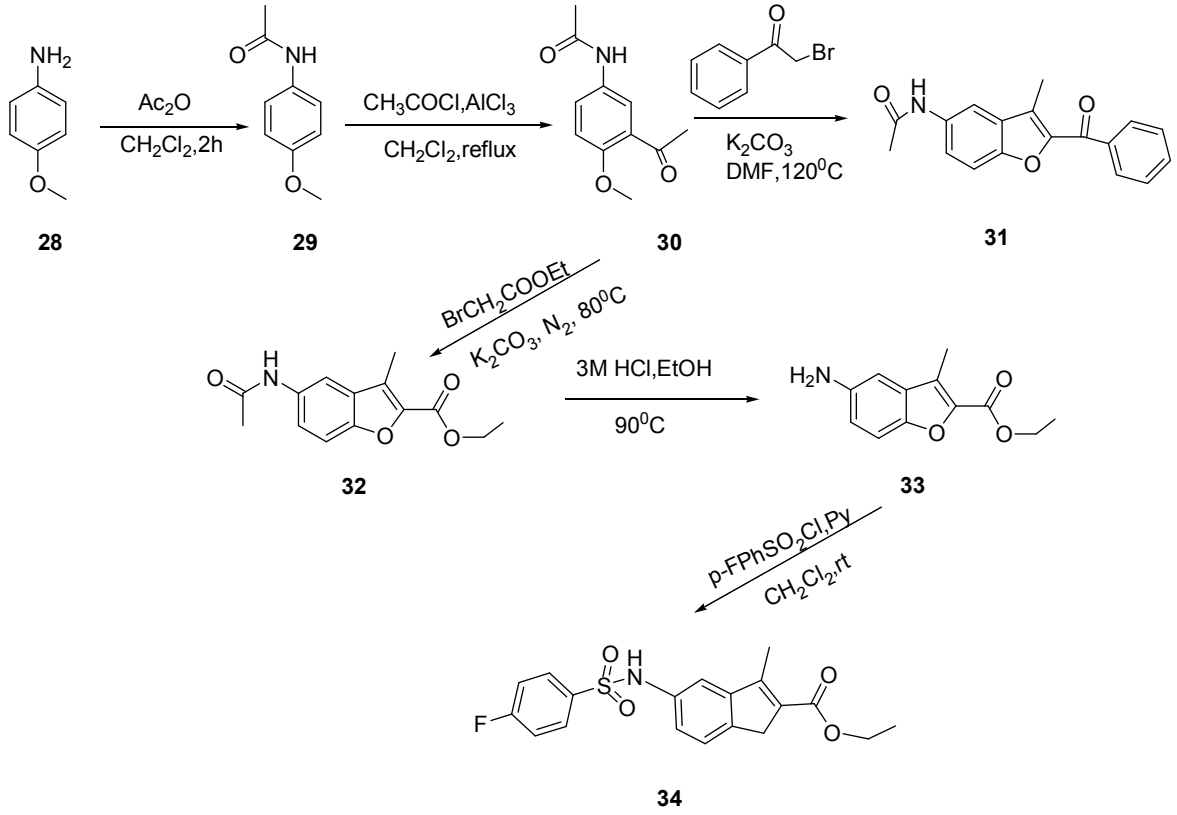


R_1	H	Cl	C_6H_5	p-OHC_6H_4	p-ClC_6H_4	p-$NO_2C_6H_4$	$C_{10}H_7$	p-$CH_3C_6H_4$
R_2	H	Cl	C_6H_5	p-OHC_6H_4	p-ClC_6H_4	p-$NO_2C_6H_4$	$C_{10}H_7$	p-$CH_3C_6H_4$

Scheme 7

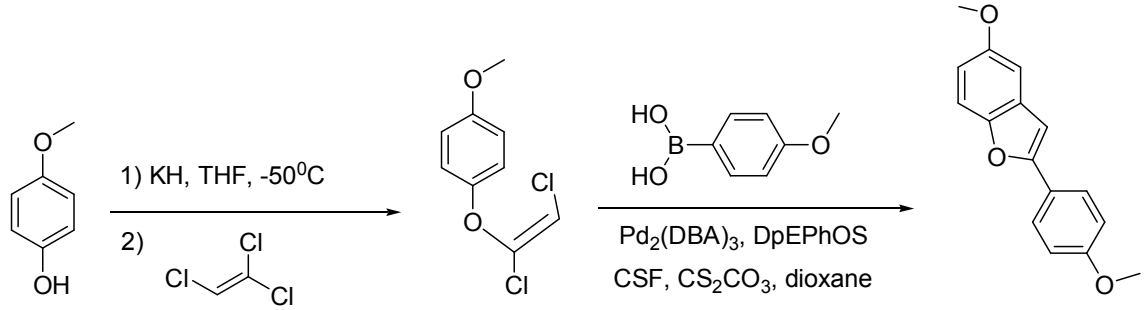
8) Starting with aniline derivative 5-(4-Fluoro-benzenesulfonylamino)-3-methyl-benzofuran-2-carboxylic acid ethyl ester 34 was formed. Compound 28 was acylated with acetyl chloride in presence of aluminium chloride to form N-(3-acetyl-4-hydroxy-phenyl) acetamide30. This compound 30 when react with ethyl bromoacetate or benzoyl bromide in DMF for 1 hour give N-(2-benzoyl-3-methylbenzofuran-5-yl)-

acetamide31 and 5-acetylamino-3-methyl-benzofuran-2-carboxylicacid ethyl ester 32. Further hydrolyzed 32 with HCl obtained 33 which on react with p-fluorobenzenesulfonyl chloride in basic condition and dichloromethane as solvent to yield aimed compound 34 (Scheme 8).[25]



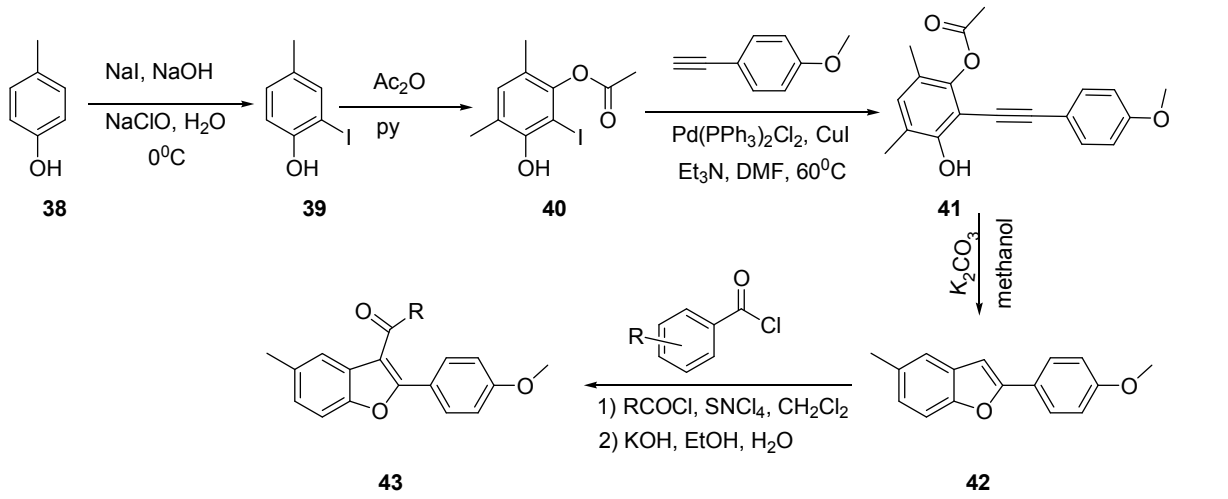
Scheme 8

9) Bis ethers 36 was formed by the treatment of 4-methoxyphenol 35 with trichloro ethylene in tetrahydrofuran , which further reacted with 4- methoxyphenylboronic acid in 1,4-dioxane solvent to give desired benzofuran derivative 37 (Scheme 9).[26-29]



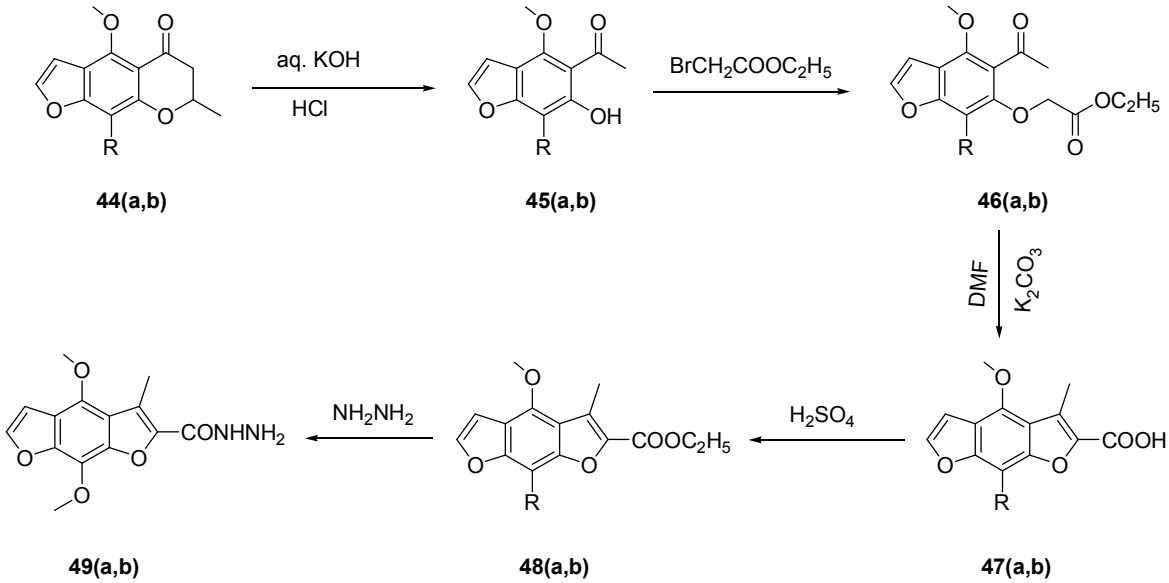
Scheme 9

10) p-substituted phenol 38 reaction with sodium iodide in presence of sodium hydroxide and NaClO at low temperature gave iodination of phenol as monoiodine phenol 39 which on treatment with acetic anhydride in pyridine produced intermediates 40 which coupled with 1-ethynyl-4-methoxybenzene using Sonogashiracouping reagent Pd(PPh3)2Cl2/CuI in triethylamine base gave diarylethyne41 then intramolecular cyclization was done by potassium carbonate in methanol afforded benzofuran42 . Benzofuran42 underwent Friedel–Crafts bezoylation with acid chloride to give benzoylatedbenzofuran43 (Scheme 10).[30]



Scheme 10

11) Started reaction of visnagen44(a) and khellin44(b) in aqueous potassium hydroxide gave visnagenone45(a) and khellinone45(b) respectively.[31,32,] Then treated with ethyl bromoacetate to gave 4-methoxy-5-acetylbenzofuran-6-yloxy)acetic acid ethyl ester[33] 46(a) and 4,7-dimethoxy-5-acetylbenzofuran-6-yloxy)acetic acid ethyl ester ,46(b) which again reacted with potassium carbonate in DMF solvent afforded 4-methoxy-3-methylbenzo[1,2-b:5,4-b]difuran-2-carboxylicacid 47(a) and 4,8-dimethoxy-3-methylbenzo[1,2-b:5,4-b]difuran-2-carboxylicacid 48(b).Then compound 48(a,b) and 49(a,b) were obtained by treatment with sulfuric acid and hydrazine hydrate respectively (Scheme 11).[34]

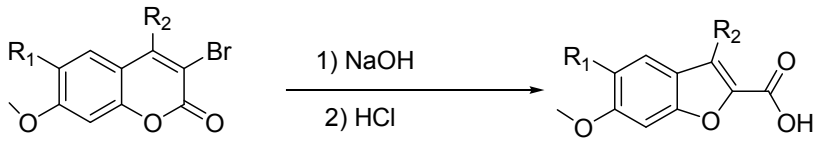


a) Visnagen R=H **b)** Khellin R=OCH_3

Scheme 11

12) From Coumarin

Reaction of substituted 3-bromocoumarin 50 firstly with basic and then with acidic condition to afforded substituted benzofuran-2-carboxylic acid 51 via Perkin Rearrangement (Scheme 12).[35]

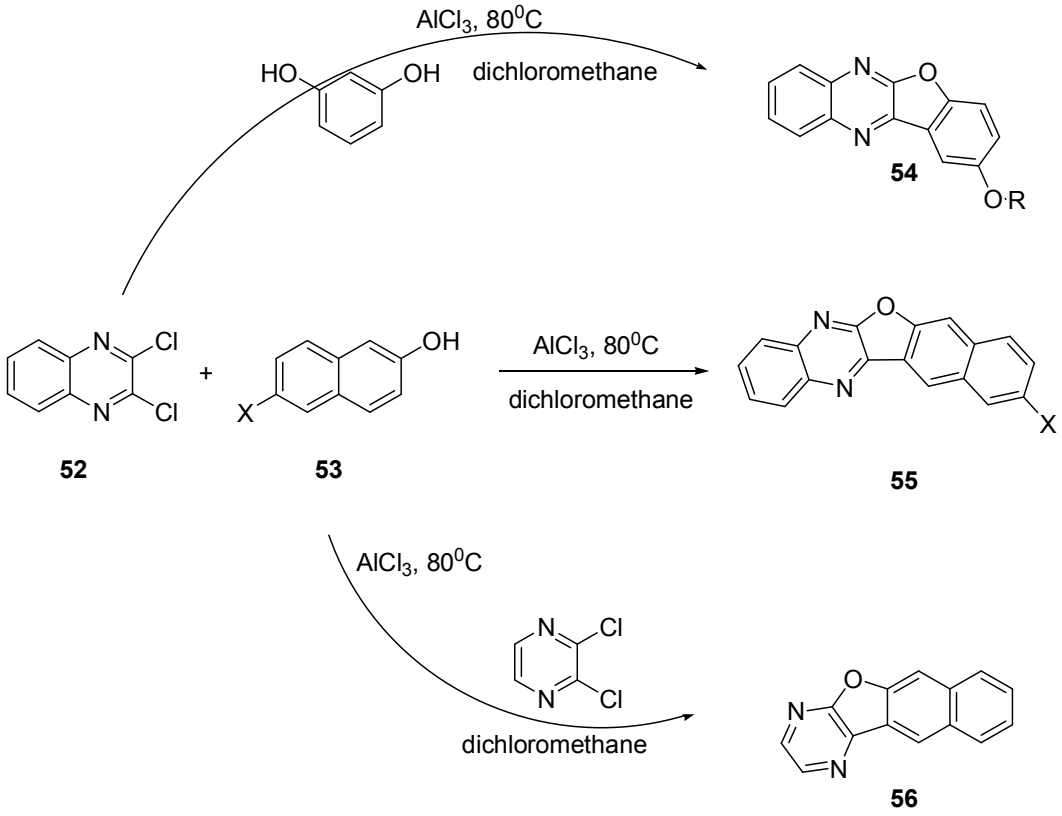


50 **51**

R_1	R_2
OCH_3	CH_3
H	CH_3
OCH_3	H
H	H

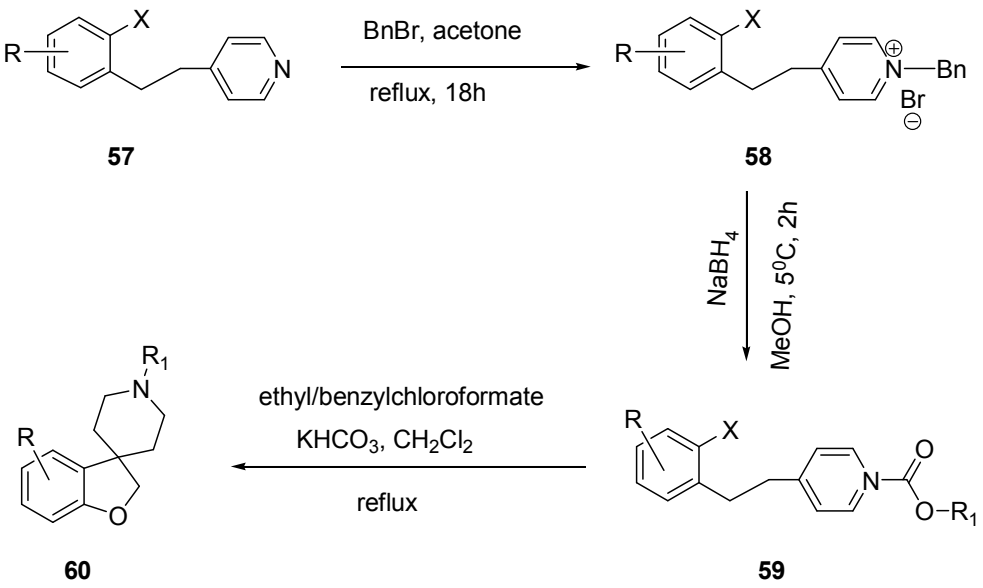
Scheme 12

13) Here two component systems were synthesized by one pot reaction with aluminium chloride at 80̊C in dichloromethane to afford 54, 55 and 56 (Scheme 13).[36]



Scheme 13

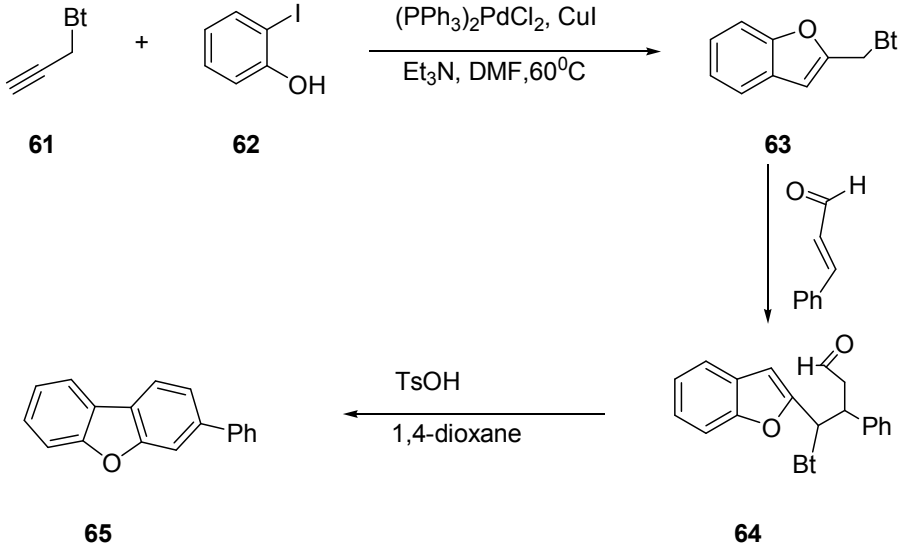
14) Here Spiro benzofuran(2H-Spiro[1-benzofuran-3,4-piperidin]ol) 60 was obtained via Heck Cyclization of three different series of compounds (Scheme 14).[37]



57 **58** **59** **60**

Scheme 14

15) Sonogashiracouping reagent Pd (PPh3)2Cl2/CuI in triethylamine base was used to synthesized 2-(benzotriazol-1-ylmethyl) benzo[b]furan 63 from 1-propargyl benzotriazole61 and o-Iodophenol62. Further alkylation was done by trans-cinnamaldehyde to gave64 and intramolecular cyclization with TSOH in dioxane afforded dibenzofuran 65 (Scheme 15).[38]

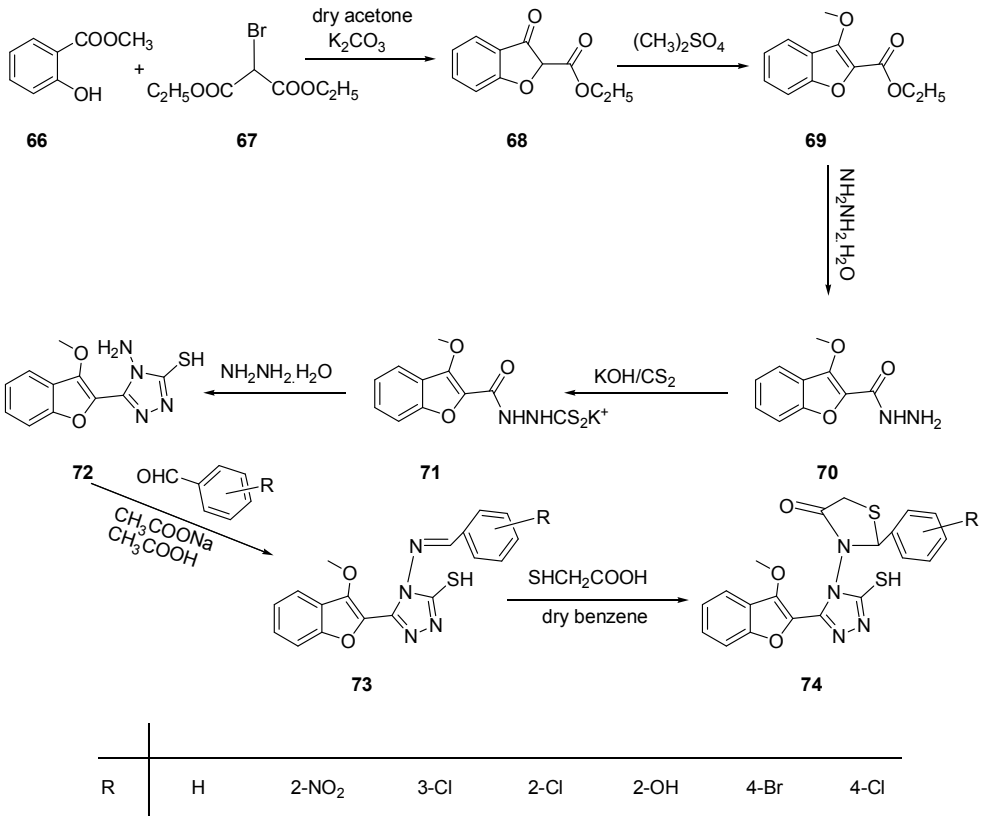


61 **62** **63** **64** **65**

Bt=benzotriazole

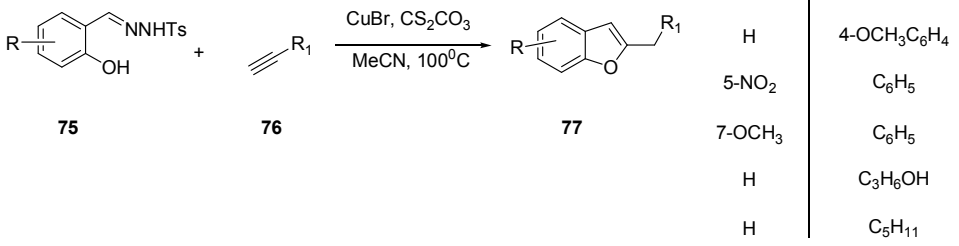
Scheme 15

16) 2-carbethoxy-3(2H) benzo furanone68 was synthesized by heating methylsalicylate66 with diethylbromo malonate 67 in anhydrous potassium carbonate base and dry acetone .Then diethylsulphate was used for alkylation to gave 2-carbethoxy 3-methoxy benzofuran69. Further reaction with hydrazine hydrate formed hydrazide derivatve70 and again reaction with carbon disulfide in basic condition formed potassium salt 71 which again reacted with hydrazine hydrate afford amino triazole derivative 72 which further treated with benzaldehyde derivative gave 73 and 73 reflux with mercaptoacetic acid to synthesized thiazoline derivatives 74 (Scheme 16).[39]



Scheme 16

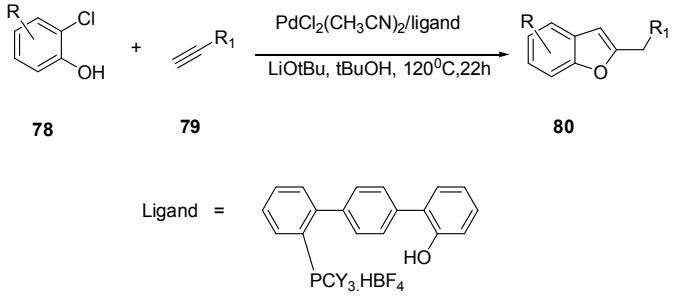
17) N-tosylhydrazone75 and terminal alkynes 76 were treated with copper bromide in ligand free condition to obtained benzofuran derivatives 77 (Scheme 17).[40]



R	R_1
H	$4\text{-}CF_3C_6H_4$
H	$4\text{-}OCH_3C_6H_4$
$5\text{-}NO_2$	C_6H_5
$7\text{-}OCH_3$	C_6H_5
H	C_3H_6OH
H	C_5H_{11}

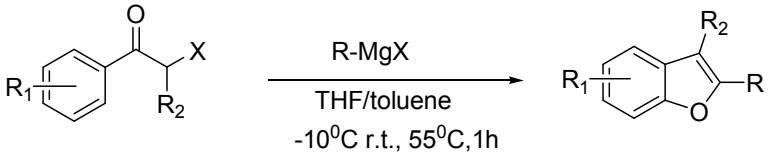
Scheme 17

18) One pot benzofuran derivatives 80 were obtained by reaction of 2-chlorophenols 78 and alkynes 79 in presence of Pd catalyst with hydroxyl-terphenyl-phosphine ligand (Scheme 18).[41]



Scheme 18

19) 1-(2-hydroxyphenyl)-2-chloroethanones 81 were reacted with Grignard reagent to form [1,2]-aryl migrated and [1,3]-aryl migrated product. Here [1,2]-aryl migration was obtained by controlled temperature to gavebenzofuran derivatives 82 (Scheme 19).[42]

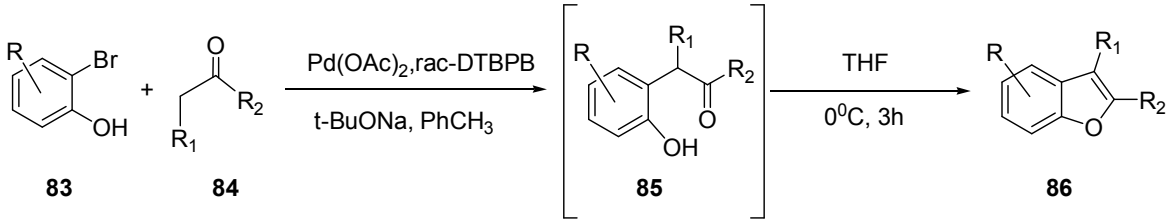


81 **82**

R	R_1	R_2
C_2H_5	H	H
C_6H_{11}	H	H
C_4H_9	H	CH_3
$CH_2C(CH_3)_2Ph$	H	H
2-thienyl	H	H
4-Cl-C_6H_4	5-Br,7-CH_3	H

Scheme 19

20) Pdcatalysedenolatearylation was done on substituted phenol 83 and ketone derivatives 84 to yield benzofurans derivatives 86 via one pot reaction (Scheme 20).[43]

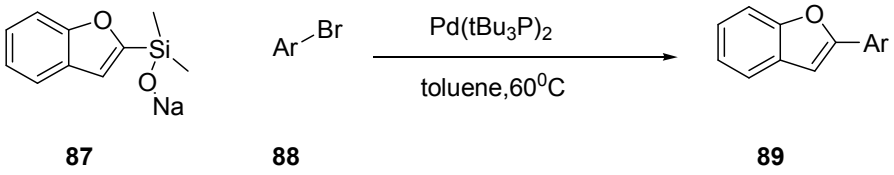


83 **84** **85** **86**

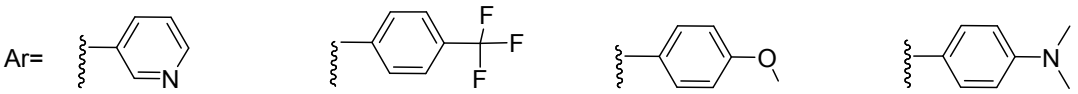
R	R_1	R_2
H	C_2H_5	C_6H_5
H	H	3,5-$OCH_3C_6H_3$
H	CH_3	thienyl
H	$CH_2C(CH_3)_2CH_2CH_2$	$CH_2C(CH_3)_2CH_2CH_2$
5-CH_3	CH_3	C_6H_5
6-F	CH_3	C_6H_5
5-Cl	CH_3	C_6H_5
5-NO_2	CH_3	C_6H_5
5-NH_2	CH_3	C_6H_5

Scheme 20

21) Cross-Coupling reaction proceed with the use of bis (tri-tert-butylphosphine) palladium on a large number of electron-rich, electron-poor, and sterically hindered aryl- and hetero aryl silanols of alkali metal salt 87 and arylbromides88 in mild condition to afford 2-arylbenzofuran 89 (Scheme 21).[44]

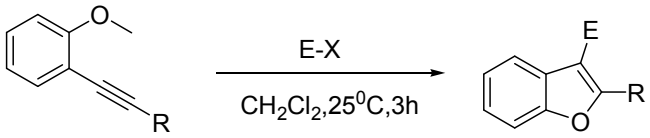


87 **88** **89**



Scheme 21

22) With terminal alkynes and different o-iodoanisoles formed aryl- and vinylic substituted alkynes 90 which gave 2,3-disubstituted benzo[b]furans 91 in mild condition via coupling followed by electrophilic cyclization (Scheme 22).[45]



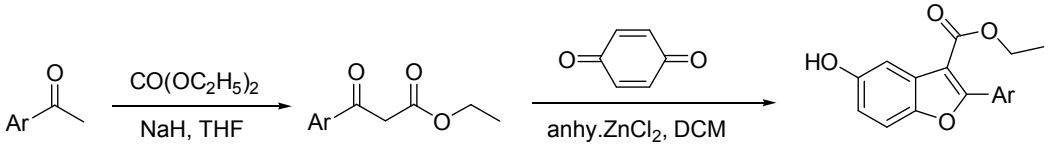
90 **91**

R	E
C_6H_5	I
C_6H_5	SePh
C_6H_5	$SC_6H_4NO_2$-p
p-$OCH_3C_6H_4$	I
p-$OCH_3C_6H_4$	SePh
C_6H_5	I

E-X=I_2,PhSeCl,$NO_2C_6H_4SCl$

Scheme 22

23) 3-oxo-3-aromatic-propionic acid ethyl ester 93 was prepared by reaction of substituted ketone 92 with diethyl carbonates and further reaction with benzoquinone to gave 5-hydroxy-2-aryl-benzofuran-3-carboxylic acid ethyl ester 94 (Scheme 23).[46]



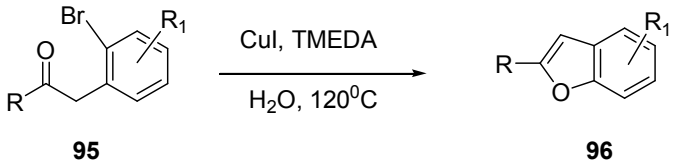
92 **93** **94**

Ar	4-$OCH_3C_6H_4$	4-$CH_3C_6H_4$	2-naphthyl

Scheme 23

With Copper Iodide

24) CuI and TMEDA(tetramethylethylenediamine) was used to convert different type of ketones 95 into benzo[b]furans 96 (Scheme 24).[47]

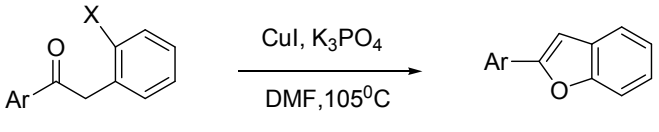


95 **96**

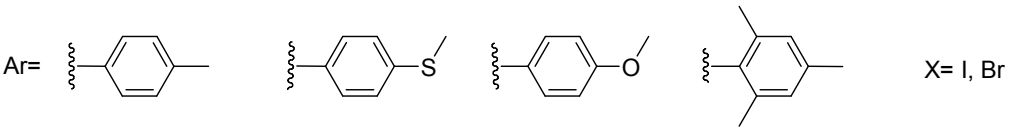
R	R_1
$2\text{-}ClC_6H_4$	H
$2\text{-}ClC_6H_4$	5,6-diF
$2\text{-}NO_2C_6H_4$	H
CH_3	H
C_6H_5	$5,6\text{-}diOCH_3$
$p\text{-}OCH_3C_6H_4$	H

Scheme 24

25) Using CuI, ring closure reactions proceed by using different type of 2-haloaromatic ketones 97, 99 to afford variety of benzofurans98, 100 (Scheme 25, 26).[48]

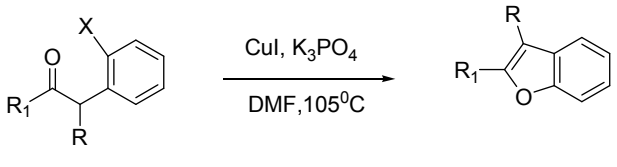


97 **98**



Scheme 25

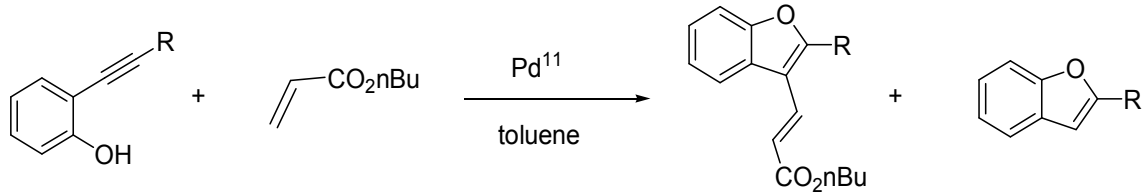
R	R_1
CH_3	$p\text{-}OCH_3\text{-}C_6H_4$
$COOC_2H_5$	C_6H_5
CN	C_6H_5
$-CH_2\text{-}o\text{-}Br\text{-}C_6H_4$	CH_3
$-CH_2\text{-}o\text{-}Br\text{-}C_6H_4$	H



99 **100**

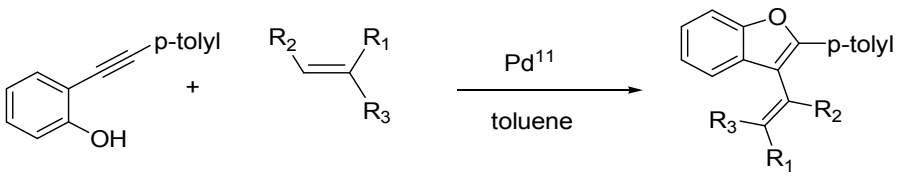
Scheme 26

26) Synthesis of different benzofurans103, 104 were done by using Pd catalyst on 2-ethynyl-phenol derivatives 101, 105 with acrylic acid derivatives (Scheme 27, 28).[49]



101 **102** **103** **104**

Scheme 27

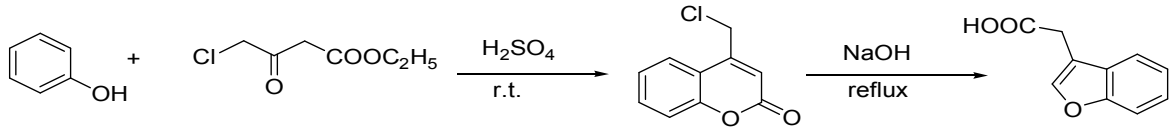


105 **106** **107**

R_1= $COCH_3$,CN,SO_2CH_3,C_6H_5,$CONH_2$,$COOCH_3$
R_2=H,CH_3
R_3=H,CH_3

Scheme 28

27) By using substituted phenols 108 and ethyl-4-chloroacetate 109 to afford 4-chloro- methylcoumarin110 in sulphuric acid and then further reflux with NaOH to obtained required benzofuran-3-acetic acid 111 (Scheme 29).[50]

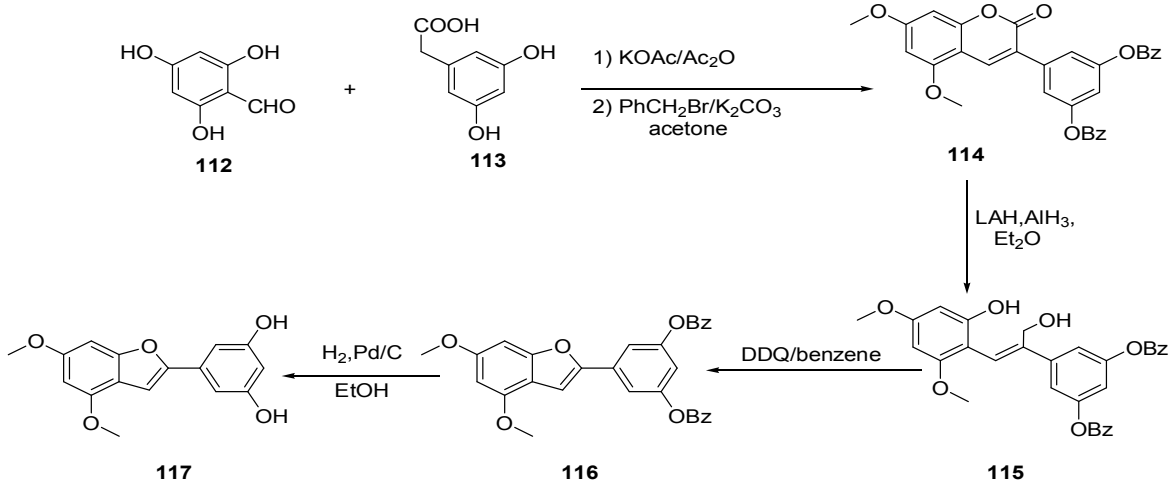


108 **109** **110** **111**

R=3-OH, 4-CH_3, 4-OCH_3

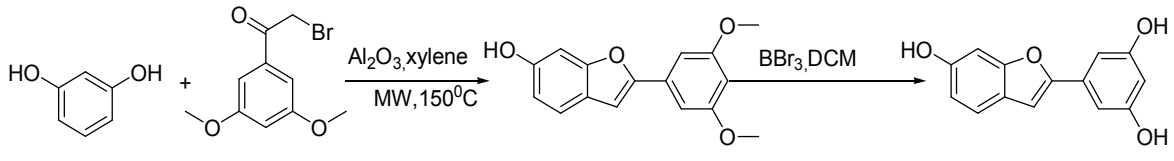
Scheme 29

28) Perkin condensation was done on 2,4,6-trihydroxybenzaldehyde 112 and 2-(3,5-dihydroxyphenyl) acetic acid 113 to yield 3-phenylcoumarin derivatives 114 and then further reaction with LAH/AlH3 and DDQ afford corresponding 2-phenylbenzofurans 116 then debenzylation done by Pd/C in presence of hydrogen to obtained Moracin A 117 (Scheme 30).[51]



Scheme 30

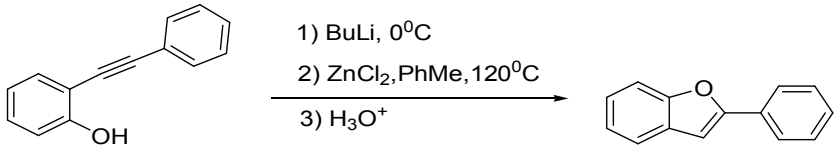
29) Benzofuran derivatives120, 121 were derived from resorcinol 118 and α-bromoacetophenone119 in presence of neutral alumina using xylene at 150̊ (Scheme 31).[52]



118 **119** **120** **121**

Scheme 31

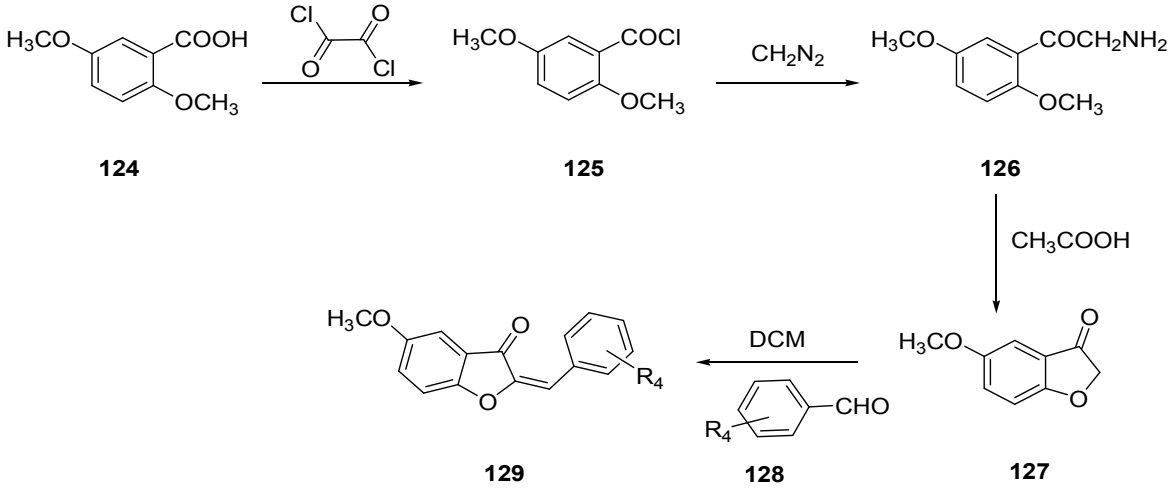
30) Reaction of ortho-alkynylphenols122 with Zn catalyst to afford benzofuran derivative 123 via intramolecular hydroalkoxylation reactions (Scheme 32).[53,54]



122 **123**

Scheme 32

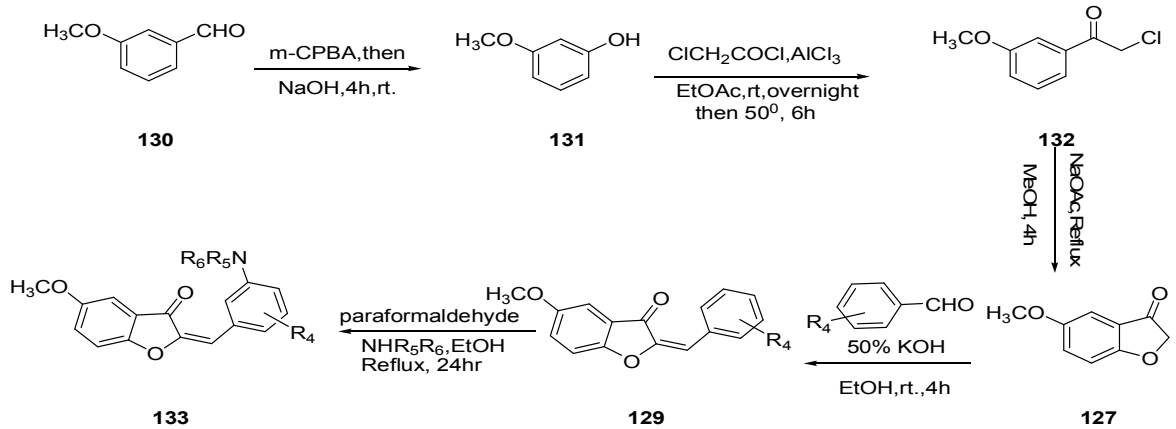
31) Refluxing of 2,5-dimethoxy-benzoic acid 124 with oxalyl dichloride gave 2,5-dimethoxy-benzoyl chloride 125, which reacted with diazomethane to afford 126. The latter compound 126 refluxed in acetic acid to give 5-methoxy-benzofuran-3-one 127 , which condensed with 3,4-dihydroxybenzaldehyde give 2-(3,4-dihydroxy-benzylidene)-5-methoxy-benzofuran-3-one 129 (Scheme33).[55]



124 **125** **126** **127** **128** **129**

Scheme 33

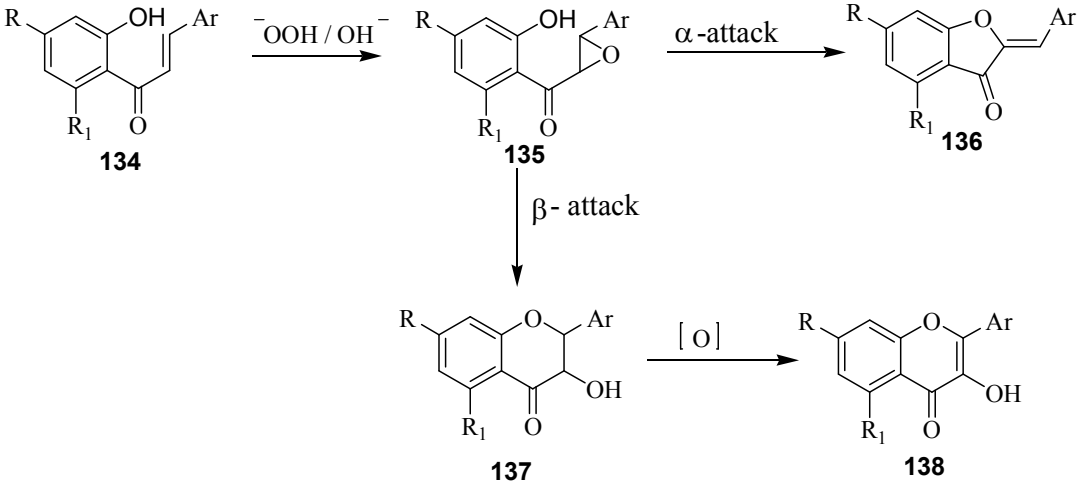
32) Compound 131 was synthesized from 3-methoxybenzaldehyde 130 in good yield according to an improved solvent-free Daking oxidation protocol. Compound 127 was produced from 131 after Fries rearrangement and cyclization reaction. The key intermediates 129 were afforded by the condensation of 127 with m- or p-hydroxybenzaldehyde, respectively, in ethanolic 50% KOH solution. As reported in many literature, only Z stereoisomers were isolated. The stereochemistry of the auronediastereomers has been elucidated by NMR spectroscopic measurement sand by X-ray diffraction analysis. Mannich reactions of compounds 129 with paraformaldehyde and different secondary amines in EtOH gave the novel auroneMannich base derivatives 133 (Scheme 34).[56-58]



130 **131** **132** **133** **129** **127**

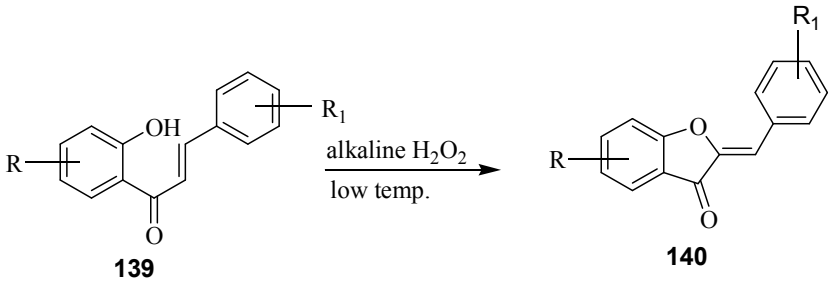
Scheme 34

33) In literature, aurones are generally obtained from chalcones by oxidation of 2'-hydroxychalcones with alkaline hydrogen peroxide using Algar-Flynn-Oyamaoda (A.F.O) reaction. This reaction takes place via the formation of epoxide intermediate which further involves intramolecular displacement of the oxirane oxygen by the phenoxide ion at the α position to give aurones, or at β position to give dihydroflavonols, and subsequently flavonols (Scheme 35).[59,60]



Scheme 35

34) Wheeler et al. however reported that the product obtained by oxidative cyclisation of 2'-hydroxychalcone using alkaline hydrogen peroxide is temperature dependent. Chalcones on treatment with hydrogen peroxide at low temperature afforded the corresponding 2-arylidenecoumaran-3-ones (Scheme 36).[61]



Scheme 36

CONCLUSION

Benzofuran is a fused bicyclic compound. Its derivatives constitute a major class of heterocyclic compounds. A varity of synthesis of benzofuran shows that these compounds are of much interest. The present study has covered past 10 years method of synthesis and isolation of benzofuran and benzofuran derivatives.

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