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RECENT ADVANCES IN THE MICROWAVE ASSISTED SYNTHESIS OF BENZOFURAN AND INDOLE DERIVATIVES

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Dedicated with great respect to Professor Yasuyuki Kita for his outstanding contributions in Organic Synthesis

Abstract – Microwave (MW) assisted syntheses are environment friendly, efficient, rapid and convenient methodology for the synthesis of organic compounds. Benzene ring fused to a five membered ring containing N or O atom exhibits wide range of biological activities. Benzofuran is present in polymers, pharmaceuticals, and bioactive natural products. Benzofuran is significant as insecticides, herbicides, anti-inflammatory and anti-viral agents. Indoles are well known scaffold showing noteworthy activities like anti-tumor, anti-viral, anti-microbial and anti-oxidant. Indole derivatives are valuable moiety in different therapeutically active drug molecules. On account of the biological significance of benzofuran and indole scaffold, this review describes the recent advances in microwave assisted synthesis of benzofurans and indoles, and covers literature from 2012-2020.

1. INTRODUCTION

Benzofuran and indole are aromatic heterocyclic organic compounds with a bicyclic structure, consisting of a benzene ring fused to a five membered ring containing a heteroatom such as O or N respectively.[1] The enormous biological activities of these heterocycles encouraged medicinal chemists to design more efficient and green protocols towards its synthesis.[2] The aspect of green chemistry turned the attention of scientific community to microwave assisted methodology and succeeded in applying this strategy to organic synthesis.[3,4] Microwave assisted organic synthesis resulted in rapid and selective reactions under uniform heating process.[5]

Microwave irradiation is one of the most popular nonconventional activation methods which has upgraded organic synthesis during the past thirty years. This alternative source of heating turned out to be an attractive tool in chemical synthesis due to substantial reduction of reaction time (hours to minutes) and higher yield compared to the conventional heating method. The possibility of fine tuning of reaction parameters and low chemical waste formation make this technique a choice of organic chemists. Advantages like short reaction time, elimination of side reactions and cost-effective reaction execution also enhanced the popularity of microwave assisted reactions.[6,7] This distinctive strategy has been extensively used in the efficient synthesis of several interesting bioactive compounds including several heterocycles. The first MW mediated organic reaction was reported in 1969; but the technique was popularized by the work of Gedye and Giguere.[8] During the reaction, organic molecules undergo interaction with MW energy resulting in dielectric heating. Polar molecules like acetonitrile, ethanol water etc. undergo efficient interaction with MWs resulting in speedy heat generation. The convection mode of MW heating improves the reaction rate whereas external heating source in conventional heating results in decrease of energy transfer leading to difference in the rate of reaction.[9] Naturally, this methodology offers higher yields compared to other conventional methods.[10] Earlier domestic ovens was used for microwave irradiated chemical synthesis; but now, it was replaced by sophisticated monomode and multimode microwave instruments. This unique activation technique has brought remarkable improvements in organic synthesis and is still a choice for many thermal reactions, especially those with high activation energy.

Benzofuran is a heterocyclic compound consisting of fused benzene and furan rings. This heterocycle is well known for its anti-inflammatory,[11] anti-hypertensive,[12] anti-tubercular[13] and anti-hyperglycaemia[14] activities. Benzofurans are important moiety present in polymers and natural products.[15]

Indole is a nitrogen heterocycle with a six membered benzene ring fused to a pyrrole ring. Indole derivatives have received substantial attention in the field of drug discovery and derivatives are used as drugs as anti-tubercular,[16] anti-microbial,[17] anti-asthmatics[18] and anti-psychotics.[19] Indoles are also important in cancer therapy due to the successful usage of indole based vinca alkaloids as anticancer drugs.[20-22] Many indole derivatives were found to exhibit anti-oxidant,[23] anti-proliferative,[24] anti-rheumatoidal,[25] anti-neoplastic,[26] anti-HIV,[27] and anti-estrogenic[28] activities. Tryptophan,[29] serotonin[30] and indomethacin[31] are some pharmacologically important molecules possessing indole skeleton.

In view of the wide variety of biological and pharmacological properties of substituted benzofurans and indoles, several methods were reported so far for the synthesis of these compounds. These include C-H activation through intramolecular annulation method for benzofuran,[32] synthesis of novel heterocycles containing benzofuran motif using thiocarbohydrazide as precursor,[33] Zn catalysed Sonogashira

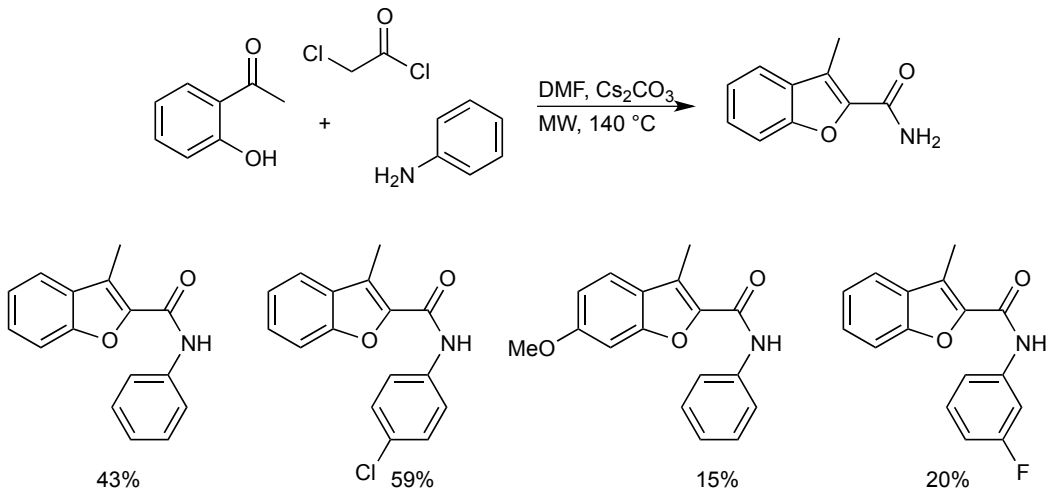
cyclisation strategy for substituted benzofurans and indoles,[34] C-H amination protocol for substituted indoles[35] and so on. Although there are several reviews on the synthesis of substituted benzofurans and indoles, so far no review is reported yet on MW assisted synthesis of these important compounds. This review summarises recent advances in the synthesis of benzofuran and indole derivatives via microwave assisted methodologies covering literature from 2012-2020.

2. MICROWAVE ASSISTED SYNTHESIS OF BENZOFURAN DERIVATIVES

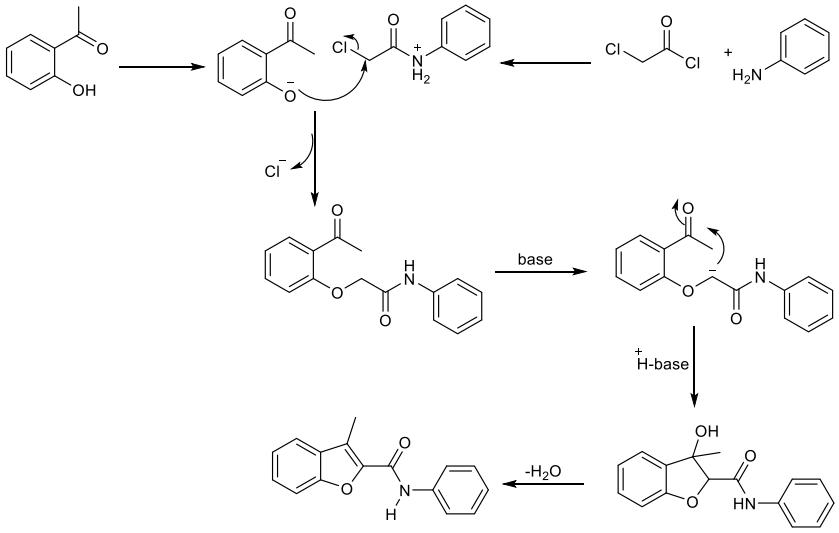
2.1 SYNTHESIS OF BENZOFURAN-2-CARBOXYLIC ACID DERIVATIVES

Benzofuran-2-carboxylic acid derivatives have broad application in pharmaceutical and biological field. These compounds are major components of certain drugs which are useful for cancer and various central nervous system disorders.

Radi *et al.* succeeded in achieving substituted benzofuran-2-carboxamides via microwave assisted multicomponent reaction of anilines, α-chloroacetyl chloride and 2'-hydroxyacetophenones.[36] The reaction exhibited good functional group tolerance under the optimized conditions (Cs_2CO_3 as base, in dry DMF upon microwave irradiation at 140 °C) (**Scheme 1**). When electron-donating substituents were attached to 2'-hydroxyacetophenones, the yield of the corresponding product got reduced rapidly. A plausible mechanism for the transformation is also proposed (**Scheme 2**).

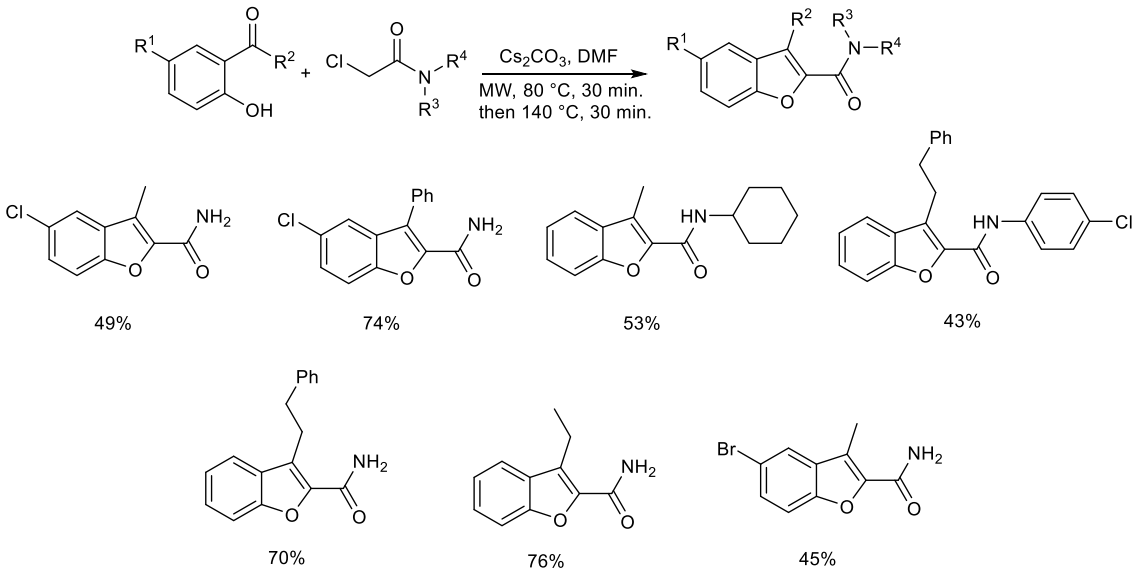


Scheme 1. Microwave assisted multicomponent protocol for benzofuran-2-carboxamides



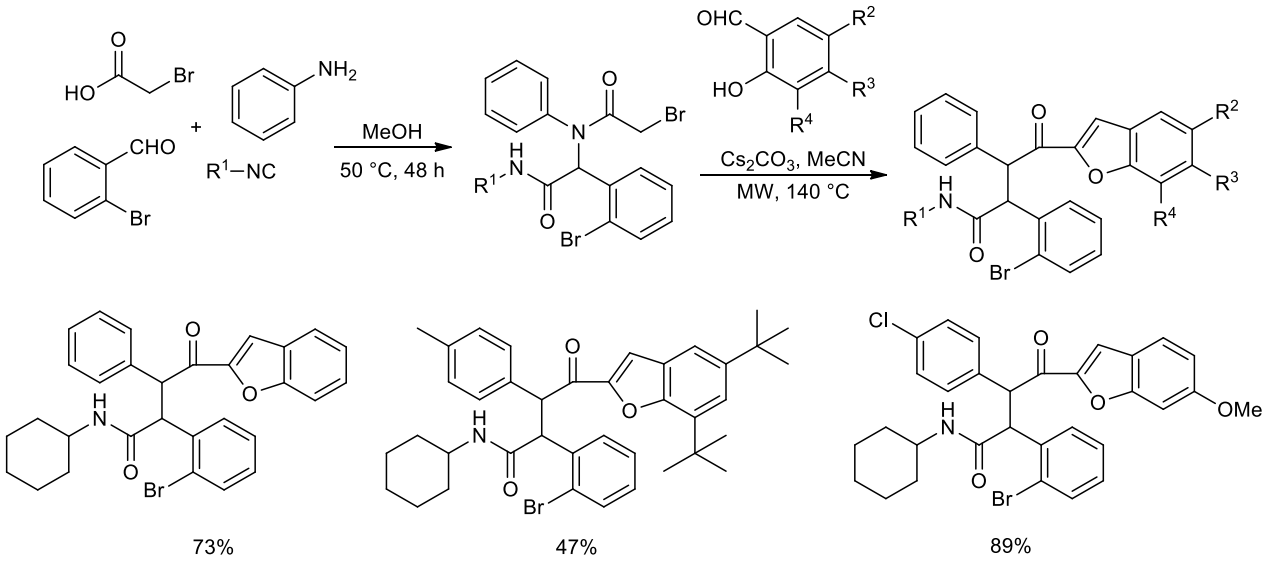
Scheme 2. Plausible mechanism for the preparation of benzofuran-2-carboxamides [Reproduced with permission from ref. 36]

The importance of benzofuran-2-carboxamides in pharmaceutical and biological field promoted scientists to develop new methodologies for the synthesis of this class of compounds. The reaction between (2-chloroacetyl)amides and 2-acyl/formylphenols via *O*-alkylation followed by Knoevenagel condensation reaction furnished benzofuran-2-carboxamides (**Scheme 3**).[37] From the substrate scope studies it is revealed that phenols with electron-withdrawing group substituted aryl rings gave comparatively low yields. Better results were obtained for aryl amides bearing electron-withdrawing group than those with electron-donating groups. Most of the synthesised compounds exhibit anti-inflammatory, anti-pyretic and analgesic properties.

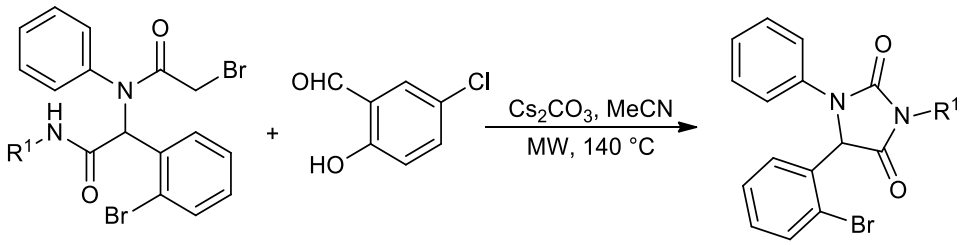


Scheme 3. Synthesis of benzofuran-2-carboxamides via Knoevenagel condensation

Dai and co-workers achieved highly functionalised benzofuran-2-carboxamides via Ugi reaction, a multicomponent reaction between an isocyanide, a carboxylic acid, an amine and a ketone or aldehyde.[38] In this methodology, aromatic amines, 2-bromobenzaldehyde, 2-bromoacetic acid and isocyanides reacted resulting in the formation of *N*-aryl-2-bromoacetamides. Further reaction of this *N*-aryl-2-bromoacetamides with salicylaldehydes via Rap–Stoermer reaction in the presence of Cs_2CO_3 under microwave irradiation at 90-140 °C generated benzofuran-2-carboxamides (**Scheme 4**). However, the use of electron-deficient salicylaldehyde in presence of Cs_2CO_3 furnished 1,3,5-trisubstituted hydantoins instead of the expected benzofuran-2-carboxamides (**Scheme 5**). The effect of steric hindrance of salicylaldehydes on Rap–Stoermer reaction was confirmed from the lower yields obtained for 3,5-di-*tert*-butylsalicylaldehyde.



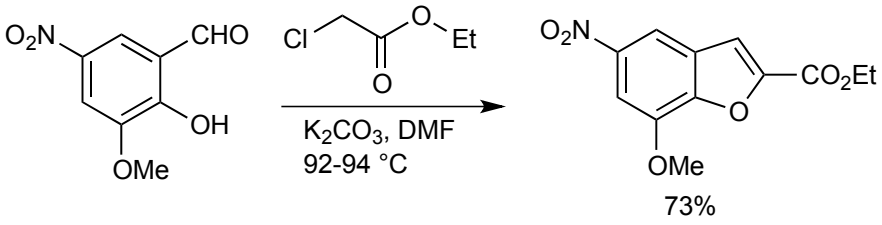
Scheme 4. Synthesis of benzofuran-2-carboxamides by Rap–Stoermer reaction



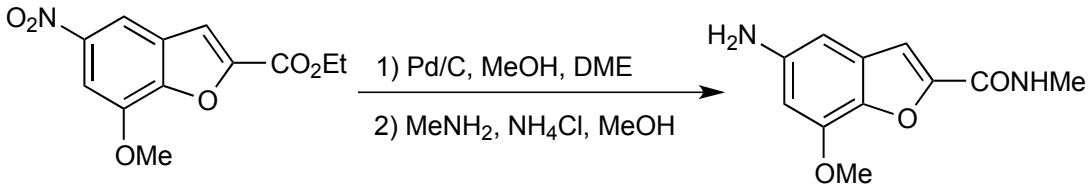
Scheme 5. 1,3,5-Trisubstituted hydantoin formation from electron-deficient salicylaldehydes

Selective cytotoxicity of benzofuran-2-carboxylic acid derivatives encouraged scientists to develop efficient methodologies for the synthesis of these compounds. The synthesis of benzofuran-2-carboxylic acid ethyl esters has been established by Kowalewska and co-workers.[39] Benzofuran-2-carboxylic acid

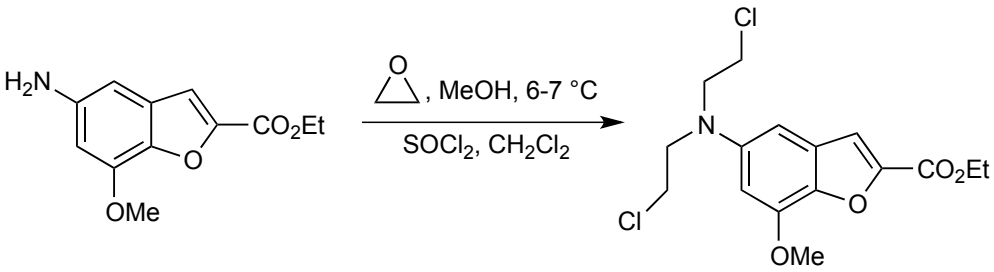
ethyl esters were prepared by heating 2-hydroxybenzaldehyde, ethyl chloroacetate with anhydrous potassium carbonate in DMF at 92-94 °C for 4 h (**Scheme 6**). Suitable procedures for halogen-substituted benzofuran-2-carboxylic acid and amides of benzofuran-2-carboxylic acid from benzofuran-2-carboxylic acid ethyl esters were also discussed in the report (**Scheme 7&8**).



Scheme 6. Synthetic approach to benzofuran-2-carboxylic acid derivatives

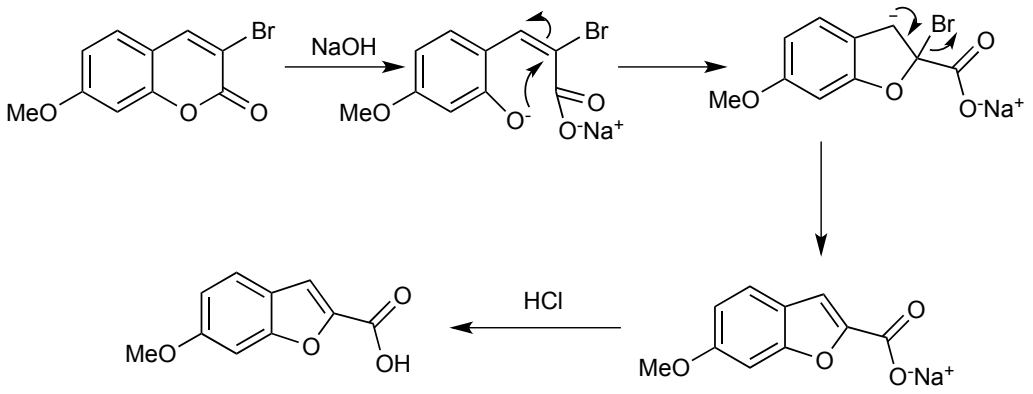


Scheme 7. Synthetic approach to amides of benzofuran-2-carboxylic acid derivatives



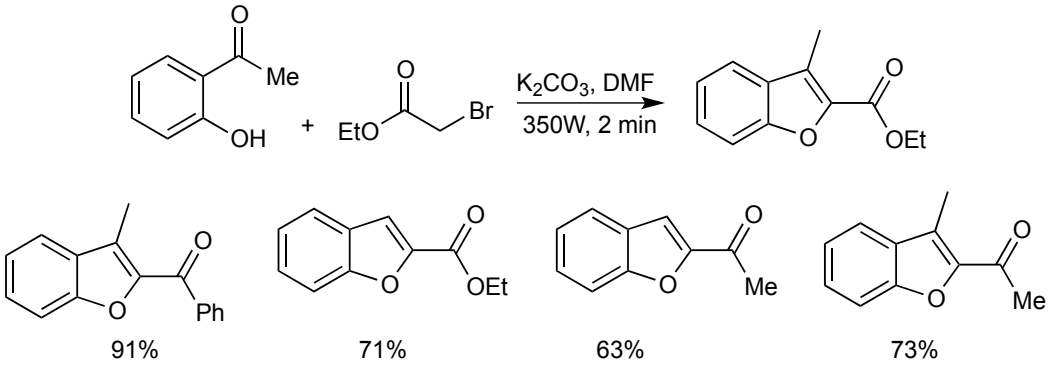
Scheme 8. Synthetic approach to halogen substituted benzofuran-2-carboxylic acid derivatives

Marriott *et al.* disclosed an efficient method for the synthesis of benzofuran-2-carboxylic acids from 3-halocoumarins through Perkin rearrangement carried out in ethanol under microwave irradiation power of 300W for 5 min at 79 °C.[40] The conventional synthesis of benzofuran-2-carboxylic acids from 3-halocoumarins was done in the presence of a base under reflux for 3 h. The prolonged reaction time for conventional method attested the real importance of microwave assisted method in organic synthesis. This methodology was found suitable for a wide variety of 3-halocoumarins, which confirmed the synthetic utility of this method. A mechanistic pathway is also depicted (**Scheme 9**).



Scheme 9. Mechanistic approach to benzofuran-2-carboxylic acids [Reproduced with permission from ref. 40]

Liu and co-workers established a microwave assisted strategy for the synthesis of substituted benzofuran derivatives.[41] Condensation of *o*-hydroxyacetophenone with ethyl bromoacetate in presence of the base, potassium carbonate in DMF under microwave irradiation at 350W for 2 min afforded benzofuran derivatives (**Scheme 10**). This MW assisted methodology offers several advantages such as shorter reaction time, higher yields and simple workup procedures.



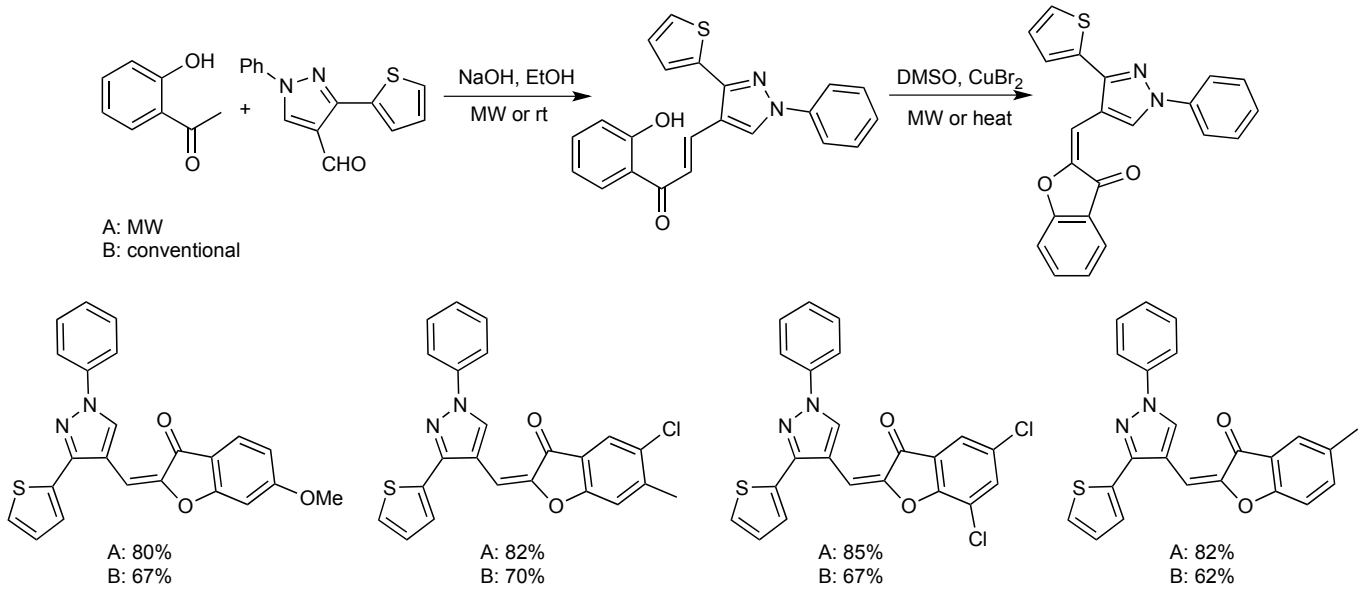
Scheme 10. Synthesis of substituted benzofuran derivatives via condensation of *o*-hydroxyacetophenone with ethyl bromoacetate

2.2 SYNTHESIS OF PYRAZOLE OR INDOLE BASED BENZOFURAN DERIVATIVES

The pronounced medicinal applications of different heterocycles encouraged scientists to develop new compounds via incorporation of two or more heterocyclic rings. As a result of research in this area, wide variety of compounds having fused heterocyclic ring system was established. Pyrazole and benzofuran are well known for its spectacular application in medicinal field.[42,43] These medicinal applications were impetus to develop new heterocyclic compounds by incorporating pyrazole and benzofuran systems. The

astonishing activity of pyrazole-benzofuran ring system against certain multidrug resistant bacteria further confirms the relevance of this compound.[44]

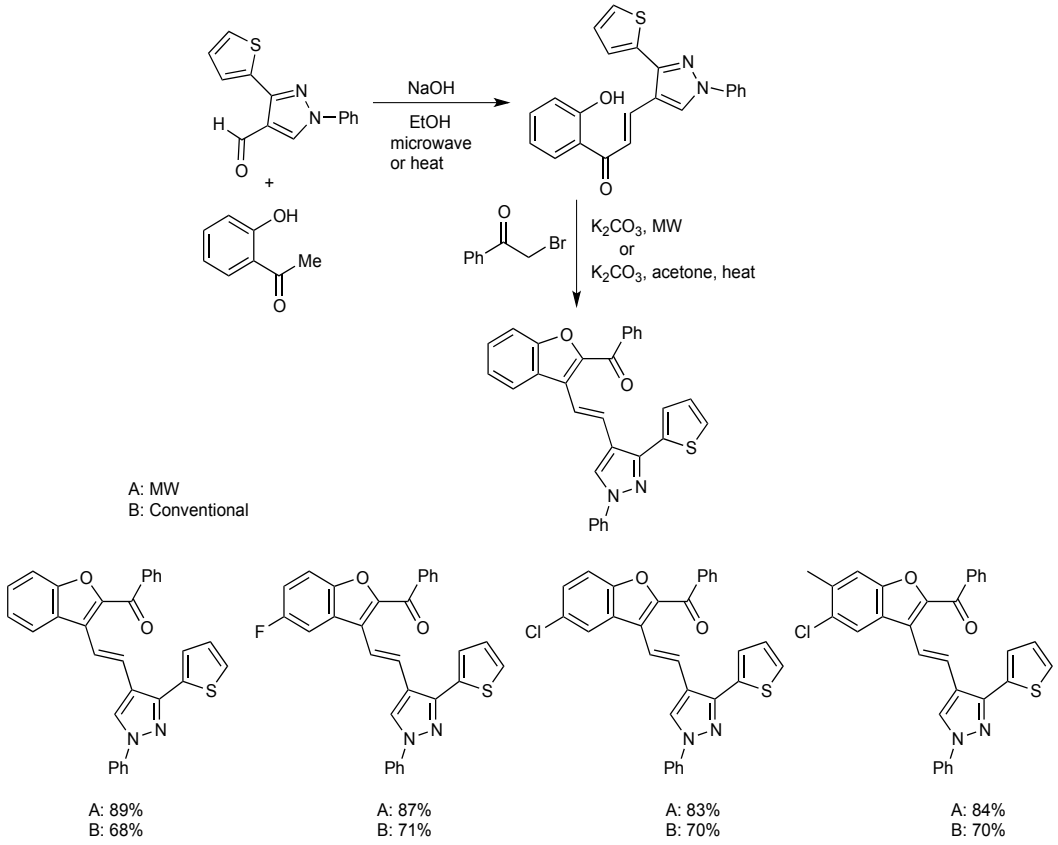
Excellent anti-microbial activity of pyrazole, thiophene and benzofuran scaffolds encouraged Ashok and his co-workers to synthesise (*Z*)-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-ones.[45] The starting material for this strategy, (*E*)-1-(2-hydroxyphenyl)-3-[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]prop-2-en-1-ones, was prepared via condensation of 2-hydroxyacetophenones with 1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazole-4-carbaldehyde in presence of alkali under microwave irradiation. Refluxing (*E*)-1-(2-hydroxyphenyl)-3-[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]prop-2-en-1-ones with $CuBr_2$ in 10 mL DMSO for 2-3 h afforded the desired product in moderate to good yields (**Scheme 11**). The reaction mixture in the second step when subjected to microwave irradiation at 180W for 5-6 min afforded the product in higher yields compared to the conventional method. Some of the prepared compounds exhibited anti-microbial activity, which was confirmed by testing against certain microorganisms.



Scheme 11. Synthesis of (*Z*)-2-{[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]methylene}benzofuran-3(2*H*)-ones via microwave assisted methodology

Later, the same group established an environmentally benign protocol for the synthesis of substituted (*E*)-phenyl{3-(2-[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]vinyl)benzofuran-2yl}methanones.[46] Here, both conventional and microwave assisted methodologies towards the synthesis of this class of compounds were compared. (*E*)-1-(2-Hydroxyphenyl)-3-[1phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]prop-2-en-1-one and 2-bromo-1-phenylethanone and K_2CO_3 were refluxed in ethanol for 5-6 h (**Scheme 12**). The same reaction under microwave irradiation at 160W afforded the desired product in 45 min. The anti-microbial

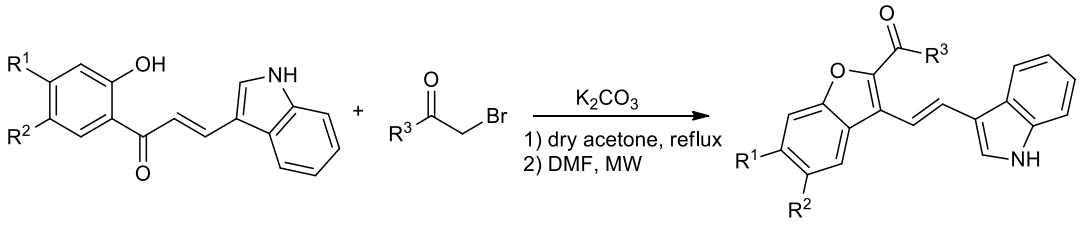
activity of some of the synthesised compounds further enhances the importance of this synthetic strategy in biological and medical field.



Scheme 12. Synthetic route to substituted (*E*)-phenyl{3-(2-[1-phenyl-3-(thiophen-2-yl)-1*H*-pyrazol-4-yl]vinyl)benzofuran-2-yl}methannones

Pyrazolobenzofurans are important scaffolds known to exhibit anti-viral and anti-cancer activity. An environment friendly microwave assisted synthesis of pyrazolyl benzofuran derivatives was established.[47] Condensation of benzofuran-2-carbonylhydrazide with different acetones and chloroacetones followed by treatment with DMF and $POCl_3$ under microwave irradiation furnished pyrazolyl benzofuran derivatives. Indole based benzofuran are well known for its anti-microbial activity and anti-oxidant activities.[48]

In 2016 Ashok *et al*. reported a strategy for indole based benzofuran derivatives via cyclisation of 1-(2-hydroxyphenyl)-3-(1*H*-indol-3-yl)prop-2-en-1-one derivatives with 2-bromo-1-(4-bromophenyl)ethanone or 1-bromo-3,3-dimethylbutan-2-one (**Scheme 13**).[49] Here, both conventional and microwave irradiation methods were used. Conventional method includes reflux of reaction mixture in dry acetone for 6-7.5 h. At the same time microwave assisted methodology was carried out in DMF under microwave irradiation at 180W for 5-6 min.

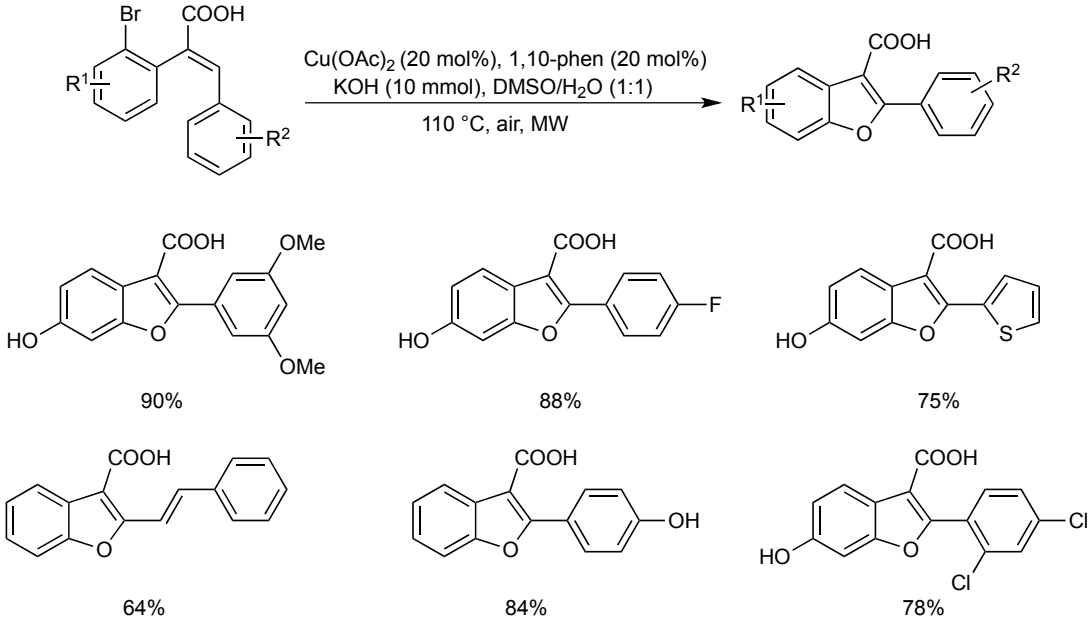


			Yield (%)	
R^1	R^2	R^3	MW	Conventional
H	H	4-bromophenyl	77	55
H	F	4-bromophenyl	81	51
H	Cl	4-bromophenyl	79	47
H	H	*tert*-butyl	85	49
H	Cl	*tert*-butyl	76	50

Scheme 13. Microwave assisted methodology for indole based benzofuran derivatives

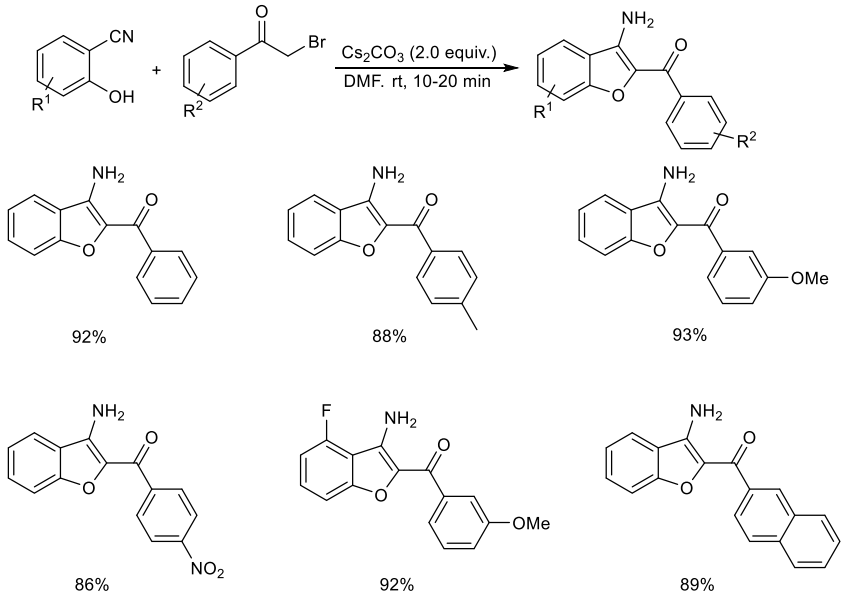
2.3 SYNTHESIS OF SUBSTITUTED BENZOFURAN WITH MISCELLANEOUS GROUP

Zou and co-workers demonstrated a facile protocol for the preparation of 2-arylbenzofuran-3-carboxylic acids from (*E*)-2-(2-bromophenyl)-3-arylacrylic acids.[50] The optimized conditions for this reaction includes $Cu(OAc)_2$ (20 mol%), 1,10 phenanthroline, (20 mol%), KOH (10 mmol) in DMSO/H_2O (1:1) solvent for 1 h under microwave irradiation (**Scheme 14**). Substrate scope studies revealed that (*E*)-2-(2-bromophenyl)-3-phenylacrylic acids with various substituents were compatible with this method and furnished the required product in excellent yields.

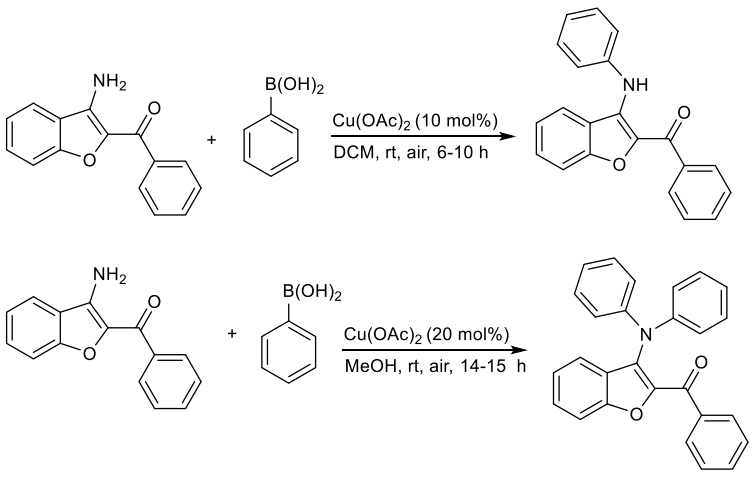


Scheme 14. Synthesis of 2-arylbenzofuran-3-carboxylic acids

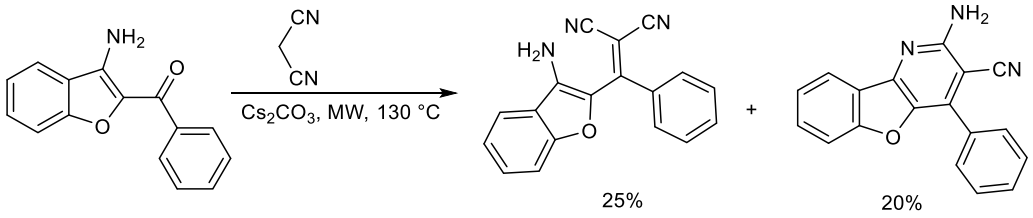
Choudhury and co-workers introduced a method for the synthesis of 3-amino-2-aroylbenzofuran derivatives by the reaction between 2-hydroxybenzonitriles and 2-bromoacetophenones.[51] Initially they performed the reaction using 2-hydroxybenzonitrile and 2-bromoacetophenone and the optimized conditions were recognized as Cs_2CO_3 (1 equiv.) as base in DMF solvent at room temperature for 10-20 min (**Scheme 15**). Functional groups such as −Me, −OMe, $-NO_2$, −F, −Cl, and –Br on aromatic ring of 2-hydroxybenzonitrile and 2-bromoacetophenone derivatives provided excellent yields of products. They extended the scope of the reaction by the synthesis of mono- or *bi*-*N*-aryl derivatives of aminobenzofurans from the obtained products by treating it with arylboronic acids (**Scheme 16**). A microwave assisted strategy was also suggested for the synthesis of fluorescent conjugated alkenes and pyridine-fused benzofurans by the reaction of 3-amino-2-aroylbenzofurans and malononitrile (**Scheme 17**).



Scheme 15. Synthesis of 3-amino-2-aroylbenzofuran derivatives from 2-hydroxybenzonitriles and 2-bromoacetophenones

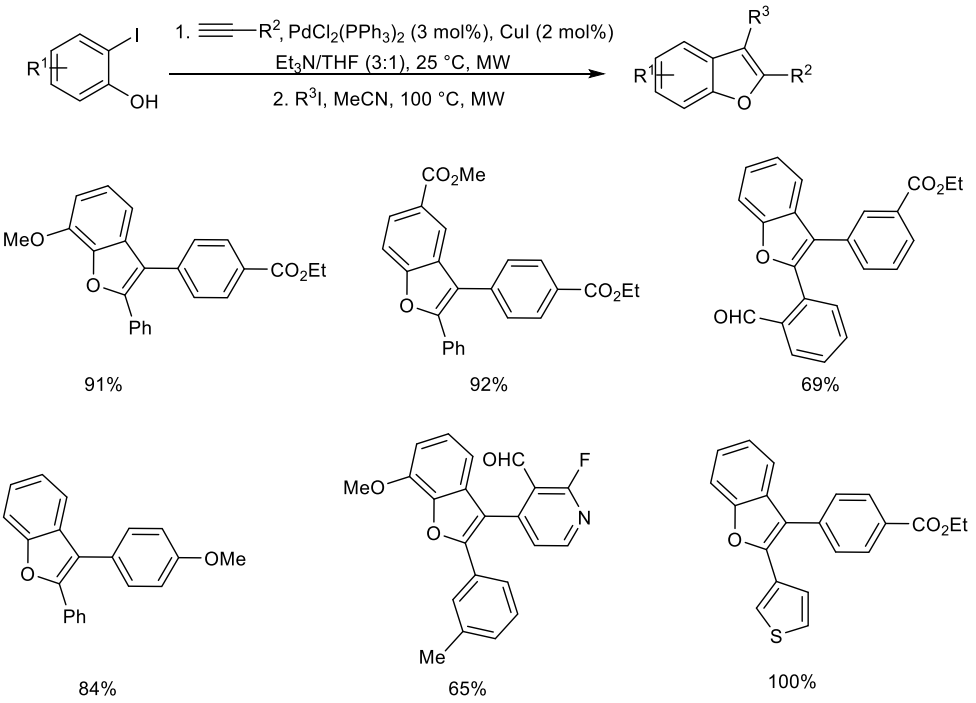


Scheme 16. Synthesis of mono- or *bi*-*N*-aryl derivatives of aminobenzofurans



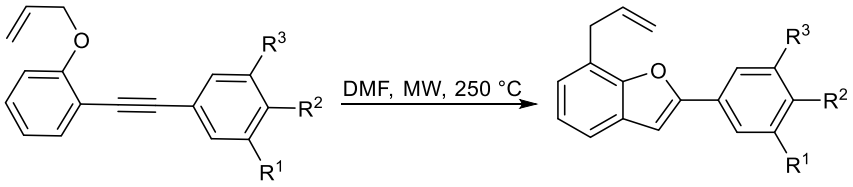
Scheme 17. Microwave promoted synthesis of fluorescent conjugated alkenes and pyridine-fused benzofurans

Larock and co-workers synthesised 2,3-disubstituted benzo[*b*]furans from 2-iodophenols, terminal acetylenes and aryl iodides (**Scheme18**).[52] Sonogashira coupling between 2-iodophenols and terminal acetylenes was identified as the initial step for this reaction. This coupling reaction leads to the formation of 2-(1-alkynyl)phenol, which undergoes cyclisation in the presence of aryl iodides to form expected 2,3-disubstituted benzo[*b*]furans in good yields. Both electron-deficient and electron-rich iodophenols were well participated in the reaction. Heterocycle substituted terminal alkynes were also well compatible under the optimized conditions. A wide substrate scope for aryl iodides was also disclosed.

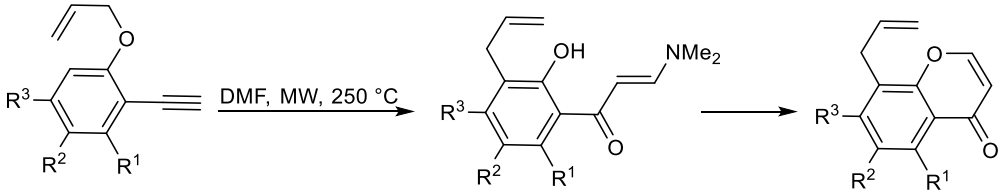


Scheme 18. Synthesis of 2,3-disubstituted benzo[*b*]furans

Microwave promoted approach towards the preparation of 7-allylsubstituted benzofurans from *ortho*-allyloxyalkenylbenzenes was established (**Scheme 19**).[53] The reaction was described to proceed via Claisen-rearrangement, followed by 5-*endo-dig*-cyclisation forming 7-allylsubstituted benzofurans. For monosubstituted alkynes under optimized conditions (DMF solvent, 250 °C, MW), an unexpected formation of enaminoketones was observed which on cyclisation yielded chromen-4-ones (**Scheme 20**).

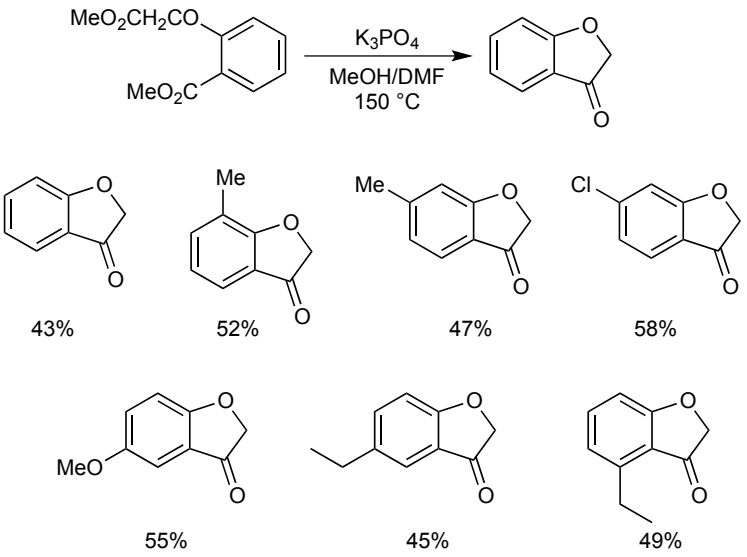


Scheme 19. Synthesis of 7-allylsubstituted benzofurans from *ortho*-allyloxyalkenylbenzenes



Scheme 20. Synthesis of chromen-4-ones from monosubstituted alkynes through enaminoketones

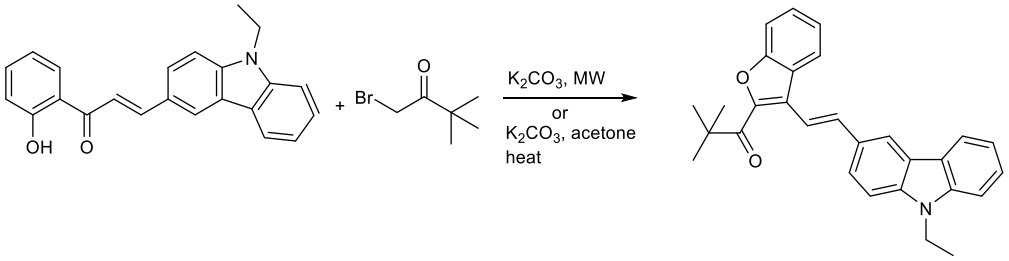
Fang *et al.* described the preparation of benzofuran-3(2*H*)-ones from methyl 2-(2-methoxy-2-oxoethoxy)benzoate.[54] In this protocol methyl 2-(2-methoxy-2-oxoethoxy)benzoate with 0.75 equiv. of K_3PO_4 in MeOH/DMF solvent system upon microwave irradiation at 150 °C for 30 min cyclised to benzofuran-3(2*H*)-ones in 43% yields (**Scheme 21**). The method exhibited good functional group tolerance, but the lower yield of the products remained as a major drawback of this method.



Scheme 21. Synthesis of benzofuran-3(2*H*)-ones from methyl 2-(2-methoxy-2-oxoethoxy)benzoate

Ashok and co-workers established the synthesis of (*E*)-1-{3-[2-(9-ethyl-9*H*-carbazol-3-yl)vinyl]benzofuran-2-yl}-2,2-dimethylpropan-1-ones.[55] This efficient methodology includes Claisen-Schmidt condensation of substituted 2-hydroxyacetophenones with 9-ethyl-9*H*-carbazole-3-carbaldehyde in the presence of KOH in EtOH to afford

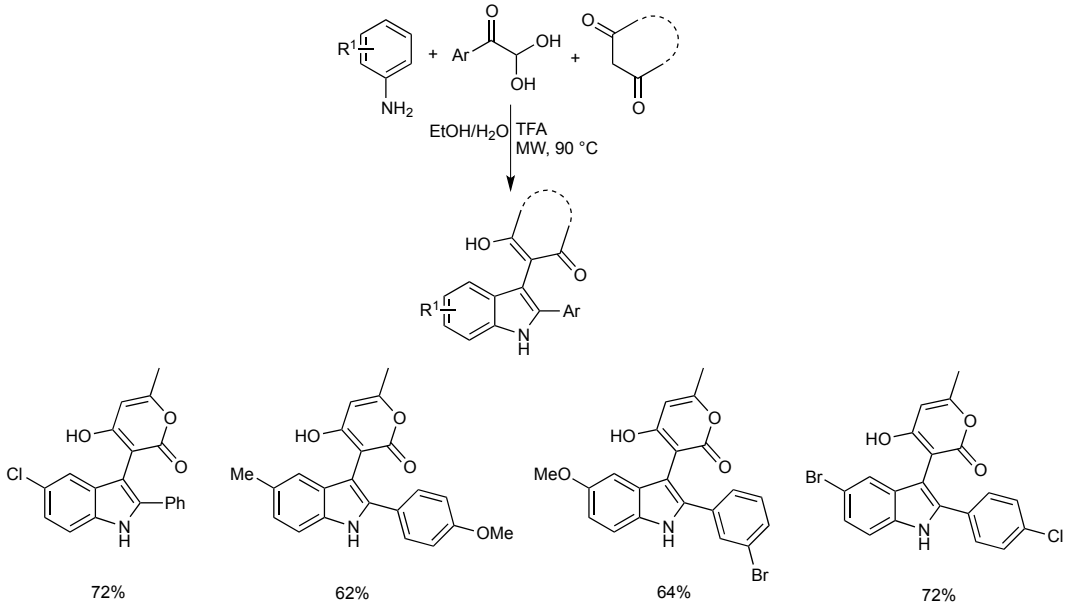
(*E*)-1-{3-[2-(9-ethyl-9*H*-carbazol-3-yl)vinyl]benzofuran-2-yl}-2,2-dimethylpropan-1-ones (**Scheme 22**). They also proposed microwave assisted methodology for this reaction, and was found more efficient, as the reaction time reduced to 5-8 min from 9-12 h.



Scheme 22. Synthetic route to (*E*)-1-{3-[2-(9-ethyl-9*H*-carbazol-3-yl)vinyl]benzofuran-2-yl}-2,2-dimethylpropan-1-ones via Claisen-Schmidt condensation

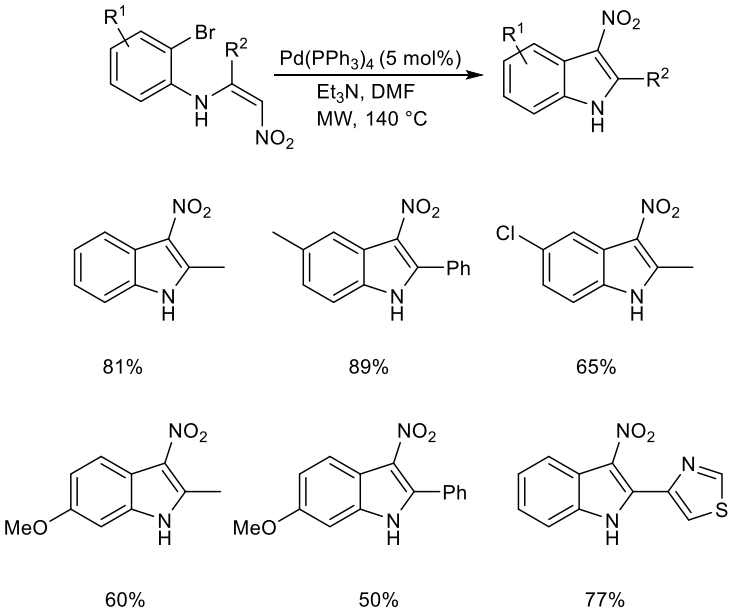
3. SYNTHESIS AND REACTIONS OF INDOLE DERIVATIVES

The practical simplicity and green characteristics of MW assisted methodology encouraged scientists to adapt this methodology in organic synthesis. Huang *et al.* developed a multicomponent regioselective synthesis of 3-functionalized indole derivatives using anilines, arylglyoxal monohydrates and 1,3-dicarbonyl compounds (**Scheme 23**).[56] Under the optimized conditions, catalytic amount of trifluoroacetic acid (TFA) in 1:1 (v/v) EtOH/water as a solvent at 90 °C formed 3-functionalized indole derivatives in 40 min.

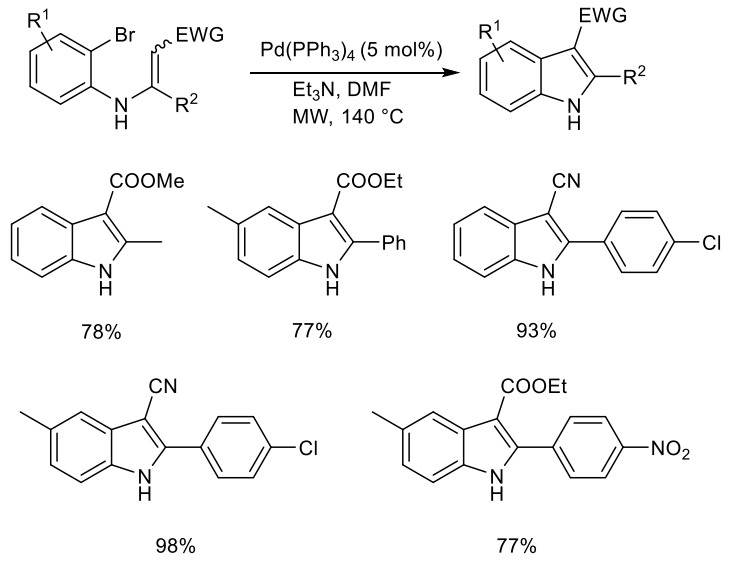


Scheme 23. Microwave assisted methodology for 3-functionalized indole derivatives from anilines, arylglyoxal monohydrates and 1,3-dicarbonyl compounds

Microwave assisted methodology towards the synthesis of 3-nitroindoles from *N*-aryl-*β*-nitroenamines through palladium-catalysed intramolecular coupling reaction was established.[57] Under optimized conditions ($Pd(PPh_3)_4$ (5 mol%), Et_3N (5 equiv.), DMF, 140 °C, MW) good yields of products were obtained from a wide variety of electron-withdrawing and electron-donating enamines (**Scheme 24**). The substrate scope studies revealed the higher reactivity of aryl enamines compared to the aliphatic enamines. This method furnished wide variety of indoles with substitution at 2-position mainly including aryl, alkyl and heterocyclic groups. Synthesis of 3-carboalkoxy- and 3-cyanoindoles via this strategy further confirmed the wide application of this method in organic synthesis (**Scheme 25**).

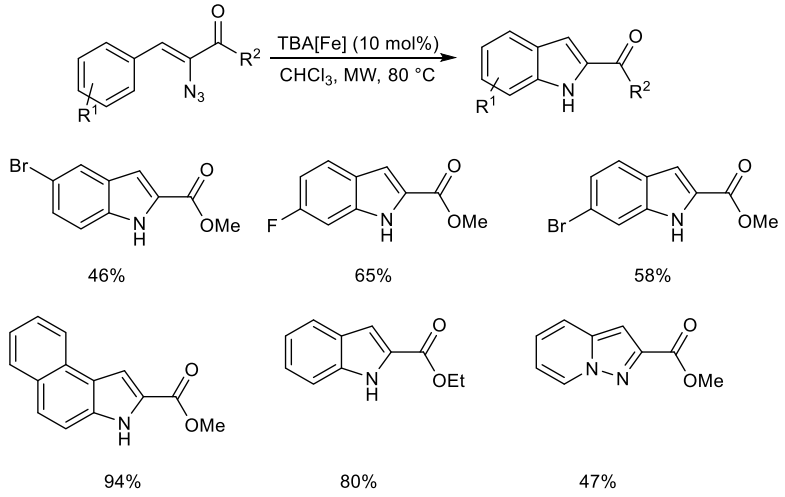


Scheme 24. Microwave assisted synthesis of 3-nitroindoles



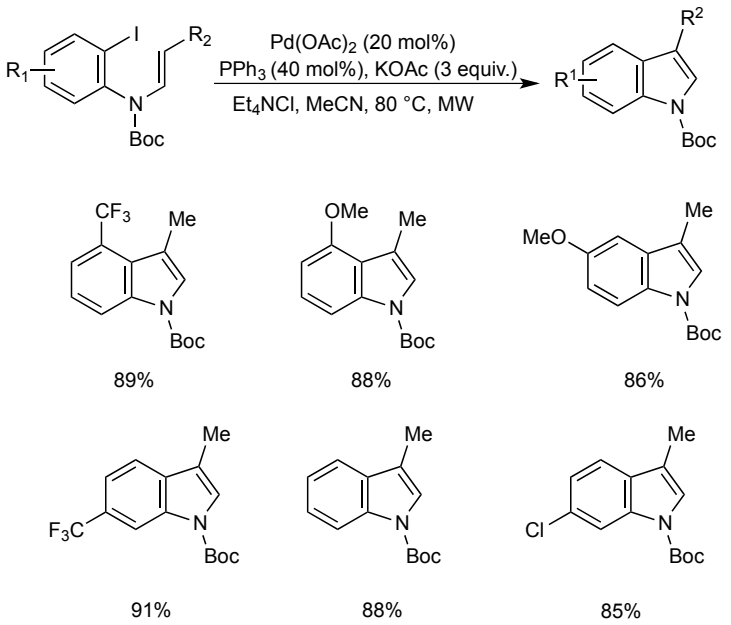
Scheme 25. Synthesis of 3-carboalkoxy- and 3-cyanoindoles

Plietker and co-workers reported an iron catalyzed C(sp2)–H-amination of vinyl azides for the synthesis of indole derivatives (**Scheme 26**).[58] The optimized condition includes the use of $Bu_4N[Fe(CO)_3(NO)]$-(TBA[Fe]) as catalyst in $CHCl_3$ solvent at 80 °C under microwave irradiation furnishing indole derivatives in moderate to good yields. A wide variety of substrates underwent the reaction successfully affording the required products in excellent yields.



Scheme 26. Iron catalysed synthesis of indole derivatives

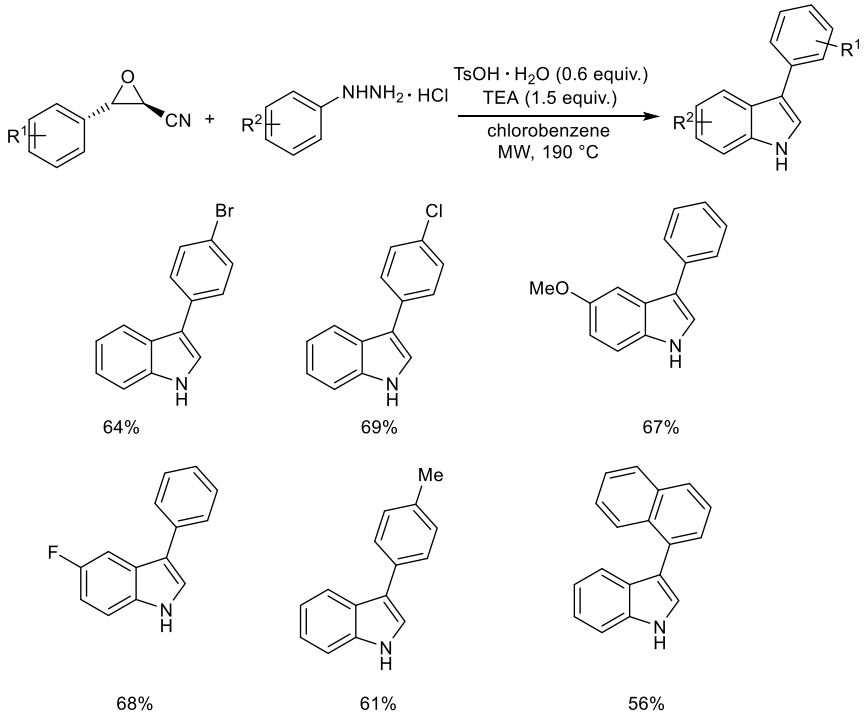
A microwave assisted synthesis of 3-substituted indole derivatives was achieved via intramolecular arene-alkene coupling of *o*-iodoanilinoenamines (**Scheme 27**).[59] The authors initiated the reaction by the preparation of enamine substrates from *N*,*O*-acetal TMS ethers upon treatment with $BF_3 \cdot Et_2O$ in the presence of Hünig's base. Different substituted *o*-iodoanilinoenamines reacted smoothly irrespective of the electronic and steric effect of substituents.



Scheme 27. Synthesis of 3-substituted indole derivatives from *o*-iodoanilinoenamines

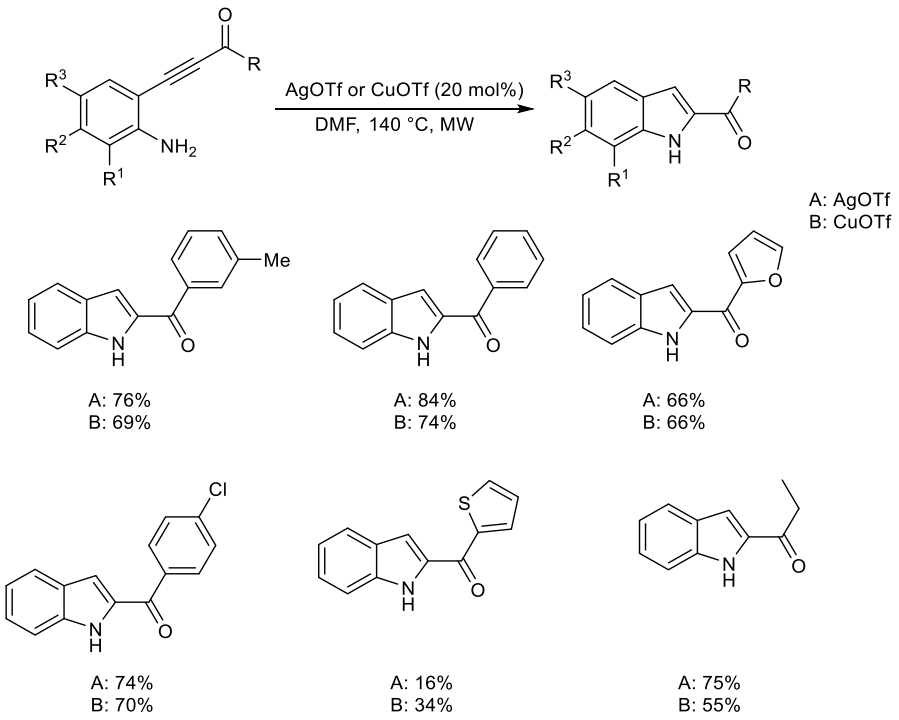
Microwave assisted strategy for the synthesis of substituted indoles from phenylazocarboxylates was reported.[60] This new methodology offers a unique synthetic approach to ^{18}F-substituted indoles. *tert*-Butyl-4-[^{18}F]fluorophenylazocarboxylate on treatment with a wide variety of ketones including phenylacetone, 2-indanone and 2-tetralone underwent the reaction successfully furnishing the corresponding 5-fluoroindole derivatives in moderate to good yields.

Xu and co-workers reported a new approach towards the synthesis of 3-arylindoles by the reaction between 3-aryloxirane-2-carbonitriles and arylhydrazine hydrochlorides (**Scheme 28**).[61] The optimized conditions were found to be *p*-toluenesulfonic acid monohydrate (TsOH·H_2O) (0.6 equiv.) along with the base triethyl amine (1.5 equiv.) in 3 mL chlorobenzene at 190 °C under microwave heating. Both electron-deficient and electron-rich 3-aryloxirane-2-carbonitriles were well tolerated in this reaction. The major advantage of this protocol includes broad substrate scope and high regiospecifity.



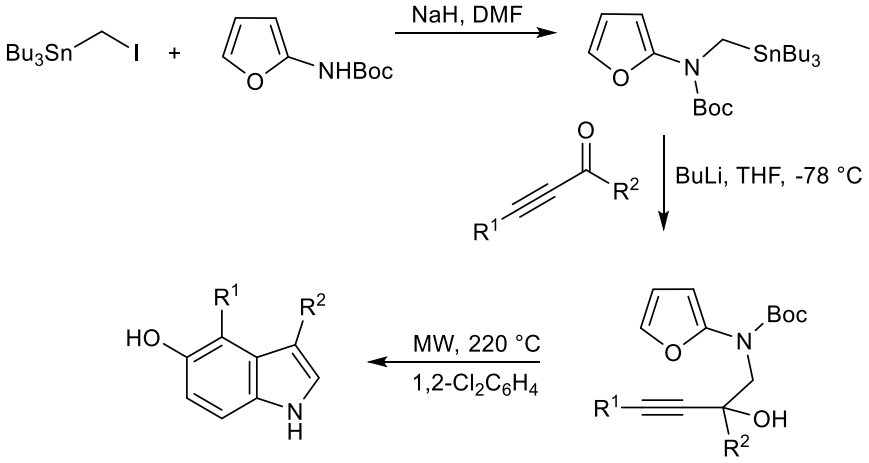
Scheme 28. Synthesis of 3-arylindoles

Marinelli and co-workers established a methodology for the synthesis of 3-unsubstituted 2-acylindoles from *β*-(2-aminophenyl)-*α,β*-ynones (**Scheme 29**).[62] The optimized condition includes AgOTf (0.04 mmol) as the catalyst in DMF solvent at 140 °C under microwave irradiation. They also performed the reaction using CuOTf as the catalyst under the same reaction conditions and found that it was less active compared to AgOTf. However, in case of thienyl substituted ynones CuOTf was found more efficient in achieving the desired product in higher yields compared to AgOTf.



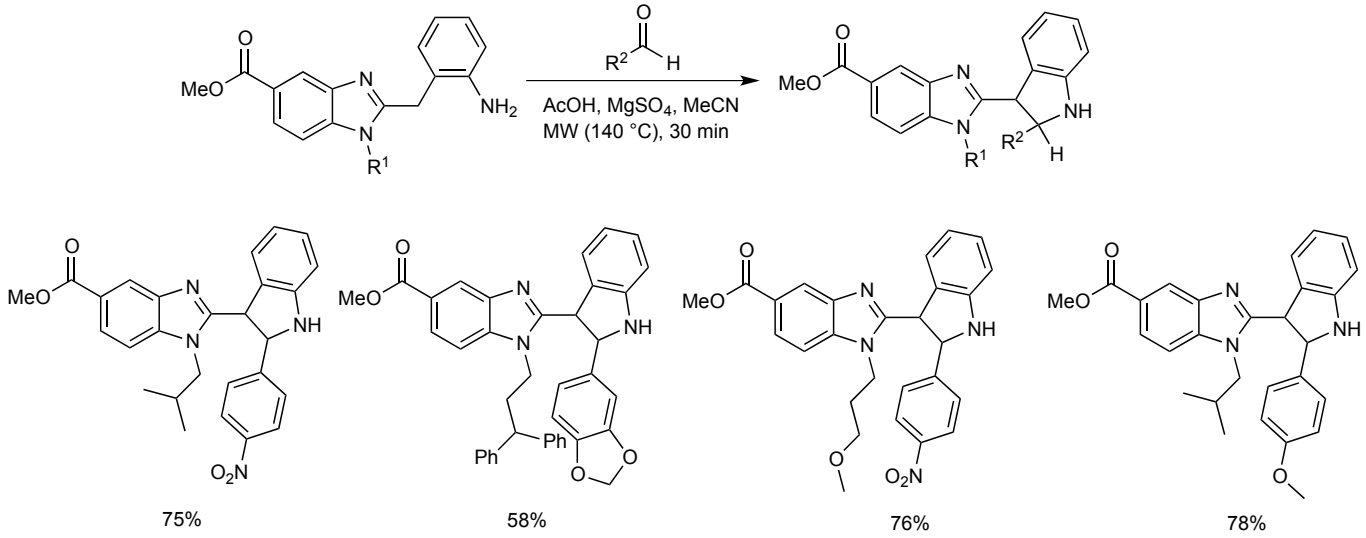
Scheme 29. Microwave assisted method for the synthesis of 3-unsubstituted 2-acylindoles

Synthesis of 3,4-disubstituted 5-hydroxyindoles from furanyl-stannane and alkynone was reported.[63] The reaction was initiated by the transmetallation reaction of furanyl-stannane on treatment with *n*-BuLi, followed by the addition of alkynone to give allylic alcohol. The most important step of this method was the intramolecular [4+2] cycloaddition reaction of the allylic alcohol to give 5-hydroxyindoles under microwave heating (**Scheme 30**). The reaction was found to exhibit well functional group tolerance.

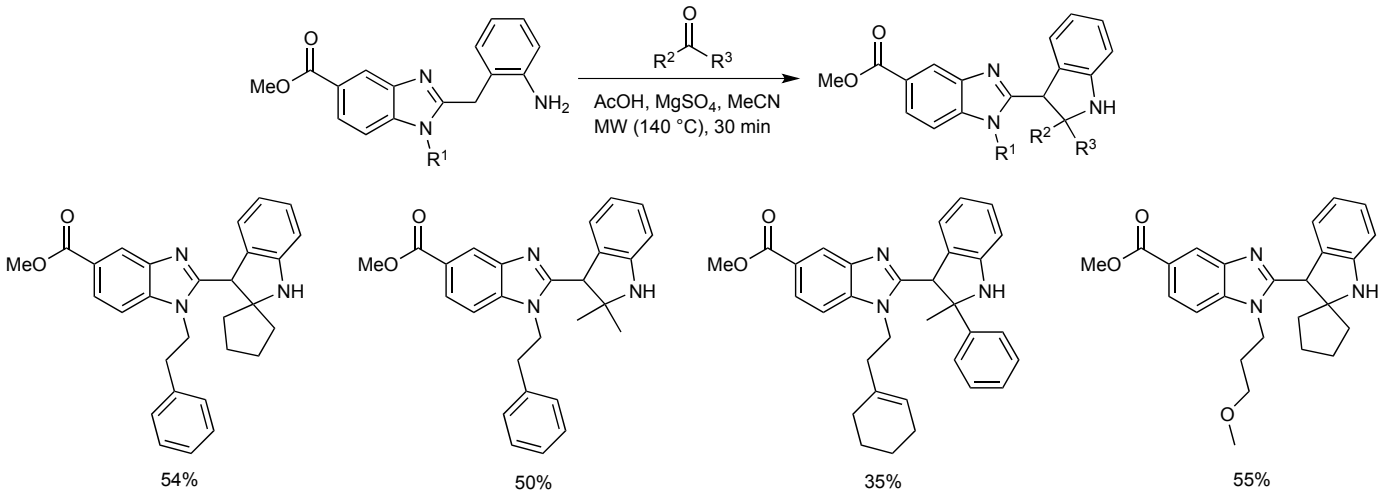


Scheme 30. Schematic pathway for the synthesis of 3,4-disubstituted 5-hydroxyindoles [Reproduced with permission from ref. 63]

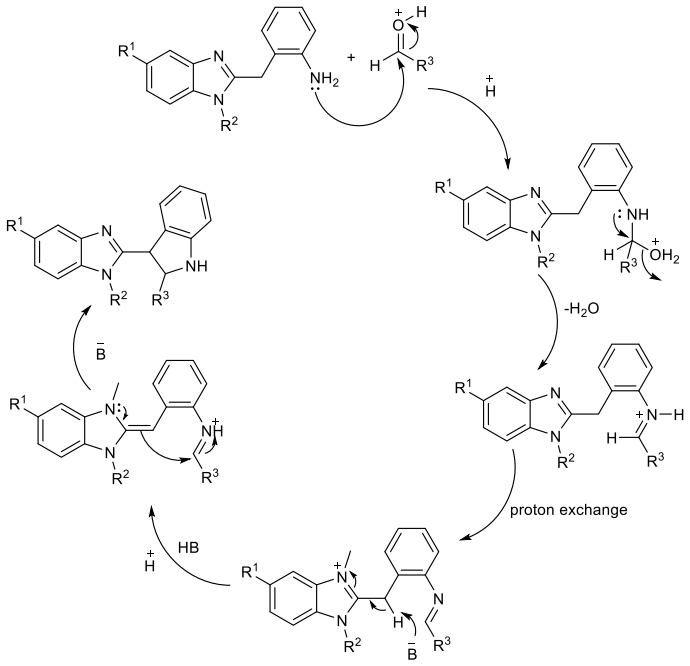
Sun *et al*. established a MW assisted Pictet-Spengler type condensation of C-2 linked *o*-aminobenzyl-benzimidazole with aldehydes and ketones to form benzimidazole-linked indoline hybrids.[64] The reaction exhibited good functional group tolerance under optimized condition (C-2-linked amino benzyl-benzimidazoles (1.48 mmol), aldehydes or ketones (4.44 mmol) with 10 mol% of acetic acid in 4 mL acetonitrile (MeCN) under microwave radiation at 140 °C for 30 min) (**Schemes 31&32**). Oxidation of the obtained benzimidazole-linked indoline hybrids with DDQ generated the corresponding benzimidazole-linked indole hybrids. Utilization of 2-carboxyaldehydes to synthesise tetracyclic pyrroloindole benzoimidazolecarboxylates illustrates the extension of this methodology. A plausible mechanism is also depicted (**Scheme 33**).



Scheme 31. Synthesis of benzimidazole-linked indoline hybrids from aldehydes

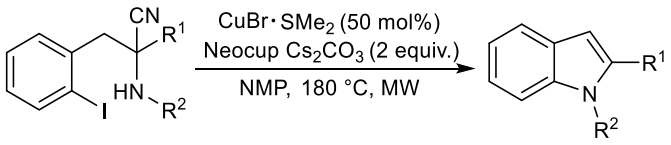


Scheme 32. Synthesis of benzimidazole-linked indoline hybrids from ketones



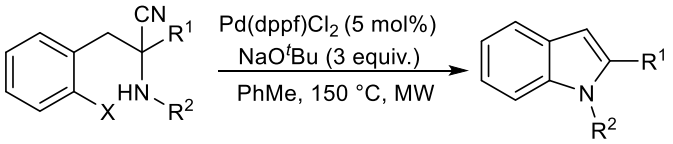
Scheme 33. Plausible mechanism for the preparation of benzimidazole-linked indoline hybrids [Reproduced with permission from ref. 64]

Opatz and co-workers developed two simple approaches to 1,2-disubstituted indoles from α-aminonitriles through copper catalysed Ullmann and palladium-mediated Buchwald−Hartwig-type ring closure reactions.[65] The optimized condition for the Ullman type ring closure involves CuBr·SMe_2 (50 mol%) as the catalytic system along with neocuproine as the ligand (copper-ligand ratio 1:1), Cs_2CO_3 (2.0 equiv.) in *N*-methyl-2-pyrrolidone (NMP) at 180 °C under microwave heating (**Scheme 34**). The authors performed Buchwald−Hartwig-type cyclisation using Pd(dppf)Cl_2 (5 mol%) as the catalytic system and NaO^{t}Bu (3 equiv.) as the base in toluene at 150 °C under microwave irradiation (**Scheme 35**). For *N*-alkyl substrates Ullmann reaction was found to be more efficient compared to Buchwald−Hartwig-type reaction. Better yields were observed for electron-withdrawing α-aminonitriles than electron donating ones.



R^1	R^2	Yield (%)
Ph	Ph	28
4-FC_6H_4	CH_2CH_2Ph	58
4-ClC_6H_4	4-ClC_6H_4	64
4-ClC_6H_4	4-$MeOC_6H_4$	56
Ph	Cy	76

Scheme 34. Synthesis of 1,2-disubstituted indoles via copper catalysed Ullmann cyclisation

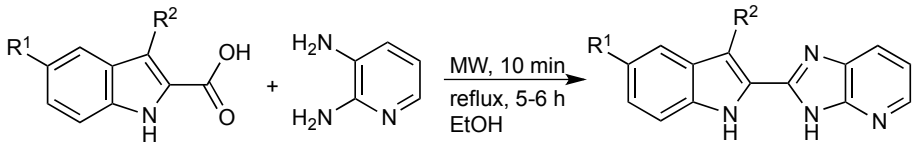


R^1	R^2	X	Yield (%)
Ph	Ph	Br	59
4-$MeOC_6H_4$	*p*-tolyl	I	21
4-ClC_6H_4	*p*-tolyl	I	55
4-ClC_6H_4	4-ClC_6H_4	I	64
4-FC_6H_4	CH_2CH_2Ph	I	49

Scheme 35. Synthesis of 1,2-disubstituted indoles via palladium catalysed Buchwald−Hartwig-type reaction

The significant biological activities of indole derivatives encouraged the scientific community to synthesise new derivatives from known compounds with indole moiety.

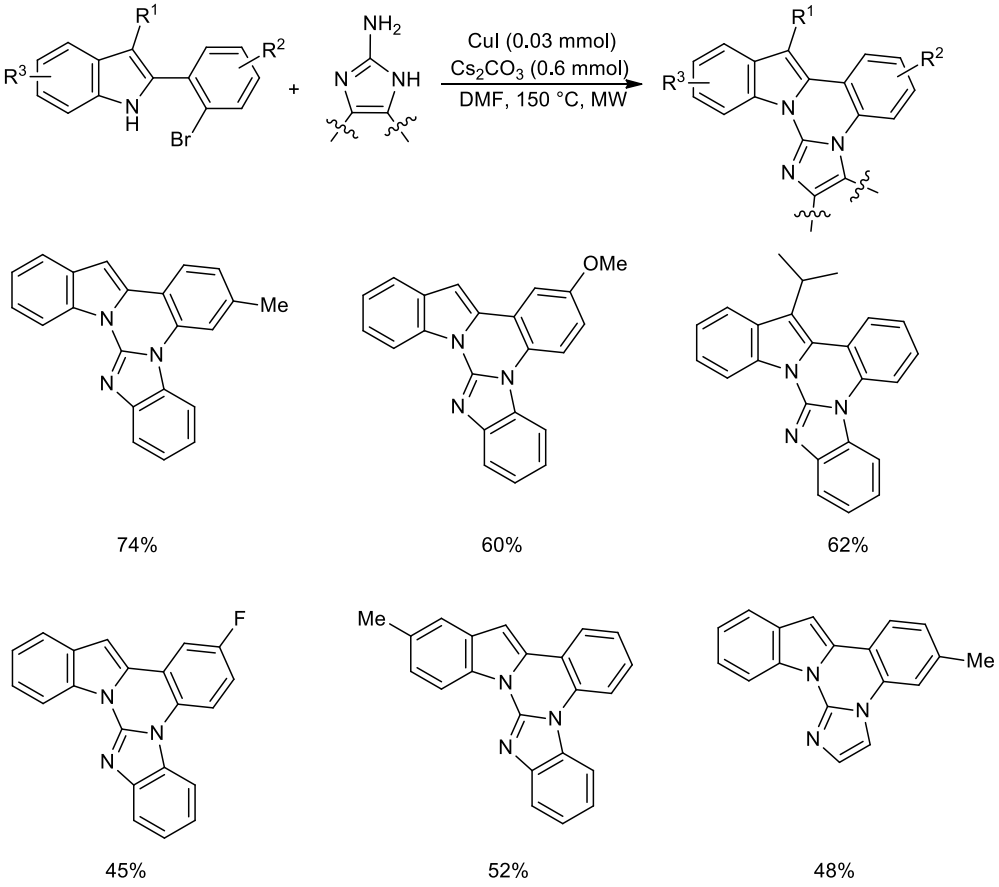
Anti-oxidant and anti-microbial activity of (imidazolopyridinyl)indole analogues imparted a significant attention to the synthesis of this compound. The prominent pharmacological activity of (imidazolopyridinyl)indole analogues inspired medicinal chemist to develop this compound from already known indole derivatives. In 2014, Biradar and co-workers succeeded in achieving an environmentally benign and catalyst free methodology for imidazolopyridinyl indole analogues from 3,5-disubstituted indole-2-carboxylic acid and 2,3-diaminopyridine.[66] They explored the reactivity of a wide variety of substrates under optimized conditions (3,5-disubstituted indole-2-carboxylic acid (0.01 mol), 2,3-diaminopyridine (0.01 mol), in 15-20 mL EtOH for 5-6 h) (**Scheme 36**). Anti-microbial and anti-oxidant activities of (imidazolopyridinyl)indole analogues were confirmed by suitable methods. Compounds having halogens, methyl or methoxy groups at fifth position and phenyl ring at third position of indole ring exhibited excellent anti-microbial and anti-oxidant activities.



R^1	R^2	Yield(%)
Cl	Ph	98
Br	Ph	97
Me	Ph	95
OMe	Ph	95
Cl	Me	98

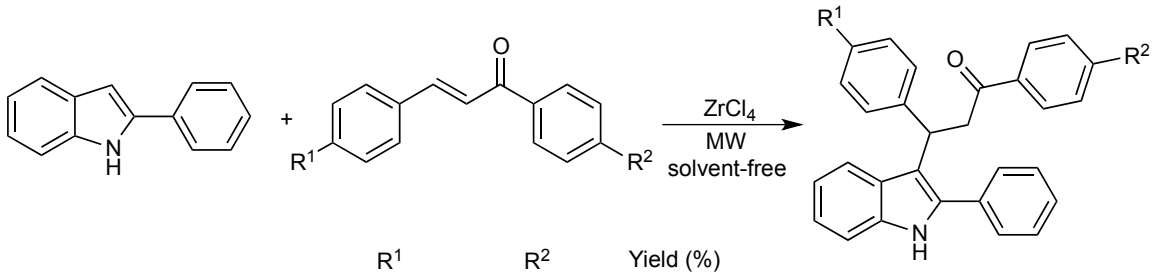
Scheme 36. Microwave assisted synthesis of (imidazopyridinyl)indole analogues

Cho and co-workers synthesised *N*-fused hybrid scaffolds by a microwave assisted reaction involving 2-(2-bromoaryl)indoles and 2-aminoazoles (**Scheme 37**).[67] Under optimized conditions (CuI (0.03 mmol), Cs_2CO_3 (0.6 mmol), DMF (3 mL), 150 °C, MW) both electron-donating and electron-withdrawing 2-aminoazoles furnished the corresponding trinuclear *N*-fused hybrid scaffolds in moderate to good yields.



Scheme 37. Synthesis of *N*-fused hybrid scaffolds

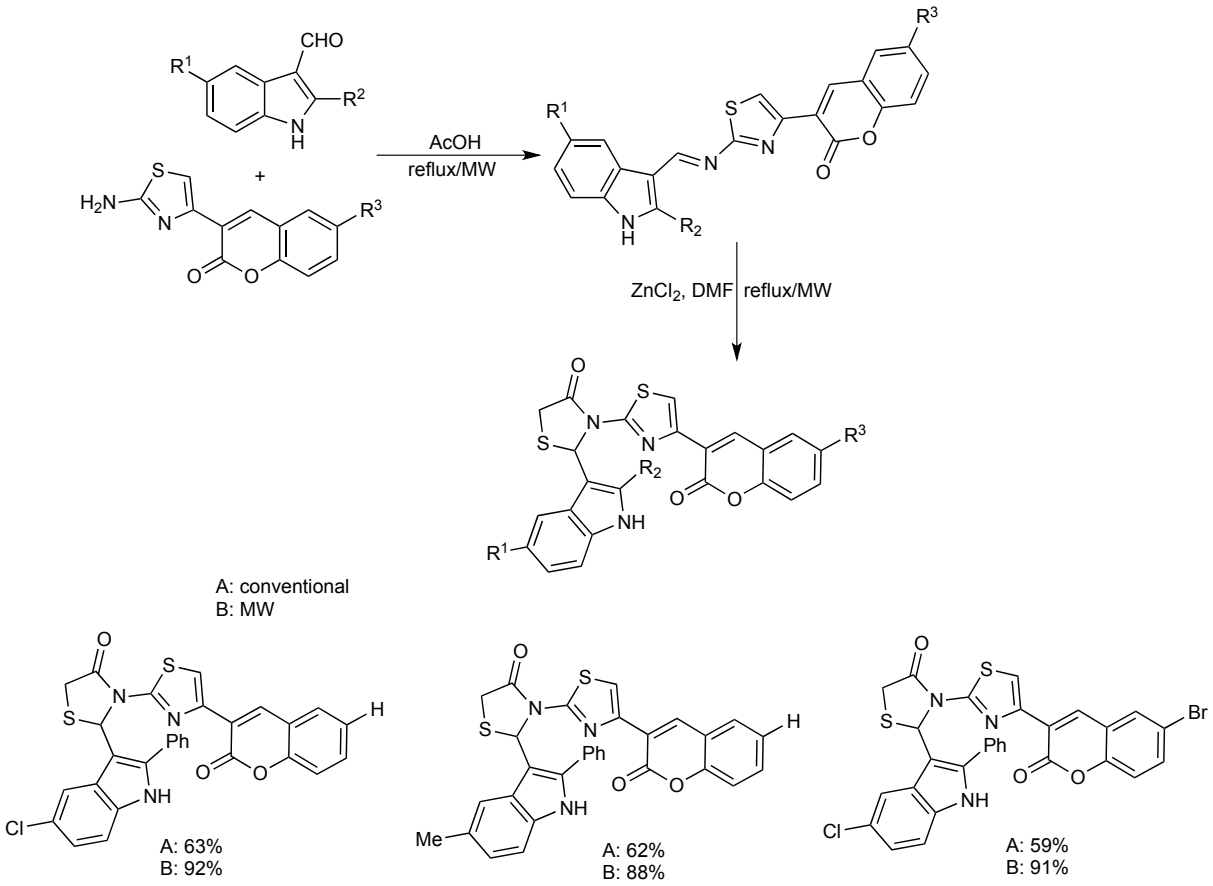
Electrophilic substitution predominantly occurs at the 3-position of indole; thus 3-substituted indole derivatives act as resourceful intermediates towards the synthesis of various substituted indoles.[68] Gayen and co-workers exploited Michael addition reaction and thereby disclosed an effective microwave assisted, solvent-free methodology for 3-(3-oxoaryl)indole derivatives from 2-phenylindole and chalcones in the presence of Lewis catalyst, $ZrCl_4$ (**Scheme 38**).[69] In the optimized reaction condition, 15 mol% of $ZrCl_4$ was used as the suitable catalyst under microwave radiation power of 280W. The reaction was more facile with chalcones bearing electron-withdrawing group compared to electron-donating ones. Activity against B16F10 and MCF7 cell lines revealed the pronouncing anti-cancer activity of these compounds.



R^1	R^2	Yield (%)
H	H	82
Br	H	78
F	H	70
OMe	H	72
Me	H	74
H	OMe	70
H	NO_2	72

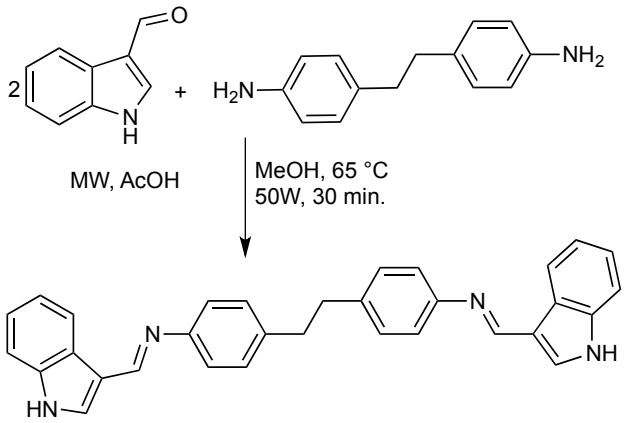
Scheme 38. Microwave assisted, solvent-free methodology for 3-(3-oxoaryl)indole derivatives

In 2018 an efficient and green methodology for indole analogues bearing thiazolidinone attached to substituted thiazolylcoumarin motifs was established.[70] First step of this procedure is the synthesis of schiffs base by the reaction of 2,5-disubstituted-1*H*-indole-3-carboxaldehyde with 3-(4-aminothiazol-2-yl)-2*H*-chromen-2-one or 3-(4-aminothiazol-2-yl)-6-bromo-2*H*-chromen-2-one in 4-5 drops of glacial acetic acid. Cyclisation of this Schiff base with thioglycolic acid in the presence of small amount of anhydrous $ZnCl_2$ in dimethylformamide (DMF) afforded the desired product in moderate to good yields (**Scheme 39**). They carried out both conventional and microwave assisted methods. In the case of conventional method this reaction needed 360 min to complete, while at the same time it gets reduced to 5 min for microwave assisted methodology. Further studies confirmed the anti-tubercular and anti-microbial activities of these compounds. Halogens at C5 position of indole and C6 position of coumarin further enhanced the anti-tubercular and anti-microbial activities of these novel compounds.



Scheme 39. Conventional and MW assisted methodology for indole analogues

Agrody and co-workers disclosed a novel microwave assisted methodology for bis-indole derivatives.[71] This strategy follows the condensation of indole-3/2/5-carbaldehydes with bifunctional aromatic amines (*p*-phenylenediamine or 4,4′-ethylenedianiline) in the presence of catalytic amount of glacial acetic acid in methanol at 65 °C under microwave radiation for 30 min to afford bis-indole derivatives in 98% yields (**Scheme 40**). Agar diffusion assay analysis showed anti-bacterial activity of some derivatives against gram positive and negative bacteria.



Scheme 40. Microwave assisted methodology for bis-indole derivatives

4. CONCLUSION

In this review we have discussed the synthetic strategies towards substituted benzofurans and indoles along with the biological activity of some of the reported compounds. Microwave assisted synthesis of benzofuran and indole derivatives has been an astonishing area in the past couple of decades. This was primarily due to the interesting applications benzofuran and indole derivatives demonstrated in pharmaceutical and biological field. Benzofuran scaffolds are also important in polymers and bioactive natural products chemistry. In view of the importance of these scaffolds several strategies were reported for the synthesis of benzofuran and indole derivatives. The scope of efficient and green microwave assisted methodology towards the synthesis of these compounds are highlighted in the review. These methodologies offer new avenues for microwave assisted synthesis of heterocyclic compounds. Compounds such as benzofuran-2-carboxylic acid derivatives, indole based benzofuran etc. continued to fascinate medicinal chemist owing to their varied biological activities, which are of great interest. Better and more efficient, ecofriendly strategies would be the future prospects in this area.

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