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PART I: Microwave-Assisted Synthesis of Benzimidazoles: An Overview (Until 2013)

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Abstract: Benzimidazole derivatives are interesting heterocycles and are found in many naturally occurring products and various drugs. They exhibit several pharmacological activities such as antitumor, diuretic, fungicidal, bactericidal, antihelmintic, antiallergic, antihistaminic, vasodilator, hypotensive, spasmolytic activities and local analgesic. Owing to the importance of these heterocyclic compounds, the aim of this review is to present the main aspects of the microwave synthetic methods of the benzimidazole derivatives until 2013.

Keywords: Benzimidazoles, benzimidazole synthesis, heterocycles, microwave.

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INTRODUCTION

Benzimidazole is a privileged heterocyclic structure for exploring chemical functionality in biological active molecules (1). They have been studied extensively due to their biological activities such as antivirutic against a lot of viruses including HIV (2,3), herpes (HSV-1) (4), RNA (5), influenza (6) and human cytomegalovirus (HCMV) (7), potent antiparasitic agents (8), topoisomerase I inhibitors (9), potential antitumor agents (10), selective neuropeptide Y Y1 receptor antagonists, angiotensin II (AII) inhibitors (11), inhibitors of the hepatitis C virus RNA polymerase (12), antibacterial (13), antifungal (14), antiulcer (15), anti-inflammatory (16), antiprotozoal (17), anticonvulsant (18), antitubercular (19), antidepressant (20), antileishmanial (21), antihypertensive (22), antioxidant (23), and anticoagulant (24, 25).

Moreover, benzimidazole structures behave as good ligands to the transition metal atoms using one of the nitrogen atom and these type of complexes have been found in a variety of biological molecules including ion-heme systems, vitamin B_{12} and its derivatives, and several metalloproteins. According to a reported study, metal complexes of biological important ligands are sometimes more effective than the free ligands (26). Therefore, their preparations have been continuously increasing and they have become the most studying heterocyclic motif by synthetic organic chemists and biologists. A number of methods have been developed for the synthesis of compounds containing a benzimidazole moiety (27). The most popular synthetic method of benzimidazoles is the dehydration of 1,2-diaminobenzenes with carboxylic acids under vigorous dehydrating reaction conditions in the presence of strong acids such as polyphosphoric acid, hydrochloric acid, boric acid, or *p*-toluenesulonic acid (28). However, the use of milder reagents, such as Lewis acids (29), inorganic clays (30), or mineral acids (31), has improved both the yield and purity of this reaction (1a). Another important synthesis method of benzimidazoles is the condensation of 1,2-diaminobenzenes with aldehydes in the presence of an oxidative reagent such as nitrobenzene, benzoquinone, sodium metabisulfite, mercuric oxide, lead tetracetate, iodine, copper (II) acetate, indium perfluorooctane sulfonates, ytterbium perfluorooctane sulfonates, and even air, have been used for this aim (32). The benzimidazoles could also be synthesized by the coupling of 1,2-diaminobenzenes with carboxylic acid derivatives such as anhydrides, lactones, orthoesters, imidates and nitriles (33). Moreover, several other catalysts, namely iodine (34), hydrogen peroxide (35), boron trifluoride diethyl etherate (36), zirconyl (IV) chloride (37), zeolite (38), and L-proline (39) have been effectively used for the synthesis of benzimidazole derivetives.

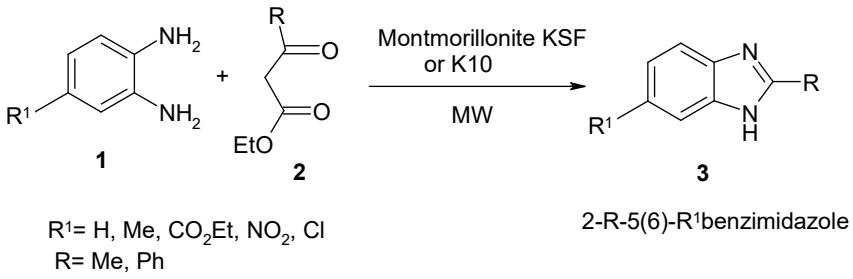
Despite their high effectiveness for the synthesis of benzimidazoles, some of the methods need to be improved for the high reaction temperature, long reaction times, toxic solvent and high-priced catalyst, *etc*. (40). Therefore, development of mild, efficient and environmentally benign protocol for the synthesis of benzimidazoles is still a hot topic for researchers. After the first reports of applications of microwaves in synthetic chemistry in 1986 (41), microwave-assisted

synthesis have become popular, particularly, last two decades due to the generally short reaction times, the high purity and yields of the resulting products. Up to now, several microwave-assisted methodologies for the synthesis of benzimidazoles have been reported.

This article aims to review the work reported, microwave-assisted synthesis of benzimidazole derivatives during past years untill 2013.

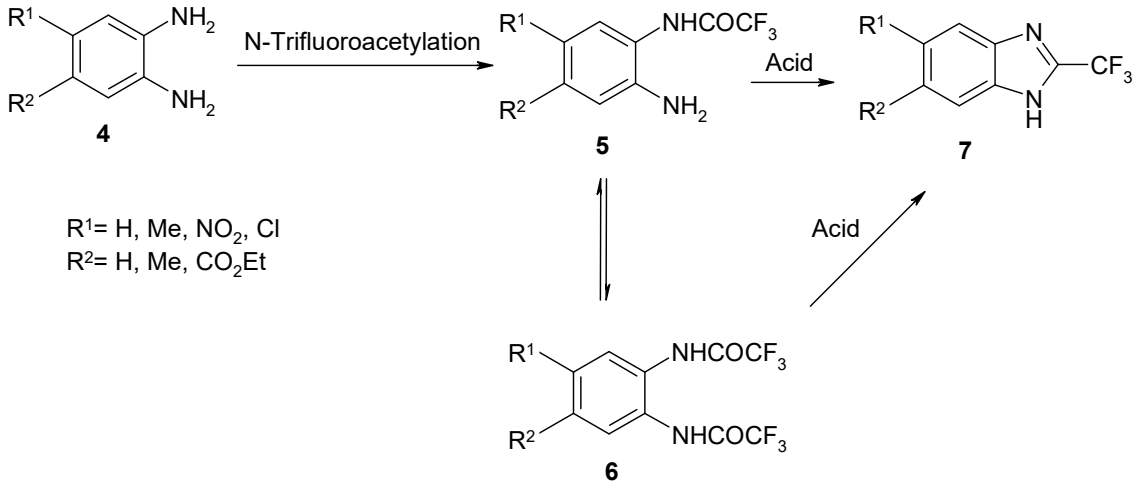
Microwave-assisted benzimidazole synthesis: a) Benzimidazole synthesis from carboxylic acids/carboxylic acid derivatives and 1,2-diaminobenzenes

The first microwave-assisted benzimidazole synthesis reported in 1995 by Bougrin and Soufaoui (42). They have described a benzimidazole synthesis method using 1,2-diaminobenzene or 4-substituted-1,2-diaminobenzene and ethyl acetoacetate or ethyl benzoylacetate on solid mineral supports in dry media under microwave irradiation in domestic ovens (Scheme 1).



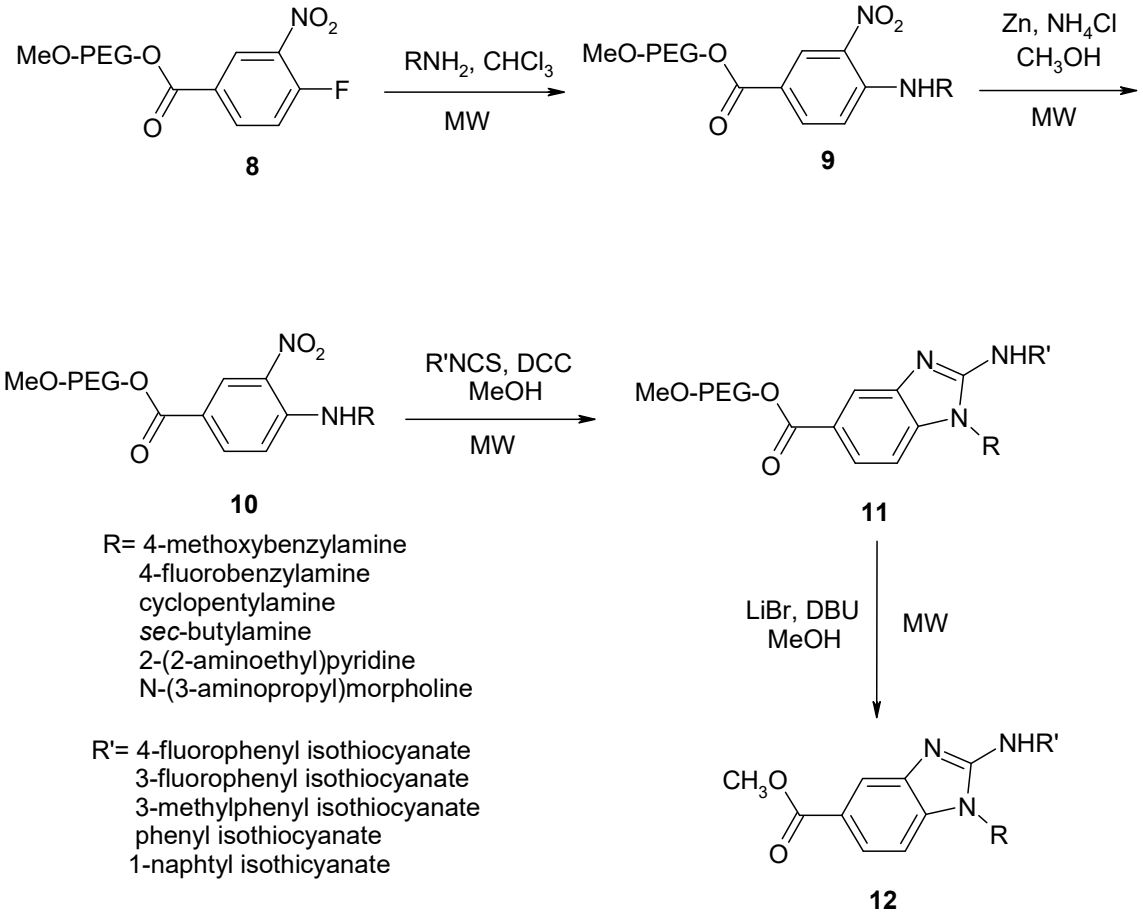
Scheme 1.

Bougrin *et al*. (43) have described in dry media synthesis of 2-trifluoromethylbenzimidazoles through cyclocondensation of N-(carbotrifluoromethyl)-*ortho*-arylenediamines on montmorillonite K10 under domestic microwave oven with good yields (Scheme 2).



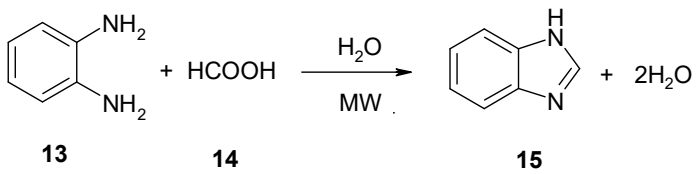
Scheme 2.

Bendale and Sun (44) have described an efficient, facile, and practical liquid-phase combinatorial synthesis of benzimidazoles under microwave irradiation in short time (Scheme 3).



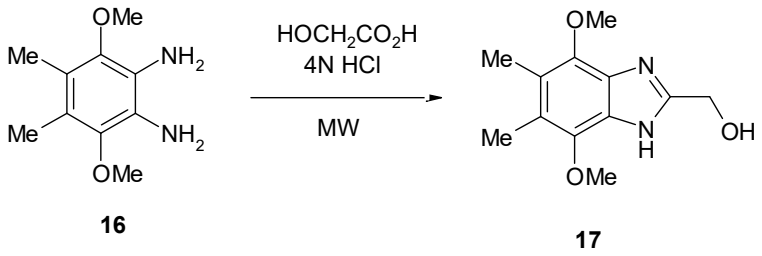
Scheme 3.

Getvoldsen *et al*. (45) developed an *in situ* monitoring method for the reactions in a microwave using UV/Vis spectroscopy. The benzimidazole synthetic reaction from 1,2-diaminobenzene and formic acid has chosen as a model reaction. They have reported that the new method would be an excellent analytical tool for monitoring the progress of a reaction, determination of end points and derivation of quantitative and kinetic data (Scheme 4).



Scheme 4.

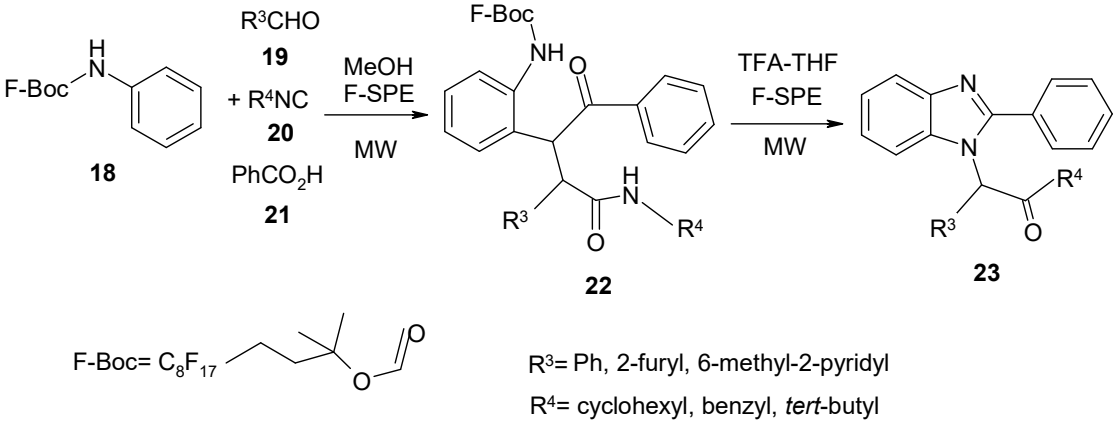
Boufatah *et al*. (46) have reported the preperation of some new biologically active benzimidazole-4,7-dione derivatives in 7 steps through the microwave irradiation for the ring closing step to obtain benzimidazole derivative (Scheme 5).



16 **17**

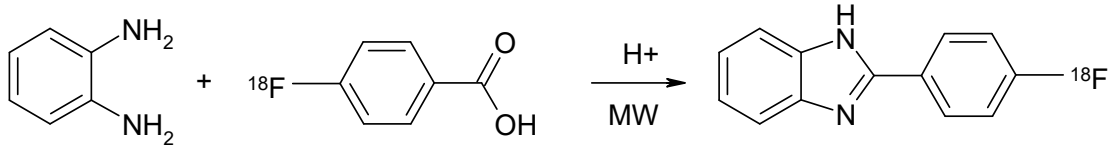
Scheme 5.

Zhang and Tempest (47) have improved the efficiency of the Ugi/de-Boc/cyclization synthesis replaced the normal Boc group with the fluorous-Boc group to protect the diamine. They were used fluorous component as a limiting agent in the Ugi reaction. Hence, they have easily separated designed condensation product containing the F-Boc group from the reaction mixture by fluorous SPE. Compared to the original Ugi/de-Boc/cyclization procedures, which take 1-2 days, the fluorous/microwave approach which modified by Zhang and Tempest has more favorable reaction and purification conditions: less than 20 min for each reaction and no need of the double scavenging step (Scheme 6).



Scheme 6.

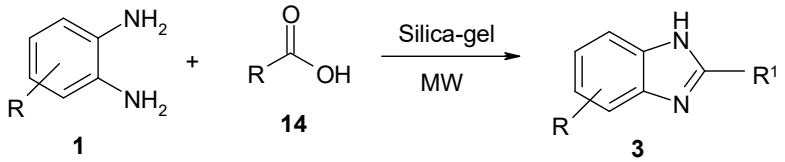
Getvoldsen *et al*. (48) have reported 2-([4-^{18}F] fluorophenyl) benzimidazole synthesis from the cyclocondensation reaction of 1,2-diaminobenzene with radiolabelled [4-^{18}F]fluorobenzoic acid in neat methanesulfonic and polyphosphoric acids under microwave (Scheme 7).



1 **24** **25**

Scheme 7.

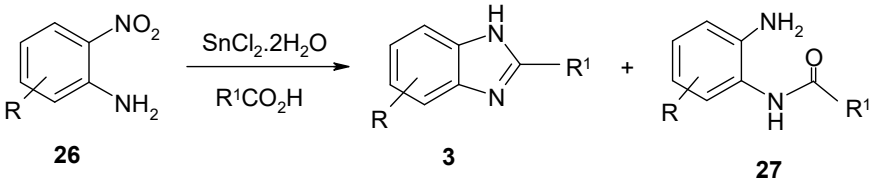
Martinez-Palou *et al*. (49) have described 2-long alkyl chain substituted benzimidazole synthesis from the reaction of 1,2-diaminobenzene and stearic acid via mono and multimode microwave irradiation with high yields (Scheme 8).



R^1= Long alkyl chain (C_9-C_{17})
R= H, Me, Cl

Scheme 8.

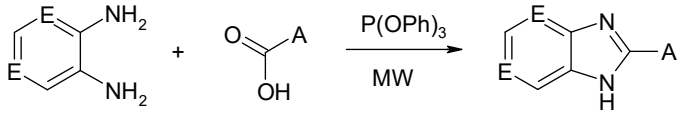
Vliet *et al*. (50) have described a simple, rapid, one pot procedure for the generation of 2-substituted benzimidazoles with high-yield directly from 2-nitroanilines using $SnCl_2$ as a reduction agent and carboxylic acid under microwave irradiation at 130 °C in 5 min (Scheme 9).



R= H, Me, OH, CO_2H, CN, CF_3, Cl
R^1= H, Me, CF_3

Scheme 9.

Lin *et al*. (51) have reported a microwave-assisted one-pot synthesis of several benzimidazole derivatives from readily available starting compounds such as 1,2-diaminobenzene, 4,5-diaminopyrimidine, *cis*-1,2-diaminocicylohexane and several carboxylic acids including heteroaraomatic carboxylic acids (Scheme 10).



E= C, N; A= R, Ar

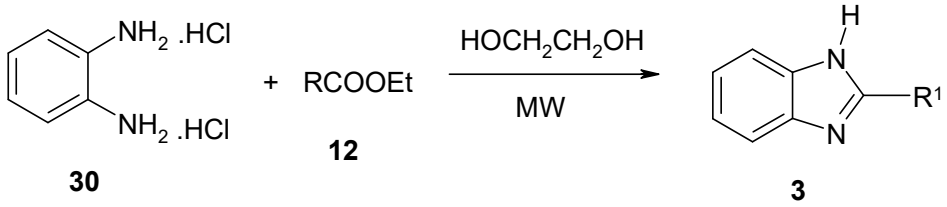
Scheme 10.

Mobinikhaledi and co-workers (38) described a selective synthesis of 2-aryl-1*H*-benzimidazoles through the reaction of 1,2-diaminobenzene with arylcarboxylic acid using zeolite as an efficient catalyst under microwave irradiation (Scheme 11).

Ar= 3-Nitrophenyl,4-nitrophenyl, 4-chlorophenyl
3-chlorophenyl, 4-tolyl, 3-tolyl, 4-methoxyphenyl
4-bromophenyl, 2-pyridyl

Scheme 11.

Jing *et al*. (52) have described a simple and rapid synthesis of benzimidazoles from 1,2-diaminobenzene dihydrochloride and esters under microwave irradiation. This is also the first report for microwave assisted benzimidazole synthesis from esters and 1,2-diaminobenzenes (Scheme 12).

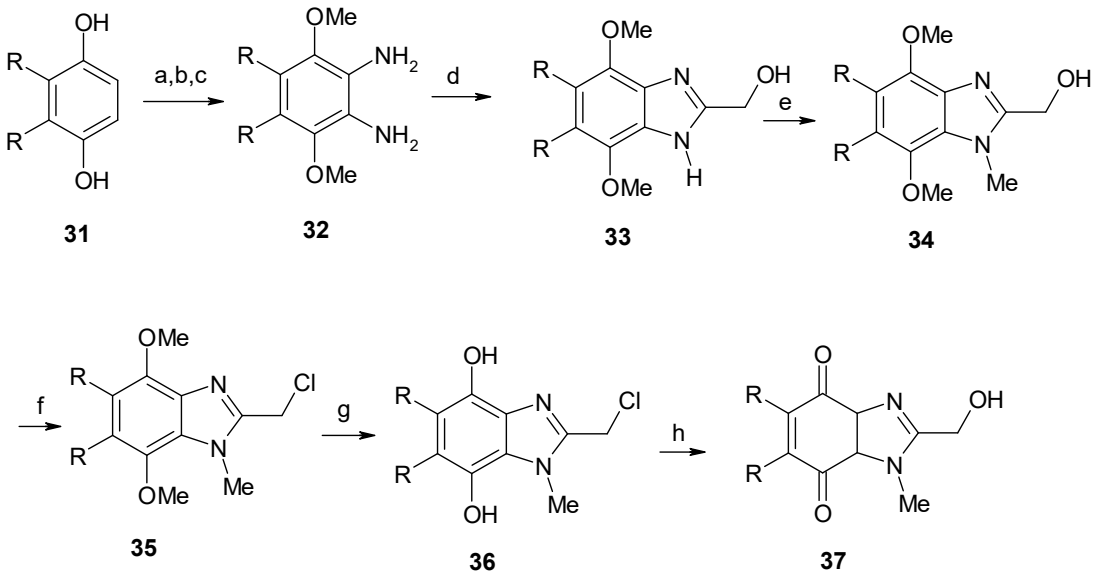


R= $ClCH_2$, CH_3,
$HOCH_2$, Et, H,
n-C_5H_{10}, CH_2CO_2Et

R_1= $ClCH_2$, CH_3,
$HOCH_2$, Et, H,
n-C_5H_{10}, 2-Benzimidazolyl

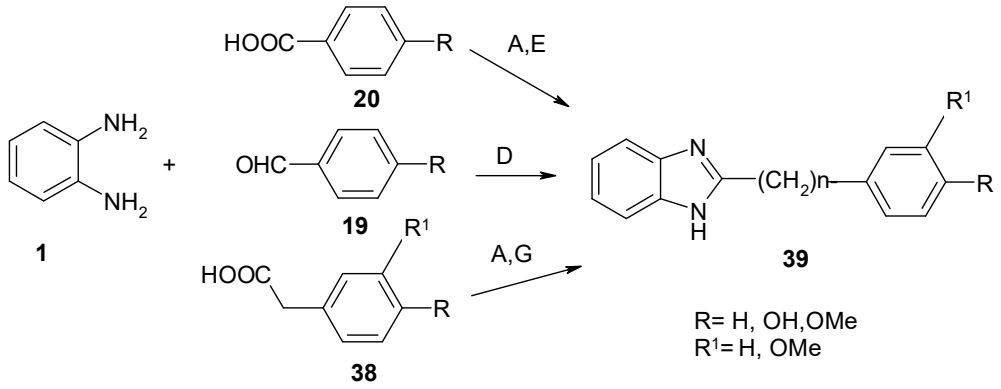
Scheme 12.

Gellis *et al*. (53) have reported the synthesis a series of variously substituted benzimidazole-4,7-diones in seven steps and antitumor activity results of them. One of them exhibit excellent cytotoxicity comparable to that of mitomycin C (Scheme 13).



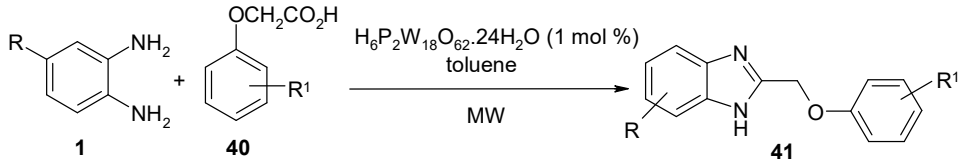
Scheme 13. Reagents and conditions: (a) KOH, $(CH_3)_2SO_4$, CH_3OH, reflux, 1 h; (b) R= H; HNO_3 62%, 1 h at rt, 1 h at 100°C or R= CH_3, $(CH_3CO)_2O$, HNO_3 fuming, 90 °C, 1 h; (c) Sn, HCl; (d) $HOCH_2CO_2H$, 4 N HCl, microwave, 800 W, 1 h 30 min; (e) $LiN(TMS)_2$, THF, 20 min, then CH_3I, 7h; (f) $SOCl_2$, $CHCl_3$, reflux, 4h; (g) BBr_3, CH_2Cl_2, -78 °C, 3 h; (h) $K_2Cr_2O_7$, H_2O, rt, 2 h.

Algül *et al*. (54) have described the synthesis of some 2-substituted benzimidazole, benzothiazole, and indole derivatives using on both microwave irradiation and conventional heating methods. They have also evaluated hyaluronidase inhibitory activity of the compounds (Scheme 14).



Scheme 14. A= PPA/MW, D= $Na_2S_2O_5$/DMF, E= PPA, G= HCl.

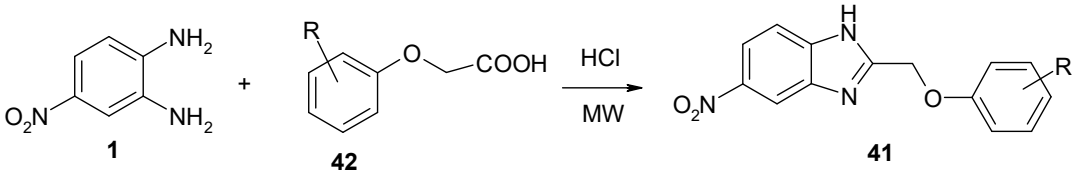
Keri *et al*. (27) have reported an expeditious, novel, and efficient method for the synthesis of benzimidazole derivatives from *o*-phenylendiamines with different phenoxy acid using a Wells-Dawson $H_6P_2W_{18}O_{62}.24\ H_2O$ catalyst (Scheme 15).



R= H, Br, Me
R^1= H, 2-Me, 3-Me, 4-Me, 2-Cl, 4-Cl, 2-NO_2, 4-NO_2, 2-NH_2, 2,4-Cl

Scheme 15.

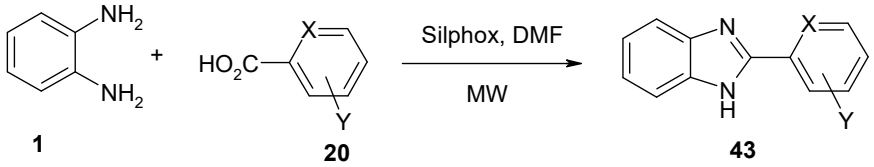
Similar to the Keri method, Hosamani and co-workers (55) described a convenient protocol for the preparation of 5-nitro-2-arylsubstituted phenoxymethyl-1*H*-benzimidazole libraries in one pot-synthesis both under microwave irradiation and conventional heating methods using hydrochloride acid as catalyst (Scheme 16).



R= H, 2-Me, 3-Me, 4-Me,
2-Cl, 4-Cl, 2-NO_2, 4-NO_2
2-NH_2, 2,4-dichloro

Scheme 16.

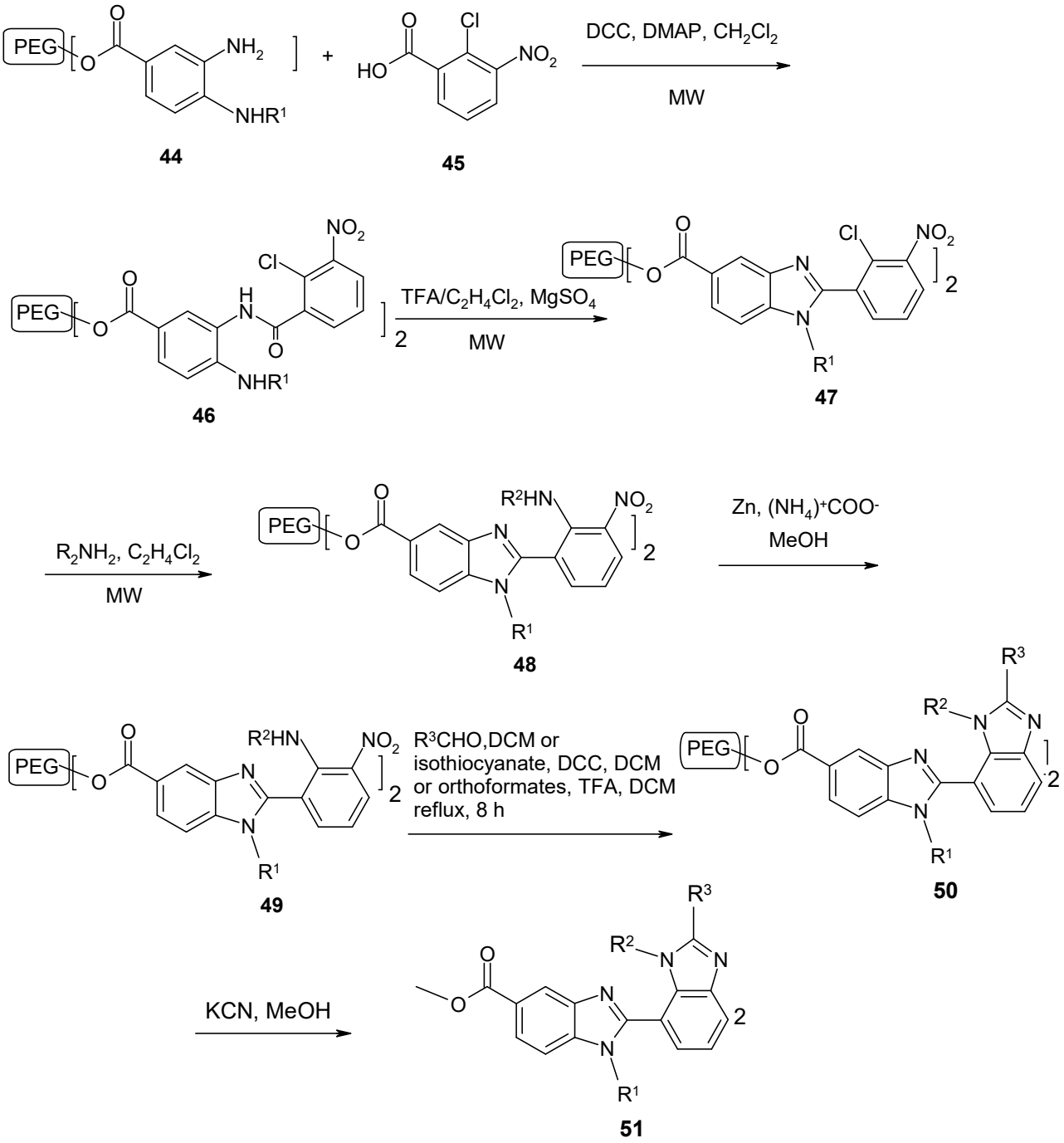
Hasaninejad *et al*. (56) have reported the synthesis of some 2-substituted benzimidazole derivatives from benzene-1,2-diamine with mono and dicarboxylic acids under microwave irradiation using silphox [$POCl_{3-n}(SiO_2)_n$] catalyst in highly yield and short reaction times (Scheme 17).



X= C, N
Y= H, Me, OMe, NO_2, Cl,Br

Scheme 17.

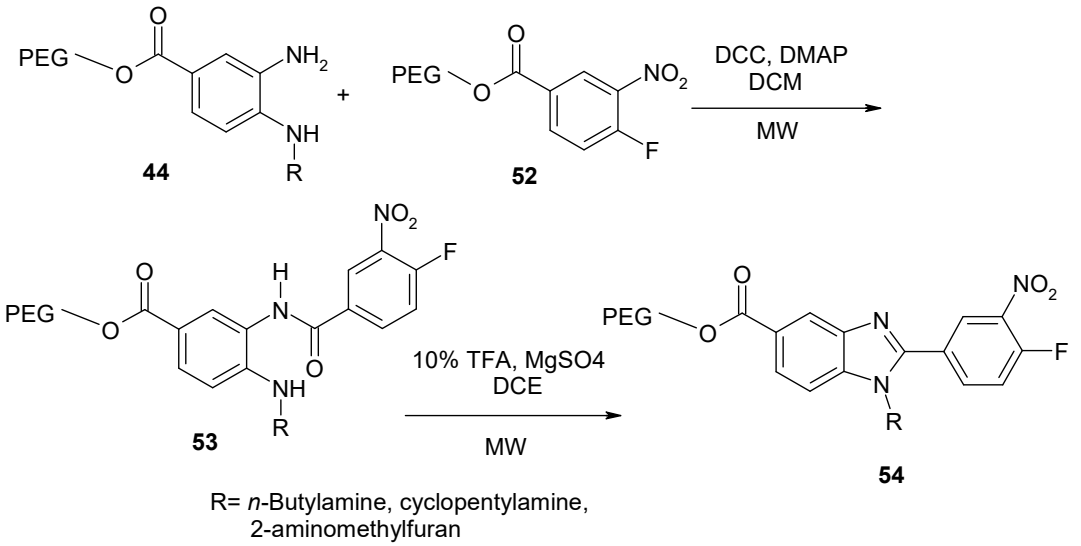
Sun and co-workers (57) synthesized angular bis-benzimidazoles on the support with three appendages with good yields and purities through soluble polymer-supported reaction. The integration of microwave irradiation and a soluble polymer support strategy provided an efficient and convenient approach for high throughput and diversity-oriented synthesis of drug-like molecules. Their preliminary screening results have shown that some of these compounds exhibited moderately to good inhabitation against VEGFR 3, which is related to the invasion and migration of cancer cells (Scheme 18).



R1= 2-(cyclohexen1-yl)ethyl, isobutyl, 3-methoxypropyl, *n*-butyl, *sec*-butyl
R2= *n*-butyl, isopropyl, 3,3-diphenylpropyl, 2-thenyl, 4-methoxybenzyl, 2-methoxyethyl
R3= *n*-butyl, 4-nitrophenyl, 2-furyl, 2-thienyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, benzylisothiocyanate

Scheme 18.

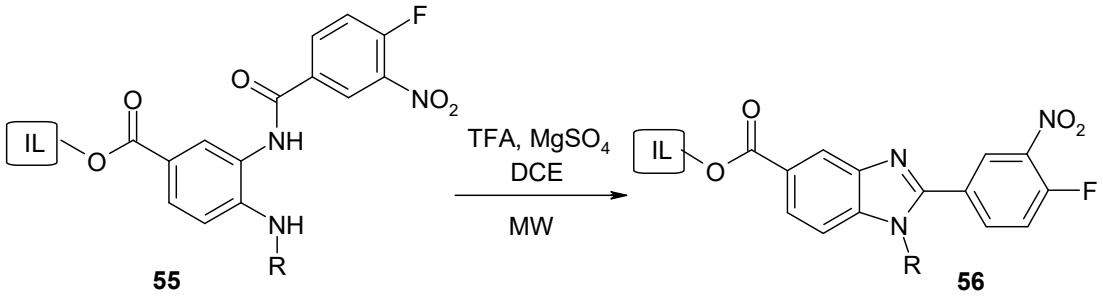
Sun and co-workers (58-60) reported a novel synthetic method for the substituted benzimidazole derivatives from the starting compounds 1,2-diaminobenzene derivative on soluble polymer support and 3-nitro-4-hydroxy/fluorobenzoic acid in a multistep process under focused microwave irradiation (Scheme 19).



R= *n*-Butylamine, cyclopentylamine, 2-aminomethylfuran

Scheme 19.

The same group has recently described the synthesis of bis-heterocyclic skeletal novel benzimidazole-linked pyrrolo-/pyridobenzimidazolones and benzimidazole-linked isoindolo-benzimidazoleones on ionic liquid support under microwave irradiation by utilizing the cascade cyclization (61) (Scheme 20).

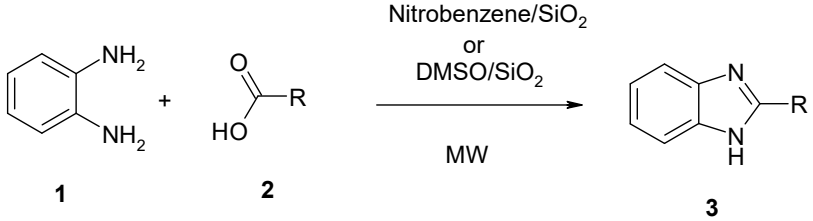


R= Isobutyl, 2-(cyclohexen-1-yl)ethyl, 3-methoxypropyl

Scheme 20.

b) Benzimidazole synthesis from aldehydes and 1,2-diaminobenzenes

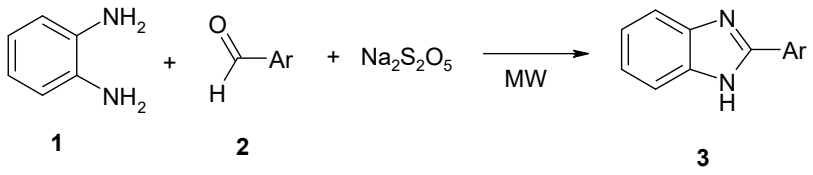
Ben-Alloum *et al*. (62) have described oxidative heterocyclization of aldehydes and o-phenylenediamine with nitrobenzene or dimethylsulfoxide impregnated on silica gel irradiated with microwave in good yields and high purity (Scheme 21).



R= Ph, 4-tolyl, 4-anisolyl, 4-ClPh, 4-NO_2Ph, 2-ClPh, 2-HOPh, 2-furyl, *n*-propyl, ethyl

Scheme 21.

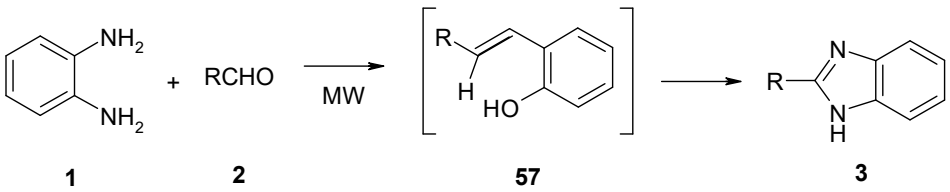
Navarrete-Vazquez and co-workers (63) described a simple, rapid, and efficient method for the preparation of several 2-(alkyoxyaryl)-1*H*-benzimidazole compounds under solvent-free conditions using readily available and inexpensive reagents utilizing microwave irradiation (Scheme 22).



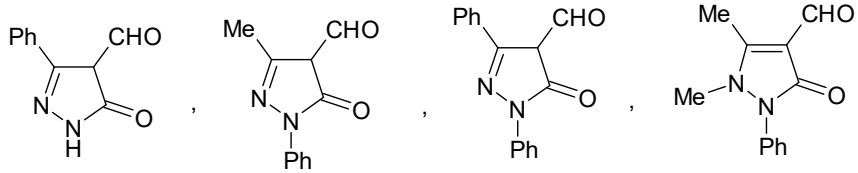
Ar= 2-HOPh, 2-MeOPh, 2-EtOPh, 2-PrOPh, 2-PhCH$_2$OPh
2-NO$_2$Ph, 4-HOPh, 4-pyridyl, 2,4,5-(trimethoxy)phenyl

Scheme 22.

Zahran and co-workers (64) described the synthesis of new heterocyclic compounds containing pyrazol-5-one coupled with benzimidazole under dry media and they also explored antitumor activity of the newly synthesized heterocycles. Some of them were found to be more effective than thalidomide (Scheme 23).



R=



Scheme 23.

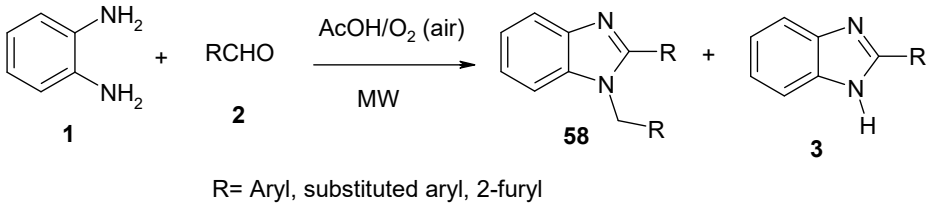
Dubey and Moorthy (65) have reported comparative synthesis of 2-alkyl and 2-aryl substituted benzimidazole derivative in the presence of polyphosphoric acid through microwave and conventional methods and also studied the effect of salt form of reactant for completion of the reaction. According to their report, the 2-substituted aryl and alkyl benzimidazole derivative synthesized via microwave and it is beneficial, in respect of yield increases up to 10 to 50%) and time (96 to 98% was reduced) than conventional method of synthesis. They also showed some remarkable inferences while the use of salt form of the reactant (1,2-diaminobenzene dihydrochloride). Navarrete-Vazquez *et al*. (66) have synthesized several benzimidazole derivatives which could be vasorelaxant and spasmolytic properties from the reaction of 1,2-

diaminobenzene with aromatic substituted aldehydes and sodium metabisulfite under microwave irradiation.

Jacob and co-workers (67) described an improved methodology for the selective synthesis of 1,2-disubstituted benzimidazoles by the condensation of 1,2-diaminobenzene and aldehydes using solid-supported catalyst ($SiO_2/ZnCl_2$) in a short time under microwave irradiation.

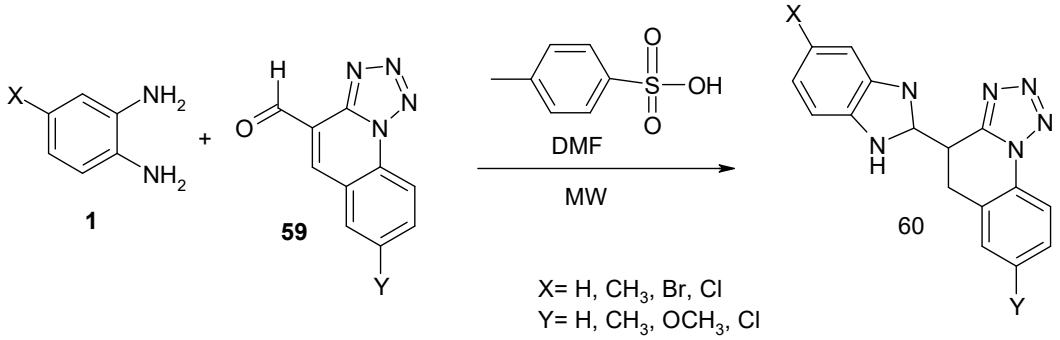
Mao *et al*. (68) have reported intermittent microwave irradiation for the synthesis 2-benzimidazole derivatives from aromatic aldehydes an 1,2-diaminobenzene only using molecular oxygen as the oxidant and inexpensive KI as the catalyst.

Rathod and co-workers (40) described eco-friendly benzimidazole synthesis from aromatic aldehydes and 1,2-diaminobenzene using $MoO_3/CeO_2.ZrO_2$ as a catalyst under solvent-free conditions both conventional and microwave heating. Azarifar *et al*. (69) have reported 2-aryl-1-(arylmethyl)1H-benzimidazole synthesis from 1,2-diaminobenzene and aldehydes through acetic acid-promoted condensation in air under microwave irradiation (Scheme 24).



Scheme 24.

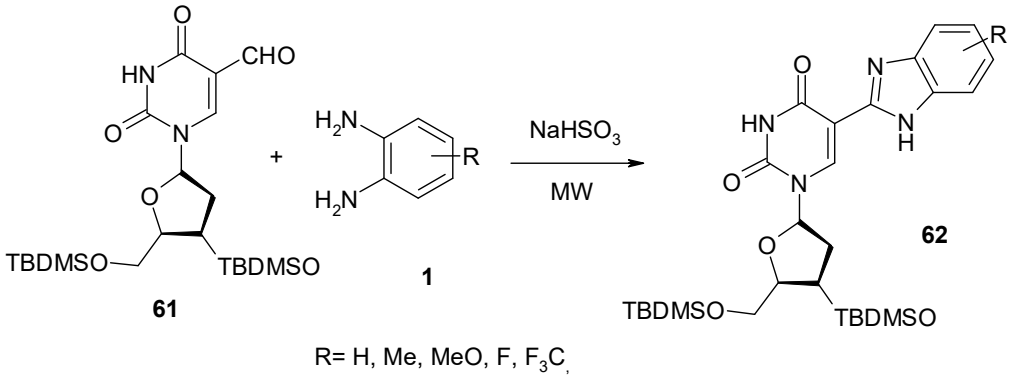
Mungra and co-workers (70) described a microwave-assisted synthesis of 4-(benzimidazol-2-yl)tetrazolo[1,5-a]quinoline from 1,2-diaminobenzene and heterocyclic aldehydes catalyzed by an organocatalyst *p*-TsOH (Scheme 25).



Scheme 25.

Krim *et al*. (71) have reported efficient synthetic routes to prepare fluorescent compounds containing benzimidazoles in the 5-position of pyrimidine nucleosides. Their synthesis is based on the straightforward condensation of 5-formyl-2'-deoxyuridine and arylenediamine

derivatives under a cooperative effect of microwave activation and $NaHSO_3$ catalysis (Scheme 26).

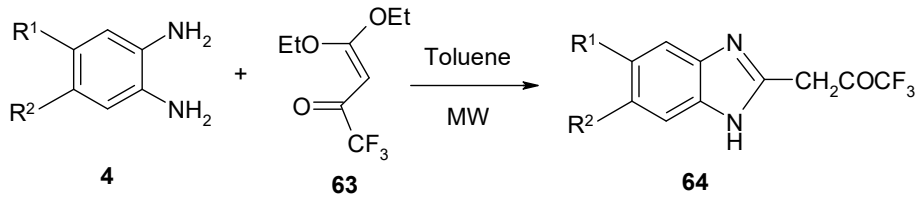


R= H, Me, MeO, F, F_3C,

Scheme 26.

c) Miscellaneous benzimidazole syntheses

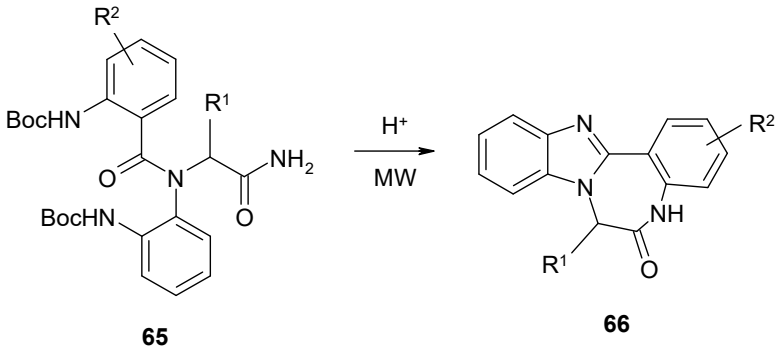
Reddy *et al*. (72) have reported microwave assisted synthesis of 5- or 5,6-disubstituted-2-trifluoroacetonylbenzimidazole derivatives (Scheme 27).



R^1=, R^2= H or Me

Scheme 27.

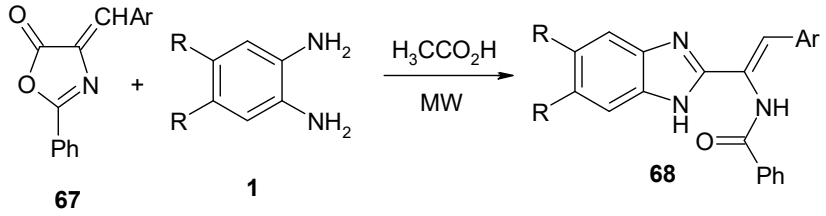
Hulme and co-workers (73) described a novel two-step solution phase protocol for the synthesis of arrays of triazadibenzoazulenones using the Ugi reaction and two tandem ring closing transfomations. They also used microwave irradiation for 5 or 10 min for the second ring closing steps (Scheme 28).



R^1= *n*-Propyl, 2-phenylethyl, *n*-butyl, isopropyl, *sec*-butyl, Me
R^2= H, Cl, MeO

Scheme 28.

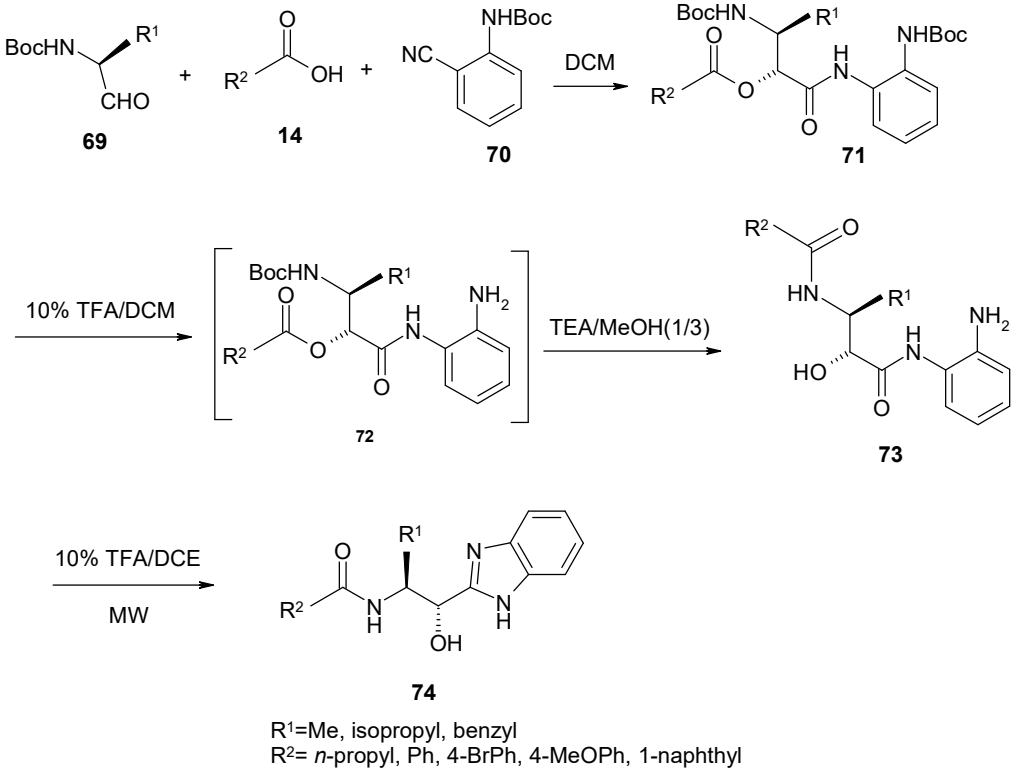
Wang *et al*. (74) reported microwave-assisted solvent-dependent chemoselective reaction dealing with 4-arylidene-2-phenyloxazol-5-ones and *ortho*-diamines to obtain benzimidazole scaffold (Scheme 29).



R= H, Me, Cl, CO_2H
Ar= Ph, 4-ClPh, 4-MeOPh, 3,4,5-trimethoxyphenyl, 2-thienyl

Scheme 29.

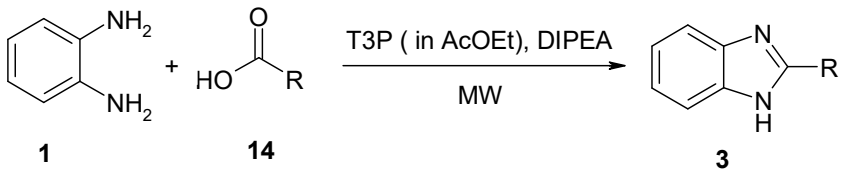
Shaw and *et al*. (75) described a novel synthetic protocol for the synthesis of unique norstatine analogs bearing benzimidazole moiety through Passerini reaction and following ring closing (Scheme 30).



R^1=Me, isopropyl, benzyl
R^2= *n*-propyl, Ph, 4-BrPh, 4-MeOPh, 1-naphthyl

Scheme 30.

Wen *et al*. (76) have reported on eco-friendly, one-pot efficient propylphosphonic anhydride (T3P) mediated synthesis of benzimidazoles from various carboxylic acids and 1,2-diaminobenzene under microwave irradiation (Scheme 31).



1 **14** **3**

R= Et, Ph, 4-substituted phenyl, 4-pyridyl, 4-chloro-2-phenylethyl

Scheme 31.

CONCLUSION

Properties of benzimidazole and its derivatives have been studied for over a hundred years. Special interest of researchers triggered by the fact that 5,6-dimethylbenzimidazole is a component of naturally occurring vitamin B-12. The benzimidazole ring is an important pharmacophore in modern drug discovery. On the other hand, in the past decade, heating and driving chemical reaction by microwave energy has been an increasingly popular theme in the scientific community. A number of methods have been developed for the synthesis of benzimidazole containing compounds. There are two main synthesis methods for the benzimidazoles: i) from the reaction of 1,2-diaminobenzenes with carboxylic acids or its derivatives, ii) condensation of 1,2-diaminobenzenes with aldehydes presence of an oxidative reagent. Despite their high efficiency for the synthesis of benzimidazoles, some of the methods are plugged by one of the drawbacks such as, high reaction temperature, prolonged reaction times, toxic solvent and expensive catalyst, *etc.* Therefore, development of mild, efficient and environmentally benign protocol for the synthesis of benzimidazoles continues to attract researchers' attentions. This article aims to review the work reported, microwave-assisted synthesis of benzimidazole derivatives published in SCI journals from the first report up to 2013.

ABBREVIATIONS

Ac= Acetyl
Ar= Aryl
Boc= *tert*-Butyloxycarbonyl
DCC= N,N'-Dicyclohexylcarbodiimide
DCE= 1,2-Dichloroethane
DCM= Dichloromethane
DEAD= Diethyl azodicarboxylate
DIPEA= N,N-Diisopropylethylamine
DMAD= Dimethylacetylene dicarboxylate
DMAP= 4-Dimethylaminopyridine
DMF= Dimethylformamide
DMSO= Dimethyl sulfoxide
HCMV= Human cytomegalovirus
HIV= Human Immunodeficiency Virus
HSV= Herpes simplex virus
Me= Methyl
MW= Microwave

PEG= Polyethylene glycol
PPA= Polyphthalamide
RNA= Ribonucleic acid
TBDMS= *tert*-butyldimethylsilyl
TFA= Trifluoroacetic acid
TEA= Triethanolamine
Ts= Tosyl
T3P= propylphosphonic anhydride
VEGFR= Vascular endothelial growth factor receptor

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