Promising Synthetic Approaches Using Aqueous Media for Assembling Various Substituted Benzimidazoles

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Abstract

In recent years, use of water as a green solvent media for synthesizing benzimidazole derivatives, draws substantial attentions to the medicinal chemists, as this approach offers relatively simple reaction conditions, improved chemo selectivity, easy work-up procedure to isolate products and accelerating reaction rates in many cases. These are the clear-cut advantages over using organic solvents as synthetic media which often associated with harsh reaction conditions like reflux temperature, hazardous catalysts, long reaction time, moreover generation of toxic vapors which is harmful for chemists himself as well as for the environment. Herein, several recent synthetic approaches are reviewed ranging from metal catalyzed condensation reactions to polymer-supported benzimidazole assembly in aqueous media.

Key words: *Benzimidazole, Organic synthesis; Green synthesis; Antiviral; Anticancer.*

Introduction

Benzimidazole ring system is a heterocyclic structure that comprises a benzene ring fused to the 4,5-positions of imidazole. This benzimidazole moiety is one of the most privileged pharmacophore in medicinal chemistry as it shows significant affinity to a variety of proteins, enzymes and receptors (Chawla et al., 2013; Mason et al., 1999). Some benzimidazole derivatives have shown to exert pharmacologically potent antimicrobial (Figure 01) and antibacterial effects (Ansari & Lal, 2009; Ed & G, 1980; Foks et al., 2006), while some other derivatives are found to have significant antiviral efficacy over several viruses such as HIV, herpes (HSV-1), influenza, and human cytomegalovirus (HCMV) (Migawa et al., 1998; Porcari et al., 1998; Roth et al., 1997; Tamm, 1957; Tebbe et al., 1997). Moreover, various substituted benzimidazoles have also been employed as topoisomerase inhibitors, angiotensin II inhibitors, serotonin receptor (5-HT3) antagonists, antitumor agents, smooth muscle cell proliferation inhibitors etc. (Denny et al., 1990; Fonseca et al., 2001; Kim et al., 1996; Kohara et al., 1996; Zarrinmayeh et al., 1999; Zhao et al., 2000).

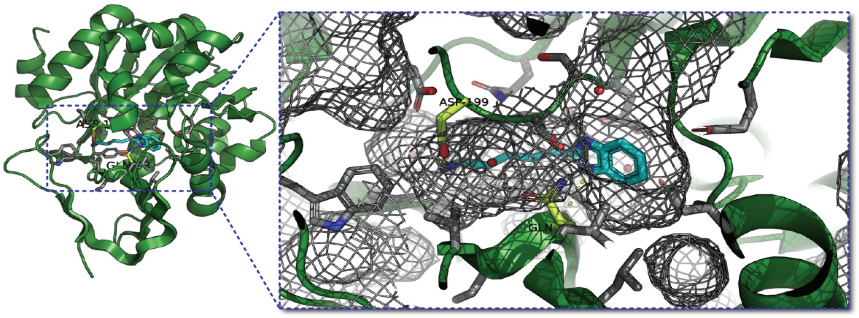

Figure 01: A benzimidazole-based derivative (cyan stick) at the active site of Spermidine Synthase (green) of *Plasmodium falciparum*; based on PDB ID 4CWA (Sprenger et al., 2015).

Because of these versatile biological activities, it is imperative for the medicinal chemists to develop efficient, fast, simple as well as environmentally benign approaches to synthesize substituted

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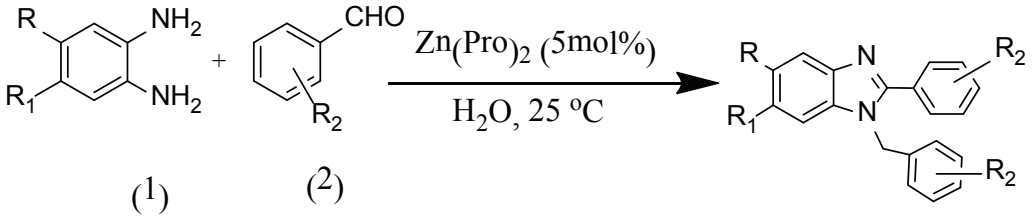
benzimidazoles. Numerous synthetic methodologies for preparing substituted benzimidazole derivatives have been reported in literatures which includes synthesis from condensation of o-phenylenediamines with carboxylic acids, acid chlorides, nitriles imidates and orthoesters under strong acidic reaction conditions (Fairley et al., 1993; Geratz et al., 1979; Lu et al., 2002; Tidwell et al., 1978); oxidative cyclodehydrogenation of o-phenylenediamine with various aldehyde derivatives in presence of different oxidants (Bachhav et al., 2011; Blacker et al., 2009; V. D. Patil et al., 2010; Riadi et al., 2011); transition-metal-catalyzed intramolecular cyclization of 2-haloanilides (Evindar & Batey, 2006; Saha et al., 2009; Yang et al., 2008); microwave radiation assisted condensation reactions of o-phenylenediamine with β-ketonitriles, β-ketoesters, or β-diketones under high temperature conditions or in the presence of a catalyst (Cai et al., 2011; Kamila et al., 2006; R. Biehl et al., 2005; Wang & Qin, 2005). These methods are widely used. But to improve the chemo selectivity, lowering the chances of formation of side products, to ease the workup procedure, to avoid toxic and hazardous chemicals, moreover, to employ economical and ecofriendly approaches for benzimidazole synthesis, synthetic chemists are utilizing water as a useful alternative solvent for several years. As water has several prospective advantages like safety, economy, ready availability and being nontoxic, suitability of reactions in water have been ascertained by the many researches dedicated to develop new processes with which they can be accomplished catalytically and with improved chemo selectively (Habibi et al., 2015).

Recent Synthetic Approaches for Benzimidazole Derivatives in Aqueous Medium

Ravi Varala et al, 2007, reported an efficient procedure (Scheme-1) for the selective synthesis of 1, 2-disubstituted benzimidazole derivatives (3) from a wide range of substituted o-phenylenediamines (1) (1 mmol) and aldehydes (2) (2 mmol) in moderate to excellent yields (42—92%) utilizing 5 mol% of Zn(proline)2-complex as catalyst in water media at ambient temperature (Ravi et al., 2007).

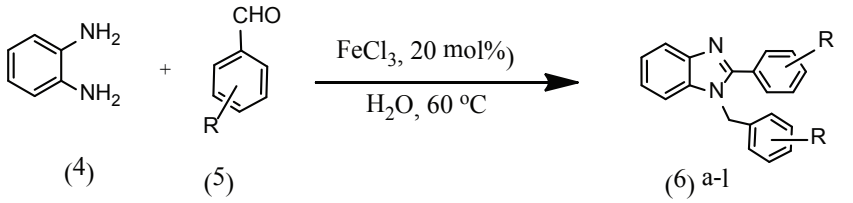


(1) (2) (3) formed exclusively

R, R_1=H
R=CH3, R_1=CH3
R=Cl, R_1=Cl
R2 = various substitution on phenyl ring

Scheme-1: Synthesis of 1, 2-disubstituted benzimidazole using Zn-proline as catalyst

Yunyun et al, 2012, developed a reaction system to synthesize 1, 2-disubstituted benzimidazoles (6) from using o-phenylenediamine (4) with various aromatic aldehyde derivatives (5) in 1:2 mmol equivalent ratio and have found good to excellent yields (63-90%) under mild reaction conditions involving water as the reaction medium in the presence of 20 mol% FeCl3 (Scheme-2). This method possesses advantages such as clean reactions system, low cost and potentially recyclable catalyst as well as good substrate tolerance (Liu & Wang, 2012).

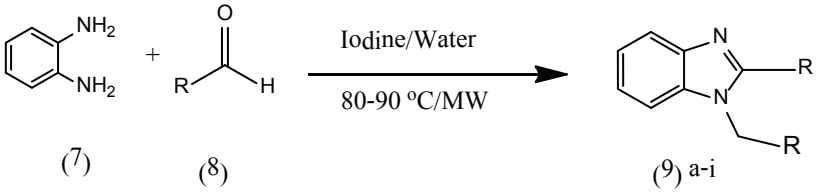


(4) (5) (6) a-l

R=H (6a), 4-Me (6b), 4-F (6c), 4-Cl (6d), 4-Br (6e), 4-NO_2 (6f), 4-OMe (6g), 2-OMe (6i), 3-NO_2 (6j), 2-OH (6k), 2-Cl (6l)

Scheme-2: Synthesis of 1, 2-disubstituted benzimidazole using 20 mol % FeCl3 as catalyst

P. P. Sun et al, 2006, utilized catalytic amount of iodine (0.02 mmol), in THF–H2O (1:1 v/v) for the condensation of variety of aldehyde derivatives (8) with o-phenylenediamine (7) in 1:1 mmol equivalent ratio to obtain substituted benzimidazoles under room temperature at good yields. The method can be exploited for the synthesis of both 2-substituted and 1, 2-disubstituted benzimidazoles (Sun & Hu, 2006). In 2015, Aniket P. Sarkate et al, demonstrated iodine catalyzed synthesis of 2-Aryl-1-arylmethyl-1H-benzimidazoles (9) by using o-phenylenediamine (7) and aldehydes (8) at 1:2 mmol equivalent amount at 80-90°C or at 70°C under microwave in aqueous media (Scheme-3). This newer approach is promising and gives moderate yields (84-95%) with high purity and selectively single product in aqueous media (Aniket et al., 2015).

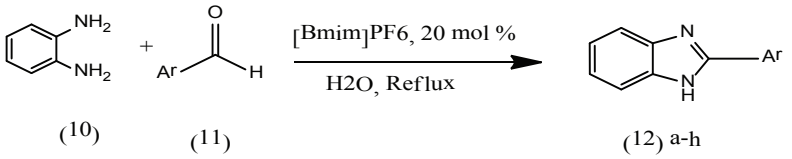


(7) (8) (9) a-i

R= Ph (9a), 4-ClC_6H_4 (9b), 3-$O_2NC_6H_4$ (9c), 4- MeC_6H_4 (9d), 4- FC_6H_4 (9e), 4-CNC_6H_4 (9f), 4-$MeOC_6H_4$ (9g), 4-$Me_2NC_6H_4$ (9h), 2-furyl (9i)

Scheme-3: Synthesis of 1, 2-disubstituted benzimidazole using I2 as catalyst

Aniruddh Bhavsar et al, 2016, demonstrated a novel and efficient route to synthesize 2-substituted benzimidazole derivatives (12) in good to excellent yield (87-96%) starting from o-phenylenediamine (10) and aryl aldehydes (11) in 1:1 mmol equivalent ratio in an aqueous media under reflux condition in presence of catalytic amount (20 mol%) of an ionic liquid, 1-Butyl-3-methylimidazolium hexafluorophosphate [BMIM-PF6] (Scheme-4). One important thing is, this ionic liquid can be reusable for further reactions after simple distillation to remove water and drying the remaining ionic liquids under vacuum (Bhavsar et al., 2016).

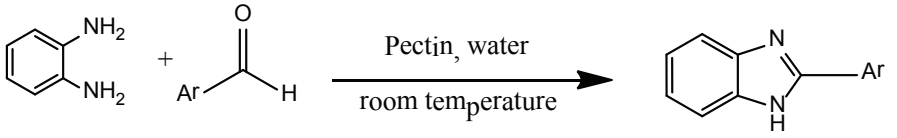


(10) (11) (12) a-h

Ar = -C_6H_5 (12a), 4-OH-C_6H_4 (12b), 4-OCH_3-C_6H_4 (12c), 4-Cl-C_6H_4 (12d), 4-Br-C_6H_4 (12e), 4-CH_3-C_6H_4 (12f), 4-C_2H_5-C_6H_4 (12g), 3-OCH_3-4-OH-C_6H_3 (12h)

Scheme-4: Synthesis of 2-substituted benzimidazole using ionic liquid [BMIM-PF6] (20 mol %) as catalyst.

Agrwal Akansha et al, 2014, developed a green procedure for synthesizing 2-substituted benzimidazole (15) by using various aromatic aldehydes (14) and o-phenylenediamine (13) (1:1 mol equivalent ratio) using pectin, a hetero polysaccharide, as a catalyst in water medium at room temperature (Scheme-5). The key advantages of this procedure were cost effectiveness of catalyst, easy workup and purification of product by non-chromatographic methods and excellent yield up to 91% depending upon various substitutions (Akansha et al., 2014).

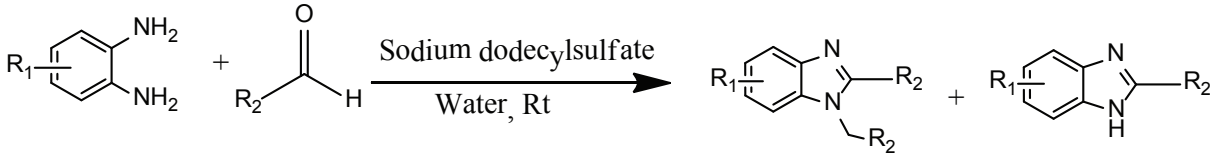


(13) (14) (15) a-k

Ar = -C_6H_5 (15a), 3-(NO_2)-C_6H_4 (15b), 4-(NO_2)-C_6H_4 (15c)
3-(OCH_3)-C_6H_4 (15d), 4-(OCH_3)-C_6H_4 (15e), 4-(Cl)-C_6H_4 (15f),
4-(OH)-C_6H_4 (15g), 3-(OH)-C_6H_4 (15h), 4-(F)-C_6H_4 (15i),
3-(Br)-C_6H_4 (15j), 4-(CH_3)-C_6H_4 (15k)

Scheme-5: Synthesis of 2-substituted benzimidazole by using pectin, a hetero polysaccharide as a catalyst and water as a solvent at room temperature.

S. D. Pardeshi et al, 2015, demonstrated a convenient procedure for the synthesis of mono substituted, 2-Aryl benzimidazoles (19) from the reaction of o-phenylenediamine (16) with aromatic aldehydes (17) at 1:1 mol equivalent ration in presence of 10 mol% sodium dodecyl sulphate using water as reaction medium at room temperature under open air atmospheric condition with and without use of sonication (Pardeshi & Thore, 2015). In 2011, P. Ghosh et al, synthesized 1, 2-disubstituted benzimidazole (18) as predominant product using 1 mmol of anhydrous SDS in the reaction mixture of o-phenylenediamine (16) and benzaldehyde (17) (1:2 mol equivalent) under same reaction condition (Scheme-6) at room temperature (Ghosh & Mandal, 2011).

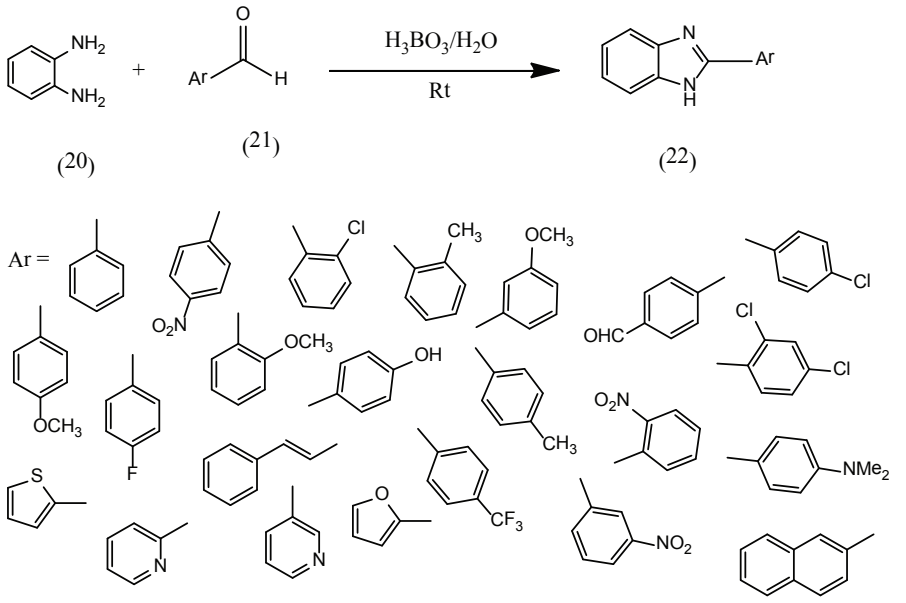


(16) (17) (18) (19)

R1 = H, 5-Cl, 3-CH3, 3-benzoyl
R2 = various aromatic substitution

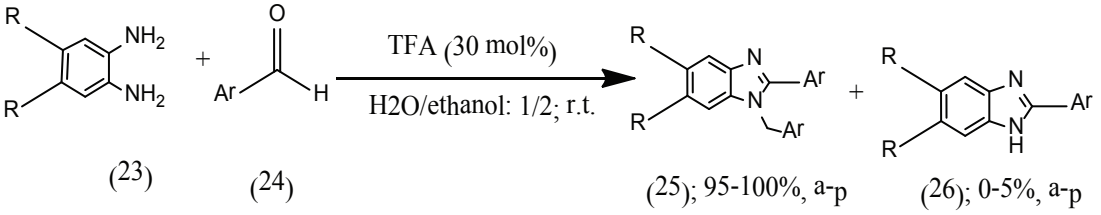
Scheme-6: Substituted benzimidazole using anhydrous SDS at room temperature

Zahed Karimi-Jaberi et al, 2012 and M. R. Poor Heravi et al, 2013, revealed a very simple, environmentally benign and efficient method for the synthesis of 2-substituted benzimidazoles (22) from o-phenylenediamine (20) and aromatic aldehydes (21), utilizing boric acid (H3BO3) as catalyst in aqueous media under room temperature in an excellent yield (85-95%) (Scheme-7). The method is applicable for both aryl and heteroaryl aldehydes. The main features of this procedure include mild reaction conditions, tolerability to a wide range of functional groups and easy separation of products from the reaction mixture (Karimi-Jaberi & Amiri, 2012; Poor Heravi & Ashori, 2013).



Scheme-7: 2-substituted benzimidazole using boric acid (H3BO3) as catalyst in aqueous media at room temperature

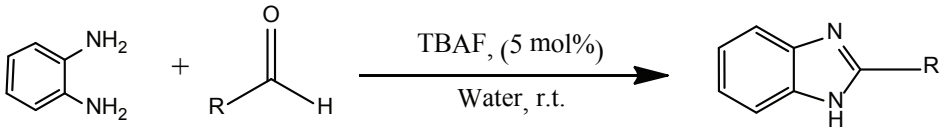
M. R. Mohammadizadeh et al, 2011, introduced a selective and eco-compatible synthesis of a 2-aryl-1-arylmethyl-1H-1,3-benzimidazoles (25) via condensation reaction between variety of o-phenylenediamine (23) and aromatic aldehyde derivatives (24) in ethanol/water solvent system at room temperature (Scheme-8) utilizing an organocatalyst Trifluoroacetic acid (TFA) at 30 mol%. This procedure provides a substituted benzimidazoles with an excellent yield of 68-97% yield (Mohammadizadeh & Taghavi, 2011).



R=H, Ar=Ph (**a**); R=H, Ar = 4-Me-Ph (**b**); R=H, Ar = 4-MeO-Ph (**c**); R=H, Ar= 4-Cl-Ph (**d**);
R=H, Ar = 4-Me_2N-Ph (**e**); R=H, Ar= 4-F-Ph (**f**); R=H, Ar= 4-NC-Ph (**g**);
R= H, Ar= 4-O_2N-Ph (**h**); R= H, Ar = 4-HO-Ph (**i**); R= H, Ar= 3-HO-Ph (**j**);
R= H, Ar= 3,4-di(MeO)-Ph (**k**); R=H, Ar= 2-Furyl (**l**); R= Me, Ar= 4-iso-propyl-Ph (**m**);
R=Me, Ar= 4-Cl-Ph (**n**); R= Me, Ar = 4-Me-Ph (**o**); R=Cl, Ar = Ph (**p**)

Scheme-8: Substituted benzimidazole in presence of an organocatalyst, Trifluoroacetic acid (TFA)

Joshi et al, 2010, developed one-pot reaction scheme for synthesizing 2-Arylbenzimidazole (29) in good to excellent yield (82-94%), utilizing o-phenylenediamine (27) as starting compound and various substituted aldehydes (28) as reactants in aqueous medium under ultrasonic irradiation at ambient temperature (Scheme-9). In this procedure 5 mol% of tetra-n-butylammonium fluoride (TBAF) was used as catalyst. As a whole green, mild and inexpensive reaction scheme with excellent chemo selectivity, and excellent yields are the main advantages of this procedure (Joshi et al., 2010).

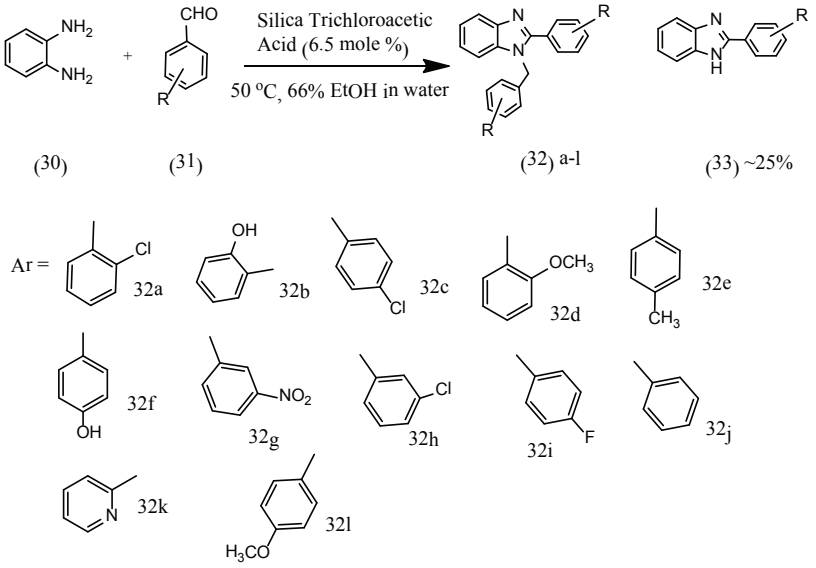


(27) (28) (29) a-m

Aldehydes (28) : Benzaldehyde **(29a)**; Anisaldehyde **(29b)**; 4-methyl benzaldehyde **(29c);** 4-chlorobezaldehyde **(29d)**; 4-flurobenzaldehyde **(29e)**; 3-bromobenzaldehyde **(29f)**; Furan-2carbaldehyde **(29g)**; Piconaldehyde **(29h)**; Nicotinaldehyde **(29i)**; 4-(1H-1,2,4-trizol-1-yl)benzaldehyde **(29_j)**; Napthaldehyde **(29k);** Cinnamaldehyde **(29l)**; 3-nitrobanzaldehyde **(29m)**

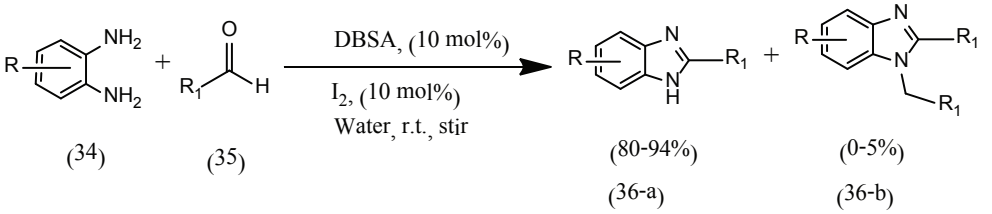
Scheme-9: Substituted benzimidazole using tetra-n-butylammonium fluoride (TBAF) as catalyst

Brajesh Kumar et al, 2014, introduced an efficient one-pot synthesis technique by utilizing silica gel supported trichloroacetic acid (SiTCA) at 50°C in aqueous medium by ultrasonic irradiation for synthesizing 2-aryl-1-arylmethyl-1H- benzimidazole derivatives (32) from o-phenylenediamine (30) and aromatic aldehydes (31) in excellent yields (Scheme-10). This scheme is advantageous to synthesize di-substituted benzimidazole due to the use of green solvent and inexpensive catalyst, requiring simple experimental procedure, shorter reaction time and higher yield (KUMAR et al., 2014).



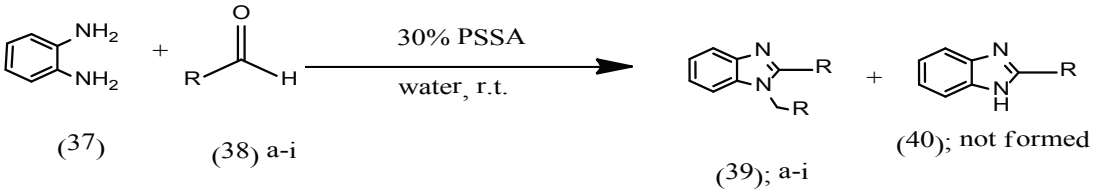
Scheme-10: Sonochemical synthesis of 1, 2-disubstituted benzimidazole derivatives in the presence of silica gel supported trichloroacetic acid (SiTCA)

V. Kumar et al, 2013, developed an efficient synthetic method for the facile synthesis of 2-substituted benzimidazoles (36-a) from various substituted o-phenylenediamine (34) and aldehyde derivatives (35) in aqueous media utilizing a surfactant, Dodecylbenzenesulfonic acid (DBSA) as catalyst (10 mol%) and I2 (10 mol%) as co-catalyst (Scheme-11). The reaction scheme described by the researchers is beneficial due to its clean and green reaction profile, operational simplicity and high chemo selectivity with excellent yields (Kumar et al., 2013).



Scheme-11: DBSA catalyzed synthesis of 2-substituted benzimidazoles.

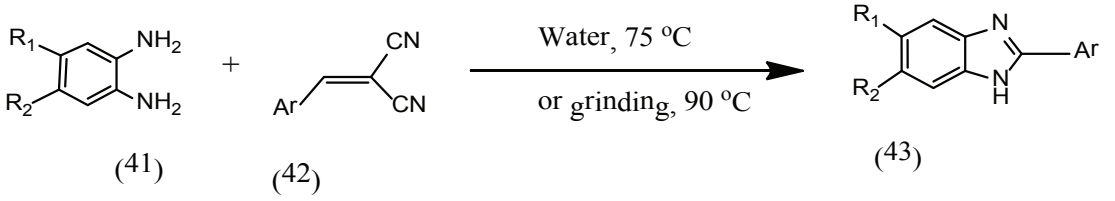
Madhukar B. Deshmukh et al, 2011, had incorporated polymer supported Polystyrene sulfonic acid (PSSA) at 30% w/v, as catalyst (Scheme-12) rendering excellent chemo selectivity in synthesizing di-substituted compound, 2-Aryl-1-Arylmethyl-1H-Benzimidazoles (39) from o-phenylene diamine (37) with several substituted aryl aldehydes (38). Several captivating features of this reaction scheme are the greenness of water solvent system and efficient, selective attainment of desired product (yield 85-90%) within a reasonably shorter reaction time of 30 - 40 min (S. Patil et al., 2011).



R = Ph **(39a)**, 2-ClC_6H_4 **(39b)**, 4-ClC_6H_4 **(39c)**, 4-$NO_2C_6H_4$ **(39d)**, 3-$NO_2C_6H_4$ **(39e)**, 4-$MeOC_6H_4$ **(39f)**, 4-OHC_6H_4 **(39g)**, 4-$Me_2NC_6H_4$ **(39h)**, 6-methoxy-2-chloro quinoline **(39j)**

Scheme-12: Synthesis of 2-aryl-1-arylmethyl-1H- benzimidazole derivatives using polymer supported Polystyrene sulfonic acid (PSSA) at 30% w/v, as catalyst.

A. Habibi et al, 2015, reported a fast, efficient and environmentally benign reaction scheme for the synthesis of 2-aryl benzimidazole derivatives (43) from reaction between 1,2-phenylenediamine derivatives (41) and arylidene malononitrile (42) under aqueous media (Scheme-13) generating 2-aryl benzimidazole derivatives with a high yield (83-91%) (Habibi et al., 2015).

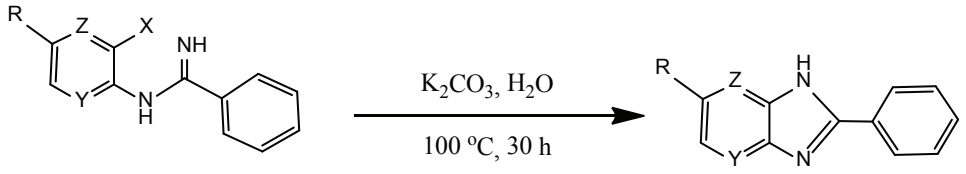


R1 , R2 = H or Me
Ar = C_6H_5, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 3-NO_2-C_6H_4, 4-NO_2-C_6H_4, 3-OCH_3-C_6H_4, 4-OCH_3-C_6H_4, 4-CH_3-C_6H_4, 4-Br-C_6H_4, 2-thiophenyl

Scheme-13: Synthesis of 2-substituted benzimidazole derivatives using 1, 2-phenylenediamine derivatives and arylidene malononitrile under aqueous media.

Chunxia Chen et al, 2012, had reported a very straightforward synthesis scheme for obtaining the benzimidazole ring system from N-(2-Halophenyl) benzamidines (44) through a carbon-nitrogen cross-coupling reaction in the presence of 2.0 equiv. of K2CO3 in water at 100° C for 30 h

(Scheme-14). In this experimental procedure, benzimidazole derivatives (45) are yielded in moderate to high yields by the intramolecular cyclization of N-(2-iodoaryl) benzamidine. This reaction progresses exclusively in water solvent and doesn't require the use of any additional reagent and/or catalyst, rendering the method highly valuable from both environmental and economic points of view (Chen et al., 2012).



(44) a-i

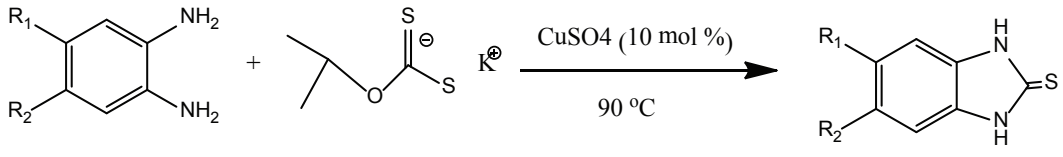
X= Br, I

(45) a-i

45a: X=I, R=H, Y=CH, Z=CH; **45b:** X=I, R=F, Y=CH, Z=CH; **45c:** X=Br, R=F, Y=CH, Z=CH; **45d:** X=Cl, R=I, Y=CH, Z=CH; **45e**: X=Br, R=I, Y=CH, Z=CH; **45f:** X=Me, R=I, Y=CH, Z=CH; **45g:** X=MeO, R=I, Y=CH, Z=CH; **45h**: X=I, R=H, Y=N, Z=CH; **45i:** X=Br, R=H, Y=N, Z=CH; **45j:** X=I, R=H, Y=CH, Z=N

Scheme-14: Base-mediated intramolecular C–N cross-coupling of benzamidine in water

Ranjbar-Karimi et al, 2016, reported an easy, efficient, simple, moreover an eco-friendly method to synthesize some benzimidazole (48) derivatives by employing the reaction between 1,2-phenylenediamines (46) with potassium isopropyl xanthate (47). In this experimental procedure, the reaction was conducted under the presence of copper sulfate (CuSO4) as a catalyst with conventional heating (at 90°C) and ultrasonic irradiation at room temperature (Scheme-15) generating high yield in relatively shorter reaction duration (6-7h) (Ranjbar-Karimi et al., 2016).



(46)

R_1= Me, R_2 = H

(47)

(48)

Scheme-15: Synthesis of benzimidazole employing the reaction of 1,2-phenylenediamines with potassium isopropyl xanthate in the presence of copper sulfate (CuSO4) as a catalyst.

Conclusion

These studies have definitely exhibited that the derivatives anchored on structurally simple benzimidazole hub demonstrated a crucial role for the treatment of many diseases. The relevant research works on drug design and discovery with fewer or no adverse effects is an active domain. The reviewed literature unveils that the opportunity exists to develop benzimidazole-based drug for the treatment of many diseases. Despite huge numbers of research publications are not available exclusively on some benzimidazole-based derivatives for some diseases like tuberculosis, the stated facts specify the likely usefulness of this class of molecules against those diseases. To comprehensively understand the performance of benzimidazole derivatives, the SAR-based investigation would apparently continue to play an indispensable role. Synthesis of benzimidazole-based derivatives is an active field of research, because these are being found as important for the treatment of mane diseases.

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None declared.

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Ethical Approval
Not required.

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