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A Convenient Approach in the Synthesis of Imidazole Derivatives Using Debus Radziszewski Reaction

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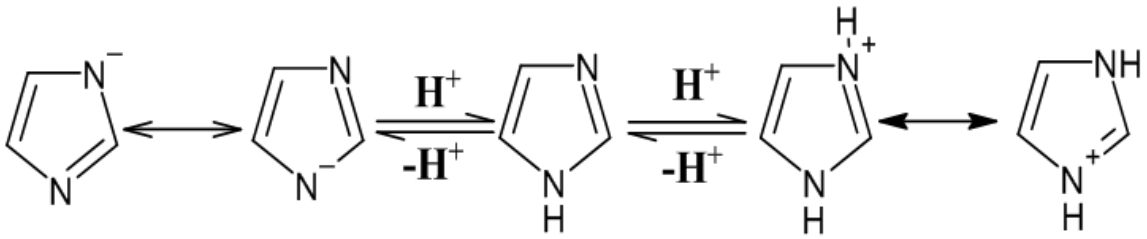
ABSTRACT: In the field of medicinal chemistry and pharmacology, Imidazole and its derivatives occupy a unique position, thus the synthesis of novel imidazole derivatives plays a vital role in the synthetic strategy of drug discovery. Imidazole derivatives have been proven for various biological activities such as antimicrobial, anti-inflammatory activity, analgesic activity, antitubercular activity, antidepressant activity, anticancer activity, anti-viral activity, and anti-leishmanial activity. Debus Radziszewski reaction is the synthesis of an imidazole derivative by the condensation of an 1,2-dicarbonyl compound, an aldehyde, and two equivalents of dry ammonia in alcohol. The problem with the Debus Radziswiski imidazole synthesis is, that gives poor yields of imidazole and side reactions. The main objective of this review is to provide the summaries and developments in the research work associated with the synthesis of tri/tetra substituted imidazole derivatives using Debus Radziswski imidazole synthesis to get better yields, decrease reaction time, economic and environmental friendly synthesis.

KEYWORDS: Debus Radziswki reaction, Imidazole, 1,2-dicarbonyl compound, condensation

I. INTRODUCTION

Imidazole is a 5-membered aromatic ring with two nitrogen atoms at 1st and 3rd positions. The solubility of Imidazole is found to be good in polar solvents and water. Due to the presence of hydrogen atoms on either of the two nitrogen atoms in the imidazole ring, it exists in two equivalent tautomeric forms i.e., 1H-imidazole and 3H-imidazole[1]. It is the main structure present in natural products such as purine, histamine, histidine, nucleic acids, etc. In the field of medicinal chemistry and pharmacology, Imidazole and its derivatives occupy a unique position, thus the synthesis of novel imidazole derivatives plays a vital role in the synthetic strategy of drug discovery[2].

Chemistry of imidazole's: Imidazole is an aromatic compound with the molecular formula $C_3N_2H_4$ and resonance value of 14.2 Kcal/mol. Imidazole's show pKa value of 14.5 and dipole moment of 3.61D. N-3 of the Imidazole ring is the basic site, protonation gives the imidazolium cation. Imidazole is a weak base and tautomeric substance since positions 4 and 5 are equivalent.The physical characteristics of imidazoles occur in colourless solid having a melting point of 89℃-91℃ and boiling point 256℃ [3].



Imidazole derivatives have been proven for various biological activities based on the research and review articles available such as anti-microbial, anti-viral activity[4],anti-inflammatory activity[5],analgesic activity[6], anti-tubercular activity, anticancer activity[7], anti-depressant activity, and antileishmanial activity[8]. The synthesis of imidazole derivatives can be done using Debus Radziswski imidazole synthesis. It is the synthesis of an imidazole derivatives by the condensation of an 1,2-dicarbonyl compound, an aromatic aldehyde and two equivalents of dry ammonia in alcohol[9].
This reaction was first reported by Debus in 1858, then developed by Radziszewski in early 1882, and

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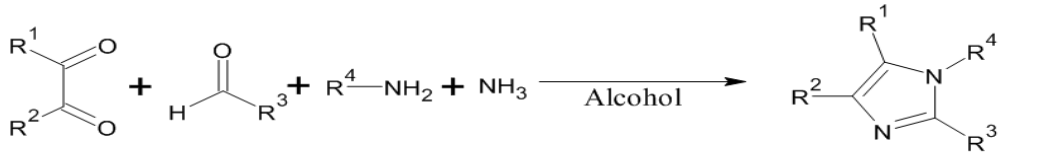
further modified by Weidenhagen in 1935. This reaction is the main synthetic reaction which has industrial importance for the synthesis of imidazole derivatives but the problem with Debus Radziswiski imidazole synthesis is that it gives poor yields of imidazoles and side reactions[10]. The main objective of this review is to provide synthetic procedures to increase the percentage yield and decrease the reaction time.

II. SYNTHESIS

General Procedure

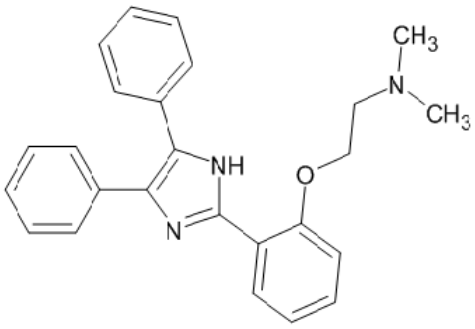
Imidazole derivatives can be synthesized by condensation of an alpha-dicarbonyl compound for example glyoxal, a substituted aldehyde and two equivalents of dry ammonia in alcohol. Probable mechanism is that ammonia or primary amine reacts with an α-dicarbonyl compound to form α-diimine, which then condenses with an aldehyde to form Imidazole derivatives **(Reaction-1)**, but the problem with the Debus Radziswiski imidazole synthesis is, it gives poor yields of imidazoles and side reactions[10]. This review provides synthetic procedures to increase the percentage yield and decrease the reaction time.



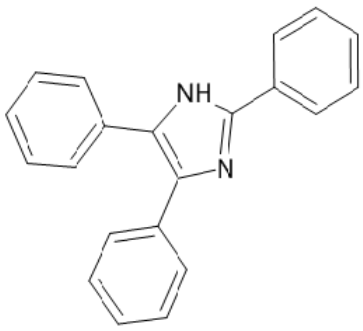
Reaction-1 (R_1~R_4 = H, alkyl, aryl)

By using catalysts

N. L. Higuera et.al., synthesized variety of triaryl-1H-imidazoles or 2-aryl-1H-phenanthro[9,10-d]imidazoles using low-melting mixture urea–$ZnCl_2$ as catalyst which gave excellent yields. When the reaction was performed at 110℃ in the presence of urea–$ZnCl_2$ DES (deep eutectic solvent), 2,4,5-triphenyl-1H-imidazole was obtained in an excellent yield of 99% after 30 min. A decrease in temperature or the use of $ZnCl_2$ as a catalyst gave lower yields. If DES was not used in the reaction, the yield was decreased to 20%. The above mentioned methodology was further used in the synthesis of the drug Trifenagrel, which gave excellent yield of 92 %[11].



Trifenagrel (1)



2,4,5-triphenyl-1*H*-imidazole (2)

S. Narayana Murthy et.al., synthesized 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazoles in the presence of DABCO (1,4-diazabicyclo[2.2. 2]octane) as catalyst using t-butanol as solvent at 60–65℃. The reaction proceeded to completion within 12 hours and yielded the corresponding imidazole in 92% yield.The condensation of benzaldehyde, ammonium acetate, and benzil to yield 2,4,5-triphenyl-1H-imidazole are also tried using triethyl amine (75%), piperidine (78%), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) (81%), and DABCO (92%) as catalyst and. However DABCO gave excellent yields[12].

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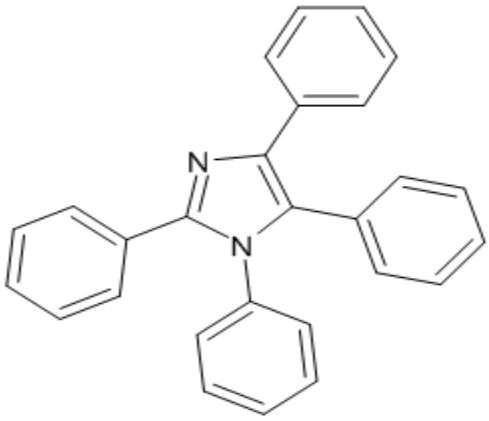
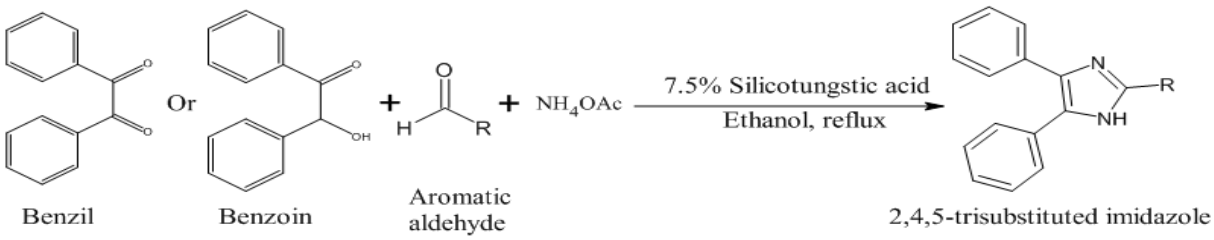


1,2,4,5-tetraphenyl-1*H*-imidazole (3)

2,4,5-trisubstituted Imidazoles derivatives were efficiently synthesized by B.P. Ankush et.al., using 7.5% silicotungstic acid as catalyst. Synthesis of trisubstituted imidazoles are done by condensation of benzyl/benzoin, ammonium acetate, and aromatic aldehydes in the presence of silicotungstic acid which act as catalyst using ethanol as solvent **(Reaction-2)**. To determine the optimum concentration of silicotungstic acid, the reaction was carried at different concentrations i.e., 2.5%, 5%, 7.5% and 10 mol% of silicotungstic acid in ethanol at reflux temperature. The yields obtained by using the following concentrations are 63%, 85%, 94% and 94% yield, respectively. This proves that using 7.5% concentration of catalyst gives excellent yields[13].



Reaction-2

Entry	Silicotungstic acid Concentration (mol %)	Yield (%)
1	2.5	63
2	5	85
3	7.5	94
4	10	94

Table 1: Concentration of catalyst vs yield

Deepika Geedkar et.al., used Titania nanoparticles hosted on silica ($TiO_2.SiO_2$ NPs) as heterogeneous catalyst in the synthesis of 2,3-diaryl 3,4-dihydroimidazo[4,5-b]indole derivatives using methanol as solvent. By using $TiO_2.SiO_2$ NPs reaction time will be decreased, there will be low catalyst loading, high product yield (92%), and catalyst can be reused up to 7 cycles makes this procedure comes under green chemistry[14].

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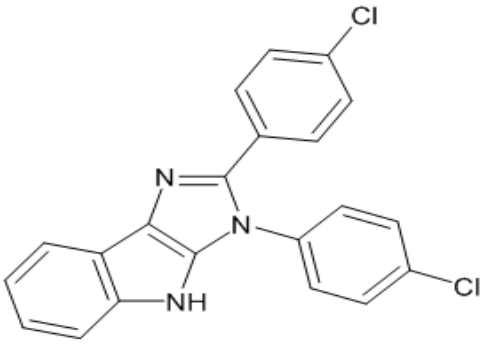
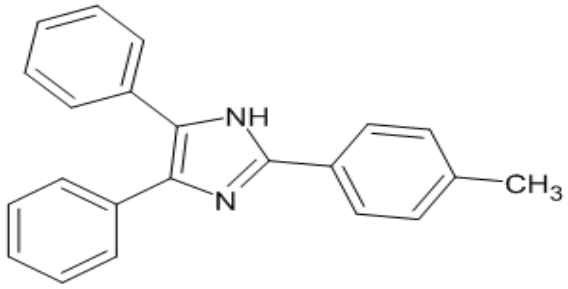


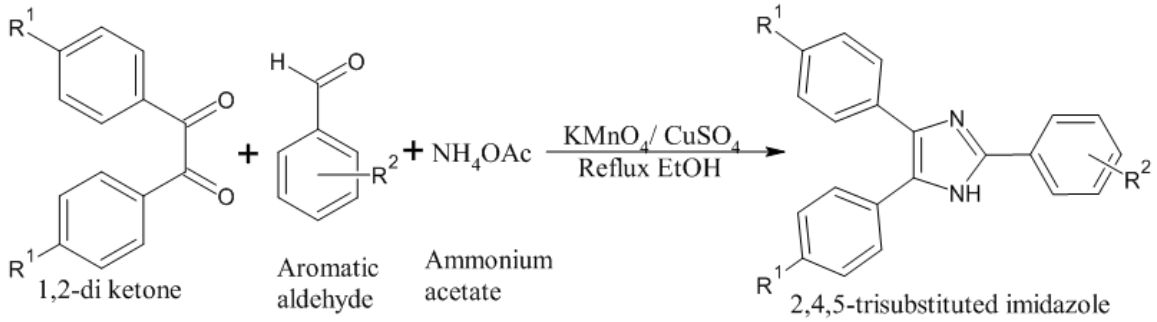
2,3-bis(4-chlorophenyl)-3,4-dihydroimidazo[4,5-*b*]indole (4)

2,4,5-triarylimidazoles are synthesized from condensation of benzoin or benzil, ammonium acetate and aromatic aldehydes using sulphanilic acid as catalyst was described by A. F. Mohammed et. al., 10 mol% sulphanilic acid is used as catalyst, 2,4,5-triaryl-1H-imidazoles were efficiently synthesized with moderate to excellent yields from benzil or benzoin. Ethanol-water was used as solvent which is relatively eco-friendly and supporting to Green Chemistry[15].



2-(4-methylphenyl)-4,5-diphenyl-1*H*-imidazole (5)

2,4,5-Triarylimidazoles have been synthesized by Ahmad Khorramabadi-zad et.al., in very good yields by the one-pot three-component condensation of bis-aryl alpha-hydroxyketones, aromatic aldehydes and ammonium acetate along with $KMnO_4/CuSO_4$ as catalyst under mild reaction conditions **(Reaction-3)**. The reaction time for bis-aryl α-hydroxyketones is much less than that of bis-aryl diketones. $KMnO_4$ and $CuSO_4$ are important for the reaction to proceed. When this mixture was used in hot EtOH media, MnO_2 was generated in by the action of $KMnO_4$ on hot EtOH during the reaction. This MnO_2 produced freshly act as mild oxidant which helps in oxidation of benzylic hydroxyl group to the corresponding carbonyl group[16].



Reaction-3

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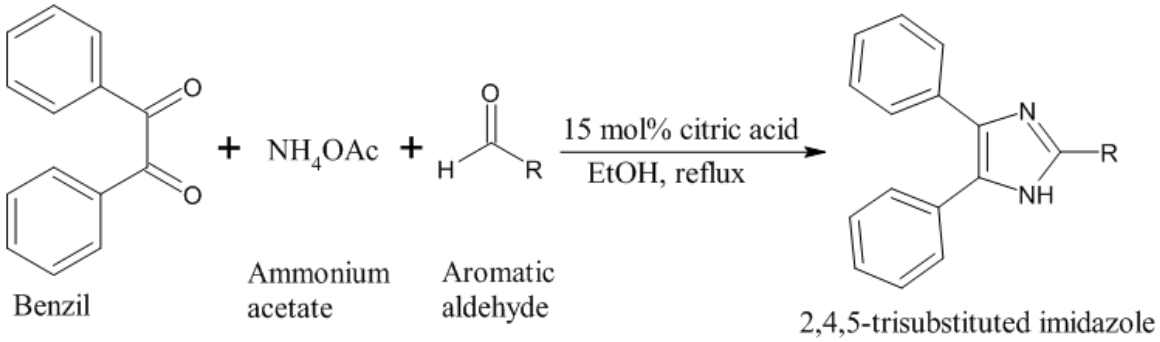
Entry	R^1	R^2	Time (min)	Yield (%)
1	H	H	65	89
2	H	2-Cl	80	91
3	H	4-Cl	70	85
4	H	4-Me	90	87
5	H	4-OMe	110	75
6	H	4-Br	80	89
7	H	2-OMe	80	88
8	H	2,4-DiCl	90	90
9	H	4-NO_2	150	82
10	4-Me	H	80	79
11	4-Me	4-Me	90	75

Table 2: Percentage yield vs time

Nora Chouha et.al., reported that 2,4,5-triarylsubstituted imidazole derivatives can be efficiently synthesized via three-component condensation reaction in the presence of citric acid at catalytic amount. 2,4,5-triphenyl-1H-imidazole was produced in 92% yield using 15 mol% citric acid in ethanol under reflux conditions for 50 min **(Reaction-4)**. But in the absence of catalyst the desired product could not be obtained even in similar reaction conditions. Advantages of using above reactions are the mild reaction conditions, easy work-up, clean reaction profiles, low catalyst loading and cost efficiency[17].



Reaction-4

Entry	R	Time (min)	Yield (%)
1	C_6H_5	50	92
2	4-CH_3-C_6H_4	75	82
3	4-CH_3O-C_6H_4	70	80
4	2-NO_2-C_6H_4	100	65
5	2-OH-C_6H_4	90	80
6	2-CH_3-C_6H_4	80	75
7	2-CH_3O-C_6H_4	70	81
8	2,4-Cl_2-C_6H_3	115	70
9	4-Cl-C_6H_4	120	78
10	4-Et-C_6H_4	360	86
11	3-Cl-C_6H_4	210	75
12	4-MeO-C_6H_4	180	90
13	3-OH-4-MeO-C_6H_3	300	64

Table 3: Percentage yield vs time

Ali Javid et.al., reported the synthesis of tetrasubstituted imidazole derivatives using benzil, aromatic aldehydes, primary amines and ammonium acetate in the presence of Preyssler-

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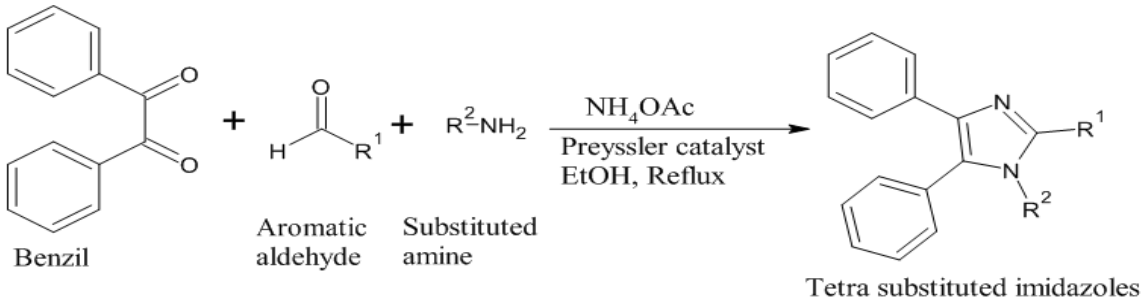
type heteropoly acid $H_{14}[NaP_5W_{30}O_{110}]$ as catalyst **(Reaction-5)**. Preyssler acid is a highly acidic catalyst fromheteropoly acid family with excellent catalytic activity in a variety of acid-catalyzed reactions. 97% yield of 1-benzyl-2,4,5-triphenyl-1H-imidazole was synthesized using above procedure[18].

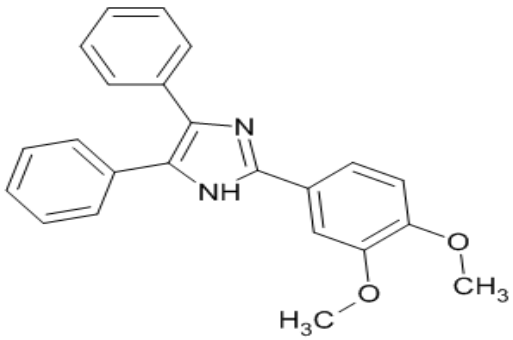


Reaction-5

Entry	R^1	R^2	Time (min)	Yield (%)
1	C_6H_5	$PhCH_2$	10	95
2	4-Cl-C_6H_4	$PhCH_2$	20	88
3	4-CH_3O-C_6H_4	$PhCH_2$	20	97
4	4-CH_3-C_6H_4	$PhCH_2$	20	92
5	4-OH-C_6H_4	$PhCH_2$	10	93
6	2-OH-C_6H_4	$PhCH_2$	30	88
7	4-Br-C_6H_4	$PhCH_2$	20	85
8	C_6H_5	CH_3	30	86
9	4-CH_3-C_6H_4	CH_3	20	85
10	4-Br-C_6H_4	CH_3	20	85
11	4-$CH_3C_6H_4$	Ph	30	89
12	4-OH-C_6H_4	Ph	-	91
13	4-NO_2-C_6H_4	Ph	-	87

Table 4: Percentage yield vs time

One pot Solvent free synthesis of 2,4,5-trisubstituted Imidazoles has been reported by Madhuri S Kulkarni et.al., using wet cyanuric chloride as productive organic catalyst. 2,4,5 trisubstituted imidazoes are synthesized by reacting substituted benzaldehydes with benzoin and ammonium acetate in presence of wet cyanuric chloride in catalytic amount using ethanol as solvent at 80℃. When the reaction is carried out by using 3,4dimethoxy benzaldehyde as substituted aldehyde, 90% yield of trisubstituted Imidazole is obtained[19].



2-(3,4-dimethoxyphenyl)-4,5-diphenyl-1*H*-imidazole (6)

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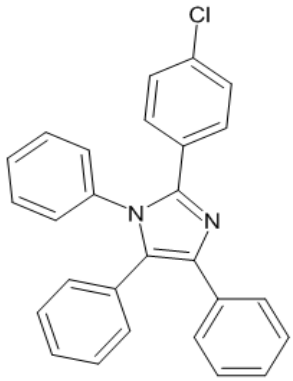
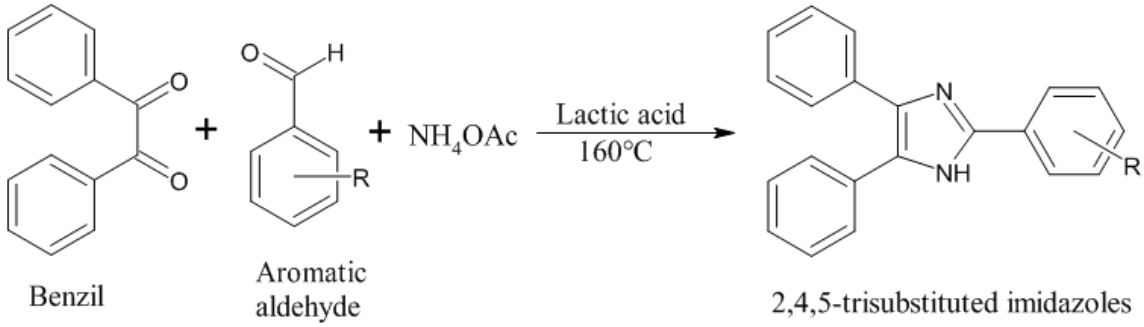
One-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted has been reported by Ghodsi Mohammadi Ziarani et.al., using SBA-Pr-SO_3H as a green nano catalyst. SBA-Pr-SO_3H as Sulfonic acid functionalized SBA-15 nanoporous material with a pore size of 6 nm was reported to be a green and effective solid acid catalyst in synthesis of tri and tetra substituted imidazoles. Synthesis of imidazole derivatives can be done by condensation of benzyl, aromatic aldehydes, aniline derivatives and ammonium acetate in presence of SBA-Pr-SO_3H under solvent free conditions. Using the following methodology 2-(4-chlorophenyl)-1,4,5-triphenyl-1H-imidazole was synthesized in 100% yield[20].



2-(4-chlorophenyl)-1,4,5-triphenyl-1*H*-imidazole (7)

Jayant Sonar et.al., synthesized 2,4,5-trisubstituted imidazoles efficiently using lactic acid as catalyst. The synthesis of 2,4,5-trisubstituted imidazole can be done by reacting aromatic aldehyde, benzil and ammonium acetate in the presence of biodegradable lactic acid at 160℃ **(Reaction-6)**. It has been reported that using 1 ml of lactic acid and 2.5 mmol of ammonium acetate in the reaction gives yield of 92%. This methodology provides a better performance and provides higher product yield for aromatic aldehydes containing electron donating and electron withdrawing groups[21].



Reaction-6

Microwave assisted synthesis

Tejpal Singh Chundawat et.al., synthesized one-pot microwave-assisted 2,4,5-trisubstituted imidazoles using a freshly prepared Schiff's base nickel catalyst (Ni-C) complex. By Using conventional method, the yield of 2,4,5-trisubstituted imidazoles were less compare to microwave assisted synthesis. It has been proved that good yields were obtained by using Ni-C as catalyst in imidazole synthesis. After the process catalyst was separated by filtration and can be reused after activation at 200℃ for 3–4 hours **(Reaction-7)**. The Ni-C catalyst exhibited remarkable catalytic activity with respect to the reaction time in the microwave reactor[22].

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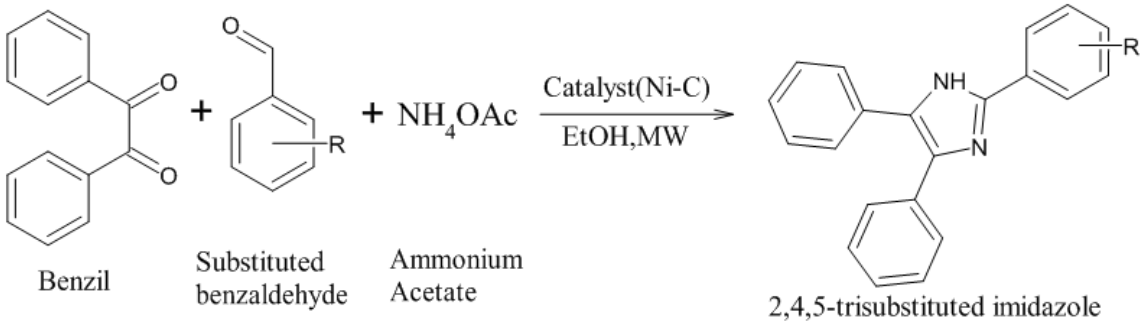
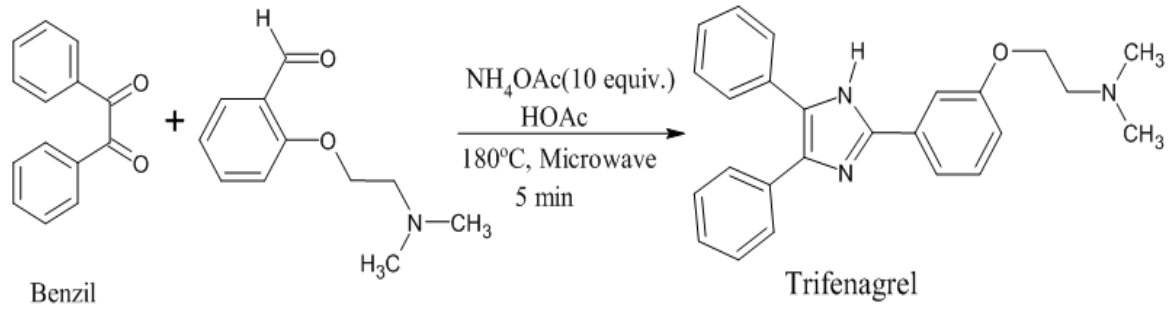


Reaction-7

Entry	R	Time(min)	Yield (%)
1	H	20	90
2	4-MeO	15	88
3	3,4-MeO	15	85
4	3-Cl	25	86
5	2-O_2N	30	85
6	4-F	20	88
7	4-F_3C	25	90

Table 5: Percentage yield vs reaction time

Microwave assisted synthesis of 2,4,5-trisubstituted imidazoles from 1,2-diketones and aldehydes in the presence of NH_4OAc has been reported by Scott E. Wolkenberg et.al., heteroaromatic, aryl, and aliphatic 1,2-diketones uniformly provide excellent yields of the substituted imidazoles ranging from 80% to 99% yields. Synthesized 2,4,5-trisubstituted imidazoles under microwave irradiation for 5min gave excellent yields compare to conventional thermal heating for 8-24 hours. By using above mentioned procedure Trifenagrel was synthesized in 99% yield in 5 min duration **(Reaction-8)**[23].



Reaction-8

Mazaahir Kidwai et.al., synthesized 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives are done by neat reaction conditions using Microwave irradiation. Solvent free synthesis of trisubstituted 1H imidazoles can be done by taking equimolar amount of benzil, substituted aldehydes and excess of ammonium acetate on exposure to microwave irradiation gave excellent yields and synthesis of 1,2,4,5-tetrasubstituted-1H-imidazoles by four component condensation of benzil, substituted aldehyde, aromatic amine and ammonium acetate **(Reaction-9)**. Direct heating or conventional heating of reactants take more time and gave low yields whereas microwave irradiation techniquegave excellent yields[24].

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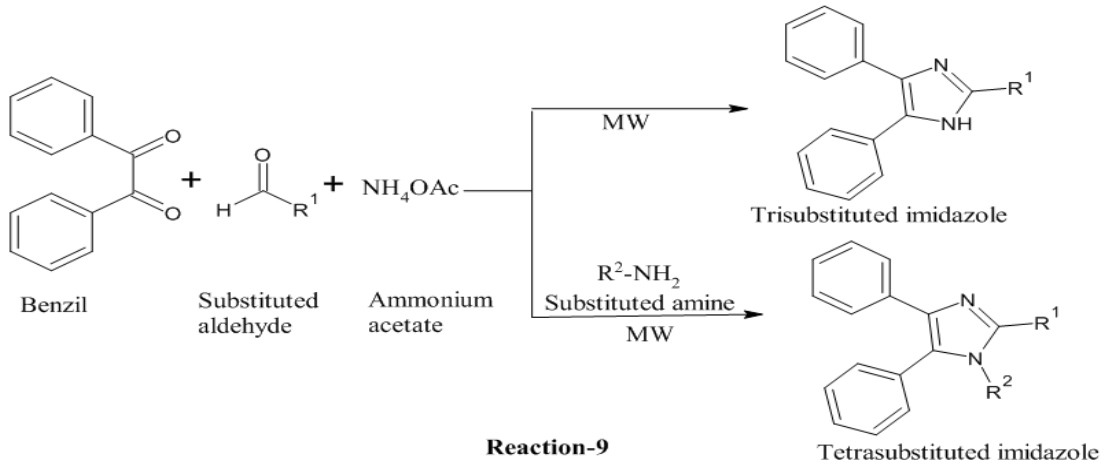
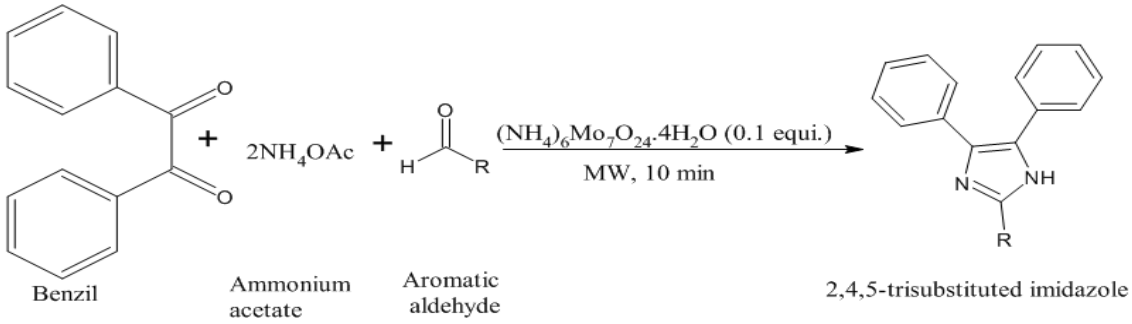


Reaction-9

Javad Safari et.al., used $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ as catalyst in the synthesis of 2,4,5-Trisubstituted imidazoles. The three-component synthesis of trisubstituted imidazoles can be done by condensation of benzil, aryl aldehydes and ammonium acetate using microwave irradiation under solvent-free conditions **(Reaction-10)**. The products synthesized by conventional heating conditions are compared with the microwave-assisted methods. It is proven that microwave assisted synthesis as shown better yields than conventional heating and also it is observed that by using a wide range of aromatic aldehydes, 2,4,5-Trisubstituted imidazoles were obtained in good yields[25].



Reaction-10

Entry	R	Time (min)	Yield (%)
1	C_6H_5	10	94
2	m-$MeOC_6H_4$	10	93
3	p-MeC_6H_4	10	98
4	p-ClC_6H_4	10	94
5	m-ClC_6H_4	10	94
6	p-$MeOC_6H_4$	10	99
7	2-Naphthyl	10	94
8	2,4-$Cl_2C_6H_3$	10	93
9	2-Thienyl	10	92
10	p-BrC_6H_4	10	93
11	m-NO_2C_4H	10	89
12	o-HOC_4H_6	10	91
13	p-$(Me)_2NC_6H_4$	10	97

Table 6: Percentage yield vs time

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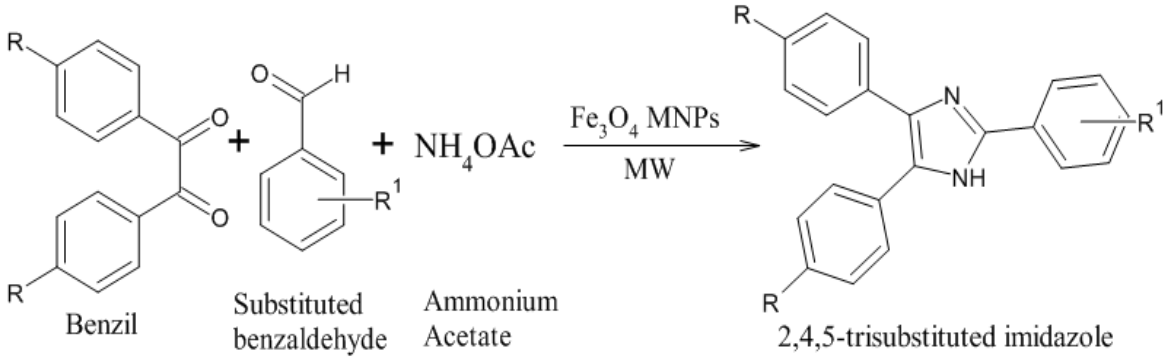
Microwave assisted synthesis of trisubstituted imidazoles has been reported by Hamid Reza Mardani et.al., using magnetically nanocatalyst i.e., Fe_3O_4 MNPs (Fe_3O_4 magnetic nanoparticles) under solvent free conditions. 2,4,5-trisubstituted imidazoles can be synthesized by three-component condensation of aromatic aldehydes, benzil and ammonium acetate in presence of magnetically nanocatalyst under low power microwave irradiation **(Reaction-11)**. Fe_3O_4 MNPs act as Lewis acid and plays an important part in increasing the electrophilic character of the aldehyde. Catalyst used in this procedure is eco-friendly, reusable, low-cost, and efficient[26].



Reaction-11

Entry	R	R^1	Time (min)	Yield (%)
1	H	H	20	85
2	H	p-OH	10	95
3	H	p-Cl	25	87
4	H	p-OCH_3	30	85
5	H	p-Br	15	80
6	H	m-NO_2	10	90
7	F	p-OH	35	90
8	O-Me	H	50	80
9	O-Me	p-OH	60	95
10	H	o-Cl	25	87

Table 7: Percentage yield vs time

Narendra Nirwan et.al., synthesized 2,4,5-trisubstituted imidazole and 4,5-disubstituted indolylimidazole derivatives using Amberlyst A-15 as green, recyclable catalyst under microwave irradiation. Synthesis of 2,4,5-trisubstituted imidazole can be done by condensation of aldehydes, benzil and ammonium acetate in the presence of Amberlyst A-15 as catalyst under Microwave irradiation and gained excelent yields **(Reaction-12)**. Similar procedure was applied for the synthesis of 4,5-disubstituted indolylimidazole derivatives which also synthesized by the condensation of benzil, indole-3-carbaldehydes and ammonium acetate along with Amberlyst A-15 under Microwave irradiation[27].

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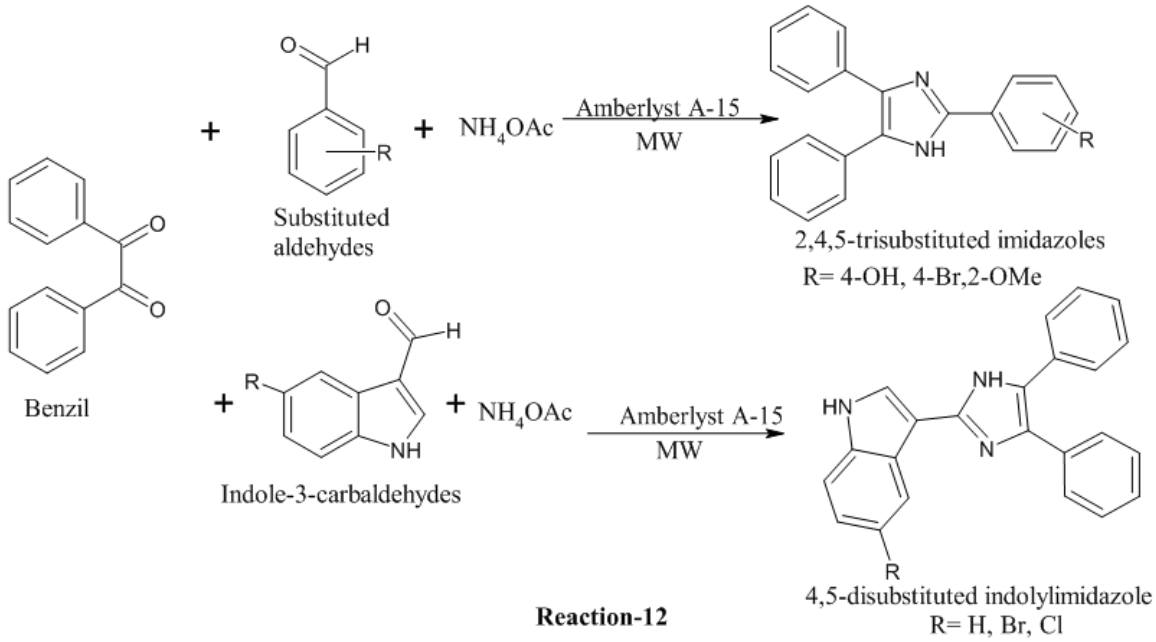
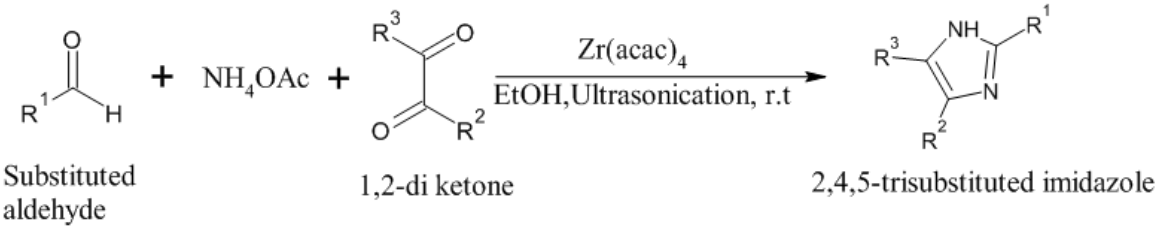


Reaction-12

Ultrasound assisted synthesis

A simple and efficientsynthetic procedure has been reported by Ahmad R. Khosropour for the synthesis of 2,4,5-trisubstituted imidazoles catalyzed by zirconium (IV) acetylacetonate ($Zr(acac)_4$) using ultrasonic irradiation. Synthesis of 2,4,5-trisubstituted imidazoles can be done by the condensation of aldehydes, benzils and ammonium acetate in the presence of 20 mol% of $Zr(acac)_4$ as catalyst using EtOH as solvent at 24 kHz under ultrasound sonication **(Reaction-13)**. The procedure mentioned above offers several merits such as high yields, easy procedure, short reaction times and mild reaction conditions[28].



Reaction-13

An efficient 2,4,5-triaryl-1H-Imidazole derivatives were synthesised by Kiran F. Shelke et.al., using Boric Acid in Aqueous media as catalyst under ultrasound irradiation. 2,4,5-triaryl-1H-imidazoles synthesized by one pot three-component condensation of benzil/benzoin, an aldehydes and ammonium acetate in aqueous media under ultrasound at room temperature. A quantitative yield of desired product was obtained in the presence of 5 mol% boric acid for 40 to 70 min **(Reaction-14)**. Advantages of using this procedure are mild reaction conditions, simple procedures, cleaner reactions, short reaction times and excellent yields of products[29].

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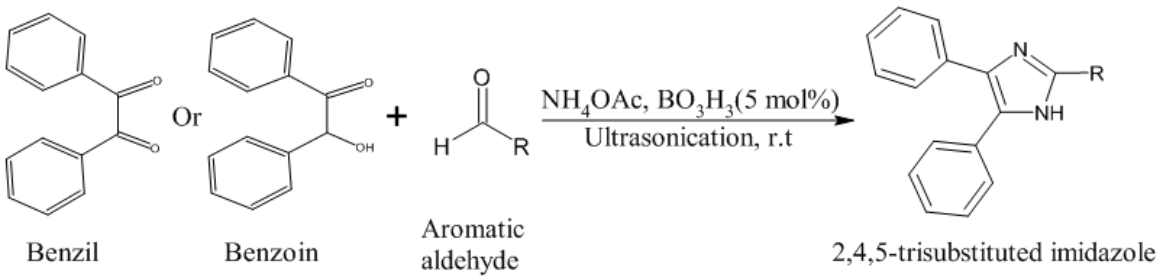
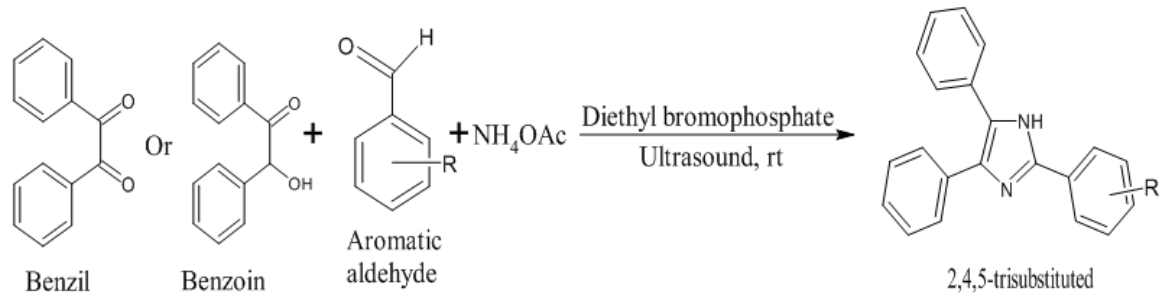


Reaction-14

Ultrasound assisted one pot synthesis of imidazole derivatives has been reported by Deepak Nagargoje et.al., in the presence of diethyl bromophosphate which act as oxidant. Trisubstituted imidazoles can be done by one pot, three-component condensation of benzoin or benzyl, an aldehyde, and ammonium acetate using diethyl bromophosphate as a mild oxidant under ultrasound irradiation in the preparation of 2,4,5-triaryl-1H-imidazole **(Reaction-15)** compounds in excellent yields. Synthesis of imidazole was performed under three different frequencies of 35, 45 and 60 kHz which gave yield of 97%, 89% and 75% respectively[30].

Entry	Aldehyde	Time (min)		Yield (%)	
		Benzil	Benzoin	Benzil	Benzil
1	Benzaldehyde	40	50	95	93
2	o-Chlorobenzaldehyde	35	45	96	91
3	p-Chlorobenzaldehyde	30	50	95	94
4	p-Toluldehyde	45	65	92	90
5	4-Methoxy benzaldehyde	35	70	98	94
6	2,4-Dimethoxy benzaldehyde	30	50	93	94
7	4-Nitrobenzaldehyde	40	80	96	93
8	4-N,N-Dimethyl benzaldehyde	45	60	98	97
9	4-Hydroxy benzaldehyde	35	40	90	92
10	4-Fluorobenzaldehyde	25	35	97	95
11	Furfuraldehyde	45	50	94	91
12	2-Formyl thiophene	35	45	97	95

Table 8: Percentage yield vs reaction time



Reaction-15

Sonochemical synthesis of 1,2,4,5-tetrasubstituted imidazoles were reported by Javad Safari et.al., using nanocrystalline $MgAl_2O_4$ as an effective catalyst. $MgAl_2O_4$ is an important acid catalyst which efficiently catalyzes the preparation of 1,2,4,5-tetrasubstituted imidazoles by one-step condensation of an aldehyde, benzil, ammonium acetate and primary aromatic amine using ethanol

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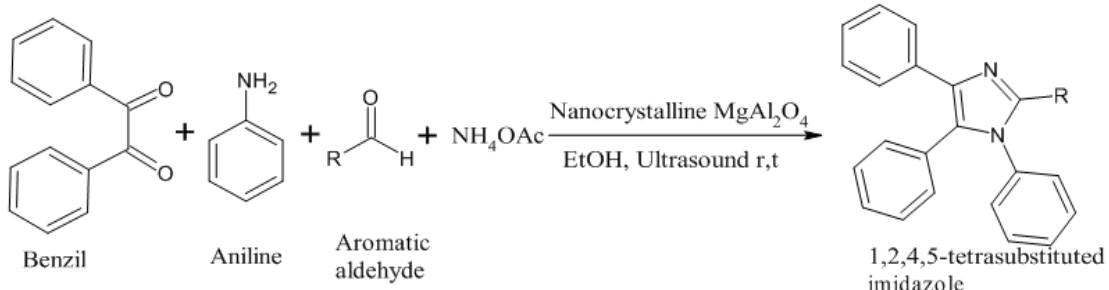
as a solvent under ultrasonic irradiation. . The maximum yield has been reported when the reaction was carried out under irradiation of 50 kHz at 60℃ for 15 min **(Reaction-16)**. The presence of $MgAl_2O_4$ as an acidic catalyst can quicken the cyclocondensation reaction by increasing the reactivity of benzaldehyde derivatives and benzyl[31].

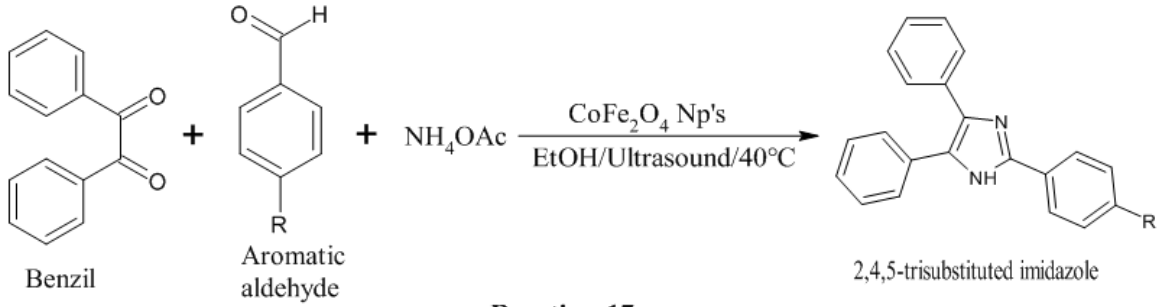


Reaction-16

Entry	R	Time (min)	Yield (%)
1	C_6H_5	15	91
2	p-MeC_6H_4	17	95
3	p-MeOC_6H_4	18	93
4	3,4-$(OMe)_2$ C_6H_3	20	90
5	p-ClC_6H_4	12	96
6	p-Br C_6H_4	12	94
7	2-F C_6H_4	15	93
8	2-OH C_6H_4	18	90
9	3,5-$(OMe)_2$ C_6H_3	14	97
10	p-OH C_6H_4	25	89

Table 9: Percentage yield vs reaction time

Esmaiel Eidi et.al., synthesized 2,4,5-trisubstituted imidazoles under ultrasound irradiation using reusable $CoFe_2O_4$ (Cobalt ferrite) nanoparticles as catalyst. Synthesis of trisubstituted imidazoles are done by condensation reaction of 1, 2 di ketone, aldehyde and ammonium acetate in presence of $CoFe_2O_4$ nanoparticles using ethanol as solvent and the mixture was irradiated in an ultrasonic bath at 40℃ for the appropriate time **(Reaction-17)**. The catalyst can be separatedby external magnet and washed several times using water and ethanol. The best outcomes are acquired by using 10 mg of catalyst, with the rate power of ultrasonic irradiation at 60%, and at 40℃ in 20 min[32].



Reaction-17

Wael Abdelgayed Ahmed Arafa reported an eco-friendly pathway in the synthesis of mono and bis-multisubstituted imidazoles using renewable [DABCO-DOL][OAc] as promoter/catalyst under sonication. Synthesis of tri/tetra substituted imidazoles can be done by condensation of aromatic aldehydes, benzyl, amines and ammonium acetate in presence of [DABCO-DOL][OAc] which act as catalyst. Compared to the traditional procedure, this

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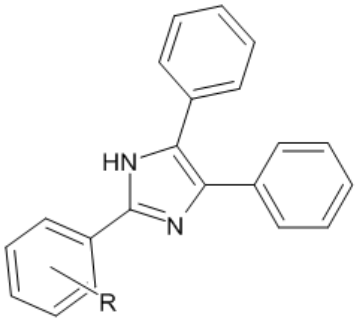
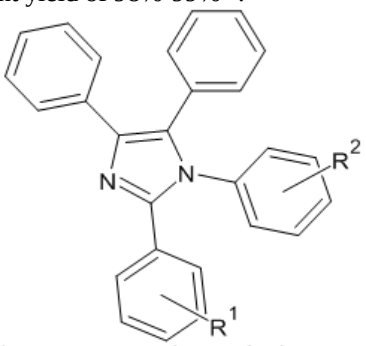
methodology can enhance the reaction rate and thereby produce excellent yields. All the substitutions which are mentioned below leads to excellent yield of 98%-99%[33].



2,4,5 trisubstituted imidazoles (8)

R=C6H5, 4-CH3O–C6H4, 2-Thienyl, CH3

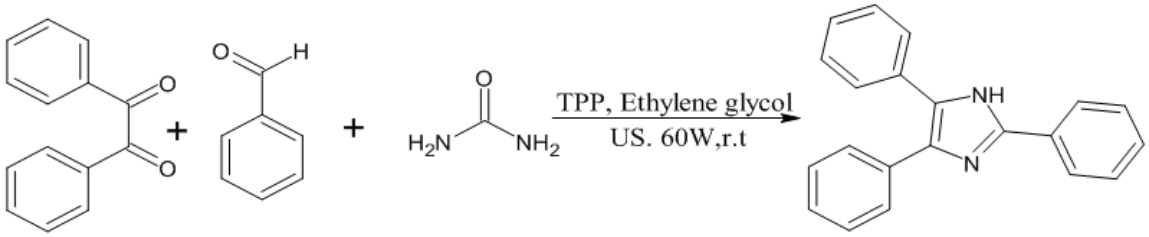


1,2,4,5 tetra substitutedimidazoles (9)

R^1= C_6H_5, 4-CH_3-C_6H_4

R^2=C_6H_5, C_6H_4-CH_2, 4-CH_3O–C_6H_4–CH_2, 4-CH_3–C_6H_4–CH_2

Three-component synthesis of 2,4,5-trisubstituted Imidazoles has been reported by Somayeh Behrouz et.al., using urea and PPh3 as the sources of nitrogen and organocatalyst under ultrasonication. One-pot, three-componentsynthesis of 2,4,5-trisubstituted imidazole by reacting benzil, aldehydes, urea which act as catalyst and ammonia source and PPh_3 using ethylene glycol as green solvent at room temperature under ultrasound irradiation **(Reaction-18)**. Utilizing ultrasonic irradiation methodology shows improved reaction yields and reaction times compared to conventional heating technique[34].



Benzil Benzaldehyde Urea 2,4,5-triphenyl imidazole

Reaction-18

Entry	Catalyst (xmol %)	Time (min)	Yield (%)
1	0	30	90
2	0.5	15	88
3	1	10	85
4	2	10	86
5	3	10	85
6	4	10	88

Table 10- Calatytic concentration vs yield

III. CONCLUSION

Debus radziswiski reaction is one of the main synthetic reactions of industrial importance for the synthesis of imidazole derivatives but this reaction gives poor yields of imidazole. Based on the procedures mentioned in this review, it was proven that by using the following methodologies in the synthesis of trisubstituted or tetrasubstituted imidazole derivatives increases the percentage yield of the product, increase in the reaction rate

and also decreases reaction time. In this review we mainly focused on the synthesis of imidazole derivatives using different catalyst, using microwave irradiation and ultrasound irradiation.

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