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A rapid and large volume synthesis of mono-, di-, tri-, and tetra-substituted imidazole derivatives via ultrasonic radiation-driven technique

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ABSTRACT

Sonochemistry under controlled conditions has proven effective in medicinal chemistry and drug development. It can substantially shorten reaction timelines from days or hours to minutes. A convenient one-pot synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives catalyzed by PTSA and benzenesulfonic acid in ethanol as solvent, under ultrasonic irradiation and without ultrasound irradiation at 50° C has been achieved successfully. These 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives synthesis were also accomplished using different solvents viz., Methanol, Ethanol, DCM, DMF, Acetonitrile and THF and PTSA as the catalyst. This method yielded the highest % synthesis of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives with PTSA as the catalyst in solvent ethanol. These reactions were also optimized for % of PTSA catalyst required to obtain the maximum yield of 2,4,5-trisubstituted and 1,2,4,5-tetrasubstituted imidazole derivatives with and without ultrasound irradiation at 50° C. Synthesis of 2,4,5-trisubstituted Imidazole derivatives reaction follows first-order rate kinetics while that of 1,2,4,5-tetrasubstituted Imidazole derivatives reaction follows the second-order rate kinetics. Furthermore, sonochemistry has higher yields, lower cost, easier workups, and higher purity than conventional thermal organic synthesis, which has lower yields, tedious workups, longer reaction periods, lower purity, and numerous byproducts.

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1. Introduction

The Piezoelectric effect is the basis of generation of mechanical vibrations, in response to an applied alternating electrical potential. This serves as the working principle of modern ultrasonic devices. The Piezoelectric phenomenon was first shown by Pierre and Jacques Curie in 1880 using a quartz sample that undergoes electrical charge when under compressive stress (*1*,*2*). On the contrary, when an electrical voltage is applied to the quartz, it causes a deformation in its crystal structure. Transducers employ the Piezoelectric effect for the conversion of electrical energy into mechanical movement. When ultrasound is exposed to organic liquid under appropriate conditions, it can cause cavitation and microstreaming resulting in the occurrence of chemical reactions (*3*). These effects provide the energy of activation by which reactions proceed fast. It is possible to propagate ultrasonic waves by inducing a series of alternating compressions and rarefactions in the medium through which the waves are transmitted (*1*). When the sound wave collides with the liquid during the rarefaction cycle, it causes the molecules in the liquid to separate (*4*). This results in the formation of bubbles, which then burst during the compression cycle. These sudden and intense implosions have the potential to produce short-lived hotspots with local temperatures of approximately 5000 degrees Celsius, pressures of approximately 1000 atm, and heating and cooling speeds that can surpass 10 billion degrees Celsius per second (*1*). These localized hot spots can somehow be recognized as micro reactors that operate when the mechanical energy of sound is converted into a functional chemical form. In addition, the violent collapse leads to the production of mechanical effects (*1*,*5*). Mason and Lorimer have provided a thorough explanation of the synthesis of reactions that can be either homogeneous or heterogeneous. They have concluded that sonochemistry may not only accelerate reactions, but also alter their path, which would result in entirely new compounds. With the use of sono-chemistry, many reactions are governed such as addition, alkylation, and reduction/oxidation reactions (*5*). In the field of polymer chemistry, ultrasound can be utilized both for the degradation of polymers and for the controlled synthesis of new polymers based on the hydrodynamic and cavitation processes that operate on the polymer chains (*5*,*6*). Sono-electrochemistry, in which the two energy sources can interact effectively in a variety of ways, such as degassing cells and lowering polarization effects, leading to enhancements in electroplating and electrochemical synthesis efficiency (*5*). There have been a lot of different uses of ultrasound in organic synthesis that have been described, and a lot of them are effective and novel. The use of ultrasonic cleaning baths and ultrasonic immersion probes, both of which typically operate at frequencies of 40 and 20 kHz, respectively, are the two primary sources of ultrasound that are utilized in organic synthesis (*7*). The former is utilized more frequently in organic synthesis due to the fact that they are less costly, even though the energy that is transferred to the reaction medium is lower than that which is the case with ultrasonic probe systems, which deposit the acoustic energy directly into the reaction medium (*8*,*9*).

Imidazole is a heterocycle ring that can be found in a wide variety of naturally occurring and pharmacologically active chemicals. Some examples of these include: histamine, histidine, biotin, alkaloids, nucleic acid, etomidate, cimetidine, omeprazole and lansoprazole encompassing diverse categories of drugs like antacid, antibacterial, fungicidal or herbicidal (*10*–*15*). These heterocyclic analogs have the ability to imitate necessary aspects of

the structure or function of proteins. The ultrasonic-assisted green synthesis of substituted imidazole is indeed an innovative approach that has proven to play a key role in the creation of combinatorial libraries of small molecules (*9*,*16*). Irradiation with ultrasonic waves has been shown to accelerate the progression of a number of different thermally driven organic reactions. In addition to this, research has shown that it can increase both yields and selectivity (*9*). Imidazole was first synthesized by Heinrich Debus in 1858, using glyoxal and formaldehyde in ammonia with a relatively low yield. Significant changes to this method were made by Radiszewski, utilizing ammonium acetate as a slow and continuous source of ammonia generated during the heating process. This modification produced imidazole with a higher yield. This modified procedure is known as Debus-Radziszewski imidazole synthesis (*17*). Bilodeau, M. T. and Cunningham, A. M. *et al.* in 2003 have synthesized 2,4,5-triarylimidazoles through the [3 + 2] cycloaddition reaction (*18*). They allowed aryl tosyl imines to react with the polymer-supported 1,3-oxazoline-5-plates (munchnones) in the presence of EDC. As a product of this, the 2,4,5-trisubstituted imidazoles were produced following cleavage employing refluxing acetic acid. The yield and purity of these compounds ranged from moderate to good. Ultrasound-assisted one-pot green synthesis of various di, tri-substituted imidazole have been reported by using various catalysts and solvent systems or without solvent (*16*,*19*–*25*). Ahmad R. Khosropour *et al.* in 2008 reported the synthesis of 2,4,5-trisubstituted imidazoles catalyzed by zirconium (IV) acetylacetonate, using ultrasonic irradiation under ambient conditions (*16*). Deepak Nagargoje et al reported the ultrasonic one-pot synthesis of 2,4,5-trisubstituted imidazole derivatives using diethyl bromophosphate as an oxidant (*19*). Javad Safari *et al.* in 2013 reported a highly efficient magnetic solid acid catalyst (SA-MNPs) for the synthesis of 2,4,5-trisubstituted imidazoles, under ultrasound irradiation (*20*). Chemical co-precipitation was used to produce Fe_3O_4 nanoparticles, which were then coated with 3-aminopropyltriethoxysilane (APTES) by a silanization reaction. The sulfamic acid-functionalized magnetic nanoparticles were produced by grafting chlorosulfuric acid onto the amino-functionalized Fe_3O_4 nanoparticles (SA-MNPs) (*20*). Recently, it has been revealed that an effective ultrasonic-assisted synthesis of imidazolium and pyridinium salts based on the Zincke reaction could well be carried out (*25*).

2. Experimental

2.1. Apparatus and analysis

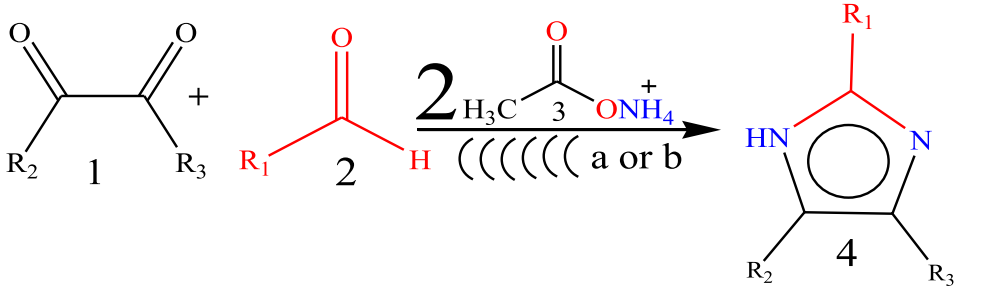
The uncorrected melting points of compounds were recorded using an open capillary in a liquid paraffin bath on the digital melting point apparatus. The values observed were compared with the reported values. Recordings of infrared spectra were made using a Perkin–Elmer Fourier Transform spectrophotometer equipped with KBr discs, and the results were given in cm^{-1}. NMR spectra were obtained by employing the solvent DMSO-d_6 and a Bruker DPX 400 MHz spectrometer. The chemical shift (σ) was measured in ppm relative to TMS, which served as the instrument's internal standard. The sonication was carried out by a UP 400S ultrasonic processor, which had a probe measuring 3 millimeters in width and 140 millimeters in length. The probe was immersed in the reaction mixture and allowed to remain there during the operation. The frequency at which the operation took place was 24 kHz, and the output power ranged from 0 to 400 watts and was adjusted manually.

2.2. General procedure for the synthesis of 2,4,5-triphenyl-1H-imidazole

Synthesis of 2,4,5-triphenyl-1H-imidazole was carried out by mixing benzil (1 mmol), benzaldehyde (1 mmol) and ammonium acetate (3 mmol) in the presence of PTSA/ benzenesulfonic acid (30 mol%) as a catalyst dissolved in ethanol (5 mL) in 250 ml. This reaction mixture was then irradiated using the ultrasonicator with an operating frequency of 24 kHz and the output power was 0–400 W at 50°C for 30 min. By employing silica gel G as the stationary phase in thin-layer chromatography (TLC) and toluene, ethyl acetate, and formaldehyde (4:4:2) as the solvent system, it was possible to demonstrate that the reaction had been completed. After letting the reaction mixture drop to ambient temperature, we put it into ice-cold water (50 mL) to precipitate the solid result. This precipitate was recovered by filtration, then rinsed with cold water, and ethanol was used to recrystallize it. The finished product was obtained with a good yield (94%) and sufficient purity for spectrum analysis after being dried in a vacuum. The synthesis of 1,2,4,5-tetrasubstituted imidazole has been carried out using a similar method, with a slight modification in the nitrogen source. Instead of using two moles of ammonium acetate, one mole of acetate and one mole of aniline are employed as nitrogen-contributing reagents in this reaction (*17*,*26*,*27*).

3. Results and discussion

Several scientific publications have described the use of ultrasonic irradiation in organic transformations, emphasizing benefits such as decreased risk, cheaper prices, simplicity of handling and high productivity. A green, facile and efficient method for the synthesis of mono, di, tri, and tetra substituted imidazoles catalyzed by two catalysts sulfonic acid and PTSA different solvent conditions under ultrasonic irradiation at temperature 50°C (Scheme 1) has been developed (Table 1 and Table 2). The conventional technique of synthesis of substituted imidazoles was compared with the ultrasonic-assisted synthesis of identical compounds using the same solvent and catalyst. The reactions were carried out at a temperature of 50°C for 20–30 min by using a mixture of aldehyde, benzyl, and ammonium acetate in the proportions of 1:1:3 mmol respectively, in the presence of 30 mol% of either benzenesulfonic acid or PTSA, and with ethanol serving as the solvent. Sonication was performed at a frequency of 24 kHz (Table 3, Table 4 and Table 5).



Scheme 1. Synthesis of 2,4,5-trisubstituted-1*H*-imidazole. a-benzenesulfonic acid, b-PTSA, —24 kHz ultrasonic waves.

Table 1. One-pot synthesis of 2,4,5-trisubstituted imidazoles catalyzed by PTSA and benzenesulfonic acid in Ethanol under ultrasound irradiation (method A) and without ultrasound irradiation (method B) at 50 °C.

				PTSA (30 mol%)				Benzenesulfonic acid (30 mol%)				
				With sonication		Without sonication		With sonication		Without sonication		
Sr. No	Dicarbonyl compound	Aldehyde (R1)	Product	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	M.P. (˚C)
1	1a	Formaldehyde	4a	80	30	40	210	76	30	60	210	90
2	1a	Acetaldehyde	4b	89	30	63	210	77	30	61	210	147
3	1a	Propanaldehyde	4c	90	30	61	210	78	30	62	210	82
4	1a	Crotonaldehyde	4d	88	30	61	210	76	30	61	210	89
5	1a	Benzaldehyde	4e	94	30	66	210	80	30	63	210	147
6	1a	Salicylaldehyde	4f	92	30	67	210	79	30	62	210	211
7	1a	Anisaldehyde	4g	94	30	66	210	81	30	62	210	77
8	1a	Cinnamaldehyde	4h	94	30	67	210	81	30	62	210	180
9	1a	2-chlorobenzaldehyde	4i	93	30	64	210	79	30	62	210	88
10	1a	3-chlorobenzaldehyde	4j	95	30	67	210	82	30	63	210	97
11	1a	4-chlorobenzaldehyde	4k	92	30	66	210	80	30	61	210	110
12	1a	*P*-dimethyl amino benzaldehyde	4l	93	30	66	210	81	30	64	210	121
13	1a	2-nitrobenzaldehyde	4m	93	30	64	210	78	30	63	210	117
14	1a	3-nitrobenzaldehyde	4n	94	30	66	210	80	30	64	210	147
15	1a	4-nitrobenzaldehyde	4o	92	30	67	210	77	30	64	210	253
16	1a	Vanillic aldehyde	4p	93	30	65	210	79	30	63	210	217
17	1b	Formaldehyde	4b1	85	30	50	210	81	30	64	210	94
18	1b	Acetaldehyde	4b1	91	30	63	210	80	30	65	210	146
19	1b	Propanaldehyde	4c1	91	30	64	210	81	30	64	210	87
20	1b	Crotonaldehyde	4d1	90	30	64	210	80	30	63	210	74
21	1b	Benzaldehyde	4e1	94	30	70	210	85	30	67	210	150
22	1b	Salicylaldehyde	4f1	95	30	71	210	86	30	67	210	95
23	1b	Anisaldehyde	4g1	95	30	69	210	85	30	68	210	225
24	1b	Cinnamaldehyde	4h1	93	30	68	210	84	30	68	210	150
25	1b	2-chlorobenzaldehyde	4i1	95	30	71	210	84	30	68	210	160

(*continued*).

Table 1. Continued.

				PTSA (30 mol%)				Benzenesulfonic acid (30 mol%)				
				With sonication		Without sonication		With sonication		Without sonication		
Sr. No	Dicarbonyl compound	Aldehyde (R1)	Product	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	M.*P*. (°C)
26	1b	3-chlorobenzaldehyde	4j1	96	30	72	210	85	30	69	210	205
27	1b	4-chlorobenzaldehyde	4k1	94	30	70	210	84	30	68	210	250
28	1b	*P*-dimethyl amino benzaldehyde	4l1	96	30	71	210	83	30	69	210	240
29	1b	2-nitrobenzaldehyde	4m1	95	30	71	210	84	30	67	210	185
30	1b	3-nitrobenzaldehyde	4n1	96	30	73	210	85	30	69	210	217
31	1b	4-nitrobenzaldehyde	4o1	95	30	72	210	86	30	67	210	251
32	1b	Vanilline aldehyde	4p1	95	30	71	210	84	30	68	210	239

[a]Benzil (1 mmol), Aldehyde (1 mmol), ammonium acetate (03 mmol), PTSA (30 mol%) & benzenesulfonic acid (30 mol%) in 5 ml Ethanol.
[b]Glyoxal (1 mmol), Aldehyde (1 mmol), ammonium acetate (03 mmol), PTSA (30 mol%) & benzenesulfonic acid (30 mol%) in 5 ml Ethanol.

Table 2. Assessment of the effect of the solvent on the model reaction[a].

			Yield (%)[b]	
Sr. No.	Solvent	Time (min)	benzenesulfonic acid (30 mol%)	PTSA (30 mol%)
1	Ethanol	20	85	94
2	Methanol	20	74	83
3	DCM	20	31	33
4	DMF	20	45	49
5	THF	20	49	56
6	Acetonitrile	20	65	70

[a]Reaction of benzil, benzaldehyde and ammonium acetate (1:1:3) in presence of benzenesulfonic acid (30 mol %) and PTSA (30 mol%) as a catalyst under ultrasonic irradiation with a power intensity of 24 kHz at 50° C.
[b]Isolated yield based on aldehyde.

Table 3. Assessment of the effect of the mol% PTSA concentration on the model reaction.

		With sonication		Without sonication	
Sr.no	mol% PTSA	Time (min)	Yield (%)	Time (min)	Yield (%)
1	0	30	6	210	9
2	10	30	38	210	21
3	20	30	69	210	47
4	30	30	94	210	70
5	40	30	95	210	83
6	50	30	96	210	85
7	60	30	96	210	87
8	70	30	96	210	87
9	80	30	96	210	87
10	90	30	96	210	87

When 24 kHz ultrasound radiation was exposed to the above reaction mixture under appropriate conditions, it causes cavitation and microstreaming resulting in chemical reactions (*3*). These effects provide the energy of activation to both of our reactants viz. a dicarbonyl compound and aldehyde. Due to this, the reactions proceed very fast with minimum energy requirement. This rapid and violent crumbling generates short-lived regions with high temperatures and pressures. Due to this, the heating and cooling rates change dynamically within a second. These localized hot spots can be regarded as micro vessels that contain the mechanical energy of sound and are transformed into a chemical form that can be employed. Sonochemistry can not only accelerate reactions but also change their course. This can result in a distinct mechanistic path leading to the same products. Thus, sono-chemistry is useful for the synthesis of imidazole. It also helps in the cyclization step by reducing the energy and time of cyclization. The experiments were conducted under both conditions viz. with sonication and without sonication. Synthesis of imidazole by conventional method without sonication requires more energy and leads to fewer product yields as compared to reactions employing ultrasonication.

Benzaldehyde was first reacted with benzyl and ammonium acetate in ethanol (5 mL) for 30 min under ultrasound irradiation in the presence of each catalyst (0.2 equiv.) separately in an initial study for the purpose of examining the catalytic activity of various catalysts, such as benzenesulfonic acid and PTSA, in this condensation reaction. This was done to determine the catalytic activity of different catalysts. We discovered that PTSA was the most efficient catalyst in terms of the yield of the triaryl imidazole (94%), whereas other catalysts

Table 4. One-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles catalyzed by PTSA and benzenesulfonic acid in Ethanol under ultrasound irradiation (method A) and without ultrasound irradiation (method B) at 50 ^{0}C.

					PTSA (30 mol%)				benzenesulfonic acid (30 mol%)				
					With sonication		Without sonication		With sonication		Without sonication		
Sr. No	Dicarbonyl compound	Aldehyde (R1)	Aniline (5)	Product	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	M.*P.* (˚C)
1	1a	Formaldehyde	5	4a	86	30	64	210	78	30	61	210	230
2	1a	Acetaldehyde	5	4b	87	30	65	210	79	30	62	210	260
3	1a	Propanaldehyde	5	4c	88	30	65	210	80	30	62	210	283
4	1a	Crotonaldehyde	5	4d	87	30	64	210	79	30	61	210	271
5	1a	Benzaldehyde	5	4e	88	30	67	210	81	30	63	210	221
6	1a	Salicylaldehyde	5	4f	88	30	67	210	81	30	62	210	257
7	1a	Anisaldehyde	5	4g	89	30	68	210	82	30	64	210	245
8	1a	Cinnamaldehyde	5	4h	90	30	68	210	82	30	64	210	228
9	1a	2-chlorobenzaldehyde	5	4i	90	30	67	210	81	30	63	210	170
10	1a	3-chlorobenzaldehyde	5	4j	91	30	68	210	83	30	64	210	155
11	1a	4-chlorobenzaldehyde	5	4k	90	30	67	210	81	30	62	210	167
12	1a	*P*-dimethyl amino benzaldehyde	5	4l	92	30	69	210	83	30	64	210	188
13	1a	2-nitrobenzaldehyde	5	4m	92	30	67	210	81	30	63	210	255
14	1a	3-nitrobenzaldehyde	5	4n	90	30	68	210	82	30	64	210	270
15	1a	4-nitrobenzaldehyde	5	4o	90	30	66	210	81	30	63	210	262
16	1a	Vanillic aldehyde	5	4p	89	30	67	210	81	30	63	210	290
17	1b	Formaldehyde	5	4a1	87	30	69	210	80	30	62	210	145(B.*P.* ˚C)
18	1b	Acetaldehyde	5	4b1	88	30	70	210	81	30	63	210	98
19	1b	Propanaldehyde	5	4c1	89	30	69	210	81	30	63	210	130
20	1b	Crotonaldehyde	5	4d1	89	30	69	210	80	30	62	210	143
21	1b	Benzaldehyde	5	4e1	91	30	70	210	82	30	65	210	185
22	1b	Salicylaldehyde	5	4f1	91	30	70	210	82	30	65	210	209
23	1b	Anisaldehyde	5	4g1	92	30	71	210	83	30	66	210	202
24	1b	Cinnamaldehyde	5	4h1	92	30	71	210	83	30	67	210	195
25	1b	2-chlorobenzaldehyde	5	4i1	91	30	69	210	81	30	67	210	145

(*continued*).

Table 4. Continued.

					PTSA (30 mol%)				benzenesulfonic acid (30 mol%)				
					With sonication		Without sonication		With sonication		Without sonication		
Sr. No	Dicarbonyl compound	Aldehyde (R1)	Aniline (5)	Product	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	M.*P*. (°C)
26	1b	3-chlorobenzaldehyde	5	4j1	93	30	71	210	83	30	68	210	133
27	1b	4-chlorobenzaldehyde	5	4k1	91	30	70	210	82	30	68	210	139
28	1b	*P*-dimethyl amino benzaldehyde	5	4l1	92	30	72	210	83	30	67	210	160
29	1b	2-nitrobenzaldehyde	5	4m1	91	30	70	210	81	30	67	210	215
30	1b	3-nitrobenzaldehyde	5	4n1	92	30	71	210	83	30	68	210	198
31	1b	4-nitrobenzaldehyde	5	4o1	91	30	69	210	81	30	67	210	205
32	1b	Vanillic aldehyde	5	4p1	92	30	69	210	80	30	66	210	242

[a]Benzil (1 mmol), Aldehyde (1 mmol), ammonium acetate (03 mmol), PTSA (30 mol%) & benzenesulfonic acid (30 mol%) in 5 ml Ethanol.
[b]Glyoxal (1 mmol), Aldehyde (1 mmol), ammonium acetate (03 mmol), PTSA (30 mol%) & benzenesulfonic acid (30 mol%) in 5 ml Ethanol.

Table 5. Assessment of the effect of the solvent on the model reaction[a].

			Yield (%)[b]	
Entry	Solvent	Time (min)	Benzenesulfonic acid	PTSA
1	Ethanol	20	80	91
2	Methanol	20	72	83
3	DCM	20	50	42
4	DMF	20	55	59
5	THF	20	60	64
6	Acetonitrile	20	52	47

[a]Reaction of benzil, benzaldehyde, aniline and ammonium acetate (1:1:3:3) in presence of benzenesulfonic acid (30 mol%) and PTSA (30 mol%) as a catalyst under ultrasonic irradiation with a power intensity of 24 kHz at 50 ^{0}C.
[b]Isolated yield based on aldehyde.

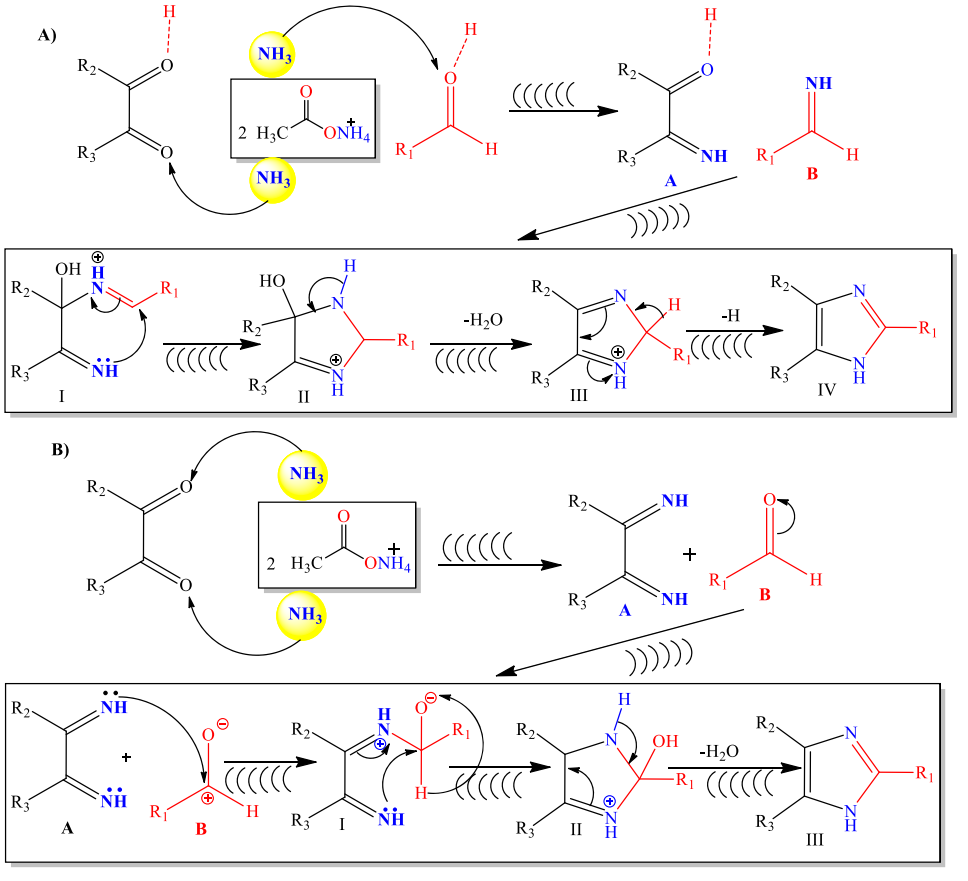
Table 6. Assessment of the effect of the mol% PTSA concentration on the model reaction.

		With sonication		Without sonication	
Sr. No.	mol% PTSA	Time (min)	Yield (%)	Time (min)	Yield (%)
1	0	30	7	210	6
2	10	30	33	210	25
3	20	30	61	210	51
4	30	30	91	210	68
5	40	30	92	210	84
6	50	30	92	210	86
7	60	30	93	210	87
8	70	30	93	210	87
9	80	30	94	210	88
10	90	30	94	210	89

yielded the product with yields ranging from 65 to 82%. It was revealed that the yield of the product was significantly reduced when a catalyst was not present.

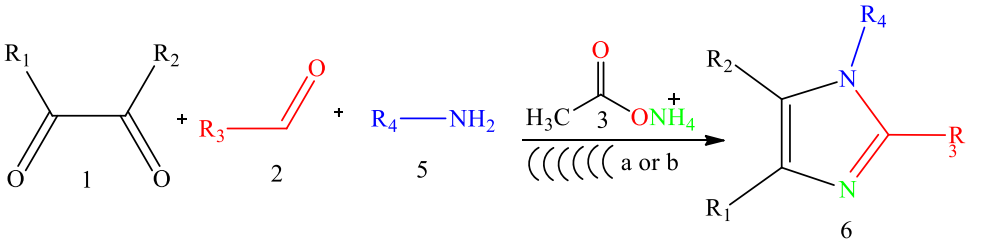
The synthesis of 2,4,5-triphenyl-1*H*- imidazole was investigated as a typical example in order to observe the effect that ultrasonic irradiation has on these reactions. The experiment was conducted in the presence of 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90 mol% of PTSA, both with and without ultrasonic irradiation (Table 3 and Table 6). Under the impact of sonication, the results of the experiments reveal that the reaction durations are reduced, but at the same time, the yields of the products are increased to a greater extent. The best results were obtained using 30 mol% of the catalyst under ultrasonic exposure resulted in a yield of 94% and while 50 mol% of the catalyst without sonication resulted in a yield of 70% as shown in Table 1 and Table 3. Thus, ultrasound irradiation not only improves the reaction times and yields but also increases the efficiency of the catalyst activity as less amount of catalysts is required to produce the maximum yields as compared to the synthesis without employing ultrasound.

The study of imidazole formation through the [3 + 2] cycloaddition reaction mechanism involves the steps as shown in Scheme 2 and Scheme 3. As the reaction proceeds under the influence of the heat supply and ultrasonic exposure, ammonium acetate starts converting to ammonia. Thus, it acts as the slow source of ammonia which reacts with one of the carbonyl groups of dicarbonyl compounds like benzil or glyoxal and with an aldehyde to form the A and B product separately, with the secondary amine functionality as the



Scheme 2. Mechanism of reaction of synthesis for 2,4,5-trisubstituted-1*H*-imidazole.

amine derivative of dicarbonyl compound and aldehyde with the removal of the hydroxyl group. The protons generated by acetic acid through the conversion of ammonium acetate form the hydrogen bonds with the carbonyl groups of both dicarbonyl compound and aldehyde which helps in dissociation, making the compounds reactive. A and B react with each other to form the acyclic quaternary ammonium complex (I) in which the amine group of aldehyde derivative reacts with the second carbonyl group of dicarbonyl compound derivative through lone pair of amine. This I undergo [3 + 2] cyclization through intermolecular rearrangement to form the cyclic quaternary imidazolium compound (II) with cation and the double bond on one of the nitrogen atoms. Subsequently, the high energy imidazolium compound readily removes the hydrogen from the nitrogen to liberate the water molecule and generate (III) imidazolium compound with the two-double bond in the ring and one cation on the nitrogen atom. As shown in step III, it loses the hydrogen from the carbon adjacent to nitrogen so as to maintain the aromaticity and stabilization thereby forming imidazole, similar to in case of electrophilic substitution reaction of benzene where the intermediate carbocations readily lose the protons in order to maintain the aromaticity and stabilization resulting in the substituted product instead of additional product.



Scheme 3. Mechanism of reaction of synthesis for 1,2,4,5-trisubstituted imidazole.

The rate of reaction was faster (*i.e.* less energy requirement) in the case of PTSA while in the case of benzenesulfonic acid, the reaction proceeds at a slower rate (*i.e.* more energy requirement). Thus, the chemical nature of the catalyst also governs the rate of reaction and the path of the reaction mechanism. PTSA is a strong organic acid (one million times stronger than benzoic acid with the Pka of - 3). It is a stronger acid than the benzenesulfonic acid (Pka 3.25) due to the presence of the amine group which undergoes the resonance and activates the benzene ring toward the ortho, para-directing nature and destabilizes the sulfone group. PTSA, with the methyl group at the para position, shows the electron-donating effects via the inductive effect and not by resonance and hence this stabilizes the solphone group. Thus, PTSA is more acidic than benzenesulfonic acid and it progresses the reaction faster. In presence of benzenesulfonic acid, the reaction probably follows the second path of mechanism as shown in Scheme 2. As PTSA is the stronger acid, it may lead to activating both the reactants viz. dicarbonyl compound and aldehyde to render the energy of activation more vigorously.

3.1. Kinetics of reactions

In Chemistry, The field of research known as kinetics focuses on the rate at which chemical reactions take place. It serves the purpose of understanding the underlying mechanisms of change and enables the prediction of the degree of change that will take place after a specified amount of time. The starting rate of the reaction and the time-integrated rate of the reaction are the two approaches that may be taken for this analysis. The reliance on time is associated with a particular power law in the concentration of the reactants in the forward direction and the products in the reverse reaction. There are two types of power laws: those that pertain to the inclusive order of the reaction, for which the power law must be determined through experimentation, and those that pertain to the molecularity of the reaction, which are typically associated with the individual steps that make up the reaction mechanism (*26*).

3.1.1. Reaction rate

It refers to the shift that takes place over time in the concentration of a reactant or a product (mol/sec or mol/min or mol/hours). *i.e.*

Reactant (A) → Products (B)

$$\text{Average rate} = \frac{\text{Change in number of moles of B}}{\text{Change in time}}$$

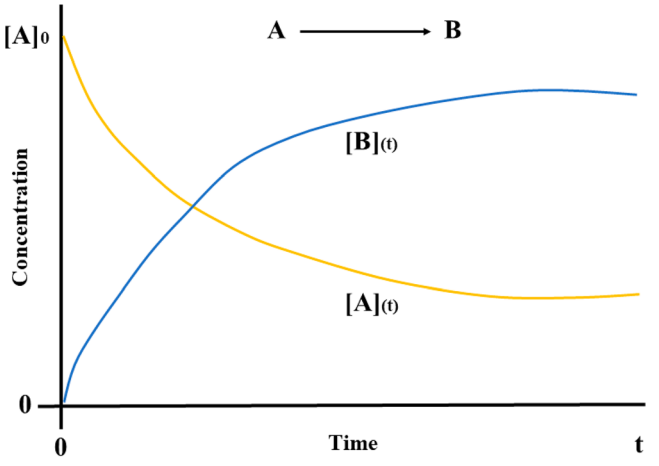


Figure 1. Graph of concentration of A & B with time (t).

$$\text{Average rate} = \frac{\Delta(\text{moles of B})}{\Delta t}$$

$$\text{Average rate} = \frac{\Delta[B]}{\Delta t}$$

Here, the concentration of product (B) will go on increasing with time while the concentration of reactant (A) it will goes on decreasing. Therefore,

$$\text{Average rate} = -\frac{\Delta[A]}{\Delta t}$$

The graph of concentrations of reactant and product with time clears the idea, *i.e.* given in Figure 1.

3.2. Order of reaction

3.2.1. First-Order reaction

First-order reactions are those in which the rate of the reaction is proportional to the concentration of a single ingredient raised to the first power. Here, the reaction will only start after the active participation of that reactant. As a result, the rate of reaction is directly proportional to the concentration of the substance that is reacting, and this relationship can be stated as follows:

$$\text{Rate of concentration decrease} = \frac{-dCx}{dt} = KCX \tag{1}$$

Where, K is the rate constant in the rate law

If the concentration of reactant X is 'a' at beginning of the reaction when t = 0, & if the amount that has reacted after time t is denoted by x then the amount of X remaining at time t will be (a-x).

Therefore equation (1) can be rewritten as:

$$\text{Rate of concentration decrease} = \frac{-dCx}{dt} = K(a-x)$$

$$\text{Rate of concentration decrease} = \frac{dCx}{(a-x)} = -Kdt \tag{2}$$

Integrating equation (2) between time limit 0 to t,

$$\int_{a}^{a-x} \frac{-dCx}{dt} = -K \int_{0}^{t} dt$$

$$ln\,(a-x) - ln\,a = -Kt$$

$$log\,(a-x) - log\,a = -\frac{Kt}{2.303}$$

$$log\,(a-x) = log\,a - \frac{Kt}{2.303} \tag{3}$$

Rearranging equation (3) we have,

$$K = \frac{2.303}{t} \log\left(\frac{a}{a-x}\right) \tag{4}$$

The unit of K for the first-order is **time^{-1}** *i.e.* SI unit is (sec)$^{-1}$ because K is inversely proportional to t.

3.2.2. s-Order reaction

Here, the rates at which reactions proceed are directly proportional to the concentrations of the two reactants. The reaction will proceed only when there is the active participation of both reactants. The rate at which product and reactant concentrations change is proportional to the second power of the concentration of a single reactant or the first power of the concentration of two reactants.

$$\text{Rate of concentration decrease} = \frac{-dCx}{dt} = K[X][Y] \tag{5}$$

$$\text{Rate of concentration decrease} = \frac{-dCx}{dt} = K[X]^2 \tag{6}$$

Let us discuss equation (5) in detail,

Here decrease in concentrations of **Y** is similar to **X**. If concentrations of **X** and **Y** at time **t = 0** are **a** and **b** respectively, and the concentration of each substance that has reacted after time **t** is equal to **x** then the concentration of **X** and **Y** remaining will be **(a-x)** & **(b-x)** respectively.

In case when (a ≠ b),

$$\frac{-dx}{dt} = K(a-x)(b-x) \tag{7}$$

Where $\frac{-dx}{dt}$ = rate of decrease in concentrations of **X** or **Y**

Integrating equation (7) we get,

$$Kt = \frac{2.303}{(a-b)} log \frac{b(a-x)}{a(b-x)} \tag{8}$$

Rearranging equation (8) we get,

$$log \frac{(a-x)}{(b-x)} = \frac{(a-b)}{2.303} Kt + log \frac{a}{b} \tag{9}$$

Let us discuss equation (6) in detail, in the case when (a = b),

Integrating equation (6) gives,

$$Kt = \frac{x}{a(a-x)} \tag{7}$$

The rearrangement of equation (7) gives us,

$$Kt = \frac{1}{(a-x)} - \frac{1}{a} \tag{8}$$

The unit of second-order reaction is concentration^{-1} time^{-1} and the SI unit is mol^{-1} sec^{-1}.

3.3. Synthesis of 2,4,5-trisubstituted imidazoles

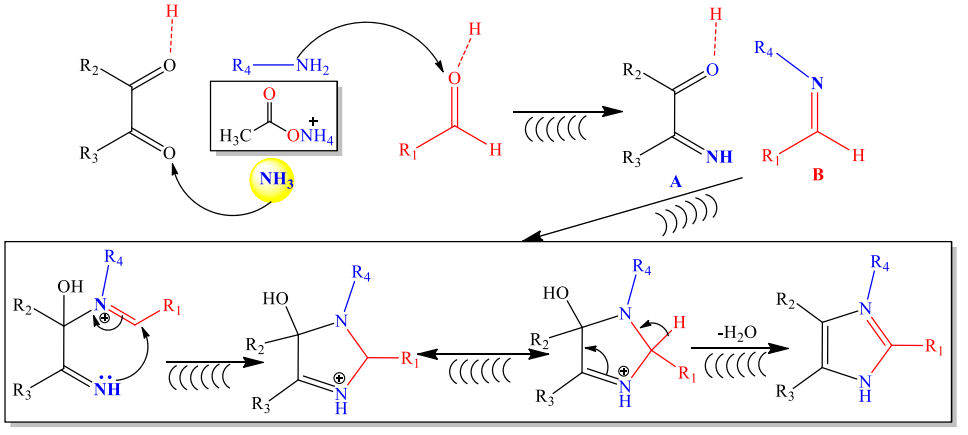
Ammonium acetate acts as a reservoir for the release of ammonia. 2 moles of ammonia are liberated from ammonium acetate, one of which reacts with the aldehyde molecule while the other reacts with the diketone molecule to form the intermediates. This is the rate-limiting step in this reaction and is totally depends upon the concentration of ammonium acetate. Therefore, this reaction follows first-order rate kinetics. Two moles of ammonia will react with aldehyde & diketone molecule & converts the C = O group to the C = NH group by losing water molecule. Here, one proton is lost from ammonia while OH is lost from the diketone molecule.

To calculate the rate constant for the synthesis of 2,4,5-trisubstituted imidazole at t = 600, 1200, 1800 sec., the concentration of ammonium acetate used was 3 moles which decrease gradually with time like 3, 2, 1 mol & 0 mol. Thus, equation (4) will take the form,

$$K = \frac{2.303}{t} \log \frac{[Conc.\ of\ Ammonium\ acetate]}{[Conc.\ of\ Ammonium\ acetate\ -\ Conc.\ of\ Ammonium\ acetate\ After\ 900\ sec]}$$

3.4. Synthesis of 1,2,4,5-tetrasubstituted imidazoles

In the present synthesis of 1,2,4,5-tetrasubstituted imidazole, ammonia was liberated from substituted primary amines & ammonium acetate as represented in Scheme 4 and Table 4. One mole of ammonia is liberated from amine & one mole is from ammonium acetate. The rate of reaction in this reaction will depend upon both of these components, amines as well as ammonium acetate. Thus, the rate of the reaction follows the second-order rate kinetics. The reaction will not get initiated until both of these liberates ammonia. Two moles of ammonia gas will react with aldehyde & diketone molecule & converts the -C = O group to the -C = NH group by losing the water molecule. Here, one proton is lost from ammonia while OH is lost from the diketone molecule.



Scheme 4. Synthesis of 1,2,4,5-tetrasubstituted imidazole. a-benzenesulfonic acid, b-PTSA, —24 kHz ultra sonic waves.

Now, the concentrations of amines & ammonium acetate used were the same *i.e.* 3 moles. To calculate the rate of reaction equation (8) will be,

$$Kt = \frac{1}{\left(\begin{array}{c}\textit{Conc. of Ammonium acetate or Amines} \\ -\textit{Conc. of Ammonium acetate or Amine after time } t\end{array}\right)} - \frac{1}{\textit{Conc. of Ammonium acetate or Amine}}$$

4. Conclusion

This green synthesis of mono-, di-, tri-, and tetrasubstituted imidazole derivatives using ultrasonic radiation is a great example of the one-pot organic transformations made possible by ultrasound, which simplifies experimental procedures and speeds up reaction times. These results showed that PTSA functions as the best catalyst for the cyclization of imidazole in ethanol as compared to other organic solvents. Lower % mol. PTSA quantity is required to produce significantly higher yields of imidazole derivatives. The usage of this method is helpful in overcoming many of the challenges that are present in the reactions that are typically used in conventional synthesis. In the cyclization reaction for heterocyclic compounds, it offers advantages related to the process as well as those linked to the environment.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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