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Synthesis of Substituted Imidazoles *via* a Multi-Component Condensation Catalyzed by *p*-toluene Sulfonic Acid, PTSA

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Abstract

A robust and reliable one pot synthetic method has been developed for 2,4,5-trisubstituted and 1,2,4,5-tetra substituted imidazoles. The synthetic sequence, via a multi-component condensation catalyzed by p-toluenesulfonic acid (PTSA), provides good isolated yields under mild conditions. The structural features have been arrived at from their micro analytical, infra red, mass and ^{1}H NMR spectral data. Short synthesis, mild reaction conditions, inexpensive reagents and high yield illustrate the utility of this approach.

***Keywords*:** Multicomponent reaction, one-pot synthesis, substituted imidazoles, *p*-toluenesulfonic acid, (PTSA).

Introduction

Imidazole represents an important class of compound being the main components of many naturally occurring products, as well as synthetic derivatives. Imidazole ring has been of great interest for organic chemist due to their useful biological and pharmacological aspects. They act as inhibitors of p38 MAP kinase[1], B-Raf kinase[2], transforming growth factor b1 (TGF-b1) type 1 activin receptor-like kinase (ALK5)[3], cyclooxygenase-2 (COX-2)[4] and biosynthesis of interleukin-1 (IL-1)[5]. Appropriately substituted imidazoles are extensively used as glucagon receptors[6] and CB1 cannabinoid receptor antagonists[7], modulators of P-glycoprotein (P-gp)-mediated multidrug resistance (MDR)[8], antitumor[9], antibacterial[10] and anti-inflammatory agents. It can also be employed as fungicides, herbicides[11] and plant growth regulators[12]. Imidazoles as ionic liquid and imidazole related N- hetrocyclic carbenes are well known green solvent.

Due to pharmacological properties and industrial applications the preparation of imidazole has been attracted considerable attention in recent years. Various synthetic protocols have been developed for the synthesis of Imidazole such as the hetero-Cope rearrangement[13], four-component condensation of arylglyoxals, primary amines, carboxylic acids and isocyanides on Wang resin[14], reaction of N-(2-oxo)-amides with ammonium tri fluoroacetate, 1, 2-aminoalcohols in the presence of PCl_5, diketones, aldehyde, amine and ammonium acetate in phosphoric acid and in acetic acid, organo catalyst in acetic acid as well as H_2SO_4 and DMSO. Several microwave (MW) assisted syntheses of imidazoles from 1, 2-diketones and aldehydes in the presence of a variety of catalysts such as silica-gel, silica-gel/HY, Al_2O_3, DMF, acetic acid[15], $ZrCl_4$[16], $NiCl_2.6H_2O$[17] and ionic liquid[18] has been reported. Many of the synthetic protocols for the synthesis of imidazole reported so far suffer from one or more disadvantages such as harsh reaction conditions, poor yields, prolonged time period, use of hazardous and often expensive acid catalysts. So, development of an improved synthetic protocol for the generation of substituted imidazole to lead optimization is of considerable interest.

As a part of our ongoing efforts towards the development of new procedure for the highly substituted heterocycles through multi-component reaction[19], we have discovered an efficient and environment friendly procedure for the synthesis of substituted imidazole. Here we describe the synthesis of highly substituted imidazoles by one-pot condensation of benzil with a substituted benzaldehyde, ammonium acetate and aniline in the presence of *p*-toluenesulphonic acid (PTSA) a non-toxic and inexpensive catalyst.

Material and Methods

Chemicals used in the experiment were of analytical grade. Analytical TLC's were performed on pre-coated Merck silica gel 60 F254 plates; the spots were detected either under UV light or by placing in iodine chamber. Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were obtained on Perkin-Elmer FTIR-1710 spectrophotometer using Nujol film. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Advance Spectrospin at 300 and at 75 MHz, respectively, using TMS as internal standard.

General procedure for the synthesis of 2,4,5-triarylimidazole (4a-4d): A mixture of benzil 1 (10 mmol), ammonium acetate 2 (20 mmol), aromatic aldehyde 3a-3d (20 mmol) and PTSA (5 mol %) stirred at 80 ºC in ethanol (5 ml) for the appropriate time as mentioned in table 1. The completion of reaction was monitored by TLC. After completion of reaction, the reaction

mixture was cooled to room temperature and diluted with excess of cold water. The solid imidazole products that separated out, were filtered, washed with excess of water and was further recrystallized with 9:1 acetone-water to result a pure compound of 2,4,5-triarylimidazole (4a-4d), scheme 1.

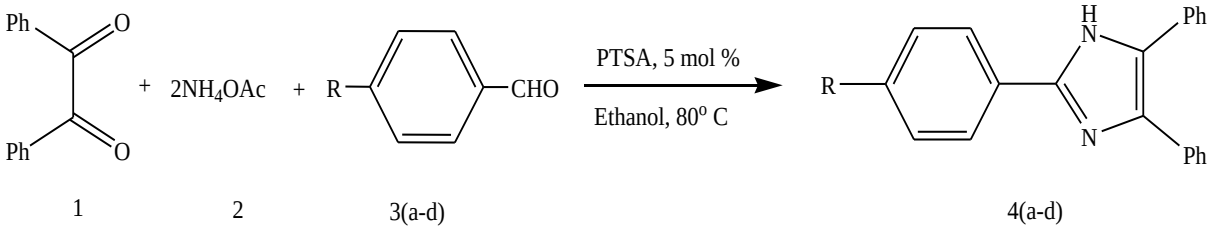
General procedure for the synthesis of 1,2,4,5-tetraarylimidazole (6a–6d): A mixture of benzil 5 (10 mmol), ammonium acetate 2 (10 mmol), aniline 5 (10 mmol), aromatic aldehyde 3a-3d (10 mmol), and PTSA (5 mol %) stirred at 80 °C in ethanol (5 ml) for the appropriate time as mentioned in table 2. The completion of reaction was monitored by TLC. To obtain pure compounds of 1,2,4,5-tetraarylimidazole (6a-6d) after completion of reaction, work-up procedure followed was similar to the synthesis of 2,4,5-triarylimidazole. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ^{1}H, ^{13}C NMR and CHN data), scheme 2.

Table-1
Analytical and physical data of the tri-substituted imidazole compounds

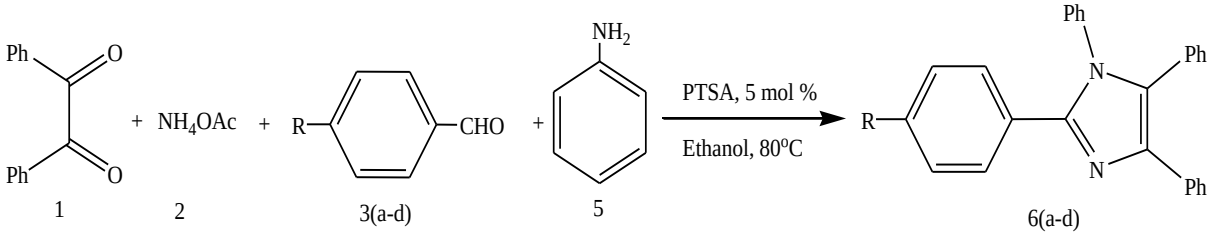
Entry	Product	R	Time (h)	Yield (%)	MP (obs)ºC	M.P (rep)ºC
3a	4a	H	1	90	275	273
3b	4b	CH_3	1.5	82	240	235
3c	4c	OCH_3	1.5	87	225	222-224
3d	4d	Cl	2	80	265	261-262

Table-2
Analytical and physical data of the tetra-substituted imidazole compounds

Entry	Product	R	Time (h)	Yield (%)	MP (obs) ºC	M.P (rep) ºC
3a	6a	H	1	84	117	121
3b	6b	CH_3	1.5	81	188	185
3c	6c	OCH_3	1.5	91	186	184
3d	6d	Cl	2	85	154	151



Scheme-1
Synthesis of tri-substituted imidazoles



Scheme-2
Synthesis of tetra-substituted imidazoles

Results and Discussion

Careful literature analyses revealed that a variety of acidic catalyst have been used for this multicomponent reaction. It has been reported that *p*-toluenesulphonic acid (PTSA) acts as a mild, useful, non-toxic and inexpensive Lewis acid catalyst which makes the process convenient, more economic and environmentally benign. The mild reaction conditions, operational simplicity and the excellent yields make the catalyst more versatile. The reaction is rapid, facile, and efficient and is devoid of unnecessary derivatization and generation of hazardous substance. Knowing the importance of PTSA we used it as a catalyst for these multicomponent reactions. We were please to know that high yield product was obtained on using only 5 mol% of PTSA in ethanol. A wide range of substituted aromatic aldehydes underwent multicomponent condensation with benzil and ammonium acetate to give high yield tri-substituted imidazole. In addition to above reactants if aniline was added it resulted into tetra-substituted imidazole. We also tried aqueous ethanol and PEG as solvent but the results were not satisfactory. All the utilized functionalities were found to be compatible under the reaction conditions (table 1 and table 2).

Spectroscopic Data of the Synthesized Compounds: Compound 4a *2, 4, 5-triphenyl 1H- imidazole*: M.P. 275^{0}C. IR (cm^{-1}, Nujol): 3385, 3116, 1638, 1522, 1420. ^{1}H NMR (DMSO-d_6,): δ = 12.32 (s, 1H), 7.21-8.10 (m, 15H) ppm. ^{13}C NMR (DMSO-d_6): δ 123.2, 126.7, 128.2, 129.0,135.6 ppm; Anal. Calcd. (Found) for $C_{21}H_{16}N_2$: C, 85.10 (85.01); H, 5.44 (5.51); N, 9.44 (9.39).

Compound 4b *2-(4-Methyl-phenyl)-4,5-dipheny-1H-imidazole:* M.P. 240^{0}C. IR (cm^{-1}, KBr): 2920, 1602, 1493, 1486, 1453 1218. ^{1}H NMR (DMSO-d_6): δ = 2.32(s, 3H), 7.39-8.49 (m, 14H), 12.87 ppm; ^{13}C NMR (DMSO-d_6): δ = 48.8, 126.1, 127.4, 128.3, 128.9, 129.5, 130.6, 134.4, 138.2, 147.3 ppm; Anal. Calcd. (Found) for $C_{22}H_{18}N_2$: C, 85.13 (84.90); H, 5.85 (5.66); N, 9.02 (9.31).

Compound 4c *2–(4–Methoxy–phenyl)–4,5 diphenyl–1H-imidazole*: M.P: 225°C; IR (cm^{-1}, Nujol): 3433, 1619, 1527; ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ = 3.72 (s, 3H), 6.92–6.96 (d, 2H), 7.18–7.31 (m, 10H), 7.82–7.85 (d, 2H), 12.48 (br, s, NH) ppm; ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ = 56.1, 114.3, 123.1, 126.3, 126.6, 128.0, 128.3, 134.2, 146.0, 158.9 ppm; Anal. Calcd. (Found) for $C_{22}H_{18}N_2$: C, 80.96 (81.01); H, 5.55 (5.49); N, 8.56 (8.39).

Compound 4d *2-(4-chlorophenyl)-4,5-diphenyl 1H imidazole*: M. p. 265°C. IR (cm^{-1}, KBr): 3447, 1620, 1519. ^{1}H NMR ($CDCl_3$/DMSO-d_6): δ = 12.71 (br, s, 1H), 7.76-7.89(d, 2H), 7.44 - 7.51 (d, 2H), 7.10-7.41 (m, 10H) ppm. ^{13}C NMR ($CDCl_3$/DMSO-d_6): δ = 124.9, 126.3, 126.8, 128.1, 129.2, 129.9, 132.3, 143.9 ppm; Anal. Calcd. (Found) for $C_{21}H_{16}N_2$: C, 76.25 (76.14); H, 4.53 (4.55); N, 8.47 (8.37).

Compound 6a *1,2,4,5-Tetraphenylimidazole*: M.P: 117°C; IR (cm^{-1}, Nujol): 3008, 1621, 1521, 1421; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ = 7.10–7.91 (m, 20H) ppm; ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ = 123.2, 124.5, 125.1, 126.0, 127.4, 128.7, 128.8, 129.2, 129.5, 129.9, 136.9 ppm; Anal. Calcd. (Found) for $C_{27}H_{20}N_2$: C, 87.07 (87.10); H, 5.41 (5.39); N, 7.52 (7.45).

Compound 6b *2-(4-Methylphenyl)-1,4,5-triphenylimidazole:* M.P: 188°C; IR (cm^{-1}, Nujol): 1610, 1582; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ = 2.09 (s, 3H), 7.58 - 6.80 (m, 19H); ^{13}C NMR ($CDCl_3$/DMSO-d_6) δ = 47.20, 120.06, 122.43, 126.76, 127.06, 129.06, 132.80, 138.09, 141.87, 145.76 ppm; Anal. Calcd. (Found) for $C_{28}H_{22}N_2$: C, 87.01 (87.05); H, 5.74 (5.81); N, 7.23 (7.29).

Compound 6c *2-(4-Methoxy-phynyl)-1,4,5-triphenyl-1H-imidazole*: M.P: 186°C; IR (cm^{-1}, Nujol): 1624, 1585; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ = 3.69 (s, 3H), 6.83–6.86 (d, 2H), 7.11–7.32 (m, 15H), 7.50–7.52 (d, 2H) ppm; ^{13}C NMR ($CDCl_3$/DMSO d_6) δ = 56.2, 113.8, 125.6, 126.3, 127.1, 128.0, 128.3, 128.5,128.8, 129.4, 130.8, 131.5, 131.9, 135.5, 136.9, 138.4, 147.1, 159.5 ppm; Anal. Calcd. (Found) for $C_{28}H_{22}N_2O$: C, 83.56 (83.58); H, 5.51 (5.45); N, 6.96 (6.90).

Compound 6d *2-(4-Chloro-phenyl)-1,4,5-triphenyl-1H-imidazole*: M.P: 154°C, IR (cm^{-1}, Nujol): 1620, 1584; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ = 7.21–7.55 (m, 15H), 7.64–7.67 (d, 2H), 7.90–7.94 (d, 2H) ppm; ^{13}C NMR ($CDCl_3$/ DMSO-d_6) δ = 123.6, 124.4, 126.1, 127.5, 128.0, 129.1, 130.5, 130.7, 132.5, 134.1, 138.9, 144.1, 144.7 ppm; Anal. Calcd. (Found) For $C_{27}H_{19}N_2Cl$: C, 79.70 (79.78); H, 4.71 (4.69); N, 6.88 (6.81).

Conclusion

Imidazoles enjoy an outstanding status due to their biological importance. PTSA, a non toxic and inexpensive catalyst is optimized for the synthesis of tri- and tetra- substituted imidazoles. Existing synthetic approaches are currently somewhat limited by issues of poor yields, harsh reaction conditions, expensive catalysts etc. hence; the present one-pot synthetic method provides an alternate methodology to obtain excellent yield of product, under reflux condition with 5 mol % of PTSA.

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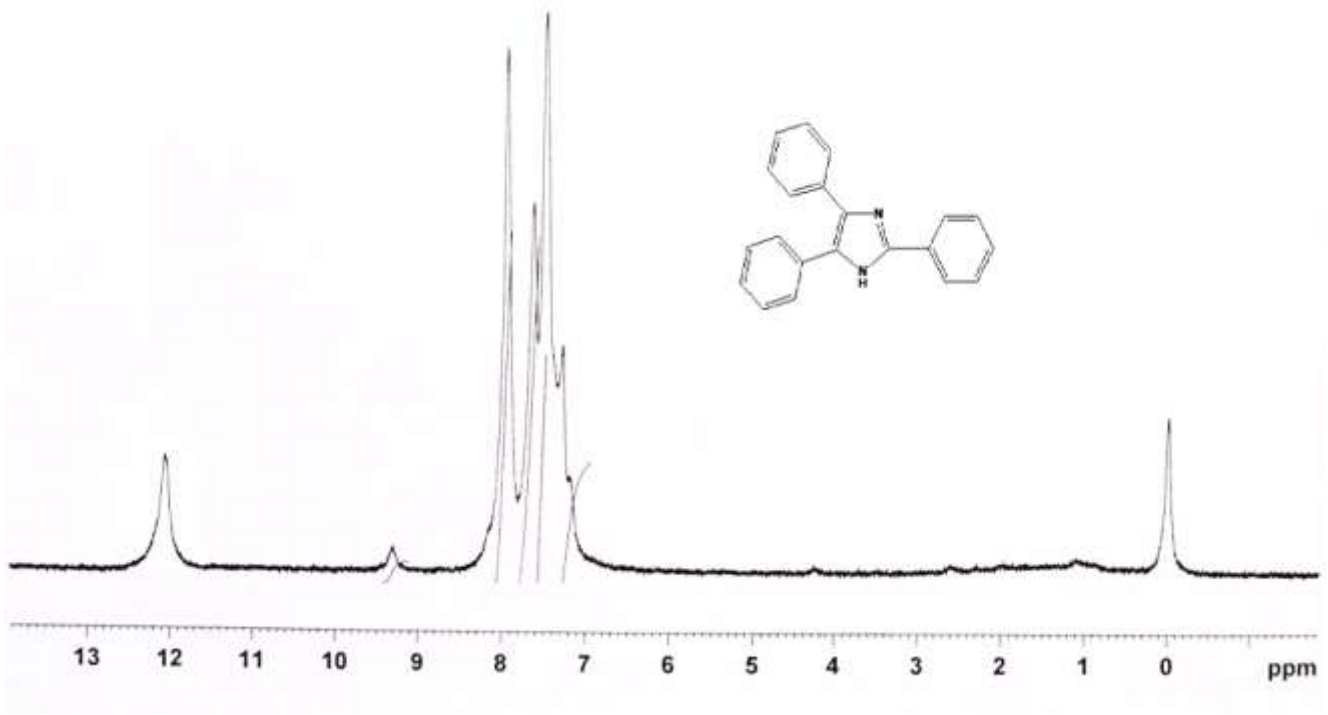

Figure-1a
NMR spectra of 2, 4, 5-triphenyl *1H*- imidazole

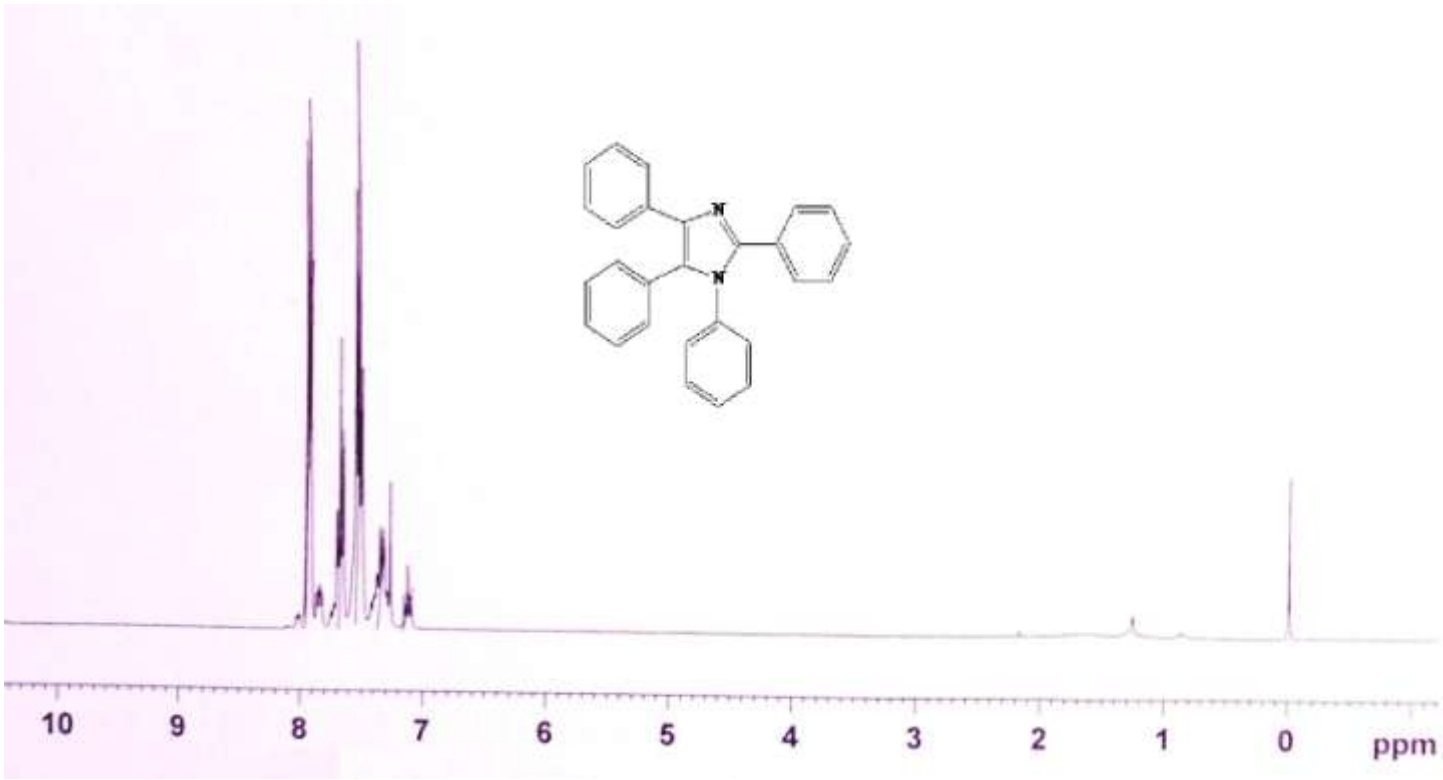

Figure-1b
NMR spectra of 1,2,4,5-tetraphenylimidazole

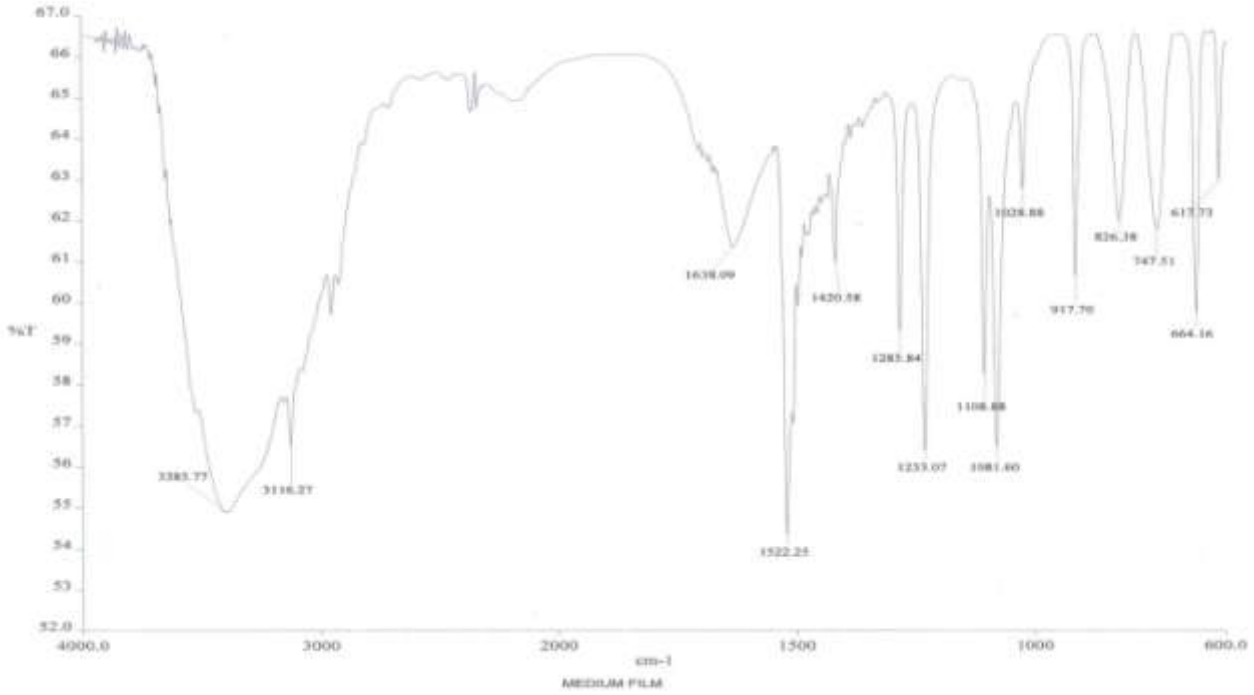

Figure - 2a
IR spectra of 2, 4, 5-triphenyl *1H*- imidazole

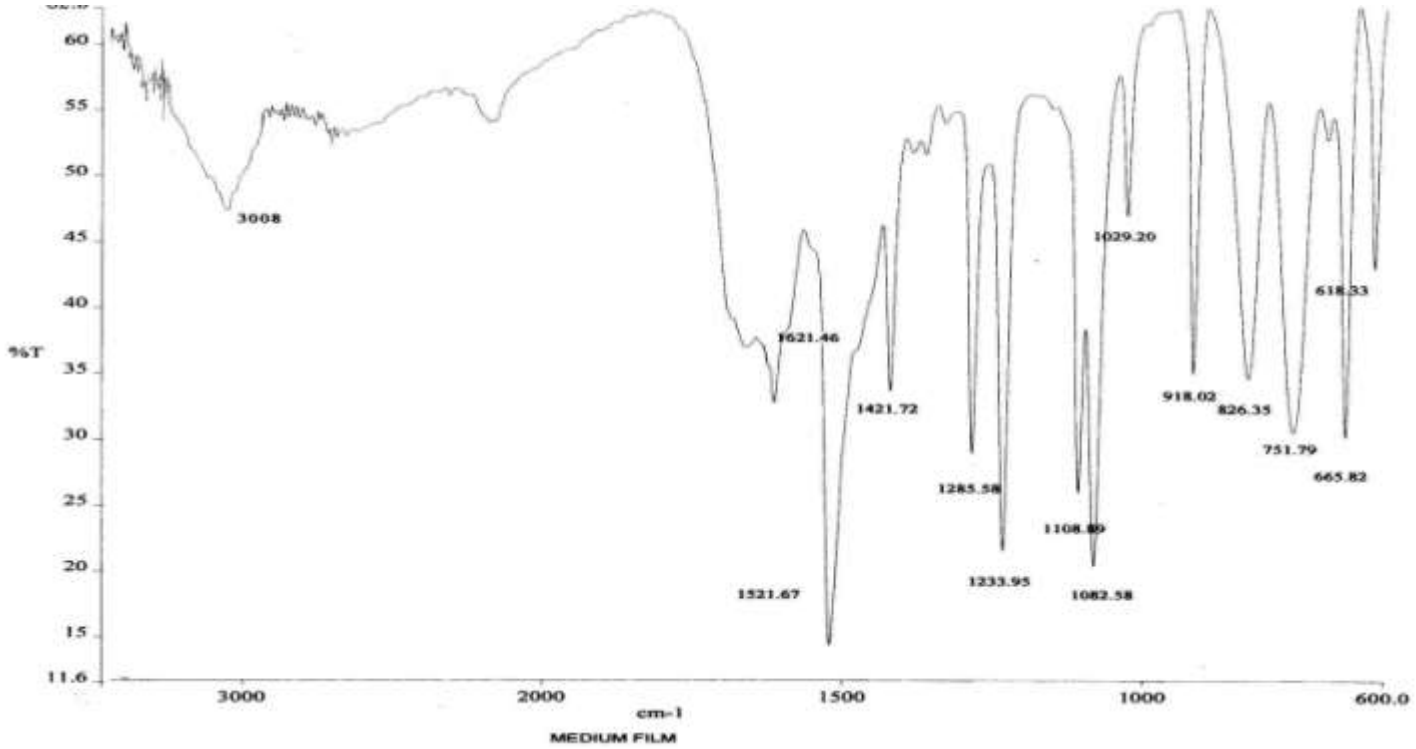

Figure-2b
IR spectra of 1,2,4,5-tetraphenylimidazole