IJPSR (2023), Volume 14, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 14 May 2022; received in revised form, 28 June 2022; accepted, 29 July 2022; published 01 January 2023

A SIMPLE, EFFICIENT AND GREEN PROCEDURE FOR THE SYNTHESIS OF 2, 4, 5-TRISUBSTITUTED IMIDAZOLE DERIVATIVES USING NOVEL PEG-SOCl AS A CATALYST

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Keywords:

Multicomponent reaction, PEG-SOCl, Microwave, Green solvent, Imidazole derivatives

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ABSTRACT: A facile, highly efficient, simple, and convenient method for synthesizing 2, 4, 5-trisubstituted imidazole derivatives from the condensation of various substituted benzaldehyde, benzil, and ammonium acetate by using a catalytic amount of PEG-SOCl in the presence of water at room temperature or under microwave irradiation. PEG-SOCl is an effective heterogeneous catalyst and easy to separate. We have investigated that PEG-SOCl catalytic system was excellent recycled and reused three times without any loss of catalytic activity. PEG-SOCl act as a green catalyst, low-cost, non-volatile, non-hazardous, environmental friendly catalyst, and water is a green solvent reaction carried out at room temperature or under microwave radiation method shows greater advantages because it has contributed in the green chemistry aspects. The prepared catalyst was analyzed by analytical methods such as infrared spectrum (IR), X-Ray diffraction pattern (XRD), thermo-gravimetric analysis (TGA), and BET surface analysis. Spectroscopic techniques identified the synthesized pure product (1j), including infra-red (IR) spectrum, ^{1}H and ^{13}C NMR spectrum and Mass (LC-MS) spectrometry.

INTRODUCTION: Imidazole derivatives are important and famous heterocyclic compound which shows the general and key structure of features of a variety of medicinal Pharmaceutical and natural products. Essential and synthetic imidazole derivatives occupy the main place among pharmaceutically and medicinally important compounds due to their different interesting and widespread medicinal Pharmaceutical and biological activity such as anti-oxidant [1-2], anti-viral [3-4], anti-cancer [5-6], anti-inflammatory [7-8], anti-tuberculosis [9-10], anti-bacterial [11-12], antifungal [13-14], anti-diabetic [15-16], anti-microbial [17-18], anti-convulsant [19], cytotoxic [20-21], antiproliferative [22], anticandidal [23], antiamoebic [24] activity, *etc*.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(1).434-43

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.14(1).434-43

Imidazole and its derivatives involve one pot and the multicomponent reaction of substituted benzaldehyde, benzil, and ammonium acetate by using a PEG-SOCl as a green catalyst in aqueous media at room temperature or under microwave irradiation. The various synthetic methods have been developed for the synthesis of imidazole derivatives in the presence of different catalysts such as poly (4-vinylpyridine) supported $TiCl_4$ or [P_4-VP]-Ti(IV) [25], Amberlite IR 120H+ [26], Appel reagent (Ph_3P/CCl_4) [27], Sulfonic Acid Magnetic Graphene Oxide (Fe3O4@GO-Pr-SO_3H) [28], Fly Ash Supported Bi_2O_3–ZnO [29], Pyrrolidinium Hydrogen Sulfate (PHS) as the ionic liquid catalyst [30], Pd/AlO(OH) NPs [31], Urea/Hydrogen Peroxide (UHP) [32], Nano-Zirconia (nano ZrO_2) [33], Silver nanoparticles [34], Copper Oxide nanoparticles [35] *etc*.

Green chemistry aims for alternative, environmentally friendly reaction media to increase reaction rates and lower reaction temperatures. Green chemistry principle that the method in chemical sciences that readily uses renewable raw

substances, removing waste and avoiding the use of toxic, volatile, and hazardous chemicals, reagents, catalysts, and solvents in the production, manufacture, and application of chemical products. PEG-SOCl was an effective heterogeneous catalyst; this catalyst has greater advantages due to being non-toxic, easy to handle, low cost, easy for separation, easy to work up, and environmentally benign catalyst. In the present work, we have described a highly efficient, convenient, and one-pot synthesis of 2, 4, 5-trisubstituted imidazole derivatives for the condensation of benzil, ammonium acetate, and substituted benzaldehyde by using PEG-SOCl as a green catalyst in the presence of water at room temperature or under microwave radiation method.

MATERIAL AND METHOD: All chemicals used were of analytical reagent (AR) grade purchased from the commercial distributor and used without further purification melting point of the synthesized product was recorded in open capillaries tube and uncorrected. All synthetic experiments under microwave irradiation were carried out in a microwave synthesis system has a maximum power of 700W. The reaction clarity and progress were monitored by thin layer chromatography (TLC) using Silica gel coated aluminium sheets, and the constituents were visualized under a UV chamber.

General Procedure:

Preparation of the PEG-SOCl Catalyst: To a mixture of poly (ethylene glycol) (PEG-6000) (1 mmol) in 15 mL of dichloromethane was added in 10 mmol of Thionyl chloride at cold temperature (0-8 °C).the resultant solution was mechanically stirred for 12 h. The mixture was filtered and washed with 25 mL of diethyl ether, and the product was dried at room temperature to give a pure white colored as a PEG-SOCl formed.

For the synthesis of 2, 4, 5-trisubstituted Imidazole Derivatives:

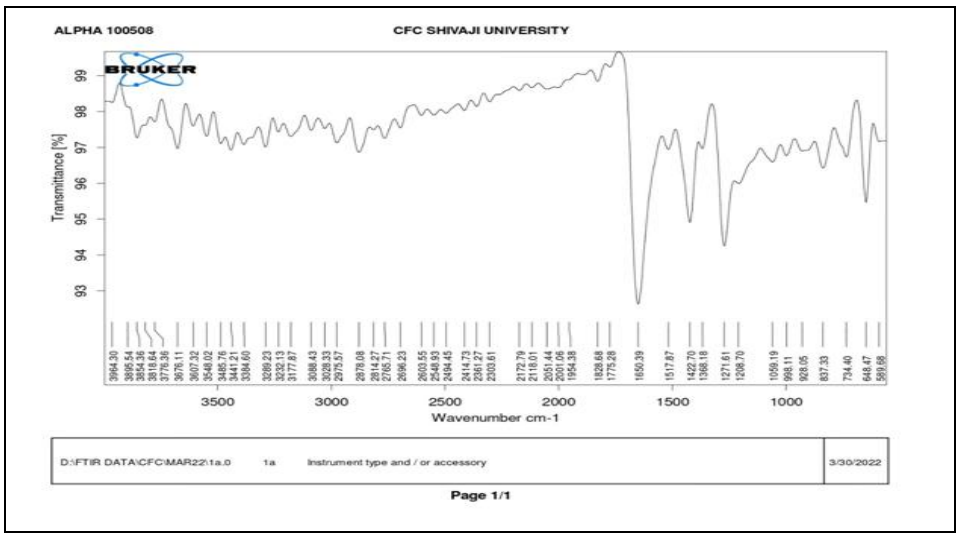
For Conventional Method: In a three naked RBF, a mixture of benzil (1 mole), ammonium acetate (3 mole), and various substituted benzaldehyde (1 mmol) by using a catalytic amount of PEG-SOCl (0.2g) was added to the presence of aqueous media, and the mixture was stirred at room temperature for the appropriate time. The progress of the reaction was monitored by TLC silica gel pre-coated aluminium sheet in a solvent (Ethyl acetate: n-Hexane, 4:1). After completion of the reaction, ethyl acetate was added to the reaction mixture, and the catalyst was separated by filtration and evaporated under reduced pressure to form a product. The crude solid product was purified and recrystallized from ethanol.

For Microwave Irradiation Method: In a three naked RBF, benzil (1 mmol), ammonium acetate (3 mmol), substituted benzaldehyde (1 mmol), were mixed properly, then a catalytic amount of PEG-SOCl (0.2 g) was added, and the reaction mixture was irradiated in the microwave oven 210 W for a definite time after next, the procedure is similar to the conventional method.

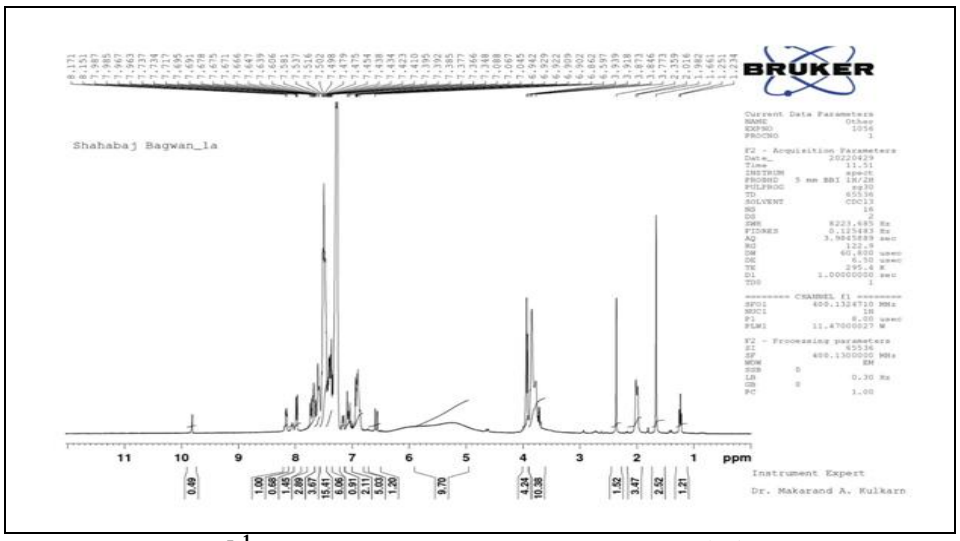
Spectral Data: 1j) 2-(4-hydroxy-3-methoxy)-4, 5-diphenyl imidazole (1j). White Solid, M. P. 222-224 $^{\circ}$C FT-IR (KBr, cm^{-1}):- 3676.11, 2878.08, 1650.39, 1422.70, 1271.61, 837.33, 734.40, 648.47. ^{1}H-NMR (400MHz, $CDCl_3$):- δH 7.434-7.666 (m, 10H, Ar-H), δH 7.088-6.902 (dd, 2H, ArH), δH 6.597 (s, 1H, OH), δH 3.939 (s, 3H, OCH_3). C^{13}-NMR ($CDCl_3$):- δC 147.02-143.26, δC 134.78-132.18, δC 129.90-126.44, δC 78-75, δC 56.24. (+)ESI-HRMS *m/z*: calculated for [$C_{22}H_{18}N_2O_2$+ H^+] 342.0, observed for [$C_{22}H_{18}N_2O_2 + H^+$] 343.0.

RESULTS AND DISCUSSION: At the present report were carried out by a simple and efficient synthesis of 2, 4, 5-tri substituted imidazole derivatives from the reaction of various substituted benzaldehyde, benzil, and ammonium acetate by using PEG-SOCl acts as a green catalyst in aqueous media at room temperature in convenient method or under microwave irradiation method the synthesis of 2,4,5-trisubstituted imidazole derivatives in different solvents or solvent free conditions by using PEG-SOCl catalyst in conventional method. It was investigated that the reaction condition in excellent yield of product in aqueous medium from **Table 1** to obtain the optimized the reaction condition. The reaction route was carried out with the different amount of PEG-SOCl catalyst (0.05 g to 0.4 g) for the synthesis of 2, 4, 5-trisubstituted imidazole derivatives. The product yield increased especially from 22% to 96%; after increasing the concentration amount of catalyst, the synthesis of

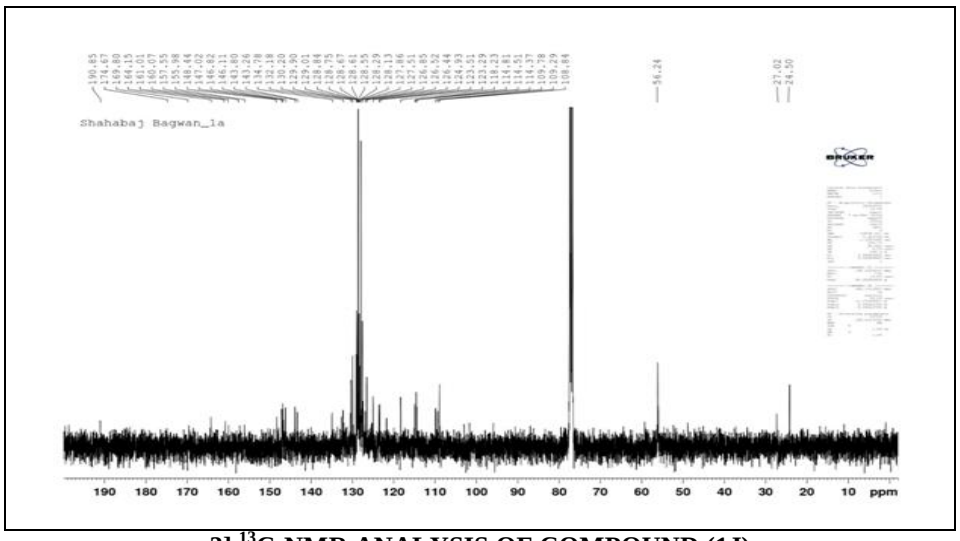
2. 4, 5-trisubstituted imidazole derivatives was optimum catalyzed by 0.2 g of PEG-SOCl in aqueous media for both conventional method and microwave irradiation method.



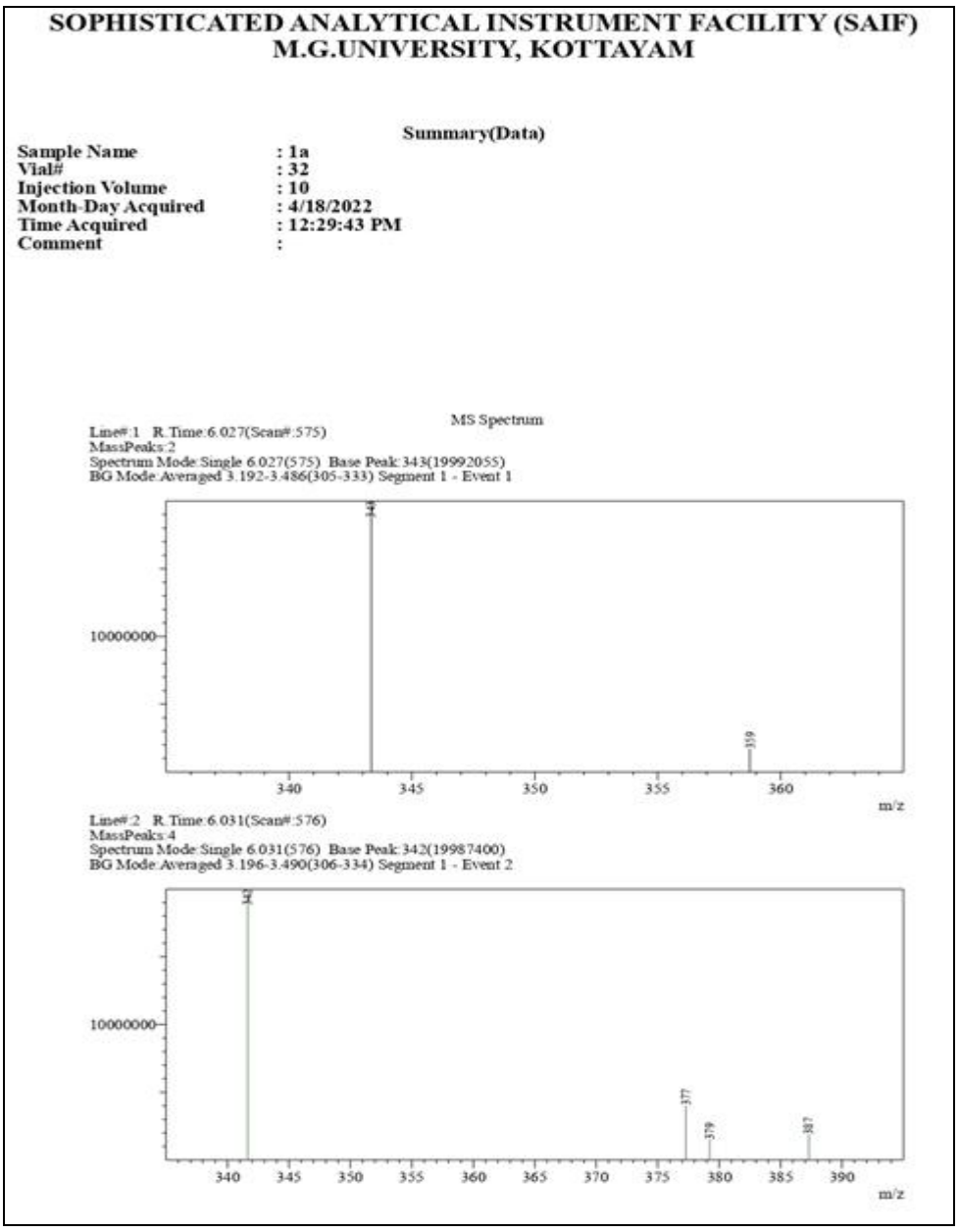
1] FT-IR ANALYSIS OF COMPOUND (1J)



2] ^{1}H-NMR ANALYSIS OF COMPOUND (1J)



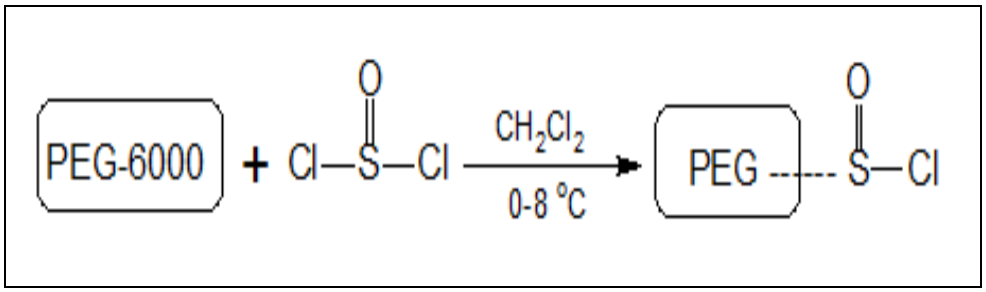
3] ^{13}C-NMR ANALYSIS OF COMPOUND (1J)



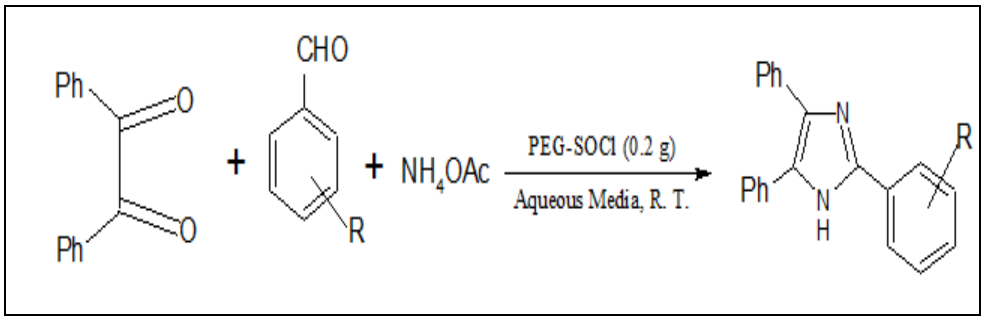
4] MASS ANALYSIS OF COMPOUND (1J)

Further, we also changed or increased the temperature but the amount of catalyst of PEG-SOCl (0.2 g) was sufficient to increase the amount of yield of product from **Table 2.** To establish most efficient and green method for the synthesis of 2,4,5-trisubstituted imidazole derivatives for the reaction of various benzaldehyde, benzil and ammonium acetate for conventional method in good to excellent yield of product (92% to 96%) in less reaction time (20 min) and for microwave irradiation method in excellent yield of product (96%) in minimum reaction time (2 min) from **Table 3**. For earlier reaction methods give up to good to high yield of product and adopted a wide range of substituted benzaldehyde for the tendency of the electron donating and electron withdrawing for substituents. The reactivity of different aromatic aldehydes was affected by their natural character and the position of the substituents on the aromatic aldehydes ring system. The aromatic aldehyde compound containing electron-withdrawing substituents was highly reactive. It showed an excellent yield of the product with a short reaction time. In contrast, the aromatic aldehyde compound containing electron-donating substituents was less reactive and showed lower yield of product with a longer reaction time from **Table 3.** In all examinations, the crude product was isolated by simple filtration, washed with water, and crystallized by ethanol. Compared with other

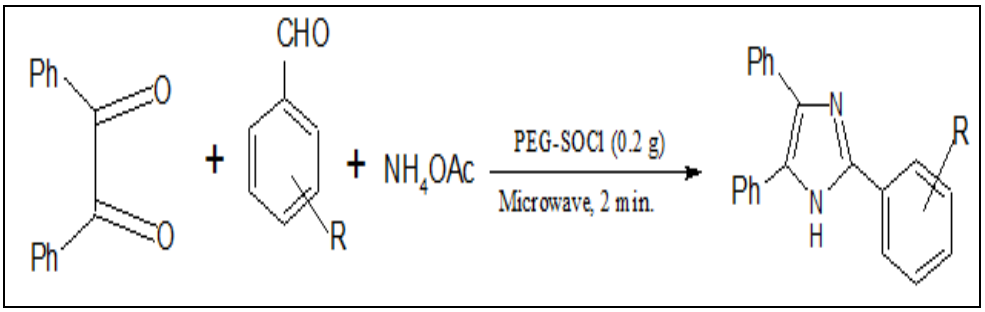
catalysts for synthesizing 2,4,5-trisubstituted imidazole derivatives for the reaction of various benzaldehyde, benzil, and ammonium acetate in the presence of PEG-SOCl as a catalyst, PEG-SOCl showed much excellent catalytic activity in terms of very less reaction time and mild reaction condition from **Table 4.**



SCHEME 1: PREPARATION OF PEG-SOCL



SCHEME 2: FOR CONVENTIONAL METHOD



SCHEME 3: FOR THE MICROWAVE IRRADIATION METHOD

TABLE 1: OPTIMIZED CONDITIONS FOR SYNTHESIS OF 2,4,5-TRISUBSTITUTED IMIDAZOLE BY THE CONVENTIONAL METHOD

S. no.	Amount of catalyst (g)	Solvents	Temp(°C)	Time (Min)	Yield
1	0.1	Ethanol	R.T.	60	46 %
2	0.1	Methanol	R.T.	60	47%
3	0.1	Acetonitrile	R.T.	60	39 %
4	0.1	Chloroform	R.T.	60	42%
5	0.1	Ethyl acetate	R.T.	60	39 %
6	0.1	THF	R.T.	60	36%
7	0.1	Dichloromethane	R.T.	60	40%
8	0.1	Acetone	R.T.	60	45%
9	0.1	Water	R.T.	60	55 %
10	0.2	Water	R.T.	20	96%
11	0.05	Water	R.T.	60	22%
12	0.15	Water	R.T.	40	72%
13	0.3	Water	R.T.	60	96%
14	0.4	Water	R.T.	60	96 %
15	0.2	Water	60	60	96 %
16	0.2	Water	80	60	96 %
17	0.2	Water	100	60	96 %

TABLE 2: OPTIMIZATION OF CATALYST FOR SYNTHESIS OF 2, 4, 5-TRISUBSTITUTED IMIDAZOLE DERIVATIVES BY MICROWAVE IRRADIATION

S. no.	Amount of catalyst (g)	Power of Microwave Irradiation (%)	% Yield
1	----	40	18 %
2	0.05	40	26 %
3	0.1	40	56 %
4	0.15	40	73 %
5	0.2	40	96 %
6	0.2	20	55 %
7	0.3	40	96 %
8	0.4	40	96 %
9	0.2	60	96 %
10	0.2	80	96 %
11	0.2	100	96 %

TABLE 3: SYNTHESIS OF 2, 4, 5-TRISUBSTITUTED IMIDAZOLE DERIVATIVES BY PEG-SOCL CATALYZED REACTION OF BENZIL, AMMONIUM ACETATE WITH SUBSTITUTED BENZALDEHYDE UNDER MICROWAVE IRRADIATION AND CONVENTIONAL CONDITIONS METHOD

Entry	R	Product	Conventional Method		Microwave Method		M.P.
			Time (Min)	Yield (%)	Tim (Min)	Yield (%)	
1a	H	2, 4, 5-triphenyl imidazole	20	96	2	96	271-272°C
1b	4-Cl	2-(4-Chlorophenyl)- 4, 5-diphenyl imidazole	20	96	2	96	257-259°C
1c	4-OH	2-(4-Hydroxyphenyl)- 4, 5-diphenyl imidazole	20	96	2	96	233-234°C
1d	4-NO_2	2-(4-Nitrophenyl)- 4, 5-diphenyl imidazole	20	96	2	96	200-202°C
1e	2-Cl	2-(2-Chlorophenyl)- 4, 5-diphenyl imidazole	20	96	2	96	194-196°C
1f	3-NO_2	2-(3-Nitrophenyl)- 4, 5-diphenyl imidazole	20	96	2	96	297-298°C
1g	2-OH	2-(2-Hydroxyphenyl)- 4, 5-diphenyl imidazole	20	96	2	96	208-209°C
1h	4-OCH_3	2-(4-Methoxyphenyl)- 4, 5-diphenyl imidazole	20	95	2	95	228-230°C
1i	Furfural	2-(Furfural-2-yl)- 4, 5-diphenyl imidazole	20	96	2	96	200-202°C
1j	Vanillin	2-(4-hydroxy-3-methoxy)- 4, 5-diphenyl imidazole	20	95	2	95	222-224°C

TABLE 4: COMPARISON OF PEG-SOCLCATALYST WITH OTHER CATALYSTS FOR THE SYNTHESIS OF 2, 4, 5-TRISUBSTITUTED IMIDAZOLE DERIVATIVES

S. no.	Catalyst used [Ref]	Amount of catalyst	Temp. (°C)	Time (Min)	Yield (%)
1	$SbCl_3/SiO_2$[36]	0. 1 g	120	15	94
2	HNO_3/MeCN[37]	1.0 equiv	70	5	89
3	CAN/HNO_3[38]	0.05/0.4 mol	70	25	82
4	HMDS/ TMSOTf[39]	5.0/0.1 equiv	150	30	93
5	N-heterocyclic carbine (NHC)[40]	10 % Mol	350 W	5	91
6	Non-chloroaluminate Ionic Liquids[41]	2 mL	150	4	91
7	p-TSA[42]	15% mol	500 W	50	74
8	PEG-SOCl [Present Work]	0.2 g	50 (MW)	2	96

Reusability of a PEG-SOCl Catalyst: The reusability of a catalyst is one of the most important advantages of chemical reactions. The catalyst was investigated by reused during three consecutive runs without any activity loss. It can be observed that the yield of product in second, third uses were almost same as that of first consecutive run. The reaction route is quite eco-friendly because no solvent is used in this method. It was seen that the use of the microwave irradiation method has a great effect on the speed-up of the reaction rates providing excellent yields of products in a shorter reaction time. Compared with the microwave irradiation method, the convenient route

shows that the study reaction rate, the lower yields of expected product with longer a reaction time.

Characterization of PEG-SOCl Catalyst:

Infra-Red Spectral Analysis of the catalyst: Infra-red (IR) spectral analysis of the prepared catalyst is shown in **Fig. 1**.

It can be observed that there are three significant absorption peaks in the spectrum of PEG-SOCl catalyst.

The sharp absorption bands as about 1504.04 cm^{-1}, 1022.77 $cm^{-1,}$ and 687.51 cm^{-1}corresponding to S=O, S-O, and S-Cl stretching vibrations.

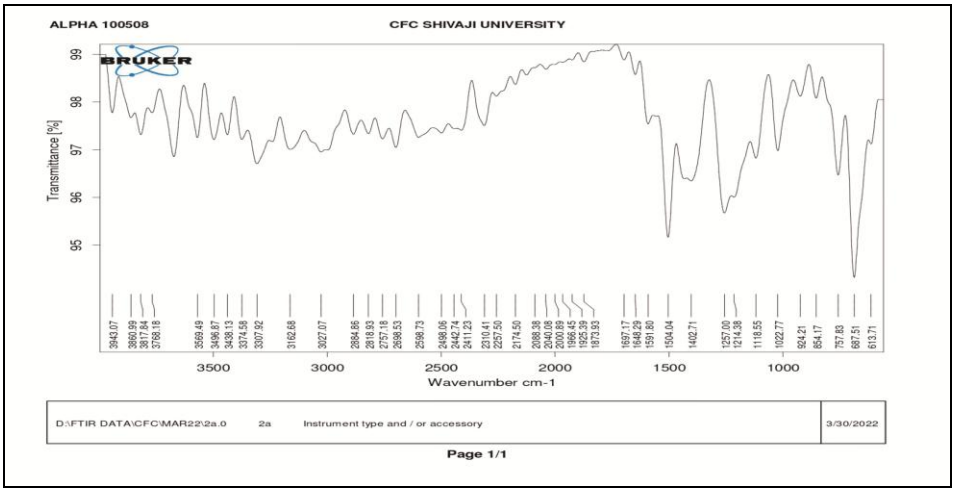


FIG. 1: INFRA-RED (IR) ANALYSIS OF THE PREPARED CATALYST

X-Ray Diffraction Pattern Studies of the Catalyst: The prepared catalyst was further characterized by X-Ray Diffraction. The XRD pattern of synthesized PEG-SOCl as shown in **Fig. 2**. The sharp peaks is observed at 2θ = 11.58°, 23.96° and 29.80° are assigned to (011), (022), and (023) lattice planes respectively. The X-ray Diffraction pattern studies of prepared catalyst is crystalline and triclinic structure.

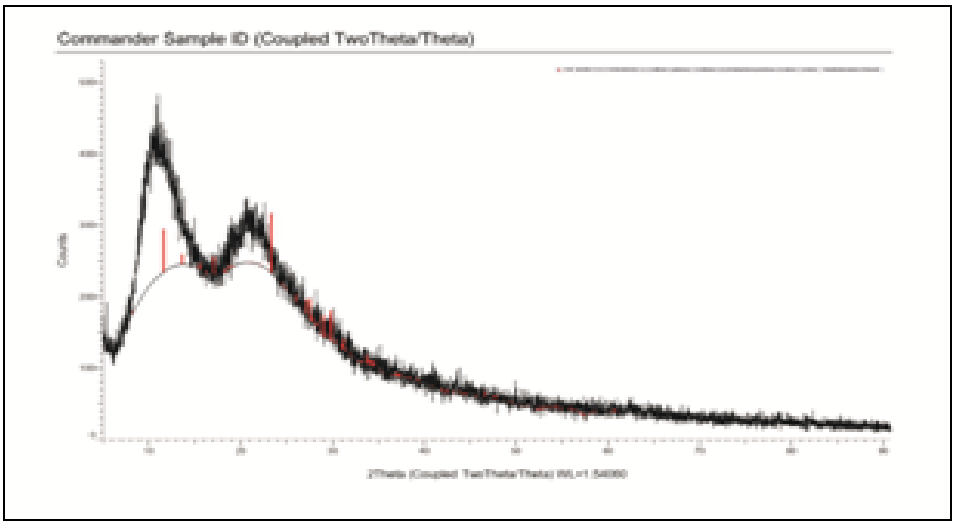


FIG. 2: XRD PATTERN STUDIES OF THE PREPARED CATALYST

TGA Analysis of the Catalyst: Thermo-gravimetric (TG) analysis was the most commonly used thermal analytical method to characterize crystalline and amorphous organic, inorganic and pharmaceutical compounds. The thermogravimetric (TG) was used to examine the thermal stability of prepared compounds.

The thermal stability of the prepared catalyst was characterized by thermogravimetric analysis (TGA) are, shown in **Fig. 3**. The TGA thermogram of the catalyst shows initial stage weight loss at 110° C. the final stage involves the decomposition of the catalyst, which begins after 110° C and continues up to 650° C.

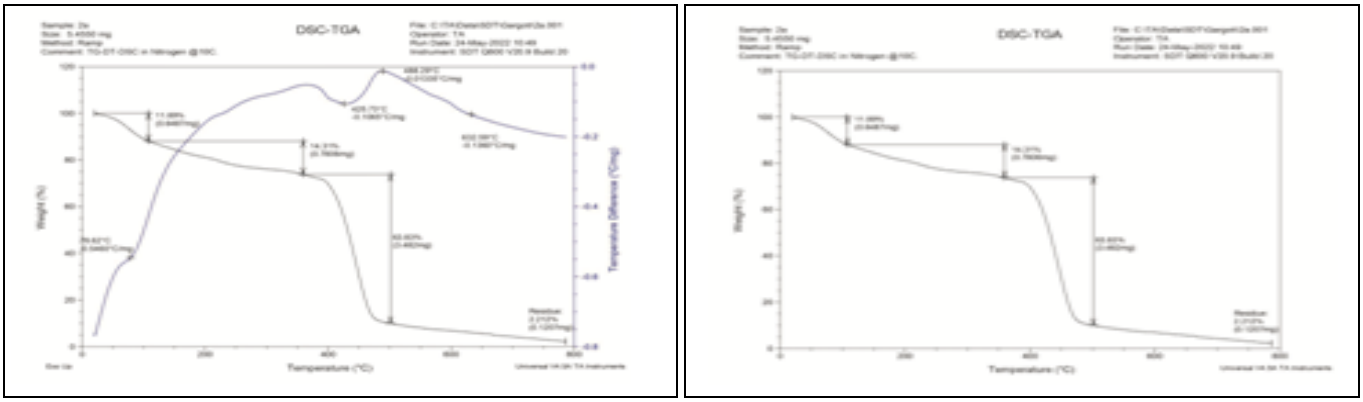


FIG. 3: TGA THERMOGRAM OF THE PREPARED CATALYST

BET Analysis of the Catalyst: BET surface area analyzers were used to determine a solid's total surface area by suspending a powdered analysis in an inert gaseous bath and measuring the adsorption of gas molecules to the surface and its porous structures. The PEG-SOCl catalyst was further investigated by BET or N2adsorption-desorption analysis, shown in fig 4. The BET surface area of the catalyst data shows that the estimated surface area is 129.774 m^2 g^{-1} and 287.72 m^2 $g^{-1,}$ respectively. These figure values were indicated by complete monolayer adsorption coverage and highly non-porous structure bearing mesopores and macropores, respectively.

TABLE 5: BET SURFACE AREA RESULTS OF THE CATALYST

S. no.	Catalyst	BET Surface Area [m2/g]	Pore Volume [cc/g]	Pore Size [nm]
1	PEG-SOCl	287.72	2.663	374.3

TABLE 6: SUMMARY OF BET ANALYSIS OF THE CATALYST

S. no.	Summary of BET analysis	
1	Slope	7.516
2	Intercept	4.588e+00
3	Correlation Coefficient (r)	0.998421
4	C-Constant	2.638
5	Surface Area	287.72 m^2/g

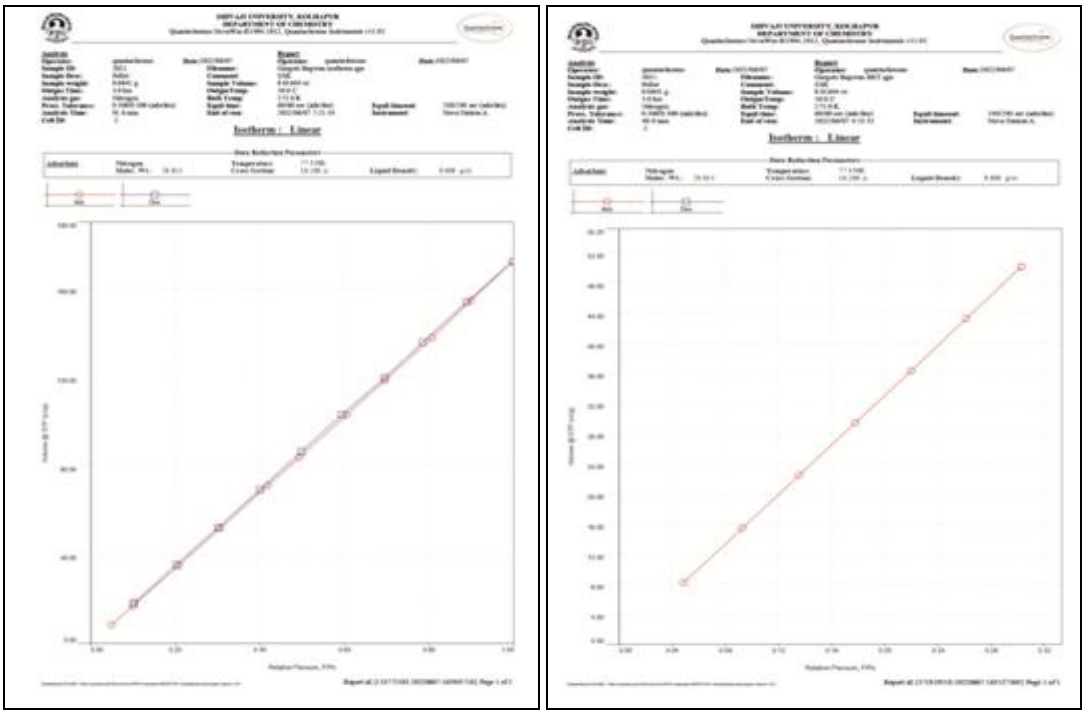


FIG. 4: BET SURFACE ANALYSIS OF THE PREPARED CATALYST

CONCLUSION: In summary, a highly efficient and green catalyst PEG-SOCl was developed to synthesize 2,4,5-trisubstituted imidazole derivatives via the reaction of benzil, ammonium acetate, and various substituted benzaldehyde in the presence of water for both conventional and microwave irradiation method. PEG-SOCl catalysts can indicate an excellent yield of product, reusability, inexpensive, non-toxic, easy for separation, and green catalyst. It was found that the microwave irradiation method is an excellent method as compared to the conventional method. The remarkable feature of the present procedure is the fast rate of reaction, high product yield, cost-efficient, mild reaction condition, environmentally friendly, and green synthetic protocol.

ACKNOWLEDGEMENT: The corresponding author is thankful to the UGC-Maulana Azad National Fellowship (MANF-2018-2019-MAH-96698) in New Delhi, India, for providing financial support. We also acknowledged Dr. Arif Pathan, Director, Maulana Azad College, Aurangabad, for constant support and encouragement.

CONFLICTS OF INTEREST: All the authors declare no conflict of interest in this research article.

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How to cite this article:
Bagwan SM, Quazi S, Farooqui M and Asif M: A simple, efficient and green procedure for the synthesis of 2, 4, 5-trisubstituted imidazole derivatives using novel peg-socl as a catalyst. Int J Pharm Sci & Res 2023; 14(1): 434-43. doi: 10.13040/IJPSR.0975-8232.14(1).434-43.