Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Special Issue [1]2022 : 1555-1562
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Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
ORIGINAL ARTICLE **OPEN ACCESS**

Ultrasound Assisted One-Pot Green Synthesis of Highly Substituted Pyrazoles Catalyzed by [DBUH][OAc] Ionic Liquid

Sanket R. Rathod[1,2], **Rahul A. Waghmare**[2], **Shantilal D. Rathod**[2*]
[1]Department of Chemistry, Balwant college, Vita, Dist Sangli-415311, Maharashtra, India
[2]Department of Chemistry, Milind College of Science, Nagsenvana, Aurangabad-431002, Maharashtra, India
***Corresponding Author:**:sdr_rathod@yahoo.in

ABSTRACT

A significant, one-pot synthesis of highly substituted pyrazoles derivativevia three-component condensations of Aromatic aldehyde, Malononitrile, along with Phenylhydrazine in the presence of ionic liquid [DBUH][OAc]. The present technique provides significant advantages, including reduced environmental impact, simple procedure, shorter reaction time, mild condition, and ease of product recovery. The ionic liquid reusability and recovery make the protocol eco-friendly. Also, a series for 5-amino-1,3-diphenylpyrazole-4-carbonitrile analogues were synthesised. For the comparison between conventional and ultrasound techniques. It was observed that the ultrasound irradiation technique gave excellent yield and shorter reaction time than the conventional technique.

Keywords: *pyrazole, multicomponent reaction, ionic liquid, [DBUH][OAc], ultrasound irradiation.*

Received 14.03.2022 Revised 26.03.2022 Accepted 29.04.2022

INTRODUCTION

In pharmaceutical research, five-membered N-linked heterocyclic molecules have attracted much interest. For synthesizing five-membered heterocyclic compounds, the condensation reaction suitable sequential compound is the most popular alternative approach [1-4]. Pyrazole ring is a prominent motif which among the provide reported as having outstanding pharmacological and biological activity such as antimicrobial [5], antiviral [6], anti-inflammatory [7], anticonvulsant [8], anti-depressant [9], antitumor [10], as well as fungicidal properties [11,12]. Several pyrazole derivatives exhibit significant pharmacological properties and are valuable materials in pharmaceutical research. Some of the pyrazole-containing drugs like Antipyrine, Celecoxib, Mepirizole, Rimonabant, Lonazolac, and Tepoxalin, etc. The structure of drugs has been shown in Figure 1[13-18].

Multicomponent reactions (MCRs) is the preferable approach because it allows for high throughput chemical synthesis at a low cost and in a shorter reaction time. Because it generates significant compounds in a single step by forming multiple new bonds in a one-opt, the approach has prompted a lot of interest in organic chemistry. In both drug discovery and green chemistry [19,20]. in the last decade, the growth of three and four-component reaction has been considerable and there is still a lot of effort being put into developing new MCRs [21,22].In currentcenturies, ionic liquids (ILs) have obtained a noteworthy attention in the context of eco-friendly green synthesis since they can also be used as effective media for organic synthesis [23-25]. Non-volatility, non-explosive, low vapour pressure, reusable, easily operated, as well as thermally stable over a wide temperature range are only several of the physicochemical features of ILs. Due to their specific ionic character and structural organization, ionic liquids can be regarded as alternative greener solvents [26,27]. In organic synthesis, there are numerous reports about the application of ILs such as Biginelli reaction [28], Friedel-Crafts reaction [29], Beckmann rearrangement [30], Diels-Alder reaction [31], Heck reaction [32], Pechmann condensation [33], and more reactions [34-38].Recently, the technique of synthesizing organic molecules using ultrasound irradiation is very effective and attractive. Ultrasound irradiation is used to increase the rate of a chemical reaction by ultrasonic cavitation mechanism, mass transfer in the microenvironment can be accelerated, which is the formation of microbubbles, growth, and impulsive collapse. High temperature and pressure are generated by collapsing bubbles, resulting in hot spots with enough energy to promote chemical reactions [39-43]. This method is considered in terms of conserving energy, reducing reaction time, improving yield and waste minimization [44,45]. In the current work, effective implementation of

[DBUH][OAc] ionic liquid and ultrasound has been established for synthesis of highly substituted pyrazoles [Scheme 1]. Use of the catalyst [DBUH][OAc] is associated with ultrasound irradiation technique for the synthesis substituted pyrazoles is investigated for first time. A comparative study by conventional as well as ultrasonication technique.

MATERIALS AND METHODS

Analytical grade of all chemicals and were purchased from a commercial source. Merck 60 F250 TLC analytical silica gel plat is used to monitor reaction progress and purity of compounds. Bondelin sonorex (frequency of 40 MHz and 100W) was used to ultrasound bath. Using of Avance-II(Bruker) instrument for ^{1}H-NMR and ^{13}C-NMR their frequency 400MHz and 100 MHz, recorded in Dimethyl sulfoxide-d6. RZX (Perkin Elmer) spectrometer using KBr, IR spectra were recorded. The melting points were determined by using the open capillary tube is uncorrected.

General procedure for the preparation of I.L.[DBUH][OAc]

In a round bottom flask add acetic acid (1 eq.) was added over a time span of 5 min. to DBU (1 eq.) In an ice bath under ultrasound at 5°C. At normal temperature, the reaction mixture was irradiated with ultrasound for an increased 30 minutes. As result, the lightyellow viscous liquid of [DBUH][OAc] was obtained.

General experimental procedure for the synthesis of 5-amino-1,3-diphenylpyrazole-4-carbonitrile 4(a-j)

Conventional Method

A mixture of Aromatic aldehydes (**1a-j**, 1mmol), Malononitrile (**2,** 1mmol), along with Phenylhydrazine (**3,** 1mmol), and 20 mol % [DBUH]OAc] in 5 mL ethanol was placed In a round bottom flask. At 80 °C, the mixture was heated. TLC (eluent: pet ether/ethyl acetate, 7:3)by using the progress of a reaction. After that, the reaction was completed and the reaction mixture was cooled to normal temp. and poured over ice-cold water and the product obtained was isolated by filtration. The obtained product was crystallized in ethanol to get pure products. The catalyst [DBUH] [OAc] is recovered from the water below reduced pressure and reused. All the products are confirmed by melting point and compared with the literature **[Scheme 1]**.

Ultrasound method

A mixture of Aromatic aldehydes (**1a-j**, 1mmol), Malononitrile (**2,** 1mmol), along with Phenylhydrazine (**3,** 1mmol), and 20 mol % [DBUH]OAc] in 5 mL ethanol was placed In a round bottom flask. At 50 °C, the mixture was irradiated with ultrasound. TLC (eluent: pet ether/ethyl acetate, 7:3) by using the progress of a reaction. After that, the reaction mixture was cooled to normal temp. and poured over ice-cold water and the solid product obtained was isolated by filtration. The obtained products were crystallized in ethanol to get pure products. The catalyst [DBUH] [OAc] is recovered from the water below reduced pressure and reused. All the products are confirmed by melting point and compared with the literature **[Scheme 1]**.

Spectral data of synthesized compounds

5-amino-3-(4-chlorophenyl)-1-phenylpyrazole-4-carbonitrile(4d): chrome yellow crystal. melting point 127-130°C. yield 95%.^{1}H-NMR (DMSO-d6, 400MHz) δ 7.5 (J=5.65Hz, d, 2H), 7.46 (J=6.6Hz, t, 2H), 7.32 (t, 1H), 7.42 (J=4.5Hz, d, 2H), 7.43 (J=5.31Hz, d, 2H), 5.40 (s, 2H). ^{13}C NMR (DMSO-d6, 100MHz) δ 158.80, 148.87, 139.62, 135.11, 133.83, 130.12, 129.93; 129.83, 129.41, 129.12, 128.39, 126.69, 126.3, 118.92, 117.98, 96.05. M.S. (m/z) (M$^+$) Calculated $C_{16}H_{11}ClN_4$ (294.0676 and (M+2)$^+$ 296.0682, found 294.0678. & 296.0685).

5-amino-3-(4-methoxyphenyl)-1-phenylpyrazole-4-carbonitrile(4e): light-yellow crystal. melting point. 107-109°C. yield 96%. ^{1}H-NMR (DMSO-d6, 400MHz) δ 7.24 (t, 1H), 7.37 (J=3.33 Hz, t, 2H), 7.54 (J=3.11 Hz, t, 2H), 7.45 (J=5.11 Hz, d, 2H), 6.89 (J=2.13 Hz, d, 2H) 4.58 (s, 2H), 3.77 (s, 3H). ^{13}C-NMR (DMSO-d6, 100MHz) δ 160.10, 148.55, 139.69, 132.16, 129.19, 128.45, 124.98, 124.32, 121.89, 121.46, 121.01, 118.96, 117.91, 114.69, 113.80, 94.79, 56.24. M.S. (m/z) Calculated $C_{17}H_{14}N_4O$ ((M$^+$) 290.0653, found 290.0650).

5-amino-3-(4-bromophenyl)-1-phenylpyrazole-4-carbonitrile(4g): creamy-white crystal. melting point 165-167°C. yield 94%.^{1}H-NMR (DMSO-d6, 400MHz) δ 6.91 (t, 1H), 7.35 (J=2.15Hz, t, 2H), 7.77 (J=2.25Hz, t, 2H), 7.43 (J=3.35Hz, d, 2H), 7.48 (J=3.55Hz, d, 2H), 5.89 (s, 2H). ^{13}C-NMR (DMSO-d6, 100MHz) δ 158.23, 147.96, 138.01, 137.52, 134.99, 132.26, 129.91, 129.09, 128.76, 126.46, 123.29, 118.93, 118.12, 98.94. M.S. (m/z) Calculated $C_{16}H_{11}BrN_4$ ((M$^+$) 338.1021 and (M+2)$^+$ 340.1023, found 338.1020 and 340.1022).

5-amino-3-(4-hydroxyphenyl)-1-phenylpyrazole-4-carbonitrile(4h): Pale-yellow. melting point 175-177°C. yield 95%.^{1}H-NMR (DMSO-d6, 400MHz) δ 7.62 (J=4.35Hz, d, 2H), 7.43 (J=4.25Hz, t, 2H), 7.25 (t, 1H), 7.35 (J=6.1Hz, d, 2H), 6.75 (J=2.4Hz, d, 2H), 5.52 (s, 2H), 5.15 (s, 1H). ^{13}C-NMR (DMSO-d6, 100MHz, δ ppm): 165.65, 155.97, 147.98, 139.31, 138.26, 135.47, 130.05, 129.87. 129.49, 129.28, 128.36, 128.08, 128.01, 118.78, 118.09, 116.34, 96.92. M.S. (m/z) Calculated $C_{16}H_{12}N_4O$ ((M^+) 276.1016, found 276.1012).

1,8-diazabicyclo [5,4,0] undec-7-enium acetate [DBUH][OAc]: light-yellow viscous liquid, ^{1}H-NMR (DMSO-d6, 400MHz, δ) δ=3.53-3.22 (m, 6H), 2.53 (J = 3.16 Hz, d, 2H), 1.83 (J = 5.11 Hz, d, 2H), $1.85-1.75$ (m, 3H), $1.70-1.43$ (m, 7H). IR (potassium bromide), v_{max}/cm^{-1}, $2928-2856$, 1643, 1549, 1445, 1379, 1310, 1192, 1113, 1073, 911, 685. The spectral data is in according to literature [38,48].

RESULTS AND DISCUSSION

In view of the diverse pharmacological activity of substituted pyrazoles, we have planned to develop an eco-friendly synthetic protocol. Also, it was assumed worthwhile to investigate the catalytic role of [DBUH][OAc] for the synthesis of highly substituted pyrazole derivatives *via* a 3-component reaction involving Aromatic aldehydes (1a-j, 1mmol), Malononitrile (2, 1mmol), along with Phenylhydrazine (3, 1mmol) under the conventional and ultrasound technique [Scheme 1].

In order to optimize the reaction conditions and to obtain the finest catalytic activity of [DBUH][OAc], the reaction of benzaldehyde (1a, 1mmol), malononitrile (2, 1mmol), and phenylhydrazine (3, 1mmol) was used model reaction. The model reaction was initially performed in a variety of solvents, including H_2O, EtOH, MeOH, Acetone, and solvent free conditions, using the conventional method to study the efficiency of the catalyst (Table 1, entries 1-5). In this study, it was experiential that ethanol was preferred solvent with respect to reaction time and yield (Table 1, entry 3).To determine the suitable conc. of [DBUH][OAc], the model reaction was investigated at different concentrations such as 5, 10, 15, 20, and 25 mol%. The product was found in trace, 60, 70, 82, 85, and 85% yield, respectively (Table 2, entries 1-5). This indicates that 20 mol% of [DBUH][OAc] is sufficient to carry out the reaction efficiently (Table 2, entry 4). To demonstrate the result of ultrasound irradiation the same reaction was done under the ultrasound method. It was observed that in ultrasonic irradiations the reaction rate decreased and product yield was increased. Evidently, the sonochemical effect might be a key factor to the high efficiency for the synthesis of substituted pyrazoles derivative which was superior to conventional method with respect to yields, reaction times, easiness, and safeties. A comparative study by conventional as well as ultrasonication technique whereas the conventional condition observed that 4a compound gave 89% yield within 60 min. and ultrasound irradiation condition gave 97% yield within 35 min. In order to the extremely interesting scope of the reaction. We intended to apply our methodology to a wide range of aromatic aldehydes in presence of [DBUH][OAc] 20 mol% under the conventional and ultrasound methods. As expected, satisfactory results were obtained for both electron-donating ($-OCH_3$, -O,) as well as electron-withdrawing ($-NO_2$, -Cl, -Br,) groups (Table 3). We herein proposed a mechanism for condensation aromatic aldehyde (1a-j), malononitrile (2), and phenylhydrazine (3) in presence of [DBUH][OAc]. The reaction proceeds throughout condensations of aromatic aldehyde along with malononitrile by using Knoevenagel condensation (5), by adding phenylhydrazine the reaction carried out Michael addition (6), along with intramolecular cyclization, followed by air oxidation was converted into the final product (4a-j) [Scheme 2]. The reusability and recovery of the ILs [DBUH][OAc] significant advantage. For reason, we've chosen the model reaction Benzaldehyde (1a), Malononitrile (2), and Phenylhydrazine (3) in[DBUH][OAc] 20 mol% under conventional heating. After the completions reaction product was poured into ice-cold water and filtration of the product was isolated. Below the reduced pressure, the ILs was recovered for recycling at least 5 times. In terms of the product, the catalytic activity is decreasing (Figure 2). Recovered IR spectra of ionic liquid after 5th cycles we are equated with the 1st cycle. As confirmed shown in Figure 3. Recovered IR spectra of ionic liquid shown to be close to identical to the 1st cycle.

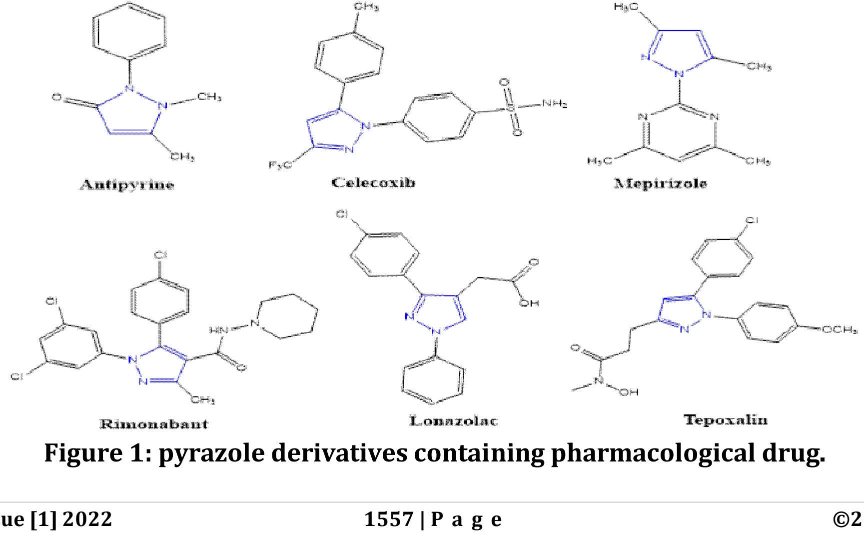
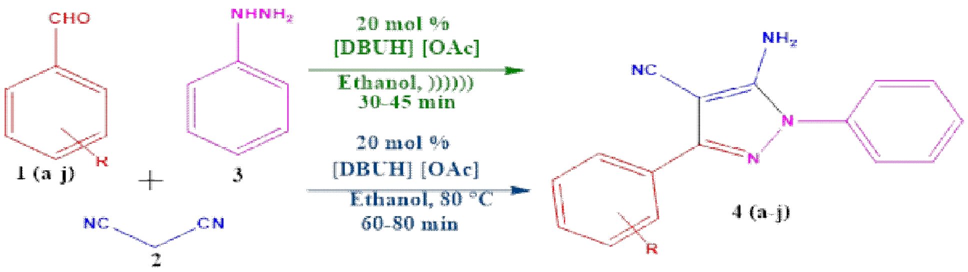


Figure 1: pyrazole derivatives containing pharmacological drug.



Scheme 1: synthesis of highly substituted pyrazoles with [DBUH][OAc] under the ultrasound and conventional methods.

Table 1: Screening of Solvents[a]

Entry	Solvents	Time(min.)	[b]Yield(%)
1	Solvent free	60	76
2	Water	60	70
3	**Ethanol**	**60**	**85**
4	Methanol	60	74
5	Acetone	60	75

[a]Reaction condition: Benzaldehyde (**1a,** 1mmol), Malononitrile (**2,** 1mmol), along with Phenylhydrazine (**3,** 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under conventional heating.[b]Isolated yields.

Table 2: Effect of Catalyst Concentration[a]

Entry	[DBUH][OAc] mol (%)	Time (min.)	Yield[b] (%)
1	5	150	60
2	10	120	70
3	15	90	82
4	**20**	**60**	**85**
5	25	60	85

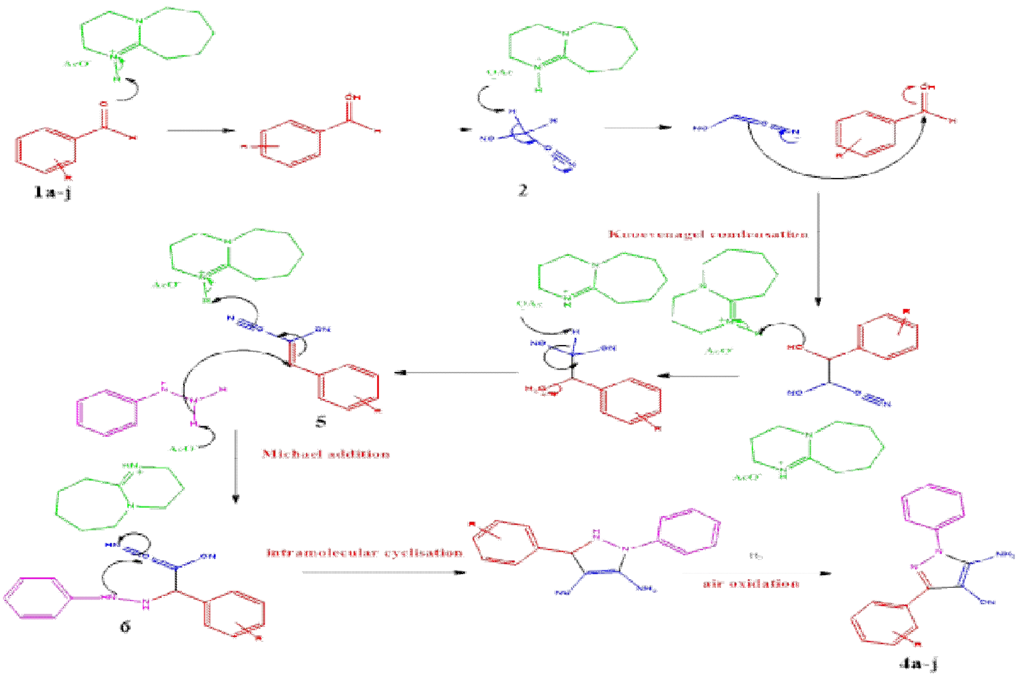
[a]Reaction condition: Benzaldehyde (**1a,** 1mmol), Malononitrile (**2,** 1mmol), along with Phenylhydrazine (**3,** 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under conventional heating.[b]Isolated yields.

Table 3. Synthesis of highly substituted pyrazoles in presence of [DBHU][OAc] 20 mol% under the Conventional and ultrasound methods. 4(a-j)

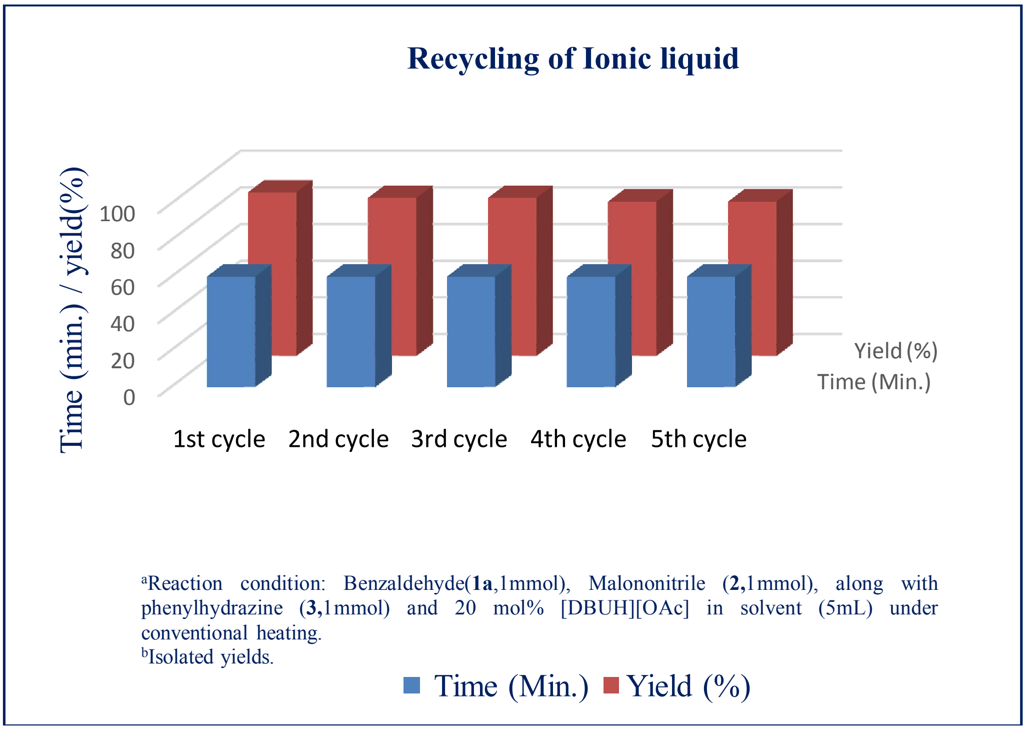
Entry	R	[a]Ultrasound Method		[a]Conventional Method		M.P. (°C)	
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)	Found	[c]Literature
4a	-H	35	97	60	89	158-160	159-161
4b	2-OH	38	94	60	87	159-162	160-162
4c	3,4-OCH_3	40	92	75	85	119-121	120–123
4d	4-Cl	35	95	50	87	127-130	128-130
4e	4-OCH_3	45	96	60	88	107-109	106-108
4f	4-NMe_2	40	93	60	85	156-158	157-159
4g	4-Br	35	94	60	88	165-167	164-166
4h	4-OH	35	95	60	86	207-209	208-210
4i	4-NO_2	45	92	60	85	163-165	164–165
4j	4-CH_3	38	94	60	88	115-117	117–118

[a]Reaction condition: Aromatic aldehydes (**1a-j,** 1mmol), Malononitrile (**2,** 1mmol), along with Phenylhydrazine (**3,** 1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under ultrasound method and conventional method. [b]Isolated yields.

[c]All the product was confirmed by melting point and compared with the literature **[46,47,49]**



Scheme 2: Propose a mechanism for highly substituted pyrazoles by using[DBUH][OAc] ionic liquid.



ᵃReaction condition: Benzaldehyde(**1a**,1mmol), Malononitrile (**2**,1mmol), along with phenylhydrazine (**3**,1mmol) and 20 mol% [DBUH][OAc] in solvent (5mL) under conventional heating.
ᵇIsolated yields.

Figure 2:Reuse of[DBUH] [OAc]for synthesized compound (4a).

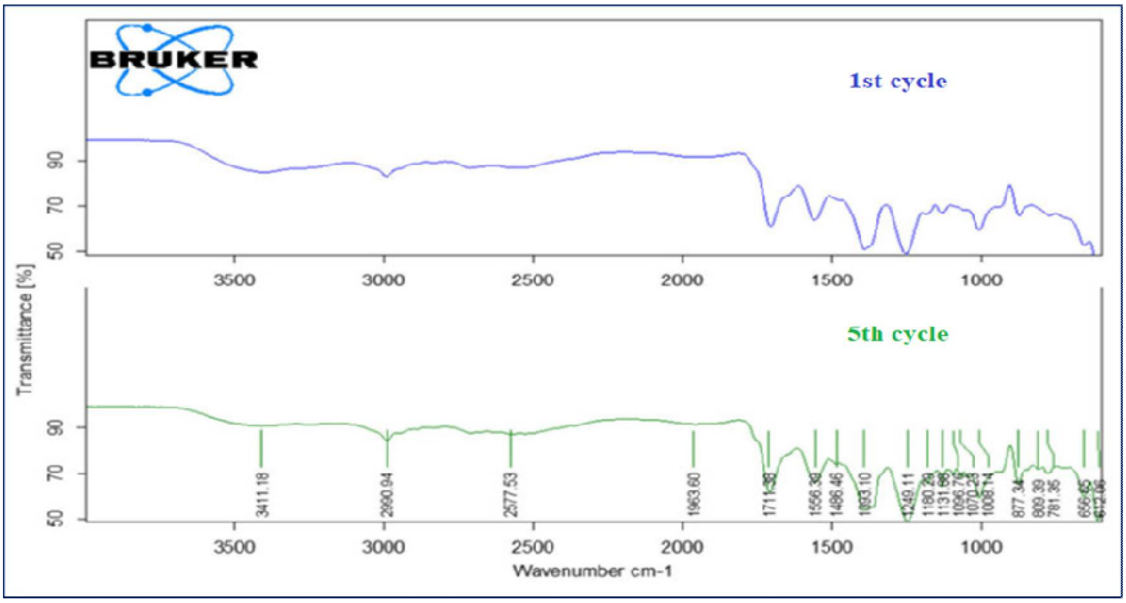


Figure 3:IR Spectra of Recycling ionic liquid[DBUH][OAc] IR Spectra.

CONCLUSION

Finally, we have developed an efficient technique for synthesizing highly substituted pyrazole derivatives. The producers described here are simple, mild and efficient, which gives this synthesis strategy a significant advantage over others. The benefits of using an ionic liquid catalyst include Increased rate and reactivity, as well as ease of product recovery and recycling. The use of ultrasonication of non-classical energy sources provides better energy stability to conventional methods. The ultrasound irradiation technique gave excellent yield, shorter reaction time, and simplified work procedure than the conventional technique. Present work is the reported first time forsynthesis of highly substituted pyrazoles using [DBUH][OAc] ionic liquid under ultrasound irradiation technique.

ACKNOWLEDGMENTS

The authors are appreciative to the Principal, Milind College of Science, Nagsenvana, Aurangabad-431002, Maharashtra, India, And Principal, Balwant college, Vita, Dist Sangli-415311, Maharashtra, India, for providing the necessary laboratory facilities for research work. We honestly thank SAIF, Punjab University, Chandigarh, India for provided that spectral analysis data. The author S.R.R. is very much grateful to the CSIR, New Delhi, for the award JRF.

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CITATION OF THIS ARTICLE

S R. Rathod, R A. Waghmare, S D. Rathod. Ultrasound Assisted One-Pot Green Synthesis of Highly Substituted Pyrazoles Catalyzed by [DBUH][OAc] Ionic Liquid. Bull. Env.Pharmacol. Life Sci., Spl Issue [1] 2022 : 1555-1562