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Ultrasound-promoted catalyst-free one-pot four component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in neutral ionic liquid 1-butyl-3-methylimidazolium bromide

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ABSTRACT

A catalyst-free one-pot four component methodology for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones under ultrasonic irradiation at room temperature using 1-butyl-3-methylimidazolium bromide, [Bmim]Br, as a neutral reaction medium is described. A broad range of structurally diverse aldehydes (aromatic aldehydes bearing electron withdrawing and/or electron releasing groups as well as heteroaromatic aldehydes) were applied successfully, and corresponding products were obtained in good to excellent yields without any byproduct.

1. Introduction

The efficient high-throughput synthesis of organic compounds is one of the most important objectives in modern drug discovery. Organic reactions should be fast and facile, and the target products should be easily separated and purified in high yields. From this point of view, there is much interest in the implementation of new processes and new synthetic strategies. In this regard, nonclassical methods, microwave-assisted synthesis, ultrasonic irradiation, and supercritical fluids, find application as appealing methods to achieve these goals [1]. Ultrasonic activation, based on cavitation effects leading to mass transfer improvement, is widely used today to promote numerous organic reactions [2]. A survey of literature shows that the synthesis of heterocyclic compounds has been accelerated by ultrasound irradiation. Compared with traditional methods, this technique is more convenient and easily controlled and is more appropriate in the consideration of green chemistry concepts [3]. In this way, Cella and Stefani have recently published an important review concerning to the use of ultrasound in heterocyclic chemistry [4]. Ultrasound irradiation have also been used for the synthesis of a wide variety of heterocycles such as tetrahydropyrimidines [5], 4*H*-benzo[*b*]pyran derivatives [6], 1,8-dioxooctahydroxanthene derivatives [7], 1,5-benzodiazepines [8], pyrido[2,3-*d*]pyrimidine derivatives [9], 3,4-dihydropyrimidin-2-ones [10], 1,3,5-thiadiazole and bi(1,3,5-thiadiazole) [11], benzoacridinones [12], 2-(3,5-diaryl-4,5-dihydro-1*H*-pyrazol-1-yl)-4-phenylthiazoles [13]. In all cases, the reactions occurred under mild conditions with good to excellent yields and in a few minutes.

In the other hand multi-component reactions (MCRs) play an important role in combinatorial chemistry because of the ability to synthesize target compounds with greater efficiency and atom economy by generating structural complexity in a single step from three or more reactants. Moreover, MCRs offer the advantage of simplicity and synthetic efficiency over conventional chemical reactions [14].

Moreover one of the most important aspects in green chemistry is the use of ionic liquids (ILs) as greener solvents in organic reactions that is in combination with some advantages such as control of product distribution [15], enhanced rate [16] and/or reactivity [17], ease of product recovery [18], catalyst immobilization [19], and recycling [20]. Since ILs are neither completely nonvolatile nor non-flammable, use of ILs omits the risk of combustion by replacement of volatile organic compounds widely used as solvents in organic reactions.

In combination with the use of ILs in organic transformations, catalyst-free methodologies for the synthesis of organic compounds have attracted much interest because of their ease of experimental procedures as well as workup, low cost, possibility of using acid or base sensitive substrates, and environmentally

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benign nature [21]. Many organic transformations were studied under catalyst-free conditions such as synthesis of 2-amino thiazols,[22] N-benzyloxycarbonylation of amines,[23] synthesis of benzoic and benzyl esters,[24] gembisillylation of carboxylic acids,[25] synthesis of polyorganosyloxanes [26] and one-pot four component synthesis of poly substituted imidazoles [27].

Nitrogen heterocycles containing a phthalazine moiety are important because they show biological and pharmacological activities such as anticonvulsant, cardiotonic, and vasorelaxant, and also unique electrical and optical properties [28]. Despite many methods being available for the synthesis of phthalazine derivatives,[29–33] their broad utility has accentuated the need to develop new synthetic routes for these compounds. Recent protocols have employed three-component condensations of aldehydes and dimedone (5,5-dimethylcyclohexane-1,3-dione) with 2,3-dihydro-1,4-phthalazinedione (phthalhydrazide) and/or one-pot four component reaction between aldehydes and dimedone (5,5-dimethylcyclohexane-1,3-dione), hydrazinium hydroxide and phthalic anhydride using various catalytic systems such as *p*-toluenesulfonic acid (*p*-TSA) [34a], H_2SO_4 [34b], heteropoly acids (HPAs) [34c], starch sulfate [35a], $CeSO_4{\cdot}4H_2O$ [35b] and silica supported poly phosphoric acid [35c]. These protocols have limitations such as the formation of by-products and the use of toxic organic solvents, acidic conditions, large amounts of catalyst, and tedious work-up procedures. According to the principle of safe chemistry, synthetic methods should be designed to use substances that exhibit little or no toxicity to human health and the environment [36].

As a part of our continuing studies in developing efficient catalyst-free synthetic methodologies in organic preparations,[27,37] we found that synthesis of 2*H*-indazolo [2,1-*b*] phthalazine-triones *via* a one-pot four component reaction can be efficiently achieved without any catalyst with the use of neutral ILs under ultrasonic irradiation at room temperature.

2. Methods

2.1. Apparatus and analysis

Reagents and solvents were purchased from Merck, Fluka or Aldrich. The IL was prepared according to the reported method [38]. Melting points were determined in capillary tubes in an electro-thermal C14500 apparatus. The progress of the reaction and the purity of compounds were monitored by TLC analytical silica gel plates (Merck 60 F250). All known compounds were identified by comparison of their melting points and ^{1}H NMR data with those in the authentic samples. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Chemical shifts are given as δ values against tetramethylsylane as the internal standard and *J* values are given in Hz. Microanalysis was performed on a Perkin–Elmer 240-B microanalyzer. The ultrasound apparatus was cleaning bath Wiseclear 770 W (Seoul, Korea). The operating frequency was 40 kHz and the output power was 200 W, estimated calorimetrically. The reaction flasks were located in the maximum energy area in the water bath, where the surface of reactants (reaction vessel) is slightly lower than the level of the water, and the addition or removal of water controlled the temperature of the water bath. The temperature of the water bath was controlled at 25–30 °C. All experiments performed in this work were repeated three times. The yield reported represents the average of the values obtained for each reaction.

2.2. General procedure for the synthesis of 2H-indazolo[2,1-b] phthalazine-triones

Dimedone (1 mmol), aromatic aldehyde (1 mmol), hydrazinium hydroxide (1.2 mmol) and phthalic anhydride (1 mmol) were added to [Bmim]Br (0.5 g) in a 25 mL Pyrex flask. The mixture was continuously irradiated for the appropriate time (Table 2) at room temperature. The reactions were followed by thin layer chromatography (TLC) using hexane/ethyl acetate (3:1) as an eluent. The ultrasonic apparatus used showed the temperature automatically so the temperature was controlled and fixed at room temperature by pouring cold water in the bath in the case of any elevation of temperature. After completion of the reaction, water (20 mL) was added and stirred magnetically for 5 min. Insoluble crude products were filtered, dried, and recrystallized from ethanol. To recover the [Bmim]Br, after the isolation of insoluble products, water was evaporated, and the remaining viscous liquid was washed with ethyl acetate (5 mL) and dried under reduced pressure ([Bmim]Br was recovered in 97% yield).

2.3. Selected Spectral data

2.3.1. 3,3-dimethyl-13-phenyl-3,4-dihydro-1H-indazolo[1,2-b] phthalazine-1,6,11(2H,13H)-trione (Compound 5a)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.23 (s, 6H), 2.33 (Distorted AB system, 2H), 3.25 (AB System, *J* = 18.0 Hz, 1H), 3.48 (AB System, *J* = 18.0 Hz, 1H), 6.44 (s, 1H), 7.41–8.42 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.2, 28.4, 34.3, 38.0, 50.4, 64.5, 118.6, 127.0, 127.5, 127.7, 128.3, 128.6, 129.1, 133.4, 134.2, 136.3, 150.9, 151.7, 154.2, 156.8, 192.3. Anal. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52%, Found: C, 74.23; H, 5.40; N, 7.61%.

2.3.2. 13-(4-chlorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo [1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5b)

White powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.21 (s, 3H), 1.23 (s, 3H), 2.33 (Distorted AB System, 2H), 3.26 (AB System, *J* = 18.5 Hz, 1H), 3.44 (AB System, *J* = 18.5 Hz, 1H), 6.45 (s,1H), 7.33–8.42 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.3, 28.4, 34.5, 38.1, 50.6, 64.4, 118.2, 127.7, 128.0, 128.4, 128.5, 128.7, 129.0, 133.3, 134.4, 134.6, 134.9, 151.0, 154.2, 156.0, 192.2. Anal. Calcd for $C_{23}H_{19}ClN_2O_3$: C, 67.90; H, 4.71; N, 6.89%, Found: C, 67.81; H, 4.77; N, 6.95%.

2.3.3. 13-(4-fluorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo [1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5d)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.23 (s, 6H), 2.35 (Distorted AB System, 2H), 3.22 (AB System, *J* = 18.5 Hz, 1H), 3.43 (AB System, *J* = 18.0 Hz, 1H), 6.41 (s, 1H), 7.01–8.44 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.5, 28.6, 34.8, 38.1, 50.5, 64.2, 115.6, 115.9 (d, $^1J_{C-F}$ = 275 Hz), 118.0, 127.3, 128.0, 128.9, 129.0, 132.4, 133.5, 134.6, 151.1, 152.0, 154.3, 156.0, 192.1. Anal. Calcd for $C_{23}H_{19}FN_2O_3$: C, 70.76; H, 4.91; N, 7.18%, Found: C, 70.82; H, 4.85; N, 7.29%.

2.3.4. 3,3-dimethyl-13-p-tolyl-3,4-dihydro-1H-indazolo[1,2-b] phthalazine-1,6,11(2H,13H)-trione (Compound 5h)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.25 (s, 6H), 2.31 (s, 3H), 2.38 (Distorted AB System, 2H), 3.22 (AB System, *J* = 18.0 Hz, 1H), and 3.45 (AB System, *J* = 18.0 Hz, 1H), 6.43 (s, 1H), 7.16–8.42 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 21.3, 28.5, 28.9, 34.6, 38.1, 50.6, 64.6, 118.3, 127.0, 127.7, 127.9, 128.8, 129.3, 129.5, 133.4, 133.6, 134.2, 138.5, 150.9, 154.3, 156.3, 192.1. Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25%, Found: C, 74.66; H, 5.71; N, 7.39%.

2.3.5. 13-(4-isopropylphenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo [1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5o)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.22 (s, 3H), 1.25 (s, 6H), 1.27 (s, 3H), 2.37–2.38 (Distorted AB System, 2H), 2.89–2.94 (m, 3H), 6.24 (s, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.38 (d,

J = 8.5 Hz, 2H), 7.43–7.48 (m, 1H), 7.52–8.35 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 24.3, 28.8, 29.1, 34.2, 35.1, 35.9, 51.7, 64.3, 120.5, 126.0, 127.44, 127.48, 129.1, 129.7, 131.2, 134.5, 149.4, 149.9, 151.0, 151.3, 154.3, 156.3, 191.3. Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76%, Found: C, 75.43; H, 6.33; N, 6.85%.

2.3.6. 13-(1H-indol-3-yl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5p)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.23 (s, 6H), 2.33 (Distorted AB System, 2H), 3.24 (AB System, J = 18.5 Hz, 1H), 3.43 (AB System, J = 18.0 Hz, 1H), 6.43 (s, 1H), 7.32–8.46 (m, 9H), 9.87 (brs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 24.2, 28.5, 29.0, 34.1, 35.3, 35.9, 51.9, 64.8, 111.3, 112.0, 114.6, 118.3, 119.2, 121.4, 123.0, 123.9, 127.2, 127.5, 128.35, 128.39, 132.21, 132.29, 135.5, 136.8, 156.4, 158.8, 191.3. Anal. Calcd for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21%, Found: C, 72.82; H, 5.19; N, 10.29%.

2.3.7. 3,3-dimethyl-13-(thiophen-2-yl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5q)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.22 (s, 6H), 2.34 (Distorted AB System, 2H), 3.25 (AB System, J = 18.5 Hz, 1H), 3.46 (AB System, J = 18.0 Hz, 1H), 6.24 (s, 1H), 6.79 (d, J = 9.0 Hz, 1H), 6.98 (t, J = 9.0 Hz, 1H), 7.09 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 24.4, 28.1, 29.3, 34.4, 35.0, 35.6, 51.9, 64.7, 116.0, 123.5, 125.6, 126.6, 127.0, 127.4, 128.5, 128.9, 132.1, 132.5, 135.7, 139.0, 155.4, 158.6, 191.3. Anal. Calcd for $C_{21}H_{18}N_2O_3S$: C, 66.65; H, 4.79; N, 7.40%, Found: C, 66.78; H, 4.86; N, 7.49%.

2.3.8. 3,3-dimethyl-13-(naphthalen-2-yl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (Compound 5r)

Yellow powder, ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.24 (s, 3H), 1.25 (s, 3H), 2.37 (Distorted AB System, 2H), 2.97 (AB System, J = 15.0 Hz, 1H), 3.01 (AB System, J = 15.0 Hz, 1H), 6.41 (s, 1H), 7.42–7.56 (m, 8H), 7.85–7.86 (m, 1H), 7.88–8.29 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 28.7, 29.1, 35.2, 36.0, 51.7, 64.8, 120.6, 124.5, 126.0, 126.8, 126.9, 127.2, 128.1, 128.7, 131.1, 133.6, 133.8, 134.5, 135.7, 137.1, 138.2, 149.5, 151.1, 151.5, 154.3, 156.3, 192.3. Anal. Calcd for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63%, Found: C, 76.83; H, 5.32; N, 6.70%.

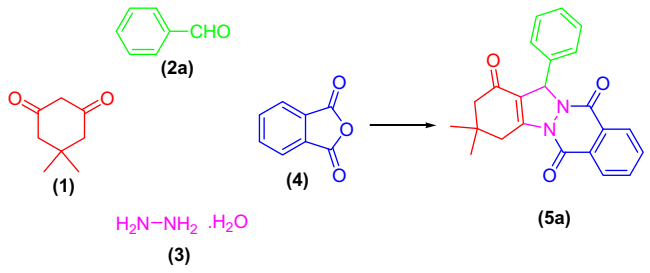
3. Results and discussions

To find an appropriate reaction medium for the catalyst-free synthesis of the titled compounds, one-pot four component reaction between dimedone (**1**) (1 mmol), benzaldehyde (**2a**) (1 mmol), hydrazinium hydroxide (**3**) (1.2 mmol) and phthalic anhydride (**4**) (1 mmol) was selected as a model reaction (Scheme. 1) and was examined in several reaction medium (0.5 g) and the yield and reaction times were monitored in the presence of ultrasonic irradiation at room temperature. The obtained results are summarized in Table 1.

Table 1
Catalyst-free one-pot four component reaction between dimedone (**1**) (1 mmol), benzaldehyde (**2a**) (1 mmol), hydrazinium hydroxide (**3**) (1.2 mmol) and phthalic anhydride (**4**) (1 mmol) in several reaction medium in the presence of ultrasonic irradiation at room temperature.

Entry	Reaction medium	Time (min)	Yield (%)[a]
1	H_2O (0.5 mL)	60	31
2	EtOH (0.5 mL)	60	63
3	CH_3CN (0.5 mL)	60	44
4	$CHCl_3$ (0.5 mL)	60	31
5	PEG 400 (0.5 mL)	60	77
6[b]	SiO_2 (0.5 g)	60	79
7	[Bmim]Br (0.5 g)	10	93

[a] Isolated yield.
[b] Reaction conditions: substrates were mixed with SiO_2 truly and the obtained mixture was irradiated under the neat condition.



Scheme. 1. The one-pot four component reaction between dimedone (**1**) (1 mmol), benzaldehyde (**2a**) (1 mmol), hydrazinium hydroxide (**3**) (1.2 mmol) and phthalic anhydride (**4**) (1 mmol).

Table 2
Catalyst-free one-pot four component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in [Bmim]Br in the presence of ultrasonic irradiation at room temperature.

Entry	R	Compound	Time (min)	Yield (%)[a]	M.P. (°C)	
					Found	Reported
1	C_6H_5	**5a**	10	93	206–208	207–209[35c]
2	4-ClC_6H_4	**5b**	7	91	260–262	259–261[35c]
3	4-BrC_6H_4	**5c**	7	92	262–263	258–260[35c]
4	4-FC_6H_4	**5d**	10	93	222–223	224–226[35c]
5	4-$NO_2C_6H_4$	**5e**	3	95	215–217	217–219[35c]
6	2-ClC_6H_4	**5f**	10	91	266–267	264–266[35c]
7	3-$NO_2C_6H_4$	**5g**	5	94	272–274	270–272[35c]
8	4-$CH_3C_6H_4$	**5h**	10	91	227–229	226–228[35c]
9	2-$CH_3C_6H_4$	**5i**	14	90	239–241	241–243[35c]
10	3-ClC_6H_4	**5j**	8	92	206–207	204–206[35c]
11	2-$CH_3OC_6H_4$	**5k**	15	90	242–243	240–241[35a]
12	4-$CF_3C_6H_4$	**5l**	5	92	215–217	214–216[35a]
13	4-$CH_3OC_6H_4$	**5m**	15	90	218–220	216–217[35a]
14	3-$PhOC_6H_4$	**5n**	12	89	183–185	180–182[35a]
15	4-*iso*$C_3H_7C_6H_4$	**5o**	10	93	230–232	-
16	3-indolyl	**5p**	15	92	248–250	-
17	2-thienyl	**5q**	8	90	232–234	-
18	2-naphthyl	**5r**	15	93	240–242	-

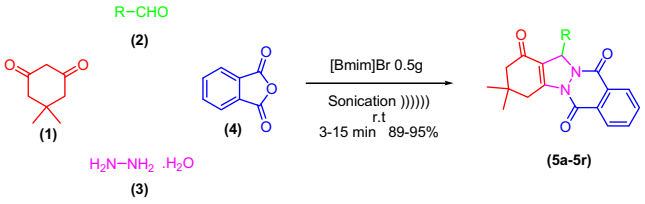
[a] Isolated yield.

As it is clear form Table 1, the best results were obtained in the presence of [Bmim]Br as a reaction medium.

In the next step the scope and efficiency of the process was explored under the optimized conditions. For this purpose, a broad range of structurally diverse aromatic aldehydes (**2**) were condensed with dimedone (**1**), hydrazinium hydroxide (**3**) and phthalic anhydride (**4**) in the presence of ultrasonic irradiation at room temperature (Scheme. 2), and the results are displayed in Table 2.

The yields obtained were good to excellent without formation of any side-products and all reactions proceed rapidly in short times. Aromatic aldehydes having electron withdrawing groups (Table 2, entries 5, 7, 12) reacted at faster rate compared with aromatic aldehydes substituted with electron releasing groups (Table 2, entries 11, 13, 14, 16). Beside this, our methodology has been used successfully for heteroaromatic aldehydes, and corresponding products were obtained in excellent yields and without any byproduct. (Table 2, entries 16, 17). All the products obtained were fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and by comparison with the reported spectral data.

Many recent studies have established that hydrogen bonding can occur between the solute and the cationic or anionic component of ILs [39]. Based on these facts, Deb and Bhuyan have suggested for the synthesis of bis(indolyl)methanes *via* condensation of indoles with aldehydes that hydrogen bond formation between a carbonyl group and solvent leads to activation of aldehydes [40]. Moreover, Crowhurts et al. demonstrated that imidazolium ILs are able to act as strong hydrogen bond acids as well as hydrogen bond bases at the same time [39c]. They shown that acidity of ILs is determined by the cation and it has been suggested that the hydrogen bond acidity is controlled by the ability of cation to act as a hydrogen bond acceptor; so a strong anion–cation interaction reduces the ability of the cation to hydrogen bond with the substrate. In the other hand hydrogen bond basicity of ILs was dominated by the choice of anion. It is well known that the hydrogen bonding between cationic component of an IL and negatively charged parts of electrophiles (hydrogen bond acidity) in combination with the hydrogen bonding between anionic component of the applied IL with the positively charged polar hydrogens of nucleophiles (hydrogen bond basicity) obviously enhance the reaction rate and yields. Accordingly we think that in the case of buthyl methylimidazolium based ILs ([Bmim]X, X = Cl^-, Br^- and I^-) the best results in order of reaction rate an yields most be obtained in the presence of [Bmim]Br as a reaction medium for the synthesis of titled compounds due to the moderate interaction between cationic component (buthyl methylimidazolium) and the anionic component (Br^-) that leads to the sufficient hydrogen bond acidity and hydrogen bond basicity of the IL. In order to establish the our theory in this case, the model reaction was examined in the presence of three ILs ([Bmim]Cl, [Bmim]Br and [Bmim]I) and the obtained results are summarized in Table 3. As it is clear form Table 3, the best results were obtained in the presence of [Bmim]Br as we expected.



Scheme. 2. Catalyst-free one-pot four component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in [Bmim]Br in the presence of ultrasonic irradiation at room temperature.

Table 3
Catalyst-free one-pot four component reaction between dimedone (**1**) (1 mmol), benzaldehyde (**2a**) (1 mmol), hydrazinium hydroxide (**3**) (1.2 mmol) and phthalic anhydride (**4**) (1 mmol) in the presence of [Bmim]Cl, [Bmim]Br and [Bmim]I under ultrasonic irradiation at room temperature.

Entry	Reaction medium	Time (min)	Yield (%)[a]
1	[Bmim]Cl (0.5 g)	20	93
2	[Bmim]Br (0.5 g)	10	93
3	[Bmim]I (0.5 g)	25	91

[a] Isolated yield.

According to these observations, we suggest a mechanism for this reaction in which the IL serves two catalytic functions; first, to electrophilically activate the aldehyde carbonyl through hydrogen-bonding to the carbonyl oxygen, and second, to enhance the nucleophilicity of the hydrazinium hydroxide through deprotonation of the N–H bond, as shown in the Scheme. 3. Our proposed mechanism contains two steps. Initial formation of the phthalhydrazide (**6**) by nucleophilic addition of hydrazinium hydroxide (**3**) to phthalic anhydride (**4**) followed by dehydration occurs.

The second step involves initial formation of heterodiene (**7**) by standard Knoevenagel condensation of dimedone (**1**) and aldehyde (**2**). Subsequent Michael-type addition of the phthalhydrazide followed by cyclization affords the corresponding product (**5**). (Scheme. 3)

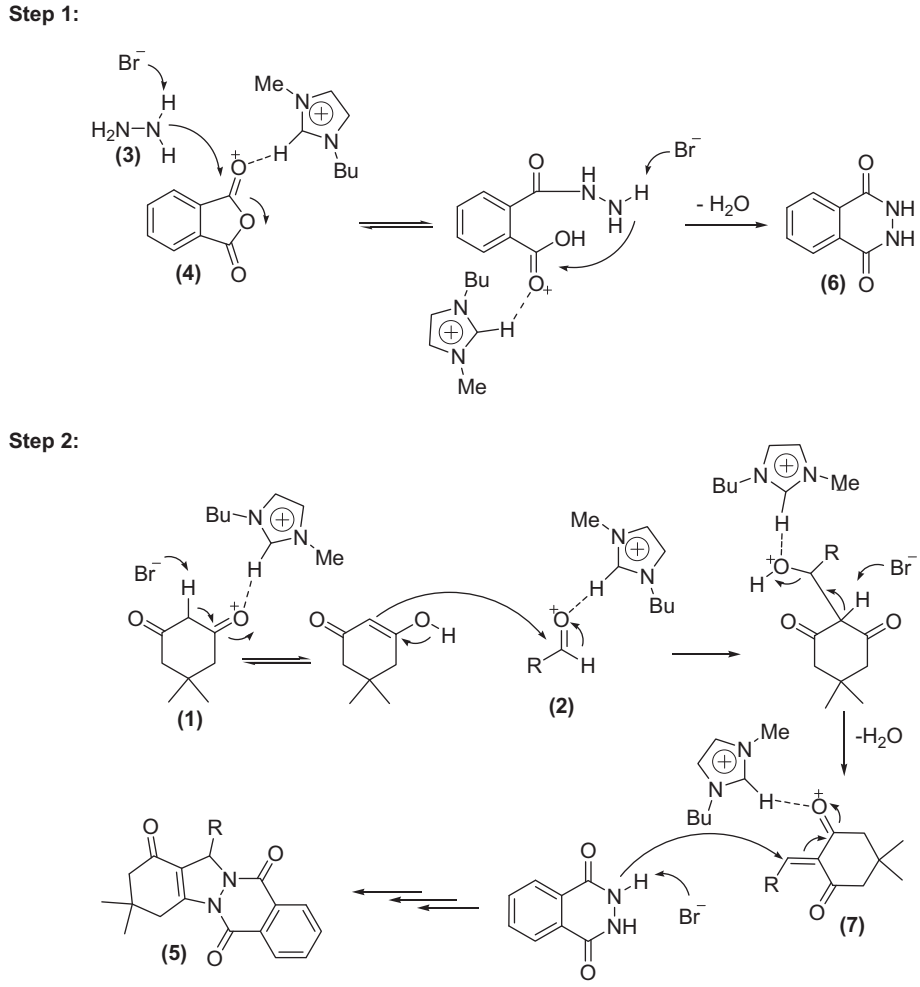
To investigate the role of ultrasonic irradiation in this method, the reactions were carried out in the presence of the same amount of [Bmim]Br under stirring condition at room temperature. The results are summarized in Table 4. It is clear that, under the same reaction conditions, reactions under ultrasonic irradiation led to relatively higher yields and shorter reaction times.

It is presumed that the efficiency using ultrasound irradiation is due to the cavitation phenomena. An ultrasonic wave is a pressure wave with alternate compressions and rarefactions which is able to break the intermolecular forces maintaining the cohesion of the liquid and produces a cavity in the rarefaction section of the wave. The chemical and physical effects of ultrasound derive primarily from acoustic cavitation which includes formation, growth and collapse of the cavity [41–43]. Bubble collapse in liquids results in an enormous concentration of energy from the conversion of kinetic energy of liquid motion into heating of the contents of the bubble. The high local temperatures and pressures produced by cavitation lead to a diverse set of applications of ultrasound [44]. As it is

Table 4
Catalyst-free one-pot four component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in [Bmim]Br under stirring condition at room temperature.

Entry	R	Compound	Time (min)	Yield (%)[a]
1	C_6H_5	**5a**	180	31
2	4-ClC_6H_4	**5b**	180	36
3	4-BrC_6H_4	**5c**	180	33
4	4-FC_6H_4	**5d**	180	39
5	4-$NO_2C_6H_4$	**5e**	180	55
6	2-ClC_6H_4	**5f**	180	25
7	3-$NO_2C_6H_4$	**5g**	180	49
8	4-$CH_3C_6H_4$	**5h**	180	21
9	2-$CH_3C_6H_4$	**5i**	180	Trace
10	3-ClC_6H_4	**5j**	180	22
11	2-$CH_3OC_6H_4$	**5k**	180	Trace
12	4-$CF_3C_6H_4$	**5l**	180	46
13	4-$CH_3OC_6H_4$	**5m**	180	Trace
14	3-$PhOC_6H_4$	**5n**	180	No reaction
15	4-*iso*$C_3H_7C_6H_4$	**5o**	180	Trace
16	3-Indolyl	**5p**	180	No reaction
17	2-Thienyl	**5q**	180	22
18	2-Naphthyl	**5r**	180	25

[a] Isolated yield.



Scheme. 3. Suggested mechanism for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in the presence of [Bmim]Br.

shown in Scheme. 3 our proposed mechanism for the one-pot four components synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in the presence of ultrasonic irradiation in [Bmim]Br consist of two steps contain the nucleophilic addition of hydrazinium hydroxide to phthalic anhydride, Knoevenagel condensation between dimedone and carbonyl compounds and Michael-type addition of the phthalhydrazide. It is well known that all of these reactions have negative activation volumes owing to the condensation of the molecules into a reactive intermediate. In this regard, it is well-known that reactions with negative activation volumes are accelerated with pressure [45]. On the other hand, ultrasound irradiation [46,47] as well as solvophobic interactions of ionic liquids generates a microscopic internal pressure in the solvent cavity [48]. So owning to the ultrasonic cavitations, microscopic internal high pressures and high temperatures have been generated in reaction media [49]. Accordingly, it is reasonable to assume that these effects should accelerate this type of four components condensation reaction.

4. Conclusion

In conclusion, an extremely efficient method has been developed for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in [Bmim]Br under ultrasonic irradiation and catalyst-free conditions at room temperature. This method is bestowed with several unique merits, such as high conversions, simplicity in operation, cost efficiency, and use of [Bmim]Br as a solvent, and thus significantly contributes to the practice of green chemistry. The use of [Bmim]Br as a nonvolatile medium, simple workup, neutral reaction conditions, and high yields of the products make our methodology a valid contribution to the existing processes in the field of 2*H*-indazolo[2,1-*b*]phthalazine-triones synthesis.

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