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Solvent-free synthesis of 2*H*-indazolo[2,1-*b*] phthalazine-triones promoted by cavitational phenomenon using iodine as catalyst

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ABSTRACT

An environmentally benign, simple and efficient protocol for the synthesis of 2*H*-indazolo[2,1-*b*] phthalazine-triones by condensation of phthalhydrazide, aromatic aldehydes and dimedone under solvent-free ultrasound assisted conditions employing a safe, readily available iodine as catalyst has been described. This process is a valuable addition as it devoids the use of any solvent and takes place in short duration of time giving good yield of the products.

1. Introduction

In the past few decades, development of efficient and environmentally safe protocols for synthesis of heterocyclic compounds has been a subject of great interest. Heterocyclic compounds occur widely in nature and are essential to life [1]. Among a large variety of heterocyclic compounds, nitrogen-containing heterocycles are widespread and their applications in biologically active pharmaceuticals, agrochemicals, and functional materials are becoming more and more important [2-6]. Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing bridgehead hydrazine have received considerable attention because of their pharmacological properties and clinical applications [7-16]. One such group of heterocyles are phthalazine derivatives, they were reported to possess cardiotonic [17], vasorelaxan [18], cytotoxic [19], antimicrobial [20], antifungal [21], anticancer [22], anti-inflammatory [23] and anticonvulsant [24] activities.

Looking into their importance, various researchers have reported different protocols [1,24-31] for the synthesis of these phthalazine derivatives. Some of the recently developed procedures for the synthesis of 2*H*-Indazolo[2,1-*b*]phthalazine trione via a three-component condensation reaction of phthalhydrazide, dimedone, and aromatic aldehydes employing catalyst like $H_3PW_{12}O_{40}$ in ionic liquid [32], H_2SO_4 in water-ethanol or ionic liquid [33], *p*-TSA [1], *N*,*N*,*N*',*N*'-tetrabromo benzene-1,3-disulfonamide and poly(*N*-bromo-*N*-ethyl benzene-1,3-disulfonamide) [34], (S)-camphorsulfonic acid [35], 1-butyl-3-methylimidazolium bromide [36], and $Ce(SO_4)_2{\cdot}H_2O$ [37], Me_3SiCl [38], silica sulfuric acid [39] and $Mg(HSO_4)_2$ [40] and silica supported poly phosphoric acid [41]. Despite the available methods, the development of new simple synthetic routes for the synthesis of phthalazine ring fragment still remains an important challenge, as the reported methods are associated with one or more disadvantages like use of expensive, corrosive or non-biodegradable catalyst, use of solvents, involves additional preparation of catalyst (which makes use of reagents which are corrosive and not easy to handle), high catalyst loading [1,33,39-41] and long reaction time [33].

Multicomponent reactions (MCRs), defined as one pot reactions in which at least three starting materials react to form a product, has been steadily gaining importance in synthetic organic chemistry [42-45]. They play a great role in the rapid assembly of molecular diversity and in the construction of heterocyclic "*drug-like*" libraries [46-48]. Speed, diversity, atom-efficiency, environmental amiability, straight-forward reaction design, substantial minimization of waste, time, and cost are some of the key features of this class of reactions [49-54].

On the other hand organic reactions under solvent-free conditions have also attracted much interest from chemists particularly from the viewpoint of green chemistry [34]. Green chemistry approaches are significant due to the reduction in produced waste, reduction in byproducts, reduction of energy and cost [34]. The possibility of performing multicomponent reactions under solvent-free conditions using an environmentally friendly catalyst could enhance the efficiency from an economic as well as ecological point of view [55]. In recent years, iodine has gained special attention as a catalyst in organic synthesis because many advantages such as simple handling, excellent yield, inexpensiveness, eco-friendly nature, ready availability and high reactivity [56]. Recently, several synthetically useful organic transformations using iodine as a catalyst have been reported in the literature [57,58].

Among the methods in chemical synthesis that have been recognized to have a green value, are the ones that make use of ultrasound and the non-hazardous microwave irradiation [59-61]. Ultrasonic irradiation has been found useful as support for quite a few organic reactions [62].

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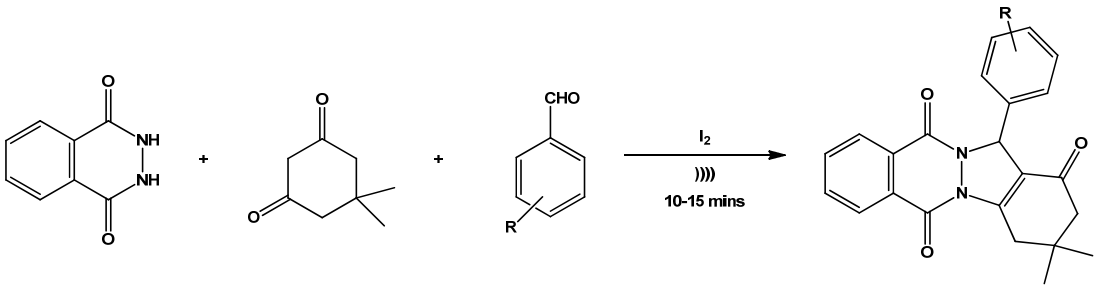


Scheme 1

In recent years, ultrasound has been widely used in carrying out organic synthesis [63-65]. Ultrasound irradiation enables many chemical reactions to proceed efficiently, which are unable to be achieved under conventional condition. Ultrasound is used in carrying out a number of organic transformations because it can enhance the reaction rate and can alter selectivity performance of the reaction [66-68]. Comparing traditional methods with ultrasound assisted method, reveals that ultrasound mediated protocols are more convenient and easily controlled. Hence a large number of organic reactions have been carried out in higher yield, shorter reaction time and milder condition under ultrasound irradiation [69-71].

In continuation of our work on development of green protocols for the synthesis of biologically active compounds and taking into consideration the advantages associated with multicomponent strategy, solvent-free reaction conditions, the applicability of iodine and ultrasound radiation, we have aimed at developing a highly green protocol incorporating all the above green strategies to synthesize 2*H*-indazolo[2,1-*b*] phthalazine-triones via a three-component condensation reaction of phthalhydrazide, dimedone, and aromatic aldehydes in the presence of iodine under ultrasonic irradiation (Scheme 1).

2. Experimental

All starting materials were commercial products, and all were used without further purification except liquid aldehydes, which were distilled before use. Progress of the reaction was monitored on TLC. TLC was carried out on Merck made silica gel 60F_{254} plates with ethylacetate: hexane (1:4, *v:v*) system. The formation of product was confirmed by recording the melting points, IR spectra and ^{1}H NMR spectra. IR spectra were recorded using Bruker alpha-T ATR/FTIR spectrometer and Nuclear magnetic resonance spectra recorded on a 400 MHz Bruker AMX instrument in DMSO-d_6 using TMS as a standard. All the reactions were studied using SIDILU, Indian make sonic bath working at 35 kHz maintained at 25-30 ^{o}C without mechanical stirring. Melting points were measured on Veego VMP-D melting point apparatus. Yields refer to isolated yields of the products.

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

A mixture of phthalhydrazide (2 mmol), aromatic aldehydes (2 mmol), dimedone (2 mmol) and iodine (0.1 g) were sonicated in a sonic bath working at 35 kHz maintained at 25-30 ^{o}C (by circulating water). For aldehydes which are solids, dichloromethane (0.5 mL) was added to the mixture. After completion of the reaction (monitored by TLC), product was dissolved in ethyl acetate (10 mL), washed successively with $Na_2S_2O_3$ solution and water (5 mL), and then dried over anhydrous sodium sulphate to get the crude compound in almost pure form. The analytical grade of the product was obtained by recrystallization from aq. ethanol.

3,3-Dimethyl-13-phenyl-3,4-dihydro-2H-indazolo[1,2-b] phthalazine-1,6,11(13H)-trione (**4a**): Yellow. Yield: 95%. M.p.: 207-208 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3020 (C-H) (Ar), 1720 (C=O) (ketone), 1650 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1080 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11 (s, 6H, -(CH_3)$_2$), 2.25(s, 2H, -C(CH$_3$)$_2$-CH_2-C=), 2.71 (s, 2H, -C(CH$_3$)$_2$-CH_2-CO), 6.22 (s, 1H, Ar-C*H*-N), 6.82-6.85 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.10-7.16 (m, 3H, Ar-*H*), 7.94-8.24 (m, 4H, Ar-*H*).

13-(4-Methoxyphenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**4b**): Yellow. Yield: 95%. M.p.: 220-221 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 2959 (C-H) (Ar), 1722 (C=O) (ketone), 1655 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1267 (C-O) (methoxy), 1082 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.12 (s, 6H, -(CH_3)$_2$), 2.26 (s, 2H, -C(CH$_3$)$_2$-CH_2-C=), 2.72 (s, 2H, -C(CH$_3$)$_2$-CH_2-CO), 3.71(s, 3H, O-CH_3), 6.24 (s, 1H, Ar-C*H*-N), 6.83-6.86 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.33-7.36 (d, *J* = 9 Hz, 2H, Ar-*H*),7.94-8.25 (m, 4H, Ar-*H*).

3,3-Dimethyl-13-p-tolyl-3,4-dihydro-2H-indazolo[1,2-b] phthalazine-1,6,11(13H)-trione (**4c**): Yellow. Yield: 95%. M.p.: 226-228 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3020 (C-H) (Ar), 1720 (C=O) (ketone), 1652 (C=O) (amide), 1626 (C=C), 1600 (C=C) (Ar), 1078 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11 (s, 6H, -(CH_3)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-CH_2-C=), 2.34 (s, 3H, Ar-CH_3), 2.72 (s, 2H, -C(CH$_3$)$_2$-CH_2-CO), 6.22 (s, 1H, Ar-C*H*-N), 6.84-6.87 (d, *J* = 9 Hz, 4H, Ar-*H*), 7.61-8.24 (m, 4H, Ar-*H*).

3,3-Dimethyl-13-m-tolyl-3,4-dihydro-2H-indazolo[1,2-b] phthalazine-1,6,11(13H)-trione (**4d**): Yellow. Yield: 92%. M.p.: 233-235 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3010 (C-H) (Ar), 1720 (C=O) (ketone), 1652 (C=O) (amide), 1625 (C=C), 1602 (C=C) (Ar), 1078 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11 (s, 6H, -(CH_3)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-CH_2-C=), 2.35 (s, 3H, Ar-CH_3), 2.72 (s, 2H, -C(CH$_3$)$_2$-CH_2-CO), 6.22 (s, 1H, Ar-C*H*-N), 6.83 (s, 1H, Ar-*H*), 6.85-7.01 (m, 3H, Ar-*H*), 7.90-8.23 (m, 4H, Ar-*H*).

13-(3,4-Dimethylphenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**4e**): Pale yellow. Yield: 90%. M.p.: 251-253 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 3018 (C-H) (Ar), 1725 (C=O) (ketone), 1650 (C=O) (amide), 1626 (C=C), 1600 (C=C) (Ar), 1080 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.12 (s, 6H, -(CH_3)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-CH_2-C=), 2.34 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH$_3$), 2.72 (s, 2H, -C(CH$_3$)$_2$-CH_2-CO), 6.23 (s, 1H, Ar-C*H*-N), 6.84 (m, 3H, Ar-*H*), 7.92-8.25 (m, 4H, Ar-*H*).

3,3-Dimethyl-13-(3,4,5-trimethoxyphenyl)-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**4f**): Pale yellow. Yield: 90%. M.p.: 230-232 ^{o}C. FT-IR (KBr, ν, cm^{-1}): 2960 (C-H) (Ar), 1726 (C=O) (ketone), 1655 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1266 (C-O) (methoxy), 1080 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.12 (s, 6H, -(CH_3)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-CH_2-C=), 2.72 (s, 2H, -C(CH$_3$)$_2$-CH_2-CO), 3.72(s, 9H, O-CH_3), 6.25 (s, 1H, Ar-C*H*-N), 6.64 (s, 2H, Ar-*H*), 7.92-8.24 (m, 4H, Ar-*H*).

13-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo [1,2-b]phthalazine-1,6,11(13H)-trione (**4g**): White. Yield: 92%.

M.p.: 261-263 °C. FT-IR (KBr, ν, cm^{-1}): 3020 (C-H) (Ar), 1720 (C=O) (ketone), 1656 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1080 (C-N), 700 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11 (s, 6H, -(C*H*$_3$)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-C=), 2.71 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-CO), 6.23 (s, 1H, Ar-C*H*-N), 7.01-7.03 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.15-7.18 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.92-8.23 (m, 4H, Ar-*H*).

13-(3-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo [1,2-b]phthalazine-1,6,11(13H)-trione (**4h**): White. Yield: 90%. M.p.: 207-209 °C. FT-IR (KBr, ν, cm^{-1}): 3020 (C-H) (Ar), 1720 (C=O) (ketone), 1654 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1080 (C-N), 702 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.12 (s, 6H, -(C*H*$_3$)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-C=), 2.71 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-CO), 6.22 (s, 1H, Ar-C*H*-N), 7.02 (s, 1H, Ar-*H*), 7.04-7.21 (m, 3H, Ar-*H*), 7.91-8.24 (m, 4H, Ar-*H*).

13-(2-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo [1,2-b]phthalazine-1,6,11(13H)-trione (**4i**): White. Yield: 90%. M.p.: 266-268 °C. FT-IR (KBr, ν, cm^{-1}): 3020 (C-H) (Ar), 1726 (C=O) (ketone), 1655 (C=O) (amide), 1625 (C=C), 1600 (C=C) (Ar), 1082 (C-N), 700 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11 (s, 6H, -(C*H*$_3$)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-C=), 2.72 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-CO), 6.22 (s, 1H, Ar-C*H*-N), 7.01-7.22 (m, 4H, Ar-*H*), 7.90-8.23 (m, 4H, Ar-*H*).

13-(2,4-Dichlorophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo[1,2-b]phthalazine-1,6,11(13H)-trione (**4j**): White. Yield: 90%. M.p.: 220-222 °C. FT-IR (KBr, ν, cm^{-1}): 3010 (C-H) (Ar), 1720 (C=O) (ketone), 1656 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1080 (C-N), 702 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11 (s, 6H, -(C*H*$_3$)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-C=), 2.72 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-CO), 6.22 (s, 1H, Ar-C*H*-N), 6.98-7.21 (m, 3H, Ar-*H*), 7.91-8.24 (m, 4H, Ar-*H*).

13-(4-Bromophenyl)-3,3-dimethyl-3,4-dihydro-2H-indazolo [1,2-b]phthalazine-1,6,11(13H)-trione (**4k**): White. Yield: 95%. M.p.: 266-268 °C. FT-IR (KBr, ν, cm^{-1}): 3018 (C-H) (Ar), 1720 (C=O) (ketone), 1655 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1080 (C-N), 620 (C-Br). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.11 (s, 6H, -(C*H*$_3$)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-C=), 2.71 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-CO), 6.23 (s, 1H, Ar-C*H*-N), 7.02-7.05 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.17-7.20 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.91-8.24 (m, 4H, Ar-*H*).

3,3-Dimethyl-13-(4-nitrophenyl)-3,4-dihydro-2H-indazolo [1,2-b]phthalazine-1,6,11(13H)-trione (**4l**): Yellow. Yield: 90%. M.p.: 215-217 °C. FT-IR (KBr, ν, cm^{-1}): 3020 (C-H) (Ar), 1720 (C=O) (ketone), 1655 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1402 (N=O) (nitro), 1080 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.12 (s, 6H, -(C*H*$_3$)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-C=), 2.71 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-CO), 6.23 (s, 1H, Ar-C*H*-N), 7.13-7.16 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.42-7.45 (d, *J* = 9 Hz, 2H, Ar-*H*), 7.91-8.24 (m, 4H, Ar-*H*).

3,3-Dimethyl-13-(4-nitrophenyl)-3,4-dihydro-2H-indazolo [1,2-b]phthalazine-1,6,11(13H)-trione (**4m**): Yellow. Yield: 87%. M.p.: 270-272 °C. FT-IR (KBr, ν, cm^{-1}): 3020 (C-H) (Ar), 1720 (C=O) (ketone), 1655 (C=O) (amide), 1626 (C=C), 1602 (C=C) (Ar), 1410 (N=O) (nitro), 1080 (C-N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 1.12 (s, 6H, -(C*H*$_3$)$_2$), 2.25 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-C=), 2.71 (s, 2H, -C(CH$_3$)$_2$-C*H*$_2$-CO), 6.23 (s, 1H, Ar-C*H*-N), 7.38 (s, 1H, Ar-*H*), 7.40-7.66 (m, 3H, Ar-*H*), 7.91-8.24 (m, 4H, Ar-*H*).

3. Results and discussion

Herein we report the solvent-free three-component reaction of phthalhydrazide (**1**), dimedone (**2**), and aromatic aldehydes (**3**) under ultrasonic irradiation in the presence of a catalytic amount of iodine within 10-15 mins, allowing the `one-pot' formation of 2*H*-indazolo[2,1-*b*] phthalazine-triones (**4**) in excellent overall yield.

The complete process represents an example of the one-pot and sequential steps reaction (often referred to as tandem or cascade reaction) where reagents and catalysts are mixed together and experimental conditions are set up in such a way to promote the reaction cascade [72-74].

To optimize the reaction conditions for the synthesis of 2*H*-indazolo[2,1-*b*] phthalazine-triones, the reaction of phthalhydrazide, dimedone with 4-chlorobenzaldehyde was chosen as a model in the presence of iodine as catalyst, reaction was done under silent, thermal and ultrasonic conditions.

The rate of the reaction is markedly affected by the use of ultrasound as shown in (Figure 1) The ultrasound unassisted reactions afforded the corresponding 2*H*-indazolo[2,1-*b*] phthalazine-trione in 20% yield after 30 mins under silent condition and 60% yield after 30 mins under thermal condition, whereas the presence of the ultrasound strongly increased the rate of the process and compound is produced in 92% yield after 10 mins. This drastic increase in yield of product is attributed to the activation of reactants due to acoustic cavitation produced by ultrasonic irradiation. Like any sound wave ultrasound is propagated *via* a series of compression and rarefaction waves of the medium through which it passes. At sufficiently high power the rarefaction cycle may exceed the attractive forces of the molecules of the liquid and cavitation bubbles will form. Such bubbles grow by a process known as rectified diffusion *i.e.* small amounts of vapour (or gas) from the medium enters the bubble during its expansion phase and is not fully expelled during compression [76]. The bubbles grow over a period of a few cycles to an equilibrium size for the particular frequency applied. It is the fate of these bubbles when they collapse in succeeding compression cycles which generates the energy for chemical and mechanical effects [76]. In systems operating at an ultrasonic frequency of 20 kHz each cavitation bubble collapse acts as a localised "*hotspot*" generating temperatures of about 4,000 K and pressures in excess of 1000 atmospheres [76]. Cavitation bubble collapse occurs in the bulk liquid symmetrically, or near to a surface of reaction flask in an unsymmetrical manner because the surface provides resistance to liquid flow from that side. The result is an inrush of liquid predominantly from the side of the bubble remote from the surface resulting in a powerful liquid jet being formed, targeted at the reaction mixture. The effect is equivalent to high pressure jetting and is the reason for using ultrasound in reaction rate enhancement. This effect can also activate solid catalysts by breaking it down into smaller fragments and thereby increasing the surface area of the catalyst and in turn accelerating the reaction [77,78]. This combined overall effect of bubble collapse and activation of catalyst iodine has led to rate enhancement of the reaction.

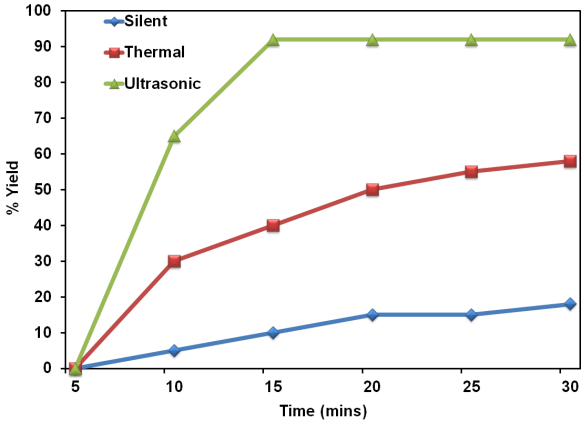


Figure 1. Reactivity of phthalhydrazide, dimedone, and 4-chlorobenzaldehyde in the presence of iodine in the under silent, thermal and ultrasonic conditions as a function of time.

Table 1. Synthesis of 2*H*-indazolo[2,1-*b*] phthalazine-triones (4) using iodine from aromatic aldehydes, phthalhydrazide and dimedone.

Entry	R	Product (4)[a]	Time (mins)	Yield (%)[b]	Mp [Lit. M.p.] (°C)
1	C_6H_5	4a	15	95	207-208 (204-206) [33]
2	4-MeO-C_6H_4	4b	10	95	220-221 (218-220) [39]
3	4-Me-C_6H_4	4c	10	95	226-228 (226-231) [33]
4	3- Me-C_6H_4	4d	10	92	233-235 (232-233) [75]
5	3,4-$(Me)_2$-C_6H_3	4e	10	90	251-253 (250-251) [75]
6	3,4,5-MeO-C_6H_2	4f	15	90	230-232 (232-234) [33]
7	4-Cl-C_6H_4	4g	10	92	261-263 (258-260) [33]
8	3-Cl-C_6H_4	4h	15	90	207–209 (204-206) [41]
9	2-Cl-C_6H_4	4i	15	90	266–268 (264-266) [39]
10	2,4-Cl_2-C_6H_3	4j	15	90	220–222 (219-221) [41]
11	4-BrC_6H_4	4k	15	95	266–268 (265-267) [1]
12	4-NO_2-C_6H_4	4l	10	90	215-217 (216-218) [33]
13	3-NO_2-C_6H_4	4m	15	87	270-272 (269-271) [33]

[a] All compounds were characterized by recording their melting points, IR spectra and ^{1}H NMR spectra and comparing with data reported in literature.
[b] Isolated yields.

Table 2. Comparative study on the present method with the reported methods for the synthesis of 13-(4-chloro-phenyl)-3,3-dimethyl-2,3,4,13-tetrahydro-indazolo[1,2-*b*]phthalazine-1,6,11-trione.

Catalyst	Catalyst load (mol %)	Temperature (°C)	Time (min)	Yield (%)
Silica sulfuric acid	6.5	100	**7**	91
[Bmim]BF_4/ H_2SO_4	15	80	30	94
p-Toluenesulfonic acid	30	80	10	93
Poly phosphoric acid-SiO_2	5	100	6	93
PBBS	0.1 g	100	25	67
(S)-camphorsulfonic acid	20	RT	20	90
Iodine /))))*	**10**	**25-30**	**10**	**92**

*Advantages: Iodine is readily available, inexpensive and highly eco-friendly, yield is good, short reaction time, ambient temperature, overall mild and green reaction conditions,)))) = Ultrasonic condition.

After establishing the technique which lead to the maximum product yield, the reaction time was optimised by subjecting the reaction mixture to sonication and monitoring by TLC at an interval of 2 mins each, at every interval there was noticeable increase in the yield. Finally after 10 mins maximum formation of 13-(4-chloro-phenyl)-3,3-dimethyl-2,3,4,13-tetra-hydro-indazolo[1,2-*b*]phthalazine-1,6,11-trione (92%) was observed, irradiation further did not improve the yield.

Optimization of catalyst loading was the next concern, to start off with 25 mol% of iodine was used, decrease of catalyst loading to 20 mol% did not alter the product yield, further reduction in the amount of catalyst to 10 mol% did not affect the yield of product formed, but reduction to below 10 mol% led to decrease in the formation of product.

After these successful trial experiments, a library synthesis was conducted using various aromatic aldehydes containing electron-donating groups like OCH_3, OH, CH_3 and electron-withdrawing substituents such as NO_2, F, Cl, Br and found that both reacted well with phthalhydrazide and dimedone, to give high to excellent yield of the desired products as shown in (Table 1).

To show the merit of the present work results were compared with the reported results in the literature as shown in (Table 2).

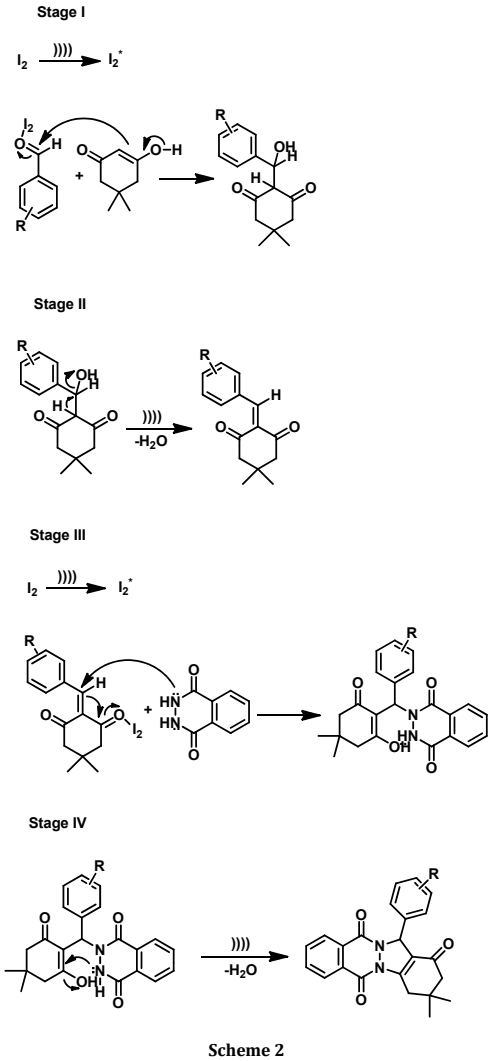
The probable mechanism outlined in (Scheme 2) proceeds in four stages.

Stage I

The reaction was initiated by ultrasound assisted surface activation of the catalyst iodine by breaking it down into finely divided very reactive particles and hence increasing its surface area, this was followed by the attack of enolic form of dimedone on the carbonyl carbon of aromatic aldehyde complexed to the activated iodine (thereby making it more electrophillic) to give different substituted 2-(hydroxy-phenyl-methyl)-5,5-dimethyl-cyclohexane-1,3-diones.

Stage II

The various 2-(hydroxy-phenyl-methyl)-5,5-dimethyl-cyclohexane-1,3-diones formed undergoes dehydration readily with the aid of ultrasound, which is the crucial stage for further progress of the reaction. Ultrasound works by the phenomenon of cavitation; which involves the growth, oscillation, and collapse of bubbles under the action of an acoustic field.



Scheme 2

The acoustic field experienced by the bubble is not stable because of the interference of other bubbles forming and resonating around it [76]. As a result some bubbles suffer sudden expansion to an unstable size and collapse violently. It is the fate of these cavities when they collapse which generates the energy for chemical and mechanical effects of each cavitation bubble acts as a localised microreactor which, generates temperatures of several thousand degrees and pressures in excess of one thousand atmospheres [76]. The high temperature and pressure generated helps in facile removal of water to afford substituted 2-benzylidene-5,5-dimethylcyclohexane-1,3-diones.

Stage III

The 2-benzylidene-5,5-dimethylcyclohexane-1,3-diones obtained get activated by iodine as discussed in stage I, and then reaction of activated 2-benzylidene-5,5-dimethylcyclo hexane-1,3-diones with phthalhydrazide to give 2,3-dihydro-2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)(phenyl)methyl)phthalazine-1,4-diones.

Stage IV

2,3-Dihydro-2-((2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)(phenyl) methyl) phthalazine-1,4-diones undergo loss of water with the help of ultrasound to give the desired products in good yield.

4. Conclusion

In conclusion, the preparation of various substituted 2*H*-indazolo[2,1-*b*] phthalazine-triones was efficiently achieved by a solvent-free one pot condensation of phthalhydrazide, dimedone, and aromatic aldehydes in the presence of readily available, inexpensive and environmentally benign iodine as catalyst accelerated by ultrasound. To the best of our knowledge only a few solvent-free reactions are carried out under ultrasonic conditions. We feel this method is a very good alternative to the other existing methods possessing high green value.

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References

[1]. Sayyafi, M.; Seyyedhamzeh, M.; Khavasi, H. R.; Bazgir, A. *Tetrahedron* **2008**, *64*, 2375-2378.
[2]. Franklin, E. C. *Chem. Rev*. **1935**, *16*, 305-361.
[3]. Bergstrom, F. W. *Chem. Rev*. **1944**, *35*, 77-277.
[4]. Lichtenthaler, F. W. *Acc. Chem. Res.* **2002**, *35*, 728-737.
[5]. Litvinov, V. P. *Russ. Chem. Rev.* **2003**, *72*, 69-85
[6]. Xu, Y.; Guo, Q-X. *Heterocycles* **2004**, *63*, 903-974.
[7]. Vaughan, W. R. *Chem. Rev.* **1948**, *43*, 447-508.
[8]. Clement, R. A. *J. Org. Chem.* **1960**, *25*, 1724-1727.
[9]. Heine, H. W.; Henrie, R.; Heitz, L.; Kovvali, S. R. *J. Org. Chem.* **1974**, *39*, 3187-3191.
[10]. Heine, H. W.; Baclawski, L. M.; Bonser, S. M.; Wachob, G. D. *J. Org. Chem.* **1976**, *41*, 3229-3232.
[11]. Sheradsky, T.; Moshenberg, R. *J. Org. Chem.* **1986**, *51*, 3123-3125.
[12]. Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007-4013.
[13]. Indelicato, J. M.; Pasini, C. E. *J. Med. Chem*. **1988**, *31*, 1227-1230.
[14]. Kappe, T.; Kos, C. *Synthesis* **1989**, 629-630.
[15]. Turk, C.; Svete, J.; Stanovnik, B.; Goli, C. L.; Grdadolnik, S.; Golobi, C. A.; Seli Helv, C. L. *Chim. Acta*. **2001**, *84*, 146-156.
[16]. Clark, M. P.; Laughlin, S. K.; Laufersweiler, M. J.; Bookland, R. G.; Brugel, T. A.; Golebiowski, A.; Sabat, M. P.; Townes, J. A.; VanRens, J. C.; Djung, J. F.; Natchus, M. G.; De, B.; Hsieh, L. C.; Xu, S. C.; Walter, R. L.; Mekel, M. J.; Heitmeyer, S. A.; Brown, K. K.; Juergens, K.; Taiwo, Y. O.; Janusz, M. J. *J. Med. Chem.* **2004**, *47*, 2724-2727.
[17]. Nomoto, Y.; Obase, H.; Takai, H.; Teranishi, M.; Nakamura, J.; Kubo, K. *Chem. Pharm. Bull. (Tokyo)* **1990**, *38*, 2179-2183.
[18]. Watanabe, N.; Kabasawa, Y.; Takase, Y.; Matsukura, M.; Miyazaki, K.; Ishihara, H.; Kodama, K.; Adachi, H. *J. Med. Chem*. **1998**, *41*, 3367-3372.
[19]. Kim, J. S.; Rhee, H. K.; Park, H. J.; Lee, S. K.; Lee, C. O.; Park Choo, H. Y. *Bioorg. Med. Chem.* **2008**, *16*, 4545-4550.
[20]. El-Sakka, S. S.; Soliman, A. H.; Imam, A. M. *Afinidad* **2009**, *66*, 167-172.
[21]. Ryu, C. K.; Park, R. E.; Ma, M. Y.; Nho, J. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2577-2580.
[22]. Li, J.; Zhao, Y. F.; Yuan, X. Y.; Xu, J. X.; Gong, P. *Molecules* **2006**, *11*, 574-582.
[23]. Sinkkonen, J.; Ovcharenko, V.; Zelenin, K. N.; Bezhan, I. P.; Chakchir, B. A.; Al-Assar, F.; Pihlaja, K. *Eur. J. Org. Chem*. **2002**, *13*, 2046-2053.
[24]. Grasso, S.; DeSarro, G.; Micale, N.; Zappala, M.; Puia, G.; Baraldi, M.; Demicheli, C. *J. Med. Chem.* **2000**, *43*, 2851-2859.
[25]. Sheradsky, T.; Moshenberg, R. *J. Org. Chem*. **1986**, *51*, 3123-3125.
[26]. Heine, H. W.; Baclawski, L. M.; Bonser, S. M.; Wachob, G. D. *J. Org. Chem*. **1976**, *41,* 3229-3232.
[27]. Ramtohup, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem*. **2002**, *67*, 3169-3178.
[28]. Liu, L. P.; Lu, J. M.; Shi, M. *Org. Lett.* **2007**, *9*, 1303-1306.
[29]. Csampai, A.; Kormendy, K.; Ruff, F. *Tetrahedron* **1991**, *47*, 4457-4464.
[30]. Amarasekara, A. S.; Chandrasekara, S. *Org. Lett.* **2002**, *4*, 773-775.
[31]. Hwang, J. Y.; Choi, H. S.; Gong, Y. D. *Tetrahedron Lett.* **2005**, *46*, 3107-3110.
[32]. Fazaeli, R.; Aliyan, H.; Fazaeli, N. *Open Catal. J.* **2010**, *3*, 14-18.
[33]. Khurana, J. M.; Magoo, D. *Tetrahedron Lett.* **2009**, *50*, 7300-7303.
[34]. Vaghei, R. G.; Karimi-Nami, R.; Toghraei-Semiromi, Z.; Amiri, M.; Ghavidel, M. *Tetrahedron* **2011**, *67*, 1930-1937.
[35]. Shukla, G.; Verma, R. K.; Verma, G. K.; Singh, M. S. *Tetrahedron Lett.* **2011**, *52*, 7195-7198.
[36]. Shekouhy, M.; Hasaninejad, A. *Ultrasonics Sonochemistry* **2012**, *19,* 307-313.
[37]. Mosaddegh, E.; Hassankhani, A. *Tetrahedron Lett.* **2011**, *52*, 488-490.
[38]. Nagarapu, L.; Bantu, R.; Hari Babu, M. *J. Heterocyclic Chem.* **2009**, *46*, 728-731.
[39]. Shaterian, H. R.; Ghashang, M.; Feyzi, M. *Appl Catal A Gen* **2008**, *345,* 128-133.
[40]. Shaterian, H. R.; Khorami, F.; Amirzadeh, A.; Doostmohammadi, R.; Ghashang, M. *J. Iran. Chem. Res*. **2009**, *2*, 57-62.
[41]. Shaterian, H. R.; Hosseinian, A.; Ghashang, M. *Arkivoc* **2009**, *2*, 59-67.
[42]. Toure, B. B.; Hall, D. G. *Chem. Rev*. **2009**, *109*, 4439-4486.
[43]. Bondock, S.; Fadaly, W.; Metwally, M. A. *J. Sulfur Chem*. **2009**, *30*, 74-107.
[44]. Ganem, B. *Acc. Chem. Res*. **2009**, *42*, 463-472.
[45]. Domling, A. *Chem. Rev*. **2006**, *106*, 17-89.
[46]. Gerencser, J.; Dormon, G.; Darvas, F. *QSAR Comb. Sci*. **2006**, *25,* 439-448.
[47]. Ramon, D. J.; Yus, M. *Angew. Chem. Int.* **2005**, *44*, 1602-1634.
[48]. Hulme, C.; Gore, V. *Curr. Med. Chem*. **2003**, *10*, 51-80.
[49]. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575-579.
[50]. Staben, S. T.; Blaquiere, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 325-328.
[51]. Yue, T.; Wang, M. X.; Wang, D. X.; Masson, G.; Zhu, J. *J. Org. Chem*. **2009**, *74*, 8396-8399.
[52]. Trofimov, B. A.; Andriyankova, L. V.; Belyaeva, K. V.; Malkina, A. G.; Nikitina, L. P.; Afonin, A. V.; Ushakov, I. A. *Eur. J. Org. Chem.* **2010**, *9*, 1772-1777.
[53]. Ma, N.; Jiang, B.; Zhang, G.; Tu, S. J.; Wever, W.; Li, G. *Green Chem* **2010**, *12*, 1357-1361.
[54]. Kategaonkar, A. H.; Sonar, S. S.; Shelke, K. F.; Shingate, B. B.; Shingare, M. S. *Org. Commun*. **2010**, *3:1*, 1-7.
[55]. Kumar, A.; Maurya, R. A. *Tetrahedron* **2007**, *63*, 1946-1952.
[56]. Ali, S. S. *Archives of Applied Science Research* **2010**, *2*, 121-125.
[57]. Kidwai, M.; Mothsra, P.; Bansal, V.; Goyal, R. *Mont. Fur. Chem*. **2006**, *137*, 1189-1194.
[58]. Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959-1961.
[59]. Singh, A. K.; Shukla, S. K.; Quraishi, M. A. *J. Mater. Environ. Sci*. **2011**, *2*, 403-406.
[60]. USEPA website, EPA's Green Chemistry Program, http://www.epa.gov/opptintr/greenchemistry/index.htm
[61]. Singh, A. K.; Shukla, S. K.; Ahamad, I.; Quraishi, M. A. *J. Heterocycl. Chem.* **2009**, *46,* 571-574.
[62]. Luche, J. L. Synthetic Organic Sonochemistry, Plenum Press: New York, 1998.
[63]. Feng, R.; Li, H. M. Sheng Huexue Jiqi Yingyong; Anhui Science & Technology Press, Hefei, 1992.
[64]. Wang, L. M.; Tian, H.; Jingxi Youji Hecheng Xinfangfa; Chemical Industry Press: Beijing, 2004, pp. 396.
[65]. Li, J. T.; Yang, W. Z.; Wang, S. X.; Li, S. H.; Li, T. S. *Ultrason. Sonochem.* **2002**, *9*, 237-239.
[66]. Mason, T. J. Advances in Sonochemistry, JAI Press: London, 1990.
[67]. Shibata, K.; Katsuyama, I.; Matsui, M.; Muramatsu, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3710-3712.
[68]. Nandurkar, N. S. Synthetic Organic Sonochemistry, Plenum Press: New York, 1998.
[69]. Li, J. T.; Chen, G. F.; Yang, W. Z.; Li, T. S. *Ultrason. Sonochem*. **2003**, *10*, 123-126.

[70]. Li, J. T.; Chen, G. F.; Xu, W. Z.; Li, T. S. *Ultrason. Sonochem*. **2003**, *10,* 115-118.
[71]. Ding, L.; Wang, W.; Zhang, A. *Ultrason. Sonochem*. **2007**, *14*, 563-567.
[72]. Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937-6963.
[73]. DoÈmling, A.; Herdtweck, F.; Ugi, I. *Acta Chem. Scand.* **1998**, *52*, 107-113.
[74]. Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366-374.
[75]. Hong-Juan, W.; Xiao-Nan, Z.; Zhan-Hui, Z. *Monatsh. Chem*. **2010,** *141*, 425-430.
[76]. Timothy, J. M. *Chemical Society Reviews*, **1997**, *26*, 443-451.
[77]. Richards, W. T.; Loomis, A. L. *J. Am. Chem. Soc*. **1927**, *49*, 3086-3100;
[78]. Luche, J. L. Synthetic Organic Sonochemistry, Plenum Press; New York, 1998.