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Lewis acid free synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones promoted by 1,1,1,3,3,3-hexafluoro-2-propanol

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Abstract

A convenient, environmentally friendly and efficient procedure for the synthesis 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione derivatives have been developed *via* multi-component and one-pot reactions of various aldehydes with cyclic 1,3-diketones and phthalhydrazide 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). In simple and mild reaction conditions, the use of HFIP is explored as an easy workup and a green catalyst for the one-pot three-component synthesis 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones. Thus, this practical method is developed as a notable medium for these derivatives *via* a multicomponent reaction.

Key words:
3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones, 1,1,1,3,3,3-Hexafluoro-2-propanol, Cyclic 1,3-diketones, Phthalhydrazide, Aldehyde

Introduction

Multi-component reactions (MCRs) enable multiple reactions[1] leading to motivating heterocyclic framework which are useful for the construction of poly-functionalized heterocyclic 'drug like' libraries.[2,3] These reactions have been investigated widely in organic and diversely oriented synthesis. In the past few decades, the synthesis of novel heterocyclic compounds has been received a great deal of attention, most notably for the construction of heterocyclic compounds.[4,5] Nitrogen-containing heterocyclic compounds are widespread in

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nature, and their applications to pharmaceuticals, agrochemicals, and functional materials are becoming more and more important.[6] 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones which are important *N*-heterocycles, comprise a key structural of numerous natural and synthetic bioactive molecules.[7] Moreover, fused Phthalazines were found to possess multiple pharmacological and biological activities such as antimicrobial,[8] antifungal,[9] anticancer,[10] anti-inflammatory,[11] anticonvulsant,[12] cardiotonic,[13] and vasorelaxant.[14] These target molecules also could be promising materials for new luminescence or fluorescence probes.[15]

Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives. Nonetheless the development of new synthetic methods for the proficient preparation of heterocycles containing phthalazine ring fragment is an interesting challenge. In recent years, much attention has been directed toward synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione derivatives. Synthesis of these derivatives have been reported using *p*-TSA,[16] Me_3SiCl,[17] silica sulfuric acid,[18] H_2SO_4,[19] $Mg(HSO_4)_2$,[20] and silica supported poly phosphoric acid,[21] montmorillonite K-10,[22] P_{38} MAP kinase,[23] and *N,N,N,N*-tetramethylguanidinium acetate [TMG][Ac][24] as catalysts. Since many of these methods are associated with more disadvantages such as use of expensive catalyst or toxic organic solvents,[17,20] strong acidic conditions,[16,19] and harsh reaction conditions,[16-21] synthetic methods should be designed to use substances that exhibit little or no toxicity to human health and the environment.

Results and Discussion

In recent years, the fluorous solvents have attracted a grabbing attention and an increasing interest in the context of green reaction media, as catalyst and co-solvent (additive). Fluorinated alcohols were reported to possess lower boiling points and higher melting points than their non-fluorinated counterparts, high polarity, generally selective, without effluents,

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strong hydrogen bond donation properties and the ability to solvate water. Reactions in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) have a facile isolation of the product and can be easily recovered by distillation.[25-27] HFIP has been used in organic synthesis because these fluorinated alcohols are available on a commercial scale. They can be well dispersed in the reaction mixtures in solvolysis reaction, where the generated cationic intermediates can be trapped by nucleophiles. Moreover, HFIP takes part in the reactions as both catalyst and solvent. The electron withdrawing character of CF_3 confers high acidity to the hydrogen of the hydroxyl group.[28] In addition this property, fluorinated alcohols are not nucleophiles or hydrogen bond acceptors. Thus, the degree of auto-association of fluorinated alcohols is low. The chief advantage of fluorinated alcohols, for instance hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE), is the possibility to carry out, in the absence of promoting agents, reactions that usually require the aid of Lewis acids or catalysts.[29,30]

HFIP provides as a dominant hydrogen-bond donor, as was indicated not only by the spectral studies and calorimetric measurements, but also by the isolation of extremely stable complexes with a number of nucleophilic species.[31] Compared to other solvents, HFIP (bp = 58ºC) are unique due to their high ionizing powers, strong hydrogen bond donor abilities, mild acidic characters (pKa = 12.4 and pKa = 9.3, respectively), and low nucleophilicity.[32,33] In recent decades, approaches for the synthesis of biologically interesting products via multi-component reactions were developed. The challenge in this field was developing efficient and rapid green methods. Green chemistry approaches are most important due to the reduction in byproducts, a reduction in produced waste, and reduction of energy cost. In this report, based on earlier success in the preparation of heterocycles with nucleous nitrogen,[34] we present the results of an extended investigation on the activity this solvent, as an efficient medium for the synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones (Scheme 1).

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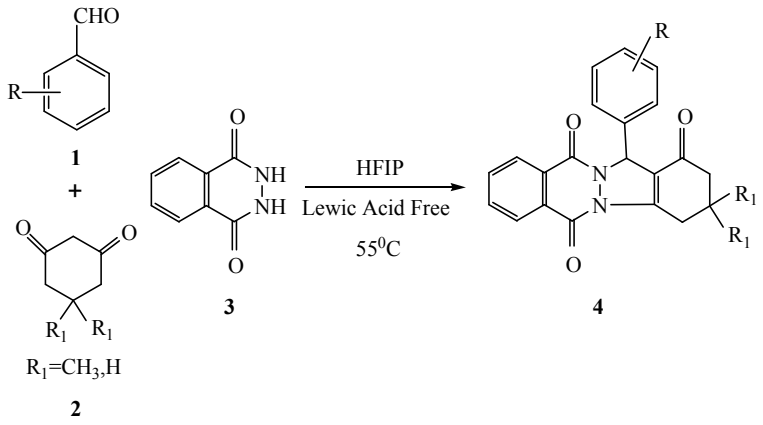

Scheme 1 One-pot synthesis of 1*H*-Indazolo[1,2-b]phthalazine-triones.

We decided to explore the possibility of a simple and facile synthesis 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione derivatives by a three-component condensation reaction of cyclic 1,3-diketones, aromatic aldehydes and phthalhydrazide in the presence of HFIP as a novel and reusable solvent.

First, we examined the amount of HFIP and the reaction temperature using dimidone (1 mmol), benzaldehyde (1 mmol) and phthalhydrazide (1 mmol) to the consequent 3,3-dimethyl-13-phenyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione was studied under reaction conditions in the presence of HFIP at different temperatures and amount of HFIP. The best results were achieved in 0.3 ml at 55°C. No product was observed in the absence of HFIP at 55°C after one day.

Based on the optimized reaction conditions, a range of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione derivatives was synthesized by the reaction of cyclic 1,3-diketones, aldehyde and phthalhydrazide (Table 1). The structures of the products were established from their spectral properties (^{1}H NMR, ^{13}C NMR and elemental analysis) and also by comparison with available literature data.

As shown in Table 1, the direct multi-component reactions worked fit with a variety of aldehydes together with those bearing electron-withdrawing and electron-donating groups

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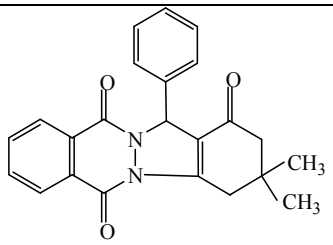
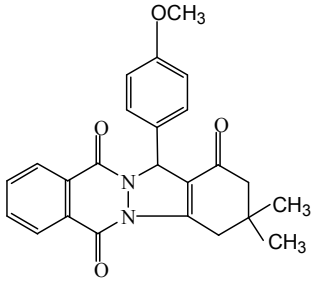
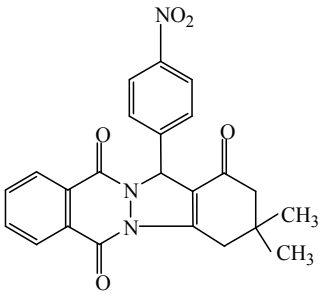
such as Me, OMe, Cl, F, Br or NO_2, and the target molecules were obtained in high to excellent yields.

Table 1

Synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione derivatives using HFIP

Entry	Product	Time (h)	Yield % [ref]
1	 **4a**	8	92[17]
2	 **4b**	9	90[17]
3	 **4c**	10	92[20]

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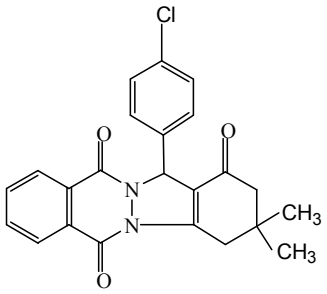
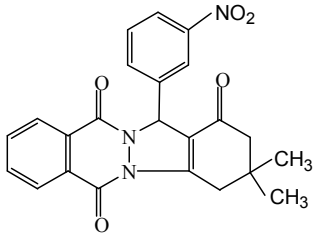
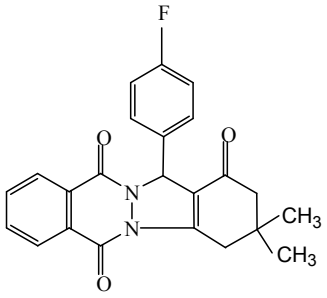
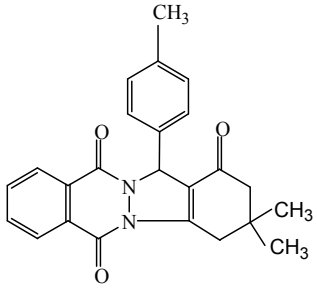
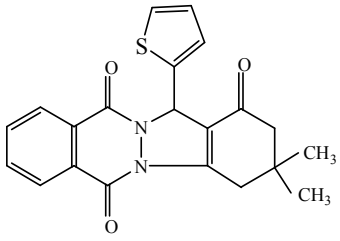
4	 **4d**	8	85[20]
5	 **4e**	11	79[17]
6	 **4f**	15	90[19]
7	 **4g**	12	89[17]
8	 **4h**	9	83[23]

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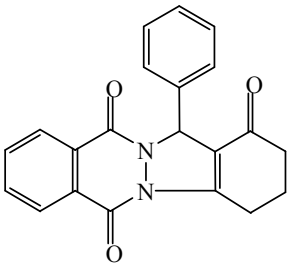
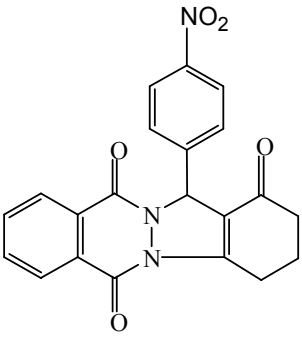
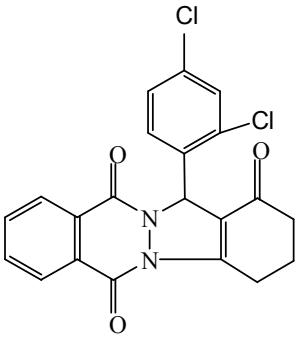
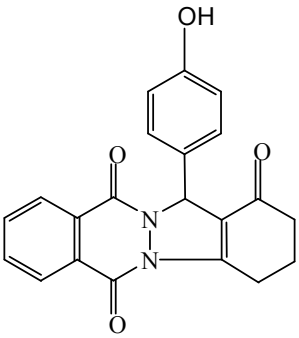
9	 **4i**	8	83[20]
10	 **4j**	10	88[17]
11	 **4k**	8	75[20]
12	 **4l**	9	82[20]

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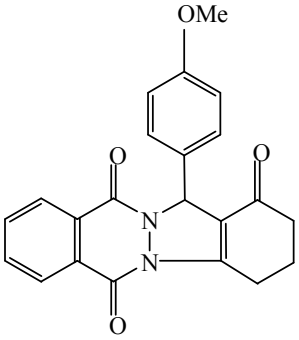
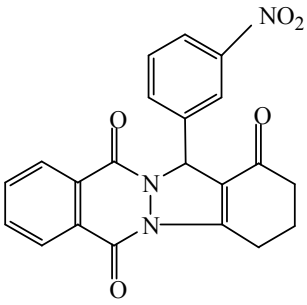
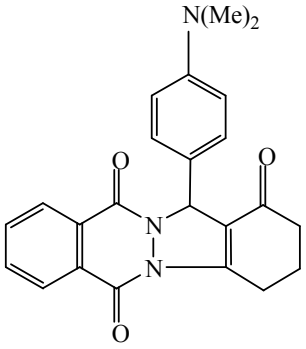
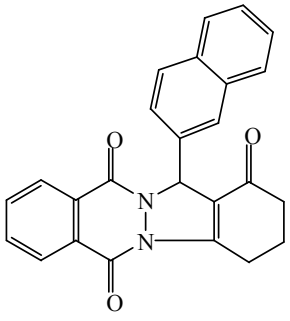
13	 **4m**	10	90[17]
14	 **4n**	9	90[20]
15	 **4o**	12	86[20]
16	 **4p**	10	90[19]

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In continuation of our studies in this field, we decided to synthesize 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones in shorter times and better yields with HFIP. The reaction between 4-fluorobenzaldehydes (1.0 mmol), dimedone (1.0 mmol) with phthalhydrazide (1 mmol) was carried out with HFIP (0.5 ml) at 55^0C. The target molecule (**4f)** of this reaction was obtained with 90% of yield in 15h.

Trifluoroethanol (TFE) is a solvent with similar physicochemical properties of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). In order to examine the catalytic activity of TFE in this reaction, benzaldehyde (1.0 mmol), dimedone (1.0 mmol) with phthalhydrazide (1 mmol) and TFE (0.3 ml) was selected as the model at 70^0C. After 8h, only 78% of expected 3,3-dimethyl-13-phenyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione **(4a)** was obtained.

The formation of strong hydrogen bonds with C=O groups facilitates all reaction routes. In this process, HFIP with a strong H-bond donor (α=1.96, pK_a=9.3), high ionizing power (Y_{OTs}=3.79), and polarity (P_s=11.08) could activate the C=O groups and play a significant role in increasing the electrophilic character.[25-27] Therefore, The formation of products **4a-p** can be rationalized by initial formation of heterodiene by standard Knoevenagel condensation of cyclic 1,3-diketones and aromatic aldehydes in the presence of a catalytic amount. Subsequent Michael-type addition of phthalhydrazide to the heterodienes followed by cyclization and dehydration afford the corresponding products **4a-p** (Scheme 2).

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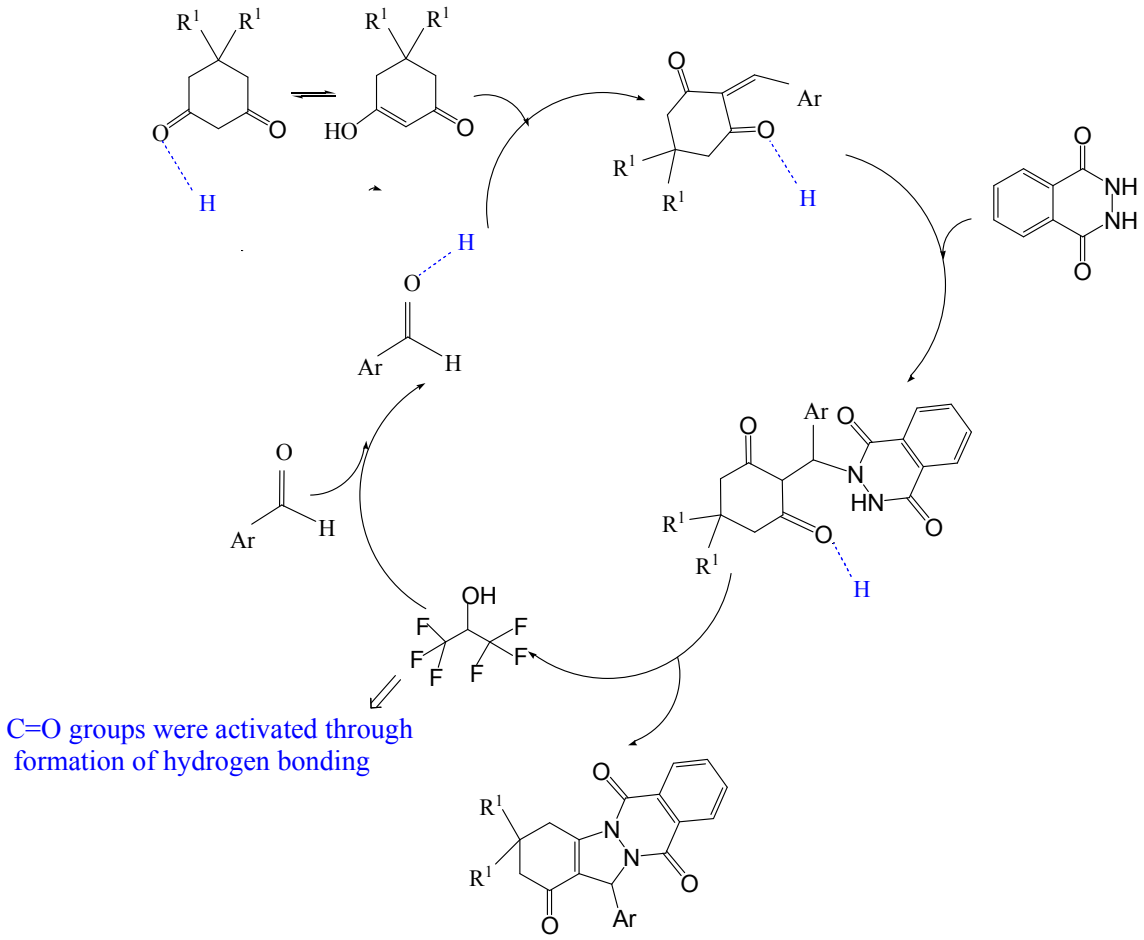

Scheme 2 Proposed mechanism.

To recognize the capability of the present method in comparison with reported methods for the preparation of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione derivatives, the model reaction of dimedone, benzaldehyde and phthalhydrazide was studied in the literature. Their results clearly demonstrate that HFIP is efficient for this three-component reaction (Table 2).

Table 2

Comparison of Methods for the Synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones

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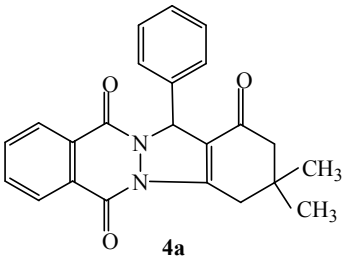
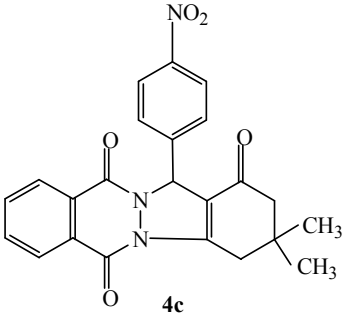
Entry	Compounds 4	Conditions	Time (h)	Yield (%)[a]
1	 **4a**	PMA-SiO_2/Solvent-Free/80 °C[17]	0.66	85
		[bmim]BF_4/H_2O-EtOH/reflux[20]	0.58	88
		1-butyl-3-methylimidazolium bromide/Ultrasound[19]	0.25	90
		HFIP/55 °C	8	92
2	 **4c**	[bmim]BF_4/H_2O-EtOH/reflux[20]	0.5	92
		Silica-SO_3H/Solvent-free/125 °C[19a]	0.11	85
		Sulfuric acid-modified/Solvent-free/80 °C[19b]	0.25	90
		HFIP/55 °C	10	92

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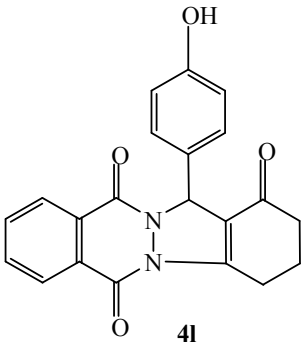
3	 **4l**	PMA-SiO_2/Solvent-Free/80°C[17]	0.66 82
		Sulfuric acid-modified/Solvent-free/80°C[19]	1.16 50
		HFIP/55°C	9 82

The reusability of the catalyst was checked by separating HFIP from mixture and reuse in subsequent reactions. The recovered HFIP can be reused for at least three additional times in subsequent reactions with 92, 90 and 84% of yields in 8h for **4a** without significant loss in product yield.

Experimental

Chemicals were obtained from Merck and Fluka. IR spectra were recorded on a Shimadzu 435-U-04 spectrophotometer (KBr pellets). ^{1}H NMR spectra were obtained using a Jeol FT NMR 300 MHz spectrometer in $CDCl_3$ using TMS as an internal reference. Melting points were determined in open capillary tubes in a Stuart BI Branstead Electrothermal Cat No:IA92003 apparatus and are uncorrected. Mass spec techniques were conducted in GCMS-QP1100EX.

General procedure for the synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones (4a-p)

To a mixture of various aldehydes (1.0 mmol), dimedone or 1,3 cyclohexadione (1.0 mmol) with phthalhydrazide (1 mmol) and HFIP (0.3 ml) was stirred magnetically at 55°C for an appropriate time as mentioned in Table 1. After completion of the reaction (monitored by TLC; n-hexane/ethylacetate, 4/1), the reaction mixture was diluted with EtOH (96%, 0.1 ml)

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and stirred for 2 min in 55°C. Next, the resulting crude product was poured into crushed ice and the solid product, which separated was filtered, recrystallized from ethanol (96%, 3 ml) to get pure 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones **(4a-p)**. Then, the HFIP was separated by distillation and reused in the next run.

3,3-dimethyl-13-phenyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4a). Yellow powder, mp: 200-202 °C, (206-208 °C)[17]; IR (KBr, cm^{-1}): 2958, 1661, 1575; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.23 (6H, s, 2Me), 2.35 (2H, s, CH_2CO), 3.26 and 3.44 (2H, AB system, J = 18.6 Hz, CH_aH_bCO), 6.47 (1H, s, CHN), 7.33-8.37 (9H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 28.5, 28.7, 34.7, 38.1, 50.9, 64.9, 118.6, 127.1, 127.7, 127.9, 128.7, 128.9, 129.1, 133.6, 134.5, 136.4, 150.9, 154.3, 156.1, 192.2; MS, m/z (%): 372 (M, 15), 295 (100), 104 (84), 76 (67).

3,3-dimethyl-13-(4-methoxyphenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4b). Yellow powder, mp: 207-209 °C, (207-209 °C)[17]; IR (KBr, cm^{-1}): 2958, 1663, 1628, 1604, 1513, 1465, 1425, 1361,1312, 1265, 1242, 1172, 1099, 1027, 842, 797, 699; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.25-8.35 (m, 2H), 7.82-7.85 (m, 2H), 6.84-7.35 (m, 4H), 6.42 (s, 1H), 3.76 (s, 3H), 3.23 and 3.42 (2H, AB system, J = 19.2 Hz), 2.34 (s, 2H), 1.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 192.23, 159.74, 156.07, 154.28, 150.75, 134.47, 133.47, 129.18, 128.98, 128.51, 128.36, 127.93, 127.71, 118.58, 114.14, 64.59, 55.21, 50.99, 38.07, 34.65, 28.71, 28.51; MS, m/z (%): 402.

3,3-dimethyl-13-(4-nitrophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4c). Yellow powder, mp: 226-228 °C, (224-225 °C)[20]; IR (KBr, cm^{-1}): 2924, 1695, 1659, 1615; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.21 (3H, s, Me), 1.23 (3H, s, Me), 2.33 and 2.38 (2H, AB system, J = 16.5 Hz, CH_aH_bCO), 3.26 and 3.43 (2H, AB system, J = 19.2 Hz, CH_aH_bCO), 6.52 (1H, s, CHN), 7.61-8.41 (8H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 28.4, 28.7, 34.7, 38.0, 50.8, 64.2, 117.3, 124.1, 127.8, 128.1, 128.3,

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128.6, 128.9, 133.9, 134.9, 143.4, 147.9, 151.7, 154.6, 155.9, 192.1; MS, m/z (%): 417 (M, 5), 295 (100), 104 (48), 76 (75).

3,3-dimethyl-13-(4-chlorophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4d). White powder, mp: 263-265 °C, (260-262 °C)[20]; IR (KBr, cm^{-1}): 2957, 1656, 1623; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.22 (3H, s, Me), 1.23 (3H, s, Me), 2.35 (2H, s, CH_2CO), 3.25 and 3.43 (2H, AB system, J = 19.1 Hz, CH_aH_bCO), 6.43 (1H, s, CHN), 7.31-8.39 (8H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 28.5, 28.7, 34.7, 38.0, 50.9, 64.3, 118.1, 127.7, 128.1, 128.5, 128.8, 128.9, 129.0, 133.7, 134.5, 134.6, 134.9, 151.1, 154.3, 156.0, 192.2 ppm; MS, m/z (%): 406 (M, 5), 295 (100), 104 (43), 76 (46).

3,3-dimethyl-13-(3-nitrophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4e). Yellow powder, mp: 270-272 °C, (270-272 °C)[17]; IR (KBr, cm^{-1}): 2926, 1660, 1625; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.12 (6H, s, 2Me), 2.27 (2H, s, CH_2CO), 3.23 (2H, br s, CH_2CO), 6.46 (1H, s, CHN), 7.60-8.37 (8H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 28.3, 28.9, 34.6, 38.2, 51.5, 64.2, 116.9, 127.3, 127.3, 128.4, 128.7, 129.2, 129.8, 131.5, 132.7, 133.1, 133.6, 134.5, 135.5, 151.8, 154.4, 156.4, 192.2; MS, m/z (%): 417 (M, 10), 295 (100), 104 (48), 76 (75).

3,3-dimethyl-13-(4-methylphenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4g). Yellow powder, mp: 227-229 °C, (227-229 °C)[17]; IR (KBr, cm^{-1}): 2956, 1663, 1621; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.23 (6H, s, 2Me), 2.30 (3H, s, CH_3), 2.35 (2H, s, CH_2CO), 3.24 and 3.43 (2H, AB system, J = 18.5 Hz, CH_aH_bCO), 6.43 (1H, s, CHN), 7.12-8.38 (8H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 21.3, 28.5, 28.8, 34.7, 38.1, 50.9, 64.9, 118.7, 127.1, 127.7, 127.9, 128.9, 129.2, 129.5, 133.4, 133.5, 134.5, 138.5, 150.8, 154.2, 156.1, 192.2; MS, m/z (%): 386 (M, 10), 295 (100), 104 (45), 76 (46).

3,3-dimethyl-13-(thiophen-2-yl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4h). Yellow powder, mp: 219-222 °C, (218-220 °C)[23]; IR (KBr, cm^{-}

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^{1}): 2958, 1661, 1575; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 1.22 (6H, s, 2Me), 2.31 (2H, s, CH_2CO), 3.19 and 3.35 (2H, AB system, J = 18.6 Hz, CH_aH_bCO), 6.48 (1H, s, CHN), 7.29-8.35 (7H, m, Ar); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 28.6, 28.7, 34.7, 38.0, 50.9, 64.9, 118.6, 127.1, 127.7, 127.9, 128.7, 128.9, 129.1, 133.6, 134.5, 136.4, 150.9, 154.3, 156.0, 192.1; MS, m/z (%): 372 (M, 15), 295 (100).

13-(phenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4i). Yellow powder, mp: 223–225 °C, (223-225 °C)[20]; IR (KBr, cm^{-1}): 2954, 1659, 1623, 1366, 1304, 1267, 702; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.24-8.36 (m, 2H), 7.82–7.85 (m, 2H), 7.31-7.43 (m, 5H), 6.44 (s, 1H), 3.29-3.60 (m, 2H), 2.44-2.62 (m, 2H), 2.23-2.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ ppm) δ 192.50, 156.01, 154.21, 152.29, 144.35, 136.33, 134.51, 133.52, 129.04, 128.65, 128.07, 127.95, 127.69, 119.64, 64.94, 36.89, 24.47, 22.26; MS, m/z (%): 344.

13-(4-hydroxyphenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4l). White powder, mp: 267-269 °C, (265-266 °C)[20]; IR (KBr, cm^{-1}): 3424, 2899, 1642, 1612, 1371, 1310, 1279,703; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.83 (s, 1H), 8.23-8.35 (m, 2H), 7.83-7.86 (m, 2H), 7.23 (d, 2H, J = 8.7 Hz), 6.78 (d, 2H, J = 8.4 Hz), 6.37 (s, 1H), 3.35-3.60 (m, 2H), 2.46-2.47 (m, 2H), 2.24-2.28 (m,2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 197.29, 162.42, 160.57, 158.79, 157.08, 139.25, 138.28, 137.07, 133.73, 133.38, 132.66, 132.09, 131.80, 130.27, 124.18, 120.28, 69.25, 41.68, 29.16, 27.02; MS, m/z (%): 360.

13-(4-methoxyphenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4m). Yellow powder, mp: 245–247 °C, (242-244 °C)[17]; IR (KBr, cm^{-1}): 2950, 1657, 1624, 1365, 1306, 1246, 703; ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.25-8.35 (m, 2H), 7.82-7.86 (m,2H), 7.32-7.37 (m, 2H), 6.83-6.87 (m, 2H), 6.42 (s, 1H), 3.75 (s, 3H), 3.28-3.60 (m, 2H), 2.44-2.49 (m, 2H), 2.23–2.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 192.60,

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159.73, 156.05, 154.22, 152.19,134.48, 133.47, 129.16, 128.94, 128.55, 128.30, 127.93, 127.69,119.65, 114.09, 64.58, 55.23, 36.96, 24.51, 22.34; MS, m/z (%): 374.

13-(3-nitrophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4n). Yellow powder, mp: 232-234 °C, (228-230 °C)[20]; IR (KBr, cm^{-1}): 2926, 1662, 1624, 1369, 1305, 1285, 697; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.22-8.40 (m, 2H), 8.14-8.17 (m, 2H), 7.52-7.92 (m, 4H), 6.52 (s, 1H), 3.31-3.65 (m, 2H), 2.46-2.50(m, 2H), 2.23-2.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 192.46, 164.62, 155.99, 154.65, 153.21, 148.53, 138.60, 134.78, 129.62, 128.27, 127.76, 123.69, 121.70, 118.26, 64.25, 36.79, 24.54, 22.23; MS, m/z (%): 389.

13-(4-*N,N*-dimethylphenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4o). White powder, mp: 257-259 °C, (256-258 °C)[20]; IR (KBr, cm^{-1}): 2923, 1661, 1616, 1364, 1305,1280, 699; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.25-8.34 (m, 2H), 7.80-7.83 (m, 2H), 7.26-7.29 (m, 2H), 6.63-6.66 (m, 2H), 6.40 (s, 1H), 3.35-3.61 (m, 2H), 2.89 (s, 6H), 2.46-2.48 (m, 2H), 2.24-2.28 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 192.59, 156.12, 154.12, 151.89, 150.64, 134.34, 133.28, 129.39, 128.98, 128.92, 128.21, 127.84, 127.70, 123.41, 119.95, 112.40, 112.26, 64.83, 40.64, 40.36, 37.02, 24.53, 22.39; MS, m/z (%): 387.

13-(naphthalen-2-yl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (4p). Yellow powder, mp: 248-250 °C, (248-250 °C)[19b]; IR (KBr, cm^{-1}): 2961, 1655, 1626; ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 1.22 (6H, s, 2Me), 2.33 (2H, s, CH_2C), 3.24-3.50 (2H, AB system, J =18.6 Hz, CH_aH_bCO), 6.62 (1H, s, CHN), 7.45-8.38 (11H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$, ppm); δ 28.4, 28.7, 34.6, 38.1, 50.9, 65.1, 118.6, 124.2, 126.2, 126.3, 126.8, 127.6, 127.7, 127.9, 128.2, 128.7, 129.0, 129.6, 133.2, 133.4, 133.5, 133.6, 134.5, 150.8, 154.2, 156.1, 192.1; MS, m/z (%): 422 (M, 5), 295 (100), 104 (40), 76 (56).

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Conclusion

In summary, a novel and highly efficient methodology for the synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones by a three-component condensation reaction of cyclic 1,3-diketones, aromatic aldehydes and phthalhydrazide in the presence of HFIP was reported. In contrast to the existing methods using potentially hazardous catalysts/additives, this new method offers the following competitive advantages such as avoiding the use of any base, metal, or Lewis acid catalysts. To the best of our knowledge, this method represents the first example of the synthesis 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones in the absence of catalyst.

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Graphical Abstract

Lewis acid free synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones promoted by 1,1,1,3,3,3-hexafluoro-2-propanol

Behrooz Maleki*, Samaneh Sedigh Ashrafi, Reza Tayebee

- ✓ For the first time a Lewis acid catalyst free is proposed for the synthesis of 3,4-dihydro-1*H*-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-triones derivatives
- ✓ Avoiding of any base, metal, or Lewis acid catalysts
- ✓ Reusability of the catalyst