

Heteropoly Acid in Ionic Liquid - An Efficient Catalyst for the Preparation of 2H-Indazolo[2,1-b]Phthalazine-Triones

Razieh Fazaeli*, Hamid Aliyan* and Nahid Fazaeli

Department of Chemistry, Islamic Azad University, Shahreza Branch, 86145-311, Iran

Abstract: 2H-Indazolo[2,1-b]phthalazine-1,6,11(13H)-trione derivatives were synthesized in a simple and efficient method from the three-component condensation reaction of phthalhydrazide, dimedone, and aromatic aldehydes by $H_3PW_{12}O_{40}$ in ionic liquid in good to excellent yields and short reaction times. The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) offered the best results in terms of yield of the products. It was observed that a homogeneous reaction medium proved beneficial for the yield of the reaction.

Keywords: Heteropoly acids (HPAs), dimedone, phthalhydrazide, indazolophthalazine, one-pot reaction, ionic liquid.

INTRODUCTION

Nitrogen-containing heterocyclic compounds spread out over a large area in nature, and their act of applying to biologically active pharmaceuticals, agrochemicals, and functional materials are becoming to a larger and larger degree important [1]. Phthalazine derivatives were reported to possess vasorelaxant [2], cardiotoxic [3], and anticonvulsant [4], activities. Therefore, a number of methods have been reported in the literature for the synthesis of phthalazine derivatives [4-11]. Unfortunately, many of these processes suffer from one or other limitations such as harsh reaction conditions, low product yields, tedious work-up procedures, relatively long reaction times, and co-occurrence of several side products, and difficulty in recovery and reusability of the catalysts. Moreover, some of the reagents employed are very expensive. Therefore, the search continues for a better catalyst for the synthesis of heterocycles containing phthalazine ring fragment in term of operational simplicity, reusability, economic viability, and greater selectivity. Recently the synthesis of 2H-indazolo[2,1-b]phthalazine-triones has been reported by Bazzir and co-workers using *p*-TSA as catalyst [12].

In recent years, the use of ionic liquids as a recyclable reaction medium, to replace volatile organic solvents has received considerable attention [13]. Ionic liquids, also called "the designer solvents", have been largely successful in replacing obnoxious organic solvents. Their high thermal stability and ability to solvate various substrates have made them highly useful in a variety of organic reactions [14-16].

In recent decades, uses of heteropoly acids (HPAs) as catalysts for fine organic synthetic processes have been developed and are important for industries related with fine chemicals [17], including flavors, pharmaceuticals and food industries [18]. Heteropoly acids are more active catalysts than conventional inorganic and organic acids for various

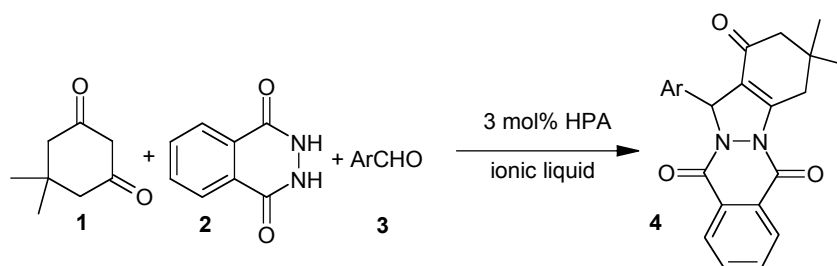
reactions in solutions [19]. They are used as industrial catalysts for several liquid phase reactions [20-23]. Among heteropoly acids, polytungstic acids are the most widely used catalysts owing to their high acid strengths, thermal stabilities, and low reducibilities. Catalysts based on heteropoly acids as Brønsted acids have many advantages over liquid acid catalysts. They are non-corrosive and environmentally benign, presenting fewer disposal problems. Solid heteropoly acids have attracted much attention in organic synthesis owing to easy work-up procedures, easy filtration, and minimization of cost and waste generation due to reuse and recycling of the catalysts [24-26]. Supported heteropoly acid on silica gel has been used as effective catalyst for Diels Alder [27] and Fries rearrangement [28], Friedel-Crafts reactions [29].

In continuation of our work on the catalytic properties of heteropoly acids [30], herein, we wish to report a suitable method for the use of $H_3PW_{12}O_{40}$ in ionic liquid as catalyst for Preparation of 2,2-dimethyl-13-phenyl-2,3-dihydro-1H-indazolo[2,1-b]phthalazine-4,6,11(13H)-trione (Scheme 1).

RESULT AND DISCUSSION

At first, for optimization of the reaction conditions, the reaction of benzaldehyde (1.2 mmol), dimedone (1 mmol) and phthalhydrazide (1 mmol) in CH₃CN at room temperature in the presence of a catalytic amount of $H_3PW_{12}O_{40}$ (5 mol%) was studied. The analysis of the reaction mixture showed that the desired product 2,2-dimethyl-13-phenyl-2,3-dihydro-1H-indazolo[2,1-b]phthalazine-4,6,11(13H)-trione was produced in only 75% after 3 h plus unreacted starting materials (Table 1, entry 1). We have also observed that even the prolonged reaction time to 7 h did not affect the yield of the product. Then, we decided to study the catalytic ability of $H_3PW_{12}O_{40}$ in ionic liquid. We observed that the reaction of benzaldehyde (1.2 mmol) dimedone (1 mmol) and phthalhydrazide (1 mmol) in CH₃CN in the presence of the $H_3PW_{12}O_{40}$ (2 mol%) in ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) was performed smoothly and the desired product; 2,2-dimethyl-13-phenyl-2,3-dihydro-1H-indazolo[2,1-b]phthalazine-4,6,11(13H)-trione was obtained in 92%

*Address correspondence to these authors at the Department of Chemistry, Islamic Azad University, Shahreza Branch, 86145-311, Iran; Tel: +98 321 3232706; Fax: +98 321 3232701-2; E-mails: fazaeli@iaush.ac.ir, aliyan@iaush.ac.ir



Scheme 1. Preparation of 2,2-dimethyl-13-phenyl-2,3-dihydro-1H-indazolo[2,1-b]phthalazine-4,6,11(13H)-trione.

yield after 30 min (Table 1, entry 6). We have also studied the similar reaction only in the presence of ionic liquid ([bmim]BF₄). The reaction did not proceed at all and the starting materials were remained intact after 10 h (Table 1, entry 9). These results show the strong synergistic effect of ionic liquid upon the catalytic activity of H₃PW₁₂O₄₀ in the reaction of benzaldehyde with dimedone and phthalhydrazide.

We carried out the reaction in various other hydrophilic as well as hydrophobic ionic liquids and conventional organic solvents to compare the outcome of the reaction in terms of the yield and the rate of the reaction. HPA dissolved in organic solvents like DMF, and acetonitrile and hydrophilic ionic liquids, such as 1-butyl-3-methylimidazolium chloride ([bmim]Cl) to produce a homogenous system. However, HPA was insoluble in hydrophobic ionic liquids, such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆). Better yields were obtained when catalyst was soluble in the reaction medium compared with those obtained when the catalyst was insoluble in the reaction solvent (Table 1, entries 6,7). From these observations, it can be deduced that the solubility of the catalyst in the medium plays an important role in enhancing the outcome of the reaction and that a homogeneous system produces better yields. Amongst the various ionic liquids and organic solvents that were employed for the present study, [bmim]BF₄ was employed for further investigation.

Table 1. Phosphotungstic Acid (HTP) Catalyzed Preparation of 2,2-Dimethyl-13-Phenyl-2,3-Dihydro-1H-Indazolo[2,1-b]Phthalazine-4,6,11(13H)-Trione in Various Solvents at Room Temperature^a

Entry	Solvent	Time (h)	Yield ^b (%)
1	Acetonitrile	3	75
2	Ethanol	5	43
3	Water	7	28
4	Dichloromethane	5.5	40
5	DMF	9	55
6	[bmim]BF ₄	0.5	92
7	[bmim]PF ₆	8	80
8	[bmim]Cl	3.5	90
9	[bmim]BF ₄ ^c	10	no reaction

^aReaction conditions: benzaldehyde (1.2 mmol), dimedone (1 mmol), phthalhydrazide (1 mmol), and HTP (2 mol%) was used in various solvents (5 ml) at room temperature. ^b Isolated yields. ^cWithout HTP.

The results of the synthesis of 3,4-dihydro-3,3-dimethyl-13-phenyl-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (4a) using a variety of heteropolyacids as catalyst in [bmim]BF₄ are shown in Table 2. We employed four different HPAs, H₃PW₁₂O₄₀, H₃PMo₁₂O₄₀, H₄SiW₁₂O₄₀, H₄SiMo₁₂O₄₀ (Keggin series) for the reaction. All the HPAs completely dissolved in the ionic liquid. 3 mol % of each of these HPAs were used. The reaction mixture was stirred at room temperature. Comparison of these HPAs showed that the higher activity and selectivity could be achieved using H₃PW₁₂O₄₀. This catalyst is more efficient than others and gave the highest yield of the desired product. Comparison of the obtained yields of all reactions at the same time, 20 min, confirmed this result (Table 2).

Table 2. Comparison of Different Heteropoly Acids (HPAs) Employed for Preparation of 2,2-Dimethyl-13-Phenyl-2,3-Dihydro-1H-Indazolo[2,1-b]Phthalazine-4,6,11(13H)-Trione in [bmim]BF₄ at Room Temperature After 20 Min^a

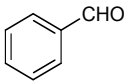
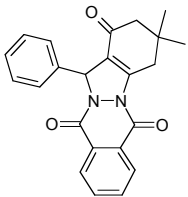
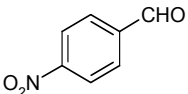
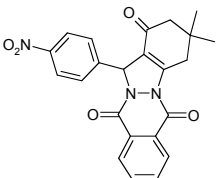
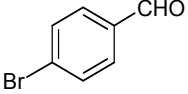
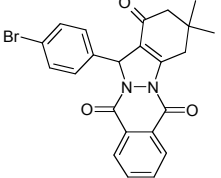
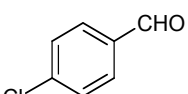
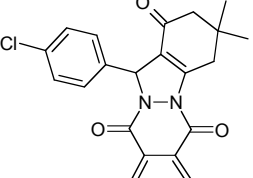
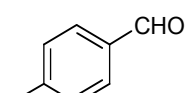
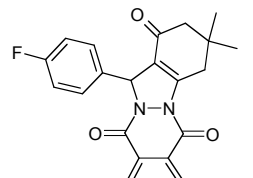
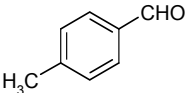
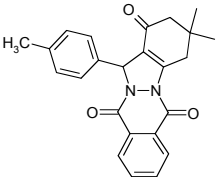
Heteropoly Acid ^a	Catalyst (Mol %)	Yield ^b (%)
H ₃ PW ₁₂ O ₄₀	1	78
H ₃ PW ₁₂ O ₄₀	3	98
H ₃ PW ₁₂ O ₄₀	5	98
H ₃ PMo ₁₂ O ₄₀	3	74
H ₄ SiW ₁₂ O ₄₀	3	75
H ₄ SiMo ₁₂ O ₄₀	3	68

^aReaction conditions: benzaldehyde (1.2 mmol), dimedone (1 mmol) and phthalhydrazide (1 mmol) was used in various catalysts in [bmim]BF₄ (2 mL) at room temperature. ^bIsolated yields.

In order to show the general applicability of the protocol, we have applied this catalytic system for the preparation of 2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione derivatives from several types of aldehydes. Aromatic aldehydes carrying either electron donating or withdrawing substituents afforded high product yields with high purity (Table 3, entries 4a-e) with exception of the electron donating methyl group (Table 3, entry 4f), which takes a slightly longer reaction time.

In order to show the merit of the present work in comparison with recently reported protocols, we compared the results of the 2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione derivatives synthesis from various aldehydes in the presence of silica-SO₃H, *p*-TSA, and HTP/[bmim]BF₄ with respect to the amounts of the catalysts used, reaction times and yields of the products (Table 4).

Table 3. Preparation of 2H-Indazolo[2,1-b]Phthalazine-1,6,11(13H)-Trione Derivatives 4^a

Entry	Substrate	Product	Time (min)	Yield (%) ^b	m.p. (lit. m.p.) ^{ref}
a			10	90	203-205 (203-205) ¹⁰
b			7	87	223-225 (226-228) ¹⁰
c			7	92	265-267 (266-268) ¹⁰
d			8	92	261-263 (261-263) ¹⁰
e			7	90	218-220 (218-220) ¹⁰
f			18	82	227-229 (226-228) ¹⁰

^aReaction conditions: aldehyde (1.2 mmol), dimedone (1 mmol), phthalhydrazide (1 mmol), and mixture of [bmim]BF₄ (2 mL) and HTP (3 mol%), room temperature.

Comparison of Keggin type heteropoly acid with these catalysts for this reaction show that activity of HTP/[bmim]BF₄ seems to be higher than or equal with other known catalysts (Table 4).

The combination of the heteropoly acid and [bmim]BF₄ provides a homogeneous system for the reaction; hence this prompted us to investigate the possibility of recycling the complete system of HPA and ionic liquid. The result was quite fruitful. The entire product could be isolated from the reaction mixture simply by ether extraction, and the system of the catalyst and ionic liquid could be recovered and recharged with fresh substrates. We screened the system for

three subsequent runs; the product was obtained in 98 %, 96% and 87% yields, respectively (Table 5).

EXPERIMENTAL

All solvents and reagents were purchased from Fluka, Aldrich and Merck chemical Companies. The products were purified by column or thick layer chromatography techniques. Products were characterized by comparison of spectroscopic data (IR, ¹H NMR spectra) and melting points with authentic samples. FT-IR spectra were recorded on a Shimadzu DR-8001 spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250MHz instrument.

Table 4. Comparison of HTP/[bmim]BF₄ with Two Catalysts for Synthesis of 2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione Derivatives

Entry	Aldehyde (Ar)	Time (min): Yield (%)		
		HTP/[bmim]BF ₄	Silica-SO ₃ H [10]	<i>p</i> -TSA [12]
1	Ph-C ₆ H ₄	10 : 90	8 : 87	10 : 86
2	4-NO ₂ -C ₆ H ₄	7 : 87	7 : 85	10 : 91
3	4-Br-C ₆ H ₄	7 : 92	7 : 86	10 : 90
4	4-Me-C ₆ H ₄	18 : 82	35 : 80	20 : 83

Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX. Melting points are not corrected.

Table 5. Recycling of HTP^a

Run	Yield ^b (%)
1	98
2	96
3	87
4	51

^aReaction conditions: benzaldehyde (1.2 mmol), dimedone (1 mmol) and phthalhydrazide (1 mmol), HTP (3 mol%), [bmim]BF₄ (2 mL), room temperature.

^bIsolated yields.

Typical Procedure for the Preparation of 2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione Derivatives 4

To a mixture of ionic liquid (2 mL) and phosphotungstic acid (3 mol%), dimedone (0.14 g, 1 mmol), phthalhydrazide (0.16 g, 1 mmol) and an aldehyde (1.2 mmol) were added. The resulting mixture was stirred at room temperature for the appropriate time as indicated in Table 3. The progress of the reaction was monitored by TLC. The crude product was isolated by extracting the reaction mixture with diethyl ether (4×15 mL). The combined ether extractions were dried over Na₂SO₄, concentrated and the residue recrystallized from ethyl acetate/*n*-hexane (1:3) to afford the pure product. The products 4a-4f are known compounds, and their structures were deduced by comparison of their physical and spectroscopic data with those previously reported [9-12].

Spectroscopic Data for 3,4-Dihydro-3,3-Dimethyl-13-(Phenyl)-2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione (4a)

Yellow powder. Mp 203–205 °C; IR (KBr) (ν_{\max} , cm⁻¹): 2953, 1565, 1573; δ_{H} (300 MHz, CDCl₃) 1.21 (3H, s), 1.23 (3H, s), 2.35 (2H, s), 3.25 and 3.40 (2H, AB system), 6.45 (1H, s), 7.29–8.35 (9H, m); δ_{C} (75 MHz, CDCl₃) 28.5, 28.8, 34.6, 38.1, 50.9, 64.9, 118.6, 127.2, 127.7, 127.9, 128.6, 128.9, 129.2, 133.6, 134.5, 136.4, 150.9, 154.3, 156.2, 192.2; MS, *m/z* (%): 372 (M⁺, 15), 295 (100), 104 (84), 76 (67). Anal. Calcd for C₂₃H₂₀N₂O₃: C, 74.18; H, 5.41; N, 7.52%. Found: C, 74.10; H, 5.16; N, 7.46%.

Spectroscopic Data for 3,4-Dihydro-3,3-Dimethyl-13-(4-Nitrophenyl)-2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione (4b)

Yellow powder. Mp 223–225 °C; IR (KBr) (ν_{\max} , cm⁻¹): 2922, 1692, 1647, 1610; δ_{H} (300 MHz, CDCl₃) 1.21 (3H, s), 1.24 (3H, s), 2.33 (2H, s), 3.25 and 3.41 (2H, AB system),

6.50 (1H, s), 7.60–8.43 (8H, m); δ_{C} (75 MHz, CDCl₃) 28.4, 28.7, 34.7, 38.2, 50.8, 64.4, 117.3, 124.3, 127.6, 128.2, 128.3, 128.6, 128.9, 134.0, 134.9, 143.1, 147.9, 151.9, 154.7, 155.7, 192.3.

Spectroscopic Data for 3,4-Dihydro-3,3-Dimethyl-13-(4-Bromophenyl)-2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione (4c)

Yellow powder. Mp 265–267 °C; IR (KBr) (ν_{\max} , cm⁻¹): 2958, 1543, 1618; δ_{H} (300 MHz, CDCl₃) 1.21 (3H, s), 1.22 (3H, s), 2.34 (2H, s), 3.24 and 3.42 (2H, AB system), 6.41 (1H, s), 7.29–8.37 (8H, m); δ_{C} (75 MHz, CDCl₃) 28.4, 28.9, 34.6, 38.0, 50.9, 64.3, 118.1, 122.9, 127.8, 128.1, 128.8, 128.8, 129.1, 131.7, 133.7, 134.7, 135.4, 151.3, 154.1, 156.2, 192.2.

Spectroscopic Data for 3,4-Dihydro-3,3-Dimethyl-13-(4-Chlorophenyl)-2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione (4d)

Yellow powder. Mp 261–263 °C; IR (KBr) (ν_{\max} , cm⁻¹): 2952, 1652, 1628; δ_{H} (300 MHz, CDCl₃) 1.23 (3H, s), 1.25 (3H, s), 2.32 (2H, s), 3.26 and 3.44 (2H, AB system), 6.44 (1H, s), 7.33–8.36 (8H, m); δ_{C} (75 MHz, CDCl₃) 28.4, 28.9, 34.9, 38.1, 50.9, 64.6, 118.2, 127.7, 128.2, 128.4, 128.8, 128.9, 129.2, 133.4, 134.5, 134.5, 151.3, 154.3, 156.0, 192.0.

Spectroscopic Data for 3,4-Dihydro-3,3-Dimethyl-13-(4-Fluorophenyl)-2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione (4e)

Yellow powder. Mp 218–220 °C; IR (KBr) (ν_{\max} , cm⁻¹): 2951, 1668, 1660; δ_{H} (300 MHz, CDCl₃) 1.20 (3H, s), 1.22 (3H, s), 2.35 (2H, s), 3.24 and 3.43 (2H, AB system), 6.43 (1H, s), 8.34 (8H, m); δ_{C} (75 MHz, CDCl₃) 28.4, 28.5, 34.5, 38.1, 50.9, 64.4, 115.5, 115.9, 118.3, 127.2, 128.2, 128.9, 129.2, 132.1, 133.8, 134.6, 151.4, 154.2, 156.2, 192.0.

Spectroscopic Data for 3,4-Dihydro-3,3-Dimethyl-13-(4-Methylphenyl)-2*H*-Indazolo[2,1-*b*]Phthalazine-1,6,11(13*H*)-Trione (4f)

Yellow powder. Mp 227–229 °C; IR (KBr) (ν_{\max} , cm⁻¹): 2954, 1659, 1628; δ_{H} (300 MHz, CDCl₃) 1.21 (3H, s), 1.23 (3H, s), 2.30 (3H, s), 2.35 (2H, s), 3.24 and 3.42 (2H, AB system), 6.43 (1H, s), 7.13–8.35 (8H, m); δ_{C} (75 MHz, CDCl₃) 21.3, 28.9, 34.7, 38.2, 50.9, 64.6, 118.9, 127.0, 127.5, 127.9, 129.2, 129.0, 129.1, 133.3, 133.4, 134.5, 138.5, 150.5, 154.3, 156.0, 192.4.

CONCLUSIONS

We have described an efficient and one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones *via* a cyclocondensation reaction of dimedone, phthalhydrazide, and aromatic

aldehydes using a combination of heteropoly acid and ionic liquid under solvent-free conditions. Both the catalyst and ionic liquid could be easily recovered and recycled. The absence of undesirable side-products and ambient reaction conditions also enhanced the synthetic utility of the reaction.

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