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ENVIRONMENT-FRIENDLY GREEN APPROACHES FOR AN EFFICIENT SYNTHESIS OF 2H-INDAZOLO [2,1-b] PHTHALAZINE-1,6,11 (13H)-TRIONES CATALYZED BY TANNIC ACID

Davood SHEIKH,[a*] Ali VARASTEH MORADI[b] and Zahra HEKMATIAN [a]

[a] Young Researchers & Elite Club, Hamedan Branch, Islamic Azad University, Hamedan, Iran.
[b] Department of Chemistry, Gorgan Branch, Islamic Azad University, Gorgan, Iran

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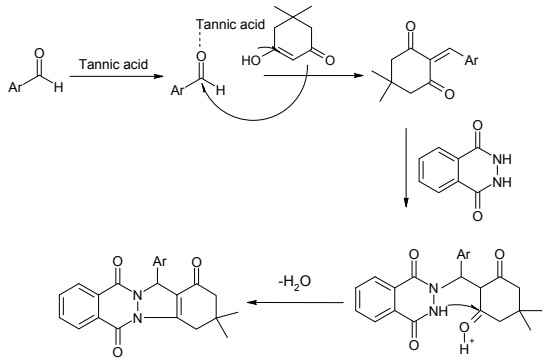
This article describes a facile pathway for one-pot synthesis of 2H-indazolo[2,1-b] phthalazine-triones in the presence of tannic acid as an ecofriendly catalyst. The reactions proceed smoothly at room temperature to afford the products in high yields.



INTRODUCTION

Development of a simple, eco-benign and low cost protocol, using a heterogeneous and reusable catalyst in synthetic organic chemistry still remains as an attractive goal for researchers.[1]

Tannic acid is a specific commercial form of tannin, a type of polyphenol. The chemical formula for commercial tannic acid is given as $C_{76}H_{52}O_{46}$, *i.e.*, a molecule with deca-galloyl glucose. Glucose occupies the central core position in the tannic acid structure whose hydroxyl groups are attached to one or more galloyl residues. Polyphenolic nature of tannic acid may be explored for its weak acidity, catalytic efficiency, antioxidant activity, redox properties and hydrogen donor's capability. Due to this properties, tannic acid be used as mild acid catalyst in the synthesis of compounds such as benzodiazepines and amidoalkylnaphthols.[2–3]

On 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.[4] Among a large variety of heterocyclic compounds, heterocycles containing phthalazine moiety are of interest because the show some pharmacological and biological activities.[5–7] Many methods have been developed for the synthesis of phthalazine derivatives.[8–17]

Solvent-free reaction condition has been demonstrated to be an efficient technique for

* Correspondence to: Tel.: +98(811) 34494000; fax: +98(811) 34494026. E-mail: davood.sheikh@gmail.com

various organic reactions. It often leads to a remarkable decrease in reaction time, increased yields, easier workup, and enhancement of regio and stereo-selectivity of reaction.[18]

The aim of the present study is to investigate the catalytic capability and enhancement of the efficiency of the tannic acid for the synthesis of 2H-indazolo[2,1-b] phthalazine-triones.

RESULT AND DISCUSSION

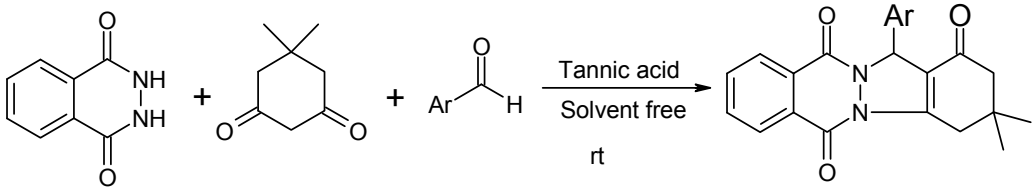
In continuation of our research and interest in the development of novel synthetic methodologies and heterocyclic compounds,[19–25] we would like to report that tannic acid is an efficient, cheap and non-toxic catalyst for the formation of 2H-indazolo [2,1-b] phthalazine-triones at room temperature by one-pot three component reaction of phthalhydrazide, dimedone and aromatic aldehydes under solvent-free conditions (Scheme 1).

In order to establish the conditions of the titled reactions, we preliminary examined the model condensation reaction between phthalhydrazide (1 mmol), dimedone (1 mmol) and benzaldehyde (1 mmol) as test compounds. The effects of solvent, and conditions on the reaction were studied by using different solvents such as EtOH, MeCN, and H_2O (Table 1). As seen in this Table, it was noticed that, the reaction worked out best at room temperature under solvent-free conditions using tannic acid (10 mol%) (entry 8). To substantiate the importance of the catalyst, the reaction was carried out at room temperature in the absence of the catalyst under solvent-free conditions. As a result, only trace amount of the product was formed (entry 6).

Under the optimized conditions, (room temperature, 10 mol% catalyst), phthalhydrazide, dimedone and aromatic aldehydes were reacted (Table 2). In all cases, high yields of products were obtained.

To show the advantage this method, we have compared some of our outcome with various catalytic systems were reported (Table 3). As indicated in the Table 3, tannic acid in comparison with other catalysts performs this alteration in milder reaction condition.

A possible catalytic mechanism that explains the formation of products is shown in Scheme 2. This mechanism is similar to the one suggested in literature.[2] The first step of the catalytic cycle is the coordination of tannic acid to the aldehyde to form intermediate. Then in step 2, the standard Knoevenagel condensation of dimedone with the aromatic aldehyde is carried out. Subsequent Michael-type addition of phthalhydrazide to intermediate followed successively by cyclization, dehydration and air oxidation affords the corresponding products.



Scheme 1 – Synthesis of 2H-indazolo[2,1-b] phthalazine-triones using tannic acid.

Table 1

Optimization of the model reaction between phthalhydrazide, dimedone and benzaldehyde [a]

Entry	Temperature (°C)	Solvent	Catalyst (mol%)	Time (min)	Yield (%) [b]
1	r.t	EtOH	10	100	65
2	r.t	H_2O	10	100	38
4	r.t	EtOH/H_2O	10	100	60
5	r.t	MeCN	10	100	45
6	r.t	Solvent free	None	120	Trace
7	r.t	Solvent free	5	85	75
8	r.t	Solvent free	10	40	88
9	r.t	Solvent free	15	85	86
10	r.t	Solvent free	20	100	83

[a] Conditions: Phthalhydrazide (0.16 g, 1 mmol), Dimedone (0.14 g, 1 mmol), Benzaldehyde (1 mmol) and tannic acid.
[b] Isolated yields

Table 2

Synthesis of 2H-indazolo[2,1-b] phthalazine-triones using tannic acid from aromatic aldehydes, phthalhydrazide and dimedone [a]

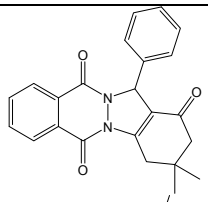
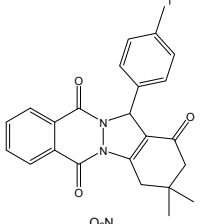
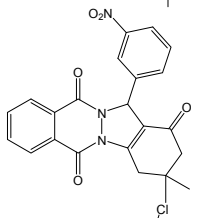
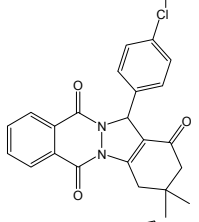
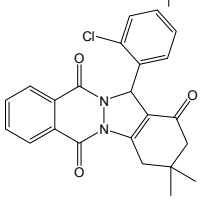
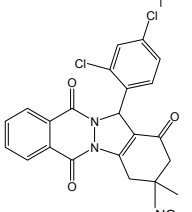
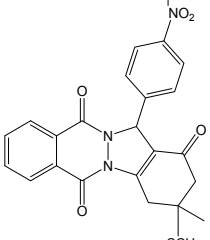
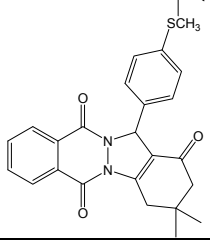
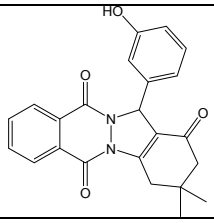
Entry	Aldehyde	Product	Time (min)	Yield (%) [b]
a	Benzaldehyde		40	88
b	4-methylbenzaldehyde		45	75
c	3-nitrobenzaldehyde		30	87
d	4-chlorobenzaldehyde		35	93
e	2-chloro benzaldehyde		40	80
f	2,4-di chlorobenzaldehyde		35	91
g	4-nitro benzaldehyde		30	80
h	4-thiomethylbenzaldehyde		35	88

Table 2 (continued)

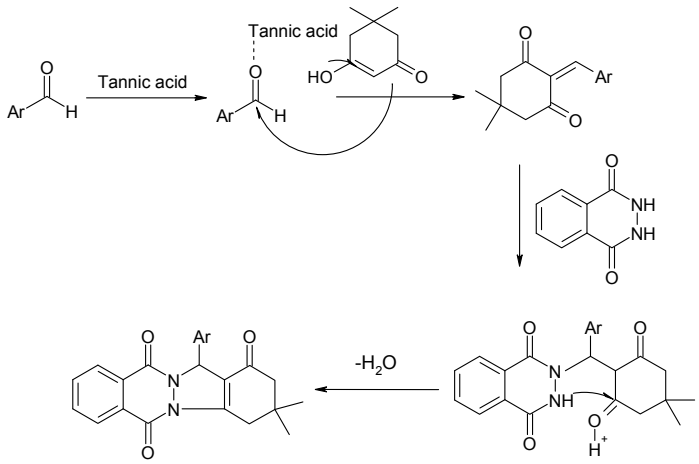
i	3-hydroxy benzaldehyde		40	84

[a] All compounds were characterized by recording their melting points, IR spectra, ^{1}H NMR, ^{13}CNMR spectra and comparing with data reported in literature.
[b] Isolated yields.

Table 3

Synthesis of indazolo[2,1-b]phthalazine-1,6,11(13H)-trione by tannic acid in comparison with other catalysts

Entry	Catalyst	Catalyst load (mol %)	Condition (°C)	Time (min)	Yield (%)[a]	References
1	Tannic acid	10	r.t	40	88	This work
2	H_2SO_4	15	Reflux	30	86	[13]
3	PBBS	0.2 g	100	25	65	[11]
4	Silica sulfuric acid	65	100	8	87	[16]
5	I_2	10	Ultrasound	15	95	[15]
6	p-TSA	30	80	10	86	[17]
7	$ZrOCl_2.8H_2O$	30	80	60	82	[14]



Scheme 2 – Plausible mechanism for Synthesis of 2H-indazolo[2,1-b] phthalazine-triones using tannic acid.

EXPERIMENTAL

Materials used in this article were prepared from Fluka and Merck companies and utilized without purification. Melting points were measured on a SMPI apparatus. The solvent was evaporated by Rota vapor IKA R-300. Products were isolated and their physical information was matched with those of known specimen. IR (KBr) spectra were recorded on a Shimadzu 470 and Perkin-Elmer 781 spectrophotometer. ^{1}H NMR spectra were obtained in $CDCl_3$ solution from a Bruker Avance AC-400 MHz and ^{13}C NMR spectra at 100 MHz on the aforementioned instrument.

Typical Procedure for the Synthesis of 2H-indazolo [2,1-b] phthalazine-triones

To a mixture of Aldehyde (1 mmol) and tannic acid (0.1 mmol) taken in round bottom flask was added dimedone (1 mmol), phthalhydrazide (1 mmol) and the reaction mixture

was stirred at room temperature for appropriate time (Table 2). The progress of reaction was checked by TLC. The reaction mixture was cooled, washed with ethyl acetate (10 ml). Removal of the solvent under reduced pressure gave the crude product that was recrystallized from ethanol to afford the pure product. The products were characterized by IR, ^{1}H and ^{13}C NMR.

Physical and spectroscopic data of products are given below:

3,4-dihydro-3,3-dimethyl-13-phenyl-2H-indazolo[2,1-b]phthalazine-1,6,11(13H) triones **(entry a)**:
M.P: 205-207 °C. IR (cm^{-1}) 1687, 1656. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.22 (s, 6H), 2.35 (s, 2H), 3.46-3.23 (AB system, J = 19.2 Hz, 2H), 6.26 (s, 1H), 7.44-7.29 (m, 5H), 7.87-7.85 (m, 2H), 8.32-8.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 192.1, 156.0, 154.2, 150.9, 136.4, 134.5, 133.5, 129.0, 128.9, 128.7, 128.7, 127.9, 127.7, 127.1, 118.6, 64.9, 50.9, 38.0, 34.6, 28.7, 28.4.

3,4-dihydro-3,3-dimethyl-13-(4-methylphenyl)-2H-indazolo[2,1-b] phthalazine-1,6,11 (13H)-triones **(Table 3, entry b):**
M.P: 228-230 °C. IR (cm^{-1}) 1679, 1668. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.23 (s, 6H), 2.32 (S, 3H), 2.36 (s, 2H), 3.46-3.23 (AB system, J = 19.2 Hz, 2H), 6.44 (s, 1H), 7.17-7.15 (m, 2H), 7.30-7.28 (m, 1H), 7.34-7.29 (m, 2H), 7.38-7.36 (m, 1H), 7.87-7.85 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.2, 156.0, 154.2, 150.7, 138.5, 134.4, 133.5, 133.4, 129.4, 129.1, 129.0, 127.9, 127.7, 127.0, 118.7, 64.8, 50.9, 38.0, 34.6, 28.7, 28.5, 21.2.

3,4-dihydro-3,3-dimethyl-13-(3-nitrophenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11 (13H)-triones **(Table 3, entry c):**
M.P: 268-271 °C. IR (cm^{-1}) 1684, 1661. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.23 (s, 6H), 2.35 (s, 2H), 3.47-3.24 (AB system, J = 18.9 Hz, 2H), 6.53 (s, 1H), 8.4-7.53 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 192.1, 155.9, 154.3, 150.8, 148.5, 138.4, 134.7, 134.2, 133.9, 129.6, 128.9, 128.6, 127.7, 123.7, 121.5, 117.1, 64.1, 50.8, 38.0, 34.7, 28.7, 28.4.

3,4-dihydro-3,3-dimethyl-13-(4-cholorophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11 (13H)-triones **(entry d):**
M.P: 263-265 °C. IR (cm^{-1}) 1664, 1622. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.23 (s, 6H), 2.36 (s, 2H), 3.45-3.24 (AB system, J = 19.2 Hz, 2H), 6.44 (s, 1H), 7.40-7.29 (m, 4H), 7.90-7.88 (m, 2H), 8.39-8.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 192.2, 156.0, 154.4, 151.1, 135.0, 134.7, 134.6, 133.7, 129.1, 129.0, 128.9, 128.6, 127.8, 118.1, 64.4, 50.9, 38.1, 34.7, 28.7, 28.5.

3,4-dihydro-3,3-dimethyl-13-(2-cholorophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11 (13H)-triones **(Table 3, entry e):**
M.P: 260-262 °C. IR (cm^{-1}) 1685, 1654. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.23 (s, 6H), 2.34 (s, 2H), 3.45-3.23 (AB system, J = 18.0 Hz, 2H), 6.60 (s, 1H), 8.35-7.20 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.2, 156.2, 154.2, 151.6, 134.5, 133.6, 133.0, 132.7, 132.5, 129.9, 129.0, 128.6, 128.0, 127.5, 116.6, 64.0, 50.0, 39.1, 34.5, 29.7, 28.4.

3,4-dihydro-3,3-dimethyl-13-(2,4-dicholorophenyl)-2H-indazolo[2,1-b] phthalazine-1,6,11 (13H)-triones **(Table 3, entry f):**
M.P: 219-221°C. IR (cm^{-1}) 1655, 1640. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.21 (s, 6H), 2.33 (s, 2H), 3.43-3.22 (AB system, J = 18.0 Hz, 2H), 6.70 (s, 1H), 8.39-7.22 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.1, 156.4, 154.3, 152.4, 134.7, 134.2, 133.7, 130.7, 129.0, 128.5, 128.1, 127.6, 127.5, 64.4, 50.8, 38.0, 34.6, 28.8, 28.4.

3,4-dihydro-3,3-dimethyl-13-(4-nitrophenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11 (13H)-triones **(Table 3, entry h):**
M.P: 222-224 °C. IR (cm^{-1}) 1655, 1625. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.21 (s, 3H), 1.25 (s, 3H), 2.35 (s, 2H), 3.44-3.23 (AB system, J = 18.0 Hz, 2H), 6.50 (s, 1H), 8.40-7.26 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.2, 155.8, 154.6, 151.8, 148.0, 143.5, 134.9, 134.1, 128.9, 128.6, 128.2, 128.1, 127.1, 124.1, 117.4, 64.2, 50.9, 50.7, 38.1, 34.8, 28.8, 28.5.

3,4-dihydro-3,3-dimethyl-13-(3-hydroxyphenyl)-2H-indazolo [2,1-b] phthalazine-1,6,11 (13H)-triones **(Table 3, entry i):**
M.P: 265-267 °C. IR (cm^{-1}) 3357, 1663. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.21 (s, 6H), 2.32 (s, 2H), 3.44-3.21 (AB system, J = 18.0 Hz, 2H), 5.97 (b, 1H), 6.41 (s, 1H), 7.19-6.71 (m, 4H), 7.90-7.84 (m, 2H), 8.27-8.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=192.3, 156.1, 154.0, 151.0, 137.9, 134.64, 133.6, 129.9, 128.9, 128.0 (2C), 127.7, 118.6, 118.5, 115.9, 114.6, 64.7, 50.9, 38.0, 34.6, 28.6, 28.5.

CONCLUSIONS

In conclusion, an efficient, mild and three-component preparation of indazolo [2,1-b]phthalazine-1,6,11(13H)-trione derivatives in presence of tannic acid as a heterogeneous and ecofriendly catalyst were examined. Various derivatives of aldehydes are used. The advantages of this method are simple work up, ambient temperature, non-toxic and solvent-free conditions. We believe that the present methodology would be an important addition to existing methodologies.

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