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SYNTHESIS OF PHENYL 1*H*-INDAZOLO [1,2-*b*] PHTHALAZINE TRIONE DERIVATIVES WITH THEIR BIOLOGICAL EVALUATION

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Abstract:

Heterocyclic compounds are the most global moieties in chemical compounds which exhibit wide spectrum of pharmacological activities. Multicomponent reactions are important tool in the hands of organic chemist's,researcher. Since they offer improved atom economy for construction of complex molecules over the stepwise liner convergent synthesis. A simple, efficient and green protocol has been developed for the synthesis phenyl 1H-Indazolo [1,2-b] Phthalazine trione derivatives from a one pot four componant condensation of Phthalic anhydride, Hydrazine hydrate, Dimedone and different substituted aromatic aldehydes was refluxed independently in ethanol using Cesium Chloride as an efficient catalyst. Synthesized compounds were screened for their Anti-oxidant activity. These newly synthesized compounds were evaluated by their spectral analysis.

Keywords: *MCRs, Phthalic anhydride, Hydrazine hydrate, Dimedone, Aromatic aldehyde*

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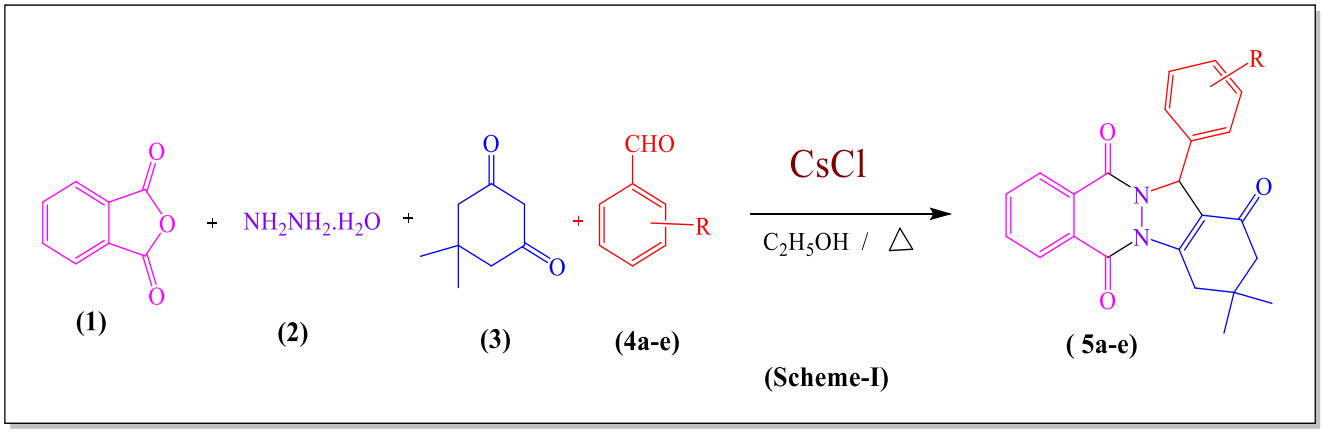
INTRODUCTION:

Multi-component reactions (MCRs) offer a number of fascinating and challenging transformations in organic synthesis [1-7]. 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 heterocycles [8]. Heterocyclic compounds occur very extensively in nature and are essential to life. Among a large variety of heterocyclic compounds, heterocycles containing phthalazine moiety [9,10] are of importance because they show some pharmacological and biological activities [11]. Phthalazine derivatives which have two bridgehead nitrogen atoms in a fused ring system were reported several activities such as anticonvulsant [12], cardiotonic [13], and vasorelaxant activities [14-18], cytotoxic [19], antimicrobial [20], antifungal [21], anticancer [22] and anti-inflammatory [23]. Moreover, these compounds exhibited good promise as new luminescent materials or fluorescence probes [24]. Despite the available methods, the development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment is therefore an interesting challenge.

Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives. Recently, three-component reactions of Dimedone (5, 5-dimethylcyclohexane- 1,3-dione), aromatic aldehyde, and phthalhydrazide to give 2*H*-indazolo[2,1-*b*] phthalazine-triones have attracted the interest of the synthetic community. Various catalytic systems including *p*-TSA [25], Me_3SiCl [26], silica sulfuric acid [27], H_2SO4 [28], cyanuric chloride [29], heteropolyacids [30], and N-halo sulfonamides [31] have been reported. The direct four-component condensations have also been achieved by employing $Ce(SO4)_2{\cdot}4H_2O$ [32], sulfuric acid-modified PEG-6000 [33] under solvent-free conditions. However, some of these methods suffered from several drawbacks such as hazardous organic solvents, high cost, long reaction time, use of stoichiometric and excess amounts of acids. Therefore, the development of a new, efficient, and environment-friendly procedure is still in demand.

Now a days, the catalytic activity of Cesium chloride is useful as an efficient, reusable for sulfonylation and desulfonylation of heteroatom's, acid imparting high regio and chemo selectivity in chemical reaction, it is active for the transesterification of diethyl carbonate by different alcohols and diols with an activity nearly independent of the structure of the substrate.

RESULT AND DISCUSSION:



(Scheme-I)

We initially focused on optimization reaction condition. The reaction mixture of Phthalic anhydride, hydrazine hydrate, Dimedone and different substituted aromatic aldehydes was refluxed independently in ethanol using Cesium chloride as an efficient and novel catalyst, was considered as a model reaction (**Scheme 1**) for investigating the effectiveness of different polar and non polar solvent using catalytic amount of Cesium chloride (15 mol%). Solvent optimization clearly noted that ethanol is the best solvent for the desired transformation due to fast reaction rate and high yield (Table1, entry 6). The other polar protic solvents gives moderate yield (Table1, entry 5).While other aprotic solvent like DCM, Acetonitrile, THF, DMF, displayed slow reaction rates leading lower yield (Table1, entry 1-4).

We have carried out the model reaction using different stoichiometric amount of catalyst. The catalyst screening result are summarized in Table 2. It was observed that the excellent yield was achieved by using 15 mol% of Cesium chloride (Table 2, entry 5).

Further investigating the influence of different parameters on the model reaction, we turned our attention towards the 13-substituted derivatives of 2,3,4,13-tetrahydr-13-phenyl-3,3-dimethyl-1*H*-indazolo [1,2-*b*] phthalazine-1,6,11-trione **(5a-e)** using one pot four component reaction of Phthalic anhydride **(1)**, hydrazine hydrate **(2)**, Dimedone **(3)** and different substituted aldehydes **(4a-e)**, was refluxed independently in ethanol using Cesium chloride, and the result are summarized in Table 3. With the both electron-poor and electron-rich benzaldhydes (Table 3, entries 1-3 and 4-5), the corresponding 13-substituted derivatives of 2,3,4,13-tetrahydr-13-phenyl-3,3-dimethyl-1*H*-indazolo [1,2-*b*] phthalazine-1,6,11-trione **(5a-e),** were obtained to excellent yields. These synthesized products **(5a-e)** were characterized from IR, ^{1}H-NMR, Mass and ^{13}C-NMR spectroscopic technique and also elemental analysis.

The Cesium Chloride acting as phase transfer catalyst that's why reaction mechanism was accelerated, we proposed tentative plausible mechanism for the formation of 2,3,4,13-Tetrahydr-13-phenyl-3,3-dimethyl-1*H*-indazolo [1,2-*b*] phthalazine-1,6,11-trione **(5a-e),** in the presence of Cesium chloride. The overall, mechanism takes place according to Knoevenagels-Micheal reaction **(Scheme-II).**

Table 1: Optimization of the reaction conditions using different solvents.[a]

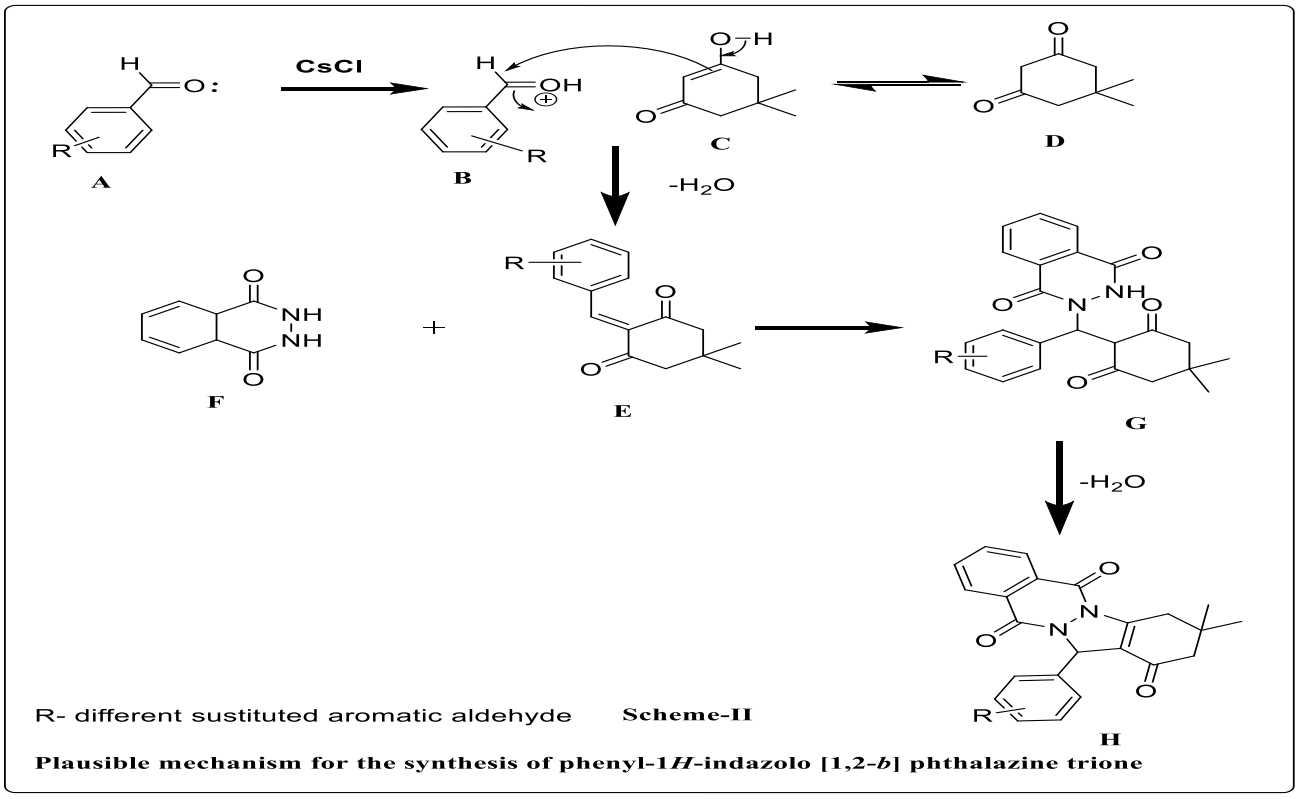
Entry	Solvent	Reaction Time (h)	Yield (%)[b]
1	DCM	6.0	30
2	Acetonitrile	7.5	38
3	DMF	8.0	40
4	THF	6.0	45
5	Ethylene glycol	5.5	68
6	Ethanol	4.0	82

[a] ***Reaction conditions:*** Phthalic anhydride(1 mmol), hydrazine hydrate(1 mmol), dimedone (1 mmol) and different substituted aldehydes(1 mmol) was refluxed at 60^0 C.
[b] Isolated yields.

Table 2: Optimization Study for the amount of Cesium Chloride.[a]

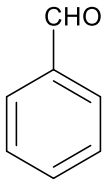
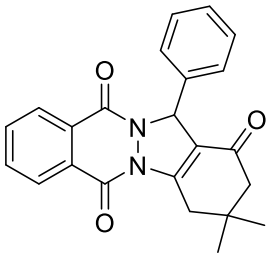
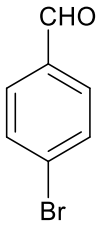
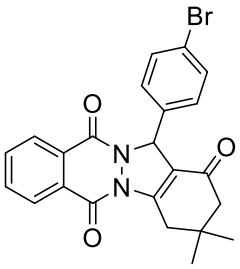
Entry	Catalyst (mole %)	Temperature (^{0}C)	Reaction Time (h)	Yield %[b]
1	01	60	4.0	42
2	02	60	5.0	50
3	05	60	4.0	60
4	08	60	5.0	68
5	10	60	4.0	75
6	15	60	5.0	82
7	20	60	4.0	82

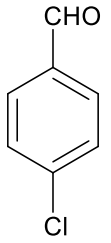
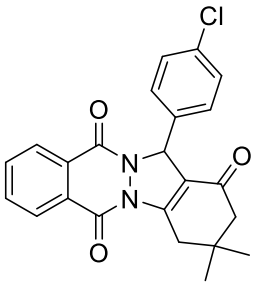
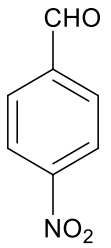
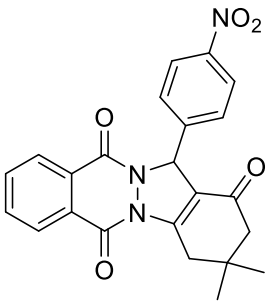
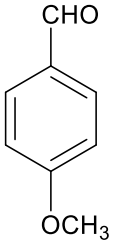
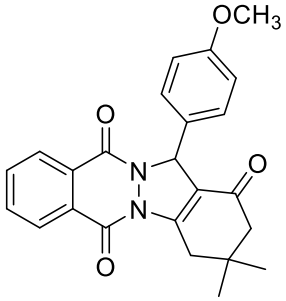
[a] ***Reaction conditions:*** Phthalic anhydride(1 mmol), hydrazine hydrate(1 mmol), dimedone (1 mmol) and different substituted aldehydes(1 mmol) was refluxed at 60^0 C
[b] Isolated yields.



Plausible mechanism for the synthesis of phenyl-1*H*-indazolo [1,2-*b*] phthalazine trione

Table 3: Four component reaction of Phthalic anhydride (1), hydrazine hydrate (2), dimedone (3), aromatic aldehydes (4a-e), and for the synthesis of (5a-4e).[a]

Entry	Aldehyde (3a-e)	Products (4a-4e)	Time (h)	Yield (%)[b]	M.P. (^{0}C)
1			3.0	70	205-207
2			3.5	82	265-267

3			4.0	80	261-263
4			3.5	78	224-226
5			3.0	76	207-209

[a] ***Reaction conditions:*** (1) (1 mmol), (2) (1 mmol), (3) (1 mmol), (4a-e) (1 mmol) and ethanol in Cesium Chloride were refluxed at 60°. [b] Isolated yields.

EXPERIMENTAL:

Open capillary tubes were used for melting points of isolated synthesized compounds and are uncorrected. Perkin-Elmer FTIR spectrophotometer was used for IR (KBr) spectra of compounds. Mass spectral data were recorded on liquid chromatography mass spectrometer (Shimadzu 2010Ev) using ESI probe. The ^{1}H and ^{13}C NMR spectra were recorded on various spectrometers at 300 & 400MHz using TMS as an internal standard.

General procedure for the synthesis of 13-substituted derivatives of 2,3,4,13-Tetrahydro-13-phenyl-3,3-Dimethyl-1*H*-indazolo[1,2-*b*] phthalazine-1,6,11 trione (5a-e) :

A mixture of Phthalic anhydride **(1)**, Hydrazine hydrate **(2)**, Dimedone (10 mmol) **(3)** was refluxed independently in ethanol and Cesium Chloride with different substituted aromatic aldehydes **(4a-e)**, to afford the respective products **(5a-e)**. The reaction mixture was cooled to room temperature and poured into ice cold water. The solid obtained was filtered, washed with water and recrystallized by ethanol to give **(5a-e)**. The reaction was monitored by TLC. These synthesized compounds **(5a-e)** were completely characterized from IR, ^{1}H-NMR, Mass and ^{13}C-NMR spectroscopic technique and also elemental analysis.

Spectral Analysis:

2,3,4,13-Tetrahydro-13-phenyl-3,3-Dimethyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (5a) :

M.P. 205-207 ^{0}C, Yield 70 %. IR (KBr, νmax, cm^{-1}) 2930, 1650, 1620, 1340, 1282, 730; ^{1}H NMR (400MHz, DMSO-d$_6$, ppm) δ 8.30-8.25 (m, 1H), 8.26-8.22 (m, 1H), 7.80-6.72 (m, 5H, Ar-H), 6.40 (s, 1H, Ar-CH), 3.60 (s, 3H), 3.45 and 3.24 (AB system, J = 19.1 Hz, 2H), 2.35 (s, 2H), 1.20 (s, 3H), 1.30 (s, 3H); EI-MS (m/z: RA %): 372 ($M^{+\cdot}$, 100%). Elemental analysis Calculated data for $C_{23}H_{20}N_2O_3$; C, 73.24; N, 08.13. Found: C, 73.22; N, 08.11.

2,3,4,13-Tetrahydro-13-(4-Bromo-phenyl)-3,3-dimethyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (5b) :

M.P. 265-267 ^{0}C , Yield 82 %. IR (KBr, *v*max , cm^{-1}) 2950, 2880, 1654, 1352, 1286; ^{1}H NMR (400MHz, DMSO-d_6 , ppm) δ 8.30-8.35 (m, 1H), 8.29- 8.26 (m, 1H),7.82-7.89 (m, 2H), 7.12–7.55 (m, 4H, Ar-H), 6.45 (s, 1H Ar-CH), 3.42 and 3.68 (AB system, *J* = 19.0 Hz, 2H), 2.40 (s, 2H), 1.25 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (400 MHz, DMSO–d_6, ppm): δ 192.0, 158.0, 154.0, 151.9, 135.5, 131.6, 130.5, 128.2, 127.6., Elemental analysis calculated data for $C_{21}H_{15}BrN_2O_3$; C, 59.58; N, 06.65 . Found: C, 59.56; N, 06.53.

2,3,4,13-Tetrahydro-13-(4-Chloro-phenyl)-3,3-dimethyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (5c) :

M.P. 261-263 ^{0}C, Yield 80% .IR (KBr, *v*max, cm^{-1}) 2960, 1665, 1629, 1365, 1320, 1253, 796; ^{1}H NMR (400MHz, DMSO-d_6 , ppm) δ 8.22-8.40 (m, 2H), 7.82-7.89 (m, 2H), 7.25-7.38 (m, 4H, Ar-H), 6.45 (s, 1H, Ar-CH), 3.20 and 3.42 (AB-q system, *J* = 19.04 Hz, 2H), 2.35 (s, 2H), 1.20 (s, 3H, CH3), 0.98 (s, 3H, CH3) ; EI-MS (m/z: RA %): 406 ($M^{+\cdot}$, 100%); ^{13}C NMR (400 MHz, DMSO–d_6, ppm) δ: 194.1, 162.6, 150.7, 149.0, 144.2, 136.6, 134.0, 130.7, 128.1,128.0, 127.6, 114.2, 66.3, 55.8, 40.2, 29.5, 27.6. Elemental analysis calculated data for $C_{23}H_{19}ClN_2O_3$; C, 67.90; N, 06.89. Found: C, 67.92; N, 06.91.

2,3,4,13-Tetrahydro-13-(4-nitro-phenyl)-3,3-Dimethyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (5d) :

M.P. 224-226 ^{0}C, Yield 78%. IR (KBr, *v*max, cm^{-1}) 3010, 2960, 1697, 1590, 1380, 1350, 1260, 845; ^{1}H NMR (400MHz, DMSO-d_6 , ppm) δ 8.20-8.40 (m, 2H), 7.84-7.90 (m, 2H), 7.25-7.65 (m, 4H, Ar-H), 6.49 (s, 1H, Ar-CH), 3.20 and 3.45 (AB-q system, *J* = 21.2 Hz, 2H), 2.50 (s, 2H), 1.20 (s, 3H, CH3), 1.18 (s, 3H, CH3); EI-MS (m/z: RA %): 417 ($M^{+\cdot}$, 100),. ^{13}C NMR (400 MHz, DMSO–d_6, ppm) δ 193.1, 163.9, 150.4, 149.4, 144.2, 141.8, 130.7, 130.7, 129.0, 124.6, 123.0, 115.9, 64.1, 50.7, 40.9, 29.2, 27.3; Elemental analysis calculated data for $C_{23}H_{19}N_3O_5$; C, 66.19; N, 10.07. Found: C, 66.21; N, 10.09.

2,3,4,13-Tetrahydro-13-(4-Methoxy-phenyl)-3,3-dimethyl-1*H*-indazolo[1,2-*b*]phthalazine-1,6,11-trione (5e) :

M.P. 207-209 ^{0}C, Yield 76%.IR (KBr, *v*max, cm^{-1}) 3012, 2895, 1662, 1499, 1367, 1309, 1268, 795); ^{1}H NMR (400MHz, DMSO-d_6 / ppm) δ 8.20-8.40 (m, 2H), 7.81-7.89(m, 2H), 6.75-7.14 (m, 4H, Ar-H), 6.38 (s, 1H, Ar-CH), 3.63 (s, 3H, OCH3), 3.16 and 3.45 (AB-q system, *J* = 19.1 Hz, 2H), 2.44 (s, 2H), 1.09 (s, 3H, CH3), 1.04 (s, 3H, CH3); EI-MS (m/z: RA %): 402 ($M^{+\cdot}$ +1, 100%),. ^{13}C NMR (400 MHz, DMSO–d_6, ppm) δ: 192.5, 163.2, 154.6, 158.2, 145.6, 138.2, 131.4, 129.9, 128.4, 127.2. 116.8, 110.4, 56.1, 52.1, 44.0, 32.6, 29.0, 27.8. Elemental analysis calculated data for $C_{24}H_{22}N_2O_4$; C, 71.62; N, 06.95. Found: C, 71.65; N, 06.97.

Biological Activity:

Antioxidant Activity:

A) DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay:

DPPH (1,1-diphenyl-2-picrylhydrazyl) radical scavenging assay was performed as per earlier reported method. The reaction cocktail was prepared by mixing individual newly synthesized organic compounds is added to equal volume of 0.1 mM solution of DPPH radical in absolute ethanol. After 20 minutes of incubation at room temperature, the DPPH reduction was calculated by reading the absorbance at 517 nm using UV-Visible spectrophotometer. Ascorbic acid (1mM) was used as reference compound.

The compound **(5b and 5d)** shows remarkable antioxidant activity against DDPH radical scavenging activity with reference of ascorbic acid (91.4 ±0.021).

B) OH radical scavenging assay:

Hydroxy radicals scavenging activity was measured with Fenton's reaction (Rollet –Labelle et al., 1998). The reaction mixture contained 60 µl of $FeCl_2$ (1mM), 90 µl of 1,10-phenanthroline(1mM), 2.4 ml of phosphate buffer (pH 7.8),150 µl of 0.17M H_2O_2 and 1.5 ml of individual newly synthesized organic compounds (1mM). The reaction mixture was kept at room temperature for 5 minutes incubation and the absorbance was recorded at 560 nm using UV-Visible spectrophotometer. Ascorbic acid (1mM) was used as the reference compound.

The compound **(5b, 5c and 5d)** shows good OH radical scavenging activity as compared with Ascorbic acid (89.5 ± 0.021).

Table 4: Antioxidant activity of tested compounds (5a-5e).

Entry	Compound Code	% Radical scavenging activity	
		DPPH radical scavenging	OH radical scavenging
1	**5a**	40.2 ± 0.60	51.1 ± 1.22
2	**5b**	80.6 ± 0.82	84.0 ± 1.60
3	**5c**	78.2 ± 1.84	82.2 ± 1.06
4	**5d**	88.4 ± 1.36	86.9 ± 0.21
5	**5e**	65.4 ± 0.30	70.2 ± 1.25
6	**Ascorbic Acid (Standard)**	**91.4 ± 0.021**	**89.5 ± 0.021**

CONCLUSION:

In conclusion, we have developed an efficient, green and easy protocol for synthesis of 13-substituted derivatives of 2,3,4,13-Tetrahydro-13-phenyl-3,3-Dimethyl-1*H*-indazolo[1,2-*b*] phthalazine-1,6,11 trione by reaction of corresponding substituted aldehydes, phthalic anhydride, hydrazine hydrate, and Dimedone in presence Cesium Chloride in ethanol. The product can be easily isolated by simple workup technique, short time, less expensive, requires ambient reaction condition, and give excellent yield. Among these synthesized compounds shows potent Antioxidant activity.

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