Ionic Liquid 4-(3-Methyl-1-imidazolio)-1-butanesulfonic Acid Hydrogen Sulfate-catalyzed Synthesis of Phthalazinetrione Derivatives

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A simple method for the synthesis of phthalazinetrione derivatives by a one-pot three-component condensation reaction of phthalhydrazide, 1,3-dicarbonyl compounds and aldehydes catalyzed by the ionic liquid 4-(3-methyl-1-imidazolio)-1-butanesulfonic acid hydrogen sulfate ($[BSO_3HmIm]HSO_4$) is reported. Good to excellent yields were obtained in short reaction times in the solvent PEG 600 (polyethylene glycol 600) at 120 °C. The strategy proved to be efficient and environmentally benign. The catalyst/solvent system could easily be recovered and reused for at least 5 times without noticeable loss of activity.

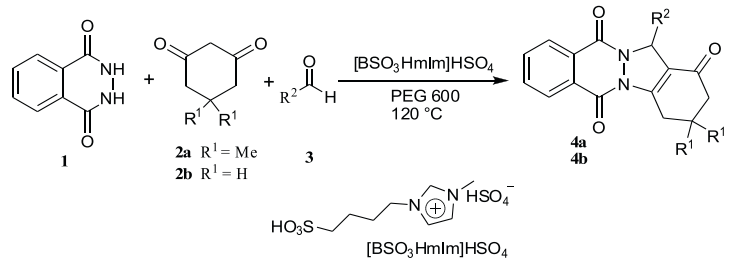
Key words: Multicomponent Reaction, One-pot, Ionic Liquid, Phthalazinetrione Derivative

Introduction

Multicomponent reactions (MCRs), which have emerged as a powerful tool for the construction of novel and complex molecules [1], have attracted increasing attention. These types of reactions have some advantages over conventional linear syntheses, including lower costs, shorter reaction times, higher degrees of atom economy, the possibility for combinatorial surveying of structural variations, and environmental friendliness [2].

In the past few years, heterocyclic compounds have received great interest because they are common in Nature and often essential to life. Heterocycles containing the phthalazine moiety show some pharmacological and biological activities [3]. Phthalazine derivatives have been reported to possess anticonvulsant [4], cardiotonic [5], vasorelaxant [6], cytotoxic [7], antimicrobial [8], antifungal [9], anticancer [10], and anti-inflammatory activities [11]. In addition, these compounds show good promise as new luminescence materials and fluorescence probes [12]. There are several methods to synthesize phthalazine derivatives, including the reaction of phthalhydrazide, aldehydes and dimedone or cyclohexane-1,3-dione catalyzed by *p*-TSA [13], H_2SO_4 [14], $H_4SiW_{12}O_{40}$ [15], $H_3PW_{12}O_{40}$ [16], silica sulfuric acid [17], silica-supported polyphosphoric acid [18], TMSCl [19], phosphomolybdic acid (PMA)-SiO_2 [20], *N*,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide and poly(*N*-bromo-*N*-ethylbenzene-1,3-disulfonamide) [21]. Most recently a one-pot four-component reaction for the synthesis of phthalazine derivatives was reported using $Ce(SO_4)_2 \cdot 4H_2O$ [22] as catalyst. However, these methods have limitations such as the use of toxic metals, toxic organic solvents, expensive or large amounts of catalysts, and tedious work-up procedures. Besides, the recovery of catalysts or solvents is difficult for the existing methods. From the viewpoint of green chemistry, there is still an urgent need to develop new strategies for the preparation of heterocycles containing the phthalazine ring fragment.

Ionic liquids have attracted intensive interest recently. Compared to traditional volatile organic solvents, they have unique advantages, such as negligible vapor pressure, recyclability and solvophobic properties. By virtue of the incorporated functional groups, ionic liquids can act not only as solvents but also as



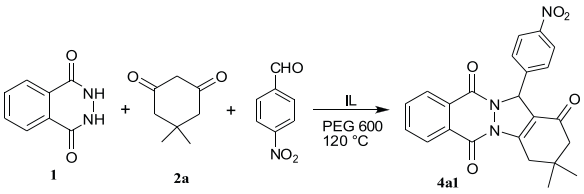
Scheme 1. The synthesis of phthalazinetrione derivatives catalyzed by $[BSO_3HmIm]HSO_4$ (R^2 = aryl or alkyl).

catalysts [23]. $[BmIm]BF_4$ has been used as solvent for the synthesis of phthalazine derivatives [14, 16]. However, the dosages of $[BmIm]BF_4$ were very large. To our knowledge, up to now there was no report about the synthesis of phthalazine derivatives catalyzed by ionic liquids. As an ionic liquid, $[BSO_3HmIm]HSO_4$ is relatively cheap and commercially available or easily synthesized [24]. For this reason, there have been some reports about the application [25, 26] of $[BSO_3HmIm]HSO_4$. Polyethylene glycol (PEG) has been widely used as a medium for organic synthesis in recent years because it is non-toxic, inexpensive, non-volatile, thermally stable, biologically acceptable, and eco-friendly, and allows many useful organic transformations to occur under mild reaction conditions [27]. Herein we wish to report a green and simple strategy for the synthesis of phthalazinetriones catalyzed by the ionic liquid $[BSO_3HmIm]HSO_4$ in PEG 600 at 120 °C (Scheme 1).

Results and Discussion

In our initial study, the one-pot, three-component condensation reaction of phthalhydrazide, dimedone and 4-nitrobenzaldehyde was used as a model reaction. Various ionic liquids (ILs) were tested as catalysts in PEG 600 (1.0 mL) at 120 °C, and the results are listed in Table 1. No product was detected in the absence of IL in PEG 600 at 120 °C even after 240 min (Table 1, entry 1). Among the tested ILs (15 mol-%), $[BSO_3HmIm]HSO_4$ showed the best catalytic activity for the model reaction, which gave a good yield of 81 % after 30 min (Table 1, entry 6). $[BmIm]HSO_4$ also catalyzed the reaction (Table 1, entry 5), while other tested ILs had little effect (Table 1, entries 2–4). Thus, $[BSO_3HmIm]HSO_4$ was chosen as the catalyst for the reaction. Next, we investigated the effect of catalyst loading on the model reaction. When 10 mol-% of catalyst was used, the product was obtained only in 73 % yield after 30 min (Table 1, entry 7). The catalyst loading of 15 mol-% led to a satisfactory yield of 81 % (Table 1, entry 6), however no obvious improvement was observed by further increasing the catalyst loading to 25 mol-% (Table 1, entries 8 and 9). Therefore, 15 mol-% of $[BSO_3HmIm]HSO_4$ was used as the optimized catalyst for the following study.

Table 1. The effects of different catalysts and catalyst loading on the three-component reaction[a].



Entry	Catalyst (mol-%)	Time (min)	Yield (%)[b]
1	None	240	n. d.
2[c]	$[BmIm]BF_4$ (15)	240	n. d.
3[c]	$[BmIm]PF_6$ (15)	240	n. d.
4[c]	[BmIm]Ac (15)	240	n. d.
5[c]	$[BmIm]HSO_4$ (15)	60	65
6	$[BSO_3HmIm]HSO_4$ (15)	30	81
7	$[BSO_3HmIm]HSO_4$ (10)	30	73
8	$[BSO_3HmIm]HSO_4$ (20)	30	81
9	$[BSO_3HmIm]HSO_4$ (25)	30	82

[a] Experimental conditions: phthalhydrazide (1.0 mmol), dimedone (1.0 mmol), 4-nitrobenzaldehyde (1.2 mmol) and IL in PEG 600 (1.0 mL) at 120 °C; [b] isolated yields; n. d. = not determined; [c] [BmIm]: 1-butyl-3-methylimidazolium.

In order to find a suitable solvent for the reaction, water and ethanol were also investigated as solvents using the model reaction. After refluxing for 30 min, a low yield of 38 % was obtained in water (Table 2, entry 1), but only a trace amount of product was observed in ethanol (Table 2, entry 2). The results indicated that PEG 600 was the best choice (Table 2, entry 3). Next, since the concentration of reactants and catalyst can

Table 2. The effects of solvent and temperature on the three-component reaction[a].

Entry	Solvent (mL)	T (°C)	Yield (%)[b]
1	water (1.0)	100	38
2	ethanol (1.0)	80	trace
3	PEG 600 (1.0)	120	81
4	PEG 600 (0.5)	120	79
5	PEG 600 (2.0)	120	62
6	PEG 600 (3.0)	120	45
7	PEG 600 (1.0)	100	70
8	PEG 600 (1.0)	140	83
9	PEG 600 (1.0)	160	84

[a] Experimental conditions: phthalhydrazide (1.0 mmol), dimedone (1.0 mmol), 4-nitrobenzaldehyde (1.2 mmol) and $[BSO_3HmIm]HSO_4$ (0.15 mmol) in a specified solvent at the temperature listed in Table 2 for 30 min; [b] isolated yields.

affect the yield and rate of a reaction, it was necessary to confirm the optimum solvent volume. Thus, we screened the volume of PEG 600 from 0.5 to 3.0 mL for 1 : 1 : 1.2 mmol of reactants (Table 2, entries 3–6), and the best yield of 81 % was obtained in 1.0 mL of PEG 600 (Table 2, entry 3). A relatively low yield of 79 % was received in 0.5 mL of solvent probably due to the low solubility of phthalhydrazide and product (Table 2, entry 4). However, the reaction in 2.0 or 3.0 mL of solvent was too dilute to proceed effectively, and only gave the product in low yields of 62 and 45 %, respectively (Table 2, entries 5 and 6). Hence, we chose 1.0 mL of PEG 600 as the optimized solvent volume. Then, we further investigated the effects of temperature on the reaction. When the reaction was performed at 100 °C, it provided the product in a yield of 70 % after 30 min (Table 2, entry 7). Raising the temperature to 120 °C led to a good yield of 81 % (Table 2, entry 3), but further increase of the temperature to 160 °C hardly improved the yield (Table 2, entries 8 and 9). So we chose 120 °C as the optimum temperature for the three-component reaction.

To further optimize the reaction conditions for the three-component reaction, the effects of molar ratio of phthalhydrazide (**1**), dimedone (**2a**) and 4-nitrobenzaldehyde (**3**) on the yield of phthalazinetrione **4a1** were studied, and the results are listed in Table 3. In consideration of the potential oxidation of aldehydes, the amount of 4-nitrobenzaldehyde (**3**) was used in 0.2 molar excess over **2a**. It was obvious that the yields could be improved by increasing the molar ratio of reactants. The best yield of 95 % was obtained with the molar ratio of **1** : **2a** : **3** = 1 : 1.4 : 1.6 (Table 3, entry 5), which was therefore chosen as the optimized molar ratio for the three-component reaction.

Table 3. The effects of molar ratio on the three-component reaction[a].

Entry	**1** (mmol)	**2a** (mmol)	**3** (mmol)	Yield (%)[b]
1	1.0	1.0	1.2	81
2	1.0	1.1	1.3	85
3	1.0	1.2	1.4	88
4	1.0	1.3	1.5	93
5	1.0	1.4	1.6	95
6	1.0	1.5	1.7	95

[a] Experimental conditions: phthalhydrazide (**1**), dimedone (**2a**), 4-nitrobenzaldehyde (**3**) and $[BSO_3HmIm]HSO_4$ (0.15 mmol) in PEG 600 (1.0 mL) at 120 °C for 30 min; [b] isolated yields.

With the optimized reaction conditions in hand, the scope and limitations of the one-pot three-component reaction for the synthesis of phthalazinetriones catalyzed by $[BSO_3HmIm]HSO_4$ in PEG 600 were explored using phthalhydrazide, dimedone or cyclohexane-1,3-dione and a variety of aldehydes. The results are summarized in Table 4. In general, aromatic aldehydes bearing electron-withdrawing or electron-donating functional groups at different positions reacted with the other two components in the presence of catalyst to generate the corresponding products in good to excellent yields. The nature and electronic properties of the aldehydes did affect the reaction yields. Aromatic aldehydes containing electron-withdrawing groups gave superior yields. For instance, when reacting with phthalhydrazide and dimedone, 4-nitrobenzaldehyde gave an excellent yield of 95 % after 30 min (Table 4, entry 1), however 4-methoxybenzaldehyde only provided the product in 70 % yield after 60 min, and prolonging the reaction time to 120 min did not give a better yield (Table 4, entry 9). The procedure was also applicable to aliphatic aldehydes, which gave satisfactory yields although longer reaction times were required in comparison with aromatic aldehydes (Table 4, entries 10 and 11). In addition, the three-component reactions using dimedone (Table 4, entries 1–9) generally gave better yields than cyclohexane-1,3-dione (Table 4, entries 12–19).

Finally, we investigated the reusability of the catalyst/solvent system using the model reaction. That both the ionic liquid and PEG 600 have little vapor pressure and high boiling points made it possible to recycle and reuse the catalyst/solvent system by distillation. After the completion of the reaction, water was added to

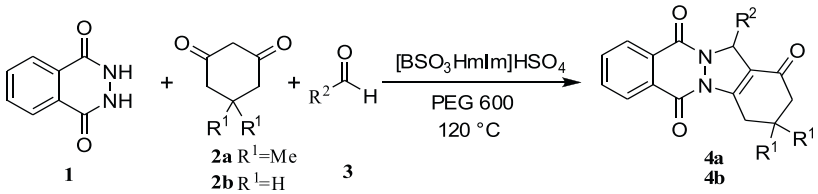


Table 4. $[BSO_3HmIm]HSO_4$-catalyzed synthesis of phthalazinetrione derivatives[a].

Entry	R^2	R^1	Product	Time (min)	Yield (%)[b]	M. p. (°C) found/reported [Ref.]
1	4-$NO_2C_6H_4$	Me	**4a1**	30	95	223–225/223–225 [13]
2	3-$NO_2C_6H_4$	Me	**4a2**	40	95	269–271/270–272 [13]
3	4-FC_6H_4	Me	**4a3**	40	87	219–222/217–219 [13]
4	4-ClC_6H_4	Me	**4a4**	30	93	261–262/262–264 [13]
5	2-ClC_6H_4	Me	**4a5**	40	92	264–266/264–266 [13]
6	4-BrC_6H_4	Me	**4a6**	30	96	263–266/265–267 [13]
7	2,3-$Cl_2C_6H_3$	Me	**4a7**	40	94	252–254/251–253 [21]
8	C_6H_5	Me	**4a8**	40	82	204–206/204–206 [13]
9	4-$CH_3C_6H_4$	Me	**4a9**	60 (120)[c]	70 (71)[c]	225–228/227–229 [14]
10	CH_3CH_2	Me	**4a10**	120	73	144–146/145–147 [21]
11	$CH_3CH_2CH_2$	Me	**4a11**	120	70	135–138/136–138 [21]
12	4-$NO_2C_6H_4$	H	**4b1**	30	94	251–253/252–254 [20]
13	3-$NO_2C_6H_4$	H	**4b2**	30	84	228–230/228–230 [14]
14	4-FC_6H_4	H	**4b3**	40	86	257–260/258–260 [14]
15	4-ClC_6H_4	H	**4b4**	30	86	270–272/272–273 [19]
16	4-BrC_6H_4	H	**4b5**	30	88	278–281/280–281 [19]
17	2,4-$Cl_2C_6H_3$	H	**4b6**	30	83	275–277/274–275 [19]
18	C_6H_5	H	**4b7**	40	80	223–225/222–224 [14]
19	4-$CH_3C_6H_4$	H	**4b8**	40	82	245–248/244–246 [14]

[a] Experimental conditions: phthalhydrazide (1.0 mmol), dimedone or cyclohexane-1,3-dione (1.4 mmol), aldehyde (1.6 mmol), $[BSO_3HmIm]HSO_4$ (0.15 mmol) in PEG 600 (1.0 mL) at 120 °C; [b] isolated yields; [c] when the reaction time was 120 min, the yield was 71 %.

the cooled reaction mixture to dissolve the catalyst and solvent, and the residue (product and some unreacted reactants) precipitated during the process and could be separated from the solution by filtration. The residue was then washed with ethanol to get NMR-pure products, and unreacted reactants could be washed into the filtrate. The filtrate was then distilled to remove water and ethanol, and the $[BSO_3HmIm]HSO_4$/PEG 600 system containing some unreacted reactants was easily recovered and could be reused for the next cycle by loading new reactants without adding any new catalyst and solvent. The molar ratio of reactants **1** : **2** : **3** = 1.0 : 1.4 : 1.6 was used for the first cycle, but **1** : **2** : **3** = 1 : 1 : 1 was used for the next cycles because there were already excess **2** and **3** (or Knoevenagel intermediates generated by them) left in the recovered system. The model reaction was performed five times using the same catalyst/solvent system (Table 5). No obvious decrease in the isolated yield was observed for the first four cycles, and an excellent yield of 92 % was obtained at the fourth cycle after 30 min (Table 5, cycles 1–4). The fifth cycle still provided a good yield of 87 % (Table 5, cycle 5).

Table 5. Reuse of the catalyst/solvent system.

Cycle	Time (min)	Yield (%)[a]
1[b]	30	95
2[c]	30	94
3[c]	30	94
4[c]	30	92
5[c]	30	87

[a] Isolated yields; [b] experimental conditions: phthalhydrazide (1.0 mmol), dimedone (1.4 mmol), 4-nitrobenzaldehyde (1.6 mmol), and $[BSO_3HmIm]HSO_4$ (0.15 mmol) in PEG 600 (1.0 mL) at 120 °C; [c] experimental conditions: phthalhydrazide (1.0 mmol), dimedone (1.0 mmol) and 4-nitrobenzaldehyde (1.0 mmol) in the catalyst/solvent system recovered from the previous cycle at 120 °C.

Conclusion

In summary, we have developed a simple and efficient green method to synthesize phthalazinetrione

derivatives through a one-pot three-component reaction using phthalhydrazide, dimedone or cyclohexane-1,3-dione and a variety of aromatic or aliphatic aldehydes. $[BSO_3HmIm]HSO_4$ was employed as an inexpensive, non-toxic, non-metallic, readily available, and environmentally benign catalyst. The chosen solvent of this reaction was PEG 600, which is non-toxic, inexpensive, non-volatile, thermally stable, biologically acceptable, and eco-friendly. In most cases, NMR-pure products could be readily obtained in good to excellent yields just through filtration and washing with ethanol. The catalyst/solvent system can be easily recovered by distillation. The attractive features of this procedure are the efficiency, clean reaction profiles, inexpensive starting materials, and an environmentally friendly reusable catalyst/solvent system.

Experimental Section

General

All solvents and chemicals were obtained commercially and were used as received. ^{1}H and ^{13}C NMR spectra were recorded at a 300 and 75 MHz spectrometer. Chemical shifts (δ) are expressed in ppm with TMS as internal standard, and coupling constants (J) are reported in Hz. Routine monitoring of reactions was performed by TLC using precoated Haiyang GF254 silica gel TLC plates. Column chromatography separations were done by using silica gel (200 – 300 mesh) at increased pressure. Melting points were determined on an X-4 digital display micro melting point apparatus and are uncorrected.

*General procedure for the preparation of **4** (**4a1**–**4a9**, **4b1**–**4b8**)*

A mixture of phthalhydrazide (1.0 mmol), dimedone or cyclohexane-1,3-dione (1.4 mmol), aldehyde (1.6 mmol), and $[BSO_3HmIm]HSO_4$ (0.15 mmol) in PEG 600 (1.0 mL) was stirred at 120 °C for the specified time. The reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool to r. t. Then water (5 mL) was added to the cooled reaction mixture, and the mixture was stirred for 5 min. The residue precipitated during the process was separated from the solution by filtration, and the filter cake was washed with ethanol to yield NMR-pure **4**.

*General procedure for the preparation of **4a10** and **4a11***

A mixture of phthalhydrazide (1.0 mmol), dimedone (1.4 mmol), aldehyde (1.6 mmol), and $[BSO_3HmIm]HSO_4$ (0.15 mmol) in PEG 600 (1.0 mL) was stirred at 120 °C for the specified time. The reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool to r. t. Then saturated brine (10 mL) was added to the cooled reaction mixture which was stirred for 5 min. The mixture was extracted twice with dichloromethane (2 × 10 mL), and the solvent was removed under reduced pressure to give the crude product which was purified by flash chromatography using petroleum ether-ethyl acetate (3 : 1, v/v) as eluent to afford the pure product.

*Procedure for the recovery of the catalyst/solvent system (**4a1**)*

A mixture of phthalhydrazide (1.0 mmol), dimedone (1.4 mmol), 4-nitrobenzaldehyde (1.6 mmol), and $[BSO_3HmIm]HSO_4$ (0.15 mmol) in PEG 600 (1.0 mL) was stirred at 120 °C for 30 min. After the reaction was complete, the reaction mixture was allowed to cool to r. t. Then water (5 mL) was added and the mixture stirred for 5 min. The residue precipitated during the process was separated by filtration and was washed with ethanol to give product **4a1**. The filtrate was then distilled to remove water and ethanol which gave the residue containing $[BSO_3HmIm]HSO_4$ and PEG 600 as the recovered catalyst/solvent system. This system was then used for the second cycle by loading new reactants (molar ratio was 1 : 1 : 1) without adding any new $[BSO_3HmIm]HSO_4$ and PEG 600.

*3,3-Dimethyl-13-(4-nitrophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a1**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37–8.19 (4H, m, Ph), 7.89, 7.62–7.59 (4H, m, Ph), 6.51 (1H, s, CHN), 3.44–3.22 (2H, AB system, J = 18.99 Hz, CH_aH_bCO), 2.34 (2H, s, CH_2C), 1.22, 1.19 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.98, 155.87, 154.50, 151.66, 147.80, 143.43, 134.73, 133.89, 128.89, 128.66, 128.54, 128.15, 128.03, 127.66, 123.94, 123.80, 117.20, 64.09, 50.74, 37.96, 34.65, 28.61, 28.29.

*3,3-Dimethyl-13-(3-nitrophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a2**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39–8.18 (4H, m, Ph), 7.89 (3H, m, Ph), 7.59–7.53 (1H, m, Ph), 6.52 (1H, s, CHN), 3.47–3.24 (2H, AB system, J = 19.22 Hz, CH_aH_bCO), 2.35 (2H, s, CH_2C), 1.22 (6H, s, 2Me).

*13-(4-Fluorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a3**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.34–8.27 (2H, m, Ph), 7.85 (2H, m, Ph), 7.40 (2H, m, Ph), 7.02 (2H, m, Ph), 6.43 (1H, s, CHN), 3.38–3.27 (2H, AB system), 2.34 (2H, s, CH_2C), 1.21 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.10, 155.96, 154.33, 150.97,

134.53, 133.57, 132.21, 132.17, 128.99, 128.93, 128.88, 127.97, 127.65, 118.15, 115.80, 115.51, 64.23, 50.86, 37.98, 34.60, 28.62, 28.40.

*13-(4-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a4**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.34$–8.25 (2H, m, Ph), 7.85 (2H, m, Ph), 7.37–7.28 (4H, m, Ph), 6.40 (1H, s, CHN), 3.43–3.20 (2H, AB system, $J = 19.10$ Hz, CH_aH_bCO), 2.33 (2H, s, CH_2C), 1.20 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.06$, 155.96, 154.34, 150.95, 134.52, 133.56, 132.22, 132.17, 128.99, 128.95, 128.91, 128.87, 127.97, 127.65, 118.16, 115.80, 115.50, 64.23, 50.88, 37.99, 34.59, 28.62, 28.40.

*13-(2-Chlorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a5**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.37$–8.24 (2H, m, Ph), 7.85–7.84 (2H, m, Ph), 7.49–7.47 (1H, m, Ph), 7.33–7.29 (2H, m, Ph), 7.23–7.21 (1H, m, Ph), 6.68 (1H, s, CHN), 3.44–3.20 (2H, AB system, $J = 19.09$ Hz, CH_aH_bCO), 2.32 (2H, s, CH_2C) 1.21 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.05$, 156.11, 154.17, 151.80, 134.47, 133.53, 132.96, 132.51, 130.47, 129.82, 128.98, 128.65, 127.97, 127.61, 127.16, 125.65, 116.60, 64.01, 50.80, 37.96, 34.54, 28.74, 28.34.

*13-(4-Bromophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a6**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.35$–8.27, 7.86 (4H, m, Ph), 7.47–7.28 (4H, m, Ph), 6.40 (1H, s, CHN), 3.43–3.20 (2H, AB system, $J = 19.09$ Hz, CH_aH_bCO), 2.33 (2H, s, CH_2C), 1.20 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.04$, 155.93, 154.33, 151.09, 135.44, 134.57, 133.63, 131.84, 128.88, 128.84, 128.77, 128.00, 127.66, 122.69, 117.92, 64.33, 50.83, 37.97, 34.61, 28.64, 28.36.

*13-(2,3-Dichlorophenyl)-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a7**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.37$–7.26 (7H, m, Ph), 6.70 (1H, s, CHN), 3.43–3.21 (2H, AB system, $J = 17.98$ Hz, CH_aH_bCO), 2.33 (2H, s, CH_2C), 1.21 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.05$, 156.07, 154.24, 152.13, 135.30, 134.58, 134.10, 133.67, 130.85, 130.68, 130.18, 128.94, 128.49, 128.05, 127.62, 127.50, 116.11, 64.43, 50.77, 37.95, 34.56, 28.70, 28.40.

*3,3-Dimethyl-13-phenyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a8**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.35$–8.27 (2H, m, Ph), 7.85 (2H, m, Ph), 7.40–7.27 (5H, m, Ph), 6.45 (1H, s, CHN), 3.45–3.21 (2H, AB system, $J = 19.06$ Hz, CH_aH_bCO), 2.33 (2H, s, CH_2C), 1.21 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.02$, 155.98, 154.23, 150.79, 136.36, 134.43, 133.45, 129.05, 128.94, 128.64, 128.61, 127.90, 127.67, 127.07, 118.55, 64.91, 50.91, 38.00, 34.58, 28.63, 28.40.

*3,3-Dimethyl-13-p-tolyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a9**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.35$–8.27 (2H, m, Ph), 7.84 (2H, m, Ph), 7.31–7.29 (2H, m, Ph), 7.15–7.12 (2H, m, Ph), 6.42 (1H, s, CHN), 3.45–3.20 (2H, AB system, $J = 19.02$ Hz, CH_aH_bCO), 2.33 (2H, s, CH_2C), 2.29 (3H, s, Me), 1.21 (6H, s, 2-Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 192.08$, 155.99, 154.19, 150.68, 138.42, 134.38, 133.39, 129.39, 129.12, 128.94, 127.86, 127.66, 127.01, 118.64, 64.79, 50.92, 38.01, 34.58, 28.64, 28.40, 21.15.

*13-Ethyl-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a10**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$–8.33 (2H, m, Ph), 7.93–7.84 (2H, m, Ph), 5.72 (1H, s, CHN), 3.38–3.11 (2H, AB system, $J = 19.15$ Hz, CH_aH_bCO), 2.59–2.50 (1H, m, CH), 2.39 (2H, s, CH_2C), 2.19–2.10 (1H, m, CH), 1.23–1.20 (6H, s, 2-Me), 0.77–0.72 (3H, t, Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.01$, 156.02, 154.66, 151.84, 134.41, 133.37, 128.94, 128.83, 127.83, 127.45, 116.64, 63.43, 50.93, 38.02, 34.43, 28.79, 28.32, 22.05, 7.21.

*13-Butyl-3,3-dimethyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4a11**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$–8.32 (2H, m, Ph), 7.92–7.83 (2H, m, Ph), 5.70 (1H, s, CHN), 3.36–3.10 (2H, AB system, $J = 19.25$ Hz, CH_aH_bCO), 2.44–2.38 (3H, m), 2.12–2.03 (1H, m), 1.22–1.10 (8H, m), 0.89–0.84 (3H, t, Me). – ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 193.00$, 156.02, 154.66, 151.56, 134.39, 133.34, 128.95, 128.82, 127.80, 127.45, 117.22, 62.77, 50.93, 37.98, 34.40, 31.46, 28.69, 28.39, 16.69, 13.67.

*13-(4-Nitrophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b1**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.39$–8.19 (4H, m, Ph), 7.90–7.89 (2H, m, Ph), 7.63–7.60 (2H, m, Ph), 6.51(1H, s, CHN), 3.60–3.32 (2H, AB system, $J = 19.23$ Hz, CH_aH_bCO), 2.48–2.36 (2H, m), 2.33–2.27 (2H,

m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.28, 155.91, 154.48, 153.00, 147.85, 143.28, 134.77, 134.76, 133.88, 128.87, 128.59, 128.56, 128.19, 128.06, 127.74, 123.94, 118.34, 64.15, 36.72, 24.47, 22.16.

*13-(3-Nitrophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b2**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39–8.25 (2H, m, Ph), 8.17(2H, m, Ph), 7.89 (3H, m, Ph), 7.56 (1H, Ph), 6.52 (1H, s, CHN), 3.63–3.33 (2H, AB system, J = 18.76 Hz, CH_aH_bCO), 2.48 (2H, m), 2.28 (2H, m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.42, 155.91, 154.57, 153.17, 138.54, 135.78, 134.70, 134.18, 133.86, 129.54, 128.90, 128.58, 128.19, 127.66, 123.60, 121.55, 118.17, 64.17, 36.71, 24.46, 22.16.

*13-(4-Fluorophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b3**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.27 (2H, m, Ph), 7.85 (2H, m, Ph), 7.41–7.39 (2H, m, Ph), 7.04–6.99 (2H, m, Ph), 6.44 (1H, s, CHN), 3.60–3.29, 2H, AB system, J = 19.24 Hz, CH_aH_bCO), 2.47–2.45 (2H, m), 2.28–2.24 (2H, m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.43, 155.98, 154.29, 152.37, 134.53, 133.56, 132.13, 132.09, 129.04, 128.95, 128.92, 128.87, 127.98, 127.66, 119.25, 115.75, 115.46, 64.24, 36.84, 24.43, 22.23.

*13-(4-Chlorophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b4**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.36–8.27 (2H, m, Ph), 7.86 (2H, m, Ph), 7.36–7.31(4H, m, Ph), 6.42 (1H, s, CHN), 3.59–3.29 (2H, AB system, J = 18.30 Hz, CH_aH_bCO), 2.47 (2H, m), 2.25 (2H, m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.39, 155.95, 154.29, 152.47, 134.82, 134.57, 134.51, 134.45, 133.61, 128.86, 128.52, 128.00, 127.67, 119.08, 64.29, 36.81, 24.43, 22.21.

*13-(4-Bromophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b5**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.25 (2H, m, Ph), 7.85 (2H, m, Ph), 7.46–7.44 (2H, m, Ph), 7.32–7.29 (2H, m, Ph), 6.39 (1H, s, CHN), 3.58–3.28 (2H, AB system, J = 19.29 Hz, CH_aH_bCO), 2.46–2.44 (2H, m), 2.26–2.24 (2H, m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.40, 155.94, 154.29, 152.51, 135.35, 135.15, 134.58, 133.63, 131.80, 128.85, 128.82, 128.01, 127.67, 122.70, 119.02, 64.35, 36.81, 24.44, 22.22.

*13-(2,4-Dichlorophenyl)-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b6**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.37–8.25 (2H, m, Ph), 7.87 (2H, m, Ph), 7.42–7.27 (3H, m, Ph), 6.62 (1H, s, CHN), 3.54–3.25 (2H, AB system,), 2.46–2.26 (4H, m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.34, 156.05, 154.25, 153.43, 135.06, 134.57, 133.65, 133.33, 131.63, 130.28, 128.92, 128.54, 128.06, 127.62, 127.54, 117.18, 111.41, 63.62, 36.74, 24.42, 22.20.

*13-Phenyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b7**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.25 (2H, m, Ph), 7.84 (2H, m, Ph), 7.43–7.31(5H, m, Ph), 6.45 (1H, s, CHN), 3.60–3.29 (2H, AB system, J = 19.27 Hz, CH_aH_bCO), 2.47–2.45 (2H, m), 2.27–2.23 (2H, m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.47, 155.97, 154.18, 152.27, 136.29, 134.47, 133.48, 129.00, 128.88, 128.60, 127.90, 127.65, 127.11, 119.60, 111.41, 64.90, 36.85, 24.43, 22.22.

*13-p-Tolyl-3,4-dihydro-1H-indazolo[1,2-b]phthalazine-1,6,11(2H,13H)-trione (**4b8**)*

Yellow solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35–8.26 (2H, m, Ph), 7.84 (2H, m, Ph), 7.32–7.26 (2H, m, Ph), 7.15–7.12 (2H, m, Ph), 6.42 (1H, s, CHN), 3.60–3.29 (2H, AB system, J = 19.09 Hz, CH_aH_bCO), 2.46 (2H, m), 2.29 (3H, s, Me), 2.25 (2H, m). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 192.50, 155.91, 154.08, 152.18, 138.37, 134.41, 133.42, 133.34, 129.33, 129.03, 128.86, 127.82, 127.59, 127.07, 119.64, 64.77, 36.87, 24.43, 22.24, 21.19.

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