Brønsted acidic deep eutectic solvent catalysed the one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones

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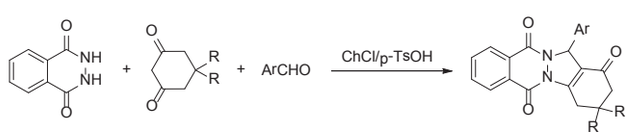
An efficient and facile protocol for the one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones in the presence of a Brønsted acidic deep eutectic solvent has been developed. The Brønsted acidic deep eutectic solvent was readily prepared via heating the mixture of choline chloride and *p*-toluenesulfonic acid. In addition, the deep eutectic solvent is non-toxic, cost-effective and recyclable.

Keywords: deep eutectic solvent, 2*H*-indazolo[2,1-*b*]phthalazine-triones, multicomponent reactions, *p*-toluene sulfonic acid

In the past few decades, the synthesis of new nitrogen heterocycles containing a phthalazine moiety has been a subject of great interest due to their biological and pharmacological activities such as anticonvulsant, cardiotonic and vasorelaxant.[1–3] Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives. Among them, multicomponent reactions of phthalhydrazide, an aldehyde, and dimedone to give 2*H*-indazolo[2,1-*b*]phthalazine-triones have recently attracted the interest of the synthetic community because the formation of different condensation products can be expected depending on the specific conditions and structure of the building blocks. Thus, a series of catalysts such as *p*-TSA,[4] Me_3SiCl,[5] silica sulfuric acid,[6] cyanuric chloride,[7] heteropolyacids,[8] N-halosulfonamides[9] have been reported to catalyse such transformation. The direct four-component condensations have also been achieved under solvent-free conditions using $Ce(SO_4)_2.4H_2O$[10] and sulfuric acid-modified PEG-6000[11] as catalysts. However, some of these methods suffered with several drawbacks such as hazardous organic solvents, high cost as well as use of stoichiometric and excess amounts of acids. Therefore, the development of an efficient and environment friendly procedure is in demand.

Recently, deep eutectic solvents (DES) have invoked enormous interest as green potential solvents or catalysts in organic reactions.[12,13] DES are similar to conventional ionic liquids in terms of low vapour pressure and low flammability. In addition, they are biodegradable, non-toxic, and inexpensive. Generally, DES are mainly prepared by combining choline chloride with different hydrogen bond donors, such as urea, Lewis acids as well as Brønsted acids.[14] It should be mentioned that choline is a naturally occurring biocompatible compound and choline chloride is commercially produced on a large scale as a chicken feed additive.[10] However, their ability to serve as catalysts as well as solvents has not been adequately explored in the field of synthetic organic chemistry except for a few reported examples.[15–19]

We report here an efficient and reusable catalytic system for one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones using deep eutectic solvents based on choline chloride and *p*-toluenesulfonic acid (Scheme 1).



Scheme 1 ChCl/*p*-TsOH catalysed the one-pot synthesis of 2*H*-indazolo [2,1-*b*]phthalazine-triones.

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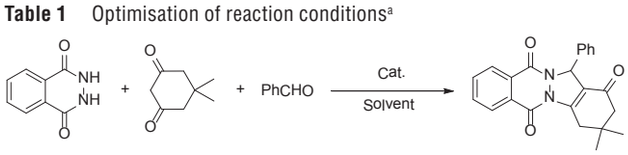
p-Toluenesulfonic acid is an important Brønsted acid catalyst which is widely used in organic synthetic processes due to its strong acidity as well as the ease of operation. However, it is very deliquescent and difficult to recover. Recently, it was reported that *p*-toluenesulfonic acid and choline chloride could form a deep eutectic solvent *via* hydrogen bonding and such a DES not only showed good catalytic activity but also could be recovered and reused.[20]

The DES ChCl/*p*-TsOH was readily prepared by mixing the choline chloride 1 (0.1 mol) with *p*-toluenesulfonic acid (0.1 mol) at 100 °C until a clear solution was obtained (40 min) which was used for reactions without any purification. The method gave this DES with 100% atom economy since it completely forms a eutectic mixture with no by-product formation.

With the DES in hand, we started to optimise the reaction conditions *via* condensation of phthalhydrazide (1 mmol), benzaldehyde (1 mmol) and dimedone (1 mmol) in different catalytic systems (Table 1). The reaction medium played an important role for the reaction. Good yields were obtained when methanol and ethanol were used (86 and 82% yield, respectively). Other organic solvents such ethyl acetate and toluene gave much lower yields. When the reaction proceeded in pure water, only trace amounts of product were detected. However, good yields were obtained when ethanol/water and

Table 1 Optimisation of reaction conditions[a]



Entry	Reaction medium	DES catalyst/mol%	Yield/%[b]
1	MeOH	ChCl/*p*-TsOH (15)	86
2	EtOH	ChCl/*p*-TsOH (15)	82
3	H_2O	ChCl/*p*-TsOH (15)	trace
4	EtOH/H_2O(1:1)	ChCl/*p*-TsOH (15)	79
5	MeOH/H_2O(1:1)	ChCl/*p*-TsOH (15)	81
6	CH_3CN	ChCl/*p*-TsOH (15)	63
7	EtOAc	ChCl/*p*-TsOH (15)	30
8	toluene	ChCl/*p*-TsOH (15)	trace
9	MeOH	–	trace
10	MeOH	ChCl (15)	trace
11	MeOH	p-TsOH (15)	52
12	MeOH	ChCl/urea (15)	37
13	MeOH	ChCl/malonic acid (15)	44
14	MeOH	ChCl/glycerol (15)	28
15	MeOH	ChCl/*p*-TsOH (5)	49
16	MeOH	ChCl/*p*-TsOH (10)	67
17	MeOH	ChCl/p-TsOH (20)	88

[a]Reaction conditions: phthalhydrazide (1 mmol), benzaldehyde (1 mmol), dimedone (1 mmol), solvent (2 mL), reflux for 4 h.
[b]Isolated yields.

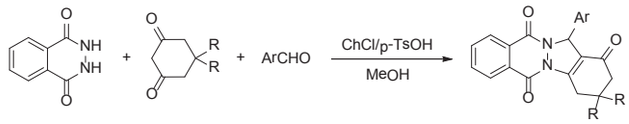
methanol/water were used as the reaction media. This can be explained as DES shows excellent solubility in polar solvents and the reaction proceeds in a homogeneous system. Various deep eutectic mixtures as well as the catalyst amount were also evaluated (Table 1, entries 9–17). A trace amount of product was obtained in the absence of any catalyst. *p*-Toluenesulfonic acid, when used alone, could also promote the reaction, albeit with a moderate (52%) yield. Other deep eutectic mixtures generated from urea, malonic acid and glycerol gave lower yields owing to their lesser acidity than ChCl/*p*-TsOH. The optimisation of the quantity of catalyst suggested 15 mol% of ChCl/*p*-TsOH (relative to phthalhydrazide) in methanol as the best choice.

The generality and functional group tolerance of this protocol was examined by employing a number of substituted aromatic aldehydes under the optimised conditions (Table 2). It was obvious that this method showed good substrate compatibility for aromatic aldehydes. Both aromatic aldehydes bearing electron-donating groups and electron-withdrawing groups gave the products in good to excellent yields (83–93%). In the same way, the reactions of 1,3-cyclohexanedione for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones under the optimum conditions were examined and the desired products were obtained in high yields (Table 2, entries 9–11). In addition, the product could be easily purified by washing using an ethanol/water mixture (1: 3 v/v). Thus, this method offers significant improvements with regard to the scope of the transformation, simplicity, and green aspects.

One of the most important advantages employing DES as solvent or catalyst is their recyclability. A batch reaction between phthalhydrazide, benzaldehyde and dimedone was scaled up to 10 mmol to examine the recycling process. The recovery was very simple involving evaporation of the solvent and water after isolation of product by extraction with ethyl acetate. The deep eutectic solvent was reused without obvious loss in activity in five consecutive runs (86, 87, 82, 82 and 80% yield, respectively).

In summary, we have developed a simple, green and efficient catalytic system using deep eutectic mixtures for rapid synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives. The reaction gave high yields in short reaction times. In addition, the DES catalyst could also be easily recycled and reused at least up to five runs without any considerable loss in yields.

Table 2 Synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives[a]



Entry	Ar	R	Product	Yield/%[a]
1	C_6H_5	CH3	**a**	86
2	4-$CH_3C_6H_4$	CH3	**b**	90
3	4-$CH_3OC_6H_4$	CH3	**c**	85
4	4-FC_6H_4	CH3	**d**	87
5	4-ClC_6H_4	CH3	**e**	91
6	2-ClC_6H_4	CH3	**f**	83
7	4-BrC_6H_4	CH3	**g**	85
8	4-$NO_2C_6H_4$	CH3	**h**	93
9	4-OHC_6H_4	H	**i**	86
10	2-Naphthyl	H	**j**	89
11	4-$CH_3C_6H_4$	H	**k**	88

[a]Reaction conditions: phthalhydrazide (1 mmol), aldehyde (1 mmol), dimedone or 1,3-cyclohexanedione (1 mmol), ChCl/*p*-TsOH (15 mol%), methanol (2 mL), reflux for 4 h.
[b]Isolated yields.

Experimental

All reagents were obtained from local commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 500 analyser. All the products are known compounds and were identified by comparing of their physical and spectra data with those reported in the literature.

Synthesis of 2H-indazolo[2,1-b]-phthalazine-triones; typical procedure
In a 25 mL round-bottomed flask, phthalhydrazide (1 mmol), aromatic aldehyde (1 mmol) and dimedone or 1,3-cyclohexandione (1 mmol) were taken in the presence of 15 mol% (relative to phthalhydrazide) of ChCl/*p*-TsOH in methanol (2 mL). Then the reaction mixture was stirred at 65 °C for an appropriate time as monitored by TLC. After completion of the reaction, the volume of the reaction mixture was reduced, diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then the solvent was removed under reduced pressure. The crude product was washed with ethanol/water mixture (1: 3 v/v) (5 mL) and recrystallised from ethanol to obtain the pure product.

3,4-Dihydro-3,3-dimethyl-13-phenyl-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**a**): M.p. 208–209 °C (lit.[4] 204–206 °C)[4]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 6H), 2.35 (s, 2H), 3.25–3.43 (m, 2H), 6.46 (s, 1H), 7.32–7.40 (m, 3H), 7.44–7.46 (m, 2H), 7.76–7.86 (m, 2H), 8.30–8.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (EI) *m/z* 372 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(4-methylphenyl)-2H-indazolo[2,1-b] phthalazine-1,6,11(13H)-trione (**b**): M.p. 226–228 °C (lit.[4] 227–229 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (s, 6H), 2.30 (s, 3H), 2.36 (s, 2H), 3.23–3.42 (m, 2H), 6.42 (s, 1H), 7.12–7.14 (m, 2H), 7.30–7.38 (m, 2H), 7.84–7.87 (m, 2H), 8.28–8.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 (EI) *m/z* 386 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(4-methyoxylphenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**c**): M.p. 216–218 °C (lit.[21] 218–220 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.34 (s, 2H), 3.23–3.42 (m, 2H), 3.76 (s, 3H), 6.42 (s, 1H), 6.84–6.86 (m, 2H), 7.35–7.37 (m, 2H), 7.82–7.86 (m, 2H), 8.26–8.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 28.7, 34.6, 38.1, 51.0, 55.2, 64.6, 114.1, 118.6, 127.7, 127.9, 128.4, 128.5, 129.0, 129.2, 133.5, 134.5, 150.7, 154.2, 156.0, 159.7, 192.2; MS (EI) *m/z* 402 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(4-fluorophenyl)-2H-indazolo[2,1-b] phthalazine-1,6,11(13H)-trione (**d**): M.p. 220–222 °C (li.[4] 217–219 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 6H), 2.33 (s, 2H), 3.22–3.40 (m, 2H), 6.42 (s, 1H), 6.99–7.03 (m, 2H), 7.38–7.43 (m, 2H), 7.84–7.88 (m, 2H), 8.26–8.35 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 28.7, 34.7, 38.0, 50.9, 64.3, 115.5, 115.9, 118.2, 127.7, 128.0, 128.9, 129.1, 132.2, 133.7, 134.6, 151.1, 154.4, 156.0, 192.2; MS (EI) *m/z* 390 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(4-chlorophenyl)-2H-indazolo[2,1-b] phthalazine-1,6,11(13H)-trione (**e**): M.p. 262–264 °C (lit.[4] 262–264 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.23 (s, 3H), 2.35 (s, 2H), 3.25–3.43 (m, 2H), 6.43 (s, 1H), 7.31–7.33 (m, 2H), 7.37–7.41 (m, 2H), 7.85–7.88 (m, 2H), 8.26–8.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 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; MS (EI) *m/z* 406 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(2-chlorophenyl)-2H-indazolo[2,1-b] phthalazine-1,6,11(13H)-trione (**f**): M.p. 268–270 °C (lit.[4] 264–266 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.23 (s, 3H), 2.33 (s, 2H), 3.24–3.42 (m, 2H), 6.69 (s, 1H), 7.25–7.34 (m, 2H), 7.49–7.50 (m, 2H), 7.84–7.89 (m, 2H), 8.25–8.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4, 28.8, 34.6, 38.0, 50.9, 64.0, 116.7, 127.2, 127.6, 128.0, 128.7, 129.0, 129.9, 130.5, 132.6, 133.0, 133.6, 134.5, 151.9, 154.2, 156.2, 192.1; MS (EI) *m/z* 406 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(4-bromophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**g**): M.p. 264–266 °C (lit.[4] 265–267 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.22 (s, 3H), 2.35 (s, 2H), 3.24–3.41 (m, 2H), 6.41 (s, 1H), 7.29–7.31 (m, 2H), 7.35–7.38 (m, 2H), 7.82–7.84 (m, 2H), 8.27–8.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 28.7, 34.7, 38.0, 50.9, 64.4, 118.0, 122.8, 127.8, 128.1, 128.8, 128.9, 129.0, 131.9, 133.7, 134.7, 135.5, 151.1, 154.4, 156.0, 192.1; MS (EI) *m/z* 451 (M^+).

3,4-Dihydro-3,3-dimethyl-13-(4-nitrophenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**h**): M.p. 220–222 °C (lit.[4] 223–225 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.23 (s, 3H), 2.33–2.38 (m, 2H), 3.26–3.43 (m, 2H), 6.52 (s, 1H), 7.62–7.64 (m, 2H), 7.90 (m, 2H), 8.21 (m, 2H), 8.24–8.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.4, 28.7, 34.7, 38.0, 50.8, 64.2, 117.3, 124.1, 127.8, 128.1, 128.3, 128.6, 128.9, 133.9, 134.9, 143.4, 147.9, 151.7, 154.6, 155.9, 192.1; MS (EI) *m/z* 417 (M^+).

3,4-Dihydro-13-(4-hydroxyphenyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**i**): M.p. 258–260 °C (lit.[7] 265–266 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24–2.28 (m, 2H), 2.46–2.47 (m, 2H), 3.35–3.60 (m, 2H), 6.37 (s, 1H), 6.78 (d, 2H), 7.23 (d, 2H), 7.83–7.86 (m, 2H), 8.23–8.35 (m, 2H), 8.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.0, 29.2, 41.7, 69.3, 120.3, 124.2, 130.3, 131.8, 132.1, 132.7, 133.4, 133.7, 137.1, 138.3, 139.3, 157.1, 158.8, 160.6, 162.4, 197.3; MS (EI) *m/z* 360 (M^+).

3,4-Dihydro-13-(naphthalen-2-yl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**j**): M.p. 261–262 °C (lit.[7] 262–264 °C)[7]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.21–2.29 (m, 2H), 2.43–2.47 (m, 2H), 3.28–3.65 (m, 2H), 6.60 (s, 1H), 7.41–7.50 (m, 3H), 7.75–7.91 (m, 6H), 8.20–8.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.3, 24.5, 36.9, 65.1, 119.7, 124.3, 126.2, 126.3, 126.7, 127.6, 127.7, 128.0, 128.2, 128.6, 129.0, 129.1, 133.2, 133.4, 133.5, 133.6, 134.5, 152.3, 154.3, 156.1, 192.4; MS (EI) *m/z* 394 (M^+).

3,4-Dihydro-13-(p-tolyl)-2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-trione (**k**): M.p. 244–246 °C (lit.[21] 248–250 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.23–2.27 (m, 2H), 2.29 (s, 3H), 2.44–2.48 (m, 2H), 3.29–3.60 (m, 2H), 6.42 (s, 1H), 7.12–7.32 (m, 4H), 7.81–7.87 (m, 2H), 8.25–8.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ21.2, 22.3, 24.5, 36.9, 64.8, 119.8, 127.1, 127.7, 127.9, 129.0, 129.2, 129.4, 133.3, 133.4, 134.5, 138.5, 152.1, 154.2, 156.1, 192.5; MS (EI) *m/z* 358 (M^+).

Recycling study; typical procedure

Phthalhydrazide (10 mmol), benzaldehyde (10 mmol) and dimedone (10 mmol) were reacted in the presence of 15 mol% of a batch of ChCl/*p*-TsOH in methanol (20 mL) under reflux for an appropriate time as monitored by TLC. After completion of the reaction, the mixture was concentrated, diluted with water and extracted with ethyl acetate. The recovery was very simple by evaporation of water.

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