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Solvent-free sonochemical one-pot three-component synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones

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ABSTRACT

A rapid and efficient one-pot three-component protocol for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones **4** and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **6** has been developed by domino coupling of phthalhydrazide, 1,3-diketones, and aldehydes under solvent-free conditions at 80 °C as well as under solvent-free ultrasound irradiation at room temperature promoted by (*S*)-camphorsulfonic acid.

The continual upsurge in facile and non-polluting synthetic procedures urges synthetic chemists to increase tools of their arsenal, because of the increasing concern for the harmful effects of organic solvents on the environment. Ultrasound-promoted syntheses[1] have attracted much attention during the last few years, and extensively utilized to accelerate a number of organic transformations.[2] Simple experimental procedure, clean reaction, short reaction time, high yields, and improved selectivity of many ultrasound induced organic transformations offer additional convenience in the field of synthetic organic chemistry.[3] Recently, numerous important heterocycles have been synthesized under solvent-free conditions accelerated by ultrasound irradiation.[4]

Over the years, multicomponent reactions[5] (MCRs) have become increasingly popular tools to ensure sufficient molecular diversity and complexity. They have gained significant popularity in recent years due to their atom-economy and straightforward reaction design due to substantial minimization of waste, labor, time, and cost.[6] MCRs leading to interesting heterocyclic scaffolds are particularly useful for the construction of diverse chemical libraries of 'drug like' molecules.[7,8] Many organic reactions have been reported to proceed efficiently under solvent-free conditions[9–11] showing enhanced selectivities and excellent yields. 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones constitute a key structural motif in a number of natural and synthetic bioactive molecules. They are important *N*-heterocycles possessing multiple biological activities[12] such as anticonvulsant,[13] cardiotonic,[14] vasorelaxant,[15] antimicrobial,[16a] antifungal,[16b] anticancer,[16c] and anti-inflammatory[17] along with unique electrical and optical properties.[18]

Despite many methods being available for the synthesis of phthalazine derivatives,[19] their broad utility has accentuated the need to develop eco-compatible and clean synthetic routes. Recently, several elegant multicomponent strategies for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones by the cyclocondensation of phthalhydrazide, aldehydes, and 1,3-diketones utilizing different types of catalysts have been reported.[20,21] The reported methods show varying degrees of successes as well as limitations such as harsh reaction conditions, expensive catalyst/reagent, toxic organic solvents, low product yields, long reaction times, and co-occurrence of several side products. Therefore, there still remains a high demand for the development of more general, efficient, economically viable, and eco-compatible protocol to assemble such scaffolds. Camphorsulfonic acid (CSA) has emerged as a highly efficient and effective potential organic acid catalyst imparting high stereoselectivity in various chemical transformations.[22] We therefore became interested in devising more general and green methods for the synthesis of indazolo[2,1-*b*]phthalazine-1,6,11-triones and pyrazolo[1,2-*b*]phthalazine-5,10-diones under solvent-free ultrasound irradiation utilizing (*S*)-CSA as the catalyst.

Our literature survey at this stage revealed that there are no reports on the synthesis of indazolo[2,1-*b*]phthalazine-1,6,11-triones

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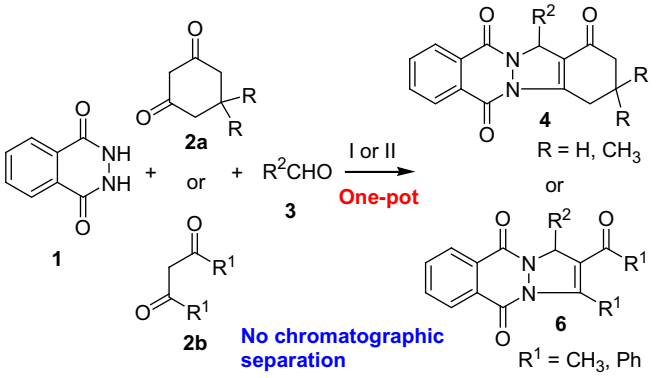
and pyrazolo[1,2-*b*]phthalazine-5,10-diones under solvent-free ultrasound irradiation at room temperature mediated by (*S*)-camphorsulfonic acid. Our main strategy is to develop a green organic reaction enhancement methodology, which is relatively faster and cleaner than the conventional reactions. As part of our ongoing research program on the development of clean protocols under solvent-free conditions[23] herein, we report a facile one-pot synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones **4** and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **6** via the three-component coupling of phthalhydrazide **1**, 1,3-diketones **2**, and aldehydes **3** under solvent-free conditions at 80 °C as well as under solvent-free ultrasound irradiation at room temperature (Scheme 1).[24]

Initial study was carried out utilizing phthalhydrazide **1** (1.0 mmol), dimedone **2** (1.1 mmol), and 4-nitrobenzaldehyde **3a** (1.1 mmol) under solvent-free conventional heating (method I) and under ultrasound irradiation at room temperature separately, in the absence of a catalyst. We did not observe a trace of the desired product even after 12 h under the above two conditions (Table 1, entries 1 and 14). To explore suitable reaction conditions, the above model reaction was performed in the presence of various catalysts such as L-proline, P_2O_5, $InCl_3$, NH_2HSO_3, $BF_3.OEt_2$, and (*S*)-CSA separately, under solvent-free conditions at 80 °C as well as under ultrasound irradiation at room temperature. The results are summarized in Table 1. L-proline could not trigger the reaction even after 12 h of heating, whereas P_2O_5, $InCl_3$, NH_2HSO_3, and $BF_3.OEt_2$ were found to catalyze the reaction to give the desired 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-trione **4a** in moderate yields along with Knoevenagel condensation product **5** in 15–25% yields as a side product. To our delight (*S*)-CSA provided the desired compound **4a** in a 94% yield as an exclusive product under solvent-free conditions at 80 °C. Subsequently, catalyst loading was optimized and 20 mol % loading of the (*S*)-CSA provided the maximum yield

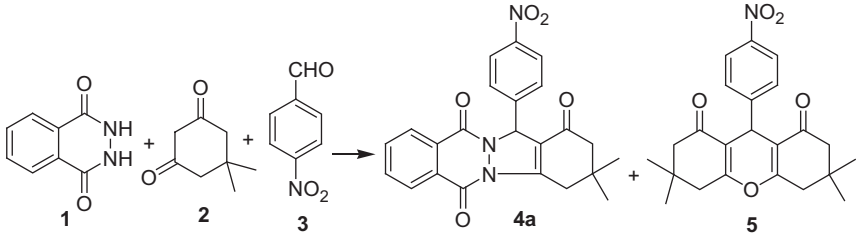


Scheme 1. Synthesis of indazolo[2,1-*b*]phthalazine-1,6,11-triones **4** and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **6**. Reagents and conditions: (I) (*S*)-CSA (20 mol %),80 °C, solvent-free; (II) (*S*)-CSA (20 mol %), rt,))))), solvent-free.

in minimum time (Table 1, entry 11). A further increase in the amount of (*S*)-CSA did not have any significant effect on the product yield or reaction time, whereas the yield was reduced by decreasing the amount of (*S*)-CSA (Table 1, entries 12 and 13).

Recently, organic synthesis involving multicomponent reaction under ultrasonic irradiation has attracted much attention. Therefore, we explored the possibility of obtaining the target compounds under ultrasonic irradiation. We performed the above test reaction in the presence of 20 mol % of (*S*)-CSA under ultrasound irradiation at room temperature. The desired product **4a** was obtained exclusively in a 92% yield within 20 min (Table 1, entry 15). Thus, 20 mol % of (*S*)-CSA was found to be optimum for both conditions I and II. Although, the yields are found to be almost parallel under

Table 1
Optimization of reaction conditions for the synthesis of **4**[a]



Entry	Catalyst	Loading (mol %)	Method I and II	Time	Yield[b] (%) **4a**	Yield (%) **5**
1	None	—	80 °C	12 h	—	—
2	L-proline	20	80 °C	12 h	—	—
3	P_2O_5	20	80 °C	50 min	40	25
4	P_2O_5	30	80 °C	40 min	55	20
5	$InCl_3$	20	80 °C	40 min	50	20
6	$InCl_3$	30	80 °C	25 min	55	15
7	H_2NHSO_3	20	80 °C	30 min	65	15
8	H_2NHSO_3	30	80 °C	20 min	70	12
9	$BF_3.OEt_2$	20	80 °C	30 min	60	15
10	$BF_3.OEt_2$	30	80 °C	25 min	65	20
11	(*S*)-CSA	20	80 °C	15 min	94	—
12	(*S*)-CSA	30	80 °C	14 min	92	—
13	(*S*)-CSA	10	80 °C	35 min	78	Trace
14	None	—	)))), rt	12 h	—	—
15	(*S*)-CSA	20	)))), rt	20 min	92	—
16	(*S*)-CSA	10	)))), rt	40 min	75	Trace
17	(*S*)-CSA	30	)))), rt	20 min	90	—
18	$InCl_3$	20	)))), rt	50 min	45	20
19	H_2NHSO_3	20	)))), rt	35 min	60	20
20	$BF_3.OEt_2$	20	)))), rt	40 min	55	15

[a] Reaction of phthalhydrazide (1.0 mmol), dimedone (1.1 mmol), and 4-nitrobenzaldehyde (1.1 mmol).
[b] Isolated pure yields.

Table 2
Synthesis of 2*H*-indazolo[2,1-*b*]phthalazinetriones **4** and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **6**.

Entry	R	R^1	R^2	Time I/II (min)	Yield[a] I/II (%)	mp (°C)[Lit.]
4a	Me	—	4-$NO_2C_6H_4$	15/20	94/92	(224–225)[21a,b]
4b	Me	—	3-$NO_2C_6H_4$	20/25	88/85	(268–267)[20a]
4c	Me	—	C_6H_5	15/20	90/87	(206–208)[20a]
4d	Me	—	4-$OMeC_6H_4$	20/25	82/80	(218–220)[21b]
4e	Me	—	4-ClC_6H_4	15/20	92/90	(260–262)[20b]
4f	Me	—	3-ClC_6H_4	20/25	85/83	(205–207)[21b]
4g	Me	—	4-BrC_6H_4	15/20	92/90	(265–267)[20b]
4h	H	—	2,4-$Cl_2C_6H_3$	20/30	90/88	(274–276)[20b]
4i	H	—	4-$NO_2C_6H_4$	20/25	94/92	(263–265)[21b]
4j	H	—	4-$CH_3C_6H_4$	25/35	92/90	(248–250)[20b]
4k	H	—	3-OHC_6H_4	25/30	92/88	(265–268)[20b]
4l	Me	—	4-$CHOC_6H_4$	25/30	85/80	260–262
4m	Me	—	2-Thienyl	20/25	68/65	217–219
4n	Me	—	2-Pyridyl	20/30	62/60	230–232
4o	Me	—	*n*-C_7H_{15}	35/40	52/50	88–90
4p	H	—	Cyclohexyl	30/40	90/85	214–216
6a	—	Me	4-$NO_2C_6H_4$	35/40	85/82	217–218
6b	—	Ph	4-$CH_3C_6H_4$	40/45	82/80	233–234
6c	—	Me	Isopropyl	60/70	52/50	Viscous oil
6d	—	Ph	Cyclohexyl	65/70	50/45	Viscous oil

[a] Isolated pure yields under both conditions I and II.

both conditions, ultrasound irradiation appears milder than the conventional heating, and offers significant improvements in terms of simplicity and green aspects by avoiding high temperature.

Subsequently, with optimal conditions in hand, the generality and synthetic scope of this coupling protocol were demonstrated by synthesizing a series of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones **4a–p** and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **6a–d** (Table 2). Gratifyingly, a wide range of aldehydes (aromatic, heteroaromatic, and aliphatic), and cyclic and acyclic 1,3-diketones were well tolerated under the optimized reaction conditions. However, in comparison to aromatic aldehydes, aliphatic aldehydes gave lower yields (Table 2, entries **4o**, **6c**, and **6d**). Moreover, when cyclic 1,3-diketones such as indane-1,3-dione, 1,3-dimethylbarbituric acid, and 4-hydroxycoumarin were treated with phthalhydrazide and aldehyde under the optimized reaction conditions failed to give the expected product and furnished the Knoevenagel condensation product exclusively, thus limiting the scope of this reaction to some extent. The time taken for complete conversion (monitored by TLC) and the isolated yields are recorded in Table 2. All new compounds were characterized by their satisfactory elemental analyses and spectral (IR, ^1H, ^{13}C NMR and mass) studies, and known compounds by comparison of their physical and spectral data with those of the reported ones.[20,21]

In summary, we have devised a simple and efficient one-pot approach to construct the structurally diverse 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11-triones **4** and 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **6** via three-component coupling of phthalhydrazide, 1,3-diketones, and aldehydes under solvent-free conditions at 80 °C as well as under solvent-free ultrasound irradiation at room temperature promoted by (*S*)-camphorsulfonic acid through domino Knoevenagel condensation/Michael addition/intramolecular cyclodehydration sequence. The advantages of operational simplicity, economic viability, high atom-economy together with ecologically benign nature make this protocol a very efficient alternative to the literature methods, which could be directly used for biological assays. The economical factors (time, money, waste etc.) for these three-component reactions hold promise for the future of organic synthesis.

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24. *General procedure for the synthesis of compounds* ***4*** *and* ***6****: (I) Conventional Method*: To a thoroughly homogenated mixture of phthalhydrazide **1** (1.0 mmol), cyclic/acyclic 1,3-diketone **2** (1.1 mmol), and aldehyde **3** (1.1 mmol), (*S*)-CSA (0.046 g, 0.2 mmol) was added. The reaction mixture was heated at 80 °C for a stipulated period of time (Table 2). After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and washed twice with water. The product obtained was purified by crystallization from ethyl acetate-*n*-hexane (1:3) or by column chromatography (in case of acyclic 1,3-diketones) over silica gel (Merck, 60–120 mesh, ethyl acetate-*n*-hexane, 1:3). *(II) Ultrasound Irradiation*: To a thoroughly homogenated mixture of **1** (1.0 mmol), **2** (1.1 mmol), and **3** (1.1 mmol), (*S*)-CSA (0.046 g, 0.2 mmol) was added. The reaction mixture (solid paste using a drop of acetonitrile was prepared in case of solid aldehydes) was subjected to ultrasound irradiation (Qualigen ultrasonic cleaner with power of 200 W) under solvent-free conditions at room temperature until completion of the reaction (monitored by TLC). The desired product obtained was purified as mentioned above. Analytical and spectral data for the selected products: *Compound* ***4m****: 3,3-Dimethyl-13-thiophen-2-yl-2,3,4,13-tetrahydro-indazolo[2,1-b]phthalazine-1,6,11-trione*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.34–8.29 (m, 2H, ArH), 7.86–7.83 (m, 2H, ArH), 7.33 (s, 1H, ArH), 7.23–7.22 (m, 1H, ArH), 6.99–6.96 (m, 1H, ArH), 6.82 (s, 1H, CH), 3.44 and 3.19 (d, J = 18.9 Hz, 2H, CH_2), 2.39 (s, 2H, CH_2), 1.29 and 1.22 (s, 6H, 2 × CH_3).^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 154.1, 151.5, 138.6, 134.4, 133.4, 128.7, 128.2, 127.9, 127.5, 126.9, 125.8, 117.0, 59.2, 50.7, 37.8, 34.3, 28.8, 28.1. IR (KBr): ν = 2945, 1669, 1374, 1301, 1257, 800 cm^{-1}. ESI MS (m/z): 379 [M+1]$^+$. Anal. Calcd for $C_{21}H_{18}N_2O_3S$ (378.4): C, 66.65; H, 4.79; N 7.40%. Found C, 66.75; H, 4.89; N, 7.31%. *Compound* ***4p****: 13-Cyclohexyl-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.36–8.30 (m, 2H, ArH), 7.91–7.81 (m, 2H, ArH), 5.58 (s, 1H, CH), 3.35–3.50 and 3.18–3.09 (m, 2H, CH_2), 2.63–2.20 (m, 5H, CH_2), 2.04–1.92 (m, 1H, CH), 1.74–1.58 (m, 6H, CH_2), 1.21–1.10 (m, 3H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 155.2, 154.4, 153.0, 133.8, 132.7, 131.6, 128.2, 128.0, 127.1, 126.7, 124.8, 117.3, 65.6, 40.5, 36.3, 27.5, 25.6, 25.4, 23.7, 21.3. IR (KBr): ν = 2962, 1667, 1365, 1294, 1243 cm^{-1}. ESI MS (m/z): 351 [M+1]$^+$. Anal. Calcd for $C_{21}H_{22}N_2O_3$ (350.4): C, 71.98; H, 6.33; N 7.99%. Found C, 71.75; H, 6.52; N, 7.71%. *Compund* ***6a****: 2-Acetyl-3-methyl-1-(4-nitrophenyl)-1H-pyrazolo[1,2-b]phthalazine-5,10-dione*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.38–8.35 (m, 1H, ArH), 8.21 (d, J = 8.7 Hz, 3H, ArH), 7.86–7.83 (m, 2H, ArH), 7.65 (d, J = 8.7 Hz, 2H, ArH), 6.55 (s, 1H, CH), 3.09 (s, 3H, $COCH_3$), 2.23 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.0, 156.0, 153.9, 147.6, 146.0, 143.6, 134.3, 133.6, 129.1, 128.8, 128.0, 127.9, 127.0, 123.7, 119.1, 65.0, 30.5, 14.6. IR (KBr): ν = 2924, 1662, 1616, 1521, 1351, 1310 cm^{-1}. ESI MS (m/z): 378 [M$^+$+1]. Anal. Calcd for $C_{20}H_{15}N_3O_5$ (377.3): C, 63.66; H, 4.01; N 11.14%. Found: C, 63.78; H, 4.12; N, 11.01%. *Compound* ***6b****: 2-Benzoyl-3-phenyl-1-p-tolyl-1H-pyrazolo[1,2-b]phthalazine-5,10-dione*: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.28–8.22 (m, 2H, ArH), 7.84–7.75 (m, 2H, ArH), 7.44 (d, J = 7.8 Hz, 2H, ArH), 7.35–7.31 (m, 4H, ArH), 7.21–7.13 (m, 6H, ArH), 7.07–7.02 (m, 2H, ArH), 6.83 (s, 1H, CH), 2.27 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.8, 154.7, 142.4, 138.6, 137.2, 134.0, 133.5, 133.4, 132.0, 130.0, 129.8, 129.6, 128.8, 128.5, 127.9, 127.7, 127.5, 127.4, 127.0, 123.2, 68.1, 21.2. IR (KBr): ν = 3046, 2925, 2856, 1739, 1662, 1412, 1339 cm^{-1}. ESI MS (m/z): 471 [M$^+$+1]. Anal. Calcd for $C_{31}H_{22}N_2O_3$ (470.5): C, 79.13; H, 4.71; N 5.95%. Found: C, 79.24; H, 4.82; N, 6.01%.