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# Dodecylphosphonic acid (DPA): a highly efficient catalyst for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones under solvent-free conditions

Mazaahir Kidwai [a,*], Anwar Jahan [a], Ritika Chauhan [a], Neeraj Kumar Mishra [a]

[a] *Green Chemistry Research Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India*

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ABSTRACT

A new green protocol has been developed for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones via one-pot, three-component condensation reaction of aromatic aldehydes with 1,3-dicarbonyl compounds and phthalhydrazide using reusable dodecylphosphonic acid (DPA) as heterogeneous solid acid catalyst under solvent-free conditions. This protocol provides a novel and improved method for obtaining 2*H*-indazolo[2,1-*b*]phthalazine-triones in terms of good yields with little catalyst loading.



The development of new methods for solvent-free organic synthesis involving multicomponent reactions is an important and attractive area of synthetic research.[1,2] Organic reactions should be fast and facile and the target products should be easily separated and purified in high yields without the isolation of any intermediate.[3] From this point of view, solvent-free multicomponent reactions[4] find application as appealing methods to achieve these goals. Multicomponent protocol emphasizes as one-pot reaction in which three or more reactants are combined together to generate a single product with greater efficiency.[5,6] Multicomponent reactions (MCRs) enable multiple reactions leading to interesting heterocyclic scaffolds which are useful for the construction of poly-functionalized heterocyclic 'drug like' libraries.[7,8]

In the past few decades, the synthesis of nitrogen-containing heterocyclic compounds has gained prominence as they are widespread in nature.[9] Also their applications to biologically active pharmaceuticals, agrochemical and functional materials are becoming increasingly important.[10–12]

Among a large variety of N-containing heterocyclic compounds, heterocycles containing hydrazine moiety as 'fusion site' have received considerable attention because of their pharmacological properties and clinical applications.[13] Moreover, fused phthalazines were found to possess multiple biological activities such as antimicrobial,[14] anticonvulsant,[15] antifungal,[16] anticancer,[17] and anti-inflammatory activities.[18] Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives.[19,20] However, some of these methods suffered with several drawbacks such as hazardous organic solvents, high cost, long reaction time, use of stoichiometric, and excess amounts of acids and harsh reaction conditions with non-recyclable catalyst. Therefore, the development of a new, efficient, and environment friendly procedure is necessary, which allow the ready synthesis of heterocycles containing phthalazine ring fragment.

In recent years, solid acid catalysts have found several applications in organic synthesis, as they may be easily recovered and recycled. In this connection, dodecylphosphonic acid (DPA) was used as mild, harmless to the environment, recyclable, non-toxic, and commercially available heterogeneous solid acid catalyst with stability toward humidity.[21,22] Despite its great importance, only a few papers are reported on its catalytic application in organic synthesis.[21,22]

In combination with the use of heterogeneous catalyst in organic transformations, solvent-free methodologies for the synthesis of organic compounds have attracted much interest because of their ease of experimental procedures as well as work-up, low cost, clean, efficient, environmentally benign, and high yielding processes.[23,24] According to the principle of safe chemistry, synthetic methods should be designed to use substances that exhibit little or no toxicity to human health and the environment.[25]

As a part of our continuing studies in developing efficient synthetic methodologies[26,27] in organic preparations, we found that the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives via a one-pot, three-component condensation reaction of aldehydes

* Corresponding author at present address: Vice-chancellor, Jiwaji University, Gwalior (M.P.), India (On Deputation from Department of Chemistry, University of Delhi, Delhi 110 007, India). Tel./fax: +91 11 27666235.
*E-mail address:* kidwai.chemistry@gmail.com (M. Kidwai).

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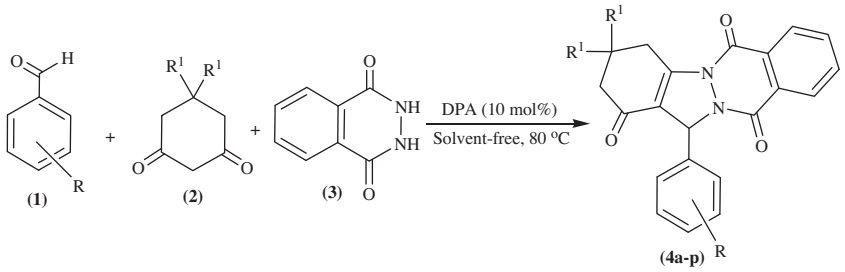
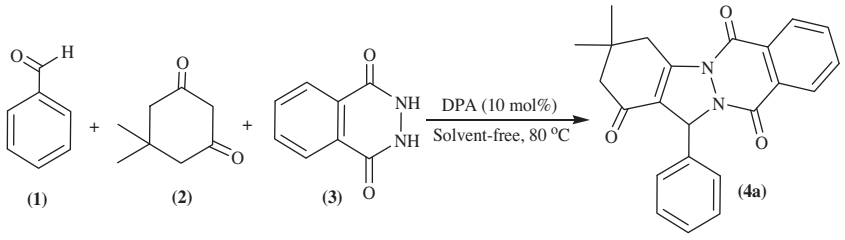



**Scheme 1.** DPA catalyzed synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives.




**Scheme 2.** DPA catalyzed model reaction.

(**1**) with 1,3-dicarbonyl compounds (**2**) and phthalhydrazide (**3**) can be efficiently achieved without any solvent with the use of dodecylphosphonic acid under mild conditions at 80 °C (Scheme 1).

To optimize the reaction conditions, we first examined the reaction of benzaldehyde (1 mmol), dimedone (1 mmol), and phthalhydrazide (1.5 mmol) at 80 °C without catalyst under solvent-free conditions in order to recognize the capability of the catalyst. The reaction did not proceed even after prolonged reaction time and no desired product was formed which supported the catalytic activity of DPA. When the reaction was performed in the presence dodecylphosphonic acid, it proceeded effectively to produce the desired product (**4a**) in high yields (Scheme 2).

Some other solid acid catalysts such as L-proline, montmorillonite K-10, Amberlyst-15, *p*-TSA, PMA-$SiO_2$, silica sulfuric acid, and $HClO_4$–$SiO_2$ exhibited moderate to good catalytic properties. In most of these cases comparative yields of the desired product were obtained. Following the DPA-catalyzed procedure, the reported methods required expensive catalyst, toxic or organic solvents, strong acidic conditions, high catalyst loading, and long reaction times. These results clearly demonstrated that DPA is a more efficient catalyst for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones. The results are summarized in Table 1.

Besides this, we observed that the concentration of the catalyst played a major role in catalyzing the condensation reaction for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones. Using a model reaction as described above and varying just the concentration of DPA from 2 mol % to 10 mol %, the yield of product was increased from 82% to 96%. This shows that 10 mol % of DPA is the suitable choice for the optimum reaction rate and yield of 2*H*-indazolo[2,1-*b*]phthalazine-triones (Table 1, entries 9–11).

Next, the effect of temperature was also evaluated for the model reaction. It was observed that fast reaction occurred on raising the temperature from 20 °C to 80 °C and the yield of desired product increased considerably. We were pleased to find that the reaction proceeded smoothly and almost complete conversion of reactants was observed at 80 °C to afford the desired product (**4a**) in 96% yield within 10 min (Table 2). However, at room temperature a lower yield of product was obtained even after longer reaction times.

With the optimistic results in hand, we chose a variety of structurally diverse aromatic aldehydes and 1,3-dicarbonyl compounds to understand the scope and efficiency of the dodecylphosphonic acid promoted synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones. It was observed that aromatic aldehydes having electron-withdrawing groups (Table 3, entries 2 and 3) afforded high yield of products as compared to aromatic aldehydes substituted with electron-donating groups (Table 3, entries 4 and 5). Heterocyclic aldehydes also displayed good reactivity (Table 3, entry 7). Besides this, our methodology has been used successfully with cyclohexane-1,3-dione in place of dimedone and corresponding products were

**Table 1**
Influence of different catalysts on the reaction of benzaldehyde, dimedone and phthalhydrazide[a]

| Entry | Catalyst | Amount (mol %) | Time (min) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | No | — | 3600 | Trace |
| 2 | L-Proline | 10 | 600 | Nil |
| 3 | Montmorillonite K-10 | 10 | 30 | 65 |
| 4 | Amberlyst-15 | 10 | 12 | 83 |
| 5 | *p*-TSA | 30 | 10 | 86 |
| 6 | PMA-$SiO_2$ | 10 | 30 | 85 |
| 7 | Silica sulfuric acid | 6.5 | 7 | 91 |
| 8 | $HClO_4$–$SiO_2$ | 10 | 12 | 86 |
| 9 | DPA | 2 | 20 | 82 |
| 10 | DPA | 5 | 10 | 92 |
| 11 | DPA | 10 | 10 | 96 |

[a] Reaction conditions: Benzaldehyde (1 mmol), dimedone (1 mmol) and phthalhydrazide (1.5 mmol); temperature: 80 °C.
[b] Isolated yields.

**Table 2**
Effect of temperature[a]

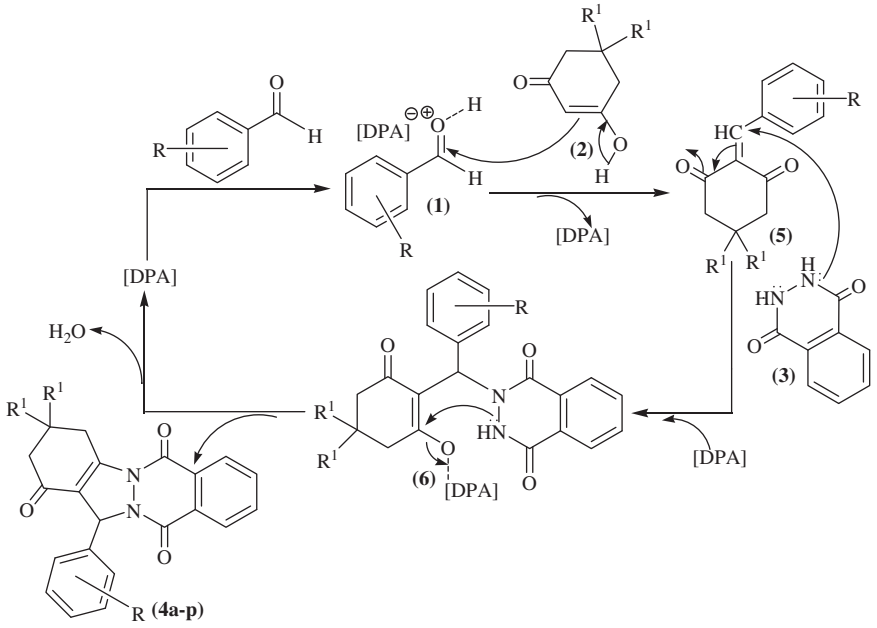
| Entry | Temperature (°C) | Time (min) | Yield[b] (%) |
|---|---|---|---|
| 1 | 20 | 60 | 25 |
| 2 | 40 | 35 | 65 |
| 3 | 60 | 20 | 90 |
| 4 | 80 | 10 | 96 |

[a] Reaction conditions: Benzaldehyde (1 mmol), dimedone (1 mmol), and phthalhydrazide (1.5 mmol); catalyst: DPA (10 mol %); at different temperatures.
[b] Isolated yields.

**Table 3**
Dodecylphosphonic acid (DPA) catalyzed synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-triones **(4a–p)**[a]

| Entry | R | $R^1$ | Product | Time (min) | Yield[b] (%) | Mp (°C) |
|---|---|---|---|---|---|---|
| 1 | H | $CH_3$ | **4a** | 10 | 96 | 203–205[20a] |
| 2 | 4-Cl | $CH_3$ | **4b** | 5 | 90 | 263–265[20a] |
| 3 | 4-$NO_2$ | $CH_3$ | **4c** | 10 | 94 | 224–226[20a] |
| 4 | 4-$OCH_3$ | $CH_3$ | **4d** | 10 | 88 | 217–219[28a] |
| 5 | 4-$CH_3$ | $CH_3$ | **4e** | 10 | 85 | 226–228[20a] |
| 6 | 2-OH | $CH_3$ | **4f** | 10 | 83 | 185–187 |
| 7 | Piperonyl | $CH_3$ | **4g** | 10 | 79 | 196–198 |
| 8 | 1-Naphthyl | $CH_3$ | **4h** | 15 | 82 | 263–265[29] |
| 9 | H | H | **4i** | 10 | 94 | 222–225[28b] |
| 10 | 3-$NO_2$ | H | **4j** | 5 | 92 | 228–231[28a] |
| 11 | 4-$CH_3$ | H | **4k** | 10 | 84 | 245–246[28a] |
| 12 | 3-OH | H | **4l** | 10 | 80 | 266–268[28b] |
| 13 | 4-Br | H | **4m** | 10 | 87 | 279–282[28b] |
| 14 | 4-HO-3-MeO | H | **4n** | 10 | 91 | 203–205 |
| 15 | 4-$(CH_3)_2N$ | H | **4o** | 10 | 86 | 255–257[28a] |
| 16 | 1-Naphthyl | H | **4p** | 15 | 80 | 259–261[28b] |

[a] Reaction conditions: Aromatic aldehydes (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and phthalhydrazide (1.5 mmol); catalyst: DPA (10 mol %); temperature: 80 °C.
[b] Isolated yields.




**Scheme 3.** Plausible mechanism for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-trione derivatives.

obtained in excellent yields under similar reaction conditions (Table 3, entries 9–16). The scope of the reaction was also investigated with aliphatic and α,β-unsaturated aldehydes as substrates and incomplete conversion of the starting materials to the product was observed.

A plausible mechanism[29] for the formation of 2*H*-indazolo[2,1-*b*]phthalazine-triones[30] is shown in Scheme 3. The reaction is thought to proceed in a stepwise manner. Firstly, we assumed that the reaction occurs via a Knoevenagel condensation between 1,3-dicarbonyl compounds **2** and aromatic aldehydes **1** to form the intermediate **5** in the presence of DPA, which suffers immediate Michael addition of phthalhydrazide **3** to the C=C bond of **5**. The concerted cyclocondensation of amino and carbonyl of the Michael adduct **6** was performed to afford the corresponding products (**4a–p**). During the reaction process, the hydrogen ion is donated by the dodecylphosphonic acid. The hydrogen ion helps in the enolization of 1,3-dicarbonyl compounds to form the enolate intermediate.

**Table 4**
Recycling yields[a]

| No of Cycles[a] | Fresh | Run 1 | Run 2 | Run 3 | Run 4 | Run 5 |
|---|---|---|---|---|---|---|
| Yield[b] | 96 | 96 | 95 | 92 | 90 | 86 |
| Time (min) | 10 | 10 | 10 | 10 | 10 | 10 |

[a] Reaction conditions: Benzaldehyde (1 mmol), dimedone (1 mmol), and phthalhydrazide (1.5 mmol); catalyst: DPA (10 mol %), temperature: 80 °C.
[b] Isolated yields.

The recyclability of DPA was also examined. When the reaction was completed, water was added and the product was filtered. The aqueous solution was evaporated under reduced pressure and the powder obtained (catalyst) was washed with diethyl ether, dried, and reused for the same reaction again. It was observed that, with an increase in reusability runs, the catalytic activity of DPA decreased slightly (Table 4).

In conclusion, we have developed a solvent-free reaction for the synthesis of 2*H*-indazolo[1,2-*b*]phthalazine-triones via one-pot, three-component condensation reaction of aromatic aldehydes with 1,3-dicarbonyl compounds and phthalhydrazide using dodecylphosphonic acid (DPA) as a novel, efficient, and recyclable catalyst . The salient features of this protocol are high product yields, shorter reaction time, solvent-free condition, low catalyst loading, and relatively mild acid catalyst with easy work-up procedure, which make this procedure quite simple, more convenient, and environmentally benign. Hopefully, our methodology could be a valid contribution to the existing processes in the field of 2*H*-indazolo[2,1-*b*]phthalazine-triones synthesis.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.095.

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30. *General procedure for the synthesis of 2H-indazolo[2,1-b]phthalazine-trione derivatives*: In a 50 mL round bottom flask, the required amount of aromatic aldehydes (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and dodecylphosphonic acid (DPA) (10 mol %) were added and the mixture was stirred over a magnetic stirrer. After 5 min, to this stirred mixture, phthalhydrazide (1.5 mmol) was added and the contents were stirred at 80 °C for an appropriate time. The progress of reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and washed with water. The crude product was crystallized with ethanol, which was further purified by silica gel column chromatography (hexane/ethylacetate 70:30) to give the desired products. All the products were characterized by comparing their physical (MPs) and spectral data with those reported earlier. After the evaporation of aqueous layer, the catalyst was recovered and reused for next reaction.