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Palladium(0) nanoparticles: an efficient catalyst for the one-pot synthesis of polyhydroquinolines

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ABSTRACT

A mild, concise, and efficient protocol for the synthesis of polyhydroquinoline via four component reaction of aromatic aldehydes, dimedone, ethyl acetoacetate or ethyl cyanoacetate, and ammonium acetate using Pd-nanoparticles is described. The same phenomenon was observed in the case of arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones), ethyl acetoacetate, ammonium acetate, and Pd-nanoparticles in one-pot. The present method also allows us to synthesize highly functionalized title compounds from simple and readily available inputs.

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Design of highly efficient chemical reaction sequence that provides maximum structural complexity and diversity with a minimum number of synthetic steps to assemble compounds with increasing properties is a major challenge of modern drug discovery.[1] Recently, multicomponent reaction has emerged as a highly valuable synthetic tool in the context of modern drug discovery. The atom-economy and convergent character, the simplicity of one-pot procedure, the possible structural variation, the accessible complexion of the molecule, and the very large number of accessible compounds are among the described advantages of multicomponent reaction.[2] Thus, they are perfectly amenable to automation for combinatorial synthesis.[3]

Polyhydroquinolines are an important group of nitrogen containing heterocycles that have attracted much attention because of their diverse therapeutic and pharmacological properties, such as calcium channel blockers, vasodilator, hepatoprotective, antiatherosclerotic, bronchodilator, antitumor, geroprotective, antidiabetic activity, etc.[4,5] Furthermore, recent studies have revealed several other medicinal applications that include neuroprotectant and platelet anti-aggregatory activity, cerebral anti-ischemic activity in the treatment of Alzheimer's disease, and as a chemosensitizer in tumor therapy.[6]

Therefore, several methods have been developed for the preparation of polyhydroquinoline derivatives by using various catalysts, including molecular iodine,[7] ionic liquid,[8] rare earth metal triflates,[9] $HClO_4$–SiO_2,[10] HY-zeolites,[11] TMSCl-NaI,[12] ceric ammonium nitrate,[13] grinding technique,[14] ultrasound,[15] montmorillonite K-10,[16] *p*-TSA,[17] polymer,[18,19] hetrapolyacid,[20] organic catalyst,[21] L-proline,[22] Bakers' yeast,[23] $ZrCl_4$,[24] MCM-41,[25] solar heat,[26] $Hf(NPf_2)_4$,[27] $Yb(OTf)_3$,[28] $Cu(OTf)_2$,[29] triphenyl phosphine,[30] and liquid phase.[31] Although most of these processes offer distinct advantages, they also suffer from certain drawbacks, such as longer reaction time, unsatisfactory yields, high costs, harsh reaction conditions, stoichiometric amounts of catalyst, and also environmentally toxic catalysts. In recent time, interest in nanoparticles catalysis has increased considerably because of its improved efficiency (higher surface to volume ratio)[32,33] under mild and environmentally benign conditions in the context of green chemistry and palladium nanoparticles have been found to be active species in various C–C bond formation reaction, namely Heck, Sonogashira, and Suzuki, coupling reactions and thus showed great promise for further applications.[33]

To the best of our knowledge, however, any palladium nanoparticles promoted synthesis of polyhydroquinoline derivatives has not been reported till date. In the present work, we report here a novel, ligand-free protocol for the synthesis of polyhydroquinolines catalyzed by palladium(0) nanoparticles. The overall process involves the Knoevenagel condensation of dimedone with aryl aldehydes, followed by in situ Michael addition of ethyl acetoacetate in a single operation.

In continuation of our research work in the development of highly expedient methodologies for the synthesis of biologically important heterocyclic compounds,[34] we became interested in

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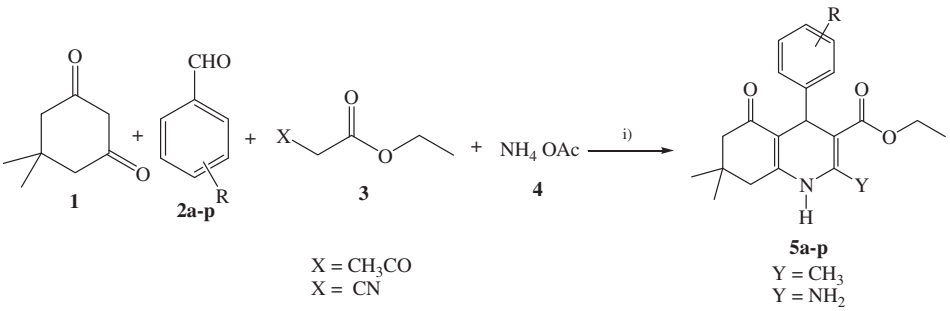


Scheme 1. Synthesis of polyhydroquinoline derivatives **5a–p** from dimedone. Reagents and conditions: (i)$PdCl_2$, Na_2CO_3, TBAB, THF, refluxed 4–5 h.

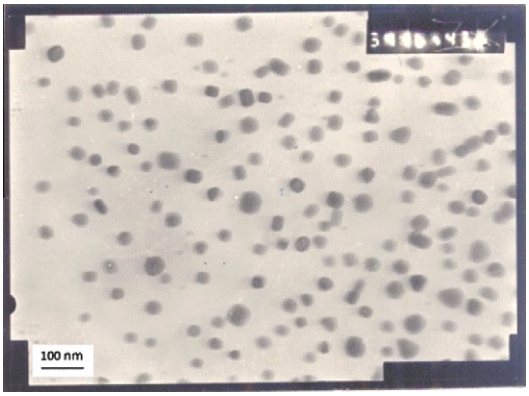


Figure 1. TEM image of palladium nanoparticles.

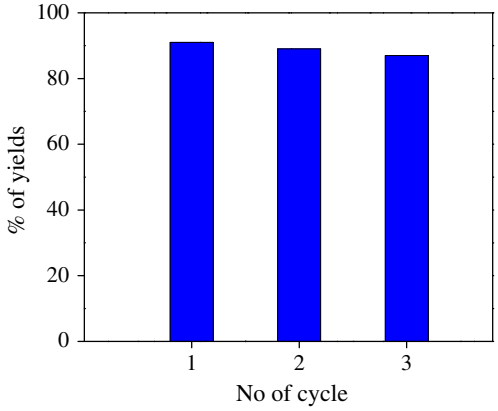


Figure 2. Recyclability chart.

developing a methodology for the synthesis of polyhydroquinoline derivatives using various aromatic aldehydes, ethyl acetoacetate or ethyl cyanoacetate, ammonium acetate, and dimedone under Pd-nanoparticles mediated reaction condition. As a model reaction, we selected 1 equiv of dimedone **1**, 1 equiv of benzaldehyde **2a**, 1 equiv of ethyl acetoacetate **3**, 2 equiv of ammonium acetate **4**, 0.04 equiv of $PdCl_2$, 1 equiv of TBAB, and 3 equiv of Na_2CO_3 in THF under refluxing condition and obtained **5a** in 89% yield (Scheme 1). The formation of Pd-(0) nanoparticles in situ from this reagent system was detected from the analysis of the reaction mixture by transmission electron microscope (TEM) (Fig. 1) and X-ray diffraction (XRD) (Fig. 3). The morphology and grain size of the palladium nanoparticles were investigated by TEM. They had spherical with a narrow size distribution from 10 to 40 nm. The presence of some larger particles should be attributed to aggregating or overlapping of smaller particles. The data were in good agreement with the previously reported results.[35] Encouraged by the initial success, we extended the scope of the present protocol for the synthesis of polyhydroquinolines from aryl aldehydes (Scheme 1). As shown in the Table 1, aromatic aldehydes carrying either electron donating or withdrawing substituent worked well, giving excellent yields of products with high purity, but aliphatic aldehydes under similar condition did not produce any polyhydroquinolines. Only starting materials were recovered.

The Knoevenagel condensation followed by Michael addition reaction of dimedone with several aromatic aldehydes, ammonium acetate, and ethyl acetoacetate in the presence of palladium nanoparticles was investigated using a range of different solvents. The results of Table 2 indicate that solvents affected the efficiency of the reaction. In general, solvent like dichloromethane, acetonitrile,

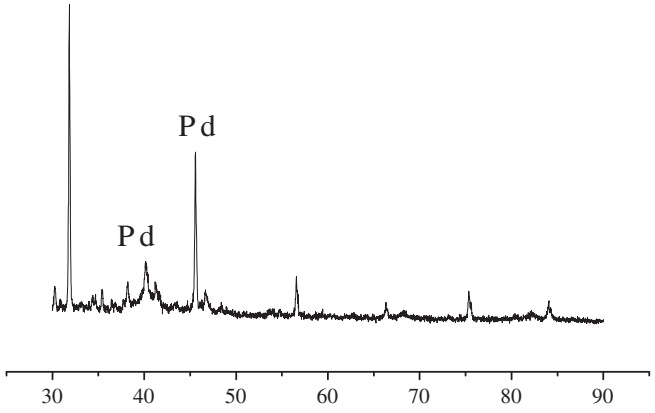


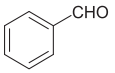
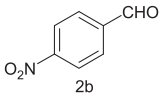
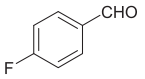
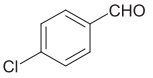
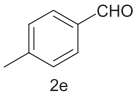
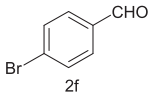
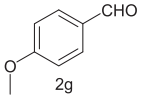
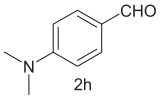
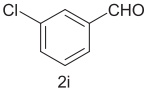
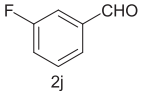
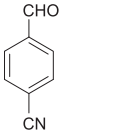
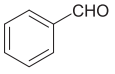
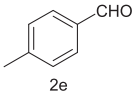
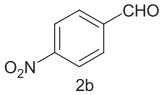
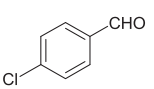
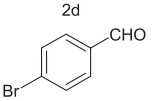
Figure 3. Powder XRD pattern with characteristic dihedral angels at 40.17° and 45.73° corresponding to Pd nanoparticles.

and water led to low yields (Table 2, entries 1–3) under refluxing condition, but the best conversion was observed when the reaction was carried out in tetrahydrofuran (Table 2, entry 4).

In transition metal catalyzed reactions, ligands play an important role. Various phosphine and nonphosphine ligands for palladium catalyzed coupling reactions are described in the literature. Most of these ligands are air and moisture sensitive, difficult to prepare, and expensive. Thus, catalysis by a ligand-free condition is an area of high importance.[36]

In evaluating the effect of catalyst concentration, the best yields were obtained in the presence of just 0.04 mmol of palladium

Table 1
Synthesis of polyhydroquinoline derivatives **5a–p**

Entry	Aldehydes (**2a–k**)	X	Y	Product	Time (h)	Yield (%)[a]
1	 2a	$COCH_3$	CH_3	**5a**	4	89
2	 2b	$COCH_3$	CH_3	**5b**	4	92
3	 2c	$COCH_3$	CH_3	**5c**	4	88
4	 2d	$COCH_3$	CH_3	**5d**	4	87
5	 2e	$COCH_3$	CH_3	**5e**	4.3	86
6	 2f	$COCH_3$	CH_3	**5f**	4	88
7	 2g	$COCH_3$	CH_3	**5g**	5	86
8	 2h	$COCH_3$	CH_3	**5h**	5	85
9	 2i	$COCH_3$	CH_3	**5i**	4.3	89
10	 2j	$COCH_3$	CH_3	**5j**	4.3	88
11	 2k	$COCH_3$	CH_3	**5k**	4.0	89
12	 2a	CN	NH_2	**5l**	4	87
13	 2e	CN	NH_2	**5m**	5	89
14	 2b	CN	NH_2	**5n**	4	88
15	 2d	CN	NH_2	**5o**	4	87
16	 2f	CN	NH_2	**5p**	4	88

[a]Isolated yields

nanoparticles. A higher amount of catalyst 0.06, 0.08, and 1.0 mmol did not improve the yield of the desired product. On decreasing the Pd concentration from 0.04 to 0.02 and 0.01 mmol, the yield of polyhydroquinoline dropped even after 6 h. The reaction without the catalyst has also been carried out but no polyhydroquinoline derivatives were witnessed and only dimedone and aryl aldehyde were recovered. Reusability is one of the important properties of this catalyst. In this study, the catalyst was recovered and reused in another run. The catalyst was recovered by a simple filtration using centrifugation method and reused during three consecutive runs without any apparent loss of activity for the same reaction (Fig. 2).

Table 2
Optimization of solvent effect

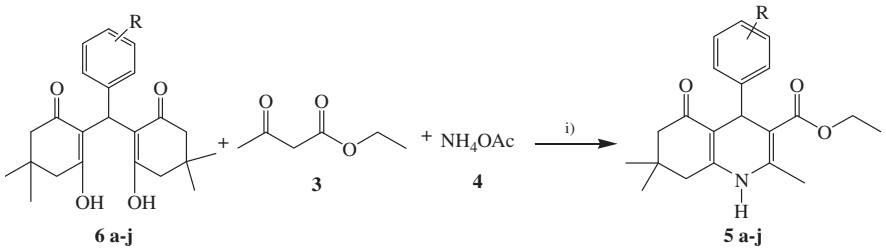
Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	DCM	Reflux	4	67
2	CH_3CN	Reflux	4	59
3	Water	Reflux	4	52
4	THF	Reflux	4	89
5	THF	Reflux	6	89

Kumar et al.[23] reported the conversion of arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) to polyhydroquinoline using Bakers' yeast as a catalyst. Encouraged by our initial results, we extended the scope of our present protocol for the synthesis of polyhydroquinoline from arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) **6a–j** and it afforded polyhydroquinoline (**5a–j**) (Scheme 2) in good to excellent yields (Table 3). The mechanism for the formation of polyhydroquinoline **5a–j** from arylmethylene bis(3-hydroxy-2-cyclohexene-1-one) **6a–j** is still uncertain. All the products were analytically pure and structures were determined by the spectral methods.

In summary, we have developed a novel, mild, and efficient strategy for the synthesis of polyhydroquinoline from dimedone, aryl aldehydes, and ammonium acetate and ethyl acetoacetate or ethyl cyanoacetate via Knoevenagel condensation followed by Michael addition reaction using Pd-nanoparticles as catalyst. The methodology is simple, rapid, and relatively inexpensive affording good to excellent yields with operational simplicity.

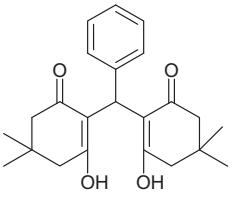
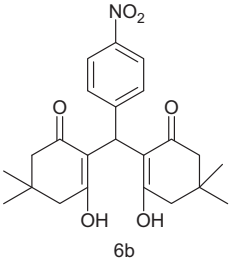
Acknowledgments

We thank Department of Chemistry (NEHU), UGC-SAP, and SAIF (NEHU) and IACS (Kolkata) for analytical support. We are also thankful to Professor R. K. Poddar and Dr. Rama Ranjan Bhattacharya.



Scheme 2. Synthesis of polyhydroquinoline derivatives **5a–j** from arylmethylene bis(3-hydroxy-2-cyclohexene-1-one). Reagents and conditions: (i) $PdCl_2$, Na_2CO_3, TBAB, THF, refluxed 4–5 h.

Table 3
Synthesis of polyhydroquinoline (**5a–j**) derivatives from arylmethylene *bis*(3-hydroxy-2-cyclohexene-1-ones) **6a–j**

Entry	Arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) 6a-j	Product	Time (h)	Yields (%)[a]
1	 6a	**5a**	4.3	87
2	 6b	**5b**	4	91

(*continued on next page*)

Table 3 (*continued*)

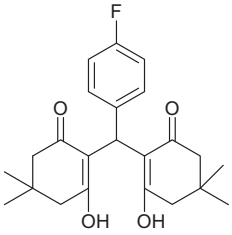
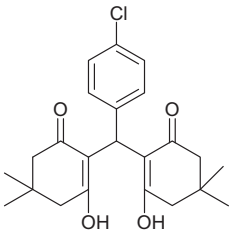
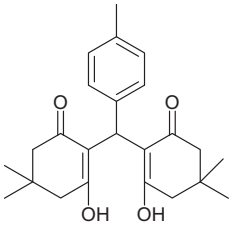
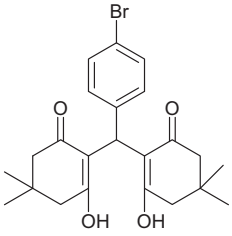
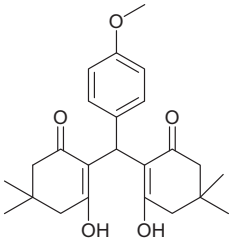
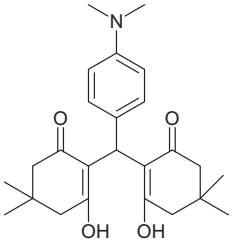
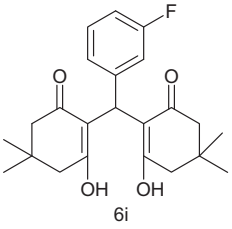
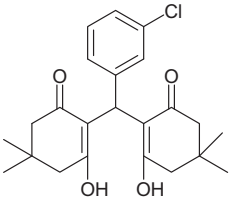
Entry	Arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) 6a-j	Product	Time (h)	Yields (%)[a]
3	 6c	**5c**	4	88
4	 6d	**5d**	4	87
5	 6e	**5e**	4.3	85
6	 6f	**5f**	4	88
7	 6g	**5g**	5	83
8	 6h	**5h**	5	81

Table 3 (*continued*)

Entry	Arylmethylene bis(3-hydroxy-2-cyclohexene-1-ones) 6a-j	Product	Time (h)	Yields (%)[a]
9	 6i	**5i**	4.3	87
10	 6j	**5j**	4.3	89

[a] Isolated yields

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