

Pd nanoparticles: an efficient catalyst for the solventfree synthesis of 2,3-disubstituted-4-thiazolidinones

Rajkumar R. Harale¹ · Praveen V. Shitre¹ · Bhaskar R. Sathe¹ · Murlidhar S. Shingare¹

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Abstract Palladium nanoparticles (Pd NPs: \sim 5-nm diameter) catalysed an efficient, solvent-free protocol for the cyclocondensation reaction of the aldehydes, anilines and mercaptoacetic acid has been developed. This method offers a rapid, relatively economical and ecofriendly protocol for the synthesis of 2,3-disubstituted-4-thiazolidinones for the first time. Moreover, the catalyst can also be easily recovered and recycled with no loss of catalytic activity.

Graphical Abstract



- Murlidhar S. Shingare prof_msshingare@rediffmail.com
- ¹ Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, India

Keywords 4-Thiazolidinones · Cyclocondensation reaction · Palladium nanoparticles

Introduction

4-Thiazolidinone derivatives are of considerable and remarkable interest in the field of medicinal chemistry. The 4-thiazolidinone heterocycles exhibit a wide range of biological activities such as anti-cancer [1], anti-malarial [2], anti-bacterial [3], anti-HIV [4] and nematicidal [5] activities, etc. Moreover, their end derivatives are also important precursors for the synthesis of useful pharmaceutical compounds, such as pyrazolothiazole derivatives [6], monofluoro β -lactam [7] and also for the synthesis of polymethine cyanine dyes [8]. Due to this diversity of the motif in the biological profile, 4-thiazolidinones have attracted much attention of the research community to explore the catalytic pathways for its synthesis.

The most recently used methods for the synthesis of thiazolidinone include condensation of aldehydes, anilines and mercaptoacetic acid using catalyst such as DCC [9], *Saccharomyces cerevisiae* [10], HBTU [11], [bmim][PF₆] [12], Bi(SCH₂COOH)₃ [13], silica chloride [14], silica gel [15], etc. Attempts have also been made to accelerate the cyclocondensation by simultaneous removal of reaction water azeotropically or by using dehydrating agents such as molecular sieves [16], trimethyl orthoformate [17], sodium sulphate [18], and ZnCl₂ [19]. Although most of the processes offer distinct advantages, moreover, they also suffer from certain drawbacks such as longer reaction times, unsatisfactory yields, harsh reaction conditions, stoichiometric amounts of catalysts and also environmentally toxic catalysts. To circumvent these difficulties and to speed up the synthesis, we focused on developing an alternate and novel route for the solvent-free synthesis of 4-thiazolidinones.

Most organic solvents are well-known for their unrecoverability and unavoidable polluting characteristics which results from their use in many industrial organic processes [20]. Hence, there is an urgent need to develop efficient and cost-effective synthetic methodologies that avoid using organic solvents (i.e. solvent-free conditions). As a result, the development of such methodologies has become a vital challenge for synthetic chemists. In addition to reducing pollution, solvent-free reactions also reduce overall costs and enhance the simplicity of processing and handling the resulting compounds.

Moreover, the properties of the nano-sized metals may differ from those of the bulk metals [21]; for example, the catalytic properties of metal nanoparticles (NPs) are as a function of their size, shape and dispersity. Among the other metal NPs, it has been proved that palladium (Pd) NPs acts as efficient catalysts due to their large surface to volume ratio at their tiny dimensions [22], chemo-selectivity, environmental compatibility and end recoverability. Recently, Pd NPs were found to be proficient catalysts for organic reactions [23–25] such as Heck, Sonogashira and Hiyama cross-couplings [26]. Herein, we report first time use of Pd NPs along with solvent-free reaction conditions for the synthesis of 4-thiazolidinones.

Preparation of Pd bulk catalyst

In brief, the preparation of Pd bulk catalyst involves, initially, aqueous $Pd(OAc)_2$ (1 mmol) stirred at room temperature (RT) for 30 min with Pd^{2+} ions subsequently being reduced via drop-wise addition of 20 mL of 0.1-M aq. NaBH₄ solution. Upon the slow addition of NaBH₄, the pale yellow color of Pd^{2+} turned reddish violet indicating the formation of Pd bulk catalyst.

Preparation of Pd NPs

Pd NPs were prepared by a modified Brust synthesis route using 9-decen-1-ol (DOL) as the capping agent. In brief, NPs were synthesized in a biphasic mixture of water and toluene (v:v; 1:1) using a 1:3 mol ratio of Pd acetate to DOL. The biphasic mixture was stirred at RT for 30 min and Pd^{2+} ions were subsequently reduced using drop-wise addition of 20 mL of 0.1-M aq. NaBH₄ solution. Upon the slow addition of NaBH₄, the pale yellow color of Pd^{2+} turned reddish violet, indicating the formation of Pd NPs. Furthermore, after rigorous stirring for 3 h, Pd NPs were found to be shifted to the organic phase, turning the upper layer blackish. Subsequently, the particles were precipitated repeatedly using acetone to remove excess/unbound capping agent and other by-products. Furthermore, the formation of Pd NPs along with their morphology and grain size has been proved by the transmission electron microscopy (TEM) images at different magnifications. Accordingly, Fig. 1a shows a low-magnification TEM image of as-synthesised Pd NPs, and it confirms particles



Fig. 1 Transmission electron microscopy (TEM) images of mono-dispersed Pd NPs at different **a** low and **b** high magnification having an average particle diameter of 5 ± 0.4 nm. **c** TEM analysis after four cycles, **d** along with the X-ray diffraction (XRD) pattern of Pd NPs using CuK α (1.54 Å) radiation; the patterns (111), (200) and (220) reveal the FCC structures

were well- and mono-dispersed with an interconnected network between them due to the bifunctional nature of the capping agent (DOL). Figure 1b shows high magnification of Pd–DOL NPs having a size of 5 ± 0.4 nm. X-ray diffraction (XRD) analysis was further carried out to investigate the crystallinity of these assynthesised Pd–DOL NPs and also to evaluate their size distribution. Figure 1c shows the XRD patterns corresponding to Pd NPs having a face-centered cubic (FCC) crystal structure as in agreement with the previous reports [23], although there are slight differences in the orientation. Moreover, the particle size was calculated from the full width at the half maxima (FWHM) of the strongest peak; (111) for Pd– DOL NPs using the Scherrer formula. The calculated crystallite size is comparable with the corresponding size from TEM analysis shown in Fig. 1a–c.

General procedure for synthesis of 2,3-diaryl-4-thiazolidinones (4a-q)

A mixture of aromatic aldehydes (1a–h; 0.002 mol), aromatic amines (2a–c; 0.002 mol) and mercaptoacetic acid (3; 0.004 mol) with a catalytic amount of Pd NPs (10 mol%) were mixed followed by stirring at 100 °C. The reaction progress was monitored by thin-layer chromatography (TLC) using ethyl acetate: *n*-hexane (3:7) composition. After completion of the reaction, the reaction mass was poured on cold water and washed with NaHCO₃, and the obtained crude products were filtered and recrystallised from ethanol.

Spectral data for the representative compounds

2-(4-Chlorophenyl)-3-phenylthiazolidin-4-one (4c): Proton nuclear magnetic resonance (1H NMR; 300 MHz, acetone-d6) δ ppm: 7.49 (d, 2H, ArH), 7.35 (d, 2H, ArH), 7.30 (d, 2H, ArH), 7.26 (d, 2H, ArH), 7.15 (m, 1H, ArH), 6.47 (s, 1H, methine), 4.00 (d, J = 15.6 Hz, CH₂), 3.87 (d, J = 15.6 Hz, CH₂); Carbon-13 NMR (13C NMR; 75 MHz, acetone-d6): δ 171.22, 140.34, 139.04, 134.66, 130.53, 129.94, 129.67, 129.64, 129.31, 127.36, 126.54, 126.11, 64.51, 33.57; MS (ESI) *m/z* 290.1 [M + H]⁺; Anal. calcd. for C₁₅H₁₂ClNOS: C 62.17, H 4.17, N 4.83, S 11.07 %; found C 61.96, H 4.24, N 4.75, S 11.11 %.

Results and discussion

In the search for better catalytic systems for this 4-thiazolidinone derivative, optimization of the reaction conditions was carried out by taking benzaldehyde 1a (0.002 mol), aniline 2a (0.002 mol) and mercaptoacetic acid 3 (0.004 mol) as model substrates (Scheme 1).

To initiate our study, the model reaction was carried out at 100 °C by constant stirring in the absence of catalyst for 60 min under solvent-free conditions, but the desired product was not formed (Table 1, entry 1) Moreover, we studied the same reaction with different catalyst amounts having 5 and 10 mol% loading of Pd NPs



Scheme 1 Standard model reaction for the synthesis of 4-thiazolidinones

Table 1 Screening of the catalyst with concentration	Entry	Catalyst	Pd-based catalysts (mol%)	Yield ^a (%)
	1	No catalyst	_	No condensation
	2	Pd NPs	5	80
			10	89
			15	88
	3	Pd bulk	5	62
			10	70
			15	70
Reaction conditions: 1a (0.002 mol), 2a (0.002 mol), 3	4	Pd (OAC) ₂	5	45
			10	56
(0.004), stirred at 100 °C	5	Pd Cl ₂	5	42
^a Isolated yield			10	45

under the same reaction conditions and we observed 80 and 89 % of the product, respectively (Table 1, entry 2).

We also carried out the same reaction using higher catalyst loading (15 mol%) to generalize our findings (Table 1, entry 2). In conclusion, the best result was obtained with 10 mol% of Pd NPs while stirring at 100 °C under solvent-free conditions. A higher Pd NP loading did not have much effect on conversion efficiency (decreasing the reaction time and increasing product formation). Furthermore, to evaluate the uniqueness of Pd NPs, we also screened the activities of other Pd-based catalysts such as $Pd(OAc)_2$ and $PdCl_2$ with 5 and 10 mol% loading for the above-said reaction, respectively; the screenings, however, resulted in moderate yields summarised in Table 1, entries 3–4.

We screened various solvents including tetrahydrofuran (THF), 1,4-dioxane, acetonitrile, dimethylformamide (DMF), water and ethanol, and the results are shown in Table 2, entries 1–6. Interestingly, the results shows that there was no condensation under the same reaction conditions, possibly be due to thermodynamical control.

One of the advantages of using a heterogenous catalyst is the possibility to recycle the catalyst, thus reducing the cost and environmental impact of the process.

Moreover, the reusability of the Pd NP catalyst was examined. It was found that the catalyst can be reused for another four consecutive runs under similar reaction

Table 2Screening of solventsReaction conditions: 1a(0.002 mol), 2a (0.002 mol), 3(0.004) Pd NPs catalyst (10 mol	Entry	Solvent	Temp.	Time (min)	Yield ^a (%)
	1	THF	Reflux	60	No condensation
	2	1,4-Dioxane	Reflux	60	No condensation
	3	Acetonitrile	Reflux	60	No condensation
	4	DMF	Reflux	60	No condensation
	5	Water	Reflux	60	No condensation
	6	Ethanol	Reflux	60	No condensation
^a Isolated yield	7	Solvent-free	100 °C	60	89
Table 3 Recovery and recycling of Pd NPs	Entry		Run		Yield ^a (%)
	1		Ι		89
Reaction conditions: 1a	2		II		87
(0.002 mor), 2a (0.002 mor), 3 (0.004), Pd NP catalyst	3		III		85
(10 mol%), stirred at 100 °C (solvent-free) for 60 min	4		IV		80

conditions. After each run, the reaction mixture was centrifuged at 4000 rpm at RT for 5–7 min and filtered. Then, the residue was washed with water and reused.

To investigate this key feature, four successive condensations of 1a were performed with Pd NPs which were recovered by centrifugation after each cycle and reused in the next reaction. It was observed that the recovered Pd NPs worked with good efficiency up to 2nd run (Table 3, entries 1–2), while in the 3rd and 4th runs (Table 3, entries 3 and 4), the yield of the product was decreased slightly.

Catalyst behavior

We report one-pot, three-component synthesis of 4-thiazolidinone derivatives catalyzed by Pd NPs as the heterogenous catalyst under solvent-free conditions. While performing the whole experiment, it was observed that the catalyst was recovered and reused four times for the model reaction with no significant loss of activity and mass loss (Table 3). Moreover, Pd NPs were free from leaching and nanosalts with a –SH substrate group. It is clear from TEM analysis that the Pd NP catalyst recovered after four cycles showed no major changes in its morphology (Fig. 1c).

Having been inspired by these observations and to generalize the synthetic procedure, a variety of electronically divergent aromatic aldehydes and aromatic amines were treated with mercaptoacetic acid at 100 °C in the presence of Pd NPs. Aromatic aldehydes with several functionalities such as -Cl, -OH, $-CH_3$, $-OCH_3$ and $-NO_2$ were found to be compatible under the optimized reaction conditions. Our conclusive findings say that aldehydes having no substituent on the phenyl ring reacted smoothly and products were obtained in excellent yields, ranging from 89 to 90 % (Table 4, entries 1–2). Electron-donating groups such as $-OCH_3$, $-CH_3$ and -

Table 4 Synthesis of 4-thiazolidinone derivatives	H + +	NH ₂ + HS	о	Pd N 100° Solveni	$\frac{P_S}{C}$	\mathbf{x}_{1}
	R (1 a-h)	R ₁ (2 a-c)	3	Solven	ince	(4 a-q)
	Entries	Compounds	R	R_1	Yield ^a (%)	M.P. ^b (°C)
	1	4a	Н	Н	89	105–107
	2	4b	Н	Cl	90	111-113
	3	4c	Cl	Н	84	130-132
	4	4d	Cl	Cl	75	124-126
	5	4e	OH	Cl	81	158-160
	6	4f	CH_3	Н	73	115-117
	7	4g	CH_3	Cl	65	155-157
	8	4h	OH	Н	88	182–184
	9	4i	OCH ₃	Н	71	110-111
	10	4j	OCH ₃	Cl	83	158-160
Reaction conditions: aldehydes (0.002 mol), 2a (0.002 mol), 3 (0.004 mol), Pd NP catalyst (10 mol%), stirred at 100 °C for	11	4k	OCH ₃	CH_3	85	148-150
	12	41	Н	CH_3	78	112-114
	13	4m	OH	CH_3	75	210-211
	14	4n	NO_2	Н	73	105-107
60 min	15	40	NO_2	Cl	80	139–141
^a Isolated yields	16	4p	F	Cl	86	132–134
^b Melting points were in good agreement with literature values	17	4q	Br	Cl	82	118-120

OH present in the parent aldehydes afforded moderate yields in the products (Table 4, entries 6–11). The presence of the $-NO_2$ group in the aldehydes (Table 4, entries 14–15) showed enhancement in the product yield. Furthermore, the 4-thiazolidinone products were isolated and characterized, and their melting points were found to be in good agreement with those reported in the literature [27, 28]. To show the merits of this work over the methods reported in the literature, comparison of results obtain by use of Pd NPs with different catalysts like, [bmim][PF6], PEG-400, Bi(SCH₂COOH)₃, HClO₄–SiO₂, Silica gel, *Saccharomyces cerevisiae* shown in Table 5.

In a plausible mechanism, the electrophilic characteristics of the carbonyl carbon of aldehydes and mercaptoacetic acid have been enhanced due to non-covalent interaction with Pd NPs [23]. The nucleophilic addition of a mercapto group of mercapto acetic acid on the imino intermediate (generated in situ) resulted in intermediate (A). The intermediate (B) plays an important role in the rate of reaction, because the rate of the reaction depends upon the rate of dehydration from this intermediate. Especially (1) the non-covalent interaction of Pd NPs and (2) solvent-free stirring at 100 °C, these two conditions might be responsible for accelerating the rate of reaction by rapid removal of water molecules (dehydration step) (Scheme 2).

Entry	Catalyst/solvent	Temperature (°C)	Time (h)	Yield (%)
1	[bmim][PF6]	80	5–9	47–92
2	PEG-400	50	2	58-92
3	Bi(SCH ₂ COOH) ₃ , solvent-free	70	2	75–90
4	$HClO_4$ –SiO ₂ , toluene	100	3–6	70-87
5	Silica gel, DCM	RT	3–7	77–96
6	Saccharomyces cerevisiae, THF	RT	40	71–72
7	Pd NPs, solvent-free	100	1	65–90

 Table 5
 Comparative study of Pd NPs (our studies) and other catalysts reported for synthesis of 4-thiazolidinone derivatives



Scheme 2 Plausible mechanism for 4-thiazolidinones

Conclusion

In conclusion, a novel and efficient synthetic method has been developed for the preparation of 2,3-disubstituted-4-thiazolidinone derivatives by using as-synthesised Pd NPs as a recyclable catalyst. The key features of this protocol are its simple reaction conditions, excellent product yields, applicability to a wide range of substrates and its benign nature by avoiding the use of volatile and poisonous conventional organic solvents; these features make this present protocol more innovative than existing ones.

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