

Nickel nanoparticles: A highly efficient catalyst for one pot synthesis of tetraketones and biscoumarins

JITENDER M KHURANA* and KANIKA VIJ

Department of Chemistry, University of Delhi, Delhi 110 007, India

e-mail: jmkhurana1@yahoo.co.in

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Abstract. A novel and practically useful protocol has been designed wherein, polyvinyl pyrrolidone (PVP) stabilized nickel nanoparticles have been used as a catalyst for promoting the synthesis of 2,2'-aryl-methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one), 2,2'-aryl-methylene bis(3-hydroxy-2-cyclohexene-1-one), also known as tetraketones, and biscoumarins *via* Knoevenagel condensation followed by rapid Michael addition.

Keywords. PVP-stabilized Ni nanoparticles; ethylene glycol; tetraketones; biscoumarins; cyclo-condensation.

1. Introduction

Tetraketones such as 2,2'-aryl-methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) or tetraketones (**3**), are important precursors extensively used in the synthesis of acridinediones, as laser dyes and for the synthesis of various heterocyclic compounds.¹ Tetraketones show significant lipoxxygenase inhibitor activity and strong anti-oxidant potential.² They exhibit broad spectrum of therapeutic and biological properties.^{3–5} 3,3'-(4-aryl methylene) bis-(4-hydroxycoumarin), commonly known as biscoumarins (**4**), are of considerable interest due to their biological activities, e.g., anticoagulant activity,⁶ prevention and treatment of thrombosis,⁷ urease inhibitors.⁸ Various methods have been reported for the synthesis of compounds belonging to these classes: (**3** and **4**).^{9–18} Each of these methods have their own advantages but also suffer from certain disadvantages such as prolonged reaction time, tedious work-up processes, low yield, high temperature and hazardous reaction conditions.

Transition metal nanoparticles have gained tremendous importance due to their interesting electrical, optical, magnetic, chemical properties, and especially catalytic properties, which cannot be achieved by their bulk counterparts.^{19–21} Recently, there has been growing interest in using nickel nanoparticles in organic synthesis owing to their easy preparation, potent catalytic activity, possible processability, high stability and ease of recyclability compared to traditional

Raney Ni catalyst. Ni nanoparticles have been used as catalyst for functional group transformations like transfer hydrogenation of carbonyl compounds,^{22–24} reductive amination of aldehydes,²⁵ alkylation of ketones and indirect *aza*-Wittig reaction with alcohols,²⁶ oxidative coupling of thiols²⁷ and Hantzsch condensation for polyhydroquinoline derivatives.²⁸ Recently, we have reported the Knoevenagel condensation of aldehydes with barbituric acids²⁹ and with *o*-phenylene diamine and 2-aminothiophenol³⁰ catalyzed efficiently by PVP-stabilized Ni(0) nanoparticles in ethylene glycol prepared by the polyol method.³¹ We have also reported nickel nanoparticles catalyzed chemoselective Knoevenagel condensation of Meldrum's acid and tandem enol lactonizations *via* cascade cyclization sequence.³² One of the prime steps in the synthesis of tetraketones and biscoumarins is the Knoevenagel condensation of aldehydes with dimedone. Therefore, we envisaged the possibility of applying nickel nanoparticles for the synthesis of **3** and **4**.

2. Experimental

2.1 General

All the chemicals used were of research grade and were used without further purification. The size and morphology of nickel nanoparticles were characterized with the help of TEM (JEOL 2100-F operating at 200 kV) and QELS analysis (PHOTOCOR-FC-1135P). ¹HNMR spectra were recorded on Bruker Spectrospin AVANCE (300 MHz). IR spectra were recorded on

*For correspondence

Perkin-Elmer FT-IR SPECTRUM-2000. X-ray diffraction pattern was obtained on BRUKER D8.

2.2 Preparation of Ni nanoparticles

Nickel nanoparticles were prepared by the modified polyol process.³¹ 2×10^{-4} molL⁻¹ solution of NiCl₂·6H₂O in ethylene glycol was reduced with NaBH₄ in the presence of PVP (Ni²⁺: PVP:: 1: 5 wt%) at 140°C. The sample for TEM was prepared by addition of acetone to the nickel nanoparticles dispersion in ethylene glycol, followed by centrifugation (6000 rpm). The particles, so obtained, were washed free of any residual components using ethanol. Methanol dispersion of the nickel nanoparticles was placed on carbon coated Cu grid (mesh size 300). The ethylene glycol dispersion was used as such for QELS analysis. Sample for the X-ray diffraction was obtained by depositing a thin-coating of the isolated nickel nanoparticles (dispersed in absolute ethanol) onto a glass plate followed by vacuum drying.

2.3 General procedure for the synthesis of 2,2'-aryl-methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 2,2'-aryl-methylene bis(3-hydroxy-2-cyclohexene-1-one) (3a-z)

In a typical experiment, 4-bromobenzaldehyde (2 mmol) was added to a well stirred dispersion of nickel nanoparticles in ethylene glycol (2 mL/0.1 g of **1**) in a 25 mL reaction flask. Dimedone (**2**, 4 mmol) was added to the mixture and the stirring was continued. The progress of the reaction was monitored by TLC using petroleum ether: ethyl acetate (70:30, v/v) as eluent. After completion of the reaction, the solid

product was filtered using a pump, washed with water, dried and recrystallised from hot ethanol. 2, 2'-(4-bromophenyl)-methylene bis(3-hydroxy-5, 5-dimethyl-2-cyclohexene-1-one) (**3a**, 93%) was obtained as identified by m.p. 155°C (lit 158–159°C) and spectral data.

3a: M.P. = 155°C (lit.⁹ 158–159°C); IR (KBr, cm⁻¹) ν_{\max} = 3053, 2959, 2873, 1723, 1594. ¹H NMR (300 MHz, CDCl₃) δ : 1.13 (s, 6H, 2Me), 1.23 (s, 6H, 2Me), 2.20–2.53 (m, 8H, 4CH₂), 5.47 (s, 1H, CH), 6.96 (d, 2H, J = 6.6 Hz, H-Ar), 7.38 (d, 2H, J = 6.6 Hz), 11.93 (brs, 1H, OH).

2.4 General procedure for the synthesis of 3,3'-(4-aryl methylene) bis-(4-hydroxycoumarins) (4a-f)

In a typical experiment, 4-chlorobenzaldehyde (2 mmol) was added to a well-stirred dispersion of nickel nanoparticles in ethylene glycol (2 mL/0.1 g of **1**) in a 25 mL reaction flask. 4-Hydroxycoumarin (4 mmol) was added to the mixture and the stirring was continued. The progress of the reaction was monitored by TLC using petroleum ether: ethyl acetate (60:40, v/v) as eluent. After completion of the reaction, the solid product was filtered using a pump, washed with water, dried and recrystallized from hot ethanol. 3, 3'-(4-chlorophenylmethylene)-bis-(4-hydroxycoumarin) (**4a**, 92%) was obtained as identified by m.p. 250°C (lit. 252–254°C) and spectral data.

4a: M.P. = 250°C (lit.¹⁷ 252–254°C); IR (KBr cm⁻¹): ν_{\max} = 3075, 2919, 2733, 1663, 1612, 1567. ¹H NMR (300 MHz, CDCl₃) δ : 6.03 (s, 1H, CH), 7.13–7.29 (m, 4H, H-Ar), 7.35–7.42 (m, 4H, H-Ar), 7.60–7.66 (m, 2H, H-Ar), 7.97–8.07 (m, 2H, H-Ar), 11.31 (s, 1H, OH), 11.53 (s, 1H, OH).

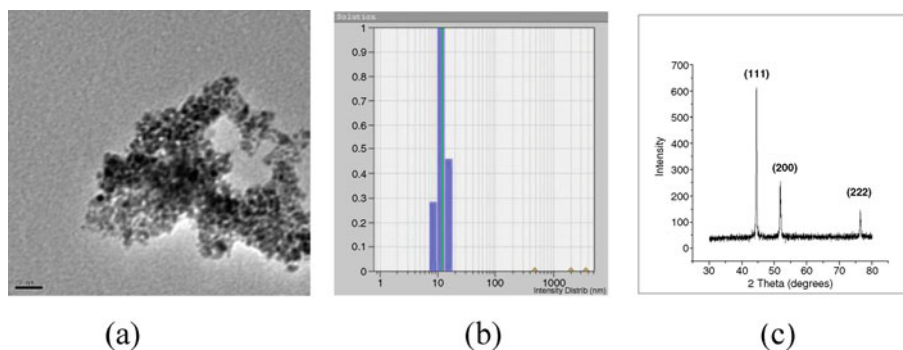
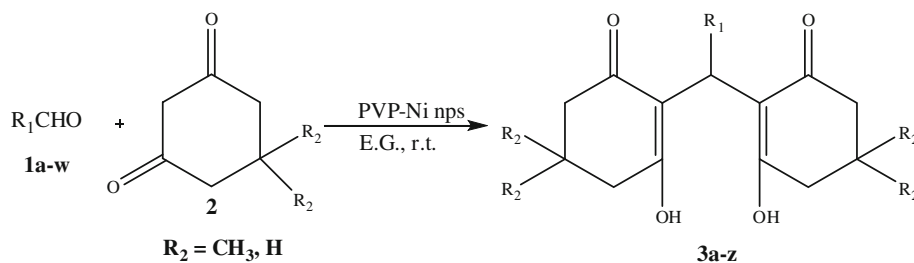


Figure 1. (a) HRTEM image of Ni nanoparticles. The scale bar corresponds to 20 nm in the images; (b) QELS data of Ni nanoparticles: plot of population distribution in percentile versus size distribution in nanometers (nm); (c) X-ray diffraction pattern of PVP-Ni nanoparticles.



Scheme 1. PVP-Ni nanoparticles catalyzed synthesis of tetraketones (**3a-z**).

2.5 General procedure for the recyclability of the catalyst

Aldehyde (**1a**, 2 mmol) was added to nickel nanoparticle dispersion in ethylene glycol (2 mL/0.1 g **1**) in 25 mL reaction flask. Dimedone (**2**, 4 mmol) was added to the reaction mixture and it was stirred. Upon complete formation of **3a** as monitored by TLC, 10.0 mL of ethyl acetate was added to the reaction mixture. The reaction mixture was stirred until complete dissolution

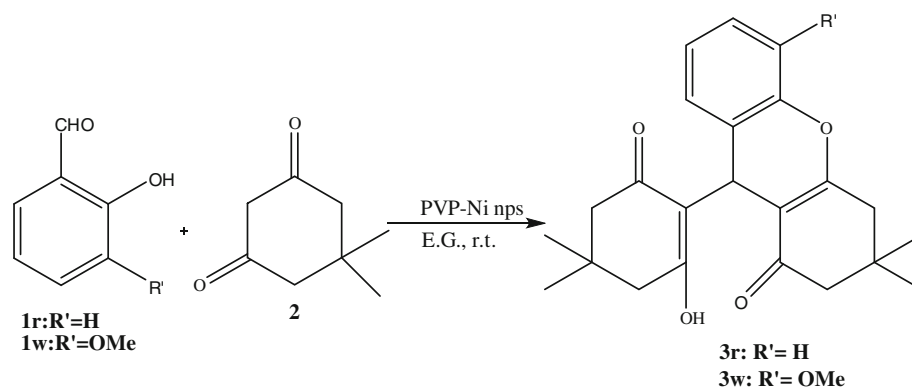
of **3a** in ethyl acetate was observed. The two layers were then separated. The ethylene glycol layer was sonicated for 5–10 min and reused for the same experiment for over five cycles.

3. Results and discussion

We report here a simple and highly efficient route for the synthesis of 2,2'-aryl-methylene bis(3-hydroxy-5,5-

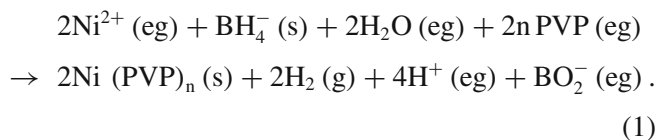
Table 1. PVP stabilized Ni nanoparticles catalysed synthesis of 2,2'-aryl-methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) and 2,2'-aryl-methylene bis(3-hydroxy-2-cyclohexene-1-one) (**3a-z**).

Entry	R ₁	R ₂	Product	Time (min.)	Yield (%)	M.P. (°C)	
						Obs.	Lit.
1.	4-BrC ₆ H ₄ (1a)	CH ₃	3a	10	93	155	158–159 ¹¹
2.	4-MeOC ₆ H ₄ (1b)	CH ₃	3b	10	90	138	142–143 ⁹
3.	3,4,5-(MeO) ₃ C ₆ H ₂ (1c)	CH ₃	3c	10	96	186	189–191 ¹⁵
4.	C ₆ H ₅ (1d)	CH ₃	3d	10	88	204	194–195 ⁹
5.	4-O ₂ NC ₆ H ₄ (1e)	CH ₃	3e	10	91	190	188–190 ⁹
6.	4-MeC ₆ H ₄ (1f)	CH ₃	3f	15	86	132	126–128 ²
7.	4-ClC ₆ H ₄ (1g)	CH ₃	3g	10	92	144	141–143 ¹¹
8.	2-BrC ₆ H ₄ (1h)	CH ₃	3h	10	92	187	194–195 ¹⁰
9.	3-O ₂ NC ₆ H ₄ (1i)	CH ₃	3i	10	90	190	197–198 ⁹
10.	2,4-Cl ₂ C ₆ H ₃ (1j)	CH ₃	3j	10	89	200	203–204 ¹¹
11.	4-Me ₂ NC ₆ H ₄ (1k)	CH ₃	3k	10	90	193	195–196 ⁹
12.	4-HOC ₆ H ₄ (1l)	CH ₃	3l	10	87	180	187–189 ⁹
13.	4-FC ₆ H ₄ (1m)	CH ₃	3m	10	93	165	167–168 ¹⁴
14.	CH ₃ CH ₂ CH ₂ (1n)	CH ₃	3n	10	88	130	134–135 ⁹
15.	C ₆ H ₅ CH=CH (1o)	CH ₃	3o	15	89	204	215–217 ⁹
16.	1-Naphthyl (1p)	CH ₃	3p	10	91	190	195 ¹²
17.	2-Pyridinyl (1q)	CH ₃	3q	15	89	172	175–177 ¹⁰
18.	2-HOC ₆ H ₄ (1r)	CH ₃	3r	10	94	202	205–206 ⁹
19.	2-Furanyl (1s)	CH ₃	3s	8	89	146	152–153 ²
20.	CH ₃ CH=CH (1t)	CH ₃	3t	10	88	186	193–194 ⁹
21.	(CH ₃) ₂ CH (1u)	CH ₃	3u	10	88	152	153–154 ⁹
22.	n-C ₆ H ₁₃ (1v)	CH ₃	3v	12	86	100	101–103 ⁹
23.	2-HO-3-MeO-C ₆ H ₃ (1w)	CH ₃	3w	10	87	225	229–231 ¹⁶
24.	4-ClC ₆ H ₄ (1g)	H	3x	8	90	200	202–203 ¹³
25.	4-BrC ₆ H ₄ (1a)	H	3y	10	92	236	240–241 ¹³
26.	4-O ₂ NC ₆ H ₄ (1e)	H	3z	7	89	190	194–196 ¹³



Scheme 2. PVP-Ni nanoparticles catalyzed reaction of ortho-hydroxy benzaldehydes and dimedone.

dimethyl-2-cyclohexene-1-one) and 2,2'-aryl-methylene bis(3-hydroxy-2-cyclohexene-1-one) (**3**) starting from aldehydes and dimedone, and also the synthesis of biscoumarins (**4**) from aldehydes and 4-hydroxycoumarin, using highly monodispersed nickel nanoparticles as catalyst in ethylene glycol. The nickel nanoparticles were obtained as air-stable nanoparticulate monodispersion by modified polyol method³¹ in ethylene glycol from nickel chloride hexahydrate and sodium borohydride using polyvinylpyrrolidone (PVP) as the stabilizing agent (equation 1).



The metal dispersion so obtained was characterized by TEM analysis which revealed the formation of coated Ni nanoparticles with average diameter 11 nm (figure 1a) which was further supported by QELS analysis that showed a maximum population distribution centred around 11 nm (figure 1b). XRD analysis further supported the results (figure 1c).

The versatility of the catalyst was investigated for the condensation of dimedone with aldehydes. The

reactions of 4-bromobenzaldehyde (**1a**) and dimedone with varying amounts of nickel nanoparticulate dispersion in ethylene glycol were monitored by TLC. The reaction was complete using 1:2 molar ratio of aldehyde to dimedone in 10 min and 93% of 2,2'-(4-bromophenyl)-methylene bis(3-hydroxy-5,5-dimethyl-2-cyclohexene-1-one) (**3a**) was obtained as identified by mp and spectral data. The reaction of **1a** and dimedone in equimolar ratio gave a mixture of **3a** and unreacted aldehyde. Subsequent reactions of dimedone with several aldehydes containing electron-donating as well as electron-withdrawing groups underwent smooth and effective one-pot Knoevenagel condensation followed by Michael addition in the presence of PVP-coated Ni nanoparticles to give tetraketones (**3b-w**). The aldehydes also underwent efficient Knoevenagel condensation and Michael addition with cyclohexane-1,3-dione to give the corresponding 2,2'-aryl-methylene bis(3-hydroxy-2-cyclohexene-1-one) (**3x-z**) (scheme 1, table 1). The condensation could be achieved with aryl, alkyl, α , β -unsaturated (**1o** and **1t**) as well as heteroaryl aldehydes (**1q** and **1s**). The products (**3r** and **3w**)

Table 2. Reactions to confirm involvement of Ni nanoparticles during synthesis of **3**.

S. No.	Reaction condition	Time	Yield (3a , %)
1.	Ethylene glycol alone	6 h ^a	40
2.	Ni powder (size < 150 micron)	— ^a	45
3.	NiCl ₂ .6H ₂ O alone in EG	8 h ^a	42
4.	NaBH ₄ alone in EG	5 h ^b	—
5.	Isolated Ni nanoparticles redispersed in EG	15 min	90

^aincomplete reaction; ^bmixture of products

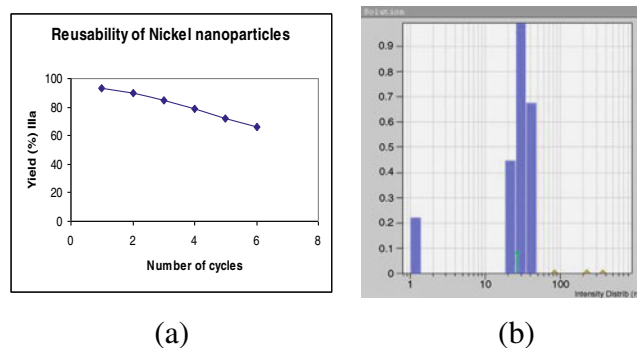
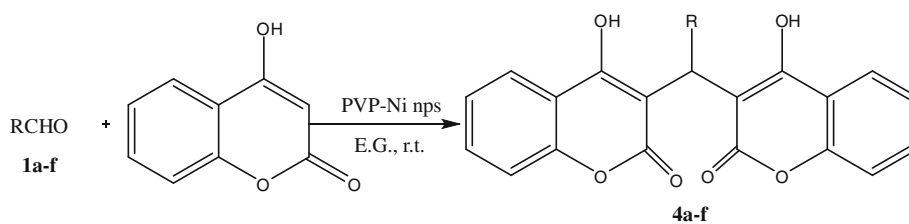


Figure 2. (a) Recyclability data of PVP-Ni nanoparticles; (b) QELS data of recycled Ni nanoparticles after 4th cycle: Plot of population distribution in percentile versus size distribution in nanometers (nm).



Scheme 3. PVP-Ni nanoparticles catalyzed synthesis of biscoumarins (**4a-f**).

obtained from the reaction of salicylaldehyde (**1r**) and 2-hydroxy-3-methoxy benzaldehyde (**1w**) with dimedone has been assigned a pyran structure (scheme 2).

The role of nickel nanoparticles in catalyzing the formation of tetraketones (**3a-z**) was confirmed by a blank reaction of **1a** with dimedone in ethylene glycol in the absence of catalyst. The reaction was incomplete even after 6 h of stirring though formation of a small amount of **3a** was observed. The reaction of **1a** with dimedone was also attempted with Ni powder (size < 150 micron). The reaction was only 45% complete even after stirring for 24 h. One of the most crucial result came from the reaction of **1a** with dimedone in the presence of isolated Ni nanoparticles (obtained from the dispersion by the polyol method) which were washed repeatedly with absolute ethanol followed by dispersal in ethylene glycol. The reaction was found to be complete in 15 min and 90% of **3a** was isolated. All these results have been summarized in table 2.

Reusability of nickel nanoparticles was examined by the reaction of *p*-bromobenzaldehyde (**1a**) with dimedone in the presence of PVP-Ni nanoparticles. Upon completion, the product (**3a**, 93%) was extracted in ethyl acetate followed by isolation of ethylene glycol layer which was then used for subsequent cycles. The catalyst retained optimum activity up to four cycles after which a drop in yield (74%) of the product (**3a**)

was observed along with a increase in the particle size as is evident from the QELS data (figure 2).

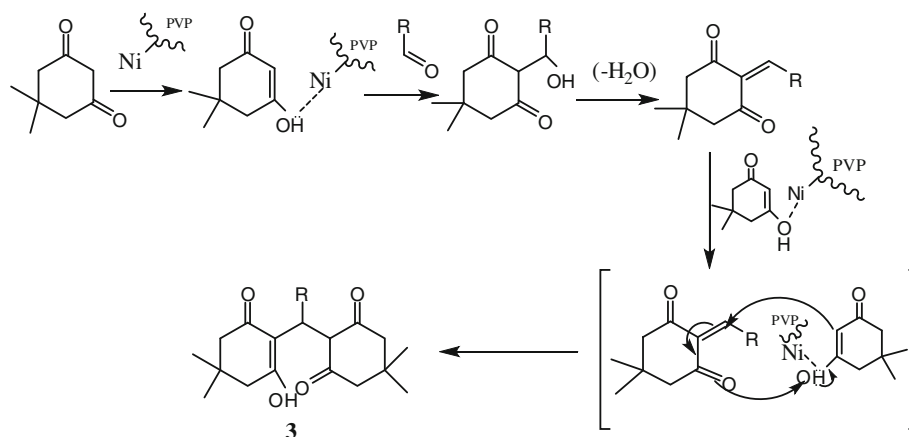
The applicability of the catalyst was further extended to the reaction of 4-chlorobenzaldehyde with 4-hydroxycoumarin under otherwise identical conditions. The reaction was complete in 15 min and 92% of 3,3'-(4-chlorophenyl methylene)-bis (4-hydroxycoumarin) (**4a**) was obtained after work up. Subsequently, reactions of other aldehydes with 4-hydroxycoumarin also gave the corresponding biscoumarins in high yields (scheme 3, table 3).

Scheme 4 represents a plausible mechanism for the formation of tetraketones in the presence of PVP-stabilized Ni nanoparticles. It is believed that Ni nanoparticles promote enolization in dimedone and facilitate domino Knoevenagel condensation Michael addition reaction leading to tetraketones. Also, it is a well known fact that polymer capped nanoparticles represent semi-heterogeneous catalytic system, as presence of polymer increases the interaction in the organic phase. So, in addition to promoting enolization, PVP-stabilized Ni nanoparticles act as semi-heterogeneous high surface area catalyst and promote rapid tetraketone or biscoumarin formation.

Ethylene glycol, besides being a green solvent, proved advantageous for this transformation based on the solubility difference of the starting materials and the

Table 3. PVP stabilized Ni nanoparticles catalyzed synthesis of biscoumarins (**4a-f**) in ethylene glycol from aldehyde and 4-hydroxycoumarin.

Entry	R	Product	Time (min)	Yield (%)	M.P. (°C)	
					Obs.	Lit.
1.	4-ClC ₆ H ₄ (1a)	4a	15	92	250	252–254 ¹⁷
2.	4-O ₂ NC ₆ H ₄ (1b)	4b	15	93	230	232–234 ¹⁸
3.	4-HOC ₆ H ₄ (1c)	4c	20	87	198	222–224 ¹⁸
4.	2-HOC ₆ H ₄ (1d)	4d	15	94	244	247–248 ¹⁸
5.	3,4-(CH ₃ O) ₂ C ₆ H ₃ (1e)	4e	20	90	270–272	273–275 ¹⁷
6.	Piperonyl (1f)	4f	15	89	244–246	247–248 ¹⁸



Scheme 4. Plausible mechanism for the formation of tetraketones in the presence of Ni nanoparticles.

final product. Hence, during the course of the reaction, the product precipitated out and was isolated simply by filtration and washing.

4. Conclusion

We have developed a practically efficient and novel protocol for the synthesis of tetraketones (**3**) and bis-coumarins (**4**) using air stable PVP coated nickel nanoparticles as the catalyst in ethylene glycol at room temperature. The yields and the reaction time completely highlight the practical synthetic efficiency of this novel protocol.

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