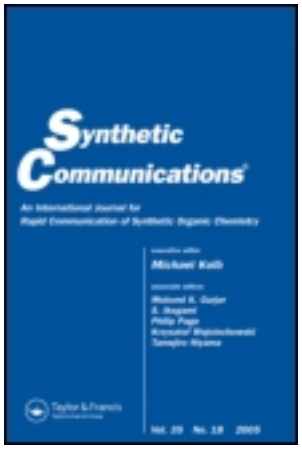

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Nickel Nanoparticles as Semiheterogeneous Catalyst for One-Pot, Three-Component Synthesis of 2-Amino-4H-pyrans and Pyran Annulated Heterocyclic Moieties

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NICKEL NANOPARTICLES AS SEMIHETEROGENEOUS CATALYST FOR ONE-POT, THREE-COMPONENT SYNTHESIS OF 2-AMINO-4*H*-PYRANS AND PYRAN ANNULATED HETEROCYCLIC MOIETIES

Jitender M. Khurana and Kanika Vij
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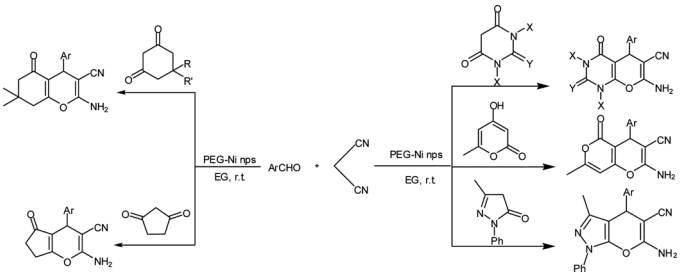
GRAPHICAL ABSTRACT



Abstract *An efficient route for the synthesis of 2-amino-4*H*-pyrans and pyran annulated heterocyclic moieties has been reported via one-pot tandem Knoevenagel–cyclocondensation of aldehydes, malononitrile, and carbocyclic/heterocyclic 1,3-diones in the presence of stabilized nickel nanoparticles in ethylene glycol at room temperature. A wide range of aromatic aldehydes undergo the condensation readily to afford the pharmacologically important compounds in excellent yields. Bis-pyranization has been observed in the reactions of terephthaldehyde.*

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Keywords Aromatic aldehydes; 1,3-dicarbonyls; 4*H*-pyrans; malononitrile; nickel nanoparticles

INTRODUCTION

In recent years, 4*H*-pyrans and its derivatives have attracted strong interest because of their useful biological and pharmacological properties, such as anticoagulant, spasmolytic, anticancer, and antianaphylactin activities.[1] 2-Amino-4*H*-pyrans have been employed as photoactive materials[2] and biodegradable agrochemicals.[3] Substituted 4*H*-pyrans also constitute structural units of a series of natural

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products.[4] Also, dihydropyrano[2,3-*c*]pyrazoles represent an interesting template for medicinal chemistry as many of these compounds are known as antimicrobial,[5] insecticidal[6] and anti-inflammatory[7]agents.

In view of their importance, different methods for the synthesis of 2-amino-4*H*-pyran derivatives have been reported.[8–15] Conventional syntheses of 2-amino-3-cyano-4*H*-pyrans use complicated workup procedures and lead to poor yields of products.[16] Recently, 2-amino-3-cyano-4*H*-pyrans have been synthesized under exposure to microwave[17] and also in aqueous media.[18] Two-component[19] and three-component[18,20] condensations have been introduced for the synthesis of 2-amino-3-cyano-4*H*-pyrans. Each of these methods have their own merits and demerits.

Transition-metal nanoparticles are attractive alternatives to conventional catalysts.[21] Besides their special characteristics such as high stability, easy preparation, possible processability, and ease of recyclability, they are reported to catalyze organic reactions.[22–24] Nanoparticles are reported to promote chemoselectivity in some reactions[25,26] and also assist in convenient isolation of products in catalytic reactions.[27] Recently, we have reported the Knoevenagel condensation of aldehydes with barbituric acids,[28] *o*-phenylene diamine, and 2-aminobenzothiazole[29] catalyzed by PVP-stabilized Ni(0) nanoparticles [Ni(0) NP] in ethylene glycol; Knoevenagel condensation of aldehydes and Meldrum's acid, followed by cascade enol lactonization of arylidene Meldrum's acids with active methylenes catalyzed by PEG-stabilized Ni(0) NP in ethylene glycol;[30] and synthesis of tetraketones and biscoumarins using PVP-stabilized Ni(0) NP as the catalyst.[31] Our investigations using Ni(0) NP as the active catalyst have led us to believe that this promotes Knoevenagel as well as Michael addition reactions. In continuation of our ongoing interest in newer applications of Ni(0) NP, we have investigated a new methodology for the synthesis of highly functionalized pyran derivatives, using Ni(0) NP stabilized by polyethylene glycol (PEG) (av. molar mass 4000) instead of conventional polyvinyl pyrrolidone (PVP).[32]

RESULTS AND DISCUSSION

We report in this article a three-component, one-pot synthesis of highly functionalized annulated pyran libraries, namely, 4*H*-benzo[*b*]pyrans and cyclopenta[*b*]pyrans, pyrano[2,3-*d*]pyrimidines, pyrano[3,2-*c*]pyran-5(4*H*)-ones, and pyrano[2,3-*c*]pyrazoles. The synthesis has been achieved by one-pot, three-component tandem Knoevenagel–cyclocondensation reaction of aromatic aldehydes, malononitrile, and carbocyclic/heterocyclic 1,3-diones using PEG-stabilized Ni(0) NP as semiheterogeneous catalysts with high catalytic activity and reusability in ethylene glycol at room temperature.

Highly monodispersed Ni(0) NP were prepared in ethylene glycol by the reduction of Ni^{2+} ($NiCl_2 \cdot 6H_2O$) with $NaBH_4$ in the presence of PEG-4000 in ethylene glycol as reported earlier.[30] The metal dispersion so obtained was characterized by transition electron microscopy (TEM) analysis, which revealed the formation of coated Ni(0) NP with diameter in the range 6–8 nm (Fig. 1a, and b). The metallic nature of nanoparticles was confirmed by X-ray diffraction (XRD) analysis (Fig. 1c) and energy-dispersive X-ray analysis (EDAX) data of the sample

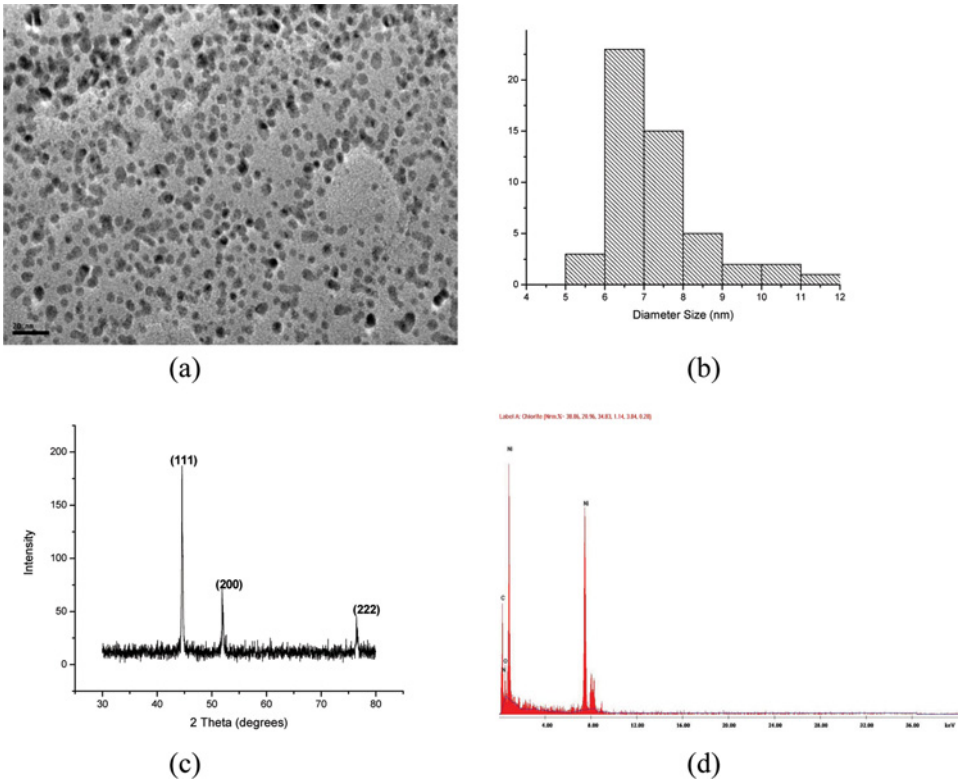
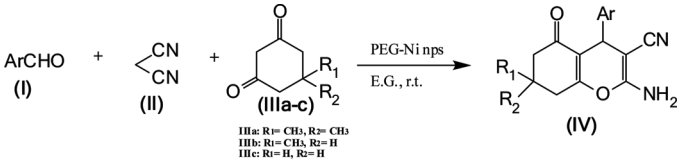


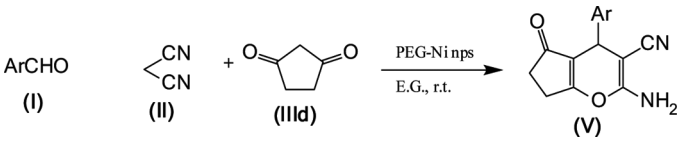
Figure 1. (a) TEM image of PEG-Ni nanoparticles; (b) size histogram of PEG-Ni nanoparticles; (c) x-ray diffraction pattern of PEG-Ni nanoparticles; and (d) EDAX data of PEG-Ni nanoparticles. (Figure is provided in color online.)

(Fig. 1d). The size from the XRD data was calculated to be 6.9 nm and is consistent with TEM results.

The PEG-coated Ni(0) NP were used as such for the reactions. A reaction of 4-chlorobenzaldehyde (**Ia**, 1.0 mmol), malononitrile (**II**, 1.1 mmol), and 5,5-dimethylcyclohexa-1,3-dione (**IIIa**, 1.0 mmol) was attempted in the presence of Ni(0) NP (used as a dispersion in ethylene glycol 2.0 mL/0.1 g of I, equivalent to 0.06 mol% of Ni) at room temperature. The reaction was complete in 5 min, and 95% of 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**IVa**) was obtained simply by filtration after dilution since ethylene glycol served as a suitable solvent because of the solubility difference of the product and the starting materials. Subsequently, reactions of other aldehydes, malononitrile and various cyclohexa-1,3-diones, namely, dimedone, cyclohexane-1,3-dione, and 5-methylcyclohexane-1,3-dione (**IIIa–c**) also gave the corresponding tetrahydrobenzo[*b*]pyran derivatives (**IVa–r**) (Scheme 1) in good yields. A new class of compounds, namely, tetrahydrocyclopenta[*b*]pyran derivatives (Va-h) were obtained in high yields when cyclopenta-1,3-dione (**IIId**) was used as the cyclic diketone (Scheme 2). It can be inferred that the reactions can tolerate a variety of substituents. All these results are summarized in Table 1.



Scheme 1. PEG-stabilized Ni nanoparticles catalyzed the synthesis of tetrahydro-4*H*-benzo[*b*]pyran derivatives.



Scheme 2. PEG-stabilized Ni nanoparticles catalyzed the synthesis of tetrahydro-cyclopenta[*b*]pyran derivatives.

The protocol was further extended to heterocycle-based 1,3-diketo compounds (α-C-H acids). Reaction of 4-chlorobenzaldehyde (**Ia**, 1.0 mmol), malononitrile (**II**, 1.1 mmol), and 1,3-dimethyl barbituric acid (**IIIe**, 1.0 mmol) was attempted

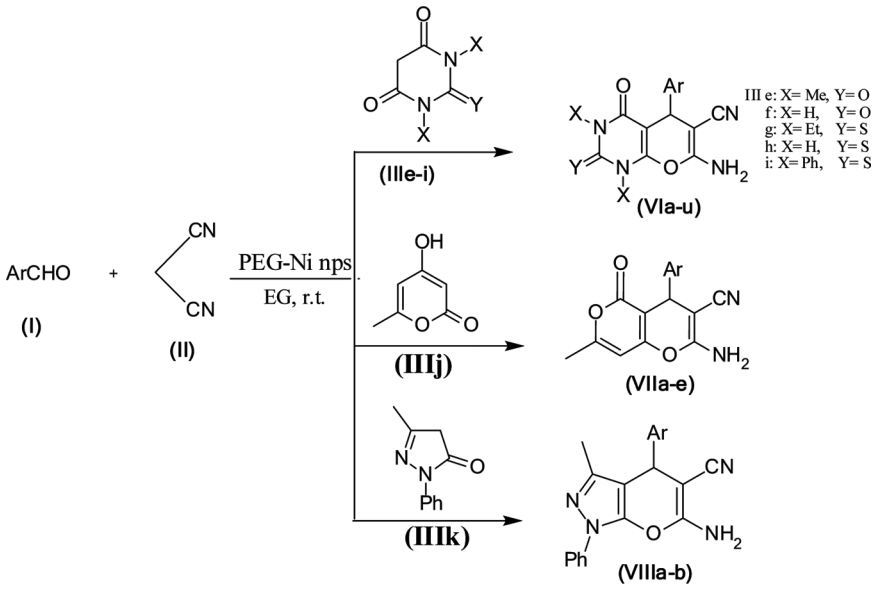
Table 1. PEG-Ni nanoparticle–catalyzed synthesis of 4*H*-pyran derivatives

No.	Ar	1,3-Dicarbonyl	Product	Time (min)	Yield (%)	Mp (°C) (obs.)[Ref.]
1	4-ClC_6H_4 (Ia)	IIIa	IVa	5	95	206[9a]
2	4-HOC_6H_4 (Ib)	IIIa	IVb	7	89	205[20d]
3	4-$O_2NC_6H_4$ (Ic)	IIIa	IVc	5	92	177[9a]
4	3,4-$(MeO)_2C_6H_3$ (Id)	IIIa	IVd	10	87	170–172[13]
5	3-BrC_6H_4 (Ie)	IIIa	IVe	5	92	285[9a]
6	2-Furanyl (If)	IIIa	IVf	5	95	214–216[13]
7	2-Naphthyl (Ig)	IIIa	IVg	7	88	248[14]
8	2,4-$Cl_2C_6H_3$ (Ih)	IIIb	IVh	7	93	116–118
9	4-FC_6H_4 (Ii)	IIIb	IVi	5	88	200
10	2,5-$(MeO)_2C_6H_3$ (Ij)	IIIb	IVj	10	87	202
11	4-$(CH_3)_2CHC_6H_4$ (Ik)	IIIb	IVk	10	90	196
12	4-$F_3CC_6H_4$ (Il)	IIIb	IVl	7	92	210
13	Terephthalyl (Im)	IIIb	IVm	5	94	270 (d)
14	2,4-$Cl_2C_6H_3$ (Ih)	IIIc	IVn	5	96	218[20c]
15	3-$O_2NC_6H_4$ (In)	IIIc	IVo	5	93	204–206[20c]
16	3,4,5-$(MeO)_3C_6H_2$ (Io)	IIIc	IVp	10	87	210–212
17	Piperonyl (Ip)	IIIc	IVq	10	89	206[15]
18	2-ClC_6H_4 (Iq)	IIIc	IVr	7	96	212[15]
19	4-ClC_6H_4 (Ia)	IIId	Va	7	86	182
20	3-$O_2NC_6H_4$ (In)	IIId	Vb	10	89	195
21	3,4-$(MeO)_2C_6H_3$ (Id)	IIId	Vc	12	87	190
22	2-Br-Piperonyl (Ir)	IIId	Vd	5	91	263 (d)
23	2,5-$(MeO)_2C_6H_3$ (Ij)	IIId	Ve	10	87	215
24	2-Thiophenyl (Is)	IIId	Vf	10	91	170
25	Terephthalyl (Im)	IIId	Vg	10	93	276 (d)
26	2-BrC_6H_4 (It)	IIId	Vh	7	90	206

in the presence of Ni(0) NP at room temperature, and 94% of 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrano[2,3-*d*]pyrimidine-6-carbonitrile (**VIa**) was obtained in 5 min. To demonstrate the efficiency and the applicability of the present method, we extended the reaction for a variety of arylaldehydes (**I**), malononitrile (**II**), and variously substituted barbituric acids (**IIIe–i**). The reactions were complete in 5–15 min and quantitative yields of corresponding pyran derivatives (**VIa–u**) were obtained. The pyran formation was observed selectively in the case of electron withdrawing substituents in arylaldehydes. Subsequently, reactions of aryl aldehydes (**I**) and malononitrile (**II**) were also attempted with 4-hydroxy-6-methyl-2*H*-pyran-2-one (**IIIj**) and 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**IIIg**). These reactions yielded the corresponding pyran derivatives (**VIIa–e** and **VIIIa–b**, respectively) in short time span with good yields. All these reactions are illustrated in Scheme 3 and the results are summarized in Table 2.

Interestingly, reactions of terephthaldehyde (**Im**) with greater molar ratios of reactants (I– II– III 1:2.2:2.0) led to bis-pyranization (double condensation) under otherwise identical reaction conditions as illustrated in Scheme 4.

The involvement of Ni(0) NP is essential for the reactions as confirmed by a blank reaction of **Ia**, malononitrile, and **IIIa** in ethylene glycol (containing traces of PEG) in the absence of Ni(0) NP. The reaction was incomplete after 8 h and only 76% of **IVa** was isolated compared to 95% of **IVa** in 5 min in the presence of Ni(0) NP. Similar results were obtained when this reaction was repeated with Ni^{2+} or $NaBH_4$ alone in ethylene glycol at room temperature. In another experiment, isolated Ni(0) NP were redispersed in ethylene glycol, and the dispersion so obtained was then used for the reaction of **Ia, II**, and **IIIa**. The reaction was complete within



Scheme 3. PEG-stabilized Ni nanoparticles catalyzed the synthesis of 2-amino-4-aryl-4*H*-pyran-3-carbonitrile derivatives.

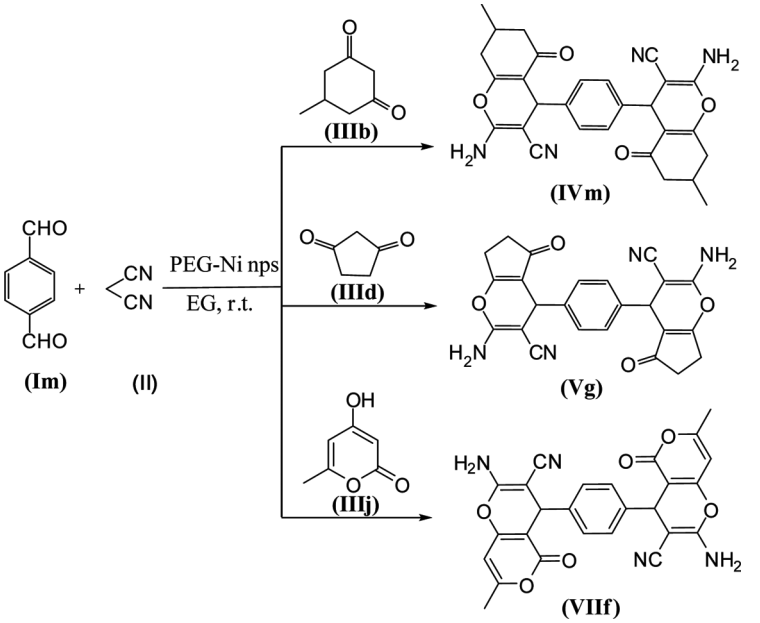
Table 2. PEG-stabilized Ni nanoparticle–catalyzed synthesis of 2-amino-4-aryl-4*H*-pyran-3-carbonitrile derivatives

No.	Ar(I)	III	Product	Time (min)	Yield (%)	Mp (°C) (obs.)[Ref.]
1	4-ClC_6H_4 (Ia)	IIIe	VIa	5	94	200[20c]
2	4-$O_2NC_6H_4$ (Ic)	IIIe	VIb	5	91	212[20c]
3	2,5-$(CH_3O)_2C_6H_3$ (Ij)	IIIe	VIc	15	87	198
4	4-BrC_6H_4 (Iu)	IIIe	VId	5	92	204[20c]
5	4-FC_6H_4 (Ii)	IIIe	VIe	7	89	193[20c]
6	3,4-$(CH_3O)_2C_6H_3$ (Id)	IIIe	VIf	12	87	190
7	2,4-$Cl_2C_6H_3$ (Ih)	IIIe	VIg	10	94	165
8	4-$F_3CC_6H_4$ (Il)	IIIe	VIh	5	90	182[20c]
9	4-$CH_3C_6H_4$ (Iv)	IIIe	VIi	15	89	170
10	2-Naphthyl (Ig)	IIIe	VIj	10	92	186
11	C_6H_5 (Iw)	IIIe	VIk	10	90	216[20c]
12	2-$O_2NC_6H_4$ (Ix)	IIIe	VIl	5	93	206 (d)
13	3-BrC_6H_4 (Ie)	IIIe	VIm	7	91	138
14	4-ClC_6H_4 (Ia)	IIIf	VIn	10	89	238[9b]
16	4-$F_3CC_6H_4$ (Il)	IIIg	VIo	5	92	142
17	2,4-$Cl_2C_6H_3$ (Ih)	IIIg	VIp	10	93	136
18	4-FC_6H_4 (Ii)	IIIg	VIq	10	91	146
19	2-$O_2NC_6H_4$ (Ix)	IIIg	VIr	5	94	184
19	4-BrC_6H_4 (Ia)	IIIh	VIs	15	92	234[9b]
20	3-$O_2NC_6H_4$ (In)	IIIi	VIt	5	89	192 (d)
21	4-BrC_6H_4 (Iu)	IIIi	VIu	5	94	110
22	4-ClC_6H_4 (Ia)	IIIj	VIIa	5	92	198[15]
23	3-$O_2NC_6H_4$ (In)	IIIj	VIIb	7	89	212
24	3-BrC_6H_4 (Ie)	IIIj	VIIc	7	93	246[9b]
25	3,4-$(MeO)_2C_6H_3$ (Id)	IIIj	VIId	12	88	186[9b]
26	2-Furanyl (If)	IIIj	VIIe	5	94	210 (d)
27	Terephthaldehyde (Im)	IIIj	VIIf	10	93	>300 (d)
27	4-ClC_6H_4 (Ia)	IIIk	VIIIa	10	93	175[15]
28	4-$O_2NC_6H_4$ (Ic)	IIIk	VIIIb	10	91	190[15]

10 min and 93% of **IVa** was isolated, thereby confirming the involvement of Ni(0) NP. The reaction of **Ia, IIa**, and **IIIa** was also attempted with Ni powder (size <150 micron) in ethylene glycol. The reaction was only 60% complete even after stirring for 10 h, unlike complete reactions in 10–15 min in the presence of Ni(0) NP. Another important aspect of the reactions is the ease of recyclability of Ni(0) NP, which was examined by the reaction of 4-chlorobenzaldehyde (**Ia**), malononitrile, and dimedone in the presence of PEG-stabilized Ni(0) NP. Upon completion, the product (**IVa**, 95%) was extracted in ethyl acetate followed by isolation of the ethylene glycol layer, which was then used for subsequent cycles. The catalyst retained optimum activity up to four cycles (94–85%), after which a drop in yield (74%) of the product (**IVa**) was observed. The particle analysis after the fifth catalytic cycle indicated agglomeration along with increase in size, which could be a possible reason for drop in catalytic activity.

A reasonable mechanism for the formation of the product via tandem Knoevenagel–cyclocondensation is outlined in Scheme 5.

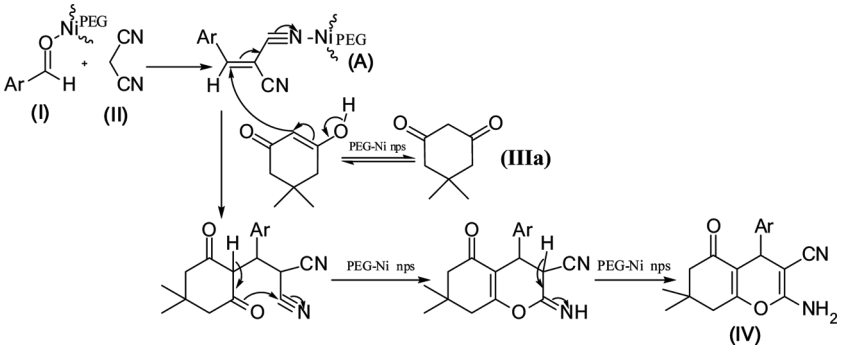
The reaction occurs via initial formation of arylidene malononitrile (A) from the Knoevenagel condensation of arylaldehyde (**I**) and malononitrile (**II**), which



Scheme 4. PEG-Ni nanoparticles catalyzed the formation of pyran-3-carbonitrile derivatives corresponding to terephthaldehyde (**Im**).

reacts with **III** and subsequently cyclizes to afford the desired product (**IV–VIII**) after proton transfer and tautomerization. This has been confirmed by the independent reaction of arylidene malononitrile (A) with **IIIa** in otherwise identical conditions that led to the formation of **IVa**.

In conclusion we have reported PEG-stabilized Ni(0) NP as an effective catalyst that provides a new and useful method for the synthesis of 2-amino-4*H*-pyrans and pyran annulated heterocycles by the condensation of aldehydes, malononitrile, and cyclic 1,3-diketones. The procedure offers advantages such as good yields, operational simplicity, and clean reaction conditions.



Scheme 5. Plausible mechanistic pathway for the PEG-Ni nanoparticle–catalyzed synthesis of 4*H*-pyrans.

EXPERIMENTAL

All the chemicals used were of research grade and were used without further purification. The size and morphology of Ni(0) NP were characterized with the help of TEM and EDAX analysis using TECNAI G^2 U-TWIN (300 kV). XRD was obtained on a Bruker D8. ^{1}H NMR spectra were recorded on Brucker Spectrospin Avance (300 MHz) and Jeol JNM ECX-400P (400 MHz) instruments with $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) as the solvent and tetramethylsilance (TMS) as the internal standard. Infrared (IR) spectra were recorded on Perkin-Elmer Fourier transform (FT)–IR Spectrum-2000. Mass spectra were recorded on KC-455-TOF spectrometer. Melting points were recorded on a Tropical Labequip apparatus and are uncorrected.

Preparation of Ni Nanoparticles

Ni(0) NP were synthesized in ethylene glycol (20.0 mL) from $NiCl_2 \cdot 6H_2O$ (2×10^{-4} M) and $NaBH_4$ by the modified polyol process,[30] and polyethylene glycol (PEG-4000, Ni^{2+}–PEG 1:5 wt%) was used as the stabilizing agent instead of the conventional polyvinyl pyrrolidone (PVP). The size and morphology of PEG-stabilized Ni(0) NP match satisfactorily with the conventional protocol.

General Procedure for the Synthesis of 4*H*-Pyran Derivatives

In a typical general procedure, a mixture of aromatic aldehyde (1.0 mmol), malononitrile (1.1 mmol), 1,3-diketone (1.0 mmol), and Ni(0) NP dispersion in ethylene glycol (2 mL/0.1 g I) was stirred thoroughly at room temperature in a 50-mL, round-bottom flask. Completion of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate–petroleum ether (45:55) as the eluent. Upon completion of the reaction, the reaction mixture was diluted with water and the solid product was filtered, washed with water, dried, and recrystallized from ethanol. 4*H*-Pyran derivative was obtained as identified by their mp and spectral data. In case of terephthaldehyde, the molar ratios of **I– II– III** required for complete bis-pyranization were 1:2.2:2 under otherwise identical reaction conditions.

2-Amino-4-(2,4-dichlorophenyl)-7-methyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (IVh)

Colorless solid; yield = 93%; mp.: 116–118 °C. IR (KBr, cm^{-1}) $\upsilon_{max} = 3494$, 3367, 3330, 3163, 2960, 2189, 1682, 1660, 1471, 1371, 1211. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07–1.11 (m, 3H, Me), 2.00–2.10 (m, 1H, CH), 2.21–2.46 (m, 3H), 2.55–2.62 (m, 1H), 4.79 (s, 1H, CH), 4.83 (s, 2H, NH_2), 7.09–7.19 (m, 2H, Ar-H), 7.33 (s, 1H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.69, 27.97, 33.53, 44.90, 50.72, 60.64, 112.98, 118.44, 127.41, 129.93, 131.35, 133.39, 133.99, 138.55, 157.98, 164.03, 196.04. $[M + H]^+ = 349$.

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