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Full Paper

Highly Monodispersed PEG-stabilized Ni Nanoparticles: Proficient Catalyst for the Synthesis of Biologically Important Spiropyrans

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A convenient and efficient synthesis of biologically and pharmacologically important spiropyrans from the condensation of malononitrile, 1,3-dicarbonyl compounds and ninhydrin/acenaphthequinone/isatin has been reported using recyclable heterogeneous polyethylene glycol (PEG)-stabilized Ni nanoparticles in ethylene glycol. This new protocol affords products in high yields and less reaction time.

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Introduction

Spiro compounds represent an important class of naturally occurring substances known for their biological properties.[1,2] Among them, spiropyrans have attracted strong interest owing to their potential activity as hypertensive and analgesic agents[3] and applications to industrial fields.[4] Oxindole derivatives are known to possess biological activities, such as potent inhibition of monoamine oxidase in human urine and rat tissues,[5] inhibition of several enzymes such as acetylcholinesterase[6] and atrial natriuretic peptide-stimulated guanylate cyclase, and potent antagonist of in vitro receptor binding by atrial natriuretic peptide,[7] besides possessing a wide range of central nervous system activities.[8] The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids.[9–11] On the other hand, ninhydrin is a unique tricarbonyl compound that is widely used in biochemical and medical settings for the analysis of amino acids.[12]

In recent years, a variety of synthetic methodologies for constructing spiro-fused pyran derivatives via multi-component condensation reactions have been reported.[13–17] Each of the known procedures for the synthesis of spiropyrans has its merits and demerits but the development of facile, greener and economical synthetic routes is still essential. Owing to the high surface area to volume ratio, metal nanoparticles have proved to be very efficient catalysts in comparison to the traditional catalysts. Ni nanoparticles, in particular, have gained much attention over the decade owing to their ease of preparation, high reaction yields and recyclability. Ni nanoparticles overcome the shortcoming of recyclability of homogeneous nickel catalysts thereby behaving as efficient heterogeneous catalysts. Pioneering work using Ni nanoparticles includes selective hydrogenation,[18] C-C coupling namely Suzuki coupling,[19] Heck reaction,[20] Nigeshi coupling,[21] Kumada coupling,[22] Mizoroki-Heck coupling,[23] and other Ni nanoparticle-catalyzed reactions.[24,25] Recently, we have reported PVP-stabilized Ni^0 nanoparticle-catalyzed Knoevenagel condensation of aldehydes with barbituric acids,[26] *o*-phenylenediamine and 2-aminobenzothiazole[27] in ethylene glycol. We have also reported the Knoevenagel condensation followed by cascade enol lactonization using arylidene Meldrum's acid and active methylenes catalyzed by PEG-stabilized Ni nanoparticles in ethylene glycol.[28] In continuation of our efforts to explore the catalytic applications of Ni nanoparticles in organic synthesis, we wish to report a novel and highly efficient protocol for the synthesis of spiro-fused pyran derivatives using Ni nanoparticles as catalyst.

Results and Discussion

We report, herein, the synthesis of a variety of spiro-2-amino-4*H*-pyrans, spiroacenaphthylenes and spirooxindoles by the one-pot condensation of ninhydrin/acenaphthequinone/isatin with malononitrile and a variety of α-methylene carbonyl compounds in the presence of Ni nanoparticles in ethylene glycol at room temperature.

Catalyst Characterization

The average size of Ni nanoparticles was found to be 7 nm through transmission electron microscopy (TEM) (Fig. 1a) and XRD analysis (Fig. 1b). Energy dispersive X-ray (EDAX) data (Fig. 1c) and the XRD pattern confirmed the metallic nature of Ni nanoparticles. As per the X-ray diffraction plot, the peaks at $2\theta = 44.5°$, 51.8° and 76.4°, corresponding to the (111), (200) and (222) lattice planes respectively, clearly indicate the presence of pure elemental Ni with face-centred cubic (FCC) structure. The size from the XRD data was calculated to be 6.9 nm and is consistent with TEM results.

Ni Nanoparticle-catalyzed Synthesis of Spiropyrans

Ni nanoparticle dispersion in ethylene glycol was used as such for the reactions. We investigated the condensation of ninhydrin (**1a**, 1 equiv.), malononitrile (1.1 equiv.) and

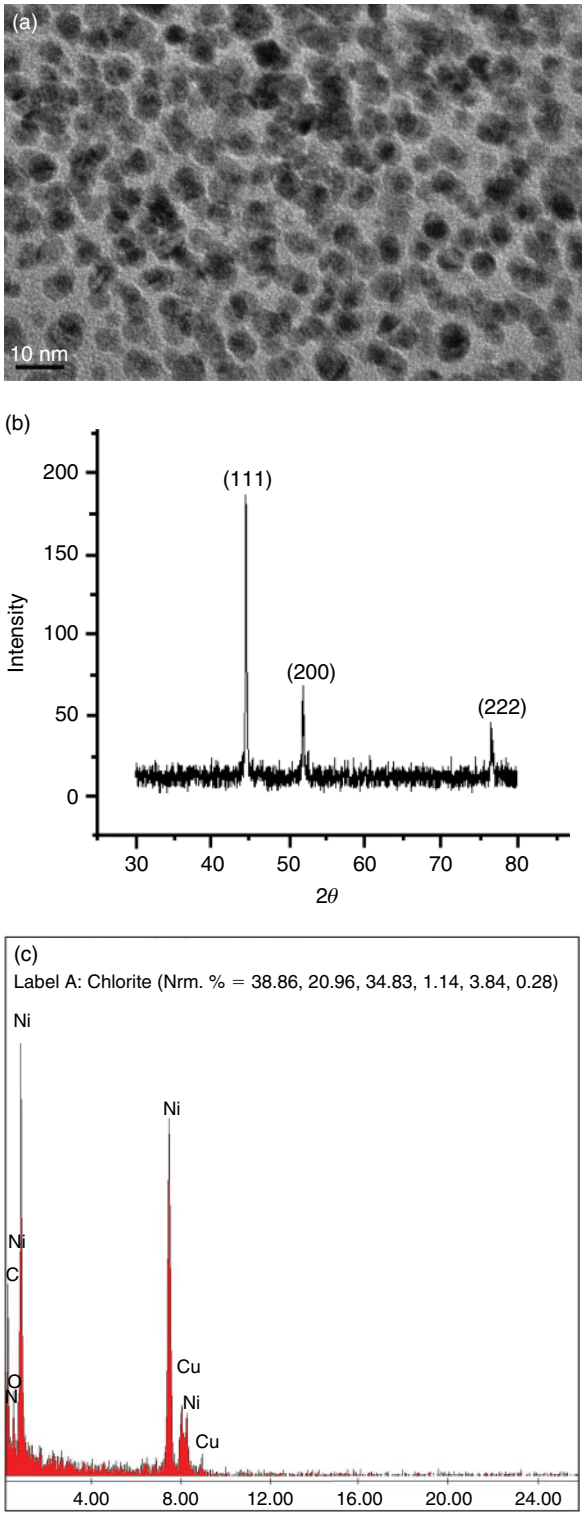


Fig. 1. (a) TEM image of PEG-stabilized Ni nanoparticles. (b) X-ray diffraction pattern of PEG-Ni nanoparticles. (c) EDAX data of PEG-Ni nanoparticles.

dimedone (1 equiv.) in the presence of Ni nanoparticles dispersed in ethylene glycol by varying reaction conditions. It was observed that **4a** was formed in 7 min in 93 % yield using a catalytic amount of Ni nanoparticles in ethylene glycol [2 mL of dispersion (0.0235 wt % Ni)/0.1 g ninhydrin] at room temperature. Condensations of malononitrile and dimedone with acenaphthequinone (**1b**) or isatin (**1c**) in place of ninhydrin (**1a**) also resulted in the formation of corresponding spiroacenaphthylene (**5a**) and spirooxindole (**6a**) in high yields under the same reaction conditions. Ethylene glycol served as a suitable solvent for these transformations. Based on the solubility difference of the products and starting materials, the products separated readily from the reaction mixture upon completion, thereby facilitating their easy isolation simply by filtration. Subsequently, the reactions of ninhydrin, acenaphthequinone and isatin with malononitrile and various 1,3-dicarbonyl compounds gave the corresponding spiro-2-amino-4*H*-pyrans, spiroacenaphthylenes and spirooxindoles (Chart 1) in high yields. All results have been summarized in Table 1.

Catalyst Role Justification

The role of Ni nanoparticles was elucidated by a control experiment which was conducted with ninhydrin (1 equiv.), malononitrile (1.1 equiv.) and dimedone (1 equiv.) in ethylene glycol in the absence of Ni nanoparticles. This resulted in the formation of **4a** after 7 h with only 55 % yield. Also low yields were obtained when the reaction was carried out with Ni^{2+} salt alone in ethylene glycol at room temperature, whereas when the reaction was carried out in the presence of a catalytic amount of $NaBH_4$, a mixture of products was obtained. The nanoparticles were isolated from the ethylene glycol dispersion, washed with absolute ethanol several times and redispersed in ethylene glycol. This dispersion was then used for carrying out the reaction between **1a**, **2** and **3a**. The reaction resulted in formation of **4a** in 90 % yield in 8–10 min. The reaction was also attempted with Ni powder (size $<$150 micron) in ethylene glycol. The reaction was only 62 % complete even after 8 h of stirring. The results have been recapitulated in Table 2.

Recyclability of Catalyst

The catalyst could be recycled simply by solvent extraction of the product several times from the reaction mixture using ethyl acetate, becuase it was completely immiscible with ethylene glycol at room temperature. Upon sonication, the ethylene glycol layer containing the Ni nanoparticles could be reused for the subsequent cycles. The relationship between the number of cycles of the reaction and the catalytic activity in terms of yields is presented in Fig. 2a. It was found that the catalyst retained optimum activity until four cycles after which a drop in yield was observed. The plausible reason for this could be the decreased stability of the nanoparticles with subsequent recycling which resulted in diminished catalytic activity owing to agglomeration of nanoparticles, as shown in Fig. 2b.

Mechanism

A rational mechanism for the formation of the spiropyrans via tandem Knoevenagel-cyclo-condensation is outlined in Scheme 1. The reaction occurs via initial formation of Knoevenagel condensate (**I**) from ninhydrin (**1a**) and malononitrile (**2**), which reacts with dimedone (**3a**) and subsequently cyclizes to afford the desired product **4a** after proton transfer and tautomerization.

Conclusions

In conclusion, we have successfully developed a novel and efficient method for the synthesis of diverse spiropyrans through a three-component one-pot reaction catalyzed by PEG-stabilized Ni nanoparticles. The protocol offers advantages such

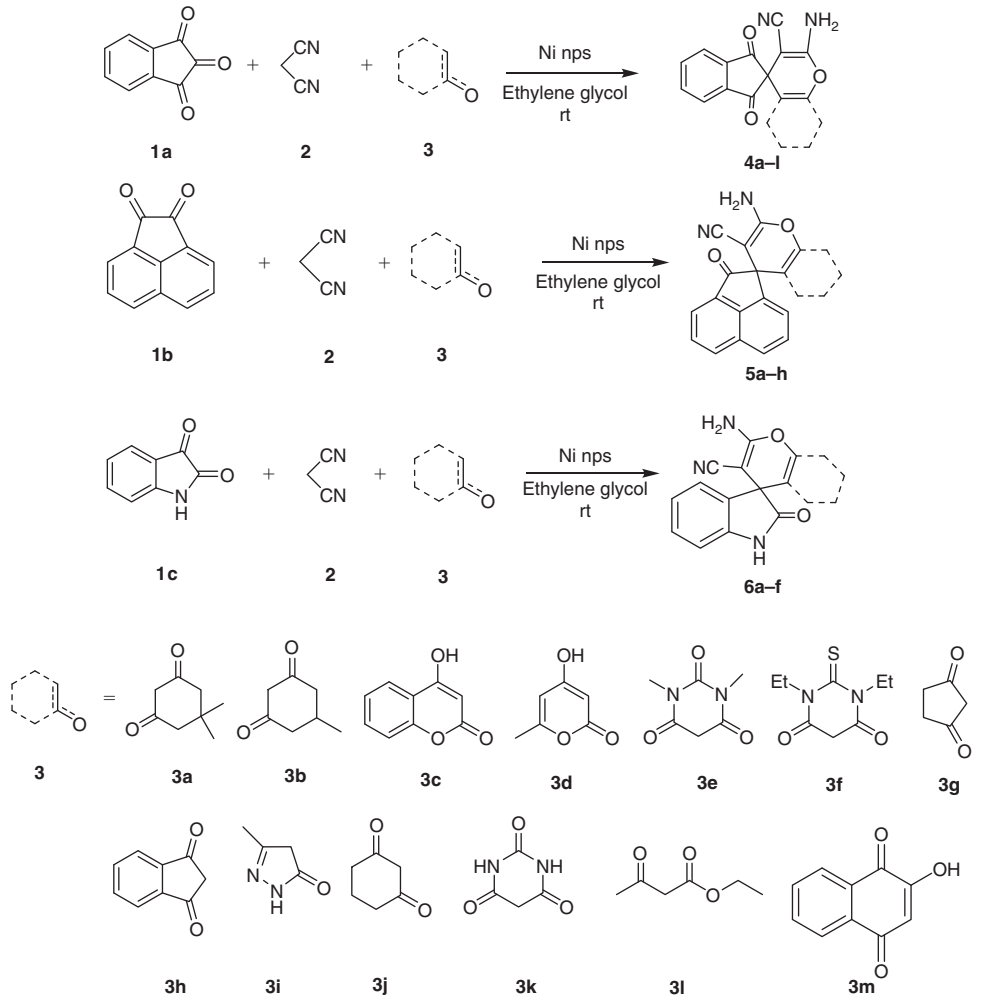


Chart 1. PEG-stabilized Ni nanoparticle-catalyzed synthesis of spiropyrans.

Table 1. PEG-Ni nanoparticle-catalyzed synthesis of spiropyrans 4, 5, and 6

Sr. No.	1	1,3-dicarbonyl	Product	Time [min]	Yield [%]	mp [°C][13–17]
1.	**1a**	**3a**	**4a**	7	93	290–292 (>300)[13b]
2.	**1a**	**3b**	**4b**	5	90	270–272
3.	**1a**	**3c**	**4c**	5	89	280–285 (>300)[13b]
4.	**1a**	**3d**	**4d**	10	91	290–295[17]
5.	**1a**	**3e**	**4e**	10	92	258–260
6.	**1a**	**3f**	**4f**	8	92	235–237 (242–244)[13a]
7.	**1a**	**3g**	**4g**	15	90	230–235
8.	**1a**	**3h**	**4h**	12	89	255–260*
9.	**1a**	**3i**	**4i**	10	91	290–295 (250–252)[13a]
10.	**1a**	**3j**	**4j**	12	90	280–282 (282–282)[13a]
11.	**1a**	**3k**	**4k**	15	89	275–277 (>300)[13b]
12.	**1a**	**3l**	**4l**	20	88	220–225
13.	**1b**	**3a**	**5a**	10	93	270 (268–270)[16]
14.	**1b**	**3b**	**5b**	10	89	275–280
15.	**1b**	**3d**	**5c**	8	93	290–295
16.	**1b**	**3e**	**5d**	5	92	280–282 (>300)[13b]
17.	**1b**	**3f**	**5e**	12	90	180–185
18.	**1b**	**3g**	**5f**	8	90	260–265
19.	**1b**	**3h**	**5g**	8	94	270–272 (>300)[16]
20.	**1b**	**3i**	**5h**	6	94	250–255 (298)[16]
21.	**1c**	**3a**	**6a**	5	92	295–300 (290–292)[14]
22.	**1c**	**3b**	**6b**	10	92	275–280*
23.	**1c**	**3d**	**6c**	10	90	280–282 (278–280)[14a]
24.	**1c**	**3e**	**6d**	20	89	220–225 (230)[14b]
25.	**1c**	**3f**	**6e**	8	91	205–210 (221)[14b]
26.	**1c**	**3m**	**6f**	20	88	260–265 (295)[17b]

*Compound known but mp reported for first time.

Table 2. Reactions validating the involvement of Ni nanoparticles for the synthesis of 4a

Sr. No.	Reaction conditions	Time	Yield [**4a**, %]
1.	Ethylene glycol (EG) alone	7 h[A]	55
2.	$NiCl_2{\cdot}6H_2O$ alone in EG	7 h[A]	58
3.	$NaBH_4$ alone in EG	6 h[B]	–
4.	Isolated Ni nanoparticles redispersed in EG	10 min	90
5.	Ni powder (size <150 micron)	8 h[A]	62

[A]Incomplete reaction.
[B]Mixture of products; no **4a** observed.

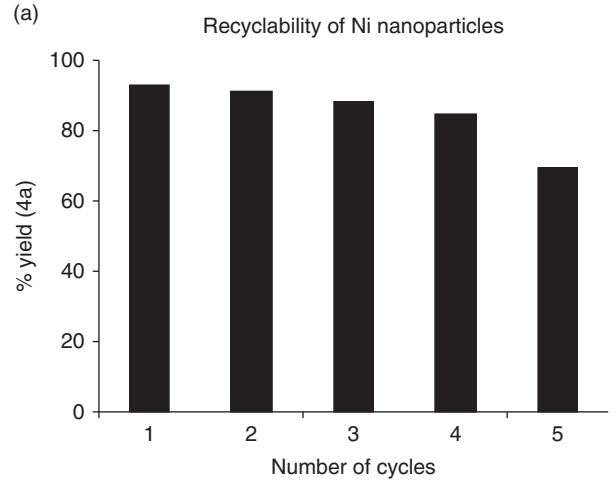


Fig. 2. (a) Recyclability of Ni nanoparticles: plot of yield (%) of 4a versus number of cycles. (b) TEM image of Ni nanoparticles obtained after five cycles.

as high yields, mild reaction conditions and an environmentally benign procedure. Moreover, the nanocatalysts are stable to leaching and can be reused without significantly affecting the yields.

Experimental

All the chemicals used were of research grade and were used without further purification. Transmission electron microscopy for size and morphology characterization was obtained on TECNAI G^2 U-TWIN (300 kV) and JEOL 2100-F (200 kV) instruments. X-ray diffraction pattern was obtained on a BRUKER D8 diffractometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM ECX-400P (400 MHz) spectrometer with DMSO-d_6 as the solvent and TMS as the internal standard. IR spectra were recorded on a Perkin-Elmer FT-IR SPECTRUM-2000. Mass spectra were recorded on JEOL-AccuTOF JMS–T100 mass spectrometer having a DART source. Melting points were recorded on a Tropical Labequip apparatus and are uncorrected.

Preparation of Ni Nanoparticles

Ni nanoparticles were prepared by a modified polyol method as reported in literature.[28] To a 2×10^{-4} M solution of $NiCl_2{\cdot}6H_2O$ (0.0048 g) in ethylene glycol (100 mL) placed in a 250 mL round bottom flask fitted with a reflux condenser, PEG 4000 (0.024 g, Ni^{2+}:PEG: 1:5 wt %) was added. The mixture was stirred until complete dissolution of PEG. The solution was heated in an oil bath maintained at 120°C. At this temperature, 0.36 g $NaBH_4$ was added to the solution. The system was maintained under magnetic stirring at 120°C for 2 h. The sample for TEM analysis was obtained by the addition of acetone to the Ni nanoparticles dispersion in ethylene glycol, followed by centrifugation (6000 rpm). The particles, so obtained, were washed free of any residual components using ethanol. Subsequently, a drop of methanol dispersion of Ni nanoparticles was placed on a carbon coated Cu grid (mesh size 300). A sample for the X-ray diffraction study was obtained by depositing a thin coating of the isolated Ni nanoparticles (dispersed in absolute ethanol) onto a glass plate followed by vacuum drying.

General Procedure for the Synthesis of Spiropyrans

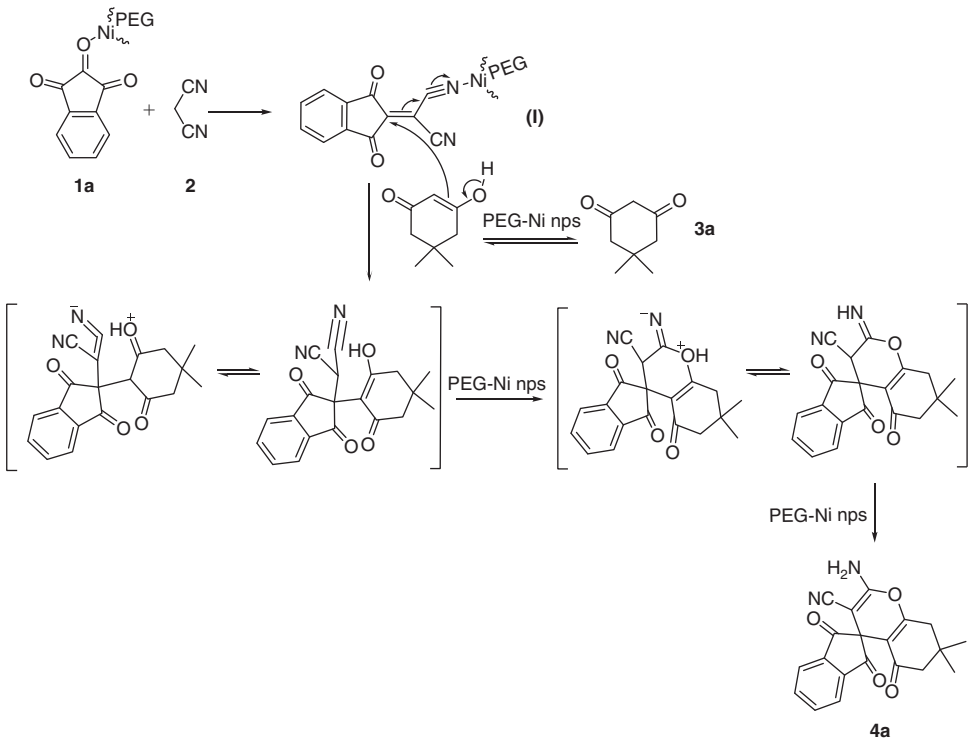
Ninhydrin/acenaphthequinone/isatin (1 equiv.), malononitrile (1.1 equiv.), 1,3-dicarbonyl compound (1 equiv.) and a well stirred dispersion of Ni nanoparticles in ethylene glycol [2 mL of dispersion (0.0235 wt % Ni)/0.1 g **1a**/**1b**/**1c**] was added to a 50 mL round bottom flask. The mixture was stirred at room temperature. The reaction progress was monitored by thin column chromatography (TLC), using petroleum ether/ethyl acetate (6:4) as eluent. All the reactions were complete in 10–15 min. Upon completion, 15 mL water was added to the reaction mixture and the solid product was filtered at the pump, washed with water, dried and recrystallized from hot ethanol. The products were identified by spectral data.

*2-Amino-7-methyl-1′,3′,5-trioxo-1′,3′,5,6,7,8-hexahydrospiro[chromene-4,2′-indene]-3-carbonitrile **4b***

Mp 270°C (dec.). ν_{max} (KBr)/cm^{-1} 3365, 3299, 3181, 2969, 2195, 1713, 1676, 1642, 1420, 1365, 1216, 1051. δ_H (400 MHz, DMSO-d_6) 8.03–7.99 (m, 4H, Ar-H), 7.65 (s, 2H, NH_2), 2.71–2.66 (m, 1H), 2.56–2.54 (m, 1H), 2.31–2.22 (m, 2H), 2.13–2.07 (m, 1H), 1.01 (s, 3H). δ_C (100 MHz, DMSO-d_6) 19.88, 27.55, 33.85, 43.10, 51.83, 53.08, 110.61, 116.85, 123.10, 123.16, 136.62, 140.47, 140.59, 159.83, 167.49, 196.04, 199.70, 199.78. *m/z* (ESI) 335.1 $[M+H]^+$.

*7′-Amino-1′,3′-dimethyl-1,2′,3,4′-tetraoxo-1,1′,2′,3,3′,4′-hexahydrospiro[indene-2,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile **4e***

Mp 260°C (dec.). ν_{max} (KBr)/cm^{-1} 3381, 3292, 3195, 2194, 1749, 1694, 1386, 1193. δ_H (400 MHz, DMSO-d_6) 8.05–8.04 (m, 4H, Ar-H), 7.97 (s, 2H, NH_2), 3.37 (s, 3H), 3.00 (s, 3H). δ_C (100 MHz, DMSO-d_6) 199.74, 160.47, 159.47, 153.08, 149.55, 140.45, 137.01, 123.32, 116.38, 85.64, 53.25, 52.08, 29.82, 28.78. *m/z* (ESI) 365.1 $[M+H]^+$.



Scheme 1. Plausible mechanistic pathway for the PEG-Ni nanoparticle-catalyzed synthesis of spiropyrans.

*2-Amino-1′,3′,5-trioxo-1′,3′,6,7-tetrahydro-5*H*-spiro[cyclopenta[*b*]pyran-4,2′-indene]-3-carbonitrile* ***4g***

Mp 230–235°C. ν_{max} (KBr)/cm^{-1} 3500, 3363, 2924, 2196, 1745, 1714, 1673, 1592, 1342, 1263. δ_H (400 MHz, DMSO-d$_6$) 8.11–8.04 (m, 4H, Ar-H), 7.90 (s, 2H, NH$_2$), 2.90–2.89 (m, 2H, CH$_2$), 2.42–2.39 (m, 2H, CH$_2$). δ_C (100 MHz, DMSO-d$_6$) 200.50, 198.84, 198.47, 179.64, 161.64, 140.85, 140.23, 137.53, 136.62, 123.58, 123.43, 117.13, 113.45, 111.40, 76.00, 52.52, 51.79, 32.92, 30.36, 25.53. *m/z* (ESI) 307.2 [M+H]$^+$.

Ethyl 2′-amino-3′-cyano-6′-methyl-1,3-dioxo-1,3-dihydrospiro[indene-2,4′-pyran]-5′-carboxylate ***4l***

Mp 220°C (dec.). ν_{max} (KBr)/cm^{-1} 3334, 3176, 2926, 2192, 1659, 1429, 1275, 1166, 1089, 1013; δ_H (400 MHz, DMSO-d$_6$) 7.95–7.94 (m, 2H, Ar-H), 7.88–7.66 (m, 2H, Ar-H), 7.74 (s, 2H, NH$_2$), 4.22–4.13 (m, 2H), 2.22 (s, 3H), 1.32 (t, *J* 7.32, 3H). δ_C (100 MHz, DMSO-d$_6$) 193.43, 167.94, 166.71, 163.25, 142.52, 137.12, 135.70, 132.72, 124.97, 124.54, 119.44, 116.99, 105.54, 67.68, 59.83, 53.37, 14.00, 13.84. *m/z* (ESI) 338 [M]$^+$.

*2′-Amino-7′-methyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-chromene]-3′-carbonitrile* ***5b***

Mp 270°C (dec.). ν_{max} (KBr)/cm^{-1} 3352, 3195, 2194, 1740, 1657, 1459, 1213. δ_H (400 MHz, DMSO-d$_6$) 8.26–8.23 (m, 1H, Ar-H), 7.93–7.91 (m, 2H, Ar-H), 7.81–7.80 (m, 1H, Ar-H), 7.64–7.62 (m, 1H, Ar-H), 7.40–7.38 (m, 1H, Ar-H), 7.30 (s, 2H, NH$_2$), 2.74–2.65 (m, 1H, CH$_2$), 2.57–2.54 (m, 1H, CH$_2$), 2.26–2.14 (m, 2H, CH$_2$), 2.04–1.98 (m, 1H, C*H*CH$_3$), 0.99 (s, 3H, CH$_3$). δ_C (100 MHz, DMSO-d$_6$) 203.69, 203.54, 195.36, 165.92, 165.31, 158.73, 143.24, 140.44, 131.45, 129.77, 128.90, 128.48, 124.53, 121.44, 121.36, 120.03, 119.90, 117.55, 112.78, 112.60, 58.01, 51.02, 43.94, 34.37, 34.16, 27.43, 20.07, 19.91. *m/z* (ESI) 357.1 [M+H]$^+$.

*2′-Amino-7′-methyl-2,5′-dioxo-2*H,5′H*-spiro[acenaphthylene-1,4′-pyrano[4,3-*b*]pyran]-3′-carbonitrile* ***5c***

Mp 290°C (dec.). ν_{max} (KBr)/cm^{-1} 3473, 3340, 2725, 2186, 1738, 1699, 1633, 1463, 1418, 1360, 1231. δ_H (400 MHz, DMSO-d$_6$) 8.32–8.30 (m, 1H, Ar-H), 7.99–7.97 (m, 3H, Ar-H), 7.86–7.82 (m, 1H, Ar-H), 7.69–7.66 (m, 1H, Ar-H), 7.52 (s, 2H, NH$_2$), 6.41 (s, 1H), 2.22 (s, 3H, CH$_3$). δ_C (100 MHz, DMSO-d$_6$) 203.43, 163.92, 160.60, 159.90, 158.60, 141.91, 141.05, 132.09, 131.34, 129.76, 128.97, 128.62, 125.02, 121.91, 120.72, 117.22, 99.21, 98.04, 57.92, 50.90, 19.28. *m/z* (ESI) 356 [M]$^+$.

*7′-Amino-1′,3′-dimethyl-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydro-2*H*-spiro[acenaphthylene-1,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* ***5d***

Mp 280–282°C. ν_{max} (KBr)/cm^{-1} 3404, 3323, 3192, 2960, 2192, 1713, 1679, 1491, 1382, 1189. δ_H (400 MHz, DMSO-d$_6$) 8.42–8.19 (m, 1H, Ar-H), 7.95 (s, 2H, NH$_2$), 7.83 (s, 1H, Ar-H), 7.65–7.53 (m, 4H, Ar-H), 3.41 (s, 3H, CH$_3$), 2.90 (s, 3H, CH$_3$).

*7′-Amino-1′,3′-diethyl-2,4′-dioxo-2′-thioxo-1′,2′,3′,4′-tetrahydro-2*H *spiro[acenaphthylene-1,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* ***5e***

Mp 180–185°C (dec.). ν_{max} (KBr)/cm^{-1} 3303, 3134, 2924, 2726, 2210, 1720, 1684, 1623, 1464, 1377, 1281, 1113. δ_H (400 MHz, DMSO-d$_6$) 8.31–8.29 (m, 1H, Ar-H), 7.98–7.96 (m, 3H, Ar-H), 7.86–7.82 (m, 1H, Ar-H), 7.73 (s, 2H, NH$_2$), 7.63–7.61 (m, 1H, Ar-H), 4.67–4.56 (m, 2H, C*H*$_2$CH$_3$), 4.16–4.05 (m, 2H, CH$_2$CH$_3$), 1.37–1.34 (m, 3H, CH$_2$C*H*$_3$), 0.94–0.91 (m, 3H, CH$_2$C*H*$_3$). δ_C (100 MHz, DMSO-d$_6$) 202.83, 174.33, 157.85, 157.51, 151.98, 141.84, 140.67, 131.98, 131.50, 129.78, 128.93, 128.52, 124.95, 121.77, 121.03, 116.73, 92.84, 57.90, 51.44, 45.00, 42.81, 12.58, 10.99. *m/z* (ESI) 431.2 [M+H]$^+$.

*2′-Amino-2,5′-dioxo-6′,7′-dihydro-2*H*,5′*H*-spiro[acenaphthylene-1,4′-cyclopenta[*b*]pyran]-3′-carbonitrile* ***5f***

Mp 260°C (dec.). ν_{max} (KBr)/cm^{-1} 3324, 3296, 2725, 2190, 1749, 1713, 1669, 1586, 1377, 1345, 1236, 1160. δ_H (400 MHz, DMSO-d_6) 8.34–8.32 (m, 1H, Ar-H), 8.00–7.97 (m, 2H, Ar-H), 7.88–7.84 (m, 1H, Ar-H), 7.71–7.68 (m, 1H, Ar-H), 7.57 (s, 2H, NH_2), 7.48–7.46 (m, 1H, Ar-H), 2.87–2.86 (m, 2H, CH_2), 2.34–2.33 (m, 2H, CH_2). δ_C (100 MHz, DMSO-d_6) 202.98, 200.10, 177.79, 160.60, 141,35, 140.71, 132.30, 131.28, 129.81, 129.06, 128.71, 125.05, 122.02, 121.05, 117.66, 115.78, 62.72, 56.98, 50.91, 33.07, 30.62, 25.03. *m/z* (ESI) 329.1 $[M+H]^+$.

2-Amino-7-methyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile ***6b***

Mp 275–280°C (dec.). ν_{max} (KBr)/cm^{-1} 3307, 3159, 2964, 2194, 1725, 1655, 1602, 1470, 1330, 1216, 1062. δ_H (400 MHz, DMSO-d_6) 10.29 (s, 1H, NH), 7.11 (s, 2H, NH_2), 7.03–7.00 (m, 1H, Ar-H), 6.88–6.85 (m, 1H, Ar-H), 6.78–6.75 (m, 1H, Ar-H), 6.67–6.65 (m, 1H, Ar-H), 2.57–2.52 (m, 1H, CH_2), 2.38–2.31 (m, 1H, CH_2), 2.17–2.08 (m, 2H, CH_2), 1.97–1.87 (m, 1H, C*H*CH_3), 0.89 (s, 3H, CH_3). δ_C (100 MHz, DMSO-d_6) 194.95, 178.15, 178.09, 165.49, 164.91, 158.72, 142.03, 134.55, 134.46, 128.17, 123.23, 123.08, 121.67, 117.39, 111.59, 111.38, 109.18, 62.44, 57.46, 46.87, 44.29, 34.40, 34.16, 27.38, 20.03, 19.99.

*7′-Amino-1′,3′-diethyl-2,4′-dioxo-2′-thioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-*d*]pyrimidine]-6′-carbonitrile* ***6e***

Mp 205°C. ν_{max} (KBr)/cm^{-1} 3435, 3345, 2921, 2208, 1722, 1681, 1668, 1463, 1385, 1119. δ_H (400 MHz, DMSO-d_6) 10.56 (s, 1H, NH), 7.65 (s, 2H, NH_2), 7.19–7.21 (m, 2H, Ar-H), 6.81–6.91 (m, 2H, Ar-H), 4.52–4.63 (m, 2H, CH_2CH$_3$), 4.16–4.18 (m, 2H, CH_2CH$_3$), 1.31 (s, 3H, CH$_2$CH_3), 1.02 (s, 3H, CH$_2$CH_3). δ_C (100 MHz, DMSO-d_6) 177.18, 174.32, 158.00, 157.21, 151.99, 142.13, 133.06, 128.75, 124.08, 121.93, 116.65, 109.41, 92.11, 69.82, 57.25, 47.61, 45.19, 42.63, 12.62, 11.23. *m/z* (ESI) 396.1 $[M+H]^+$.

2-Amino-2′,5,10-trioxo-5,10-dihydrospiro[benzo[g]chromene-4,3′-indoline]-3-carbonitrile ***6f***

Mp 260–265°C. ν_{max} (KBr)/cm^{-1} 3394, 3347, 2926, 2207, 1733, 1668, 1635, 1344, 1200. δ_H (400 MHz, DMSO-d_6) 10.68 (s, 1H, NH), 8.06–8.04 (m, 1H, Ar-H), 7.85–7.80 (m, 3H, Ar-H), 7.56 (s, 2H, NH_2), 7.22–7.17 (m, 2H, Ar-H), 6.91–6.86 (m, 2H, Ar-H). δ_C (100 MHz, DMSO-d_6) 181.86, 177.61, 176.42, 158.66, 150.48, 141.72, 134.88, 134.53, 130.58, 130.33, 128.91, 126.29, 126.04, 124.29, 122.00, 119.46, 117.03, 109.63, 62.82, 56.89, 48.06.

Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of compounds **4b**, **4e**, **4g**, **4l**, **5b**, **5c**, **5e**, **5f** and **6f** are available on the Journal's website.

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