RSC Advances

This article can be cited before page numbers have been issued, to do this please use: F. Sen, T. Demirci, B. Çelik, Y. Yldz, S. Eri, M. Arslan and B. Kilbas, *RSC Adv.*, 2016, DOI: 10.1039/C6RA13142E.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C6RA13142E

Journal Name

ARTICLE

One-Pot Synthesis of Hantzsch Dihydropyridines Using Highly Efficient and Stable PdRuNi@GO Catalyst

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

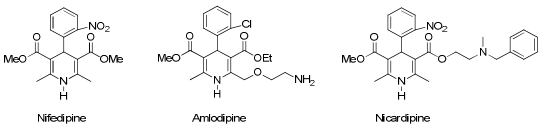
www.rsc.org/

Tuna Demirci,[‡a] Betül Çelik,[‡b] Yunus Yıldız,[b] Sinan Eriş,[b] Mustafa Arslan,[c] Fatih Sen*[b] and Benan Kilbas*[d]

Addressed herein, highly monodisperse PdRuNi nanoparticles furnished with graphene oxide (PdRuNi@GO NPs) have been prepared as novel, stable, efficient and exceptional reusable heterogeneous catalyst for 1,4-Dihydropyridine synthesis via multicomponent condensation reactions of various aldehydes with dimedone, ammonium acetate and ethyl acetoacetate at 70°C in DMF with efficient catalytic performance. These synthesized novel materials were characterized by transmission electron microscopy (TEM), the high resolution electron micrograph (HRTEM), X-ray diffraction (XRD) and X-ray photoelectron spectroscopy (XPS). This presented one pot catalytic process was described as a new methodology of Hantzsch synthesis which can be assessed as a quite simple and efficient as well as exceptional reusable. At the end of the reaction, one of the highest yield and the shortest time has been obtained for the model reaction in the presence of novel monodisperse PdRuNi@GO NPs.

Introduction

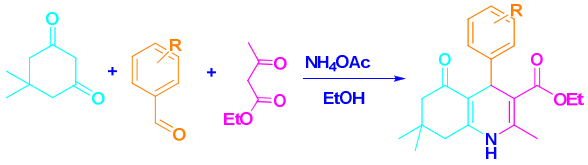
The six-membered heterocyclic compounds are very important components in organic chemistry. Recently, chemists have devoted considerable attention to 1,4-dihydropyridine compounds, due to their important roles such as medical,[1,2] biological[3] and pharmacological activities.[4] They are also used as key compounds of drugs.[5,6] For instance, 1,4-dihydropyridine is the common feature for various pharmacological activities such as cyclooxygenase-2 inhibitors,[3] inhibitors against α-glucosidase,[7] anti-inflammatory activity,[8] myorelaxant activity of gastric fundus,[9] antimicrobial[10] and antihypertensive.[11,12] Nifedipine, nicardipine and amlodipine like dihydropyridine derivatives are also known in pharmacology as calcium channel blockers, used in the treatment of hypertension[13] (Scheme 1).



Scheme 1 Examples of 1,4-dihydropyridine derivatives

1,4-dihydropyridine compounds are also acted as catalysts in different types of organic reactions. For instance, those compounds are used as H_2 surrogate for hydrogenation of α,β-epoxy ketones,[14] alkenes,[15] enamides[16] and they are key compounds both in cyclization reactions of 1,6-diynes with ruthenium[17] and in asymmetric aza-pinacol cyclization.[18]

Hantzsch dihydropyridine synthesis is a multi-component organic reaction of an aldehyde with α,β-keto ester and nitrogen surrogate such as ammonium acetate[19] (Scheme 2).



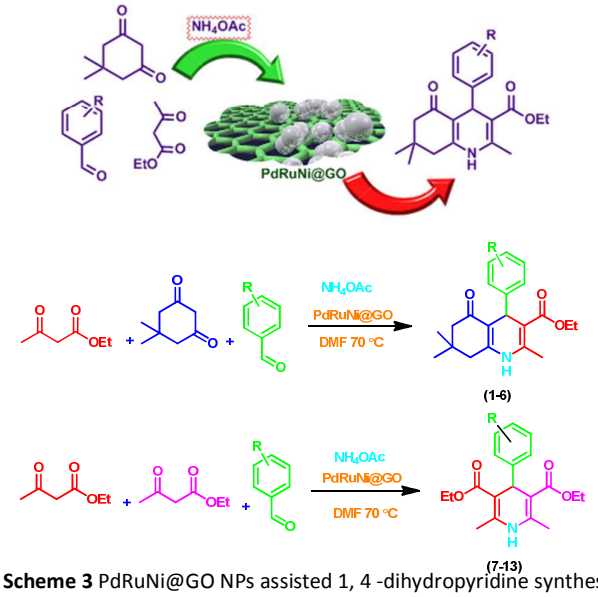
Scheme 2 Synthesis of 1, 4-dihydropyridines

In recent years, various catalysts are well established for Hantzsch dihydropyridine formations in literature such as chitosan nanoparticles,[20] $Yb(OTf)_3$[21], $Sc(OTf)_3$,[22] ceric ammonium nitrate (CAN),[23] bismuth nitrate,[24] La_2O_3,[25] Zn-VCO_3 hydrotalcite,[26] sodium perchlorate,[27] triton X-100,[28] samarium chloride,[29] $Zr(H_2PO_4)_2$,[30] ASA(alumina sulfuric acid)[31] and PtNPs@GO.[32] Presently, heterogenous catalysts are particularly attractive features because of using minimum catalytic amount, reusability, recoverability and tolerable metal leaching to the solution.[33]

[a] Scientific and Technological Research Laboratory, Duzce University, Konuralp Campus, 81620 Konuralp, Duzce, Turkey
[b] Sen Research Group, Biochemistry Department, Faculty of Arts and Science, Dumlupınar University, Evliya Çelebi Campus, 43100 Kütahya, Turkey. E-mail: fatih.sen@dpu.edu.tr
[c] Chemistry Deparment, Faculty of Arts and Sciences, Sakarya University, Esentepe Campus, 54187, Serdivan, Sakarya, Turkey
[d] Department of Chemistry, Faculty of Sciences, Duzce University, 81620 Duzce, Turkey. E-mail: benankilbas@duzce.edu.tr.
† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x
‡These authors contributed equally to this work.

View Article Online
DOI: 10.1039/C6RA13142E

Herein, a novel monodispersed heterogeneous catalyst PdRuNi@GO NPs was used for dihydropyridine formation. The reaction was carried out at mild condition and product yields are quite high (Scheme 3).



Scheme 3 PdRuNi@GO NPs assisted 1, 4 -dihydropyridine synthesis

Results and discussion

Graphene oxide (GO) (Fig. S1-S4) and monodisperse PdRuNi@GO NPs have been characterized by using XRD, TEM, HRTEM and XPS techniques. For example, Fig. 1 shows the XRD pattern of PdRuNi@GO NPs which show similar diffraction pattern as that of Pd@GO but with a slight shift to higher 2Θ values due to formation of alloy. The diffraction pattern at around 2Θ = 40.20, 46.72, 68.36 can be related to (111), (200) and (220) planes of Pd (JCPDS card numbers 87-0637 of Pd). The diffraction peak at around 2Θ= 25.5^0 corresponds to the characteristic hexagonal structure of the graphene oxide. The inset in Fig. 1 represents the extended (111) and (200) peaks showing a slight shift in peak position and there is no evidence any peaks relating to the metal oxides. The average crystallite size of PdRuNi@GO NPs was calculated from the related XRD patterns by the help of Scherrer equation and it was found to be 3.64 nm as crystalline particle size.[34-41]

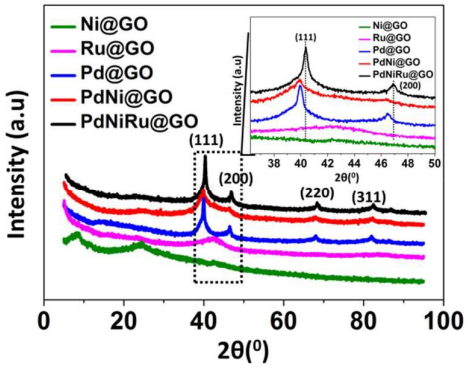


Figure 1. XRD pattern of PdRuNi@GO NPs

Particle size distribution and bulk structure were portrayed by TEM and HR-TEM which are appeared in Fig. 2. TEM picture of PdRuNi@GO (Fig. 2a) demonstrates that fine particles are homogeneously distributed on graphene oxide support. Moreover, HR-TEM picture for monodisperse PdRuNi@GO have additionally been used to analyse the atomic lattice fringes in Fig. 2b. As an effect of these edges, Pd (111) plane were seen with separating of 0.22 nm on the prepared catalyst, which is exactly same with nominal Pd (111) dividing of 0.22 nm, respectively.[42] A particle size histogram was performed for a distribution test of 100 particles and the it was shown that the distribution is Gaussian and the most plausible size of the particles was around 3.72 ± 0.41 nm (Fig. 2c). Particle size got from TEM results coordinate well with XRD results. As induced from ICP-OES, the atomic composition of PdRuNi@GO in aqua regia solution are 70 : 20 : 10, individually which coordinated well with those by EDX investigation.

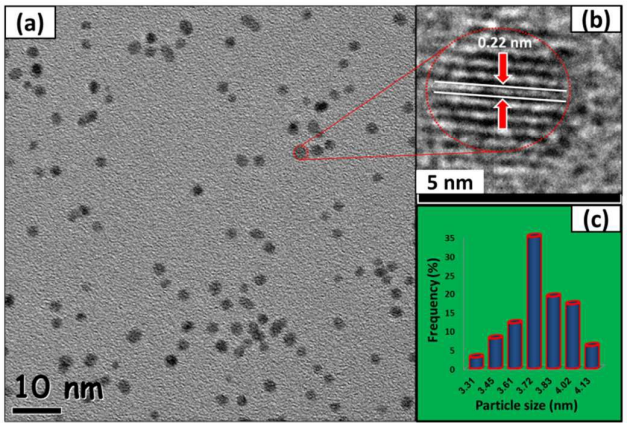


Figure 2. (a) TEM, (b) HR-TEM image and (c) particle size histogram of PdRuNi@GO NPs

XPS investigations have been performed in order to analyse the electronic structure and surface organization of PdRuNi@GO. Fig. 3a-c demonstrates the Pd (3d), Ru (3p) and Ni (2p) XPS spectra of PdRuNi@GO NPs. The Pd 3d region consists of two spin–orbit part peaks of Pd $3d_{5/2}$ and Pd $3d_{3/2}$ states[43]. Every peak was deconvoluted with various Pd oxidation conditions of metallic Pd (0) and PdO (+2) (Fig. 3a). The ratios of the metallic state and oxidized Pd species were ascertained on the premise of the coordination of their individual parts. It was found that the ratio of metallic Pd species to the oxidized Pd species have been found to be 2.1. Furthermore, as shown in Fig. 3b, Ru(3p) XPS range of PdRuNi@GO NPs have been investigated rather than Ru(3d) owing to the overlapping peaks between C (1s) and Ru (3d). For the situation of the Ru 3p state, two recognizable peaks of various intensities at 463.1 and 483.2 eV are likely ascribed to Ru-C and $RuO_2{\cdot}xH_2O$, respectively. [44-48] Another two recognizable peaks of Ni(2p) spectra ($2p_{1/2}$, $2p_{3/2}$) are situated at binding energies of 855.3 and 873.3 eV, individually, which are directly related to Ni(0) and Ni(II) as appeared in Fig. 3c. The noises in the Ni 2p spectra are relatively high due to the low nickel contents in the catalyst, they are not obstructing the effective information.

View Article Online
DOI: 10.1039/C6RA13142E

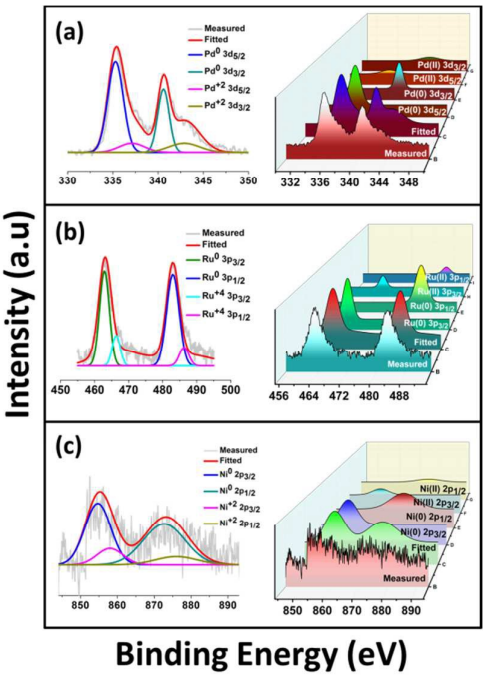


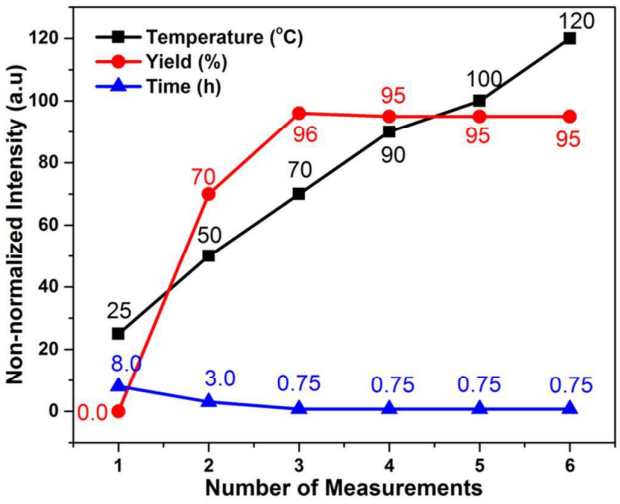
Figure 3 (**a**)Pd 3d, (**b**)Ru 3p, (**c**) Ni 2p XPS spectra of PdRuNi@GO nanoparticles.

Table 1 Comparisons of catalytic efficiency for 1, 4-dihydropyridine formation

Catalyst	Reaction Condition	Time	Yield
None[19]	Amonnium acetate (2 mmol), ethylaceto acetate (2 mmol),benzaldehyde (1 mmol), EtOH (5 ml), 70 °C	5h	50
ASA[30]	Amonnium acetate (4.5 mmol), ethylaceto acetate (6 mmol), benzaldehyde (3 mmol), catalyst (0.6 mmol), water (2 ml), 70 °C	5 h	87
$NaOCl_3$[27]	Amonnium acetate (1.5 mmol), ethylaceto acetate (2 mmol), benzaldehyde (10 mmol), catalyst (%10 mmol), AcCN (10 ml), 70°C	3 h	89
$Yb(OTf)_3$[21]	Amonnium acetate (2 mmol), dimedone (2 mmol), ethylacetoacetate (2 mmol), benzaldehyde (2 mmol), catalyst (%5 mmol), EtOH (5 ml), RT	5 h	90
$Sc(OTf)_3$[22]	Amonnium acetate (1 mmol),dimedone (1 mmol), ethylacetoacetate (1 mmol), benzaldehyde (1 mmol), catalyst (%5 mmol), EtOH (5 ml), RT	4 h	93
$SmCl_3$[29]	Amonnium acetate (2.2 mmol), ethyl acetoacetate (4.4 mmol), benzaldehyde (2 mmol), catalyst (0.2 mmol), AcCN (10 ml), 70 °C	3 h	85
PdNiRu@GO	**Amonnium acetate (2 mmol), ethylaceto acetate (1 mmol), dimedone (1 mmol), benzaldehyde (1 mmol), catalyst (6 mg), DMF (2 ml), 70 °C**	**45 min**	**88**
	Amonnium acetate (2 mmol), ethyl aceto acetate (2 mmol), benzaldehyde (1 mmol), catalyst (6 mg), DMF (2 mL), 70 °C	**45 min**	**93**

Adsorption-desorption N_2 experiments have been carried out and BET method has been used for the calculation of the specific surface area which was found at 136.2 m^2/g. The comparison of 1,4-dihydropyridine formation was examined with previous published works. PdRuNi@GO assisted 1,4-dihydropyridine formation was accomplished with high yields. In addition, the reaction was performed in a short time respect to the previous works as seen Table 1. Morover, PdRuNi@GO was a monodispersed heterogenous catalyst, therefore it can be successfully reused more than five times with the same strong effect.

Table 2 The effect of temperature for 1,4-dihydropyridine formation

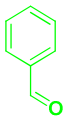
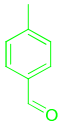
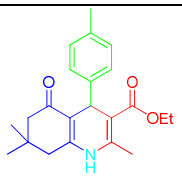
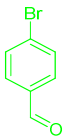
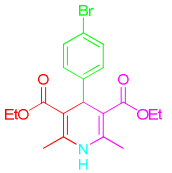
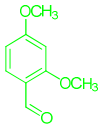
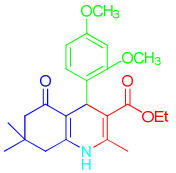
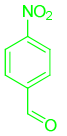
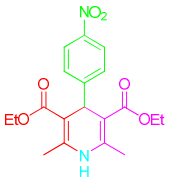
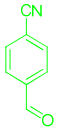
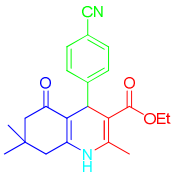
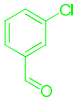
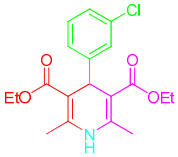
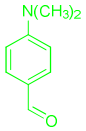
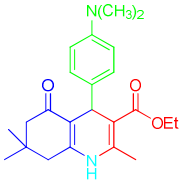
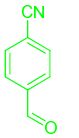
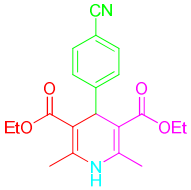
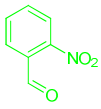
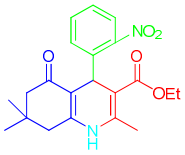
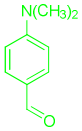
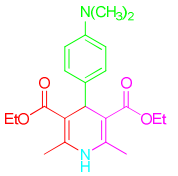
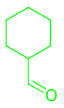
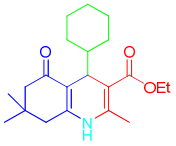
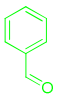
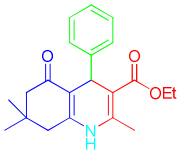
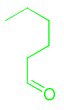
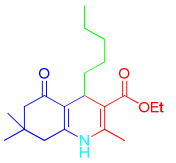
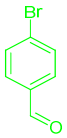
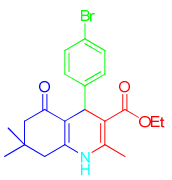
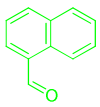
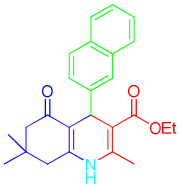


Reaction Conditions: *Amonnium acetate (2 mmol), ethylacetoacetate (1 mmol), dimedone (1 mmol), 4-nitrobenzaldehyde (1 mmol) and 6 mg PdRuNi@GO catalyst (%9.3 wt metal content) were added in 2 ml DMF.*

In the present work, optimization process was dealed with adjustment amount of catalyst, type of solvent system and ambient temperature. DMF was chosen as solvent because facilitates reactions that follow polar mechanisms such as nucleophilic reactions. The present synthesis is a nucleophilic reaction to the aldehyde carbonyl carbon. DMF's boiling point 152 to 154 °C[49]. Next, the effect of temperature was studied. While the reaction was kept 1 day at room temperature, the reaction was not completed. Even elevated temperature up to 50 °C was applied, starting material was still observed (%70 conversion). 1,4-Dihydropyridine derivative was succesfully obtained around 90% yield when the reaction was carried out at 70 °C with only 45 min using PdNiRu@GO catalyst (Table 2) .

View Article Online
DOI: 10.1039/C6RA13142E

Table 3 The result of Hantzsch dihydropyridine synthesis using PdNiRu@GO catalyst[a]

Entry	Substrate	Product	TON/TOF(h^{-1})	Yield[b] *(%)*	Entry	Substrate	Product	TON/TOF(h^{-1})	Yield[b] *(%)*
1			153.1/204.1	88	10			160.1/213.4	92
2			149.6/199.5	86	11			163.5/218.1	94
3			160.1/213.4	92	12			165.3/220.4	95
4			158.3/211.1	91	13			161.8/215.7	93
5			158.3/211.1	91	14			156.6/208.8	90
6			156.6/208.8	90	15			153.1/204.1	88
7			161.8/215.7	93	16			154.8/206.4	89
8			160.1/213.4	92	17			161.8/215.7	93

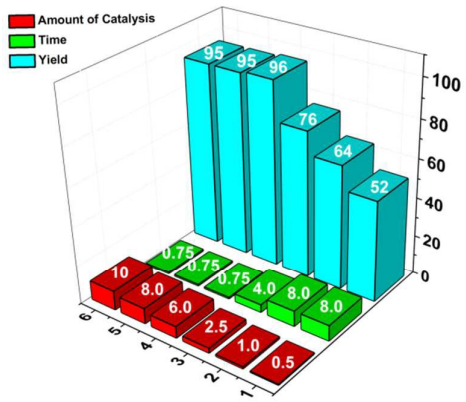
View Article Online
DOI: 10.1039/C6RA13142E

9	167.0/222.7	96	**18**	158.3/211.1	91

[a]Reaction Conditions: Amonnium acetate (2 mmol), ethylacetoacetate (2 mmol) or ethylacetoacetate (1 mmol)-dimedone (1mmol) , aldehyde (1 mmol) and 6 mg PdRuNi@GO NPs (*%9.3 wt metal content*) were added in 2 ml DMF for 45 minutes at 70 °C. [b] Isolated yield determined by ^{1}H NMR. All characterizations are given in Supporting Info.

As a result, the reaction condition was well established by using 6 mg of corresponding catalyst, 2 ml of DMF for 45 minutes at 70 °C (Table 3).

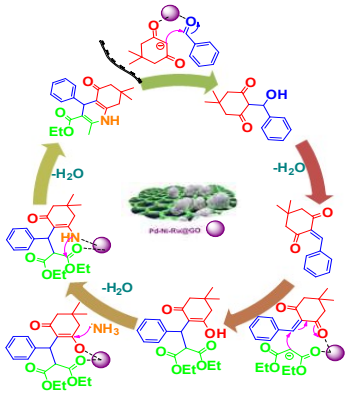
Table 4 The efficiency of catalytic amount over 1, 4-dihydropyridine formation



Reaction Conditions: *Amonnium acetate (2 mmol), ethylacetoacetate (1mmol), dimedone (1 mmol), 4-nitrobenzaldehyde (1 mmol) and 6 mg PdRuNi@GO catalyst were added in 2 ml DMF for 45 minutes at 70 °C.*

The reaction performance was also monitored by different amount of PdRuNi@GO catalyst. 6 mg of catalyst is sufficient when 1 mmol of reactants were used as seen in Table 4.

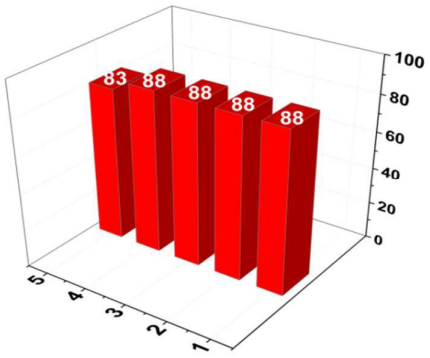
According to the plausible mechanism, PdRuNi@GO NPs provide more positive carbonyl group of dimedone as illustrated in scheme 4. For this reason, elimination of methylenic proton adjacent to the carbonyl groups becomes easier which affords easy and fast nucleophilic addition to the aldehyde carbonyl carbon.



Scheme 4 Suggested mechanistic pathway of 1,4-dihydropyridine synthesis

Reuse of the heterogeneous catalyst was tested as shown in Table 5. After completion of the reaction, PdRuNi@GO was easily separated from reaction medium by using centrifuge, washed with methanol, water and dried under vacuum and reused again. As a consequence, PdRuNi@GO catalyst was able to be reused more than five times without any decrease about catalytic function. Palladium, ruthenium and nickel content was approximately 0.6 ppm in solution after 5 times uses occured by ICP-OES analyses. Furthermore, SEM and EDX image of PdRuNi@GO have been analyzed before and after the 5th usage as shown in Fig. S5 and S6 and it was observed that there is not much change in the metal content of PdRuNi@GO as shown in EDX spectra..

Table 5 Reusability Analysis of PdRuNi@GO NPs



View Article Online
DOI: 10.1039/C6RA13142E

Reaction Conditions: *Amonium acetate (2 mmol), ethylacetoacetate (2 m mol), benzaldehyde (1mmol) and 6 mg PdRuNi@GO catalyst in 2 ml DMF for 45 minutes at 70 °C.*

Conclusions

In conclusion, traditional 1,4-dihydropyridine synthetic methods have several disadvantages such as long reaction time, tedious work-up procedure, low yield, and hard refluxing conditions. However, a novel monodisperse PdRuNi@GO NPs provided one of the highest yield and the shortest time as novel, stable, long-lived, efficient and exceptional reusable heterogeneous catalyst for 1,4-dihydropyridine synthesis via multicomponent condensation reactions of various aldehydes with dimedone, ammonium acetate and ethyl acetoacetate at 70°C in DMF with efficient catalytic performance. The current catalytic process was described as an easy, effective, practical and exceptional reusable synthetic method for Hantzsch synthesis. This nano sized heterogeneous catalyst showed excellent catalytic activity for model reaction in mild condition most likely due to high monodispersity, low crystalline particle size and high % metal (0) contents of the prepared PdRuNi@GO NPs. Since the given methodology is efficient and practical, this method would be a rather attractive synthetic method in near future.

Experimental

The preparation of monodisperse Pd-Ni-Ru@GO NPs

Monodisperse PdRuNi@GO NPs have been prepared by using sonochemical double solvent reduction method. Summarizing this process, superhydride and ethanol were used to reduce the mixture of 0.25 mmol of precursor of Pd, Ni and Ru lysed in small amount of dehydrated tetrahydrofuran and 0.25 mmol of octanethiol (OT) ligand in an ultrasonic conditions. The brown-black color solution indicates the formation of PdRuNi NPs.[39-41] Finally, in the room temperature, the solid Pd-Ni-Ru NPs were dried under vacuum. The prepared PdNiRu NPs were mixed in a 1:1 (moles) ratio with GO by using tip sonicator in order to get PdRuNi@GO NPs. The ultrasonication method was employed to increase PdRuNi@GO NPs dispersion on GO. The data show that the route is very effective for uniform distribution of PdRuNi@GO NPs on GO and for agglomeration problem of NPs.

General procedure of 1,4-dihydropyridine synthesis

Amonnium acetate (2 mmol), ethylacetoacetate (2 mmol), aldehyde (1 mmol) and 6 mg PdRuNi@GO catalyst were added in 2 ml DMF. The reaction was kept 45 min at 70 °C. After completion of the reaction, catalyst was removed by centrifugation (6000 rpm) and PdRuNi@GO catalyst was washed with methanol, water and dried. DMF solution was poured into 20 ml of ice-cold water. The resulting precipitate was filtered off and solid was allowed to dry.

Diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (1)[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (6H, t, J = 7.05 Hz, $-CH_3$), 2.31 (6H, s, $-CH_3$), 4.09 (4H, q, J = 6.80 Hz, $-OCH_2$), 4.99 (1H, s, –CH), 5.81 (NH, s), 7.14-7.25 (5H, m, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.52, 19.81, 39.84, 60.02, 104.12, 126.31, 128.06, 128.21, 144.45, 148.02, 168.09.

Diethyl 4-(4-bromophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (2)[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.22 (6H, t, J = 7.10 Hz, $-CH_3$), 2.33 (6H, s, $-CH_3$), 4.06 (4H, q, J = 6.70 Hz, $-OCH_2$), 4.95 (1H, s, –CH), 5.61 (NH, s), 7.16 (2H, d, J = 8.80 Hz, Ar-H), 7.26 (2H, d, J= 8.80 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 19.9, 39.5, 60.0, 104.0, 120.11, 130.0, 131.11, 144.1, 147.0, 167.6.

Diethyl 2,6-dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (3)[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (6H, t, J = 7.20 Hz, $-CH_3$), 2.37 (6H, s, $-CH_3$), 4.21 (4H, q, J = 6.70 Hz, $-OCH_2$), 5.31 (1H, s, –CH), 6.05 (NH, s), 7.43 (2H, d, J = 9.01 Hz, Ar-H), 8.09 (2H, d, J = 9.01 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.81, 30.77, 39.83, 113.48, 124.04, 128.72, 144.17, 146.88, 153.32, 197.27.

Diethyl 4-(3-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (6H, t, J = 7.20 Hz, $-CH_3$), 2.25 (6H, s, $-CH_3$), 4.07 (4H, q, J = 6.75 Hz, $-OCH_2$), 5.06 (1H, s, –CH), 5.80 (1H, NH), 7.08 (1H, t, –CH), 7.11(2H, d, J = 9.01 Hz, Ar–H), 8.10 (1H, s, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.41, 19.87, 40.12, 60.21, 103.65, 121.53, 123.38, 128.81, 134.73, 144.81, 148.32, 150.11, 167.37.

Diethyl 4-(4-cyanophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5): ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 1.17 (6H, t, J = 7.2 Hz, $-CH_3$), 2.39 (6H, s, $-CH_3$), 4,05 (4H, q, J = 6.70 Hz, $-OCH_2$), 5.06 (H, s, –CH), 5,92 (NH, s), 7.43 (2H, d, J = 7.80 Hz, Ar-H), 7.52 (2H, d, J = 7.71 Hz, Ar-H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 14.12, 50.87, 115.42, 109.71, 111.49, 119.52, 129.17, 132.13, 144.29, 148. 64, 152.62, 167.14.

Diethyl 4-(4-(dimethylamino)phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6)[49]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.26 (6H, t, J = 7.21 Hz, $-CH_3$), 2.32 (6H, s, $-CH_3$), 2.90 (6H, s, $-CH_3$), 4.15 (4H, q, J = 6.70 Hz, $-OCH_2$), 4.81(1H, s, –CH), 5.51 (NH, s), 6.70 (2H, d, J = 8.60 Hz, Ar-H), 7.10 (2H, d, J = 8.60 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.23, 21.36, 40.32, 43.21, 62.78, 103. 62, 114.25, 129. 82, 135.26, 146. 73, 150.76, 168. 22.

Ethyl 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7)[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (3H, s,–CH_3), 1.04 (3H, s,–CH_3), 1.21 (3H, t, J = 7.20 Hz, $-CH_3$), 2.10 – 2.26 (4H, m, $-CH_2$), 2.30 (3H, s,–CH_3), 4.06 (2H, q, J = 7.20 Hz, $-OCH_2$), 4.66 (1H,s,–CH) 5.05 (NH, s), 7.11-7.31 (5H, m, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.42, 19.55, 27.33, 29.77, 32.93, 36.88, 41.02, 51.04, 60.03, 106.17, 112.13, 126.22, 128.18, 128.23, 144.08, 147.33, 149.26, 167.73, 196.09.

Ethyl 4-(4-bromophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (8)[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ0.91 (3H, s, $-CH_3$), 1.06 (3H, s, $-CH_3$), 1.19 (3H, t, J = 7.10 Hz, $-CH_3$), 2.14 – 2.32 (4H, m, $-CH_2$), 2.35 (3H, s, $-CH_3$), 4.05(2H, q, J = 7.10 Hz, $-OCH_2$), 5.00 (1H, s, –CH), 6.58 (NH, s), 7.19 (2H, d, J = 7.60 Hz, Ar-H), 7.30 (2H, d, J = 7.70 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.44, 19.63, 27.35, 29.74, 32.98, 36.54, 41.18, 50.98, 60.14, 105.89, 111.84, 120.09, 130.04, 131.10, 144.14, 146.46, 149.06, 167.54, 195.98.

Ethyl 2,7,7-trimethyl-4-(4-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (9): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (3H, s, $-CH_3$), 1.08 (3H, s, $-CH_3$), 1.82 (3H, t, J = 7.10 Hz, $-CH_3$), 2.16 – 2.36 (4H, m, $-CH_2$), 2.40 (3H, s, $-CH_3$), 4.04 (2H, q, J = 7.80 Hz, $-OCH_2$), 5.15 (1H, s, –CH), 6.31 (NH, s), 7.50 (2H, d, J = 7.80 Hz, Ar-H), 8.09 (2H, d, J = 7.8 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.33,

View Article Online
DOI: 10.1039/C6RA13142E

18.97, 27.03, 29.57, 32.54, 37.29, 50.74, 59.79, 103.47, 110.27, 123.14, 129.03, 145.99, 146.04, 150.294, 155.23, 167.14, 195.47.

Ethyl 2,7,7-trimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (10)[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.94 (3H, s, –CH_3), 1.06 (3H, s, –CH_3), 1.22 (3H, t, J = 6.40 Hz, –CH_3), 2.11 – 2.21 (4H, m,–CH_2), 2.25 (3H, s,–CH_3), 2.33 (3H, s,–CH_3), 4.07 (2H, q, J = 6.40 Hz, –OCH_2), 5.00 (1H, s,–CH), 6.49 (NH, s), 7.00 (2H, d, J = 7.60 Hz, Ar-H), 7.19 (2H, d, J = 8.0 Hz Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.51, 19.52, 21.36, 27.43, 29.79, 32.93, 36.39, 41.14, 51.09, 60.04, 106.36, 112.39, 128.13, 128.80, 135.63, 143.82, 144.51, 148.94, 167.87, 195.92.

Ethyl 4-(2,4-dimethoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (11)[31]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.91 (3H, s, –CH_3), 1.03 (3H, s, –CH_3), 1.20 (3H, t, J = 7.20 Hz, –CH_3), 2.06 – 2.22 (4H, m, –CH_2), 2.27 (3H, s, –CH_3), 3.73 (3H, s, –OCH_3), 3.76 (3H, s, –OCH_3), 3.99 – 4.06 (2H, q, J = 7.20 Hz, –OCH_2), 5.16 (1H, s, –CH), 6.35 (2H, d, J = 7.20 Hz, Ar-H), 6.52 (NH, s, Ar-H), 7.19 (1H, s, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.43, 19.41, 26.92, 29.86, 32.72, 33.26, 41.13, 51.03, 55.47, 55.52, 59.86, 98.53, 104.25, 105.24, 110.93, 127.72, 131.81, 143.43, 149.35, 158.62, 159.27, 168.32, 195.87.

Ethyl 4-(4-cyanophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (12): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (3H, s, –CH_3), 1.08 (3H, s, –CH_3), 1.17 (3H, t, J = 7.20 Hz, –CH_3), 2.18 (2H, s, –CH_2), 2.23 (2H, s, –CH_2), 2.39 (3H, s, –CH_3), 4.05 (2H, q, J = 7.20 Hz, –OCH_2), 5.09 (H, s, –CH), 6.22 (NH, s) , 7.42 (2H, d, J = 7.80 Hz, Ar–H), 7.51 (2H, d, J = 7.8 Hz, Ar–H), ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.11, 19.72, 27.37, 29.52, 32.94, 37.42, 41.25, 50.72, 100.29, 115.14, 109.86, 111.42, 119.55, 129.12, 132.11, 144.21, 148.63, 152.52, 167.01, 195.92.

Ethyl 4-(4-(dimethylamino)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate(13)[22]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.98 (3H, s, –CH_3), 1.09 (3H, s, –CH_3), 1.24 (3H, t, J = 7.20 Hz, –CH_3), 2.29–2.36 (4H, m, –CH_2), 2.88 (6H, s, –NCH_3), 4.09 (2H, q, J = 7.20 Hz, –OCH_2), 4.96 (1H, s, –CH), 5.88 (NH, s), 6.62 (2H, d, J = 7.60 Hz, Ar–H), 7.16 (2H, d, J = 7.60 Hz, Ar–H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.62, 20.11, 27.95, 33.21, 41.36, 41.62, 42.81, 52.42, 63.25, 110.91, 11.35, 129.21, 135.68, 147.83, 148.25, 150.92, 168.18, 192.02.

Ethyl 2,7,7-trimethyl-4-(2-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (14)[50]: ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.88 (3H, s, –CH_3), 0.96 (3H, t, j = 7.20 Hz, –CH_3), 1.01 (3H, s, –CH_3), 2.14-2.20 (4H, m, –CH_2), 2.31 (3H, s, –CH_3), 3.99 (2H, m, –OCH_2), 5.64 (1H, s, CH), 6.66 (NH, s), 7.66-7.32 (4H, m, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.14, 167.90, 151.98, 147.91, 146.25, 140.94, 133.53, 130.99, 127.56, 124.90, 111.01, 105.69, 58.95, 51.05, 32.89, 32.63, 29.99, 26.12, 19.25, 14.83.

Ethyl 4-cyclohexyl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (15): ^{1}HNMR ($CDCl_3$, 300 MHz): δ 0.80 (2H, m, -CH_2), 1.08 (3H, s, –CH_3), 1.10 (3H, s, –CH_3), 1.10-1.12(4H, m, -CH_2), 1.18 (3H, t, J = 7.10 Hz, -CH_3), 1.61-1.42 (5H, m), 2.19 (3H, s, -CH_3), 2.15-2.55 (4H, m, CH_2), 3.90 (1H, d, J = 4.60 Hz, -CH), 4.10 (2H, m, -OCH_2), 5.88 (NH, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.42, 170.83, 151.78, 145.96, 109.23, 100.99, 60.25, 51.17, 47.99, 32.57, 30.09, 29.25, 27.78, 25.99, 25.72, 19.57, 14.58.

Ethyl 2,7,7-trimethyl-5-oxo-4-pentyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (16)[53]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (3H, t, J = 6.60 Hz, –CH_3), 0.99 (3H, s, –CH_3), 1.04 (3H, s, –CH_3), 1.19-1.15 (11H, m, -CH/-CH_2), 2.32 (3H, s, –CH_3), 2.54 (4H, m, –OCH_2), 6.88(NH, s). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.20, 168.00, 151.02, 148.30, 108.36, 103.22, 59.99 51.23, 36.55, 31.04, 30.03, 29.18, 29.16, 26.38, 23.56, 22.15, 18.99, 13.88, 13.65.

Ethyl 2,7,7-trimethyl-4-(naphthalen-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (17)[51]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.88 (3H, s, –CH_3), 0.92 (3H, t, J = 7.10 Hz, –CH_3), 0.99 (3H, s, –CH_3), 2.14(4H, m, -CH_2), 2.31 (3H, s, –CH_3), 4.06 (2H, m, -OCH_2), 5.02 (1H, s, CH), 6.86 (NH, s), 7.90-7.22(6H, m, Ar-H), 8.68 (1H, m, Ar-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 195.38, 167.56, 150.05, 148.21, 143.99, 134.12, 130.93, 127.61, 126.56, 126.47, 126.26, 126.11, 125.58, 125.32, 112.09, 106.99, 60.24, 50.87, 32.85, 31.12, 28.25, 27.08, 18.97, 14.53.

Ethyl 4-(furan-2-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (18)[52]: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.92 (3H, s,–CH_3), 0.99 (3H, s,–CH_3), 1.11 (3H, t, J = 6.90 Hz), 2.18-2.10 (2H, m, –CH_2), 2.24 (3H, s, –CH_3), 2.40-2.28 (2H, m, –CH_2), 4.08 (2H, t, J = 6.40 Hz, –OCH_2), 5.00 (1H, s), 5.77 (NH, s), 5.90 (1H, s), 6.20 (1H, s, Ar-H), 7.28 (1H, s, Ar-H), 9.13 (1H, s, Ar-H). ^{13}CNMR ($CDCl_3$, 75 MHz): δ 192.61, 168.32, 159.24, 151.25, 146.87, 140.99, 110.46, 107.57, 103.99, 101.86, 61.64, 51.73, 30.99, 30.86, 29.24, 26.23, 19.86, 16.72.

Acknowledgements

This research was supported by Dumlupinar (2014-05, 2015-35 and 2015-50) and Duzce University Research Fund (Grant no. 2016.05.03.410). The partial supports by Science Academy and FABED are gratefully acknowledged.

Notes and references

1 N. Nakamichi, Y. Kawashita and M. Hayashi, *Synthesis (Stuttg).,* 2004, 1015-1020.
2 N. Nakamichi, Y. Kawashita and M. Hayashi *Org. Lett.,* 2002, **4**, 3955-3957.
3 I. Sabakhi, V. Topuzyan, Z. Hajimahdi, B. Daraie, H. Arefi and A. Zarghi, *Iranian J. Pharm. Res.* 2015, **14**, 1087-1093.
4 G. Swarnalatha and G. Prasanthi, *Int. J.* , 2011, **3**, 75–89.
5 R. Miri, K. Javidnia, H. Sarkarzadeh and B. Hemmateenejad, *Bioorg. Med. Chem.*, 2006, **14**, 4842–4849.
6 R. Budriesi, A. Bisi, P. Ioan, A. Rampa, S. Gobbi, F. Belluti, L. Piazzi, P. Valenti and A. Chiarini, *Bioorganic Med. Chem*., 2005, **13**, 3423–3430.
7 H. Niaz, H. Kashtoh, J. a. J. Khan, A. Khan, A.- Wahab, M. T. Alam, K. M. Khan, S. Perveen and M. I. Choudhary, *Eur. J. Med. Chem.*, 2015, **95**, 199–209.
8 J. S. R. Surendra Kumar, A. Idhayadhulla and A. Jamal Abdul Nasser, J. Serb. *Chem. Soc*, 2011, 1–11.
9 C. Şafak, M. G. Gündüz, S. Ö. İlhan, R. Şimşek, F. İşli, Ş. Yıldırım, G. S. Ö. Fincan, Y. Sarıoğlu and A. Linden, *Drug Dev. Res.*, 2012, **73**, 332–342.
10 R. Simsek, Y. Altas, C. Safak, U. Abbasoglu and B. Ozçelik, *Farmaco*, 1995, **50**, 893–894.
11 P. A. Datar and P. B. Auti, *J. C. Methods and M. Des*, 2012, **2**, 85–91.
12 R. Bansal, G. Narang, C. Calle, R. Carron, K. Pemberton and A. L. Harvey, *Drug Dev. Res.*, 2013, **74**, 50–61.

View Article Online
DOI: 10.1039/C6RA13142E

13 F. Bossert, H. Meyer and E. Wehinger *Angew. Chem. Int. Ed.*, 1981, **20**, 762– 769.

14 a) X.-F. Zhou, P.-F. Wang, Y. Geng and H.-J. Xu, *Tetrahedron Lett.*, 2013, **54**, 5374–5377. b) Z. Zhang, J. Gao, J.-J. Xia and G.-W. Wang, *Org. Biomol. Chem.*, 2005, **3**, 1617-1619.

15 L. A. Chen, W. Xu, B. Huang, J. Ma, L. Wang, J. Xi, K. Harms, L. Gong and E. Meggers, *J. Am. Chem. Soc.*, 2013, **135**, 10598–10601.

16 G. Li and J. C. Antilla, *Org. Lett.*, 2009, **11**, 1075–1078.

17 Y. Yamamoto, S. Mori and M. Shibuya, *Chem. Eur. J.*, 2013, **19**, 12034–12041.

18 L. J. Rono, H. G. Yayla, D. Y. Wang, M. F. Armstrong and R. R. Knowles, *J. Am. Chem. Soc.*, 2013, **135**, 17735–17738.

19 a) A. Hantzsch*, Justus Liebigs Ann. Chem.*, 1882, 215
b) G. Giorgi, M. F. A. Adamo, F. Ponticelli and A. Ventura, *Org. Biomol. Chem*., 2010, **8**, 5339.

20 J. Safari, F. Azizi and M. Sadeghi, *New J. Chem.*, 2015, **39**, 1905–1909.

21 L. M. Wang, J. Sheng, L. Zhang, J. W. Han, Z. Y. Fan, H. Tian and C. T. Qian, *Tetrahedron*, 2005, **61**, 1539–1543.

22 J. L. Donelson, R. a. Gibbs and S. K. De, *J. Mol. Catal. A Chem.*, 2006, **256**, 309–311.

23 S. Ko and C. F. Yao, *Tetrahedron*, 2006, **62**, 7293–7299.

24 D. Bandyopadhyay, S. Maldonado, B. K. Banik, *Molecules,* **2012**, *17*, 2643-2662.

25 B. P. Gangwar, V. Palakollu, A. Singh, S. Kanvah and S. Sharma, *RSC Adv.*, 2014, **4**, 55407–55416..

26 R. Pagadala, S. Maddila, V. D. B. C. Dasireddy and S. B. Jonnalagadda*, Catal. Commun.*, 2014, **45**, 148–152.

27 S. S. Makone and D. B. Vyawahare, *Int. J. ChemTech Res.*, 2013, **5**, 1550–1554.

28 P. P. Ghosh, P. Mukherjee and A. R. Das, *RSC Adv.*, 2013, **3**, 8220

29 Y. P. Sarnikar, Y. D. Mane, S. M. Survarse and B. C. Khade, *Der Pharma Chemica,* 2015, **7**, 1–4.

30 Ş. Beşoluk, M. Kucukislamoglu, M. Zengin, M. Arslan and M. Nebioğlu, *Turkish J. Chem.*, 2010, **34**, 411–416.

31 M. Arslan, C. Faydali, M. Zengin, M. Küçükislamoğlu and H. Demirhan, *Turkish J. Chem.*, 2009, **33**, 769–774.

32 H. Pamuk, B. Aday, F. Şen and M. Kaya, *RSC Adv.*, 2015, **5**, 49295–49300.

33 a) H. Goksu, *New. J. Chem*., 2015, **39**, 8498-8504; b) H. Goksu, Y. Yıldız, B. Celik, M. Yazici, B. Kilbas and F. Sen, *Catal. Sci. Technol*., 2016, **6**, 2318-2324. c) L. Wang and Y. Yamauchi, *J. Am. Chem. Soc.,* 2009, **131**, 9152-9153. d) B. Dam, S. Nandi and A. K. Pal, *Tetrahedron Let*t, 2014, **55**, 5236-5240. e) M. Abaszadeh, M. Seifi and A. Asadipour, *Res. Chem. Intermed.*, 2015, **41**, 5229-5238. f) A. Maleki, M. Kamalzare and M. Aghaei, *J. Nanostruct. Chem.*, 2015, **5**, 95-105. g) C. Li , Y. Yamauchi, *PCCP*., 2013, **15(10)**, 3490-3496.h) Y. Li, B.P. Bastakoti, V. Malgras, C. Li, J. Tang, J.H. Kim, Y. Yamauchi, *Angewandte Chemie International Edition*, 2015, *54 (38),* 11073-11077.

34 H. Pamuk, B. Aday, F. Şen and M. Kaya, *RSC Adv.,* 2015, **5**, 49295-49300.

35 E. Erken, H. Pamuk, Ö. Karatepe, G. Başkaya, H. Sert, O. M. Kalfa, F. Sen, *J. Cluster Sci.,* 2016, **27**, 9-23.

36 E. Erken, İ. Esirden, M. Kaya, F. Sen, *RSC Adv.*, **5,** 68558-68564.

37 E. Erken, İ. Esirden, M. Kaya, F. Sen, *Catal. Sci. Technol.*, 2015, **5***,* 4452-4457.

38 F.Sen, Y. Karataş, M.Gülcan, M. Zahmakiran, *RSC Adv.,* 2014, **4**, 1526-1531.

39 B.Aday, Y.Yıldız, R.Ulus, S. Eriş, M. Kaya, F. Sen, *New J. Chem.,* 2016, **40**, 748-754.

40 B.Çelik, S.Kuzu, E.Erken, H.Sert, Y.Koşkun, F.Sen *Int. J. Hydrogen Energy,* 2015, **12**, 138.

41 B. Çelik, E. Erken, S.Eriş, Y. Yıldız, B. Şahin, H. Pamuk, F. Sen, *Catal. Sci. Technol.,* 2016, **6**, 1685-1692.

42 ZY. Li, Z. Liu, JC. Liang, CW. Xu, X. Lu*, J. Mater. Chem. A.*, 2014, **2**, 18236.

43 C. M. Shen, Y. K. Su, H. T. Yang and T. Z Yang, H. J. Gao *Chem Phys Lett.* 2003, **373**, 39-45.

44 Briggs D, Seah MP. Practical surface analysis. In: Auger and X-ray photoelectron spectroscopy. 2nd ed., vol. 1. Chischester: John Wiley & Sons 1990.

45 C.J. Jenks, S.L. Chang, J.W. Anderegg, P.A. Thiel and D.W. Lynch, Phys. Rev. B: *Condens. Matter. Mater. Phys.,* 1996, **54**, 6301–6303

46 C. Wagner, W.M. Riggs, L.E. Davis, J.F. Moulder and G.E. Muilenberg, Handbook of X-ray Photoelectron Spectroscopy, vol. 55, Physical Electronic Division, PerkinElmer, Eden Prairie, MN, 1979.

47 G. Schmid, Clusters and Colloids: From Theory to Applications, VCH Publishers, New York, 1994.

48 J. C. Calderona, G. Garcia, L. Calvillo, J. L. Rodriguez, M. J. Lazaro and E. Pastor, *Appl. Catal. B*, 2015, **165**, 676–686.

49 a) https://en.wikipedia.org/wiki/Dimethylformamide
b) Y. Venkateswarlu, S. R. Kumar and P. Leelavathi, *Int. J. Ind. Chem.*, 2012, **3**, 18-23.

50 A. Rajendran, C. Kartikeyan and K. Rajathi, *Int. J. ChemTech. Res.*, 2011, **3**, 810-816.

51 D. Biswanath, M. Srilatha, B. Veeranjaneyulu and B. S. Kanth, *Helv. Chim. Acta*, 2011, **94**, 885-891.

52 M. M. Heravi, M. Saeedi, N. Karimi, M. Zakeri, Y. S. Beheshtiha and A. Davoovnia, *Synth Commun.* 2010, **40**, 523-529.

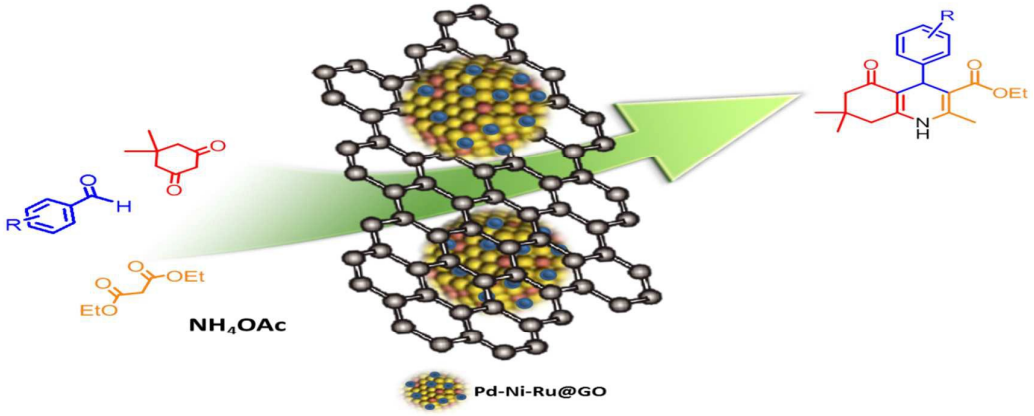
53 K.K. Pasunooti, C. N. Jensen, H. Chai, M. L. leow, Da. W. Zhang and X. W. Liu, *J. Comb. Chem*, 2010, **12**, 577-581.

View Article Online
DOI: 10.1039/C6RA13142E

Table of contents entry

One-Pot Synthesis Of Hantzsch Dihydropyridines Using Highly Efficient and Stable PdNiRu@GO Catalyst

Tuna Demirci[‡a], Betül Çelik[‡b], Yunus Yıldız[b], Sinan Eriş[b], Mustafa Arslan[c], Fatih Sen[*b] and Benan Kilbas[*d]



The method for the synthesis of 1,4 dihydropyridine compounds has been developed in the presence of Pd-Ni-Ru@GO which is simple, effective and productive.