FULL PAPER

WILEY Applied Organometallic Chemistry

Synthesis of Pyrazolo-[4,3:5,6]pyrido[2,3-d]pyrimidinediones Catalyzed by a Nano-sized Surface-Grafted *Neodymium* Complex of the Tungstosilicate *via* Multicomponent Reaction

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Majid M. Heravi, Department of Chemistry, School of Sciences, Alzahra University, Vanak, Tehran, Iran. Email: mmheravi@alzahra.ac.ir; mmh1331@yahoo.com Masoud Mirzaei, Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, Mashhad, Iran. Email: mirzaeesh@um.ac.ir; mirzaei487@yahoo.com

Funding information

Alzahra University, Tehran, Iran., Grant/ Award Number: Alzahra University, Tehran, Iran.; Ferdowsi University of Mashhad, Mashhad, Iran., Grant/Award Number: Ferdowsi University of Mashhad, Mashhad, Iran. An inorganic–organic hybrid based on lanthanide clusters and Keggin type polyoxometalates (POMs) (Na[Nd (pydc-OH)(H₂O)₄]₃][SiW₁₂O₄₀]) was used the first time as trinuclear catalyst for one pot synthesis of pyrazolo[4,3:5,6] pyrido[2,3-*d*]pyrimidine-diones, *via* two different four and five-component reactions involving hydrazine hydrate, ethyl acetoacetate, aryl aldehydes, and 6-amino-1,3-dimethyl uracil or barbituric acid with ammonium acetate as alternative materials in green condition. To evaluate potential application of the as-made hybrid in adsorption and separation processes, nitrogen adsorption was performed at 77 K through simulation study. The hybrid catalyst was further characterized *via* powder X-ray diffraction (PXRD) at room temperature which indicated the good phase purity of the catalyst. The results show that the catalytic activity of the hybrid catalyst has increased relative to each parent component due to the special interaction between Keggin anions and pydc-OH ligands.

KEYWORDS

anticancer agents, Heteropoly acid, inorganic–organic hybrids, Polyoxometalates, Pyrazolo-[4,3:5,6] pyrido[2,3-*d*]pyrimidine-diones

1 | INTRODUCTION

The World Health Organization (WHO) has recently reported the rate of cancer will rise globally by about 75% up to 2030. The number may be duplicated in some of the regressive societies an developing countries.^[1] Cancer is as a result of the uncontrolled growth of cells, tissue damage, invasion and metastases. The advances in drug discovery related to the cancer therapy is actually associated with the severe side effects, resistance to the conventional medicines, as well as an inadequate chemical space, leading to high demand for design and discovery of new chemotherapeutic medicines.^[2,3] So far, many

efforts have been made for the discovery of new scaffolds, especially heterocyclic systems through both industrial and academic projects. Among the heterocyclic compounds, the fused pyrimidines have become as promising targets due to their pharmacological significance.

In the midst of polyfunctionalized heterocycles, pyridopyrimidines are the most favored structures for developing drug discovery due to providing a wide range of pharmacological activities, such as anti-cancer,^[4] antimicrobial,^[5] anti-HIV,^[6] anti-inflammatory,^[7] antimalarial^[8] and anti-tubercular.^[9] Moreover, such compounds are valuable in chemotherapy research due to their potential properties as inhibitors of 5-phosphoribosyl-1-

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pyrophosphate synthetase,^[10] dihydrofolate reductase,^[11] and specifically, tyrosine kinase as an important enzyme in regulating cell division.^[12] In addition, fused pyrimidine derivatives are well-known as anticancer agents, and many researches describe the function of pyrimidines in chemotherapy and treatment of cancers (Figure 1).^[13]

In recent years biological activities of pyrazole, pyridine and pyrimidine based organic molecules have been approved, thus, heterocyclic systems containing the basic aforementioned heterocycles have attracted the attention of synthetic organic chemists.^[14]

Polyoxometalates (POMs), as a unique class of anionic metal oxide clusters, are gaining more interest due to numerous advantageous properties and widespread applications.^[15] Among the various applications of POMs, catalysis is one of the most important area of applications.^[16-19] In POM structures protons can act as Brønsted acids, while the metal ions show Lewis acidity originated from unoccupied orbitals as electron pair accepters. Thus, POMs with strong Brønsted and Lewis acidity exhibit promise as unrivaled acid catalysts for vartransformations.^[20,21] acid-catalyzed organic ious Although POMs are efficient homogeneous catalysts, the accessibility to the active sites is hindered because of their small surface area.

A promising synthetic strategy to improve POM catalyst system is the combination of POM with metalorganic coordination complexes to construct crystalline inorganic–organic hybrid compounds-based POMs with high-dimensional supramolecular networks.^[22–24] In comparison with the traditional POMs, inorganic–organic hybrid of POMs can merge the merits of both components, and the combination may lead to desirable catalytic activity.^[25] Among various coordination compounds, lanthanoid coordination complexes are particularly valuable in this context because of their particular optical, Lewis acid catalytic and magnetic properties.^[26–29]

We are interested in heteocyclic chemistry^[30–33] and their synthesis *via* multicomponent reaction under green conditions.^[34–36]

In two decades ago, we promoted heteropoly acids (HPAs) and their POMs as efficient and green catalysts in organic transformations including in the synthesis of heterocycles.^[37–40]

Given the importance of pyrazolopyridopyrimidines, we decided to try the synthesis of heterocyclic system based on pyridopyrimidines. In this regard we, used two different methods, four and five component reactions, using inexpensive and available starting materials in the presence of a suitable catalyst under the environmentally friendly conditions.

For this aim, we used inorganic–organic hybrid compound based on neodymium cluster and Keggin type POMs, {Na[Nd (pydc-OH)(H₂O)₄]₃}[SiW₁₂O₄₀]•15H₂O (Nd/POM hybrid) Accessibility of active sites, enhanced the Lewis acid strength in presence of the lanthanoid ions and insolubility of hybrid catalyst, encouraged us to examine the catalytic activity of this hybrid in organic transformation for the first time (Schemes 1,2).

2 | RESULTS AND DISCUSSION

2.1 | Catalyst characterization

The lower charge density on the spherical surface of HPAs is the most main reason that they are commonly employed as acidic catalysts. Due to the interest in POM-based coordination complexes, in the last years, our research team introduced different lanthanoid coordination complexes into the POMs systems and obtained a series of novel POM-based lanthanide clusters, which demonstrated unusual topologies and improved properties.^[41-45]

The hybrid catalyst contains a trinuclear neodymium organic cluster that is bound to three terminal oxygen atoms of the $[SiW_{12}O_{40}]^{4-}$ moiety to yield discrete flower-like hybrid (Figure 2). The discrete molecules are further packed into 3D supramolecular network by means of hydrogen bonds and anion- π interactions. The crystalline water molecules reside as guests in the interspaces of the 3D supramolecular structures through extensive hydrogen-bonding interactions. All of these contacts play an important role in the stabilization of the crystal structure of the hybrid catalyst.

The morphology of catalyst was studied by SEM analyses, Figure 3. As can be seen, the catalyst has fine particles with a regular structure.







Piromidic Acid (Antibacterial)

Tisopurine (Anticancer)



FIGURE 1 Pyrimidine and fused pyrimidine marketed drugs



FIGURE 2 Representation of hybrid catalyst, Red: $[SiW_{12}O_{40}]^-$, Green: lanthanoid cluster



FIGURE 3 SEM analyses of Nd/POM hybrid

The FTIR spectrum of catalyst are depicted in Figure 4. The band appears between 3300 and 3500 cm⁻¹ are assigned to the -OH vibration of coordinated molecules. The bands at 1522 cm⁻¹ and 1630 cm⁻¹ are representative of C=O asymmetric stretching. The observed band at 1459 cm⁻¹ can be due to symmetric stretching of C=O groups.

As shown in Figure 5 hybrid catalyst was characterized via powder X-ray diffraction (PXRD) at room temperature. The PXRD patterns measured for the synthesized samples were in good agreement with the PXRD patterns simulated from the respective single-crystal X-ray data (CCDC-995731) which indicates the good phase purity of the catalyst. WILEY Organometallic 3 of 9 Chemistry

To evaluate potential application of the as-made structures in adsorption and separation processes, nitrogen adsorption was performed at 77 K through simulation study. Grand Canonical Monte Carlo simulation was implemented for N₂ adsorption isotherm prediction over the hybrid and parent Keggin catalysts. The trueness of simulated N₂ isotherm in textural characterization of porous materials has been previously reported.^[46–48] As it has been illustrated in the Figure 6, the N₂ uptake has been increased rather two times over hybrid catalyst compared to the parent Keggin. It is worthwhile mentioning nitrogen adsorption uptakes over both catalysts imply potential application of the structures in separation and adsorption processes.

2.2 | Catalytic activity

In the sequel to our recent studies to synthesize heterocyclic compounds using various heterogeneous catalysts, we are looking for a simple and sufficient protocol to synthesize pyrazolo-[4,3:5,6]pyrido[2,3-d]pyrimidine-diones.

In this regard, firstly, the role of the catalyst on the reaction efficiency and the time was determined. For this aim, ethyl acetoacetate, hydrazine hydrate, 6-amino-1,3-dimethyl uracil and benzaldehyde were employed to treat as the model reaction and water was selected as solvent. When the catalyst was missed, the reaction progressed slowly and only a trace amount of the desired product was formed.

The next try was optimizing the catalyst amount. TLC technique (7:3 n-hexane/ethylacetate) was used for tracing the reaction progress and thus, the clean and smooth treatment of starting materials was observed along with the production of the favored product. To reach the optimized reaction conditions, the impact of temperature, solvent, and the amount of catalyst were investigated in the model reaction. By examining different polar and nonpolar solvents in this reaction, the best one was found and its results were compared with that of obtained under solvent-free system. The results concluded from solvents such as H₂O, EtOH, H₂O/EtOH, CH₃CN, CH₂Cl₂ and DMF were summarized in Table 1. Water as the greenest solvent gave the desired product in highest yield of 94% which was the best one (Table 1, entry 1). So water was chosen as the reaction solvent. To increase the efficiency, the catalyzed model reaction was conducted under reflux condition and the highest yield of product was obtained, while at room temperature it gave only 60% yield. Lastly, to find the effect of the optimal amount of catalyst, the model reaction was catalyzed with different amounts of catalyst. 10 mol% of the catalyst was selected as an optimized amount. The increase of the product yield was



FIGURE 4 IR spectrum of Nd/POM hybrid



FIGURE 5 X-ray powder diffraction patterns of catalyst: red, calculated from single-crystal X-ray data; green, experimental data

directly related to the increase of the Na[Nd (pydc-OH) $(H_2O)_4]_3$][SiW₁₂O₄₀] quantity that is in turn attributed to the enhancement of the number of active sites increasing the contact and collision opportunity among the catalyst surface and the molecules of reagents.

In the hybrid catalyst structure, increasing the specific surface areas and number of active sites, resulted in better catalytic efficiency than parent compound. For comparing the catalytic activities of the hybrid catalyst with parent Keggin and Lanthanopolyoxotungstate compound, the target reaction catalyzed by $H_4SiW_{12}O_{40}$, $Na_9[NdW_{10}O_{36}]$ and $Na[Nd (pydc-OH)(H_2O)_4]_3$ [Si $W_{12}O_{40}$] was performed under the optimum conditions, and the results are listed in Table 1. As exhibited in Table 1, it is found that the hybrid catalyst showed high catalytic activity, and the yield of product is 91%. These

results proved that the synergistic effect of POMs and lanthanoid complexes in the inorganic–organic hybrid compounds leads to the enhanced catalytic properties. Furthermore, the coordination of the $SiW_{12}O_{40}$ anion to the neodymium ions results in a feature of the nano-size hybrid with the activity of the acid surface, making the facilitation of the accessibility to active sites.

Using these results, we synthesized the target molecules using a one pot four component reaction of hydrazine hydrate, ethyl acetoacetate, 6-amino-1,3-dimethyl uracil and benzaldehyde in the presence of catalytic amount of Nd/POM hybrid (0.04 g) and in water as solvent.

The extension of the present method was studied by employing various substituted aldehydes, including either electron withdrawing or electron donating groups.



FIGURE 6 N2 adsorption isotherms over parent Keggin and hybrid catalysts at 77 K

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)	Catalyst amount (mol%)
1	H ₂ O	reflux	2	94	10
2	EtOH	reflux	3	89	10
3	H ₂ O/EtOH	reflux	2.5	92	10
4	CH ₃ CN	reflux	3.5	90	10
5	CH_2Cl_2	reflux	4	75	10
6	DMF	reflux	3	80	10
7	H ₂ O	r.t.	6	60	10
8	H_2O	50	5	84	10
9	H ₂ O	reflux	3	89	5
10	H ₂ O	reflux	2	97	15
11	H_2O	reflux	2.5	80	10 (H ₄ SiW ₁₂ O ₄₀)
12	H ₂ O	reflux	2.5	88	10 (Na ₉ [NdW ₁₀ O ₃₆])

TABLE 1 Optimization of the reaction conditions

The corresponding pyrazolo pyrido pyrimidine-dione derivatives were produced with excellent yields, without the formation of any by-products in a relatively short time. The results are summarized in Table 2. All compounds were known and identified by comparison of their physical and spectroscopic data of those authentic samples abd were found indentical (See supporting information).^[49,50]

In the next step, we decided to synthesize various derivatives of pyrazolo-[4,3:5,6]pyrido[2,3-d]pyrimidinediones *via* a five-component reaction using ammonium acetate as a source of nitrogen. This reaction was also extended by using various substituted aldehydes to produce the desired compounds. The results are summarized in Table 3.

2.3 | Reaction mechanism

According to previous reports, a reliable mechanical pathway for the four-component reaction catalyzed by Nd/POM hybrid has been proposed (Scheme 3). Firstly, (E)-4-benzylidene-3-methyl-1H-pyrazol-5(4H)-one was

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TABLE 2 One pot, four-component synthesis of pyrazolo-[4',3':5,6]pyrido[2,3-*d*]pyrimidinediones in refluxing water in the presence of Nd/POM hybrid

Entry	Ar	R	Time (h)	Yield (%)	Mp. (°C)	Mp. rep. (°C) ^[49,50]
1	C_6H_5	Н	2	94	195–198	194–196
2	$4F-C_6H_4$	Н	1.5	91	280-284	281-283
3	$4\text{Cl-C}_6\text{H}_4$	Н	1.8	93	282-285	285-286
4	$4Br-C_6H_4$	Н	2	90	285-288	286-288
5	$2,4-Cl_2-C_6H_3$	Н	1.5	91	284-286	285-287
6	$4\mathrm{NO}_2\text{-}\mathrm{C}_6\mathrm{H}_4$	Н	1.8	94	172–174	172-173
7	$3NO_2$ - C_6H_4	Н	2	90	220-224	221-223
8	4-N (Me) ₂ C ₆ H ₄	Η	2.5	90	221-225	222-224
9	C_6H_5	Ph	3	91	207-210	208-210
10	$4F-C_6H_4$	Ph	2.5	90	206-207	207-208
11	$4\text{Cl-C}_6\text{H}_4$	Ph	2.8	91	200-203	200-202
12	$4Br-C_6H_4$	Ph	3.1	89	161-163	160–161

obtained by nucleophilic substitution of benzaldehyde on 3-methyl-1-pyrazolone. Simultaneously, aldehyde is activated by the catalyst. Finally, the desired 1 pyrazole based pyrido[2,3-*d*]pyrimidine-dione is achieved through catalyzed cycloaddition.

3 | EXPERIMENTAL

3.1 | Materials

The chemicals employed for the investigating the catalytic activity includes ethyl acetoacetate, hydrazine hydrate/phenyl hydrazine, 1,3-dimethylbarbituric acid, ammonium acetate, 6-amino-1,3-dimethyl uracil and aryl aldehyde. All reagents were obtained from Merck and

TABLE 3 One pot, five-component reaction in the presence ofNd/POM hybrid

Entry	Ar	R	Time (h)	Yield (%)	Мр. (°С)	Mp. rep. (°C)
1	C_6H_5	Н	3	92	194–198	194–196
2	$4F-C_6H_4$	Н	2.2	90	280-283	281-283
3	$4\text{Cl-C}_6\text{H}_4$	Н	2.5	94	284-287	285-286
4	$4\mathrm{Br}\text{-}\mathrm{C}_{6}\mathrm{H}_{4}$	Н	2.8	90	286-289	286-288
5	$2,4-Cl_2-C_6H_3$	Η	2.8	90	284-288	285-287
6	$4NO_2-C_6H_4$	Η	2.5	92	171–174	172–173
7	$3NO_2-C_6H_4$	Н	3	91	221-224	221-223
8	4-N (Me) ₂ C ₆ H ₄	Η	3.4	88	222-224	222-224
9	C_6H_5	Ph	4	92	207-210	208-210
10	$4F-C_6H_4$	Ph	3.5	89	208-210	207-208
11	$4\text{Cl-C}_6\text{H}_4$	Ph	4	92	202-204	200-202
12	$4\mathrm{Br}\text{-}\mathrm{C}_{6}\mathrm{H}_{4}$	Ph	4.4	87	160-163	160-161

used without purification. All synthesized compounds were known and indentified by comparison of their physical and spectroscopic data with those of authuntic samples and were found identical^[49,50]

3.2 | Preparation and characterization of {Na[Nd (pydc-OH)(H₂O)₄]₃}[SiW₁₂O₄₀] •15H₂O hybrid catalyst

{Na[Nd (pydc-OH)(H₂O)₄]₃}[SiW₁₂O₄₀]•15H₂O hybrid were synthesized and characterized according to the procedure reported previously.^[45] A mixture of Nd (NO₃)₃•6H₂O (110 mg, 0.25 mmol), H₂pydcOH•H₂O (50 mg, 0.25 mmol), H₄SiW₁₂O₄₀•nH₂O (288 mg, 0.1 mmol) in 15 ml H₂O was stirred for about an hour in air and the pH value was adjusted to about 4 with





SCHEME 2 Model five-component reaction for pyrazole based pyrido[2,3-*d*] pyrimidine-dione synthesis.



SCHEME 3 Proposed mechanism for the model reaction.

NaOH solution. Then, the mixture was transferred into a Teflon-lined autoclave and kept under autogenous pressure at 120 °C for 3 days. After slow cooling to room temperature, yellow prismatic crystals were obtained. $C_{21}H_{63}N_3NaNd_3O_{82}SiW_{12}$ (4359.70): Calcd. C 5.79, H 1.46, N 0.96; found C 5.90, H 1.38, N 0.86, IR (KBr pellet, cm⁻¹) ν : 3420(br. s), 1600 (s), 1573 (s), 1492 (w), 1428 (s), 1338 (m), 1246 (m), 1123 (m), 1028 (s), 973 (s), 924 (s), 881 (m), 795 (s), 702 (w).

3.3 | Synthesis of Pyrazolo-[4,3:5,6] pyrido[2,3-*d*]pyrimidine-diones: Using 4-component reaction

Initially, 1.2 mmol of hydrazine hydrate or phenyl hydrazine was added drop wise to an aqueous suspension of ethyl acetoacetate to produce 3-methyl-pyraxole-1-one as a white precipitate, then 6-amino-1,3- dimethyl uracil (1 mmol), an appropriate aldehyde (1 mmol) and catalytic amount of Nd/POM hybrid (0.04 g) were added and the resulting mixture was heated at reflux for appropriate time. The progress was monitored by TLC. Upon completion of the reaction, the mixture was cooled and filtered off. The resulting solid was purified by recrystallization from CH_2Cl_2 .

3.4 | Synthesis of Pyrazolo-[4,3:5,6] pyrido[2,3-*d*]pyrimidine-diones: Using 5-component reaction

Ethyl acetoacetate (1 mmol), hydrazine hydrate or phenyl hydrazine (1.2 mmol), 1,3-dimethylbarbituric acid (1 mmol) and aryl aldehyde (1 mmol) were mixed in water (10 ml). Then, Nd/POM hybrid (10 mol%) was added and the reaction mixture was refluxed for the appropriate time. After completion of the reaction as indicated by TLC (n-hexane–ethyl acetate; 7:3), the reaction mixture was cooled to room temperature and recrystallized by dichloromethane. To recycle the catalyst, the recovered was washed with chloroform $(2 \times 10 \text{ ml})$, dried in an oven and used in reaction runs under the same conditions.

3.4.1 | 3,6,8-Trimethyl-4-phenyl-8,9dihydro-1H-pyrazolo[4',3':5,6]pyrido[2,3-d] pyrimidine-5,7-(4H,6H)-dione

¹H NMR (400 MHz, DMSO-d6): δ 10.46 (brs, 2H, 2-NH), 7.15–7.19 (t, 2H, Ar-H), 7.00–7.08 (m, 3H, Ar-H), 5.63 (s, 1H, CH), 3.07 (s, 3H, CH₃), 2.81 (s, 3H, CH₃), 2.22 (s, 3H, CH3). IR (KBr) $\nu_{max} = 3332$, 2971, 1654, 1248 cm⁻¹; m. p. = 195–195 °C.

3.4.2 | 4-(4-Fluorophenyl)-3,6,8-trimethyl-8,9-dihydro-1*H*-pyrazolo[4',3':5,6]pyrido[2,3*d*]pyrimidine-5,7(4*H*,6*H*)-dione

¹H NMR (400 MHz, DMSO-d₆): δ 11.99 (s, NH), 9.81 (s, NH), 7.36–7.38 (d, J = 7.6 Hz, 2H, Ar-H), 7.14–7.16 (d, J = 7.6 Hz, 2H, Ar-H), 4.99 (s, CH), 3.46 (s, 3H, CH₃), 3.06 (s, 3H, CH₃), 1.96 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d6) δ: 158.24, 150.19, 149.62, 142.28, 137.31, 135.63, 134.57, 130.41, 125.06, 106.23, 88.63, 33.84, 30.28, 27.15, 10.02; m. p. = 280–284 °C; IR (KBr) $\nu_{max} = 3312, 2956, 1663, 1280 \text{ cm}^{-1}.$

3.4.3 | 3,6,8-Trimethyl-1,4-diphenyl-8,9dihydro-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*] pyrimidine-5,7(4*H*,6*H*)-dione

¹H NMR (400 MHz, DMSO-d6): δ 11.77 (s, NH), 7.87–7.89 (d, *J* 8.0 Hz, 4H, Ar–H), 7.42–7.46 (t, *J* 8.0 Hz, 6H, Ar–H), 5.09 (s, CH), 2.82 (s, 3H,CH₃), 2.70 (s, 3H, CH₃), 1.55 (s, 3H, CH₃), m. p. = 207–210 °C; IR (KBr) ν_{max} = 3315, 2936, 1650, 1241.

3.4.4 | 4-(4-Chlorophenyl)-3,6,8-trimethyl-8,9-dihydro-1*H*-pyrazolo[4',3':5,6]pyrido[2,3*d*]pyrimidine-5,7(4*H*,6*H*)-dione(5 1)

¹HNMR (400 MHz, DMSO-d6): δ 11.97 (s, NH), 7.96–7.98 (d, 2H, J 7.6 Hz, Ar–H), 7.54–7.56 (d, 2H, J 7.6 Hz, Ar–H), 7.14–7.19 (m, 5H, Ar–H), 4.86 (s, CH), 3.46 (s,3H, CH3), 2.88 (s, 3H,CH₃), 1.96(s, 3H, CH₃), m. p. = 202–204 °C; IR (KBr) ν_{max} = 3321, 2946, 1641, 1273.





Catalyst recycling 3.5

Recyclability is an important feature of catalysts economically. In the hybrid catalyst, highly stable crystalline 3D supramolecular structure makes catalyst stable and recyclable. In addition, good dispersion of POMs at the molecular level prohibits conglomeration and high immobilization of POMs overcomes catalyst leaching and deactivation.

To test whether Nd/POM hybrid is recyclable, the recycled catalyst was subjected to further reaction. The results (Figure 7) show that catalyst recovery can be done to five runs, and after each recycling; only a slight decrease in catalytic activity can be seen.

CONCLUSIONS 4

In summary, we report a green and efficient strategy for the synthesis of pyrazolo-[4,3:5,6]pyrido[2,3-d]pyrimidine-dione derivatives via a four and five component reaction from the condensation of ethyl acetoacetate, hydrazine hydrate or phenyl hydrazine, aryl aldehydes, 6-amino-1,3-dimethyl uracil or 1,3-dimethyl barbituric acid and ammonium acetate in the presence of Na[Nd $(pydc-OH)(H_2O)_4]_3$ [SiW₁₂O₄₀] under triply green conditions. The use of the hybrid catalyst offers benefits such as the easy operation, short reaction and excellent yields of the products. This will not only lead to the creation of a synthetic method, but will also enhance the versatility of clean organic reactions in water.

ACKNOWLEDGMENTS

The authors appreciate partial financial supports from Alzahra University. MMH is also thankful to Iran National Science Foundation (INSF) for the individual given grant. MM is thankful to research council of Ferdowsi University of Mashhad, Mashhad, Iran.

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SUPPORTING INFORMATION

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How to cite this article: Daraie M, Heravi MM, Mirzaei M, Lotfian N. Synthesis of Pyrazolo-[4,3:5,6]pyrido[2,3-d]pyrimidine-diones Catalyzed by a Nano-sized Surface-Grafted Neodymium Complex of the Tungstosilicate via Multicomponent Reaction. Appl Organometal Chem. 2019;e5058. https://doi.org/10.1002/aoc.5058