

A Novel *pseudo*-Four-Component Domino Reaction for the Synthesis of Naphtho[2,1-*b*]furan-2(1*H*)-ones Using a Nanocatalyst

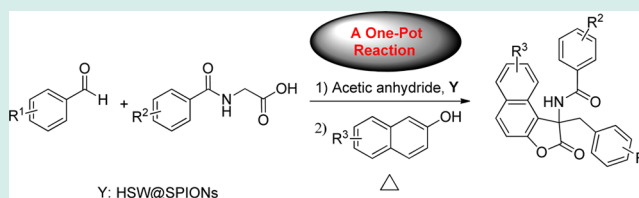
Elmira Salami-Ranjbaran, Ahmad R. Khosropour,* Iraj Mohammadpoor-Baltork,* Majid Moghadam, Shahram Tangestaninejad, and Valiollah Mirkhani

Department of Chemistry, University of Isfahan, Isfahan 81746-73441, Iran

S Supporting Information

ABSTRACT: In this article, an original one-pot method is utilized to synthesize a variety of derivatives of naphtho[2,1-*b*]furan-2(1*H*)-one via a *pseudo*-four-component domino reaction of aryl aldehydes, acetic anhydride, hippuric acids, and 2-naphthols catalyzed by HSW@SPIONs. This reaction illustrates an array of attractive features including, with particular interest in this report, a convenient and unique process of creating and utilizing a powerful recyclable nanocatalyst.

KEYWORDS: tungstosilicic acid hydrate, naphthofuran, nanocatalyst, heterocycles, multicomponent reaction, domino reaction



INTRODUCTION

Naphthofuran derivatives are valuable frameworks for active pharmaceutical heterocyclic compounds due to their presence in biologically relevant natural sources.¹ Additionally, due to the plethora of biological activities such as antimicrobial,² anticancer,^{1c,3} antidiabetic,⁴ anti-inflammatory,⁵ antifertility,⁶ antiparasitic,⁷ growth inhibitory,⁸ estrogenic,⁹ analgesic,¹⁰ and mutagenic properties in bacteria and mammalian cell systems,¹¹ they play a prominent role in medical chemistry. With respect to the aforementioned importance, naphthofuran analogs have attracted much attention, and several approaches have been developed for their synthesis.¹² A recent review of these methods demonstrates that the majority of these synthetic procedures are limited by the partial diversity^{12e,g} and complexity^{12f} associated with usage of toxic organic solvents^{12a-c} and multistep reactions under harsh conditions.^{1c} In the case of naphtho[2,1-*b*]furan-2(1*H*)-one scaffolds, despite their applications in proteomics research,¹³ the synthetic reports are surprisingly limited. To the best of our knowledge, only a few contributions for the preparation of these compounds have been presented thus far.^{3a,14} Hence, exploring an improved green strategy to synthesize polysubstituted naphthofuranones is desired.

The design and utilization of nanocatalysts for efficient organic transformations has been an important challenge in recent years.¹⁵⁻¹⁷ Developing core-shell structured catalysts through impregnation of polyoxometalates (POMs) on a magnetic nanoparticle has gained much attention^{18,19} owing to the high surface area of nanocatalysts, efficient recycling of magnetic carriers, stability and resistivity of magnetic microspheres to sintering and leaching, and high activity for catalytic organic transformations.^{20,21} Beyond introducing functionalities to the surface, dispersal of polyoxometalates on nanostructure components results in the enhancement of accessibility of

heteropoly acids, active sites through interaction between neighbors, which leads to amelioration of catalytic activity.²²⁻²⁹ Moreover, these nanocatalysts allow development of green protocols with high atom-efficiency and yield within a one-pot system, especially in tandem reactions.¹⁹

As a result of our ongoing research on the synthesis of heterocyclic compounds in our group,³⁰ herein, we report a novel one-pot multicomponent reaction of aldehydes, hippuric acids, acetic anhydride, and 2-naphthols catalyzed by H₄[Si(W₃O₁₀)₄].xH₂O (HSW) immobilized on silica-coated magnetite nanoparticles; SiO₂@Fe₃O₄ (SPIONs) as a new magnetic nanocomposite catalyst for the high-yielding synthesis of naphtho[2,1-*b*]furan-2(1*H*)-one derivatives.

RESULTS AND DISCUSSION

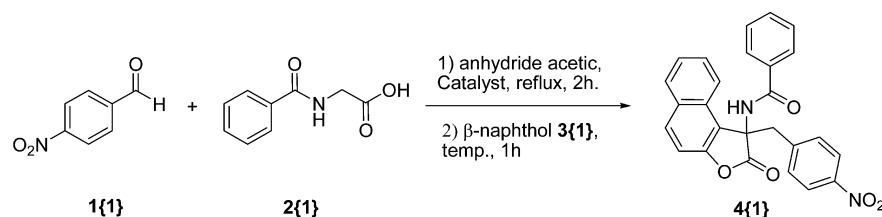
SiO₂@Fe₃O₄ was synthesized according to the literature.²⁹ Through treatment of the nanoparticles with HSW utilizing the wet impregnation method, the desired magnetite nanocatalyst was prepared and characterized (Supporting Information). The FT-IR spectrum of HSW@SPIONs showed absorption bands at 3277 cm⁻¹ (OH stretching vibration), 1191–1019 cm⁻¹ (Si–O stretching vibration), 979–926 cm⁻¹ (W=O), 880–790 (W–O–W). and 586–457 cm⁻¹ (Fe–O) SPIONs. HR-TEM and AFM images of HSW@SPIONs revealed that it appears to have almost a spherical structure with the average size about 10.3 nm.

The catalytic activity of HSW@SPIONs was evaluated in the template reaction of hippuric acid (0.2 mmol), *p*-nitrobenzaldehyde (0.2 mmol), acetic anhydride (0.5 mmol), and

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Table 1. Optimization of Reaction Conditions for *pseudo*-Four-Component Synthesis of 4{1,1,1}^a

entry	catalyst	catalyst [mol %]	T [° C]	yield [%] ^b
1	Nb ₂ O ₅	10	120	0
2	NiCl ₂	10	120	0
3	CeCl ₃ ·7H ₂ O	10	120	0
4	InCl ₃	10	120	trace
5	Fe ₃ O ₄	10	120	0
6	Zr(acac) ₂	10	120	trace
7	H ₃ BO ₃	10	120	0
8	Bi(OTf) ₃	10	120	44
9	Bi(TFA) ₃	10	120	32
10	Zn(OTf) ₂	10	120	24
11	CuBr ₂	10	120	28
12	<i>p</i> -TSA	10	120	65
13	H ₃ PW ₁₂ O ₄₀	10	120	10
14	HSW	10	120	70
15 ^c	HSW/SiO ₂ @Fe ₃ O ₄	0.52	120	76
16 ^c	HSW/SiO ₂ @Fe ₃ O ₄	0.82	120	79
17 ^c	HSW/SiO ₂ @Fe ₃ O ₄	1.4	120	84
18 ^c	HSW/SiO ₂ @Fe ₃ O ₄	2	120	85
19 ^d	HSW/SiO ₂ @Fe ₃ O ₄	1.4	120	77
20 ^e	HSW/SiO ₂ @Fe ₃ O ₄	1.4	120	85
21 ^c	HSW/SiO ₂ @Fe ₃ O ₄	1.4	125	86
22 ^c	HSW/SiO ₂ @Fe ₃ O ₄	1.4	110	51
23 ^{c,f}	HSW/SiO ₂ @Fe ₃ O ₄	1.4	110	10
24 ^{c,g}	HSW/SiO ₂ @Fe ₃ O ₄	1.4	82	6

^aA mixture of *p*-nitrobenzaldehyde (0.2 mmol), acetic anhydride, (0.5 mmol), hippuric acid (0.2 mmol), and catalyst was refluxed for 2 h. Afterward, β -naphthol (0.2 mmol) was added and refluxed for one more hour. ^bIsolated yields. ^c100 mg of catalyst. ^d80 mg of catalyst. ^e120 mg of catalyst. ^fToluene (2 mL) was used as the solvent. ^gCH₃CN (2 mL) was used as the solvent.

subsequent addition of β -naphthol (0.2 mmol) to the reaction mixture.

In the optimization study, we assessed various catalysts to evaluate which HSW demonstrated better reactivity compared to the others (Table 1, entry 14). As illustrated in Table 1, no reaction occurred by using Lewis or Brønsted acids such as Nb₂O₅, NiCl₂, CeCl₃·7H₂O, InCl₃, Fe₃O₄, Zr(acac)₂, or H₃BO₃ (Table 1, entries 1–7). Additional investigation manifested that furnishing the reaction with stronger Lewis acids such as Bi(OTf)₃, Bi(TFA)₃, Zn(OTf)₂, or CuBr₂ produced the desired product in low yields (Table 1, entries 8–11). Furthermore, it proved that Brønsted acids could be more effective in this transformation. Surprisingly, it was obvious that by comparison of strong Brønsted acids like *p*-TSA or heteropoly acids such as H₃PW₁₂O₄₀ and HSW, only tungstosilicic acid hydrate shows exceptional catalytic activity and provides the product in acceptable yield (Table 1, compare entries 12–14).

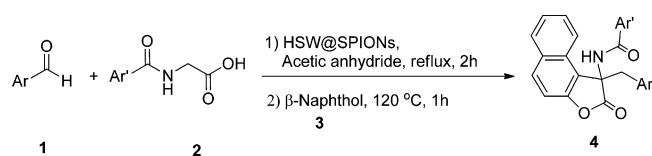
To improve the reaction yield, we investigated the immobilization of HSW on silica-coated magnetite nanoparticles. It is noteworthy that the yield of the desired product increased to 76% when utilizing 100 mg of the catalyst containing 0.52 mol % HSW (Table 1, entry 15). It can be observed that increasing the loading from 0.52 to 1.4 mol % lead to an improvement in the yield (Table 1, entries 15–17). A further increase to 2 mol % only raised the yield very slightly

(Table 1, entry 18). Moreover with additional experiments, 100 mg of the nanocatalyst containing 1.4 mol % HSW was determined as the optimum amount (Table 1, compare entries 17, 19, and 20).

After extensive evaluation and experimentation of key parameters, including temperature, we discovered raising the temperature up to 125 °C, led to a slight yield increase (Table 1, entry 21); however, lowering the temperature to 110 °C decreased the reaction yield dramatically (Table 1, entry 22). Finally, the solvent effect was also investigated. As shown in Table 1, the best yield was obtained under solventless conditions (Table 1, compare entries 17, 23, and 24). Upon determining the set of optimized conditions, the synthetic scope of naphthofuranone derivatives via sequential multi-component reaction in the presence of this novel nano-composite catalyst was investigated (Scheme 1).

A series of aromatic aldehydes and hippuric acid derivatives with electron-donating as well as electron-withdrawing substituents (Figure 1) was treated with acetic anhydride sequenced with β -naphthol derivatives to provide the corresponding naphtho[2,1-*b*]furan-2(1*H*)ones in good to excellent yields (Table 2).

As evidenced by the results in Table 2, aryl aldehyde with different substituents reacted with hippuric acid (Ar':Ph) and produced the corresponding products in generally good to

Scheme 1. Domino Synthesis of Naphtho[2,1-*b*]furan-2(1*H*)-ones Using HSW@SPIONs as a Nanocatalyst


excellent yields. It was observed that the efficiency of this transformation significantly is influenced by the electronic properties of the substituents on the aromatic rings. This protocol was found to be tolerant to a variety of functional groups such as NO₂ 4{1,1,1}, CN 4{2,1,1}, F 4{3,1,1}, Cl 4{4,1,1} - 4{6,1,1}, Br 4{8,1,1} - 4{9,1,1}, Me 4{10,1,1}, MeO 4{11,1,1}, or naphthyl 4{14,1,1} on the aryl aldehyde. To our

delight, we also surveyed the scope of the reaction with respect to the hippuric acid components. In general, it was found that electronic effect on Ar' (2) is more effective than Ar (1) group. For instance, the presence of strong electron-deficient groups on the hippuric acid 2 did not lead to the formation of the desired product under the same reaction condition, and the starting material was recovered intact. This may be attributed to their low reactivity in producing the azlactone intermediate (Table 2, 4{1,5,1}, 4{4,5,1}, 4{9,5,1}, 4{11,5,1}). Furthermore, the same result can be observed with strong electron-donating substituent such as *N,N*-dimethylamino group on the aldehyde (Table 2, 4{13,1,1}). To our disappointment, the corresponding product 4{15,1,1} was not obtained for thiophene-2-carbaldehyde (Table 2). However, when the CH₃ or Cl group was introduced into the phenyl ring of hippuric acid 2, the

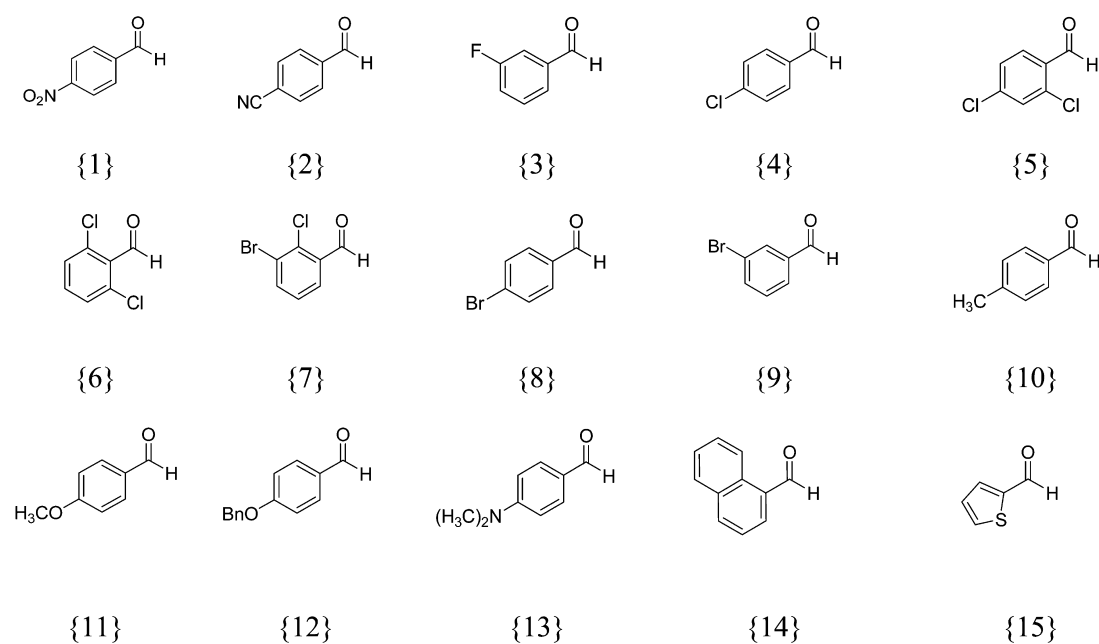
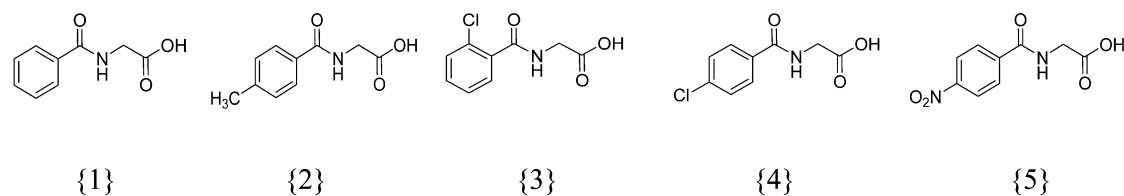
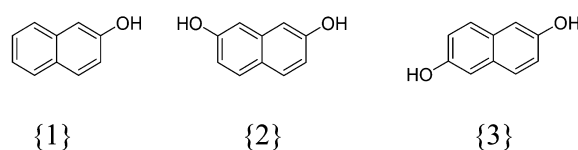
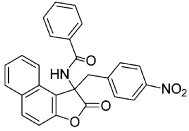
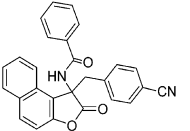
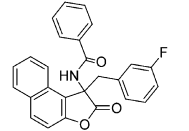
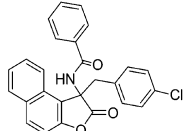
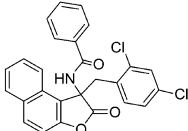
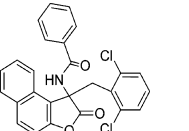
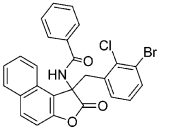
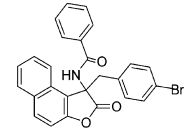
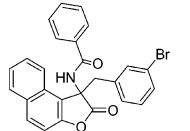
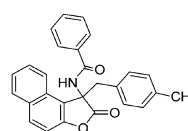
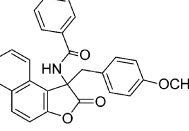
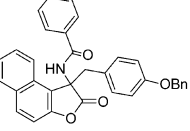
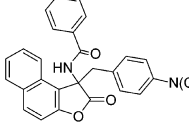
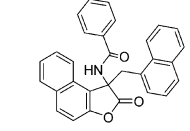
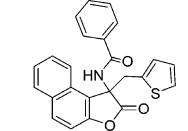
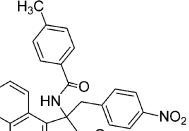
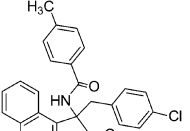
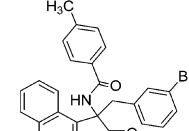
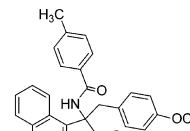
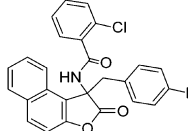
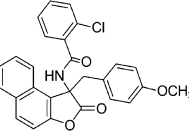
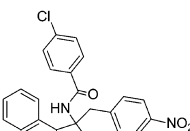
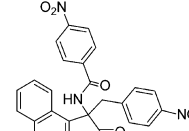
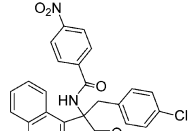
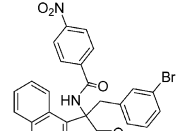
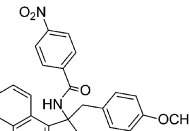
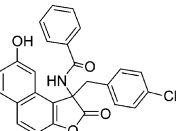
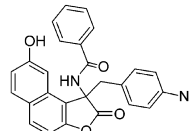
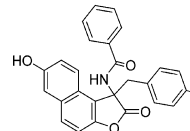
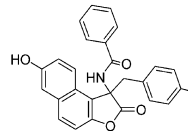
Aldehydes:

Hippuric acids:

 β -Naphthols:


Figure 1. Diversity of substrates tested in this investigation.

Table 2. Synthesis of Naphthofuran Derivatives in the Presence HSW@SPIONs under Solvent-Free Conditions^a

				
4{1,1,1} yield, 84%	4{2,1,1} yield, 87%	4{3,1,1} yield, 88%	4{4,1,1} yield, 83%	4{5,1,1} yield, 91%
				
4{6,1,1} yield, 73%	4{7,1,1} yield, 75%	4{8,1,1} yield, 92%	4{9,1,1} yield, 79%	4{10,1,1} yield, 65%
				
4{11,1,1} yield, 73%	4{12,1,1} yield, trace	4{13,1,1} yield, trace	4{14,1,1} yield, 77%	4{15,1,1} yield, trace
				
4{1,2,1} yield, trace	4{4,2,1} yield, 51%	4{9,2,1} yield, 57%	4{11,2,1} yield, 46%	4{1,3,1} yield, 61%
				
4{11,3,1} yield, 48%	4{1,4,1} yield, 66%	4{1,5,1} yield, trace	4{4,5,1} yield, trace	4{9,5,1} yield, trace
				
4{11,5,1} yield, trace	4{4,1,2} yield, 75%	4{1,1,2} yield, 71%	4{4,1,3} yield, 86%	4{1,1,3} yield, 68%

^aA mixture of aldehyde (0.2 mmol), acetic anhydride, (0.5 mmol), hippuric acid (0.2 mmol), and HSW@SPIONs (100 mg, 1.4 mol %) were refluxed for 2h. Afterward, β -naphthol (0.2 mmol) or dihydroxynaphthalene (0.4 mmol) was added to the reaction mixture and was heated for one additional hour.

desired products were produced successfully in moderate to good yields (46–66%).

In order to expand the reaction scope and the diversity of this procedure, we decided to test dihydroxynaphthalene derivatives in order to obtain naphthobisfuranones. It is worthwhile to note that when 2,6- and 2,7-dihydroxynaphthalenes were subjected to this procedure instead of 2-

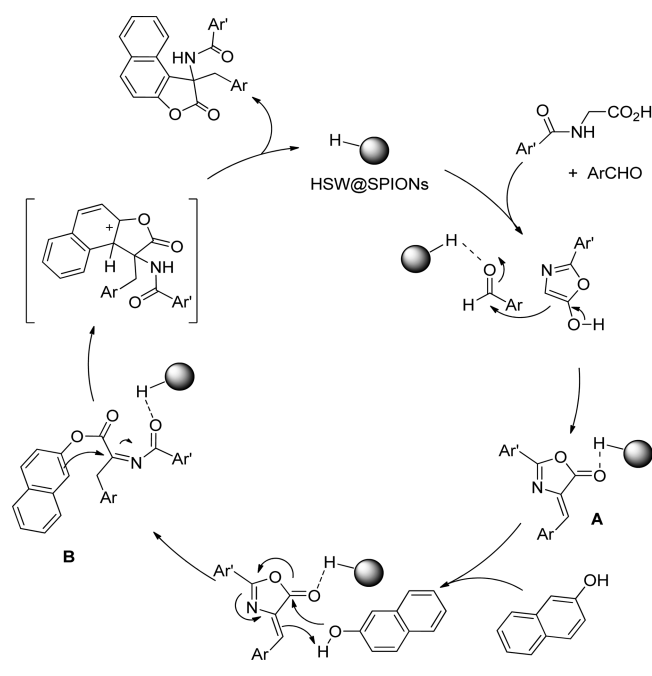
naphthol, the reaction proceeded smoothly, and the corresponding naphtho[2,1-*b*]furan-2(1*H*)-ones were obtained in 68–86% yields (Table 2, 4{4,1,2}–4{1,1,3}).

The scope of the reaction was further examined under the same conditions by using derivatives of dihydroxynaphthalene such as 2,3-dihydroxynaphthalene and 2,8-dihydroxynaphthalene as substrates, which, however, led to the formation of an

inseparable complex mixture and the expected products were not obtained.

The plausible mechanism of this reaction is illustrated in Scheme 2. After azlactone intermediate **A** was formed by the

Scheme 2. Proposed Mechanism



multicomponent reaction of arylaldehyde, hippuric acid, and acetic anhydride in the presence of the nanocatalyst via the Erlenmeyer reaction, the activated oxazolone ring would be exposed to a transesterification reaction by the attack of β -naphthol to give the ring-opening intermediate **B**.

Migration of the acidic proton occurs, followed by the addition of the naphthalene portion to the carbon in the enamide moiety through the *pseudo*-Friedel–Crafts reaction. The aromatization reaction through elimination of a proton would immediately lead to the naphtho[2,1-*b*]furan-2(1*H*)-one product.

The structure of compound 4{9,1,1} as an example was established through both extensive ^1H NMR, ^{13}C NMR, HMQC, HMBC (Figure 2), and NOE experiments and analyses. The corresponding product was formed exclusively as a single regioisomer, and the structure of other derivatives were determined firmly with comparison of their NMR spectra with 4{9,1,1} (Supporting Information).

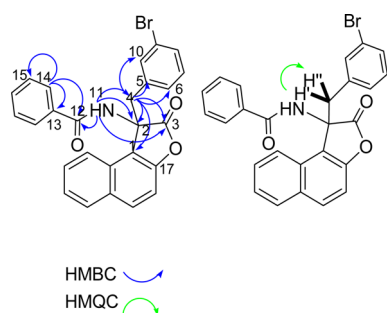


Figure 2. Key HMBC and HMQC correlations of 4{9,1,1}.

Finally, the reusability of the catalyst was examined in the model reaction. After completion of the reaction, it was cooled, and acetone (10 mL) was added. The catalyst was separated with a permanent magnet, washed with ethanol and water, and dried at 120 °C. The results illustrated that the catalyst preserved its activity even after five successive runs.

Table 3. Reusability of the Catalyst for Synthesis of 4{1,1,1}

run	yield [%] ^a
1	84
2	84
3	82
4	81
5	79
6	76

^aIsolated yields.

CONCLUSION

In summary, we have successfully established a new *pseudo*-four-component domino reaction catalyzed by HSW@SPIONs as a powerful super paramagnetic nanocatalyst as an efficient way for the synthesis of diverse naphtho[2,1-*b*]furan-2(1*H*)-one derivatives. Through this protocol, multiple fundamental reactions (cyclization, condensation, cascade, and aromatization reaction) were self-sequentially assembled in a single reactor. Use of inexpensive and readily available starting materials and simple reusability of the catalyst are other significant advantages of this method, which led to the increased efficacy of the reaction. Although at the present stage, the yield in some of the reactions are limited, the results already serve as a starting point for further investigations either for the development of new drugs or total synthesis of natural products. Our lab is currently investigating these potential applications, and the results will be issued in due course.

EXPERIMENTAL PROCEDURES

General Information. Chemicals were purchased from Fluka and Merck chemical companies. $\text{SiO}_2@\text{Fe}_3\text{O}_4$ (SPIONs) was prepared using literature procedures.²⁹ The progress of reactions were monitored by thin layer chromatography (TLC) using 0.25 mm precoated silica gel HF254 plates. NMR spectra were recorded on BrukerAvance 400 and 500 MHz Fourier-transform spectrometers. ^1H and ^{13}C NMR spectra were referenced to residual solvent. Coupling constants are reported in hertz. FT-IR spectra were recorded on a Nicolet-Impact 400D instrument in the range of 400–4000 cm^{-1} . Mass spectra were recorded on a Platform II spectrometer from Micromass, EI mode at 70 eV. Elemental analysis was done on a LECO, CHNS-932 analyzer. High resolution mass spectrometry (HRMS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE premier) using electrospray ionization (ESI) in positive or negative mode, depending on the analyte. Melting points were determined using Stuart Scientific SMP2 apparatus and are uncorrected. The TGA curve was obtained with a heating rate of 10 K/min on a TG 50 Mettler thermogravimetric analyzer in the range 30–600 °C. TEM images were taken with a Philips CM120 unit operated at 200 kV. FEM images were also taken with a DME SPM Dual Scope C-26 apparatus. The tungsten content of the catalyst was determined by Jarrell-Ash 1100 ICP instrument. The magnet-

ization of the sample was measured with a vibrating sample magnetometer (VSM) (MeghnatisDaghigKavir Co). Silica gel (230–400 mesh) was used for column chromatography.

Preparation of HSW@SPIONs. Under sonication, SPIONs (0.6 g) was dispersed in 50 mL Milli-Q water, and 0.14 M HSW H₂O (10 mL) solution was added slowly afterward. After sonication for 15 min and subsequent stirring at room temperature for 5 h, the magnetite nanoparticles were separated from the reaction mixture by an external permanent magnet, washed with ethanol, and dried at 150 °C for 2 h.

Typical Procedure for the Synthesis of *N*-(1-(4-nitrobenzyl)-1,2-dihydro-2-oxonaphtho[2,1-*b*]furan-1-yl) benzamide 4{1,1,1}. A mixture of 4-nitrobenzaldehyde (0.0302 g, 0.2 mmol), acetic anhydride, (0.0645 g, 0.5 mmol), hippuric acid (0.0358 g, 0.2 mmol), and HSW@SPIONs (100 mg, containing 1.4 mol % HSW) was refluxed for 2 h, and subsequently β -naphthol (0.0288 g, 0.2 mmol) was added and the mixture was heated at 120 °C for an additional hour. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ethyl acetate, 2:1). After completion of the reaction, the mixture was cooled to room temperature and acetone (10 mL) was added. The catalyst was separated by an external magnetic field. After evaporation of the solvent, the organic layer was washed with water (3 mL \times 10 mL) and dried. The reaction mixture was purified by column chromatography (silica-gel: *n*-hexane/ethyl acetate, 4:1) to obtain the pure product 4{1,1,1} as a white solid. Mp 227–229 °C. IR (KBr): ν_{\max} = 3389, 2923, 2854, 1784, 1662 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 8.05 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.76–7.79 (m, 3H), 7.60 (t, *J* = 7.0 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.29 (s, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 3.91 (d, *J* = 12.2 Hz, 1H), 3.62 (d, *J* = 12.2 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃): δ = 175.00, 166.67, 151.54, 147.51, 138.99, 132.58, 131.94, 131.71, 131.19, 130.83, 130.32, 128.78, 128.70, 128.22, 127.33, 124.87, 123.25, 120.93, 116.99, 111.67, 63.53, 41.83. MS: *m/z* (%) = 439 (M⁺⁺, 5.3), 438 (M⁺, 16.8), 317 (13.2), 302 (77.4), 169 (39.2), 140 (19.2), 114 (22.6), 105 (100.0). C₂₆H₁₈N₂O₅ (438.122): calcd. C 71.23, H 4.14, N 6.39; found C 71.15, H 4.21, N 6.41.

■ ASSOCIATED CONTENT

Supporting Information

¹H and ¹³C NMR spectra for all products, HMBC and HMQC spectra for compound 4{9,1,1}, and NOE spectra for compounds 4{5,1,1} and 4{9,1,1}. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00018.

■ AUTHOR INFORMATION

Corresponding Authors

*Fax: +98(31)36689732. Phone: +98(31) 37932705. E-mail: khosropour@chem.ui.ac.ir (A.R.K.).

*Fax: +98(31)36689732. Phone: +98(31) 37932705. E-mail: imbaltork@sci.ui.ac.ir (I.M.-B.).

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Notes

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