Three-component synthesis of pyrano[2,3-d]-pyrimidine dione derivatives facilitated by sulfonic acid nanoporous silica (SBA-Pr-SO₃H) and their docking and urease inhibitory activity

Ghodsi Mohammadi Ziarani1*, Sakineh Faramarzi1, Shima Asadi1, Alireza Badiei2, Roya Bazl3 and Massoud Amanlou3*

Abstract

Background: A straightforward and efficient method for the synthesis of pyrano[2,3-d]pyrimidine diones derivatives from the reaction of barbituric acid, malononitrile and various aromatic aldehydes using SBA-Pr-SO₃H as a nanocatalyst is reported.

Results: Reactions proceed with high efficiency under solvent free conditions. Urease inhibitory activity of pyrano[2,3-d]pyrimidine diones derivatives were tested against Jack bean urease using phenol red method. Three compounds of 4a, 4d and 4l were not active in urease inhibition test, but compound 4a displayed slight urease activation properties. Compounds 4b, 4k, 4f, 4e, 4j, 4g and 4c with hydrophobic substitutes on phenyl ring, showed good inhibitory activity (19.45-279.14 μM).

Discussion: The compounds with electron donating group and higher hydrophobic interaction with active site of enzyme prevents hydrolysis of substrate. Electron withdrawing groups such as nitro at different position and meta-methoxy reduced urease inhibitory activity. Substitution of both hydrogen of barbituric acid with methyl group will convert inhibitor to activator.

Keywords: SBA-Pr-SO₃H, Barbituric acid, Pyrano[2,3-d]pyrimidine diones, Multicomponent reaction (MCRs), Urease inhibitory

Introduction

Pyran derivatives are ordinary structural subunits in a variety of important natural products, including carbohydrates, alkaloids, polyether antibiotics, pheromones, and iridoids [1]. Uracil and its fused derivatives, such as pyrano[2,3-d]pyrimidines, pyrido[2,3-d]pyrimidines or pyrimido[4,5-d]pyrimidines are well recognized by synthesis as well as biological chemists. These annelated uracils have received considerable attention over the past years due to their wide range of biological activity. Compounds with these ring systems have diverse pharmacological properties such as antiallergic [2], antihypertensive [3], cardiotonic [4], bronchodilator [5], antibronchitic [6], or antitumour activity [7]. The synthesis of the mentioned compounds containing a pyran and an uracil ring poses significant synthetic challenges. Therefore, for the preparation of these complex molecules large efforts have been directed towards the synthetic manipulation of uracils. As a result, a number
of reports have described in literature [8-12] which usually require drastic conditions, long reaction times and complex synthetic pathways and the yields are poor. Thus new routes for the synthesis of these molecules have attracted considerable attention in search for a rapid entry to these heterocycles.

The general procedures for the preparation of pyrano[2,3-d] pyrimidine-2,4(1H,3H)-diones include the reaction of arylidenemalononitriles with barbituric acid under traditional hot reaction conditions [13,14] or microwave irradiation [15]. In these methods the arylidenemalononitriles are previously derived from malononitrile and aldehydes. Recently, direct condensation of aldehydes, malononitrile and barbituric acid in aqueous media has been reported under ultrasound irradiation [16], or catalyzed by diammonium hydrogen phosphate [17].

Different catalysts such as L-proline [18], N-methylmorpholine [19], [BMIm]BF4 [20], 1,4-dioxane [13,21], H3[NaP5W30O110] [22] and [K Al(SO4)2] [23] under heating also 3-deoxy-D-arabino-heptulosonate 7-phosphate (DAHP) [17] and L-proline [24] under room temperature condition have been researched for the synthesis of pyrano[2,3-d]pyrimidine diones derivatives. In addition, Et3N was examined under microwave irradiation [25]. The catalys free procedures for the preparation of the pyrano pyrimidine diones were also investigated using microwave irradiation [15], ultrasonic [16], heating with water [26] and ball-milling technique [27].

Mesoporous materials are a special type of nanomaterials with ordered arrays of uniform nanochannels. These materials have important applications in a wide variety of fields such as separation, catalysis, adsorption, advanced nanomaterials, etc [28-33]. SBA-15 has many advantages such as: largest pore-size mesoporous material with highly ordered hexagonally arranged meso-channels, with thick walls, adjustable pore size from 3 to 30 nm, and high hydrothermal and thermal stability [34-38], therefore it is expected to be an useful catalyst in the synthesis of organic compounds.

The surface of SBA-15 was modified by acidic functional groups (e.g., -SO3H) to prepare nano-solid acid catalyst which can use in the synthesis of various heterocyclic compounds [35]. Recently, we have also reported the use of this catalyst for the synthesis of quinoxaline derivatives [39], polyhydroquinolines [40], triazoloquinazolinones and benzimidazoquinazolinones [41].

Moreover, to the best of our knowledge there is no report on the use of these materials as nanoreactors in the synthesis of pyrano pyrimidine diones derivatives. In the present work, we report our results on the research of convenient and green way for the synthesis of pyrano[2,3-d]pyrimidine diones derivatives using SBA-Pr-SO3H as a nanocatalyst and their urease inhibitory activity was investigated.

Material and methods

Gc-Mass analysis was performed on a Gc-Mass model: 5973 network mass selective detector, Gc 6890 Agilent. IR spectra were recorded from KBr disk using a FT-IR Bruker Tensor 27 instrument. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. The 1H-NMR (250 MHz) was run on a Bruker DPX, 250 MHZ. Nitrogen adsorption and desorption isotherms were measured at -196°C using a Japan Belsorb II system after the samples were vacuum dried at 150°C overnight. Surface areas were calculated by the Brunauer-Emmett-Teller (BET) method, and pore sizes were calculated by the Barrett-Joyner-Halenda (BJH) method. Thermogravimetry analysis (TGA) was carried out in Perkin Elmer Pyris Diamond instrument from ambient temperature to 800°C using 20°C/min ramp rate.

Preparation of catalyst

**Synthesis and functionalization of SBA-15**

The nanoporous compound SBA-15 was synthesized and functionalized according to our previous report and the modified SBA-15-Pr-SO3H was used as nanoporous solid acid catalyst in the following reactions [40-43].

**General procedure for the preparation pyrano[2,3-d] pyrimidine diones**

The SBA-Pr-SO3H (0.02 g) was activated in vacuum at 100°C and then after cooling to room temperature, barbituric acid (0.265 g, 2 mmol), 4-nitrobenzaldehyde (0.362 ml, 2.4 mmol) and malonitrile (0.132 g, 2 mmol) was added to the catalyst in a reaction vessel (Scheme 1). The reaction mixture was heated for 15 min in bath oil at 140°C. After the completion of reaction as indicated.
The generated solid was recrystallized in DMF and ethanol to afford pure product 4. The resulting solid product was dissolved in DMF, and then filtered for removing the unsolvable catalyst and then the filtrate was cooled to afford the pure product as a solid.

Spectral data for product

7-Amino-6-cyano-5-(3-methy lphenyl)-5H-pyrano[2,3-d]pyrimidine-2,4(1H,3H)-diones 4f: IR (KBr): \( \nu_{\max} = 3411 \) and 3320 (NH\(_2\)), 2961 and 2740 (CN), 1733 and 1700 (C=O) cm\(^{-1}\). \( ^{1}H \) NMR (250 MHz, CDCl\(_3\)): \( \delta = 2.47 \) (s, 3H, CH\(_3\)), 4.13 (s, 1H, CH), 6.95-7.17 (m, 6H, ArH & NH\(_2\)), 11.09 (s, 1H, NH) 12.00 (s, 1H, NH) ppm. Mass (m/z): 296 (M\(^{+}\)), 285, 149 (100).

7-Amino-6-cyano-5-(3-methoxyphenyl)-5H-pyrano[2,3-d]pyrimidine-2,4(1H,3H)-diones 4h: IR (KBr): \( \nu_{\max} = 3183 \) and 2834 (NH\(_2\)), 2246 and 2200 (CN), 1690 and 1538 (C=O), 1459, 1375 cm\(^{-1}\). \( ^{1}H \) NMR (250 MHz, CDCl\(_3\)): \( \delta \)....

| Table 1 Optimization of the reaction conditions in the synthesis of 4i |
|---|---|---|---|
| Entry | Solvent | Time | Yield (%) |
| 1 | H\(_2\)O | 7 h | 32 |
| 2 | EtOH | 5 h | 31 |
| 3 | EtOH (1:1)/H\(_2\)O | 6 h | 28 |
| 4 | CH\(_3\)CN | 5 h | 50 |
| 5 | neat (140°C) | 15 min | 90 |
| 6 | neat (140°C) | 20 min | 30 |

* Reaction conditions: barbituric acid (2 mmol), 4-nitrobenzaldehyde (2.4 mmol), malonitrile (2 mmol) and catalyst (0.02 g).

* Isolated yields.

The spectroscopic and analytical data for selected compounds are presented in the following part. The catalyst was washed subsequently with acetonitrile, diluted acid solution, distilled water and then acetone, dried under vacuum and re-used for several times without loss of significant activity.

Scheme 2 Plausible mechanism for the formation of pyrano[2,3]pyrimidine dione derivatives 4.
Table 2 Synthesis of pyrano[2,3-d]pyrimidine diones derivatives 4 under optimized conditions

| Entry | Ar     | R<sub>1</sub>, R<sub>2</sub> | Product Structure<sup>a</sup> | Time (min) | Yield<sup>b</sup> (%) | M.p. (°C)       | Found | Reported |
|-------|--------|-----------------------------|-------------------------------|------------|------------------------|-----------------|-------|----------|
|       |        |                             |                               |            |                        |                 |       |          |
| 1     | Ph     | Me, Me                      | ![4a](image)                  | 5          | 65                     | 236–238         | 260–262 | [26]     |
| 2     | 2,4-(Cl)<sub>2</sub>-Ph | H, H                       | ![4b](image)                  | 20         | 61                     | 242–243         | 243–246 | [16]     |
| 3     | 4-Me-Ph| H, H                        | ![4c](image)                  | 25         | 62                     | 226–227         | 225    | [18]     |
| 4     | 3-NO<sub>2</sub>-Ph | H, H                        | ![4d](image)                  | 15         | 80                     | 255–226         | 255–257 | [18]     |
| 5     | 4-Cl-Ph | H, H                        | ![4e](image)                  | 45         | 30                     | 234–235         | 234–237 | [15]     |
| 6     | 3-Me-Ph| H, H                        | ![4f](image)                  | 30         | 80                     | 224–225         | –      |          |
| Entry | R Group | Solvents | T (°C) | Yield (%) | λ_{max} range (nm) | λ_{max} (nm) | Ref. |
|-------|---------|----------|--------|-----------|------------------|-------------|------|
| 7     | 4-OMe-Ph | H, H    | 35     | 71        | 280–284          | 280         | 18   |
| 8     | 3-OMe-Ph | H, H    | 10     | 75        | 200–206          | –           |      |
| 9     | 4-NO\_2-Ph | H, H   | 15     | 90        | 227–228          | 227–229     | 15   |
| 10    | 4-Br-Ph  | H, H    | 15     | 81        | 235–236          | 229–230     | 24   |
| 11    | 2,6-(Cl)\_2-Ph | H, H | 15     | 72        | 227–228          | –           |      |
Table 2 Synthesis of pyrano[2,3-d]pyrimidine diones derivatives 4 under optimized conditions (Continued)

| Entry | Catalyst | Solvent | Condition | Time (min) | Yield (%) |
|-------|----------|---------|-----------|------------|-----------|
| 12    | -        | -       | -         | 140°C      | 5-45 min  |

a All the compounds were characterized by IR, NMR, MS, and Mp.

b Isolated yields.

Docking approach
AutoDockTools 1.5.4 (ADT) [44], Autogrid 4.2 [45] and Autodock 4.2 [45] were used to prepare input files, calculate grid box and docking experiments. A grid map consisted of 40 × 40 × 40 Å points around the active site was used. The center of the grid was set to the average coordinates of the two Ni2+ ions in the α chain of *H. pylori* urease (pdb ID: 3LA4). A Lamarckian genetic algorithm (LGA) was used for the conformational search. The reliability of the applied docking protocol was assessed by re-docking acetohydroxamic acid (AHA) into the active site of the *H. pylori* urease. Each Lamarckian

Table 3 Comparison of SBA-Pr-SO3H and various catalysts in the synthesis of pyrano[2,3-d]pyrimidine diones derivatives 4

| Entry | Catalyst | Solvent | Condition | Time (min) | Yield (%) | Year/Ref. |
|-------|----------|---------|-----------|------------|-----------|-----------|
| 1     | Et3N     | DMF     | MW        | 10–12 min  | 65–70     | 2003 [25] |
| 2     | L-proline| EtOH    | Reflux    | 30–60 min  | 80–90     | 2009 [26] |
| 3     | N-methylmorpholine | [bmim][PF6] | 70°C       | 15 min     | 85–89     | 2004 [19] |
| 4     | -        | H2O     | MW        | 3–5 min    | 86–94     | 2004 [15] |
| 5     | H2[NaP5W30O110] | EtOH | Reflux    | 30–60 min  | 85–90     | 2010 [22] |
| 6     | -        | 1,4-dioxane/H2O | 80°C       | 18 min     | 65–87     | 2007 [17] |
| 7     | [BMIm]BF4 | [BMIm]BF4 | 90°C       | 3–5 h      | 82–95     | 2005 [20] |
| 8     | -        | H2O     | 80°C      | 7.5–11 h   | 72–81     | 2007 [26] |
| 9     | -        | 1,4-dioxane/H2O | Reflux    | 1–2 min    | 60–70     | 1997 [21] |
| 10    | L-proline| EtOH    | rt        | 30–150 min | 68–88     | 2009 [24] |
| 11    | -        | Ball-milling | rt        | 15–90 min  | 94–99     | 2009 [27] |
| 12    | -        | H2O     | US        | 1–3 h      | 62–78     | 2005 [16] |
| 13    | DAHP     | EtOH    | rt        | 2 h        | 71–81     | 2008 [17] |
| 14    | [KAl(SO4)2] | H2O     | 80°C      | 40–50 min  | 80–90     | 2010 [23] |
| 15    | SBA-Pr-SO3H | -      | 140°C     | 5–45 min   | 91        | This work |

[BMIm]BF4: 1-Butyl-3-methylimidazolium Tetrafluoroborate.
DAHP: 3-deoxy-D-arabino-heptulosonate 7-phosphate.
The job consisted of 250 runs. The initial population was 150 structures, and the maximum number of energy evaluations and generations was $2.5 \times 10^7$. The other parameters were set to default values. The final structures were clustered and ranked according to the most favorable docking energy. This protocol was then similarly applied to all synthesized compounds [46].

**Computational resources**

The computational studies were carried out on a computer cluster comprising four sets of HP Proliant ML370-G5 tower servers equipped with two quad-core Intel Xeon E5355 processors (2.66 GHz) and 4 GB of RAM, running a Linux platform (SUSE 10.2).

**Urease inhibitory assay**

All the chemicals used were of analytical grade from Merck Co., Germany. All aqueous solutions were prepared in MilliQ (Millipore, USA) water. Jack-bean urease was obtained from Merck (5 units/mg). After proper dilution, the concentration of enzyme solution adjusts at 2 mg/ml which is determined by UV spectroscopy at $\lambda = 280$ nm. Urease activity was measured by rapid phenol red urease test contains phenol red 0.1% (w/v) and 100 mM urea in 10 mM phosphate buffer, pH 7.0. Based on this method, the colour change from yellow (pH 6.8) to bright pink (pH 8.2) of phenol red pH indicator as a result of urea hydrolysis to ammonia was measured. The urease activity of the synthesized compounds (10 μl in DMSO) was monitored spectrophotometrically at 560 nm after incubation at 37°C for 30 min [47].

**Results and discussion**

In this article, we want to report the use of SBA-Pr-SO$_3$H as a nano and green solid acid catalyst and nano-reactor in the synthesis of 7-amino-6-cyano-5-aryl-5H-pyrano[2,3-d]pyrimidinones by the Knoevenagel–Michael condensation reaction. The procedure consisted of the mixture of malonitrile, aromatic aldehydes, and barbituric acid derivatives. The reaction proceeded in high yields in the presence of SBA-Pr-SO$_3$H as catalyst at room temperature and solvent free conditions to obtain our desired products 4a-4l (Scheme 1).

First the suitable conditions for the above transformation are examined with various solvents in different temperatures in the presence of SBA-Pr-SO$_3$H as nanocatalyst as shown in Table 1. The results revealed when the reaction proceeds in the absence of solvent, the desired product was obtained in high yield (90%) and very short reaction time. By increasing the temperature of the media to 130°C, the reaction time decreases to 15 minutes so the best reaction conditions were obtained (entry 5, Table 1). The same reaction was done without using any catalyst and a very low yield of product was obtained.

A reasonable mechanism for the formation of the product 4 is outlined in Scheme 2. First the oxygen of carbonyl group in benzaldehyde 2 was protonated and malonitrile 3 tautomerized to 6. The Knoevenagel condensation of compounds 5 and 6 was occurred to form the cyano-olefin 8. Subsequently, the tautomerized barbituric acid 7 endures nucleophilic attack to 8 and gives the Michael adduct 9. The intermediate 9 tautomerizes in the presence of acidic catalyst to generate intermediate 10 which cyclizes to give compound 11 which subsequently tautomerized to afford the fully aromatized compound 4.

Table 2 shows the obtained results in the reaction of a series of representative aldehydes with malononitrile and barbituric derivatives. The most derivatives were obtained in short reaction time ranging 5-45 minutes in very high yields. The effect of substituents on the aromatic ring did not show special effects in terms of yields under these reaction conditions.

Literature surveys revealed that various conditions have been employed in this reaction as demonstrated in Table 3.
Table 4 Urease inhibitory activities (IC$_{50}$ in μM) and interaction energies (kcal mol$^{-1}$) of pyrano[2,3-$d$]pyrimidine diones derivatives 4

| Entry | Product | Docking energy (kcal/mol) | IC$_{50}$ (μM) | Structure |
|-------|---------|---------------------------|----------------|-----------|
| 1     | 4a      | −5.46                     | 98.77          | ![Structure](image) |
| 2     | 4b      | −6.43                     | 19.45          | ![Structure](image) |
| 3     | 4c      | −5.65                     | 71.92          | ![Structure](image) |
| 4     | 4d      | −5.46                     | 98.93          | ![Structure](image) |
| 5 | **4e** | -5.87 | 49.65 |
|---|---|---|---|
| 6 | **4f** | -5.98 | 41.13 |
| 7 | **4g** | -5.73 | 62.92 |
| 8 | **4h** | -5.42 | 106.29 |

Table 4 Urease inhibitory activities (IC$_{50}$ in μM) and interaction energies (kcal mol$^{-1}$) of pyrano[2,3-d]pyrimidine diones derivatives 4 (Continued)
Table 4 Urease inhibitory activities (IC$_{50}$ in μM) and interaction energies (kcal mol$^{-1}$) of pyrano[2,3-$d$]pyrimidine diones derivatives 4 (Continued)

|   | 4i   |   |    |
|---|------|---|----|
| 9 |      |   |    |

- $IC_{50}$: 4.85 μM
- Interaction energy: 279.14 kcal mol$^{-1}$

|   | 4j   |   |    |
|---|------|---|----|
| 10|      |   |    |

- $IC_{50}$: 5.85 μM
- Interaction energy: 51.31 kcal mol$^{-1}$

|   | 4k   |   |    |
|---|------|---|----|
| 11|      |   |    |

- $IC_{50}$: 5.99 μM
- Interaction energy: 41.0 kcal mol$^{-1}$
The results illustrated that SBA-Pr-SO$_3$H was an efficient catalyst in the synthesis of these compounds.

**Preparation of catalyst**

Pure Nanoporous compound SBA-15 was synthesized according to the well-established method designed by Zhao & coworkers [42] with triblock poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) copolymer (Pluronic, EO$_{20}$PO$_{70}$EO$_{20}$, P$_{123}$) as the template. The SBA-15 silica was functionalized with (3-mercaptopropyl)trimethoxysilane (MPTS) and then, the thiol groups were oxidized to sulfonic acid by hydrogen peroxide. Analyzing of the catalyst surface was performed by various methods such as TGA, BET and CHN methods which demonstrated that the propylsulfonic acids were immobilized into the pores. Calculating average pore diameter of the surface area was performed by the BET method and pore volume of SBA-Pr-SO$_3$H are 440 m$^2$ g$^{-1}$, 6.0 nm and 0.660 cm$^3$ g$^{-1}$, respectively, which are smaller than those of SBA-15 due to the immobilization of sulfonosilane groups into the pores [40]. The TGA analysis of SBA-Pr-SO$_3$H confirmed the amount of organic groups on SBA-15. The weight reduction of SBA-Pr-SO$_3$H in the temperature range between 200-600°C indicated that the amount of organic group was 1.2 mmol/g. SEM image of SBA-Pr-SO$_3$H (Figure 1a) shows uniform particles about 1μm. The same morphology was observed for SBA-15. It can be concluded that morphology of acid catalyst was saved without change during the surface modifications. On the other hand, the TEM image (Figure 1b) reveals the parallel channels, which resemble to the pores configuration of SBA-15. This indicates that the pore of SBA-Pr-SO$_3$H was not collapsed during two steps reactions.

**Table 4 Urease inhibitory activities (IC$_{50}$ in μM) and interaction energies (kcal mol$^{-1}$) of pyrano[2,3-d]pyrimidine diones derivatives 4 (Continued)**

|   |   | IC$_{50}$ (μM) | Interaction (kcal mol$^{-1}$) |
|---|---|---------------|-----------------------------|
| 11 | 4l | -5.41         | 107.62                      |

* Green and red arrows are presented H-bond donor and acceptor interactions, respectively.

* Yellow areas are parts with hydrophobic interactions.

* Blue lines depict the electrostatic interactions.

* The IC$_{50}$ values for activator.

**Figure 2** SBA-Pr-SO$_3$H act as a nano-reactor in this reaction.
The pyrano[2,3-d]pyrimidine diones structurally similar to barbituric acids. The antibacterial and urease inhibitory activity of barbituric acid derivatives were reported [46,48,49]. Many urease inhibitors have been synthesized and tested, but because of their toxicity and instability use of them in vivo is impossible [48-50]. Thus, the search is still on for finding strong and specific urease inhibitors.

As shown in Table 4, all prepared pyrano[2,3-d]pyrimidine diones are demonstrated different profile of activity. This might be due to similarity of synthesised compounds to substrate of enzyme. While compounds 4a, 4d and 4l were not active in urease inhibition test, compound 4a displayed slight urease activation properties. Compounds 4b, 4k, 4f, 4e, 4j, 4g and 4c with hydrophobic substitutes on phenyl ring, show good inhibitory activity (Table 4). These compounds with electron donating group and subsequent hydrophobic interaction with active site of enzyme prevents the hydrolysis of substrate. Electron withdrawing groups such as nitro, 3-methoxy reduced urease inhibitory activity due to decreasing partial charge on nitrogen atoms of barbiturate moiety on pyrano[2,3-d] pyrimidine ring which is essential for inhibitory activity. Substitution of both hydrogen of barbituric acid with methy groups will convert the inhibitor to activator.

Conclusions

In conclusion we have developed a nano-catalyzed multicomponent synthesis of pyrano pyrimidine diones in good to very good yields. In comparison with previous investigations (Table 3), we presented SBA-Pr-SO₃H as an efficient and active nano-reactor (Figure 2). Our method is simple as no special apparatus, reagents or chemicals, and work up are required, and the formed compound is filtered and purified just by simple crystallization. This synthesis is also advantageous in terms of atom economy as well as is devoid of any hazardous chemicals. The urease inhibitory activity of pyrano[2,3-d]pyrimidine dione derivatives were reported for first time.

Competing interest

The authors declare that they have no competing of interests related to this publication.

Authors’ contributions

GMZ: Collaboration in design and identifying of the structures of target compounds, manuscript preparation. SF: Synthesis of the intermediates and some target compounds. SA: Synthesis of some target compounds and collaboration in identifying of the structures of target compounds. AB: Synthesis and characterization of nano catalyst. RB: Collaboration in docking study and evaluation of urease inhibitory test. MA: Collaboration in design of docking study, management of urease test and manuscript preparation. All authors read and approved the final manuscript.

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Author details

1. Department of Chemistry, Alzahra University, Vanak Square, P.O. Box 19938939973, Tehran, Iran. 2. School of Chemistry, College of Science, University of Tehran, Tehran, Iran. 3. Drug Design and Development Research Center and Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

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