

Green Synthesis of 4*H*-Pyrans and 4*H*-Chromenes in Magnetized Distilled Water

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ABSTRACT: *An efficient, facile, and green synthesis of 4*H*-pyran and 4*H*-chromene derivatives in Magnetized Distilled Water (MDW) has been described. In this work, magnetized distilled water was applied as a green-promoting medium for a practical, and environmentally benign three-component reaction of an aldehyde, ethyl acetoacetate/resorcinol, and malononitrile in the presence of potassium carbonate as a catalyst at 70 °C. This method offers the advantages of simplicity, low costs, high reaction yields, being green, and no need for any organic solvent. Also, the chemical structures of the synthesized new compounds were confirmed using Nuclear Magnetic Resonance (NMR), and InfraRed (IR) spectroscopy analysis.*

KEYWORDS: *4*H*-pyran; 4*H*-chromene; Multi-component reaction; Magnetized distilled water.*

INTRODUCTION

4*H*-Pyrans and 4*H*-chromenes have a broad range of applications. They exhibit various therapeutic applications such as antitumor [1], antibacterial [2-4], anti-HIV [5], antifungal [6], and anti-inflammatory [7]. Moreover, they are often used in pigments [8], laser dyes [9], and fluorescence markers [10]. Recently, various catalysts such as piperidine [11], NaOH [12], Na₂CO₃ [13], Et₃N [14], KSF [15], TiCl₄ [16], InCl₃ [17], MgO [18], K₃PO₄ [19], sodium malonate [20], and hetero-polyacid [21] are reported for the synthesis of 4*H*-Pyrans and 4*H*-chromenes, but all these protocols suffer from the drawbacks like the restricted substrate scope, the use of organic solvents and toxic metals, low achievement, and a tedious workup process. Therefore, it is necessary to develop a green and simple procedure for the preparation of these compounds.

Among the commonly used solvents in organic synthesis, water is nontoxic, and it is the most economical,

most abundant, safest, and most environmentally friendly medium. Sometimes water shows higher reactivity and selectivity compared to the other conventional organic solvents because of its strong hydrogen-bonding ability. These characteristics allow water to act as a solvent, or a reactant, making it different from conventional organic solvents [22].

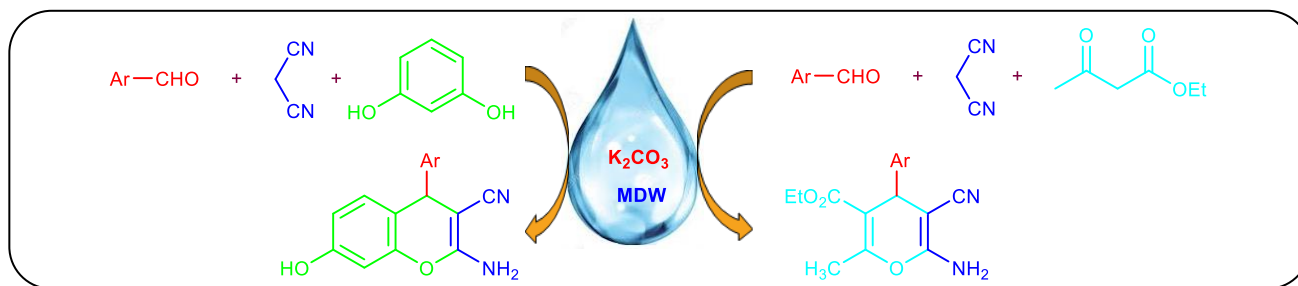
The water magnetization technique is an easy one without extra energy consumption when a permanent external magnet is utilized. Such a magnet can be installed on a previously established water tube system, resulting in no additional energy requirement for water magnetization. The applied magnetic field directly affects the structure of water such as density, penetration, specific heat, refractive index, electric dipole moment, vaporization enthalpy, surface tension, and viscosity change compared with non-magnetic water [23-27]. Two primary methods of making MDW has been reported. The first method

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1021-9986/2023/3/853-862

10/\$/6.00



Scheme 1: Synthesis of pyrans and chromenes in MDW.

is passing water through a magnetic field, and the second is using a permanent magnet near a particular volume of water.

In continuation to our recent research on MDW, including the synthesis of pyrano [2, 3-c] pyrazoles [28], pyrazolopyranopyrimidines [29], pyrano [2, 3-d] pyrimidines [30], and 9*H*-diuracilopyrans pyrans [31], we report here an eco-friendly and economical approach to a three-component reaction towards an easy synthesis of pyrans and chromenes in MDW (Scheme 1).

EXPERIMENTAL SECTION

General

The reagents and solvents used were supplied from Merck, Fluka, or Aldrich. Melting points were determined using an electro-thermal C14500 apparatus. The reaction progress and the purity of compounds were monitored using TLC analytical silica gel plates (Merck 60 F250). The ^1H NMR (300 MHz) spectra were obtained using a Bruker Advance DPX-250 FT-NMR spectrometer. The chemical shift values were given as δ values against tetramethylsilane (TMS), as the internal standard, and the J values were given in Hz. IR spectra were recorded on a Shimadzu IR-435 grating spectrophotometer.

Preparation of MDW

MDW has been prepared using our previous report [30]. Deionized water (5 mL) was first put in a test tube, which was then put between two neodymium magnets NdFeB (10 cm \times 5 cm \times 4 cm) with a magnetic field of 0.8 T for 15 min. The test tube was subsequently removed from the instrument and used for the reaction (Fig. 1).

General procedure for the preparation of pyrans (4a-4g) and chromenes (6a-6h).

An aldehyde (1.0 mmol), ethyl acetoacetate/resorcinol (1.0 mmol), malononitrile (1.0 mmol), and K_2CO_3 (1.0 mmol) were stirred at 70 $^\circ\text{C}$ in 3 mL of MDW. After completion

(as indicated by TLC), the crude product formed was separated, washed with cold water and the products were purified by recrystallization using EtOH.

Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4*H*-pyran-3-carboxylate (4a)

FT-IR (KBr): 3410, 3330, 2200, 1691 cm^{-1} ; ^1H NMR (DMSO- d_6) δ : 1.05 (t, 3H, $J=7.2$ Hz, CH_3), 2.34 (s, 3H, CH_3), 4.04 (m, 2H, CH_2), 4.32 (s, 1H, CH), 6.94 (s, 2H, NH_2), 7.26 (m, 3H, ArH), 7.36 (m, 2H, ArH).

Ethyl 6-amino-5-cyano-2-methyl-4-(4-chlorophenyl)-4*H*-pyran-3-carboxylate (4b)

FT-IR (KBr): 3410, 3331, 2192, 1693 cm^{-1} ; ^1H NMR (DMSO- d_6) δ : 1.07 (t, 3H, $J=7.2$ Hz, CH_3), 3.38 (s, 3H, CH_3), 4.04 (m, 2H, CH_2), 4.33 (s, 1H, CH), 6.93 (s, 2H, NH_2), 7.20 (d, 2H, $J=8.7$ Hz, ArH), 7.39 (d, 2H, $J=8.4$ Hz, ArH).

Ethyl 6-amino-5-cyano-2-methyl-4-(4-bromophenyl)-4*H*-pyran-3-carboxylate (4c)

FT-IR (KBr): 3408, 3329, 2194, 1689 cm^{-1} ; ^1H NMR (DMSO- d_6) δ : 1.05 (t, 3H, $J=7.2$ Hz, CH_3), 2.33 (s, 3H, CH_3), 4.02 (m, 2H, CH_2), 4.31 (s, 1H, CH), 6.99 (s, 2H, NH_2), 7.13 (d, 2H, $J=8.4$ Hz, ArH), 7.53 (d, 2H, $J=8.4$ Hz, ArH).

Ethyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4*H*-pyran-3-carboxylate (4d)

FT-IR (KBr): 3406, 3331, 2197, 1693, 1530 cm^{-1} ; ^1H NMR (DMSO- d_6) δ : 1.08 (t, 3H, $J=7.2$ Hz, CH_3), 2.37 (s, 3H, CH_3), 4.03 (q, 2H, $J=6.9$ Hz, CH_2), 4.49 (s, 1H, CH), 7.11 (s, 2H, NH_2), 7.46 (d, 2H, $J=8.7$ Hz, ArH), 8.23 (d, 2H, $J=8.7$ Hz, ArH).

Ethyl 6-amino-5-cyano-2-methyl-4-(3-nitrophenyl)-4*H*-pyran-3-carboxylate (4e)

FT-IR (KBr): 3402, 3328, 2191, 1692, 1531 cm^{-1} ; ^1H NMR (DMSO- d_6) δ : 1.04 (t, 3H, $J=7.2$ Hz, CH_3),

2.39 (s, 3H, CH₃), 4.03 (m, 2H, CH₂), 4.54 (s, 1H, CH), 7.12 (s, 2H, NH₂), 7.70 (m, 1H, ArH), 7.99 (s, 1H, ArH), 8.13 (d, 2H, *J*=6.6 Hz, ArH).

Ethyl 6-amino-5-cyano-2-methyl-4-(2-nitrophenyl)-4H-pyran-3-carboxylate (4f)

FT-IR (KBr): 3401, 3331, 2189, 1691, 1534 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 0.93 (t, 3H, *J*=7.2 Hz, CH₃), 2.35 (s, 3H, CH₃), 3.93 (q, 2H, *J*=6.9 Hz, CH₂), 5.03 (s, 1H, CH), 7.10 (s, 2H, NH₂), 7.56 (m, 2H, ArH), 7.75 (d, 1H, ArH), 7.87 (d, 1H, *J*=8.4 Hz, ArH).

Ethyl 6-amino-5-cyano-2-methyl-4-(2,6-dichlorophenyl)-4H-pyran-3-carboxylate (4g)

FT-IR (KBr): 3400, 3330, 2190, 1680 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 0.96 (t, 3H, *J*=7.2 Hz, CH₃), 2.28 (s, 3H, CH₃), 4.01 (m, 2H, CH₂), 5.37 (s, 1H, CH), 7.03 (s, 2H, NH₂), 7.33 (t, 1H, *J*=7.2 Hz, ArH), 7.46 (d, 1H, *J*=7.2 Hz, ArH), 7.57 (d, 1H, *J*=7.2 Hz, ArH).

2-Amino-3-cyano-7-hydroxy-4-phenyl-4H-chromene (6a)

FT-IR (KBr): 3460, 3338, 2193, 1649 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 4.63 (s, 1H, CH), 6.43 (d, 1H, *J*=2.4 Hz, ArH), 6.51 (dd, 1H, *J*_A=8.4 Hz, *J*_B=2.4 Hz, ArH), 6.80 (d, 1H, *J*=2.4 Hz, ArH), 6.88 (s, 2H, NH₂), 7.24 (m, 3H, ArH), 7.34 (m, 2H, ArH), 9.72 (s, 1H, OH).

2-Amino-3-cyano-7-hydroxy-4-(4-chlorophenyl)-4H-chromene (6b)

FT-IR (KBr): 3463, 3339, 2190, 1650 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 4.68 (s, 1H, CH), 6.43 (d, 1H, *J*=2.4 Hz, ArH), 6.51 (dd, 1H, *J*_A=8.4 Hz, *J*_B=2.4 Hz, ArH), 6.81 (d, 1H, *J*=8.4 Hz, ArH), 6.93 (s, 2H, NH₂), 7.22 (d, 2H, *J*=1.2 Hz, ArH), 7.40 (d, 2H, *J*=2.4 Hz, ArH), 9.75 (s, 1H, OH).

2-Amino-3-cyano-7-hydroxy-4-(4-nitrophenyl)-4H-chromene (6c)

FT-IR (KBr): 3460, 3340, 2190, 1645, 1530 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 4.88 (s, 1H, CH), 6.41 (d, 1H, *J*=2.1 Hz, ArH), 6.52 (dd, 1H, *J*_A=8.4 Hz, *J*_B=2.4 Hz, ArH), 6.84 (d, 1H, *J*=8.4 Hz, ArH), 7.05 (s, 2H, NH₂), 7.47 (d, 2H, *J*=8.7 Hz, ArH), 8.23 (d, 2H, *J*=8.7 Hz, ArH), 9.88 (s, 1H, OH).

2-Amino-3-cyano-7-hydroxy-4-(3-nitrophenyl)-4H-chromene (6d)

FT-IR (KBr): 3465, 3340, 2191, 1643, 1533 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 4.93 (s, 1H, CH), 6.46 (d, 1H,

J=2.1 Hz, ArH), 6.54 (dd, 1H, *J*_A=8.4 Hz, *J*_B=2.4 Hz, ArH), 6.87 (d, 1H, *J*=8.4 Hz, ArH), 7.05 (s, 2H, NH₂), 7.70 (m, 2H, ArH), 8.04 (d, 1H, *J*=1.8 Hz, ArH), 8.13 (m, 1H, ArH), 9.81 (s, 1H, OH).

2-Amino-3-cyano-7-hydroxy-4-(2,4-dichlorophenyl)-4H-chromene (6e)

FT-IR (KBr): 3463, 3340, 2190, 1640 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 5.15 (s, 1H, CH), 6.43 (d, 1H, *J*=2.4 Hz, ArH), 6.52 (dd, 1H, *J*_A=8.4 Hz, *J*_B=2.1 Hz, ArH), 6.74 (d, 1H, *J*=8.4 Hz, ArH), 6.99 (s, 2H, NH₂), 7.23 (d, 1H, *J*=8.1 Hz, ArH), 7.43 (d, *J*=2.4 Hz, 1H, ArH), 7.60 (d, 1H, *J*=2.1 Hz, ArH), 9.83 (s, 1H, OH).

2-Amino-3-cyano-7-hydroxy-4-(2-nitrophenyl)-4H-chromene (6f)

FT-IR (KBr): 3465, 3341, 2192, 1645, 1531 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 5.17 (s, 1H, CH), 6.46 (d, 1H, *J*=2.4 Hz, ArH), 6.54 (dd, 1H, *J*_A=8.4 Hz, *J*_B=2.4 Hz, ArH), 6.82 (d, 1H, *J*=8.4 Hz, ArH), 7.03 (s, 2H, NH₂), 7.33 (d, 1H, *J*=1.5 Hz, ArH), 7.51 (t, 1H, *J*=6.9 Hz, ArH), 7.69 (t, 1H, *J*=6.9 Hz, ArH), 7.88 (d, 1H, *J*=8.1 Hz, ArH), 9.85 (s, 1H, OH).

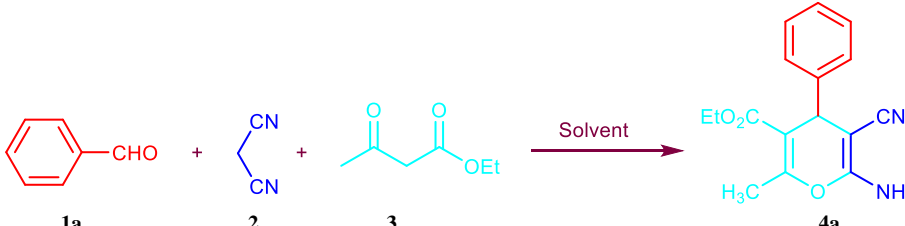
2-Amino-3-cyano-7-hydroxy-4-(2,6-dichlorophenyl)-4H-chromene (6g)

FT-IR (KBr): 3464, 3340, 2191, 1642 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ: 2.27 (s, 3H, CH₃), 4.58 (s, 1H, CH), 6.41 (d, 1H, *J*=1.8 Hz, ArH), 6.50 (dd, 1H, *J*_A=8.4 Hz, *J*_B=2.4 Hz, ArH), 6.80 (d, 1H, *J*=8.4 Hz, ArH), 6.85 (s, 2H, NH₂), 7.07 (d, 2H, *J*=8.1 Hz, ArH), 7.45 (d, 2H, *J*=8.1 Hz, ArH), 9.70 (s, 1H, OH).

RESULTS AND DISCUSSION

The MDW was prepared according to previously reported [30]. The deionized water (5 mL) was put in a test tube, which was then put in a magnetic field (0.8 T) at different times. The tube was subsequently removed from the instrument and used for the reaction (Fig. 1).

We selected 1.0 mmol of benzaldehyde (**1a**), 1.0 mmol of malononitrile (**2**), and 1 mmol of ethyl acetoacetate (**3**), as substrates in the model multicomponent reaction. Initially, various solvents including H₂O, EtOH, MeOH, CH₃CN, DMF, and THF were screened to identify an optimized condition (Table 1).

Table 1: Optimization experiments^a.


Entry	Solvent	Base	Temperature (°C)	Yield ^b (%)
1	H ₂ O	-	50	40
2	EtOH	-	50	20
3	MeOH	-	50	15
4	CH ₃ CN	-	50	-
5	DMF	-	50	25
6	THF	-	50	5
7	MDW	-	50	70
8	MDW	K ₂ CO ₃	50	85
9	MDW	KOH	50	80
10	MDW	Na ₂ CO ₃	50	75
11	MDW	NaOH	50	73
12	MDW	DABCO	50	60
13	MDW	Et ₃ N	50	45
14	MDW	DIPEA	50	35
15 ^c	MDW	K ₂ CO ₃	90	95
16 ^d	MDW	K ₂ CO ₃	90	77
17	MDW	K ₂ CO ₃	70	95
18	MDW	K ₂ CO ₃	90	96

a) Reaction conditions: benzaldehyde **1a** (1.0 mmol), malononitrile **2** (1.0 mmol), ethyl acetoacetate **3** (1.0 mmol), reaction time (3 h), solvent (3 mL), base (1 mmol), magnetization time (15 min). b) Isolated yield. c) K₂CO₃ (2 mmol). d) K₂CO₃ (0.5 mmol).



Fig. 1. The pilot for solvent magnetization apparatus.

As shown in Table 1, product (**4a**) is formed in low yields (Table 1, entries 1-6). Significantly, an improvement in the product yield was observed when the reaction was carried out in MDW (Table 1, entry 7). The efficacy of various parameters such as bases, and reaction temperature was tested. The role of bases including K₂CO₃, KOH, Na₂CO₃, NaOH, DABCO, triethylamine, and diisopropylethylamine (DIPEA) was investigated in the model reaction (Table 1, entries 8-14). According to Table 1, the reaction led to a higher yield in the presence of K₂CO₃ (Table 1, entry 8). Increasing the amount of K₂CO₃ to 2.0 mmol was not necessary and helpful for the reaction (Table 1, entry 15). When 0.5 mmol of K₂CO₃ was used, product **4a** was obtained with only 77% yield (Table 1, entry 16). In addition, when the reaction was performed at various temperatures ranging

Table 2: Reaction times, melting points, and yields of 4H-pyran **4**^a.

5		4.5		94	183-185	187-188 [33]
6		3		90	176-178	179-181 [33]
7		5		82	168-170	---

^aReaction conditions: aldehyde **1** (1.0 mmol), malononitrile **2** (1.1 mmol), ethyl acetoacetate **3** (1.0 mmol), K₂CO₃ (1.0 mmol), temperature (70 °C), magnetization time (15 min), MDW (3 mL).

^bIsolated yield.

from 50 °C to 90 °C, an excellent product yield (95%) was obtained at 70 °C (Table 1, entry 17).

The multicomponent reaction has been performed in MDW for six aldehydes to investigate the generality of the procedure for this reaction (Table 2).

According to Table 2, the reactions of various aldehydes, lead to products (**4a-4g**) in high-to-excellent yields (82-95%). The Unsubstituted, benzaldehyde was converted into excellent yield of product (**4a**) (Table 2, entry 1). Notably, the reactions of aryl aldehydes with electron-withdrawing functionalities like 4-nitro and 3-nitro with active methylene compounds was found to form excellent yields of products (Table 2, entries 4, and 5). Moreover, a sterically hindered aldehyde such as 2-nitrobenzaldehyde, and 2,6-dichlorobenzaldehyde also produced high yields of the products (Table 2, entries 6, and 7).

The applicability of MDW has also been studied for the preparation of 4H-chromenes using the optimized reaction conditions (Table 1, entry 17), and the results are illustrated in Table 3. A variety of aldehydes underwent the reaction to give the corresponding 4H-chromenes in high-to-excellent yields (83-96%). Various aldehydes including 4-nitrobenzaldehyde, 3-nitrobenzaldehyde, and 2,4-dichlorobenzaldehyde react to give 4H-chromenes in excellent products (Table 3, entries 3-5). However, the product yield was slightly decreased with 2-nitrobenzaldehyde (Table 3, entry 6). Finally, the aldehyde-bearing methyl group gave the corresponding 4H-chromene (**6g**) an excellent yield of about 94% (Table 3, entry 7).

Table 4 compares the efficiency of MDW as a green solvent to some reported methods in synthesis of 4H-pyran (**4a**) and 4H-chromene (**6a**). It shows that this method

Table 3. Synthesis of 4H-chromenes 6^a.

Entry	Ar	Time (h)	Product	Yield ^b (%)	m.p. (°C)	m.p. (°C) [Ref.]
1		3		96	233-235	235-236 [32]
2		4		90	223-225	223-225 [34]
3		3		90	168-170	170-172 [32]
4		4		96	166-168	169-170 [32]
5		5		92	257-259	256-258 [35]
6		4		83	160-162	164-166 [36]
		4.5		85	184-186	186-187 [32]

a) Reaction conditions: An aldehyde **1** (1.0 mmol), malononitrile **2** (1.1 mmol), resorcinol **5** (1.0 mmol), K_2CO_3 (1.0 mmol), MDW (3 mL), magnetization time (15 min), temperature (70 °C). b) Isolated yield.

Table 4: Comparison between this work and the priorly reported for the synthesis of 4H-pyran (4a) and 4H-chromene (6a).

Product	Catalyst	Conditions	Yield (%)	[Ref.]
4a	KF-Al ₂ O ₃	EtOH, r.t, 3 h	77	[37]
4a	Fe ₃ O ₄ @GA@ Isinglass	EtOH, reflux, 50 min	88	[38]
4a	[bmim]OH	Neat, 60 °C, 45 min	90	[39]
4a	Fe ₃ O ₄ @gC ₃ N ₄	EtOH, 60 °C, 3 h	80	[40]
4a	K ₂ CO ₃ /LD30	EtOH:H ₂ O, ultrasound, 50 °C, 25 min	95	[41]
4a	[2-aemim] [PF6]	H ₂ O, MW, 100 °C, 3 min	87	[42]
4a	NH ₄ OAc	Neat, grinding, r.t, 15 min	78	[43]
4a	K ₂ CO ₃	MDW, 70 °C, 3 h	95	This work
6a	Lemon Fruit Shell Ash	Microwave, 8 min	84	[44]
6a	polyoxometalate@Dysprosium	EtOH, H ₂ O, reflux, 25 min	88	[45]
6a	Fe ₃ O ₄ @SiO ₂ -nanocatalyst	EtOH, H ₂ O, ultrasound, r.t, 10 min	95	[46]
6a	CTABr	Ultrasound, 110 °C, 6 h	80	[47]
6a	Hydrotalcite	H ₂ O, 60 °C, 5 h	90	[48]
6a	Polyamine	EtOH, H ₂ O, reflux, 3 h	86	[49]
6a	Tungstic acid-SBA-15	H ₂ O, 100 °C, 12 h	86	[50]
6a	MIL-101(Cr)-SO ₃ H.	H ₂ O, 100 °C, 6 h	80	[36]
6a	L-Proline	EtOH, H ₂ O, 60 °C, 1.5 h	95	[51]
6a	K ₂ CO ₃	MDW, 70 °C, 3 h	96	[This work]

has high efficiency in reaction conditions for synthesis of 4H-pyran (**4a**) and 4H-chromene (**6a**).

CONCLUSIONS

In conclusion, an efficient, green, and convenient method was proposed for the one-pot three-component synthesis of pyrans and chromenes in MDW. Here, we used MDW as an inexpensive and 'green' solvent for the reaction medium. Eco-friendly, low costs, column-free workup condition, and high-to-excellent yields make this present procedure an interesting alternative to multistep approaches

Acknowledgment

We wish to express our thanks to the Research Council of the Shahrood University of Technology for the financial support of this work.

Received : Feb. 7, 2022 ; Accepted : May 30, 2022

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