

# 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], Na<sub>2</sub>CO<sub>3</sub> [13], Et<sub>3</sub>N [14], KSF [15], TiCl<sub>4</sub> [16], InCl<sub>3</sub> [17], MgO [18], K<sub>3</sub>PO<sub>4</sub> [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].

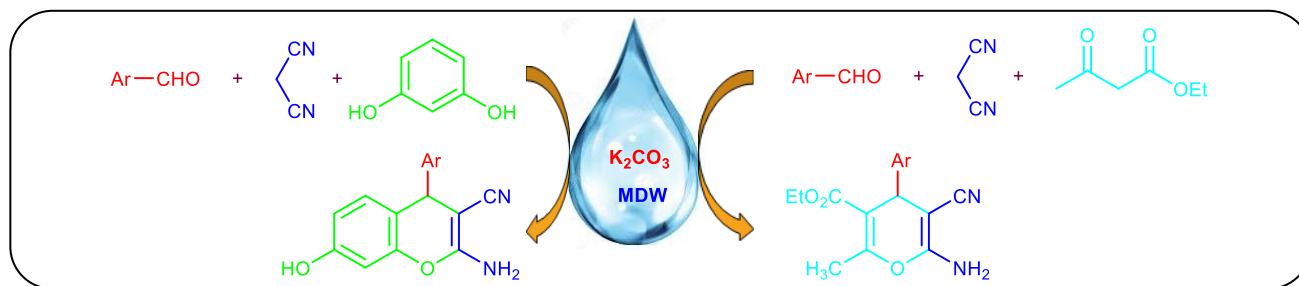
The water magnetization technique is an easy one without extra energy consumption when a permanent external magnet is utilized. Such a magnet can be installed on a previously established water tube system, resulting in no additional energy requirement for water magnetization. The applied magnetic field 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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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  $^1\text{H}$  NMR (300 MHz) spectra were obtained using a Bruker Advance DPX-250 FT-NMR spectrometer. The chemical shift values were given as  $\delta$  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  $\text{K}_2\text{CO}_3$  (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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 1.05 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ), 2.34 (s, 3H,  $\text{CH}_3$ ), 4.04 (m, 2H,  $\text{CH}_2$ ), 4.32 (s, 1H, CH), 6.94 (s, 2H,  $\text{NH}_2$ ), 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 1.07 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ), 3.38 (s, 3H,  $\text{CH}_3$ ), 4.04 (m, 2H,  $\text{CH}_2$ ), 4.33 (s, 1H, CH), 6.93 (s, 2H,  $\text{NH}_2$ ), 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 1.05 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ), 2.33 (s, 3H,  $\text{CH}_3$ ), 4.02 (m, 2H,  $\text{CH}_2$ ), 4.31 (s, 1H, CH), 6.99 (s, 2H,  $\text{NH}_2$ ), 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 1.08 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ), 2.37 (s, 3H,  $\text{CH}_3$ ), 4.03 (q, 2H,  $J=6.9$  Hz,  $\text{CH}_2$ ), 4.49 (s, 1H, CH), 7.11 (s, 2H,  $\text{NH}_2$ ), 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$ : 1.04 (t, 3H,  $J=7.2$  Hz,  $\text{CH}_3$ ),

2.39 (s, 3H, CH<sub>3</sub>), 4.03 (m, 2H, CH<sub>2</sub>), 4.54 (s, 1H, CH), 7.12 (s, 2H, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 0.93 (t, 3H,  $J=7.2$  Hz, CH<sub>3</sub>), 2.35 (s, 3H, CH<sub>3</sub>), 3.93 (q, 2H,  $J=6.9$  Hz, CH<sub>2</sub>), 5.03 (s, 1H, CH), 7.10 (s, 2H, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 0.96 (t, 3H,  $J=7.2$  Hz, CH<sub>3</sub>), 2.28 (s, 3H, CH<sub>3</sub>), 4.01 (m, 2H, CH<sub>2</sub>), 5.37 (s, 1H, CH), 7.03 (s, 2H, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 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, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 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, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 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, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 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, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 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, NH<sub>2</sub>), 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<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 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, NH<sub>2</sub>), 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).

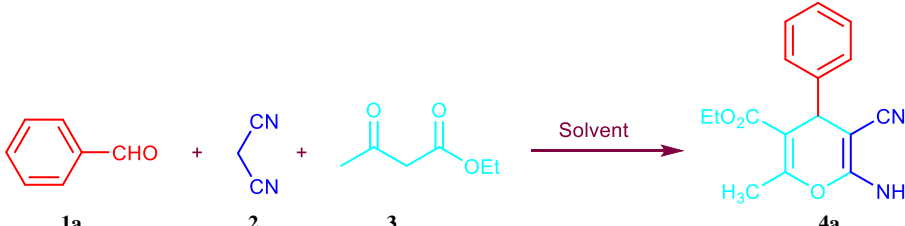
**2-Amino-3-cyano-7-hydroxy-4-(2,6-dichlorophenyl)-4H-chromene (6g)**

FT-IR (KBr): 3464, 3340, 2191, 1642 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$ : 2.27 (s, 3H, CH<sub>3</sub>), 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, NH<sub>2</sub>), 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 H<sub>2</sub>O, EtOH, MeOH, CH<sub>3</sub>CN, DMF, and THF were screened to identify an optimized condition (Table 1).

Table 1: Optimization experiments<sup>a</sup>.


Entry	Solvent	Base	Temperature (°C)	Yield <sup>b</sup> (%)
1	H <sub>2</sub> O	-	50	40
2	EtOH	-	50	20
3	MeOH	-	50	15
4	CH <sub>3</sub> CN	-	50	-
5	DMF	-	50	25
6	THF	-	50	5
7	MDW	-	50	70
8	MDW	K <sub>2</sub> CO <sub>3</sub>	50	85
9	MDW	KOH	50	80
10	MDW	Na <sub>2</sub> CO <sub>3</sub>	50	75
11	MDW	NaOH	50	73
12	MDW	DABCO	50	60
13	MDW	Et <sub>3</sub> N	50	45
14	MDW	DIPEA	50	35
15 <sup>c</sup>	MDW	K <sub>2</sub> CO <sub>3</sub>	90	95
16 <sup>d</sup>	MDW	K <sub>2</sub> CO <sub>3</sub>	90	77
17	MDW	K <sub>2</sub> CO <sub>3</sub>	70	95
18	MDW	K <sub>2</sub> CO <sub>3</sub>	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) K<sub>2</sub>CO<sub>3</sub> (2 mmol). d) K<sub>2</sub>CO<sub>3</sub> (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 K<sub>2</sub>CO<sub>3</sub>, KOH, Na<sub>2</sub>CO<sub>3</sub>, 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 K<sub>2</sub>CO<sub>3</sub> (Table 1, entry 8). Increasing the amount of K<sub>2</sub>CO<sub>3</sub> to 2.0 mmol was not necessary and helpful for the reaction (Table 1, entry 15). When 0.5 mmol of K<sub>2</sub>CO<sub>3</sub> 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<sup>a</sup>.

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

<sup>a</sup>Reaction conditions: aldehyde **1** (1.0 mmol), malononitrile **2** (1.1 mmol), ethyl acetoacetate **3** (1.0 mmol), K<sub>2</sub>CO<sub>3</sub> (1.0 mmol), temperature (70 °C), magnetization time (15 min), MDW (3 mL).

<sup>b</sup>Isolated 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<sup>a</sup>.

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

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## REFERENCES

- [1] Zhang G., Zhang Y., Yan J., Chen R., Wang S., Ma Y., Wang R., One-Pot Enantioselective Synthesis of Functionalized Pyranocoumarins and 2-Amino-4 H-Chromenes: Discovery of a Type of Potent Antibacterial Agent, *The Journal of Organic Chemistry*, 77: 887-878 (2012).
- [2] Wang J. L., Liu D., Zhang Z. J., Shan S., Han X., Srinivasula S. M., Croce C. M., Alnemri E. S., Huang Z., Structure-Based Discovery of an Organic Compound that Binds Bcl-2 Protein and Induces Apoptosis of Tumor Cells, *Proceedings of the National Academy of Sciences*, 97: 7124-7129 (2000).
- [3] El-Saghier A.M., Naili M.B., Rammash B.K., Saleh N.A., Kredan K.M., Synthesis and Antibacterial Activity of Some New Fused Chromenes, *Arkivoc*, Xvi, 16: 83-91 (2007).

- [4] Kumar R.R., Perumal S., Senthilkumar P., Yogeeswari P., Sriram D., An Atom Efficient, Solvent-Free, Green Synthesis and Antimycobacterial Evaluation of 2-amino-6-methyl-4-aryl-8-[(E)-arylmethylidene]-5, 6, 7, 8-tetrahydro-4H-pyrano [3, 2-c] pyridine-3-Carbonitriles, *Bioorganic & Medicinal Chemistry Letters*, **17**: 6459-6462 (2007).
- [5] Rueping M., Sugiono E., Merino E., Asymmetric Organocatalysis: An Efficient Enantioselective Access to Benzopyranes and Chromenes, *Chemistry—A European Journal*, **14**: 6329-6332 (2008).
- [6] Raj T., Bhatia R. K., Sharma M., Saxena A. K., Ishar M. P. S., Cytotoxic Activity of 3-(5-phenyl-3H-[1,2,4] dithiazol-3-yl) chromen-4-ones and 4-oxo-4H-chromene-3-carbothioic acid N-Phenylamides, *European Journal of Medicinal Chemistry*, **45**: 790-794 (2010).
- [7] Moon D.O., Kim K. C., Jin C.Y., Han M. H., Park C., Lee K.J., Kim, G.Y., Inhibitory Effects of Eicosapentaenoic Acid on Lipopolysaccharide-Induced Activation in BV<sub>2</sub> Microglia, *International Immunopharmacology*, **7**: 222-229 (2007).
- [8] Ellis G.P., "Chemistry of Heterocyclic of Compounds. Chromenes, Harmonesand Chromones"; Weissberger, A. Taylor, EC, Eds.; John Wiley: New York, 11-13 (1977).
- [9] Reynolds G. A., Drexhage K. H., New Coumarin Dyes with Rigidized Structure for Flashlamp-Pumped Dye Lasers, *Optics Communications*, **13**: 222-225 (1975).
- [10] Bissell E. R., Mitchell A. R., Smith R. E., Synthesis and chemistry of 7-amino-4-(trifluoromethyl) Coumarin and its Amino Acid and Peptide Derivatives, *The Journal of Organic Chemistry*, **45**: 2283-2287 (1980).
- [11] Marak B.N., Sran B.S., Singh V.P., Multicomponent Synthesis, Crystal Structure, Hirshfeld Surface Analysis, and Molecular Docking of 4H-Pyrans, *Chemistry Select*, **6**: 11249-11260 (2021).
- [12] Zhang A.Q., Zhang M., Chen H.H., Chen J., Chen H.Y., Convenient method for Synthesis of Substituted 2-Amino-2-chromenes, *Synthetic Communications*, **37**: 231-235 (2007).
- [13] Naimi-Jamal M. R., Mashkouri S., Sharifi A., An Efficient, Multicomponent Approach for Solvent-Free Synthesis of 2-amino-4H-chromene Scaffold, *Molecular Diversity*, **14**: 473-477 (2010).
- [14] Shaabani A., Ghadari R., Ghasemi S., Pedarpour M., Rezayan A.H., Sarvary A., Ng S.W., Novel One-Pot Three-And Pseudo-Five-Component Reactions: Synthesis of Functionalized Benzo [g]- and Dihydropyrano [2, 3-g] chromene Derivatives, *Journal of Combinatorial Chemistry*, **11**: 956-959 (2009).
- [15] Ballini R., Bigi F., Conforti M.L., De Santis D., Maggi R., Oppici G., Sartori G., Multicomponent Reactions under Clay Catalysis, *Catalysis Today*, **60**: 305-309 (2000).
- [16] Kumar B.S., Srinivasulu N., Udupi R.H., Rajitha B., Reddy Y.T., Reddy P.N., Kumar P.S., An Efficient Approach Towards Three-Component Coupling of One Pot Reaction for Synthesis of Functionalized Benzopyranes, *Journal of Heterocyclic Chemistry*, **43**: 1691-1693 (2006).
- [17] Shanthi G., Perumal P.T., An Eco-Friendly Synthesis Of 2-Aminochromenes and Indolyl Chromenes Catalyzed by InCl<sub>3</sub> in Aqueous Media, *Tetrahedron Letters*, **48**: 6785-6789 (2007).
- [18] Kumar D., Reddy V.B., Mishra B. G., Rana R.K., Nadagouda M.N., Varma R.S., Nanosized Magnesium Oxide as Catalyst for the Rapid and Green Synthesis of Substituted 2-Amino-2-Chromenes, *Tetrahedron*, **63**: 3093-3097 (2007).
- [19] Zhou Z., Yang F., Wu L., Zhang A., Potassium Phosphate Tribasic Trihydrate as Catalyst for the Rapid and Clean one-Pot Synthesis of 2-Amino-4H-Chromenes under Solvent-Free Conditions, *Chemical Science Transactions*, **1**: 57-60 (2012).
- [20] Tazari M., Kiyani H., Expedient Synthesis of 2-amino-4H-chromenes and 2-amino-4H-pyran-3-Carboxylates Promoted by Sodium Malonate, *Current Organic Synthesis*, **16**: 793-800 (2019).
- [21] Heravi M.M., Bakhtiari K., Zadsirjan V., Bamoharram F.F., Heravi O.M., Aqua Mediated Synthesis of Substituted 2-Amino-4H-Chromenes Catalyzed by Green and Reusable Preyssler Heteropolyacid, *Bioorganic & Medicinal Chemistry Letters*, **17**: 4262-4265 (2007).
- [22] Torii H., Nakadai M., Ishihara K., Saito S., Yamamoto H., Asymmetric Direct Aldol Reaction Assisted by Water and a Proline-Derived Tetrazole Catalyst, *Angewandte Chemie International Edition*, **43**: 1983-1986 (2004).



- [23] Golovleva V. K., Dunaevskii G. E., Levdikova T. L., Sarkisov Y. S., Tsyganok Y. I., Study of the Influence of Magnetic Fields on the Properties of Polar Liquids, *Russian Physics Journal*, **43**:1009-1012 (2000).
- [24] Ignatov I., Mosin O., Basic Concepts of Magnetic Water Treatment, *European Journal of Molecular Biotechnology*, **4**: 72-85 (2014).
- [25] Mosin O., Ignatov I., Magnetohydrodynamic Cell for Magnetic Water Treatment, *Nanotechnology Research and Practice*, **2**: 81-92 (2015).
- [26] Esmaeilnezhad E., Choi H.J., Schaffie M., Gholizadeh M., Ranjbar M., Characteristics and Applications of Magnetized Water as a Green Technology, *Journal of Cleaner Production*, **161**: 908-921 (2017).
- [27] Absalan Y., Gholizadeh M., Choi H. J., Magnetized Solvents: Characteristics and Various Applications, *Journal of Molecular Liquids*, **335**: 116167 (2021).
- [28] Bakherad M., Keivanloo A., Gholizadeh M., Doosti R., Javanmardi M., Using Magnetized Water as a Solvent for a Green, Catalyst-Free, and Efficient Protocol for the Synthesis of Pyrano [2, 3-*c*] Pyrazoles and Pyrano [4', 3': 5, 6] pyrazolo [2, 3-*d*] pyrimidines, *Research on Chemical Intermediates*, **43**: 1013-1029 (2017).
- [29] Bakherad M., Doosti R., Keivanloo A., Gholizadeh M., Amin A. H., A New, Simple, Catalyst-Free Method for the Synthesis of Pyrazolopyranopyrimidines in Magnetized Water, *Letters in Organic Chemistry*, **14**: 510-516 (2017).
- [30] Bakherad M., Bagherian G., Rezaeifard A., Mosayebi F., Shokoohi B., Keivanloo A., Synthesis of Pyrano [2, 3-*d*] Pyrimidines and pyrido [2, 3-*d*] Pyrimidines in the Magnetized Deionized Water Based on UV-Visible Study, *Journal of the Iranian Chemical Society*, **18**: 839-852 (2021).
- [31] Bakherad M., Moosavi-Tekyeh Z., Keivanloo A., Gholizadeh M., Toozandejani Z., A Catalyst-Free and Green Method for Synthesis of 9-Substituted-9 H-Diuracilopyrans in Magnetized Water: Experimental Aspects and Molecular Dynamics Simulation, *Research on Chemical Intermediates*, **44**: 373-387 (2018).
- [32] Dekamin M. G., Eslami M., Highly Efficient Organocatalytic Synthesis of Diverse and Densely Functionalized 2-amino-3-cyano-4H-pyrans under Mechanochemical Ball Milling, *Green Chemistry*, **16**: 4914-4921 (2014).
- [33] Zonouz A., Moghani D., Okhravi S., A facile and Efficient Protocol for the Synthesis of 2-amino-3-cyano-4H-pyran Derivatives at Ambient Temperature, *Current Chemistry Letters*, **3**: 71-74 (2014).
- [34] Hiremath P.B., Kamanna K., A Microwave Accelerated Sustainable Approach for the Synthesis of 2-amino-4H-chromenes Catalysed by WEPPA: A Green Strategy, *Current Microwave Chemistry*, **6**: 30-43 (2019).
- [35] Safari J., Zarnegar Z., Heydarian M., Magnetic Fe<sub>3</sub>O<sub>4</sub> Nanoparticles as Efficient and Reusable Catalyst for the Green Synthesis of 2-amino-4 H-chromene in Aqueous Media, *Bulletin of the Chemical Society of Japan*, **85**: 1332-1338 (2012).
- [36] Saikia M., Saikia L., Sulfonic Acid-Functionalized MIL-101 (Cr) as a Highly Efficient Heterogeneous Catalyst for One-Pot Synthesis of 2-Amino-4H-Chromenes in Aqueous Medium, *RSC Advances*, **6**: 15846-15853 (2016).
- [37] Kharbanger I., Rohman R., Mecadon H., Myrboh B., KF-Al<sub>2</sub>O<sub>3</sub> as an Efficient and Recyclable Basic Catalyst for the Synthesis of 4H-pyran-3-Carboxylates and 5-acetyl-4H-pyrans, *International Journal of Organic Chemistry*, **2**: 282-286 (2012).
- [38] Pourian E., Javanshir S., Dolatkah Z., Molaei S., Maleki A., Ultrasonic-Assisted Preparation, Characterization, and Use of Novel Biocompatible Core/Shell Fe<sub>3</sub>O<sub>4</sub>@GA@Isinglass in the Synthesis of 1,4-dihydropyridine and 4H-pyran Derivatives, *ACS Omega*, **3**: 5012-5020 (2018).
- [39] Khurana J. M., Chaudhary A., Efficient and Green Synthesis of 4H-pyrans and 4H-pyrano[2,3-*c*] Pyrazoles Catalyzed by Task-Specific Ionic Liquid [bmim]OH Under Solvent-Free Conditions, *Green Chemistry Letters and Reviews*, **5**: 633-638 (2012).
- [40] Najmedin A., Ahoie T. S., Hashemi M. M., Yavari I., Magnetic Graphitic Carbon Nitride-Catalyzed Highly Efficient Construction of Functionalized 4H-pyrans, *Synlett*, **29**: 645-649 (2018).
- [41] Pham D.D., Thanh G.-V., Le T.N., Efficient and green synthesis of 4H-pyran Derivatives under Ultrasound Irradiation in the Presence of K<sub>2</sub>CO<sub>3</sub> Supported on Acidic Montmorillonite, *Synthetic Communications*, **47**: 1684-1691 (2017).

- [42] Peng Y., Song G., Amino-Functionalized Ionic Liquid as Catalytically Active Solvent for Microwave-Assisted Synthesis of 4H-pyrans, *Catalysis Communications*, **8**: 111–114 (2007)
- [43] Smits R., Belyakov S., Plotniece A., Duburs G., Synthesis of 4H-pyran Derivatives Under Solvent-Free and Grinding Conditions, *Synthetic Communications*, **43**: 465–475 (2013).
- [44] Kantharaju K., Khatavi S.Y., Microwave Accelerated synthesis of 2-Amino-4H-Chromenes Catalyzed by WELFSA: A Green Protocol, *ChemistrySelect*, **3**: 5016-5024 (2018).
- [45] Hosseinzadeh-Baghan S., Mirzaei M., Eshtiagh-Hosseini H., Zadsirjan V., Heravi M. M., Mague J. T., An Inorganic–Organic Hybrid Material Based on a Keggin-Type Polyoxometalate@ Dysprosium as an Effective And Green Catalyst in the Synthesis of 2-amino-4H-chromenes via Multicomponent Reactions, *Applied Organometallic Chemistry*, **34**: e5793 (2020).
- [46] Mohammadi R., Esmati S., Gholamhosseini-Nazari M., Teimuri-Mofrad R., Synthesis and Characterization of a Novel Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-BenzIm-Fc[Cl]/BiOCl Nanocomposite and its Efficient Catalytic Activity in the Ultrasound-Assisted Synthesis of Diverse Chromene Analogs, *New Journal of Chemistry*, **43**: 135-145 (2019).
- [47] Ballini R., Bosica G., Conforti M. L., Maggi R., Mazzacani A., Righi P., Sartori G., Three-Component Process for the Synthesis of 2-amino-2-chromenes in Aqueous Media, *Tetrahedron Letters*, **57**: 1395-1398 (2001).
- [48] Kale S.R., Kahandal S.S., Burange A.S., Gawande M.B., Jayaram R. V., A Benign Synthesis of 2-amino-4H-Chromene in Aqueous Medium Using Hydrotalcite (HT) as a Heterogeneous Base Catalyst, *Catalysis Science & Technology*, **3**: 2050-2056 (2013).
- [49] Magar R.L., Thorat P.B., Jadhav V.B., Tekale S.U., Dake S.A., Patil B.R., Pawar R.P., Silica Gel Supported Polyamine: A Versatile Catalyst for One Pot Synthesis of 2-amino-4H-chromene Derivatives. *Journal of Molecular Catalysis A: Chemical*, **374**: 118-124 (2013).
- [50] Kundu S.K., Mondal J., Bhaumik A., Tungstic Acid Functionalized Mesoporous SBA-15: A Novel Heterogeneous Catalyst for Facile One-Pot Synthesis of 2-amino-4H-chromenes in Aqueous Medium, *Dalton Transactions*, **42**: 10515-10524 (2013).
- [51] Moghadasi Z., One-Pot Synthesis of 2-amino-4H-Chromenes Using L-Proline as a Reusable Catalyst, *Journal of Medicinal and Chemical Sciences*, **2**: 35-37 (2019).