Scientific paper

Sodium Saccharin as an Effective Catalyst for Rapid One-pot Pseudo-five Component Synthesis of Dihydropyrano[2,3-*g*]chromenes under Microwave Irradiation

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Received: 06-04-2017

Abstract

One-pot microwave-assisted synthesis of dihydropyrano[2,3-*g*]chromenes catalyzed by sodium saccharin as an efficient, mild and green catalyst was studied. The method presented is a safe and eco-friendly approach for the multicomponent synthesis of dihydropyrano[2,3-*g*]chromene derivatives with many merits including short reaction times (in comparison with other reported results), high yields and easy work up.

Keywords: Dihydropyrano[2,3-*g*]chromenes; Sodium saccharin; Pseudo-five component reactions; Microwave irradiation

1. Introduction

One pot multicomponent reactions (MCRs) with high atom economy^{1,2} play an important role in combinatorial chemistry. Consequently, this field has attracted great attention in recent years.^{3–5} During MCRs, target compounds are produced with greater efficiency by generating structural complexity in a single step from three or more reactants.^{6,7}

Chromenes and their derivatives have a wide range of applications in various fields of chemistry, biology and pharmacology.⁸ Some of these compounds exhibit spasmolytic, diuretic, anticoagulant, anticancer and antimicrobial activities.^{9–11}

During attempts to synthesize the title compounds, some shortcomings were observed, such as long reaction time. Consequently, to overcome this drawback, the microwave irradiation method was used in the present study. Microwave irradiation (MW) as a form of electromagnetic energy that falls at the lower-frequency end of electromagnetic spectrum (300–300000 MHz), uses the ability of some liquids and solids to transform electromagnetic radiation into heat to drive chemical reactions.^{12,13} In fact, use of microwaves has some advantages, such as spectacular decrease of the reaction time, improved conversions, formation of cleaner products and wide scope for the development of new reaction conditions.^{14–16}

Development of catalytic systems composed of low-cost, clean, environmentally benign and commercially available materials, has been a challenge in organic synthesis. Saccharin as an artificial sweetener with no food energy, has been employed extensively in a variety of foods and beverages, such as drinks, juices, cookies, medicines, toothpaste and gelatin. It is also used in cosmetics, pharmaceutical products and nutritive and non nutritive sweeteners.^{17–20}

Recently, sodium saccharin as a basic green and easy available compound was used as catalyst in some organic syntheses.^{21,22} We now report a new efficient and simple synthetic method, taking place via addition and subsequently cyclization of 2,5-dihydroxy-1,4-benzoquinone, arylaldehydes and malononitrile in the presence of a catalytic amount of sodium saccharine under microwave irradiation. Green and low-cost catalyst, easy workup, short reaction time in comparison with other reported results,²³ are just some of the advantages of the presented method.

2. Experimental

2. 1. Materials and Apparatus

All chemicals were obtained from Merck and Sigma–Aldrich and used as received. Melting points were de-

terminated in an open capillary using a Thermo Scientific 9300 apparatus. FTIR spectra were recorded with a Perkin–Elmer FTIR 550 spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded in $\text{DMSO}-d_6$ using Bruker DRX-400 spectrometer operating at 400 and 100 MHz, respectively. The elemental analyses (CHN) were obtained from a Carlo Erba model EA 1108 analyzer carried out on Perkin–Elmer 240c analyzer. Microwave-assisted reactions were performed with a Milestone ETHOS EZ apparatus, keeping irradiation power fixed and monitoring the internal reaction temperature. Mass spectra were recorded on a Finnigan MAT 44S by Electron Ionization (EI) mode with an ionization voltage of 70 eV.

2. 2. General Procedure for the Synthesis of Dihydropyrano[2,3-*g*]chromenes

A mixture of arylaldehyde (2.0 mmol), malononitrile (0.13 g, 2.0 mmol), 2,5-dihydroxy-1,4-benzoquinone (0.14 g, 1.0 mmol), $\text{H}_2\text{O}/\text{EtOH}$ (1:1, 5 mL) and a catalytic amount of sodium saccharin (10 mol%) was irradiated in a microwave oven (100 W) at 30 °C for appropriate times. After completion of the reaction (monitored by TLC), the precipitated product was separated from the reaction mixture by simple filtration and then washed with EtOH to afford the products (Scheme 1).

Scheme 1. Synthesis of dihydropyrano[2,3-*g*]chromene derivatives catalyzed by sodium saccharin under microwave irradiation.

2. 3. Spectral and Analytical Data

2,7-Diamino-4,9-bis(4-nitrophenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-*g*]chromene-3,8-dicarbonitrile (4a). Brown powder ($\text{C}_{26}\text{H}_{14}\text{N}_6\text{O}_8$); FTIR (KBr): ν_{max} 3345 (NH_2), 3180 ($=\text{C}-\text{H}$ aromatic), 2196 (CN), 1592 ($\text{C}=\text{C}$ aromatic) cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.7(s, 2H, 2CH), 7.39–8.18 (m, 12H, H–Ar, 2 NH_2) ppm. Anal. Calcd for $\text{C}_{26}\text{H}_{14}\text{N}_6\text{O}_8$: C 58.00, H 2.62, N 15.61%. Found: C 58.10, H 2.61, N 15.65%.

2,7-Diamino-4,9-bis(2-hydroxyphenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-*g*]chromene-3,8-dicarbonitrile (4b). Orange powder ($\text{C}_{26}\text{H}_{16}\text{N}_4\text{O}_6$); FTIR (KBr): ν_{max} 3459(OH), 3303 (NH_2), 3180 ($=\text{C}-\text{H}$ aromatic), 2189

(CN), 1579 ($\text{C}=\text{C}$ aromatic) cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 3.67 (2H, bs, 2OH), 4.74 (s, 2H, 2CH), 6.6–7.1 (m, 12H, H–Ar, 2 NH_2) ppm. Anal. Calcd for: $\text{C}_{26}\text{H}_{16}\text{N}_4\text{O}_6$: C 65.00, H 3.36, N 11.66%. Found: C 65.10, H 3.33, N 11.65%.

2,7-Diamino-4,9-di-*ortho*-tolyl-5,10-dioxo-4,9-dihydropyrano[2,3-*g*]chromene-3,8-dicarbonitrile (4c). Brown powder ($\text{C}_{28}\text{H}_{20}\text{N}_4\text{O}_4$); FTIR (KBr): ν_{max} 3182 (NH_2), 3053 ($=\text{C}-\text{H}$ aromatic), 2201 (CN), 1596 ($\text{C}=\text{C}$ aromatic) cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.48 (s, 6H, 2 CH_3), 5.37 (s, 2H, 2CH), 6.95–7.30 (m, 12H, H–Ar, 2 NH_2) ppm. Anal. Calcd for $\text{C}_{28}\text{H}_{20}\text{N}_4\text{O}_4$: C 70.58, H 4.23, N 11.76%. Found: C 70.61, H 4.22, N 11.75%.

2,7-Diamino-4,9-diphenyl-5,10-dioxo-4,9-dihydropyrano[2,3-*g*]chromene-3,8-dicarbonitrile (4d). Brown powder ($\text{C}_{26}\text{H}_{16}\text{N}_4\text{O}_6$); FTIR (KBr): ν_{max} 3296 (NH_2), 3179 ($=\text{C}-\text{H}$ aromatic), 2202 (CN), 1595 ($\text{C}=\text{C}$ aromatic) cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.46 (s, 2H, 2CH), 7.24–7.40 (m, 12H, H–Ar, 2 NH_2) ppm. Anal. Calcd for $\text{C}_{26}\text{H}_{16}\text{N}_4\text{O}_6$: C 69.64, H 3.60, N 12.49%. Found: C 69.61, H 3.62, N 12.46%.

2,7-Diamino-4,9-bis(4-chlorophenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-*g*]chromene-3,8-dicarbonitrile

(4e). Brown powder ($\text{C}_{26}\text{H}_{14}\text{N}_4\text{O}_4\text{Cl}_2$); FTIR (KBr): ν_{max} 3317 (NH_2), 3173 ($=\text{C}-\text{H}$ aromatic), 2197 (CN), 1591 ($\text{C}=\text{C}$ aromatic) cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.45 (s, 2H, 2CH), 7.29–7.32 (m, 12H, H–Ar, 2 NH_2) ppm. Anal. Calcd for $\text{C}_{26}\text{H}_{14}\text{N}_4\text{O}_4\text{Cl}_2$: C 60.36, H 2.73, N 10.83%. Found: C 60.28, H 2.75, N 10.81%.

2,7-Diamino-4,9-bis(4-bromophenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-*g*]chromene-3,8-dicarbonitrile (4f). Brown powder ($\text{C}_{26}\text{H}_{14}\text{N}_4\text{O}_4\text{Br}_2$); FTIR (KBr): ν_{max} 3321 (NH_2), 3179 ($=\text{C}-\text{H}$ aromatic), 2199 (CN), 1589 ($\text{C}=\text{C}$ aromatic) cm^{-1} . ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 4.45 (s, 2H, 2CH), 7.22–7.51 (m, 12H, H–Ar, 2 NH_2) ppm. Anal. Calcd for: $\text{C}_{26}\text{H}_{14}\text{N}_4\text{O}_4\text{Br}_2$: C 51.51, H 2.33, N 9.24%. Found: C 51.60, H 2.36, N 9.26%.

2,7-Diamino-4,9-bis(2,4-dichlorophenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-g]chromene-3,8-dicarbonitrile (4g).

Brown powder ($C_{26}H_{12}N_4O_4Cl_4$); FTIR (KBr): $\nu_{\max}$ 3326 (NH_2), 3178 ($=C-H$ aromatic), 2203 (CN), 1590 ($C=C$ aromatic) cm^{-1} . 1H NMR (400 MHz, $DMSO-d_6$): δ 5.00 (s, 2H, 2CH), 7.34–8.52 (m, 10H, H-Ar, $2NH_2$), ppm. ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 33.2 (CH), 56.08, 117.2, 119.9, 128.4, 129.1, 132.4, 133.4, 139.8, 147.5, 158.7, (C-alkene and Ar), 177.3 ($2C=O$) ppm. MS m/z (%): 586 (M^+), 522 (3), 431 (9), 366 (25), 339 (41), 274 (82), 186 (32), 115 (44), 91 (100), 65 (58). Anal. Calcd for $C_{26}H_{12}N_4O_4Cl_4$: C 53.24, H 2.04, N 9.55%. Found: C 53.78, H 2.09, N 9.32%.

2,7-Diamino-4,9-bis(3-nitrophenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-g]chromene-3,8-dicarbonitrile (4h).

Brown powder ($C_{26}H_{14}N_6O_8$); FTIR (KBr): $\nu_{\max}$ 3345 (NH_2), 3207 ($=C-H$ aromatic), 2195 (CN), 1593 ($C=C$ aromatic) cm^{-1} . 1H NMR (400 MHz, $DMSO-d_6$): δ 4.71 (s, 2H, 2CH), 7.39–8.15 (m, 12H, H-Ar, $2NH_2$), ppm; ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 36.2 (CH), 56.7, 117.0, 119.3, 123.0, 130.07, 130.5, 135.2, 145.4, 147.2, 148.2, 158.8 (C-alkene and Ar), 177.52 ($2C=O$) ppm. MS m/z (%): 538 (M^+), 417 (2), 348 (4), 281 (4), 257 (9), 222 (12), 152 (14), 131 (21), 104 (75), 91 (26), 76 (73), 57 (55), 43 (100). Anal. Calcd for $C_{26}H_{14}N_6O_8$: C 57.99, H 2.60, N 15.61%. Found: C 58.00, H 2.40, N 15.88%.

2,7-Diamino-4,9-bis(thiophen-2-yl)-5,10-dioxo-4,9-dihydropyrano[2,3-g]chromene-3,8-dicarbonitrile (4i).

Brown powder ($C_{22}H_{12}N_4O_4S_2$); FTIR (KBr): $\nu_{\max}$ 3333 (NH_2), 3102 ($=C-H$ aromatic), 2195 (CN), 1576 ($C=C$ aromatic) cm^{-1} . 1H NMR (400 MHz, $DMSO-d_6$): δ 3.80 (s, 2H, 2CH), 6.90–8.73 (m, 10H, H-Ar, $2NH_2$), ppm. ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 76.4, 129.7, 131.02, 135.7, 139.1, 140.9, 153.9 (C-alkene, C-thiophene), 187.6 ($2C=O$) ppm. MS m/z (%): 460 (M^+), 374 (8), 342 (12), 314 (18), 160 (92), 147 (15), 133 (30), 109 (34), 76 (38), 66 (50), 49 (100). Anal. Calcd for $C_{22}H_{12}N_4O_4S_2$: C 57.39, H 2.60, N 12.17, S 13.91%. Found: C 57.10, H 2.60, N 12.10, S 13.33%.

2,7-Diamino-4,9-bis(4-hydroxyphenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-g]chromene-3,8-dicarbonitrile (4j).

Brown powder ($C_{26}H_{16}N_4O_6$); FTIR (KBr): $\nu_{\max}$ 3417 (OH), 3346 (NH_2), 3219 ($=C-H$ aromatic), 2198 (CN), 1599 ($C=C$ aromatic) cm^{-1} . 1H NMR (400 MHz, $DMSO-d_6$): δ 4.10 (s, 2H, 2CH), 6.90–8.30 (m, 12H, H-Ar, $2NH_2$), 11.08 (s, 2H, 2OH) ppm. ^{13}C NMR (100 MHz, $DMSO-d_6$): δ 34.2 (2CH), 75.5, 107.2, 114.6, 115.5, 117.1, 123.2, 134.3 (C-alkene and Ar), 160.96, 164.4 ($2C=O$) ppm. MS m/z (%): 480 (M^+), 454 (9), 313 (48), 274 (25), 238 (38), 198 (18), 187 (46), 170 (100), 94 (69). Anal. Calcd for $C_{26}H_{16}N_4O_6$: C 65.00, H 3.33, N 11.66%. Found: C 64.88, H 3.59, N 11.1%.

2,7-Diamino-4,9-di(*para*-tolyl)-5,10-dioxo-4,9-dihydropyrano[2,3-g]chromene-3,8-dicarbonitrile (4k).

Brown powder ($C_{28}H_{20}N_4O_4$); FTIR (KBr): $\nu_{\max}$ 3436 (NH_2), 2922 ($=C-H$ aromatic), 2198 (CN), 1584 ($C=C$ aromatic) cm^{-1} . 1H NMR (400 MHz, $DMSO-d_6$): δ 2.25 (s, 6H, $2CH_3$), 4.45 (s, 2H, 2CH), 6.94–7.86 (m, 12H, H-Ar, $2NH_2$) ppm. MS m/z (%): 476 (M^+), 388 (2), 313 (48), 265 (11), 299 (8), 168 (21), 140 (42), 115 (34), 104 (72), 91 (40), 69 (80), 42 (100). Anal. Calcd for $C_{28}H_{20}N_4O_4$: C 70.58, H 4.20, N 11.76%. Found: C 70.91, H 4.10, N 11.91%.

2,7-Diamino-4,9-bis(4-methoxyphenyl)-5,10-dioxo-4,9-dihydropyrano[2,3-g]chromene-3,8-dicarbonitrile (4l).

Brown powder ($C_{28}H_{20}N_4O_6$); FTIR (KBr): $\nu_{\max}$ 3321 (NH_2), 2926 ($=C-H$ aromatic), 2196 (CN), 1584 ($C=C$ aromatic) cm^{-1} . 1H NMR (400 MHz, $DMSO-d_6$): δ 3.65 (s, 6H, $2OCH_3$), 4.45 (s, 2H, 2CH), 6.72–7.20 (m, 12H, H-Ar, $2NH_2$) ppm. MS m/z (%): 508 (M^+), 445 (16), 380 (45), 355 (8), 339 (28), 290 (34), 274 (49), 198 (39), 128 (22), 105 (80), 91 (100), 77 (28). Anal. Calcd for $C_{28}H_{20}N_4O_6$: C 66.14, H 3.93, N 11.02%. Found: C 66.70, H 3.70 and N 11.10%.

3. Results and Discussion

In the initial stages of the presented research optimization of the catalyst amounts, solvent and power of microwave irradiation were investigated. In the first step, catalyst optimization was studied. For determining the best quantity of sodium saccharin, 2 mmol of 4-nitrobenzaldehyde, 2 mmol of malononitrile and 1 mmol of 2,5-dihydroxybenzoquinone were used (as a model reaction). The reaction was performed in the presence of various amounts of the catalyst. As shown in Table 1, it is clearly observed that 0.019 g (10 mol%) of sodium saccharin lead to the highest yield of **4a** (Table 1, entry 5).

Table 1. Effect of catalyst amounts on the time and yield of **4a**^a

Entry	Cat. (mol%)	Time (min)	Yield (%) ^b
1	—	20	—
2	2	15	47
3	5	12	71
4	8	10	83
5	10	8	90
6	12	8	90
7	15	8	88
8 ^c	10	19 ^d	88

^a 1 mmol of **1**, 2 mmol of **2** and 2 mmol of **3a** in 5 mL EtOH/ H_2O (1:1) and power of 100 W. ^b Isolated yield. ^c Thermal condition (35 °C). ^d Time in hours.

The obtained results show that excellent yield was achieved using 10 mol% (0.019 g) of sodium saccharin (Table 1, entry 5). It should be considered that due to the very low solubility of products in general organic solvents, homogeneous catalysts are the best choice for the synthesis of dihydropyrano[2,3-*g*]chromenes.

In continuation of the research, the power of microwave irradiation was examined. Model reaction was run at several powers. Results in Table 2 show that the power of 100 W was the optimized condition for the synthesis of **4a** (Table 2, entry 4).

Table 2. Optimization of microwave power^a

Entry	Power (W)	Time (min)	Yield (%) ^b
1	100	2	50
2	100	4	55
3	100	6	70
4	100	8	90
5	100	10	90
6	200	5	55
7	200	8	42
8	300	5	45
9	300	8	40

^a 1 mmol of **1**, 2 mmol of **2** and 2 mmol of **3a** in the presence of 10 mol% of catalyst in EtOH/H₂O (1:1). ^b Isolated yield.

In last step, the effect of the solvent on the time and yield of the reaction was studied. Depending on the results presented in Table 3, in contrast to other solvents, H₂O/EtOH in ratio of 1:1 is the proper solvent for the synthesis of **4a** in high yield (Table 3, entry 4).

Table 3. Solvent effect on synthesis of **4a**^a

Entry	Solvent	Time (min)	Yield (%) ^b
1	EtOH	5	35
2	H ₂ O	8	70
3	CH ₃ CN	12	65
4	EtOH/H ₂ O (1:1)	8	90
5	EtOH/H ₂ O (1:2)	8	75
6	MeOH	8	41
7	Dioxane	10	52

^a 1 mmol of **1**, 2 mmol of **2** and 2 mmol of **3a**, in the presence of 10 mol% of sodium saccharin and power of 100 W. ^b Isolated yield.

According to the optimization results, the procedure was extended to various aldehydes (with electron withdrawing and electron donating groups). As can be seen in Table 4, aldehydes containing electron withdrawing groups (especially at the *para* position), have the highest yields (Table 4, entries 1, 8), also low yield products were obtained using aldehydes with a group at the *ortho* position (Table 4, entries 2, 3, 7). As a result, the reaction proceeded very efficiently and led to the formation of dihydropyrano[2,3-*g*]chromene derivatives **4a–l** in high yields and in short reaction times. The structures of **4a–l** was deduced from their FTIR, mass spectroscopy, elemental analysis, ¹H NMR and ¹³C NMR techniques.

Scheme 2. The plausible mechanism of dihydropyrano[2,3-*g*]chromenes formation

Table 4. Pseudo-five-component synthesis of dihydropyrano[2,3-g]chromene derivatives **4**^a

Entry	Product	ArCHO 3a-l	Time (min)	Yield (%) ^b	m.p. (°C)	Ref.
1	4a		8	90	290–293	23
2	4b		14	80	264–266	23
3	4c		16	78	280–282	23
4	4d		19	82	287–289	23
5	4e		13	85	273–275	23
6	4f		16	85	264–266	23
7	4g		19	80	263–265	–
8	4h		13	90	242–244	–
9	4i		13	85	258–260	–
10	4j		18	80	208–210	–
11	4k		18	78	260–263	–
12	4l		18	82	>300	–

^a 1 mmol of **1**, 2 mmol of **2** and 2 mmol of **3a-l**, in the presence of 10 mol% of sodium saccharin in EtOH/H₂O (1:1), and power of 100 W. ^b Isolated yield.

A plausible mechanism of the reaction is presented in Scheme 2. In the first step of the reaction, acidic proton of malononitrile has been separated by sodium saccharin as a basic catalyst. Then, the Knoevenagel condensation of malononitrile anion and aldehyde leads to the intermediate **I**. In the next step, cyclization and tautomerization lead via **II** to the product **III**. The same process occurs on the other side of 2,5-dihydroxy-1,4-benzoquinone (due to its special structure) and finally, a dual chromene structure is produced.

The efficiency of sodium saccharin in comparison with other catalysts in the synthesis of dihydropyrano[2,3-*g*]chromenes was also investigated. Results presented in Table 5 clearly show that sodium saccharin can be mentioned as a powerful, highly efficient catalyst for the synthesis of dihydropyrano[2,3-*g*]chromenes under microwave irradiation.

Table 5. The effect of various catalysts on the synthesis of **4a** under optimized conditions

Entry	Catalyst (10 mol %)	Time	Yield (%) ^a
1	Meglumine	15	43
2	[BMIM]BF ₄ ^b	8	57
3	Sodium phthalimide	10	70
4	Sodium benzoate	25	64
5	NEt ₃	20	75
6	Saccharin	30	52
7	Sodium saccharin	8	90

^a Isolated yield. ^b 0.02 g.

4. Conclusion

We have developed an efficient, novel and eco-friendly method for the synthesis of dihydropyrano[2,3-*g*]chromenes in the presence of sodium saccharin as the catalyst under microwave irradiation. The procedure described provides clean reaction conditions with easy work-up, simple filtration and short reaction times with high yields of products.

5. Acknowledgments

We thank the Research Council of the University of Kashan for support of this work.

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Povzetek

Raziskalo smo »one-pot« sintezo dihidropirano[2,3-*g*]kromenov pod pogoji obsevanja z mikrovalovi in z uporabo natrijevega saharinata kot učinkovitega, milega in zelenega katalizatorja. Metoda predstavlja varen in okolju prijazen pristop k multikomponentni sintezi dihidropirano[2,3-*g*]kromenskih derivatov; odlikujejo jo mnoge prednosti v primerjavi z ostalimi doslej objavljenimi pristopi, kot so krajši reakcijski časi, višji izkoristki in enostavnost izolacije.