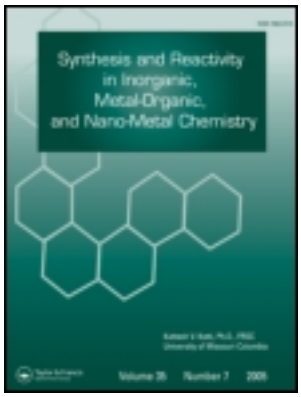

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Microwave-Assisted One-Pot Synthesis of 2-Amino-2-chromenes Using Piperazine as a Catalyst Under Solvent-Free Conditions

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A simple and efficient procedure for the synthesis of substituted 2-amino-2-chromenes employing one-pot three-component condensation reaction of aromatic aldehydes with malononitrile and activated phenols has been developed by using the odorless and easy to work piperazine in the absence of solvents under microwave irradiation. The present method is operationally simple and offers several advantages such as high yields, short reaction time, and simple workup.

Keywords 2-amino-2-chromenes, microwave irradiation, multicomponent, piperazine, solvent-free

INTRODUCTION

Multicomponent reactions (MCRs) under solvent-free conditions are valuable procedures in organic synthesis because a multistep reaction may produce considerable amounts of environmentally unfavorable wastes mainly due to a series of complex isolation procedures, which often needs expensive, toxic, and hazardous solvents after each step. Thus, MCRs are extensively investigated for combinatorial library syntheses, and finding their applications in the discovery process for new drugs and agricultural chemicals.[1−4] Further, the use of solvent-free synthesis in conjunction with microwave irradiation (MWI) develops a facile procedure associated with advantages of short reaction times, uniform heating, higher yields, enhanced selectivity, and associated ease of manipulation.[5,6]

2-amino-chromenes are an important class of heterocycles as they are the main constituents of many natural products. They are widely used as cosmetics, pigments,[7] and potential biodegradable agrochemicals.[8] Fused chromenes are biologically active compounds with a wide range of activities such as antimicrobial,[9] mutagenicitical,[10] antiviral,[11] sex pheromonal,[12] antitumoral,[13] and central nervous system activities.[14] Thus, the synthesis of 2-amino-2-chromenes is very important for organic chemists.

The most important synthetic method for the preparation of these compounds involves the multi-component condensation reaction of aldehyde, malononitrile, and an activated phenol in organic solvents (i.e., ethanol, acetonitrile) and in the presence of piperidine, which are frequently utilized in stoichiometric amounts and refluxing for several hours.[15] Various modified procedures have been reported for the preperation of substituted 2-amino-2-chromenes using CTACl,[16] TEBA,[17] γ-alumina,[18] K_2CO_3,[19] $H_{14}[NaP_5W_{30}O_{110}]$,[20] p-TSA,[21] and KF/Al_2O_3[22] as a catalyst. However, most of these methods suffer from one or more drawbacks such as moderate yields of the products, the use of toxic solvents, longer reaction time, and laborious workup procedure.

EXPERIMENTAL

General

All chemicals used were obtained commercially. Melting points were measured by using capillary tubes on an electro thermal digital apparatus and are uncorrected. Microanalyses were performed by the elemental analyzer (Elemental, Vario EL III) at the Arak University. The products were characterized by IR spectra, NMR spectra, and by comparison of their melting points with literature values. IR spectra were recorded as KBr disc on a galaxy series FT-IR 5000 spectrometer. NMR spectra were recorded on a Brucker spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard. Microwave irradiation was carried out in a National Microwave Oven, Model No. NN-K571MF (2450 MHz, 1000 W).

General Procedure for Preparation of 2-Amino-chromene Derivatives

In a round bottomed flask, piperazine (0.1 mmol) was added to a mixture of aldehyde (1 mmol), phenol (1 mmol), and malononitrile (1 mmol). The mixture was irradiated with microwaves under solvent-free conditions for the appropriate time

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TABLE 1
Optimization of reaction conditions

Entry	Solvent	Conditions	Piperazine (mol%)	Time/min	Yield/ %[a]
1	Ethanol	Reflux	10	300	61
2	Chloroform	Reflux	10	300	81
3	Tetrahedrofuran	Reflux	10	300	55
4	Acetonitrile	Reflux	10	300	80
5	Solvent-free	120 °C	10	60	80
6	Solvent-free	MW (450 W)	10	8	65
7	Solvent-free	MW (600 W)	10	8	84
8	Solvent-free	MW (900 W)	10	8	83
9	Solvent-free	MW (600 W)	20	8	84

[a] Isolated yields.

according to Table 1. After completion of the reaction, as indicated by TLC, the mixture of ethanol-water (2:1, 5 mL) was added to the reaction mixture and then the solution filtered. The crude product was washed with water and purified by recrystallization using ethanol. The products were obtained in 86–95% yields.

Physical and Spectroscopic Data for Selected Compounds

Compound **4a** (Table 2, entry 1): IR (KBr): ν_{max} = 3418, 3340, 3020, 2918, 2189, 1649, 1587, 1508, 1404, 1155, 1111, 1043, 856, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, J = 6.2 Hz, 2H), (d, J = 5.5 Hz, 1H), 7.42-7.38 (m, 2H), 7.24-7.08 (m, 5H), 5.22 (s, 1H), 4.59 (br, 2H), 2.30 (s, 3H).

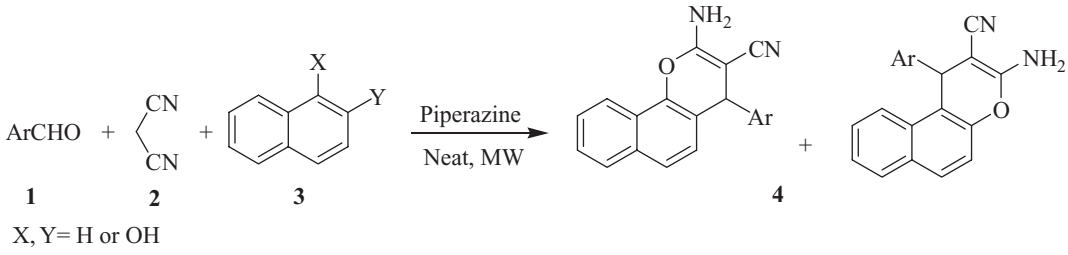
Compound **4e** (Table 2, entry 5): IR (KBr): ν_{max} = 3416, 3323, 3194, 3051, 2193, 1641, 1591, 1485, 1410, 1234, 1080, 1012, 819, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 6.4 Hz, 1H), 7.45-7.40 (m, 3H), 7.27 (d, J = 6.3 Hz 2H), 7.07 (d, J = 8.4 Hz 2H),), 5.23 (s, 1H), 4.64 (br, 2H); ^{13}C NMR(75 MHz, $CDCl_3$): δ = 160.2, 147.3, 145.6, 132.1, 131.3, 130.5, 130.2, 129.7, 129.0, 127.7, 125.5, 124.0, 120.6, 120.2, 117.3, 115.5, 57.4, 37.8; Anal calcd for $C_{20}H_{13}BrN_2O$: C, 63.68; H, 3.47; N, 7.43. Found: C, 63.56; H, 3.52; N, 7.45.

Compound **4k** (Table 2, entry 11): IR (KBr): ν_{max} = 3474, 3344, 3072, 2868, 2173, 1645, 1589, 1518, 1410, 1267, 1217, 1084, 831, 769 cm^{-1}; ^1H NMR (300 MHz, DMSO-d6): δ = 9.70 (s, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.87-6.76 (m, 5H), 6.51

TABLE 2
Synthesis of substituted 2-amino-2-chromenes

Entry	Ar (aldehyde)	Phenol	Compound	Time/min	Yield/%[a]	Mp (°C) Found	Mp (°C) Reported [lit.]
1	4-MeC_6H_4	2-naphthol	**4a**	6	91	268–269	270–271 [29]
2	C_6H_5	2-naphthol	**4b**	8	84	285–287	287–288 [29]
3	2-ClC_6H_4	2-naphthol	**4c**	7	82	268–270	270–271 [29]
4	4-$MeOC_6H_4$	2-naphthol	**4d**	7	90	189–190	190–191 [29]
5	4-BrC_6H_4	2-naphthol	**4e**	8	95	228–231	—
6	4-MeC_6H_4	1-naphthol	**4f**	7	89	204–205	206–207 [29]
7	C_6H_5	1-naphthol	**4g**	8	88	215–217	216–217 [29]
8	4-ClC_6H_4	1-naphthol	**4h**	8	80	235–236	231–232 [29]
9	4-$NO_2C_6H_4$	1-naphthol	**4i**	7	81	238–240	240–241[29]
10	4-MeC_6H_4	resorcinol	**4j**	6	93	186–188	182–184 [30]
11	4-$MeOC_6H_4$	resorcinol	**4k**	6	89	230–231	111–112[30]
12	C_6H_5	resorcinol	**4l**	7	90	234–235	232–234 [19]
13	4-FC_6H_4	resorcinol	**4m**	7	87	188–189	187–189 [30]
14	C_6H_5	2,7-naphthalenediol	**4n**	8	81	253–254	249–251 [31]
15	4-ClC_6H_4	2,7-naphthalenediol	**4o**	8	83	265–266	263–267 [31]
16	3-$MeOC_6H_4$	2,7-naphthalenediol	**4p**	8	80	238–240	—

[a] Isolated yields.



SCH. 1.

(d, J = 8.6 Hz, 1H), 6.39 (d, J = 2 Hz, 1H), 4.56(s, 1H), 3.71 (s, 3H); ^{13}C NMR(75 MHz, DMSO-d6): δ = 160.6, 158.4, 157.4, 149.2, 139.0, 130.4, 128.9, 121.3, 114.5, 114.4, 112.8, 102.6, 57.1, 55.4, 39.7; Anal calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9,52. Found: C, 69.27; H, 4.69; N, 9.61.

Compound **4p** (Table 2, entry 16): IR (KBr): ν_{max} = 3454, 3354, 3205, 2974, 2179, 1651, 1608, 1489, 1406, 1217, 1140, 1045, 829, 754, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d6): δ = 9.88 (s, 1H), 7.76 (t, J = 9.4 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 7.08-6.94 (m, 5H), 6.76-6.63 (m, 3H), 4.98 (s, 1H), 3.69 (s, 3H); ^{13}C NMR(75 MHz, DMSO-d6): δ = 160.2, 159.8, 156.8, 147.7, 147.5, 132.6, 130.6, 130.4, 129.7, 125.7, 121.1, 119.6, 117.6, 114.1, 113.9, 113.6, 111.5, 106.1, 58.3, 55.4, 38.8; Anal calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.12; H, 4.65; N, 8.07.

RESULTS AND DISCUSSION

During the course of our recent studies directed toward the development of practical safe and environmentally friendly procedures for some important transformations,[23–28] we wish to report a simple and efficient procedure for the synthesis of 2-amino-chromenes from condensation of aromatic aldehydes with malononitrile and activated phenols in the presence of piperazine as a catalyst in the absence of solvents under microwave irradiation (Scheme 1).

First, the condensation reaction of benzaldehyde with malononitrile and 2-naphthol in the presence of piperazine was explored in order to search for the optimal conditions, such as the amount of catalysts and reaction conditions (Table 1). As shown in Table 1, the best conditions for this reaction were solvent-free, 10 mol% of piperazine and microwave irradiation, since the reaction could be carried out in high yield (Table 1, entry 7).

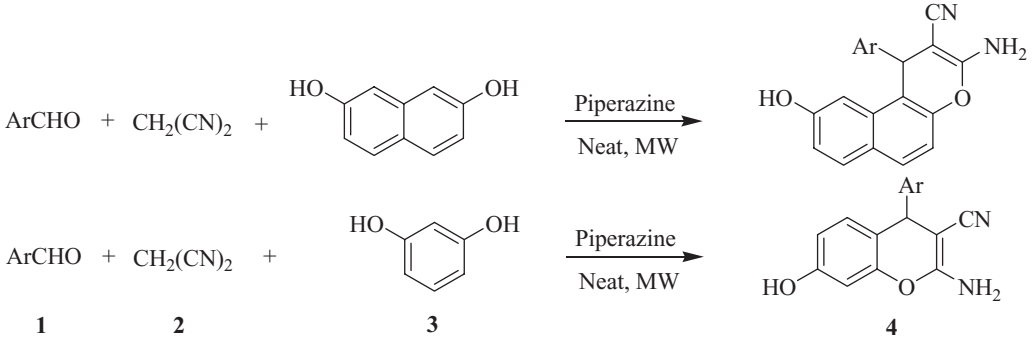
TABLE 3
Different catalysts for synthesis of **4b**

Entry	Catalysts	Time/h	Yield/ %[a]
1	Piperazine	0.12	91
2	$H_{14}[NaP_5W_{30}O_{110}]$	3	93 [20]
3	[bmim]OH	0.16	90[29]
4	*p*-TSA	3	90 [21]
5	KF/Al_2O_3	6	83 [22]
6	Basic alumina	3	96 [18]

[a] Isolated yields.

Encouraged by this success, a wide variety of aromatic aldehydes, containing both electron withdrawing and donating substitutes were treated under the optimized conditions and afforded the corresponding 2-amino-chromenes (Table 2) in good to high yields. Similarly, 1-naphthol also was reacted under the same conditions and provided the desired products without any difficulties.

To extend the preparative utility and generality of this multicomponent reaction, a variety of aldehydes and malononitrile were treated with other activated phenols such as 2,7-naphthalenediol and resorcinol under the same experimental



SCH. 2.

conditions (Scheme 2). The corresponding 2-amino-chromene derivatives were obtained in good to high yields (Table 2).

The results obtained with benzaldehyde, malononitrile and 1-naphthol under the optimized conditions were compared with the best ones published so far for this reaction using inorganic or organic alkali catalysts; the data is listed in Table 3. It showed that the piperazine was fairly a good catalyst for this reaction.

CONCLUSION

In summary, we have developed a simple and efficient methodology for the synthesis of 2-amino-chromene derivatives by a one-pot, multi-component reaction. Some advantageous of this solvent-free protocol include a simple reaction set-up, high products yields, short reaction times, and elimination of toxic solvents.

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