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ARTICLE

Synthesis of 1*H*-isochromenes, 4*H*-chromenes, and ortho-aminocarbonitrile tetrahydronaphthalenes from the same reactants by using metal-free catalyst

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Abstract

A facile and rapid multicomponent synthesis of pharmaceutically diverse 1*H*-isochromenes, 4*H*-chromenes, and ortho-aminocarbonitrile tetrahydronaphthalenes has been developed from benzaldehyde, malononitrile, and cyclohexanone. Three different methods from the same reactants, solvent, temperature, and catalyst lead to three products with excellent yields. All the reactions were followed with the Michael addition and cyclization. In this study, morpholine was used as an active metal-free base catalyst that increases the yields of products and decreases the time of reactions.

1 | INTRODUCTION

Multicomponent reactions (MCRs) are a great idea for the synthesis of a complicated organic product. Multicomponent reactions have three or more reactants to form a new applied product. This reaction converts all or most material atoms to a new form of atom. The products that are synthesized from the MCR are used in medicine, pharmacology, and industries.[1–3] The optimum conditions for MCR to find high yield, low cost, shorter reaction time, energy conservation, and comfortable and cheap purification processes have been explored.[4–8] One of the famous MCRs was the synthesis of α,β-unsaturated nitrile, which was synthesized from Michael reaction as the active intermediate for the synthesis of several useful products.[9–11] Derivatives of bicyclic ortho-aminocarbonitrile from cyclic ketones, malononitrile, and benzaldehyde create important organic products.[12–14] Some of these products were tetrahydronaphthalene, 1*H*-isochromene, and 4*H*-chromene. Ortho-aminocarbonitrile tetrahydronaphtha-lene is useful as a precursor and significant for its optical properties.[15,16] The various derivatives of 1*H*-isochromene are present in a diversity of natural products, pharmaceuticals, and bioactive molecules.[17,18] These benefit structure applied in biological and pharmacy products such as an antitumor compound.[19–22] 4*H*-Chromenes can be employed as cognitive enhancers for cure of neurodegenerative illnesses (such as Huntington disease, Parkinson disease, Alzheimer disease, and amyotrophic lateral sclerosis) and other dangerous neurodegenerative illnesses such schizophrenia.[23–26] Numerous methods and catalyst are reported for the synthesis of the α,β-unsaturated nitrile and the related product, for example, nanocatalyst, transition metal catalyst, and metal-free catalyst. One special straightforward and economical reaction has been the use of a metal-free catalyst.[27,28] This catalyst has high activity without any heavy metal such as Et_3N, guanidine, and morpholine. Morpholine is a great base catalyst that can be applied in different MCRs.[29] In the present report, we hope to study the MCRs of cyclohexanone, malononitrile, and benzaldehyde for the synthesis of three products with excellent yield using different methods.

2 | RESULTS AND DISCUSSION

2.1 | Investigation of various methods

At the beginning of our study, all the reactants were mixed at the same time, and the reaction flowed under

different acid and base catalysts, solvents, and temperatures. Consequently, in a better condition, we obtained three products in low yields (Scheme 1).

Since malononitrile is the active reactant and was rapidly added to the Michael addition with a double-bond or carbonyl compound, the reaction was probed step by step. In the first reaction, cyclohexanone was mixed to malononitrile under different catalysts and solvents, and after 10 to 20 minutes, benzaldehyde was added to the mixture. In this reaction, under the best conditions, 1*H*-isochromene (**4a**) was synthesized in excellent yield (Scheme 2).

In the other reaction, first, benzaldehyde and malononitrile were mixed under different conditions; and after 20 to 25 minutes, cyclohexanone was added to the mixture; and then the reaction followed for 15 to 20 minutes. In the best condition, the 4*H*-chromene (**5a**) product was formed with good yield (Scheme 3).

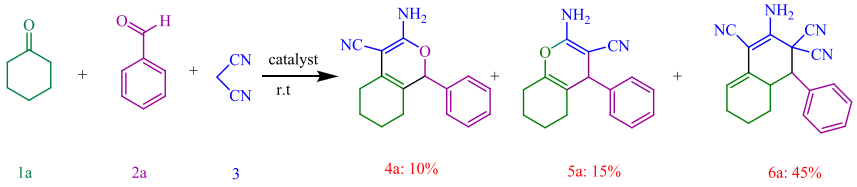
To increase the yield of 4*H*-isochromene, another method was used. In this reaction, the first benzaldehyde and cyclohexanone were mixed under several conditions. After formation of the α,β-unsaturated carbonyl compound during 15 to 20 minutes, malononitrile was added to the mixture. So 4*H*-chromene (**5a**) was a product in excellent yield (Scheme 4).

For the synthesis of ortho-aminocarbonitrile tetrahydronaphthalene (**6a**), two equivalents of malononitrile was used: one reacts with cyclohexanone, and the other with benzaldehyde. So the two methods was examined increasing the yield of the product. The first was a one-pot reaction with cyclohexanone, benzaldehyde, and two equivalents of malononitrile under the best condition. The product of this reaction was obtained in good yields (Scheme 5).

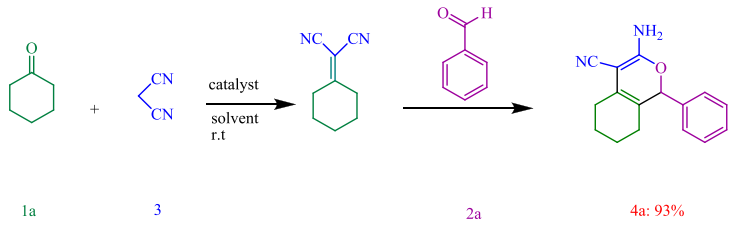
For increase of the yield of ortho-aminocarbonitrile tetrahydronaphthalene (**6a**), another method was probed. In this method, first, the intermediate from the reaction of cyclohexanone and malononitrile, also the intermediate forms of benzaldehyde and malononitrile were synthesized. Then, both of the intermediates were mixed together to form the final product (Scheme 6). The yield of the reaction under the best condition was excellent.

2.2 | Investigation of catalytic activity

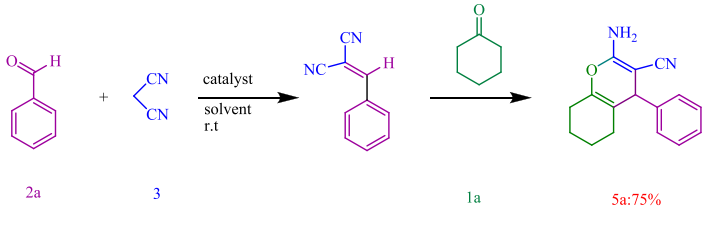
To select the best condition for the desired reactions, they were examined in the presence of different catalysts, solvents, and temperatures for the reaction. To analyze the



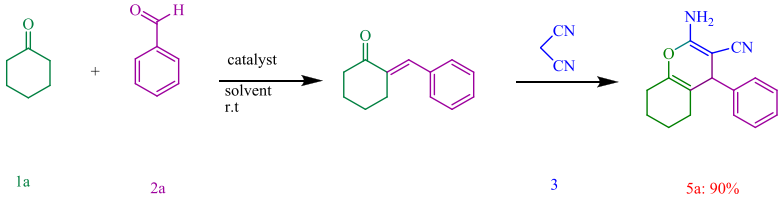
SCHEME 1 Synthesis of three products from cyclohexanone, benzaldehyde, and malononitrile [Color figure can be viewed at wileyonlinelibrary.com]



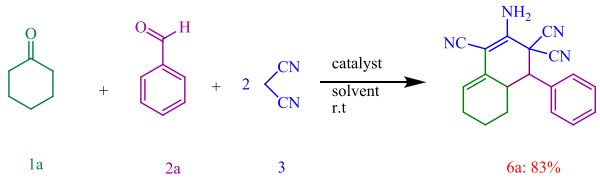
SCHEME 2 Synthesis of 1*H*-isochromene from cyclohexanone, malononitrile, and benzaldehyde [Color figure can be viewed at wileyonlinelibrary.com]



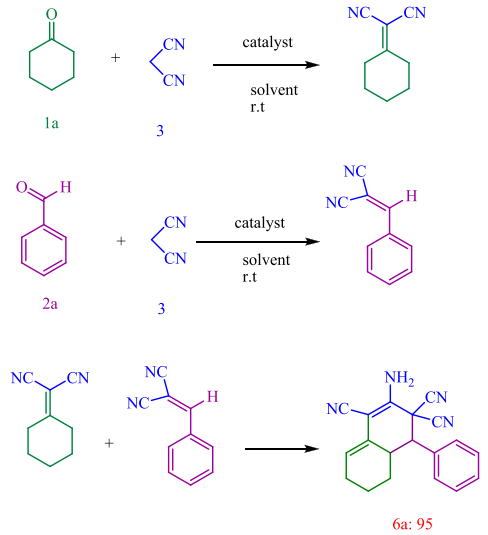
SCHEME 3 Synthesis of 4*H*-chromene from benzaldehyde, malononitrile, and cyclohexanone [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 4 Synthesis of 4*H*-chromene from cyclohexanone, benzaldehyde, and malononitrile [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 5 One-pot synthesis of ortho-aminocarbonitrile tetrahydronaphthalene from cyclohexanone, malononitrile, and benzaldehyde [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 6 Synthesis of ortho-aminocarbonitrile tetrahydronaphthalene in two steps from cyclohexanone, malononitrile, and benzaldehyde [Color figure can be viewed at wileyonlinelibrary.com]

applicants of catalyst, first, the reactions were studied without catalyst at ambient and reflux temperatures (Table 1, entry **1**), but the yield of the product was very low. The reactions were probed by altering the acid and a base catalyst such as *p*-toluenesulfonic acid (PTSA), Fe_2O_3, Et_3N, guanidine, morpholine, NaOH, and MgO (Table 1). The observation of the small amount of product was noticed in the presence of acid catalysts, such as PTSA and Fe_2O_3 (Table 1 entries **2** and **3**), and clearly shows that yields were increased under the bases of MgO and NaOH and nitrogen-containing bases such as guanidine, Et_3N, and morpholine. Among the base catalysts, morpholine was found superior with the increase of yield and decrease of reaction time. Also, different amounts of catalyst (mmol) were studied, and the results are reported in Table 1, entries **9** to **11**.

The reactions were studied in several solvents such as chloroform, dichloromethane, acetonitrile methanol, and ethanol. Consequently, ethanol has the best condition for the reactions. So the reactions were tested in ethanol with morpholine catalyst under various temperature, with the reactions at room temperature having excellent yield (Table 2).

After optimization of the reactions by the different catalysts, solvents, and temperatures, the reaction condition was determined. So the best catalyst that was selected for the synthesis of 1*H*-isochromene and 4*H*-isochromene from cyclohexanone (1 mmol), malononitrile (1 mmol), and benzaldehyde (1 mmol) and for ortho-aminocarbonitrile tetrahydronaphthalene from cyclohexanone (1 mmol), malononitrile (2 mmol), and benzaldehyde (1 mmol) was morpholine, and the best solvent was ethanol. Therefore, the different derivatives of 1*H*-isochromene, 4*H*-isochromene, and ortho-aminocarbo-nitrile tetrahydronaphthalene (Table 3) were synthesized at room temperature in 30 to 50 minutes.

2.3 | Proposed reaction mechanism

Synthesis of 1*H*-isochromene was done in two steps: the first included the mixing of cyclohexanone with malononitrile in ethanol under a great base condition from morpholine. The reaction was followed by vinylogous Michael addition for the synthesis of vinylmalononitriles A. Then benzaldehyde was added to the mixture, and the processes were followed by cycle creation of C–C (D) and C–O (E) bonds. In the end, 1*H*-isochromene (**4a**) was synthesized with cyclization and loss the hydrogen from intermediate via the base catalyst (Scheme 7).

For the synthesis of 4*H*-chromene, the first cyclohexanone and benzaldehyde were mixed in ethanol using morpholine as a catalyst for synthesis of desired chalcone (F) from condensation reaction. Then malononitrile was added to the mixture for the synthesis of intermediate G from Michael addition. The processes were flowing by the formation of C–O bond, and at the end of reaction, 4*H*-chromene (**5a**) was synthesized with the rearrangement of double bonds (Scheme 8).

The first step for synthesis of ortho-aminocarbonitrile tetrahydronaphthalene (**6a**) includes the Michael addition of cyclohexanone and malononitrile with the formation of intermediate A. Another equivalent of malononitrile concurrently reacts with benzaldehyde **2a** to obtain intermediate **I**. Then, by the action of morpholine, intermediate **J** forms, which attack anion B to intermediate **I**, and the processes were flowing by cyclization of two C–C bonds. At the end of the processes, ortho-aminocarbonitrile tetrahydronaphthalene (**6a**) was formed with losses in hydrogen via base catalyst and rearrangement of the molecules (Scheme 9).

TABLE 1 Analysis of catalytic activity and catalyst amount (mmol) for synthesis of 1*H*-isochromene,[a] 4*H*-chromene,[b] and ortho-aminocarbonitrile tetrahydronaphthalene[c]

Entry	Catalyst	Yield, %[d]/Tim,e h**4a**	Yield, %[d]/Time, h[d]**5a**	Yield, %[d]/Time, h**6a**	Catalyst Amount, mmol
1	None	10/24	5/24	-/24	-
2	PTSA	5/24	5/24	-/24	0.1
3	Fe_2O_3	7/24	6/25	-/24	0.1
4	NaOH	50/1.5	65/2	60/1.45	0.1
5	Et_3N	70/1	73/1.5	75/1	0.1
6	Pyridine	65/1	60/1.5	70/1	0.1
7	Guanidine	80/0.6	83/0.75	85/0.6	0.1
8	MgO	76/1	70/1.5	80/1.5	0.1
9	Morpholine	93/0.3	92/0.3	95/0.3	0.1
10	Morpholine	93/0.3	92/0.3	95/0.3	0.2
11	Morpholine	93/0.75	87/0.6	90/0.75	0.05

Abbreviation: PTSA, *p*-toluenesulfonic acid.
[a]Reaction conditions: cyclohexanone (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol), and 5 mL of solvent.
[b]Reaction conditions: benzaldehyde (1 mmol), cyclohexanone (1 mmol), malononitrile (1 mmol), and 5 mL of solvent.
[c]Reaction conditions: benzaldehyde (1 mmol), cyclohexanone (1 mmol), malononitrile (2 mmol), and 5 mL of solvent.
[d]Isolated yield.

TABLE 2 Analysis of the solvent role and the reaction temperature for the synthesis of 1*H*-isochromene,[a] 4*H*-chromene,[b] and ortho-aminocarbonitrile tetrahydronaphthalene[c]

Entry	Solvent	Temperature, °C	Yield, %[d]/Time, h**4a**	Yield, %[d]/Time, h**5a**	Yield, %[d]/Time, h**6a**
1	Chloroform	25	75/0.66	60/0.70	65/0.75
2	Dichloromethane	25	78/0.75	65/0.8	65/0.83
3	Methanol	25	89/0.58	80/0.66	85/0.6
4	Acetonitrile	25	75/0.83	75/0.85	70/0.6
5	Ethanol	25	93/0.5	92/0.5	95/0.33
6	Ethanol	40	85/0.75	84/0.8	87/0.6
7	Ethanol	50	83/1	82/0.75	85/0.6
8	Ethanol	60	80/1	75/1.5	83/1

[a]Reaction conditions: cyclohexanone (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol), and 0.1 mmol of morpholine.
[b]Reaction conditions: benzaldehyde (1 mmol), cyclohexanone (1 mmol), malononitrile (1 mmol), and 0.1 mmol of morpholine.
[c]Reaction conditions: benzaldehyde (1 mmol), cyclohexanone (1 mmol), malononitrile (2 mmol), and 0.1 mmol of morpholine.
[d]Isolated yield.

3 | CONCLUSIONS

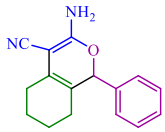
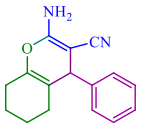
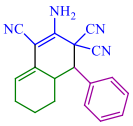
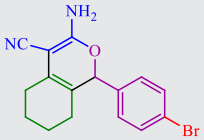
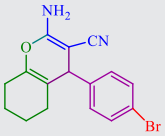
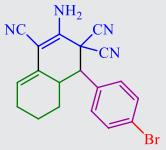
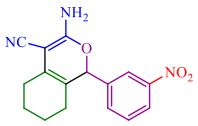
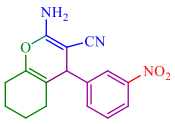
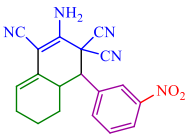
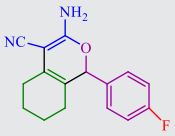
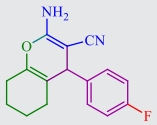
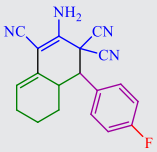
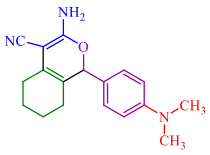
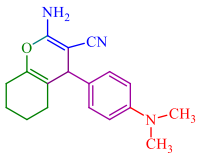
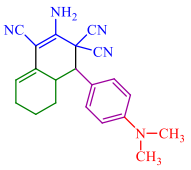
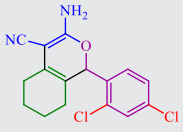
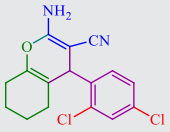
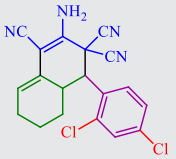
In summary, we have investigated three reactions from the same reactants by using the different methods for obtaining the specific product with excellent yield. The products contain 1*H*-isochromene, 4*H*-chromene, and ortho-aminocarbonitrile tetrahydronaphthalene that were synthesized from cyclohexanone, malononitrile, and benzaldehyde. All the reactions were in an ethanol solvent under a base condition at room temperature. In the end, the products from three reactions were recognized by melting points and IR and ^{1}H NMR spectra.

4 | EXPERIMENTAL SECTION

4.1 | Chemicals

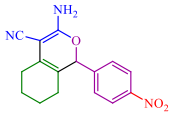
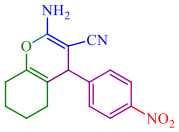
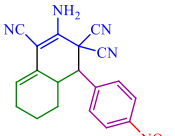
All reactants and solvents were used as the starting resources; cyclohexanone, benzaldehyde, and morpholine were acquired from Sigma; malononitrile and ethanol were purchased from Merck Chemical Company. The products were assessed with ^{1}H NMR, Fourier transform infrared (FTIR), and melting point analysis; ^{1}H NMR spectra were register in DMSO-d_6 and chloroform-*d* solvents with a Bruker DRX-400 spectrometer with

TABLE 3 Synthesis of various derivatives of 1*H*-isochromene, 4*H*-chromene, and ortho-aminocarbonitrile tetrahydronaphthalene and determination of the yield and reaction time in the presence of morpholine catalyst

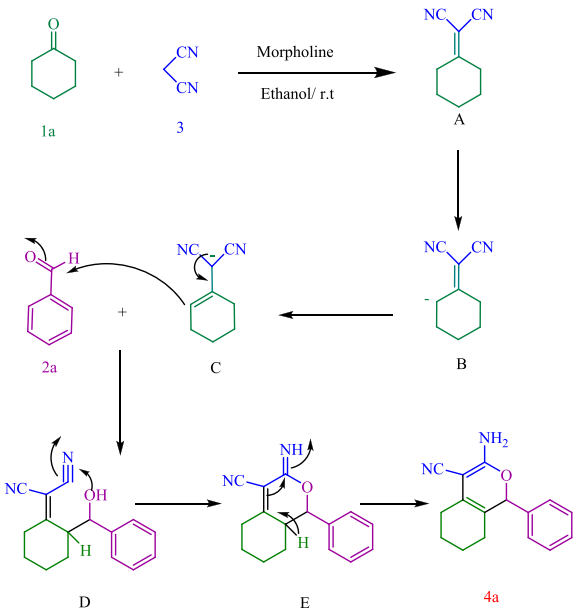
4a-h,[a] Yield %,[d] Time min	5a-h,[b] Yield %,[d] Time min	6a-h,[c] Yield %,[d] Time min
 X=H, 92, 30	 X=H, 90, 30	 X=H, 95, 20
 X=Br, 89, 25	 X= Br, 88, 30	 X= Br, 92, 30
 X= NO_2, 91, 25	 X= NO_2, 90, 35	 X= NO_2, 90, 25
 X=F, 88, 25	 X= F, 89, 20	 X= F, 90, 25
 X=N,N dimethyl, 85, 45	 X= N,N dimethyl, 88, 45	 X= N,N dimethyl, 90, 40
 X=2,4 dichloro, 88, 30	 X=2,4 dichloro, 86, 35	 X=2,4 dichloro, 89, 30

(Continues)

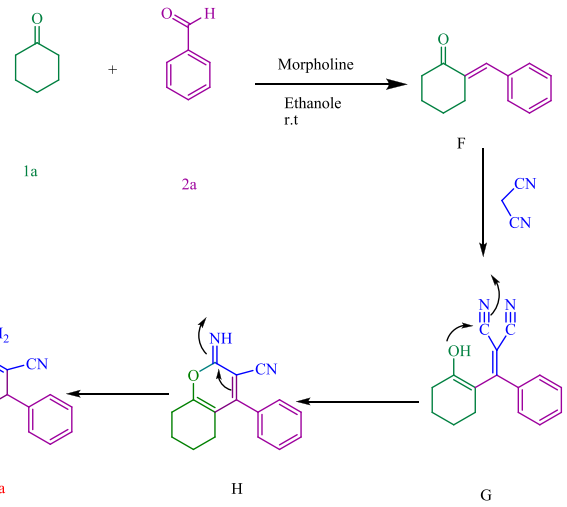
TABLE 3 (Continued)

4a-h,[a] Yield %,[d] Time min	5a-h,[b] Yield %,[d] Time min	6a-h,[c] Yield %,[d] Time min
 X=NO_2, 93, 25	 X= NO_2, 93, 25	 X= NO_2, 93, 20

[a]Reaction conditions: cyclohexanone (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol), 0.1 mmol of morpholine, and ethanol solvent (5 mL), rt.
[b]Reaction conditions: benzaldehyde (1 mmol), cyclohexanone (1 mmol), malononitrile (1 mmol), 0.1 mmol of morpholine, and ethanol solvent (5 mL), rt.
[c]Reaction conditions: benzaldehyde (1 mmol), cyclohexanone (1 mmol), malononitrile (2 mmol), 0.1 mmol of morpholine, and ethanol solvent (5 mL), rt.
[d]Isolated yield.



SCHEME 7 Reaction mechanism for synthesis of 1*H*-isochromene [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 8 Reaction mechanism for synthesis of 4*H*-chromene [Color figure can be viewed at wileyonlinelibrary.com]

tetramethylsilane as the internal reference. Fourier transform infrared spectra were reached as KBr pellets and register with PerkinElmer 781 spectrophotometer by an Impact 400 Nicolet FTIR spectrophotometer. Melting points were measured on a Yanagimoto micromelting point apparatus.

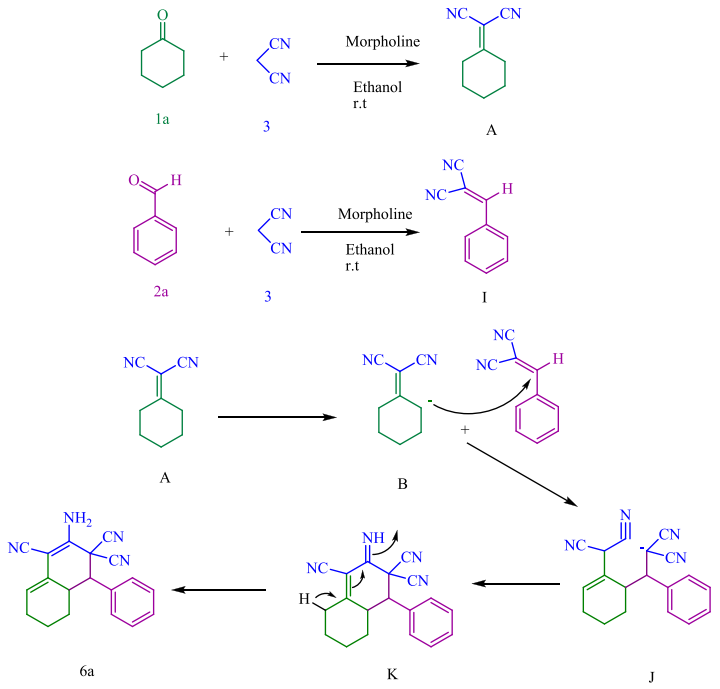
4.2 | General multicomponent procedure for synthesis of 1*H*-isochromene

1*H*-Isochromene was synthesized from the MCR. In this reaction, 1 mmol of cyclohexanone (**1a**) with 1 mmol of malononitrile was mixed in an ethanol solvent. Then, 0.1 mmol of morpholine was added to the mixture and stirred for 10 to 20 minutes at ambient temperature. After the reaction is completed, 1 mmol of benzaldehyde (**2a**-**f**) was added to the mixture and followed by the reaction for 10 to 20 minutes at room temperature. In the end, 5 mL water was added to the mixture for the formation of the pure product. The product was characterized by melting points and IR and ^{1}H NMR spectra.

4.2.1 | 3-Amino-1-phenyl-5,6,7,8-tetrahydro-1*H*-isochromene-4-carbonitrile (4a)

White solid; mp: 280-282°C (lit. mp 285-288°C)[13]; IR (KBr) ν = 3418, 3339, 3253, 2933, 2210, 1648, 1601 1451, 1392, 1276, 1080, 713, 581 cm^{-1}, ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.46-7.58 (m, 5H), 6.05 (s. 1H), 4.86 (s, 2H, NH_2), 3.07-3.10 (d, J = 12.5 Hz, 1H), 2.88-2.91 (m, 1H), 2.27-2.32 (m, 1H), 2.15-2.18 (m, 1H), 1.79-1.82 (m, 1H), 1.67-1.70 (m, 1H), 1.49-1.58 (m, 1H), 0.91-1.00 (m, 1H).

SCHEME 9 Reaction mechanism for synthesis of ortho-aminocarbonitrile tetrahydronaphthalene [Color figure can be viewed at wileyonlinelibrary.com]



4.2.2 | 3-Amino-1-(4-bromophenyl)-5,6,7,8-tetrahydro-1*H*-isochromene-4-carbonitrile (4b)

White solid; mp: 260-263°C; IR (KBr) ν = 3422, 3343, 3250, 2928, 2210, 1643, 1600, 1488, 1390, 1274, 1075, 834, 509 cm^{-1}, ^1H NMR (400 MHz, chloroform-*d*) δ 7.42-7.78 (m, 3H), 7.17-7.19 (d, J = 8.3 Hz, 1H), 6.10-6.05 (m, 1H). 4.85 (s, 2H, NH_2), 3.05-3.09 (d, J = 12.3 Hz, 1H), 2.85-2.88 (d, J = 12.5 Hz, 1H), 2.29-2.33 (m, 1H), 2.03-2.26 (m, 1H), 1.80-1.86 (m, 1H), 1.41-1.73 (m, 2H), 0.73-1.09 (m, 1H).

4.2.3 | 3-Amino-1-(3-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-isochromene-4-carbonitrile (4c)

White solid; mp: 248-250°C; IR (KBr) ν = 3440, 3356, 3249, 2948, 2209, 1638, 1530, 1441, 1351, 906, 828, 546 cm^{-1}, ^1H NMR (400 MHz, chloroform-*d*) δ 7.46-7.48 (d, J = 8.2 Hz, 2H), 7.35-7.21 (m, 2H), 6.03-6.06 (m, 1H), 4.87 (s, 2H, NH_2), 3.04-3.07 (d, J = 12.4 Hz, 1H), 2.77-2.93 (m, 1H), 2.15-2.19 (m, 1H), 1.81-1.83 (m, 1H), 1.70-1.73 (m, 1H), 1.47-1.63 (m, 2H), 0.89-1.02 (m, 1H).

4.2.4 | 3-Amino-1-(4-fluorophenyl)-5,6,7,8-tetrahydro-1*H*-isochromene-4-carbonitrile (4d)

White solid; mp: 262-265°C; IR (KBr) ν = 3421, 3336, 3250, 2948, 2212, 1648, 1599, 1454, 1390, 1272, 829, 515 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.27-7.64 (m, 6H, CH, NH_2), 5.71 (s, 1H), 3.60-3.62 (d, J = 12.2 Hz, 1H), 2.77-2.79 (d, J = 13.3 Hz, 1H), 2.18-2.20 (d, J = 18.8 Hz, 1H), 2.06 (s, 1H), 1.67 (s, 1H), 1.36-1.58 (m, 2H), 0.82-0.86 (q, J = 12.5, 12.1 Hz, 1H).

4.2.5 | 3-Amino-1-(4-(dimethylamino) phenyl)-5,6,7,8-tetrahydro-1*H*-isochromene-4-carbonitrile (4e)

White solid; mp: 248-250°C; IR (KBr) ν = 3447, 3355, 3206, 2916, 2213, 1617, 1525, 1446, 1357, 1271, 1116, 947, 524 cm^{-1}. ^1H NMR (400 MHz, chloroform-*d*) δ 7.34-7.71 (m, 1H), 7.16-7.12 (d, J = 8.5 Hz, 1H), 6.60-6.88 (m, 2H), 6.01-6.05 (m, 1H), 4.87 (s, 2H, NH_2), 3.00 (s, 6H), 2.75-2.91 (m, 1H), 2.25-2.33 (m, 1H), 2.14 (m, 1H), 1.76-1.81 (m, 2H), 1.42-1.65 (m, 2H), 0.86-1.03 (m, 1H).

4.2.6 | 3-Amino-1-(2,4-dichlorophenyl)-5,6,7,8-tetrahydro-1*H*-isochromene-4-carbonitrile (4f)

White solid; mp: 276-279°C; IR (KBr) ν = 3445, 3355, 3203, 2942, 2214, 1624, 1592, 1475, 1338, 1269, 11088, 1051, 879, 562 cm^{-1}, ^1H NMR (400 MHz, chloroform-*d*) δ 7.52-7.68 (m, 2H), 7.41-7.43 (m, 1H), 6.06-6.10 (m, 1H), 4.88 (s, 2H, NH_2), 3.95-3.99 (d, J = 12.3 Hz, 1H), 2.80-2.97 (t, J = 12.2 Hz, 1H), 2.31-2.33 (m, 1H), 2.09-2.24 (m, 1H), 1.75-1.87 (m, 1H), 1.44-1.60 (m, 2H), 0.96-0.99 (m, 1H).

4.2.7 | 3-Amino-1-(4-nitrophenyl)-5,6,7,8-tetrahydro-1*H*-isochromene-4-carbonitrile (4g)

White solid; mp: 229-232°C (lit. mp 232-236°C)[13]; IR (KBr) ν = 3418, 3347, 3286, 2938, 2206, 1644, 1523, 1448, 1348, 1132, 1041, 859, 558 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 8.28-8.54 (m, 2H), 8.18-8.22 (t, J = 7.8 Hz, 1H), 7.70-8.05 (m, 1H), 7.35-7.70 (m, 1H), 6.67 (s, 2H, NH_2), 5.67 (s, 1H), 3.49-3.51 (d, J = 12.5 Hz, 1H), 3.42 (s, 1H), 2.85-3.87 (d, J = 12.5 Hz, 1H), 2.11-2.15 (m, 1H), 1.61-1.71 (m, 1H), 1.41-1.45 (t, J = 19.3 Hz, 1H), 0.85-0.88 (m, 1H).

4.3 | General multicomponent procedure for synthesis of 4*H*-chromene

4*H*-Chromene was synthesized from the three-component reaction. For this reaction, 1 mmol of cyclohexanone (**1**) with 1 mmol of benzaldehyde (**2a**-**h**) was mixed in an ethanol solvent, and then 0.15 mmol of morpholine as a catalyst was added to the mixture. After 15 to 20 minutes, 1 mmol of malononitrile was added to the mixture. The reaction was followed with thin-layer chromatography (TLC). At the end of the reaction, 5 mL of water was added to the mixture for the formation of the pure product. The product was filtered and recognized with FTIR and ^1H NMR spectra and melting point.

4.3.1 | 2-Amino-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5a)

White solid; mp: 233-235°C (lit. mp 240-241°C)[30]; IR (KBr) ν = 3453, 3317, 3177, 2954, 2828, 2183, 1668, 1629 1483, 1411, 1382, 1253, 1132, 1069, 819, 514 cm^{-1}, ^1H NMR (400 MHz, chloroform-*d*) δ 7.33-7.37 (m, 4H), 6.88 (s, 1H), 4.52 (s, 1H), 3.97 (s, 2H, NH_2), 2.68-2.77 (m, 1H), 2.54-2.64 (m, 1H), 1.93-2.05 (m, 2H), 1.46-1.72 (m, 4H).

4.3.2 | 2-Amino-4-(4-bromophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5b)

White solid; mp: 220-222°C; IR (KBr) ν = 3446, 3335, 3235, 2935, 2863, 2214, 1667, 1663 1595, 1484, 1413, 1258, 1128, 1008, 822, 512 cm^{-1}, ^1H NMR (400 MHz, chloroform-*d*) δ 7.47 (m, 1H), 7.13-7.17 (m, 2H), 6.79 (s, 1H), 4.54 (s, 2H, NH_2), 3.95 (s, 1H), 2.66 (s, 1H), 2.54 (s, 1H), 1.94-1.98 (d, J = 17.5 Hz, 2H), 1.57-1.63 (d, J = 24.8 Hz, 4H).

4.3.3 | 2-Amino-4-(3-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5c)

White solid; mp: 120-122°C; IR (KBr) ν = 3460, 3363, 3085, 2931, 2863, 2189, 1669, 1633 1527, 1410, 1349, 1130, 809, 735, 680 cm^{-1}, ^1H NMR (400 MHz, chloroform-*d*) δ 8.11-8-17 (d, J = 22.4 Hz, 1H), 7.63-7.65 (m, 2H), 6.95 (s, 1H), 4.68 (s, 2H, NH_2), 4.16 (s, 1H), 2.66-2.79 (m, 1H), 2.59-2.62 (d, J = 11.7 Hz, 1H), 2.06-2.10 (d, J = 17.6 Hz, 1H), 1.83-1.99 (m, 1H), 1.45-1.77 (m, 4H).

4.3.4 | 2-Amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5d)

White solid; mp: 223-225°C; IR (KBr) ν = 3448, 3346, 3057, 2955, 2863, 2187, 1671, 1635 1592, 1412, 1254, 1139, 700, 515 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.33-7.37 (d, J = 8.2 Hz, 1H), 7.20 (s, 2H, NH_2), 6.93 (s, 1H), 6.81 (s, 2H), 4.00 (s, 1H), 3.34 (s, 1H), 2.59-2.62 (d, J = 15.3 Hz, 1H), 2.43-2.46 (d, J = 10.4 Hz, 1H), 2.01-2.05 (d, J = 17.1 Hz, 1H), 1.76-1.77 (d, J = 6.5 Hz, 2H), 1.39-1.61 (m, 2H).

4.3.5 | 2-Amino-4-(4-(dimethylamino) phenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5e)

White solid; mp: 223-225°C; IR (KBr) ν = 3445, 3325, 3021, 2892, 2835, 2192, 1668, 1635 1595, 1417, 1247, 1133, 754, 699, 561 cm^{-1}, ^1H NMR (400 MHz, chloroform-*d*) δ 7.18-7.19 (d, J = 7.0 Hz, 1H), 7.14 (s, 2H), 6.84 (s, 1H), 4.49 (s, 2H, NH_2), 3.93 (s, 1H), 2.69-2.72 (d, J = 9.0 Hz, 1H), 2.58 (m, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 1.97-1.99 (d, J = 5.1 Hz, 2H), 1.62 (m, 4H).

4.3.6 | 2-Amino-4-(2,4-dichlorophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5f)

White solid; mp: 130-132°C; IR (KBr) ν = 3466, 3319, 3180, 2942, 2836, 2186, 1669, 1631 1596, 1486, 1410, 1259, 1090, 824, 512 cm^{-1},^1H NMR (400 MHz, chloroform-*d*) δ 7.38-7.45 (m, 1H), 7.20-7.24 (dd, J = 18.6, 10.7 Hz, 1H), 6.85 (s, 1H), 4.64-4.67 (s, 2H, NH_2), 3.70-3.74 (q, J = 7.0 Hz, 1H), 2.34-2.65 (m, 2H), 2.18-2.01 (m, 1H), 1.87 (m, 1H), 1.59-1.62 (d, J = 12.2 Hz, 2H), 1.37-1.52 (m, 1H), 1.23-1.26 (t, J = 7.0 Hz, 1H).

4.3.7 | 2-Amino-4-(4-nitrophenyl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (5g)

White solid; mp: 180-183°C; IR (KBr) ν = 3466, 3378, 2934, 2191, 1640, 1517, 1443, 1343 11032, 855, 705 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 2H, NH_2) 7.57-7.59 (d, J = 8.5 Hz, 1H), 7.49-7.50 (d, J = 8.3 Hz, 1H), 7.07 (s, 1H), 7.02 (s, 1H), 4.27 (s, 1H) , 2.62-2.77 (m, 1H), 2.54-2.56 (d, J = 7.1 Hz, 1H), 2.03-2.19 (m, 2H), 1.71-1.88 (m, 2H), 1.56-1.57 (d, J = 4.6 Hz, 2H).

4.4 | General multicomponent procedure for synthesis of ortho-aminocarbonitrile tetrahydronaphthalene

For the synthesis of ortho-aminocarbonitrile tetrahydronaphthalene with a four-component reaction, cyclohexanone (1 mmol) (**1**) was reacted with malononitrile (1 mmol), and at the same time, benzaldehyde (1 mmol) (**2a**-**h**) was reacted with malononitrile (1 mmol). This was followed with both reactions in ethanol solvent with 0.1 mmol of morpholine. After completion of the reactions, both intermediate products were mixed and the processes monitored by TLC. At the end of the reaction, 5 mL water was added to the reaction mixture for the formation of the pure product. The final product was determined with a melting point and FTIR and ^1H NMR spectra.

4.4.1 | 2-Amino-4-phenyl-4*a*,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (6a)

White solid; mp: 256-260°C (lit. mp 255-257°C)[31]; IR (KBr) ν = 3446, 3356, 2950, 2856, 2216, 1623, 1525 1477, 1390, 1271, 1040, 748, 501 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.25-7.65 (m, 7H, NH_2, CH), 5.72 (s, 1H), 3.52-3.55 (d, J = 12.3 Hz, 1H), 2.80 (s, 1H), 2.06-2.15 (d, J = 36.6 Hz, 2H), 1.64-1.68 (d, J = 12.8 Hz, 1H), 1.44 (s, 2H), 0.83-0.86 (d, J = 11.4 Hz, 1H).

4.4.2 | 2-Amino-4-(4-bromophenyl)-4*a*,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (6b)

White solid; mp: 251-253°C (lit. mp 244-246°C)[31]; IR (KBr) ν = 3421, 3336, 3250, 2947, 2865, 2212, 1646, 1599 1454, 1390, 1037, 830, 586 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.41-7.48 (m, 1H), 7.35 (s, 2H, NH_2), 7.33-7.24 (m, 2H), 7.22 (s, 1H), 5.71 (s, 1H), 3.44-3.47 (d, J = 12.5 Hz, 1H), 2.76 (s, 1H), 2.49 (s, 1H), 2.01-2.20 (m, 2H), 1.67 (s, 1H), 1.43-1.50 (m, 1H), 0.72-0.97 (m, 1H).

4.4.3 | 2-Amino-4-(3-nitrophenyl)-4*a*,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (6c)

White solid; mp: 265-267°C (lit. mp 262-264°C)[32]; IR (KBr) ν = 3445, 3356, 2949, 2853, 2216, 1622, 1472, 1389, 1270, 1023, 746, 506 cm^{-1},^1H NMR (400 MHz, DMSO-d_6) δ 7.64-7.71 (m, 2H), 7.54-7.56 (d, J = 7.9 Hz, 1H), 7.39 (s, 3H), 5.72 (s, 1H), 3.60-3.63 (d, J = 12.5 Hz, 1H), 2.76-2.61 (t, J = 10.1 Hz, 1H), 2.24-1.92 (m, 2H), 1.65 (s, 1H), 1.43-1.45 (d, J = 9.9 Hz, 2H), 0.79-0.88 (q, J = 12.1 Hz, 1H).

4.4.4 | 2-Amino-4-(4-fluorophenyl)-4*a*,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (6d)

White solid; mp: 264-266°C (lit. mp 262-264°C)[31]; IR (KBr) ν = 3448, 3356, 3210, 2957, 2839, 2212, 1618, 1518, 1449, 1387, 1230, 1120, 930, 824, 525 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.34-7.38 (d, J = 20.5 Hz, 2H), 7.29-7.20 (m, 1H), 7.05-6.91 (m, 1H), 5.69 (s, 1H), 3.73 (s, 2H, NH_2), 3.40-3.33 (m, 1H), 2.84-2.63 (m, 1H), 2.08-2.14 (dd, J = 47.5, 12.6 Hz, 2H), 1.65 (s, 1H), 1.43-1.47 (d, J = 20.9 Hz, 1H), 0.80-0.84 (d, J = 12.5 Hz, 1H).

4.4.5 | 2-Amino-4-(4-(dimethylamino) phenyl)-4*a*,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (6e)

White solid; mp: 263-265°C; IR (KBr) ν = 3447, 3355, 2952, 2803, 2214, 1617, 1525, 1272, 1168, 947, 816, 525 cm^{-1}, 1H NMR (400 MHz, DMSO-d_6) δ 7.32 (s, 3H, NH_2, CH), 7.17-7.19 (d, J = 8.5 Hz, 1H), 6.76-6.89 (m, 1H), 6.62-6.76 (m, 1H), 5.69 (s, 1H), 3.32-3.33 (d, J = 7.9 Hz, 1H), 2.91 (s, 6H), 2.70 (s, 1H), 2.14-2.19 (d, J = 18.1 Hz, 1H), 2.04 (s, 1H), 1.65 (s, 1H), 1.50-1.53 (d, J = 10.6 Hz, 1H), 1.44 (s, 1H), 0.73-0.97 (m, 1H).

4.4.6 | 2-Amino-4-(2,4-dichlorophenyl)-4*a*,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (6f)

White solid; mp: 260-264°C (lit. mp 262-264°C)[31]; IR (KBr) ν = 3446, 3357, 2943, 2860, 2214, 1623, 1593, 1476,

1388, 1268, 1109, 880, 562, 501 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.72-7.94 (m, 2H), 7.63-7.65 (d, J = 8.2 Hz, 1H), 7.44 (s, 2H, NH_2), 5.75 (s, 1H), 3.85-3.88 (d, J = 12.3 Hz, 1H), 2.85 (s, 1H), 2.09-2.14 (d, J = 23.6 Hz, 2H), 1.64 (s, 1H), 1.39-1.41 (d, J = 18.9 Hz, 2H), 0.78-0.81 (d, J = 11.9 Hz, 1H).

4.4.7 | 2-Amino-4-(4-nitrophenyl)-4*a*,5,6,7-tetrahydronaphthalene-1,3,3(4*H*)-tricarbonitrile (6g)

White solid; mp: 256-260°C (lit. mp 264-266°C)[31]; IR (KBr) ν = 3419, 3343, 3252, 2943, 2867, 2212, 1645, 1602 1492, 1390, 1094, 837, 567 cm^{-1}, ^1H NMR (400 MHz, DMSO-d_6) δ 7.56-7.63 (q, J = 8.2 Hz, 2H), 7.51-7.53 (d, J = 8.1 Hz, 1H), 7.44-7.46 (d, J = 7.8 Hz, 1H), 7.39 (s, 2H, NH_2), 5.72 (s, 1H), 3.62-3.65 (d, J = 12.5 Hz, 1H), 2.79 (s, 1H), 2.07-2.15 (m, 2H), 1.65 (s, 1H), 1.43-1.46 (d, J = 9.7 Hz, 2H), 0.79-0.88 (q, J = 11.7 Hz, 1H).

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