Tetrahedron 69 (2013) 1074–1085

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Potassium phthalimide-*N*-oxyl: a novel, efficient, and simple organocatalyst for the one-pot three-component synthesis of various 2-amino-4*H*-chromene derivatives in water

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ARTICLE INFO

Article history:
Received 29 August 2012
Received in revised form 2 November 2012
Accepted 20 November 2012
Available online 28 November 2012

Keywords:
Potassium phthalimide-*N*-oxyl (POPINO)
Transition metal-free catalysis
Multi-component reactions (MCRs)
2-Amino-4*H*-chromene
Green chemistry

ABSTRACT

A wide variety of 2-amino-4*H*-chromene derivatives with diverse substituents on the 4*H*-chromene ring were efficiently prepared via one-pot, three-component reaction of an aromatic aldehyde, malononitrile (or ethyl cyanoacetate), and diverse enolizable C–H activated acidic compounds in the presence of low loading of potassium phthalimide-*N*-oxyl (POPINO), as a new organocatalyst, in aqueous media. This procedure is a clean, transition metal-free, and environmentally friendly approach to prepare different 2-amino-4*H*-chromen derivatives that offers many advantages including short reaction time, high to quantitative yields, low cost, and straightforward work-up.

1. Introduction

Multi-component reactions (MCRs) have emerged as an attractive and powerful strategy for organic synthesis compared to multi-step reactions due to the creation of several new bonds in a one-pot reaction, low number of reaction and purification steps, selectivity, synthetic convergence, high atom economy, simplicity, and synthetic efficiency.[1] Therefore, academic and industrial research groups have increasingly focused on the use of MCRs to synthesize a broad range of products.[2] In fact, development of MCRs can lead to new efficient synthetic methodologies to afford many small organic compounds in the field of modern organic, bioorganic, and medicinal chemistry.[1–3] Hence, MCRs are considered as a pivotal theme in the synthesis of many important heterocyclic compounds such as chromene derivatives nowadays. The chromene moiety, including that of 2*H*-chromene and 4*H*-chromene, belongs to a major class of natural oxygen-containing heterocyclic compounds, which are widely found in edible fruits and vegetables.[4] These compounds have occupied an important place in drug research because of their various biological and pharmacological activities such as antioxidant, antileishmanial, antibacterial, antifungal, hypotensive, anticoagulant, antiviral, diuretic, antiallergenic, and antitumor activities.[5] Generally, the biological and pharmacological activities of chromenes depend on the nature of substituents being either on the 4*H*-pyran or the adjacent rings.

Especially, among various chromene derivatives, 2-amino-4*H*-chromene with cyano-functionality has a potential applications in the treatment of rheumatoid, psoriasis, and cancer.[6] Other properties such as laser dyes,[7] optical brighteners,[8] fluorescence markers,[9] pigments,[10] cosmetics, and potent biodegradable agrochemicals[11] are well known for decades.

Due to the important aforementioned properties of chromene derivatives, considerable attention has been focused on the development of environmentally friendly methodologies to synthesize 2-amino-4*H*-chromene scaffold by cyclization of an aromatic/aliphatic aldehyde, malononitrile (or ethyl cyanoacetate), and diverse enolizable C–H activated acidic compounds. Malononitrile or ethyl cyanoacetate has been used as a nucleophile in organic syntheses.[12] A literature survey shows that several modified methods have been reported using different homogeneous or heterogeneous catalysts such as cetyltrimethylammonium chloride/bromide[13,14] tetrabutylammonium bromide,[15] triethylbenzylammonium chloride,[16] *N*,*N*-dimethylaminoethylbenzyldimethylammonium chloride,[17] chitosan,[18] KSF,[19] K_3PO_4,[20] K_2CO_3,[21] Na_2CO_3 under grinding,[22] nano-sized MgO,[23] heteropolyacid,[24] Mg/Al hydrotalcite,[25] $TiCl_4$,[26] methane sulfonic acid,[27] TMG-[bmim][x],[28] [BMIm]BF_4,[29] [2-aemim][PF_6],[30] DBU,[31] and piperidine under microwave irradiation.[32,33] However, many proposed methods for the

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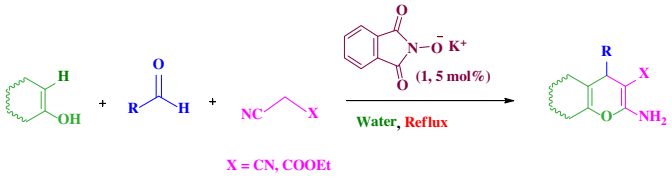
http://dx.doi.org/10.1016/j.tet.2012.11.068

synthesis of these compounds suffer from disadvantages including relying on multi-step conditions, the use of toxic organic solvents or catalysts containing transition metals, tedious work-up procedure, troublesome waste discarding, high reaction time, and low yields.[33] Thus, obviation of these limitations is necessary to develop a simple and green synthesis of 2-amino-4*H*-chromenes.

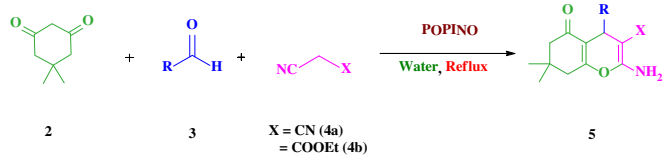
In continuation of our interest to develop the catalytic scope of phthalimide-*N*-oxyl (PINO) anion as an effective, easy to handle, and readily available Lewis base for cyclotrimerization of isocyanates,[34] cyanosilylation of carbonyl compounds,[35] and protection of alcohols and phenols with trimethylsilyl group,[36] we decided to investigate a transition metal-free route for synthesis of 2-amino-4*H*-chromene with diverse substituents in the presence of potassium phthalimide-*N*-oxyl **1** (POPINO) in water. Furthermore, the use of water, as a green, natural, and high abundance solvent, strongly enhances the rate of reaction due to its strong hydrogen bonding ability, hydrophobic effects and high polarity (Scheme 1).[37]



Scheme 1. One-pot three-component reaction of different enols, aldehydes, and active methylene nitriles catalyzed by POPINO in water.

2. Results and discussion

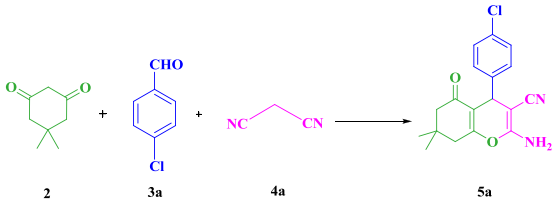
To find the optimized conditions, a systematic study considering different variables affecting the reaction yield was carried out for the reaction of dimedone (**2**), 4-chlorobenzaldehyde (**3a**), and malononitrile (**4a**) (molar ratio: 1:1:1.1) as the model reaction (Scheme 2). The results have been summarized in Table 1. Only



Scheme 2. One-pot three-component reaction of dimedone (**2a**), different aldehydes (**3**), and active methylene nitriles (**4a**,**b**) catalyzed by POPINO in water.

a trace amount of the desired 2-amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene (**5a**) was obtained under solvent-free conditions even at 100 °C (entries 1 and 2). However, the use of water, as solvent, improved the yield of the desired product **5a** slightly (entries 3 and 4). Interestingly, the use of PINO anion with different countercations, as soluble organic salts in water, at 10 mol % loading afforded high to quantitative yield of the desired product **5a** in refluxing water. POPINO afforded higher yield compared to other salts including Li^+, Na^+, and Mg^{2+} (entries 5–8). Furthermore, the product of reaction is completely precipitated out from the reaction mixture after cooling to rt. Hence, filtering the reaction mixture simply afforded the pure desired product **5a**. Then, the effect of catalyst loading on the completion of the reaction was studied in the next step (entries 7, 10, and 11, Table 1). As it can be seen, 5 mol % catalyst loading gave the best results among all by considering the catalyst turnover number (TON) and turnover frequency (TOF) values. On the other hand, the use of other solvents such as EtOH and MeCN afforded lower yield of the desired product **5a** under similar conditions (entries 11–13, Table 1).

Table 1
Optimization of the three-component reaction of dimedone (**2**), 4-chlorobenzaldehyde (**3a**), and malononitrile (**4a**) under various conditions[a]



Entry	Catalyst	Catalyst loading (mol %)	Solvent	Temperature (°C)	Time (min)	Yield[b] (%)	TON	TOF (h^{-1})
1	—	—	—	rt	15	Trace	—	—
2	—	—	—	100	15	Trace	—	—
3	—	—	H_2O	rt	15	20	—	—
4	—	—	H_2O	Reflux	15	35	—	—
5	LIPINO[c]	10	H_2O	Reflux	15	69	6.9	27.6
6	NAPINO[d]	10	H_2O	Reflux	15	75	7.5	30
7	POPINO	10	H_2O	Reflux	10	96	9.6	57.6
8	MAPINO[e]	10	H_2O	Reflux	15	72	7.2	28.8
9	POPINO	10	H_2O	rt	15	65	6.5	26
10	POPINO	7.5	H_2O	Reflux	15	98	13.1	52.4
11	POPINO	5	H_2O	Reflux	15	96	19.2	76.8
12	POPINO	5	EtOH	Reflux	15	63	12.6	50.4
13	POPINO	5	MeCN	Reflux	15	51	10.2	40.8

[a] Reaction conditions: 4-chlorobenzaldehyde (1 mmol), dimedone (1 mmol), malononitrile (1.1 mmol), water (2 mL), and required amount of the catalysts.
[b] The yields refer to the isolated product.
[c] Lithium phthalimide-*N*-oxyl.
[d] Sodium phthalimide-*N*-oxyl.
[e] Magnesium phthalimide-*N*-oxyl.

In order to generalize the optimum conditions, different derivatives of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**5a**–**r**) were prepared from the one-pot reaction mixture of dimedone (**2**), appropriate aldehyde (**3a**–**n**), and malononitrile (**4a**) or ethyl cyanoacetate (**4b**) in the presence of a catalytic amount of POPINO (5 mol %) in water under reflux conditions (Scheme 2). The results have been summarized in Table 2.

As shown in Table 2, aromatic aldehydes with electron-withdrawing groups (entries 1–4 and 15, 16) accelerate the reaction compared to the electron-donating groups (entries 6–10 and 18, Table 2). In addition to the aromatic aldehydes, the reaction was also proceeded smoothly using heterocyclic, alkenyl, and aliphatic aldehydes in high to excellent yields (entries 11–14, Table 2). It is also noteworthy that ethyl cyanoacetate (**4b**) required longer reaction time compared to malononitrile (**4a**) (entries 15–18, Table 2). This may be attributed to the capability of the cyanide group in stabilizing the reaction intermediates compared to the ester group.

On the next step, various derivatives of 2-amino-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene (**7a**–**o**) were synthesized from the aqueous reaction mixture of 2-hydroxynaphthalene-1,4-dione (**6**), aromatic aldehydes (**3a**–**p**), and malononitrile (or ethyl cyanoacetate) in the presence of catalytic amount of POPINO (5 mol %) under reflux conditions (Scheme 3). The results have been summarized in Table 3. The trend of reactivity for different aldehydes is similar to the previous ones in the case of dimedone (**2**).

After that, 4-hydroxycoumarin (**8**) was used as enolic component to synthesize 2-amino-3,4-dihydropyrano[3,2-*c*]chromene (**9a**–**n**) derivatives under the optimized conditions mentioned above, which led to the advantage of a lower reaction time (Scheme 4).

In addition to the enolizable compounds such as dimedone, 2-hydroxynaphthalene-1,4-dione, and 4-hydroxycoumarin, activated phenols including resorcinol (**10**), 1-naphthol (**11a**), and

Table 2
Synthesis of derivatives of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**5**) via condensation of dimedone (**2**), different aldehydes (**3**), and malononitrile or ethyl cyanoacetate (**4a**,**b**) in the presence of POPINO[a]

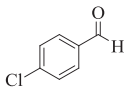
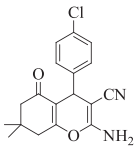
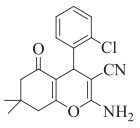
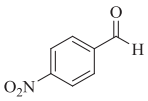
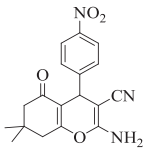
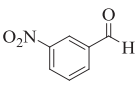
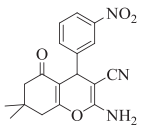
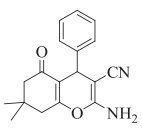
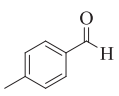
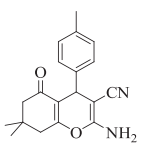
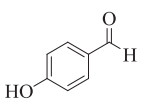
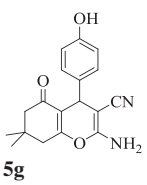
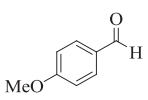
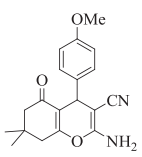
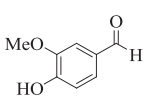
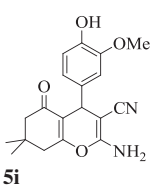
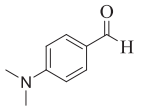
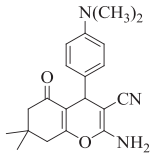
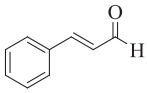
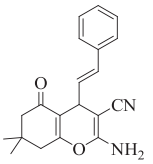
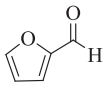
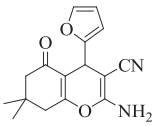
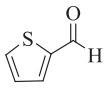
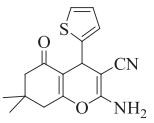
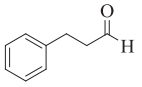
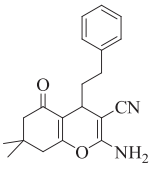
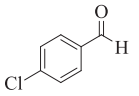
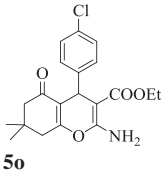
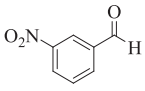
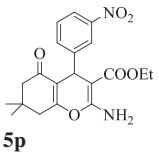
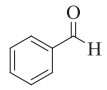
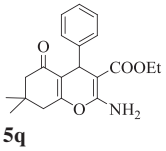
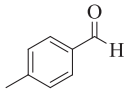
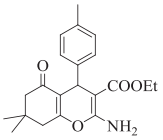
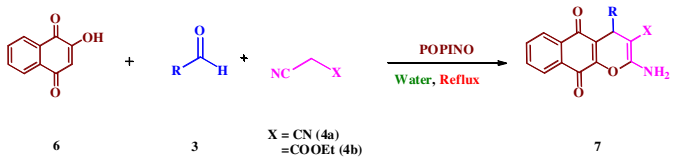
Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (obsd) (°C)	Mp (lit.) (°C)
1	 **3a**	**4a** (CN)	 **5a**	15	96	216–218	215–217[38a]
2	 **3b**	**4a** (CN)	 **5b**	20	98	214–215	214–215[38b]
3	 **3c**	**4a** (CN)	 **5c**	15	88	180–182	179–180[38c]
4	 **3d**	**4a** (CN)	 **5d**	10	92	217–219	214–216[38a]
5	 **3e**	**4a** (CN)	 **5e**	15	95	234–236	234–235[38d]
6	 **3f**	**4a** (CN)	 **5f**	20	94	219–221	220–222[38e]
7	 **3g**	**4a** (CN)	 **5g**	20	92	226–228	224–226[38d]
8	 **3h**	**4a** (CN)	 **5h**	25	89	201–203	201–202[38d]
9	 **3i**	**4a** (CN)	 **5i**	40	98	240–242	238–230[38f]

Table 2 (*continued*)

Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (obsd) (°C)	Mp (lit.) (°C)
10	 **3j**	**4a** (CN)	 **5j**	30	95	210–212	210–212[38g]
11	 **3k**	**4a** (CN)	 **5k**	25	93	183–185	182–184[38h]
12	 **3l**	**4a** (CN)	 **5l**	20	96	220–222	220–223[38i]
13	 **3m**	**4a** (CN)	 **5m**	30	95	226–228	224–226[38j]
14	 **3n**	**4a** (CN)	 **5n**	35	88	203–205	199–200[38k]
15	 **3a**	**4b** (COOEt)	 **5o**	50	91	153–155	153–154[38e]
16	 **3d**	**4b** (COOEt)	 **5p**	50	94	156–157	154–156[38g]
17	 **3e**	**4b** (COOEt)	 **5q**	60	87	148–150	151–153[38e]
18	 **3f**	**4b** (COOEt)	 **5r**	60	90	153–155	151–152[38g]

[a] Reaction conditions: dimedone (1 mmol), aldehyde (1mmol), malononitrile or ethyl cyanoacetate (1.1 mmol), water (2 mL, reflux), POPINO (5 mol %).
[b] All compounds are known and their structures were established from their spectral data and melting points as compared with literature values.
[c] The yields refer to isolated products.



6 3 7

Scheme 3. One-pot three-component reaction of 2-hydroxynaphthalene-1,4-dione (**6**), different aldehydes (**3**), and malononitrile or ethyl cyanoacetate (**4a**,**b**).

2-naphthol (**11b**) were also used in the synthesis of 2-amino-4*H*-chromene derivatives containing fused aromatic rings (**12**–**14**) (Scheme 5). According to the data given in Table 5, resorcinol reacted at position-6 instead of position-2 because of the steric hindrance between two hydroxyl groups (entries 1–10, Table 5).

Generally, the reactions described in Schemes 2–5 are straightforward and the desired products are precipitated out

Table 3
Synthesis of derivatives of 2-amino-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromene (**7**) via condensation of different aldehydes (**3**), malononitrile or ethyl cyanoacetate (**4a**,**b**), and 2-hydroxynaphthalene-1,4-dione (**6**) in the presence of POPINO[a]

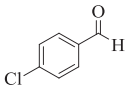
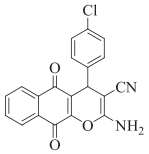
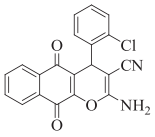
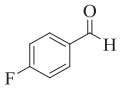
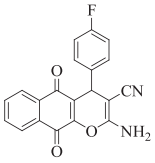
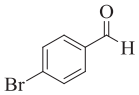
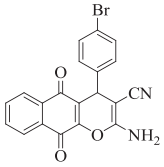
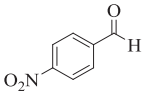
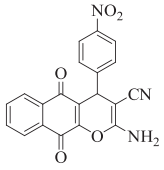
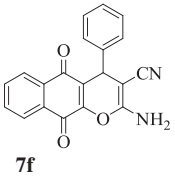
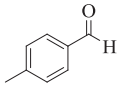
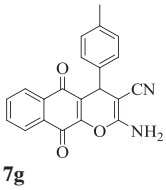
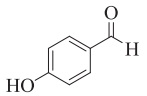
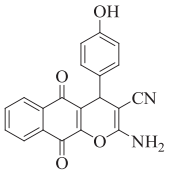
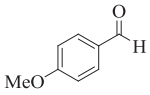
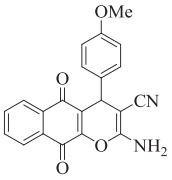
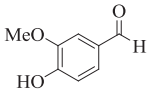
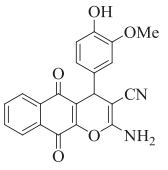
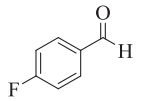
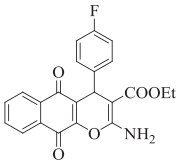
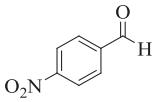
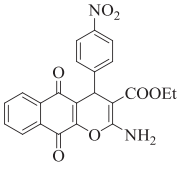
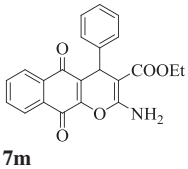
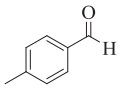
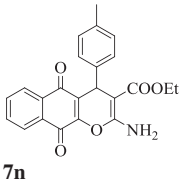
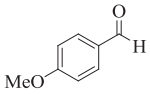
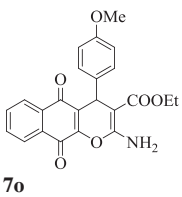
Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (obsd) (°C)	Mp (lit.) (°C)
1	 **3a**	**4a** (CN)	 **7a**	30	98	243–244	240–242[31]
2	 **3b**	**4a** (CN)	 **7b**	20	96	248–250	250–252[39a]
3	 **3o**	**4a** (CN)	 **7c**	25	97	244–246	240–242[39a]
4	 **3p**	**4a** (CN)	 **7d**	30	92	249–251	252–254[31]
5	 **3c**	**4a** (CN)	 **7e**	25	98	232–234	236–238[39a]
6	 **3e**	**4a** (CN)	 **7f**	20	91	263–264	260–262[31]
7	 **3f**	**4a** (CN)	 **7g**	40	94	240–242	242–244[31]

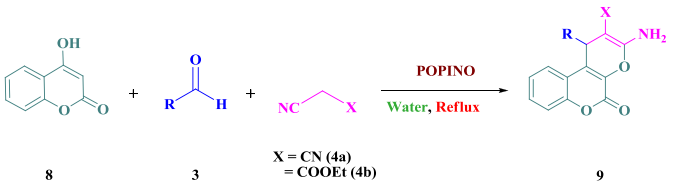
Table 3 (*continued*)

Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (obsd) (°C)	Mp (lit.) (°C)
8	 **3g**	**4a** (CN)	 **7h**	30	93	258–260	255–257[39a]
9	 **3h**	**4a** (CN)	 **7i**	30	90	243–245	244–246[39a]
10	 **3i**	**4a** (CN)	 **7j**	40	89	245–247	243–245[39a]
11	 **3o**	**4b** (COOEt)	 **7k**	40	93	209–211	214–216[31]
12	 **3c**	**4b** (COOEt)	 **7l**	40	96	197–199	194–196[31]
13	 **3e**	**4b** (COOEt)	 **7m**	50	94	185–187	188[39b]
14	 **3f**	**4b** (COOEt)	 **7n**	50	90	207–209	211–214[39a]
15	 **3h**	**4b** (COOEt)	 **7o**	50	89	224–226	220–222[39b]

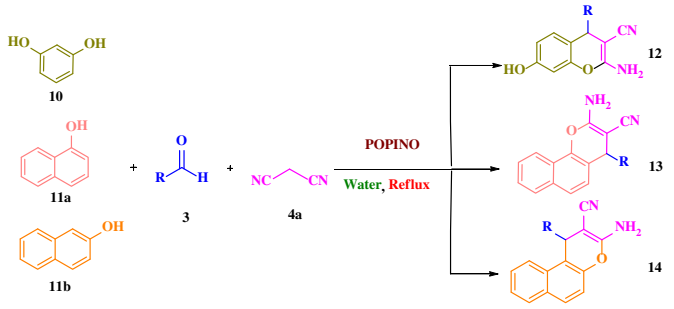
[a] Reaction conditions: aldehyde (1 mmol), 2-hydroxynaphthalene-1,4-dione (1 mmol), malononitrile or ethyl cyanoacetate (1.1 mmol), water (2 mL, reflux), POPINO (5 mol %).

[b] All compounds are known and their structures were established from their spectral data and melting points as compared with literature values.

[c] The yields refer to isolated products.



Scheme 4. One-pot three-component reaction of 4-hydroxycoumarin (**8**), different aldehydes (**3**), and malononitrile or ethyl cyanoacetate (**4a**,**b**).



Scheme 5. One-pot three-component reaction of activated phenols (**10**,**11**), different aldehydes (**3**), and malononitrile or ethyl cyanoacetate (**4a**,**b**).

from the reaction mixture. Therefore, simple filtration of the reaction mixture affords essentially pure products without any laborious step for isolation of the catalyst or evaporation of organic solvent. On the other hand, in some protocols for synthesis of 2-amino-3-cyano-4*H*-chromenes, hydrolysis of cyano groups, which produce undesirable side products have been reported.[24,26,27] Furthermore, acid sensitive aldehydes such as cinnamaldehyde or electron-rich heterocyclic furfural and thiophene-2-carbaldehyde (**3k**–**m**) reacted smoothly under optimized reaction conditions to afford desired products in all studied cases without formation of any polymerization products.[3b,c] Fortunately, the present methodology did not lead to any undesirable side products.

The mechanism suggested in Scheme 6 seems to be reasonable for the one-pot three-component reaction of different enols, aldehydes, and active methylene nitriles catalyzed by POPINO (**1**) in water. The first step includes cyanocinnamonitriles or ethyl cyanocinnamates (**18**) formation from the reaction between aldehyde and malononitrile (or ethyl cyanoacetate). Then, Michael addition of the enolizable component (**2**, **6**, **8**, **10** or **11**) on the intermediate (**18**), cyclization and final tautomerization of intermediates **19** and **20**, respectively, in the presence of POPINO affords the desired product (**5**, **7**, **9**, **12**–**14**).

Table 4
Synthesis of derivatives of 2-amino-3,4-dihydropyrano[3,2-*c*]chromene (**9**) via condensation of different aldehydes (**3**), malononitrile or ethyl cyanoacetate (**4a**,**b**), and 4-hydroxycoumarin (**8**) in the presence of POPINO[a]

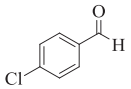
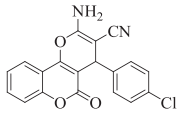
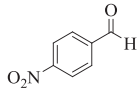
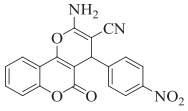
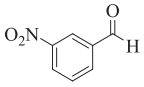
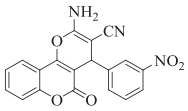
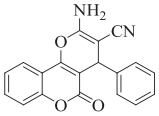
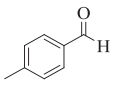
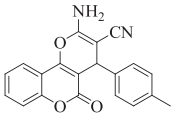
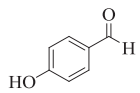
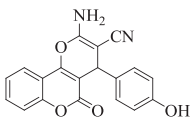
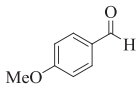
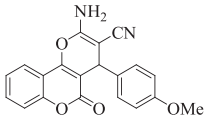
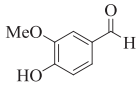
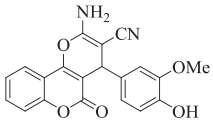
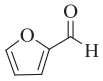
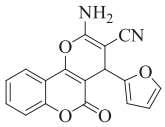
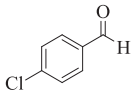
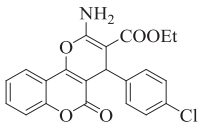
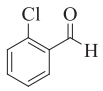
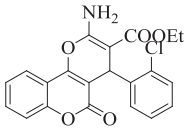
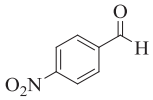
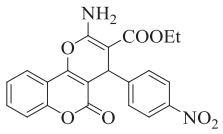
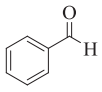
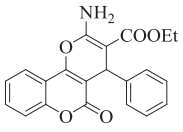
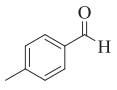
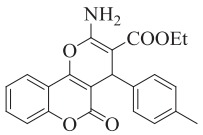
Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (obsd) (°C)	Mp (lit.) (°C)
1	 **3a**	**4a** (CN)	 **9a**	10	96	265–267	264–266[38g]
2	 **3c**	**4a** (CN)	 **9b**	10	95	250–252	250–252[40a]
3	 **3d**	**4a** (CN)	 **9c**	10	90	263–265	264–266[40b]
4	 **3e**	**4a** (CN)	 **9d**	12	97	261–263	260–262[40c]
5	 **3f**	**4a** (CN)	 **9e**	12	88	257–259	253–255[31]
6	 **3g**	**4a** (CN)	 **9f**	15	98	258–260	259–260[40d]

Table 4 (*continued*)

Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (obsd) (°C)	Mp (lit.) (°C)
7	 **3h**	**4a** (CN)	 **9g**	15	91	235–237	233–236[40e]
8	 **3i**	**4a** (CN)	 **9h**	20	96	256–257	253–254[40f]
9	 **3l**	**4a** (CN)	 **9i**	15	95	253–255	254–257[40a]
10	 **3a**	**4b** (COOEt)	 **9j**	20	86	188–190	192–194[31]
11	 **3b**	**4b** (COOEt)	 **9k**	15	87	211–213	209–212[38g]
12	 **3c**	**4b** (COOEt)	 **9l**	15	95	232–233	232–234[40g]
13	 **3e**	**4b** (COOEt)	 **9m**	20	90	209–211	210–212[40h]
14	 **3f**	**4b** (COOEt)	 **9n**	35	92	193–195	199–201[40g]

[a] Reaction conditions: aldehyde (1 mmol), 4-hydroxycoumarin (1 mmol), malononitrile or ethyl cyanoacetate (1.1 mmol), water (2 mL, reflux), POPINO (5 mol %).
[b] All compounds are known and their structures were established from their spectral data and melting points as compared with literature values.
[c] The yields refer to isolated products.

A comparison of the catalytic efficiency of POPINO to prepare the product of model reaction (**5a**) using the selected previously known catalysts is shown in Table 6 to demonstrate that the present protocol is indeed superior to several of the others.

3. Conclusion

In summary, we have developed a highly efficient and green one-pot methodology for the synthesis of a wide range of 2-amino-4*H*-chromene derivatives, which are often encountered in biologically and pharmacologically actives compounds. The present methodology requires low catalyst loading of POPINO as a mild Lewis base organocatalyst. The most important advantages of this method include the use of cost-effective and mild organocatalyst, aqueous conditions, excellent yields, clean and simple work-up procedure, and avoidance of using hazardous organic solvents that makes this method an instrumental alternative to the previous methodologies for the scale-up of these one-pot three-component reactions.

Table 5
Synthesis of fused aromatic rings of 2-amino-7-hydroxy-4*H*-chromenes (**12**–**14**) via condensation of different aldehydes (**3**), malononitrile or ethyl cyanoacetate (**4a**,**b**), and resorcinol (**10**) or naphthol isomers (**11a**,**b**) in the presence of POPINO[a]

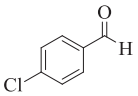
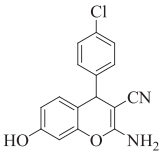
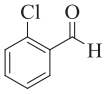
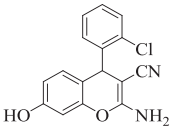
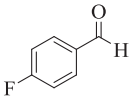
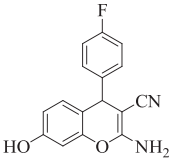
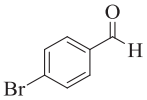
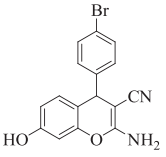
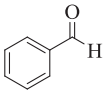
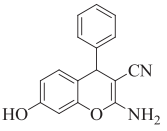
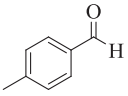
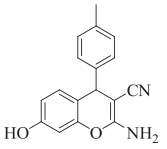
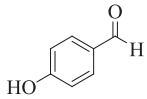
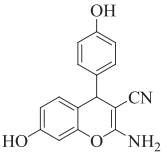
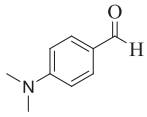
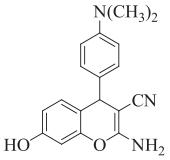
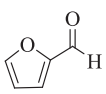
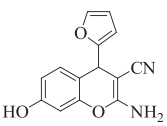
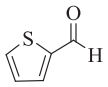
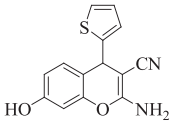
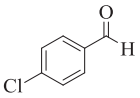
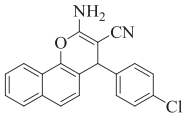
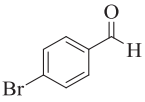
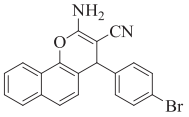
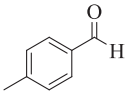
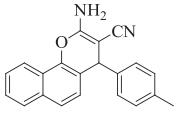
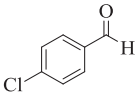
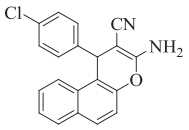
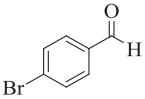
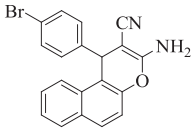
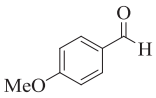
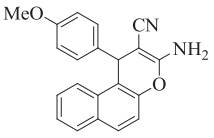
Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (°C)	Mp (lit.) (°C)
1	 **3a**	**4a** (CN)	 **12a**	15	92	162–163	163[41a]
2	 **3b**	**4a** (CN)	 **12b**	20	95	188–190	185–187[41b]
3	 **3o**	**4a** (CN)	 **12c**	22	87	190–192	187–189[41c]
4	 **3p**	**4a** (CN)	 **12d**	15	93	228–230	225–227[41a]
5	 **3e**	**4a** (CN)	 **12e**	20	90	230–232	232–234[41a]
6	 **3f**	**4a** (CN)	 **12f**	30	91	182–184	185–187[41a]
7	 **3g**	**4a** (CN)	 **12g**	20	88	252–254	249[41d]
8	 **3j**	**4a** (CN)	 **12h**	30	86	190–192	193–195[41d]
9	 **3l**	**4a** (CN)	 **12i**	25	89	185–187	189–191[32]

Table 5 (*continued*)

Entry	RCHO (**3**)	Carbon acid (**4**) (X)	Product[b]	Time (min)	Yield[c] (%)	Mp (°C)	Mp (lit.) (°C)
10	 **3m**	**4a** (CN)	 **12j**	25	84	207–209	204–205[32]
11	 **3a**	**4a** (CN)	 **13a**	10	93	233–235	232–234[41e]
12	 **3p**	**4a** (CN)	 **13b**	10	90	234–236	234–235[41f]
13	 **3f**	**4a** (CN)	 **13c**	15	87	200–202	205–206[31]
14	 **3a**	**4a** (CN)	 **14a**	12	88	207–208	206–208[41g]
15	 **3p**	**4a** (CN)	 **14b**	15	92	238–240	241–243[17]
16	 **3h**	**4a** (CN)	 **14c**	15	83	185–187	182–183[41g]

[a] Reaction conditions: aldehyde (1 mmol), resorcinol (1 mmol), malononitrile or ethyl cyanoacetate (1.1 mmol), water (2 mL, reflux), POPINO (5 mol %).
[b] All compounds are known and their structures were established from their spectral data and melting points as compared with literature values.
[c] The yields refer to isolated products.

4. Experimental

4.1. General

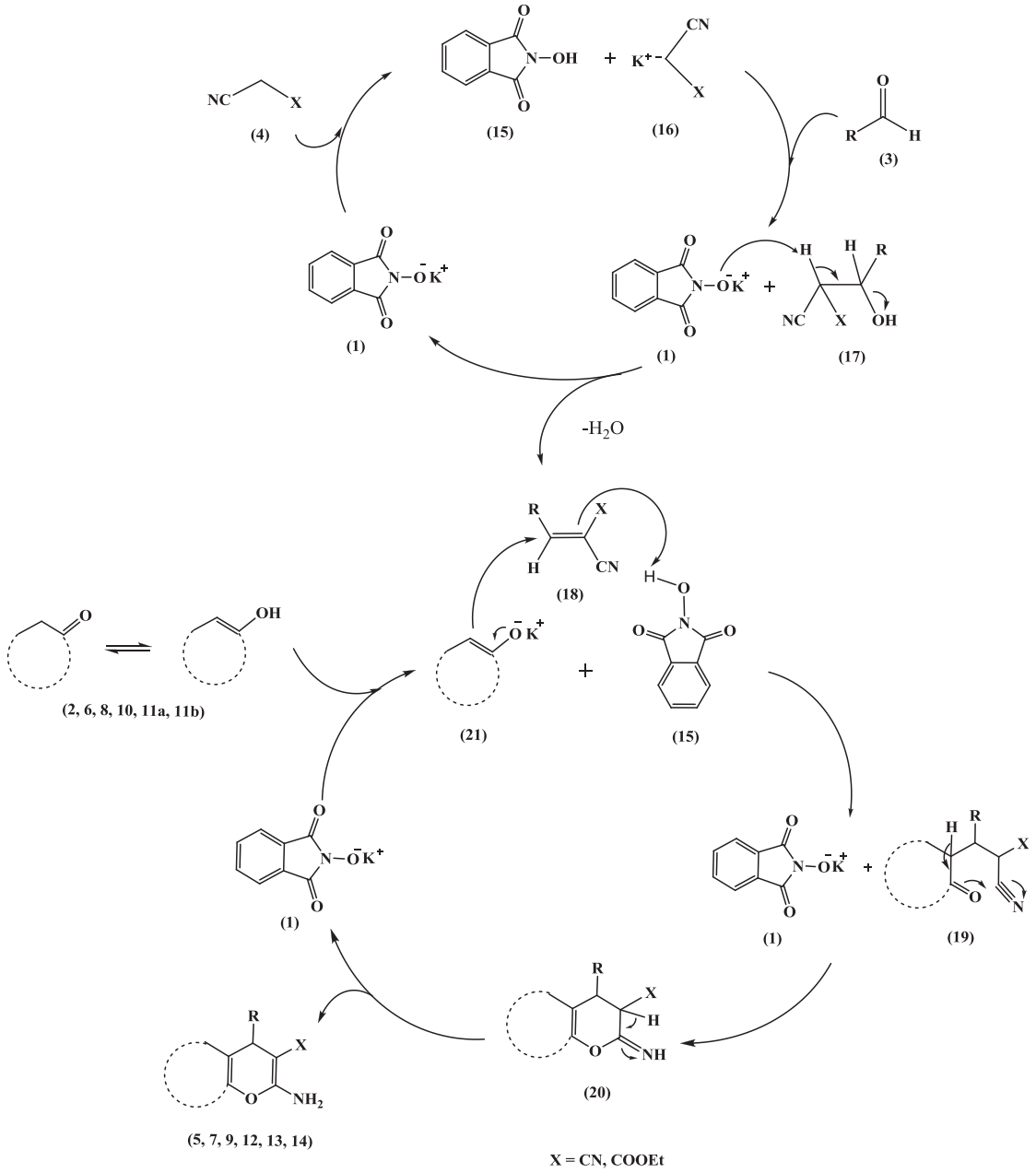
All of the chemicals and laboratory grade reagents were purchased from Merck and Aldrich without further purification, except for benzaldehyde, which was used as a fresh distilled sample. POPINO and other salts of PINO anion were synthesized according to our previously reported experimental procedure.[34a] Analytical thin layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates. Products were characterized by spectroscopy data (IR, ^{1}H NMR, and ^{13}C NMR spectra) and melting points. FTIR spectra were recorded as KBr pellets on a Shimadzu FT IR-8400S spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded using Bruker DRX-500 Avance spectrometer in $CDCl_3$ at ambient temperature. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected.

4.2. General procedure for preparation of POPINO (1)

POPINO (**1**) was simply prepared in high yield and purity by the reaction of *N*-hydroxyphthalimide (1.63 g, 10 mmol) with an equivalent amount of the KOH in EtOH (20 mL) under reflux conditions after 5 min. The obtained deep red salt was filtered, washed with cold EtOH (5 mL), and characterized by FTIR spectroscopy.[34a]

4.3. Typical procedure for the synthesis of 2-amino-4*H*-chromene derivatives (5, 7, 9, 12–14)

In a 5 mL round bottom flask equipped with a magnetic bar and condenser, enolizable compound (**2**, **6**, **8**, **10** or **11**, 1 mmol), aldehyde (**3a**–**p**, 1 mmol), and malononitrile (or ethyl cyanoacetate)



Scheme 6. A plausible mechanism for the one-pot three-component reaction of different enols (**2**, **6**, **8**, **10**, **11**), aldehydes (**3**), and active methylene nitriles (**4**) catalyzed by POPINO (**1**) in water.

Table 6
Comparative synthesis of compound **5a** using the reported methods versus the present method

Entry	Catalyst	mol %	Solvent	Temp (°C)	Time (min)	Yield (%)	TOF (h^{-1})	Reference
1	4-(Dimethylamino)pyridine (DMAP)	20	EtOH	Reflux	15	94	18.8	38g
2	LiBr	10	H_2O	Reflux	15	95	38	42
3	Magnesium oxide	50	—	rt	25	86	17.2	5e
4	Tetrabutylammonium fluoride (TBAF)	10	H_2O	Reflux	30	94	18.8	38d
5	Nickel nitrate hexahydrate ($Ni(NO_3)_2{\cdot}6H_2O$)	10	H_2O	Reflux	20	88	26.4	43
6	*N*,*N*-Dimethylaminoethylbenzyldimethylammoniumchloride ($[PhCH_2Me_2N^+CH_2CH_2NMe_2]Cl^-$)	5	—	50	30	91	36.4	17b
7	Triethylbenzylammonium chloride (TEBA)	100	H_2O	90	420	94	0.13	44
8	*N*-Methylimidazole	20	H_2O	rt	90	90	3	45
9	1,4-Diazabicyclo[2.2.2]octane (DABCO)	10	H_2O	Reflux	120	94	4.7	46
10	POPINO	5	H_2O	Reflux	15	95	78.6	This work

(**4**, 1.1 mmol) were added to distilled water (2 mL). Then, the reaction mixture was refluxed for appropriate time as shown in Tables 2–5. The reaction progress was monitored by TLC as well as precipitating out of the products from the reaction mixture. After completion of the reaction, the mixture was cooled to rt and the solid product was filtered, washed with cold distilled water (2 mL) to obtain essentially pure products. The solid products were recrystallized from ethanol if necessary.

Acknowledgements

We are grateful for the financial support from The Research Council of Iran University of Science and Technology (IUST), Tehran, Iran (grant no. 160/354).

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