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Highly efficient organocatalytic synthesis of diverse and densely functionalized 2-amino-3-cyano-4*H*-pyrans under mechanochemical ball milling

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2014,
Accepted 00th January 2014

DOI: 10.1039/x0xx00000x

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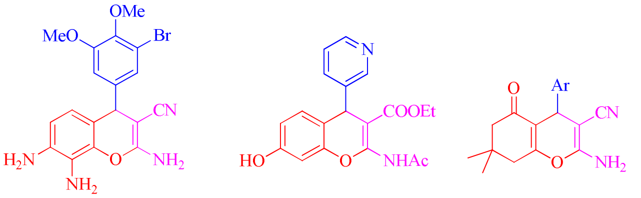
An improved one-pot three-component and environmentally benign approach for the synthesis of a wide range of densely functionalized 2-amino-3-cyano-4*H*-pyran annulated derivatives has been described by the reaction of aryl aldehydes, malononitrile and diverse phenols or enolizable C─H activated acidic compounds under mechanochemical ball milling conditions in the presence of potassium phthalimide (POPI), as a mild basic organocatalyst, at ambient temperature. In comparison to the conventional methods, the remarkable advantages of this green protocol are high to quantitative yields, avoiding the use of any hazardous transition metal-free catalyst or solvent, shorter reaction time at ambient temperature, low cost, and straightforward work-up procedure.

Introduction

With considering the increasing environmental pollution and its intensive impact on living systems, developing chemical processes using more environmentally acceptable chemicals, catalysts, solvents, atom efficient procedures, and new energy inputs have been emerged as subjects of innovation in green chemistry. Avoiding or minimizing the use of transition metals in chemical processes is a significant part of this innovation since they are often toxic and difficult to dispose off properly in large quantities. Moreover, the difficulty of transition metals separation might lead to contamination of the final product. Therefore, the presence of transition metals, even at the lowest level, in the pharmaceutical products is closely regulated due to their undesired harmful side effects on health nowadays.[1] On the other hand, development of alternative energy inputs for chemical reactions have become a major achievement since consumption of energy for heating or cooling causes a major adverse effect on the environment. In this regard, a number of chemists are engaged in the development of green chemistry protocols *i.e.* utilization of nonclassical alternative energy inputs such as mechanochemical ball milling technique or ultrasound and microwave irradiation. Furthermore, the toxic and volatile nature of many organic solvents have posed a serious threat to the environment because these solvents contribute significantly to the chemical waste. Therefore, development of protocols working under solvent-free conditions at room temperature is in great demand to avoid the use of volatile organic compounds (VOCs).[1,2] One of the most important progresses to combine economic aspects with the environmental concerns is the use of ball milling solid-state mechanochemical techniques which has provided simple and efficient synthetic methods of great promise. The elimination of toxic organic solvent during the reaction, short reaction time, better energy balance, straightforward work-up, higher safety and providing good to excellent yields with stoichiometric amounts of reactants are apparent advantages that distinguish the mechanochemical ball milling techniques from others techniques such as microwave or ultrasound irradiation.[2,3] Morever, great efforts have also been focoused on multi-component reactions (MCRs) because these reactions allow rapid and efficient coupling of several building blocks in a single step to give highly functionalized organic molecules. The outstanding potential of these strategy is creation of several new bonds in a one-pot reaction, lower number of reaction and purification steps, synthetic efficiency and convergence, high atom economy, selectivity, and operational simplicity. Therefore, academic and industrial research groups have increasingly focused on the development of MCRs that can lead to new efficient synthetic methodologies to afford many small organic compounds such as biologically-active heterocyclic compounds.[4]

Fused benzo-4*H*-pyran, namely, 4*H*-chromene moiety is the key building block of many oxygen-containing heterocyclic natural products which their pharmacological and biological activity has been known for a long time.[5] Indeed, edible fruits and vegetables are among of food resources that being characterized by the natural products containing chromene moiety in their structures.[6] These compounds demonstrate antitumor, antioxidant, antibacterial, antiviral, antifungal, hypotensive, anticoagulant, antileishmanial, diuretic, and antiallergenic activities.[7] For instance, 2-amino-3-cyano-4*H*-chromene derivatives such as **A**, **B** and **C** are valuable compounds as anticancer, inhibitors of insulin-regulated aminopeptidase (IRAP) for enhancing memory and learning functions and antibacterial agents, respectively (Fig. 1).[8]

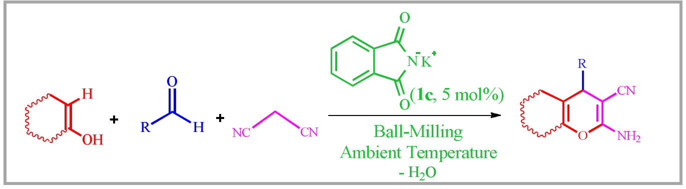


(A) Anticancer agent **(B)** IRAP inhibitor **(C)** Anibacterial agents

Fig.1 Selected examples of 4*H*-chromene derivatives demonstrating pharmacological and biological activity.

Furthermore, compounds containing 4*H*-chromene scaffold have found other applications such as laser dyes,[9] optical brighteners,[10] fluorescence markers,[11] pigments,[12] cosmetics, biodegradable agrochemicals[13] and pH sensitive fluorescent materials for visualization of biomolecules.[14] Therefore, it is not strange that different MCR strategies have been developed for the synthesis of 4*H*-pyran scaffold.[15-21] However, one of the useful strategies for the synthesis of 2-amino-3-cyano(/ethyl carboxy)-4*H*-pyran derivatives is based on catalytic MCR between malononitrile (or ethyl cyanoacetate), an aldehyde, and diverse electron-rich phenolic C—H activated or enolizable acidic compounds. Consequently, many protocols for the synthesis of 2-amino-3-cyano(/ethyl carboxy)-4*H*-pyran derivatives have been developed using homogeneous or heterogeneous catalysts due to their broad applications in many different fields as well as diversity of the reaction components.[15a,16-20] Although there is a few reports about the enol-based MCR to afford 4*H*-pyran scaffold under catalyst-free conditions for more acidic cyclic 1,3-dicarbonyl compounds such as barbituric acid (p*K*a= 4.01) and dimedone (p*K*a= 5.23) but elevated temperature and long reaction times are required compared to protocols using catalysts.[21a-c] However, less acidic acyclic 1,3-dicarbonyl compounds such as ethyl acetoacetate (p*K*a= 10.68) or activated phenols such as resorcinol (p*K*a= 9.32), 1-naphthol (p*K*a= 9.39), and 2-naphthol (p*K*a= 9.63) react only in the presence of a catalyst to afford desired products under similar reaction conditions.[15a,16-21a]

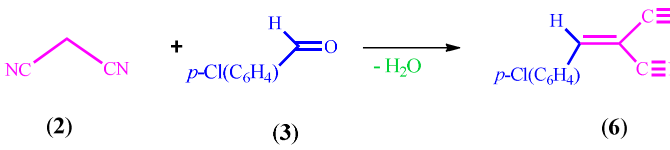
Recent catalytic systems for MCR synthesis of 2-amino-3-cyano-4*H*-pyran derivatives consist of homogeneous or heterogeneous $TiCl_4$,[16a] $Fe(HSO4)_3$,[16b] heteropolyacid,[16c] $MeSO_3H$,[16d] PEG-SO_3H,[16e] nano-sized zeolite clinoptilolite,[16f] tungstic acid functionalized mesoporous SBA-15,[16g] KSF,[16h] nano-sized $CoFe_2O_4$,[17a] CuO-CeO_2,[17b] eggshell,[17c] or MgO,[17d] Mg/Al hydrotalcite,[17e-f]Alumina,[17g] L-proline,[18a] glycine,[1f] chitosan,[18b] meglumine,[18c] imidazole,[18d] DBU,[18e] Et_3N,[8a] 4-dimethylaminopyridine,[18f] morpholine,[18g] piperidine,[8a] potassium phthalimide-*N*-oxyl,[18h] combined NaOAc/KF,[18i] different tetraalkylammonium halides[19a-d] or ionic liquids such as [BMIm]BF_4, [2-AEMIm]PF_6 and TMG-[BMIm][X],[19e-g] or an enzyme such as lipase. the use of transition metals, high catalyst loading, long reaction time, highly corrosive, fuming or expensive catalysts, odorous amines, volatile solvents and consumption of energy inputs for heating of the reaction system.[16-20] To the best of our knowledge, little efforts have been paid to the synthesis of 2-amino-3-cyano-4*H*-pyran derivatives under solvent-free conditions at ambient temperature.[21d] However, high loading of piperazine is still required. Therefore, development of eco-friendly protocols using more efficient and safer catalysts under solvent-free conditions at room temperature are in great demand. In continuation of our interest to develop the catalytic scope of potassium phthalimide for cyanosilylation of carbonyl compounds and cyclotrimerization of isocyanates,[22] we wish herein to report a quantitative, convenient and cost-effective ball milling methodology for the preparation of 2-amino-3-cyano-4*H*-pyran scaffold in the presence of potassium phthalimide (POPI, **1c**) based on MCR strategy (Scheme 1). POPI is commercially available as a transition metal-free and mild Lewis base. However, it has received less attention as a catalyst in organic synthesis.[23]



Scheme 1 Three-component reaction of different phenols or enols with aromatic aldehydes and malononitrile catalyzed by POPI (**1c**) under ball milling conditions at ambient temperature.

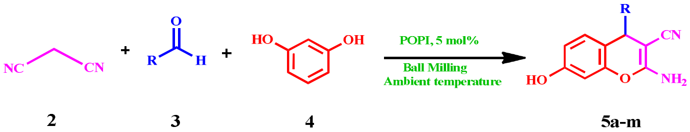
Results and discussion

First, the reaction of malononitrile (**2**), *p*-chlorobenzaldehyde (**3a**), and resorcinol (**4**, p*K*a= 9.32) (molar ratio: 1.1:1:1) was chosen as the model reaction. To prove the efficiency of both *p*-toluenesulfinate[24] and phthalimide anions under different conditions, a systematic study considering different factors affecting the yield of the desired 2-amino-4-(4-chlorophenyl)-3-cyano-7-hydroxy-4*H*-chromene (**5a**) was performed.[18h] The results are summarized in Table 1. Preliminary optimization experiments indicated that the desired product **5a** was not obtained in the absence of any catalyst in various solvents even under reflux conditions or solvent-free ball milling at ambient temperature (entries, 1-4). Indeed, only the Knoevenagel condensation product of (**2**) and (**3a**) was formed in almost quantitative yield in all studied cases (Scheme 2).[18h]



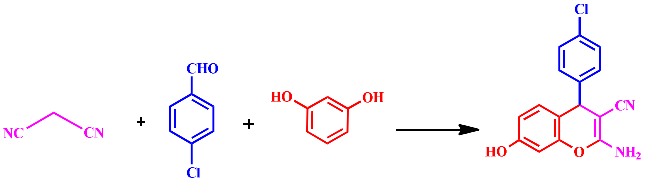
Scheme 2 Cyanocinnamonitrile intermediate (**6**) formed by the Knoevenagel condensation of malonitrile (**2**) and *p*-chlorobenzaldehyde (**3a**).

Interestingly, the desired product **5a** was obtained when a catalytic amount of alkali metal salts of *p*-toluenesulfinate or phthalimide was used in water under reflux conditions (entries 5-7). However, POPI (**1c**) afforded higher yields compared to sodium or potassium *p*-toluenesulfinate (**1a-b**) in water under reflux conditions as well as under solvent-free conditions at 80 °C. Surprisingly, almost quantitative yield of **5a** was obtained under ball milling at ambient temperature (entries, 8-11). Furthermore, simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solid of **5a**. Therefore, POPI was chosen in the next optimization experiments for the best catalyst loading (entries, 11-13). According to the obtained results, 5 mol% POPI loading under ball milling at ambient temperature, as optimized conditions, was developed to other derivatives of aldehydes (**5b-m**) (Scheme 3).[25] The results are summarized in Table 2.



Scheme 3 Three-component synthesis of different 2-amino-7-hydroxy-4*H*-chromene derivatives (**5a-m**) catalyzed by POPI (**1c**) under ball milling at ambient Temperature.

Table 1 Optimization of the reaction conditions for preparation of 2-amino-4-(4-chlorophenyl)-3-cyano-7-hydroxy-4*H*-chromene (**5a**)[a]

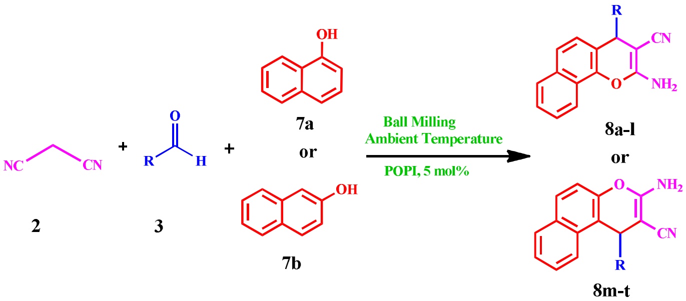


2 **3a** **4** **5a**

Entry	Catalyst (mol%)	Conditions	Temp. (°C)	Yield[b] (%)	TON	TOF (h^{-1})
1	-	H_2O	Reflux	Trace[c]	-	-
2	-	EtOH	Reflux	Trace[c]	-	-
3	-	MeCN	Reflux	Trace[c]	-	-
4	-	Ball milling	Ambient	Trace[c]	-	-
5	NATS[d] (**1a**, 10)	H_2O	Reflux	35	3.5	14
6	POTS[e] (**1b**, 10)	H_2O	Reflux	40	4.0	16
7	POPI (**1c**, 10)	H_2O	Reflux	70	7.0	18.7
8	POPI (**1c**, 10)	Solvent-free	80	82	8.2	32.8
9	POTS[e] (**1b**, 10)	Solvent-free	80	40	4.0	16
10	POPI (**1c**, 10)	Ball milling	Ambient	98[f]	9.8	39.2
11	POTS[e] (**1b**, 10)	Ball milling	Ambient	38	3.8	15.2
12	POPI (**1c**, 5)	Ball milling	Ambient	98[f]	19.6	78.4
13	POPI (**1c**, 2.5)	Ball milling	Ambient	70	7.0	28
14	POPI (**1c**, 5)	Ball milling	Ambient	99[g]	19.8	79.2
15	POPI (**1c**, 5)	Ball milling	Ambient	96[h]	19.2	76.8
16	POPI (**1c**, 5)	Ball milling	Ambient	93[i]	18.6	74.4

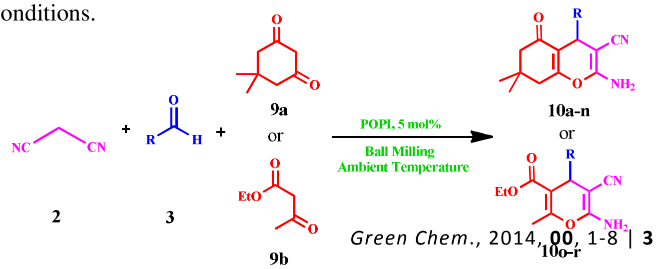
[a] Reaction conditions: Malononitrile (**2**, 1.1 mmol), 4-chlorobenzaldehyde (**3a**,1 mmol), resorcinol (**4**,1 mmol), solvent (2 mL), time (15 min) and required ammount of the catalysts. [b] The yields refer to the isolated product **5a**. [c] The Knoevenagel condensation product of (**2**) and (**3a**) was formed in almost quantitative yield. [d] Sodium *p*-toluenesulfinate. [e] Potassium *p*-toluenesulfinate. [f] Quantitative conversion of the substrates to the desired product **5a** was observed. Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solid of **5a**. [g] An experiment was run with 5 mmol of resorcinol to recycle the catalyst. [h] Second run with 3 mmol of resorcinol using recycled catalyst from entry 14. [i] Third run with 1 mmol of resorcinol using recycled catalyst from entry 15.

In order to demonstrate the scope of this new efficient methodology, the optimized reaction conditions were developed to another activated phenolic compounds, 1-naphthol (**7a**, p*K*a= 9.39) and 2-naphthol (**7b**, p*K*a= 9.63), at the next stage (Scheme 4). The results are summarized in Table **3**. Again, almost quantitative yields were obtained for the desired products (**8a-t**) under the optimized conditions.



Scheme 4 Three-component synthesis of different fused aromatic ring derivatives of 2-amino-4*H*-chromene (**8a-t**) catalyzed by POPI (**1c**) under ball milling at ambient temperature.

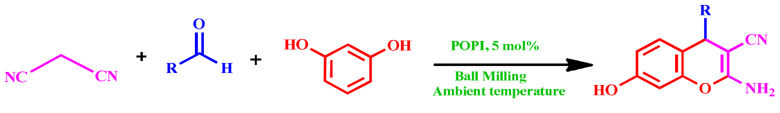
Finally, the scope of the present protocol was developed to dimedone (**9a**, p*K*a= 5.23), for quantitative preparation of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran products (**10a-n**) under ball milling (Scheme 5). The results are summarized in Table 4. It is noteworthy that dimedone, as a cyclic C–H activated acidic 1,3-dicarbonyl, required shorter reaction times compared to resorcinol (**4**) or 1-naphtol (**7a**) and 2-naphtol (**7b**), as representatives of activated phenolic components. In addition to dimedone, ethyl acetoacetate (**9b**, p*K*a= 10.68), was also examined for the synthesis of ethyl 6-amino-4-(aryl)-5-cyano-2-methyl-4*H*-pyran-3-carboxylates (**10o-s**). However, The three-component reaction of and ethyl acetoacetate (**9b**), as an acyclic 1,3-dicarbonyl, required longer reaction times compared to dimedone (**9a**) under similar reaction conditions.



Scheme 5 Three-component synthesis of various 2-amino-3-cyano-4*H*-pyran derivatives (**10a-s**) catalyzed by POPI (**1c**) under ball milling at ambient temperature.

Considering the substituent effects with the trend of reactivity of different aldehydes in the multicomponent reaction with each of enol components **4**, **7** or **9** demonstrate that electron deficiency of the carbon-carbon double bound in the cyanocinnamonitrile intermediate (**6**), formed by the Knoevenagel condensation of malonitrile (**2**) and aldehydes (**3**), is an effective factor in the completion of the reaction (Scheme 2). Therefore, electron-withdrawing groups in the *p-/o-* position of the aromatic ring of aldehyde accelerate the reaction compared to the electron-donating groups. It is also noteworthy that heterocyclic aldehydes, such as furfural and thiophen-2-carbaldehyde, required similar reaction time compared to aldehydes with electron-donation groups.

Table 2 Three-component synthesis of different 2-amino-7-hydroxy-4*H*-chromene derivatives (**5a-m**) via condensation of malononitrile (**2**), various aldehydes (**3**) and resorcinol (**4**) in the presence of POPI (**1c**) using ball milling technique at ambient temperature[a]

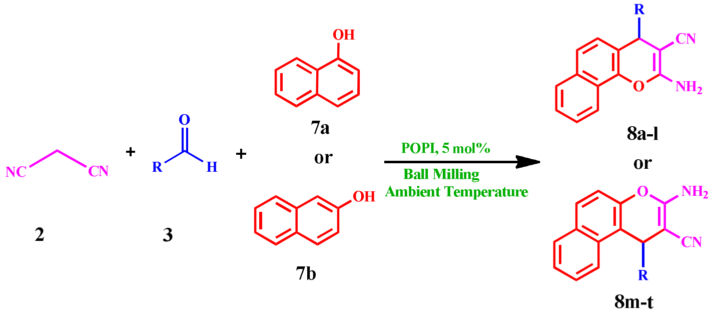


2 **3** **4** **5a-m**

Entry	Aldehyde **3**	Product[b]	Time (min)	Isolated Yeild[c](%)	M.P (Obsd) (°C)	M.P (Lit) (°C)
1	4-Chlorobenzaldehyde	**5a**	15	98	161-163	159-161[17e]
2	2-Chlorobenzaldehyde	**5b**	15	96	97-99	96-98[17e]
3	4-Fluorobenzaldehyde	**5c**	10	99	191-192	187-189[18h]
4	4-Boromobenzaldehyde	**5d**	7	98	222-224	225-227[18h]
5	4-Nitrobenzaldehyde	**5e**	12	97	166-168	162-163[17e]
6	3-Nitrobenzaldehyde	**5f**	20	96	167-169	169-170[17e]
7	Benzaldehyde	**5g**	17	97	235-237	232-234[16b]
8	4-Methylbenzaldehyde	**5h**	20	98	188-190	185-187[16b]
9	4-Methoxybenzaldehyde	**5i**	25	97	110-112	111-112[17e]
10	4-Hydroxybenzaldehyde	**5j**	20	98	250-252	248-250[17e]
11	4-Dimethylaminobenzaldehyde	**5k**	17	98	194-196	193-195[18h]
12	Furfural	**5l**	20	97	190-192	189-191[26]
13	Thiophen-2-carbaldehyde	**5m**	20	99	210-212	207-209[17e]

[a] Reaction conditions: Malononitrile (**2**, 1.1 mmol), aryl aldehyde (**3**, 1 mmol), resorcinol (**4**, 1 mmol), POPI (**1c**, 5 mol%). [b] All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values.[16b,17e,18h, 26] [c] Quantitative conversion of the substrates to the desired product **5a-m** was observed. Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solids of **5a-m**.

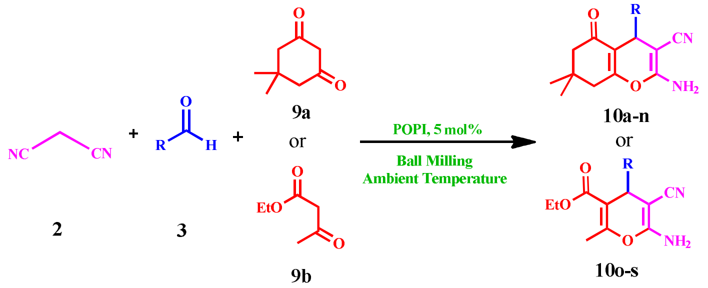
Table 3 Three-component synthesis of different fused aromatic ring derivatives of 2-amino-4*H*-chromene(**8a-t**) via condensation of malononitrile (**2**), various aldehydes (**3**) and 1-naphthol (**7**) in the presence of POPI (**1c**) using ball milling technique at ambient temperature[a]



Entry	Aldehyde **3**	Product[b]	Time (min)	Isolated Yeild[c](%)	M.P (Obsd) (°C)	M.P (Lit) (°C)
1	4-Chlorobenzaldehyde	**8a**	10	99	232-234	232-234[27a]
3	2-Chlorobenzaldehyde	**8b**	8	97	240-241	237-239[27b]
2	4-Fluorobenzaldehyde	**8c**	10	99	233-235	236-237[18e]
4	4-Nitrobenzaldehyde	**8d**	10	98	233-234	232-234[17d]
5	3-Nitrobenzaldehyde	**8e**	15	99	211-213	214-216[18e]
6	4-Cyanobenzaldehyde	**8f**	8	99	285-286	285-287[17g]
7	Benzaldehyde	**8g**	10	97	213-215	210-212[17g]
8	4-Methylbenzaldehyde	**8h**	17	96	206-208	205-206[18e]
9	4-Methoxybenzaldehyde	**8i**	20	96	187-189	184-185[27c]
10	4-Hydroxybenzaldehyde	**8j**	15	98	190-192	187-188[27a]
11	Vanillin	**8k**	15	98	141-143	137-139[27d]
12	4-Dimethylaminobenzaldehyde	**8l**	13	98	203-205	203-205[27d]
13	4-Chlorobenzaldehyde	**8m**	13	99	207-208	206-208[27e]
14	2-Chlorobenzaldehyde	**8n**	13	96	256-258	259-261[27a]
15	4-Boromobenzaldehyde	**8o**	13	97	238-240	241-243[17g]
16	4-Nitrobenzaldehyde	**8p**	13	99	187-189	188[27d]
17	3-Nitrobenzaldehyde	**8q**	13	98	232-234	232-235[27a]
18	4-Cyanobenzaldehyde	**8r**	13	99	255-257	258-260[17g]
19	Benzaldehyde	**8s**	13	97	283-285	280-282[27d]
20	4-Methoxybenzaldehyde	**8t**	13	97	188-189	188-189[27a]

[a] Reaction conditions: Malononitrile (**2**,1.1mmol), aryl aldehyde (**3**, 1mmol), 1-naphthol or 2-naphthol (**7a-b**, 1mmol), POPI (**1c**, 5 mol%). [b] All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values.[17d,g,27] [c] Quantitative conversion of the substrates to the desired product **8a-t** was observed. Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solids of **8a-t**.

Table 4 Three-component synthesis of different 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[b]pyrans (**10a-s**) via condensation of malononitrile (**2**), various aldehydes (**3**) and dimedone (**8a**) in the presence of POPI (**1c**) using ball milling technique at ambient temperature[a]



Entry	Aldehyde **3**	Product[b]	Time (min)	Isolated Yeild[c](%)	M.P (Obsd) (°C)	M.P (Lit) (°C)
1	4-Chlorobenzaldehyde	**10a**	3	99	203-205	202-203[7b]
2	4-Fluorobenzaldehyde	**10b**	1	98	214-215	210-211[27c]
3	2-Chlorobenzaldehyde	**10c**	4	96	211-213	214-215[28a]
4	4-Nitrobenzaldehyde	**10d**	3	99	181-183	179-180[28b]
5	3-Nitrobenzaldehyde	**10e**	4	98	212-213	214-216[28b]
6	4-Cyanobenzaldehyde	**10f**	1	98	184-186	180-182[28b]
7	Benzaldehyde	**10g**	6	97	232-234	234-235[27c]
8	4-Methylbenzaldehyde	**10h**	5	96	220-221	220-222[28c]
9	4-Methoxybenzaldehyde	**10i**	8	98	197-199	196-198[28c]
10	4-Hydroxybenzaldehyde	**10j**	10	99	224-226	204-205[28b]
11	Vanillin	**10k**	8	98	238-239	238-240[28d]
12	4-Dimethylaminobenzaldehyde	**10l**	10	98	213-215	210-212[18f]
13	Furfural	**10m**	5	96	223-225	226-228[27c]
14	Thiophen-2-carbaldehyde	**10n**	6	98	222-224	224-226[28e]
15	4-Chlorobenzaldehyde	**10o**	15	90	174-175	172-174[7b]
16	4-Nitrobenzaldehyde	**10p**	15	96	175-177	176–178[28f]
17	Methyl 4-formylbenzoate	**10q**	15	98	179-181	178–180[21d]
18	Benzaldehyde	**10r**	20	96	187-189	191-192[21d]
19	4-Methoxybenzaldehyde	**10s**	20	95	136-138	136-138[28f]

[a] Reaction conditions: Malononitrile (**2**, 1.1mmol), aryl aldehyde (**3**, 1mmol), dimedoneor ethyl acetoacetate (**9a-b**, 1mmol), POPI (**1c**, 5 mol%). [b] All compounds are known and their structures were established from their spectral data and melting points as compared with authentic samples or literature values.[7b,18f,21,27c,28] [c] Quantitative conversion of the substrates to the desired product **10a-s** was observed. Simple trituration of the reaction mixture in water and its subsequent filtering afforded essentially pure solids of **10a-s**.

Finally, to demonstrate the efficiency and capability of the present protocol in the synthesis of different 2-amino-3-cyano-4*H*-pyran derivatives, it has been compared with some of the previously reported and published procedures. Summarized results in Table 6, clearly show that the present protocol is indeed superior to several of the others in terms of product yield, reaction time, elimination of solvent, and reaction temperature.

Conclusion

In summary, we have introduced a highly efficient, eco-friendly and one-pot three-component protocol for the synthesis of densely functionalized 2-amino-3-cyano-4*H*-pyran annulated derivatives in the presence of potassium phthalimide under solvent-free ball milling conditions at ambient temperature. Furthermore, the present method offers several advantages such as mild conditions, quantitative yields of products in relatively short reaction times, elimination of solvent, clean reaction profile and simple work-up procedure, and savings in energy consumption that makes this method an instrumental alternative to the previous methodologies for the scale-up of these one-pot three-component reactions.

Table 6. Comparative synthesis of compound **5a**, **8j** and **10m** using the reported methods *versus* the present method

Entry	Catalyst	Catalyst loading	Solvent	Temp (°C)	Time (min)	Yield (%)	TOF (h^{-1})	Reference
1	TAFMC-1[a]	30 mg	H_2O	Reflux	900	80	4.8	16g
2	hydrotalcite[a]	15 (wt%)	H_2O	60	300	90	-	17e
3	Nanozeolite clinoptilolite[a]	10 mg	H_2O	Reflux	15	95	-	16f
4	POPI[a]	5 mol%	Ball milling	r.t	15	98	78.4	This work
5	DBU[b]	10 mol%	H_2O	Reflux	10	86	51.6	18e
6	PEG-SO_3H[b]	1 mL	-	100	135	89	-	16e
7	Na_2CO_3[b]	10 mol%	-	120	45	100	13.3	27a
8	POPI[b]	5 mol%	Ball milling	r.t	15	96	76.8	This work
9	Tetrabutylammonium fluoride[c]	10 mol%	H_2O	Reflux	10	97	58.2	19a
10	POPINO[c]	5 mol%	H_2O	Reflux	20	96	57.6	18h
11	POPI[c]	5 mol%	Ball milling	r.t	5	94	225.6	This work

[a] Obtained results for the synthesis of compound **5a**. [b] Obtained results for the synthesis of compound **8j**. [c] Obtained results for the synthesis of compound **10m**.

Experimental

General

All commercially available chemicals were obtained from Merck and Aldrich, and used without further purifications, except for benzaldehyde, which was used as a fresh distilled sample. The ball mill was a Retsch MM 400 swing mill. 10 mL stainless steel ball mill vessels were applied for 1-5 mmol runs. Two stainless steel balls with 12 mm diameter were used, and the milling frequency was at 28 Hz at the ambient temperatures. Analytical thin layer chromatography (TLC) for monitoring reactions was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. ^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on a Bruker DRX-500 Avance spectrometers with $CDCl_3$ as solvent at ambient temperature and tetramethylsilane (TMS) as the internal standard. All chemical shifts are given relative to TMS. Infrared (IR) spectra were acquired on a Shimadzu FT-IR-8400S spectrometer. All yields refer to the isolated products.

General procedure for the preparation of 2-amino-3-cyano-4*H*-pyran derivatives (5, 8, 10)

A clean and dry 10 mL ball mill vessel with 2 stainless steel balls was charged with malononitrile **2** (1.1 mmol), aromatic aldehydes **3** (1 mmol), phenol or C-H acidic compounds **4**, **7**, **9** (1 mmol), and POPI **1c** (9.2 mg, 5 mol%). The vessel was closed, and the milling was started at ambient temperatures at a speed of 28 Hz for the specific times indicated in Tables 2, 3 and 4 until products **6, 8** or **10** were formed completely. The reaction progress was monitored by TLC. After completion of the reaction, the product was triturated in a 10 mL beaker containing 5 mL of water for 5 minute. The obtained solid was filtered on a Buchner funnel and dried in an oven at 60 °C to afford the pure products. The filtrate was evaporated to dryness under reduced pressure and then EtOH (1 mL) was added. POPI **1c**, as a white solid, was filtered off and dried in an oven at 75 °C for the next experiments.

Acknowledgements

We are grateful for the financial support from The Research Council of Iran University of Science and Technology (IUST), Tehran, Iran (Grant no. 160/8034).

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PAPER

Highly efficient organocatalytic synthesis of diverse and densely functionalized 2-amino-3-cyano-4*H*-pyrans under mechanochemical ball milling

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An improved one-pot three-component and environmentally benign approach for the synthesis of a wide range of densely functionalized 2-amino-3-cyano-4H-pyran annulated derivatives has been described by the reaction of aryl aldehydes, malononitrile and diverse phenols or enolizable C─H activated acidic compounds under mechanochemical ball milling conditions in the presence of potassium phthalimide (POPI), as a mild basic organocatalyst, at ambient temperature. In comparison to the conventional methods, the remarkable advantages of this protocol are high to quantitative yields, avoiding the use of any hazardous transition metal-free catalyst or solvent, shorter reaction time at ambient temperature, low cost, and straightforward work-up procedure.