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FULL-LENGTH PAPER

$CaCl_2$ as a bifunctional reusable catalyst: diversity-oriented synthesis of 4*H*-pyran library under ultrasonic irradiation

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Abstract $CaCl_2$ is applied as an efficient reusable and eco-friendly bifunctional catalyst for the one-pot three-component synthesis of 4*H*-pyrans under ultrasonic irradiation. A broad range of substrates including the aromatic and heteroaromatic aldehydes, indoline-2,3-dione (isatin) derivatives, acenaphthylene-1,2-dione (acenaphthenequinone) and 2, 2-dihydroxy-2*H*-indene-1,3-dione (ninhydrin) were condensed with carbonyl compounds possessing a reactive α-methylene group and alkylmalonates. All reactions are completed in short times, and the products are obtained in good to excellent yields. The catalyst could be recycled and reused several times without any loss of efficiency.

Keywords Multi-component reactions · MCRs · Diversity-oriented synthesis · DOS · Ultrasound-promoted synthesis · Calcium chloride · 4*H*-pyrans · Combinatorial chemistry

Introduction

In the past decade, growing interest in green chemistry has expanded, and it encompasses a wide variety of areas of the chemical enterprise and is an alternative way to reduce drastic requirements of materials that maybe hazardous for the environment. There is a need for facile, efficient, and nonpolluting synthetic procedures that require using organic solvents and toxic reagents. Diversity-oriented synthesis (DOS) continues to be an important area at the interface of organic synthesis and biochemical processes [1]. At the heart of DOS, there is a need for methods that are highly efficient for the generation of multi-functional small molecules, especially those possessing skeletons found in natural products and drug-like materials [2]. Perhaps the most promising and powerful method for the synthesis of such molecules is by sequential multi-component reactions (MCRs) that generate more complex and diverse molecules [3].

Ultrasound, an efficient and virtually innocuous means of activation in synthetic chemistry, has been employed for decades with various successes. This high-energy input not only enhances mechanism effects in heterogeneous processes but also induces new reactivity leading to the formation of unexpected chemical species. The remarkable phenomenon of cavitation makes sonochemistry unique. The effects of ultrasound observed during organic reactions are due to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in an irradiated liquid. Cavitation induces very high local temperatures and pressures inside the bubbles, leading to turbulent flow of the liquid and enhances mass transfer. When compared to conventional methods, ultrasound-accelerated chemical reactions can give higher yields in shorter reaction times and milder conditions [4]. Because of these advantages, ultrasound irradiation has been used for the synthesis of a wide variety of organic compounds [5–9].

It is well known that pyrans are important core units in a number of natural products and photochromic materials [10]. Compounds with the pyran ring system have many pharmacological properties and play important roles in biochemical

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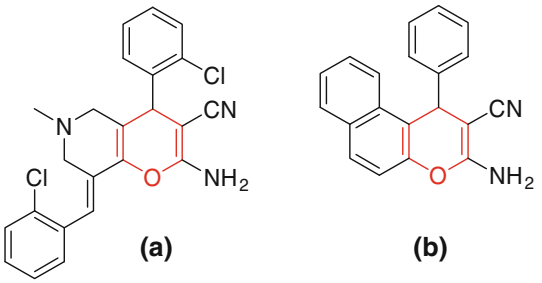
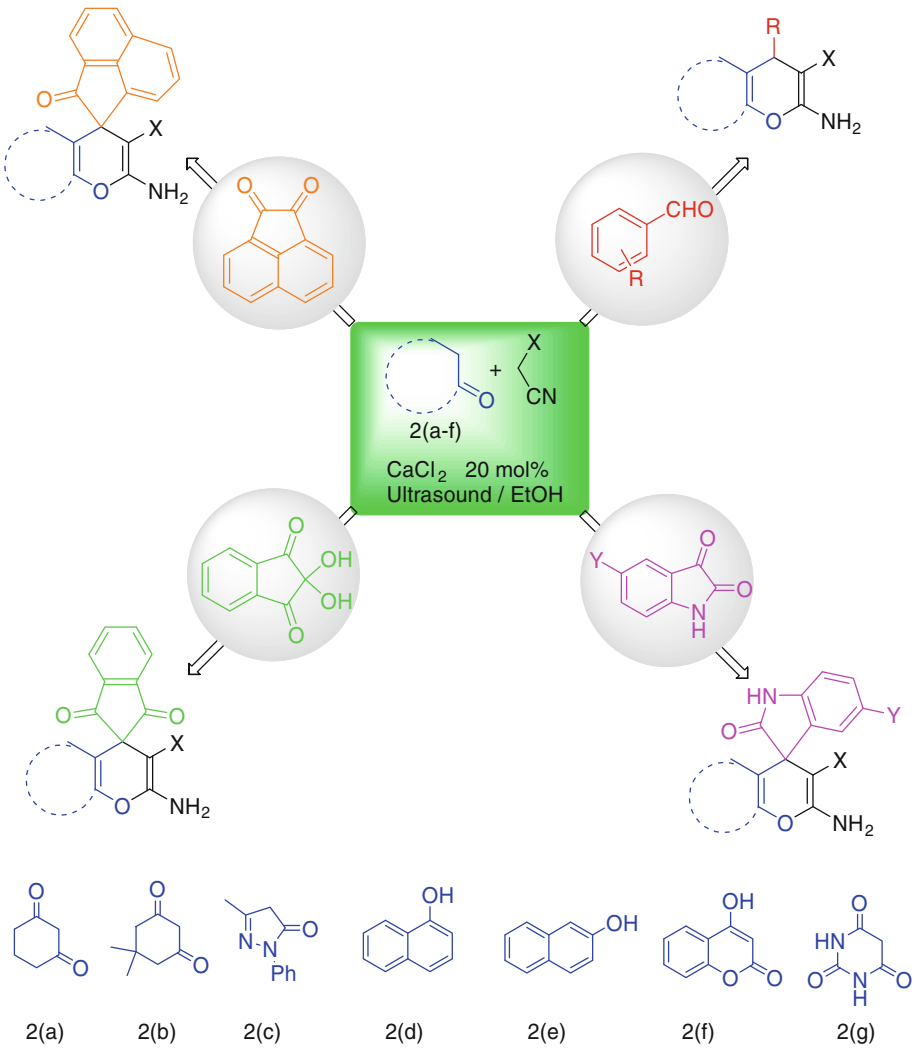


Fig. 1 Two representative structures of 4*H*-pyrans with antibacterial activity [10]

processes (Fig. 1) [10]. Moreover, 4*H*-pyrans are useful intermediates for the synthesis of various compounds, such as pyranopyridine derivatives [11], polyazanaphthalenes [12], pyrano[2]pyrimidines [13], and pyridin-2-ones [14]. Therefore, preparation of this heterocyclic nucleus has gained great importance in organic synthesis.

The routine procedure for the synthesis of 4*H*-pyrans is the condensation reaction of aldehydes with β-dicarbonyl compounds and alkylmalonates via a three-component reactions. Various catalytic systems such as hexadecyltrimethyl ammonium bromide (HMTAB) [15], triethylbenzylammonium chloride (TEBA) [16], rare earth perfluorooctanoate ($RE(PFO)_3$) [17], (*S*)-proline [18], amino functionalized ionic liquids [19], MgO [20], SiO_2 nanoparticles [21] and silica-bonded *n*-propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride (SB-DABCO) [22] have been used for the synthesis of 4*H*-benzo[*b*]pyrans so far. However, most of these methods suffer from several drawbacks such as low yields, long reaction times, harsh reaction conditions, tedious work-up, tedious steps for the preparation of catalyst, application of toxic and expensive catalysts, application of hazardous solvents for the work-up and lack of generality. Moreover, in most cases, the catalysts are not recyclable. Therefore, the development of an efficient and more practical procedure with high generality for the synthesis of 4*H*-pyrans is of considerable interest.

Scheme 1 The one-pot three-component synthesis of 4*H*-pyrans under ultrasound irradiation at room temperature

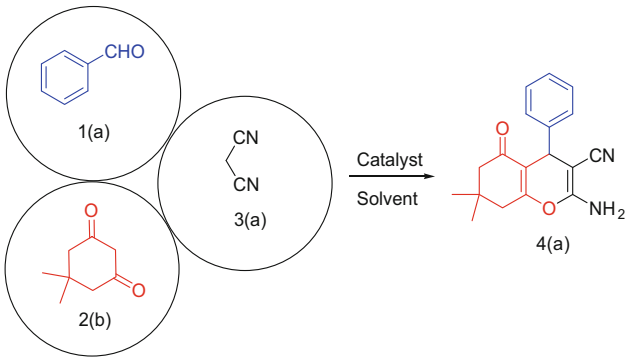


The reactions promoted by Lewis acids and bases are fundamental in organic synthesis. However, most of such reactions are merely stoichiometric. Therefore, the development of catalytic reactions that use Lewis acids and those Lewis base catalysts under neutral and mild conditions are particularly important. $CaCl_2$ is an inexpensive, water stable, environmentally benign and commercially available reagent that can act as a Lewis base [23] as well as Lewis acid [24] in organic transformations. A literature survey shows that the three-component one-pot synthesis of 4*H*-pyrans can be catalyzed successfully in the presence of acid as well as base catalysts. Based on the above facts and as a part of our research program to develop selective, efficient and green methods in organic synthesis [9,22], we report here the application of $CaCl_2$ as a bifunctional (Lewis acid as well as Lewis base), water tolerant, reusable and neutral environmentally benign catalyst for the DOS of 4*H*-pyrans via a one-pot three-component condensation reaction between carbonyl compounds **1**, carbonyl compounds possessing a reactive α-methylene group **2** and alkylmalonates **3** under ultrasonic irradiation (Scheme 1).

Results and discussion

In order to find the best reaction conditions for the synthesis of 4*H*-pyran derivatives, the one-pot three-component condensation of benzaldehyde (**1a**) (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**2b**) (1 mmol) and malononitrile (**3a**) (1 mmol) was examined in the presence of various Lewis acids and Lewis bases in different solvents at room temperature (Scheme 2) and the obtained results are summarized in Table 1.

As it is clear from Table 1, the best results were obtained in the presence of $CaCl_2$ (0.2 mmol, 20 mol%) in ethanol as a solvent. The reaction was also checked without the catalyst in which the reaction did not proceed even after 3 h. These observations established the crucial rule of $CaCl_2$ for the expedition of the reaction time and the product yield. The model reaction was also examined in the presence of $TiCl_4$ as a stronger Lewis acid and HCl as a strong Brönsted acid under the optimized conditions (Table 1, entries 7 and 8). As it can be seen from Table 1, $TiCl_4$ and HCl catalyze the reaction in shorter times and admissible yields, but they were not reusable under the applied conditions (Table 1, entry 7). It is well known that titanium tetrachloride immediately hydrolyzes when it comes into contact with humidity. Hence, titanium polyoxo species and hydrochloric acid are formed. Moreover, HCl is a liquid Brönsted acid that is not recoverable from the reaction mixture and may cause to the formation of hazardous residue. Application of this type of catalyst is not in accordance with the green chemistry protocols.



Scheme 2 The one-pot three-component condensation reaction of benzaldehyde (**1a**) (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**2b**) (1 mmol) and malononitrile (**3a**) (1 mmol) in the presence of various Lewis acids and bases in different solvents at room temperature

Table 1 The one-pot three-component condensation reaction of benzaldehyde **(1a)** (1 mmol), 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**2b**) (1 mmol) and malononitrile (**3a**) (1 mmol) in the presence of various Lewis acids and bases in different solvents at room temperature

Entry	Cat. (mol%)	Solvent (5 mL)	Time (min)	Yield (%)[a]
1	$NiCl_2$ (20)	Ethanol	180	78
2	$CoCl_2$ (20)	Ethanol	180	67
3	$CuCl_2$ (20)	Ethanol	180	51
4	$BiCl_3$ (20)	Ethanol	180	35
5	NaCl (20)	Ethanol	180	20
6	–	Ethanol	180	Trace
7	$TiCl_4$ (20)	Ethanol	35 (180)[b]	95 (62)[b]
8	HCl (20)	Ethanol	40	92
9	$CaCl_2$ (20)	Ethanol	50	96
10	$CaCl_2$ (10)	Ethanol	180	83
11	$CaCl_2$ (30)	Ethanol	50	96
12	$CaCl_2$ (20)	H_2O	180	25
13	$CaCl_2$ (20)	Ethyl acetate	180	36
14	$CaCl_2$ (20)	CH_3CN	180	74
15	$CaCl_2$ (20)	CH_2Cl_2	180	33
16	$CaCl_2$ (20)	THF	180	59
17	$CaCl_2$ (20)	DMF	180	40

[a] Isolated yield
[b] Reaction was proceeded in the presence of recovered catalyst

Considering the ability of ultrasonic irradiation for the acceleration of organic reactions, we examined the model reaction under ultrasonic irradiation at room temperature expecting to observe shorter reaction times. Nonetheless, synthesis of organic compounds under ultrasound irradiation has been limited by the need for a specialized apparatus that may not be accessible in many laboratories. Because of this limitation, herein we report both ultrasound-promoted and classical methodology for the synthesis of the titled compounds.

The scope and efficiency of the process was explored under the optimized conditions. For this purpose, a broad range of structurally diverse aldehydes (aromatic and heteroaromatic) as well as carbonyl compounds possessing a reactive α-methylene group and alkylmalonates were condensed and the results are displayed in Table 2.

As it can be seen from Table 2, all reactions proceeded efficiently and the desired products were obtained in good to excellent yields in relatively short reaction times without formation of any byproducts. Moreover, it is clear that, under the same reaction conditions, reactions under ultrasonic irradiation led to shorter reaction times. Aromatic aldehydes containing electron-withdrawing groups (Table 2, entries 4ad, 4ai, 4at, 4aw, 4az, 4pk, 4bn, 4bo and 4bq) reacted at a faster rate when compared with those that contained electron-donating groups (Table 2, entries 4al, 4ao, 4ap, 4at, 4ax, 4az and 4bp). Moreover, our methodology has been successfully used for heteroaromatic aldehydes that are acid-sensitive species, and the corresponding 4*H*-pyrans were obtained in excellent yields and without the formation of any byproduct (Table 2, entries 4ab, 4aj, 4as, 4bb, 4be and 4bi).

Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties. It is well known that the spirooxindole moiety is the core structure of many natural alkaloids and various kinds of pharmaceutical agents [15]. Spiro compounds containing pyrans show good activity as hypertensive agents [16] and are the subject of great interest as potential novel analgesic agents [17]. Considering these facts, our methodology was applied successfully for the synthesis of a broad range of spiro-4*H*-pyrans (Table 3) via a one-pot three-

Table 2 The one-pot three-component synthesis of 4*H*-pyrans in the presence of $CaCl_2$ in ethanol under ultrasonic irradiation at room temperature

Entry	Sub.	R	X	No ultrasonic		Ultrasonic-enhanced		MP (°C)
				Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]	
4aa	2b	Ph	CN	50	96	8	96	225–227
								226–228 [25]
4ab	2b	4-Cl-Ph	CN	50	94	8	94	213–215
								215–217 [25]
4ac	2b	4-OEt-Ph	CN	120	92	15	93	232–233
								233–235 [22]
4ad	2b	4-NO_2-Ph	CN	35	96	5	97	177–178
								175–177 [25]
4ae	2b	2-Naphthalene	CN	60	93	10	93	257–258
								258–260 [22]
4af	2b	Ph-CO-	CN	55	91	8	94	222–223
4ag	2b	3-OPh-Ph	CN	70	89	15	91	192–194
								193–194 [22]
4ah	2b	2-Naphthalene	CO_2Et	90	91	25	90	189–191
								188–190 [22]
4ai	2b	4-CF_3-Ph	CO_2Et	45	95	8	93	157–158
								155–156 [22]
4aj	2b	2-Thionyl	CN	70	92	12	92	219–221
								220–222 [22]
4ak	2b	4-CN-Ph	CO_2Me	40	95	7	93	182–184
								180–182 [22]
4al	2b	4-C_3H_7-Ph	CN	80	94	16	93	187–189
4am	2a	4-OEt-Ph	CN	110	91	13	91	234–236
4an	2a	4-OEt-Ph	CO_2Me	140	93	12	90	150–152
								149–150 [22]
4ao	2a	4-Me-Ph	CN	90	92	14	92	233–235
								232–233 [22]
4ap	2a	3-OMe-Ph	CN	80	94	13	94	245–246
4aq	2a	3-Cl-Ph	CN	110	91	15	94	252–254
								254–255 [22]

Table 2 continued

Entry	Sub.	R	X	No ultrasonic		Ultrasonic-enhanced		MP (°C)
				Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]	
4ar	2a	2-Cl-Ph	CN	70	95	10	96	210–212
								209–211 [22]
4as	2c	2-Thionyl	CN	120	91	11	92	166–167
								168–169 [22]
4at	2c	4-CF_3-Ph	CN	100	93	9	96	183–185
								182–184 [22]
4au	2c	4-OEt-Ph	CO_2Me	180	90	15	92	165–167
4av	2c	2-Naphthalene	CN	160	93	15	95	232–234
4aw	2c	4-CN-Ph	CN	55	95	7	96	219–220
								217–219 [22]
4ax	2c	4-C_3H_7-Ph	CN	100	92	10	95	160–162
								158–160 [22]
4ay	2d	Ph	CN	60	94	8	94	218–219
								216–217 [26]
4az	2d	4-NO_2-Ph	CN	45	95	5	96	242–243
								240–241 [26]
4ba	2d	4-OMe-Ph	CN	100	91	14	93	194–195
								195–196 [26]
4bb	2d	2-Furyl	CN	70	93	10	95	170–172
								170–171 [26]
4bc	2e	Ph	CN	60	94	8	93	288–290
								287–288 [26]
4bd	2e	4-F-Ph	CN	75	91	10	91	232–233
								231–232 [26]
4be	2e	2-Furyl	CN	80	92	10	91	226–228
								226–227 [26]
4bf	2f	Ph	CN	80	90	10	94	255–257
								256–258 [27]
4bg	2f	4-Br-Ph	CN	80	93	12	94	253–255
								252–254 [27]
4bh	2f	4-Me-Ph	CN	110	92	15	96	254–256
								253–255 [27]
4bi	2f	2-Furyl	CN	100	90	10	91	251–253
								250–252 [27]
4bj	2f	4-Cl-Ph	CO_2Et	160	91	20	93	194–195
								192–194 [27]
4bk	2f	4-NO_2-Ph	CO_2Et	140	93	18	95	243–244
								241–243 [27]
4bl	2g	4-Cl-Ph	CN	120	91	10	94	263–265
4bm	2g	2-OMe-Ph	CN	190	89	18	92	231–232
4bn	2g	4-NO_2-Ph	CN	90	93	10	95	262–263
4bo	2g	2-NO_2-Ph	CN	90	91	10	91	264–266
4bp	2g	2-Cl-Ph	CN	110	90	10	93	228–229
4bq	2g	3-NO_2-Ph	CN	90	92	9	94	264–265
4br	2g	3-Cl-Ph	CN	120	90	11	92	266–268
4bs	2g	4-Cl-Ph	CO_2Et	120	91	10	93	>300

Table 2 continued

Entry	Sub.	R	X	No ultrasonic		Ultrasonic-enhanced		MP (°C)
				Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]	
4bt	2g	4-Cl-Ph	CO_2Me	120	92	10	92	>300
4bu	2g	3-Cl-Ph	CO_2Me	120	91	10	91	278–279
4bv	2g	3-Cl-Ph	CO_2Et	130	90	10	90	283–284
4bw	2g	4-OMe-Ph	CO_2Et	170	92	15	92	297–289
4bx	2g	4-OMe-Ph	CO_2Me	150	91	14	92	>300

[a] Isolated yield

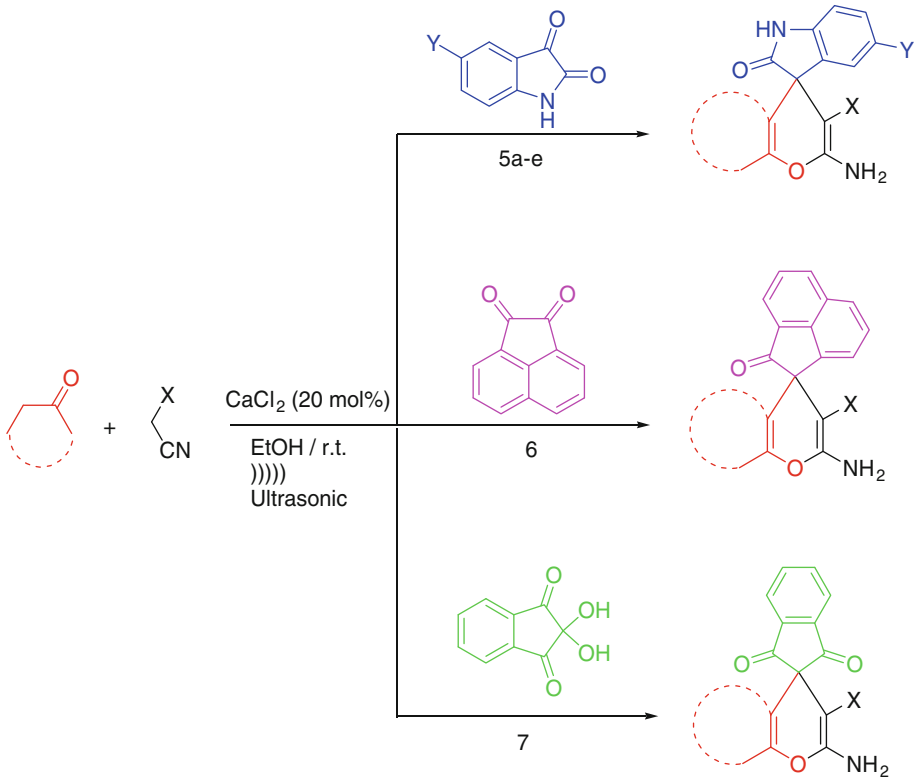
Table 3 The one-pot three-component synthesis of spiropyrans in the presence of $CaCl_2$ in ethanol under ultrasonic irradiation at room temperature

Entry	Subs./X	Carbonyl compound	No ultrasonic		Ultrasonic-enhanced		MP (°C)	Reported
			Time (min)	Yield (%)[a]	Time (min)	Yield (%)[a]	Founded	
8aa	2b/CN	5a	100	93	10	96	291–292	290–292 [28]
8ab	2a/CN	5a	110	92	10	93	296–298	298–299 [28]
8ac	2c/CN	5a	110	91	12	95	246–248	248 [29]
8ad	2d/CN	5a	130	90	12	93	223–224	222 [29]
8ae	2e/CN	5a	130	92	11	94	234–235	236 [29]
8af	2d/CO_2Et	5a	180	90	16	91	227–228	229 [29]
8ag	2c/CN	5a	180	92	15	93	205–207	208 [29]
8ah	2f/CN	5a	150	91	13	92	282–283	283–285 [30]
8ai	2f/CN	5c	150	92	12	92	>300	>300 [30]
8aj	2f/CN	5e	150	90	13	90	>300	>300 [30]
8ak	2c/CO_2Me	5a	180	92	15	93	226–227	–
8al	2b/CO_2Et	5a	180	91	18	91	238–239	–
8am	2b/CN	5e	170	93	14	93	279–281	278–280 [31]
8an	2a/CN	5d	150	91	13	93	281–282	–
8ao	2c/CN	5d	160	93	15	96	241 (dec.)	–
8ap	2a/CO_2Et	5d	180	91	18	91	274–276	273–274 [32]
8aq	2b/CN	5b	150	93	14	96	>300	>300 [31]
8ar	2f/CN	5b	180	90	18	93	277–278	278–280 [31]
8as	2a/CO_2Me	5b	180	93	15	94	274 (dec.)	–
8at	2a/CN	5e	160	91	14	94	280–281	–
8au	2f/ CO_2Et	6	220	93	20	94	240–242	–
8av	2c/CN	6	180	90	17	91	197–198	–
8aw	2g/CN	5a	160	93	12	93	296–298	–
8ax	2g/CN	7	160	92	11	95	191–193	–
8ay	2g/CO_2Et	5a	190	90	16	95	228–230	–
8az	2g/CO_2Me	5a	180	91	15	92	242–244	–
8ba	2g/CO_2Et	7	190	90	17	91	225–227	–
8bb	2g/CO_2Me	7	180	92	15	92	259–261	–
8bc	2g/CO_2Et	5c	190	90	18	91	272–274	–

[a] Isolated yield

component reaction of indoline-2,3-dione (isatin) derivatives (**5a–e**), acenaphthylene-1,2-dione (acenaphthenequinone) (**6**) and/or 2,2-dihydroxy-2*H*-indene-1,3-dione (ninhydrin) (**7**) with carbonyl compounds possessing a reactive α-methylene group and alkylmalonates (Scheme 3) and the obtained results are summarized in Table 3.

In order to assess the capability and efficiency of our methodology with respect to the reported catalysts for the



Scheme 3 The one-pot three component reaction of indoline-2,3-dione (isatin) derivatives (**5a–e**, acenaphthylene-1,2-dione (acenaphthenequinone) (**6**) and/or 2,2-dihydroxy-2*H*-indene-1,3-dione (ninhydrin) (**7**) with carbonyl compounds possessing a reactive α-methylene group and alkylmalonates

Table 4 Comparative condensation of malononitrile with benzaldehyde and 5,5-dimethylcyclohexane-1,3-dione (dimedone) using the reported catalysts versus $CaCl_2$

Entry	Reagents and conditions	Time (min)	Yield (%)	References
1	Na_2SeO_4, 0.1 g, ethanol/H_2O, reflux	60	97	[33]
2	Hexadecyldimethyl benzyl ammonium bromide (HDMBAB), 12 mol%, H_2O, 90 °C	360	92	[15]
3	Tetra-methyl ammonium hydroxide (TMAH), 10 mol%, H_2O, r.t.	120	81	[34]
4	Rare earth perfluorooctanoate ($RE(PFO)_3$), 5 mol%, ethanol, 60 °C	300	90	[17]
5	SB-DABCO, 6 mol%, ethanol, r.t.	35	96	[22]
6	SiO_2NP, 5 mg, ethanol, r.t.	30	94	[21]
7	$CaCl_2$, 20 mol%, ethanol, ultrasound, r.t.	8	96	This study

preparation of 4*H*-pyrans, the results of these catalysts for the synthesis of compound **4aa** were tabulated in Table 4. As it is clear from Table 4, our methodology is more efficient.

The possibility of recycling the catalyst was examined using the reaction of benzaldehyde (**1a**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**2b**) with malononitrile (**3a**) under the optimized conditions. Upon completion, water (5 mL) was added to the reaction mixture, shacked truly and insoluble products separated by simple filtration and recrystallized from ethanol. In order to recover the catalyst, the solvent was evaporated under reduced pressure, and the resulting solid was washed with CH_2Cl_2, and dried. The recovered catalyst was reused fifteen times in the condensation reaction of benzaldehyde (**1a**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**2b**) with malononitrile (**3a**) and smooth loss of catalytic activity was observed from the 10th time of reuse (Fig. 2).

In order to find the structure of recovered catalyst, the IR spectra of $CaCl_2$, the recovered $CaCl_2$ after the first use and the recovered $CaCl_2$ after the 10th time of reuse as a catalyst in model reaction under the optimized conditions were compared and any obvious differences were not observed (Fig. 3). So this was concluded that the structure of $CaCl_2$ is stable under the applied conditions even after the 10th time of recovery and reuse.

Recently, Hasaninejad et al. [22] discussed the possibility of the formation of various byproducts when carbonyl compounds reacted with derivatives of cyanoacetic acid

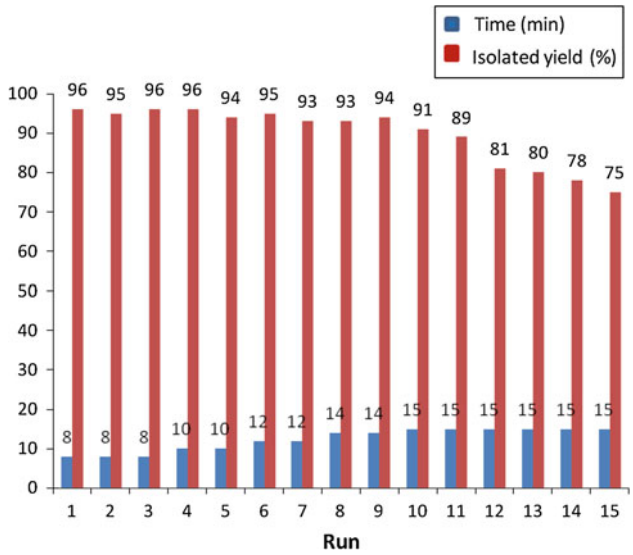


Fig. 2 The catalytic activity of $CaCl_2$ in 15 cycles for the reaction of benzaldehyde (**1a**) and 5,5-dimethylcyclohexane-1,3-dione (dimedone) (**2b**) with malononitrile (**3a**) under ultrasonic irradiation at room temperature

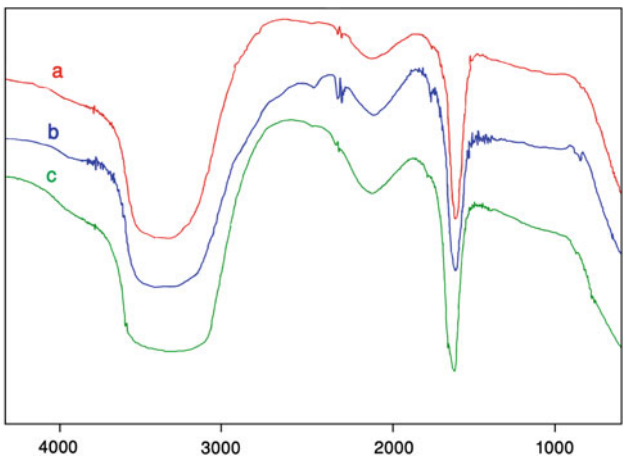


Fig. 3 IR spectra of $CaCl_2$ (*a*), the recovered $CaCl_2$ after the first use (*b*) and the recovered $CaCl_2$ after the 10th time of reuse (*c*)

(Scheme 4). In our attempts, we only obtained 4*H*-pyrans **4**. Using this method, 79 compounds were obtained in good yield (90 % minimum purity) without the need of additional purification.

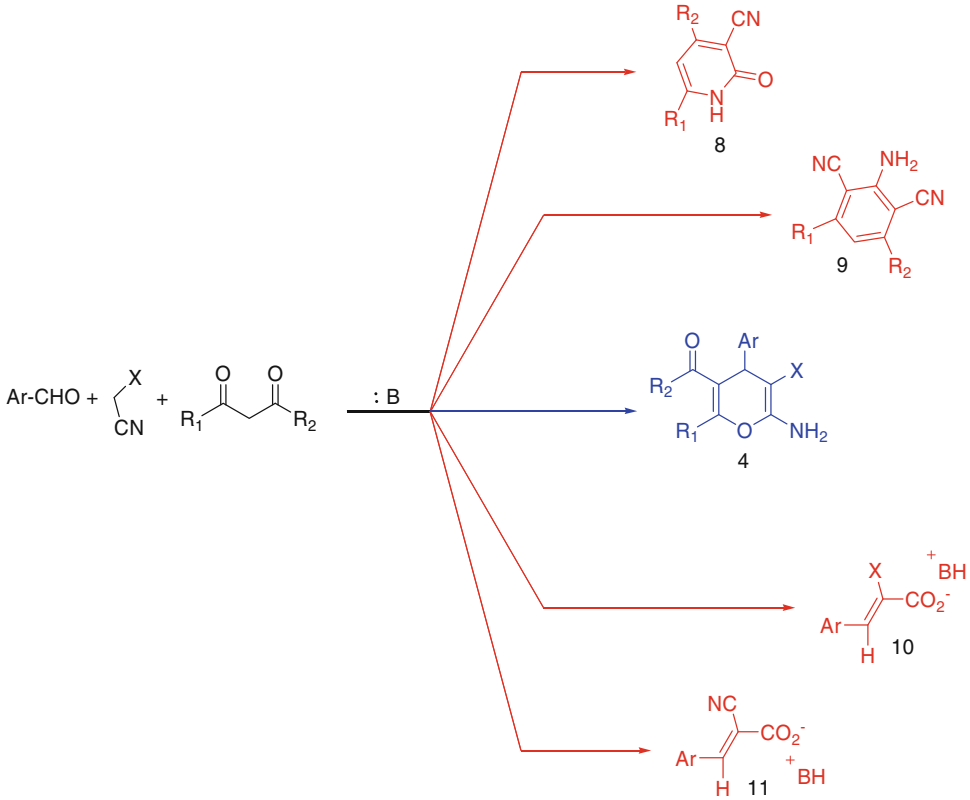
The selectivity in the synthesis of 4*H*-pyrans **4** in the presence of $CaCl_2$ can be explained by the strict sequence of reactions in Scheme 5. Based on this mechanism, $CaCl_2$ is an effective bifunctional catalyst (Lewis acid as well as Lewis base) for the formation of olefin **9** which readily prepares in situ from Knoevenagel condensation of aldehyde **1** with highly active CH-acidic cyanoacetic ester derivative **3**. Then carbonyl compound **3** in the presence of $CaCl_2$ converts to its corresponding enolate form **13** and adds to the unsaturated nitrile **9** by Michael addition to produce intermediate **14**, and enolate oxygen attacks nucleophilically nitrile group (Thorpe–Ziegler-type reaction). Finally, after a tautomeric proton shift, 4*H*-pyrans **4** are formed. As it is shown in Scheme 5, we suggest that the $CaCl_2$ serves two catalytic functions: first, to electrophilically activate the aldehyde carbonyl through the interaction between Ca^{2+} and the carbonyl oxygen, and second, to enhance the nucleophilicity of the alkylmalonates through deprotonation of the Cα-H with Cl^-.

As it is shown in Scheme 5, our proposed mechanism for the one-pot three-component synthesis of 4*H*-pyrans in the presence of $CaCl_2$ under ultrasonic irradiation consists of two steps containing the Knoevenagel condensation between alkylmalonates and aldehydes and Michael-type addition of the enolizable carbonyl compounds. It is well known that all these reactions have negative activation volumes owing to the condensation of the molecules into a reactive intermediate. In this regard, it is well known that reactions with negative activation volumes are accelerated with pressure [35]. On the other hand, ultrasound irradiation generates a microscopic internal pressure in the solvent cavity [36]. Therefore, owning to the ultrasonic, microscopic internal high pressures and high temperatures have been generated in the reaction media [37]. Accordingly, it is reasonable to assume that these effects should accelerate this type of three-component condensation reaction. As it is obviously shown in Tables 2 and 3, the effect of substitutions on the reaction rate is the same under both reported conditions (ultrasonic irradiation and traditional condition). As it is clear from Table 2, aromatic aldehydes having electron-withdrawing groups (Table 2, entries 4ad, 4ai, 4at, 4aw, 4az, 4pk, 4bn, 4bo and 4bq) reacted at a faster rate compared with those substituted with electron-releasing groups (Table 2, entries 4al, 4ao, 4ap, 4at, 4ax, 4az and 4bp) under both conditions (in the presence as well as in the absence of ultrasonic irradiation). Moreover, it is obviously shown that less reactive alkylmalonates such as ethyl or methyl cyanoacetate required longer times to react than malononitrile under both conditions (Table 2, entries 4ah, 4ai, 4ak, 4an, 4au, 4bj, 4bk, 4bs, 4bt, 4bu, 4bv, 4bw and 4bx).

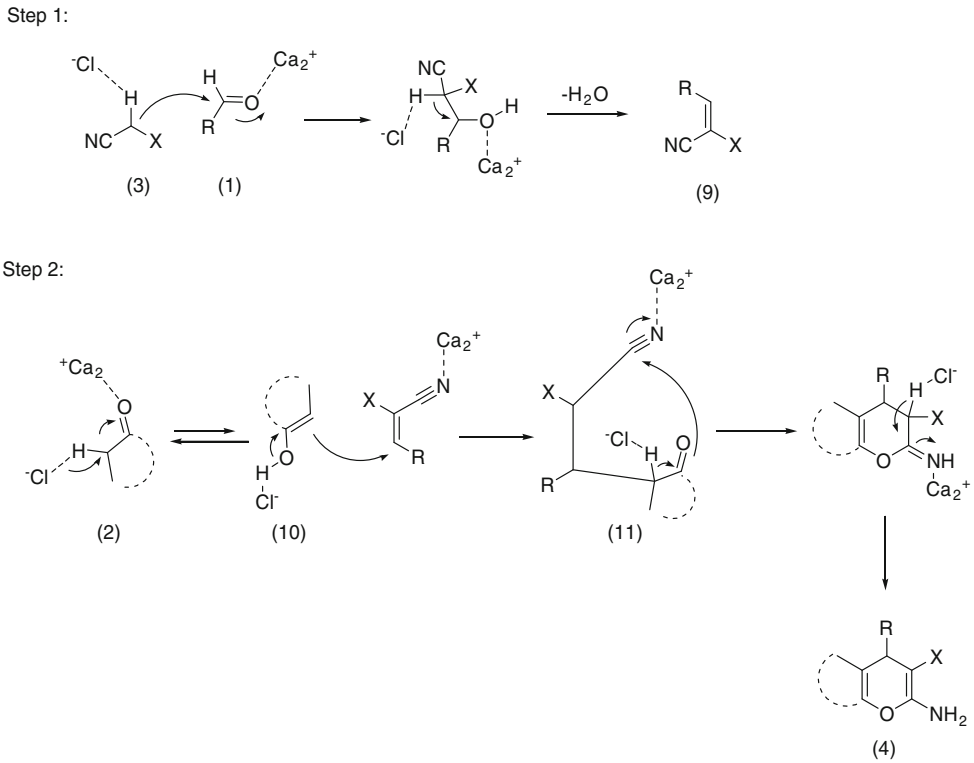
Conclusions

In summary, we have reported a highly efficient and green method for the one-pot three-component synthesis of 4*H*-pyran derivatives using $CaCl_2$ as a very cheap, biodegradable, commercially available and reusable bifunctional catalyst. This method not only offers substantial improvements in reaction rates and yields but also avoids using hazardous catalysts or solvents. The advantageous points for the present methodology are efficiency, high generality, high yield, short reaction time, ease of handling of the catalyst, cleaner reaction profile, ease of product isolation, simplicity,

Scheme 4 Three-component synthesis of 4*H*-pyrans (*blue*) and theoretically possible byproducts (*red*). (Color scheme online)



Scheme 5 Proposed mechanism for the synthesis of 4*H*-pyrans in the presence of $CaCl_2$



potential for recycling of the catalyst and agreement with the green chemistry protocols, which all make it a useful and attractive process for the synthesis of 4*H*-pyran derivatives. Moreover, in the presence of ultrasonic irradiation as an accelerator doer, reaction rates were significantly increased and the desired products were obtained in very short times with excellent yields.

Experimental

Chemical and apparatus

Reagents and solvents were purchased from Merck, Fluka or Aldrich and they were used as-received without further pre-treatments. Melting points were determined in capillary tubes in an electro-thermal C14500 apparatus; uncorrected. The progress of the reaction was monitored and the purity of the products was assessed by TLC analytical silica gel plates (Merck 60 F250). All known compounds were confirmed by comparing their melting points and ^{1}H NMR data with authentic samples. The ^{1}H NMR (500 and 400 MHz) and ^{13}C NMR (125 and 100 MHz) were recorded on a Bruker Avance DPX-250, FT-NMR spectrometer. Chemical shifts are given as δ values against tetramethylsylane as the internal standard and *J* values are given in Hertz. Microanalysis were performed on a Perkin-Elmer 240-B microanalyzer. The ultrasound apparatus was a Wiseclear 770W cleaning bath (Seoul, Korea). The operating frequency was 40 kHz and the output power was 200 W, estimated calorimetrically. Reaction flasks were placed in the maximum energy area in the water bath, where the surface of reactants (reaction vessel) is slightly lower than the level of the water, and the addition or removal of water controlled the temperature of the water bath. The water bath temperature was set at 25–30 °C. All experiments performed in this study were repeated three times. Reported yields represent the average of the values obtained for each reaction.

General procedure for the synthesis of 4*H*-pyran derivatives

Carbonyl compounds possessing a reactive α-methylene group (1 mmol), alkylmalonates (1 mmol) and aromatic aldehydes (1 mmol) were added in a 25 mL round-bottomed flask containing $CaCl_2$ (0.2 mmol, 20 mol%) and ethanol (5 mL). The mixture was stirred at room temperature for an appropriate time (Table 2). In order to ultrasound-promotion of the reaction, the mixture was continuously irradiated for the appropriate time (Table 2) at room temperature. The ultrasonic apparatus used showed the temperature automatically so the temperature was controlled and fixed at room temperature by pouring cold water in the bath in the case of any elevation of temperature. After the completion of reaction, water (5 mL) was added to the reaction mixture, shacked truly and insoluble products separated by simple filtration and recrystallized from ethanol. In order to recover the catalyst, the solvent was evaporated under reduced pressure, and the resulting solid was washed with CH_2Cl_2, and dried.

Selected physical and spectral data of the products

2-Amino-4-benzoyl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (compound **4af***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.05 (s, 3H), 1.07 (s, 3H), 2.12 (ABd, J = 16.0 Hz, 1H), 2.34 (ABd, J = 16.0 Hz, 1H), 2.41 (ABd, J = 17.5 Hz, 1H), 2.61 (ABd, J = 17.5 Hz, 1H), 4.98 (s, 1H), 7.23 (s, 2H), 7.55 (t, J = 7.75 Hz, 2H), 7.68 (t, J = 7.5 Hz, 1H), 8.05(d, J = 7.5 Hz, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 27.2, 29.5, 33.2, 36.7, 50.4, 53.0, 111.5, 119.9, 129.5, 129.7, 134.4, 136.6, 160.9, 164.8, 196.8, 199.4. Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.83; H, 5.62; N, 8.72.

2-Amino-4-(4-isopropylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (compound **4al***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.97 (s, 3H), 1.03 (s, 3H), 1.16 (d, J = 6.8 Hz 6H), 2.11 (ABd, J = 16.0 Hz, 1H), 2.24 (ABd, J = 16.0 Hz, 1H), 2.49–2.51 (m, 2H), 2.81–2.86 (m, 1H), 4.13 (s, 1H), 6.95 (s, 2H), 7.04 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H). ^{13}C NMR (DMSO-d_6,125 MHz): δ 24.6, 24.7, 27.7, 29.2, 32.6, 33.8, 36.0, 50.8, 59.4, 113.7, 120.6, 127.1, 127.8, 143.0, 147.3, 159.3, 163.3, 196.5. Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.91; H, 7.22; N, 8.19.

2-Amino-4-(4-ethoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (compound **4am***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.29 (t, J = 7.0 Hz, 3H), 1.85–1.94 (m, 2H), 2.23–2.29 (m, 2H), 2.49–2.60 (m, 2H), 3.94–3.99 (m, 2H), 4.14 (s, 1H), 6.80–6.83 (m, 2H), 6.93 (s, 2H), 7.04–7.06 (m, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.1, 21.3, 28.9, 36.6, 38.9, 58.2, 64.5, 113.1, 114.5, 119.0, 129.3, 135.3, 155.0, 156.7, 159.1, 198.5. Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.71; H, 5.88; N, 9.12.

2-Amino-4-(3-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (compound **4ap***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.87–1.96 (m, 2H), 2.27–2.31 (m, 2H), 2.58–2.63 (m, 2H), 3.72

(s, 3H), 4.16 (s, 1H), 6.67–6.77 (m, 3H), 6.97 (s, 2H), 7.20 (t, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 20.6, 27.3, 36.1, 37.1, 55.7, 58.9, 112.2, 114.1, 114.5, 120.1, 120.6, 130.3, 147.2, 159.3, 160.0, 165.3, 196.6. Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.01; H, 5.45; N, 9.49.

6-Amino-3-methyl-4-(naphthalen-2-yl)-1-phenyl-1, 4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (compound **4av***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.75 (s, 3H), 4.86 (s, 1H), 7.26 (s, 2H), 7.31–7.37 (m, 2H), 7.48–7.51 (m, 4H), 7.80–7.93 (6H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.4, 37.8, 58.9, 99.2, 120.8, 126.7, 126.8, 127.0, 127.1, 128.4, 128.6, 129.3, 130.2, 133.1, 133.7, 138.4, 141.7, 144.8, 146.2, 160.3. Anal. Calcd for $C_{24}H_{18}N_4O$: C, 76.17; H, 4.79; N, 14.81. Found: C, 76.21; H, 4.81; N, 14.85.

7-Amino-5-(4-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (compound **4bl***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.37 (s, 1H), 6.97 (s, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 9.2 (s, 1H), 11.1 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.8, 59.3, 80.1, 119.1, 127.9, 130.0, 131.1, 142.6, 150.4, 159.3, 160.3, 163.1. Anal. Calcd for $C_{14}H_9ClN_4O_3$: C, 53.09; H, 2.86; N, 17.69. Found: C, 53.14; H, 2.92; N, 17.77.

7-Amino-5-(2-methoxyphenyl)-2,4-dioxo-2,3,4, 5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (compound **4bm***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.64 (s, 3H), 4.29 (s, 1H), 6.84–6.88 (m, 2H), 6.87–6.89 (m, 3H), 7.13 (d, J = 8.0 Hz, 1H), 9.01 (s, 1H), 10.88 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 29.1, 54.3, 58.8, 78.9, 112.1, 119.0, 120.6, 121.3, 125.9, 130.0, 151.4, 158.8, 159.3, 160.0, 163.5. Anal. Calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.62; H, 3.82; N, 7.98.

7-Amino-5-(4-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (compound **4bn***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.29 (s, 1H), 7.08 (s, 2H), 7.49 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H), 9.41 (s, 1H), 10.93 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.4, 58.2, 79.9, 119.3, 123.5, 125.9, 143.8, 150.5, 150.8, 159.0, 160.1, 163.8. Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.45; H, 2.84; N, 21.49.

7-Amino-5-(2-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (compound **4bo***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.48 (s, 1H), 7.04 (s, 2H), 7.49–7.56 (m, 2H), 7.74 (d, J = 8.0 Hz, 2H), 8.01 (d, J = 8.5 Hz, 1H), 9.08 (s, 1H), 10.89 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 31.6, 59.2, 79.5, 119.3, 123.9, 126.9, 129.8, 130.9, 133.7, 147.1, 150.6, 159.0, 160.6, 163.3. Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.46; H, 2.71; N, 21.49.

7-Amino-5-(2-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (compound **4bp***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.31 (s, 1H), 6.98 (s, 2H), 7.16–7.34 (m, 3H), 7.58 (d, J = 8.1 Hz, 1H), 9.12 (s, 1H), 11.08 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 30.9, 58.4, 80.1, 119.0, 126.7, 126.9, 127.6, 128.8, 131.5, 142.9, 149.6, 157.5, 160.4, 163.4. Anal. Calcd for $C_{14}H_9ClN_4O_3$: C, 53.09; H, 2.86; N, 17.69. Found: C, 53.17; H, 2.81; N, 17.72.

7-Amino-5-(3-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (compound **4bq***)*

Yellowish Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.33 (s, 1H), 7.03 (s, 2H), 7.56-7.63 (m, 2H), 8.01 (d, J = 8.0 Hz, 1H), 8.16 (s, 1H), 9.15 (s, 1H), 11.13 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 34.9, 58.0, 79.9, 119.2, 120.8, 121.5, 132.9, 133.6, 143.1, 145.6, 150.0, 158.5, 160.6, 163.7. Anal. Calcd for $C_{14}H_9N_5O_5$: C, 51.38; H, 2.77; N, 21.40. Found: C, 51.32; H, 2.81; N, 21.49.

7-Amino-5-(3-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (compound **4br***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 4.59 (s, 1H), 7.06 (s, 1H), 7.13 (d, J = 8.3 Hz, 1H), 7.24–7.33 (m, 2H), 7.41 (s, 1H), 9.11 (s, 1H), 10.91 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.9, 59.1, 80.1, 119.0, 124.9, 125.7, 127.9, 130.1, 133.8, 142.9, 150.6, 158.8, 160.4, 163.9. Anal. Calcd for $C_{14}H_9ClN_4O_3$: C, 53.09; H, 2.86; N, 17.69. Found: C, 53.18; H, 2.80; N, 17.75.

Ethyl 7-amino-5-(4-chlorophenyl)-2,4-dioxo-2,3,4, 5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (compound **4bs***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.98 (t, J = 7.5 Hz, 3H), 3.98 (m, 2H), 4.91 (s, 1H), 7.06 (s, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 9.11 (s, 1H), 10.98 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, 35.5, 61.3, 76.4, 80.4, 127.8, 130.1, 131.2, 142.0, 143.3, 160.7, 162.3, 163.7, 167.9. Anal. Calcd for $C_{16}H_{14}ClN_3O_5$: C, 52.83; H, 3.88; N, 11.55. Found: C, 52.88; H, 3.91; N, 11.59.

Methyl 7-amino-5-(4-chlorophenyl)-2,4-dioxo-2,3,4, 5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (compound **4bt***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 3.54 (s, 3H), 4.94 (s, 1H), 7.05 (s, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 9.09 (s, 1H), 11.01 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.4, 61.5, 76.4, 80.3, 127.8, 130.0, 131.3, 142.1, 143.6, 160.5, 162.5, 163.7, 167.4. Anal. Calcd for $C_{15}H_{12}ClN_3O_5$: C, 51.51; H, 3.46; N, 12.02. Found: C, 51.61; H, 3.48; N, 12.11.

Methyl 7-amino-5-(3-chlorophenyl)-2,4-dioxo-2,3,4, 5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (compound **4bu***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 3.83 (s, 3H), 4.06 (s, 1H), 6.98 (s, 2H), 7.10–7.21 (m, 2H), 7.29 (d, J = 8.1 Hz, 1H), 7.36 (s, 1H), 9.12 (s, 1H), 10.98 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.8, 52.6, 76.9, 78.8, 124.9, 125.0, 127.7, 129.6, 133.3, 143.1, 150.0, 160.1, 160.4, 163.3, 167.1. Anal. Calcd for $C_{15}H_{12}ClN_3O_5$: C, 51.51; H, 3.46; N, 12.02. Found: C, 51.54; H, 3.41; N, 12.08.

Ethyl 7-amino-5-(3-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (compound **4bv***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 0.99 (t, J = 7.5 Hz, 3H), 3.83 (m, 2H), 4.11 (s, 1H), 6.99 (s, 2H), 7.11–7.25 (m, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.37 (s, 1H), 9.10 (s, 1H), 11.01 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.6, 35.7, 52.8, 76.9, 78.8, 124.8, 125.0, 127.9, 129.6, 133.5, 143.0, 150.2, 160.1, 160.3, 163.2, 167.2. Anal. Calcd for $C_{16}H_{14}ClN_3O_5$: C, 52.83; H, 3.88; N, 11.55. Found: C, 52.90; H, 3.3.84; N, 11.61.

Ethyl 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-2,3,4, 5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (compound **4bw***)*

Yellow Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.01 (t, J = 7.3 Hz, 3H), 3.84–3.89 (m, 5H), 4.86 (s, 1H), 6.84 (d, J = 8.0 Hz, 2H), 7.03 (s, 2H), 7.13 (d, J = 8.0 Hz, 2H), 9.09 (s, 1H), 11.0 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.3, 36.9, 56.2, 61.3, 76.4, 79.5, 114.1, 130.0, 135.5, 136.9, 150.5, 156.3, 160.9, 162.3, 163.3, 167.6. Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.89; H, 4.82; N, 11.75.

Methyl 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-2,3,4, 5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carboxylate (compound **4bx***)*

Yellow Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 3.42 (3, 3H), 3.76 (s, 3H), 4.91 (s, 1H), 6.81 (d, J = 8.2 Hz, 2H), 7.01 (s, 2H), 7.15 (d, J = 8.2 Hz, 2H), 9.06 (s, 1H), 10.99 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 36.6, 56.1, 61.2, 76.6, 79.4, 114.0, 130.2, 135.6, 136.7, 150.6, 156.1, 160.0, 162.4, 163.5, 167.9. Anal. Calcd for $C_{16}H_{15}N_3O_6$: C, 55.65; H, 4.38; N, 12.17. Found: C, 55.71; H, 4.31; N, 12.20.

Methyl 2-amino-5′-bromo-2′,5-dioxo-5,6,7, 8-tetrahydrospiro[chromene-4,3′-indoline]-3-carboxylate (compound **8as***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.86–1.88 (m, 2H), 2.17–2.21 (m, 2H), 2.62–2.64 (m, 2H), 3.27 (s, 3H), 6.62 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 7.19 (dd, J = 2.0, 8.0 Hz, 1H), 7.87 (s, 1H), 10.29 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 20.4, 27.8, 37.8, 47.9, 51.0, 76.9, 110.7, 112.9, 114.4, 126.1, 130.7, 139.3, 144.1, 159.8, 165.7, 168.3, 180.4, 195.8. Anal. Calcd. for $C_{18}H_15BrN_2O_5$: C, 51.57; H, 3.61; N, 6.68. Found C, 51.60; H, 3.62; N, 6.65.

2-Amino-5′-methyl-2′,5-dioxo-5,6,7, 8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (compound **8at***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.76–1.78 (m, 2H), 2.18 (s, 3H), 2.21–2.23 (m, 2H), 2.41–2.44 (m, 2H), 6.68 (d, J = 7.0 Hz, 1H), 6.76 (s, 1H), 6.96 (d, J = 7.75 Hz, 1H), 7.16 (s, 2H), 10.28 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 20.4, 27.8, 37.8, 47.9, 51.0, 76.9, 110.7, 112.9, 114.4, 126.1, 130.7, 139.3, 144.1, 159.8, 165.7, 168.3, 177.4, 195.8. Anal. Calcd. for $C_{18}H_{15}N_3O_3$: C, 67.28; H, 4.71; N, 13.08. Found C, 67.35; H, 4.77; N, 13.15.

Ethyl 2′-amino-2,5′-dioxo-2H,5′H-spiro[acenaphthylene-1,4′-pyrano[2,3-b]chromene]-3′-carboxylate (compound **8au***)*

Yellowish Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.22 (t, J = 7.0 Hz, 3H), 3.32–3.37 (m, 2H), 7.42 (d, J = 7.5 Hz, 2H), 7.52–7.57 (m, 2H), 7.72–7.79 (m, 2H), 7.67 (d, J = 7.5 Hz, 2H), 8.08 (d, J = 7.5 Hz, 1H), 8.17–8.20 (m, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.1, 52.1, 59.5, 77.3, 105.8, 113.4, 117.3, 120.8, 120.9, 123.6, 123.7, 125.2, 125.7, 128.8, 129.2, 130.1, 131.1, 134.3, 135.8, 142.2, 144.7, 152.7, 154.9, 159.6, 159.7, 167.8, 205.6. Anal. Calcd. for $C_{26}H_{17}NO_6$: C, 71.07; H, 3.90; N, 3.19. Found C, 71.14; H, 3.96; N, 3.22.

6′-Amino-3′-methyl-2-oxo-1′-phenyl-1′H,2H-spiro[acenaphthylene-1,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (compound **8av***)*

Yellowish Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.06 (s, 3H), 7.35–7.37 (m, 1H), 7.51–7.54 (m, 2H), 7.59–7.64 (m, 3H), 7.78–7.82 (m, 3H), 7.92–7.95 (m, 1H), 8.08–8.11 (m, 2H), 8.42 (d, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.9, 53.6, 58.6, 116.5, 118.9, 121.1, 122.5, 124.6, 125.3, 125.6, 126.8, 128.9, 129.7, 129.9, 130.8, 131.4, 132.7, 136.2, 141.9, 152.5, 177.3, 197.8. Anal. Calcd. for $C_{25}H_{16}N_4O_2$: C, 74.25; H, 3.99; N, 13.85. Found C, 74.31; H, 4.05; N, 13.90.

7′-Amino-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (compound **8aw***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 6.95 (s, 2H), 7.05 (t, J = 8.3 Hz, 1H), 7.21-7.30 (m, 3H), 9.03 (s, 1H), 9.66 (s, 1H), 11.03 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 47.6, 58.2, 79.8, 114.5, 117.1, 123.9, 127.81, 127.86, 129.3, 140.9, 150.4, 158.6, 159.9, 163.9, 168.8. Anal. Calcd. for $C_{15}H_9N_5O_4$: C, 55.73; H, 2.81; N, 21.66. Found C, 55.78; H, 2.85; N, 21.72.

7′-Amino-1,2′,3,4′-tetraoxo-1,1′,2′,3,3′,4′-hexahydrospiro[indene-2,5′-pyrano[2,3-d]pyrimidine]-6′-carbonitrile (compound **8ax***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 7.01 (s, 2H), 8.01 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H), 9.08 (s, 1H), 11.03 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 58.1, 64.2, 80.0, 116.5, 124.6, 131.3, 140.9, 151.1, 158.9, 160.8, 162.3, 196.4. Anal. Calcd. for $C_{16}H_8N_4O_5$: C, 57.15; H, 2.40; N, 16.66. Found C, 57.21; H, 2.44; N, 16.72.

Ethyl 7′-amino-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carboxylate (compound **8ay***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.03 (s, 3H), 3.96 (m, 2H), 6.98 (s, 2H), 7.10 (m, 1H), 7.21–7.30 (m, 3H), 9.12 (s, 1H), 9.76 (s, 1H), 11.06 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.9, 57.6, 61.5, 79.8, 80.1, 114.3, 123.6, 127.66, 127.69, 129.1, 140.9, 149.8, 160.0, 162.3, 163.5, 167.1, 168.4. Anal. Calcd. for $C_{17}H_{14}N_4O_6$: C, 55.14; H, 3.81; N, 15.13. Found C, 55.19; H, 3.88; N, 15.15.

Methyl 7′-amino-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carboxylate (compound **8az***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 3.92 (S, 3H), 7.01 (s, 2H), 7.11 (m, 1H), 7.21-7.29 (m, 3H), 9.10 (s, 1H), 9.71 (s, 1H), 11.01 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 53.2, 61.7, 79.5, 80.0, 114.2, 123.6, 127.62, 127.67, 129.1, 140.8, 149.8, 160.3, 162.3, 163.7, 167.1, 168.6. Anal. Calcd. for $C_{16}H_{12}N_4O_6$: C, 53.94; H, 3.39; N, 15.73. Found C, 53.98; H, 3.33; N, 15.80.

Ethyl 7′-amino-1,2′,3,4′-tetraoxo-1,1′,2′,3,3′,4′-hexahydrospiro[indene-2,5′-pyrano[2,3-d]pyrimidine]-6′-carboxylate (compound **8ba***)*

Yellowish Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.06 (t, J = 7.6 Hz, 3H), 3.95 (m, 2H), 7.03 (S, 2H), 8.06 (d, J = 8.7 Hz, 2H), 8.13 (d, J = 8.7 Hz, H), 9.11 (s, 1H), 10.96 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.1, 61.3, 63.9, 78.8, 79.3, 125.1, 132.9, 141.0, 152.3, 159.8, 161.9, 162.3, 163.8, 167.6, 196.8. Anal. Calcd. for $C_{18}H_{13}N_3O_7$: C, 56.40; H, 3.42; N, 10.96. Found C, 56.46; H, 3.45; N, 10.91.

Methyl 7′-amino-1,2′,3,4′-tetraoxo-1,1′,2′,3,3′,4′-hexahydrospiro[indene-2,5′-pyrano[2,3-d]pyrimidine]-6′-carboxylate (compound **8bb***)*

Yellowish Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 3.93 (s, 3H), 7.01 (S, 2H), 8.04 (d, J = 8.5 Hz, 2H), 8.15 (d, J = 8.5 Hz, H), 9.08 (s, 1H), 10.98 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 59.9, 63.7, 78.5, 79.2, 125.0, 132.9, 141.0, 152.3, 159.6, 161.9, 162.7, 163.8, 167.5, 196.6. Anal. Calcd. for $C_{17}H_{11}N_3O_7$: C, 55.29; H, 3.00; N, 11.38; found C, 5.33; H, 3.07; N, 11.32.

Ethyl 7′-amino-5-chloro-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro[indoline-3,5′-pyrano[2,3-d]pyrimidine]-6′-carboxylate (compound **8bc***)*

White Powder, ^{1}H NMR (DMSO-d_6, 500 MHz): 1.09 (t, J = 7.3 Hz, 3H), 3.84 (m, 2H), 6.98 (s, 2H), 7.21 (m, 1H), 7.38 (s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 9.12 (s, 1H), 9.76 (s, 1H), 11.10 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.3, 46.9, 61.7, 78.9, 111.6, 126.9, 128.9, 129.3, 131.0, 138.9, 150.7, 160.1, 162.1, 163.9, 167.0, 168.3. Anal. Calcd. for $C_{17}H_{13}ClN_4O_6$: C, 50.45; H, 3.24; N, 13.84. Found C, 50.48; H, 3.26; N, 13.87.

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