1,8-Diazabicyclo[5.4.0]undec-7-ene: A Highly Efficient Catalyst for One-Pot Synthesis of Substituted Tetrahydro-4*H*-chromenes, Tetrahydro[*b*]pyrans, Pyrano[*d*]pyrimidines, and 4*H*-Pyrans in Aqueous Medium

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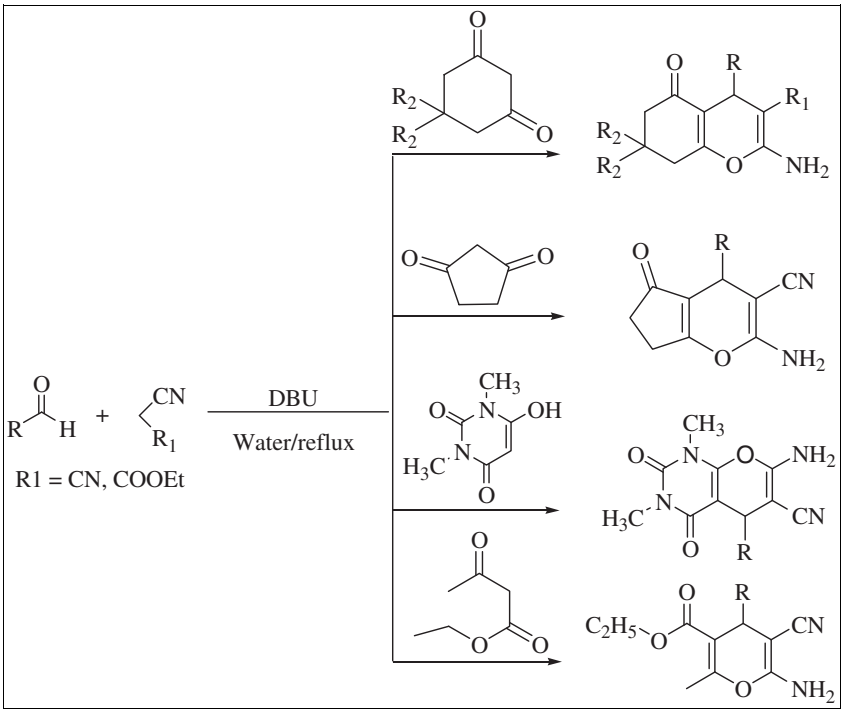


We have reported 1,8-diazabicyclo[5.4.0]undec-7-ene catalyzed one-pot synthesis of tetrahydro-4*H*-chromenes, tetrahydro[*b*]pyrans, pyrano[*d*]pyrimidines and 4*H*-pyrans from aldehydes, active methylene compounds malononitrile/ethyl cyanocacetate and activated C–H acids such as dimedone, 1,3-cyclohexanedione, 1,3-cyclopentanedione, 1,3-dimethylbarbituric acid, and ethyl acetoacetate in water under reflux. The attractive features of this process are mild reaction conditions, reusability of the reaction media, short reaction times, easy isolation of products, and excellent yields.

INTRODUCTION

In recent years, the "greening" of chemical processes to attain environmental benignness [1] and sustainability has become a major issue in academia and industry. The search for alternative reaction media to replace volatile, flammable, and often toxic solvents commonly used in organic synthesis is an important objective in the development of green chemical processes [2]. Developing multicomponent reaction (MCR) protocols in water is an active area of research in this direction. MCR offers greater possibilities for molecular diversity per step with a minimum synthetic time and effort. It constitutes an attractive synthetic strategy in drug discovery research, as they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns [3]. The network of hydrogen bonds in water influences the reactivity of the substrates, which makes it an ideal solvent [4]. It is also proposed that the reactions with negative activation volume might be facilitated by water [5]. MCRs are believed to exhibit negative activation volumes owing to the condensation of several molecules into a single reactive intermediate and product [6].

In recent years, 4*H*-pyrans and its derivatives have attracted strong interest because of their useful biological and pharmacological properties, such as anticoagulant, spasmolytic, anticancer, and antianaphylactin agents [7]. 2-Amino-4*H*-pyrans can be used as photoactive materials [8]. Furthermore, polyfunctionalized 4*H*-chromenes and 4*H*-pyrans also constitute a structural unit of many natural products [9]. 2-Amino-4*H*-chromene derivatives

are often used in cosmetics and pigments and utilized as potentially biodegradable agrochemicals [10]. 4*H*-Pyran derivatives are also potential calcium channel antagonists [11] that are structurally similar to biologically active 1,4-dihydropyridines.

The importance of these compounds has led many workers to synthesize them using methods including microwave [12] and ultrasonic irradiation [13], by using halide ions [14], (*S*)-proline [15], rare earth perfluorooctanoates [16], hexadecyltrimethylammonium bromide [17], and magnesium oxide [18] as basic catalysts or 1,1,3,3-tetramethylguanidinium trifluoroacetate [19] as an ionic liquid in one-pot reactions. Each of the beforementioned methods has its own merits and demerits. Thus, in view of the importance of chromenes/pyrans for diverse therapeutic activity and in continuation to our endeavor of developing new methodologies aimed at synthesis of polyfunctionalized heterocyclic moieties [20], we considered it necessary to develop a general rapid, high yielding, environmentally benign, and easy synthetic protocol for a variety of chromene/pyran derivatives.

RESULTS AND DISCUSSION

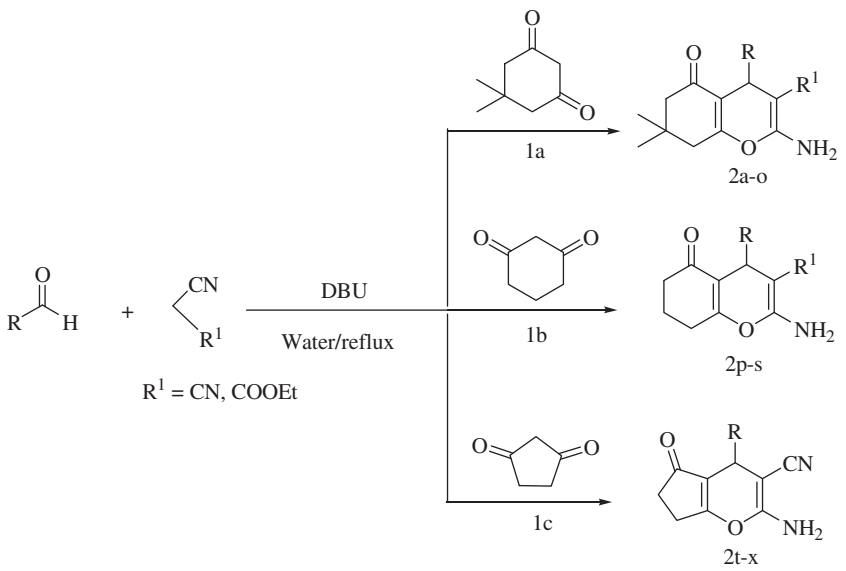
We report in this article highly efficient one-pot synthesis of a variety of chromene/pyran derivatives, namely, tetrahydro-4*H*-chromenes (**2a-s**), tetrahydro[*b*]pyrans (**2t-x**), pyrano[*d*]pyrimidines (**3a-i**), and 4*H*-pyrans (**4a-i**) catalyzed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in water under reflux. DBU was found to be far superior to other tertiary amines, and its nucleophilic nature as well as its utility in organic synthesis has also been investigated over the past decades [21].

Inspired by the recent advances based upon DBU, we examined first the efficiency of DBU as a promoter for one-pot synthesis of 2-amino-4*H*-chromenes via three-component condensation of aldehydes, malononitrile, or ethyl cyanoacetate and dimedone (**1a**), and we were pleased to find that with a substoichiometric amount of DBU, 4-chlorobenzaldehyde (1.0 equiv), malononitrile (1.0 equiv), and dimedone (1.0 equiv) underwent condensation smoothly, affording 90% of 2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**2a**) in 5 min using water as solvent under reflux.

This preliminary study prompted us to carry out in-depth investigation on this novel synthetic protocol. So when this reaction was repeated at room temperature, no desired product formation was observed because of insolubility of the starting materials. The reaction remained incomplete after 2 h at room temperature when a mixture of ethanol/water (1:1, v/v) was used, giving 76% yield of the desired product. Heating the reaction mixture at 80°C using ethanol/water (1:1, v/v) as solvent yielded 86% of the desired product in 40 min. No product formation was observed in the absence of DBU, and the use of 10 mol% of DBU was found to be sufficient for catalyzing this reaction. Thus, refluxing all the components in the presence of 10 mol% of DBU in water proved to be the optimum condition for this reaction (Scheme 1).

Thereafter, a series of reactions were carried out under identical reaction conditions. A wide range of diversely substituted aromatic aldehydes underwent this three-component cyclocondensation reaction with malononitrile and dimedone to produce 2-amino-4-aryl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (Table 1,

Scheme 1



entries **2a–g**). The substituents in the aromatic ring of aldehydes did not show any effect on the rate of the reaction and yield of the products. The heteroaryl aldehydes, such as 2-furaldehyde and 2-thiophenealdehyde (Table 1, entries **2h** and **2i**), reacted very smoothly to give the corresponding 4*H*-chromenes in good yields. These compounds have been reported to exhibit molluscicidal activity [22]. Aliphatic aldehydes also underwent this three-component cyclocondensation reaction to give corresponding 4*H*-chromene derivatives (Table 1, entry **2j**).

We then investigated the scope of extending the condensation strategy by replacing the active methylene compound, malononitrile, with ethyl cyanoacetate for reaction with aromatic aldehydes and dimedone. The reaction underwent successful condensation under similar reaction conditions to afford a series of ethyl 2-amino-7,7-dimethyl-5-oxo-4-aryl-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate derivatives in high yields (Table 1, entries **2k–o**).

To further expand the scope of the present method, the replacement of 5,5-dimethyl-1,3-cyclohexanedione (dimedone) with 1,3-cyclohexanedione (**1b**) was examined under the same reaction conditions. The reactions proceeded steadily to provide the targeted tetrahydro-4*H*-chromenes (Table 1, entries **2p–s**) in good yields. Reactions were also attempted by replacing dimedone with 1,3-cyclopentanedione (**1c**). The components underwent successful condensation to give tetrahydro [*b*]pyrans (Table 1, entries **2t–x**) in nearly quantitative yields.

Encouraged by these results, we attempted the present protocol for condensation of aldehydes, malononitrile, and 1,3-dimethyl barbituric acid. During our exploratory experiments, we observed that 4-chlorobenzaldehyde underwent the three-component condensation smoothly in the presence of 10 mol% of DBU under reflux to afford 84% of 7-amino-5-(4-chlorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-pyrano[2,3-*d*] pyrimidine-6-carbonitrile in 5 min (Table 2, entry **3a**). Thereafter, a series of differently substituted pyrano[2,3-*d*]pyrimidines were prepared from different aromatic aldehydes bearing electron-withdrawing and electron-donating groups using 10 mol% of DBU in aqueous medium under reflux in high yields (Scheme 2, Table 2, entries **3a–i**). These results clearly indicate that reactions can tolerate a wide range of differently substituted aromatic aldehydes.

Further, to realize the generality and versatility of the catalyst, this novel protocol was extended for the synthesis of 6-amino-4*H*-pyrans (Table 3, entries **4a–i**) by one-pot condensation of aromatic aldehydes (1.0 equiv), malononitrile (1.0 equiv), and ethyl acetoacetate (1.0 equiv) in aqueous media under reflux in the presence of 10 mol% of DBU (Scheme 3). In all cases, the reactions were remarkably clean, and no chromatographic separation was required.

Table 1

DBU-catalyzed three-component one-pot synthesis of substituted tetrahydro-4*H*-chromenes and tetrahydro[*b*]pyrans.

Product	R_f[a]	*R*	R^1	1,3-Dicarbonyl	Time (min)	Yield (%)	mp (°C)[b] (observed)	mp (°C) (lit. [14,16,24])
2a	0.61	4-ClC_6H_4	CN	**1a**	5	90	210–212	214–215
2b	0.39	4-$O_2NC_6H_4$	CN	**1a**	5	92	178–180	180–181
2c	0.28	4-HOC_6H_4	CN	**1a**	10	88	202–204	205
2d	0.67	4-$CH_3C_6H_4$	CN	**1a**	10	91	216–220	224–225
2e	0.58	4-$CH_3OC_6H_4$	CN	**1a**	10	90	200–202	202–203
2f	0.61	4-BrC_6H_4	CN	**1a**	5	90	204–206	202–203
2g	0.60	4-FC_6H_4	CN	**1a**	5	86	190–194	210–211
2h	0.66	2-Furanyl	CN	**1a**	5	86	220–224	225–226
2i	0.68	2-Thiophenyl	CN	**1a**	5	85	216–218	216–218
2j	0.83	$(CH_3)_2CH$	CN	**1a**	10	88	174–176	172–174
2k	0.88	4-ClC_6H_4	$COOC_2H_5$	**1a**	5	88	148–150	154–155
2l	0.85	C_6H_5	$COOC_2H_5$	**1a**	5	90	152–154	157–158
2m	0.88	4-$CH_3C_6H_4$	$COOC_2H_5$	**1a**	10	85	152–154	157–158
2n	0.82	3-$O_2NC_6H_4$	$COOC_2H_5$	**1a**	10	90	178–180	182–183
2o	0.82	4-$O_2NC_6H_4$	$COOC_2H_5$	**1a**	10	90	180–182	184–185
2p	0.46	4-ClC_6H_4	CN	**1b**	5	88	228–230	228–229
2q	0.34	4-$O_2NC_6H_4$	CN	**1b**	5	90	232–234	235–236
2r	0.43	2-Furanyl	CN	**1b**	5	87	230–232	234–235
2s	0.48	2-Thiophenyl	CN	**1b**	5	86	198–200	205–206
2t	0.23	3-$O_2NC_6H_4$	CN	**1c**	10	85	200–202	198–200
2u	0.47	2-$O_2NC_6H_4$	CN	**1c**	10	75	218–220	–[c]
2v	0.37	4-$CH_3C_6H_4$	CN	**1c**	15	68	190–192	–[c]
2w	0.21	4-HOC_6H_4	CN	**1c**	15	65	218–220	–[c]
2x	0.58	4-ClC_6H_4	CN	**1c**	20	60	202–204	–[c]

[a]TLC solvent system ethyl acetate : petroleum ether (40:60 v/v).
[b]Solvent of recrystallization, ethanol. The compounds that showed slight variation from reported melting point was further recrystallized from ethanol, but no improvement in the melting point of these compounds was noticed.
[c]Known compounds, but their melting points were not reported.

Table 2

DBU-catalyzed three-component one-pot synthesis of pyrano[*d*]pyrimidines.

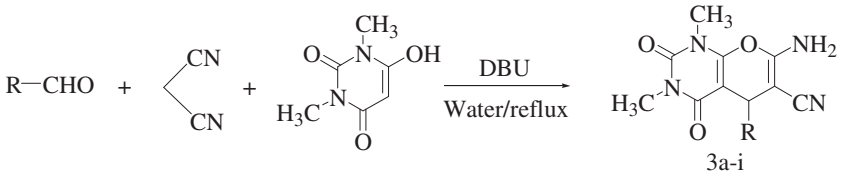
Product	R_f[a]	*R*	Time (min)	Yield (%)	mp (°C)[b] (observed)	mp (°C) (lit. [19,24])
3a	0.30	4-ClC_6H_4	5	84	206–208	–[c]
3b	0.19	4-$O_2NC_6H_4$	5	82	196–198	–[c]
3c	0.29	4-FC_6H_4	5	78	164–166	–[c]
3d	0.30	4-BrC_6H_4	5	76	206–210	–[c]
3e	0.20	4-$F_3CC_6H_4$	10	80	146–150	–[c]
3f	0.32	C_6H_5	5	85	198–202	205–207
3g	0.31	2-ClC_6H_4	5	88	218–220	–[c]
3h	0.21	3-$O_2NC_6H_4$	5	86	168–170	–[c]
3i	0.30	3-ClC_6H_4	5	87	196–198	–[c]

[a]TLC solvent system methanol : chloroform (25:75 v/v).
[b]Solvent of recrystallization, ethanol.
[c]Known compounds, but their melting points were not reported.

According to the proposed mechanism, the first step of this reaction is the formation of Knoevenagel product by the condensation of an aldehyde with malononitrile [18]. During such base-catalyzed three-component reaction, formation of many side products like enaminonitrile, higher adducts, reduced products, and malononitrile self addition products have been reported [23]. We believe that higher basicity and stability of DBU–H^+ species generated in these reactions suppress the formation of these side products, and hence the yield of the products increases.

The α-cyanocinnamonitrile or α-carbethoxycinnamonitrile formed initially by Knoevenagel condensation in the presence of DBU undergo subsequent reactions with C–H acids, for example, dimedone/1,3-cyclohexanedione/1,3-cyclopentanedione/1,3-dimethyl barbituric acid or ethyl acetoacetate in the presence of DBU to give the desired products (Scheme 4). This has been confirmed by independent reactions of α-cyano-4 chlorocinnamonitrile and α-carbethoxy-4-chlorocinnamonitrile with dimedone in the presence of DBU, which yielded the desired products in 94% and 92% yields, respectively. The three reactions in the absence of DBU showed the formation of α-cyanocinnamonitrile or α-carbethoxycinnamonitriles only. The reaction media can be reused for further reactions. For example, after completion of the reaction, the solid product was collected by filtration (entry **2a**). To the filtrate,

Scheme 2



3a-i

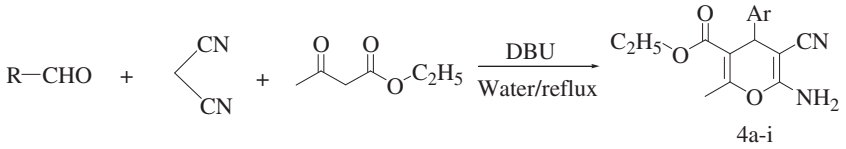
Table 3

DBU-catalyzed three-component one-pot synthesis of 4*H*-pyrans.

Product	R_f[a]	*R*	Time (min)	Yield (%)	mp (°C)[b] (observed)	mp (°C) (lit. [18,24])
4a	0.83	4-ClC_6H_4	5	95	168–170	172–174
4b	0.49	4-$O_2NC_6H_4$	5	90	176–178	180–183
4c	0.85	3-ClC_6H_4	5	92	152–154	153–156
4d	0.88	4-$CH_3C_6H_4$	10	85	178–180	177–179
4e	0.67	C_6H_5	5	88	194–195	195–196
4f	0.85	2-ClC_6H_4	5	90	167–169	–[c]
4g	0.52	3-$O_2NC_6H_4$	5	88	184–186	182–183
4h	0.15	4-HOC_6H_4	10	85	175–177	–[c]
4i	0.67	4-$CH_3OC_6H_4$	5	85	140–142	142–144

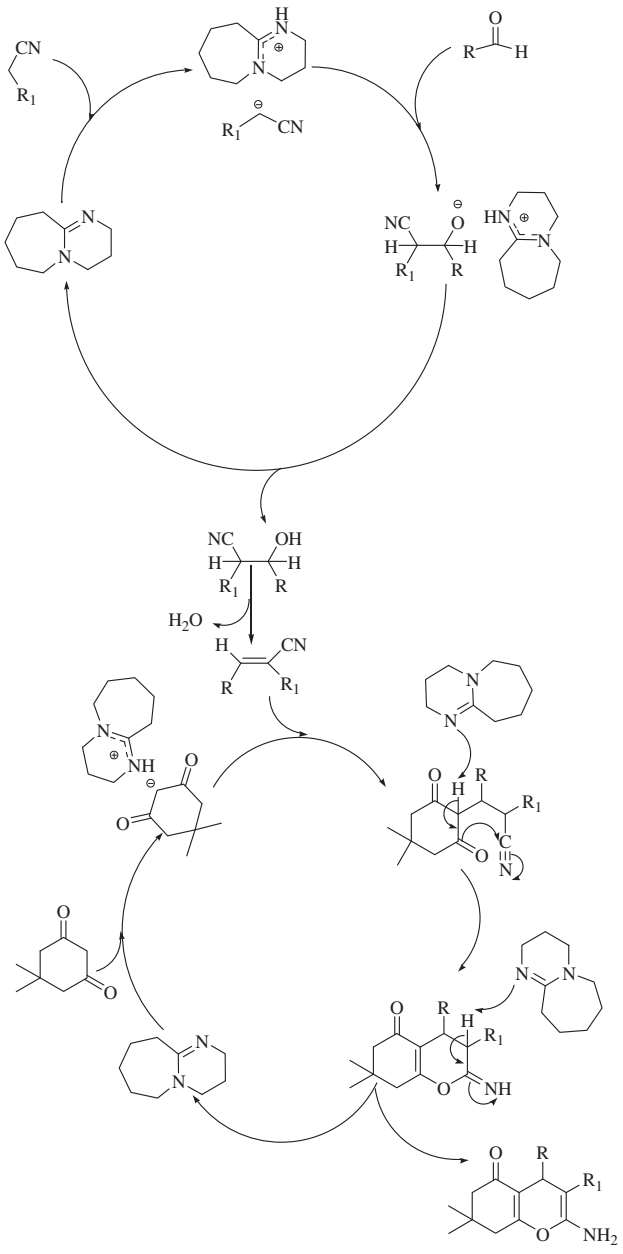
[a]TLC solvent system ethyl acetate : petroleum ether (40:60 v/v).
[b]Solvent of recrystallization, ethanol.
[c]Known compounds, but their melting points were not reported.

Scheme 3



4a-i

Scheme 4



4-chlorobenzaldehyde, malononitrile, and dimedone were added in the same molar ratio without additional load of DBU. The reaction mixture was stirred for specified time; marginal loss of the yield was observed in the first three runs (90%, 91%, and 84%), whereas in the fourth and fifth runs, the yield dropped to 74% and 63%, respectively.

CONCLUSION

DBU is an effective catalyst and provides a new and useful method to synthesize pyran annulated heterocyclic systems by condensation of aldehydes, activated C–H acid compounds, and active methylene compounds. The procedure offers several advantages including high yields, operational simplicity, clean reaction conditions, and minimum pollution of the environment, which make it a valid contribution to the existing processes in the field of pyran derivative synthesis.

EXPERIMENTAL

All of the chemicals used were purchased from Sigma-Aldrich, (Bangalore, India) and used as received. Structures of all of the compounds were identified by their melting point and spectral data. Thin layer chromatography was used to monitor reaction progress. Compounds were purified by crystallization through hot ethanol. Melting points were determined on a Tropical Labequip apparatus and are uncorrected. IR (KBr) spectra were recorded on Perkin Elmer (USA) FTIR Spectrum-1710, and the values are expressed as ν_{max} per centimeter. Mass spectral data were recorded on a Waters (USA) micromass LCT Mass Spectrometer. The NMR (^{1}H and ^{13}C) spectra were recorded on Jeol JNM ECX-400P (Tokyo, Japan) at 400 MHz using TMS as an internal standard. The chemical shift values are recorded on δ scale, and the coupling constants (*J*) are in hertz.

General procedure for 1,8-diazabicyclo[5.4.0]undec-7-ene catalyzed multicomponent synthesis. Aldehyde (2.5 mmol), malononitrile (or ethyl cyanoacetate) (2.5 mmol), and 10 mL of water were placed in a 50-mL round-bottomed flask mounted over a magnetic stirrer. DBU (10 mol%, 0.25 mmol) was added to the mixture, and the contents were stirred. To this stirred mixture, dimedone (or 1,3-cyclohexanedione or 1,3-cyclopentadione or 1,3-dimethylbarbituric acid or ethyl acetoacetate) (2.5 mmol) was added. The reaction mixture was refluxed for an appropriate time as mentioned in Tables 1, 2, or 3. The progress of the reaction was monitored by TLC (solvent system ethyl acetate : petroleum ether 40:60) for disappearance of the aldehyde. After

completion of the reaction, the reaction mixture was allowed to cool at room temperature, and water was decanted. Ethanol (3 mL) was added to the mixture, and it was stirred. The solid was collected by filtration at pump, washed with ethanol, and crystallized from hot ethanol to obtain pure products. The aqueous filtrate containing DBU was used as such for investigating the recyclability of the catalyst.

Representative analytical data.

2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (2a, $C_{18}H_{17}ClN_2O_2$). ν_{max} (KBr) 3380, 3183, 2188, 1675, 1635, 1364, 1216 cm^{-1}; δH (400 MHz, $CDCl_3$) 1.02 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.10 (d, $J = 16.1$ Hz, 1H), 2.23 (d, $J = 16.1$ Hz, 1H), 2.45 (s, 2H, CH_2), 4.38 (s, 1H, CH), 4.59 (s, br, 2H, NH_2), 7.18 (d, $J = 8.08$ Hz, 2H, Ar), 7.26 (d, $J = 6.04$ Hz, 2H, Ar); δC (400 MHz, $CDCl_3$) 27.43, 28.75, 31.00, 35.22, 41.27, 49.34, 57.85, 114.55, 118.53, 128.74, 128.99, 129.12, 141.20, 156.64, 160.68, 195.92; *m/z* 328.0669 [M^+].

Ethyl-2-amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carboxylate (2k, $C_{20}H_{22}ClNO_4$). ν_{max} (KBr) 3480, 3327, 1688, 1660, 1525, 1206 cm^{-1}; δH (400 MHz, $CDCl_3$) 0.96 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.17 (t, $J = 7.32$, 3H, CH_3), 2.17 and 2.25 (AB system, $J = 16.04$ Hz, 2H, $CH_aCH_bC(CH_3)_2$), 2.41 (s, 2H, CH_2); 4.02–4.04 (m, 2H, OCH_2), 4.46 (s, 1H, CH), 6.20 (s, br, 2H, NH_2), 7.15–7.20 (m, 4H, Ar); δC (400 MHz, $CDCl_3$) 14.18, 27.31, 29.09, 32.21, 33.39, 40.58, 50.62, 59.74, 81.04, 116.33, 127.86, 129.62, 131.6, 144.38, 158.26, 161.46, 168.92, 196.40; *m/z* 375.8429 [M^+].

2-Amino-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (2q, $C_{16}H_{13}N_3O_4$). ν_{max} (KBr) 3414, 3362, 2196, 1682, 1651, 1518, 1346, 1210 cm^{-1}; δH (400 MHz, DMSO-d_6) 1.97–1.95 (m, 2H, CH_2), 2.26–2.29 (m, 2H, CH_2), 2.64 (m, 2H, CH_2) 4.35 (s, 1H, CH), 7.19 (s, br, 2H, NH_2), 7.46 (d, $J = 8.24$ Hz, 2H, Ar) 8.17 (d, $J = 7.80$ Hz, 2H, Ar); δC (400 MHz, DMSO-d_6) 56.12, 115.24, 120.05, 123.65, 130.87, 146.43, 154.49, 158.21, 165.23, 166.54, 196.76; *m/z* 311.2716 [M^+].

2-Amino-4-(3-nitrophenyl)-5-oxo-4,5,6,7-tetrahydrocyclopenta [b]pyran-3-carbonitrile (2t, $C_{15}H_{11}N_3O_4$). ν_{max} (KBr) 3369, 3314, 3187, 2196, 1662, 1348, 1238 cm^{-1}; δH (400 MHz, DMSO-d_6) 2.36 (s, 2H, CH_2), 2.68–2.80 (m, 2H, CH_2), 4.48 (s, 1H, CH), 7.35 (s, br, 2H, NH_2), 7.62–7.72 (m, 2H, Ar), 8.05–8.11 (m, 2H, Ar); δC (400 MHz, DMSO-d_6) 24.84, 33.49, 35.17, 56.45, 115.92, 119.54, 122.27, 122.38, 130.08, 134.87, 144.85, 147.87, 159.88, 177.01, 201.33; *m/z* 297.2456 [M^+].

7-Amino-1,3-dimethyl-2,4-dioxo-5-(4-trifluoromethylphenyl)-1,3,4,5-tetrahydro-2H-pyrano [2,3-d]pyrimidine-6-carbonitrile (3e, $C_{17}H_{13}F_3N_4O_3$). ν_{max} (KBr) 3381, 3192, 2199, 1708, 1640, 1493, 1224 cm^{-1}; δH (400 MHz, DMSO-d_6) 3.02 (s, 3H, CH_3), 3.31 (s, 3H, CH_3), 4.31 (s, 1H, CH), 7.07–7.26 (m, 4H, Ar), 7.30 (s, br, 2H, NH_2); δC (400 MHz, DMSO-d_6); 27.77, 39.50, 39.70, 57.79, 85.11, 118.94, 125.29, 126.4, 128.40, 131.01, 148.86, 157.77, 160.13, 160.61; *m/z* 378.3134 [M^+].

Ethyl-6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (4e, $C_{16}H_{16}N_2O_3$). ν_{max} (KBr) 3403, 3329, 2190, 1693, 1259, 1060 cm^{-1}; δH (400 MHz, $CDCl_3$) 1.08 (t, $J = 7.17$ Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 4.00–4.01 (m, 2H, OCH_2), 4.41 (s, 1H, CH), 4.49 (s, br, 2H, NH_2), 7.24–7.70 (m, 5H, Ar); δC (400 MHz, $CDCl_3$) 13.50, 18.50, 19.51, 38.50, 60.79, 61.60, 107.37, 118.64, 126.51, 128.26, 129.58, 134.30, 134.51, 147.06, 158.41, 166.23, 166.49; *m/z* 284.3429 [M^+].

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