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Facile and One-Pot Access to Diverse and Densely Functionalized 2-Amino-3-cyano-4*H*-pyrans and Pyran-Annulated Heterocyclic Scaffolds via an Eco-Friendly Multicomponent Reaction at Room Temperature Using Urea as a Novel Organo-Catalyst

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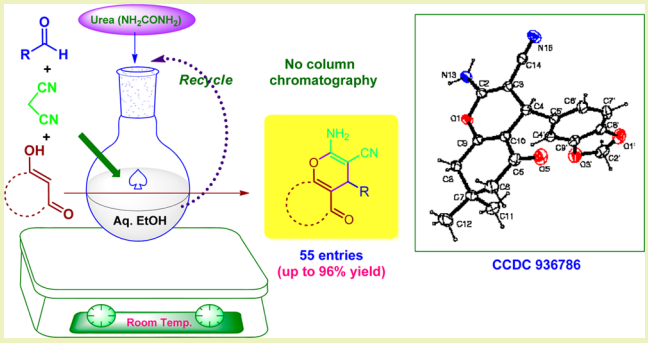
Supporting Information

ABSTRACT: A simple, straightforward, and highly efficient multicomponent one-pot synthesis of a pharmaceutically interesting diverse kind of functionalized 2-amino-3-cyano-4*H*-pyrans and pyran-annulated heterocycles has been developed based on a low-cost and environmentally benign commercially available urea as a novel organo-catalyst. The reaction occurs via tandem Knoevenagel−cyclocondensation of aldehydes, malononitrile, and C−H-activated acidic compounds in aqueous ethanol at room temperature. Following this protocol, it was possible to synthesize 2-amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)-ones (**4aa−4al**), 2-amino-3-cyano-pyrano[4,3-*b*]pyran-5(4*H*)-ones (**4ba−4be**), 2-amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-one (**4ca−4cr**), 1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones (**4da−4dd**), 2-amino-3-cyano-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromenes (**4ea−4ec**), 2-amino-3-cyano-4*H*-pyrans (**4fa−4fh**), and 1,4-dihydropyrano[2,3-*c*]pyrazoles (**4ga−4gb**). The salient features of the present protocol are mild reaction conditions, excellent yields, high atom-economy, eco-friendly standards, easy isolation of products, no column chromatographic separation, and reusability of reaction media. Bis-pyranization has also been observed in the reactions of terephthaldehyde.



KEYWORDS: *Multicomponent reactions, Pyran-annulated heterocycles, Medicinal chemistry, Urea, Aqueous ethanol, Room temperature, Chemoselectivity, No column chromatography, Green and sustainable chemistry*

INTRODUCTION

4*H*-Pyrans and 4*H*-pyran-annulated heterocyclic scaffolds represent a "privileged" structural motif well distributed in naturally occurring compounds[1−3] with a broad spectrum of significant biological activities that include anticancer,[4] cytotoxic,[5] anti-HIV,[6−8] anti-inflammatory,[9] antimalarial,[10,11] antimicrobial,[12] antihyperglycemic, and antidyslipidemic,[13] along with antineurodegenerative disorders like Alzheimer's, Parkinson disease, Huntington's disease,[14] and many more.[15,16] Figure 1 represents a glimpse of some of the naturally occurring bioactive pyran-annulated heterocyclic compounds exhibiting a diverse kind of pharmaceutical potentials.[17−28] Moreover, functionalized 4*H*-pyran derivatives have played increasing roles in synthetic approaches to promising compounds in the field of medicinal,[29,30] agrochemical,[31] cosmetics, and pigment industries.[32] It is worthwhile to mention that currently a number of drug molecules bearing the 4*H*-pyran moiety are in use in the treatment of various ailments, such as hypertension, asthma, ischemia, and urinary incontinence.[33−37] In addition, such 4*H*-pyran derivatives are also administrated to animals suffering from a disorder responsive to the positive modulation of the AMPA receptor as an effective remedy.[38] 2-Amino-3-cyano-4*H*-pyrans are found to exhibit significant photochemical activity as well.[39] Recently, a series of synthetic 2-amino-3-cyano-4*H*-pyrans (Figure 2) has been evaluated to possess potent anticancer,[40−51] antibacterial, antifungal,[52−57] and antirheumatic[58] properties. Besides, the 4*H*-pyran ring can be transformed to dihydropyridine (DHP) type systems having promising calcium antagonist properties.[59,60] Such a handful of diverse applications of 4*H*-pyrans and pyran-annulated heterocyclic scaffolds in medicinal chemistry have drawn considerable interest during the last several years among synthetic chemists to develop useful synthetic routes to these heterocycles of potential interest; as a result, a good number of methods are already reported.

Among the known procedures, the most straightforward method for the synthesis of this heterocyclic system involves a three-component tandem reaction of 1,3-diketones, aldehydes, and malononitrile utilizing a variety of homogeneous and heterogeneous catalysts, such as DMAP,[61] heteropolyacids,[62] basic ionic liquid,[63] TBAB,[64,65] DBU,[66] diammonium hydrogen

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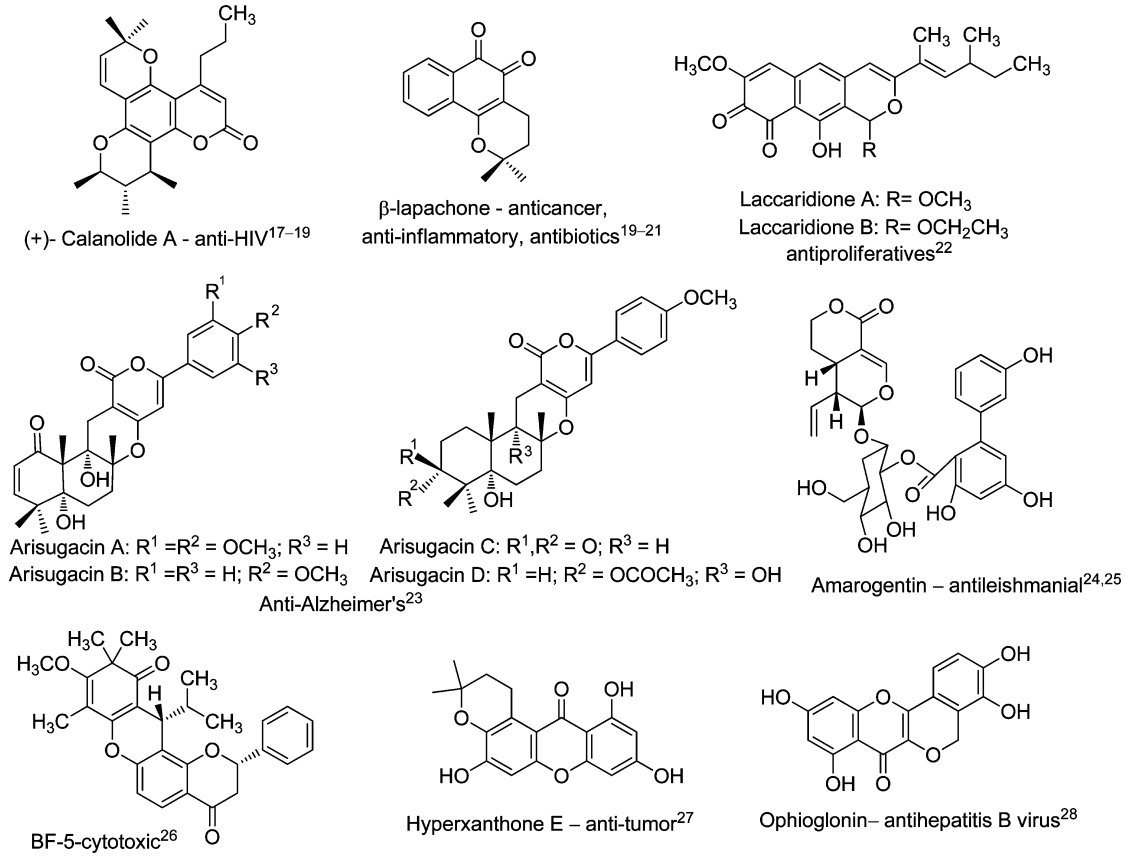

Figure 1. Some of the naturally occurring bioactive compounds bearing pyran-annulated scaffolds.[17−28]

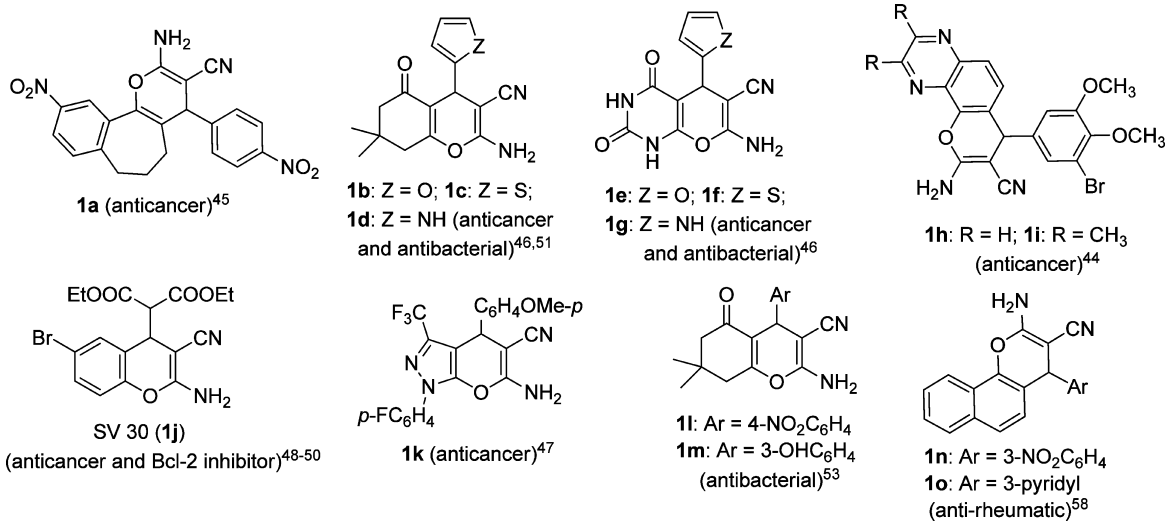

Figure 2. Representative examples of pharmacologically active synthetic 2-amino-3-cyano-4*H*-pyrans.[44−51,53,58]

phosphate,[67] nano ZnO,[68] MgO,[69] (*S*)-proline,[70] hexadecyltrimethyl ammonium bromide,[71] TMGT,[72] magnetic nanocatalyst,[73] phenylboronic acid,[74] hydroxyapatite (HAP),[75] and *per*-6-amino-*β*-cyclodextrin.[76] Although these protocols reported by others find certain merits of their own, still they suffer from a number of demerits such as long reaction time, harsh reaction conditions, heating, expensive catalyst/reagents, and high catalytic loading; besides, most of these reported methods involve the use of a limited number of C−H-activated acids (mainly, dimedone and 4-hydroxycoumarin) and aromatic aldehydes. Therefore, a search for more general, clean, efficient, feasible, and high yielding routes to this class of *O*-heterocycles remains a valid exercise.

In recent times, multicomponent reactions (MCRs) have gained eminence as a synthetic tool for producing structurally complex molecular entities with attractive biological features through the formation and breakage of several carbon−carbon and carbon−heteroatom bonds in one pot.[77−90] It is becoming increasingly important both in academia and in industry to design less toxic and more environmentally friendly MCRs. In addition, implementation of several transformations in a single manipulation in MCR strategy is highly compatible with the

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Scheme 1. Synthesis of Densely Functionalized 2-Amino-3-cyano-4*H*-pyrans and Pyran-Annulated Heterocyclic Scaffolds

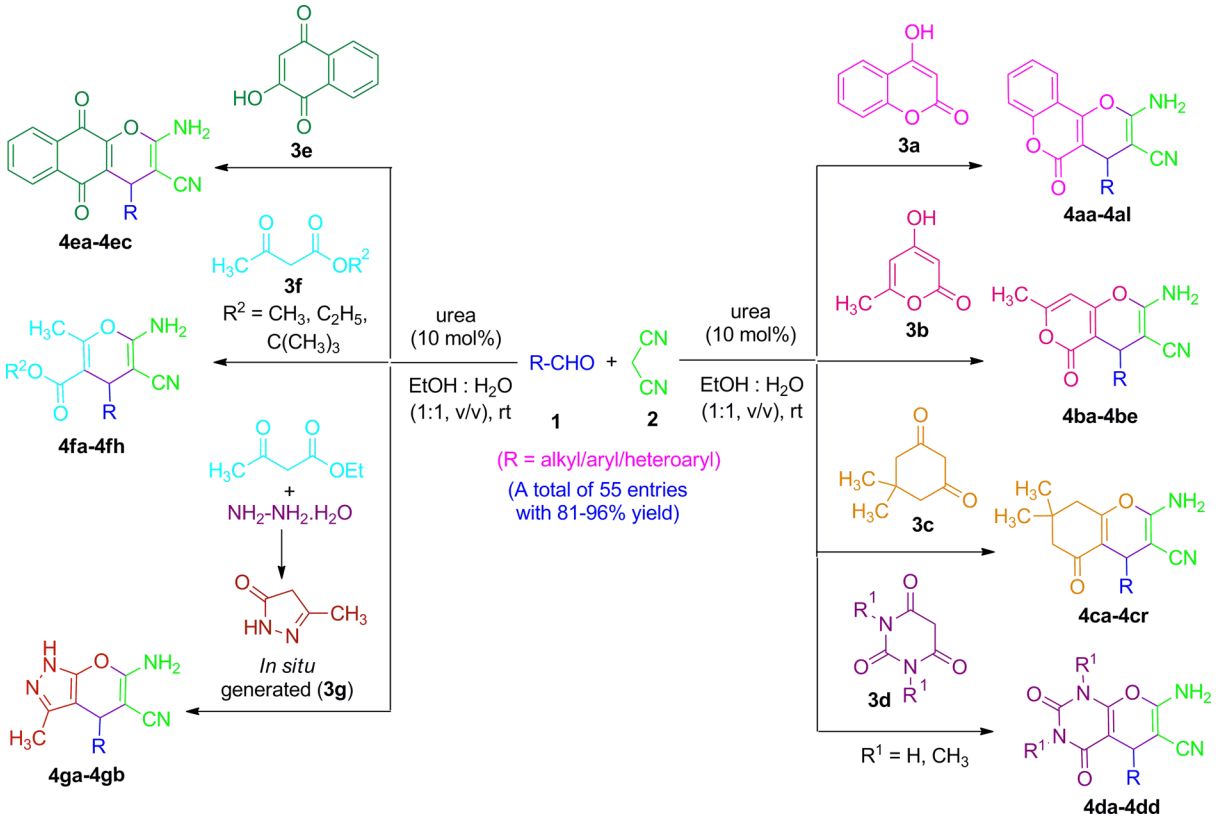
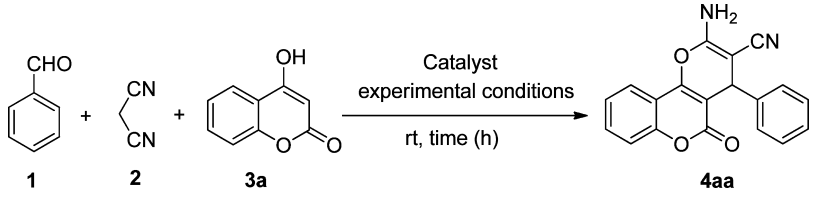


Table 1. Optimization of Reaction Conditions in the Synthesis of 2-Amino-3-cyano-4*H*-pyrans and Pyran-Annulated Heterocycles



entry	catalyst	solvent	time (h)	yield (%)[a,b]
1	no catalyst	no solvent	24	Trace
2	no catalyst	EtOH	24	39
3	urea (5 mol %)	EtOH	11	64
4	urea (10 mol %)	EtOH	8	71
5	urea (10 mol %)	H_2O	24	56
6	**urea (10 mol %)**	**EtOH:H_2O (1:1 v/v)**	**6**	**91**
7	urea (10 mol %)	no solvent	24	26
8	urea (20 mol %)	EtOH:H_2O (1:1 v/v)	4.5	87
9	urea (15 mol %)	EtOH:H_2O (1:1 v/v)	6	91
10	urea (5 mol %)	EtOH	8	71
11	thiourea (10 mol %)	EtOH:H_2O (1:1 v/v)	7	86

[a]Reaction conditions: benzaldehyde (1 mmol), malononitrile (1.1 mmol), and 4-hydroxycoumarin (1 mmol) in the presence or absence of urea/thiourea in neat/4 mL of water/ethanol/ethanol−water at room temperature. [b]Isolated yields.

goals of sustainable and "*green*" chemistry.[91,92] As part of our continuing efforts to develop green synthetic methodologies for useful organic transformations,[93−103] herein, we wish to report a straightforward, efficient, clean, and high yielding MCR protocol for the one-pot facile synthesis of biologically relevant diverse and densely functionalized 2-amino-3-cyano-4*H*-pyrans and pyran-annulated heterocyclic scaffolds from the reaction of aldehydes, malononitrile, and a variety of C−H-activated acids in aqueous ethanol at room temperature using commercially available urea as an inexpensive and environmentally benign organo-catalyst. To the best of our knowledge, this is the first-time there has been a report on the use of a catalytic amount of urea in organic synthesis. The results are summarized in Scheme 1 and Tables 1−7.

EXPERIMENTAL SECTION

General. Infrared spectra were recorded using a Shimadzu (FT-IR 8400S) FT-IR spectrophotometer using KBr disc. ^{1}H and ^{13}C NMR

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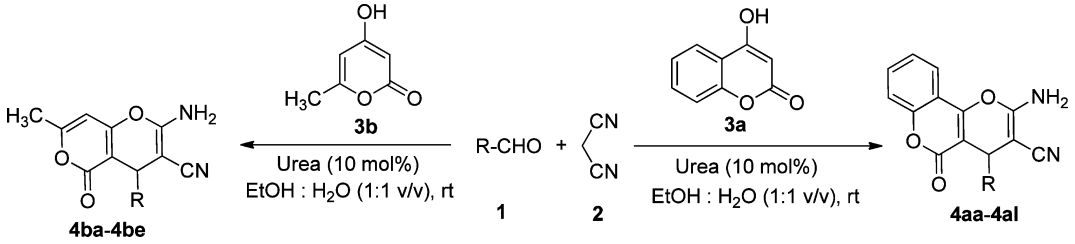
Table 2. Synthesis of 2-Amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)-ones (4aa−4al) and 2-Amino-3-cyano-pyrano[4,3-*b*]pyran-5(4*H*)-ones (4ba−4be)



entry	activated C−H acid	product	substituent (R)	time (h)	yield (%)[a,b]	melting point (°C) found	melting point (°C) reported
1	**3a**	**4aa**	C_6H_5	6	91	254−256	256−258[66]
2	**3a**	**4ab**	4-ClC_6H_4	7	93	262−264	260−262[66]
3	**3a**	**4ac**	4-FC_6H_4	11	90	261−262	262−263[66]
4	**3a**	**4ad**	4-$CH_3C_6H_4$	10	91	257−259	258−260[61]
5	**3a**	**4ae**	4-$NO_2C_6H_4$	8	86	258−260	256−258[66]
6	**3a**	**4af**	3-$NO_2C_6H_4$	3	97	254−256	257−258[70]
7	**3a**	**4ag**	4-$CF_3C_6H_4$	8	87	252−254	–
8	**3a**	**4ah**	4-OH−C_6H_4	10	89	262−264	264−266[104]
9	**3a**	**4ai**	2,4-di-Cl−C_6H_3	7	82	253−255	255−257[105]
10	**3a**	**4aj**	3-OMe, 4-OH−C_6H_3	12	87	253−255	253−254[104]
11	**3a**	**4ak**	$CH_3(CH_2)_2$	16	83	242−243	243−245[66]
12	**3a**	**4al**	$(CH_3)_2CH$	15	85	251−253	250−252[66]
13	**3b**	**4ba**	C_6H_5	3	81	218−220	221−223[66]
14	**3b**	**4bb**	3-$NO_2C_6H_4$	3	84	237−239	235−237[69]
15	**3b**	**4bc**	4-$NO_2C_6H_4$	7	83	208−210	210−212[66]
16	**3b**	**4bd**	4-FC_6H_4	6	88	224−226	–
17	**3b**	**4be**	4-CN−C_6H_4	5	80	216−218	–

[a]Reaction conditions: aldehyde (1 mmol), malononitrile (1.1 mmol), and 4-hydroxycoumarin (**3a**) or 4-hydroxy-6-methylpyrone (**3b**) (1 mmol) and 10 mol % urea as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

spectra were obtained at 400 and 100 MHz, respectively, using a Bruker DRX- 400 spectrometer and DMSO-d_6 as the solvent. Mass spectra (TOF-MS) were measured on a QTOF Micro mass spectrometer. Elemental analyses were performed with an Elementar Vario EL III Carlo Erba 1108 microanalyzer instrument. The melting point was recorded on a Chemiline CL-725 melting point apparatus and is uncorrected. Thin layer chromatography (TLC) was performed using silica gel 60 F_{254} (Merck) plates.

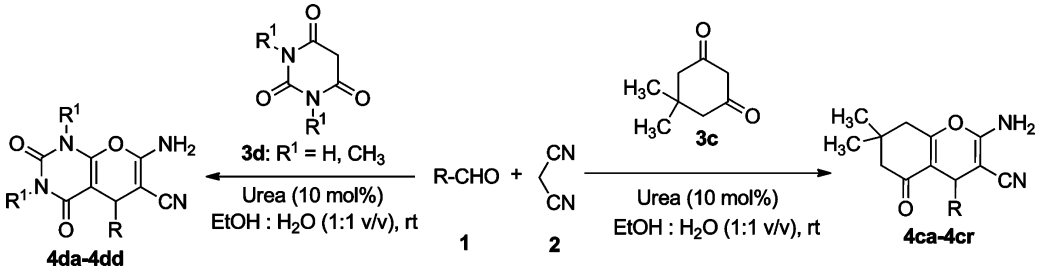
General Procedure for the Synthesis of Pyran-Annulated Heterocyclic Scaffolds 4. An oven-dried screw cap test tube was charged with a magnetic stir bar, aldehyde (**1**; 1 mmol), malononitrile (**2**; 1.1 mmol), urea (10 mol % as organo-catalyst), and EtOH: H_2O (1:1 v/v; 4 mL) in a sequential manner; the reaction mixture was then stirred vigorously at room temperature for about 20 min. After that, C−H-activated acid (**3**) (1 mmol) was added to the stirred reaction mixture, and the stirring was continued for appropriate range of time as indicated in respective tables in the text. The progress of the reaction was monitored by TLC. On completion of the reaction, a solid mass precipitated out that was filtered off followed by washing with aqueous ethanol to obtain crude product (**4**) purified just by recrystallization from ethanol without carrying out column chromatography. The filtrate containing residual solvent, catalyst, and substrates obtained upon filtration of the reaction mixture after completion of reaction could be successfully reused for a particular entry up to three times without appreciable loss of catalytic activity. The structure of each purified pyran-annulated heterocyclic scaffold was confirmed by analytical as well as spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR, and TOF-MS (Supporting Information).

Characterization Data of Few Representative Entries. 2-Amino-5-oxo-4-(4-(trifluoromethyl)phenyl)-4,5-dihydropyrano[3,2-c]-chromene-3-carbonitrile ***(4ag)***. White solid. Yield 87%. Mp: 252−254 °C. IR (KBr) ν_{max}/cm^{-1}: 3360, 3333, 3306, 3190, 3115, 3057, 2914, 2330, 2197, 1711, 1674, 1605, 1587, 1493, 1373, 1319, 1258, 1198, 1157, 1122, 1051, 951, 860, 849, 771, 754, 685, 662. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.01 (1H, d, J = 7.6 Hz, aromatic H), 7.73 (1H, d, J = 7.2 Hz, aromatic H), 7.68 (2H, d, J = 8.4 Hz, aromatic H), 7.53−7.50 (5H, m, aromatic H + NH_2), 7.46 (1H, d, J = 8.4 Hz, aromatic H), 4.60 (s, 1H, -C*H*-). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 160.00, 158.43, 154.23, 152.65, 148.32, 133.53, 129.06 (2C), 125.86 (2C), 125.15, 123.29, 122.98, 119.42, 117.03 (2C), 113.32, 103.55, 57.58, 37.25. TOF-MS: 407.0617 [M + Na]$^+$. Elemental analysis: Calcd. (%) for $C_{20}H_{11}F_3N_2O_3$: C, 62.51; H, 2.89; N, 7.29. Found: C 62.49, H 2.88, N 7.31.

2-Amino-4-(4-fluorophenyl)-7-methyl-5-oxo-4,5-dihydropyrano-[4,3-b]pyran-3-carbonitrile ***(4bd)***. White solid. Yield 88%. Mp: 224−226 °C. IR (KBr) ν_{max}/cm^{-1}: 3393, 3310, 3202, 3069, 2889, 2191, 1707, 1612, 1510, 1387, 1244, 1159, 1142, 1051, 970, 824, 613, 588. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.24−7.22 (2H, m, aromatic H), 7.21 (2H, s, NH_2), 7.12 (2H, t, J = 8.8 Hz, aromatic H), 6.25 (1H, s, CH), 4.31 (1H, s, CH), 2.20 (3H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 163.46, 162.76, 161.84, 160.35, 158.60, 158.47, 140.15, 140.13, 129.91, 129.83, 119.68, 115.63, 115.42, 100.90, 98.38, 58.17, 35.97, 19.69. TOF-MS: 321.0654 [M + Na]$^+$. Elemental analysis: Calcd. (%) for $C_{16}H_{11}FN_2O_3$: C, 64.43; H, 3.72; N 9.39. Found: C, 64.45; H, 3.69; N, 9.38.

2-Amino-7,7-dimethyl-5-oxo-4-(pyridin-4-yl)-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile ***(4cl)***. White solid. Yield 92%. Mp: 214−216 °C. IR (KBr) ν_{max}/cm^{-1}: 3389, 3312, 3038, 2962, 2878, 2341, 2330, 2183, 1674, 1653, 1599, 1529, 1479, 1360, 1213, 1149, 1041, 922, 852, 787, 658. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.49 (2H, d, J = 5.6 Hz, aromatic H), 7.19 (2H, s, NH_2), 7.18 (2H, d, J = 1.2 Hz, aromatic H), 4.23 (1H, s, CH), 2.54 (2H, s, CH_2), 2.27 (1H, d, J = 16.0 Hz), 2.14 (1H, d, J = 16.4 Hz), 1.04 (3H, s, CH_3), 0.97 (3H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 196.11, 163.69, 159.11, 153.45, 150.12 (2C), 122.93 (2C), 119.78, 111.84, 57.17, 50.27, 35.58, 32.23 (2C), 28.68, 27.36. TOF-MS: 296.0589 [M+H]$^+$. Elemental analysis: Calcd.

Table 3. Synthesis of 2-Amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-one (4ca−4cr) and 1*H*-Pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones (4da−4dd)



entry	activated C−H acid	product	substituent (R)	time (h)	yield (%)[a,b]	melting point (°C) found	melting point (°C) reported
1	**3c**	**4ca**	C_6H_5	3	90	224−226	225−227[66]
2	**3c**	**4cb**	4-ClC_6H_4	3	87	212−214	213-214[61]
3	**3c**	**4cc**	4-FC_6H_4	4	88	208−210	210−211[106]
4	**3c**	**4cd**	4-BrC_6H_4	2	93	205−207	207−209[67]
5	**3c**	**4ce**	4-$CH_3C_6H_4$	4	91	205−206	204−205[107]
6	**3c**	**4cf**	4-CN−C_6H_4	2	91	226−228	227−230[67]
7	**3c**	**4cg**	4-$NO_2C_6H_4$	5	92	183−185	184−186[107]
8	**3c**	**4ch**	3-$NO_2C_6H_4$	2	90	204−206	205−208[107]
9	**3c**	**4ci**	4-OCH_3−C_6H_4	9	87	195−196	197−199[107]
10	**3c**	**4cj**	3,4-(O−CH_2−O)−C_6H_3	12	96	212−214	211−213[71]
11	**3c**	**4ck**	3,4,5-$(OCH_3)_3$−C_6H_2	16	83	208−210	–
12	**3c**	**4cl**	4-pyridyl	6	92	214−216	–
13	**3c**	**4cm**	2-furfuryl	4	86	224−226	226−228[106]
14	**3c**	**4cn**	$CH_3(CH_2)_2$	4	85	174−176	172−174[108]
15	**3c**	**4co**	$(CH_3)_2CH$	6	84	155−157	154−156[74]
16	**3c**	**4cp**	2-$NO_2C_6H_4$	6	91	221−222	222−223[70]
17	**3c**	**4cq**	2-ClC_6H_4	7	88	215−217	217−218[71]
18	**3c**	**4cr**	3-BrC_6H_4	6	86	227−228	228−230[111]
19	**3d**[c]	**4da**	4-ClC_6H_4	14	86	236−238	234−237[109]
20	**3d**[d]	**4db**	4-FC_6H_4	12	90	194−196	–
21	**3d**[d]	**4dc**	4-CN−C_6H_4	13	91	202−204	–
22	**3d**[d]	**4dd**	2-$NO_2C_6H_4$	14	83	208−209	–

[a]Reaction conditions: aldehyde (**1**; 1 mmol), malononitrile (**2**; 1.1 mmol), dimedone (**3c**) or barbuturic acid (**3d**)[c] or *N*,*N*-dimethylbarbuturic acid (**3d**)[d] (1 mmol) and 10 mol % urea as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

(%) for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.18; H, 5.81; N, 14.21.

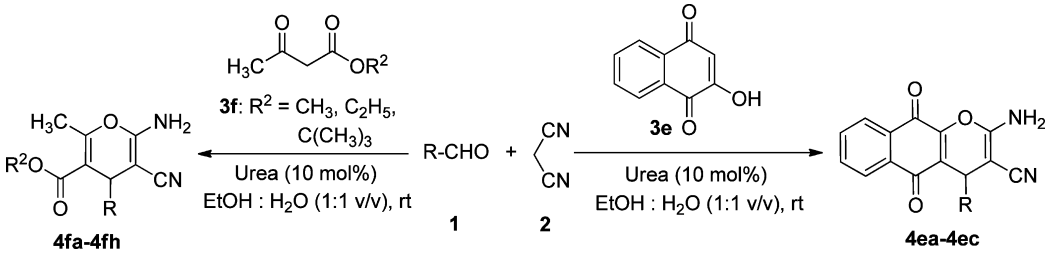
*7-Amino-1,3-dimethyl-5-(2-nitrophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (**4dd**).* White solid. Yield 83%. Mp: 208−209 °C. IR (KBr) ν_{max}/cm^{-1}: 3389, 3288, 3281, 3178, 3086, 2957, 2338, 2193, 1686, 1665, 1587, 1485, 1391, 1367, 1310, 1182, 1067, 1045, 960, 942, 921, 789, 748, 692. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.85 (1H, d, J = 8.0 Hz, aromatic H), 7.65 (1H, t, J = 8.0 Hz, aromatic H), 7.53 (1H, br s, aromatic H), 7.51 (2H, s, NH_2), 7.45 (1H, t, J = 8.0 and 7.6 Hz, aromatic H), 5.13 (1H, s, CH), 3.35 (3H, s, CH_3), 3.02 (3H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 160.95, 158.76, 151.57, 150.33, 149.50, 138.87, 133.84, 131.19, 128.47, 124.08, 118.88, 88.78, 57.07, 31.21, 29.57, 28.02. TOF-MS: 378.0814 [M + Na]$^+$. Elemental analysis: Calcd. (%) for $C_{16}H_{13}N_5O_5$: C, 54.09; H, 3.69; N, 19.71. Found: C, 54.11; H, 3.71; N, 19.69.

*2-Amino-4-(furan-2-yl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (**4eb**).* Blackish solid. Yield 91%. Mp: 266−268 °C. IR (KBr) ν_{max}/cm^{-1}: 3406, 3198, 3070, 2332, 2197, 1794, 1663, 1643, 1580, 1516, 1441, 1352, 1279, 1051, 997, 872, 787, 764, 723, 662, 573. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.27 (1H, d, J = 8.4 Hz, aromatic H), 8.13 (1H, d, J = 7.2 Hz, aromatic H), 8.06 (1H, d, J = 7.2 Hz, aromatic H), 7.99 (1H, d, J = 7.2 Hz, aromatic H), 7.93 (2H, d, J = 7.2 Hz, aromatic H), 7.85 (2H, br s, NH_2), 7.79 (1H, d, J = 8.0 Hz, aromatic H), 6.17 (1H, s, CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 185.08, 181.67, 160.02, 135.28, 134.88, 133.72, 133.63, 132.28, 130.95, 127.06, 126.48, 126.35, 125.82, 124.25, 124.19, 121.64, 111.40, 60.78. TOF-MS: 341.0541 [M + Na]$^+$. Elemental analysis: Calcd. (%) for $C_{18}H_{10}N_2O_4$: C, 67.92; H, 3.17; N, 8.80. Found: C, 67.98; H, 3.13; N, 8.82.

*Methyl 6-amino-5-cyano-4-(4-cyanophenyl)-2-methyl-4H-pyran-3-carboxylate (**4fa**).* White solid. Yield 91%. Mp: 198−200 °C. IR (KBr) ν_{max}/cm^{-1}: 3352, 3304, 3175, 3074, 2916, 2372, 2191, 1676, 1591, 1533, 1523, 1466, 1364, 1279, 1236, 1194, 1103, 974, 943, 868, 829, 793, 733, 663, 619, 565. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.72 (2H, d, J = 8.0 Hz, aromatic H), 7.43 (2H, d, J = 7.2 Hz, aromatic H), 6.62 (2H, s, NH_2), 4.52 (1H, s, CH), 3.65 (3H, s, OCH_3), 2.46 (3H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 164.44, 157.44, 156.80, 148.79, 130.94 (2C), 126.87 (2C), 118.06, 117.30, 108.94, 105.04, 55.95, 50.21, 37.80, 17.32. TOF-MS: 318.0857 [M + Na]$^+$. Elemental analysis: Calcd. (%) for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.09; H, 4.42; N, 14.26.

*tert-Butyl 6-amino-5-cyano-2-methyl-4-(4-nitrophenyl)-4H-pyran-3-carboxylate (**4fg**).* White solid. Yield 87%. Mp: 209−211 °C. IR (KBr) ν_{max}/cm^{-1}: 3406, 3325, 3209, 2972, 2341, 2195, 1681, 1670, 1591, 1506, 1348, 1267, 1169, 953, 837, 619, 488. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 8.22 (2H, d, J = 8.4, aromatic H), 7.44 (2H, d, J = 8.4 Hz, aromatic H), 7.05 (2H, s, NH_2), 4.42 (1H, s, CH), 2.32 (3H, s, CH_3), 1.21 (9H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.71, 158.86, 157.57, 153.09, 146.75, 128.98 (2C), 124.17 (2C), 119.80, 107.39. 81.30, 56.45, 39.28, 27.87 (3C), 18.54. TOF-MS: 380.1226 [M + Na]$^+$. Elemental analysis: Calcd. (%) for $C_{18}H_{19}N_3O_5$: C, 60.50; H, 5.36; N, 11.76. Found: C, 60.52; H, 5.39; N, 11.74.

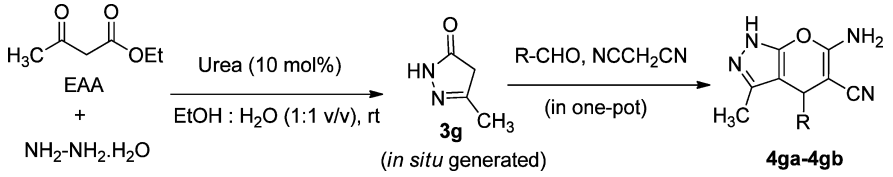
Table 4. Synthesis of 2-Amino-3-cyano-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromenes (4ea−4ec) and 2-Amino-3-cyano-4*H*-pyrans (4fa−4fh)



entry	activated C−H acid	R^2	product	substituent (R)	time (h)	yield (%)[a,b]	melting point (°C) found	melting point (°C) reported
1	**3e**	–	**4ea**	3-$NO_2C_6H_4$	6	84	248−249	248−250[110]
2	**3e**	–	**4eb**	2-furfuryl	7	91	266−268	–
3	**3e**	–	**4ec**	4-pyridyl	9	88	272−274	–
4	**3f**	$-CH_3$	**4fa**	4-CN−C_6H_4	9	91	198−200	–
5	**3f**	$-CH_3$	**4fb**	4-$NO_2C_6H_4$	10	90	192−194	–
6	**3f**	$-CH_3$	**4fc**	3-$NO_2C_6H_4$	8	92	204−206	–
7	**3f**	$-CH_3$	**4fd**	2-$NO_2C_6H_4$	11	86	200−202	–
8	**3f**	$-C_2H_5$	**4fe**	4-CN−C_6H_4	7	87	170−172	–
9	**3f**	$-C_2H_5$	**4ff**	3-$NO_2C_6H_4$	5	92	174−176	171−173[111]
10	**3f**	$-C(CH_3)_3$	**4fg**	4-$NO_2C_6H_4$	9	87	209−211	–
11	**3f**	$-C(CH_3)_3$	**4fh**	3-$NO_2C_6H_4$	6	92	188−190	–

[a]Reaction conditions: aldehyde (**1**; 1 mmol), malononitrile (**2**; 1.1 mmol), 2-hydroxynaphtahquinone (**3e**)/alkylacetoacetate (**3f**) (1 mmol), and 10 mol % urea as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

Table 5. Four-Component Synthesis of 1,4-Dihydropyrano[2,3-*c*]pyrazoles (4ga−4gb)



entry	activated C−H acid	product	substituent (R)	time (h)	yield (%)[a,b]	melting point (°C) found	melting point (°C) reported
1	**3g**	**4ga**	3-$NO_2C_6H_5$	8	86	194−196	193−195[78]
2	**3g**	**4gb**	4-ClC_6H_4	12	84	233−235	234−236[78]

[a]Reaction conditions: ethylacetoacetate (EAA; 1 mmol), hydrazine hydrate (1 mmol), aldehyde (1 mmol), malononitrile (1.1 mmol), and 10 mol % urea as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

*6-Amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]-pyrazole-5-carbonitrile (**4gb**).* White solid. Yield 84%. Mp: 233−235 °C. IR (KBr) ν_{max}/cm^{-1}: 3392, 3345, 3288, 3196, 3182, 3018, 2960, 2338, 2185, 1612, 1595, 1493, 1398, 1389, 1308, 1186, 1171, 1055, 1043, 945, 874, 746, 735, 609. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 12.14 (1H, s, NH), 7.38 (2H, d, J = 8.4 Hz aromatic H), 7.20 (2H, d, J = 8.4 Hz, aromatic H), 6.93 (2H, s, NH_2), 4.64 (1H, s, CH), 1.79 (3H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 161.33, 155.13, 143.89, 136.10, 131.65, 129.77 (2C), 128.87 (2C), 121.05, 97.61, 57.20, 35.99, 10.14. TOF-MS: 309.0513 $[M+Na]^+$. Elemental analysis: Calcd. (%) for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found C, 58.61; H, 3.89; N, 19.52.

*2-Amino-4-(4-(2-amino-3-cyano-5-oxo-4,5-dihydropyrano[3,2-c]chromen-4-yl)phenyl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (**5a**).* White solid. Yield 86%. Mp: >280 °C. IR (KBr) ν_{max}/cm^{-1}: 3377, 3277, 3269, 3178, 2326, 2197, 1695, 1603, 1587, 1383, 1188, 1051, 964, 735, 554. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.90 (2H, d, J = 6.8 Hz, aromatic H), 7.70 (2H, br s, aromatic H), 7.47 (2H, d, J = 10.8 Hz, aromatic H), 7.42 (3H, br s, aromatic H), 7.31 (3H, d, J = 6.0 Hz, aromatic H), 7.26 (4H, br s, NH_2), 4.44 (2H, s, CH). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 158.97, 158.40 (2C), 153.84, 152.53, 143.73, 133.35 (2C), 128.94 (4C), 128.03 (4C), 127.55 (2C), 125.09 (2C), 122.91 (2C), 119.65 (2C), 116.96, 113.34 (2C), 104.39, 58.40 (2C), 37.37 (2C). TOF-MS: 577.0398 $[M + Na]^+$. Elemental analysis: Calcd. (%) for $C_{32}H_{18}N_4O_6$: C, 69.31; H, 3.27; N, 10.10. Found: C, 69.28; H, 3.27; N, 10.07.

*2-Amino-4-(4-(2-amino-3-cyano-7-methyl-5-oxo-4,5-dihydropyrano[4,3-b]pyran-4-yl)phenyl)-7-methyl-5-oxo-4,5-dihydropyrano[4,3-b]pyran-3-carbonitrile (**5b**).* White solid. Yield 90%. Mp: >280. IR (KBr) ν_{max}/cm^{-1}: 3371, 3188, 2864, 2204, 1709, 1688, 1595, 1373, 1256, 1188, 1151, 1038, 955, 822, 791, 548. ^{1}H NMR (400 MHz, DMSO-d_6) δ/ppm: 7.91 (2H, d, J = 6.8 Hz, aromatic H), 7.47 (2H, d, J = 7.2 Hz, aromatic H), 7.32 (2H, s, NH_2), 7.19 (1H, s, NH_2), 7.12 (1H, s, NH_2), 6.29 (1H, s, CH), 6.26 (1H, s, CH), 4.42 (1H, s, CH), 4.25 (1H, s, CH), 2.22 (6H, s, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ/ppm: 163.76, 163.38, 161.81, 161.51, 159.04, 158.56, 150.69, 142.66, 131.27 (2C), 130.54, 129.19 (2C), 127.95, 119.48, 114.73, 113.71, 101.25, 100.03, 98.44, 81.37, 57.24, 36.83, 36.27, 19.73 (2C). TOF-MS: 505.0395 $[M + Na]^+$. Elemental analysis: Calcd. (%) for $C_{26}H_{18}N_4O_6$: C, 64.73; H, 3.76; N, 11.61. Found: C, 64.69; H, 3.74; N, 11.63.

RESULTS AND DISCUSSION

Herein, we report a facile access of a diverse range of highly functionalized 2-amino-3-cyano-4*H*-pyrans and pyran-annulated

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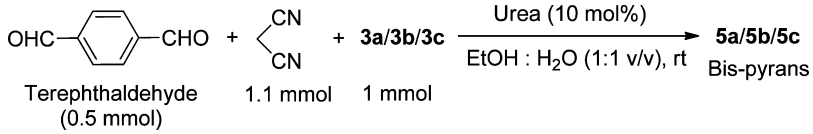
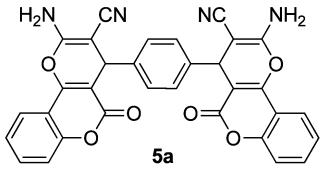
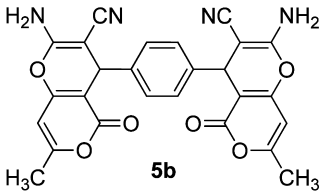
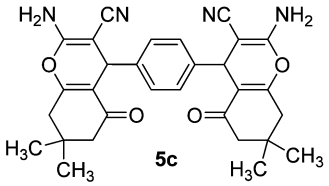
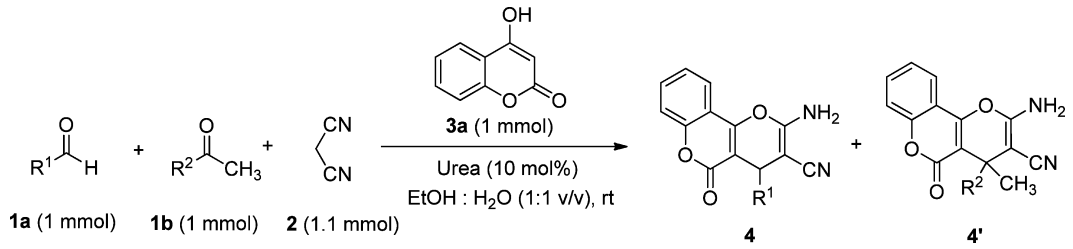
Table 6. Synthesis of Bis-pyrans 5a−5c



Entry	Activated C-H acid	Product	Time (h)	Yield (%)[a,b]	Melting point (^{0}C) Found	Reported
1	**3a**	 **5a**	20.0	86	>280	-
2	**3b**	 **5b**	22.0	90	>280	-
3	**3c**	 **5c**	18.0	92	>280	-

[a]Reaction conditions: terephthaldehyde (0.5 mmol), malononitrile (1.1 mmol), **3a**/**3b**/**3c** (1 mmol), and 10 mol % urea as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

Table 7. Effect of Catalyst on the Substrate Selectivity



entry	R^1	R^2	time (h)	**4** (% yield)[a,b]	**4′** (% yield)[a,b]
1	4-ClC_6H_4	4-ClC_6H_4	8	91	0
2	3-$NO_2C_6H_4$	4-ClC_6H_4	3	95	0
3	$(CH_3)_2CH$	CH_3	16	83	0

[a]Reaction conditions: aldehyde (**1a**; 1 mmol), ketone (**1b**; 1 mmol), malononitrile (**2**; 1.1 mmol), **3a** (1 mmol), and 10 mol % urea as catalyst in 4 mL of aqueous ethanol (1:1 v/v) at room temperature. [b]Isolated yields.

heterocyclic scaffolds, such as 2-amino-3-cyano-pyrano[3,2-*c*]-chromen-5(4*H*)-ones (**4aa**−**4al**), 2-amino-3-cyano-pyrano[4,3-*b*]-pyran-5(4*H*)-ones (**4ba**−**4be**), 2-amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-one (**4ca**−**4cr**), 1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones (**4da**−**4dd**), 2-amino-3-cyano-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromenes (**4ea**−**4ec**), 2-amino-3-cyano-4*H*-pyrans (**4fa**−**4fh**), 1,4-dihydropyrano-[2,3-*c*]pyrazoles (**4ga**−**4gb**) and bis-pyrans (**5a**−**5c**) via multi-component one-pot synthesis from the reaction of aldehydes, malononitrile, and a variety of activated C−H-activated acids in aqueous ethanol at room temperature using commercially available urea as inexpensive and environmentally benign organo-catalyst (Scheme 1).

To optimize the reaction conditions, we first conducted a series of trial reactions with benzaldehyde (**1**; 1 mmol), malononitrile (**2**; 1.1 mmol), and 4-hydroxycoumarin (**3a**; 1 mmol) in the absence or presence of urea/thiourea using water, ethanol, and/or ethanol−water (1:1 v/v) as solvent at room temperature (Table 1). From these preliminary experiments, 10 mol % of urea in aqueous ethanol (1:1 v/v) at room temperature came out as the optimized conditions for the reaction in terms of yield and time (Table 1, entry 6) for the desired product,

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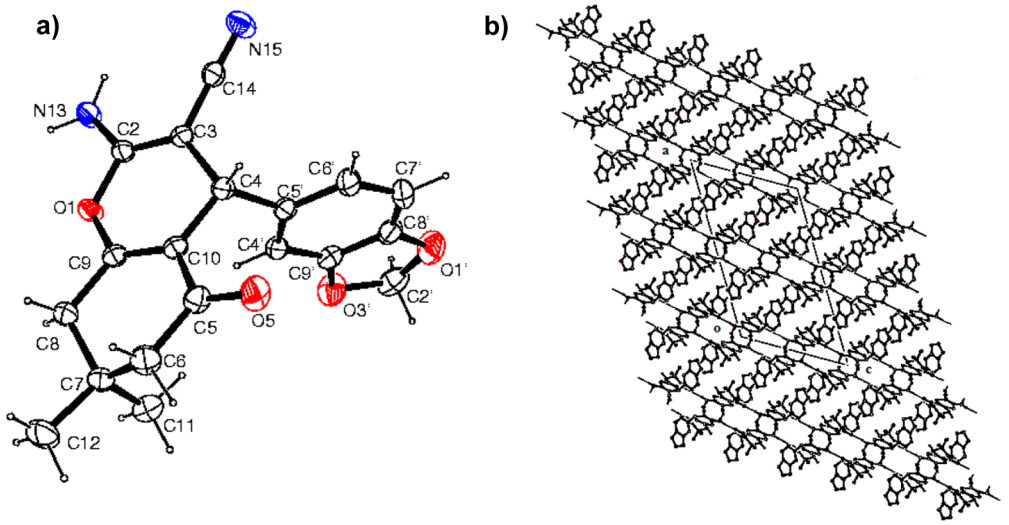


Figure 3. (a) ORTEP diagram of compound **4cj**. (b) Packing arrangement of molecules viewed down the *a*-axis.

2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (**4aa**), which was characterized by its physical and spectral properties.[66]

Under the optimized conditions, the reaction of 4-chlorobenzaldehyde with malononitrile (**2**) and 4-hydroxycoumarin (**3a**) was then carried out, and it furnished the product 2-amino-5-oxo-4-(4-chlorophenyl)-4,5-dihydropyrano[3,2-*c*]-chromene-3-carbonitrile (**4ab**) in 93% yield within 7 h (Table 2, entry 2). To check the generality as well as the effectiveness of our newly developed protocol, a number of aromatic aldehydes having substituents such as hydroxy, methoxy, nitro, halogens and methyl, and aliphatic aldehydes such as butaraldehyde and isobutaraldehyde were reacted with malononitrile and 4-hydroxycoumarin using identical reaction conditions; all of them underwent the reaction smoothly affording the corresponding 2-amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)-ones (**4ac**−**4al**) (Table 2, entries 3−12) in excellent yields (82−97%) at room temperature. To our delight, the reactions attempted by replacing 4-hydroxycoumarin (**3a**) with 4-hydroxy-6-methylpyrone (**3b**) (Scheme 1) also underwent successful condensation to produce the desired 2-amino-3-cyano-pyrano[4,3-*b*]pyran-5(4*H*)-ones (**4ba**−**4be**) in good yields (80−88%) within 3−7 h under the similar reaction conditions at room temperature (Table 2, entries 13−17). Encouraged by these results, we attempted to extend the present protocol using dimedone (**3c**) and barbutaric acid and its *N*,*N*-dimethylderivative (**3d**) as varying C−H-activated acids. These C−H-activated acids underwent smooth reactions as well with diverse aldehydes and malononitrile under the similar reaction conditions (Scheme 1). The desired products, 2-amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-one (**4ca**−**4cr**; Table 3, entries 1−18) and 1*H*-pyrano-[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones (**4da**−**4dd**; Table 3, entries 19−22) were obtained in good to excellent yields (83−96%) with reasonable time frame at room temperature under urea-catalysis (Table 3).

The scope of the present protocol was further investigated with other C−H-activated acidic compounds such as 2-hydroxy-1,4-naphthaquinone (**3e**) and *β*-ketoesters (**3f**). Both the C−H-activated acids **3e** and **3f** underwent smooth condensation under the reaction conditions furnishing the desired products, 2-amino-3-cyano-5,10-dioxo-5,10-dihydro-4*H*-benzo[*g*]chromenes (**4ea**−**4ec**) and 2-amino-3-cyano-4*H*-pyrans (**4fa**−**4fh**), respectively in good yields (84−92%) within reasonable time frame (Table 4). To our delight this reaction protocol was also successfully applied for the synthesis of pyran-annulated heterocyclic scaffolds like 1,4-dihydropyrano[2,3-*c*]pyrazoles (**4ga**−**4gb**; Table 5) via a four-component reaction leading to in situ generation of 3-methyl-1*H*-pyrazol-5(4*H*)-one (**3g**) that eventually undergoes condensation with the aldehydes and malononitrile to afford the products in good yield (84−90%). In addition, bis-pyranization from the reaction between terephthaldehyde, malononitrile and C−H-activated acids (**3a**, **3b**, and **3c**) was also achieved following this protocol (Table 6).

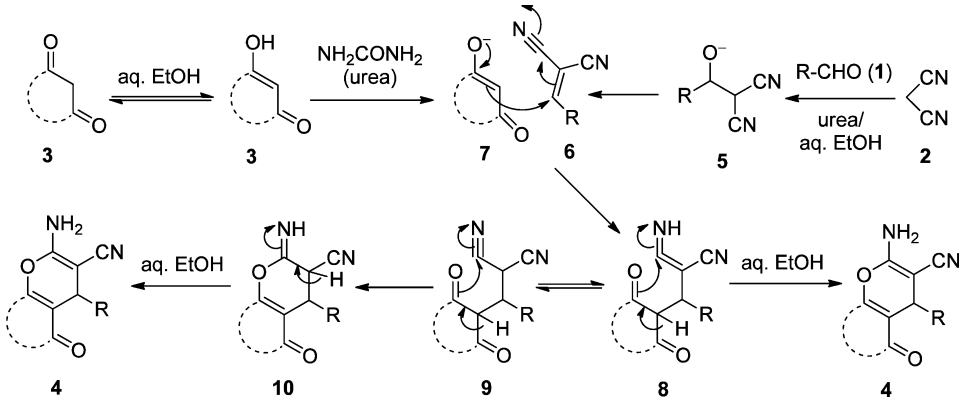
To measure the selectivity of this method, we carried out some competitive reactions for the preparation of pyrano[3,2-*c*]-chromen-5(4*H*)-one from aldehydes in the presence of ketones using 10 mol % of urea as catalyst in aqueous ethanol at room temperature. It is our delight to note that the aldehydes in the presence of ketones selectively underwent condensation with malononitrile and 4-hydroxycoumarine (**3a**) to afford the corresponding 2-amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)-ones (**4**) (Table 7, entries 1−3) in good yields and the starting ketones were recovered intact.

All the products were isolated pure just by washing with aqueous ethanol followed by recrystallization from ethanol; no tedious chromatographic purification was needed. The isolated products were fully characterized on the basis of analytical data and detailed spectral studies including FT-IR, ^{1}H NMR, ^{13}C NMR and TOF-MS. All the known compounds had physical and spectroscopic data identical to the literature values.[61,66,67,69−71,74,78,104−111] Single crystal X-ray analysis for 2-amino-4-(benzo[*d*][1,3]dioxol-5-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**4cj**) (Table 3, entry 10) was also documented in this present paper (Figure 3).[112]

We herein propose a mechanism in Scheme 2 for the formation of pyran-annulated heterocycles under the reaction conditions where urea acts as a base. It is supposed that the Knoevenagel intermediate (**6**) formed in situ is attacked by the enolate of the C−H-activated acid (**7**) giving rise to the adduct **8**/**9** which eventually undergoes ring closure to afford the desired product **4**.

It is worth noting that we reused the filtrate containing residual solvent, catalyst, and substrates obtained upon filtration of the reaction mixture after completion of the reaction up to third run in case of a representative entry (Table 2, entry 1). Addition of reactants directly into the filtrate without adding further catalyst

Scheme 2. Proposed Mechanism for the Synthesis of Pyran-Annulated Heterocycles



and solvent resulted in the formation of expected product **4aa** with slight loss of catalytic activity at least up to third run (with respective isolated yields of 91%, 82%, and 73%). However, each filtrate can only be used for the particular entry due to residual starting materials. We also examined the feasibility of the present method for a somewhat scaled-up (on the gram scale) experiment with benzaldehyde (**1**; 10 mmol), malononitrile (**2**; 10.5 mmol), and 4-hydroxycoumarin (**3a**; 10 mmol) using 10 mol % urea at room temperature in ethanol−water (1:1 v/v); the reaction was found to proceed smoothly affording the desired product, 2-amino-5-oxo-4-phenyl-4,5-dihydropyrano[3,2-*c*]-chromene-3-carbonitrile (**4aa**) in 86% isolated yield within 8 h, almost similarly in all respects with 1 mmol scale entry (Table 2, entry 1). This experiment demonstrated the efficiency of the catalyst for large-scale production as well.

CONCLUSIONS

In conclusion, we have developed a very simple, facile, energy-efficient, and conveniently practical method for easy access to a wide range of pharmaceutically interesting functionalized 2-amino-3-cyano-4*H*-pyrans and pyran-annulated heterocycles in the presence of urea as a novel organo-catalyst via one-pot tandem Knoevenagel−cyclocondensation of aldehydes, malononitrile, and C−H-activated acids in aqueous ethanol at room temperature. Mild reaction conditions, excellent yields, operational simplicity, absence of tedious separation procedures, clean reaction profiles, energy-efficiency, and high atom-economy, as well as the use of inexpensive and environmentally benign catalysts are the key advantages of the present method. Moreover, reusability of the reaction media is an added advantage to this protocol. Keeping in mind that the synthetic importance of such biologically relevant pyran-annulated heterocyclic scaffolds directly relate to medicinal chemistry, the present methodology with mild reaction conditions and operational simplicity offers the possibility of its use with cost-effective and environmentally friendlier ways for large-scale industrial syntheses as well.

ASSOCIATED CONTENT

Supporting Information

Materials and apparatus, general experimental procedure, crystallographic data, spectral data, and respective scanned spectra (^{1}H and ^{13}C NMR) of all the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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NOTE ADDED AFTER ASAP PUBLICATION

This article was published ASAP on November 19, 2013, with an error in Scheme 1 and the Table 3 graphic. The corrected version was published ASAP on December 17, 2013.