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Three-component coupling approach for the synthesis of 4*H*-pyrans and pyran-annulated heterocyclic scaffolds utilizing Ag/TiO_2 nano-thin films as robust recoverable catalyst

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As a segment of ongoing surveys and with the aim of expansion of environmentally benign processes, a series of biologically varied type of substituted 2-amino-3-cyano-4*H*-pyrans and pyran-annulated Scaffolds have been synthesized by tandem Knoevenagel-cyclocondensation of aldehydes, malononitrile, and C-H-activated acidic compounds in aqueous ethanol in the presence of Ag/TiO_2 nano-thin films as an eco-friendly, recyclable, and, robust catalyst at 60°C. The salient features of this protocol are mild reaction conditions, producing target compounds in high yields, short reaction times, high atom economy, eco-friendly catalyst, easy isolation of products and no column chromatographic separation. Also, it is observed that the catalyst is highly stable during the reaction and several reuse times without observable loss in catalytic performance.

Keywords: 2-Amino-3-cyano-4*H*-pyrans, pyran-annulated, aldehydes, malononitrile, C-H-activated acidic compounds, Ag/TiO_2 nano-thin film

4*H*-Pyran and 4*H*-pyran-annulated and their analogues constitute a substantial family of scaffolds distributed throughout nature occurring[1-3] with a wide range of remarkable biological activities that subtend anti-inflammatory[4], antimalarial[5,6], anticancer[7], cytotoxic[8], antimicrobial[9], antihyperglycemic[10], anti-HIV[11-13] and antidyslipidemic[10] apart from being identified as anti-neurodegenerative perturbations such as Huntington's disease, Alzheimer's, Parkinson disease[14], *etc*. In particular, 4*H*-pyran moiety is still being used in the treatment of diverse ailments, like asthma, ischemia, hypertension, and urinary incontinence[15-19]. Some of the naturally occurring bioactive pyran-annulated heterocyclic framework displaying a various type of pharmaceutical potentials have been illustrated in Figure 1 [20-25]. Several approaches have been designed for the synthesis of 4*H*-pyran derivatives like trisodium citrate[26], $H_6P_2W_{18}O_{62}\cdot 18H_2O$ [27], (S)-proline[28], L-Proline[29], TMGT[30], $ZnFe_2O_4$ nanoparticles[31], glycerol[32], (α-Fe_2O_3)-MCM-41-supported)[33], DMAP[34], heteropolyacids[35], basic ionic liquid[36], ionic liquid based on magnetic carbon[37], 2,2,2-trifluoroethanol[38], DBU[39], $CaCl_2$ [40] and urea[41] as catalysts.

In recent times, emergent awareness regarding ecological safety and global warming has created universal interest as to the benefit of renewable sources and decrement of wastage. In this regards, the use of green solvents and catalyst in all phases of chemical construction are considered substantial tools from the sight of green chemistry protocols[42-44]. Worldwide request for environmentally friendly chemical processes, require the design of reclaimable catalysts that provides a practical, inexpensive, operationally straightforward and high yielding approach. From this aspect, nanotechnology has presented nanocatalysts with higher catalytic activity owing to their large surface area, recoverability, small size, and catalyst loading capacity, distinctive electronic, magnetic, optical and thermal properties[45-47]. Furthermore, the active sites on their surfaces are easily available by reactants. Recently, organic synthesis catalyzed by metal/metal oxide nanoparticles has obtained notable importance.

Nowadays, TiO_2 nanoparticles have appeared as a noteworthy multi-functional substance with unique attributes like high stability, long lasting, and the safe and broad-spectrum antibiotic[48]. In particular, TiO_2 nanoparticles have been the center of notice owing to various applications[49] including optical films for photocatalysts[50], fuel cells[51], lithium-ion batteries[52],

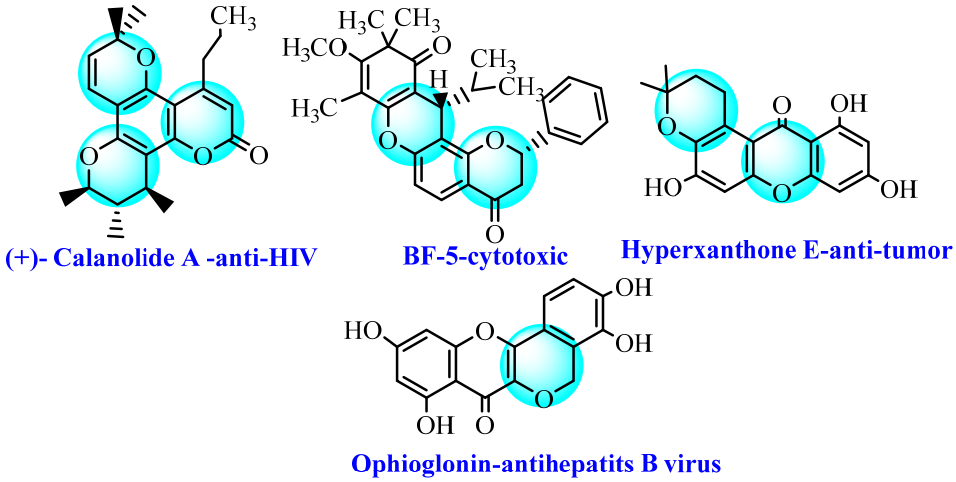


Figure 1 — Some drugs containing pyran core

sensors[53], and semiconductor materials for photochemical virtues[54,55].

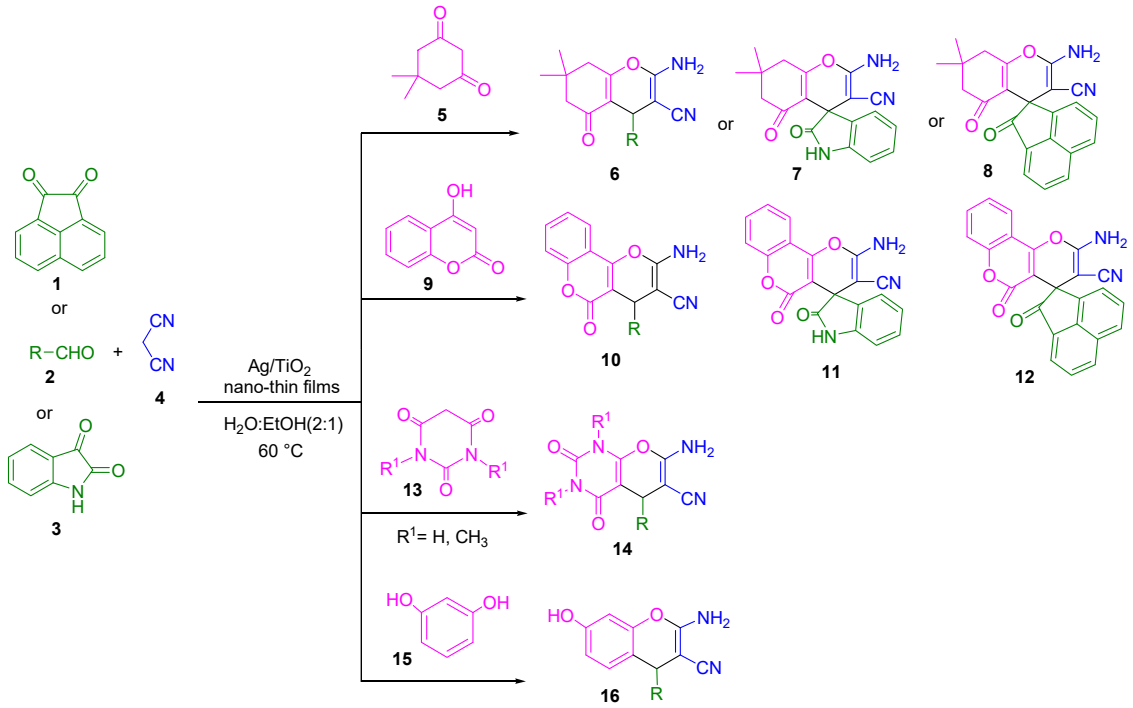
In addition, TiO_2 nanoparticles have been exerted as an eco-friendly catalyst for the synthesis of compound libraries of medicinal scaffolds[55]. Correction of nanocrystalline TiO_2 films by metal doping is progressively being considered to enlarge the photocatalytic proficiency due to increased electron traps and decreased TiO_2 bandgap[56,57]. Noble metal nanoparticles like silver are recognized to depict catalytic, electric, and special optical characters. Accordingly, the infusion of nanoparticles Ag to mesoporous TiO_2 substrate motifs could be exerted as antibacterial materials for medical utilizations and in the water therapy field processes[58].

In view of these important points and continuing our efforts on the development of green catalytic manners for substantial organic conversions[59-67], we aim to report a facile, fast and high yielding synthesis of 2-amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-ones **6**, **7** and **8**, 2-amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)-ones **10**, **11** and **12**, 1*H*-pyrano[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones **14** and 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles **16** by three-component reaction of aldehyde, malononitrile and C−H-activated acids in water medium at 60°C in the presence of Ag ion doped in TiO_2 lattice was occupied as nontoxic, cheap, and readily accessible heterogeneous catalysts (Scheme I). Ag-TiO_2 nanocomposite films were deposited on insides of beakers by spray pyrolysis technique.

Result and Discussion

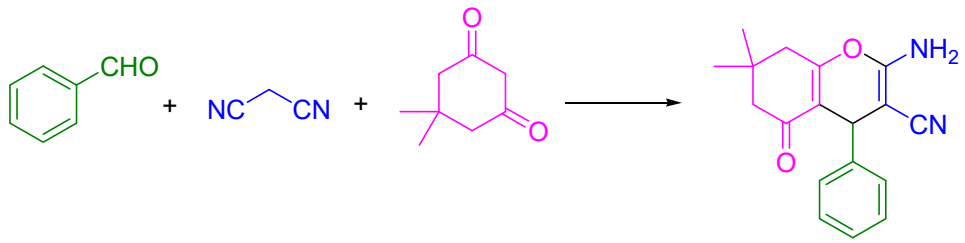
To optimize the reaction conditions, we tentatively considered the reaction between benzaldehyde (1.0 mmol), malononitrile (1.0 mmol) and dimedone (1.0 mmol) as a model reaction using Ag/TiO_2 nano-thin films as a green catalyst for the synthesis of 2-Amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-ones (Scheme I). At the outset, a test reaction was accomplished in the absence of the catalyst at 40°C and offered only 37 % yield of the desired product, as shown in (Table I, entry 1). Then, a brief screening of diverse solvents were afforded (Table I). These studies revealed that the rate 2:1 H_2O/ EtOH is better than other rates. Finally, to investigate the efficacy of reaction temperature, the model reaction was done at different temperatures. The yield growth to 93% when the reaction was carried out at 60 °C temperature (Table I, entry 8). Accordingly, the optimization of reaction conditions was established as indicated in Table I and entry 8.

After establishing the most desirable situations, to study the generality as well as the efficacy of our enlarged strategy, a various aryl aldehydes, Isatine and Acenaphthoquinone **1** were reacted with malononitrile **4** and dimedone **5**; all of them underwent the reaction furnishing the desired 2-Amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-ones (**6-8**) (Table II, entries 1-13) in good to excellent yields (80-93%). To our delight, the reactions endeavored by replacing dimedone (**5**) with 4-hydroxycoumarin (**9**) (Scheme I) also underwent favored condensation to afford the desired 2-Amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)-ones (**10-12**) (Table II, entries 14-26) in good to excellent yields (80-93%) under the analogous reaction conditions, we endeavored to developed the present strategy using barbituric acid and its *N*, *N*-dimethyl derivative (**13**) and resorcinol (**15**) as varying C-H-activated acids. These C-H activated acids underwent reactions as well as with diverse aryl aldehydes and malononitrile under the analogous reaction conditions (Scheme I).



Scheme I — Ag/TiO_2 catalyzed one-pot synthesis of functionalized 2-amino-3-cyano-4*H*-pyrans and pyran-annulated heterocyclic scaffolds

Table I — Optimization of reaction condition using benzaldehyde, malononitrile and dimedone as reactants in the presence Ag/TiO_2 nano-thin films.

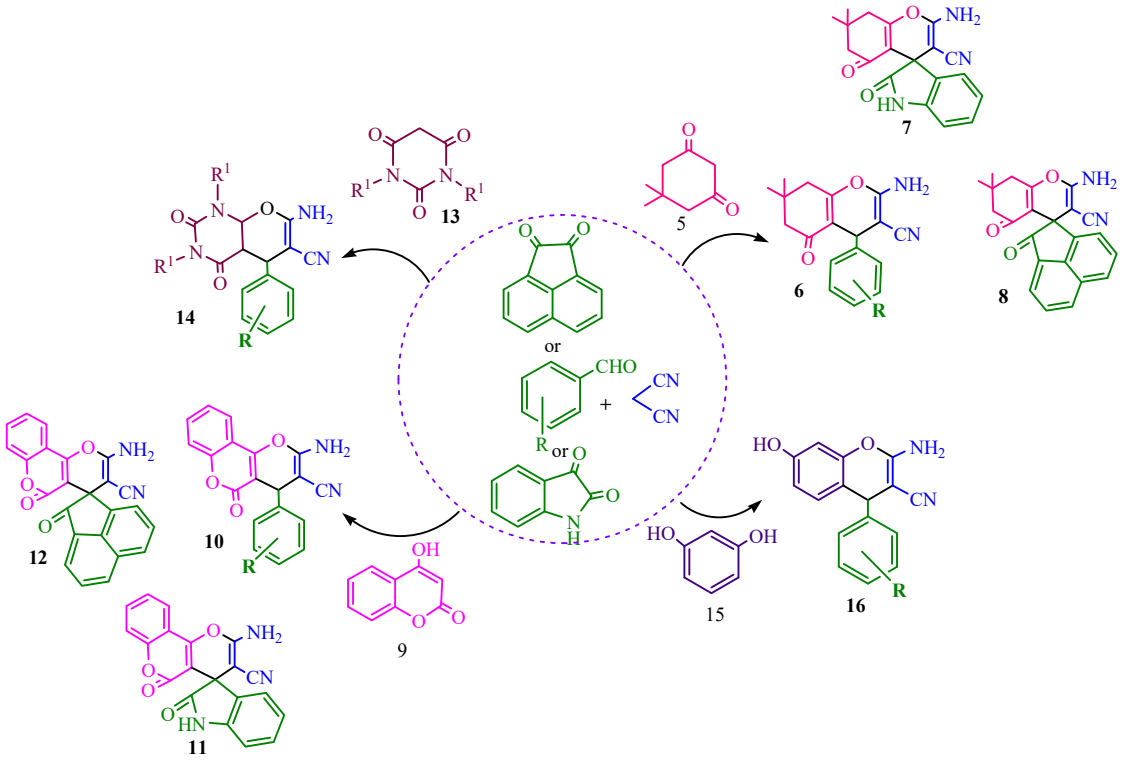


Entry	Temperature (°C)	Catalyst/Solvent	Time (min)	Isolated Yield (%)
1	40	EtOH/-	24h	37
2	40	EtOH/Cat	90	66
3	40	Cat/ H_2O: EtOH (1:1)	75	73
4	40	Cat/ H_2O: EtOH (2:1)	70	78
5	40	Cat/H_2O	75	75
6	r.t	Cat/ H_2O: EtOH (2:1)	24h	20
7	50	Cat/ H_2O: EtOH (2:1)	40	90

The desired products, 1*H*-pyrano-[2,3-*d*]pyrimidine-2,4(3*H*,5*H*)-diones (**14**) (Table II, entries 27-42)and 2-amino-7-hydroxy-4*H*-chromene-3-carbonitriles (**16**) (Table II, entries 43-51) were obtained in good to excellent yields (80-94%) with adequate time under Ag/TiO_2 nano-thin films-catalysis.

A schematic mechanism, representing the role of Ag/TiO_2 nano-thin films in the tandem synthesis of pyran-annulated heterocycles is suggested in Scheme II. Initially, Knoevenagel condensation between aldehyde 2 and malononitrile **4** is accomplished to give α-cyanocinnamonitrile **A**. Next, C-H activated acids **5** C-alkylation carries out an intermediate **B** which subsequently cyclizes *via* nucleophilic attack of O atom on the cyano moiety conformance to protonation and rearrangement to generate desired products.

Table II — Synthesis of pyran-annulated heterocycles — (*Contd.*)

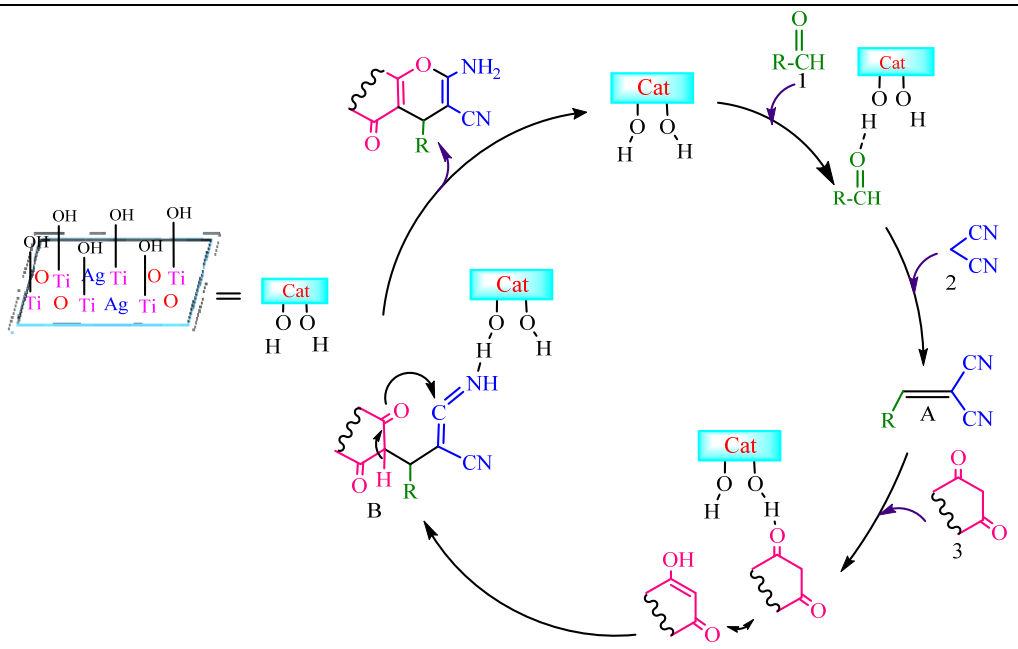


Entry	R	R^1	Product	Time (min)	Yield [a] (%)	m.p. (°C) (Lit. Ref.)
1	H	–	**6a**	20	93	230-232 (225-227) (Ref. 38)
2	2-Cl	–	**6b**	25	83	210-212 (215-217) (Ref. 41)
3	4-Cl	–	**6c**	15	90	208-210 (212-214) (Ref. 41)
4	2-NO_2	–	**6d**	35	89	227-230 (222-223) (Ref. 28)
5	3-NO_2	–	**6e**	30	90	210-213 (205-208) (Ref. 26)
6	4-NO_2	–	**6f**	20	93	183-185 (183-185) (Ref. 41)
7	4-Me	–	**6g**	30	85	208-210 (205-206) (Ref. 41)
8	4-OMe	–	**6h**	30	87	205-207 (200-202) (Ref. 39)
9	2,3-diOMe	–	**6i**	40	80	218-220 (214-216) (Ref. 65)
10	4-OH- 3-OMe	–	**6j**	45	82	228-230 (226-231) (Ref. 64)
11	4-OH	–	**6k**	55	80	206-208 (202-204) (Ref. 39)
12	Isatine	–	**7**	45	87	296-298 (291-293) (Ref. 32)
13	Acenaphthoquinone	–	**8**	50	82	268-270 (268-270) (Ref. 68)
14	H	–	**10a**	25	90	258-260 (256-258) (Ref. 38)
15	2-Cl	–	**10b**	35	86	275-276 (275-277) (Ref. 66)
16	4-Cl	–	**10c**	25	93	263-265 (262-264) (Ref. 41)
17	2,4-diCl	–	**10d**	45	80	258-260 (255-257) (Ref. 27)
18	3-NO_2	–	**10e**	35	85	260-262 (254-256) (Ref. 41)
19	4-NO_2	–	**10f**	30	93	255-257 (258-260) (Ref. 41)
20	4-Me	–	**10g**	40	87	253-255 (257-259) (Ref. 41)
21	2-F	–	**10h**	40	90	222-224 (220-223) (Ref. 64)
22	2,3-diOMe	–	**10i**	60	85	214-216 (216-218) (Ref. 66)
23	4-OH-3-OMe	–	**10j**	40	87	254-257 (255-257) (Ref. 27)
24	4-OH	–	**10k**	40	83	260-263 (262-264) (Ref. 41)
25	Isatine	–	**11**	55	90	275-277 (281-282) (Ref. 32)
26	Acenaphthoquinone	–	**12**	60	85	297-299 (>300) (Ref. 68)
28	2-Cl	H	**14b**	35	85	218-220 (213-215) (Ref. 69)
29	3-Cl	H	**14c**	30	87	260-263 (266-268) (Ref. 40)

(*Contd.*)

Table II — Synthesis of pyran-annulated heterocycles.

Entry	R	R^1	Product	Time (min)	Yield [a] (%)	m.p. (°C) (Lit. Ref.)
30	4-Cl	H	**14d**	20	93	238-240 (236-238) (Ref. 41)
31	2,4-diCl	H	**14e**	40	85	240-242 (241-242) (Ref. 29)
32	3-NO_2	H	**14f**	30	87	269-271 (264-265) (Ref. 40)
33	4-NO_2	H	**14g**	25	94	236-238 (235-236) (Ref. 69)
34	4-CN	H	**14h**	20	88	243-245 (240-241) (Ref. 29)
35	H	CH_3	**14i**	25	92	219-221 (218-220) (Ref. 31)
36	4-F	CH_3	**14j**	25	94	228-230 (227-228) (Ref. 31)
37	4- Cl	CH_3	**14k**	20	93	203-205 (206) (Ref. 31)
38	4-Br	CH_3	**14l**	20	92	231-233 (235) (Ref. 31)
39	4-NO_2	CH_3	**14m**	25	90	210-212 (217-219) (Ref. 31)
40	4-Me	CH_3	**14n**	30	87	215-218 (217-218) (Ref. 31)
41	2-F	CH_3	**14o**	30	87	236-237 (238-239) (Ref. 31)
42	H	–	**16a**	60	92	229-231 (232-233) (Ref. 33)
43	4-Cl	–	**16b**	45	90	162-163 (162-163) (Ref. 33)
44	2-F	–	**16c**	50	87	200-201 (200-202) (Ref. 33)
45	4-F	–	**16d**	45	92	186-187 (186-187) (Ref. 33)
46	4-Me	–	**16e**	60	85	181-182 (182-183) (Ref. 33)
47	4-OMe	–	**16f**	55	88	111-114 (111-112) (Ref. 33)
48	Thiophene-2	–	**16g**	60	89	188-190 (204-205) (Ref. 37)
49	Furan-2-	–	**16h**	60	90	186-189 (189-191) (Ref. 37)
50	Naphtalene-2-	–	**16i**	70	80	228-232 (231-232) (Ref. 36)



Scheme II — The proposed mechanism for the synthesis 4*H*-Pyran and 4*H*-pyran-annulated heterocycles

Ag/TiO_2 nano-thin films entrusted on the insides of beakers could be easily resumed without observable damages in catalytic proficiency. This catalytic system was checked for the condensation of benzaldehyde, malononitrile, and dimedone as a model in ten catalytic runs, and no sensible shift in activity was observed that all derivatives of each reaction were synthesized from only one beaker coated TiO_2 thin film as shown in Figure 2.

Experimental Section

Materials and Methods

Melting points and IR spectra of all compounds were determined using an Electro thermal 9100 apparatus and FTIR-JASCO-460 plus spectrometer. The ^{1}H NMR spectra of known compounds were recorded on a Bruker DRX-300 and 400 Avance instrument in DMSO-d_6 and $CDCl_3$ at 300 and

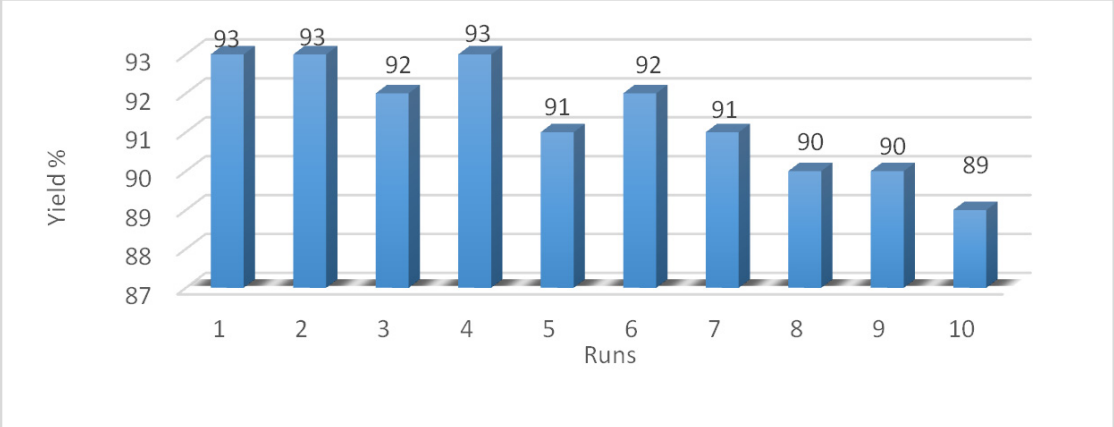


Figure 2 — Recyclability of the catalyst in the synthesis of **4a** over 10 runs

400MHz. The crystal structure was examined using Bruker D8-advanced diffractometer with CuKα radiation in the 10<2θ<70 range, the surface morphology was analyzed using of DME- SPM (2.4.2.1) AFM and optical spectroscopy was performed by T80- PG instrument double beam spectrophotometer and the Photoluminescence analysis (PL) was performed by Perkin Elmers LS-3. All the chemicals were provided from chemical producer Merck (Darmastadt, Germany) and Fluka (Buchs, Switzerland) and used without further purification.

General procedure for preparation of Ag/TiO_2 nano-thin films

For the preparation of spray precursor, titanium isopropoxide (TTIP) was applied as precursor of Ti and Acetyl Acetone (AcAc) along with Ethanol 6% used as a solution. The rate of molar composition of TTIP: AcAc in the spray solution is 1:2. The solution was magnetically stirred for 30 minutes and then silver nitrate was added as the source of Ag in a molar ratio of Ag: TTIP equal to 3:10. In continuation, the final solution was stirred for 30 min. This solution was sprayed onto well cleaned preheated substrates. Before spraying, the microscope glass slides were washed by substrate cleaner and after drying with compressed air, they were put in an ultrasonic cleaner containing acetone for 10 minutes. Catalyst characterization Optical, morphological, and structural properties of catalyst were investigated by XRD, AFM, spectrophotometry and photoluminescent spectroscopy. The outcomes of this research were mentioned in supporting information.

General procedure for the synthesis of 2-amino-3-cyano-7,8-dihydro-4*H*-chromen-5(6*H*)-ones 4 and 2-amino-3-cyano-pyrano[3,2-*c*]chromen-5(4*H*)-ones

A mixture of aromatic aldehydes (1.0 mmol), malononitrile (1.0 mmol) was stirred in $EtOH/H_2O$ (3 mL) in presence of Ag/TiO_2 nanocomposite films which have been deposited inside beakers at RT for about 20 min. After that, C-H activated acid (**5**) (1.0 mmol) was added to the stirred reaction mixture, and the stirring was continued for the appropriate time at 60°C. The progress of the reaction was monitored by thin layer chromatography (TLC). Finally, the reaction mixture was cooled to RT, and then water and ethanol (5 mL) were added to the mixture of reaction and filtered to separate the product **6**. Finally, the crude product was recrystallized from ethanol to afford the pure product. The structure of some purified pyran- annulated heterocyclic scaffold was confirmed by analytical as well as spectral studies including FT-IR and ^{1}H NMR.

Spectral data for the selected compounds

2-Amino-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4*H*-chromene-3-carbonitrile, 6a: White solid. m.p. 230-232°C. IR (KBr): 3395, 3323, 2641, 2199, 1680, 1240 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 3H), 1.14 (s, 3H), 2.23 (d, 1H, J = 16.4 Hz), 2.27 (d, 1H, J = 16.4 Hz), 2.48, (s, 2H), 4.43 (s, 1H), 4.55 (s, 2H), 7.2, 7.3 (m, 5H).

2-Amino-5,6,7,8-tetrahydro-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile, 6f: Yellow solid. m.p. 182-184°C. IR (KBr): 3375,3324, 3182, 2956, 2187, 1674, 1246 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.027 (s, 3H, CH_3), 2.12 (d, 1H, J = 16.0 Hz), 2.27 (d, 1H, J = 16.0 Hz), 2.51 (d, 2H J = 10.0 Hz), 4.36 (s, 1H,CH), 7.19 (s, br, NH_2), 7.44 (d, 2H, Ar, J = 8.0 Hz), 8.16 (d, 2H, Ar, J = 8.0 Hz).

2-Amino-5,6,7,8-tetrahydro-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile, 6g: White solid. m.p. 210-212°C. IR (KBr): 3331, 3318, 2962, 2190, 1680, 1246 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.08 (s, 3H), 1.12 (s, 3H), 2.21 (d, 1H *J* 16.4), 2.24 (d, 1H, *J* = 16.4 hz), 2.30 (s, 3H), 2.46 (s, 2H), 4.38 (s, 1H), 4.57(s, 2H), 7.10 (d, 2H, *J* = 8 Hz), 7.14 (d, 2H, *J* = 8.0 Hz).

2-Amino-5,6,7,8-tetrahydro-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile, 6h: Yellow solid. m.p. 205-207°C. IR (KBr): 3465, 3320, 2955, 2190, 1676, 1247 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.09 (d, 1H, *J* = 18.0 Hz), 2.25 (d, 1H, *J* = 18.0 Hz), 3.37 (d, 2H, *J* = 6.0 Hz), 3.72 (s, 3H, OCH_3), 4.13 (s, 1H, CH), 6.85 (d, $2H_{Ar}$, *J* = 8.0 Hz), 6.97 (br, NH_2), 7.06 (d, 2H, Ar, *J* = 8.0 Hz).

2-Amino-5,6,7,8-tetrahydro-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-4*H*-chromene-3-carbonitrile, 6k: Orange solid. m.p. 206-208°C. IR (KBr): 3285, 3160, 2960, 2185, 1675, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.20-2.29 (dd, 2H, *J* = 16.0 Hz, *J* = 20.0 Hz), 2.41-2.50 (dd, 2H, *J* = 16.0 Hz, *J* = 20.0 Hz), 4.36 (s, 1H, CH), 4.53(s, 2H, NH_2), 5.26 (s, 1H, OH), 6.71-7.28 (m, 4H, Ar).

2-Amino-4,5-dihydro-4-(phenyl)-5-oxopyrano[3,2-c]chromene-3-carbonitrile, 10a: White solid. m.p. 258-260°C. IR (KBr): 3377, 3284, 2922, 2189, 1708, 1380 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.57 (s, 1H, CH), 6.70 (s, 2H, NH_2) 7.26-8.00 (m, 11H, Ar, NH_2).

2-Amino-4,5-dihydro-4-(3-nitrophenyl)-5-oxo-pyrano[3,2-c]chromene-3-carbonitrile, 10e: White solid. m.p. 260-262°C. IR (KBr): 3402, 3322, 2202, 1703, 1380 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.75 (s, 1H, CH), 7.48-8.16 (m, 9H, Ar, NH_2).

2-Amino-4,5-dihydro-4-(2-fluorophenyl)-5-oxo-pyrano[3,2-c]chromene-3-carbonitrile, 10h: White solid. m.p. 220-223°C. IR (KBr): 3400, 3320, 2100, 1750, 1665, 1609, 1528, 1375 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.75 (s, 1H, CH), 7.10-8.39 (m, 10H, Ar, NH_2).

7-Amino-5-(3-nitrophenyl)-2,4-dioxo-1,3,4,4a,5,8a-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-6-carbonitrile, 14f: White solid. m.p. 269-271°C. IR (KBr): 3415, 3311, 3203,3102, 2951, 1710,1536, 1280 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.50 (s, 1H, CH), 7.28 (s, 2H, NH_2), 7.62 (t, 1H, *J* = 7.8, Ar), 7.76 (d, 1H, *J* = 7.2, Ar), 8.03-8.13 (m, 2H, Ar), 11.12 (br, 1H, NH), 12.17 (br, 1H, NH).

7-Amino-5-(4-nitrophenyl)-2,4-dioxo-1,3,4,4a,5,8a-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-6-carbonitrile, 14g: White solid. m.p. 236-238°C. IR (KBr): 3360, 3183, 2856, 2196, 1720,1348, 1282 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.48 (s,1H,CH), 7.38 (s, 2H, NH_2) 7.60-8.16 (m, 4H, Ar), 11.13 (br, 1H, NH), 12.19 (br, 1H, NH).

7-Amino-5-(2-fluorophenyl)-1,3-dimethyl-2,4-dioxo-1,3,4,4a,5,8a-hexahydro-2*H*-pyrano[2,3-d]pyrimidine-6-carbonitrile, 14p: White solid. m.p. 236-237°C. IR (KBr): 3360, 3183, 2856, 2196, 1720,1348, 1282 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.10 (s, 3H, CH_3), 3.39 (s, 3H, CH_3), 4.65 (s, 1H, CH), 7.11-7.39 (m, 6H, Ar, NH_2).

2-Amino-7-hydroxy-4-phenyl-4*H*-chromene-3-carbonitrile, 16a: White solid. m.p. 229-231°C. IR (KBr): 3360, 3183, 2856, 2196, 1720,1348, 1282 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.63 (s, 1H, CH), 6.42 (d, 1H, *J* = 2.1 Hz, CH), 6.50 (dd, 1H, *J* = 2.4 Hz, CH), 6.82 (d, 1H, *J* = 8.7 Hz, CH), 6.88 (s, 2H, NH_2), 7.17-7.34 (m, 5H, Ar), 9.70 (s, 1H, OH).

2-Amino-4-(2-fluorophenyl)-7-hydroxy-4*H*-chromene-3-carbonitrile, 16c: White solid. m.p. 200-201°C. IR (KBr): 3360, 3183, 2856, 2196, 1720, 1348, 1282 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.71 (s, 1H, CH), 6.45 (d, 1H, *J* = 2.4, CH), 6.53 (dd, 1H, *J* = 2.4 Hz, CH), 6.85 (d, 1H, *J* = 8.4 Hz, CH), 6.95-7.40 (m, 6H, Ar, NH_2), 9.76 (s, 1H, OH).

Concusion

Within this article, we have constructed a series of variety pharmaceutically functionalized 4H-pyrans and pyran-annulated skeletons *via* easy, facile, green, and conveniently practical procedure in the presence of Ag/TiO_2 nano-thin films as an eco-compatibility catalyst, through one-pot tandem Knoevenagel-cyclocondensation of aldehydes, malononitrile, and C−H-activated acids in aqueous ethanol at 60 °C. Mild reaction situations, high yields, lack of boring separation procedures and high atom-economy, moreover the application of cheap and the reusability of the catalyst are the key advantages of the present procedure.

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