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Graphical Abstract

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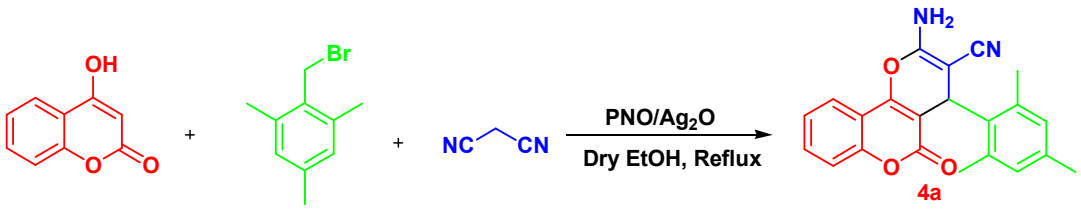

One pot synthesis of pyran-based heterocycles from benzyl halides as key reagents.

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Abstract

Pyridine *N*-oxide and silver oxide have been demonstrated to be an efficient and mild reagent for the one pot synthesis of pyran analogues from a variety of benzyl halides. Benzyl halides are oxidized *in situ* to aldehydes, which in turn undergo a three-component reaction with malanonitrile/ethylcyanoacetate and α-hydroxy C-H acids to yield pyran analogues. The attractive features of this process are mild reaction conditions, short reaction times, broad functional group tolerance, easy isolation of products and excellent yields. Thus, the current method is utilizing benzyl halides as key reagents instead of benzaldehydes.

Keywords: pyran, chromene, pyridine *N*-oxide and silver oxide

Introduction

Multi-component reactions (MCRs) have emerged as an attractive and powerful tool for organic synthesis compared to multistep reactions due to the creation of several new bonds in a one-pot reaction, least number of reaction and purification steps, shorter reaction time, high atom economy, simplicity, avoidance

of time consuming protection and de protection process. Therefore, industrial and academic research groups have continuously focused on the use of one-pot multicomponent reactions to synthesize a wide range of products.[1-3]

The synthesis of pyran analogues is an important synthetic reaction as these scaffolds are found to be a very important core in numerous synthetic, pharmaceutical and a wide variety of biologically active compounds.[4,5] A large number of compounds bearing pyran scaffolds have entered preclinical and clinical trials over the last few years. Many commercially available drugs (Figure 1) including Uvafzlelin (antimicrobial against gram-positive and acid-fast bacteria), Acronycine (to treat colon and ovary cancer), Erysenegalensein C (used in the treatment of stomach pain, female infertility and gonorrhoea), Vitamin E (antioxidant activity), Cromakalim (antihypertensive), Tephrosin (to cure lung cancer) and Kojic acid (antibiotic) are derived from pyran core entities.[6] Pyran moieties are also important as antitumor[7], antagonism of L-type Ca^{+2} channels[8], anticancer[9], antimycobacterial[10], antimicrobial[11] and antileishmanial[12]. Hence, the synthesis of pyran has evoked much attention, as a result of which a variety of synthetic methodologies have been reported[13]. The most important approaches are: (i) one-pot condensation aromatic aldehydes, malanonitrile/ethylcyanoacetate and α-hydroxy C-H acids.[14] (ii) four-component reactions of arylamine, acetylenedicarboxylate, aromatic aldehydes and cyclic 1,3-diketones[15] (iii) intramolecular alkoxycarbonylative annulation.[16] Other methods have also been developed within the last three decades.[17] In the past years, a few methods have described the one-pot multicomponent synthesis of pyran based on catalysts such as $ZnFe_2O_4$,[18] cellulose-perchloric acid,[19] meglumine,[20] per-6-amino-β-cyclodextrin,[21] nickel nano particles,[22] DBU,[23] $Fe(HSO_4)_3$,[24] $Ce(SO_4)_2.4H_2O$,[25] and ionic liquid[26] from the reaction of aromatic aldehydes,

malanonitrile/ethylcyanoacetate and α-hydroxy C-H acids. However, these methods have limitations in terms of the use of excess amounts of expensive catalysts, product diversity and yields. Hence, the development of a simple and high yielding environmentally benign protocol for the one-pot multicomponent synthesis of pyran scaffolds is still warranted.

In continuation of our work on the development of useful synthetic methodologies,[27, 28] in this study we report the use of pryridine *N*-oxide (PNO) and Ag_2O as an oxidizing and cyclising agent for the synthesis of pyran analogues under mild conditions. PNO and Ag_2O function as oxidizing agent offering several advantages such as high yields and purity, low toxicity, broad functional group tolerance and easy work up when compared to traditional reagents. Though, PNO and Ag_2O has been identified as an oxidizing agent,[29] the wider scope and synthetic utility of this reagent for oxidation, condensation and cyclisation has not been explored.

Here, we report a novel, direct approach for synthesis of pyran analogues starting from various benzyl halides, malanonitrile/ethylcyanoacetate and α-hydroxy C-H acids without the need for an additional base. The tandem process involves oxidation, condensation and cyclisation under mild condition at 70 ^{o}C .

First, the reaction of 4-hydroxy coumarin, mesitylmethyl bromide and malanonitrile was selected as the model reaction for the optimization of the reaction conditions (Scheme 1). It was hypothesized that the careful judgment of pyridine *N*-oxide and Ag_2O might efficiently oxidizes benzyl halide in to the benzaldehyde followed by condensation with active methylene compounds and cyclization with α-hydroxy C-H acids in one pot.

Results and discussion

A preliminary examination showed that PNO-Ag_2O in dry ethanol, among several other solvents, effectively oxidized, condensed and cyclized the model reaction. Upon varying the temperature of the reaction from 30 to 70 ^oC, the best yield of 4a (Table 1, entry 6) was obtained at 70 ^oC. Further increase of the temperature, neither increased the yield nor shortened the reaction time. The time taken to achieve complete conversions (monitored by TLC) and the isolated yields are recorded in Table 2. Of all the reactions using different quantities of reactant, the best results were obtained using a 1.0: 1.0: 1.0: 1.2: 1.2 ratios of 4-hydroxy coumarin, mesitylmethyl bromide, malanonitrile, pyridine *N*-oxide and Ag_2O respectively. When the benzene ring is substituted by highly electron donating groups, the reaction requires an excess of pyridine N-oxide (1.2 equiv) during a shorter time to give good yields of aldehyde. When a mixture of 4-hydroxy coumarin, mesitylmethyl bromide, malanonitrile, pyridine *N*-oxide and Ag_2O respectively in dry ethanol was refluxed at 70 ^oC for 45 min, the fused heterocyclic product, 2-amino-5-oxo-4-(2,4,6-trimethyl-phenyl)-4*a*,10*b*-dihydro-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (4a) was obtained in excellent yield (85%).

The role of the solvent on the synthesis of pyran analogues was, then, studied and the results are depicted in Table 1. Replacing ethanol by acetonitrile gave the product in high yield (entry 5) albeit lower than that obtained in ethanol (entry 6). The use of other solvents such as dioxane, chloroform, acetone, THF and methanol afforded the desired product in lower yields (23–50%, entries 3, 4, 7, 8 and 9), while DCM and toluene produced traces of yields (entries 1 and 2). The optimized conditions were established with ethanol as the solvent, a reaction

temperature of 70 ^{o}C and a time of 45 min. This remarkable activation in the reaction rate prompted us to explore the potential of this protocol for the synthesis of a variety of pyran analogues and the results are summarized in Table 2. All the aforementioned reactions proceeded expeditiously and delivered good to excellent product yields accommodating a wide range of α-hydroxy C-H acids. The overall yield ranged from 89% for 2-amino-4-(2,6-dichlorophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4b) (entry 2) to 72% for ethyl 2-amino-4-mesityl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4l) (entry 12).

A probable mechanistic pathway for the formation of pyran analogues is outlined in Figure 2, which is analogous to the established mechanism reported in the literature.[30-33] In the first step, silver oxide assists the heterolysis of the carbon–halogen bond in the substitution reaction with pyridine *N*-oxide. The resulting silver oxide ion from the reaction between halogen and silver oxide then acts as the base in the elimination reaction to aldehydes giving pyridine which in turn would able to base catalyse condensation between aldehyde and malanonitrile gives the cyanocinnamonitrile. The third step is the Michael addition of the enolizable component on the cyanocinnamonitrile, followed by cyclization and final tautomerization in the presence of pyridine to afford the desired product.

Conclusion

We have developed an efficient and a novel one pot strategy for the synthesis of pyran analogues by *in situ* oxidation of benzyl halide into benzaldehyde followed by the three component reaction of aldehyde, malanonitrile/ethylcyanoacetate and α-hydroxy C-H acids in excellent yields.

Tandem nature, mild conditions, simple and convenient work-up are the main advantage of this reaction. This protocol is also applicable to the broad range of substrates.

Experimental

General information:

The melting points were determined by the open capillary method using an electric melting point apparatus and are uncorrected. The IR spectra were recorded on a Agilent Cary 630 FT-IR Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO and CDCl3 as a solvents and TMS as the internal standard. The chemical shifts are expressed in δ ppm. The mass spectrum was recorded on Thermo LCQ Fleet. The purity of the compounds was checked by TLC. The elemental analyses were carried out using an Elemental Vario Micro Cube CHNS Rapid Analyzer. All the compounds gave satisfactory elemental analysis.

Typical procedure for the synthesis of 2-amino-5-oxo-4-(2,4,6-trimethyl-phenyl)-4*a*,10*b*-dihydro-4*H*,5*H*-pyrano[3,2-*c*]chromene-3-carbonitrile (4a)

Silver oxide (340 mg, 1.47 mmol) was added to a solution of 4-hydroxycoumarin (200 mg, 1.23 mmol), mesitylmethyl bromide (262 mg, 1.23 mmol), malanonitrile (81 mg, 1.23 mmol) and pyridine *N*-oxide (140 mg, 1.47 mmol) in dry ethanol (10 mL) in a round-bottomed flask fitted with a reflux condenser and a guard tube. The resulting reaction mixture was heated at 70 ^{o}C in an oil bath for 45 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool to room

temperature. The solid was collected by filtration at pump, washed with cold ethanol and recrystallised from ethanol to obtain pure product.

2-Amino-4-mesityl-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4a)

White solid; mp 241-243 ^{o}C; IR (ATR, cm^{-1}): 3394 (NH_2), 2018 (CN), 1706 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08 (s, 3H, -CH_3), 2.22 (s, 3H, -CH_3), 2.95 (s, 3H, -CH_3), 4.75 (s, 2H, NH_2, D_2O Exchangeable), 5.20 (s,1H, Pyran-H), 6.72-7.79 (m, 6H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 19.3, 21.2, 21.7, 31.6, 77.1, 77.4, 77.7, 104.5, 113.0, 117.4, 118.3, 122.6, 124.8, 130.2, 131.9, 133.0, 133.3, 136.7, 137.4, 138.2, 153.0, 153.9, 157.3, 160.1 ppm; Anal. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82; found: C, 73.62; H, 5.01; N, 7.76%.

2-Amino-4-(3-cyanophenyl)-5-oxo-4,5-dihydropyrano[3,2-*c*]chromene-3-carbonitrile (4c)

White solid; mp 263-265 ^{o}C; IR (ATR, cm^{-1}): 3396 (NH_2), 2233, 2201 (CN), 1720 (C=O) cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.68 (s, 1H, Pyran-H), 5.11 (s, 2H, -NH_2), 6.99-7.65 (m, 8H, Ar-H) ppm; ^{13}C NMR (400 MHz, DMSO): δ = 36.5, 57.0, 102.6, 111.3, 113.0, 116.5, 118.6, 118.9, 122.5, 124.5, 129.5, 130.9, 131.4, 132.8, 132.9, 144.8, 152.2, 153.9, 157.9, 159.5 ppm; Anal. Calcd for $C_{20}H_{11}N_3O_3$: C, 70.38; H, 3.25; N, 12.31 found: C, 70.02; H, 3.21; N, 12.21%.

2-Amino-4-(3-cyanophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4h)

White solid; mp 210-212 ^{o}C; IR (ATR, cm^{-1}): 3409 (NH_2), 2207, 2182 (CN), 1703 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 3H,-CH_3), 1.11 (s, 3H, -CH_3), 2.23 (q , 2H, J = 4 Hz, -CH_2), 2.48 (m, J = 4Hz, 2H, -CH_2), 4.44 (s, 1H, Pyran-H), 4.68 (s, 2H, -NH_2), 7.26-7.56 (m, 4H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 28.1, 29.2, 32.6, 35.0, 41.0, 51.0, 56.6, 113.1, 116.2, 117.3, 121.0, 122.5, 128.6, 132.5, 137.3, 144.1, 155.3, 161.9, 196.3 ppm; Anal. Calcd for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16 found: C, 71.28; H, 5.31; N, 13.01%.

Ethyl 2-amino-4-mesityl-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carboxylate (4l)

White solid; mp 261-263 ^{o}C; IR (ATR, cm^{-1}): 3415 (NH_2), 1710 (C=O), 1685 (ester C=O) cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 3H, -CH_3), 1.09 (s, 3H, -CH_3), 1.23 (t, 3H, J = 4Hz, -CH_3), 2.14 (s, 3H,-CH_3), 2.18 (m, 5H, -CH_3 and CH_2), 2.35 (m, 2H, -CH_2), 2.57 (s, 3H, -CH_3), 3.72 (q, J = 8 Hz, 2H, -CH_2), 4.49 (s, 2H, -NH_2), 4.93 (s, 1H, Pyran-H),6.70 (s, 1H, Ar-H), 6.84 (s, 1H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.6, 19.6, 21.2, 21.6, 28.5, 29.1, 30.5, 32.4, 41.0, 51.2, 61.3, 80.0, 117.1, 130.0, 131.7, 134.6, 136.4, 136.7, 138.0, 157.7, 161.7, 168.7, 196.8 ppm; Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.04; H, 7.62; N, 3.65 found: C, 71.93; H, 7.41; N, 3.24%.

Ethyl 6-amino-5-cyano-4-(3-cyanophenyl)-2-methyl-4*H*-pyran-3-carboxylate (4r)

White solid; mp 192-194 ^{o}C; IR (ATR, cm^{-1}): 3415 (NH_2), 2236, 2196 (CN), 1689 (C=O) cm^{-1} ; ^{1}H NMR (400 MHz, DMSO): δ = 2.49 (m, 3H, -CH_3), 3.26 (s, 3H, -CH_3), 3.96 (m, 2H, -CH_2), 4.39 (s, 1H, Pyran-H) 6.97 (s, 2H, -NH_2), 7.49-7.70 (m, Ar-H, 4H) ppm; ^{13}C NMR (400 MHz, DMSO): δ = 13.6, 18.2, 38.4, 56.4, 60.1, 105.9, 111.2, 118.6, 119.3, 129.7, 130.6, 130.8, 132.2, 146.6, 157.7, 158.4, 165.0 ppm; Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58 found: C, 65.93; H, 4.52; N, 13.32%.

Ethyl 6-amino-5-cyano-4-(2,6-dichlorophenyl)-2-methyl-4*H*-pyran-3-carboxylate (4s)

White solid; mp 146-148 ^{o}C; IR (ATR, cm^{-1}): 3457 (NH_2), 2206 (CN), 1720 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, J = 4Hz, 3H, -CH_3), 2.34 (s, 3H, -CH_3), 3.99 (q, 2H, J = 4Hz, -CH_2), 4.50 (s, 2H, -NH_2), 5.53 (s, 1H, Pyran-H), 7.08-7.26 (m, 3H, Ar-H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 14.1, 18.8, 35.1, 58.4, 61.0, 107.5, 118.7, 128.8, 129.0, 130.7, 135.4, 135.5, 144.6, 158.8, 159.3, 166.0 ppm; ESI m/z 353.02 $(M+H)^+$; Anal. Calcd for $C_{16}H_{14}Cl_2N_2O_3$: C, 54.41; H, 4.00; N, 7.93 found: C, 54.22; H, 3.88; N, 7.73%.

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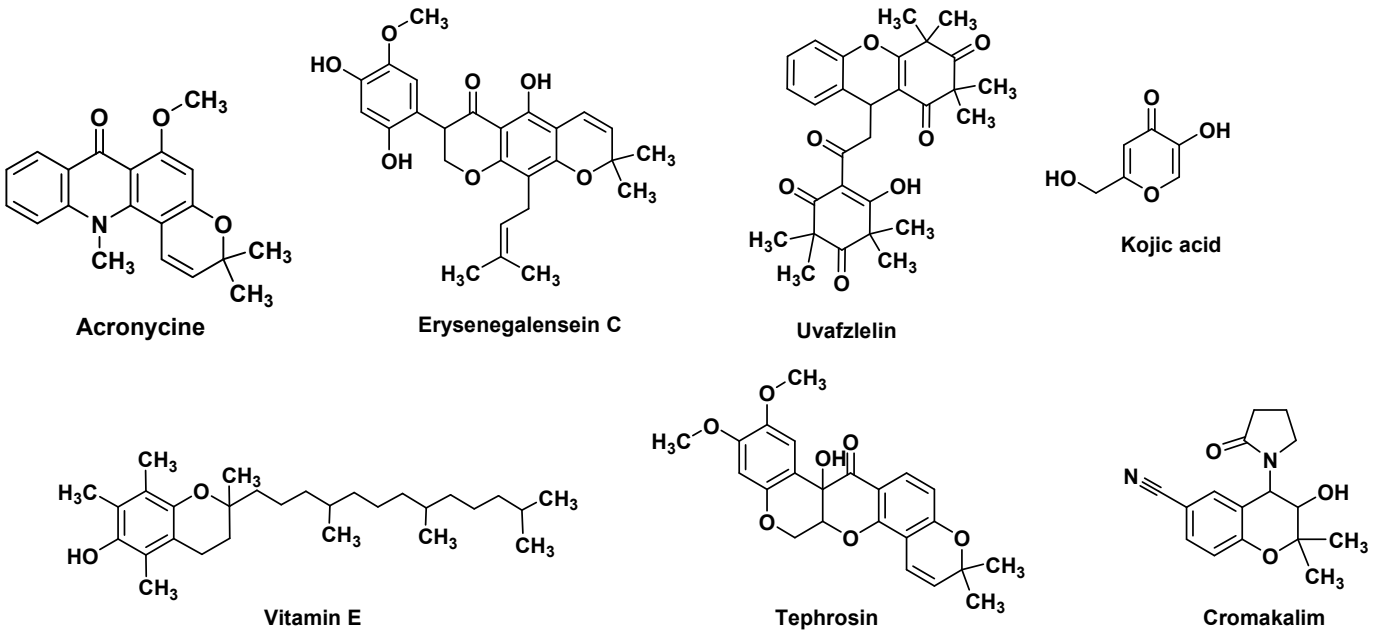
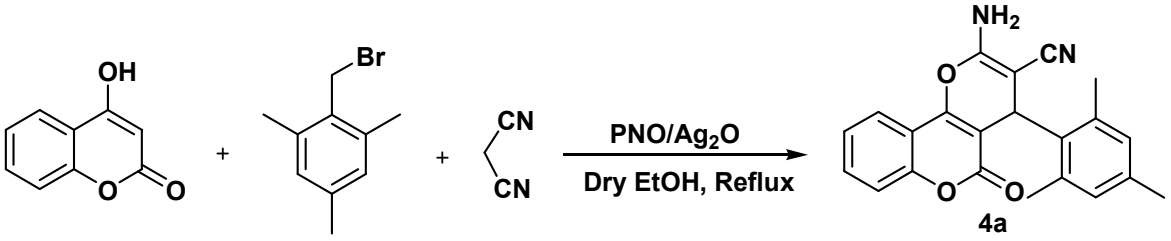


Figure 1 Pyran derived scaffolds.

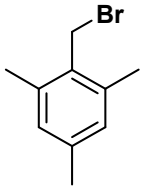
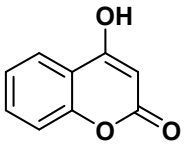
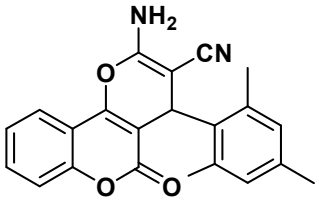
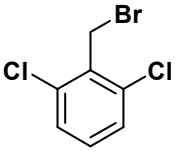
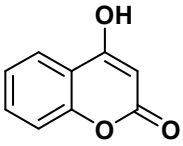
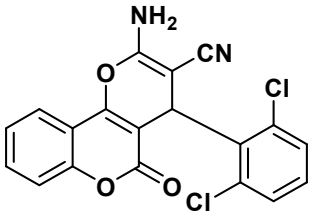
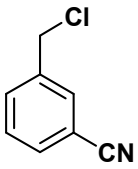
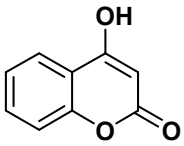
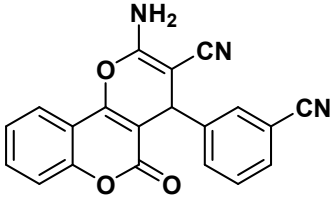
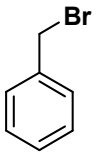
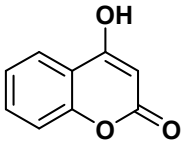
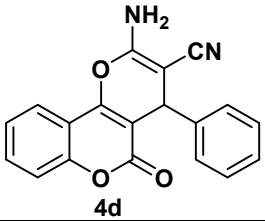
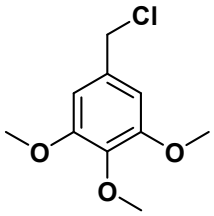
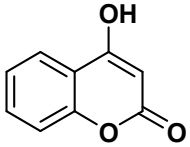
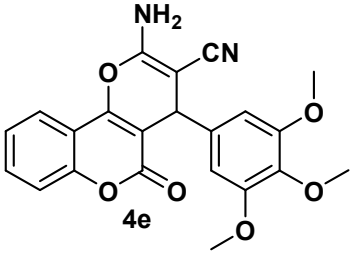


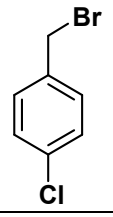
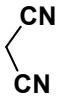
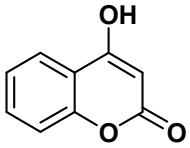
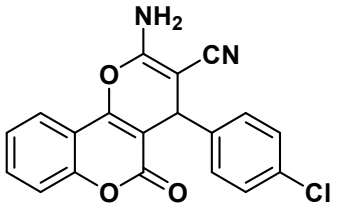
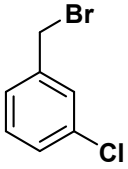
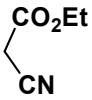
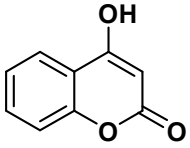
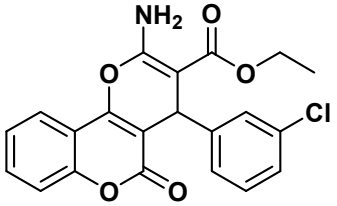
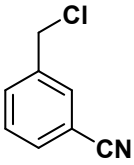
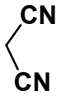
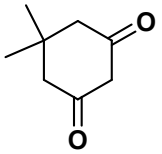
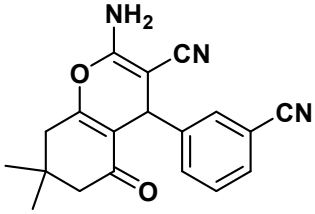
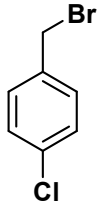
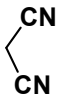
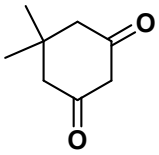
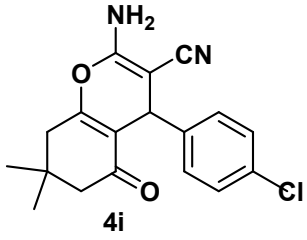
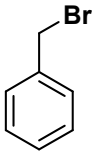
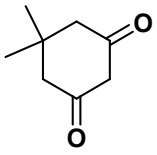
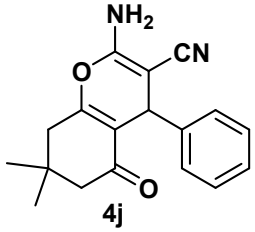
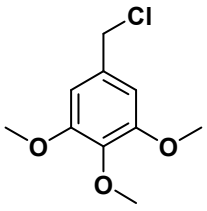
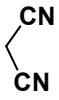
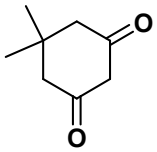
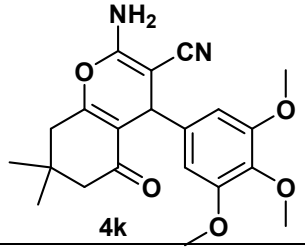
Scheme 1 Synthesis of 2-amino-4-mesityl-5-oxo-4, 5-dihydropyrano [3, 2-*c*] chromene-3-carbonitrile (**4a)** using PNO-Ag_2O reagents.

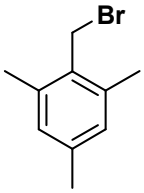
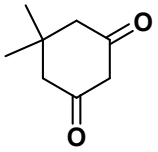
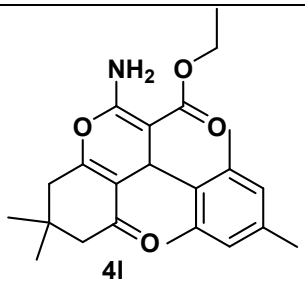
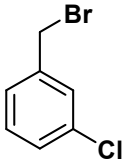
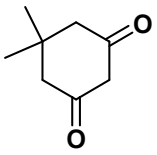
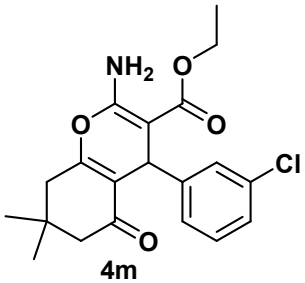
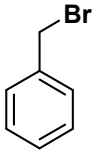
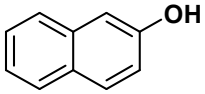
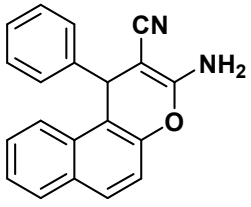
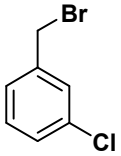
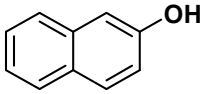
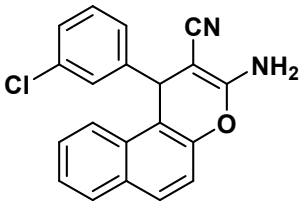
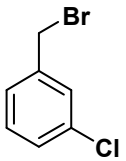
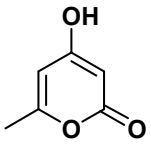
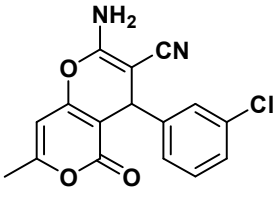
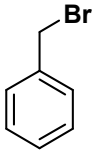
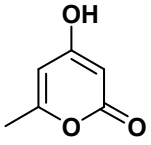
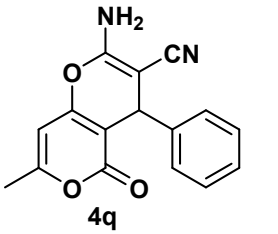
Table 1 Optimization of solvents for the synthesis (**4a)**

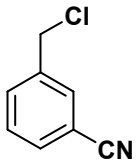
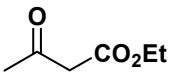
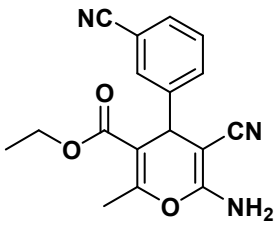
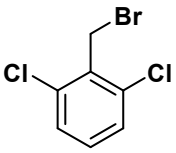
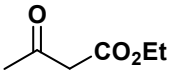
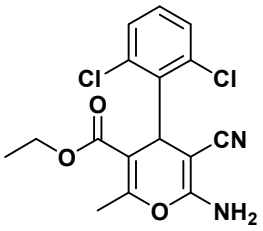
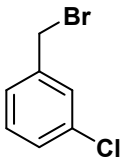
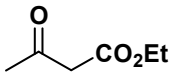
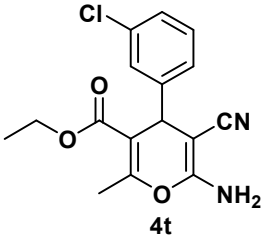
Entry	Solvents (Dry)	Time (min)	Yield (%)
1	Toluene	95	trace
2	CH_2Cl_2	95	trace
3	Dioxane	90	31
4	$CHCl_3$	85	23
5	Acetonitrile	50	80
6	**Ethanol**	**45**	**85**
7	Acetone	65	41
8	THF	60	32
9	Methanol	50	50

Table 2 Synthesis of pyran derivatives (**4a–4t**)

Entry	Benzyl halides	Active methelene compounds	α-hydroxy C-H acids	Products	Time (min)	Yield (%)
1				 **4a**	45	85
2				 **4b**	40	87
3				 **4c**	55	87
4				 **4d**	50	83
5				 **4e**	85	75

6				 4f	50	85
7				 4g	60	80
8				 4h	75	86
9				 4i	70	80
10				 4j	80	86
11				 4k	90	74

12				 4l	85	72
13				 4m	60	78
14				 4n	55	82
15				 4o	45	85
16				 4p	45	81
17				 4q	60	82

18				 4r	75	86
19				 4s	50	85
20				 4t	55	84

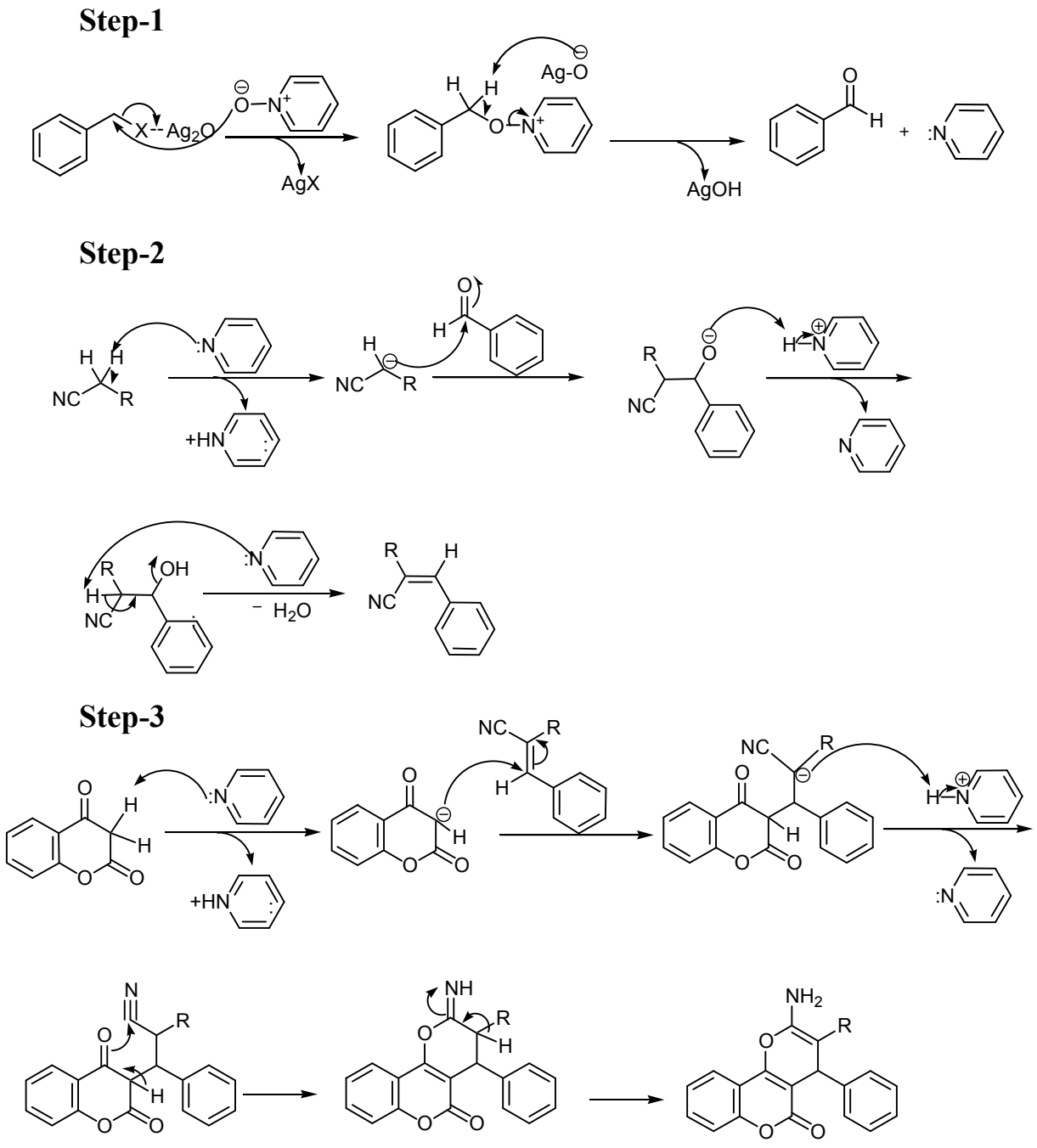


Figure 2 A plausible reaction mechanism for the formation of pyran **(4a).**