An efficient three-component synthesis of amino-substituted pyrano[3,2-*b*] pyranones

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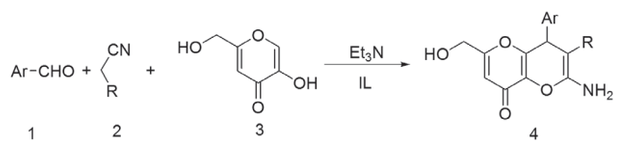
A green, efficient and mild one-pot synthesis of pyrano[3,2-*b*]pyran derivatives via a three component reaction in the ionic liquid [bmim]BF_4 is reported. This method has the advantages of environmental friendliness, operational simplicity, high yields and reuse of the ionic liquid.

Keywords: multi-component reaction, pyrano[3,2-*b*]pyranone, ionic liquid

Over the past decades, multicomponent reactions (MCRs) have proved to be very powerful and efficient bond-forming tools in organic, combinatorial and medicinal chemistry in the context of green chemistry.[1,2] MCRs with environmentally benign methods have been one of most important topics of green chemistry. One approach to reduce the environmental impact of a reaction is to conduct them in ionic liquid (IL) media. ILs have attracted extensive interest as benign reaction media in organic synthesis in recent years because of their unique properties of non-volatility, nonflammability, recyclability, and ability to dissolve a wide range of materials.[3]

Pyran and pyran derivatives are important heterocyclic compounds. They are important to the synthetic chemists due to their pronounced biological and pharmacological activities such as antibacterial,[4] anti-fungal,[5] antidiabetic,[6] antiproliferative,[7] antimicrobial,[8] antitumour,[9] anti-HIV,[10] antimalarial.[11] On the other hand, pyranopyranones are also known for their biological properties including antioxidant and cytotoxic activities.[12] So, it is very important to synthesise the pyran and pyranopyranone derivatives. A good number of methods have been already reported for the synthesis of pyran derivatives. But, so far only a few methods are available for the synthesis of pyranopyranones. Piao and Imafuku prepared pyrano[3,2-*b*]pyran-4-one derivatives by the reaction of substituted cinnamonitriles and 5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one (kojic acid) in absolute ethanol in the presence of organic bases like piperidine.[13] Shi *et al*.[14] synthesised pyrano[3,2-*c*]pyran-5-one derivatives *via* substituted cinnamonitriles and the active methylene carbonyl compound 4-hydroxy-6-methylpyran-2-one at 90 °C in an aqueous phase in the presence of triethylbenzylammonium chloride (TEBA), Wang *et al*.[15] developed a rapid and efficient method to synthesise a series of pyrano[3,2-*c*] pyrans by the reaction of aromatic aldehydes, malononitrile or cyanoacetate and 4-hydroxy-6-methylpyran-2-one in EtOH at room temperature in the presence of KF-Al_2O_3. Shestopalov synthesised a pyrano[3,2-*b*]pyran derivative by the reaction of 4-trifluoromethylthiobenzaldehyde, malonodinitrile and kojic acid in ethanol catalysed by Et_3N.[16] Parthasarathy *et al*.[17] reported



Scheme 1 The reaction of aldehyde **1**, malononitrile or cyanoacetate **2** and kojic acid **3** in ionic liquid [bmim]BF_4.

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the $Cu(OTf)_2$ catalysed synthesis of spiropyrano[3,2-*b*]pyran-4(8*H*)-ones *via* one-pot three component reaction between isatin, kojic acid, and active methylenes in 1,2-dichloroethane.[17] Banitaba *et al*.[18] prepared pyrano[3,2-*b*]pyran derivatives by the reaction of aromatic aldehydes, malononitrile and kojic acid in a heated aqueous phase using ultrasound irradiation. These methods usually require forcing conditions, complex synthetic pathways and often reaction in organic solvents. Thus, in view of the importance of pyranopyranones for their diverse therapeutic activity and in continuation of our interest in the development of new synthetic methods in heterocyclic chemistry,[19,20] we considered it useful to develop a general rapid, environmentally benign and easy synthetic protocol for a variety of pyrano[3,2-*b*]pyranone derivatives.

We now report a three-component one-pot synthesis of pyrano[3,2-*b*]pyranones in ionic liquid medium (Scheme 1). When three components of aromatic aldehyde **1**, malononitrile or cyanoacetate **2** and kojic acid **3** were treated in ionic liquid [bmim]BF_4 in the presence of Et_3N at room temperature for a few hours, the pyrano[3,2-*b*]pyranone derivatives **4** were obtained. To the best of our knowledge, this methodology has not been reported in the literature.

Results and discussion

We carried out the one-pot three-component reaction of 4-chlorobenzaldehyde **1a**, malononitrile **2** and kojic acid **3** as a model reaction. In this reaction, we found that catalysts have significant effects on the reaction time and yields (Table 1). The results indicated that this three-component reaction did not take place in the presence of proton acids such as TsOH or classical Lewis acids such as $ZnCl_2$, and $Yb(OTf)_3$ as catalysts in the

Table 1 Optimisation of the reaction conditions[a]

Entry	Catalyst/equiv.	Solvent	Time/h	Yield/%[b]
1	TsOH (1.0)	[bmim]BF_4	24	0
2	$ZnCl_2$ (1.0)	[bmim]BF_4	24	0
3	$Yb(OTf)_3$ (1.0)	[bmim]BF_4	24	0
4	Et_3N(1.0)	[bmim]BF_4	3	80
5	Pyridine(1.0)	[bmim]BF_4	3	55
6	Piperidine(1.0)	[bmim]BF_4	3	45
7	NH_4OAc(1.0)	[bmim]BF_4	3	57
8	Et_3N(1.0)	EtOH	24	0
9	Et_3N(1.0)	CH_3CN	24	0
10	Et_3N(1.0)	DMF	3	50
11	Et_3N(0)	[bmim]BF_4	3	0
12	Et_3N(0.5)	[bmim]BF_4	3	52
13	Et_3N(2.0)	[bmim]BF_4	3	78

[a]Reaction conditions: 1 mmol of 4-chlorobenzaldehyde, 1 mmol of malononitrile, 1 mmol of kojic acid, room temperature.
[b]Isolated yields.

ionic liquid [bmim]BF_4 at room temperature for 24 h, (Table 1, entries 1–3). Then, we carried out the reaction using bases as the catalysts under the same reaction conditions, using Et_3N, pyridine, piperidine, and ammonium acetate (Table 1, entries 4–7). To our delight, the desired condensation product **4a** was obtained in 80%, 55%, 45%, and 57% yields, respectively, which meant that this three-component condensation reaction of 4-chlorobenzaldehyde **1a**, malononitrile **2** and kojic acid **3** could proceed smoothly catalysed by bases. As shown in Table 1, Et_3N was found to be the most effective catalyst in terms of reaction time and yields (Table 1, entry 4). Furthermore, we found that the yields of **4a** were improved as the amount of Et_3N increased from 0.5 equiv. to 1.0 equiv., and the yields had a plateau when the amount of ammonium acetate was further increased from 1.0 equiv. to 2.0 equiv. (Table 1, entries 4, 11–13). Therefore, 1.0 equiv. of Et_3N was considered to be the most suitable. Different solvents, for example, EtOH, CH_3CN, and DMF, were tested in the presence of Et_3N as catalyst, but unfortunately they resulted in low yields or no reaction (Table 1, entries 8–10). Therefore, the best reaction conditions were obtained by using 1.0 equiv. of Et_3N as the catalyst in the ionic liquid [bmim]BF_4 at room temperature.

A series of aromatic aldehydes were employed under similar circumstances to evaluate the substrate scope of this reaction. The results are summarised in Table 2. The structures of compounds **4a–q** were fully confirmed by melting points, ^{1}H NMR, IR and HRMS. The structure of product **4i** was further confirmed by X-ray crystallography (Fig. 1).[21] The electronic effect of the aryl group on this reaction was investigated as well. Under optimised reaction conditions aldehydes having either an electron withdrawing or an electron donating substituent readily provided pyrano[3,2-*b*]pyran derivatives in high yields (Table 2). Therefore, the electronic nature of the substrate has no significant effect on this reaction.

Based on the above results, a plausible mechanism of this reaction was proposed in Scheme 2. First, aldehyde **1** and malononitrile or cyanoacetate **2** underwent Knoevenagel condensation to afford intermediate **5**. Then, Michael addition of kojic acid **3** to **5** would furnish intermediate **6.** Finally, the product **4** was obtained by an intramolecular cyclisation and dehydration.

We used the preparation of **4a** as a model to study the recovery and reuse of the ionic liquid [bmim]BF_4. Because of the poor solubility of the products in ionic liquids and water, they were easily separated by simple filtration from the mixture of water and the ionic liquid, the filtrate was then extracted with ether and dried at 90 °C in a vacuum for several hours to be then recycled. As shown in Table 2, the reaction medium can be recycled at least three times without significant decrease of the yields, ranging from 80 to 78%.

Table 2 Synthesis of **4** in ionic liquid [bmim]BF_4[a]

Entry	Ar	R	Product	Time/h	Yields/%[b]
1	4-ClC_6H_4	CN	**4a**	3	80(80,78,78)[c]
2	2-ClC_6H_4	CN	**4b**	0.3	86
3	3-ClC_6H_4	CN	**4c**	5	82
4	3,4-$Cl_2C_6H_3$	CN	**4d**	0.5	72
5	2,3-$Cl_2C_6H_3$	CN	**4e**	4.8	79
6	2-BrC_6H_4	CN	**4f**	5	79
7	2-$CF_3C_6H_4$	CN	**4g**	5	76
8	3-$CF_3C_6H_4$	CN	**4h**	5	79
9	4-$CH_3OC_6H_4$	CN	**4i**	4.5	85
10	3-$CH_3OC_6H_4$	CN	**4j**	3	67
11	4-$CH_3C_6H_4$	CN	**4k**	4.7	83
12	3-FC_6H_4	CN	**4l**	0.5	74
13	3-$NO_2C_6H_4$	CN	**4m**	5	72
14	4-BrC_6H_4	CN	**4n**	1.2	76
15	2,4-$Cl_2C_6H_3$	COOMe	**4o**	15	80
16	2-$CF_3C_6H_4$	COOMe	**4p**	10	81
17	4-ClC_6H_4	COOEt	**4q**	9	81

[a]Reaction conditions: 2 mL ionic liquid, 1 mmol aromatic aldehyde, 1 mmol malononitrile or cyanoacetate, 1 mmol kojic acid, rt.
[b]Isolated yields.
[c]The ionic liquid was reused for three runs.

Experimental

Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as an internal standard using a Bruker-400 spectrometer. HRMS data were obtained using a MicroTOF-QII instrument. The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed using a Rigaku Saturn diffractometer. Crystallographic data for the structures of **4i** reported in this paper have been deposited at the Cambridge Crystallographic Data Centre No. CCDC-926835. Crystal data for **4i**:$C_{17}H_{16}N_2O_6$, colourless, crystal dimension 0.26 × 0.20 × 0.12 mm, Monoclinic, space group P2(1)/n, a = 9.9437(16) nm, b = 11.8220(19) nm, c = 14.259(2) nm, β = 105.844(2)°, V = 1612.5(4) nm^3, Mr = 394.79, Z = 4, Dc = 1.418 g cm^{-3}, λ = 0.71073 nm, μ(Mokα) = 0.109 mm^{-1}, F(000) = 720, S = 1.042, R^1 = 0.0398, wR^2 = 0.1133.

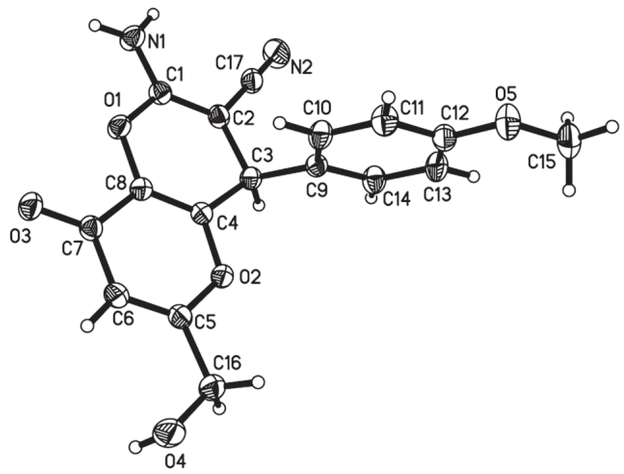
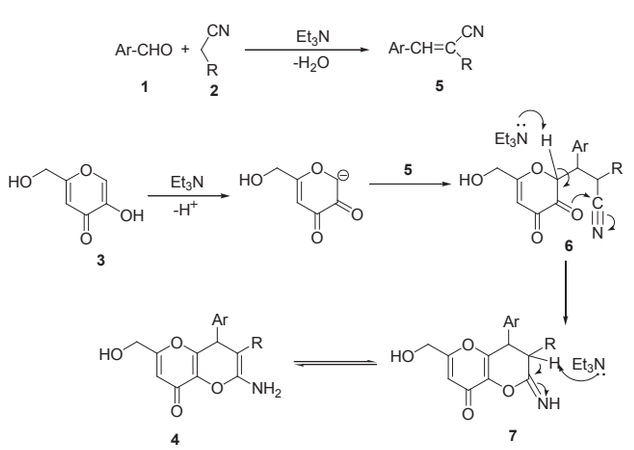


Fig. 1 X-Ray crystal structure of compound **4i**.



Scheme 2 A plausible reaction mechanism.

Synthesis of **4***; general procedure*

Et_3N(1 mmol) was added to a solution of aromatic aldehyde **1** (1 mmol), malononitrile or cyanoacetate **2** (1 mmol), kojic acid **3** (1 mmol) in ionic liquid [bmim]BF_4 (2 mL). The mixture was then stirred at room temperature. After completion of the reaction as indicated by TLC, water (5 mL) was added and the product was filtered off and washed with water. The remaining aqueous layer containing the ionic liquid was extracted with ether three times to remove the organic impurity, and then dried under vacuum at 90 °C for about 15 h to afford the ionic liquid, which was used in the subsequent runs without further purification. The crude product was purified by recrystallisation from ethanol to give **4** as a white powder.

2-Amino-4-(4-chlorophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile **(4a)**: M.p. 198–200 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.46 (d, 2H, J=8.8 Hz, ArH), 7.34 (d, 2H, J=8.8 Hz ArH), 7.29 (s, 2H, NH_2), 6.34 (s, 1H, =CH), 5.70 (s, 1H, OH), 4.11–4.24 (m, 2H, CH_2), 4.87 (s, 1H, CH); IR (KBr, ν, cm^{-1}): 3355, 3198, 2197, 1650; HRMS calcd for $C_{16}H_{11}ClN_2O_4Na$ $(M+Na)^+$: requires 353.0305, found: 353.0315.

2-Amino-4-(2-chlorophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile **(4b)**: M.p. 201–203 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.48–7.50 (m, 1H, ArH), 7.34–7.42 (m, 3H, ArH), 7.26 (s, 2H, NH_2), 6.35 (s, 1H, =CH), 5.70 (t, 1H, J=6.0 Hz, OH), 5.27 (s, 1H, CH), 4.07–4.22 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3393, 3326, 2201, 1649; HRMS calcd for $C_{16}H_{11}ClN_2O_4Na$ $(M+Na)^+$: requires 353.0305, found: 353.0316.

2-Amino-4-(3-chlorophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile **(4c)**: M.p. 201–202 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.38–7.46 (m, 3H, ArH), 7.31 (s, 2H, NH_2), 7.27–7.29 (m, 1H, ArH), 6.35 (s, 1H, =CH), 5.70 (s, 1H, OH), 4.89 (s, 1H, CH), 4.11–4.24 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3375, 3331, 2198, 1650; HRMS calcd for $C_{16}H_{11}ClN_2O_4Na$ $(M+Na)^+$: requires 353.0305, found: 353.0305.

2-Amino-4-(3,4-dichlorophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4d**): M.p. 228–230 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.67 (d, 1H, J=2.0 Hz ArH), 7.48 (dd, 1H, J_1=8,4 Hz, J_2=2.0 Hz, ArH), 7.43(d, 1H, J=8.4 Hz, ArH), 7.31 (s, 2H, NH_2), 6.35 (s, 1H, =CH), 5.71 (t, 1H, J=6.0 Hz, OH), 5.29 (s, 1H, CH), 4.09–4.22 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3339, 3193, 2195, 1644; HRMS calcd for $C_{16}H_{10}Cl_2N_2O_4Na$ $(M+Na)^+$: requires 386.9915, found: 386.9905.

2-Amino-4-(2,3-dichlorophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4e**): M.p. 235–238 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.63 (s, 1H, ArH), 7.40–7.44 (m, 2H, ArH), 7.33 (s, 2H, NH_2), 6.36 (s, 1H, =CH), 5.70 (s, 1H, OH), 5.38 (s, 1H, CH), 4.09–4.21 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3362, 3199, 2192, 1650; HRMS calcd for $C_{16}H_{10}Cl_2N_2O_4Na$ $(M+Na)^+$: requires 386.9915, found: 386.9904.

2-Amino-4-(2-bromophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4f**): M.p. 225–227 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.66 (dd, 1H, J_1=8.0 Hz, J_2=1.2 Hz, ArH), 7.42–7.46 (m, 1H, ArH), 7.36 (dd, 1H, J_1=7.6 Hz, J_2=1.6 Hz, ArH), 7.26–7.30 (m, 3H, ArH), 6.35 (s, 1H, =CH), 5.69 (s, 1H, OH), 5.28 (s, 1H, CH), 4.07–4.22 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3433, 3321, 2199, 1621; HRMS calcd for $C_{16}H_{11}BrN_2O_4Na$ $(M+Na)^+$: requires 396.9800, found: 396.9805.

2-Amino-4-(2-trifluoromethylphenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4g**): M.p. 239–242 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.76 (s, 2H, ArH), 7.55 (s, 2H, ArH), 7.31 (s, 2H, NH_2), 6.33 (s, 1H, CH), 5.66 (s, 1H, OH), 5.08 (s, 1H, CH), 4.02–4.16 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3367, 3331, 2200, 1650; HRMS calcd for $C_{17}H_{11}F_3N_2O_4Na$ $(M+Na)^+$: requires 387.0569, found: 387.0567.

2-Amino-4-(3-trifluoromethylphenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4h**): M.p. 212–213 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.64–7.71 (m, 4H, ArH), 7.32 (s, 2H, NH_2), 6.35 (s, 1H, =CH), 5.71 (s, 1H, OH), 5.04 (s, 1H, CH), 4.10–4.24 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3370, 3329, 2199, 1649; HRMS calcd for $C_{17}H_{11}F_3N_2O_4Na$ $(M+Na)^+$: requires 387.0569, found: 387.0578.

2-Amino-4-(4-methoxyphenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4i**): M.p. 220–223 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.20 (d, 4H, J=8.8, ArH), 6.95 (d, 2H, J=8.8, NH_2), 6.33 (s, 1H, =CH), 5.71 (s, 1H, OH), 4.74 (s, 1H, CH), 4.10–4.24 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3); IR (KBr, ν, cm^{-1}): 3349, 3336, 2199, 1621; HRMS calcd for $C_{17}H_{14}N_2O_5Na$ $(M+Na)^+$: requires 349.0800, found: 349.0805.

2-Amino-4-(3-methoxyphenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4j**): M.p. 268–269 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.30–7.34 (m, 1H, ArH), 7.25 (s, 2H, NH_2), 6.89–6.91 (m, 1H, ArH), 6.83 (s, 2H, ArH), 6.35 (s, 1H, =CH), 5.70 (s, 1H, OH), 4.77 (s, 1H, CH), 4.12–4.25 (m, 2H, CH_2), 3.76 (s, 3H, OCH_3); IR (KBr, ν, cm^{-1}): 3350, 3341, 2220, 1620; HRMS calcd for $C_{17}H_{14}N_2O_5Na$ $(M+Na)^+$: requires 349.0800, found: 349.0810.

2-Amino-4-(4-methylphenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4k**): M.p. 204–206 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.15–7.21 (m, 6H, ArH+NH_2), 6.33 (s, 1H, =CH), 5.72 (s, 1H, OH), 4.74 (s, 1H, CH), 4.10–4.23 (m, 2H, CH_2), 2.29 (s, 3H, CH_3); IR (KBr, ν, cm^{-1}): 3575, 3324, 2193, 1629; HRMS calcd for $C_{17}H_{14}N_2O_4Na$ $(M+Na)^+$: requires 333.0851, found: 333.0835.

2-Amino-4-(3-fluorophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4l**): M.p. 220–222 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.45 (s, 1H, ArH), 7.27 (s, 2H, NH_2), 7.16 (s, 3H, ArH), 6.35 (s, 1H, =CH), 5.72 (s, 1H, OH), 4.88 (s, 1H, CH), 4.12–4.24 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3368, 3321, 2203, 1650; HRMS calcd for $C_{16}H_{11}FN_2O_4Na$ $(M+Na)^+$: requires 337.0601, found: 337.0574.

2-Amino-4-(3-nitrophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4m**): M.p. 215–217 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 8.18 (s, 2H, ArH), 7.81 (s, 1H, ArH), 7.72 (s, 1H, ArH), 7.38 (s, 2H, NH_2), 6.36 (s, 1H, =CH), 5.71 (s, 1H, OH), 5.14 (s, 1H, CH), 4.11–4.23 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3384, 3319, 2189, 1639; HRMS calcd for $C_{16}H_{11}N_3O_6Na$ $(M+Na)^+$: requires 364.0546, found: 364.0550.

2-Amino-4-(4-bromophenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carbonitrile (**4n**): M.p. 224–226 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.42–7.46 (m, 2H, ArH), 7.35 (m, 1H, ArH), 7.24–7.28 (m, 3H, ArH+NH_2), 6.30 (s, 1H, =CH), 5.71 (s, 1H, OH), 5.26 (s, 1H, CH), 4.10–4.15 (m, 2H, CH_2); IR (KBr, ν, cm^{-1}): 3433, 3321, 2199, 1621; HRMS calcd for $C_{16}H_{11}BrN_2O_4$ $(M+Na)^+$: requires 396.9800, found: 396.9806.

Methyl 2-amino-4-(2,4-dichlorophenyl)-6-hydroxyethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carboxylate (**4o**): M.p. 230–232 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.67 (d, 1H, J=2.0 Hz, ArH), 7.48 (m, 1H, ArH), 7.43(d, 1H, J=8.4 Hz, ArH), 7.30 (s, 2H, NH_2), 6.35 (s, 1H, =CH), 5.72 (t, 1H, J=6.0 Hz, OH), 5.30 (s, 1H, CH), 4.10–4.22 (m, 2H, CH_2), 3.51 (s, 3H, OCH_3); IR (KBr, ν, cm^{-1}): 3339, 3193, 2195, 1644; HRMS calcd for $C_{17}H_{13}Cl_2NO_6Na$ $(M+Na)^+$: requires 420.0018, found: 420.0030.

Methyl 2-amino-4-(2-trifluoromethylphenyl)-6-hydroxymethyl-8-oxo-4H,8H-pyrano[3,2-b]pyran-3-carboxylate (**4p**): M.p. 227–229 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): δ : 7.60 (d, 1H, J=1.6 Hz, ArH), 7.48 (dd, 1H, J_1=8.0 Hz, J_2=1.6 Hz, ArH), 7.40 (d, 1H, J=8.4 Hz, ArH), 7.31 (s, 2H, NH_2), 6.31 (s, 1H, =CH), 5.71 (t, 1H, J=6.0 Hz, OH), 5.32 (s, 1H, CH), 4.09–4.21 (m, 2H, CH_2), 3.46 (s, 3H, OCH_3); IR (KBr, ν, cm^{-1}): 3339, 3193, 2195, 1644; HRMS calcd for $C_{18}H_{14}F_3NO_6Na$ $(M+Na)^+$: requires 420.0671, found: 420.0683.

Ethyl 2-amino-4-(4-chlorophenyl)-6-hydroxyethyl-8-oxo-4H,8H-pyrano [3,2-b]pyran-3-carboxylate (**4q**): M.p. 228–230 °C; ^{1}H NMR (DMSO-d_6, δ, ppm): 7.35 (d, 2H, J=8.4 Hz, ArH), 7.24 (d, 2H, J=8.4 Hz, ArH), 7.83 (s, 2H, NH_2), 6.30 (s, 1H, =CH), 5.67 (t, 1H, J=6.0 Hz, OH), 4.80 (s, 1H, CH), 4.18 (dd, 2H, J_1=17.2 Hz, J_2=5.6 Hz, CH_2), 3.91 (dd, 2H, J_1=6.8 Hz, J_2=2.0 Hz, CH_2), 0.98 (t, 3H, J=7.2 Hz, CH_3); IR (KBr, ν, cm^{-1}): 3393, 3326, 2201, 1649; HRMS calcd for $C_{18}H_{16}ClNO_6Na$ $(M+Na)^+$: requires 400.0564, found: 400.0558.

Conclusions

In summary, we have synthesised the pyrano[3,2-*b*]pyran derivatives *via* a three-component reaction in an ionic liquid. These methods suffer from many advantages, such as

operational simplicity, mild reaction conditions, higher yields and environmental friendliness, as well as the reuse of the ionic liquid, which could be reused three times without apparent loss of activity.

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