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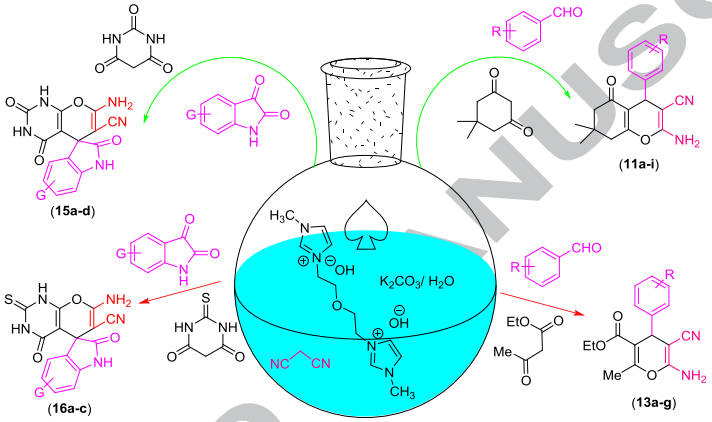

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ABSTRACT

Diethylene glycol-bis(3-methylimidazolium) dihydroxide $[DiEG(mim)_2][OH]_2$ was prepared by the reaction between sodium hydroxide and diethylene glycol-bis(3-methylimidazolium) dibromide in aqueous ethanol at room temperature. This solid, quaternized ionic liquid was employed as a recyclable catalyst for the synthesis of 4*H*-pyrane derivatives in high yields from the three-component condensation reaction of malononitrile, aromatic aldehydes and 1,3-dicarbonyls in water at room temperature. In addition, spiropyrane derivatives were synthesized from the reaction of isatin, malononitrile and 1,3-dicarbonyls in water at reflux. The dicationic ionic liquid showed the same efficiency when used in consecutive reactions.

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Ionic liquids (ILs) have been reported as green reaction media owing to their negligible volatility, excellent thermal stability, and the variety of structures available.[1-12] During the past few years a number of dicationic and polycationic ionic liquids, with a large variety of tunable interactions, have been explored.[13-19] Dicationic ionic liquids (DCILs) have been shown to possess a larger variety of tunable interactions, better thermal stabilities, and broader selectivities than conventional ILs.[20]

4*H*-Pyran derivatives represent an important class of compounds and constitute the structural unit of many natural products[21,22] and biologically interesting compounds possessing various pharmacological activities,[23] such as antiallergic,[24] antitumor,[25] and antibacterial.[26-28] 4*H*-Pyran derivatives are also potential calcium channel antagonists[29] and are structurally similar to biologically active 1,4-dihydropyridines.

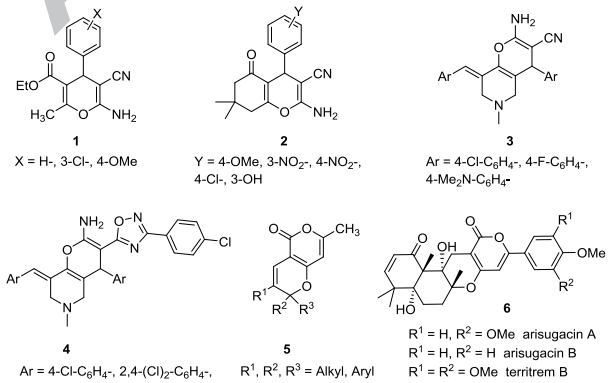

Figure 1. Representative 4*H*-pyran derivatives. **1** and **2** (inhibition of bacterial growth), **3** and **4** (*in vitro* inhibition of Mycobacterium tuberculosis H37Rv (MTB)), **5** (*in vitro* antiproliferative/cytotoxic activity), **6** (acetylcholinesterase inhibition).

Pyrano-pyridines, such as compounds **3** and **4**, show in vitro activity against Mycobacterium tuberculosis H37Rv (MTB), multi-drug resistant tuberculosis (MDR-TB), and Mycobacterium smegmatis. They are potent against MTB and MDR-TB, being 100 times more active than isoniazid against MDRTB.[33,34] Pyripyropenes **5** are characterized by a decahydro-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one skeleton and have been shown as potentially bioactive natural products.[35] Related natural products such as arisugacins and territrems (**6**) have also been reported to possess important biological activities, for example, inhibition of acetylcholinesterase.[36,37] Therefore, there is continued interest to develop efficient synthetic methods for the assembly of these motifs.[38-43]

The conventional synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes involves the condensation of dimedone with an aromatic aldehyde and malononitrile at reflux in acetic acid[44] or the two-component condensation of dimedone with α-cyanocinnamonitriles in the presence of ethanolic piperidine.[45] Other effective methods include the use of microwave,[46] ultrasonic irradiation,[47] hexadecyltrimethyl ammonium bromide (HMTAB),[48] triethylbenzylammonium chloride (TEBA),[49] KF-alumina,[50] rare earth perfluorooctanoate $(RE(PFO)_3)$,[51] amino functionalized ionic liquids,[52] tetrabutylammonium fluoride (TBAF),[53] 2-hydroxyethylammonium formate,[54] silica noanoparticles,[55] well-ordered mesoporous silica nanoparticles,[56] and $ZnFe_2O_4$,[43] as catalysts in a one-pot reaction.

However, many of these methods suffer from drawbacks such as low yields, long reaction times, harsh reaction conditions, tedious work-up procedures and the application of expensive catalysts.

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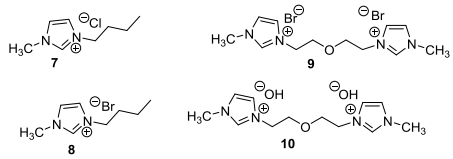
In our initial study, the evaluation of a series of imidazolium ionic liquids (**7**-**10**) was carried out for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes in aqueous medium (Scheme 1). After preliminary experiments, it was found that a mixture of dimedone, benzaldehyde, and malononitrile in water at room temperature in the presence of catalytic IL and potassium carbonate afforded 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**11a**) in excellent yield (Table 1).



Scheme 1. ILs examined as catalysts.

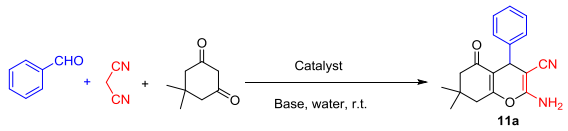


Table 1: Investigation of solvents and reaction conditions for the synthesis of 4*H*-pyran **11a**.[a]

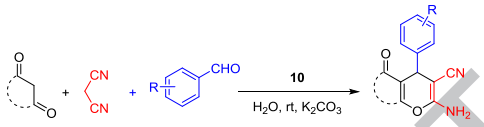
Entry	IL	IL (mol%)	Base (mol%)	Time (min)	Yield (%)[b]
1	-	-	NaOH (10)	70	30
2	-	-	K_2CO_3 (10)	70	20
3	**7**	10	K_2CO_3 (10)	60	90
4	**7**	10	K_2CO_3 (10)	20	76
5	**8**	10	K_2CO_3 (10)	70	87
6	**8**	10	K_2CO_3 (10)	20	73
7	**9**	10	NaOH (10)	30	50
8	**9**	10	K_2CO_3 (10)	40	90
9	**9**	10	K_2CO_3 (10)	20	80
10	**10**	10	-	60	30
11	**10**	10	K_2CO_3 (10)	20	92
12	**10**	5	K_2CO_3 (10)	90	80

[a] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), water (3 mL). [b] Isolated yield.

The condensation reaction conducted in water at room temperature in the presence of NaOH or K_2CO_3 (10 mol%) without IL gave the corresponding product in 30% and 20% yield, respectively, after 70 minutes (Table 1, entries 1 and 2). The best result was obtained using IL **10** (10 mol%) to give a yield of 92% (Table 1, entry 11). Additionally, this condensation conducted in the presence of other imidazolium ILs, such as **7**, **8**, and **9**, gave the corresponding product with slightly longer reaction times and lower yields (Table 1, entries 3-9). The reaction without K_2CO_3 gave only 30% yield after one hour (Table 1, entry 10).

We employed the optimized conditions, **10** (10 mol%), K_2CO_3 (10 mol%) in water, for the condensation of various 1,3-dicarbonyls, malononitrile and aromatic aldehydes to give the corresponding 4*H*-pyran derivatives (Table 2). This method worked with a variety of aromatic aldehydes. Aldehydes bearing electron-withdrawing groups such as 4-CN, 3-CN, 4-NO_2, and 3-NO_2 (Table 2, entries 5-7, 15,16), and electron-donating groups such as 3-Me, 4-EtO, and 4-*iso*-Pr (Table 2, entries 8, 9, 18, 19) were reacted with a variety of 1,3-dicarbonyls including dimedone, 1,3-cyclohexadione, and ethyl acetoacetate under the optimized conditions to give the corresponding products in 85-92% yield. Halogen substituted benzaldehydes were treated with 1,3-dicarbonyls and malononitrile to give the corresponding products in 84-91% yields (Table 2, entries 2-4,11-14).

Table 2: IL **10** catalyzed condensation of aromatic aldehydes, malononitrile, and 1,3-dicarbonyls to give the corresponding 4*H*-pyranes.[a]



Entry	Aromatic aldehyde	1,3-Dicarbonyl	Product	Time (min)	Yield (%)[b]
1	C_6H_5-CHO	Dimedone	**11a**	20	92, 91, 90, 90 88[c]
2	4-Br-C_6H_4-CHO	Dimedone	**11b**	35	90
3	4-F-C_6H_4-CHO	Dimedone	**11c**	30	91
4	2,4-$(Cl)_2$-C_6H_3-CHO	Dimedone	**11d**	40	90
5	4-NC-C_6H_4-CHO	Dimedone	**11e**	25	86
6	3-NC-C_6H_4-CHO	Dimedone	**11f**	30	85
7	4-O_2N-C_6H_4-CHO	Dimedone	**11g**	15	90
8	3-Me-C_6H_4-CHO	Dimedone	**11h**	45	89
9	4-EtO-C_6H_4-CHO	Dimedone	**11i**	45	92
10	C_6H_5-CHO	1,3-Cyclohexadione	**12a**	55	82
11	4-Br-C_6H_4-CHO	1,3-Cyclohexadione	**12b**	55	86
12	2,4-$(Cl)_2$-C_6H_3-CHO	1,3-Cyclohexadione	**12c**	55	84
13	4-Cl-C_6H_4-CHO	Ethyl acetoacetate	**13a**	40	86
14	3-Br-C_6H_4-CHO	Ethyl acetoacetate	**13b**	40	88
15	3-O_2N-C_6H_4-CHO	Ethyl acetoacetate	**13c**	35	92
16	4-O_2N-C_6H_4-CHO	Ethyl acetoacetate	**13d**	30	91
17	2-O_2N-C_6H_4-CHO	Ethyl acetoacetate	**13e**	35	91

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18	3-Me-C_6H_4-CHO	Ethyl acetoacetate	**13f**	40	90
19	4-*iso*-Pr-C_6H_4-CHO	Ethyl acetoacetate	**13g**	40	90

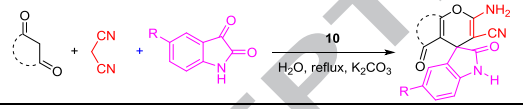
[a] Reaction conditions: aromatic aldehyde (1 mmol), 1,3-dicarbonyl (1 mmol), malononitrile (1 mmol), **10** (10 mol%), K_2CO_3 (10 mol%), water (3 mL), room temperature. [a]Isolated yield. [c]Recovered **10** was used.

Spirooxindoles are commonly occurring heterocyclic ring systems and are important structural motifs that are found in many natural products and pharmaceuticals.[57-61] In recent years, numerous efficient transformations have been developed for the construction of the spirooxindole substructure.[62-68]

To extend the catalytic ability of this dicationic ionic liquid, the synthesis of 2-amino-7,7-dimethyl-2',5-dioxo-1',2',5,6,7,8-hexahydrospiro[chromene-4,3'-indole]-3-carbonitrile (**14a**) was investigated *via* the condensation of isatin, malononitrile, and dimedone in water at reflux. After preliminary experiments, the optimized conditions was found to be isatin (1 mmol), malononitrile (1 mmol) and 1,3-dicarbonyl (1 mmol) in the presence of **10** (10 mol%) and K_2CO_3 (10 mol%) in water (3 mL) at reflux (Table 3).

As shown in Table 3, this method worked with a wide variety of substrates. A series of differently substituted isatins possessing either electron-withdrawing groups or halogens reacted with malononitrile and barbituric acid under the optimized conditions to give the corresponding products in high yields. Additionally, thiobarbituric acid was treated with various isatins and malononitrile to give the corresponding products in good to high yields (Table 3, entries 8-10). All products were characterized by m.p., IR, ^{1}H NMR, and ^{13}C NMR spectra.[69-72]

Table 3: IL **10** catalyzed condensation of isatin, 1,3-dicarbonyls, and malononitrile to give the corresponding spiropyrane derivatives.[a]



Entry	R	1,3-Dicarbonyl	Product	Time (min)	Yield (%)[b]
1	H	Dimedone	**14a**	30	92, 92, 90, 89, 88[c]
2	F	Dimedone	**14b**	25	90
3[d]	H	Dimedone	**14c**	40	90
4	H	Barbituric acid	**15a**	40	90
5	Br	Barbituric acid	**15b**	55	91
6	Cl	Barbituric acid	**15c**	45	90
7	NO_2	Barbituric acid	**15d**	30	91
8	H	Thiobarbituric acid	**16a**	60	90
9	Br	Thiobarbituric acid	**16b**	70	89
10	F	Thiobarbituric acid	**16c**	55	91

[a] Reaction conditions: isatin (1 mmol), 1,3-dicarbonyl (1 mmol), malononitrile (1 mmol), **10** (10 mol%), K_2CO_3 (10 mol%), water (3 mL), reflux. [a]Isolated yield. [c] Recovered **10** was used. [d] *N*-methyl isatin .

Finally, the reusability of the catalyst was studied for the synthesis of compounds **11a** and **14a**. After reaction completion, the precipitate was filtered and washed with ethanol. IL **10** was recycled by evaporating the aqueous ethanolic phase under reduced pressure and washing with ethyl acetate. After being air dried, the recycled catalyst could be reused four times without any significant loss in activity (Tables 2 and 3, entry 1).

In conclusion, the dicationic ionic liquid **10** and K_2CO_3 was used as an efficient catalytic system for the synthesis of 4*H*-pyrans *via* the three-component condensation reaction of an aldehyde or isatin, malononitrile, and 1,3-dicarbonyl compounds in water.

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69. Synthesis of diethylene glycol-bis (3-methylimidazolium) dibromide (**9**). The dicationic ionic liquid **9** was synthesized according to literature procedures[17,18] with slight modification. A mixture of diethylene glycol dibromide (5.0 g, 21.56 mmol) and *N*-methylimidazole (3.7 g, 45.07 mmol) in acetonitrile (30 mL) was stirred at reflux for 48 h in a two necked round bottom flask equipped with water condenser. After reaction completion (TLC), the reaction was cooled to room temperature. The solvent was evaporated under reduced pressure using a rotary evaporator at 55 °C. The reaction mixture was washed with ethyl acetate (3×10 mL) to remove unreacted starting materials and the resulting quaternized diethylene glycol-bis (3-methylimidazolium) dibromide was obtained in 95% yield (8.1 g); thick liquid; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.78 (t, 4H, J = 4.0 Hz, OCH_2), 3.91 (s, 6H, NCH_3), 4.41 (t, 4H, *J* = 4.0 Hz, NCH_2), 7.82 (d, 4H, *J* = 9.6 Hz), 9.37 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.0, 48.5, 67.9, 122.4, 123.0, 136.7.
70. Synthesis of diethylene glycol-bis (3-methylimidazolium) dihydroxide (**10**): A mixture of dicationic ionic liquid **9** (0.8 g, 2.0 mmol) and sodium hydroxide (0.5 g, 12.5 mmol) in water-ethanol (1:1) (20 mL) was stirred at room temperature. After 1 h a white precipitate formed which was filtered and washed with ethanol (3 × 10 mL) to give the quaternized diethylene glycol-bis (3-methylimidazolium) dihydroxide in 90% yield (0.486 g); white solid mp = >250 °C; ^{1}H NMR (400 MHz, D_2O): δ 3.74-3.80 (m, 10H, NMe and OCH_2), 4.25 (t, 4H, *J* = 5.0 Hz, NCH_2), 7.31 (dd, 4H, *J* = 6.8 Hz, 2.0 Hz), 8.32 (s, 2H, Ar); ^{13}C NMR (100 MHz, DMSO-d_6): δ 35.7, 49.0, 68.4, 122.5, 123.3, 166.0, 171.1. Mass m/e (%): [M-34 (2×OH)] 236 (22.9), 207 (14.6), 167 (22.9), 149 (58.3), 111 (14.6), 83 (33.3), 57 (base peak). *pH analysis of the **10***: The pH of **10** determined by pH-ISE conductivity titration controller (Denver Instrument Model 270) was 10.23 for 0.011 g of the solid base at 25 °C.
71. General procedure for the synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes: The dicationic ionic liquid **10** (27.03 mg, 10 mol%), was added to a mixture of 1,3-dicarbonyl (1 mmol), aromatic aldehyde (1 mmol), malononitrile (1 mmol), and K_2CO_3 (13.8 mg, 10 mol%) in water (3 mL). The reaction mixture was stirred at room temperature for the appropriate time. After reaction completion (TLC), the reaction mixture was filtered. The filtrate was washed with cool ethanol (3 × 5 mL) to obtain the corresponding 4*H*-pyran. The crude products were purified by recrystallization from ethanol (95%). To recover **10**, the ethanol/water phase was evaporated under reduced pressure and the crude was washed with ethyl acetate (3 × 5 mL) and air dried. **2-Amino-4-(4-bromophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (12b)**: mp 236-239 °C. IR (KBr): 3410, 3330, 3210, 2190, 1685, 1650, 1601, 1247 (cm^{-1}). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.85-2.60 (m, 6H), 4.14 (s, 1H), 7.04-7.46 (m, 6H, Ar and NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.4, 28.1, 36.7, 37.9, 59.2, 114.9, 121.2, 131.1, 132.8, 145.8, 160.1, 166.2, 197.6. Anal calcd for $C_{16}H_{13}BrN_2O_2$: C, 55.67; H, 3.80; Br, 23.15; N, 8.12. Found: C, 55.43; H, 3.93; N, 7.89. **2-Amino-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (12c)**: mp 232-235 °C. IR (KBr): 3415, 3330, 3215, 2196, 1680, 1650, 1600, 1247 (cm^{-1}). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 0.85-2.60 (m, 6H), 4.65 (s, 1H), 7.08-7.50 (m, 5H, Ar and NH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 21.4, 28.1, 34.1, 37.9, 57.9, 114.1, 120.7, 129.3, 130.2, 132.9, 134.6, 142.6, 160.1, 167.0, 197.3. Anal calcd for $C_{16}H_{12}Cl_2N_2O_2$: C, 57.33; H, 3.61; Cl, 21.15; N, 8.36. Found: C, 55.08; H, 3.71; N, 8.14.
72. General procedure for the synthesis of spiropyran derivatives: The dicationic ionic liquid **10** (27.03 mg, 10 mol%), was added to a mixture of 1,3-dicarbonyl (1 mmol), isatin (1 mmol), malononitrile (1 mmol), and K_2CO_3 (13.8 mg, 10 mol%) in water (3 mL). The reaction mixture was stirred at reflux for the appropriate time. After reaction completion (TLC), the reaction mixture was cooled to room temperature and filtered. The filtrate was washed with cool ethanol (3 × 5 mL) to obtain the corresponding 4*H*-pyran. The crude products were purified by recrystallization from ethanol (95%). To recover **10**, the ethanol/water phase was evaporated under reduced pressure and the crude was washed with ethyl acetate (3 × 5 mL) and air dried.

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