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ARTICLE TYPE

1,1'-sulfinyldipyridinium bis (hydrogen sulfate) ionic liquid: synthesis and its application towards temperature influenced synthesis of novel pyranopyrimidinediones and pyranopyrimidinetriones

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A novel robust dication homoanionic Bronsted acidic ionic liquid accessible from inexpensive, commercially available precursors efficiently catalyzes the reaction of salicylaldehyde and 6-amino uracil in ethanol medium furnished novel pyranopyrimidinediones and pyranopyrimidinetriones at ambient and reflux conditions, respectively. The mechanism for the present transformations is suggested. The advantages of this method include novelty in terms of ionic liquid as well as transformation along with high efficiency, easy work-up procedure and purification, convenient operation, mild and environmentally benign conditions.

Introduction

Designing and exploring novel methods for pharmacological agents within the framework of green chemistry is one of the most common goals for organic chemists to minimize economic burden and ecological problems.[1] In this context, ionic liquids (ILs) have touted as green solvents as well as catalysts due to unique chemical and physical properties *viz* non-volatility, non-flammability, thermal stability, and controlled miscibility.[2] ILs are now recognized in organic reactions and as providing potential improvement in the control of product distribution, enhance reactivity, ease of product recovery, catalyst immobilization and recycling.[3] ILs with sulfate functionalized Brønsted acidic sites have attracted attention because of their unique properties such as non-volatile, non-corrosive, air stable, provide easy recovery and reuse.[4] Such ILs have been explored in plethora of organic transformations as they offer the advantages of both liquid acids and solid acids thus emerged as useful alternatives to traditional mineral liquid acids such as sulfuric acid and hydrochloric acid in chemical reactions.[5] Thus, attracted the attention of both academics as well as industries lead to searching of new ionic liquid for synthetic methodologies that allow the construction of novel bioactive heterocycles.

Pyrimidines are the six member heterocyclic aromatic compounds with two nitrogen atoms at position 1 and 3. Pyrimidine embedded heterocycles are of great interest because they constitute an important class of natural and nonnatural products, many of which exhibits biological activities and clinical applications.[6] Thymine, cytosine, and uracil are building blocks of nucleic acids, DNA and RNA possess pyrimidine skeleton have widespread therapeutic applications. Some pyrimidines exhibit significant in vitro activity against unrelated DNA and RNA, viruses including polioherpes viruses, diuretic, antitumour, anti-HIV, and cardiovascular.[7] In addition to this, various analogs of pyrimidines have been found to posses

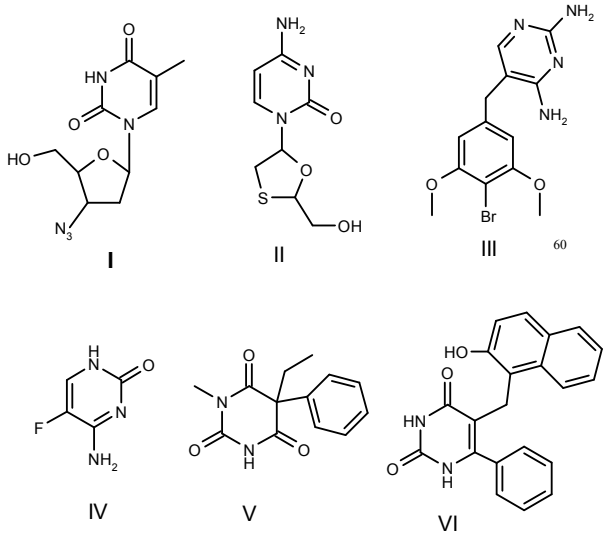


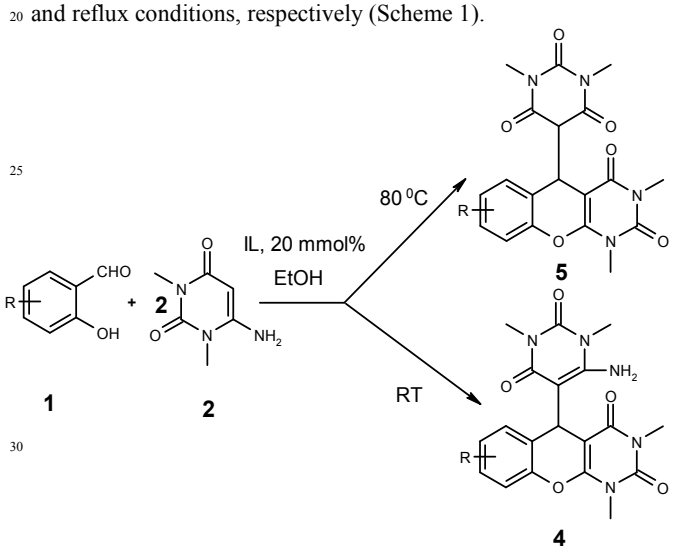
Fig 1 Drugs with pyrimidine backbone

antibacterial[8], antifungal[9], antileishmanial[10], anti-inflammatory[11], analgesic[12], antihypertensive[13], antipyretic[14],

antiviral[15], antidiabetic[16], antiallergic[17], anticonvulsant[18], antioxidant[19], antihistaminic[20], herbicidal[21], and anticancer activities[22] and many of pyrimidines were reported to possess potential central nervous system (CNS) depressant properties [23] and also act as calcium channel blockers [24]. These multifarious activities resulted into discovery of plethora of drugs with pyrimidine backbone. [Fig. 1] Previous investigation has shown that pyrimidine immobilized heterocycles *viz* zidovudine (I) and Lamivudine (II) are a sort of anti-HIV drugs [25], Brodiprim (III) and Flucytosine (IV) are an antibacterial and antifungal agent[26]. Methylphenobarbital (v) is an antiepilepticum [27], 6-aryl uracil derivatives (VI) show antitumor activity [28]. Brodiprim is effective antibacterial compound [29].

Results and Discussion

With our continued quest in devising eco-friendly methodologies for the synthesis of pyran nucleus,[30] in this letter, we reported the dramatic influence of a new task-specific ionic liquid for the synthesis of pyranopyrimidinedione as well as pyranopyrimidinetrione in ethanol medium at room temperature and reflux conditions, respectively (Scheme 1).



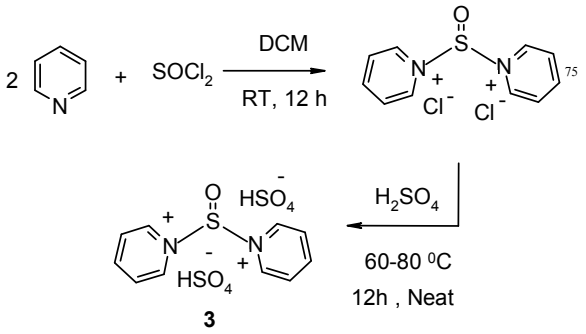
Scheme 1 Synthesis of the novel pyranopyrimidinedione and pyranopyrimidinetrione.

Firstly, we looked at optimization of reaction conditions in terms of catalyst for the model reaction of salicylaldehyde (1 mmol), 6-amino uracil. Initially, to check the effect of catalyst, the reaction was carried out in absence of catalyst (entries 1, 2, Table 1), however, the reaction did not proceed even under reflux conditions. Then attention was focused on screening of various Lewis and Bronsted acid catalysts in the formation of 4a. It is found that Lewis acids like $AlCl_3$, $ZnCl_2$, $FeCl_3$, and $(CH_2)_4SO_3Mim$, Na *p*-TSA (entries 3-5, 13, 15, Table 1) failed to carry present transformation even after long reaction time. Low yields of desired product was obtained in presence of *p*-TSA (entry 14, Table 1) and ionic liquids such as [PySOPy]Cl, [PySOPy]Cl_2, [BMim] HSO_4, [PySOCl] HSO_4 and [PySOCl] TSO (entries 6,7,10,11,12, Table 1). These observations seem that yield of reaction can be improved in presence of the strong bronsted acidic catalyst. So, ionic liquids such as $[(CH_2)_4SO_3HMim]$ HSO_4, [CMim] HSO_4, was employed and found 65-75 % yield of desired product (entries 8, 9, Table 1). Yield of product was boosted to 84 % in presence of catalytic amount of thionyl chloride (entry 16, Table 1). Which inspired us to synthesize novel ionic liquid having strong Bronsted acid cites along with thionyl (S=O) functionality for enhance the rate of the reaction.Then attempts were directed towards the synthesis of novel hydrophilic ionic liquid. ILs based on pyridynium salts have attracted particular attention, as they are easy to prepare and handle, having good solubility for many substrates and molecular catalyst. The synthesis of $[(Py)_2SO]$ $[HSO_4]_2$ hydrophilic IL 3, was achieved in two steps. Initially, $[(Py)_2SO]$ Cl_2 was prepared by reaction of pyridine with thionyl chloride in dichloromethane followed by treatment of sulphuric acid offered the desired ionic liquid in quantitative yield (Scheme 2).

Table 1 Screening of catalyst in the formation of 4[a]

Entry	Catalyst	Time (h)	Yield (%)[b]
1	No Catalyst	3	---
2	No Catalyst	3	---[c]
3	$AlCl_3$	3	---
4	$ZnCl_2$	3	---
5	$FeCl_3$	3	---
6	[PySOCl]Cl	2	20
7	[PySOPy][Cl]$_2$	2	30
8	$[(CH_2)_4SO_3HMim][HSO_4]$	1	76
9	[CMim][HSO_4]	1	66
10	[BMim] [HSO_4]	3	50
11	[PySOCl] [HSO_4]	2	53
12	[PySOCl] TSO	3	25
13	$(CH_2)_4SO_3Mim$	3	---
14	*p*-TSA	2	45
15	Na-PTSA	3	---
16	$SOCl_2$	1	84
17	[PySOPy] [HSO_4]$_2$	1	96

[a] Salicylaldehyde (1mmol), 6-amino uracil (2 mmol) and 20 mol% catalyst in ethanol at room temperature; [b] Isolated yield; [c] Reflux condition



Scheme 2 Synthesis of the novel Bronsted acidic ionic liquid

Interestingly, the dication homoanionic ionic liquid revealed exceptional catalytic activity provided the corresponding product in excellent yield due to both Lewis as well as Bronsted acidic functionality (entry 17, Table 1). Effect of amount of catalyst was evaluated by employing 5, 10, 15, 20, 25 mol % of IL for model

reaction furnished 4a in 40, 70, 84, 96, 96 %, respectively. It is found that 20 mol % of catalyst provided the maximum yield. Exceeding the catalyst quantity than 20 mol % did not affect the yield of product and reaction time.The performance of the reaction was also assessed using different solvents such as chloroform, acetonitrile, DCM, acetone, DMF and THF. Non polar solvents gave lower yields even after elongated reaction time (entries 1-4, Table 2). Ethanol is found to be best choice for the present transformation employing 20 mol % of catalyst. (entry 9, Table 2).

Table 2 Influence of solvent on the synthesis of 4a[a]

Entry	Solvent	Time (h)	Yield %[b]
1	Acetonitrile	3	46
2	DCM	3	20
3	Acetone	4	55
4	THF	4	30
5	Chloroform	3	56
6	DMF	4	77
7	Methanol	1	90
8	Water	1	80
9	Ethanol	1	96

[a] Salicylaldehyde (1mmol), 6-amino uracil (2 mmol) and catalyst (20 mol %), ethanol (5 mL), room temperature. [b] Isolated yield.

As reaction proceeds a nearly homogeneous mixture is formed Fig 2.(A) and product precipitate from ethanol Fig 2.(B) which was isolated by simple filtration and confirmed by spectral analysis. ^{1}H NMR spectrum indicates remarkable singlet at δ = 4.81 and 5.77 ppm for benzylic methine proton and two amine protons, respectively. In the IR spectrum, the absorption bands at 3445, 3388 and 1695, 1634 cm^{-1} corresponding to primary amine and two carbonyls of amide and α, β-unsaturated amide confirmed the structure of product.

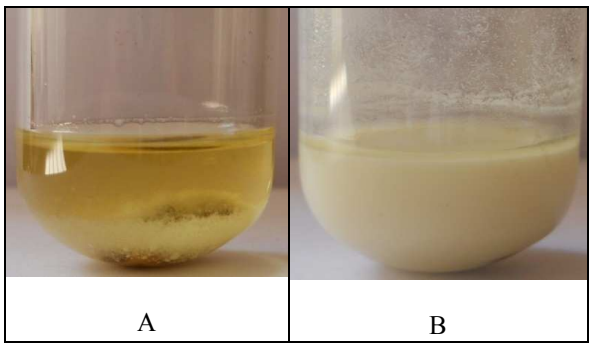
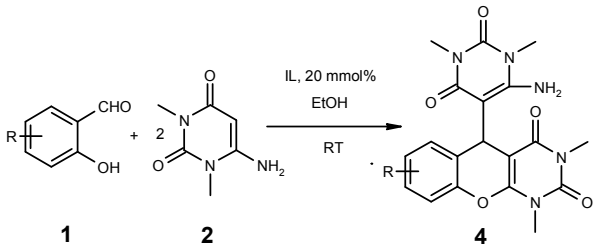


Fig 2 Reaction mixture at starting of reaction (A); reaction mixture after completion of reaction (B)

This serendipitous results led us to further explore the scope and general utility of this novel transformation. So a series of salicylaldehydes were treated with 6-amino uracil under optimized reaction conditions. Both electron-donating (entries b-g, Table 3) and electron-deficient (entry h-k, Table 3) salicylaldehydes afforded corresponding pyranopyrimidinediones in excellent yields (>82–96 %) indicating an inconspicuous stereo-electronic effect (3a-k, Table 3).

Table 3 Synthesis of novel pyranopyrimidinediones catalyzed by novel dication homoanionic Bronsted acidic ionic liquid in ethanol at room temperature [a]



1 **2** **4**

Entry	Product[b] (4)	Time (h)	Yield[c] (%)
a	R= H	1	96
b	R= 5-CH_3O	1	96
c	R= 3-CH_3CH_2O	1	98
d	R= 3-OH	1	94
e	R= 4-OH	1	92
f	R=5-OH	1	94
g	R= 3.4-OH	1	92
h	R=5-Cl	1.2	95
i	R=5-Br	1	96
j	R= 5-NO_2	1.5	93
k	R= naphthyl	1.5	90

[a] Reaction conditions: Salicylaldehyde(1 mmol); uracil (2 mmol) ; IL 20 mol % ; temp = Room temp; solvent = 5 mL 95 % ethanol; [b] All products showed satisfactory spectroscopic data (IR, ^{1}H, ^{13}C NMR and MS); [c] yields refer to pure, isolated products.

Having succeeded in the synthesis of pyranopyrimidinediones, we sought to investigate influence of temperature and performed the reaction of salicylaldehyde and 6-amino uracil in 95% ethanol at reflux temperature in presence of 20 mol % of IL 3 (Scheme 3). However, it failed to produce expected product **7**. To our delight, we observed unexpected formation of novel pyranopyrimidinetrione 5a in 87 % yield (Scheme 3). Fig. 3 depicted IR spectrum of 6-amino uracil, product 4a and 5a. Bands due to –NH_2 in 6-amino uracil and product 4a at 3445 and 3388 cm^{-1} get disappear in 5a confirmed its formation. The identification of pyranopyrimidinedione 4a–k and pyranopyrimidinetrione 5a-d is unequivocally ascertained by FT-IR, ^{1}H, ^{13}C NMR and MS analysis. The structure of 5a (Table 4) was further confirmed by X-ray crystallography, which exhibits the geometry of crystal as monoclinic and two rings twisted out-of-plane to minimize steric interactions Fig 4 [31].

In order to explore the reaction scope, other salicylaldehydes were tested and the results are summarized in Table 4. We observed that electron-rich salicylaldehydes undergo smooth reaction with 6-aminouracil afforded desired pyranopyrimidinetriones in excellent yields. It is noteworthy that in case of electron deficient salicylaldehydes product **4** is obtained instead of **5** even after prolonged heating for which we do not have any concrete answer to explain this anomaly

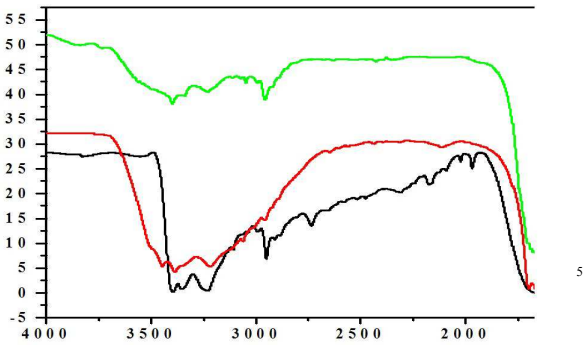


Fig 3 IR spectrum of uracil, product 4a and 5a

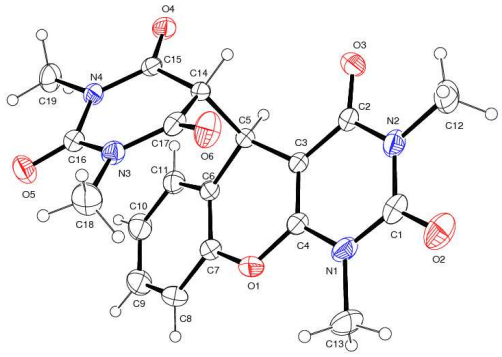
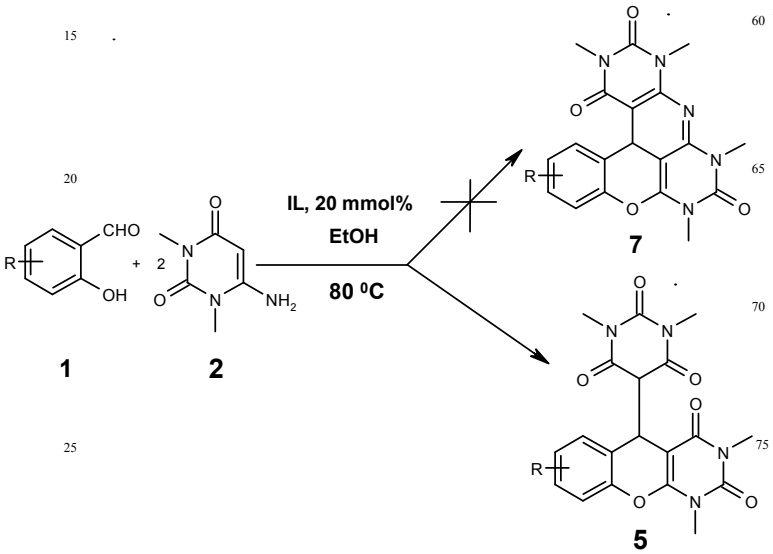


Fig 4 ORTEP diagram of 5a (Table-4)



Scheme3 Synthesis of the novel pyranopyrimidinetriones

A speculative mechanism for formation of product 4 and 5 is depicted in Scheme 4. The synergistic combination of the acidic group and the thionyl group are the key factors due to which electrophilicity of carbonyl carbon of **1** increases, favors nucleophilic attack of **2** followed by ring closure resulted into formation of intermediate **6**. Protonation of **6** by IL and subsequent Michael attack of second molecule of **2** resulted into formation of desired product **4**. Protonation of amino group by IL **3** under thermal condition took place followed by nucleophilic attack of water yielded corresponding product **5** by keto enol tautomerisation.

Table 4 Temperature influenced synthesis of novel pyranopyrimidinetriones catalyzed by dication homoanionic Bronsted acidic ionic liquid in ethanol [a]

Entry	Product[b] (5)	Time (h)	Yield[c] (%)
a	R= H	5	94
b	R= 5-CH_3O	6	92
c	R= 3-CH_3CH_2O	6	94
d	R=5-OH	6	92
e[d]	R= 5-NO_2	10	80
f[d]	R= 3,5 Cl	10	84

[a] Reaction conditions: Salicylaldehyde (1mmol); Uracil (2 mmol); IL 20 mol % ; temp = 80 ^{0}C ; solvant = 5 mL 95% ethanol; [b]All products showed satisfactory spectroscopic data (IR, ^{1}H and ^{13}C NMR and MS); [c] yields refer to pure, isolated products; [d] For electron withdrowing substituent formation of product 4 was observed instead of product 5.

Recycling of catalyst is one of the most significant criteria of green chemistry, hence recovery and reuse of the ionic liquid as catalyst was examined.The separation of product was very easy as mere filtration through an ordinary filter paper. Then ionic liquid was conveniently recovered and reused after heat treatment under vacuum at 70 ^{0}C for 2 hours. Reusability of recovered catalyst was studied for a fresh reaction and found that ionic liquid was reused at least five times without significant decrease in the reaction yield 96, 93, 90, 89, 88 %, respectively (fig. 5).

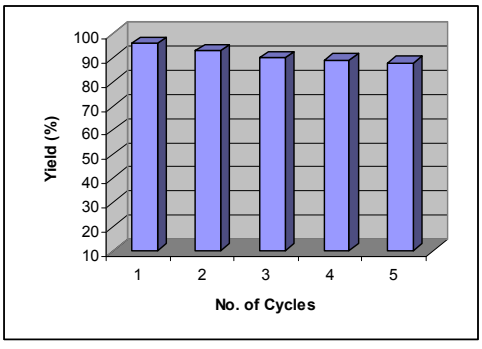


Fig 5 Recycling of catalyst

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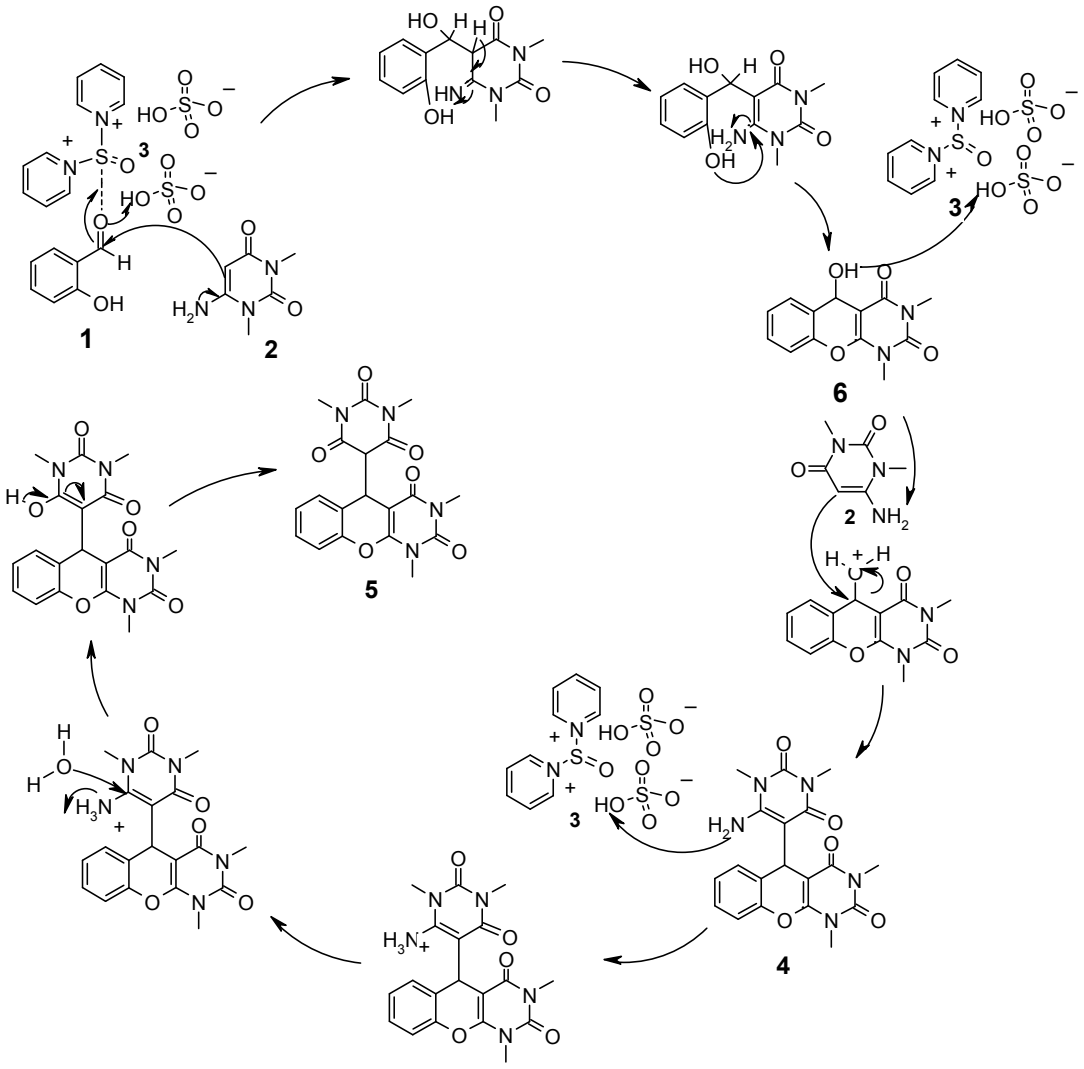

Scheme 4 A plausible mechanism for formation of product 4 and 5.

Conclusion

In summary, we have introduced a temperature influenced ionic liquid catalyzed reaction of salicyaldehyde and 2-amino uracil led new class of pyranopyrimidinediones and pyranopyrimidinetriones. The detailed mechanism is suggested. In general, all the reactions are very clean and reasonably fast. This method offers marked improvements with regard to operational simplicity, reaction time, mild reaction conditions, general applicability, high isolated yields of products, and greenness of procedure, avoiding hazardous organic solvents and toxic catalysts. The ionic liquid has been reused in up to five runs without loss of activity.

Experimental Section

Various substituted salicylaldehydes (Sigma-Aldrich), 6-amino uracil (Sigma-Aldrich) were used as received. IR spectra were

recorded on a Perkin-Elmer FT-IR-783 spectrophotometer. NMR spectra were recorded on Bruker AC-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) spectrometer in DMSO-d_6 and $CDCl_3$ using TMS as an internal standard and δ values are expressed in ppm. Single crystal X-ray crystallography was recorded on Bruker Kappa APEX II from SAIF, IIT, Madras.

General Procedure:

Synthesis of ionic liquid $[(Py)_2SO]Cl_2$:

A three necked flask (100 ml) equipped with a condenser was charged with pyridine (0.79 g, 10mmol) in dry dichloromethane (50 ml). Then under rigorous stirring, 0.36 ml (5mmol) of thionyl chloride was drop wise added over a period of 30 min, then the reaction mixture was stirred for 12 h at room temperature. The ionic liquid $[(Py)_2SO]Cl_2$ was obtained by distillation of dichloromethane, washed with dry diethyl ether (3×10 ml) and purified through drying in a vacuum at 80 ^{0}C to remove the residual dichloromethane.

Synthesis of ionic liquid $[(Py)_2SO][HSO_4]_2$:

A round bottom flask (50 ml) was charged with $[(Py)_2SO]Cl_2$ (10 g, 36 mmol), then sulphuric acid (7.056 g, 72 mmol) was added over a period of 5 min at 0-5^{0}C. Afterward, the reaction mixture was stirred for 12 h at 80^{0}C furnished $[(Py)_2SO]$ $[HSO_4]_2$ in 98% yield.

Synthesis of Pyranopyrimidinedione:

A mixture of salicylaldehyde (1 mmol) and 6-amino uracil (2 mmol) in Bronsted acidic ionic liquid $[(Py)_2SO]$ $[HSO_4]_2$ (20 mol%) was stirred at ambient temperature for the time indicated in Table 3. The progress of the reaction was monitored by TLC. After completion of reaction, the precipitated product was filtered and washed with water and ethanol.

Synthesis of Pyranopyrimidinetrione:

A mixture of salicylaldehyde (1 mmol), uracil (2 mmol) and Bronsted acidic ionic liquid $[(Py)_2SO]$ $[HSO_4]_2$ (20 mol%) in refluxing ethanol (5 mL) was stirred for time mentioned in Table 4. After completion of the reaction confirmed by TLC, the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered and washed with water (10 mL) and methanol (5 mL) afforded the pure product.

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31. Crystallographic data for compound 5a in this Paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1005214. These data can be obtained free of charge, on application to from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Email: deposit@ccdc.cam.ac.uk; Phone: +44-1223-336-408; fax: (+44)-1223-336- 033.

GRAPHICAL ABSTRACT

1, 1'-sulfinyldipyridinium bis (hydrogen sulfate) ionic liquid: synthesis and its application towards temperature influenced synthesis of novel pyranopyrimidinediones and pyranopyrimidinetriones

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