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Ionic liquid mediated and promoted eco-friendly preparation of thiazolidinone and pyrimidine nucleoside–thiazolidinone hybrids and their antiparasitic activities

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ABSTRACT

Without any catalyst, 2,3-disubstituted-1,3-thiazolidin-4-one derivatives were synthesized efficiently via the three-component reaction of aldehyde, amine and mercaptoacetic acid in [bmim][PF_6]. The whole procedure is simple and straightforward and no aqueous work-up is needed. By employing this protocol, a series of novel pyrimidine nucleoside–thiazolidin-4-one hybrids were prepared and their preliminary antiparasitic activities were also studied and reported.

It is well known that thiazolidinone and their derivatives are important heterocyclic compounds due to their broad biological activities such as anti-inflammatory,[1] antiproliferative,[2] anti-cyclooxygenases (COX-1 and COX-2),[3] anti-histaminic[4] and anti-bacterial activities.[5] More importantly, some of the 2,3-diaryl-1,3-thiazolidin-4-ones were found to be highly effective against HIV-1 replication, thereby acting as non-nucleoside HIV-I reverse transcriptase inhibitors (NNRTIs).[6] Recently, they were also found to be potent as inhibitors for HCV NS5B RNA polymerase.[7] As a result, various protocols have been developed to prepare more structurally diverse thiazolidinones and related compounds for quantitative structure–activity relationship (QSAR) studies. Generally, the thiazolidinone ring was constructed by a three-component reaction of aldehyde, amine and mercaptoacetic acid via a sequence of imine formation, sulfur nucleophilic attack on the imine carbon and intramolecular cyclization. Usually, the above process is realized in benzene or toluene under reflux with a Dean–Stark trap or molecular sieves to remove the in situ formed water and drive the reaction to complete.[6b,d,f,8] There are also reports using anhydrous $ZnCl_2$[9] or sodium sulfate[10] as desiccant to assist the formation of thiazolidinone derivatives. Katti et al. reported a novel process by employing DCC to promote the reaction and the product was obtained with high yield.[11] Bazureau et al. also reported an alternative method by using a combination of task-specific ionic liquid and microwave dielectric heating.[12] More recently, Yan et al. reported a microwave-assisted fluorous synthesis of 2-aryl-substituted thiazolidinone library.[13] However, some of these reported methods still suffered one or more limitations such as using either poisonous solvent or expensive catalyst, employing specific apparatus, necessitating long reaction period and tedious handling processes, resulting in low or moderate yields. Therefore, it is of interest to develop highly efficient and more practical method for the preparation of this important heterocyclic framework.

The development of environmentally friendly catalysts and solvents for organic chemistry and medicinal chemistry is an area of considerable importance. From both economical and environmental points of view, the use of non-volatile solvents and green catalysts is very promising. In the last a few years room temperature ionic liquids (RTILs) have been recognized as a possible environmentally benign alternative to chemical volatile solvents because, in contrast with the conventional organic solvents, they are non-volatile, non-explosive, easy to handle, thermally robust and recy-

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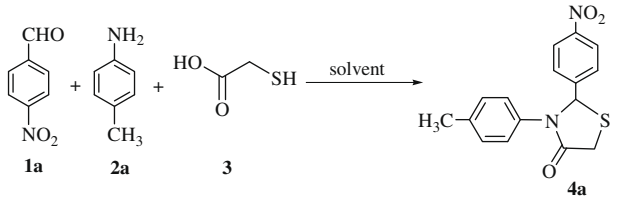
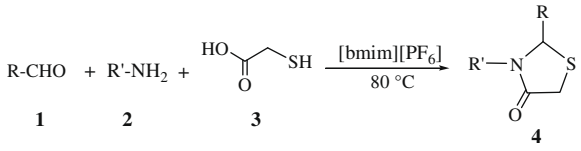


Scheme 1.



Scheme 2.

Table 1
Preparation of **4a** under different reaction conditions[a]

Entry	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
1	[bmim][PF_6]	rt	10	50
2	[bmim][PF_6]	50	8	76
3	[bmim][PF_6]	70	6	82
4	[bmim][PF_6]	80	5	87
5	[bmim][PF_6]	90	5	87
6	[bmim][BF_4]	80	8	74
7	CH_2Cl_2	Reflux	24	55
8	EtOH	Reflux	24	10
9	THF	Reflux	24	30
10	Toluene	Reflux	8	85

[a] Reaction conditions: 1 mmol of **1a**, **2a** and **3**, respectively; 1.5 g of [bmim][PF_6] for entries 1–6, or 4 mL of solvent for entries 7–10.

Table 2
Studies on the recovery and reuse of [bmim][PF_6][a]

Round	Time (h)	Temperature (°C)	Yield (%)	IL recovered (w/w%)
1	5	80	87	98
2	5	80	88	97
3	5	80	85	97
4	5	80	83	95
5	5	80	80	93

[a] Reaction conditions: 1 mmol of **1a**, **2a** and **3**, respectively; 1.5 g of [bmim][PF_6] was used for the first run.

Table 3
Preparation of compound **4** in [bmim][PF_6][a]

Entry	R	R′	Product	Reaction time (h)	Yield[b] (%)
1	*p*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	**4a**	5	87
2	*p*-$NO_2C_6H_4$	*p*-ClC_6H_4	**4b**	5	91
3	*p*-ClC_6H_4	*p*-ClC_6H_4	**4c**	7	76
4	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	**4d**	7	80
5	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	**4e**	6	83
6	*p*-FC_6H_4	*p*-$CH_3C_6H_4$	**4f**	7	81
7	*p*-ClC_6H_4	2-Pyridyl	**4g**	9	47
8	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	**4h**	7	56
9	*p*-BrC_6H_4	*p*-$CH_3C_6H_4$	**4i**	7	75
10	*p*-BrC_6H_4	*p*-ClC_6H_4	**4j**	7	80
11	*p*-FC_6H_4	*p*-ClC_6H_4	**4k**	7	81
12	*p*-FC_6H_4	2-Pyridyl	**4l**	7	48
13	*p*-ClC_6H_4	*p*-BrC_6H_4	**4m**	7	82
14	*p*-BrC_6H_4	*p*-BrC_6H_4	**4n**	7	85
15	*p*-FC_6H_4	*p*-BrC_6H_4	**4o**	7	80
16	*p*-$CH_3C_6H_4$	*p*-BrC_6H_4	**4p**	7	81
17	*p*-$NO_2C_6H_4$	*p*-BrC_6H_4	**4q**	7	92
18	*o*-ClC_6H_4	*p*-ClC_6H_4	**4r**	7	76
19	*o*-BrC_6H_4	*p*-BrC_6H_4	**4s**	7	80
20	*o*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4$	**4t**	7	88
21	*o*-$NO_2C_6H_4$	*p*-BrC_6H_4	**4u**	7	90
22	*o*-$NO_2C_6H_4$	*p*-ClC_6H_4	**4v**	7	87

[a] Reaction conditions: 1 mmol of **1**, **2** and **3**, respectively; 1.5 g of [bmim][PF_6]; 80 °C.
[b] Isolated yields.

clable.[14] Accordingly they are emerging as novel replacements for volatile organic solvents in organic synthesis.[15]

Considering the fact that ILs have been used as useful and efficient media for esterification reactions in despite of the in situ formation of water[16] because they can create an opportunity to drive the equilibrium, we studied the possibility of employing the easily made 1,3-dialkylimidazolium cation based ionic liquid as green and efficient solvent for the preparation of thiazolidinone derivatives via the three-component condensation of aldehyde, amine and mercaptoacetic acid.

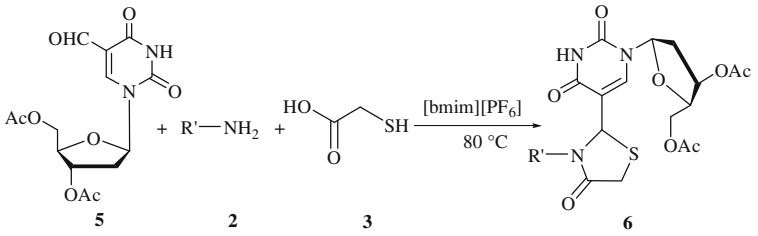
Our study was initiated by the reaction of 4-nitrobenzaldehyde (**1a**), 4-methylphenylamine (**2a**) and mercaptoacetic acid (**3**) (Scheme 1). The effect of different solvents, various temperature conditions on the condensation process was studied and the results were summarized in Table 1.

It turned out that the multi-component reaction of **1a**, **2a** and **3** went smoothly in an ionic liquid, [bmim][PF_6], 1-butyl-3-methylimidazolium hexafluorophosphate, and gave the corresponding 2,3-disubstituted-1,3-thiazolidin-4-one (**4a**). The yield of **4a** increased remarkably with the temperature increasing until 80 °C (Table 1, entries 1–5). Interestingly, of the two ILs studied, namely [bmim][PF_6] and [bmim][BF_4], [bmim][PF_6] gave better result (Table 1, entries 4 and 6), presumably due to its hydrophobic activation activity. It is postulated that water formed in situ from the condensation process is miscible with hydrophilic [bmim][BF_4] and thus detained, which prevents the reaction from going completely. In contrast, the hydrophobic nature of [bmim][PF_6] would create a micro-environment to drive the equilibrium by extruding water out of the ionic liquid phase and thus result in a higher conversion.

The same reaction was also run in several conventional organic solvents and the results were also included in Table 1. Comparing with CH_2Cl_2, EtOH and THF, ionic liquids exhibited enhanced reactivity by reducing reaction time and improving the yields significantly. For example, treatment of **1a**, **2a** and **3** in [bmim][PF_6] afforded **4a** in 87% over 5 h at 80 °C whereas the same reaction in refluxing CH_2Cl_2 gave **4a** in a yield of 55% over 24 h (Table 1, entries 4 and 7). When EtOH or THF was used, the yield of **4a** was even lower (Table 1, entries 8 and 9) with the corresponding imine as the main product. On the other hand, toluene gave comparable result in terms of yield (Table 1, entry 10). However, as one of the environmental priority pollutants, toluene poses a serious threat to the environment.[17] Therefore it is not a solvent of choice for sustainable chemistry. In contrast, [bmim][PF_6] is non-volatile and easy to handle, thus acting as a benign and efficient medium.

The recovery and reuse of [bmim][PF_6] were also studied, and **1a**, **2a** and **3** were used as model substrates. Upon completion of the condensation process, **4a** was obtained by thorough extraction with diethyl ether and the remaining ionic liquid phase was recycled in subsequent reactions. Further studies showed that the recovered [bmim][PF_6] could be successively recycled for at least five times without obvious loss in its efficiency (Table 2).

Encouraged by the results obtained above, we extended this process to various aldehyde and amine substrates to gain more insight into this reaction (Scheme 2). It turned out that in [bmim][PF_6], various aldehyde and amine substrates reacted smoothly with mercaptoacetic acid and afforded the corresponding



Scheme 3.

Table 4
Preparation of compound **6** in [bmim][PF_6][a]

Entry	R′	Product	Reaction time (h)	Yield[b] (%)
1	C_6H_5	**6a**	6	70
2	*p*-$CH_3C_6H_4$	**6b**	5	75
3	*p*-BrC_6H_4	**6c**	6	58
4	*p*-ClC_6H_4	**6d**	6	62
5	*p*-FC_6H_4	**6e**	6	65
6	*m*-$NO_2C_6H_4$	**6f**	6	60
7	2-Pyridyl	**6g**	8	53
8	6-Br-2-pyridyl	**6h**	8	50

[a] Reaction conditions: 1 mmol of **5**, **2** and **3**, respectively; 1.5 g of [bmim][PF_6]; 80 °C.
[b] Isolated yields.

Table 5
Antiparasitic activities of compounds **6a–h**[a]

Compound	*L. donovani* Promastigote IC_{50} (μM) ± SD	*T. brucei brucei* trypomastigote IC_{50} (μM) ± SD[b]
6a	>100	50
6b	>100	100
6c	ND[c]	ND[c]
6d	>100	25
6e	>100	50
6f	>100	>100
6g	>100	>100
6h	>100	50

[a] The evaluations were performed as previously described.[21]
[b] IC_{50} defined as inhibitory concentration 50%.
[c] ND, not determined.

2,3-disubstituted-1,3-thiazolinin-4-ones (**4**) in good to excellent yields (Table 3). It is worth to be noted that the procedure is simple and convenient, and does not require any aqueous work-up thereby avoiding the generation of toxic waste.

As a further respect, the 'privileged' structure of nucleosides has led to a variety of efficacious antiviral agents such as AZT, d4T, lamivudine and acyclovir. Many pyrimidine nucleoside analogues with potent biological properties have arisen by substitution at the 5-position of the uracil base, particularly in the 2′-deoxyuridine series.[18] In this regard, we have an ongoing program on the design and preparation of novel 5-substituted pyrimidine nucleoside derivatives with potential biological activities.[19] Our approach to new lead compounds has been guided by the following considerations. Firstly, the nucleosides scaffold is an excellent point of departure in the search for new compounds with potential activities; secondly, other privileged molecular scaffolds, taking thiazolidinone as an example, has also spawned a significant number of drugs and biologically active agents. With the novel procedure developed in this paper, we were interested in the preparation of novel hybrids of 5-substituted pyrimidine nucleoside and thiazolidin-4-ones to get new entities with synergetic biological activities as potential biologically active agents. To the best of our knowledge, precedent studies on the applications of ionic liquids in the preparation of nucleoside derivatives are still limited.[20]

The preparation was realized from the reaction of 5-formyl-2′-deoxyuridine, acting as an aldehyde, with amines and mercaptoacetic acid by employing [bmim][PF_6] as the reaction medium and promoter. Thus, 3′,5′-di-*O*-acetyl-5-formyl-2′-deoxyuridine (**5**), previously prepared from thymidine, was treated with aromatic amines (**2**) and mercaptoacetic acid (**3**) in [bmim][PF_6] (Scheme 3). The results were included in Table 4. It turned out that under the optimized reaction condition, **5** reacted smoothly with various amine substrates and mercaptoacetic acid and afforded the desired hybrids (**6**) in good to moderate yields.

As nucleosides are known to exhibit antileishmanial and trypanocidal activities[21], the hybrid compounds were evaluated against trypomastigote forms of *Trypanosoma brucei brucei GVR 35* and promastigote forms of *Leishmania donovani LV9*. The results are listed in Table 5.

As indicated in Table 5, part of the hybrids tested possess moderate activities against trypomastigote forms of *T. brucei brucei*, indicating they may be used as lead compounds for further elaboration. On the other hand, they are inactive against promastigote forms of *L. donovani LV9*.

In summary, a novel and efficient procedure for the preparation of 2,3-disubstituted-1,3-thiazolinin-4-one derivatives by using ionic liquids as recyclable promoter and reaction medium was developed. The notable advantages of this method include high efficiency, simple procedure and benign nature by avoiding the use of volatile and poisonous conventional organic solvents. In addition, the ionic liquids used were found to be easily recovered and efficiently reused. With this novel protocol, a series of pyrimidine nucleoside–thiazolinin-4-one hybrids were prepared and part of the hybrids possess moderate activity on trypomastigote forms of *T. brucei brucei*. The test of these hybrids as potential antivirals and the search for the application of the novel process presented herein in the synthesis of biological interesting compounds are currently underway and the results will be reported in due course.

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