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Synthesis of nucleoside-based antiviral drugs in ionic liquids

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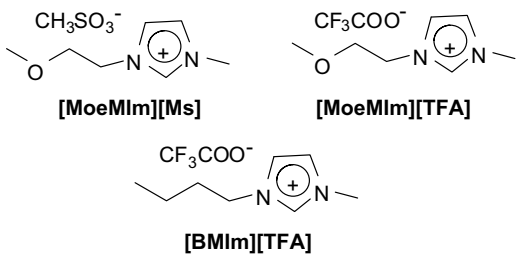
ABSTRACT

Nucleoside-based antiviral drugs have been synthesized using imidazolium-based ionic liquids as reaction medium. The ionic liquids were proved to be better solvents for all the nucleoside in terms of solubility and reaction medium as compared to conventional molecular solvents.

Nucleosides analogs are prominent drugs used for treatment of several viral infections, including HSV (herpes simplex virus), HIV (human immunodeficiancy virus), HBC (hepatitis B virus), HCV (hepatitis C virus), and HCMV (human cytomegalovirus) infections. Some well-known examples of nucleoside-based antiviral drugs already in the market are: AZT (Zidovudine), ddC (2′,3′-dideoxycytidine), d4T (Stavudine), BVDU (Brivudine), TFT (Trifluridine), IDU (Idoxuridine), etc.[1] Several structural modifications have been achieved on the heterocyclic bases and/or on the sugar moiety of natural nucleosides in search of antiviral nucleoside analogs.[1,2] However, the synthesis of modified nucleosides presents a major challenge, which is further aggravated by poor solubility of these compounds in common organic solvents. Solvents commonly used in nucleoside chemistry, *viz.* pyridine, *N*,*N*-dimethylformamide (DMF), *N*,*N*-dimethylacetamide (DMA) and *N*-methylpyrrolidone (NMP), are hazardous for human health and environment. Moreover, these solvents are difficult to remove and often get contaminated with reaction products making the workup procedures more tedious and time consuming. Hence, there is a great need for the development of new methodologies for nucleoside chemistry using environmentally benign media which could replace the conventional solvents and provide sufficient solubility to nucleosides.

Ionic liquids (ILs) have emerged as attractive alternatives to conventional organic solvents due to their advantageous properties viz. negligible vapor pressure, recyclability, high thermal stability, and their ability to dissolve wide range of compounds.[3] The possibilities of their structural variations help in designing ideal solvents suitable for any particular process.[4] Despite their attractive properties, there are only handful of reports where ILs have been used for nucleoside reactions.[5] Our earlier studies in this area have led to designing of ILs which provide high solubility for nucleosides and found to be efficient reaction medium for selective modifications, giving high yields under ambient conditions.[5e,5f] Herein, we are reporting the utility of ILs 1-methoxyethyl-3-methylimidazolium methanesulfonate ([MoeMIm][Ms]), 1-methoxyethyl-3-methylimidazolium trifluoroacetate ([MoeMIm][TFA]) and 1-butyl-3-methylimidazolium trifluoroacetate ([BMIm][TFA]) (Fig. 1)[5e,5f] as reaction medium for some of the key steps involved in the synthesis of antiviral nucleoside drugs d4T, BVDU and TFT.

Stavudine (**2**), also known as 2′,3′-didehydro-3′-deoxythymidine (d4T) is an anti-HIV drug which act as a reverse transcriptase inhibitor.[6] Although several methods for its synthesis are reported, they are associated with limitations such as tedious reaction conditions and workup, longer reaction time, use of expensive reagents, poor yields, and use of harmful solvents.[6,7] In one of



[MoeMIm][Ms] **[MoeMIm][TFA]** **[BMIm][TFA]**

Figure 1. Structures of ILs used.

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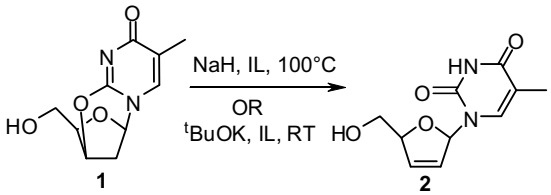
these methods, Reese et al. carried out elimination reaction on 2,3′-anhydrothymidine (**1**) by heating it with sodium hydride using DMA as solvent at 100 °C for 30 min to afford d4T in 81% yield.[7b] However, the workup procedure of this reaction was very tedious, requiring many steps e.g., neutralization, co-evaporation, extraction, and purification. In our methodology, we used ILs as solvents keeping all other conditions as reported previously. Interestingly, we observed that by replacing DMA with ionic liquids, the reaction was completed in 5–10 min giving higher product yields (Scheme 1). The workup procedure was also very simple; after completion, the reaction mixture was diluted with dichloromethane and loaded on silica gel column, which was eluted by MeOH:CH_2Cl_2 (10:90) to obtain the product. We have also carried out the same reaction using ^{t}BuOK as base (in literature, this base has never been used for this reaction) in ILs at room temperature. Although we did not observe complete conversion in these reactions but still the product was obtained in up to 62% yield (Scheme 1).

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (Brivudine or BVDU) (**4**) is an anti-HSV drug. It is a highly specific inhibitor of herpes simplex virus (HSV-1) and varicella-zoster virus (VZV) replication.[8] It is a modified form of deoxyuridine which gets incorporated into the viral DNA during replication and results in mutations by blocking base pairing due to the substitution at C-5 position.[8] It has been synthesized from its carboxylic acid analog (*E*)-5-(2-carboxyvinyl)-2′-deoxyuridine (**3**) by reacting with *N*-bromosuccinimide (NBS) using THF:H_2O (3:2)[9] or DMF[10] as solvent at room temperature in 68–95% yield (Scheme 2). We performed same reaction using ILs as solvent and monitored the progress using TLC until only desired product was formed and the reaction was stopped immediately when any side product started to appear. The product was isolated by purification using flash chromatography. Although the reactions were not carried out to complete conversion, still the product could be obtained in moderate to good yield.

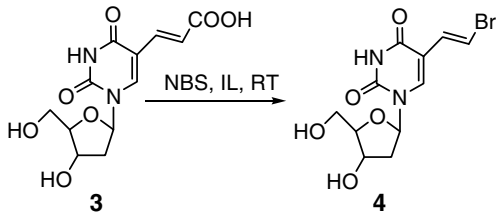
5-Trifluoromethyl-2′-deoxyuridine (Trifluridine or TFT) (**8**) is another anti-HSV antiviral drug, used primarily on the eye.[11] It can be synthesized from 2′-deoxyuridine (**5**) in three steps. The hydroxyl groups of 2′-dU (**5**) were first protected by acetylation to give 3′,5′-diacetoxy-2-deoxyuridine (**6**). Generally, this reaction is carried out in pyridine/DMAP[12] or acetonitrile/Et_3N/DMAP[13] with excess of acetic anhydride, and the reaction time varies from 2 to 12 h. We carried out this reaction in all three ILs using DMAP as catalyst and acetic anhydride (2 equiv) as acylating agent. Interestingly, the reactions were completed in 20–25 min to give the acetylated derivative in 91% yields as a single product. Moreover, no purification was required and the product was obtained by simple



Solvents	NaH/ IL/ 100°C time (min) / Yield (%)*	^{t}BuOK/ IL/ RT time (min)$/ Yield (%)*
DMA[8b]	30/81	-
[MoeMIm][Ms]	10/89	360/55
[MoeMIm][TFA]	5/93	360/60
[BMIm][TFA]	10/91	360/62

*Isolated yields.
$No further conversion was observed after this time.

Scheme 1. Synthesis of d4T in ionic liquids.



Solvent	time(hrs)	Yield(%)*
THF: H_2O[10]	0.5	95
[MoeMIm][Ms]	1.0	70
[MoeMIm][TFA]	1.5	52
[BMIm][TFA]	1.5	56

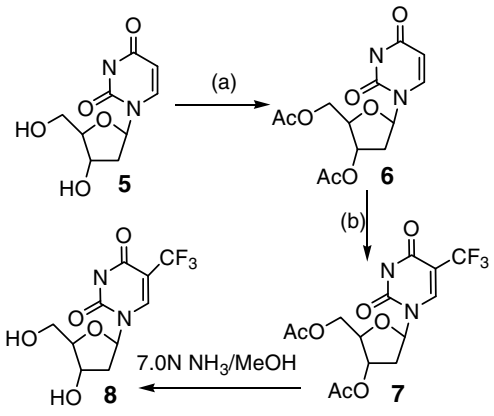
*Isolated yields.

Scheme 2. Synthesis of BVDU in ionic liquid.

Table 1
Recycling of ILs for acetylation reaction of 2′dU

No. of cycles	Reaction time (min)/yield (%)		
	[MoeMIm][Ms]	MoeMIm][TFA]	[BMIm][TFA]
0	20/91	25/90	25/90
1	20/90	25/90	30/89
2	25/90	35/89	30/89
3	25/89	35/89	35/85

extraction and all the three ILs for this step were reused up to four times with no loss in yield (Table 1). The diacetyl derivative **6** was then treated with CF_3COOH and XeF_2 to carry out trifluoromethylation at C-5 position. It is known in literature that XeF_2 and



a) Ac_2O, DMAP, IL, RT;
b) CF_3COOH (2.5eq.), XeF_2 (2.0 eq.), IL, RT

Solvents	Reaction (a) time(min)/yield(%)*	Reaction (b) time(min)/yield 9%)*
Pyridine[12]	NA/96	-
Acetonitrile[13]	120/NA	-
CF_3COOH[14a]	-	120/33
[MoeMIm][Ms]	20/91	60/35
[MoeMIm][TFA]	25/90	60/40
[BMIm][TFA]	25/90	60/36

*Isolated yields.

Scheme 3. Synthesis of TFT in ionic liquids.

CF_3COOH reacts together to form xenon (II) trifluoroacetate which decomposes to give CO_2 and CF_3 radical which can attack at C-5 position of **6** to give **7**.[14] Similar reaction has been reported earlier using excess of CF_3COOH with 33% yield.[14a] When we carried out this reaction in ILs, the yields are slightly higher and the compound **7** could be obtained up to 40% yield. The reason for lower conversions in this reaction could be due to dimerization of highly reactive CF_3 radical to give hexafluoroethane gas. Finally the deprotection of **7** using NH_3/MeOH afforded trifluridine (**8**) (Scheme 3).

It is important to mention here that in all these cases, for 1 mmol scale reaction, 15–20 ml of molecular solvents are required, while only 1.5 ml of ILs were needed for the same scale of reaction (due to the high solubility of substrate in ILs), i.e., there is 10-fold decrease in the solvent consumption which makes the use of ILs more viable and economical. Moreover, in all the systems, products were obtained with high purity as characterized by ^1H, ^{13}C NMR spectra and LC HRMS data.

In conclusion, we have successfully synthesized nucleoside-based antiviral drugs d4T, BVDU, and TFT using ionic liquids as reaction medium. Ionic liquids proved to be superior solvents in comparison of conventionally used solvents for nucleosides in terms of solubility. Reactions in ILs proceed at much faster rate and also the solvent requirement is reduced by 10-fold.

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Supplementary data

Detailed experimental procedures, ^1H NMR (400 MHz) and ^{13}C NMR (101 MHz) data can be obtained from the supporting information. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2008.08.090.

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