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Enhanced solubility and selective benzoylation of nucleosides in novel ionic liquid

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Abstract—Solubility and benzoylation study of both ribo- and deoxyribonucleosides is reported in a new ionic liquid MoeMIM·TFA; high selectivity for O-benzoylation is achieved.

Chemical synthesis of therapeutic oligonucleotides has undergone a renaissance during the last decade due to the emergence of antisense oligonucleotides and siRNA as potential and selective inhibitors of gene expression.[1] Furthermore, the discovery of AZT, ddC, d4T, etc. as anti-HIV agents,[2] has thrown new challenges before the organic chemists to develop rapid and economical process for the synthesis of these molecules. In fact, it may now be possible to synthesize an oligomer, by solid phase, in less time than it takes to protect the nucleosides used in the synthesis. Thus, the methods for suitable and selective protection/deprotection for the synthesis of nucleoside monomers have become equally important.

One of the most preferred and frequently used approach for their protection is benzoylation. This is due to its stability towards many commonly encountered reaction conditions, easy deprotection in basic medium[3] and less pronounced attitude to vicinal migration.[4] The methods reported for nucleoside benzoylation using benzoyl chloride,[5] benzoyltetrazole,[6] benzoyltriazole[7] and benzoyl cyanide[8–10] showed lack of selectivity. Furthermore, most of these studies are limited to deoxyriboseries[11,12] leaving ribonucleosides quite unexplored. One of the major reasons for this is the poor solubility of these compounds, specially ribonucleosides in common organic solvents. Most commonly used solvents in nucleoside chemistry such as pyridine and DMF have hazardous properties and other environment issues associated with them. Hence, there is a great need for the development of new methodologies for manipulation of different functionalities in nucleosides using environmentally benign media which could replace the conventional solvents and provide sufficient solubility to nucleosides, specially the ribonucleosides.

In recent years, ionic liquids (ILs) have attracted attention as green alternative to organic solvents and high-tech reaction media of the future.[13] This is owing to their unique properties such as negligible vapour pressure, high thermal stability, unprecedented ability to dissolve a broad range of compounds of organic and inorganic nature and their recyclability. One key reason for considering ILs as reaction media in the nucleoside chemistry is the potential to tune their physical property by changing their structure and thereby, design a solvent which could provide high solubility of nucleosides and, hopefully also desirable selectivity. ILs with ether side chain are known to dissolve glycolipids.[14] Similarly, a solubility study on deoxyribonucleosides found that 1-methoxyethyl-3-methylimidazolium methanesulfonate (MoeMIM·Ms) provide good affinity to dissolve deoxynucleosides but gave no selectivity for their acylation reactions and per-acyl derivative was the final product.[15] Our initial study of benzoylation in ionic liquids using benzoyl cyanide as benzoylating agent, gave high selectivity of sugar hydroxyl groups over amine group of the base of nucleosides.[10] But limitation of this process was the evolution of HCN as by product which is highly toxic.

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We are glad to report that our efforts of finding suitable ILs for nucleoside chemistry have led to synthesis of a new ionic liquid 1-methoxyethyl-3-methylimidazolium trifluoroacetate (MoeMIM·TFA) (Fig. 1), which for the first time provides high solubility and selectivity in the benzoylation of both deoxyribo- and ribonucleosides.

The solubility of thymidine was first studied in ionic liquids having 1-methoxyethyl-3-methylimidazolium as cation with different anions namely PF_6, BF_4, Tf_2N, CF_3COO. Interestingly hydrophobic ionic liquids MoeMIM·PF_6 and MoeMIM·Tf_2N and also hydrophilic ionic liquid MoeMIM·BF_4 showed poor solubility for thymidine.[16] On the other hand, the new ionic liquid MoeMIM·TFA showed good solubility for thymidine which is comparable with MoeMIM·Ms. The solubility of thymidine in 1-butyl-3-methyimidazolium trifluoroacetate (BMIM·TFA) and *N*-ethyl pyridinium trifluoroacetate (EtPy·TFA) was also found to be better than several other solvents tested by us and others.[15] The solubility analysis of thymidine in different ILs is shown in Figure 2. As it show, anion of ionic liquid has significant influence on the IL properties.[17]

Next we studied the solubility of three ribonucleosides viz. adenosine, cytosine and guanosine in ILs which were found to be best in case of thymidine. The solubility in ILs, MoeMIM·TFA, MoeMIM·Ms, BMIM·TFA, EtPy·TFA was compared with conventionally used solvents pyridine and DMF (Fig. 3). MoeMIM·Ms and EtPy·TFA were found to be the best solvents followed by MoeMIM·TFA and BMIM·TFA, respectively. In general, the ILs tested in this study were found to be far better solvents as compared to pyridine and DMF. The enhanced solubility of ribonucleosides in these ILs may be because these oxygenated anions may form hydrogen bonding with the nucleosides which can increase their solubility, as also suggested earlier in the

Figure 1. 1-Methoxyethyl-3-methylimidazolium trifluoroacetate (MoeMIM·TFA).

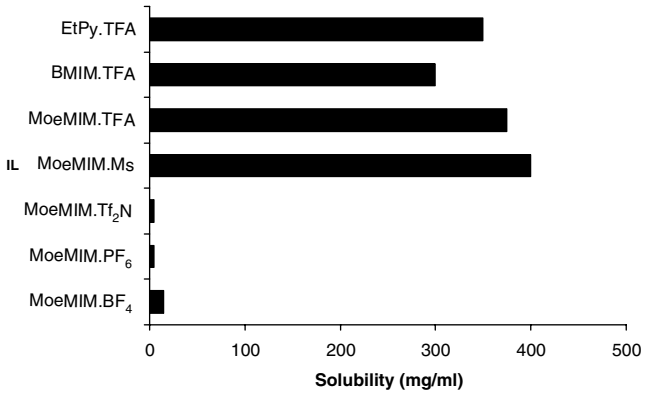


Figure 2. Solubility analysis of thymidine in different ionic liquids.

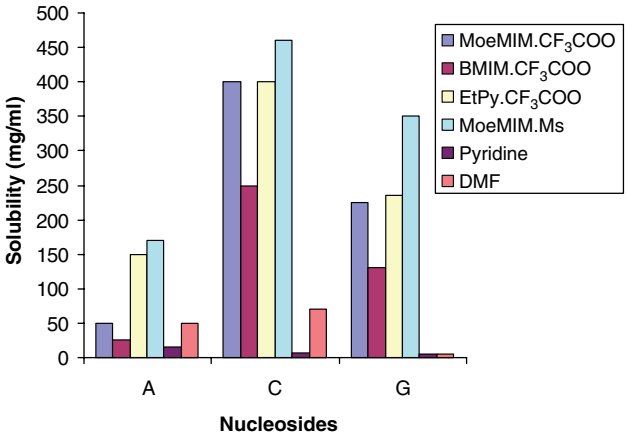
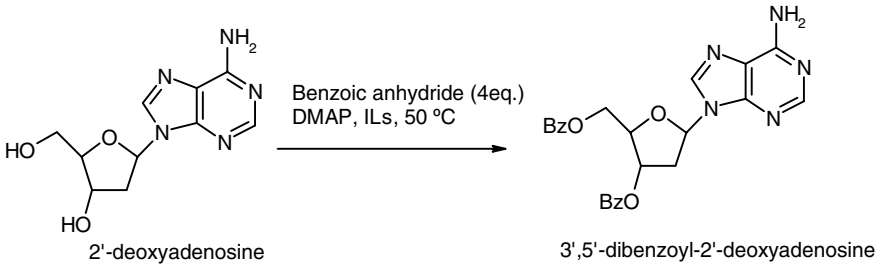


Figure 3. Solubility comparison of ribonucleosides in ILs and organic solvents.

literature.[15] However, the change of cation had no significant influence on the solubility.

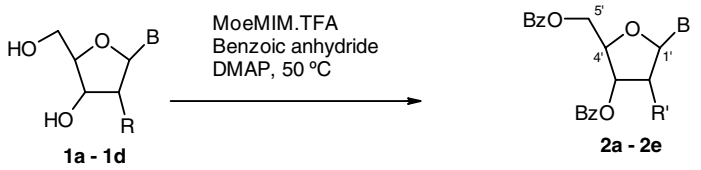
With high solubility of nucleosides achieved in these ILs, the next step was to find their utility in benzoyl protection of nucleosides. As a representative example, benzoylation reactions on 2′-dA was carried out using benzoic anhydride and DMAP (as catalyst) at 50 °C in three ILs (MoeMIM·Ms, MoeMIM·TFA and BMIM·TFA) in which high solubility was obtained (Scheme 1). Initially the reactions were carried out using 1 equiv of benzoic anhydride but the conversion was only around 30% to give a mixture of 5′-*O*-benzoyl, 3′-*O*-benzoyl and 5′,3′-di-*O*-benzoyl derivatives. Further addition of 3 equiv of benzoic anhydride was required for complete benzoylation, which gave 5′,3′-di-*O*-benzoyl-2′-deoxyadenosine as single product. The reactions were continued until all the starting material was consumed. We found that with 4 equiv of benzoic anhydride, the reaction proceed rapidly in all three ILs. Most importantly the selectivity is very high for O-benzoylation in these cases. Due to poor solubility of 2′-dA in MoeMIM·Tf_2N, MoeMIM·PF_6 and MoeMIM·BF_4 the reaction took long time (more than 24 h) and also no selectivity was observed. Interestingly however, using EtPy·TFA, gave highest solubility for both ribo- and deoxyribo- nucleosides, but the benzoylation was very slow and reactions did not complete even after three days. The new ionic liquid MoeMIM·TFA turned out to be the best solvent for this system, as it took least time to get the maximum selectivity (Scheme 1). When the same reactions were carried out at room temperature, the reaction profile was same but the conversion was very slow and the reactions were not complete even after 24 h. Similar reactions were also carried out using vinyl benzoate as benzoylating agent in different ILs, but no selectivity was observed and the reaction ends up in a complex mixture of compounds.

Inspired by these results we used MoeMIM·TFA to study benzoylation of other nucleosides (both *ribo* and *deoxyribo*-) under the same reaction conditions (Scheme 2).



Entry	Ionic liquids	Time (h)	% Yield
1	MoeMIM.Ms	8	86
2	MoeMIM.TFA	6	90
3	BMIM.TFA	10	84

Scheme 1. Benzoylation of 2′-dA in different ILs using benzoic anhydride.



1a, B = thymin-1-yl, R = H
1b, B = thymin-1-yl, R = OH
1c, B = adenin-9-yl, R = H
1d, B = adenin-9-yl, R = OH
1e, B = cytosin-1-yl, R = OH
1f, B = guanin-9-yl, R = H
1g, B = guanin-9-yl, R = OH

2a, B = thymin-1-yl, R = H
2b, B = thymin-1-yl, R = OBz
2c, B = adenin-9-yl, R = H
2d, B = adenin-9-yl, R = OBz
2e, B = cytosin-1-yl, R = OBz
2f, B = guanin-9-yl, R = H
2g, B = guanin-9-yl, R = OBz

Starting compd.	Bz_2O (equiv)	Reaction time (h)	Product	Yield%
1a	3	2.0	**2a**	93
1b	4	2.0	**2b**	90
1c	4	6.0	**2b**	90
1d	5	2.5	**2c**	92
1e	5	6.0	**2d**	68
1f	4	6.0	**2f**	80
1g	5	4.0	**2e**	70

Scheme 2. Benzoylation of nucleosides in MoeMIM·TFA using benzoic anhydride.

In all cases the selectivity is high and O-benzoylated derivatives were formed in good yields. This could be due to high ionic character of the ILs polarizing the –O–H bond, thereby making the hydroxyl moiety more nucleophilic then the $–NH_2$ group of nucleosides. This results in the selective O-benzoylation in all the cases.

Further we tested the recyclability of ionic liquid MoeMIM·TFA for benzoylation of adenosine.[18] There was no considerable drop in the selectivity and yield of O-benzoylated derivative. However, we do observe about 5–8% loss of IL in recovery. The results of recyclability studies with MoeMIM·TFA are given in Table 1.

Table 1. Recyclability studies of MoeMIM·TFA[a]

No. of cycles	Time taken (h)	Bz_2O (equiv)	% Yield
0	2.5	5	92
1	3.0	5	90
2	3.0	5	89

[a] Recovered from benzoylation of adenosine.

In summary we have synthesized a new ionic liquid MoeMIM·TFA which provides high solubility for nucleosides. Also, it is an efficient reaction medium for a selective benzoylation of nucleosides giving high yields under ambient conditions. Also, for the first time high solubility and selective derivatization of ribonucleoside has been achieved with MoeMIM·TFA, which otherwise is a tedious task in the conventional organic solvents.

Ionic liquids MoeMIM·BF_4,[19] MoeMIM·Tf_2N,[19] MoeMIM·PF_6,[19] MoeMIM·Ms,[15] BMIM·TFA,[20] EtPy·TFA[21] were prepared by following the literature procedure.

Synthesis of MoeMIM·TFA: To MoeMIM·Cl[19] (20 g, 0.113 mol) taken in acetone (150 ml), CF_3CO_2Na (24.63 g, 0.181 mol) was added. The mixture was stirred

at room temperature for 24 h, the resulting precipitate was filtered and washed with acetone (2×50 ml). The filtrate was concentrated under vacuum and purified by chromatography over silica gel using CH_2Cl_2 as solvent to get the desired IL (25 g, 87%). ^{1}H NMR (300 MHz, acetone-d_6); $\delta = 3.30$ (3H, s), 3.79 (2H, t, $J = 5.0$ Hz), 4.03 (3H, s), 4.54 (2H, t, $J = 4.9$ Hz), 7.77–7.79 (2H, m), 9.46 (1H, s). ^{13}C NMR (75 MHz, acetone-d_6); 36.39, 50.01, 58.73, 70.95, 118.26 (q, $J = 295.8$ Hz), 123.82, 124.45, 138.53, 161.55 (q, $J = 33.0$ Hz). MS (esp−): m/z 112.8 (100%, TFA), (esp+) m/z 141 (100%, MoeMIM).

General procedure for benzoylation: In a typical experiment, the nucleoside (1 mmol) was taken in the ionic liquid (1 ml), DMAP (20 mg) and benzoic anhydride (amount for different nucleosides mentioned in Scheme 2) were added. The reaction mixture was stirred at 50 °C till consumption of starting compound (TLC, MeOH/$CHCl_3$). Then water (10 ml) was added to the reaction mixture and the benzoylated derivative was precipitated out and filtered. The filtrate was proceeded to recover IL and benzoylated derivative was further washed with hot water to remove benzoic acid (which is the byproduct here) and further purified by silica gel column chromatography using MeOH/$CHCl_3$ as solvent system. It is worth mentioning that all reactions were carried out in a close flask, but without any inert atmosphere. All the benzoylated derivatives were characterized by matching their spectral data with those in the literature.[9,10]

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