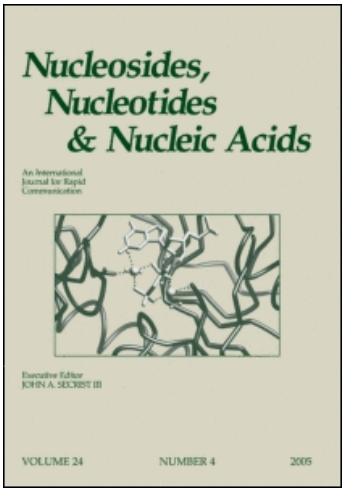

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MILD, EFFICIENT, SELECTIVE AND "GREEN" BENZOYLATION OF NUCLEOSIDES USING BENZOYL CYANIDE IN IONIC LIQUID

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▫ *Use of benzoyl cyanide (BzCN) for benzoylation of nucleosides has been studied, both in pyridine and in ionic liquid. BzCN in 1-methoxyethyl-3-methylimidazolium methanesulfonate as ionic liquid has been found to be a "green" alternative compared to the pyridine-BzCN system. An efficient and selective benzoylation of nucleosides of both, the 2′-deoxy- and the ribo-series at ambient temperature was accomplished.*

INTRODUCTION

One of the intrinsic problems, during the course of multistep synthetic protocols in nucleic acid chemistry, is the selective manipulation of hydroxyl and amino groups using labile protecting groups. This problem is further aggravated by poor solubility of nucleosides in common organic solvents. One of the most frequently used and preferred protecting groups for the protection of hydroxyl and amino groups in nucleoside and nucleotide chemistry is the benzoyl group. This is due to its less pronounced tendency to vicinal migration in comparison to acetyl group.[1] The classical method for benzoylation of hydroxyl and amino groups is treatment of the substrate with benzoyl chloride/benzoic anhydride in the presence of pyridine, which usually requires extended time periods, elevated temperatures

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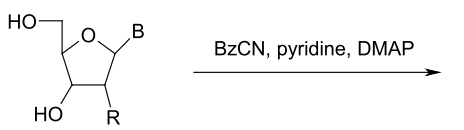


1a - 1d and **2a - 2d**

3a - 3e and **4a - 4e**

1a, B = thymin-1-yl, R = H
1b, B = adenin-9-yl, R = H
1c, B = cytosin-1-yl, R = H
1d, B = guanin-9-yl, R = H
2a, B = thymin-1-yl, R = OH
2b, B = adenin-9-yl, R = OH
2c, B = cytosin-1-yl, R = OH
2d, B = guanin-9-yl, R = OH

3a, B = thymin-1-yl, R = H
3b, B = adenin-9-yl, R = H
3c, B = cytosin-1-yl, R = H
3d, B = N^4-benzoylcytosin-1-yl, R = H
3e, B = N^2-benzoylguanin-9-yl, R = H
4a, B = thymin-1-yl, R = OBz
4b, B = adenin-9-yl, R = OBz
4c, B = N^6-benzoyladenin-9-yl, R = OBz
4d, B = N^4-benzoylcytosin-1-yl, R = OBz
4e, B = N^2-benzoylguanin-9-yl, R = OBz

FIGURE 1

or time-consuming work-up procedure. Holy and Soucek[2] have demonstrated the application of benzoyl cyanide (BzCN) in acetonitrile/dimethylformamide as a mild benzoylating agent for the protection of nucleosides. However, these authors did not study this reagent on all the eight natural 2′-deoxy- and ribonucleosides. Our ongoing interest in acylation reactions on this class of compounds encouraged us to expand and thoroughly investigate the application of BzCN as a suitable benzoylation reagent.[3–7] Herein, we report results of benzoylation studies on nucleosides of both, the 2′-deoxy- and the ribo-series using BzCN in pyridine and in 1-*m*eth*o*xy*e*thyl-3-*m*ethyl*im*idazolium *m*ethane*s*ulfonate (MoeMIM.Ms) as an ionic liquid (IL).

Benzoylation of Nucleosides Using BzCN in Pyridine as Solvent

Since most of the unprotected nucleosides are soluble in pyridine at high concentrations, it was chosen as a solvent of choice. In a typical experiment, nucleoside (1 mmol) was dissolved in pyridine (5 mL) and DMAP (10 mg) was added, followed by the addition of BzCN (2.5–8.0 mmol). The reaction was stirred at 40°C (at 115°C in case of 2′-deoxyguanosine and guanosine) and the progress monitored by TLC. On completion, the reaction mixture was poured over crushed ice while stirring in a fume hood. The precipitate was filtered off and washed with water, followed by petroleum ether to afford benzoylated nucleosides as white crystalline compounds in 11.0–96.5% yields. The results of benzoylation are summarized in Figure 1.

FIGURE 2 1-Methoxyethyl-3-methylimidazolium methanesulphonate (MoeMIM.Ms).

TABLE 1

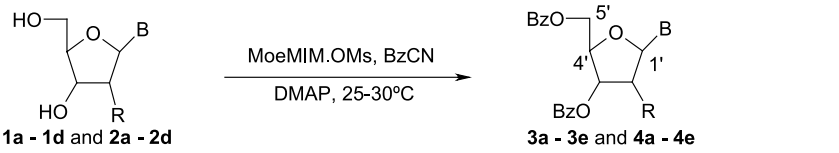
Starting compd.	BzCN (equiv.)	Reaction time/temp	Product(s)	Yield (%)*	HRMS Calcd./Obs.
1a	2.5	5 h/40°C	**3a**	94.0	$[M + H]^+$ 451.1505/451.1521
1b	2.1	6 h/40°C	**3b**	93.0	$[M + H]^+$ 460.1621/460.1636
1c	2.2	2 h/40°C	**3c**	79.3*	$[M + H]^+$ 436.1509/436.1511
			3d	17.2*	$[M + H]^+$ 540.1771/540.1794
1c	8.0	2 h/40°C	**3d**	96.5*	$[M + H]^+$ 540.1771/540.1794
1d	6.0	4 h/115°C	**3e**	89.0	$[M + H]^+$ 580.1832/580.1886
2a	5.0	3 h/40°C	**4a**	89.0	$[M + H]^+$ 571.1717/571.1736
2b	6.0	5 h/40°C	**4b**	71.5*	$[M + Na]^+$ 602.1652/602.131
			4c	11.0*	$[M + Na]^+$ 682.1801/682.1901
2c	6.8	7 h/40°C	**4d**	92.0	$[M + Na]^+$ 682.1801/682.1901
2d	7.0	7 h/115°C	**4e**	88.5*	$[M + Na]^+$ 722.1863/722.1981

*The yields reported are on the basis of LC-MS analysis data.

Benzoylation of Nucleosides Using BzCN in Ionic Liquid as Solvent

In recent years, room-temperature ILs have attracted much attention as the "green" solvents of the future. This is because of their negligible vapor pressure, thermal stability, unprecedented ability to dissolve a broad range of compounds of organic and inorganic nature and easy reuse. We have investigated the applications of BzCN as benzoylating agent in the IL MoeMIM.Ms (Figure 2). This IL was chosen as reaction medium (or solvent) because of its ability to dissolve a variety of nucleosides[5] (Table 1).

In a typical experiment, nucleoside (1 mmol) was dissolved in MoeMIM.Ms (1 ml) and catalytic amount of 4-DMAP was added, followed by the addition of BzCN (2.5–3.5 mmol). The reaction mixture was stirred at room temperature (25–30°C) and the progress monitored by TLC. On completion of the reaction, water



1a - 1d and **2a - 2d**

1a, B = thymin-1-yl, R = H
1b, B = adenin-9-yl, R = H
1c, B = cytosin-1-yl, R = H
1d, B = guanin-9-yl, R = H
2a, B = thymin-1-yl, R = OH
2b, B = adenin-9-yl, R = OH
2c, B = cytosin-1-yl, R = OH
2d, B = guanin-9-yl, R = OH

3a - 3e and **4a - 4e**

3a, B = thymin-1-yl, R = H
3b, B = adenin-9-yl, R = H
3c, B = cytosin-1-yl, R = H
3d, B = *N*⁴-benzoylcytosin-1-yl, R = H
3f, B = guanin-9-yl, R = H
4a, B = thymin-1-yl, R = OBz
4b, B = adenin-9-yl, R = OBz
4g, B = cytosin-1-yl, R = OBz
4d, B = *N*⁴-benzoylcytosin-1-yl, R = OBz
4h, B = guanin-9-yl, R = OBz

FIGURE 3

TABLE 2

Starting compd.	BzCN (equiv.)	Reaction time	Product(s)	Yield (%)*	HRMS Calcd./Obs.
1a	2.5	1.5 h	**3a**	92	$[M + Na]^+$ 473.1325/473.1349
1b	2.5	2.0 h	**3b**	91	$[M + Na]^+$ 482.1440/482.1441
1c	2.5	2.5 h	**3c**	68	$[M + H]^+$ 436.1509/436.1511
			3d	10	$[M + H]^+$ 540.1771/540.1804
1d	3.0	2.5 h	**3f**	65	$[M + H]^+$ 476.1570/476.1601
2a	3.5	1.5 h	**4a**	96	$[M + Na]^+$ 593.1536/593.1604
2b	3.0	1.5 h	**4b**	85	$[M + H]^+$ 580.1832/580.1878
2c	3.0	2.0 h	**4g**	70	$[M + H]^+$ 556.1720/556.1751
			4d	12	$[M + Na]^+$ 682.1801/682.1901
2d	3.5	2.5 h	**4h**	70	$[M + Na]^+$ 618.1601/618.1664

*Isolated yields.

(20 ml) was added and the product extracted with ethyl acetate (3 × 20 mL). The organic layer was separated, dried over sodium sulfate, concentrated, and the residue purified by silica gel column chromatography to afford the corresponding *O*-benzoylated nucleosides as white solids in 65–96% yields; minor amounts of perbenzoylated nucleosides were also obtained in case of 2′-deoxycytidine and cytidine (Figure 3).

The benzoylation of nucleosides of 2′-deoxy- and ribo-series with BzCN in IL is very selective and efficient as this combination exclusively/preferably benzoylated the hydroxyl groups of the nucleosides over their amino group (Figure 3). One of the major advantages of using IL in organic synthesis is that they are reusable. To verify the reusability, the IL was recovered from the aqueous portion of the reaction and used up to three cycles without any appreciable loss of its activity, except small loss of the IL in handling. The structures of all benzoylated nucleosides were unambiguously established on the basis of their spectral analysis (IR, ^1H and ^{13}C NMR, and LC-MS) and comparison of their melting points and/or spectral data with those reported in the literature (Ref. [7] and references therein, and Ref. [8]) (Table 2).

CONCLUSION

The benzoylation reaction carried out on 2′-d*eoxy*- and *ribo*-series of nucleosides with BzCN in pyridine was non-selective in most of the cases and required longer reaction times, elevated temperature and led to the formation of corresponding perbenzoylated products. Whereas, the BzCN in MoeMIM.Ms (IL) selectively/preferentially benzoylated the hydroxyl groups over amino groups of nucleosides at ambient temperature (25–30°C). Also we have demonstrated that IL was recovered after benzoylation reactions. In conclusion, the ionic liquid MoeMIM.Ms is found to be an improved and "greener" alternative to the hazardous conventional solvents such as pyridine commonly employed in nucleoside chemistry.

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