

‘Green’ methodology for efficient and selective benzylation of nucleosides using benzoyl cyanide in an ionic liquid[☆]

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Abstract—Benzoyl cyanide in the ionic liquid 1-methoxyethyl-3-methylimidazolium methanesulfonate has been employed as a ‘green’ alternative and mild reaction condition protocol to conventional pyridine–benzoyl chloride system for efficient and selective benzylation of nucleosides (of both the ribo- and deoxyribo-series) at ambient temperatures. The use of benzoyl cyanide–ionic liquid combination has been successfully extended for highly efficient benzylation of phenols, aromatic amines, benzyl alcohol, aliphatic diols, 3-aminophenol and 2-aminobenzylalcohol, which indicates the versatility of this benzylation system.

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1. Introduction

Nucleoside chemistry is emerging as one of the important areas of research for drug discovery. Three important factors: (i) the discovery of AZT, ddC, d4T, etc. as anti-HIV agents,^{1–6} (ii) the emergence of antisense and antigene oligonucleotides as potential and selective inhibitors of gene expression^{7–12} and (iii) application of modified nucleosides as building blocks for the synthesis of oligonucleotides useful as probes for diagnostic purposes¹³ are mainly responsible for the sharply rising focus on nucleoside chemistry.

Synthesis of modified nucleosides requires manipulation of different hydroxyl- and amino-groups present in the molecule. One of the intrinsic problems in nucleoside chemistry is selective protection of these functionalities, which is further aggravated by poor solubility of the compounds in common organic solvents. This is one

of the main reasons that most of the protection–deprotection studies have been reported on nucleosides of deoxyribo-series.^{14–16} Highly polar solvents traditionally used in nucleoside chemistry, such as pyridine, *N,N*-dimethylformamide (DMF) and *N*-methylpyrrolidone (NMP), are quite hazardous and are on blacklists of environment regulatory agencies. Hence, there is a great need for the development of new methodologies for manipulation of different functionalities in nucleosides using environmentally benign media that which could replace the conventional solvents and provide sufficient solubility to nucleosides. In recent years, room-temperature ionic liquids (compounds that consist only of ions and are liquid at room temperature) have attracted attention as green- and high-tech reaction media of the future.^{17–20} This is because of their negligible vapour pressure, thermal stability, unprecedented ability to dissolve a broad range of compounds of organic and inorganic nature and their recyclability.

Benzylation remains one of the most frequently used methods for the protection of hydroxyl and amino functions in nucleoside and nucleotide chemistry. The benzoyl group is preferred over other acyl groups due to stability towards many commonly encountered reaction conditions and their less pronounced attitude to vicinal migration.²¹ The classical method of benzylation of hydroxyl groups of nucleosides with benzoyl chloride or benzoic anhydride results in non-selective reactions.²²

Keywords: Antisense; Antigene; Benzylation; Nucleosides; Ionic liquids.

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Other mild benzoylating agents such as benzoyltetrazole,²³ benzoyltriazole²⁴ and benzoyl cyanide (BzCN)^{25–27} have been reported for this purpose. However, lower selectivity has been observed towards the acylation of different hydroxyl functions and none of these studies has been extended on to nucleosides of ribo-series.

Recently, we have reported the use of benzoyl cyanide in pyridine as a mild benzoylating agent for the benzoylation of nucleosides.²⁸ In most of the cases, the reaction was non-selective and led to perbenzoylation of nucleosides. In case of benzoylation of dG and G, the reaction had to be performed at elevated temperature because of the insolubility of the substrate at ambient temperature, which would have also contributed to perbenzoylation of substrates. Uzagare et al.²⁹ have recently investigated the application of ionic liquids for the acylation of nucleosides of deoxyribo-series with three different acylating agents, viz. acetic anhydride, benzoyl chloride and isobutyryl chloride, and have observed peracylation in all cases. Our ongoing interest in acylation reactions encouraged us to expand and thoroughly investigate

the applications of BzCN as benzoylating agent in an ionic liquid.

2. Results and discussion

The ionic liquid (IL) 1-methoxyethyl-3-methylimidazolium methanesulfonate (MoeMIM.Ms, Fig. 1) was chosen as reaction medium (or solvent) because of its ability to dissolve both ribo- and deoxyribonucleosides. Such ILs containing ether side chain have been termed as ‘sugarphilic’ as they can dissolve glycolipids.³⁰ Furthermore, we decided to use DMAP as catalyst due to its known beneficial effects.³¹

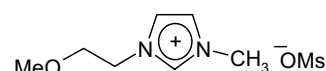
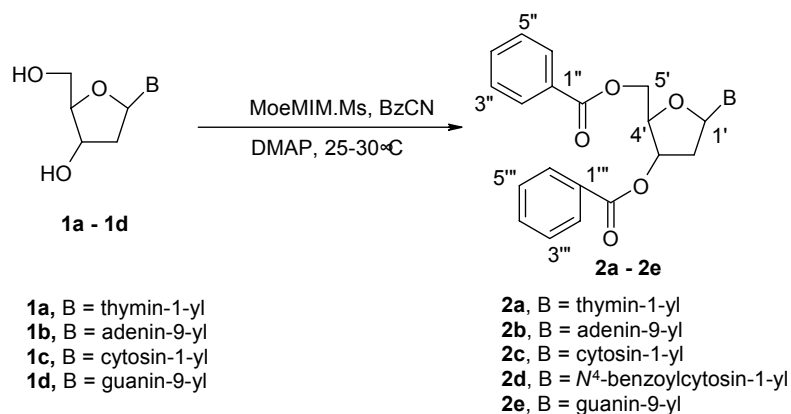
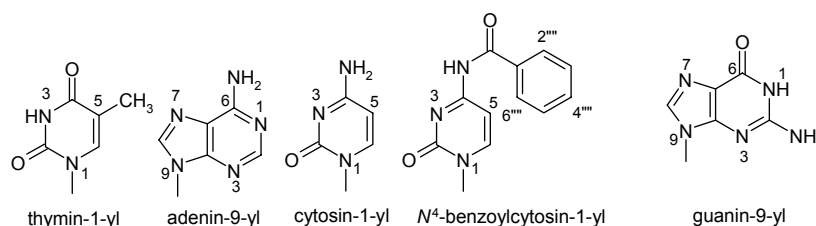


Figure 1. 1-Methoxyethyl-3-methylimidazolium methanesulfonate (MoeMIM.Ms).



Starting compd.	BzCN (equiv.)	Reaction time	Product(s) ^{lit}	Yield (%) [*]	HRMS: Calcd. / Obs. (Mol. Formulae)
1a	2.5	1.5h	2a ³³	92	[M+Na] ⁺ 473.1325 / 473.1349 / (C ₂₄ H ₂₂ N ₂ O ₇)
1b	2.5	2.0h	2b ³⁴	91	[M+Na] ⁺ 482.1440 / 482.1441 / (C ₂₄ H ₂₁ N ₅ O ₅)
1c	2.5	2.5h	2c ³⁵	68	[M+H] ⁺ 436.1509 / 436.1511 / (C ₂₃ H ₂₁ N ₃ O ₆)
			2d ³⁷	10	[M+H] ⁺ 540.1771 / 540.1804 (C ₃₀ H ₂₅ N ₃ O ₇)
1d	3.0	2.5h	2e ^{23,36}	65	[M+H] ⁺ 476.1570 / 476.1601 (C ₂₄ H ₂₁ N ₅ O ₆)

^{*}All the yields reported are isolated yields.

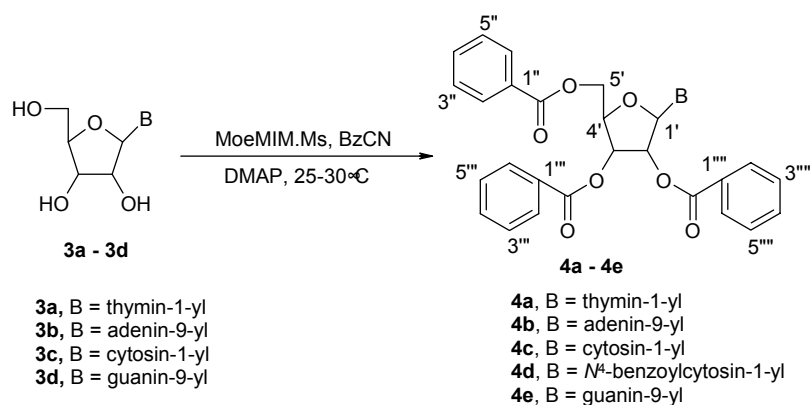


Scheme 1.

In a typical experiment, thymidine (**1a**, 1 mM) was dissolved in MoeMIM.Ms (1 ml) and catalytic amount of 4-DMAP was added followed by the addition of BzCN³² (2.5 mM). The reaction completed in 1.5 h at room temperature (25–30 °C), as evident by TLC. After completion of the reaction, water (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 was purified by silica gel column chromatography to afford 3',5'-di-*O*-benzoylthymidine (**2a**)³³ as a white solid in 92% yield (Scheme 1). The benzoylation of 2'-deoxyadenosine (**1b**), 2'-deoxycytidine (**1c**) and 2'-deoxyguanosine (**1d**) under similar conditions with 2.5, 2.5 and 3.0 equiv of benzoyl cyanide afforded the corresponding di-*O*-benzoylated derivatives: 3',5'-di-*O*-benzoylated 2'-deoxyadenosine (**2b**),³⁴ 3',5'-di-*O*-benzoylated 2'-deoxycytidine (**2c**)³⁵ and 3',5'-di-*O*-benzoylated 2'-deoxyguanosine (**2e**)³⁶ in 91%, 68% and 65% yields, respectively (Scheme 1). In case of benzoylation of 2'-deoxycytidine (**1c**), the corresponding perbenzoylated product **2d**³⁷ was also obtained as a minor product. This observation indicates that benzoyl cyanide in MoeMIM.Ms selectively/preferentially benzoylates the hydroxyl groups over amino

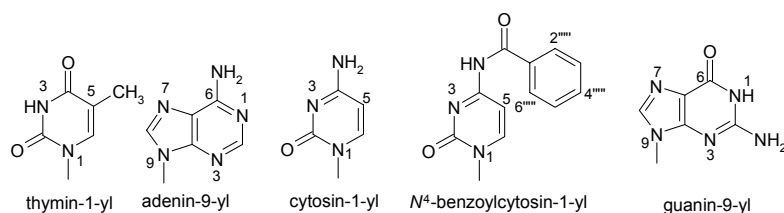
groups of nucleosides **1b–d**. A test reaction on benzoylation of 2'-deoxyadenosine (**1b**) under identical condition but in absence of DMAP remained incomplete even after 24 h. The benzoylation reaction carried out on all these four nucleosides **1a–d** in MoeMIM.Ms using benzoyl chloride as benzoylating agent does not exhibit any selectivity.²⁹ Another disadvantage with the use of benzoyl chloride is that it is always required in excess, that is, 3–4 times more than benzoyl cyanide. The benzoylation reaction carried out on nucleosides of deoxyribo- and ribo-series with benzoyl cyanide in pyridine was also non-selective in most of the cases and led to the formation of corresponding perbenzoylated products;²⁸ moreover the benzoylation reaction under these conditions takes longer time and elevated temperature to dissolve the substrate is required.

Encouraged by selective and efficient benzoyl transferring nature of benzoyl cyanide in MoeMIM.Ms, the benzoylation study was extended to more polar nucleosides of ribo-series, that is, 5-methyluridine (**3a**), adenosine (**3b**), cytidine (**3c**) and guanosine (**3d**). Benzoylation of 5-methyluridine (**3a**) gave the corresponding 2',3',5'-tri-*O*-benzoylated nucleoside **4a**³⁸ in 96% yield (Scheme



Starting compd.	BzCN (equiv.)	Reaction time	Product (s) ^{lit.}	Yield (%) [*]	HRMS: Calcd. / Obs. (Mol. Formulae)
3a	3.5	1.5h	4a ³⁸	96	[M+Na] ⁺ 593.1536 / 593.1604 (C ₃₁ H ₂₆ N ₂ O ₉)
3b	3.0	1.5h	4b ^{38,39}	85	[M+H] ⁺ 580.1832 / 580.1878 (C ₃₁ H ₂₅ N ₅ O ₇)
3c	3.0	2.0h	4c ⁴⁰	70	[M+H] ⁺ 556.1720 / 556.1751 (C ₃₀ H ₂₅ N ₃ O ₈)
			4d ³⁸	12	[M+Na] ⁺ 682.1801 / 682.1901 (C ₃₇ H ₂₉ N ₃ O ₉)
3d	3.5	2.5h	4e ⁴¹	70	[M+Na] ⁺ 618.1601 / 618.1664 (C ₃₁ H ₂₅ N ₅ O ₈)

* All the yields reported are isolated yields.



Scheme 2.

Table 1. Benzoylation of phenols, aromatic amines, aryl-carbinols and aliphatic diols with benzoyl cyanide in MoeMIM.Ms at room temperature (25–30 °C)

Starting compd	Reaction time (min)/ BzCN (equiv)	Products (lit.)	Yield (%)	Mp (°C)		HRMS (EI) [M] ⁺ peak	
				Obsd	Lit.	Calcd	Found
4-Nitrophenol (5)	40/1	4-Nitrophenyl benzoate ⁴²	93	144–145	142 ⁴²	243.0532	243.0530
4-Methoxyphenol (6)	15/1	4-Methoxyphenyl benzoate ⁴²	94	86	87 ⁴²	228.0786	228.0778
2-Naphthol (7)	30/1	2-Naphthyl benzoate ⁴²	97	98–100	107 ⁴²	248.0837	248.0830
4-Nitroaniline (8)	50/1	4-Benzamidonitrobenzene ⁴²	91	198–199	199 ⁴²	242.0691	242.0697
2,4-Difluoroaniline (9)	15/1	1-Benzamido-2,4-difluorobenzene ⁴³	94	120–122	^b	233.0652	233.0660
Benzyl alcohol (10)	30/1	Benzyl benzoate ⁴²	94	Oil	21 ⁴²	212.0837	212.0824
3-Phenoxy-1,2-propanediol (11) ^a	30/2	1,2-Dibenzoyloxy-3-phenoxypropane ⁴⁴	93	Oil	^b	376.1311	376.1292
1,2-Propanediol (12) ^a	40/2	1,2-Dibenzoyloxypropane ⁴⁵	92	Oil	^b	284.1049	284.1066
3-Aminophenol (13) ^a	40/2	3-Benzamidophenyl benzoate ⁴⁶	88	125–128	152–53 ⁴⁶	317.1052	317.1055
2-Aminobenzyl alcohol (14) ^a	40/2	2-Benzamidobenzyl benzoate	97	112–115	—	331.1208	331.1198

^a Benzoylation of compounds **11–14** with BzCN led to the formation of corresponding dibenzoylated derivatives.

^b Although benzoyl derivatives of compounds **9**, **11** and **12** are reported in the literature, their mps/physical states were not mentioned.

2). In case of other three ribo-nucleosides, that is, **3b–d** having amino group in their bases, selective/preferential benzoyl transfer takes place on hydroxyl functions of nucleosides leading to the formation of 2',3',5'-tri-*O*-benzoylated adenosine (**4b**),^{38,39} 2',3',5'-tri-*O*-benzoylated cytidine (**4c**)⁴⁰ and 2',3',5'-tri-*O*-benzoylated guanosine (**4e**)⁴¹ in 85%, 70% and 70% yields, respectively (Scheme 2). Benzoylation of cytidine (**3c**) with benzoyl cyanide in MoeMIM.Ms also resulted in the formation of *N*⁴,*O*^{2'},*O*^{3'},*O*^{5'}-tetrabenzoylcytidine (**4d**)³⁸ as a minor product. The benzoylation of ribo-nucleosides with benzoyl cyanide in MoeMIM.Ms is highly efficient and selective than the benzoylation carried out with benzoyl cyanide–pyridine system as it requires almost half of the benzoyl cyanide and all reactions went to completion in much shorter time, that too at ambient temperatures (25–30 °C).

To explore the generality of benzoyl cyanide in MoeMIM.Ms as a benzoylating agent, we further studied the benzoylation of compounds other than nucleosides (Table 1), that is, phenols **5–7**, aromatic amines **8** and **9**, benzyl alcohol (**10**), aliphatic diols **11** and **12**, 3-aminophenol (**13**) and 2-aminobenzyl alcohol (**14**). The benzoyl cyanide–IL benzoylating system was found to be very efficient and converted the hydroxy and/or amino substrates **5–14** into their corresponding benzoylated products in 88–97% yields (Table 1). In case of 3-aminophenol (**13**) and 2-aminobenzyl alcohol (**14**), both having amino and hydroxyl functions, benzoyl cyanide in MoeMIM.Ms failed to discriminate between the two protectable groups (unlike in nucleosides **1b–d** and **3b–d**). However, the benzoylation reaction on compounds **5–14** with benzoyl cyanide in MoeMIM.Ms takes 1.5–8-fold less time than benzoylation with benzoyl cyanide–pyridine (unpublished results). The structures of benzoylated nucleosides, phenols, aromatic amines, benzyl alcohol, aliphatic diols, 3-aminophenol and 2-aminobenzyl alcohol were unambiguously established on the basis of their spectral analysis (IR, ¹H, ¹³C NMR and HRMS data). 2-Benzamidobenzyl benzoate obtained from benzoylation of 2-aminobenzyl alcohol (**14**) was found to be a new compound. The structures of known

Table 2. Study on recycling of MoeMIM.Ms recovered from the reaction of 2'-deoxyadenosine

No. of cycles	%Yield
1	85 (1st reaction)
2	84 (1st cycle)
3	82 (2nd cycle)

compounds were further confirmed by comparison of their melting points and/or spectral data with those reported in the literature.^{33–46} Matsuda et al.³⁶ have reported the melting point of benzoylated nucleoside **2e** as 214 °C and Stawinski et al.²³ have reported that the compound decomposes on heating. We have observed that this compound decomposes at 150 °C.

One of the major advantages of using ionic liquids in organic synthesis is that they are reusable. To verify the reusability of MoeMIM.Ms used in the present benzoylation reaction, the aqueous portion of the reaction in case of adenosine was further washed with ethyl acetate (2 × 20 ml) and concentrated under vacuum to afford the recovered MoeMIM.Ms. The recovery of IL was reduced by 5–8% in each cycle. The recovered IL was used for the benzoylation of adenosine as above and it was observed that in 1st- and 2nd-cycle, the benzoylation reaction resulted in the formation of same product in 84% and 82% yields, respectively (Table 2). This result indicates that there is no appreciable loss of activity of MoeMIM.Ms up to three cycles of benzoylation reaction, except its small loss in handling.

3. Conclusion

In conclusion, the ionic liquid MoeMIM.Ms is found to be selective, and better and 'greener' alternative to the hazardous conventional solvents being employed in nucleoside chemistry. Further, lesser reactivity of benzoyl cyanide in comparison with benzoyl chloride or benzoic anhydride may be the reason for selective formation of favoured *O*-benzoyl over *N*-benzoyl derivatives

of all NH₂-bearing nucleosides in an ionic liquid as this media has very high polarizability and polarizes (practically ionizes) the –O–H bond, thereby making the hydroxy group more nucleophilic than the amino group of the nucleosides. However in pyridine, such polarization (or ionization) of –O–H function does not occur and both amino and hydroxy functions of nucleosides undergo acylation. The great solubilizing nature of IL MoeMIM.Ms made it possible to carry out the benzylation of ribo-nucleosides at room temperature. The present study has also revealed that by careful selection of acylating agent, high efficiency and selectivity can be achieved in IL.

4. Experimental

Melting points were determined on a Mettler FP 62 instrument or in a sulfuric acid bath and are uncorrected. The IR spectra were recorded on a Perkin–Elmer model 2000 FT-IR spectrometer by making KBr discs for solid samples and thin films for oils. The ¹H and ¹³C NMR spectra were recorded on a Bruker AC-300 Avance spectrometer at 300 and at 75 MHz, respectively, using TMS as internal standard. Analytical TLCs were performed on pre-coated Merck silica gel 60 F₂₅₄ plates; the spots were detected either under UV light or by charring with 4% alcoholic H₂SO₄. Benzoyl cyanide and DMAP were purchased either from Aldrich Chemical Co. or Fluka Chemicals Co., USA and used without further purification. The ionic liquid 1-methoxyethyl-3-methylimidazolium methanesulfonate (MoeMIM.Ms) was obtained as a gift from Sai Life Sciences Laboratories Ltd, Hyderabad, India.

4.1. General experimental procedure for benzylation of nucleosides, phenols, aromatic amines, benzyl alcohol, aliphatic diols, 3-aminophenol and 2-aminobenzyl alcohol

The starting compound (1 mM) was dissolved in the ionic liquid MoeMIM.Ms (1 ml) followed by the addition of DMAP (10 mg) and BzCN (1.0–1.16 equiv/OH group in nucleosides; 1.0 equiv/OH and/or NH₂ group in other compounds). The reaction mixture was allowed to stir at room temperature (25–35 °C) and the progress of the reaction was followed by TLC. Upon completion, water (20 ml) was added to the reaction mixture and the product was extracted with ethyl acetate (3 × 20 ml). The combined organic layer was then washed with distilled water (25 ml) and concentrated under vacuum to get the crude product, which was purified on silica gel column using chloroform/methanol as eluent in increasing order of polarity to afford the benzyolated product. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ¹H, ¹³C NMR and High Resolution Mass spectral data). All the benzyolated products were found to be known in the literature, except 2-benzamidobenzyl benzoate obtained from 2-aminobenzyl alcohol. The structures of known compounds were further confirmed by comparison of their melting points and/or spectral data with those reported in the literature.^{33–46} In some cases the observed melting points of benzyolated compounds

were not matching with those reported in literature, however we have confirmed the structures of all our compounds unequivocally from their complete spectral data. We report herein the complete spectral data of the new compound, 2-benzamidobenzyl benzoate and the ¹H and ¹³C NMR spectral data of the benzyolated nucleosides **2e**, **4c** and **4e**; the ¹H and ¹³C NMR spectral data of all other nucleosides have been reported by us earlier.²⁸

4.1.1. 3',5'-Di-O-benzoyl-2'-deoxyguanosine (2e). White solid (309 mg, 65%); mp 150 °C (dec) [lit.³⁶ mp 214 °C (dec)]; ¹H NMR (300 MHz, CDCl₃): δ 2.71 (1H, dd, *J* = 13.7 and 4.4 Hz, C-2'H_a), 3.10–3.15 (1H, m, C-2'H_b), 4.54–4.65 (3H, m, C-4'H and C-5'H), 5.74 (1H, br s, C-3'H), 6.30 (1H, t, *J* = 6.9 Hz, C-1'H), 6.47 (2H, s, NH₂), 7.49–8.06 (11H, m, 10 aromatic protons and C-8H) and 10.66 (1H, s, NH); ¹³C NMR (75 MHz, CDCl₃): δ 36.60 (C-2'), 65.17 (C-5'), 76.17 (C-3'), 82.28 (C-4'), 83.79 (C-1'), 117.85 (C-2), 129.64, 130.11 and 130.24 (C-2'', C-2''', C-3'', C-3''', C-5'', C-5''', C-6'' and C-6'''), 134.35 and 134.55 (C-4'' and C-4'''), 136.11 (C-1'' and C-1'''), 151.90 (C-4), 154.61 (C-5), 157.55 (C-8), 166.07 (2 × ester CO) and 166.34 (C-6).

4.1.2. 2',3',5'-Tri-O-benzoylcytidine (4c). White solid (389 mg, 70%); mp 183–188 °C (lit.⁴⁰ mp 185–187 °C); ¹H NMR (300 MHz, CDCl₃): δ 1.90 (2H, br s, NH₂), 4.63–4.81 (3H, m, C-4'H and C-5'H), 5.81–5.87 (1H, m, C-3'H), 5.96 (1H, t, *J* = 5.6 Hz, C-2'H), 6.21 (1H, d, *J* = 4.2 Hz, C-1'H) and 7.32–8.09 (17H, m, 15 aromatic protons, C-5H and C-6H); ¹³C NMR (75 MHz, CDCl₃): δ 63.71 (C-5'), 71.06 (C-3'), 74.37 (C-4'), 79.73 (C-2'), 90.28 (C-1'), 95.72 (C-5), 128.35, 128.48, 129.62, 129.71 and 129.81 (C-6, C-2'', C-2''', C-2''', C-3'', C-3''', C-3''', C-5'', C-5''', C-5''', C-6'', C-6'' and C-6'''), 133.26 and 133.44 (C-4'' and C-4'''), 141.36 (C-1'', C-1''' and C-1'''), 155.39 (C-4), 165.19, 165.30 and 165.85 (3 × ester CO) and 166.08 (C-2).

4.1.3. 2',3',5'-Tri-O-benzoylguanosine (4e). White solid (417 mg, 70%); mp 250 °C (dec) (lit.⁴¹ mp 252–256 °C); ¹H NMR (300 MHz, CDCl₃): δ 4.68–4.84 (3H, m, C-4'H and C-5'H), 6.20 (1H, t, *J* = 4.9 Hz, C-3'H), 6.29–6.35 (2H, m, C-2'H and C-1'H), 6.45 (2H, s, NH₂), 7.40–8.03 (16H, m, 15 aromatic protons and C-8H) and 10.76 (1H, s, NH); ¹³C NMR (75 MHz, CDCl₃): δ 64.08 (C-5'), 71.63 (C-3'), 73.80 (C-4'), 79.67 (C-2'), 86.31 (C-1'), 117.61 (C-2), 128.41, 128.61, 128.72, 128.90, 129.62 and 129.68 (C-2'', C-2''', C-2''', C-3'', C-3''', C-3''', C-5'', C-5''', C-5''', C-6'', C-6'' and C-6'''), 133.62, 133.96 and 134.08 (C-4'', C-4''' and C-4'''), 136.36 (C-1'', C-1''' and C-1'''), 151.23 (C-4), 154.19 (C-5), 157.10 (C-8), 164.81 and 164.96 (3 × ester CO) and 165.75 (C-6).

4.1.4. 2-Benzamidobenzyl benzoate. White solid (321 mg, 97%); mp 112–115 °C; IR: (KBr) 3274.9 (NH), 1716.5 (COO), 1649.0 (CONH), 1604.7, 1521.7, 1490.9, 1440.7, 1307.5, 1274.9, 1259.4, 1093.6, 1068.5 and 1026.1 cm⁻¹; UV (CHCl₃) λ_{max}: 275 and 212 nm; ¹H NMR (300 MHz, CDCl₃): δ 5.38 (2H, s, CH₂),

7.17–8.10 (14H, m, aromatic protons) and 9.75 (1H, s, NH); ^{13}C NMR (75 MHz, CDCl_3): δ 64.51 (CH_2), 125.18, 125.70, 127.42, 127.87, 128.85, 129.12, 130.26, 130.36, 130.56, 132.03, 132.30, 133.96, 134.99, 137.22 (aromatic carbons), 166.36 (ester CO) and 167.83 (amidic CO).

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