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Rapid, clean, and mild *O*-acetylation of alcohols and carbohydrates in an ionic liquid

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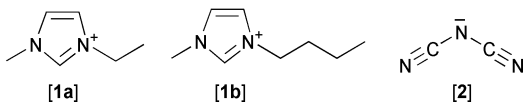
Archetypal *O*-acetylation reactions of alcohols and carbohydrates proceed rapidly in high yield under mild conditions in a dicyanamide based ionic liquid, that is not only an effective solvent but also an active base catalyst.

The application of ionic liquids as reaction media for a wide variety of synthetic processes is an area of intense research. Ionic liquids provide a vapourless, thermally stable and reusable 'green' solvent for chemical reactions.[1] Some ionic liquids have also been shown to act as catalysts further augmenting their widespread introduction into general synthetic chemistry.[2] We have recently reported a series of novel ionic liquids based on the dicyanamide anion [**2**], which are low viscosity solvents that dissolve a wider range of inorganic and organic compounds, including unprotected saccharides,[3] than previously reported ionic liquids. The dicyanamide ionic liquids allowed us to explore reactions of carbohydrates, and other alcohols, which until now have been inaccessible in other ionic liquids. Initial studies have been carried out on the acetylation of a range of alcohols including; naphthol, tertiary butyl alcohol, cyclohexanol and a number of saccharides as more complex polyols.

Hydroxy group *O*-acetylation is used extensively in carbohydrate chemistry as a protection strategy, and for the isolation and identification of sugars. The standard *O*-acetylation reaction uses acetic anhydride as the primary reagent and a wide range of solvents and catalysts. Pyridine is the most widely used solvent/catalyst for the acetylation of saccharides even though it is known to have acute toxicity.[4] Derivatives of pyridine such as 4-(dimethylamino)pyridine and 4-(1-pyrrolidino)pyridine also catalyse the acetylation, in some cases 10^4 times faster than pyridine.[5] Sodium acetate is also commonly used as a catalyst;[6] in the acetylation of D-glucose it yields exclusively the β-acetylated product.[7] Other reagents that have been shown to catalyse acetylation of saccharides by acetic anhydride include: Lewis/Bronsted acids such as $ZnCl_2$,[6] $HClO_4$,[6] $FeCl_3$,[8] H_2SO_4,[9] iodine;[10] heterogeneous catalysts such as tetrabutylammonium bromide–NaOH,[11] anionic surfactants,[12] Montmorillonite K-10,[13] H-beta zeolite,[14] zirconium sulfophenyl phosphonate[15] and enzyme catalysts such as lipases.[16] A variety of other reagents used to catalyse *O*-acetylation of alcohols are also known.[17]

We report here that dicyanamide based ionic liquids are not only effective solvents for alcohols and saccharides but also active base catalysts for their *O*-acetylation. The reaction appears quite general for a range of alcohols. The ionic liquids investigated were butylmethylimidazolium dicyanamide [bmIm][dca] and ethylmethylimidazolium dicyanamide [emIm][dca] (Fig. 1). Glucose is soluble in these liquids to greater than 10 weight percent at room temperature. The solubility of disaccharides (*e.g.* sucrose) and trisaccharides (*e.g.* raffinose) is less than glucose, although solubility of all saccharides increases with rising temperature. The dicyanamide ionic liquids appear to be unique, thus far, among families of ionic liquids in presenting high solubility to saccharides. In contrast, for example, the same imidazolium cations with bis(trifluoromethanesulfonyl)amide [tfsa], chloride [Cl],[18] hexafluorophosphate [PF_6][18] and tetrafluoroborate [BF_4] anions offer low to very low solubility. The acetylated products were also completely soluble in the dicyanamide ionic liquid reaction mixtures.



[1a] [1b] [2]

Fig. 1 Imidazolium cation [**1a**] or [**1b**] and dicyanamide anion [**2**].

In a typical reaction procedure (Entry 1, Table 1), acetic anhydride (1.42 g, 13.9 mmol) was added to α-D-glucose (0.5 g, 2.78 mmol) and [bmIm][dca] ionic liquid (1.14 g, 5.56 mmol). The mixture was stirred at room temperature until completion of reaction (indicated by disappearance of α-D-glucose on TLC). Most of the reactions were carried out on beyond-saturation suspensions of the reactant saccharide, with the reaction mixtures becoming completely homogenous solutions as the reactions proceeded. This approach allowed the use of minimal quantities of the ionic liquid. At completion of the reaction, water was added to precipitate penta-*O*-acetyl-D-glucopyranose (isolated yield 89%). The product, the extent of acetylation and the anomeric ratio were determined using ^{1}H NMR for samples of crude reaction mixture and isolated product. All reactions using the dicyanamide ionic liquid yielded the completely acetylated product.

Table 1 summarises results of acetylation on a range of alcohols and saccharides using dicyanamide ionic liquid and acetic anhydride. All hydroxy groups were successfully acetylated, indicating the generality of this reaction. Notably, none of these reactions involved the use of an added catalyst. The saccharide examples in Table 1 illustrate the acetylation of a range of primary and secondary hydroxy groups of varying reactivity. A number of simple alcohols such as 2-naphthol and tertiary butyl alcohol have also been rapidly acetylated, further expanding the generality of this reaction to aromatic and tertiary alcohols. The final entry in Table 1 describes an attempted reaction using butylmethylimidazolium bis(trifluoromethanesulfonyl)amide ionic liquid [bmIm][tfsa]. This reaction failed to produce any product and all D-glucose was recovered, as is the case when no ionic liquid is present. The first entry in Table 1 describes the acetylation of 1 molar equiv. of glucose by 5 molar

Table 1 Acetylation reactions using no added catalyst

Substrate	Solvent (eq)[a]	Ac_2O (eq)	Temp. (°C)	Time (h)	Yield % (α/β)
α-D-Glucose	2 [bmIm][dca]	5	rt[b]	0.2	89 (54/46)
α-D-Glucose	2 [bmIm][dca]	5	50	0.1	98 (48/53)
β-Me-Glucose	2 [bmIm][dca]	4.5	rt	0.2	92
Neu5Ac [**3**]	2 [emIm][dca]	5	rt	24	72
Sucrose [**4**]	4 [bmIm][dca]	8	rt	24	93
Raffinose [**5**]	6 [emIm][dca]	11	rt	24	90
2-Naphthol	2 [emIm][dca]	1	rt	24	85
t-BuOH	2 [emIm][dca]	1	rt	24	88
Cyclohexanol	2 [emIm][dca]	1	rt	0.5	90
α-D-Glucose	2 [bmIm][tfsa]	5	rt	24	0

[a] Denotes molar equivalents. [b] Room temperature is approx. 25 °C.

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equiv. of acetic anhydride in 2 molar equiv. of [bmIm][dca] ionic liquid at room temperature (25 °C). When the same reaction was conducted at 50 °C the reaction was complete within 5 min. The acetylation of β-methyl glucopyranoside proceeded just as quickly and efficiently as with D-glucose and without any observed effect on the glycosidic linkage.

N-Acetylneuraminic acid [**3**] (Fig. 2), a polyfunctional ulosonic acid with five hydroxy groups of differing reactivity,[19] the disaccharide sucrose [**4**], and the trisaccharide raffinose [**5**], represent complex saccharides that have a variety of different hydroxy groups. All of these hydroxy groups were acetylated within 24 hours at room temperature. It is expected that an increase in reaction temperature will speed up the reaction rate for the more complex saccharides by increasing their solubility in the ionic liquid.

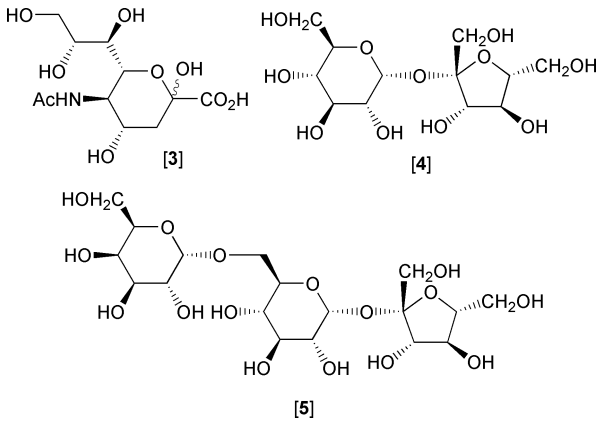

Fig. 2 [**3**] Neu5Ac, [**4**] sucrose and [**5**] raffinose.

Table 2 details a variety of acetylation reactions of α-D-glucose in the presence of different added catalysts and solvents. The traditional acetylation catalysts, pyridine and sodium acetate, continue to achieve the anomeric selectivity that they are known to produce,[6] although the presence of some alternate anomer suggests that the dicyanamide ionic liquid is playing a competitive catalytic role in the reaction.

Reactions with triethylamine (Et_3N) as catalyst were carried out at room temperature in either [bmIm][dca] or the common volatile organic solvents; acetone, acetonitrile or dimethylformamide (DMF). The long reaction times and lower yields in the organic solvents illustrate the usefulness of dicyanamide based ionic liquids compared to more traditional solvents. This is especially evident when considering the solvent-related 'green' benefits of the re-usable ionic liquid. To confirm the latter possibility, recovered [emIm][dca] was re-used in an acetylation reaction; a similar reaction time was required for complete acetylation (data not shown).

Table 2 Acetylation reactions of α-D-glucose using added catalyst

	Solvent (eq)[a]	Ac_2O (eq)	Catalyst (eq)	Temp. (°C)	Time (h)	Yield % (α/β)
1	1 [emIm][dca]	5	0.5 NaOAc	50	0.5	95 (11/89)
2	10 [bmIm][dca]	10	10 Pyridine	50	0.2	98 (95/5)
3	1 [bmIm][dca]	5	0.5 Pyridine	0	4	83 (75/25)
4	10 [bmIm][dca]	5	5 Et_3N	rt[b]	0.2	95 (60/40)
5	2 [bmIm][dca]	5	5 Et_3N	0	4	80 (58/42)
6	2 [bmIm][dca]	5	5 Et_3N	rt	0.1	97 (17/83)
7	10 DMF	5	5 Et_3N	rt	24	88 (28/72)
8	10 Acetone	5	5 Et_3N	rt	48	75 (11/89)
9	10 Acetonitrile	5	5 Et_3N	rt	48	69 (8/91)
10	0.5[emIm][dca]	5	No catalyst	50	0.2	92 (46/54)

[a] Denotes molar equivalents. [b] Room temperature is approx. 25 °C.

The observation that the reactions in Table 1 proceed just as rapidly, in the absence of catalyst, as the catalysed reactions in Table 2 indicates that the ionic liquid has a more crucial role than simply as an inert solvent. In order to investigate whether the dicyanamide compound may have a role as a reactant, or as a base catalyst, a reaction (final entry in Table 2) was carried out using only 0.5 molar equiv. of ionic liquid and no catalyst. This reaction proceeded to full acetylation despite the dicyanamide compound only representing 0.1 molar equiv. with respect to hydroxy groups. This suggests that the ionic liquid is acting as a regenerating catalyst. The mechanism of this catalysis is currently under investigation, but it is most likely related to the basicity of the dicyanamide anion. The absence of any reaction in the case of the [bmIm][tfsa] ionic liquid (Table 1) further supports this proposition.

In conclusion, we have developed a rapid, clean and mild method for *O*-acetylation of alcohols and saccharides using a dicyanamide based ionic liquid. The ionic liquid is not only an excellent solvent for a range of hydroxylated compounds but also an effective base catalyst for *O*-acetylation.

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