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ARTICLE TYPE

Regioselective acetylation of carbohydrates and diols catalyzed by tetramethyl-ammonium hydroxide in water

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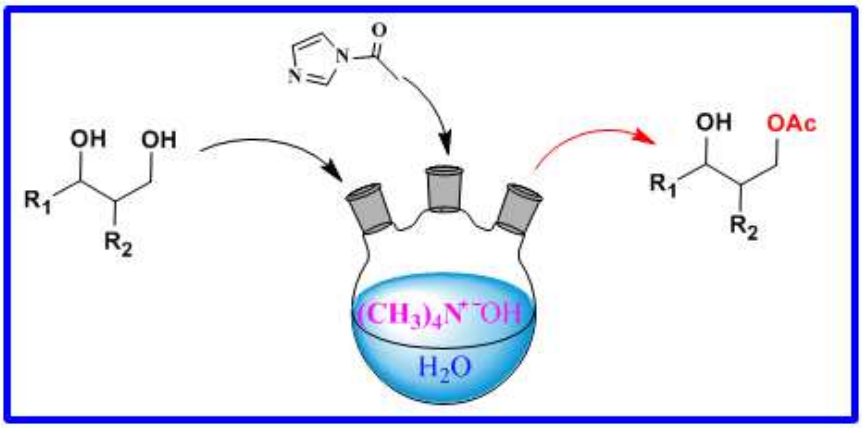
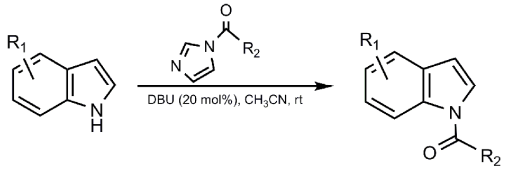
A novel method for an efficient regioselective acetylation of carbohydrates and diols in aqueous solution is described. Treatment of substrates with 1-acetylimidazole, tetramethyl-ammonium hydroxide (TMAH) in water under mild conditions gave highly regioselective acetylation for primary hydroxyl groups. This discovery provides an eco-friendly way for selective acetylation of non-protected glycosides and diols in water, avoiding the use of toxic organic solvents and the necessity of pre-protection of secondary hydroxyl groups.



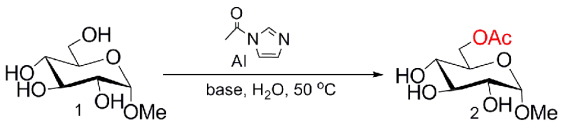
Regioselective protection of polyols and diols under mild and eco-friendly conditions represents a central challenge in chemical synthesis.[1] Carbohydrates, which are important and classic polyols, contain hydroxyl groups with similar reactivities. Regioselective protection of carbohydrates with several hydroxyl groups is a long-standing problem.[2] Recently, several protection methods have been developed to this end by using certain reagents as promoters to enlarge small differences between reactivities of hydroxyl groups in carbohydrates and diols. Examples include reactions employing organotin,[3] organoboron,[4] organosilicon,[5] and metal salts,[6] organo-catalytic method,[7] and enzymatic method.[8] However, many of these promoters have short-comings in selective protection of carbohydrates and diols, including environmental toxicity, expensive reagents, moisture intolerance, and the necessity of pre-protection of secondary hydroxyl groups. Hence, there is an urgent need to find a mild, non-toxic and eco-friendly method for selective protection of carbohydrates and diols, where the reaction is best carried out in water since reactions in aqueous solution have recently attracted considerable attention from the standpoint of green chemistry.[9]

In this study, we sought to develop a green approach for selective acetylation of primary hydroxyl groups in carbohydrates and diols. It was known that carbonylimidazole derivatives constitute a class of highly active acetylation reagents, particularly in preparation of esters and amides.[10] In several cases, the carbonylimidazole derivatives have shown superior selectivity for N-acetylation of oxindoles and indoles (Scheme 1).[11] However, the reactions mentioned above were run in organic solvents because of poor water solubility of carbonylimidazole derivatives. Inspired by this work, we decided to explore the possibility of 1-acetylimidazole (AI) as an acetylation reagent for replacing toxic and unstable acid halides in water.



Scheme 1 N-acetylation of heterocycles with carbonylazoles

In another aspect, we sought to find an eco-friendly basic catalyst for the acetylation of carbohydrates and diols. The quaternary ammonium hydroxide as a classical strong organic alkali attracted our attention due to its unique features: $R_4N^+OH^-$ zwitterionic form, non-toxicity, easy degradation, good water solubility, cheap and commercial availability. Earlier, Wang used tetraethylammonium hydroxide (TEAH) as catalyst for selectively protecting the primary hydroxyl group of ribonucleotides and ribonucleosides in DMF.[12] Recently, tetramethylammonium hydroxide (TMAH) has been used in several important organic transformations.[13] All these previous studies encouraged us to investigate TMAH as a basic catalyst in the selective acetylation of carbohydrates and diols with AI in water.



Scheme 2 Regioselective acetylation of methyl α-D-glucopyranoside

Taking methyl α-D-glucopyranoside (**1**) as substrate, the regioselective acetylation of **1** in water was catalyzed by base in the presence of AI (Scheme 2). To improve water solubility of AI, the reaction temperature was increased to 50 °C. The catalytic effects of a range of bases, including TMAH, have been investigated (Table 1). As can be seen in Table 1, DBN, NaOH, and Na_2CO_3 led to low yields (Entry 2, 4 and 5). However, as we hoped, the best yield was obtained with TMAH as catalyst.

Table 1 Optimization of methyl α-D-glucopyranoside acetylation [a]

Entry	Base	Yield[c] (%)
1	DBU	30
2	DBN	18
3	LiOH	35
4	NaOH	23
5	Na_2CO_3	26
6	K_2CO_3	32
7	TMAH	45 (52[b])
8	TEAH	33

[a]AI: 2.0 equiv., base: 0.5 equiv., Temp: 50 °C, time: 24 h; [b]AI: 3.0 equiv., TMAH: 1.2 equiv., Temp: 60 °C, time:16 h; [c]Isolated yield. DBU: 1,8-diazabicyclo[5.4.0]-undec-7-ene, DBN: 1,5-diazabicyclo-[4.3.0]non-5-ene, TMAH: tetramethylammonium hydroxide, TEAH: tetraethylammonium hydroxide.

In a series of optimization studies, methyl α-D-glucopyranoside was allowed to react with various quantities of TMAH (0.2 to 2.0 equiv) in the presence of AI (1.2 to 4.0 equiv) in water at temperature range from rt to 80 °C. It was found that methyl 6-*O*-acetyl-α-D-glucopyranoside (**2**) was synthesized in the presence of TMAH (1.2 equiv) and 1-acetylimidazole (3.0 equiv) at 60 °C in water for 16 h with an acceptable yield of 52%. It was also observed that an amount of TMAH more than 2.0 equiv disfavored the formation of product **2.**

With these findings in hand, the optimized catalyst system found above was further used for selective monoacetylation with a wide range of substrates (Table 2), including non-protected methyl D-pyranoside (entry 1-5), partially protected methyl D-pyranoside (entry 6-8) and diols (entry 9-16). The common feature of the substrates is that they all contain a primary and one or more secondary hydroxyl groups. The reaction condition has been successfully applied for the selectively monoacetylating carbohydrates and diols, where only minute quantities of by-products were detected by ^{1}H NMR (Fig. 1). Especially, the non-protected methyl D-pyranosides showed high regioselectivity for primary hydroxy group and had almost no secondary acetylated product (entry 1-3 and 5, only trace amount of byproduct detected). The partially protected methyl D-pyranosides had good selectivity for primary hydroxy group as well. The byproduct yield was no higher than 7% (see Fig. 1a, methyl 3-*O*-benzyl-α-D-galactopyranoside acetylated byproduct **12b** only about 5%; Fig. 1b, methyl 3-*O*-benzyl-β-D-galactopyranoside byproduct **14b** only about 7%). When the method was expanded to protect the primary hydroxyl group of various diols, good regioselectivity and yields were also obtained. The byproduct yield is less than 8% (Fig. 1c, 1-phenyl-1, 2-ethanediol acetylated byproduct **20b** only about 8%; Fig. 1d guaifenesin acetylated byproduct **30b** only about 6%).

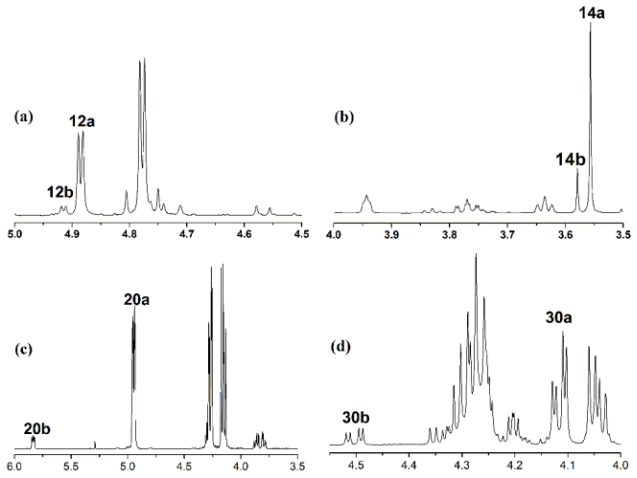
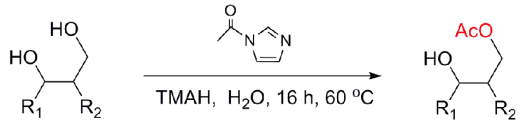
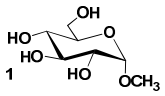
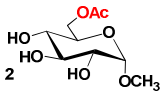
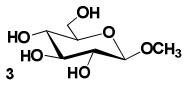
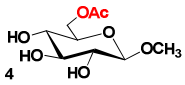
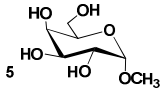
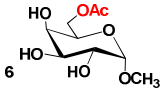
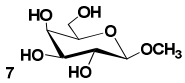
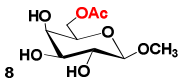
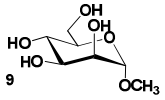
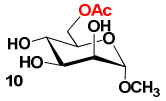
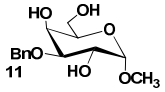
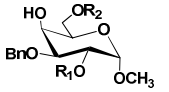
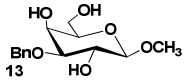
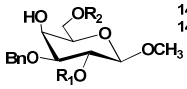
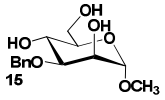
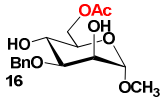
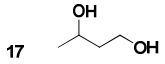
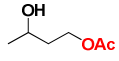
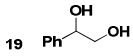
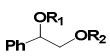
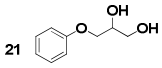
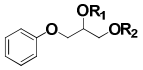
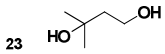
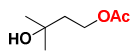
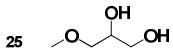
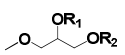
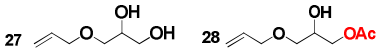
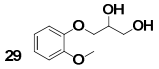
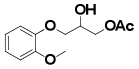
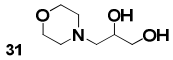
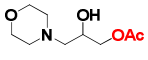


Fig. 1 ^{1}H NMR spectra of product mixtures resulting from different substrates: (a) methyl 3-*O*-benzyl-6-*O*-acetyl-α-D-galactopyranoside (**11**), (b) methyl 3-*O*-benzyl-6-*O*-acetyl-β-D-galactopyranoside (**13**), (c) 1-phenyl-1,2-ethanediol (**19**), (d) guaifenesin (**29**).

Because the ^{1}H NMR spectra of product mixture resulting from substrate **21** (entry 11) and **25** (entry 13) lack suitable characteristic peaks for comparison, we isolated their byproducts (**22b** yield 5% and **26b** yield 6%) by chromatography. Moreover, no byproducts were detected by ^{1}H NMR when the substrates were **7** (methyl β-D-galactopyranoside, entry 4), **17**, **23**, and **31** (diols, entry 9, 12 and 16). To the best of our knowledge, this is the first report for regioselective acetylation of carbohydrates and diols in water with AI as acetylation reagent in the presence of TMAH, where acetylation was performed by transacylation reactions of imidazolides under strong basic condition.[14] Based on the previous studies,[12a,15] we proposed a mechanism for the regioselective acetylation of primary hydroxyl group using TMAH as a catalyst in water. In this hypothesis, both primary and secondary hydroxyl groups can be deprotonated in the presence of strong base TMAH. The acylation of primary hydroxyl group are more preferably produced due to its less steric hindrance and stronger nucleophilicity than the other hydroxyl groups.[12a,15] Moreover, Edgar and co-worker reported that

Table 2 1-acetylimidazole used for selective acetylation of primary hydroxyl group in carbohydrates and diols



Entry	Substrates	Major products	Byproducts	Conversion (%)[c]	Isolated yield (%)	Ref
1			Trace amount	60	52	18
2			Trace amount	62	56	9d
3			Trace amount	64	59	19
4			–	74	70	20
5			Trace amount	50	44	21
6			12a:R_1=H, R_2=OAc 12b:R_1=OAc, R_2=H 5% of **12b** based on NMR	58	50	–
7			14a:R_1=H, R_2=OAc 14b:R_1=OAc, R_2=H 7% of **14b** based on NMR	61	52	21
8			Trace amount	48	43	21
9			–	39	36	22
10			20a:R_1=H, R_2=Ac 20b:R_1=Ac, R_2=H 8% of **20b** based on NMR	70	60	19
11			22a:R_1=H, R_2=Ac 22b:R_1=Ac, R_2=H 5% of **22b** product was isolated.	64	56	23
12			–	73[b]	70	24
13			26a:R_1=H, R_2=Ac 26b:R_1=Ac, R_2=H 6% of **26b** product was isolated	65	55	25
14			Trace amount	54	50	25
15			30a:R_1=H, R_2=Ac 30b:R_1=Ac, R_2=H 6% of **30b** based on NMR	71	62	26
16			–	60[b]	55	27

Notes: [a] reaction conditions: AI (3.0 equiv.); TMAH (1.2 equiv.); [b] TMAH (1.5 equiv.); [c] NMR ratio.

deacylation of cellulose triesters in DMSO by adding TBAOH aqueous solution, mainly affording cellulose-6-O-esters, which demonstrated primary ester is more stable than secondary esters in the basic condition.[16] Leino and co-worker studied the acyl groups migration for β-D-galactopyranosides in D_2O, which demonstrated the secondary esters is easier to migration to produce primary ester at basic condition (C2⇆C3⇆C4→C6 migration).[17]

Unlike the known methods, where the selective acetylation required pre-preparation of catalysts, toxic organic solvents, or pre-protection of secondary hydroxide groups, the method we developed in this work has no such disadvantages, and is therefore simple, eco-friendly, and highly regioselective. While yields are moderate, they compare quite favorably in general to the overall yields of the complex protection, acylation, and deprotection sequences that they can replace. For example, regioselective acetylation of **7** and 3-methyl-1,3-butanediol **23** under the optimized conditions yielded the corresponding acetylated products in 70% yield (see Entry 4 and 12). These results indicated that TMAH was successfully used to regioselectively acylate carbohydrates as well as diols.

Conclusions

For the first time, an eco-friendly approach for regioselective acetylation of carbohydrates and diols in aqueous solution has been developed. Highly regioselective acetylation for primary hydroxyl groups can be obtained by using 1-acetylimidazole as an acetylation reagent in the presence of TMAH, avoiding the complex, costly, time-consuming protection and deprotection schemes. The acetylation reaction can be conveniently carried out in water, avoiding the use of toxic and flammable organic solvents. With these particular merits, this method will provide a novel approach to an environmentally benign process for regioselective acetylation of primary hydroxyl groups in carbohydrates and diols.

Experimental

General Acetylation procedure of substrates (methyl D-pyranosides or diols)

To a solution of substrate (1 equiv.) in water (0.2 mL) was added TMAH (25% aq. 1.2 equiv.), and the mixture was allowed to stir at 60 °C for 5 min. 1-acetylimidazole (3.0 equiv.) was added to the reaction mixture in two portions and it was allowed to stir at 60 °C for 16 h. Water was removed under reduced pressure and the resulting mixture was purified by flash column chromatography (ethyl acetate/petroleum ether: 30% to 100% gradient) to afford acetylated products.

Methyl 3-*O*-benzyl-6-*O*-acetyl-α-D-galactopyranoside (14):

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.32 (m, 5H, Ph), 4.83 (d, J = 3.9 Hz, 1H, H_1), 4.73 (m, 2H, $PhCH_2$), 4.38-4.24 (m, 2H, H_{6a}, H_{6b}), 4.08-3.89 (m, 3H, H_2, H_4, H_5), 3.63 (d, J = 9.6 Hz, 1H, H_3), 3.41 (s, 3H, OMe), 2.44 (s, 1H, OH), 2.15 (d, J = 8 Hz, 1H, OH), 2.08 (s, 3H, OAc).; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 137.8, 128.7, 128.2, 127.9, 99.5, 78.2, 72.3, 68.5, 67.8, 67.0, 63.6, 55.4, 20.9; $[\alpha]^{20}_D$ = +53.5(c = 1.6, CH_3OH). HRMS calcd for $C_{16}H_{22}O_7$ [M + Na] 349.1263. Found 349.1261.

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Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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