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Selective cleavage of sugar anomeric *O*-acyl groups using $FeCl_3 \cdot 6H_2O$

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ABSTRACT

A convenient method has been developed for regioselective anomeric deacylation of carbohydrate derivatives using $FeCl_3 \cdot 6H_2O$ in CH_3CN. Operational simplicity, economic consideration, high yield, and low toxicity are key features associated with this protocol.

Selective deacylation on C-1 of carbohydrate residue often plays an important role in anomeric functional group transformations, especially in the preparation of glycosyl trichloroacetimidates[1] and glycosyl halide.[2,3] A great number of reagents have been suggested for this purpose, such as hydrazine acetate,[4] bis(tributyltin)oxide,[5] tributyltin methoxide,[6] mercuric chloride/mercuric oxide[7] benzylamine,[8] ammonium salts,[9] piperidine,[10] $HClO_4$–SiO_2,[11] and lanthanide triflates.[12] Some of these methods, however, suffered from either highly toxic, expensive, harsh reaction conditions, low regioselectivity, or low general applications. Therefore, providing alternatively less toxic, high regioselective, and environmentally benign protocols for anomeric deacylation of carbohydrates would be very necessary and valuable.

In conversion of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose into its corresponding oxazoline using ferric chloride as catalyst,[13] the anomeric deacetylated derivative was surprisingly obtained as the major product under our reaction conditions. Literature search suggested that ferric chloride has been applied in O-isopropylidenation, acetylation, anomerization, detritylation, debenzylation, deprotection of acetals, and coupling reactions.[14] Here we would like to report our findings in anomeric deacylation using ferric chloride hexahydrate.

The exploration started from per-O-acetylated D-glucose and anhydrous ferric chloride, combining with commercial 1,2-dichloroethane (DCE) or water-containing DCE (Table 1, entries 1–3). The experiments suggested that a good yield of 1-OH derivative, that is, 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose, could be obtained in the presence of certain amount of water under reflux. To test the reaction conditions, the same procedure was thus carried out in commercial acetonitrile and water-containing acetonitrile (Table 1, entries 4–6). The results indicated that both water content and reaction temperature were key elements for this reaction. Further optimization of the reaction conditions suggested that the best result could be obtained using $FeCl_3 \cdot 6H_2O$ in CH_3CN at 70 °C.

Table 1
Optimization of the reaction conditions for the preparation of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
(1) Anhydrous $FeCl_3$ (1–2 equiv)	Commercial DCE	Reflux	7–10	60–80
(2) Anhydrous $FeCl_3$ (1–2 equiv)	DCE–H_2O = 19:1	Reflux	5–8	60–80
(3) Anhydrous $FeCl_3$ (1 equiv)	DCE–H_2O > 20:1	Reflux	7	Complex
(4) Anhydrous $FeCl_3$ (1 equiv)	Commercial CH_3CN	Reflux	10	Complex
(5) Anhydrous $FeCl_3$ (1 equiv)	CH_3CN–H_2O = 19:1	Reflux	1	85
(6) Anhydrous $FeCl_3$ (1–2 equiv)	CH_3CN–H_2O = 19:1	rt	12	<5%
(7) $FeCl_3 \cdot 6H_2O$ (1 equiv)	CH_3CN	70	0.5	92

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Table 2

Anomeric deacylation of sugar derivatives using $FeCl_3 \cdot 6H_2O$ in CH_3CN

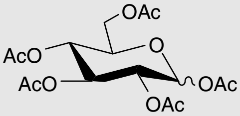
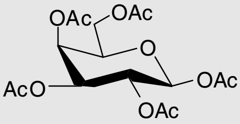
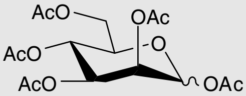
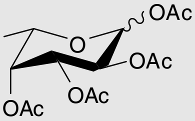
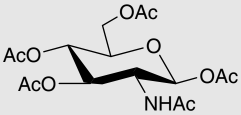
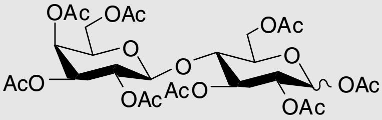
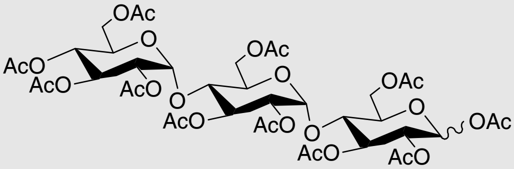
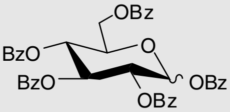
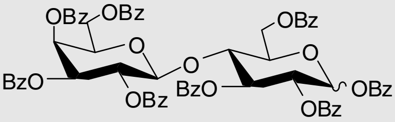
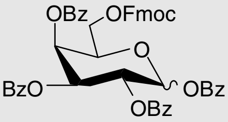
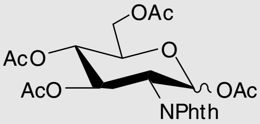
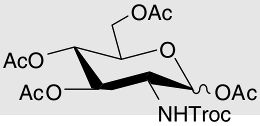
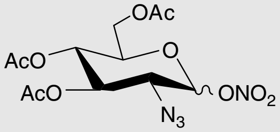
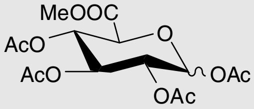
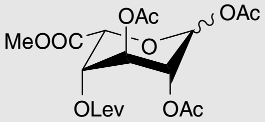
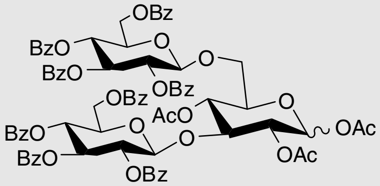
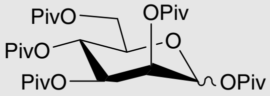
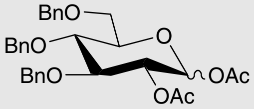
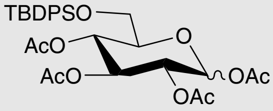
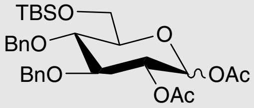
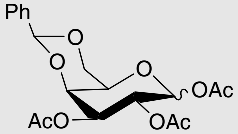
Entry	Substrate	$FeCl_3 \cdot 6H_2O$ (equiv)	Temp (°C)	Time (h)	Yield[a,b] (%)
1		1	70	0.5	92
2		1	70	0.5	91
3		1	70	0.5	89
4		1	40	0.5	85
5		2	Reflux	1.5	90
6		2	Reflux	1.5	83
7		2	Reflux	2.5	80
8		2	Reflux	3	86
9		2	Reflux	5	78
10		2	Reflux	3	85
11		2	Reflux	2	88
12		2	Reflux	1.5	86

Table 2 (*continued*)

Entry	Substrate	FeCl$_3$·6H$_2$O (equiv)	Temp (°C)	Time (h)	Yield[a,b] (%)
13		2	Reflux	2.5	81
14		2	Reflux	2.5	83
15		2	Reflux	2.5	86
16		2	Reflux	9	80
17		4	Reflux	20	70
18		1	50	0.5	78[c]
19		2	50	2.5	53[c]
20		1	40	0.5	n.d.[c]
21		1	40	0.5	n.d.[c]

[a] Isolated yields as average.

[b] The α,β ratios, based on TLC or ^{1}H NMR spectra, were variable from batch to batch.

[c] Higher temperature causes decomposition.

To investigate the scope and the limitation of this reaction, more protected sugar derivatives were subjected to this reaction system and the results are summarized in Table 2. All of the examined reactions proceeded smoothly under indicated reaction conditions, and the products were obtained in good to excellent yields (entries 1–19). The reaction was equally effective for the removal of both α- and β-acetates (entries 1–5). For L-fucose acetate (entry 4), lower temperature (optimized as 40 °C) significantly shrunk side products. In some cases (entries 5–17), reflux conditions were applied considering both yield and time consumption. Moreover, anomeric benzoate (entries 8–10) and nitrate groups (entry 13[15]) could also be removed under the similar reaction conditions. For di- and trisaccharides (entries 6, 7, 9, and 16), interglycosidic linkage remained unaffected under this mild condition. A variety of hydroxyl protecting groups, such as Fmoc (entry 10[16]), Phth (entry 11), Troc (entry 12[17]), COOMe (entries 14 and 15[18]), Piv (entry 17), Bn (entry 18[19]), and even TBDPS (entry 19) under lower reaction temperature, are compatible to the conditions. However, acid labile TBS group (entry 20[20]) and benzylidene group (entry 21) cannot be survive under this condition. More impressively, the yield for removal of anomeric acetate from trisaccharide derivative (entry 16) was significantly improved using $FeCl_3·6H_2O$ in CH_3CN, comparing to that of using NH_3 in MeOH and THF co-solvent.[21] No significant amount of required products was observed using $Fe_2(SO_4)_3·xH_2O$ in CH_3CN or other apolar solvents (CH_2Cl_2, THF, etc.).

A typical experimental procedure is depicted as follows: To a solution of 1-*O*-acyl protected sugar (1.0 mmol) in CH_3CN (5 mL) was added $FeCl_3·6H_2O$ (1–2 mmol), and the reaction mixture was stirred under the appropriate conditions as mentioned in Table 2. After reaction completion (monitored by TLC), the reaction mixture was concentrated directly under diminished pressure, in case of small-scale reaction, and the corresponding residue was further purified on column chromatography. For large-scale preparation, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ first, and then centrifuged. The liquid phase was collected and extracted with CH_2Cl_2 three times. The combined organic phase was evaporated to dryness, and the residue was purified by column chromatography to gain desired product.

In summary, we have demonstrated that $FeCl_3·6H_2O–CH_3CN$ system is highly efficient toward regioselective anomeric deacylation of carbohydrate derivatives. The mild reaction conditions, experimental simplicity, low cost, excellent yield, convenience in large scale preparation, and the environmental benign nature are major advantages of this new approach. Most commonly used protecting groups are matching with current chemistry, and some highly toxic and expensive reagents can be avoided. We expected that this green complimentary method would provide a general application in organic synthesis.

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16. *For 2,3,4-tri-O-benzoyl-6-O-(9-fluorenylmethoxycarbonyl)-*D*-galactopyranose*: ^1H NMR (400 MHz, $CDCl_3$): δ 2.61 (br s, 1H, O*H*-α), 3.27 (br s, 0.2H, O*H*-β), 4.10–4.39 (m, 6.4H), 4.62 (dd, 1H, *J* 3.7, 10 Hz, H-3α), 4.76 (t, 1H, *J* 6.0 Hz, C*H* of Fmoc α), 4.82 (t, 0.2H, *J* 6.0 Hz, C*H* of Fmoc β), 5.70 (dd, 0.2H, *J* 3.2, 10 Hz, H-2β), 5.78 (dd, 1H, *J* 3.2, 10 Hz, H-2α), 6.01 (d, 1H, *J* 3.1 Hz, H-1α), 6.05 (d, 0.2H, *J* 3.6 Hz, H-4β), 6.76 (d, 1H, *J* 3.7 Hz, H-4α), 7.30–8.13 (m, 27.6H, Ph). MALDITOF-MS: calcd for $C_{42}H_{34}O_{11}$: 714.21; found: 737.43 $[M+Na]^+$.
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