ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 2146–2148

www.rsc.org/chemcomm

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Iron(III) chloride-tandem catalysis for a one-pot regioselective protection of glycopyranosides†

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Received 13th October 2010, Accepted 14th December 2010
DOI: 10.1039/c0cc04398b

Tandem catalysis by using iron(III) chloride hexahydrate leads to carbohydrate building blocks displaying an orthogonal protecting group pattern as illustrated by the regioselective protection of trehalose and maltose disaccharides.

For the selective preparation of complex oligosaccharides and glycoconjugates requiring typically lengthy multi-step routes for the construction of building blocks, the development of alternative and efficient strategies continues to be of major importance in synthetic carbohydrate chemistry. Among the approaches utilized, catalyzed reactions in tandem are very attractive since this method increases the efficiency of the process by reducing the number of chemical steps and the time-consuming isolation and purification of intermediates.[1]

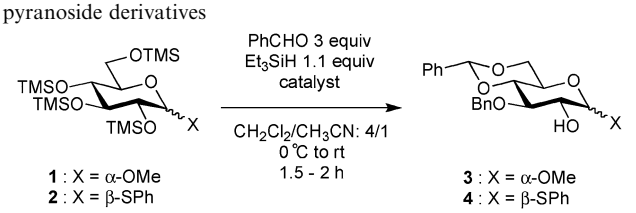
We have recently reported a regioselective one-pot protection of carbohydrates, optimized on persilylated monosaccharides, employing, as a single catalyst, copper(II) triflate (0.5 to 10 mol%) usable under easy conditions (0 °C or room temperature).[2] A wide range of useful D-glucopyranose building blocks was also constructed with a very similar strategy employing trimethylsilyltriflate (24 to 64–112 mol%) at −86 °C/−78 °C.[3,4] These one-pot tandem procedures utilize triflate-containing reagents. As a continuation of these studies, we report here the successful development of the same sequential tandem Lewis acid catalysis with the inexpensive and stable iron(III) chloride hexahydrate. Iron salts have recently attracted considerable attention as inexpensive and environmentally friendly agents in a wide range of selective processes in organic synthesis.[5] When used for its acidic properties, the hexahydrate complex was mostly applied for hydrolytic reactions.[6,7] We show that this simple hydrated catalyst is useful for programming in tandem acetal formation, reductive etherification and acylation, all transformations previously reported as single reactions with the anhydrous salt.[8–10] We also show that the unprecedented regioselective reductive opening of arylidenes catalyzed by this salt can be added as a terminating step.

In our initial studies, we examined the prototype reductive etherification of per-*O*-silylated α-methyl-D-glucopyranoside **1** with benzaldehyde (3 equiv) and triethylsilane (1.1 equiv) in the presence of a catalytic amount of iron(III) chloride, following our previously optimized solvent conditions (CH_2Cl_2 : CH_3CN ratio of 4 : 1).[2] The tandem acetalation–reductive etherification proceeded well with 5 mol% of $FeCl_3{\cdot}6H_2O$ to afford 3-*O*-benzyl-4,6-*O*-benzylidene-D-glucopyranoside **3**[11] (entry 1, Table 1) in a 77% yield.‡ Lowering the loading of catalyst to 1 mol% resulted in a lower 66% yield (entry 2). In contrast with our previous study using copper(II) triflate, this catalytic system is not air sensitive and the reaction could be performed easily on a gram-scale.

The use of other iron catalysts was studied next (entries 3–7, Table 1). Anhydrous iron chloride provided the expected compound in a similar yield (entry 3). The $Fe(acac)_3$ and $(FeCl_3)_2(TMEDA)_3$ complexes, known to be less hygroscopic than $FeCl_3$,[12] were inefficient under these reaction conditions (entries 4 and 5). The complex $Fe(NO_3)_3{\cdot}9H_2O$ led to the expected compound in a low 14% yield whereas $FeCl_2{\cdot}4H_2O$ catalyzed only the acetalation reaction in 53% yield (entries 6 and 7).

This optimized procedure was also extended to thioglucopyranoside **2**, affording product **4** in a 71% yield (entry 8),

Table 1 Iron salt-catalyzed transformations of persilylated D-glucopyranoside derivatives



1 : X = α-OMe
2 : X = β-SPh

3 : X = α-OMe
4 : X = β-SPh

Entry	X	Catalyst	Mol%	Yield%
1	α-OMe	$FeCl_3{\cdot}6H_2O$	5	77
2	α-OMe	$FeCl_3{\cdot}6H_2O$	1	66[a]
3	α-OMe	$FeCl_3$	5	75
4	α-OMe	$Fe(acac)_3$	5	—[b]
5	α-OMe	$(FeCl_3)_2(TMEDA)_3$	2.5	—[b]
6	α-OMe	$Fe(NO_3)_3{\cdot}9H_2O$	5	14[a,c]
7	α-OMe	$FeCl_2{\cdot}4H_2O$	5	—[a,d]
8	β-SPh	$FeCl_3{\cdot}6H_2O$	5	71

[a] Overnight reaction. [b] Starting material was recovered. [c] The 4,6-*O*-benzylidene derivative was obtained in 68% yield. [d] CH_2Cl_2 was used instead of CH_2Cl_2/CH_3CN; only the 4,6-*O*-benzylidene derivative was isolated in 53% yield.

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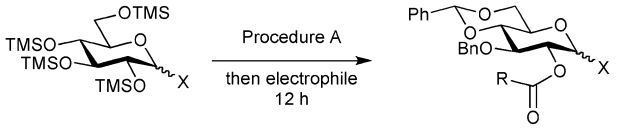
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of ^1H and ^{13}C NMR spectra for new compounds. See DOI: 10.1039/c0cc04398b

Table 2 Iron chloride hexahydrate-catalyzed one-pot regioselective protection of D-glucopyranosides **1** and **2**



1 : X = α-OMe
2 : X = β-SPh

5a : X = α-OMe, R = CH_3
5b : X = α-OMe, R = $C_{15}H_{31}$
5c : X = α-OMe, R = *tert*-Bu
6 : X = β-SPh, R = CH_3

Entry[a]	X	Electrophile (5 equiv)	Temperature	Yield%
1	α-OMe	Ac_2O	rt	**5a**: 64[b]
2	β-SPh	Ac_2O	rt	**6**: 60[b]
3	α-OMe	$C_{15}H_{31}COCl$	rt	**5b**: 58
4	α-OMe	Piv_2O	45 °C	**5c**: 60

[a] Procedure A: $FeCl_3{\cdot}6H_2O$ 5 mol%, PhCHO (3 equiv), Et_3SiH (1.1 equiv), CH_2Cl_2/CH_3CN: 4/1, 0 °C to rt, 1.5–2 h. [b] The major by-product (15–20%) was the 2,3-di-*O*-Ac-4,6-*O*-benzylidene derivative.

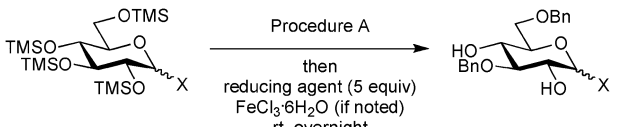
without affecting the thioglycoside functionality. In contrast, this transformation could not be performed with $Cu(OTf)_2$ catalysis in solution at room temperature,[2] without the formation of the 3,6 di-*O*-benzyl derivative as a side product, resulting from the reductive opening of the acetal.

The possibility of expanding further the tandem process by a "terminating" acylation step to obtain the orthogonally protected monosaccharide was also examined. Hence, terminal addition of acetic anhydride or palmitoyl chloride afforded the acylated compounds in good yields (entries 1–3, Table 2), including pivaloylation, which required a higher temperature to proceed (entry 4).

We then focused on a successive regioselective reductive ring opening of the 4,6-*O*-benzylidene acetal. This carbon–oxygen bond cleavage associating an acidic catalyst and a reducing agent is very well documented,[13] although iron salts were never employed before. Accordingly, persilylated pyranoside **1**, treated with procedure A followed by a further addition in the same pot of 5 equivalents of Et_3SiH, led to the 3,6-di-*O*-benzyl compound **7** in 45% yield (entry 1, Table 3).

The simultaneous addition of 5 mol% of the iron catalyst increased the yield to 55% (entry 2). These conditions applied

Table 3 Reductive ring opening of acetal mediated by $FeCl_3{\cdot}6H_2O$



1 : X = α-OMe
2 : X = β-SPh

7 : X = α-OMe
8 : X = β-SPh

Entry[a]	X	Reducing agent	Added $FeCl_3{\cdot}6H_2O$	Yield%
1	α-OMe	Et_3SiH	—	45
2	α-OMe	Et_3SiH	5%	55[b]
3	β-SPh	Et_3SiH	5%	54[c]
5	α-OMe	$BH_3{\cdot}THF$	—	—[d]

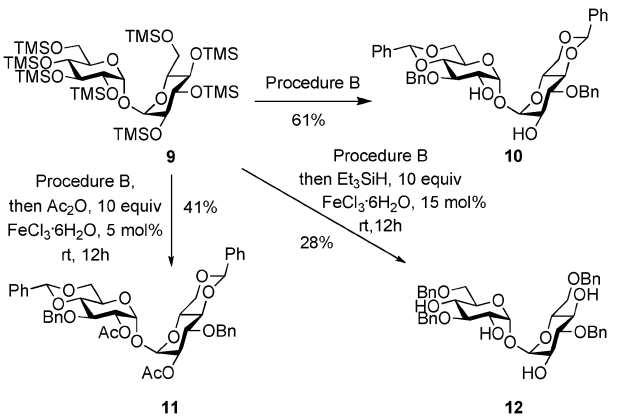
[a] Procedure A: $FeCl_3{\cdot}6H_2O$ 5 mol%, PhCHO (3 equiv), Et_3SiH (1.1 equiv), CH_2Cl_2/CH_3CN: 4/1, 0 °C to rt, 1.5–2 h. [b] 20% of the mono-3-*O*-benzyl derivative were also formed. [c] 8% of the 2,3,6-tri-*O*-benzyl derivative were also formed. [d] Only acetal **3** was isolated in 67% yield.

to silylated thioglucopyranoside **2** afforded the 3,6-di-*O*-benzyl derivative **8** in a similar yield (entry 3).[14] It is noteworthy that the single reductive opening of benzylidene **3** under these conditions ($FeCl_3{\cdot}6H_2O$, 5 mol%; Et_3SiH, 5 equiv; CH_2Cl_2/CH_3CN: 4/1 rt, overnight) provided benzyl compound **7** in only 41% yield, emphasizing the interest of the tandem process. This transformation did not proceed using $BH_3{\cdot}THF$ as a reducing agent probably due to a complexation with the catalyst (entry 5).

This tandem protocol was also applied to per-*O*-silylated-α,α-D-trehalose **9** obtained in 92% yield from trehalose (TMSCl, 10 equiv; pyridine; rt, overnight). α,α-D-Trehalose is a basic core in a number of biologically important glycoconjugates playing pivotal roles in many organisms.[15,16] The symmetric compound **10** was isolated in good yield with the same regioselectivity for the reductive etherification employing procedure B ($FeCl_3{\cdot}6H_2O$, 5 mol%; PhCHO, 6 equiv; Et_3SiH, 2.2 equiv; CH_2Cl_2/CH_3CN: 4/1 0 °C to rt, 3 h, Scheme 1). This procedure could be extended to a multi-gram scale without affecting the isolated yields.[17]

Adding, to the tandem sequence, a one-pot acetylation with an excess of acetic anhydride (10 equiv) and 5 mol% more of $FeCl_3{\cdot}6H_2O$ furnished the expected 2,2′-di-*O*-acetylated α,α-D-trehalose **11** in an isolated 41% yield. Finally, ending with a one-pot *bis*-reductive opening of the benzylidene acetals by a sequential addition of 10 equivalents of Et_3SiH and 15 mol% of the catalyst afforded the expected compound **12** in a very moderate yield of 28%, reaching the limit for this tandem procedure.[18,19]

Finally, the utility of this one-pot regioselective protection was examined on α-methyl maltoside **13** (Scheme 2). With this disaccharide, a higher load of the catalyst (15 mol%) was required to provide a practical yield (51%) of the benzylidene *bis*-benzyl derivative **14**.



Scheme 1 One-pot regioselective protection of α,α-D-trehalose. Procedure B: $FeCl_3{\cdot}6H_2O$, 5 mol%; PhCHO, 6 equiv; Et_3SiH, 2.2 equiv; CH_2Cl_2/CH_3CN: 4/1 0 °C to rt, 3 h.

Scheme 2 One-pot regioselective protection of α-methyl maltoside.

In conclusion, we have developed an efficient one-pot procedure for the regioselective protection of D-glucopyranoside derivatives by tandem catalysis mediated by $FeCl_3{\cdot}6H_2O$. Our method provides a very fast access to orthogonally protected saccharides in one vessel under very mild conditions and has been applied to the α,α-D-trehalose disaccharide and α-methyl maltoside. It is interesting to note that all four reactions, which conventionally require anhydrous conditions or dehydrating agents to be carried out, are conveniently catalyzed in this work by the easy-to-handle hydrated iron complex. Extension of this protocol to other mono-, di- and oligosaccharides of interest is currently in progress in our laboratory and will be reported in due course.

We thank the Ministère de la Recherche for a grant to AL and the CNRS for financial support.

Notes and references

‡ *Representative procedure* (*synthesis of compound* **3**): To an ice-cold solution of the per-*O*-silylated α-methyl glucopyranoside **1** (3 g, 6.2 mmol) and benzaldehyde (1.89 mL, 18.6 mmol, 3 equiv) in dichloromethane (11.0 mL), a solution of $FeCl_3{\cdot}6H_2O$ in acetonitrile (84.0 mg, 5 mol%, in 2.7 mL of CH_3CN) and triethylsilane (1.09 mL, 6.8 mmol, 1.1 equiv) was added dropwise. The reaction was stirred at room temperature and monitored by TLC. After consumption of the starting material, tetra-*n*-butylammonium (10.0 mL of a 1 M solution in THF) was added. The solution was diluted with ethyl acetate and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography to give the expected compound **3** (1.78 g, 77% yield).

1 For some key reviews see: (*a*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*b*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137; (*c*) D. E. Fogg and E. N. dos Santos, *Coord. Chem. Rev.*, 2004, **248**, 2365; (*d*) A. Ajamian and J. L. Gleason, *Angew. Chem., Int. Ed.*, 2004, **43**, 3754; (*e*) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*f*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*g*) N. Shindoh, Y. Takemoto and K. Takasu, *Chem.–Eur. J.*, 2009, **15**, 12168.

2 A. Français, D. Urban and J.-M. Beau, *Angew. Chem., Int. Ed.*, 2007, **46**, 8662.

3 C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang and S.-C. Hung, *Nature*, 2007, **446**, 896.

4 For some other recent one-pot tandem procedures, see: (*a*) Y. Vohra, M. Vasan, A. Venot and G.-J. Boons, *Org. Lett.*, 2008, **10**, 3247; (*b*) K.-K. T. Mong, C.-S. Chao, M.-C. Chen and C.-W. Lin, *Synlett*, 2009, 603; (*c*) R. A. Jones, R. Davidson, A. T. Tran, N. Smith and M. C. Galan, *Carbohydr. Res.*, 2010, **345**, 1842; (*d*) H.-C. Lin, Y. B. Chen, Z. P. Lin, F. F. Wong, C.-H. Lin and S.-K. Lin, *Tetrahedron*, 2010, **66**, 5229.

5 For selected reviews see: (*a*) C. Bolm, J. Legros, J. Le Paih and L. Zani, *Chem. Rev.*, 2004, **104**, 6217; (*b*) D. Diaz, P. Miranda, J. Padrón and V. Martín, *Curr. Org. Chem.*, 2006, **10**, 457; (*c*) D. Sherry and A. Fürstner, *Acc. Chem. Res.*, 2008, **41**, 1500; (*d*) E. B. Bauer, *Curr. Org. Chem.*, 2008, **12**, 1341.

6 (*a*) G. Wei, L. Zhang, C. Cai, S. Cheng and Y. Du, *Tetrahedron Lett.*, 2008, **49**, 5488; (*b*) S. E. Sen, S. L. Roach, J. K. Boggs, G. J. Ewing and J. Magrath, *J. Org. Chem.*, 1997, **62**, 6684; (*c*) X. Ding, W. Wang and F. Kong, *Carbohydr. Res.*, 1997, **303**, 445.

7 For cleavage bond reactions, see: (*a*) M. H. Park, R. Takeda and K. Nakanishi, *Tetrahedron Lett.*, 1987, **28**, 3823; (*b*) J. I. Padrón and J. T. Vázquez, *Tetrahedron: Asymmetry*, 1995, **6**, 857; (*c*) R. Rodebaugh, J. S. Debenham and B. Fraser-Reid, *Tetrahedron Lett.*, 1996, **37**, 5477.

8 Acetal formation promoted by anhydrous $FeCl_3$: (*a*) P. P. Singh, Y. M. Gharia, F. Dasgupta and H. C. Srivastava, *Tetrahedron Lett.*, 1977, **18**, 439; (*b*) W. Danikiewicz, M. Olejnik, J. Wójcik, S. K. Tyrlik and B. Nalewajko, *J. Mol. Catal. A: Chem.*, 1997, **123**, 25.

9 Reductive etherification catalyzed by anhydrous $FeCl_3$: (*a*) K. Iwanami, H. Seo, Y. Tobita and T. Oriyama, *Synthesis*, 2005, 183; (*b*) K. Iwanami, K. Yano and T. Oriyama, *Synthesis*, 2005, 2669; (*c*) K. Iwanami, K. Yano and T. Oriyama, *Chem. Lett.*, 2007, **36**, 38.

10 Acylation: (*a*) F. Dasgupta, P. P. Singh and H. C. Srivastava, *Carbohydr. Res.*, 1980, **80**, 346; (*b*) G. V. M. Sharma, A. K. Mahalingam, M. Nagarjan, A. Ilangovan and P. Radhakrishna, *Synlett*, 1999, 1200. With $FeCl_3{\cdot}6H_2O$ as a catalyst, see; (*c*) K. Komura, A. Ozaki, N. Ieda and Y. Sugi, *Synthesis*, 2008, 3407.

11 The regioselectivity of the reductive etherification was determined through chemical correlation after acetylation of the hydroxyl function and was in agreement with previous work. See ref. 2 and C.-C. Wang, J.-C. Lee, S.-Y. Luo, H.-F. Fan, C.-L. Pai, W.-C. Y, L.-D. Lu and S.-C. Hung, *Angew. Chem., Int. Ed.*, 2002, **41**, 2360.

12 G. Cahiez, V. Habiak, C. Duplais and A. Moyeux, *Angew. Chem., Int. Ed.*, 2007, **46**, 4364.

13 For a recent work see: K. Daragics and P. Fügedi, *Tetrahedron Lett.*, 2009, **50**, 2914 and references cited therein.

14 This sequential addition of the iron catalyst (5 mol% twice) was more efficient than adding 10 mol% at the onset of the tandem process.

15 (*a*) J.-C. Argüelles, *Arch. Microbiol.*, 2000, **174**, 217; (*b*) A. D. Elbein, Y. T. Pan, I. Pastuszak and D. Carroll, *Glycobiology*, 2003, **13**, 17; (*c*) M. Gilleron, S. Stenger, Z. Mazorra, F. Wittke, S. Mariotti, G. Böhmer, J. Prandi, L. Mori, G. Puzo and G. De Libero, *J. Exp. Med.*, 2004, **199**, 649.

16 For recent synthetic studies on substituted trehalose derivatives see: (*a*) C. D. Leigh and C. R. Bertozzi, *J. Org. Chem.*, 2008, **73**, 1008(*b*) J. Guiard, A. Collmann, M. Gilleron, L. Mori, G. De Libero, J. Prandi and G. Puzo, *Angew. Chem., Int. Ed.*, 2008, **47**, 9734; (*c*) M. K. Patel and B. G. Davis, *Org. Biomol. Chem.*, 2010, **8**, 4232.

17 Under the same conditions, but with a higher concentration, the reaction mediated by copper(II) triflate provided only 30% yield of the same compound **10**.

18 Higher loadings of catalyst did not improve the yield, probably due to the concomitant hydrolysis of the benzylidene acetals. See ref. 6*b*.

19 The direct *bis* reductive opening of the benzylidene acetals in compound **10** under identical conditions led to a complex mixture of partially reduced and/or hydrolyzed products, highlighting again the interest of the tandem procedure.

