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Diastereoselective thioglycosylation of peracetylated glycosides catalyzed by in situ generated iron(III) iodide from elemental iodine and iron

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ARTICLE INFO	ABSTRACT
Article history:	A facile in situ preparation of Fe(III) iodide from cheap, abundant elemental iodine and iron metal served
Received 7 June 2009	as an efficient catalyst for the thioglycosylation of peracetylated glycosides with various alkyl and aryl
Revised 12 July 2009	mercaptans. Due to neighboring participation, the anomerically pure β -thioglycosides were obtained in
Accepted 16 July 2009	good to high yields with exclusive diastereocontrol.
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Carbohydrate derivatives with anomeric-substituted thiol groups as stable O-glycoside analogues have attracted considerable attention in a wide array of biological activity studies.¹ In addition, thioglycosides with different substituted pendants have served as versatile building block core units to facilitate the rapid synthesis of complex oligosaccharides, known as 'Programmable One-Pot Oligosaccharide Synthesis'.² The Lewis acid-catalyzed thiolysis of peracetylated saccharides to produce thioglycosides with predominantly 1,2-trans-product has been the most extensively adopted method for many years.^{1b} Currently available catalysts such as *p*-TSA,^{3a} Amberlyst/Amberlite resin,^{3b} perchloric acid–silica,^{3c} TiCl₄,⁴ BF₃–Et₂O,⁵ AlCl₃,⁶ ZrCl₄,⁷ SnCl₄,⁸ TMSOTf,⁹ ZnI₂,¹⁰ Et₃SiH/I₂–thio-urea,¹¹ Me₃SiSiMe₃/I₂,¹² and amphoteric MoO₂Cl₂¹³ have been successfully employed, stoichiometrically or substoichiometrically, for such transformations. In most instances, the cost of the catalyst, moisture sensitivity, and toxicity issues have restricted their use in biological or pharmaceutical applications. Hence, a more simple, efficient, clean, cost-effective, and safe catalyst to replace toxic and/or precious ones, such as an iron-containing catalyst to effect catalytic thioglycosylation, remained to be explored.

Being easily accessible, inexpensive, biologically essential, and abundant on earth, iron catalysts have become popular and attractive from an environmental and economic point of view for organic transformations as well as for catalytic reactions.¹⁴ In addition, FeCl₃ has also been employed as an efficient catalyst for O-isopropylidenation, acetolysis, acylation, and activation of the anomeric acetate of carbohydrates in suprastoichiometric use.¹⁵ This inspired us to initiate an extensive search for a more sustainable iron catalyst than FeCl₃ in order to meet the standard of green chemistry. Herein we describe a new economical, efficient, and handy protocol for thioglycosylation of peracetylated glycosides by using cheap, easily available, non-toxic iodine, and iron metal.

peracetylated saccharides, we initiated catalyst screening of various Fe(II) and Fe(III) salts in the presence of 1.0 equiv penta-O-acetyl- β -D-glucopyranose **1** and 1.3 equiv *p*-toluenethiol in CH₂Cl₂ at rt for 24 h. The results indicated that the commercial 5 mol % FeI₂ and freshly prepared Fe(OTf)₃ had the highest reactivities, yielding phenyl-2,3,4,6-tetra-O-acetyl- β -D-1-thio-glucopyranoside **1a** (Table 1, entries 3 and 10). Notably, the trivalent ferric salts

In order to find the best iron catalyst for thioglycosylation of

Table 1

Effects of iron salts on catalytic thiogly cosylation of penta-O-acetyl- β -D-glucopyranose and p-toluenethiol a

	OAc			-OAc
Acont	-0 +	$/ = \backslash$	5 mol%Fe(X) n	Aco 10
Aco	∼OAc ⁱ —	\sim	SH	Aco
	ÖAc			ÖAc
1	1 eq.	1.3eq.		1 a

Entry	FeXn	Time (h)	Conversion ^d (%)	Yield ^e (%)
1	FeCl ₂	24	7	_f
2	FeBr ₂	24	13	9
3	Fel ₂	24 (48 ^b)	43 (52 ^b)	41 (51 ^b)
4	Fe(OAc) ₂	24	3	f
5	Fe(OTf) ₂	24	33	28
6	FeCl ₃	24	12	9
7	FeBr ₃	24	27	22
8	Fe(ClO ₄) ₃	24	33	30
9	Fe(OTs) ₃	24	31	27
10	Fe(OTf) ₃	24 (48 ^b)	48 (61 ^b)	45 (57 ^b)
11	FeI ₂ + 1.0 equiv I ₂	0.7 (1 ^c)	>99 (>99 ^c)	94 (95 ^c)
12	Fe + 1.6 equiv I ₂	0.7 (1 ^c)	>99 (>99 ^c)	95 (97 ^c)
13	Fe	24	0	f
14	I ₂	24	0	f

^a All reactions were performed in CH₂Cl₂ at rt.

^b 20 mol % catalyst was used.

^c 1 mol % catalyst was used.

^d Determined by ¹H NMR analysis of the reaction mixture.

^e Isolated yield after column chromatography.

^f Not determined.



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showed the best reactivities and their catalytic efficiency increased with a decrease in the basicity of the counteranion bearing the iron $(TfO^- > TsO^-, ClO_4^- > Br^- > Cl^-)$. In contrast, the ferrous salts were far less reactive than the ferric ones, except FeI₂. On the basis of these results, the best, Fe(OTf)₃ and FeI₂, were further examined. Increasing catalyst loading to 20 mol %, thiol amount to 2.0 equiv and extending the reaction time to 48 h resulted in only 10–12% improvement in yield (Table 1, entries 3 and 10, parentheses).

Since the trivalent ferric salts were more reactive than the divalent ferrous competitors and FeI2 showed remarkable catalytic efficiency, in situ prepared FeI₃ was thus targeted as the catalyst for thioglycosylation. The FeI₃ could easily be prepared by reacting Fe metal or FeI₂ with 1.5 equiv or an equal amount of iodine in anhydrous CH₂Cl₂ and served as an excellent catalyst to accelerate the asymmetric Diels–Alder addition at low temperature.¹⁶ Thus. Fel₃ was prepared in situ by stirring 1.0 equiv Fel₂ with 1.0 equiv I_2 in CH₂Cl₂ or by adding 1.6 equiv I_2 to 1.0 equiv Fe metal powder in CH₂Cl₂ for 4 h until the metal had totally dissolved. Indeed, FeI₃ was found in both reaction mixtures as evidenced by the ESI-MS spectra.¹⁷ Furthermore, both reaction mixtures were diluted to 5 mol % and individually employed as catalysts for the thioglycosylation of glucoside 1 (1.0 equiv) in the presence of 1.3 equiv p-toluenethiol in CH₂Cl₂ at rt under an N₂ atmosphere. Surprisingly, both reactions were completed in 40 min and the glucoside 1 was totally converted into **1a**, as evidenced by the ¹H NMR spectroscopic analyses of the crude reaction mixtures (entries 11 and 12). Moreover, even with the catalyst loading decreased to 1 mol %, the reaction was completed in 1 h and no epimerization side product (penta-O-acetyl- α -D-glucopyranose) was found in the crude ¹H NMR spectrum. The control reactions also revealed that I₂ or metal Fe did not catalyze thioglycosylation individually. Finally, the glycosyl donor penta-O-acetyl- α -D-glucopyranose **1** with 2-O-acetyl group cis- orientated to the anomeric leaving acetate did not effect this transformation even though 20 mol % catalyst was employed or the reaction time was prolonged, only traces (<5%) of the product were observed.

Ultimately, the cheapest and most convenient combination of 1 mol % I₂ and metal Fe in CH₂Cl₂ to generate FeI₃ in situ was chosen as the optimized condition for substrate scope investigation.¹⁸ Several alkyl and aryl thiols with different electronic and steric demands were then examined (Table 2). In general, the aliphatic mercaptans were less reactive than the aryl ones (complete reaction in 4-6 h vs 0.5-1 h) but satisfactory yields were obtained for aliphatic thiols (23-88%). In the case of tert-butyl mercaptan, even when 5.0 equiv thiol was used or the reaction time was prolonged, only 27% yield of product could be generated. Unsurprisingly, the reactivities of the alkyl mercaptans increased with a decrease in the steric substitution (Et-, Bn- > *i*-propyl- > cyclohexyl- \gg *t*-butyl-). Notably, the amide containing N-acetyl cystamine showed no reactivity (Table 2, entry 6). A similar result was found when the reaction was performed in a strong coordination solvent such as DMF.¹⁷ For aryl thiols the reactivity was influenced by the electronic nature of the substituents, with electron-withdrawing substituents giving a higher yield than electron-donating substituents. In addition, the reactivity was affected by steric demand, with the yield dropping to 44% when o-toluenethiol was employed instead of p-toluenethiol (Table 2, compare entries 9 and 11). Although the electron-withdrawing aryl thiols provided the best efficiency, the most electron-deficient 4-nitro-benzenethiol did not show any reactivity. This above disappointing result can be postulated that an interaction occurred between Fel3 and nitro group which hindered the ability of the catalyst to participate in the formation of a glycosidic linkage (Table 2, entry 14).

To expand the substrate scope, a series of peracetylated β -D-saccharides were further examined with highly reactive, cheap, and commercially available benzenethiol, Table 3. The peracety-

Table 2

Effects of thiols on thioglycosylation of penta-O-acetyl- β -D-glucopyranose catalyzed by 1 mol % of in situ prepared Fel₃^a

~OAc		-OAc
Aco O Aco Bu	SH 1 mol% Fel3	Aco 0
Aco UAc + H	CH _o Cl _o rt	Aco SR1
1 OAc	01.20.2, 14,	1a-n OAc
1 eq. 1.3	Beq.	

Entry	R ₁	Time (h)	Product	Yield ^d (%)
1	CH ₃ CH ₂ -	12	1b	87
2	PhCH ₂ -	6	1c	88
3	(CH ₃) ₂ CH-	4	1d	81
4	Cyclohexyl-	6	1e	76
5	tert-Butyl-	24 (72 ^b)	1f	23(27 ^b)
6	CH ₃ C(O)NHCH ₂ CH ₂ -	24	1g	0
7	$-(CH_2)_{10}CO_2Me$	12	1h	74
8	Ph-	0.5	1i	97
9	$4-Me-C_6H_4-$	1	1a	95
10	$4-MeO-C_6H_4-$	1 (4)	1j	62(69 ^c)
11	$2-Me-C_6H_4-$	1 (4)	1k	44(56 ^c)
12	$4-Cl-C_{6}H_{4}-$	0.5	11	95
13	2-Naphthyl-	0.5	1m	98
14	$4 - NO_2 - C_6 H_4 -$	24	1n	0

^a All reactions performed in CH₂Cl₂ at rt.

^b 5 equiv *tert*-butyl mercaptan was used.

^c Yield of isolated product after 4 h.

^d Isolated yield after column chromatography.

lated β -D-galactose **2**, D-xylose **3**, D-arabinose **4**, and furanosyl Dribose 8 were reacted with 1.3 equiv benzenethiol and proceeded smoothly in the presence of freshly prepared 3 mol % FeI₃ under the optimal condition to afford the desired 1,2-trans products 2a (97%), 3a (94%), 4a (96%), and 8a (97%), respectively. The nearly 1 to 1 anomeric mixture of peracetylated D-mannose 5 showed low reactivities and the phenyl 2,3,4,6-tetra-O-acetyl-α-D-1-thio-mannoside 5a was obtained in only 14% yield. Expectedly, the additional control reaction of the less reactive α -D-peracetylated mannoside 5' failed to produce the corresponding thioglycoside. The peracetylated β-D-2-deoxy-phthalimido- and acetamido-glucosides 6 and 7 were also tested. In one case, the strong coordination acetamido (-NHAc) group containing 7 remained unreactive and the starting acetamido precursor was totally recovered. In the other case, the weak coordinative phthalimido-masked (NPhth) glucosides 6 showed moderate reactivity under optimal conditions and afforded the phenyl 2phthalimido-2-deoxy- β -D-1-thio-glucoside **6a** with a 74% yield. The protocol was also applicable to peracetylated β-p-disaccharides derived from lactose 9 and maltose 10. The exclusive 1,2trans thioglycosides 9a and 10a were obtained in 90-92% yield within 2 h and the stereochemistry of the 1-4' glycosidic bond remained intact.

In summary, we developed a handy approach for the thioglycosylation of peracetylated saccharides by using an in situ prepared FeI₃ catalyst made from cheap iodine and metal iron in CH_2Cl_2 solution. The anchimeric assistance mechanism during the glycosylation process is suggested due to the exclusive 1,2trans diastereoselectivity of the products. The current catalytic protocol offers an alternative variant that is competitive with several existing methods in terms of its low cost, operational simplicity, and compatibility with diverse thiols and sugars, which argues well for its potential application in carbohydrate chemistry.

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Table 3

Thioglycosylation of	peracetvlated	saccharides and	benzenethiol ca	atalvzed by	1 mol % in situ-	prepared Fel ₃ ^a
0.5						

Glycosides	Time	Product	Yield ^c (%)
ACO OAC ACO OAC 2 OAC 2	1	Ac O OAc AcO SPh 2a	97
Aco OAc 3	1	AcO SPh 3a	94
Aco OAc 4	1	Aco SPh 4a	96
AcO OAc AcO OAc $α/β = 1.1/1$ 5 α/β > 99/1 5	24	AcO OAc AcO 5a SPh	14 (0 ^b)
$\begin{array}{c} OAc \\ AcO \\ AcO \\ NP_1P_2 \\ P_1 = P_2 = C(O)C_6H_4C(O) \end{array} $	6	$P_{1} = P_{2} = C(O)C_{6}H_{4}C(O)$	74
$P_1 = H, P_2 = C(O)CH_3$ 7	24	$P_1 = H, P_2 = C(O)CH_3$ /	0
AcO OAc 8	1	Aco OAc 8a	97
Ac O OAc OAc AcO OAc OAc 9 AcO OAc OAc OAc 9	2	Ac O OAc OAc AcO SPh 9a	87
AcO AcO AcO AcO AcO AcO AcO AcO AcO AcO	2	Aco Aco Aco Aco Aco Aco Aco Aco Aco SPh 10a	90

^a All reactions were performed in CH₂Cl₂ at rt in the presence of 1.3 equiv benzenethiol and 3 mol % Fel₃ as catalyst.

^b α-D-Mannose penta-O-acetate was used.

^c Isolated yield after column chromatography.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.077.

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- 17. See Supplementary data for details.
- Typical experimental procedure for thioglycosylation of peracetylated saccharide: To a solution of iron metal powder (325 mesh, 1.67 mg,

0.03 mmol) in anhydrous CH_2Cl_2 solution (2 mL) was added l_2 (12.2 mg, 0.048 mmol) at rt under nitrogen atmosphere. The resulting mixture was stirred for 4 h until the iron powder was totally dissolved. A solution of 3 mmol peracetylated glycoside and 3.9 mmol thiol in 13 mL CH_2Cl_2 was added by a cannula and the resulting dark brown mixture was stirred at ambient temperature for indicated time. The reaction was monitored by TLC analysis and quenched by adding 10 mL satd NaHCO₃ (aq) solution. The organic layer was separated, dried over MgSO₄, and filtered. The crude product was concentrated under reduced pressure and loaded directly on top of an eluent-filled silica gel column and purified by flash column chromatography.