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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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ABSTRACT

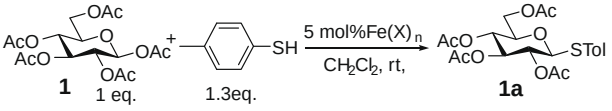
A facile in situ preparation of Fe(III) iodide from cheap, abundant elemental iodine and iron metal served as an efficient catalyst for the thioglycosylation of peracetylated glycosides with various alkyl and aryl mercaptans. Due to neighboring participation, the anomerically pure β-thioglycosides were obtained in good to high yields with exclusive diastereocontrol.

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] $TiCl_4$,[4] BF_3–Et_2O,[5] $AlCl_3$,[6] $ZrCl_4$,[7] $SnCl_4$,[8] TMSOTf,[9] ZnI_2,[10] Et_3SiH/I_2–thiourea,[11] $Me_3SiSiMe_3/I_2$,[12] and amphoteric MoO_2Cl_2[13] 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, $FeCl_3$ 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 $FeCl_3$ 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.

In order to find the best iron catalyst for thioglycosylation of 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 CH_2Cl_2 at rt for 24 h. The results indicated that the commercial 5 mol % FeI_2 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

Table 1
Effects of iron salts on catalytic thioglycosylation of penta-*O*-acetyl-β-D-glucopyranose and *p*-toluenethiol[a]



Entry	FeX_n	Time (h)	Conversion[d] (%)	Yield[e] (%)
1	$FeCl_2$	24	7	—[f]
2	$FeBr_2$	24	13	9
3	FeI_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 CH_2Cl_2 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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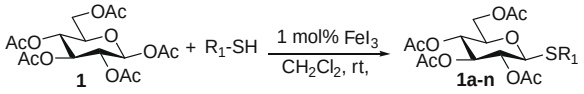
showed the best reactivities and their catalytic efficiency increased with a decrease in the basicity of the counteranion bearing the iron ($TfO^- > TsO^-$, $ClO_4^- > Br^- > Cl^-$). In contrast, the ferrous salts were far less reactive than the ferric ones, except FeI_2. On the basis of these results, the best, $Fe(OTf)_3$ and FeI_2, 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 FeI_2 showed remarkable catalytic efficiency, in situ prepared FeI_3 was thus targeted as the catalyst for thioglycosylation. The FeI_3 could easily be prepared by reacting Fe metal or FeI_2 with 1.5 equiv or an equal amount of iodine in anhydrous CH_2Cl_2 and served as an excellent catalyst to accelerate the asymmetric Diels–Alder addition at low temperature.[16] Thus, FeI_3 was prepared in situ by stirring 1.0 equiv FeI_2 with 1.0 equiv I_2 in CH_2Cl_2 or by adding 1.6 equiv I_2 to 1.0 equiv Fe metal powder in CH_2Cl_2 for 4 h until the metal had totally dissolved. Indeed, FeI_3 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 CH_2Cl_2 at rt under an N_2 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 I_2 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 % I_2 and metal Fe in CH_2Cl_2 to generate FeI_3 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- ≫ *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 FeI_3 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 peracetylated β-D-galactose **2**, D-xylose **3**, D-arabinose **4**, and furanosyl D-ribose **8** were reacted with 1.3 equiv benzenethiol and proceeded smoothly in the presence of freshly prepared 3 mol % FeI_3 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 2-phthalimido-2-deoxy-β-D-1-thio-glucoside **6a** with a 74% yield. The protocol was also applicable to peracetylated β-D-disaccharides derived from lactose **9** and maltose **10**. The exclusive 1,2-trans thioglycosides **9a** and **10a** were obtained in 90–92% yield within 2 h and the stereochemistry of the 1–4′ glycosidic bond remained intact.

Table 2
Effects of thiols on thioglycosylation of penta-*O*-acetyl-β-D-glucopyranose catalyzed by 1 mol % of in situ prepared FeI_3[a]



Entry	R_1	Time (h)	Product	Yield[d] (%)
1	CH_3CH_2–	12	**1b**	87
2	$PhCH_2$–	6	**1c**	88
3	$(CH_3)_2CH$–	4	**1d**	81
4	Cyclohexyl-	6	**1e**	76
5	*tert*-Butyl-	24 (72[b])	**1f**	23(27[b])
6	$CH_3C(O)NHCH_2CH_2$–	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_6H_4–	0.5	**1l**	95
13	2-Naphthyl–	0.5	**1m**	98
14	4-NO_2–C_6H_4–	24	**1n**	0

[a] All reactions performed in CH_2Cl_2 at rt.
[b] 5 equiv *tert*-butyl mercaptan was used.
[c] Yield of isolated product after 4 h.
[d] Isolated yield after column chromatography.

In summary, we developed a handy approach for the thioglycosylation of peracetylated saccharides by using an in situ prepared FeI_3 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 1,2-trans 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.

Acknowledgments

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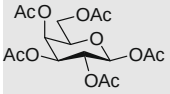
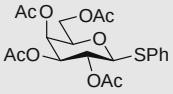
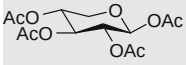
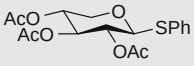
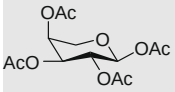
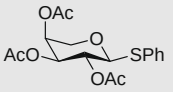
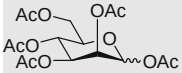
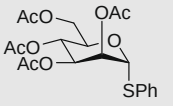
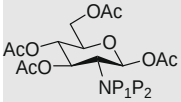
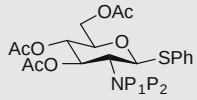
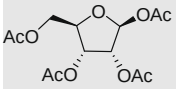
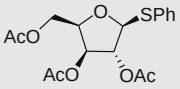
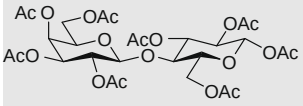
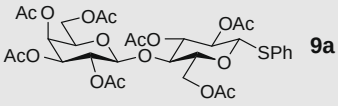
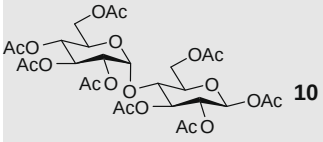
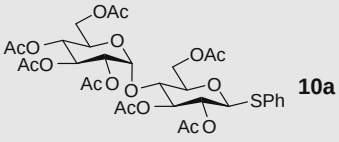
Table 3
Thioglycosylation of peracetylated saccharides and benzenethiol catalyzed by 1 mol % in situ-prepared FeI_3[a]

Glycosides	Time	Product	Yield[c] (%)
 **2**	1	 **2a**	97
 **3**	1	 **3a**	94
 **4**	1	 **4a**	96
 α/β =1.1/1 **5** α/β > 99/1 **5 '**	24	 **5a**	14 (0[b])
 $P_1 = P_2 = C(O)C_6H_4C(O)$ **6** $P_1 = H, P_2 = C(O)CH_3$ **7**	6 24	 $P_1 = P_2 = C(O)C_6H_4C(O)$ **6** $P_1 = H, P_2 = C(O)CH_3$ **7**	74 0
 **8**	1	 **8a**	97
 **9**	2	 **9a**	87
 **10**	2	 **10a**	90

[a] All reactions were performed in CH_2Cl_2 at rt in the presence of 1.3 equiv benzenethiol and 3 mol % FeI_3 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.
18. *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 I_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 $NaHCO_3$ (aq) solution. The organic layer was separated, dried over $MgSO_4$, 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.