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Note

A mild and convenient indium(III) chloride-catalyzed synthesis of thioglycosides☆

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Abstract

The efficiency of glycosidation reactions generally involves a high chemical yield, as well as high/complete stereo- and regioselectivity. All these depend on the compatibility of the reactivity of glycosyl donors and acceptors. Among glycosyl donors, thioglycosides are widely used because of their high degree of stability in many organic reactions. Although there are number of methods available for the preparation of thioglycosides, all of them have one or more disadvantages, especially concerning the time factor and cumbersome workup procedures. Here we report a convenient and high-yielding method for the preparation of thioglycosides.

Keywords: Indium(III) chloride; Thioglycoside; Thiols; Stereoselectivity

O-Glycosylation, which is crucial for attaching a sugar to other sugar moieties or aglycons, is an important chemical reaction. From a synthetic standpoint, the efficiency of the *O*-glycosylation reaction generally involves both a high chemical yield and high/complete stereo- and regioselectivity. All these depend on the general compatibility of the reactivity of glycosyl donors and acceptors. Among glycosyl donors, thioglycosides are widely used because of their high degree of stability in many organic reactions. These are also useful intermediates for the preparation of glycosyl fluorides,[1] which are also useful glycosyl donors. There are many methods available in the literature for thioglycoside preparation.[2] But all of them have one or another disadvantage such as cumbersome workup, cost of production, use of heavy metal salts like $ZnCl_2/ZnI_2$, which are also difficult to get rid of. Moreover, the use of a huge excess of thiols as reagents as well as solvent or the use of $CHCl_3$-like carcinogenic solvents are also among a few drawbacks to be mentioned. Above all, these conditions generally require a longer time for the completion of the reaction.

Recently, indium(III) halides have emerged as useful Lewis acid catalysts in organic synthesis.[3] The unique feature of indium(III) chloride is its compatibility with both organic and aqueous media, facts which have widely attracted chemists to this reagent. Because of low catalyst loading, moisture compatibility and easy removal from the reaction mixture by water wash, $InCl_3$ has been used by sugar chemists in both *O*- and *C*-glycosylation reactions in carbohydrate field.[4] Intrigued by the widespread use of this particular catalyst and cost effectiveness, we wanted to explore the utility of $InCl_3$ for the synthesis of different thioglycosides, which, to our knowledge, has not yet been reported. In this report, we present a novel method for the preparation of thioglycosides using indium(III) chloride. An example is shown in the Scheme 1 below.

For our studies we chose per-*O*-acetylglycopyranoses as substrates and acetonitrile as the solvent of choice because of its known assistance for stereospecific 1,2-trans-glycosylations. Initially, we tried to develop the reaction via the addition of a thiol to a stirred solution of per-*O*-acetylglycopyranose in acetonitrile and $InCl_3$ (20 mol%). However, the reaction was found to proceed slowly. The reaction was incomplete even after 72 h by

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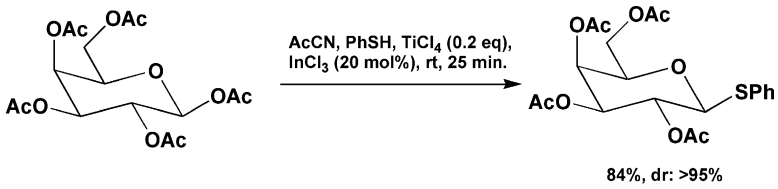

Scheme 1.

using as high as 50 mol% $InCl_3$. When a catalytic amount of $TiCl_4$ was added as co-activator along with 20 mol% (40 mol% for mannose pentaacetate) of $InCl_3$, the reactions were complete within short time with high yields. Lönn synthesised[2j] ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside using only $TiCl_4$ (1.3 equiv) as promoter, and the reaction also took a longer time to complete.

However, when we performed the reaction on per-*O*-acetylglucopyranose using $TiCl_4$ (0.2 equiv) and ethanethiol (3 equiv) in the absence of $InCl_3$, the reaction remained incomplete even after 24 h at room temperature, yielding only 11% of ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside. When the same conditions were applied with an increased amount of $TiCl_4$ (1.0 equiv), the reaction was complete within 3 h affording only 37% of the said product. In both the cases, a substantial amount of starting material was found to be decomposed. (Details are not provided in the Experimental.)

A summary of thioglycosides prepared using this method is illustrated in Table 1. The choice of amount of $InCl_3$ and $TiCl_4$ was found to be perfect for all the glycose acetates, excepting mannose pentaacetate where additional amounts of both the reagents had to be used. All the yields reported are isolated yields, and the structures of each of the compounds was deduced based on ^1H NMR spectroscopy, chemical-ionization mass spectrometry (CIMS) or electrospray-ionization mass spectrometry (ESIMS), and IR spectroscopy, which were found to be in accordance with the literature data.[5] Spectral and physical characterization data of the new compounds were satisfactory. The anomeric ratios were determined by HPLC and ^1H NMR spectroscopy. It was observed that the pentaacetate derivatives of glucose and galactose showed high β-selectivity apart from good to excellent yields. The yields of tri-*O*-acetyl-thiofucosides were high, and the selectivities were also moderate. For mannose pentaacetate the conversion rates were slow, and the yields were low because of

Table 1
Experimental data for 1-thioglycosides prepared from different sugar acetates

Starting sugar acetate	Thiogly. formed	$InCl_3$ (mol%)	$TiCl_4$ (equiv)	Yield (%)	α/β (min)	Time	Reference
β-D-Galactose	*p*-Toluoyl	20	0.2	75	>95% β	25	5a
	Phenyl	20	0.2	84	>95% β	25	5b
	Ethyl	20	0.2	98	1:19 [a]	25	5c
β-D-Glucose	*p*-Toluoyl	20	0.2	80	1:19	25	5a
	Phenyl	20	0.2	82	>95% β	75	2k
	Ethyl	20	0.2	72	1:19 [a]	25	5c
β-L-Fucose	*p*-Toluoyl	20	0.2	86	1:6	10	5a[b]
	Phenyl	20	0.2	82	1:4	10	5d[b]
	Ethyl	20	0.2	70	1:19[a]	10	5e
α-D-Mannose	*p*-Toluoyl	40	0.5	43	>95% α	180	5f
	Phenyl	40	0.5	44	19:1	180	5g
	Ethyl	40	0.5	30	>95% α	180	2d
α-L-Rhamnose	*p*-Toluoyl	20	0.2	78	4:1	20	6
	Phenyl	20	0.2	80	2:1	20	5h
	Ethyl	20	0.2	72	9:1	20	5i
2-Deoxy-2-phthalimido-β-D-Glucose	*p*-Toluoyl	20	0.2	24	>95% β	180	6
	Phenyl	20	0.2	57	>95% β	40	5j
	Ethyl	20	0.2	60	>95% β	40	2j

[a] Only from NMR spectrum.
[b] For major anomer.

degradation, although the reactions are highly stereoselective. Anomeric selectivity for the rhamnose thioglycosides has been observed to be slightly low. This could be attributed to its high reactivity, which forced the formation of kinetically controlled β-thioglycosides to a larger extent. The yields of tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranosides were moderate, although, as expected, the outcomes are stereoselective. *p*-Tolyl 2-deoxy-2-phthalimido-β-D-glucopyranoside was obtained in only 24% yield probably because of the steric interaction of phthalimido group with the *p*-tolyl group. When the reactions of tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose were conducted at 0–5 °C, the main product isolated was the 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride,[6] and no thioglycoside could be detected. This observation gives an idea about the plausible mechanism of the reaction. It seems that product formation is guided by the neighboring group, either through direct participation or through the steric bulk, thereby allowing the nucleophile to attack from the β face. It is therefore presumed that in this $TiCl_4$-mediated $InCl_3$-promoted reaction per-*O*-acetyl-glycosyl chlorides are the intermediates, which on further attack by the sulfur nucleophile give rise to 1,2-trans-products. In fact, when these reactions were performed at 10 °C with fucose tetraacetate, the reactions were complete within 15 min providing the respective thioglycosides. This fact can be attributed to the high reactivity of the 2,3,4-tri-*O*-acetyl-β-L-fucopyranosyl chloride, obtained from fucose tetraacetate, in the presence of $InCl_3$, thereby affording the final thioglycosides even at 10 °C.

In summary, our present methodology has the following advantages: (a) the promoter is used in catalytic amount; (b) cost-effective inexpensive reagents are employed; (c) short reaction times are involved; (d) good yields are obtained; (e) usually easy workups are involved, and (f) moderate-to-high stereoselectivities are observed. To conclude, we have developed a general, mild, and time-saving approach to prepare varieties of thioglycosides.

1. Experimental

1.1. General instrumentation procedures

The ^{1}H NMR spectra were recorded with tetramethylsilane (TMS, δ 0.00) as the internal standard on a Varian Gemini 200- or 400-MHz FTNMR spectrometer. ^{13}C NMR spectra were recorded with $CDCl_3$ (δ 77.00) as the internal standard at 50 MHz on a Varian Gemini 200-MHz FTNMR spectrometer. Mass spectra were either measured on Hewlett-Packard 5989A mass spectrometer (chemical ionization, CI, 20 eV) or on a Perkin–Elmer Sciex model API 3000 (electrospray-ionization, ESI, capillary voltage between +5000 and −4500 V). The IR spectra were recorded using Perkin–Elmer 1650 FTIR spectrophotometer. Melting points were measured in glass capillaries on a Büchi 535 digital melting point apparatus and are uncorrected. All chromatography solvents were distilled before use. Silica gel (100–200 mesh, SRL, India) was used for column chromatography.

1.2. General procedure

To a stirred solution of per-*O*-acetylglycopyranose (0.5 mmol) in acetonitrile (2 mL), thiol (3 equiv) and $InCl_3$ (for amount, see Table 1) were added at room temperature, followed by the addition of $TiCl_4$ (for amount, see Table 1), and the reaction was monitored by TLC. At the end point the reaction mixture was diluted with EtOAc and washed successively with satd aq Na_2CO_3 and brine, dried (Na_2SO_4) and concentrated. Filtration of the crude products through a short column of silica gel afforded the respective thioglycosides as anomeric mixtures.

1.2.1. *p*-Methylphenyl 2,3,4-tri-*O*-acetyl-1-thio-α-L-rhamnopyranoside. Syrup; IR (KBr): 2984, 1751, 1493, 1434, 1373, 1223, 1107, 1055, 981, 907 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3 H, *J* 6.2 Hz, H-6), 2.00, 2.07 and 2.16 (3s, 9 H, 3Ac), 2.32 (s, 3 H, Me), 4.06–4.22 (m, 1 H, H-5), 5.13 (t, 1 H, *J* 9.9 Hz, H-4), 5.39 (br s, 1 H, H-2), 5.56 (dd, 1 H, *J* 10.2 and 3.2 Hz, H-3), 5.93 (br s, 1 H, H-1), 7.12 (d, 2 H, *J* 7.5 Hz, Ph), 7.35 (d, 2 H, *J* 8.3 Hz, Ph). ^{13}C NMR ($CDCl_3$): δ 16.71, 20.15, 20.22, 20.29, 67.4, 69.1, 70.68, 71.47, 88.87 (C-1), 129.5, 129.6 (2C), 132.1 (2C), 137.77, 169.29, 169.37 and 169.49. CIMS: *m*/*z* 397 ($M^+ + 1$).

1.2.2. *p*-Methylphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside. Solid; mp 160–162 °C (EtOAc–petroleum ether); $[\alpha]_D$ +40° (*c* 0.5°, $CHCl_3$). IR (KBr): 2924, 1750, 1624, 1384, 1229, 1037, 912 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.84, 2.03 and 2.11 (3s, 9 H, 3Ac), 2.34 (s, 3 H, Me), 3.84–3.93 (m, 1 H, H-5), 4.11–4.30 (m, 2 H, H-6), 4.33 (t, 1 H, *J* 10.5 Hz, H-4), 5.13 (t, 1 H, *J* 9.8 Hz, H-3), 5.66 (d, 1 H, *J* 10.7 Hz, H-1), 5.79 (dd, 1 H, *J* 10.3 and 9.3 Hz, H-2), 7.08 (d, 2 H, *J* 8.3 Hz, Ph), 7.31 (d, 2 H, *J* 8.3 Hz, Ph), 7.77 (dd, 2 H, *J* 5.9 and 2.9 Hz, Ph), 7.88 (dd, 2 H, *J* 5.5 and 3.4 Hz, Ph). ^{13}C NMR ($CDCl_3$): δ 20.34, 20.56, 20.70, 21.12, 53.60, 62.17, 68.71, 71.64, 75.83, 83.09 (C-1), 123.64 (3C), 126.95, 129.61 (3C), 133.89 (3C), 134.32, 138.71, 166.89, 167.76, 169.40, 170.03 and 170.55. ESIMS: *m*/*z* 559.2 ($M + NH_4^+$), 564.2 ($M + Na^+$).

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