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Synthesis of glycosides via indium(III) chloride mediated activation of glycosyl halide in neutral condition

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Abstract—Various glycosides and disaccharides were synthesized through *coupling of glycosyl bromides with acceptors in presence of indium chloride* as a promoter. Glycosidation reactions proceeded with high stereoselectivity.

The tremendous progress in glycobiology has offered a new status to the synthesis of oligosaccharides[1] in carbohydrate synthesis. Thus the development of methods leading to the efficient and stereoselective synthesis of glycosides has been a challenging task in oligosaccharide synthesis.

In this regard various Lewis acids like $BF_3{\cdot}O(Et)_2$,[2] AgOTf,[3] $AgClO_4$,[3] TMSOTf,[4] $FeCl_3$,[5] etc. have been used for activating the glycosyl donors for the formation of a glycoside linkage. Still the development[6] in this area demands the search for a better Lewis acid that will be superior to the existing ones, with regard to toxicity, availability and handling.

Usually the glycosyl bromides are coupled with an alcohol in the presence of toxic heavy metal salts like HgO/$HgBr_2$[7]$Ag_2CO_3/AgClO_4$,[3] etc. We have found indium chloride to be very efficient for this reaction. The catalytic amount is quite effective and it was not necessary to add any acid scavenger.[8]

Indium chloride is recognized as an efficient catalyst for inducing various types of organic transformations[9] but its application as a Lewis acid in glycosylation reactions[10] has not been studied in detail. The following work illustrates the use of indium chloride as a promoter in glycosylation reactions. The reactions proceed under very mild and advantageously in neutral condition.[8] Various glycosyl bromides were coupled with different acceptors in presence of indium chloride in dichloromethane.

In all cases glycosides and disaccharides were obtained with pronounced β-stereoselectivity in good to very high yield. It was observed that in presence of indium trichloride, glycosyl bromide (**1**) coupled with methanol (**2**), benzyl alcohol (**4**), allyl alcohol (**9**) and also with isopropyl alcohol (**6**) the yield was good. In the reaction of benzyl alcohol (**4**) with 2-deoxy 2- phthalimido 3,4,6-tri-*O*-acetylglucosyl bromide (**19**), the yield was better (90%) than the reaction in presence of $Ag_2CO_3/AgClO_4$ (80%) which is usually used in oligosaccharide synthesis. In disaccharide synthesis this method was also found to be more efficient.

In conclusion, the results obtained above indicate that indium chloride is a mild and efficient promoter for carrying out glycosidation reactions. The reaction will tolerate acid sensitive protecting groups since the conditions are neutral. This method will be applied for increasing the length of the oligosaccharide chain. In our laboratory long chain oligosaccharide synthesis based on this methodology is in progress.

1. Experimental

Thin layer chromatography was performed with Merck silica gel plates (60 F_{254}). Flash column chromatography was performed on silica gel (60–120 mesh). Optical rotations were measured with a JASCO P-1020 polarimeter. IR spectra were recorded on a FT/IR/ 410 JASCO instrument. ^{1}H NMR spectra were recorded with a Bruker DPX-300 at 300 MHz Instrument using TMS as internal standard.

Compounds **3**, **5** and **10** were found identical with the compounds synthesized by usual method.[6]

1.1. Typical procedure for glycosidation

1.1.1. Isopropyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (7). The mixture containing glycosyl bromide **1** (500 mg, 1.2 mmol), acceptor **6** (0.1 ml, 1.2 mmol), freshly

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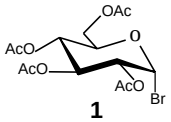
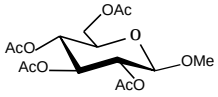
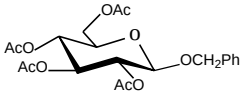
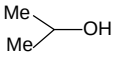
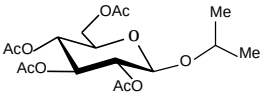
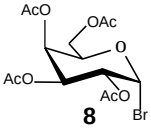
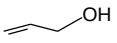
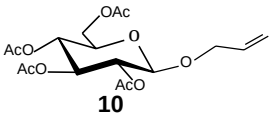
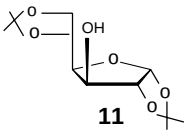
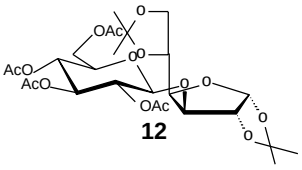
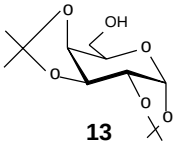
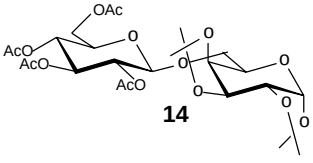
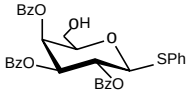
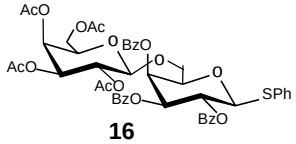
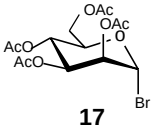
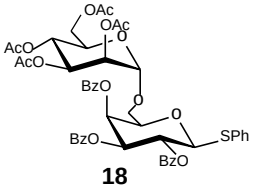
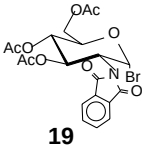
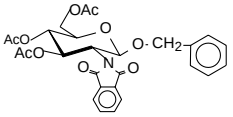
Entry	Glycosyl donor	Acceptor	Products	Yield
1	 **1**	MeOH **2**	 **3**	74%
2	**1**	$PhCH_2OH$ **4**	 **5**	68%
3	**1**	 **6**	 **7**	69%
4	 **8**	 **9**	 **10**	62 %
5	**1**	 **11**	 **12**	69%
6	**1**	 **13**	 **14**	78%
7	**1**	 **15** Bz = Benzoyl group	 **16**	86 %
8	 **17**	**15**	 **18**	88 %
9	 **19**	**4**	 **20**	90%

prepared molecular sieves 4A (500 mg) were stirred overnight in dichloromethane (8 ml). To this mixture, $InCl_3$ (110 mg, 0.5 mmol) was added and the reaction mixture was stirred overnight at room temperature. The progress of the reaction was monitored by TLC [ethyl acetate/petroleum ether (1:1)]. The reaction mixture was diluted with CH_2Cl_2, filtered over celite and washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the product was performed by flash chromatography in silica gel column. Elution with CH_2Cl_2 afforded the compound **7** (69%) as sticky mass; $[\alpha]_D=+16.6$ (c 1.25, CH_2Cl_2); R_f 0.7 [ethyl acetate/petroleum ether (1:1)]; IR (CH_2Cl_2, cm^{-1}) 1750 (ester); ^1H NMR ($CDCl_3$): δ 1.14 (d, 3H, J=6 Hz, CH_3), 1.27 (d,

3H, J=6 Hz, CH_3), 2.00, 2.02, 2.03, 2.08 (4s, 12H, 4Ac), 3.70 (m, 1H, C-5H), 3.94 (m 1H, O–*CH*<), 4.15 (m, 2H, C-6H), 4.55 (d, 1H, J=9 Hz), 4.94 (t, 1H, J=9 Hz), 5.10 (t, 1H, J=9.6 Hz), 5.20 (t, 1H, J=9.6 Hz); δ_c (75 MHz, $CDCl_3$) 170.9, 170.6, 169.9, 169.7, 100.0, 89.4, 73.3, 72.5, 72.0, 70.2, 69.0, 62.5, 23.6, 22.3, 21.1, 21.0, 21.9; FAB-MS: *m/z*, 413 (M+Na); Anal. Calcd for $C_{17}H_{26}O_{10}$: C, 52.30; H, 6.60; Found: C, 52.29; H, 6.38.

1.1.2. Methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (3). Sticky(74%) $[\alpha]_D$=−3.1 (*c* 0.83, CH_2Cl_2); R_f 0.6 [ethyl acetate/petroleum ether (1;1)]; IR (Neat, cm^{-1}): 1754 (ester); ^{1}H NMR ($CDCl_3$): δ 2.00, 2.02, 2.07, 2.09 (4s, 12H, 4Ac), 3.51 (s, 3H, OMe), 4.44 (d, 1H, J=7.8 Hz), 4.98 (t, 1H, J=8.4 Hz), 5.06 (t, 1H, J=9 Hz).

1.1.3. Benzyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (5). Sticky (68%) $[\alpha]_D$=+53.7 (*c* 0.96, CH_2Cl_2); R_f 0.5 [ethyl acetate/petroleum ether (1;1)]; IR (Neat, cm^{-1}): 1739 (ester), 743, 1246 (aromatic); ^{1}H NMR ($CDCl_3$): δ 1.99, 2.00, 2.08, 2.09 (4s, 12H, 4Ac), 3.64–3.69 (m, 1H, H-5), 4.55 (d, 1H, J=7.8 Hz), 7.27–7.35 (m, 5H, aromatic).

1.1.4. Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (10). Sticky (62%) $[\alpha]_D$=+62.6 (*c* 0.43, CH_2Cl_2); R_f 0.6 [ethyl acetate/petroleum ether (1;1)]; IR (Neat, cm^{-1}): 1733 (ester), ^{1}H NMR ($CDCl_3$): δ 1.98, 2.05, 2.06, 2.1, (4s, 12H, 4Ac), 4.5 (d, 1H, J=7 Hz), 5.85 (m, 1H, CH_2=C*H*).

1.1.5. 1,2:5,6-Di-*O*-isopropylidene-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-glucofuranose (12). Sticky(69%) $[\alpha]_D$=+68.5 (*c* 0.40, CH_2Cl_2); R_f 0.6 [ethyl acetate/petroleum ether (1:1)]; IR(Neat, cm^{-1}): 1748 (ester); ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.34 (s, 3H), 1.36 (s, 3H), 1.49 (s, 3H), 2.04, 2.05, 2.09, 2.10 (4s, 12H, 4Ac), 4.94 (t, 1H, J=4 Hz), 5.00 (d, 1H, J=4.2 Hz), 5.03 (d, 1H, J=4 Hz), 5.56 (t, 1H, J=9.6 Hz), 5.95 (d, J=3 Hz, C-1H, furan), 6.29 (d, J=6 Hz); δ_c (75 MHz, $CDCl_3$) 169.8, 169.3, 90.1, 70.8, 70.4, 69.5, 61.1, 23.8, 22.9, 22.6; MALDI-TOFMS: *m/z*, 613 (M+Na), 629 (M+K). Anal. Calcd for $C_{26}H_{38}O_{15}$: C, 52.88;H, 6.44; Found: C, 52.91; H, 6.51.

1.1.6. 1,2:3,4-Di-*O*-isopropylidene-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-α-D-galactopyranose (14). Sticky (78%) $[\alpha]_D$=−20 (*c* 1.56, CH_2Cl_2); R_f 0.6 [ethyl acetate/petroleum ether (1:1)]; IR (Neat, cm^{-1}): 1754 (ester,); ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 3H), 1.44 (s, 3H), 1.50 (s, 3H), 1.98, 2.00, 2.06, 2.09 (4s, 12H, 4Ac), 4.02 (dd, 1H, J_1=3.4 Hz, J_2=11.4 Hz) 5.19 (d, 1H, J=9.5 Hz), 5.49 (d, 1H); δ_c (75 MHz, $CDCl_3$) 170.5, 169.5, 169.4, 169.3, 101.4, 96.3, 71.7, 70.6, 69.8, 69.4, 65.9, 63.4, 61.9, 61.4, 25.0, 24.4, 24.3, 22.6, 20.7, 20.6, 20.5; MALDI-TOFMS: *m/z*, 613 (M+Na), 629 (M+K). Anal Calcd for $C_{26}H_{38}O_{15}$: C, 52.88, 6.44; Found: C, 52.90; H, 6.49.

1.1.7. Phenyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1-thio-β-D-galactopyranoside (16). Sticky (86%); $[\alpha]_D$=+60.4 (*c* 1.32, CH_2Cl_2); R_f 0.49 [ethyl acetate/petroleum ether (1:1)]; IR (CH_2Cl_2, cm^{-1}): 1734 (ester), 711, 598 (aromatic); ^{1}H NMR ($CDCl_3$): δ 1.99, 2.01, 2.03, 2.12 (4s, 12H, 4Ac), 4.53 (d, 1H, J=9 Hz), 7.21–7.84 (m, 20H, aromatic); δ_c (75 MHz, $CDCl_3$) 170.7, 170.5, 166.6, 134.1, 133.9, 133.6, 130.3, 130.2, 130.1, 129.4, 129.1, 128.9, 128.8, 128.6, 101.5, 73.5, 71.3, 71.1, 68.9, 68.6, 67.3, 21.1, 21.0, 20.9; Anal. Calcd for $C_{47}H_{46}O_{17}$ S: C, 61.71; H, 5.03; Found: C, 62.01; H, 5.18.

1.1.8. Phenyl 2,3,4-tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-1-thio-β-D-galactopyranoside (18). Sticky (88%) $[\alpha]_D$=+90 (*c* 0.44, CH_2Cl_2); R_f 0.65 [ethyl acetate/petroleum ether (1:1)]; IR (Neat, cm^{-1}): 1734 (ester), 738, 1265, 1450 (aromatic); ^{1}H NMR ($CDCl_3$): δ 2.02, 2.06, 2.09, 2.17 (4s, 12H, 4Ac), 3.67 (q, J_1=4.1 Hz, J_2=10.5 Hz, C6HA, Gal), 3.94 (q, J_1=7.5 Hz, J_2=10.4 Hz), 4.08–4.34 (m, 2H, Man), 5.05 (d, 1H, J=9.8 Hz), 5.58 (dd, 1H J_1=3 Hz, J_2=9.9 Hz, C3H, Gal), 5.76 (t, 1H, J_1=J_2=9.4 Hz, C2H, Gal), 6.09 (d, 1H J=1.8 Hz, C1HMan) 7.26–7.90 (m, 20H, aromatic); δ_c (75 MHz, $CDCl_3$) 170.9, 170.0, 169.8, 165.7, 165.5, 134.4, 133.9, 133.6, 133.5, 130.4, 130.3, 130.1, 130.1, 129.7, 129.4, 129.2, 129.1, 129.0, 128.8, 128.6, 128.3, 98.1, 91.0, 86.4, 86.0, 73.3, 71.0, 69.6, 69.4, 69.2, 68.7, 68.3, 67.4, 66.4, 66.0, 62.7, 62.5; MALDI-TOF MS: *m/z*, 937 (M+Na), 953 (M+K). Anal.Calcd for $C_{47}H_{46}O_{17}$S: C, 61.71; H, 5.03; Found: C, 62.00; H, 5.11.

1.1.9. Benzyl 2-deoxy-3,4,6-tri-*O*-acetyl-2-phthalimido-β-D-glucopyranoside (20). Sticky (90%) $[\alpha]_D$=−7.1 (*c* 0.75, $CHCl_3$); R_f 0.42 [ethyl acetate/petroleum ether (1:1)]; IR (KBr, cm^{-1}): 1750 (ester), 1716 (imide), 721 (aromatic); ^{1}H NMR ($CDCl_3$): δ 1.85, 2.02, 2.13 (3s, 9H, 3Ac), 3.85–3.89 (H-5), 4.53 (d, 1H, J=12.3 Hz), 4.85 (d, 1H, J=12.0 Hz), 5.18 (t, $J_{2,3}$=$J_{3,4}$=9 Hz, H-3), 5.37 (d, 1H, J=9 Hz), 5.78 (t, 1H, $J_{3,4}$=$J_{4,5}$=9 Hz, H=4), 7.26–7.38 (m, 4H, Phthaloyl-H), 7.72–7.85 (m, 5H, aromatic); δ_c (75 MHz, $CDCl_3$), 171.0, 170.4, 169.8, 167.8, 137.0, 134.8, 134.5, 131.8, 128.6, 128.2, 128.1, 123.9, 97.6, 72.2, 71.7, 69.5, 62.4, 55.0, 21.1, 20.9, 20.8; FAB-MS: *m/z*, 548 (M+Na); Anal.Calcd for $C_{27}H_{27}O_{10}N$: C, 61.71; H, 5.14; N, 2.67; Found: C, 61.69; H, 5.11; N, 2.66.

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