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A rapid stereoselective C-glycosidation of indoles and pyrrole via indium trichloride promoted reactions of glycosyl halides

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Abstract—Various *C*-glycosyl indoles and pyrroles were synthesized within a few minutes through coupling acetobromo sugars with suitably substituted indoles and pyrrole in the presence of catalytic amounts of $InCl_3$ at room temperature. Most of the glycosylations proceeded with a high stereoselectivity.

C-Glycosides, wherein a carbon atom replaces the glycosidic oxygen, have attracted considerable attention in carbohydrate and biological chemistry because of their stability[1] towards enzymatic and acidic hydrolysis. In particular, hexapyranosyl nucleosides as well as C-glycoconjugates bearing carbon linked nitrogen heterocycles have given rise to numerous synthetic and biological studies[2] due to their potential antiviral and antitumour activities.[3] Indole C-glycosides are model compounds for the synthesis of nucleosides of 9-deazapurines[4] and have been speculated to exist in biological systems,[5a,b] while pyrrole C-glycosides can be manipulated in remarkably diverse ways[5c,d] to generate a range of other potentially useful C-glycosides. Various approaches to C-glycosides have been developed.[6–9] The reaction of C-centred nucleophiles with an activated and electrophilic *C*-glycosyl donor[6] or glycal[7] represents by far the most common approach, although anomeric nucleophiles[8] and radicals[9] have also been used to generate such compounds. Generally *C*-glycosyl heteroaromatics are prepared from glycosyl donors such as glycosyl fluorides,[10] bromides,[11] hydroxides,[12] or *O*-glycosyl trichloroacetimidates[13] using either the heteroaryl compounds (in presence of Lewis acids such as $ZnCl_2$, BF_3–Et_2O, or TMSOTf) or the metalated heteroaryl compounds, namely, aryl aluminium[10,11] or aryl Grignard[13] species. Most of these methods suffer either from unsatisfactory yields or from low stereoselectivities. Interestingly, the reaction of indoles with per-O-benzylated glycosyl bromide[14] in the presence of Ag_2O gave C-nucleosides as anomeric mixtures in very poor yields along with other side products, while acylglycosyl halides under the above conditions yielded only 1,2-*O*-ethylidene[15] derivatives, which appear to be rather reluctant to rearrange to the desired C-glycosides. The reaction of α-glycosyl bromides with pyrrole failed to deliver significant quantities of pyrrole C-glycosides even when carried out in the presence of Ag_2CO_3–I_2,[16] while no reaction occurred when *O*-glycosyl imidates were used in the presence of $ZnCl_2$.[13a]

$InCl_3$ has recently emerged as a mild Lewis acid for a variety of organic transformations[17] due to its water stability, however, it appears that its application as a promoter for glycosylation reactions has not been studied in detail. We were the first to report[18] that it can be used as an efficient promoter for O-glycosylation using glycosyl bromides in the absence of any acid scavenger. The reagent is more advantageous than the usual strong promoters for acetobromosugars like AgOTf or $AgClO_4$ because it can bring about glycosylation at room temperature and is required only in catalytic amounts. Encouraged by these results, we studied its use as a promoter in the C-glycosylation reactions of indoles and pyrroles using glycosyl bromides. The present Letter describes the results of our efforts in this direction.

Keywords: Indium trichloride; Glycosyl halides; C-Glycosides; Indoles; Pyrrole.
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We studied the coupling of various glucosyl bromides with indoles (substituted at different positions) and pyrrole in the presence of catalytic amounts of $InCl_3$ (10 mol %) at an ambient temperature using CH_2Cl_2 as solvent. Under these conditions, the majority of the indole derivatives gave C-alkylation products, with pronounced β-stereoselectivity (Table 1). The products were identified as 3-substituted indoles from spectroscopic analysis. In the ^1H NMR spectra, the indole 3-H signals were absent. The chemical shift observed for the anomeric proton (at δ 4.7–4.8) ruled out the possibility of orthoester formation[15] (expected at δ 5.5–5.7) and the $J_{1,2}$ values (8–9 Hz) established the β-anomeric configuration.

Unsubstituted indole gave a poor yield of the product, while *N*-methylindole and indoles carrying an electron withdrawing group at the aromatic nucleus or the nitrogen atom failed to react under these conditions.

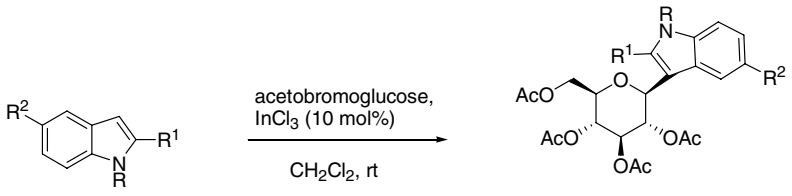
The introduction of an electron-donating group (OMe) at the 5-position of indole enhanced the yield to some extent, however, substitution at the 2-position had a more profound effect on the yields (Table 1). On the other hand, 3-methylindole provided a mixture of products, which could not be purified; this may be due to its propensity to polymerize[19] under the reaction conditions. Our efforts to increase the yield of this particular reaction by altering the reaction conditions (especially the solvent) met with only limited success. Changing the solvent to THF resulted in a low yield (10%) of N-glucosylated derivative **3**. This is, however, not surprising since N-alkylation of indole has been reported to occur with indolylbromomagnesium salts and protected furanoses when THF was used as the solvent.[20]

Compound **3** was identified as the N-glycoside from the presence of a singlet (non-exchangable) proton at δ 7.0 in the ^1H NMR assignable to H-2′, downfield shifts of the anomeric proton and carbon signals (at δ 5.61 in the ^1H NMR and 82.8 in the ^{13}C NMR) along with the absence of any signal assignable to NH. The β-anomeric configuration of this newly formed glycosidic linkage was confirmed from the $J_{1,2}$ value (8.1 Hz) in ^1H NMR. The formation of a glycosidic linkage in both cases was confirmed from mass spectroscopy.

Various other glycosyl bromides were also coupled with 2-substituted indoles in the presence of indium trichloride. In all cases, C-glycosides were obtained in a high yield with a good stereoselectivity (Table 2). Galactose, lactose and glucosamine-phthalimido acetobromo sugars, gave C-glycosides (**4a**,**b**,**e**,**f**) having β-anomeric configurations ($J_{1,2} = 9$–10 Hz), while the α-anomers ($J_{1,2}$ <1 Hz) were the exclusive products (**4c**,**d**) with mannose (Scheme 1).

Unlike unsubstituted indole, which gave a poor yield, unsubstituted pyrrole afforded a mixture of both the C-2′ and C-3′ glycosylated products in a good yield (84%) with the preponderance of the former (3:1) (Scheme 2). The stereochemistry of both compounds could be readily established by ^1H NMR analysis.[22] In particular, the resonance due to H-1 in compounds **5a** and **5b** appeared as doublets at δ 4.52 and 4.47, respectively, with J >9 Hz, thus implying the β-configuration in each case. The location of the glycosyl moiety at C2′ or C3′ on the pyrrole ring was ascertained from ^1H NMR as well as ^{13}C NMR spectra.[22] In **5a**, a two proton signal at δ 6.12 (H-3′, H-4′) and a one proton signal at δ 6.78 (H-5′) were observed, respectively, in

Table 1. Reactions of indole derivatives **1a**–**j** with acetobromoglucose

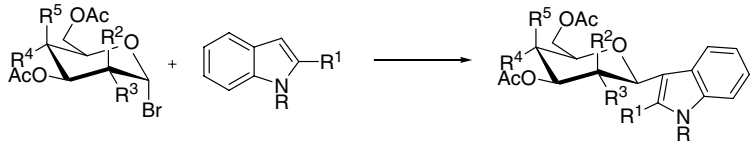


1a-j **2a-f**

Entry	Indole derivative	R	R^1	R^2	Product[a]	Time	Yield[b] (β:α)[c]
1	**1a**	H	Me	H	**2a**	30 min	82 (>9:1)
2	**1b**	H	Ph	H	**2b**	25 min	84 (>9:1)
3	**1c**	Me	Me	H	**2c**	20 min	85 (>9:1)
4	**1d**	Me	H	OMe	**2d**	2 h[d]	70 (1.8:1)
5	**1e**	H	H	OMe	**2e**	24 h[d]	40 (1.8:1)[e]
6	**1f**	H	H	H	**2f**	24 h	10 (>9:1)
7	**1g**	Me	H	H	—	24 h	5
8	**1h**	Me	H	NO_2	—	24 h	0
9	**1i**	Ts	H	H	—	24 h	0
10	**1j**	CO_2Me	H	H	—	24 h	0

[a] All products were characterized by ^1H, ^{13}C NMR and mass spectra.
[b] Isolated and unoptimized yields.
[c] Ratios of >9:1 are conservative minima; no α-product was detected.
[d] These reactions were performed at 0 °C–rt.
[e] These anomers could not be separated.

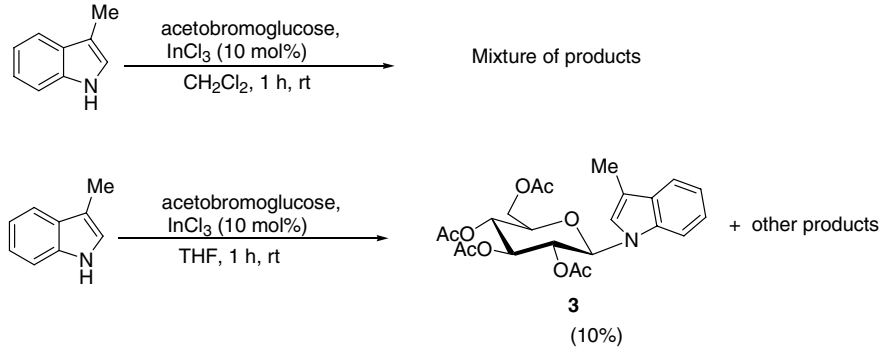
Table 2. Reactions of indole derivatives with different glycosyl bromides



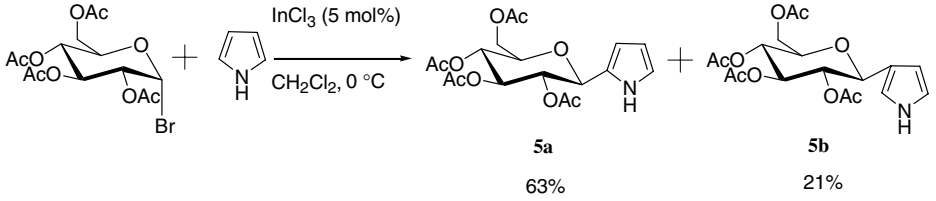
4a-f

Entry	R	R^1	R^2	R^3	R^4	R^5	Product[a]	Time (min)	Yield[b] (β:α)[c]
1	H	Me	H	OAc	H	OAc	**4a**	35	75 (>9:1)
2	H	Ph	H	OAc	H	OAc	**4b**	30	78 (>9:1)
3	H	Me	OAc	H	OAc	H	**4c**	40	72 (>1:9)
4	Me	Me	OAc	H	OAc	H	**4d**	30	82 (>1:9)
5	H	Ph	H	NPhth	OAc	H	**4e**	20	65 (>9:1)
6	H	Me	H	OAc	$OGal(OAc)_4$	H	**4f**	30	73 (>9:1)

[a] All products were characterized by ^1H, ^{13}C NMR and mass spectra.
[b] Isolated and unoptimized yields.
[c] Ratios of >9:1 are conservative minima; no α-product was detected.



Scheme 1. Reaction of 3-methylindole with glucosyl bromide.



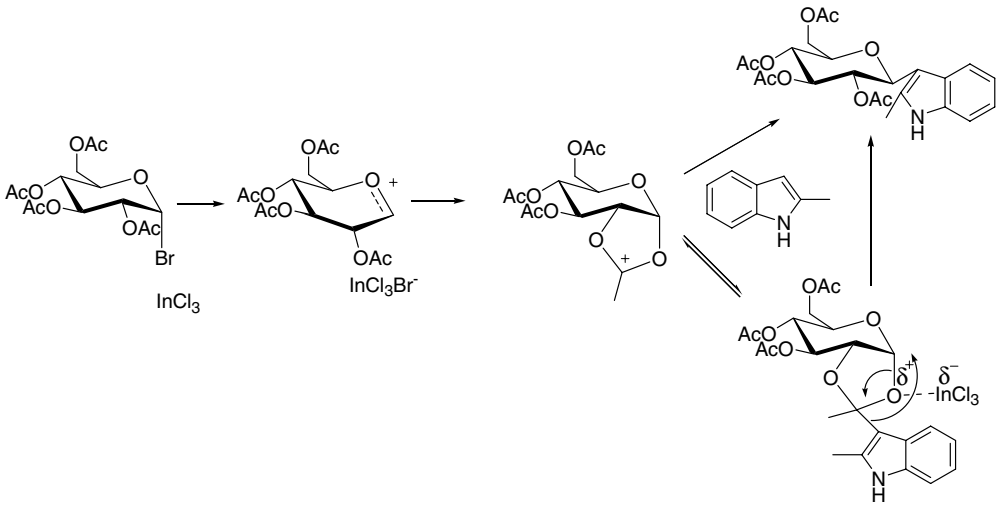
Scheme 2. Reaction of pyrrole with glucosyl bromide.

^1H NMR and resonances at δ 108.7, 108.9 (C-3′, C-4′) and 119.3 (C-5′), respectively, in ^{13}C NMR. In **5b**, resonances at δ 6.23 (H-4′), 9.73 and 6.80 (H-5′, H-2′), respectively, were observed in the ^1H NMR and at δ 108.0 (C-4′), 117.0 (C-5′) and 118.8 (C-2′), respectively, in the ^{13}C NMR.

The glycosylations appear to have proceeded through the Koenigs–Knorr process, which involves neighbouring group participation, as evident from the formation of the 1,2-*trans*-glycosides of the β-D-gluco or α-L-manno type. However, the exact mechanism is still uncertain. The reaction of indole with the acetobromosugar may initially lead to the formation of a 1,2-*O*-ethylidene derivative (as observed using Ag_2CO_3 or Ag_2O as a reagent[15]), which in the presence of $InCl_3$ rearranges to the more stable 3-C-glycoside of indole, a possible mechanism is given in Scheme 3.

The advantage of $InCl_3$ over other promoters like Ag_2O or Ag_2CO_3 lies in its ability to act not only as a halide acceptor[21] but also as a Lewis acid, facilitating rearrangement of the initially formed glycosyl orthoester to the desired C-glycoside. As anticipated, the reaction with pyrrole occurs to a greater extent at the 2-position than in the 3-position.

In summary, we have developed a novel and efficient strategy for the synthesis of C-nucleosides of indole and pyrrole from acyl glycosyl halides using $InCl_3$ as



Scheme 3. Plausible mechanism of glycosylation of indoles.

the catalyst. Further studies directed towards C-glycosylation with furan, thiophene, benzothiophene and carbazole, along with the synthesis of C-linked tryptophan glycoconjugates including biological studies (e.g., cytotoxicity) are in progress.

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22. *General procedure for the synthesis of* **2a–f**, **4a–f**: A mixture of glycosyl bromide (5 mmol), indole derivative (15 mmol) and $InCl_3$ (10 mol %) in dichloromethane (10 ml) was stirred at rt under N_2 for an appropriate time (Tables 1 and 2). The progress of the reaction was monitored by TLC (EtOAc–petroleum ether, 2:3). The reaction mixture was diluted with dichloromethane (50 ml) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (EtOAc–petroleum ether, 1:5) afforded the following compounds as white powders.
2-Methyl-3-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)indole (**2a**): $[\alpha]_D^{26}$ −3.6 (*c* 1.2, $CHCl_3$); MS (positive ion ESI): *m*/*z* 484 ($M+Na^+$); ^1H NMR (600 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.20 (m, 1H), 7.07–7.09 (m, 2H), 5.33–5.40 (m, 3H), 4.77 (d, *J* = 9.0 Hz, 1H), 4.19–4.30 (m, 2H), 3.84 (d, *J* = 8.0 Hz, 1H), 2.43 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.8, 170.0, 169.3, 135.4, 133.9, 127.5, 121.7, 120.2, 118.9, 110.7, 107.0, 76.4, 74.9, 74.8, 72.5, 69.2, 62.8, 21.2, 21.1, 20.7, 12.7; Anal. Calcd for $C_{23}H_{27}NO_9$: C, 59.86; H, 5.90; N, 3.04. Found: C, 59.81; H, 5.88; N, 3.11.
1,2-Dimethyl-3-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)indole (**4d**): $[\alpha]_D^{26}$ −41.3 (*c* 0.47, $CHCl_3$); MS (positive ion ESI): *m*/*z* 498 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.80 (d, *J* = 7.7 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.02–7.09 (m, 2H), 5.48 (t, *J* = 9.9 Hz, 1H), 5.37 (d, *J* <1Hz, 1H), 5.31 (dd, *J* = 10.6, 3.3 Hz, 1H), 5.05 (d, *J* <1 Hz, 1H), 4.23–4.33 (m, 2H), 3.81–3.84 (m, 1H), 3.60 (s, 3H), 2.31 (s, 3H), 2.10 (s, 3H), 1.98 (s, 3H), 1.90 (s, 3H), 1.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 70.6, 170.1, 169.9, 169.7, 136.5, 133.3, 126.2, 120.7, 120.5, 118.9, 108.3, 106.2, 76.4, 76.3, 72.3, 71.7, 66.1, 62.9, 29.5, 20.7, 20.6, 20.5; Anal. Calcd for $C_{24}H_{29}NO_9$: C, 60.62; H, 6.15; N, 2.95. Found: C, 60.59; H, 6.17; N, 2.98.
Procedure for the synthesis of **3**: A mixture of glucosyl bromide (5 mmol), 3-methylindole (10 mmol) and $InCl_3$ (10 mol %) in THF (5 ml) was stirred at rt under N_2 for 2 h. The progress of the reaction was monitored by TLC (EtOAc–petroleum ether, 3:5). After work-up the compound was isolated by plc (benzene–EtOAc, 6:1) as a white powder (which becomes black on prolonged exposure to light).
1-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-3-methylindole (**3**): $[\alpha]_D^{26}$ −5.7 (*c* 0.29, $CHCl_3$); MS (positive ion ESI): *m*/*z* 484 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.12–7.21 (m, 2H), 7.00 (s, 1H), 5.61 (d, *J* = 8.9 Hz, 1H), 5.53 (t, *J* = 8.9 Hz, 1H), 5.43 (t, *J* = 9.0 Hz, 1H), 5.26 (t, *J* = 9.6 Hz, 1H), 4.10–4.31 (m, 2H), 3.96–3.99 (m, 1H), 2.29 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.4, 170.2, 169.4, 168.9, 136.6, 129.6, 122.3, 121.4, 120.1, 119.3, 113.6, 109.2, 82.8, 74.4, 73.5, 70.2, 68.2, 61.9, 29.7, 20.7, 20.6, 20.6, 20.2, 9.7; Anal. Calcd for $C_{23}H_{27}NO_9$: C, 59.86; H, 5.90; N, 3.04. Found: C, 59.83; H, 5.94; N, 3.06.
Procedure for the synthesis of **5a**,**b**: A mixture of glucosyl bromide (5 mmol), pyrrole (25 mmol) and $InCl_3$ (5 mol %) in dichloromethane (5 ml) was stirred at rt under N_2 for 1 h. The progress of the reaction was monitored by TLC (EtOAc–toluene, 1:4). The reaction mixture was diluted with dichloromethane (10 ml) and washed with water. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel (100–200 mesh, EtOAc–toluene, 1:9–1:7) afforded **5a** or **5b** as a white powder (**5b** is light sensitive).
2-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)pyrrole (**5a**): $[\alpha]_D^{26}$ +2.0 (*c* 0.18, $CHCl_3$); MS (positive ion ESI): *m*/*z* 420 ($M+Na^+$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.41 (s, 1H), 6.78 (d, *J* = 1.7 Hz, 1H), 6.12 (d, *J* = 2.3 Hz, 1H), 5.31 (t, *J* = 9.1 Hz, 1H), 5.18 (m, 2H), 4.52 (d, *J* = 9.7 Hz, 1H), 4.26 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.12 (dd, *J* = 12.3, 2.0 Hz, 1H), 3.81–3.83 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.6, 169.9, 169.7, 125.9, 119.3, 108.9, 108.7, 76.4, 74.7, 74.4, 71.5, 68.9, 62.7, 21.2, 21.1, 21.0, 20.9; Anal. Calcd for $C_{18}H_{23}NO_9$: C, 54.40; H, 5.83; N, 3.52. Found: C, 54.42; H, 5.81; N, 3.54.
3-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)pyrrole (**5b**): $[\alpha]_D^{26}$ +8.2 (*c* 0.9, $CHCl_3$); MS (positive ion ESI): *m*/*z* 420 ($M+Na^+$); ^1H NMR (600 MHz, $CDCl_3$): δ 8.20 (s, 1H), 6.80 (d, *J* = 1.8 Hz, 1H), 6.73 (t, *J* = 1.8 Hz, 1H), 6.23 (s, 1H), 5.19–5.31 (m, 3H), 4.47 (d, *J* = 9.4 Hz, 1H), 4.12–4.27 (m, 2H), 3.79–3.82 (m, 1H), 2.08 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 171.2, 170.8, 169.9, 169.7, 119.7, 118.8, 117.2, 108.0, 76.1, 75.5, 75.1, 72.7, 69.2, 62.9, 62.3, 21.2, 21.1, 21.0; Anal. Calcd for $C_{18}H_{23}NO_9$: C, 54.40; H, 5.83; N, 3.52. Found: C, 54.38; H, 5.86; N, 3.51.