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A mild and environmentally friendly scandium(III) trifluoromethanesulfonate-catalyzed synthesis of bis(3′-indolyl) alkanes and bis(3′-indolyl)-1-deoxyalditols

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Abstract—Bis(3′-indolyl)alkanes and bis(3′-indolyl) derivatives containing a 1-deoxyalditol moiety were synthesized in the presence of 5 mol % of scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$] in CH_3CN or EtOH–H_2O mixture as a solvent from room temperature to 70 °C in good yields (78–97%).

Keywords: Bis(3′-indolyl)alkanes; 1-Deoxyalditol; Acyclic *C*-nucleoside; $Sc(OTf)_3$; Aqueous media

1. Introduction

A variety of synthetic methods for the preparation of the bis(3′-indolyl)alkanes, including naturally occurring products using protic or Lewis acids, have been developed.[1] The synthesis of bis(indolyl)methanes, has also been used in attempts to explore the utility of newly developed catalysts.[2] In general, the above compounds were synthesized by the condensation of 2 equiv of indole with an aldehyde or ketone using a protic or Lewis acid, and the mechanism for this reaction has been reported.[1e] Among these preparations, it has been reported that lanthanide triflates can be used efficiently in the synthesis of bis(3′-indolyl)alkanes in aqueous media.[1e] We had also reported on the *C*-glycosylation of free polyphenols with unprotected sugars using $Sc(OTf)_3$ in aqueous media.[3e,f] In a continuation of our studies of environmentally friendly and simple synthetic methods, our interest focused on the synthesis of the bis(3′-indolyl)alkanes utilizing the direct *C*-glycosylation method involving a catalytic amount of $Sc(OTf)_3$ in aqueous media. The only synthesis of bis(3′-indolyl)alkanes cross-linked to an open-chain sugar (1-deoxyalditol), reported by Mara et al.,[4] is the Grignard reaction of suitably protected aldose with *N*-indolylmagnesium bromide. The desired product was obtained in poor yield (35%). Herein, we report the first direct synthesis of bis(3′-indolyl)alkanes containing a 1-deoxyalditol from unprotected aldose (Scheme 1). The naturally occurring 3,3-bis(3′-indolyl)propane-1,3-diol (**3**)[6] (Scheme 1b) and streptindole (**2d**)[5] (Scheme 2) are also described.

2. Results and discussion

We initially examined the reaction of indole with benzaldehyde (Table 1). The optimal conditions were realized with 3 or 2 equiv of indole and benzaldehyde in CH_3CN in the presence of 5 mol % of $Sc(OTf)_3$ at room temperature for 3.5 h. Thus, an excellent yield of bis(3′-indolyl)phenylmethane (**1**) was obtained (97% and 93%) (Table 1, entries 5 and 6). In contrast, a decrease in yield was observed when an excess of benzaldehyde was used (entries 2, 3, and 4). With glyoxylic acid methyl ester instead of benzaldehyde as substrate at 40 °C for 1 h, a mixture of 2,2-bis(3′-indolyl)ethanoic acid (**2a**) and

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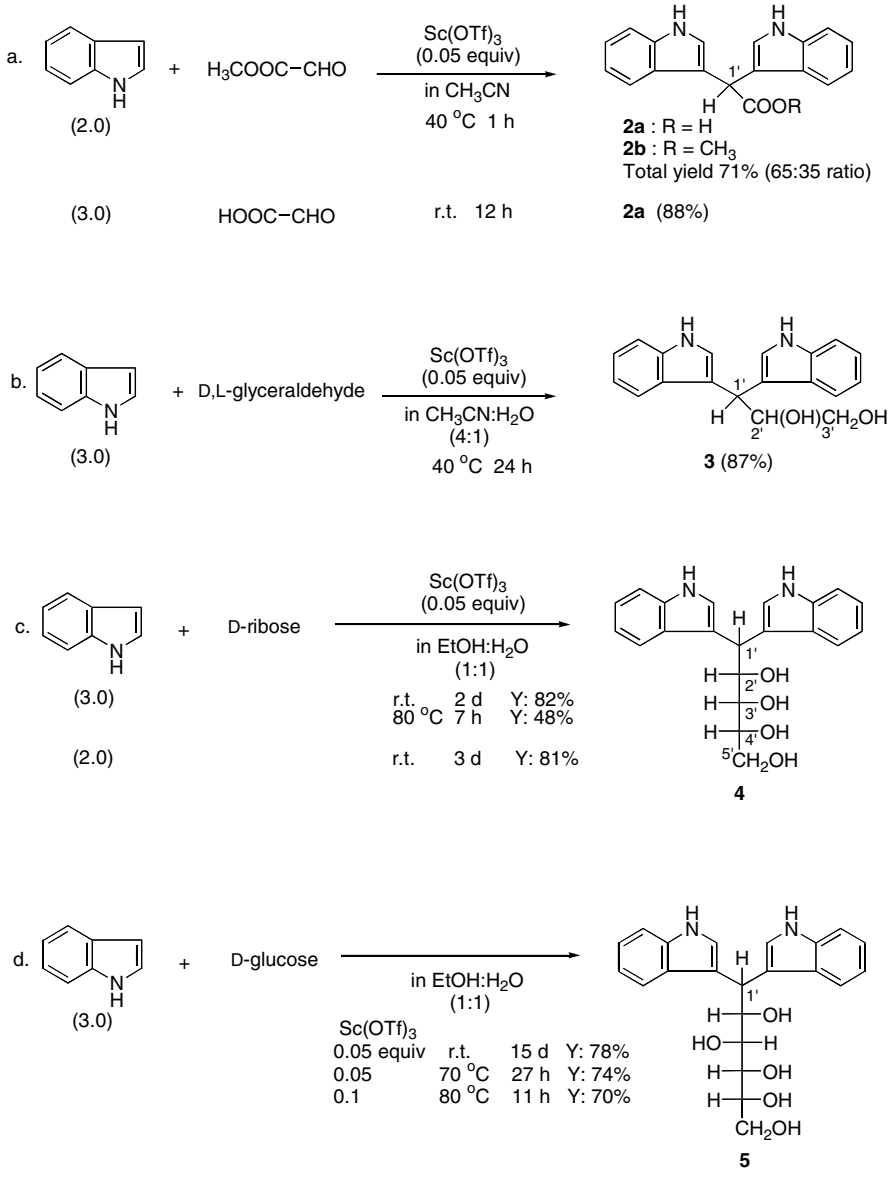
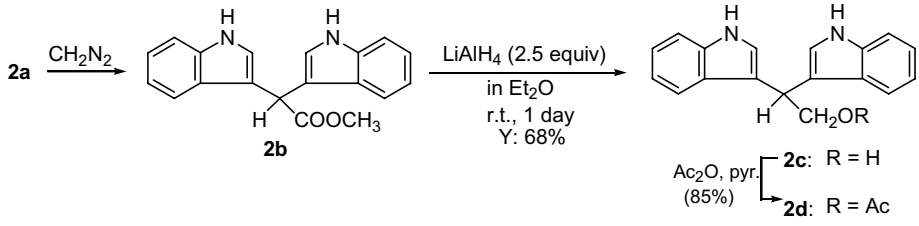


Scheme 1. Condensation of indole and various aldehydes using $Sc(OTf)_3$.



Scheme 2. Conversion of **2b** to streptindole (**2d**).

methyl 2,2-bis(3′-indolyl)ethanoate (**2b**) in 65:35 ratio was obtained in a total yield of 71% (Scheme 1a). When 3 equiv of indole reacted with glyoxylic acid as substrate at room temperature, **2a** was obtained in good yield of 88%, but with prolonged reaction time (12 h). Treatment of **2a** with diazomethane gave quantitatively **2b**, which was reduced by $LiAlH_4$ to give 2,2-bis(3′-indolyl)ethanol (**2c**) (Scheme 2). Subsequent acetylation under standard procedure gave the naturally occurring streptindole (**2d**)[5,1g] in a total yield of 51%. The reaction of indole

Table 1. Condensation of indole and benzaldehyde using $Sc(OTf)_3$

Entry	Indole (equiv)	Benzaldehyde (equiv)	$Sc(OTf)_3$ (equiv)	Temperature (°C)	Time (h)	Product (**1**) (%)
1	1.5	2.0	0	rt	24	0
2	1.5	2.0	0.05	rt	0.5	57
3	1.5	2.0	0.05	40	0.15	63
4	1.5	2.0	0.05	50	0.1	68
5	3.0	1.0	0.05	rt	3.5	97
6	2.0	1.0	0.05	rt	3.5	93

with an unprotected sugar in aqueous media was also carried out. D,L-Glyceraldehyde reacted with indole in 4:1 CH_3CN–H_2O at 40 °C for 1 day to afford 3,3-bis(3′-indolyl)propane-1,2-diol (**3**) in a yield of 87% (Scheme 1b). Interesting results were also obtained with sugars bearing more than three carbon atoms. Indeed, D-ribose at room temperature for 2 days gave the desired bis(3′-indolyl)alkane (**4**) in a yield of 82% (Scheme 1c), and D-glucose reacted with 3 equiv of indole at room temperature for 15 days to give the alditol derivative **5** in yield of 78% (Scheme 1d). The reaction time was reduced to 11 h when amount of $Sc(OTf)_3$ was increased to 0.1 equiv under heating at 80 °C. The desired compound **5** was obtained in 70% yield with some unidentified byproducts.

In conclusion, the condensation of 2 or 3 equiv of indole and aldehyde or unprotected aldose using a catalytic amount of $Sc(OTf)_3$ proceeds at room temperature or under heating to afford in good yield the desired bis(3′-indolyl)alkanes and deoxyalditols without any significant byproduct formation. This synthetic method developed herein is convenient and environmentally friendly, and may be considered one of the best synthetic methods leading to 3′-modified indoles that are substituted by alkyl or alditol groups.

3. Experimental

3.1. General methods and materials

The solvents used for this reaction were prepared by distillation. $Sc(OTf)_3$ was purchased from Taiheiyo Kinzoku Co. Ltd (Japan) and used without any further purification. Compounds were separated and purified by flash-column chromatography using silica gel (Fuji-Silysia Co., Ltd, BW-300). Melting points were determined on a Shibayama micro-melting point apparatus and are uncorrected. Mass spectra data were obtained by the fast-atom bombardment (FAB) method using 3-nitrobenzyl alcohol (NBA) as the matrix on a JEOL JMS-AX505HA instrument. Optical rotations were recorded on a JASCO DIP-370 polarimeter. Infrared spectra were recorded on a Horiba FT-720 spectrometer as KBr discs. Elemental analyses were performed on a Perkin–Elmer PE 2400 II instrument. NMR spectra were recorded on Varian Inova 500 and Mercury 200 spectrometers using Me_4Si as the internal standard.

3.2. General synthetic procedures for reaction of indole with aldehydes

3.2.1. Reaction of indole with D-ribose to give 1-deoxy-1,1-bis(3′-indolyl)-D-ribitol (4). Indole (234 mg, 1.99 mmol), D-ribose (100 mg, 0.66 mmol), and $Sc(OTf)_3$ (16.5 mg, 0.033 mmol) were dissolved in 2 mL of 1:1 ethanol–water. The solution was then stirred at room temperature for 2 days, and the reaction mixture was then evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (20:1 and 10:1 $CHCl_3$–MeOH) to give **4** (201 mg, 82%) as a colorless, white powder: mp 101–103 °C. R_f 0.28 (5:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ +52.4 (*c* 1.00, MeOH); IR (KBr) *v* 3400, 3058, 2923, 1456, 1419, 1338, 1244, 1221, 1093, 1034, 744 cm^{-1}; ^1H NMR (DMSO-d_6): δ (indolyl moiety): 6.82–7.52 (8H, ArH), 7.19 and 7.34 (each 1H, d, *J* 2.0 Hz, H-2′ and H-2″), 10.68 and 10.76 (each 1H, d, *J* 2.0 Hz, NH × 2); (ribose moiety): 3.31 (1H, dd, *J* 5.0 and 8.6 Hz, H-3), 3.43 (1H, dd, *J* 6.3 and 11.0 Hz, H-5a), 3.58 (1H, dd, *J* 3.6 and 11.0 Hz, H-5b), 3.68 (1H, ddd, *J* 5.0, 3.6, and 6.3 Hz, H-4), 4.13 (1H, dd, *J* 8.6 and 2.4 Hz, H-2), 4.97 (1H, d, *J* 2.4 Hz, H-1), 4.52, 4.57, and 4.65 (each 1H, s, OH × 3); ^{13}C NMR (DMSO-d_6): δ 136.3, 135.9 (C-7′a), 128.5, 127.2 (C-3′a), 124.5, 123.4 (C-2′), 120.7, 120.4 (C-5′), 119.7, 118.9 (C-4′), 118.3, 118.0 (C-6′), 117.9, 114.2 (C-7′), 111.4, 111.1 (C-3′); (ribose moiety): 76.2, 73.7, 72.4, 62.7 (C-5), 34.7 (C-1); FABMS (*m*/*z*) 367 $(M+H)^+$. Anal. Calcd for $C_{21}H_{22}N_2O_4 \cdot H_2O$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.28; H, 5.90; N, 7.12.

3.2.2. 1-Deoxy-1,1-bis(3′-indolyl)-D-glucitol (5). By the foregoing procedure, indole was reacted with D-glucose to give **5** as a colorless powder: mp 108–110 °C. R_f 0.12 (5:1 $CHCl_3$–MeOH); $[\alpha]_D^{20}$ +53.3 (*c*1.035, MeOH); IR (KBr) *ν* 3400, 3059, 2924, 1456, 1419, 1338, 1246, 1219, 1093, 1039, 1012, 744 cm^{-1}; ^1H NMR (DMSO-d_6): *δ* (indolyl moiety): 6.86–7.58 (8H, m, ArH), 7.16 (1H, d, *J* 2.1 Hz, H-2′), 7.37 (1H, d, *J* 1.7 Hz, H-2″), 10.68 (1H, d, *J* 2.1 Hz, NH), 10.69 (1H, d, *J* 1.7 Hz, NH); (glucose moiety): 3.30 (1H, dd, *J* 6.0 and 10.8 Hz, H-6a), 3.45 (1H, m, H-5), 3.50 (2H, m, H-4 and -6b), 3.62 (1H, dd, *J* 4.2 and 6.8 Hz, H-3), 4.46 (1H, dd, *J* 4.2 and 7.3 Hz, H-2), 4.71 (1H, d, *J* 7.3 Hz, H-1), 4.39, 4.05, and 4.60 (each 1H, s, OH × 3), 4.29 (2H, s, OH × 2); ^{13}C NMR (DMSO-d_6): *δ* 136.3, 136.2 (C-7′a), 127.9, 127.1 (C-3′a), 123.5, 123.1 (C-2′), 120.7, 120.4 (C-5′), 119.6, 119.3 (C-4′), 118.1, 117.9 (C-6′), 117.4, 115.9 (C-7′), 111.3, 111.2 (C-3′); (glucose moiety): 75.4, 73.8, 71.7, 69.4, 63.6 (C-6), 36.2 (C-1); FABMS (*m*/*z*) 397 $(M+H)^+$. Anal. Calcd for $C_{22}H_{24}N_2O_5 \cdot 0.2H_2O$: C, 66.05; H, 6.15; N, 7.00. Found: C, 66.04; H, 6.18; N, 6.92.

3.2.3. 1,1-Bis(3′-indolyl)phenylmethane (1). By the general procedure in Section 3.2.1, benzaldehyde was reacted with indole to give **1** as colorless prisms (from Et_2O): mp 151–153 °C (lit.: 150–152 °C,[7] 88–90 °C.[1h]) IR (KBr) *ν* 3398, 3051, 3022, 2923, 2854, 1612, 1599, 1493, 1456, 1419, 1336, 1091, 1008, 746 cm^{-1}; ^1H NMR (DMSO-d_6): *δ* 5.87 (1H, s, >CH–), 6.60 (1H, d, *J* 1.2 Hz, H-2), 6.61 (1H, d, *J* 0.8 Hz, H-2′), 6.87–7.41 (13H, m, ArH), 7.82 (2H, br s, NH × 2); ^{13}C NMR ($CDCl_3$): *δ* 144.0, 136.5, 128.6, 128.2, 127.0, 126.1, 121.8, 119.8, 119.5, 119.1, 111.0, 40.9 (>CH–); FABMS (*m*/*z*) 323 $(M+H)^+$.

3.2.4. 2,2-Bis(3′-indolyl)ethanoic acid (2a).[1c,d] By the general procedure in Section 3.2.1, glyoxylic acid methyl ester was reacted with indole to give **2a** as reddish yellow prisms (from AcOEt): mp 174–175 °C. IR (KBr) *ν* 3408, 3057 2924, 2854, 1705, 1618, 1458, 1338, 1010, 744 cm^{-1}; ^1H NMR (DMSO-d_6): *δ* 5.34 (1H, s, >CH–), 6.90–7.70 (10H, m, ArH), 10.91 (2H, s, NH × 2), 12.31 (1H, br s, C–OOH); ^{13}C NMR (DMSO-d_6) *δ* 174.5 (C═O), 136.5 (×2), 126.7 (×2), 123.8 (×2), 12.1 (×2), 119.2 (×2), 118.6 (×2), 113.0 (×2), 111.7 (×2), 40.5 (>CH–); FABMS (*m*/*z*) 291 $(M+H)^+$.

3.2.5. 3,3-Bis(3′-indolyl)propane-1,2-diol (3). By the general procedure in Section 3.2.1, indole was reacted with D,L-glyceraldehyde to give **3** as a white powder: mp 92–96 °C (lit.[9] 90–91 °C). IR (KBr) *ν* 3529, 3398, 3051, 2923, 2871, 1456, 1419, 1338, 1246, 1219, 1095, 1010, 744 cm^{-1}. ^1H NMR (DMSO-d_6): *δ* (indolyl moiety): 6.84–7.54 (8H, m, ArH), 7.23 (1H, d, *J* 1.5 Hz, H-2′), 7.32 (1H, d, *J* 2.0 Hz, H-2″), 10.72 (1H, d, *J* 1.5 Hz, NH), 10.74 (1H, d, *J* 2.0 Hz, NH); (propanediol moiety): 3.26 (1H, dd, *J* 10.5 and 6.5 Hz, H-3a), 3.35 (1H, dd, *J* 10.5 and 4.5 Hz, H-3b), 4.28 (1H, dd, *J* 6.0 and 4.5 Hz, H-2); ^{13}C NMR ($CDCl_3$): *δ* (indolyl moiety): 136.3, 136.1 (C-7′a), 128.1, 127.1 (C-3′a), 123.5, 123.1 (C-2′), 120.7, 120.5 (C-5′), 119.4, 119.1 (C-4′*), 118.1, 117.9 (C-6′*), 117.5, 115.4 (C-7′), 111.4, 111.2 (C-3′); (propanediol moiety): 74.4 (C-2), 64.9 (C-3), 36.1 (C-1), ∗: may be interchangeable; FABMS (*m*/*z*) 307 $(M+H)^+$.

3.3. Methyl 2,2-bis(3′-indolyl)ethanoate (2b)[1d]

To a solution of **2a** (100 mg, 0.34 mmol) in EtOAc, a solution of diazomethane in Et_2O was added dropwise until **2a** disappeared on silica gel TLC (1:1 *n*-hexane–EtOAc). The reaction mixture was evaporated in vacuo to give **2b** (105 mg, 100%) as a white powder: mp 75–78 °C (lit.[8] 45–50 °C). IR (KBr) *ν* 3410, 3128, 3055, 2950, 1728, 1618, 1458, 1431, 1338, 1199, 1170, 1095, 742 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 3.74 (3H, s, OMe), 5.51 (1H, s, >CH–), 7.03–7.64 (10H, m, ArH), 8.00 (2H, br s, NH × 2); ^{13}C NMR ($CDCl_3$): *δ* 174.1 (C═O), 136.3 (×2), 126.5 (×2), 123.4 (×2), 122.1 (×2), 119.6 (×2), 119.1 (×2), 113.3 (×2), 111.7 (×2), 52.3 (OCH_3), 40.4 (>CH–); FABMS (*m*/*z*) 305 $(M+H)^+$.

3.4. 2,2-Bis(3′-indolyl)ethanol (2c)[1d]

$LiAlH_4$ (134 mg, 3.54 mmol) was added in portions to a cooled solution of **2b** (430 mg, 1.41 mmol) in dry ether (4 mL) under stirring. The reaction mixture was stirred for 1 day at room temperature. Satd aq Na_2SO_4 was added to the reaction mixture, and the resulting solution was extracted with AcOEt (3×). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, and then evaporated in vacuo. The residue was purified by flash-column chromatography on silica gel (1:1 *n*-hexane–AcOEt) to give **2c** (264 mg, 68%) as a white powder: mp 68–70 °C [lit.[1d] 50 °C (60–80 °C, petroleum ether–toluene)]. IR (KBr) *ν* 3537, 3400, 3055, 2929, 2877, 1689, 1618, 1456, 1419, 1338, 1217, 1095, 1010, 742 cm^{-1}; ^1H NMR (DMSO-d_6): *δ* 4.06 (2H, d, *J* 6.8 Hz, CH_2), 4.53 (1H, t, *J* 6.8 Hz, >CH–), 4.62 (1H, br s, OH), 6.87 (2H, dt, *J* 6.7 and 1.1 Hz, ArH), 7.00 (2H, dt, *J* 7.8 and 1.1 Hz, ArH), 7.18 (1H, d, *J* 2.2 Hz, ArH), 7.30 (2H, d, *J* 7.1 Hz, ArH), 7.47 (2H, d, *J* 7.7 Hz, ArH), 10.76 (2H, s, NH × 2); ^{13}C NMR (DMSO-d_6): *δ* 136.5 (C-7′a), 127.2 (C-3′a), 122.7 (C-2′), 120.7 (C-5′), 119.2 (C-4′), 118.1 (C-6′), 116.6 (C-7′), 111.4 (C-3′), 65.3 (CH_2OH), 37.2 (C-2); FABMS (*m*/*z*) 277 $(M+H)^+$.

3.5. 2,2-Bis(3′-indolyl)ethyl acetate (2d, streptindole)[1d,g,5]

Product **2c** was acetylated to give **2d** as a white powder: mp 56–58 °C. ^1H NMR ($CDCl_3$): *δ* (2-acetoxyethyl moi-

ety): 1.98 (3H, s, Ac), 4.93 (2H, d, J 6.9 Hz, CH_2), 4.96 (1H, dd, J 6.9 Hz, >CH); (indole moiety): 6.96 (1H, d, J 0.7 Hz, H-2), 6.97 (1H, d, J 0.7 Hz, H-2′), 7.02–7.64 (8H, m, ArH), 7.96 (2H, br s, NH × 2); ^{13}C NMR ($CDCl_3$): δ 171.3 (C=O), 136.4 (C-7′a), 127.0 (C-3′a), 122.1 (C-2′), 122.0 (C-5′), 119.5 (C-4′*), 119.3 (C-6′), 116.2 (C-7′*), 111.1 (C-3′), 67.3 (>CH*C*H_2OH), 33.5 (>*C*HCH$_2$OH), 21.1 (CH_3), *: may be interchangeable; FABMS (m/z) 319 $(M+H)^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.carres.2005.07.019. ^{1}H and ^{13}C NMR spectra are provided for compounds **1**, **2a**–**d**, and **3**.

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