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A versatile and practical synthesis of bis(indolyl)methanes/ bis(indolyl)glycoconjugates catalyzed by trichloro-1,3,5-triazine

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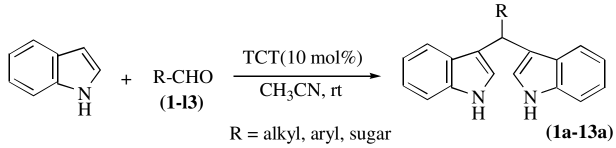
Abstract—A practical and efficient electrophilic substitution reaction of indoles with a variety of aldehydes was carried out using catalytic trichloro-1,3,5-triazine (10mol%) in acetonitrile to furnish the corresponding bis(indolyl)methanes in excellent yields. Similarly, sugar derived aldehydes gave hitherto unknown bis(indolyl)glycoconjugates in very good yields.

1. Introduction

Due to the potent biological activity exhibited by various indole derivatives,[1] there is a continuous demand for novel synthetic methods in this area. Bis(indolyl) methanes are gaining prominence in view of their occurrence in bioactive metabolites of terrestrial and marine origin.[2] The azafulvenium salts obtained from electrophilic substitution of indoles with aliphatic or aromatic aldehydes or ketones undergo further substitution to afford bis(indolyl)methanes.[3] Bis(indolyl)methanes have been obtained by reactions of indoles with various aldehydes or ketones in the presence of either protic[4] or Lewis acids.[5] Most of the previously reported methods suffer from several setbacks such as requirement of a stoichiometric amount of the Lewis acid, expensive and highly toxic catalysts, long reaction times. However these problems were overcome to some extent by recently reported methods, the use of an ionic liquid[6] and the use of I_2.[7] Hence a more efficient and practical alternative using an inexpensive and environmentally friendly reagent is still warranted. Herein, we report for the synthesis of various bis(indolyl)methanes and bis(indolyl)glycoconjugates by reaction of indoles with a variety of aldehydes in acetonitrile using trichloro-1,3,5-triazine (TCT)[8] (10mol%) as a catalyst at room temperature (Scheme 1).



Scheme 1.

Benzaldehyde (Table 1, entry 1) on reaction with indole with 10mol% of TCT in acetonitrile furnished **1a** in 92% yield. Similarly *p*-nitrobenzaldehyde (entry 4) possessing an electron withdrawing group underwent smooth reaction under the above reaction conditions to afford **4a** in 89% yield. These reactions prompted us to extend the scope of TCT as a catalyst for the synthesis of various bis(indolyl)methanes. Aromatic (entries 2 and 3), aliphatic (entry 7), alicylic (entry 8), heteroaromatic (entries 5 and 6) and α,β-unsaturated (entry 9) aldehydes similarly gave the corresponding bis(indolyl)methanes **2a**, **3a**, **5a**–**9a** in 70–94% yields within 10–15min. It is noteworthy that all the substrates reacted with equal ease in short times, furnishing the products in high yields and with no side products. Further, the reaction of a ketone (entry 10) gave the bis-indole **10a** (85%), albeit requiring 10h.

In continuation of our work on *C*-nucleosides[9] and new glycosubstances[10] we turned our attention to the construction of bis(indolyl)glycoconjugates from sugar aldehydes. Accordingly, sugar derived aldehyde, 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-pentodialdo-1,4-furanose (entry 11) underwent a facile reaction with indole to give the C-linked glycoconjugate **11a** in 85%

Keywords: Bis(indolyl)methanes; Aldehydes; Sugar aldehydes; Electrophilic substitution; Trichloro-1,3,5-triazine.

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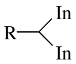
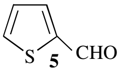
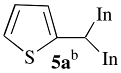
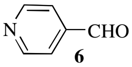
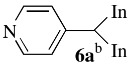
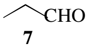
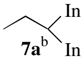
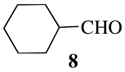
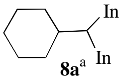
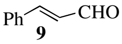
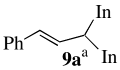
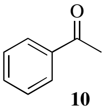
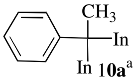
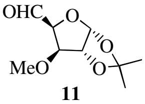
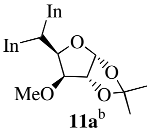
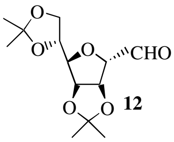
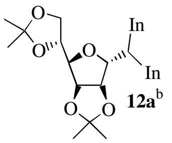
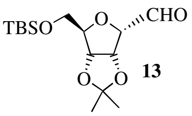
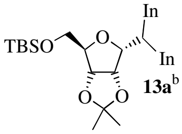
Table 1. $ZrCl_4$(10 mol%) catalyzed synthesis of bis(indolyl)methanes

Entry	Aldehyde	Product	Time (min)	Yield (%)
	R–CHO			
1	R = phenyl **1**	R = phenyl **1a**[a]	15	92
2	R = *p*-chlorophenyl **2**	R = *p*-chlorophenyl **2a**[a]	10	94
3	R = *p*-methoxyphenyl **3**	R = *p*-methoxyphenyl **3a**[a]	10	90
4	R = *p*-nitrophenyl **4**	R = *p*-nitrophenyl **4a**[a]	10	89
5	 **5**	 **5a**[b]	10	90
6	 **6**	 **6a**[b]	10	88
7	 **7**	 **7a**[b]	15	87
8	 **8**	 **8a**[a]	10	86
9	 **9**	 **9a**[a]	10	70
10	 **10**	 **10a**[a]	10 h	85
11	 **11**	 **11a**[b]	30	85
12	 **12**	 **12a**[b]	40	72
13	 **13**	 **13a**[b]	45	72

*In = 3-Indolyl.

[a] See Ref. 7.

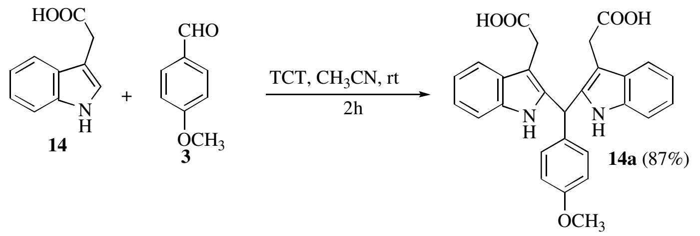
[b] All new compounds gave satisfactory data.

yield. 2,5-Anhydro-3,4:6,7-di-*O*-isopropylidene aldehydo-D-*glycero*-D-*galacto*-heptofuranose (entry 12) and 2,5-anhydro-6-*O*-*tert*-butyldimethylsilyl-3,4-*O*-isopropylidene-D-allose (entry 13) were also successfully reacted with indole to furnish bis(indolyl) *C*-nucleoside glycoconjugates **12a** and **13a**, respectively, in good yields (Table 1).

Under the above reaction conditions, indole-3-acetic acid on reaction with *p*-methoxybenzaldehyde gave **14a**[11] in 87% yield, the electrophilic substitution taking place at C-2 as C-3 was blocked (Scheme 2).

The plausible mechanism of the reaction is as shown below (Fig. 1). The adventitious moisture reacts with TCT to release 3 mol of HCl[12] and cyanuric acid (removable by water washing) as byproduct. The in situ generated HCl acts as a protic acid to activate the carbonyl oxygen to form the bis-indole derivatives.

To determine the role of adventitious moisture for 'in situ' HCl generation from TCT, treatment of indole with **3** and TCT was carried out in the presence of MS 4 Å but there was no reaction even after 24 h. When all the ingredients of the reaction were azeotropically dried and utilized, the reaction was very sluggish and less than 20% conversion was observed even after 24 h. These two experiments amply indicate that moisture is essential to release 'HCl' from TCT.



Scheme 2.

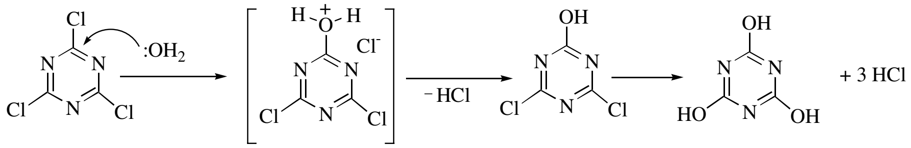


Figure 1.

In summary, we have developed an efficient TCT-catalyzed protocol for the synthesis of bis(indolyl)alkanes and bis(indolyl)glycoconjugates in short reaction times under mild reaction conditions in high yields. The readily available inexpensive TCT-catalyst makes this protocol an attractive method particularly for the synthesis of unusual *C*-nucleoside conjugates.

2. General experimental procedure

To a solution of aldehyde (1 mmol) in acetonitrile (2 mL), indole (2 mmol) was added followed by catalytic TCT (10 mol%) at room temperature. After stirring the reaction mixture for the specified time (Table 1), solvent was removed under reduced pressure, the residue diluted with water and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4) and evaporated under vacuum to give a crude product which was purified by column chromatography (silica gel 5–20% EtOAc:hexane) to furnish the product.

3. Spectral data of selected compounds

3.1. 3-[1*H*-3-Indolyl(2-thienyl)methyl]-1*H*-indole 6a

Mp 163–165 °C; IR (KBR): 3375, 2982, 2930, 1505, 1308, 1161, 1071, 1013 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.40 (d, 2H, $J = 8.3$ Hz), 7.26 (t, 3H, $J = 7.5$ Hz), 7.18–6.75 (m, 9H), 6.12 (s, 1H); EIMS: (*m*/*z*, %) 328 [M^+, 23], 245 (M^+-83, 100), 117 (42); Anal. Calcd for $C_{21}H_{96}N_2S$ (328): C, 76.80; H, 4.91. Found: C, 76.78; H, 4.95.

3.2. 3-{1*H*-3-Indolyl[6-deoxy-2,2-dimethyl-(3a*R*,5*R*,6*S*,-6a*R*)-perhydrofuro[2,3-*d*][1,3]di-oxol-5-yl]methyl}-1*H*-indole 11a

$[\alpha]_D$ −16.9 (*c* 1.0, $CHCl_3$); mp 102–105 °C; IR (KBR): 3385, 2980, 2938, 1725, 1705, 1502, 1308, 1161, 1071, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 10.30, 10.12 (2 br s, 2H), 7.64 (d, 1H, $J = 6.5$ Hz), 7.49–7.33 (m, 1H), 7.20–6.76 (m, 8H), 5.95 (d, 1H, $J = 5.3$ Hz), 4.95 (t, 2H, $J = 17.1$ Hz), 4.45 (d, 1H, $J = 5.3$ Hz), 3.29 (d, 1H, $J = 4.2$ Hz) 3.08 (s, 3H), 1.67 (s, 3H), 1.25 (s, 3H); EIMS: (*m*/*z*, %) 245 (M^+-173, 18), 233 (M^+-185, 28), 117 (M^+-301, 100), 90 (M^+-328, 37); Anal. Calcd for $C_{25}H_{26}N_2O_4$ (418): C, 71.75; H, 6.26. Found: C, 71.80; H, 6.30.

3.3. 2-{-[3-Carboxymethyl-1*H*-2-indolyl(4-methoxyphenyl)methyl]-1*H*-3-indolyl}acetic acid 14a

Mp 125–130 °C; IR (KBR): 3400, 3385, 2980, 2938, 1730, 1502, 1308, 1161, 1071, 1013 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 10.48 (br s, 2H), 7.38 (d, 2H, $J = 6.0$ Hz), 7.28 (d, 2H, $J = 5.0$ Hz), 7.12–6.90 (m, 8H), 6.78 (d, 2H, $J = 8.0$ Hz), 6.08 (s, 1H), 3.75 (d, 3H), 3.54 (s, 4H); EIMS: (*m*/*z*, %) 468 (M^+, 8), 361(M^+-107, 100), 176 (M^+-292, 63).

Acknowledgements

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12. Reaction of **3** with indole in the presence of 10 mol% HCl (prepared from commercial HCl), was complete in 10 min to give **3a** in 90% yield. However, the sugar substrates **11** and **12** gave the respective products **11a** (52%) and **12a** (40%) in comparatively low yields using HCL in this way.