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Synthesis of glycosyl dipyrromethanes

Kha Tram, Westen MacIntosh, Hongbin Yan *

Department of Chemistry, Brock University, 500 Glenridge Ave., St. Catharines, Ontario, Canada L2S 3A1

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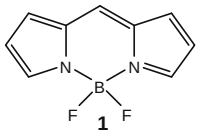
ABSTRACT

Treatment of peracetylated sugar trichloroacetimidates with dipyrromethane in the presence of boron trifluoride diethyl etherate gave peracetylated glycosyl dipyrromethanes in good yields. Regio- and stereo-selectivity of the glycosylation reactions were established.

In the past two decades, a number of methods have been developed for the synthesis of *C*-glycosides, which are useful analogues in organic synthesis, drug design, and glycobiology due to their increased resistance to enzymatic and chemical degradation.[1–12] In the course of our research, fluorophores that are suitable for labeling biomolecules such as carbohydrates and nucleic acids are required. These fluorophores should be relatively insensitive to pH and polarity changes, stable in physiological conditions, and emit intense fluorescence. Additionally, they should allow for easy incorporation into the biomolecule to be labeled. In this regard, 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacenes (BODIPY **1**)[13–16] meet most of these requirements. As such, BODIPY analogues have been used in the labeling of proteins and nucleic acids.[17–20] However, a method that allows for incorporation of BODIPY into carbohydrates via glycosydic linkages remains elusive. In this regard, an approach that enables the preparation of glycosyl dipyrromethanes (**2** where one of the R_1, R_2, or R_3 is a glycosyl substituent) is desirable. These glycosyl dipyrromethanes can be oxidized to dipyrromethene **3** by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or *p*-chloranil,[21,22] and followed by treatment with boron trifluoride diethyl etherate to give carbohydrate-derivatized BODIPY **4** (Scheme 1)



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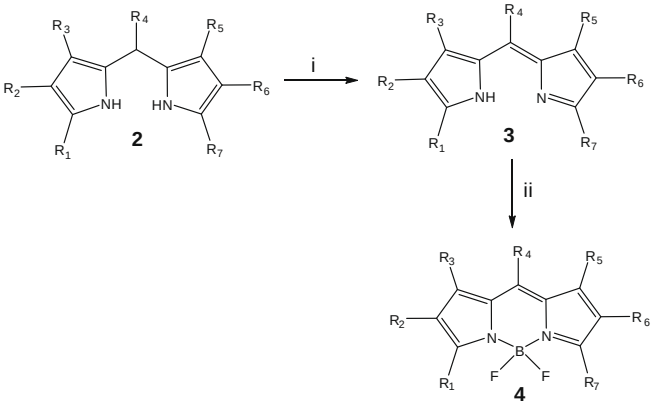
Nucleophilicity of pyrrole and its analogues has been utilized in C–C bond formation.[23–26] This approach is particularly efficient when a good electrophile, such as a carbocation, is present. An activated sugar donor, such as trichloroacetimidate, gives rise to such electrophiles when a Lewis acid, such as boron trifluoride, is present. Therefore combination of suitably protected sugar trichloroacetimidates and pyrrole analogues would enable the synthesis of *C*-glycosides bearing pyrrole substitution. Such a method has been shown to produce glycosyl pyrrole analogues.[27] We now demonstrate the synthesis of glycosyl dipyrromethanes, which can be further transformed into sugar substituted BODIPYs.

Peracetylated monosaccharides (D-glucose, D-galactose, and D-mannose) trichloroacetimidates[28] and dipyrromethane[29] were



Scheme 1. Reagents: (i) DDQ (or Chloranil); (ii) $BF_3{\cdot}Et_2O$, DBU (or NEt_3).

* Corresponding author. Tel.: +1 905 688 5550x3545; fax: +1 905 682 9020.
E-mail address: tyan@brocku.ca (H. Yan).

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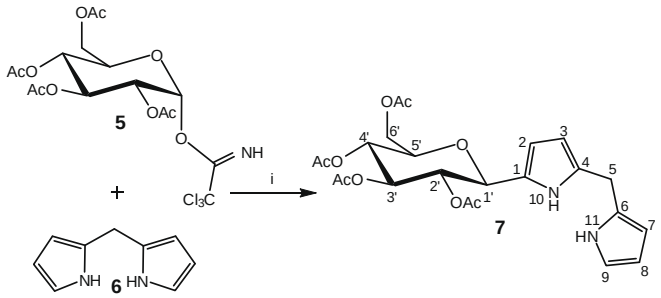

Scheme 2. Reagents and conditions: (i) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −20 °C.

readily prepared using literature methods. When 2,3,4,6-*O*-tetra-acetyl-α-D-glucosyl trichloroacetimidate **5** was mixed with five molar equivalence of dipyrromethane **6** followed by addition of boron trifluoride diethyl etherate (Scheme 2), 1-(2,3,4,6-*O*-tetra-acetyl-β-D-glucosyl) dipyrromethane **7** was isolated in 91% yield after column chromatography.[30] The excess of dipyrromethane was readily recovered by column chromatography.

The glycosylation reaction proceeds in a regio- and stereo-selective fashion for the glucosyl analogue **7**. The NOEs between H-1′ and H-3′, and H-1′ and H-5′ protons, which would not be observable in the α-anomer, suggest that β-*C*-glucoside was obtained. The stereochemistry is also evident by the relatively large coupling constant of 9.8 Hz between H-1′ and H-2′ protons (see Fig. 1).

This glycosylation chemistry was similarly effective in the formation of peracetylated D-galactosyl and D-mannosyl dipyrromethanes (Table 1). The regio- and stereo-selectivity of the *C*-glycosylation were maintained in the case of the D-galactosyl derivative **8**, but α-D-mannosyl dipyrromethane **9** was obtained as the major product in >70% yield, possibly due to neighboring 2′-*O*-acetate participation. The anomeric stereochemistry of the mannosyl analogue is evident based on the following NOE observations: (i) lack of NOEs between H-1′ and H-3′, and H-1′ and H-5′, which were observed in both β-anomers of glucosyl and galactosyl analogues (**7** and **8**), and (ii) the observed NOEs between H-2′ and H-2, H-3′ and H-2, and H-3′ and H-3 (Fig. 2).

The peracetylated glycosyl dipyrromethanes appear to be sensitive to both oxygen and light. They develop light brown and eventually dark colors upon exposure to light and oxygen, but stay virtually unchanged when exposure was avoided. The acetyl

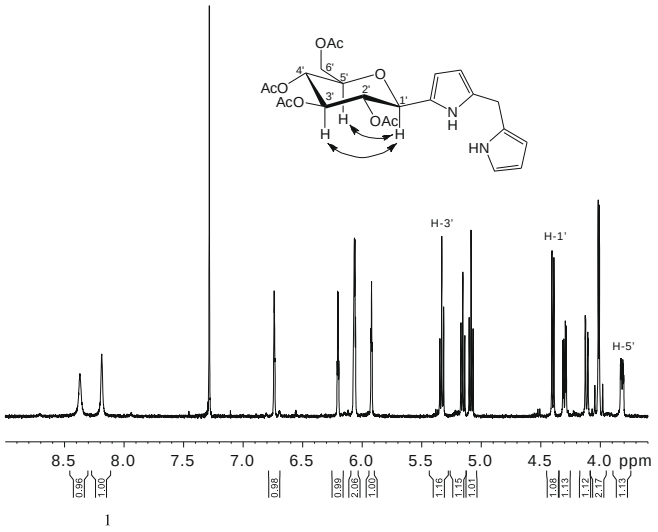

Figure 1. ^{1}H NMR and some NOEs observed in glucosyl dipyrromethane **7**.

Table 1
Isolated glycosylation yields

Entry		Yield (%)
1	Glucosyl dipyrromethane **7**	91[a]
2	Galactosyl dipyrromethane **8**	87[a]
3	Mannosyl dipyrromethane **9**	72[b]

[a] β-Anomer.
[b] α-Anomer.

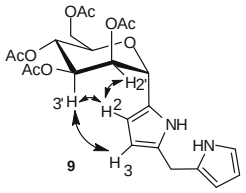

Figure 2. Selected NOEs observed in mannosyl dipyrromethane **9**.

groups were readily removable by treatment with sodium methoxide in methanol when required.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.002.

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30. 2,3,4,6-*O*-Tetraacetyl-D-glucosyl-trichloroacetimidate **5** (0.500 g, 1.017 mmol) and dipyrromethane **6** (0.730 g, 4.99 mmol) were co-evaporated with dry toluene (10 ml) and re-dissolved in dry dichloromethane (15 ml). The solution was cooled to −20 °C and boron trifluoride diethyl etherate (82 μl, 0.65 mmol) was added. After 20 min, the products were partitioned between dichloromethane (30 ml) and saturated aqueous sodium hydrogen carbonate (30 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel. The appropriate fractions, which were eluted with dichloromethane–methanol (99:1 v/v), were combined and concentrated under reduced pressure to give 1-(2,3,4,6-*O*-tetraacetyl-β-D-glucosyl)dipyrromethane **7** as a pale yellow glass (0.440 g, 91%). R_f: 0.52 (95:5 v/v dichloromethane–methanol). Recrystallization of this material from aqueous methanol gave a colorless solid. Mp 67–68 °C. Found, in material recrystallized from aqueous methanol: C, 58.10; H, 5.90; N, 5.75. Calcd for $C_{23}H_{28}N_2O_9$: C, 57.98; H, 5.92; N, 5.88. EI-MS found M = 476.17948. $^{12}C_{30}{}^{1}H_{22}{}^{14}N_1{}^{16}O_5$ requires: 476.17934. δ_H [$CDCl_3$, 600.2 MHz]: 1.92 (3H, s, CH_3), 2.03 (3H, s, CH_3), 2.06 (3H, s, CH_3), 2.10 (3H, s, CH_3), 3.81 (1H, ddd, J = 2.0, 4.7 and 12.0, H-5′), 3.99 (1H, d, J = 17.0, H-5), 4.03 (1H, d, J = 17.0, H-5), 4.11 (1H, dd, J = 1.9 and 12.4, H-6′), 4.30 (1H, dd, J = 4.8 and 12.4, H-6″), 4.40 (1H, d, J = 9.8, H-1′), 5.08 (1H, t, J = 9.7, H-2′), 5.15 (1H, t, J = 9.7, H-4′), 5.33 (1H, t, J = 9.6, H-3′), 5.92 (1H, t, J = 2.8, H-2), 6.06 (2H, m, H-3 and H-7), 6.20 (1H, dd, J = 2.8 and 5.8, H-8), 6.73 (1H, dd, J = 2.5 and 4.0, H-9), 8.19 (1H, br, NH_10), 8.37 (1H, br, NH_11). δ_C [$CDCl_3$, 150.9 MHz]: 20.6 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 26.5 (CH_2, C-5), 62.6 (C-6′), 68.5 (C-4′), 71.4 (C-2′), 73.6 (C-3′), 74.7 (C-1′), 76.1 (C-5′), 106.0 (C-3 or C-7), 107.2 (C-2), 108.4 (C-8), 109.0 (C-3 or C-7), 117.1 (C-9), 124.8, 128.8, 130.4, 169.5 (OAc), 169.6 (OAc), 170.2 (OAc), 170.8 (OAc).