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DICHLOROPHENYLBORANE, A NEW REAGENT FOR THE PREPARATION OF 2-PHENYL-4H-1,3,2-BENZODIOXABORINS

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Abstract: A novel approach in the preparation of 2-phenyl-4H-1,3,2-benzodioxaborin using dichlorophenylborane was developed. The method was applied to the synthesis of cannabinoids via an orthoquinone-methide intermediate generated from the benzodioxaborins.

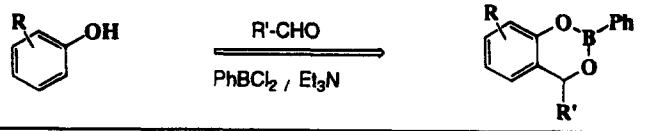
The synthesis of 2-phenyl-4H-1,3,2-benzodioxaborin was first reported by Peer[1] using phenol and paraformaldehyde in the presence of phenylboronic acid and an acid catalyst in refluxing benzene. The method was later improved by Nagata[2] and coworkers using toluene as solvent and the method was extended to a variety of aldehydes. The dioxaborin thus prepared provides a facile preparation of orthohydroxyalkyl phenol.

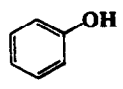
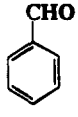
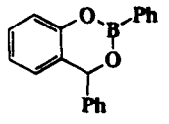
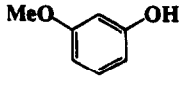
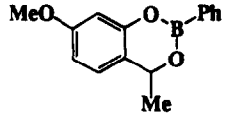
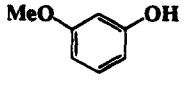
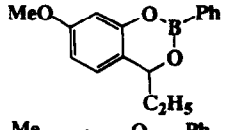
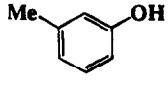
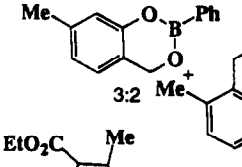
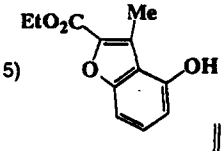
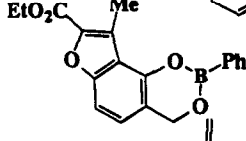
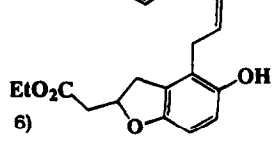
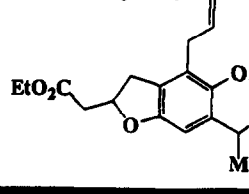
The usefulness of the dioxaborin was exploited further by Lau[3] to prepare orthoalkyl, ortho-thioalkyl and ortho-alkoxyalkyl phenols. Recognizing that the dioxaborin may serve as an orthoquinone-methide precursor, various dioxaborins were prepared which, under thermolytic condition, generated the ortho-quinone methide intermediate that was trapped by various dienophiles inter- and intramolecularly to give various substituted chromans.[4] The methodology was applied by Lau[4] and Murphy[5] to the synthesis of analogs of hexahydrocannabinols. Herein, we would like to report a new and milder method for the preparation of 2-phenyl-4H-1,3,2-benzodioxaborin using dichlorophenylborane and its application to the synthesis of cannabinoids such as analogs of HHC and THC.

The procedure for the preparation of dioxaborins developped by Nagata and Peer using phenylboronic acid under reflux conditions in toluene works well for most aldehydes but is quite harsh and unsuitable for aldehydes prone to polymerization. It is therefore desirable to develop a milder alternative method. It was found that dichlorophenylborane may be used at 0°C or room temperature to generate the dioxaborin from the corresponding phenol and aldehyde. A stoichiometric amount of dichlorophenylborane was added to a solution of phenol, triethylamine and (0.1 equivalent) DMAP in CH_2Cl_2 at 0°C. After 15 minutes, the aldehyde was added. The reaction occured at 0°C or room temperature depending on the substrate. The results are summarized in Table 1. Phenol (entry 1) and benzaldehyde under standard conditions gave 70% yield of desired dioxaborin after 20 h at room temperature. Reaction of 3-methoxy-phenol (entry 2) with acetaldehyde occured at 0°C in 2 h to give a 59% yield of a single dioxaborin, whereas the same reaction using the phenylboronic acid method gave no desired product. In the case of propionaldehyde (entry 3), reaction occured at 0°C to give 98% isolated yield of a single product after 1.5 h. Reaction of 3-methylphenol with paraformaldehyde (entry 4) gave a mixture of para- and ortho-

regioisomers in a 3 to 2 ratio in 64% combined yield. The more complex and electron poor benzofuranol (entry 5) also reacted with paraformaldehyde, although slowly, giving 40% yield of the expected dioxaborin. Entry 6 exemplifies the mildness and functional group compatibility of this procedure. This substituted dihydrobenzofuranol reacted at 0°C with acetaldehyde in only 2 h, to give a novel dioxaborin in 75% yield. Overall, the results indicate that electron rich phenols like 3-methoxyphenol tend to be more reactive and the method is advantageous over the phenylboronic acid method in most cases.

TABLE 1 PREPARATION OF 2-PHENYL-4H-BENZODIOXABORINS

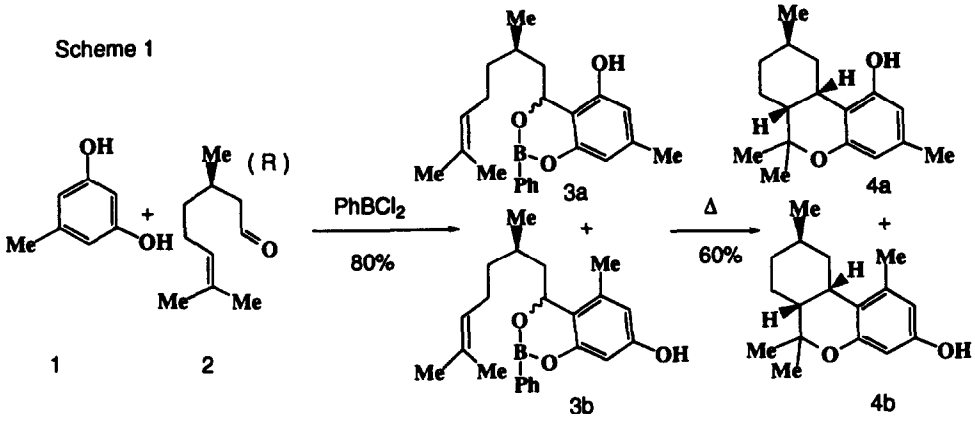


ENTRY	PHENOL	ALDEHYDE	T°,TIME	PRODUCTS	YIELD[a]
1)			RT, 3h		70%
2)		CH_3CHO	0°, 2h		59%
3)		CH_3CH_2CHO	0°,1.5h		98%
4)		$(CHO)_n$	RT, 3h		64%
5)		$(CHO)_n$	RT,69h		40%
6)		CH_3CHO	0°, 2h		75%

a) Yield of isolated products, fully characterized by ^1H NMR,IR and combustion analysis.

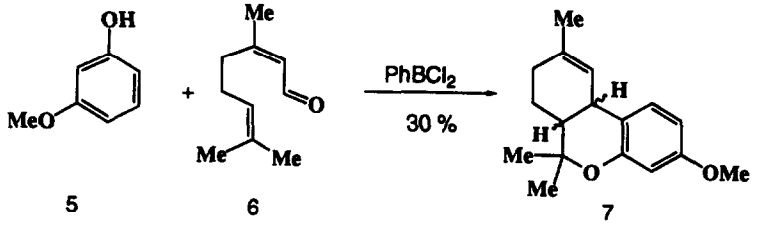
Having demonstrated the viability of the new method in the formation of benzodioxaborin, the method was then applied to the synthesis of cannabinoids. It was shown[4] that orcinol (**1**) reacted with R(+) citronellal **2** in the presence of phenylboronic acid in refluxing toluene to give a 3:2 mixture of dioxaborin regioisomers **3a**, and **3b** in 82% yield. With the new procedure using dichlorophenylborane (Scheme 1), a 1:5 ratio was obtained in 80% yield. Thermolysis of the regioisomers, as a mixture or individually, in benzene at 215°C for 18 h gave the desired HHC analogs **4a**, and **4b** in 60% combined yield.

Scheme 1



Previous attempt to prepare THC analogs using citral **6**, 3-methoxy phenol **5** with phenylboronic acid in refluxing toluene failed to give any THC analog **7**. Instead only the 7-methoxycannabichromene was isolated in 45% yield[5,6]. Using dichlorophenylborane under standard conditions, citral (**6**) reacted with 3-methoxyphenol **5** to give a 30% yield of a 2:3 mixture (cis:trans) of isomers of 3-methoxy-Δ^9-THC analog **7**[7,8,9] (Scheme 2) .

Scheme 2



In summary, we have shown that dichlorophenylborane may be used for the preparation of 2-phenyl-4H-1,3,2-benzodioxaborins. This reagent can be used in the synthesis of a number of analogs of cannabinoids via an intramolecular [4+2] cycloaddition of orthoquinone-methide intermediate generated from the corresponding 2-phenyl-1,3,2-benzodioxaborins.

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7. Compound 7 (cis+trans), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2 (d, 1H, J = 9Hz), 7.12 (d, 1H, J = 12 Hz), 6.48 (dd, 1H, J_1 = 11Hz, J_2 = 2.6Hz), 6.36 (d, 1H, J = 2.6Hz), 6.32 (d, 1H, J = 3.6Hz), 5.9 (br s, 1H), 3.74 (s, 3H), 3.48 (br t, 1H), 3.15 (br d, 1H, J = 11Hz), 1.5-2.2 (m, 5H), 1.71 (br s, 3H), 1.74 (br s, 3H), 1.44 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.70, 152.79, 134.79, 125.92, 107.36, 106.46, 101.77, 101.60, 77.4, 55.14, 44.65, 33.54, 31.64, 27.97, 25.54, 23.52, 19.6. HREIMS calcd for $C_{17}H_{22}O_2$ (M+1): 259.16980; found 259.16968.
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