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High yield protection of alcohols, including tertiary and base sensitive alcohols, as benzhydryl ethers by heating with diphenyldiazomethane in the absence of any other reagent

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This Letter marks the 80th birthday of Professor E. J. Corey

Abstract

A protecting group that can be introduced efficiently without the need for any acid or base catalysis and which is not prone to acid or base catalysed migration is a significant advantage for many syntheses. Benzhydryl [diphenylmethyl] ethers of sugar lactones are formed in high yield under neutral conditions when the corresponding alcohol is heated with diphenyldiazomethane in an inert solvent such as acetonitrile or toluene; this allows the easy protection of base sensitive and highly hindered tertiary alcohols in the absence of any other reagents.

For a long time, benzyl and silyl[1] ethers have been the most common and versatile protecting groups for alcohols.[2] There are, however, limitations in their protection of hydroxyl groups in base sensitive compounds; the introduction of benzyl ethers is almost always under base catalysis[3] or via trichloroacetimidates in the presence of triflic acid.[4] A major disadvantage of silyl ethers is the potential migration and base catalysed epimerisation during their introduction;[5] migration in subsequent reaction products from the reduction of lactones, as in the preparation of imino sugars,[6] also causes substantial practical problems.

Benzhydryl [diphenylmethyl] protecting groups have been used to protect a wide variety of functional groups such as sulfonamides,[7] amines, amides and peptides[8] and even uracils.[9] Benzhydryl esters are commonly prepared by reaction with diphenyldiazomethane,[10] diphenylmethanol[11] or tribenzhydryl phosphate[12] under acidic conditions. The benzhydryl group has been relatively rarely used for the protection of alcohols; diphenylmethyl ethers are usually prepared by treatment of an alcohol with diphenylmethanol under acid conditions,[13,14] including acid ion exchange resins[15] and silica gel-supported acid.[16] The effect on anomeric stereocontrol of *O*-alkylation of mannopyranose with diphenylmethyl trichloroacetimidate has been studied.[17]

The use of the uncatalysed decomposition of diaryldiazomethanes in carbohydrate protection has been minimal;[18] the major investigations hitherto have been on the regioselective monoalkylations of diols in the presence of catalytic amounts of tin(II) chloride.[19,20] Mechanistic studies[21] of the formation of the benzhydryl ether **5** from

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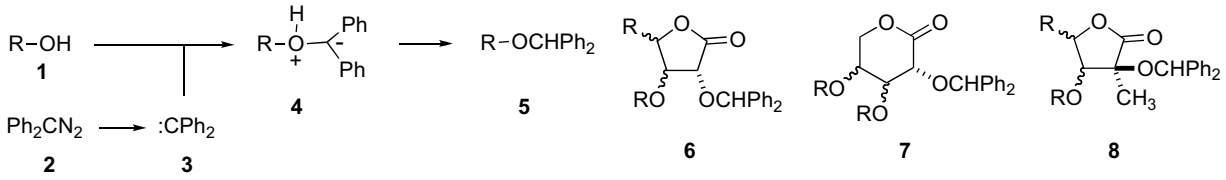
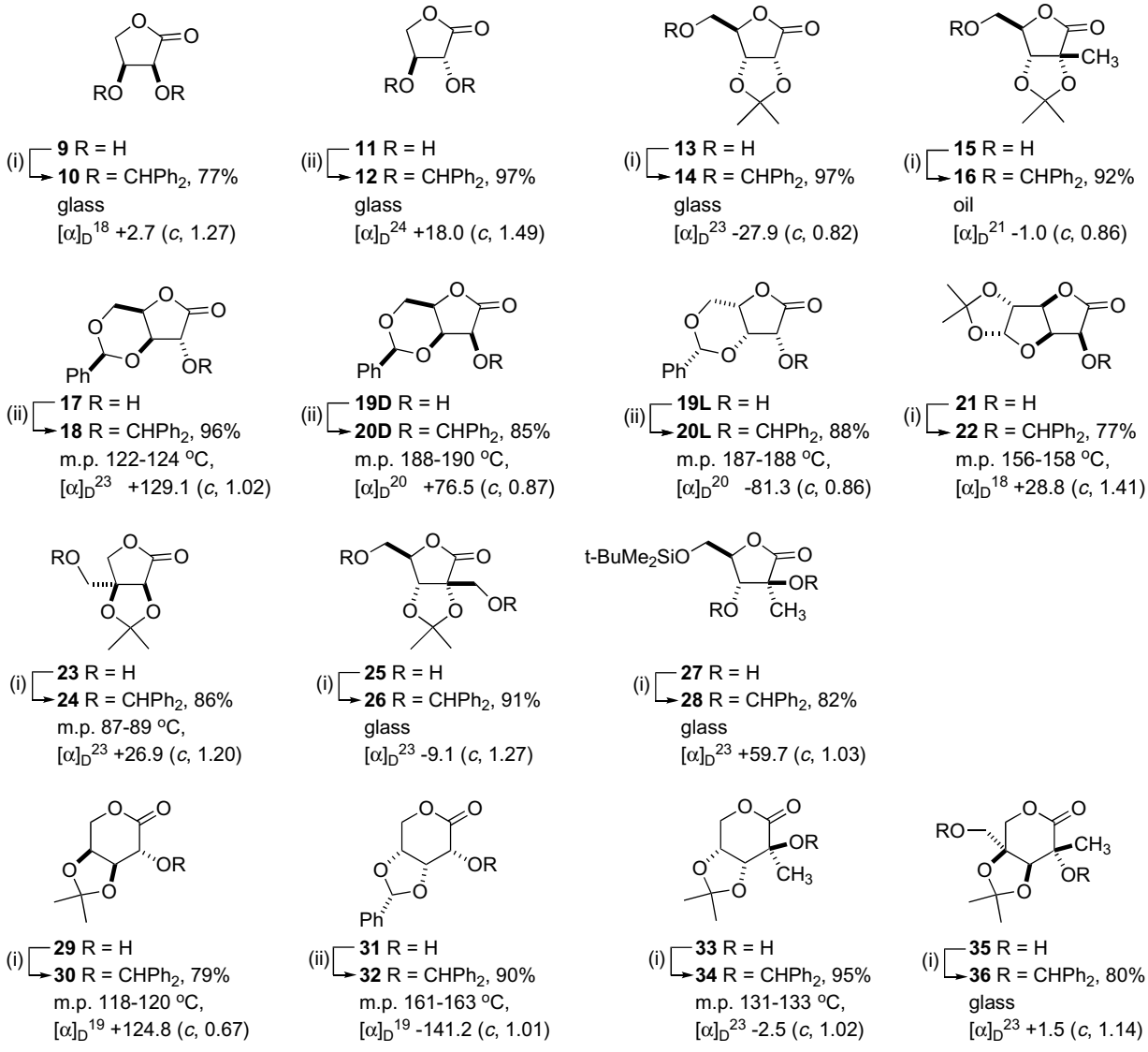


Scheme 1. Benzhydryl protection of alcohols.

an alcohol **1** with diphenyldiazomethane **2**[22] are compatible with diphenylcarbene **3** undergoing a nucleophilic addition reaction with the alcohol to form an ylide structure **4** (Scheme 1).[23]

This Letter describes the protection with the benzhydryl group under neutral conditions of hydroxyl groups in sugar lactones [such as γ- and δ-lactones **6** and **7**] which are sensitive to base catalysed epimerisation and elimination reactions; the efficient protection of hindered tertiary alcohols [such as **8**] can also be achieved. Although this procedure is likely to be particularly useful in the protection of base sensitive and highly hindered alcohols, the ease of introduction of benzhydryl ethers by this method may have attractions in the protection of a wide cohort of hydroxyl functionalities. Diphenyldiazomethane **2** can be obtained on any scale by the oxidation of benzophenone hydrazone with mercuric oxide;[24] under more environmentally friendly conditions, an alternative oxidising agent is Magtrieve™.[25]

The protection of hydroxyl groups in some 15 carbohydrate lactones by heating with diphenyldiazomethane **2** in either toluene or acetonitrile in average yields of over 85% is shown below (Scheme 2).[26]



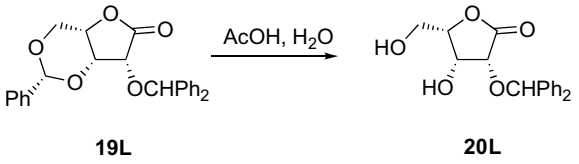
Scheme 2. Reagents and conditions: (i) Ph_2CN_2, toluene, reflux; (ii) Ph_2CN_2, MeCN, reflux.

A series of γ-lactones were protected. L-Erythrono- **9** and L-threono- **11** lactones gave the fully protected ethers **10** and **12** on heating with **2** in toluene and acetonitrile, respectively; attempted protection of such lactones by benzylation under basic conditions affords low yields of dibenzyl ethers, probably due to the acidic hydrogen at C-2. Similarly, efficient protection of the C-5 hydroxyl group in the acetonides of D-ribonolactone **13** and of 2-*C*-methyl-D-ribonolactone **15** was achieved by heating with **2** in toluene to give **14** and **16** in 97% and 92% yields.

The acidity of the proton at C-2 in carbohydrate lactones creates problems for protection under base catalysed conditions. Protection of the D-xylono- **17** as well as both enantiomers of the lyxono- **19D** and **19L** lactones with **2** gave excellent yields of the corresponding ethers **18**, **20D** and **20L**; the structure of **20D** was firmly established by X-ray crystallographic analysis, confirming that epimerisation had not occurred during the protection.[27] Additionally, the readily available acetonide of glucuronolactone **21** was protected efficiently as the corresponding benzhydryl ether **22**. The convenient protection of hindered neopentyl alcohols can be illustrated by the conversion of the L-apiono- **23** and D-hamamelono- **25** lactones to the corresponding mono- **24** and di- **26** benzhydryl ethers. Similarly, both the secondary and tertiary alcohols in the silylated 2-*C*-methyl lactone **27** were protected in excellent yield as the dibenzhydryl ether **28**. Carbohydrate δ-lactones are notoriously vulnerable to base treatment. However, both the L-arabinono- **29** and D-ribono- **31** 1,5-lactones gave excellent yields of the corresponding benzhydryl ethers **30** and **32**.

Toluene was an excellent solvent for the reaction with the decomposition of **2** [as indicated by the disappearance of the purple colour] completed within an hour. When the substrate lactones were not soluble in toluene, then acetonitrile was an alternative solvent in which the reaction time for the decomposition took several hours. Representative procedures for the diphenyldiazomethane **2** protections in both toluene[28] and acetonitrile[29] are given.

The protecting group in benzhydryl ethers and amines can be cleaved by hydrogenolysis,[30,31] acid hydrolysis[32,33] or oxidation;[34] more specialised methods, such as the ozone cleavage of benzhydryl aziridinyl esters, can be used where the circumstances warrant.[35] Acetonides or benzylidene acetals can be removed selectively without affecting the benzhydryl ether by acid hydrolysis; for example, the fully protected lyxonolactone **19L** on treatment with 80% aqueous acetic acid gave the benzhydryl lactone **20L** {oil, $[\alpha]_D^{20}$ +24.3 (*c*, 1.81)} in 87% yield (Scheme 3). This allows an efficient route to the protection of C-2 of a 1,4-lactone, a hitherto difficult transformation to achieve.



19L **20L**

Scheme 3. Partial deprotection of lactones.

In summary, this Letter reports the highly efficient protection of a series of base sensitive and/or highly hindered alcohols under neutral conditions. Although all the examples in this Letter are of sugar lactones, it is likely that the ease of introduction of the protecting group and its efficient removal by acid or hydrogenolysis will make this procedure of value in other circumstances. It is noteworthy that more than half of the ethers prepared were readily crystallised on their first preparation. The preparation of novel monosaccharides, sugar amino acids and imino sugars using the intermediates prepared in this Letter will be reported in due course.

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28. *In toluene*. Ph_2CN_2 **2** (1.012 mg, 5.22 mmol) was added to a solution of the L-arabinono-1,5-lactone **29** (555 mg, 2.95 mmol) in toluene (60 mL) at 90 °C. The reaction mixture was stirred at reflux for 1 h 15 min, after which time the purple colour had changed to yellow and TLC analysis (3:1, cyclohexane/ethyl acetate) showed complete conversion of the starting material (R_f 0.03) to one major product (R_f 0.23). The reaction mixture was concentrated in vacuo and the residue was purified by flash column chromatography (cyclohexane/ethyl acetate) to afford benzhydryl acetonide **30** (862 mg, 79%). Mp 118–120 °C; $[\alpha]_D^{19}$ +124.8 (*c*, 0.67, $CHCl_3$); ν_{max} (thin film): 1765 (s, C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.35, 1.42 (3H × 2, s × 2, CH_3 × 2), 4.16 (1H, d, H2, $J_{2,3}$ 3.0), 4.36 (1H, dd, H5, $J_{5,4}$ 2.3, $J_{5,5'}$ 12.2), 4.56 (1H, dt, H4, $J_{4,5'}$ 2.3, $J_{4,3}$ 7.5), 4.62 (1H, dd, H3, $J_{3,2}$ 3.0, $J_{3,4}$ 7.5), 4.77 (1H, dd, H5′, $J_{5',4}$ 2.3, $J_{5',5}$ 12.2), 5.66 (s, 1H, Ph_2CH), 7.27–7.40 (10H, m, ArC*H*); δ_C ($CDCl_3$, 100 MHz): 24.1, 26.0 (2 × CH_3), 67.6 (C5), 71.2 (C4), 73.8 (C2), 75.0 (C3), 82.8 (Ph_2CH), 110.5 (Me_2C), 126.77, 127.67, 127.85, 128.40, 128.45, 128.50, 128.79 (10 × Ar*C*H), 139.35, 140.75 (2 × ArC), 167.82 (C1).
29. *In acetonitrile*. Ph_2CN_2 **2** (4.13 g, 21.3 mmol) was added to a solution of the benzylidene-L-lyxono-1,4-lactone **19L** (3.08 g, 14.2 mmol) in acetonitrile (75 mL) at 70 °C. The reaction mixture was stirred at reflux for 18 h, after which time the purple colour had changed to yellow. TLC (3:1, cyclohexane/ethyl acetate) showed the formation of one major product (R_f 0.40), with remaining unreacted starting material (R_f 0.06). A further portion of Ph_2CN_2 **2** (3.21 g, 16.5 mmol) was added and the solution stirred at reflux for 18 h; TLC showed complete consumption of the starting material. The solvent was removed in vacuo and the residue was purified by column chromatography (cyclohexane/ethyl acetate) to give the benzhydryl protected lactone **20L** (4.63 g, 88%). Mp 187–188 °C; $[\alpha]_D^{20}$ −81.3 (*c*, 0.86 in $CHCl_3$); ν_{max} (thin film): 1787 (s, C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 3.99 (1H, ddd, H4, $J_{4,5'}$ 1.3, $J_{4,5}$ 2.0, $J_{4,3}$ 2.3), 4.04 (1H, dd, H5, $J_{5,4}$ 2.0, $J_{5,5'}$ 13.6), 4.26 (1H, d, H2, $J_{2,3}$ 4.0), 4.42 (1H, d, H5′, $J_{5',5}$ 13.6), 4.52 (1H, dd, H3, $J_{3,4}$ 2.3, $J_{3,2}$ 4.0), 5.42 (1H, s, PhC*H*), 5.79 (1H, s, Ph_2CH), 7.18–7.43 (15H, m, ArC*H*); δ_C ($CDCl_3$, 100 MHz): 66.4 (C5), 69.6 (C4), 72.7 (C3), 75.5 (C2), 83.0 (Ph_2CH), 98.8 (Ph*C*H), 126.3, 127.4, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 129.2 (15 × Ar*C*H), 136.9 (ArC), 140.2, 140.6 (ArC), 172.9 (C=O).
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