Benzyl Trichloroacetimidate, a Versatile Reagent for Acid-catalysed Benzylation of Hydroxy-groups

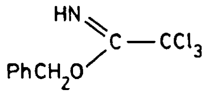
By Tommy Iversen and David R. Bundle*
(*Division of Biological Sciences, National Research Council of Canada, Ottawa, Ontario* K1A OR6)

Summary Benzyl trichloroacetimidate reacts with hydroxyl-groups under acid catalysis to give the corresponding benzyl ethers in good yield; acid-labile protecting groups such as acetals are able to survive the reaction conditions.

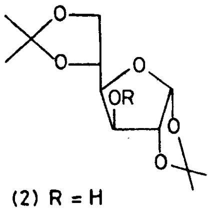
Alkyl and aryl trichloroacetimidates are known to undergo Lewis acid-catalysed reaction to give the corresponding *N*-alkyl or aryl trichloroacetamides *via* ionic intermediates.[1] Recently glycosyl trichloroacetimidates have been employed in glycoside synthesis,[2] and since benzyl trichloroacetimidate (**1**) is readily available[3] a possible route to benzyl ethers was evident.

The benzyl ether protecting group has considerable synthetic potential, particularly in carbohydrate chemistry. Typical benzylation conditions (benzyl bromide, sodium hydride in dimethylformamide[4]) are strongly alkaline and alkali-labile protecting groups are lost. For this reason, benzyl trifluoromethanesulphonate (triflate)[5,6] was introduced to permit benzylation under neutral conditions, which are compatible with groups such as acetate esters. Thus benzylation conditions which preserve the integrity of alkali- and acid-labile protecting groups are of considerable synthetic potential.

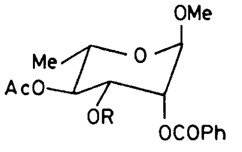
Benzylation of compounds (**2**)—(**4**) by trichloroacetimidate in hexane–methylene dichloride solution using catalytic amounts of triflic acid gave good yields of the corresponding mono-benzyl ethers (**5**)—(**7**) (Table). The three compounds, (**2**)—(**4**) were chosen to provide isolated



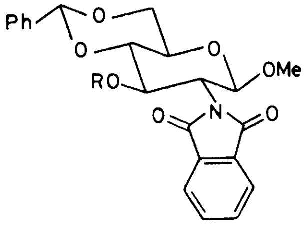
(1)



(2) R = H
(5) R = CH_2Ph



(3) R = H
(6) R = CH_2Ph



(4) R = H
(7) R = CH_2Ph

hydroxyl-groups of varying reactivity. In addition compounds (**2**) and (**4**) possess acid-labile isopropylidene and benzylidene acetal functions, whilst compounds (**3**) and (**4**) have alkali-labile ester and imide functionalities. In a typical experiment, triflic acid (catalytic amounts, <*ca.* 0·05 ml) was added to a stirred solution of the selectively blocked sugar (1·0 mmol) and benzyl trichloroacetimidate (2·0 mmol) in cyclohexane–methylene dichloride (2 : 1; 10 ml). The reaction was left for 18 h at room temperature prior to work-up in the usual manner. Acids other than triflic acid may be used as catalyst but in such cases, as with boron trifluoride–diethyl ether for example, reaction mixtures were less clean.

TABLE. Benzylation of compounds (**2**)—(**4**).

Starting material	Product	Isolated yield/%	Rotation
(**2**)[a]	(**5**)	82	$[\alpha]-21{\cdot}8°$ (c 1·0, EtOH)[b]
(**3**)[c]	(**6**)[d]	92	$[\alpha]_D^{20}+50{\cdot}4°$ (c 1·0, $CHCl_3$)
(**4**)[d]	(**7**)[d]	98	$[\alpha]_D^{20}+66{\cdot}2°$ (c 1·0, $CHCl_3$)

[a] O. Th. Schmidt, *Methods Carbohydr. Chem.*, 1963, **2**, 318. [b] Lit. $[\alpha]_D-26{\cdot}9°$, ethanol (K. Freudenberg, H. V. Hochstetter, and H. Engels, *Chem. Ber.*, 1925, **58**, 666). [c] T. Iversen and D. R. Bundle, *J. Org. Chem.*, in the press. [d] New compounds, for which elemental analyses and n.m.r. data were in full accord with the assigned structures.

Benzyl trichloroacetimidate is particularly well suited to the type of benzylations described here. Since reaction conditions are compatible with a variety of alkali- and acid-sensitive protecting groups the procedure should find general application in synthetic chemistry.

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[1] F. Cramer and N. Hennrich, *Chem. Ber.*, 1961, **94**, 976.
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[5] R. U. Lemieux and T. Kondo, *Carbohydr. Res.*, 1974, **35**, C4.