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Reactivity of Glycopyranosyl Trichloroacetimidates with Air-oxidised Samarium Diiodide in Tetrahydrofuran

Matteo Adinolfi, Gaspare Barone, Alfonso Iadonisi*[1], Rosa Lanzetta

Dipartimento di Chimica Organica e Biologica, Università di Napoli "Federico II"
Via Mezzocannone 16, I-80134 Napoli, Italy

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Abstract: Glycopyranosyl trichloroacetimidates react with SmI_2/O_2/THF to give 4-iodo-*n*-butyl 1,2-*trans*-glycopyranosides. Good to high yields can be obtained from 2α-*O*-acylated trichloroacetimidates. With armed or *manno* substrates competitive formation of α-glycopyranosyl iodides occurs.

Keywords: Samarium and compounds; Glycosidation.

In a recent work [1], we have shown that species obtained by the air oxidation of SmI_2 (formulated as "$(SmI_2)_2O$") [2] can induce a direct conversion of 2,3,4,6-tetra-*O*-benzyl aldohexoses into 1,3,4,5-tetra-*O*-benzyl ketohexoses. For this transformation we proposed a possible mechanism involving Lewis acid and base roles played by the lanthanidic center and the oxygen of the reagent, respectively. We devised that these properties could cooperate in the possible activation of anomeric trichloroacetimidates [3] in view of a possible use of this Sm^{3+} species in a mild approach for the synthesis of glycosides. The samarium center could activate the leaving trichloroacetimidate group while the basic site could act as proton scavenger. In our first experiments we have investigated the behaviour of peracetylated glycosyl trichloroacetimidates in the presence of the lanthanidic reagent and of a simple potential glycosyl acceptor such as methanol. As a matter of fact, when tetra-*O*-acetyl-D-glucopyranosyl and tetra-*O*-acetyl-D-galactopyranosyl trichloroacetimidates (**1** and **6**, resp.) were treated in THF with stoichiometric amounts of "$(SmI_2)_2O$" and MeOH at room temperature (Table, entries 1 and 11) we surprisingly observed the fast formation in good yields of 4-iodo-*n*-butyl β-glycopyranosides **9** and **14**, respectively, together with minor amounts of the corresponding methyl 1,2-*ortho*-esters. The formation of the two products can be explained (Scheme) assuming that the anomeric oxocarbenium ion resulting from the activation of the trichloroacetimidate leaving group can evolve to give an *ortho*-ester through a dioxocarbenium ion intermediate (route a). Alternatively (route b), both carbenium ions can be attacked by a THF solvent molecule from the β-side (due to the neighbouring participation of the 2-*O*-acyl group and/or to reverse anomeric effect [4]). The THF ring of the β-adduct can

[1] Fax: +39 0815521217; e-mail: iadonisi@unina.it

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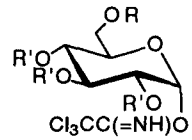
thus be opened by iodination (the behaviour of air-oxidised samarium diiodide as an iodinating reagent is well known [2]).



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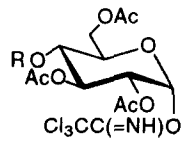
2 R = TBDPS R' = Ac
3 R = Tr R' = Ac
4 R = R' = Piv
8 R = R' = Bn



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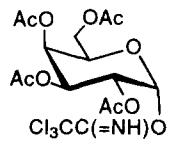

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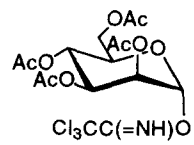

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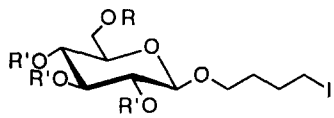

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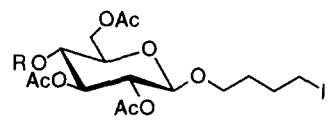
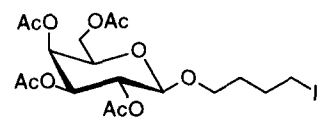
10 R = TBDPS R' = Ac
11 R = Tr R' = Ac
12 R = R' = Piv



13 R = 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl



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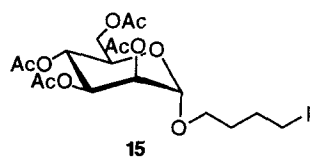

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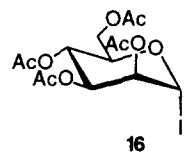

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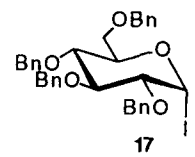

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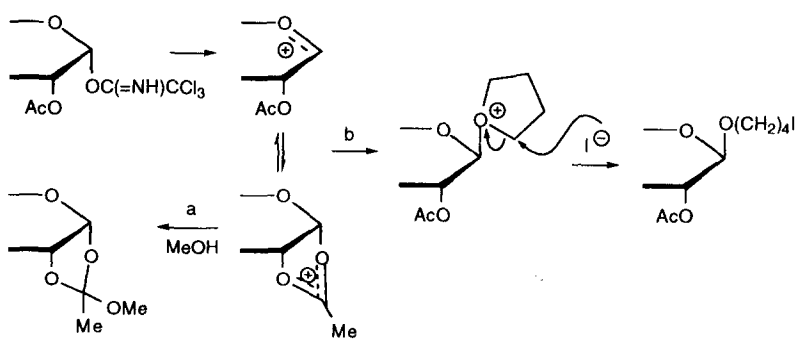
Although these reactions did not afford methyl glycosides, the high yielding formation of 4-iodo-*n*-butyl glycosides looked synthetically interesting because of the mild insertion at the anomeric position of an aglycon possessing a versatile functionality at its other end. Because of this functionalization, these spacer-connected monosaccharides can be considered as potential building blocks for the preparation of glycoconjugates. In order to investigate the generality of this reactivity, other 2-*O*-acylated glucopyranosyl trichloroacetimidates (**1**, **3**, and **4**) were submitted to the reaction and in all cases (entries 3, 6 and 8) the predominant and stereoselective formation of 4-iodo-n-butyl β-glucopyranosides was observed.

Scheme



Detectable amounts of the 4-iodo-*n*-butyl glycopyranoside **15**[2] were also yielded in the case of the *manno* derivative **7**, the major product being α-mannopyranosyl iodide **16** [5] (entry 13). While the 1,2-*trans* configuration of **15** was that expected on the basis of neighbouring participation, the minor trend of the *manno* derivative to afford iodobutyl glycoside could be explained by considering that reverse anomeric effect disfavours the addition of a THF molecule from the α-side of the anomeric carbenium ion [4].

Table

Entry	Starting compound	Alcohol	Time	Products and yields (%)[a] 4-iodo-*n*-butyl glycopyranoside		α-glycosyl iodide	
1	**1**	MeOH (2 eq.)	5 h	**9**	85[b]		
2	**1**	none	15 h	**9**	17		
3	**2**	MeOH (2 eq.)	3 h	**10**	90		
4	**2**	MeOH (0.15 eq.)	4 h	**10**	82		
5	**2**	none	15 h	**10**	51		
6	**3**	MeOH (2 eq.)	5 h	**11**	79[b]		
7	**3**	none	15 h	**11**	24		
8	**4**	MeOH (2 eq.)	20 h	**12**	81		
9	**5**	MeOH (0.15 eq.)[c]	36 h	**13**	73		
10	**5**	none	36 h	**13**	27		
11	**6**	MeOH (2 eq.)	2 h	**14**	72[b]		
12	**6**	*i*-PrOH (2 eq.)	3 h	**14**	82		
13	**7**	MeOH (2 eq.)	5 h	**15**	18[b]	**16**	50
14	**7**	*i*-PrOH (2 eq.)	7 h	**15**	26	**16**	65
15	**7**	*t*-BuOH (100 eq.)	2 h	**15**	28	**16**	65
16	**8**	none	2 h			**17**	70

[a] Isolated yields are listed for 4-iodo-*n*-butyl glycosides. Yields of glycosyl iodides were determined by ^{1}H NMR of the crude reaction product. All new compounds were indentified by spectroscopic methods (^{1}H and ^{13}C NMR).

[b] Minor amounts of methyl 1,2-*ortho*-esters were identified in the ^{1}H NMR spectrum of the crude reaction product: entry 1, <5%; entry 6, ca. 10%; entries 11 and 13, ca. 15%.

[c] Extensive deacetylation occurs in presence of 2 eq. of MeOH.

An interesting feature of the reaction of glycopyranosyl trichloroacetimidates with SmI_2/O_2/THF is that the rate of formation of the spacer-connected monosaccharides is strongly increased by the presence of an alcohol in the reaction mixture. Actually, when compound **1** was reacted with SmI_2/O_2 in absence of methanol, after 15 hours the starting product was recovered unchanged but for a 17% conversion into **9** (entry 2). Similar results were obtained with trichloroacetimidates **2**, **3**, and **5** (entries 5, 7, and 10). On the other hand, catalytic amounts of methanol were found to be sufficient to give even high yields (entries 4, 9), although longer reaction times were required. Alcohols less nucleophilic than methanol such as *i*-PrOH and *t*-BuOH turned out to be effective in depressing the formation of *ortho*-esters, thus improving the yields of iodobutyl glycosides and, in the case of *manno* derivative **7**, of glycosyl iodide (entries 12, 14, 15). The presence of alcohol was found unnecessary to the activation of the "armed" [6] tetra-*O*-benzyl glycosyl trichloroacetimidate **8**, which however gave mainly α-glycosyl iodide **17** [7] (entry 16) in keeping with the unoperativity of a

[2] The α-configuration at C-1 of **15** was assigned on the basis of the $^1J_{H,C}$ value (173 Hz).

disfavouring neighbouring partecipation by a 2α-*O*-acyl group.

In a typical experiment, the glycopyranosyl trichloroacetimidate was dissolved in a freshly air-oxidised solution of SmI_2 (2.2 eq., 0.1 M in THF). The alcohol promoter (see Table) was added. After stirring at room temperature for the period indicated in the Table (the reaction was monitored by TLC), the mixture was filtered through a short silica gel column to remove samarium species, and evaporated. The residue was analyzed by ^1H NMR. 4-Iodo-*n*-butyl O-glycosides were isolated by silica gel chromatography.

In conclusion, the above results show that a trichloroacetimidate function at the anomeric position of a sugar can be converted under mild conditions to a good leaving group by the action of air-oxidised samarium diiodide in combination with an alcoholic promoter. In tetrahydrofuran, the iodinating property of the reagent leads to the diastereoselective formation of 4-iodo-*n*-butyl 1,2-*trans*-*O*-glycosides. Preferential generation of glycosyl α-iodides has been found to occur with 2-*O*-acyl-*manno* or armed substrates. Use of different Sm(III) species for the usual glycosidation with alcohols is under investigation.

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