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A NOVEL AND CONVENIENT ROUTE TO CYCLIC AND ACYCLIC CARBONATES FROM UNPROTECTED METHYL D-GLYCOSIDES

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Abstract : *Unprotected methyl D-glycosides were selectively acylated by using thiazolidine-2-thione and 2-mercapto-5-methyl-1,3,4-thiadiazole alkoxycarbonyl or carbonyl derivatives. Under suitable conditions the corresponding 6-O-alkoxycarbonyl compounds or the cyclic five or six membered carbonates could be obtained.*

Carbonates of the primary and the secondary hydroxyl groups are useful intermediates in carbohydrate chemistry. Like esters, they can be cleaved by basic hydrolysis but under milder conditions [1]. Moreover selective cleavage of a carbonate in the presence of various other functional groups can be easily achieved [2,3]. Of particular interest are the benzyloxycarbonyl and the allyloxycarbonyl groups that can be cleaved under neutral conditions [3,4]. The latter was recently proven to be a suitable protective group in natural products chemistry [4,5]. It was also found that cyclic carbonates, that are readily cleaved under alkaline conditions, would therefore be more interesting than cyclic ketals and acetals when a glycosidic linkage has to be preserved in the unblocking step [6]. Moreover, cyclic carbonates appeared also as important intermediates for introducing a carbamoyl group in a carbohydrate [7] and for preparing some 1,2-*cis*-glycosides [8].

Partial alkoxycarbonylations and carbonylations of polyhydroxylic compounds are usually run by reaction of carbono-chloridates (chloroformates) and phosgene or its derivatives on previously protected compounds [5,7,9,10]. Although new alkoxycarbonyl donors have been proposed in recent years [11], they have not found extensive applications in selective modifications of unprotected polyols.

To overcome this problem, we report herein a study on selective modifications of free methyl D-glycosides 1-3 in order to prepare their 6-*O*-alkoxycarbonyl derivatives as well as their cyclic carbonates. For this purpose, we have used two methodologies based on i) the use of loose electrophilic ion-pairs capable of reacting on the less hindered hydroxyl, or ii) a selective activation of the more acidic hydroxyl of the substrate to the corresponding more nucleophilic oxyanion. In agreement with previous reports [12,13], we have selected the carbamates **4** and thiocarbamate **6** of 2-mercapto-5-methyl-1,3,4-thiadiazole and the 3-alkoxycarbonyl-thiazolidine-2-thiones **5** as acylating reagents.

Carbamates **4** appear to be very reactive towards alcohols, since they reacted on glycosides **1**, **3** at room temperature (RT) in pyridine without any additional initiator or catalyst (table, runs 1-2), thus affording the 6-*O*-alkoxycarbonyl derivatives **7**, **9** in moderate yields. Results could be further improved when the reaction was performed in DMF using 4-dimethylaminopyridine (DMAP) as a nucleophilic catalyst (runs 3-5). In analogous

conditions, the carbonyldiimidazole substitute **6**, obtained by reacting 2-mercapto-5-methyl-1,3,4-thiadiazole with phosgene [14], carbonylated methyl α-D-mannoside **2** to afford the corresponding 4,6- cyclic carbonate. Such 6-membered sugar carbonates are known to be unstable and had not yet been obtained, to our knowledge, from unprotected sugars. During the course of this work, we were able to isolate it as the diacetate **10** obtained in a one-pot procedure (run 6) [17].

Table - Syntheses of Acyclic 6-Monocarbonates and Cyclic Carbonates of Methyl D-Glycosides

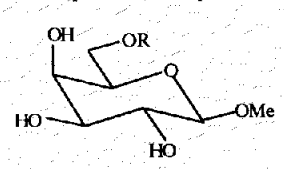
Run	Starting glycoside	Reagent	Conditions				Product [18] (yield %) [b]
			Solvent	Catalyst (equiv.)[a]	Temp. (°C)	Time (hr)	
1	**1**	**4b**	C_5H_5N	-	RT	3	**7b** (33)
2	**3**	**4c**	C_5H_5N	-	RT	4	**9c** (38)
3	**1**	**4b**	DMF	DMAP(0.05)	RT	1.5	**7b** (40)
4	**1**	**4c**	DMF	DMAP(0.04)	RT	2	**7c** (45)
5	**2**	**4b**	DMF	DMAP(0.04)	RT	1.5	**8b** (32)
6	**2**	**6**	DMF	DMAP(0.04)	RT	3	**10** (41)
7	**3**	**5a**	C_5H_5N	NaH (0.2)	RT	2	**9a** (38)
8	**3**	**5a**	C_5H_5N	NaH (0.2) and then DBU (0.25)	RT RT	2 4	 **9a** (42)
9	**2**	**5b**	C_5H_5N	NaH (0.1)	RT	4.5	[c] (45)+ **12** (16)
10	**2**	**4d**	C_5H_5N	NaH (0.2)	90	12	**12** (45)
11	**1**	**5b**	C_5H_5N	NaH (0.1)	RT	6	**11** (85)
12	**1**	**5c**	C_5H_5N	NaH (0.1)	RT	24	**11** (90)

a) Reactions were performed using glycosides **1-3** (2-3 equiv.) and reagents **4-6** (1 equiv.) ; the catalyst amounts were calculated according to substrates.
b) Compounds **7-12** could be extracted along with thiazolidine-2-thione or 2-mercapto-5-methyl-1,3,4-thiadiazole by using our usual procedure [13] for separating them from methyl D-glycosides **1-3**. The residue was then recrystallized to afford compounds **8b** ($CHCl_3$/hexane) and **11** (ethyl acetate) or chromatographied on a Merck 60H column (solvent : ethyl acetate and then ethyl acetate/methanol : 18/1 for compounds **7b-c**, **9a,c** and **12**). Excess of starting materials **1-3** could be recovered when selective extractions using *n*-butanol/ethyl acetate (1/5) and *n*-butanol were performed.
c) The reaction mixture contained three acyclic carbonates (45 % overall yield) along with cyclic carbonate **12**.

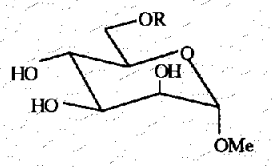
However, with methyl α-D-glucoside **3** the present strategy never afforded carbonates **9** with high yields such as we obtained using the second method [12]. Thus methyl 6-*O*-allyloxycarbonyl-α-D-glucoside **9a** was obtained by reacting the thione **5a** with glucoside **3** in anhydrous pyridine and in the presence of a catalytic amount of NaH (run 7). An additional catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) could slightly improve this yield (run 8). As a matter of fact, thiones **5** did not react within 24 hours at RT in the presence of an electrophilic catalyst such as DMAP, but needed a preliminary activation of an hydroxyl group to an alkoxide.

Under similar conditions, methyl glycosides **1** and **2** having two vicinal *cis* hydroxyl groups gave invariably the corresponding five membered cyclic carbonates. When the reaction of mannoside **2** on carbamate **5b** was achieved at room temperature for 4.5 hours (run 9), the cyclic carbonate **12** was obtained in low yield

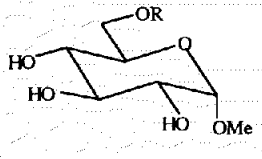
along with a mixture of acyclic alkoxycarbonates containing 30% of the 6-*O*-modified compound **8b**.[19] Nevertheless, the yield of the 2,3-carbonate **12** was improved by using the thiocarbonate **4d**, which possess two better leaving groups, as carbonyl donor at a higher temperature (run 10). Under similar conditions, the cyclic 3,4-carbonate **11** of methyl β-D-galactoside could be isolated in 85-90 % yields in reactions achieved at room temperature and using carbamates **5b-c** as carbonyl donors (run 11, 12). These reactions appear to be the first syntheses of five-membered cyclic carbonates from unprotected methyl glycosides which do not involve the toilsome protection-deprotection methodology [15].



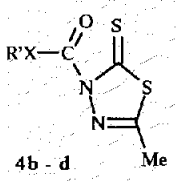
1 R = H
7 R = R'- O - CO -



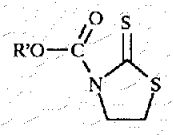
2 R = H
8 R = R'- O- CO -



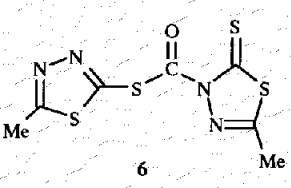
3 R = H
9 R = R'- O- CO -



4b - d

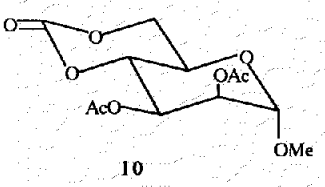


5a - c

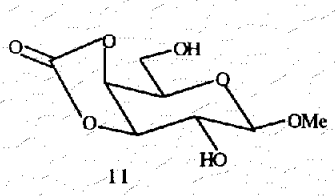


6

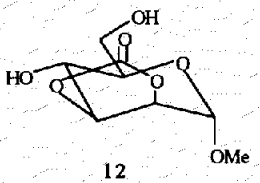
	a	b	c	d
R'X	$H_2C = CH - CH_2 - O-$	$Ph-CH_2-O-$	$Me_2CH - CH_2 - O-$	Et- S -



10



11



12

At this point it was of great interest to discover the path of formation of these cyclic carbonates. Thus when the experiment described in run 11 was achieved at lower temperature (0°C), we observed the formation of 6-*O*-benzyloxycarbonyl compound **7b** that was transformed to cyclic compound **12** at room temperature. In another experiment, compound **7b** in anhydrous pyridine containing 0.1 equivalent of NaH gave the cyclic carbonate **12** within 30 min at room temperature. Although other assays are to be made, it seems from now on that cyclic carbonates **11** and **12** result from isomerizations and cyclisations of the initially formed 6-*O*-alkoxycarbonyl compounds respectively **7** and **8**. Research is presently in progress to explore these isomerizations towards the more-substituted carbonates [16].

Conclusion

This work provides an attractive method for the direct conversion of methyl D-glycosides **1-3** into their acyclic or cyclic carbonates. We are currently trying to apply these reactions to other mono- and oligosaccharides.

Foot notes and References

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14 - Compound **6** was easily prepared by reaction of a solution of 2-mercapto-5-methyl-1,3,4-thiadiazole (purchassed from Janssen Chimica) in CH_2Cl_2 on $COCl_2$ (20 % in toluene ; Fluka) in the presence of pyridine. Reagent **6** ; m.p. 170-176°C ($CHCl_3$) ; yield : 85 %.

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17 - The diacetate **10** was isolated using the following procedure : when the carbonylation was complete, the DMF was eliminated at 0°C by extraction with a mixture of Et_2O-hexane. The residue was then acylated at room temperature within 15 hours (Ac_2O, pyridine).

18 - All new compounds were characterized by infrared and NMR spectra and gave elemental analyses as well as mass spectra consistent with assigned structures.

19 - In run 9, compounds **8b** and **12** were laboriously purified by column chromatography (Merck 60H silica gel ; solvent : ethyl acetate, then methanol/ethyl acetate : 1/50 and then methanol/ethyl acetate : 1/18).

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