Expeditious entry to *C*-alkyl and *C*-aryl pyranoid glycals: reaction of anomeric glycosyl chlorides with organolithiums

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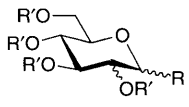
Treatment of ether-substituted glycopyranosyl chlorides with organolithium reagents gives the corresponding *C*-glycals in acceptable to good yields.

Methods for the formation of *C*-glycosides **1** continue to be of considerable interest in carbohydrate chemistry, as well as in organic synthesis.[1] Recent synthetic efforts in this area have focused on the preparation of *C*-glycals **2**[2–11] which might function as precursors for *C*-glycosides by way of the stereoselective functionalization of their enol ether double bond.[3,6c,f,7b,8,9c] Traditionally, the formation of *C*-glycosides has relied on the introduction of carbon nucleophiles at the anomeric position of suitably activated carbohydrate precursors.[1] However, methods for the preparation of *C*-glycals are generally based on the reaction of C-1 metallated glycals with electrophilic counterparts.[2–6] Some recently reported methods for the preparation of *C*-aryl glycals **2b**, which utilize a palladium-mediated cross-coupling for the C–C bond forming step, also necessitate an initial metallation step for the formation of the required C-1 substituted glycal.[7–9] In this context, recent synthetic efforts for the preparation of *C*-aryl glycosides **1b**[12] have been triggered by the antibiotic or antiviral activity that is exhibited by many of the natural products that contain this framework.[13]

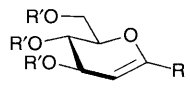
We recently reported the reaction of organolithium compounds with anomeric glycosyl sulfoxides for the formation of glycals.[14] Here, we disclose a novel entry to both *C*-aryl and *C*-alkyl pyranoid glycals, based on the reaction of organolithiums with anomeric glycosyl chlorides **3**. In this strategy, unlike the ones mentioned above, the carbohydrate functions as the electrophilic partner.

We have found that when ether-substituted glycopyranosyl chlorides **3** are treated with an excess of an organolithium reagent, the corresponding *C*-glycals **2** are produced in acceptable to good yields (Table 1).† Thus, the reaction of *manno*-pyranosyl chloride **4**[15]‡ in THF with MeLi (5 equiv.) at room temperature took place in 30 min and afforded, after work-up, *C*-methyl glycal **5a** in 50% yield (Table 1, entry 1). Analogously, treatment of **4** with BuLi, PhLi and even the sterically demanding Bu^{t}Li, resulted in the formation of the corresponding *C*-glycals **5b–d** (entries 2–4).

To gain some additional insight into the scope of the process, *manno*-pyranosyl chloride **6**[16]§ was reacted under the above mentioned conditions with a series of organolithiums. The reactions proceeded successfully, providing the corresponding C-glycosyl compounds **7a–e** (entries 6–10). We next turned our attention to the more synthetically useful benzyl protecting group and, with this aim in mind, chlorides **8** and **10**§ of the *manno* and *gluco* series, respectively, were prepared. Reaction of **8** with BuLi at room temperature led to extensive decomposition (entry 12); however, lowering the reaction temperature to −78 °C led, after 1 h, to the formation of *C*-butylglucal **9a** in 55% yield (entry 11). Analogous behaviour was observed with *gluco*-pyranosyl chloride **10**, which decomposed on treatment with BuLi at room temperature (entry 16), but afforded **9a** at −78 °C (entry 15). On the other hand, reaction of **8** and **10** with PhLi took place at 0 °C to afford the previously described *C*-

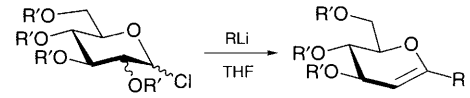


1a R = alkyl
b R = aryl

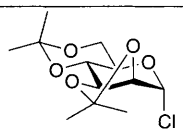
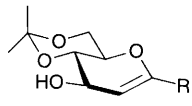
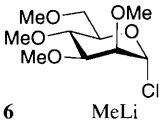
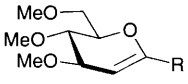
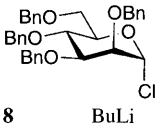
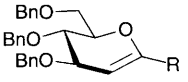
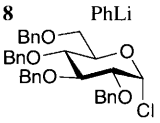


2a R = alkyl
b R = aryl

Table 1 Preparation of *C*-aryl and *C*-alkyl glycals by reaction of anomeric glycopyranosyl chlorides with organolithiums (5 equiv.) in THF



3 **2**

Entry	Substrate	Organolithium	*T*/°C	Product	Yield (%)
					
1	**4**	MeLi	room temp.	**5a** R = Me	50
2	**4**	BuLi	room temp.	**5b** R = Bu	54
3	**4**	PhLi	room temp.	**5c** R = Ph	71
4	**4**	Bu^{s}Li	room temp.	**5d** R = Bu^s	37
5	**4**	Bu^{t}Li	0	**5d** R = Bu^t	46
					
6	**6**	MeLi	room temp.	**7a** R = Me	66
7	**6**	BuLi	room temp.	**7b** R = Bu	50
8	**6**	Bu^{s}Li	room temp.	**7c** R = Bu^s	36
9	**6**	Bu^{t}Li	room temp.	**7d** R = Bu^t	40
10	**6**	PhLi	room temp.	**7e** R = Ph	70
					
11	**8**	BuLi	−78	**9a** R = Bu	55
12	**8**	BuLi	room temp.	[a]	—
13	**8**	PhLi	−78	[b]	—
14	**8**	PhLi	0	**9b** R = Ph	72
					
15	**10**	BuLi	−78	**9a** R = Bu	50
16	**10**	BuLi	room temp.	[a]	—
17	**10**	PhLi	−78	[b]	—
18	**10**	PhLi	0	**9b** R = Ph	65
19	**10**	MeLi	0	**9c** R = Me	74
20	**10**	Bu^{t}Li	0	**9d** R = Bu^t	35[c]
21	**10**	Bu^{t}Li	room temp.	[a]	—

[a] Decomposition. [b] No reaction. [c] Corrected yield based on 30% recovered starting material.

phenylglucal **9b**[7a] (entries 14 and 18). Chloride **10** also underwent reaction with MeLi and Bu^{t}Li at 0 °C to yield *C*-glycals **9c** and **9d** (entries 19 and 20).

The reactions were found to proceed smoothly at room temperature with chlorides **4** and **6** but required lower temperatures in the case of **8** and **10**, probably due to the relatively acidic nature of the benzylic protons. Accordingly, the reaction of **8** and **10** with BuLi had to be conducted at −78 °C (entries 12 and 15). On the other hand, no reaction was observed with PhLi at −78 °C (entries 13 and 17), and this seems to be related to the lower basicity of PhLi when compared with BuLi.¶ PhLi led consistently to higher yields of *C*-glycals than the corresponding alkyllithiums (compare entry 3 with entries 1, 2, 4 and 5 and entry 10 with entries 6–9). In the case of alkyllithiums, the yield seemed to decrease with the degree of substitution on the organolithium (see entries 1, 2 and 4 and entries 6, 7 and 8). Although the reaction conditions reported in this work have not been optimized, in terms of temperature and equivalents of reagent, we have observed that carrying out the reactions below room temperature can be beneficial (compare entries 4 and 5).

It is clear from the results shown in Table 1 that the reaction of pyranosyl chlorides **3** with organolithiums to afford *C*-glycals is quite general and compatible with ether protecting groups in the carbohydrate. In fact, the presence of ether protecting groups seems to be of prime importance for the reaction to proceed as shown.[17] Indeed, previous investigations of the reactions of organolithiums with acyl-substituted glycosyl chlorides resulted in the mere replacement of the anomeric chlorine to afford a mixture of *C*-glycosides.[18]

In summary, we have reported on a novel method for the preparation of synthetically important pyranoid *C*-glycals. This procedure allows a rapid entry to *C*-alkyl- and *C*-aryl-glycals from commercially available organolithiums and readily accessible glycosyl chlorides. Moreover, compounds **5a–d** are of special interest to us since they can be used in serial radical reactions of *C*- glycals for the preparation of branched chain carbohydrates.[19] Further extension of this methodology, as well as its application to the synthesis of natural products, is currently underway in our laboratory.

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Footnotes

† *Typical experimental procedure.* The organolithium reagent (5 mmol) was added to a solution of glycosyl chloride (1 mmol) in dry THF under argon, at the appropriate temperature. When TLC showed consumption of the starting material to be complete the reaction mixture was diluted with diethyl ether followed by quenching with H_2O. After separation, the organic layer was washed with brine, dried (Na_2SO_4), concentrated and the *C*-glycal purified by flash chromatography.

‡ Pyranosyl chloride **4** was prepared from its corresponding lactol according to Ireland *et al.*[15]

§ Pyranosyl chlorides **6**, **8** and **10** were prepared from their corresponding lactols according to the procedure described by Takeo *et al.*[16]

¶ This would be in agreement with a reaction mechanism in which the first step involved anomeric proton abstraction by the organolithium. See also ref. 17.

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