



An easy and efficient approach for the installation of alkoxy-carbonyl protecting groups on carbohydrate hydroxyls

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Abstract

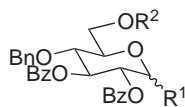
Alkoxy-carbonyl groups can be readily installed on carbohydrates by reaction with the corresponding chloroformates in the presence of TMEDA at low temperature. The mild reaction conditions can be modulated to attain regioselective protections. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: alkoxy-carbonyl group; *N,N,N',N'*-tetramethylethylenediamine; carbohydrates; protecting groups.

In the course of our efforts for the solid phase synthesis of oligosaccharides¹ we intended to prepare the imidate **1**, equipped in position 6 with a protecting allyl group selectively removable after the incorporation of this sugar unit into a polymer-bound growing saccharidic chain. During the synthesis of **1**, allylation of the intermediate **2** turned out to be problematic both under basic and acidic conditions. Thus, we considered the use of allyloxy-carbonyl as an alternative transient protecting group, whose mild and selective removal in the presence of esters was known.^{2,3} At the same time, we became aware of the efficiency of TMEDA in promoting the reactivity of acyl chlorides towards alcohols in CH₂Cl₂.⁴ We envisaged that an analogous role as nucleophilic catalyst could be played by this diamine in the activation of the less reactive alkylchloroformates. As a matter of fact allyloxy-carbonylation of compound **2** was smoothly performed at 0°C in CH₂Cl₂ in 20 min with 0.6 equiv. of TMEDA and a small excess of allylchloroformate to give **3** quantitatively after a simple extractive work-up (Fig. 1).

Encouraged by this result we explored the application of this approach for the installation of allyloxy- and benzyloxy-carbonyl groups on several differently functionalized saccharidic substrates. Alkoxy-carbonyl groups are widely employed for the protection of amino functionalities,⁵ whereas they are much less commonly used in the derivatization of hydroxyl groups and only

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- 1 $R^1 = \alpha\text{-OC(=NH)CCl}_3$,
 $R^2 = \text{All}$
 2 $R^1 = \text{OBz}$, $R^2 = \text{H}$
 3 $R^1 = \text{OBz}$,
 $R^2 = \text{COOAll}$

Figure 1.

rare examples of their exploitation in carbohydrate chemistry can be found, especially for the case of benzyloxycarbonyl groups.⁶ They are typically introduced by treatment of the alcohol with the suitable chloroformate in the presence of a mild (DMAP, TEA, DIPEA, pyridine) or even harsh (NaH, NaOH) base. However, no general procedure was established to date. In this regard, TMEDA was reported in a single example to promote allyloxycarbonylation of an allylic hydroxyl group in an ether solvent.⁷

The general efficiency of the procedure exploited for the preparation of **3** was tested with several saccharidic substrates. High yields were achieved⁸ in short reaction times (less than 1 hour) in all cases (Table 1), even at very low temperatures (Table 2) and in the presence of other protecting groups commonly used in carbohydrate chemistry.

The approach proved effective also in the installation of Troc (trichloroethoxycarbonyl), and Fmoc (9-fluorenylmethoxycarbonyl) protecting groups (Table 1, entries 6 and 7). In spite of the high reactivity of the ROCOCl/TMEDA system, a good regioselectivity was obtained when diols **4**, **5** and **6** were treated with 1.1 equiv. of benzyl- or allylchloroformate and 0.6 equiv. of TMEDA at low temperature (-78°C) (Table 2). In the cases examined the mono alkoxycarbonylated derivative at the most reactive position was the major product. No detectable amounts of the alternative mono derivative were produced, whereas substantial amounts of the fully protected product were also isolated. Interestingly, allyloxycarbonylation of **4** was reported to proceed with no regioselectivity when allylchloroformate was used in combination with TEA, whereas a comparable regioselectivity and a higher yield can be attained by using the less reactive allyl 1-benzotriazolyl carbonate.^{6c}

In conclusion, we have shown that allyloxy- or benzyloxycarbonyl groups, typically employed in the protection of amino functionalities, can be conveniently introduced on primary and secondary carbohydrate hydroxyl groups. The procedure described could contribute to increase the practical usefulness of these protecting groups,⁹ in view of the specificity and mild conditions required for their removal.^{2,6}

Acknowledgements

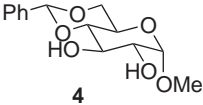
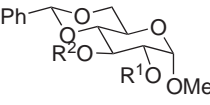
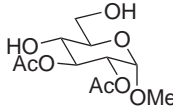
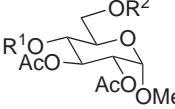
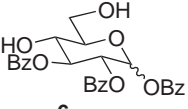
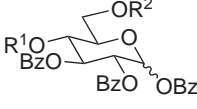
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Table 1
Alkoxy-carboxylation of carbohydrate alcohols^a

Entry	Substrate	Product and isolated yields
1		
2		R = Bn 86% R = All >95%
3		
4		R = Bn 86% R = All >95%
5		
6		R = Bn 82%
7		R = CH ₂ CCl ₃ 88%
		R = 9-fluorenylmethyl 92%
8		
9		
10		
11		
12		
13		R ¹ = R ² = Bn >95% R ¹ = R ² = Al >95%

^a Reaction conditions: see Ref. 7.

Table 2
Regioselective allyloxy- and benzyloxy-carbonylation of carbohydrate diols^a

Entry	Substrate	Product and isolated yields
1	 <p>4</p>	 <p>R¹ = R² = COOBn 21% R¹ = COOBn, R² = H 65%</p>
2		<p>R¹ = R² = COOAll 15% R¹ = COOAll, R² = H 67%</p>
3	 <p>5</p>	 <p>R¹ = R² = COOBn 15% R¹ = H, R² = COOBn 71%</p>
4		<p>R¹ = R² = COOAll 20% R¹ = H, R² = COOAll 68%</p>
5	 <p>6</p>	 <p>R¹ = R² = COOAll traces R¹ = H, R² = COOAll 72%</p>

^a Reaction conditions: see Ref. 7.

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8. Typical procedure: TMEDA (0.06 mmol for each hydroxyl to be protected) and chloroformate (0.11 mmol for each hydroxyl to be protected) are added, under argon and at 0°C, to a solution of the saccharidic substrate (0.10 mmol) in anhydrous CH₂Cl₂ (1 mL). After completion of the reaction (30–60 min, TLC), the mixture is diluted with CH₂Cl₂, washed with water, dried, evaporated and chromatographed on silica gel if necessary. Regioselective protections were performed at –78°C. Satisfactory spectral data were obtained for all products.
9. We have recently disclosed orthogonal conditions for the removal of benzyl- and benzyloxycarbonyl protecting groups: Adinolfi, M.; Guariniello, L.; Iadonisi, A.; Mangoni, L. *Synlett* **2000**, 1277–1278.