Tetrahedron Letters 50 (2009) 7051–7054

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A selective and operationally simple approach for removal of methoxy-, allyloxy-, and benzyloxycarbonyl groups from carbinols

Matteo Adinolfi, Alfonso Iadonisi *, Antonello Pastore

Dipartimento di Chimica Organica e Biochimica, Università degli Sudi di Napoli 'Federico II', Via Cinthia 4, I-80126 Napoli, Italy

ARTICLE INFO

Article history:
Received 31 August 2009
Revised 28 September 2009
Accepted 29 September 2009
Available online 2 October 2009

Keywords:
Protecting groups
Alkoxycarbonyl groups
Carbohydrates
Lithium iodide

ABSTRACT

LiI in refluxing pyridine can remove within a few hours methoxy-, allyloxy-, and benzyloxycarbonyl groups from saccharidic carbinols under conditions compatible with the maintenance of acyl groups. Addition of a stoichiometric excess of acetic acid to the reaction mixture minimizes or even suppresses intramolecular transesterifications. The procedure broadens the scope of some alkoxycarbonyl groups in organic synthesis.

Alkoxycarbonyl groups have long been extensively used in the protection of amino functionalities. However their application to carbinol functions is only currently receiving a wide interest, especially in carbohydrate chemistry.[1] Nevertheless, alkoxycarbonylated carbinols are involved in other relevant synthetic applications: O-Alkoxycarbonylated allyl alcohols are routinely used in palladium-mediated substitutions or rearrangements,[2] whereas O-methoxycarbonylated cyanohydrins are adopted for masking aldehyde or ketone carbonyl groups.[3]

An inherent advantage of alkoxycarbonyls resides in the mild basic conditions needed for their installation which are compatible with a wide range of functionalities.[1] In addition, several members of this class, that is, allyloxycarbonyl (Alloc), benzyloxycarbonyl (Z), and fluorenylmethoxycarbonyl (Fmoc) groups, can be selectively removed under specific conditions sharing a common general mechanism entailing an initial alkyl scission followed by spontaneous loss of CO_2 (Fig. 1).[4] Alternative cleavage pathways resembling an acyl nucleophilic substitution have instead been applied to de-O-methoxycarbonylation.[3,5] However these conditions are not compatible with the concomitant stability of widely used acyl protecting groups.[3]

Over the last years, we have been appreciating numerous advantages of using the methoxycarbonyl group in carbohydrate chemistry. Actually it can be quantitatively and quickly installed on saccharidic carbinols to yield products that are easily purified by a simple extractive work-up. The adopted protocol, based on the use of cheap methyl chloroformate and TMEDA, is also suited for the regioselective protection of diols.[6] In addition, methoxycarbonyl groups can be removed under Zemplen conditions at rates comparable with those of acetyls,[5] thus representing an effective alternative to the use of sterically encumbered acyl groups which are installed and removed under more forced conditions. In this

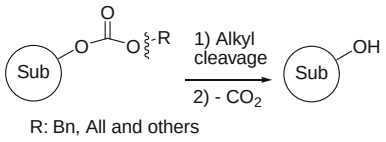
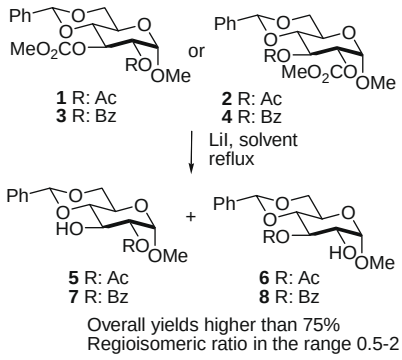


Figure 1. Common general mechanism for removal of many alkoxycarbonyl groups from alcohols.

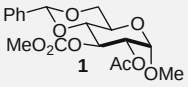
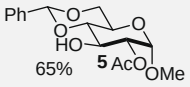
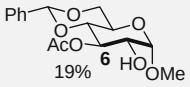
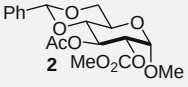
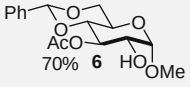
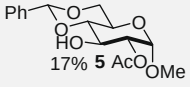
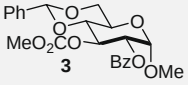
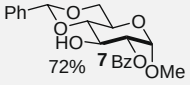
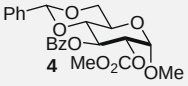
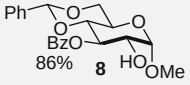
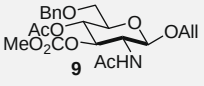
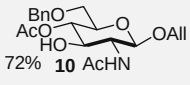
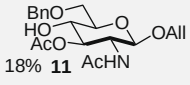
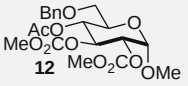
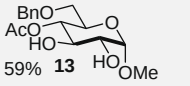
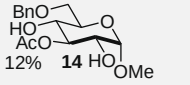
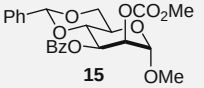
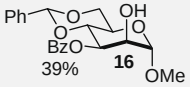
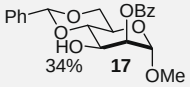
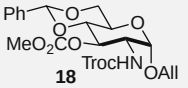
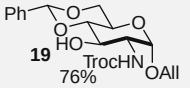
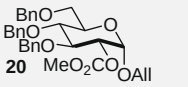
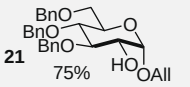
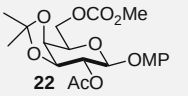
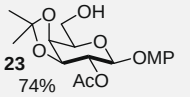
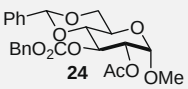
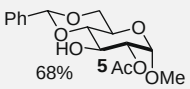
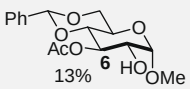
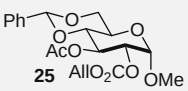
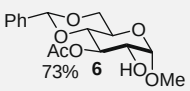
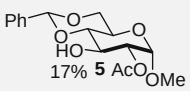
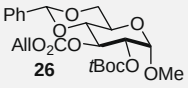
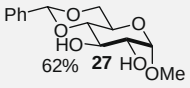
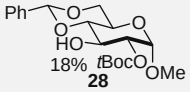


Scheme 1. Removal of methoxycarbonyl groups from O-acylated model substrates.

* Corresponding author. Fax: +39 (0)81674393.
E-mail address: iadonisi@unina.it (A. Iadonisi).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.09.174

Table 1
Removal of alkoxycarbonyl groups by the LiI/AcOH system

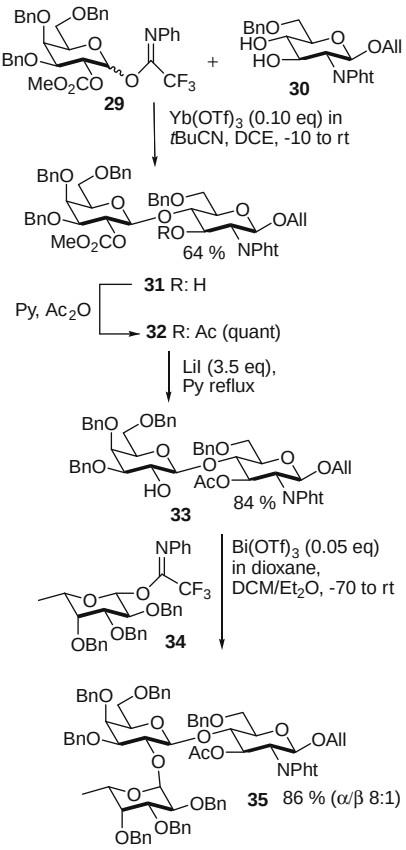
Entry	Reagents	Products and yields		Time (min)
1	 **1**	 65% **5**	 19% **6**	100
2	 **2**	 70% **6**	 17% **5**	90
3	 **3**	 72% **7**		180
4	 **4**	 86% **8**		120
5[a]	 **9**	 72% **10**	 18% **11**	90
6[b]	 **12**	 59% **13**	 12% **14**	100
7	 **15**	 39% **16**	 34% **17**	300
8	 **18**	 **19** 76%		240
9	 **20**	 **21** 75%		240
10	 **22**	 **23** 74%		150
11	 **24**	 68% **5**	 13% **6**	160
12	 **25**	 73% **6**	 17% **5**	60
13	 **26**	 62% **27**	 18% **28**	300

General conditions: LiI (3 equiv), AcOH (5 equiv), and pyridine, reflux.
[a] Regiosiomers obtained as an inseparable mixture. Yields evaluated by ^{1}H NMR.
[b] Conditions: LiI (6 equiv), AcOH (10 equiv),and pyridine, reflux. Minor regioisomer **14** could not be separated from the major one (**13**). Yields evaluated by ^{1}H NMR.

regard, methoxycarbonyl was found to serve as an excellent non-bulky participating group in 1,2-trans glycosidations conducted under very mild acidic conditions[7] where orthoester coupling products were highly produced if conventional acyl participating groups are adopted.[8] In contrast, in our experience allyloxy- and benzyloxycarbonyl groups were found to be less effective in inducing 1,2-trans selective glycosidations because of their trend to furnish undesired cyclic 1,2-carbonates.[9]

Due to emerged manifold advantages of methoxycarbonyl group, we were spurred to search for deprotection conditions which might be compatible with the stability of acyl protecting groups in order to expand the scope of methoxycarbonyl as transient protecting groups in oligosaccharide synthesis. Because of the structural analogy between a methyl ester and a methyl carbonate, we surveyed the most practical methodologies out of those described for cleaving methyl esters by an alkyl scission mechanism. A single example of methoxycarbonyl removal from a phenol with the system thiophenol/cesium carbonate in DMF is indeed reported,[10] but in preliminary experiments it did not prove very effective on such densely functionalized substrates as **1** and **2** (Scheme 1). On the other hand, use of LiI in either refluxing ethyl acetate[11] or refluxing pyridine[12] appeared as an experimentally more convenient alternative. Both protocols were thereby initially examined on model compounds **1** and **2** purposely protected with a methoxycarbonyl adjacent to an acetylated positions (Scheme 1).

As a matter of fact, the use of high-boiling pyridine was found necessary to guarantee a high yielding deprotection within short times, whereas longer reactions and higher amounts of LiI were needed in refluxing ethyl acetate. Not unexpectedly, in all cases the desired deprotections were accompanied by rearrangement processes, so that, regardless of the structure of the starting compound, comparable amounts of 2-O- and 3-O-acetylated products were observed (Scheme 1). Interestingly, the extent of the acyl transfer was not significantly reduced when the vicinal acetyl group was replaced by the benzoyl group, well known for being much more reluctant to rearrangement processes (Scheme 1).[13] Reasoning that the initially produced lithium alkoxide intermediate might cause the aforementioned transacylation, a stoichiometric excess of an acid as weak as acetic acid (5 equiv) was added to the reaction medium containing a lower excess of LiI (3 equiv) in the hope of minimizing the transacylation process. As a matter of fact, this simple procedural modification led to a significant reduction of the acetyl transfer, (compare Scheme 1 and Table 1, entries 1 and 2) whereas the intramolecular trans-benzoylation was practically suppressed with the *gluco*-precursors **3** and **4** (Table 1, entries 3 and 4). In contrast, the benzoyl shift could not be avoided in the *manno*-precursor **15** due to the *syn*-relation of *O*-2 and *O*-3 (entry 7). These improved conditions were then tested on a range of protected saccharidic derivatives (Table 1). The protocol proved effective in removing methoxycarbonyl group in the presence of a variety of different functionalities widely adopted in carbohydrate chemistry, including amino sugars N-derivatized with an acetyl (entry 5), a Troc (entry 8), and a phthalimido group (see below in Scheme 2). The procedure also worked well in removing allyloxy- and benzyloxycarbonyl groups (entries 11 and 12) as expected from an alkyl substitution mechanism. Interestingly, a benzyloxycarbonyl (Z) could be smoothly cleaved in the presence of a benzylidene (entry 11), whereas the routinely used hydrogenolytic removal[1f] of Z would affect the benzylidene functionality. Furthermore, other functions sensitive to hydrogenolysis conditions, benzyl and allyl ethers, were instead stable under the here proposed conditions (entries 5, 6, 9). Very interestingly, reaction in entry 13 shows that *tert*-buthoxycarbonyl (*t*-Boc) also proved to be a cleavable protecting group under the optimized conditions, even though in this case the direct involvement of the iodide anion in the scission step should be excluded on the basis of steric considerations. The procedure was operationally very simple and in all cases reactions took a few hours (generally less than 4 h). Besides the deprotection products, unreacted starting material generally represented the main saccharidic component of the crude reaction mixture.



Scheme 2. Synthesis of trisaccharide **32**.

Removal of a methoxycarbonyl from the nitrogen of 1,3,4,6-*O*-acetyl glucosamine was also attempted and resulted in the recovery of the starting material to indicate the chemoselectivity of the reported conditions.[14]

The feasible selective removal of methoxycarbonyl group was usefully exploited in the synthesis of protected trisaccharide **35**, a common trisaccharide motif incorporated into N-glycans. In pursuing our interest for the use of moisture-stable glycosidation promoters, initial coupling between donor **29** and acceptor **30** was best performed under the activation of catalytic $Yb(OTf)_3$ added as a solution in pivalonitrile (Scheme 2).[15] The reaction afforded in satisfying yield (64 %) the desired 4-O-linked disaccharide **31** together with minor amounts (ca. 10%) of the 3-O-linked disaccharide.[16] Acetylation of **31** yielded protected lactosamine **32** that was then submitted to the proposed de-O-methoxycarbonylation protocol to give **33** in a very good yield (84%). The latter was coupled with the fucosyl donor **34** under catalytic activation with $Bi(OTf)_3$[17] to yield the desired trisaccharide building-block **35** in high yield and α-selectivity.

In conclusion, in this Letter we have described an operationally simple approach[18] for the selective removal of methoxy-, allyloxy-, and benzyloxycarbonyl carbonyl groups from alcohols. Combined use of LiI and acetic acid minimizes or even suppresses concomitant transacylation processes. In addition, this procedure is compatible with a wide range of functional groups which could be otherwise affected under previously reported cleavage conditions. The developed protocol offers a very useful option in designing synthetic routes toward highly functionalized targets.

Acknowledgment

NMR and MS facilities of CIMCF ('Centro Interdipartimentale di Metodologie Chimico-Fisiche') are acknowledged.

Supplementary data

Experimental procedures, spectroscopic data and copies of NMR spectra of all the products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.174.

References and notes

1. For some examples: (a) Sridhar, P. R.; Chandrasekaran, S. *Org. Lett.* **2002**, *4*, 4731–4733; (b) Morere, A.; Mouffouk, F.; Jeanjean, A.; Leydet, A.; Montero, J. L. *Carbohydr. Res.* **2003**, *338*, 2409–2412; (c) Tanaka, H.; Amaya, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 3053–3057; (d) Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R. E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem. Eur. J.* **2003**, *9*, 140–169; (e) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Synlett* **2004**, 275–278; (f) Ko, K. S.; Jaipuri, F. A.; Pohl, N. L. *J. Am. Chem. Soc.* **2005**, *127*, 13162–13163; (g) de Oliveira, R. N.; Cottier, L.; Sinou, D.; Srivastavab, R. M. *Tetrahedron* **2005**, *61*, 8271–8281; (h) Kim, J. H.; Yang, H.; Khot, V.; Whitfield, D.; Boons, G.-J. *Eur. J. Org. Chem.* **2006**, 5007–5028.
2. For a recent review: Mohr, J. T.; Stoltz, B. M. *Chem. Asian J.* **2007**, *2*, 1476–1491.
3. (a) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423–1425; (b) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995–6003.
4. Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; Wiley & Sons, 2007.
5. Adinolfi, M.; Iadonisi, A.; Pezzella, A.; Ravidà, A. *Synlett* **2005**, 1848–1852.
6. Adinolfi, M.; Barone, G.; Iadonisi, A.; Guariniello, L. *Tetrahedron Lett.* **2000**, *41*, 9305–9309.
7. (a) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Schiattarella, M. *Tetrahedron Lett.* **2001**, *42*, 5967–5969; (b) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Org. Lett.* **2003**, *5*, 987–989; For an application to a biologically relevant target: (c) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *J. Org. Chem.* **2005**, *70*, 5316–5319.
8. For a recent example of a sterically bulky participating groups for 1,2-trans glycosidations: Szpilman, A. M.; Carreira, E. M. *Org. Lett.* **2009**, *11*, 1305–1307.
9. For a recent report on the generation of saccharidic cyclic carbonates arising from participation effects: Crich, D.; Hu, T.; Cai, F. *J. Org. Chem.* **2008**, *73*, 8942–8953.
10. Bouzbouz, S.; Kirschleger, B. *Synthesis* **1994**, 714–718.
11. For some examples: (a) Mayato, C.; Dorta, R. L.; Vazquez, J. T. *Tetrahedron Lett.* **2008**, *49*, 1396–1398; (b) Fisher, J. W.; Trinkle, K. L. *Tetrahedron Lett.* **1994**, *35*, 2505–2508; (c) Biron, E.; Kessler, H. *J. Org. Chem.* **2005**, *70*, 5183–5189.
12. For some examples: (a) Borch, R. F.; Grudzinskas, C. V.; Peterson, D. A.; Weber, L. D. *J. Org. Chem.* **1972**, *37*, 1141–1145; (b) Wade, J. J.; Hegel, R. F.; Toso, C. B. *J. Org. Chem.* **1979**, *44*, 1811–1816; (c) Magnus, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1984**, 389–390; (d) Sun, B.; Srinivasan, B.; Huang, X. *Chem. Eur. J.* **2008**, *14*, 7072–7081.
13. Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11.
14. For the use of N-methoxycarbonylated sugars in carbohydrate chemistry: Yeung, B. K. S.; Adamski-Werner, S. L.; Bernard, J. B.; Poulenat, G.; Petillo, P. A. *Org. Lett.* **2000**, *2*, 3135–3138.
15. Adinolfi, M.; Iadonisi, A.; Ravidà, A. *Synlett* **2006**, 583–586.
16. For the effect of the *N*-phtalimido group on regioselective glycosidations of glucosamine acceptors: (a) Ellervik, U.; Magnusson, G. *J. Org. Chem.* **1998**, *63*, 9314–9322; (b) Bohn, M. L.; Colombo, M. I.; Pisano, P. L.; Stortz, C. A.; Rùveda, E. A. *Carbohydr. Res.* **2007**, *342*, 2522–2536.
17. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Valerio, S. *Tetrahedron Lett.* **2006**, *47*, 2595–2599.
18. *Experimental procedure*: The saccharidic compound (0.3 mmol) and LiI (120 mg, 0.9 mmol) were dissolved in pyridine (1.4 mL) and to the resulting solution was added acetic acid (90 μL, 1.5 mmol). The resulting mixture was refluxed for the times indicated on Table 1, and then the vessel was cooled to rt. The mixture was diluted with DCM and the organic phase was washed with water. The aqueous phase was re-extracted with DCM and ethyl acetate. The collected organic phases were dried and concentrated in vacuo to give a residue which was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate mixtures).