Pergamon

Tetrahedron Letters 41 (2000) 10185–10188

TETRAHEDRON LETTERS

A facile cleavage of allyl ethers on solid phase

Till Opatz and Horst Kunz*

Institut für Organische Chemie, Universität Mainz, Duesbergweg 10-14, 55128 Mainz, Germany

Received 6 October 2000; accepted 13 October 2000

Abstract

A simple and efficient protocol for the cleavage of allyl ethers on solid phase using a palladium(0)-catalyzed allyl transfer reaction is reported.

Keywords: solid-phase synthesis; allyl ethers; protecting groups; palladium.

During the past decades, solid-phase synthesis has become an important tool in organic chemistry. In the context of combinatorial synthesis, many types of reactions have been performed successfully on solid support.[1–4] Nevertheless, there are several limitations concerning reaction conditions which can be applied to polymer-linked substrates. They reduce the number of protecting groups that can be utilized to allow selective manipulations on the substrate, for example in combinatorial derivatizations of polyfunctional molecules.

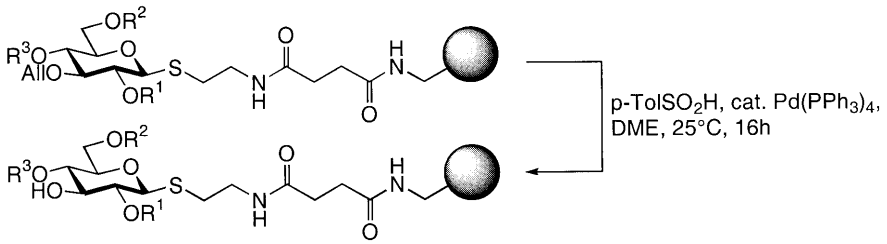
Owing to its high chemical stability, an allyl ether should be ideal as a hydroxy protecting group, but many of the methods developed for its removal including rhodium- or palladium-catalyzed isomerizations,[5,6] the use of Grignard reagents,[7] or nickel-catalyzed hydrometallation/elimination reactions,[8] do not operate or cause side reactions on polyfunctional molecules. In addition, only a few of the described methods meet the requirements for an application to solid-phase chemistry. The palladium(0)-catalyzed allyl transfer reaction[9,10] has a remarkable substrate tolerance and can be employed for the mild and selective removal of allyl esters or the allyloxycarbonyl- (Aloc-) protecting group.[5,6,11,12] Allyl ethers do not react under these classical allyl transfer conditions, because an alkoxide ion is a poor leaving group compared to a carboxylate, carbonate or carbamate. From a thermodynamic point of view, cleavage of allyl ethers using an allyl transfer reaction should be feasible, but for kinetic reasons activation of the ether oxygen by a Lewis acid is required. Allyl ethers can be cleaved by $Pd(PPh_3)_4$ and acetic acid as a proton source at room temperature, but stoichiometric amounts of the complex have to be employed.[13] In 1997, Nagakura and co-workers published a protocol for cleavage of allylic protecting groups including allyl ethers using a sulfinic acid as both allyl acceptor and proton source in combination with catalytic amounts of Pd(0).[14]

* Corresponding author. Tel: (+49) 6131-39-22272; fax: (+49) 6131-39-24786; e-mail: hokunz@mail.uni-mainz.de

0040-4039/00/$ - see front matter
PII: S0040-4039(00)01835-9

In our hands, the described deprotection of 3-*O*-allyl-1,2,5,6-di-*O*-isopropylidene-D-glucofuranose in CH_2Cl_2 turned out to be delicately dependent on parameters like concentration and reaction time. Side products were formed along with the formation of orange-colored Pd complexes. An oxidation of the catalyst[15] or the nucleophile[16] by CH_2Cl_2 could be the cause of the observed ambiguities since cleaner reactions have been performed using ethers as solvents.

Experiments with solid-phase bound allyl ethers revealed a strong influence of the type of the catalyst as well as the solvent on the cleavage efficiency, showing especially 1,2-dimethoxyethane (DME) and 1,4-dioxan to be superior to CH_2Cl_2. In addition, reactions carried out in these diethers showed reduced precipitation of finely divided Pd metal (so-called plating out), which may constitute a problem when Pd complexes with monodentate ligands are used. Catalysts with bidentate ligands such as $Pd(DIPHOS)_2$ proved to be less reactive than $Pd(PPh_3)_4$ in the described transallylation reaction. In any case, Pd metal plated out inside the resin beads when using higher concentrations of the catalyst during long reaction times can be easily removed by washing the resin with a dilute solution of ammonium pyrrolidinedithiocarbamate in MeOH/THF (Scheme 1).



Scheme 1.

The sensitive thioglycoside anchor in our solid-phase bound substrates was not affected under the reaction conditions, nor were esters, carbamates, amides, benzyl ethers, aryl chlorides and the TBDPS group. Thus, the elaborated cleavage protocol permits the use of allyl ethers as protection for hydroxy functions of complex molecules on solid phase.[19] Allyl esters as well as Aloc groups are also removed efficiently under the conditions described here.

Conversion of the allyl ethers to the corresponding alcohols (Table 1) was quantified by RP-HPLC electrospray MS analysis of the anomeric 1-*O*-ethylglycosides obtained after cleavage of the thioglycoside anchor through reaction with a mixture of NBS or bromine and 2,6-di-*tert*-butylpyridine in dry CH_2Cl_2 and subsequent ethanolysis of the produced 1-bromosugars in the presence of Et_4NBr.[17,18] Under these conditions, unreacted allyl ethers were transformed to the corresponding 2,3-dibromopropyl derivatives.

HPLC–MS chromatograms of the products revealed the formation of small amounts (about 0.5%) of the corresponding propyl ethers as the only detectable side products.

Table 1
Cleavage of allyl ethers on polyfunctionalized monosaccharide templates by Pd(0)-catalyzed allyl transfer to *p*-toluenesulfinic acid in dimethoxyethane (DME)

Compound	R^1	R^2	R^3	Repeats (see text)	Conversion (%)
1	H	*t*BuPh$_2$Si	H (galacto-configuration at C-4)	1	>99
2	Bn	4-Cl-PhNHCO	H	1	>98
3	Me	4-F-PhNHCO	4-Me-PhCH$_2$CO	2	>99
4	Me	4-F-PhNHCO	PhCO	2	>99
5	Me	4-F-PhNHCO	4-CF$_3$-PhNHCO	2	>98
6	4-F-Bn	3-CN-PhNHCO	4-F-PhNHCO	2	>99
7	4-F-Bn	3-CN-PhNHCO	4-Me-PhCH$_2$CO	2	>99
8	4-F-Bn	3-CN-PhNHCO	4-Cl-PhNHCO	1	>99
9	4-Me-Bn	4-Cl-PhNHCO	4-F-PhNHCO	2	>99
10	4-Me-Bn	4-Cl-PhNHCO	4-Me-PhCH$_2$CO	2	>99

As an example, the data obtained from ethylglycoside **11** produced by thioglycoside activation of resin **4** (Table 1) and reaction with ethanol are shown in Fig. 1. Traces of the 3-*O*-propyl derivative are the only detectable impurity formed during the deallylation reaction. The peak at $R_t = 2$ min originates from a side product formed in the second of seven synthetic steps on solid support.[17,18]

DME can be easily degassed by ultrasonication under argon. Both polystyrene- and Tentagel™-resins swell efficiently in this solvent. The catalyst as well as the sulfinic acid are stable

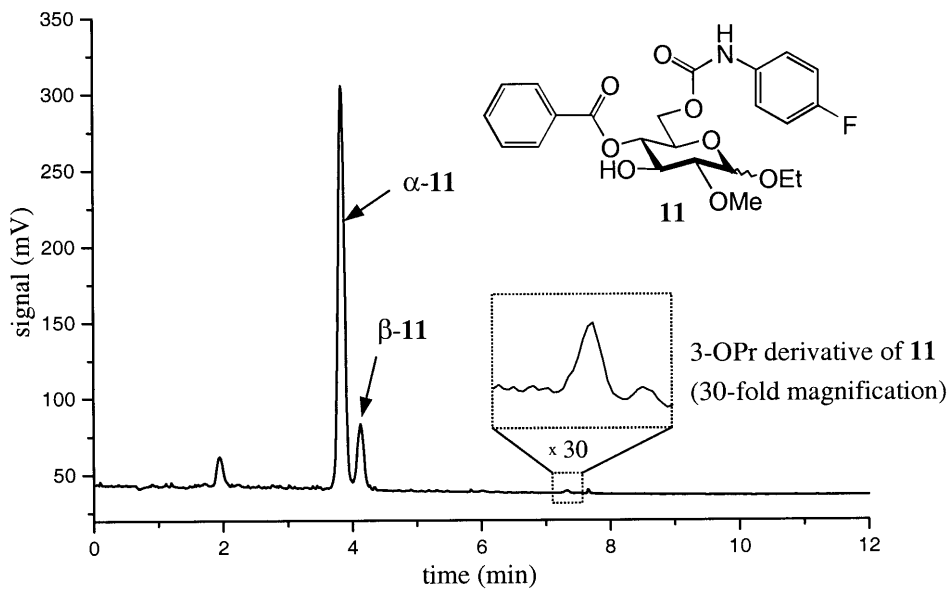


Figure 1. HPLC chromatogram (evaporative light-scattering detection) of the crude product obtained after cleavage of substrate **4** (Table 1) from the polymer

at +4°C for several months, rendering the described procedure very convenient. To our knowledge, this is the first single-step cleavage of highly functionalized alkyl allyl ethers on solid support. In addition, it only requires catalytic amounts of the expensive Pd complex.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. T.O. is grateful to the Fonds der Chemischen Industrie for a Kekulé-Stipendium.

References

1. Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 2289–2337.
2. Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 17–42.
3. Bunin, B. A. *The Combinatorial Index*; Academic: San Francisco, 1998.
4. *Combinatorial Chemistry*; Jung, G., Ed.; Wiley-VCH: Weinheim, 1999.
5. Guibé, F. *Tetrahedron* **1997**, *53*, 13509–13556.
6. Guibé, F. *Tetrahedron* **1998**, *54*, 2967–3042.
7. Lee, J.; Cha, K. *Tetrahedron Lett.* **1996**, *37*, 3663–3666.
8. Taniguchi, T.; Ogasawara, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1136–1137.
9. Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385–393.
10. Tsuji, J. *Tetrahedron* **1986**, *42*, 4361–4401.
11. Kunz, H.; Unverzagt, C. *Angew. Chem., Int. Ed.* **1984**, *23*, 436–437.
12. Kunz, H.; Waldmann, H. *Angew. Chem., Int. Ed.* **1984**, *23*, 71–72.
13. El-Abadla, N.; Lampilas, M.; Hennig, L.; Findeisen, M.; Welzel, P.; Müller, D.; Markus, A.; van Heijenoort, J. *Tetrahedron* **1999**, *55*, 699–722.
14. Honda, M.; Morita, H.; Nagakura, I. *J. Org. Chem.* **1997**, *62*, 8932–8936.
15. Balch, A. L.; Hunt, C. T.; Lee, C.-L.; Olmstead, M. M.; Farr, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 3764–3772.
16. Otto, R. *J. Prakt. Chem.* **1889**, *40*, 505–564.
17. Wunberg, T.; Kallus, C.; Opatz, T.; Schmidt, W.; Henke, S.; Kunz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2503–2505.
18. Kallus, C.; Opatz, T.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. *Tetrahedron Lett.* **1999**, *40*, 7783–7786.
19. *Typical procedure*: Under an argon atmosphere, to 400 mg of the resin **1**–**10** (load 0.5 mmol/g), 6 ml of degassed DME, 156 mg (1 mmol, 5 equiv.) of *p*-toluenesulfinic acid and 58 mg (50 μmol, 25 mol%) of $Pd(PPh_3)_4$ are added, and the mixture is agitated for 18 hours at room temperature on an orbit shaker. This process can be repeated, if applied to sterically hindered substrates. The resin is washed with dioxan and DMF and, if necessary, with a 0.1% solution of ammonium pyrrolidinedithiocarbamate in MeOH/THF (1:5).