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A photolabile protection strategy for terminal alkynes

Tina A. Gschneidtner, Kasper Moth-Poulsen *

Department of Chemical and Biological Engineering, Chalmers University of Technology, SE-412 96 Göteborg, Sweden

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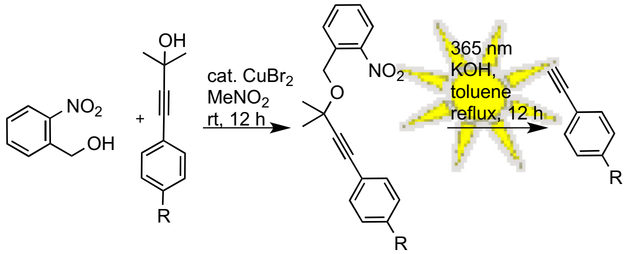
ABSTRACT

We present a strategy for photolabile protection of terminal alkynes. Several photo-caged alcohols were synthesized via mild copper(II)-catalyzed substitution between tertiary propargylic alcohols and 2-nitrobenzyl alcohol to build up robust, base stable *o*-nitrobenzyl (NB) photo-cleavable compounds. We compare the new photolabile protecting group with the commonly used alkyne protecting group, 2-methyl-3-butyn-2-ol and the results show that NB ethers are stable under the cleaving conditions for the cleavage of methylbutynol protected alkynes. Additionally, we present the synthesis of photo-cleavable NB derivatives containing thiol groups that can serve as agents for photoinduced surface functionalization reactions.

Terminal alkynes are reactive species in a number of important chemical reactions such as the 1,3-dipolar cycloaddition[1] between azides and alkynes to give 1,2,3-triazoles (click-chemistry[2]), the Sonogashira reaction and its forerunner, the Stephens–Castro reaction.[3,4] Furthermore, alkynes can undergo the Vollhardt cyclization,[5] alkyne trimerization to form aromatic compounds,[6,7] or can act as dienophiles in Diels–Alder reactions.[8] A number of protecting groups have been developed for alkyne chemistry such as trialkylsilyl, benzyl- or phenyl-substituted alkylsilyl groups and propargylic alcohols. The development of a photolabile protecting group for terminal alkynes has, to the best of our knowledge, not been described in the literature until now, and would add to the portfolio of possible chemical transformations of terminal alkynes. Such protected alkynes could also be applied in the modification of surfaces where it is highly desirable to perform spatially controlled chemoselective reactions, for example, by using chemoselective 'click chemistry'.[9]

Protected, photolabile compounds, the so called caged compounds,[10] have been used in organic synthesis,[11–13] surface science[14,15] and biochemistry,[16] for DNA-chip fabrication,[17,18] natural product synthesis,[19] and the photorelease of biological substances.[13] Among photo-cleavable groups such as the nitroindoline (Bni) group,[20,21] (coumarin-4-yl) methyl derivatives[22,23] and *p*-hydroxyphenacyl derivatives,[24,25] the *o*-nitrobenzyl (NB)[26–28] group is a very robust and a widely used group for the protection of primary alcohols.[26] Photoinduced reactions of NBs were reported as early as 1901.[29] The first reported use of the *o*-nitrobenzyl group as a protecting group for benzoic acid was by Barltrop et al.[30] in 1966, and it was further developed by Kaplan et al.,[16] who used it for the triggered release of ATP. Photolysis of *o*-nitrobenzyl-derived ethers releases the free alcohol and *o*-nitrosobenzaldehyde, due to proton abstraction by the light-activated nitro group from the benzylic ether.[13,26,31] NBs are used to release, for example, phosphoric acids,[32–34] thiols,[35] amines,[36] carboxy acids,[37,38] and alcohols,[28] and internal alkynes[39] via light activation. For an overview of this field we refer to a review.[40]



R=H **8** **1** **15**

Scheme 1. Final step in the synthesis of *o*-nitrobenzyl NB compounds. *o*-Nitrobenzyl alcohol reacts with different tertiary propargylic alcohols in the presence of catalytic amounts of CuBr$_2$. These products can be photo-cleaved under alkaline conditions to give terminal alkynes.

Herein, we introduce a photolabile protection strategy for terminal alkynes based on a combination of the photoactive NB group and tertiary propargyl ethers. The combined NB-propargyl ether groups are stable under strong alkaline conditions but release terminal alkynes after irradiation under alkaline conditions (Scheme 1).

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* Corresponding author. Tel.: +46 (0) 317723403.
E-mail address: kasper.moth-poulsen@chalmers.se (K. Moth-Poulsen).

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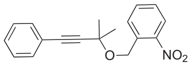
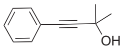
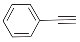
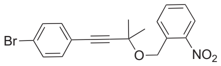
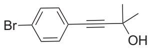
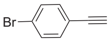
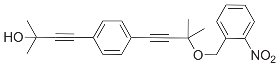
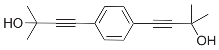
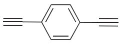
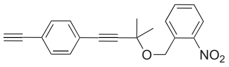
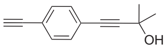
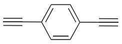
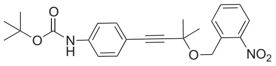
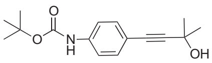
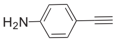
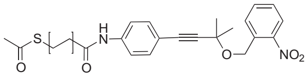
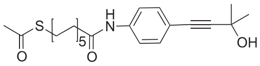
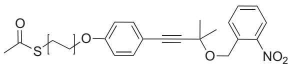
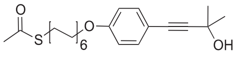
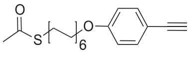
Table 1
Library of photolabile compounds synthesized as shown in Scheme 1

Photolabile compounds		Photoreaction		Alkaline photoreaction	
1 (70%)		**8** (96%)		**15** (16 h, 70%)	
2 (73%)		**9** (94%)		**16** (5 h, 78%)	
3[a]		**10** (86%)		**17** (12 h, 70%)	
4[b]		**1** (88%)		**17** (12 h, 62%)	
5 (57%)		**12** (90%)		**18** (10 h, 50%)	
6 (42%)		**13** (92%)		– (0%)	
7 (48%)		**14** (94%)		**19** (14 h, 52%)	

All compounds were deprotected to the propargylic alcohol in $CHCl_3$ in 120 mins, after irradiation with photons of 365 nm wavelength and 200 μW/cm^2 intensity. Upon UV-irradiation under alkaline conditions (KOH in toluene (reflux), 5–14 h, see above) these compounds formed terminal alkynes.

[a] Synthesized from compound **2**.

[b] Obtained via deprotection of **3**.

A library of alkynes protected with the NB cage on the tertiary propargylic alcohol was synthesized (Table 1, compounds **1**–**7**). 2-Methyl-3-butyn-2-ol was introduced by a standard Sonogashira[4] reaction with precursor molecules (aryl halides)[41] **8**, **9**, and **12**–**14** with 2-methyl-3-butyn-2-ol. These products were converted into the NB-propargylic ethers **1**–**7** via a copper-catalyzed nucleophilic substitution reaction with *o*-nitrobenzyl alcohol. In this step the tertiary propargylic alcohol was activated with $CuBr_2$ to react with *o*-nitrobenzyl alcohol at room temperature.

Propargylic ethers are interesting building blocks in organic chemistry[42,43] and terminal and secondary propargylic ethers have been prepared using Lewis acids,[44,45] or transition metal complexes with, for example, cobalt (the Nicholas reaction),[46] rhenium,[42,47] or ruthenium.[48] However, mild methods for tertiary ethers are rare, since their synthesis is not trivial. A mild method recently reported by Huang and co-workers[49] has been used in this study to form the propargylic ether via a mild copper(II)-catalyzed (S_N1) substitution.

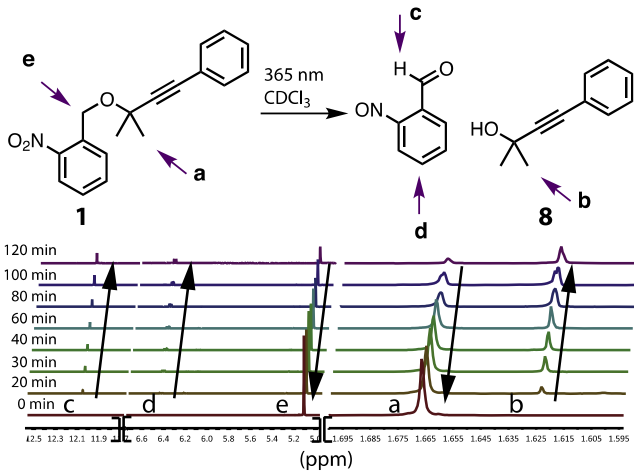


Figure 1. ^{1}H NMR spectra of **1** in $CDCl_3$ upon irradiation with UV-light (365 nm, 200 μW/cm^2) for 120 min. The formation of **8** and the by-product 2-nitrosobenzaldehyde (lit. values NMR[32]) were observed.

The obtained photolabile NB-propargylic ethers were deprotected via irradiation (365 nm, 200 μW/cm^2) to form the alcohols **8**–**14** and the terminal alkynes **15**–**19** under alkaline conditions. Figure 1 illustrates an example of the photo-cleaving reaction of 1-[(2-methyl-4-phenylbut-3-yn-2-yl)oxy]-2-nitrobenzene (**1**) in $CDCl_3$ monitored by ^{1}H NMR spectroscopy. The sample was irradiated over a period of 120 min interrupted by short breaks, in which the NMR spectra (10-min intervals) were recorded. The conversion of the starting material (signal **a**, **e**) as well as the formation of the two characteristic products *o*-nitrosobenzaldehyde (signals **c**, **d**) and 2-methyl-4-phenylbut-3-yn-2-ol (signal **b**) were monitored. The disappearance of the benzylic proton (**e**) as well as a shift of the protons of the methyl group of 2-methylbut-3-yn-2-ol (**a**–**b**), indicated the change from an ether to a free alcohol.

The versatility of the copper-catalyzed reaction using tertiary propargylic alcohols to build up NB-propargylic photo-caged derivatives was also tested on alkynes containing functional groups, such as ethers (**7**) or carbamates (**5**, **6**) (Table 1). For subsequent modification reactions, amine (**5**) bromide (**2**) and alkyne functionalities (**4**) were introduced. These functional groups can react, for example, via cross-coupling reactions, peptide-coupling strategies, or N-alkylation reactions among others. The synthesis of **3** from **2** via the Sonogashira reaction underlines the tolerance of the NB group and further modification possibilities (see Scheme 4).

A wide variety of photo-cleavable derivatives and their further use can be envisioned. As a proof of principle we synthesized the surface active compounds **6** and **7** (see Schemes 2 and 3) that can be applied for self-assembly on gold surfaces and spatially controlled photoinduced reactions. In the first step, *tert*-butyl [4-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl]carbamate (**12**) was obtained via the Pd-catalyzed reaction of 1-bromo-4-*tert*-butoxycarbonylaminobenzene and 2-methylbut-3-yn-2-ol (Scheme 2). Compound **12** was deprotected with tetra-*n*-butyl ammonium fluoride (TBAF) to give the free amine.[50] An activated N–C coupling strategy (EDC and DMAP, as used in peptide synthesis) was used to react 11-(acetylthio)undecanoic acid (synthesized according to published procedures[51]) with **12** to give **6**. Irradiation under