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Citation for the original published paper (version of record):

Gschneidtnr, T., Moth-Poulsen, K. (2013). A photolabile protection strategy for terminal alkynes. Tetrahedron Letters, 54(40): 5426-5429. <http://dx.doi.org/10.1016/j.tetlet.2013.07.144>

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A photolabile protection strategy for terminal alkynes



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ARTICLE INFO

Article history:

Received 21 May 2013

Revised 3 July 2013

Accepted 19 July 2013

Available online 2 August 2013

Keywords:

Photolabile protection

Terminal alkynes

o-Nitrobenzyl

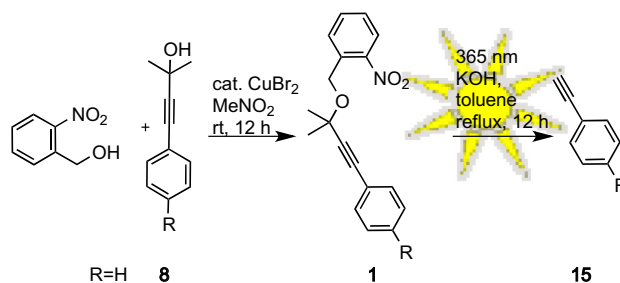
ABSTRACT

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-butyne-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.

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Terminal alkynes are reactive species in a number of important chemical reactions such as the 1,3-dipolar cycloaddition¹ between azides and alkynes to give 1,2,3-triazoles (click-chemistry²), 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



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 CuBr₂. These products can be photo-cleaved under alkaline conditions to give terminal alkynes.

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 carboxylic acids,^{37,38} and alcohols,²⁸ and internal alkynes³⁹ via light activation. For an overview of this field we refer to a review.⁴⁰

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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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 $200 \mu\text{W}/\text{cm}^2$ 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 Sonogashira⁴ 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 rhodium,^{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-workers⁴⁹ has been used in this

study to form the propargylic ether via a mild copper(II)-catalyzed ($\text{S}_{\text{N}}1$) substitution.

The obtained photolabile NB-propargylic ethers were deprotected via irradiation (365 nm, $200 \mu\text{W}/\text{cm}^2$) 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 ^1H 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**) 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 procedures⁵¹) with **12** to give **6**. Irradiation under

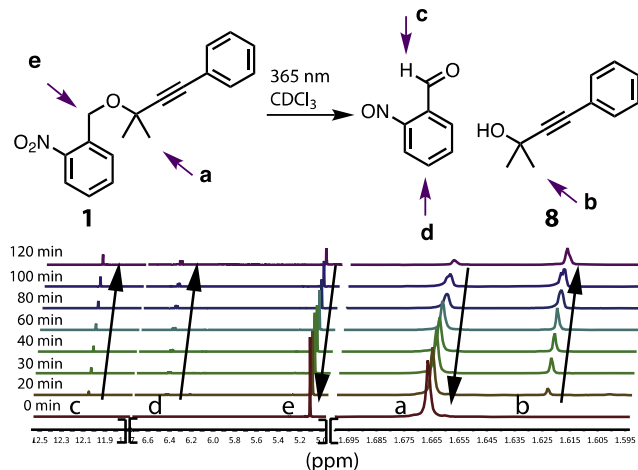
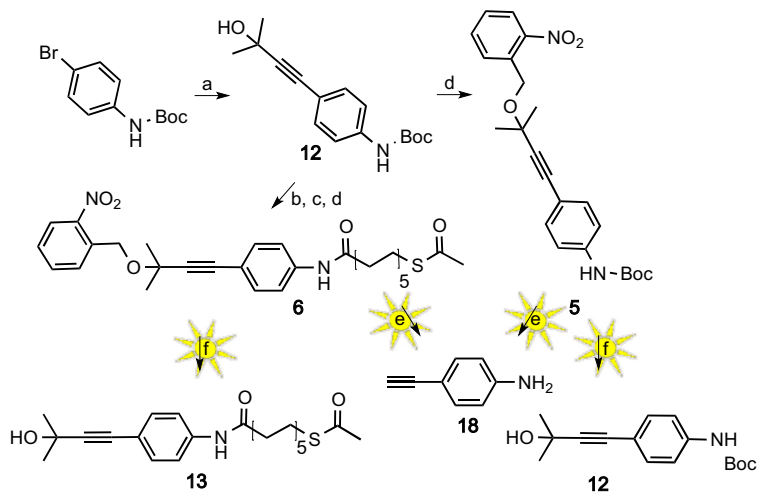
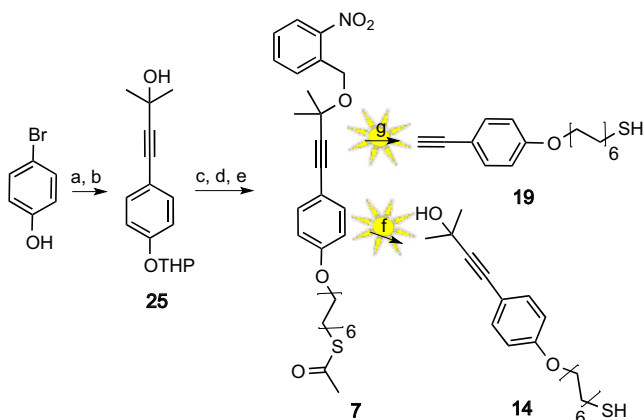


Figure 1. ^1H NMR spectra of **1** in CDCl_3 upon irradiation with UV-light (365 nm, $200 \mu\text{W}/\text{cm}^2$) for 120 min. The formation of **8** and the by-product 2-nitrosobenzaldehyde (lit. values NMR³²) were observed.



Scheme 2. Synthesis of photolabile compounds **5** and **6**. Reagents and conditions: (a) $\text{PdCl}_2(\text{PPh}_3)_2$, NEt_3 , 2-methyl-3-butyn-2-ol, CuI , PPh_3 , THF; (b) TBAF, THF; (c) EDC, DMAP, DMF, 11-(acetylthio)undecanoic acid; (d) CuBr_2 , MeNO_2 , *o*-nitrobenzyl alcohol; (e) 365 nm, KOH , toluene; (f) 365 nm, ethyl acetate.

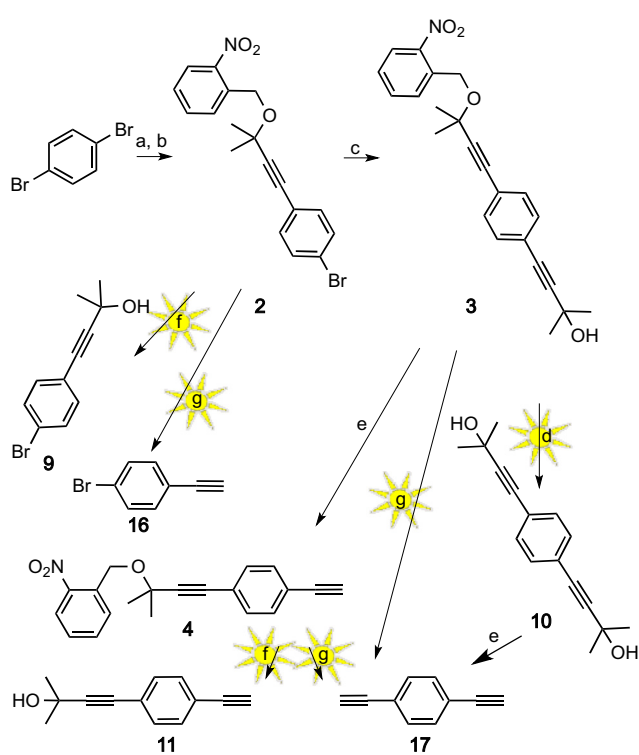


Scheme 3. Synthesis of an alkyne functionalized linker for surfaces, **19**, as well as its photolabile precursor **7**. Reagents and conditions: (a) *p*-TsOH, DCM, 3,4-dihydro-2H-pyran; (b) $\text{PdCl}_2(\text{PPh}_3)_2$, NEt_3 , 2-methyl-3-butyn-2-ol, CuI , PPh_3 , THF; (c) *p*-TsOH, THF/MeOH; (d) K_2CO_3 , DMF, *S*-(12-bromododecyl)thioacetate; (e) CuBr_2 , MeNO_2 , *o*-nitrobenzyl alcohol; (f) 365 nm, ethyl acetate; (g) 365 nm, KOH , toluene.

neutral conditions deprotected **6** and led to the release of alcohol **13**. Irradiation under alkaline conditions (365 nm, 200 $\mu\text{Watt}/\text{cm}^2$, in aq KOH , toluene) hydrolyzed the amide-functionality of photo-caged **6** to give **18**, thus the thiol linker for the gold surface was lost. As a consequence of the limited stability of compound **6** under basic conditions a more stable derivative using an ether instead of an amine (**7**) was designed (Scheme 3).

Substrate **7** was synthesized via protection of the alcohol moiety of 4-bromophenol with 3,4-dihydro-2H-pyran under weakly acidic conditions (*p*-TsOH) followed by a Sonogashira reaction to form **25**. Tetrahydropyran **25** was deprotected to give the free alcohol under acidic conditions and compound **7** was reacted via etherification with *S*-(12-bromododecyl)thioacetate (**22**) (Scheme 3). The NB ether was deprotected by irradiation under alkaline conditions to form the terminal alkyne **19**. Thus, we have shown that it is possible to obtain terminal alkynes with a thiol functionality for self-assembly on gold surfaces.

To demonstrate the use of the photolabile protecting group for terminal alkynes in synthetic organic chemistry, we compared a conventional 2-methyl-3-butyn-2-ol protected alkyne with the NB ether protected compound (Scheme 4). We synthesized compound **3**, which contains both the propargylic alcohol protecting



Scheme 4. Synthesis of the photolabile *ortho*-protecting group **3** and a bromo-substituted photo-caged **2**. Reagents and conditions: (a) $\text{PdCl}_2(\text{PPh}_3)_2$, NEt_3 , 2-methyl-3-butyn-2-ol, CuI , PPh_3 , THF; (b) CuBr_2 , MeNO_2 , *o*-nitrobenzyl alcohol; (c) $\text{PdCl}_2(\text{PPh}_3)_2$, NEt_3 , 2-methyl-3-butyn-2-ol, CuI , PPh_3 , THF; (d) 365 nm, ethylacetate; (e) KOH , toluene; (f) 365 nm, ethyl acetate; (g) 365 nm, KOH , toluene.

group for alkynes and the photo-caged propargylic alcohol. To achieve this, 1,4-dibromobenzene was reacted with 2-methyl-3-butyn-2-ol and *o*-nitrobenzyl alcohol was introduced to form photo-caged **2**. This was transformed into **3** by the Sonogashira reaction in the dark at 80 $^\circ\text{C}$, which demonstrates the high stability of this photolabile compound. Alcohol **3** was then deprotected to give **4** under basic conditions (KOH , toluene, reflux, dark), leaving the photolabile group intact. Additionally, **3** was deprotected with UV light (365 nm) to form **10** and irradiation under alkaline conditions gave the terminal alkyne **17**. We showed that the propargylic

alkyne protecting group was removed under traditional alkaline deprotection conditions, while the NB-propargylic protected alcohol group stayed intact in all cases.

In summary, we have developed a method to synthesize tertiary propargylic ether NB-photo-cages, which can release terminal alkynes upon UV-irradiation under alkaline conditions. These photo-protected propargylic alcohols add to the portfolio of alkyne protecting groups, and we envision their possible use in synthetic organic chemistry. A new light-sensitive protection strategy was applied to synthesize functional photo-cages that can be used for further post-modification reactions. The presented thiol-functionalized photocages may serve as agents for chemoselective, site-specific surface modification reactions on metal surfaces in future investigations.

Acknowledgment

This work was funded by Chalmers Materials Area of Advance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.07.144>.

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