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Synthesis and Photochemistry of a New Photolabile Protecting Group for Propargylic Alcohols

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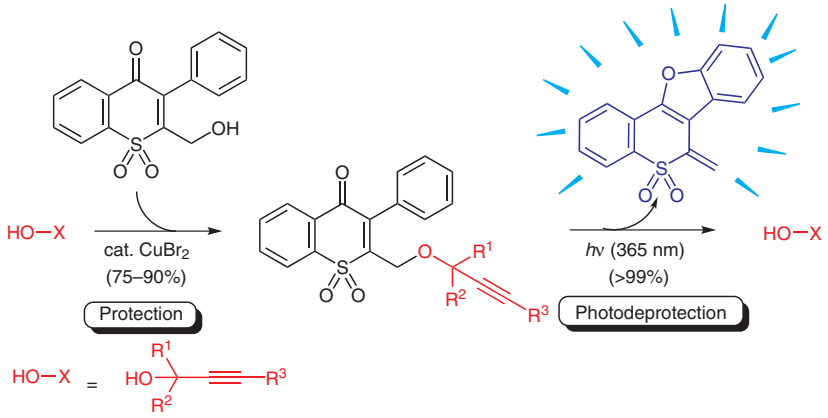

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Abstract A new and efficient thiochromenone *S*,*S*-dioxide-based photolabile protecting group for propargylic alcohols is described. Robust protection reactions were developed through copper (II)-catalyzed substitution of propargylic alcohols. Subsequent photodeprotection proceeded smoothly to give the corresponding propargylic alcohols quantitatively within 15 minutes, as demonstrated by ^{1}H NMR spectroscopy and HPLC. Notably, the photoproduct derived from the thiochromenone derivatives showed a high fluorescence quantum yield, permitting monitoring of the reaction progress by fluorescence spectroscopy. A new strategy for the synthesis of triazoles by a one-pot reaction is also presented.

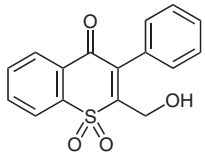
Key words thiochromenone dioxides, protecting group, propargylic alcohols, photodeprotection, photolabile groups, triazoles

In organic synthesis it is sometimes necessary to protect and subsequently deprotect functional groups under chemically selective conditions to prevent undesired side reactions and to promote desired reactions.[1] However, harsh reaction conditions involving, for example acids, bases, or highly reactive reagents, are frequently required during deprotection, leading to limitations on the range of applications of protecting groups. Therefore, mild deprotection methods are appealing for effective organic synthesis. Among the various protecting groups available, much attention has been paid to photolabile protecting groups (PLPGs), which have valuable and unique features.[2] Photodeprotection processes can be performed simply by photoirradiation under neutral and reagent-free conditions.[3] For biological and medical research, this approach with clean photochemistry provides an indispensable method for the introduction of biologically active compounds into cell or tissue cultures, where spatial and/or temporal control is desired.[4] The applications of PLPGs are by no means limited to biochemical kinetic studies and they also include photolithography, DNA synthesis and microarray fabrication, surface patterning, photolithographic preparation of high-density biochips, and solid-state synthesis.[5]

Some chromophores such as *o*-nitrobenzyl,[6] nitroindoline,[7] (coumarin-4-yl)methyl,[8] and *p*-hydroxyphenacyl groups[9] are widely used as excellent PLPGs. However, to extend the range of applications of PLPGs, the discovery of new PLPGs is required. It is well known that thiochromenone derivatives have a conjugated system that extends over the bicyclic skeleton.[10] However, their study in the field of PLPGs has seldom been reported. We recently designed and synthesized a series of efficient novel PLPGs for various alcohols, amines, carboxylic acids, phosphoric acids, ketones, and aldehydes.[11–14] These PLPGs possess a photorecognition ability based on the presence of a thiochromenone as a parent structure.

We recently developed a novel photolabile protecting group based on 2-(hydroxymethyl)-3-phenyl-4*H*-thiochromen-4-one 1,1-dioxide (**PLPG 1**; Figure 1) and we applied it initially in the protection and photodeprotection of carboxylic acids.[11] The new PLPG has some advantageous features; for example, it is easily synthesized from commercially available inexpensive materials, it has high protection/deprotection efficiencies, and it possesses remarkable stability in darkness. In particular, photodeprotection proceeds smoothly to release the target compounds almost quantitatively under irradiation. Furthermore, **PLPG 1** pro-

duces highly fluorescent products (fluorescence quantum yield ≈ 0.85).[11] Here, we reported our efforts in further enriching the scope of **PLPG 1**.



PLPG 1

Figure 1 Structure of **PLPG 1**

Among various functional groups, we were particularly interested in developing **PLPG 1** for use with propargylic alcohols (Scheme 1). Propargylic alcohols and their derivatives are an important class of organic compounds.[15] They are attractive, and have been extensively applied, as synthetic intermediates in modern organic synthesis. For example, the Meyer–Schuster rearrangement of propargylic alcohols provides an efficient strategy for the construction of various enones, carbocycles, and heterocycles.[16] However, few practically useful protecting groups for propargylic alcohols are known. Moth–Poulsen et al.[17] presented a strategy for photolabile protection of terminal alkynes that involved protection and photodeprotection of tertiary propargylic alcohols with the classical *o*-nitrobenzyl protecting group. Starke et al.[18] used cyclopropenones as photocleavable precursors that can be converted into the corresponding alkynes through UV irradiation. With continuing research in the chemistry of propargylic alcohols and their derivatives, novel PLPGs can be anticipated to appear in the future and to be applied extensively in practical syntheses.

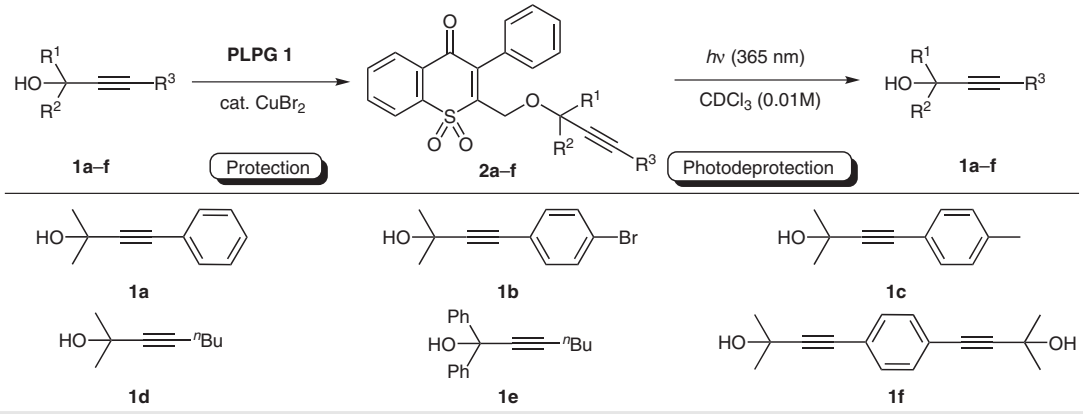
The new **PLPG 1** was promising in protecting propargylic alcohols and was therefore further examined with various substrates to determine its application scope.[19] Propargylic ethers are rarely synthesized by mild methods and are usually prepared by using Lewis acids, or transition-metal complexes of, for example, cobalt (the Nicholas reaction), rhenium, or ruthenium.[20] The protection reactions were carried out by a mild copper-catalyzed nucleophilic substitution reaction.[21] Treatment of propargylic alcohols with 1.25 equivalents of **PLPG 1** in the presence of a catalytic amount of $CuBr_2$ at room temperature gave the required protected products **2a–f** in high yields (Table 1).[22] The products **2a–f** were reasonably stable and were insensitive to laboratory lighting.[23]

Table 1 Protection and Photodeprotection of Propargylic Alcohols

Entry	Substrate	Protection[a]		Photodeprotection[b]	
		Time (h)	Yield[c] (%)	Time (min)	Yield[d] (%)
1	**1a**	12	87	15	>99 (98)
2	**1b**	10	85	14	>99 (97)
3	**1c**	13	82	15	>99
4	**1d**	11	90	15	>99
5	**1e**	12	80	13	>99 (98)
6	**1f**	10	75	15	>99 (97)

[a] Reaction conditions: **1** (0.1 mmol), **PLPG 1** (0.125 mmol), $CuBr_2$ (30 μmol), $MeNO_2$ (2.0 mL), r.t.
[b] Reaction conditions: photolysis [6 × 0.25 W UV LED lamps (365 nm)], $CDCl_3$ (0.01 M).
[c] Isolated yield.
[d] Determined by ^1H NMR spectroscopy; isolated yields are given in parentheses.

The photodeprotection reactions were carried out by using a microreactor (KeyChem-Lumino; YMC GmbH, Dinslaken) with 6 × 0.25 W UV LED lamps (365 nm), and the yield was determined by ^1H NMR spectroscopy. Deprotection proceeded smoothly under photoirradiation to give the corresponding propargylic alcohols quantitatively within 15 minutes. All the protected compounds showed similar efficiencies in photodeprotection, giving >99% yields as determined by ^1H NMR spectroscopy (Table 1). To study the



Scheme 1 Protection and photodeprotection of propargylic alcohols

photodeprotection reaction in detail, the reaction of protected product **2a** was monitored by HPLC and by ^{1}H NMR, UV–visible, and fluorescence spectroscopy.

Photodeprotection studies monitored by ^{1}H NMR spectroscopy were carried out by irradiating a 0.01 M solution of protected product **2a** in $CDCl_3$ in an NMR tube; the solution was degassed and, under a nitrogen atmosphere, transferred to the tube by using a syringe pump. Before irradiation, characteristic peaks at δ = 4.61 ppm (H_a; s, 2 H) and δ = 1.53 ppm (H_b; s, 6 H) assigned to the two methylene groups of **2a** were observed. During irradiation, these two peaks disappeared as the reaction proceeded, and a new peak appeared for **1a** at δ = 1.62 ppm ($H_{b'}$; s, 6 H) (Figure 2). After 15 minutes, these ^{1}H NMR spectra showed clearly that the protected product **2a** released the corresponding propargylic alcohol **1a** completely. After the photoreaction, work-up of the reaction mixture gave the tetracyclic compound **3** as yellow crystals, as reported previously.[11–14] ^{1}H NMR spectroscopy also suggested that no unexpected secondary effects interfered with the photolysis during the photoreaction.

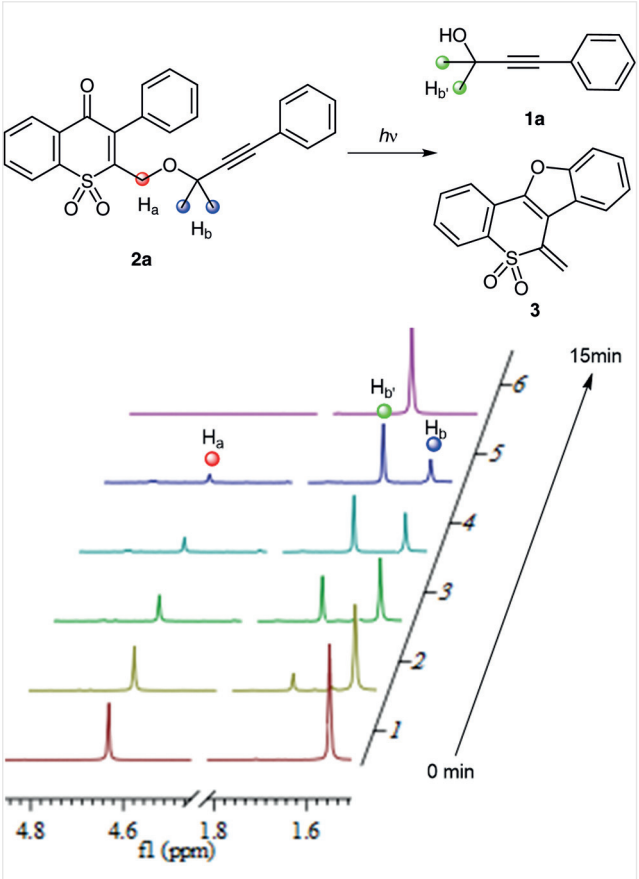


Figure 2 Sections of the ^{1}H NMR spectrum (δ = 1.5–4.8 ppm) of a 0.01 M solution of **2a** in $CDCl_3$ recorded after 0, 3, 6, 9, 12, and 15 min of irradiation.

Next, we used reversed-phase HPLC to investigate the photochemical properties during irradiation at 365 nm. Here, a 0.001 M solution of **2a** in MeOH was prepared to study the progress of the photodeprotection. The chromatography system consisted of a LC-10ATVP pump and SPD-10AVP UV–vis detector (Shimadzu Corp., Kyoto) with an injector (20 µL sample loop). The analysis was performed on a Unitary C_{18} column (5 µm, 250 × 4.6 mm^2) (Acchrom, Beijing) with a Chromatography Data System N2000 (Surwit Technology, Hangzhou). The mobile phase was 80:20 v/v MeOH–H_2O containing 0.1% HOAc, and the flow rate was set at 0.8 mL/min. The wavelength for the detector was set at 252 nm, and the injection volume was 10 µL. The HPLC chromatograms obtained during irradiation are shown in Figure 3. A peak with a retention time of 19.6 minutes, corresponding to **2a**, was observed before irradiation. During irradiation, this peak gradually disappeared as the reaction proceeded, and it was replaced by two new peaks corresponding to the propargylic alcohol **1a** (retention time 5.7 min) and the photolysis product **3** (retention time 8.5 min). After 15 minutes, the propargylic alcohol **1a** was released completely. The ratio of the released alcohol **1a** and the fluorescent compound **3** was 1:1 throughout the photodeprotection reaction. This suggests a promising method for the exact quantification of the substrate released under the photolysis conditions. Importantly, these results also confirmed that the photodeprotection reaction is not accompanied by any undesirable photochemical side reactions.

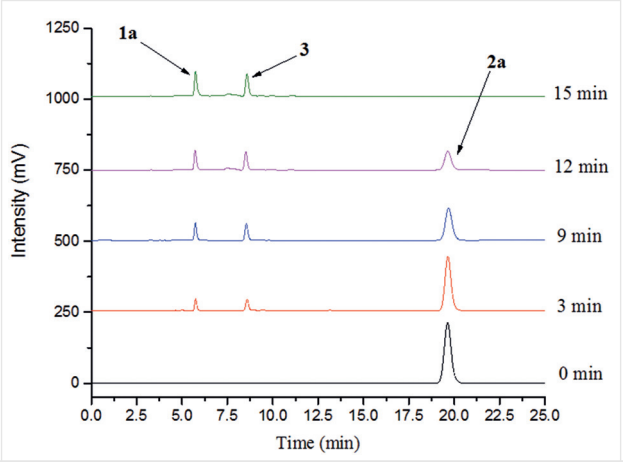


Figure 3 HPLC traces recorded during irradiation (0, 3, 9, 12, and 15 min) of propargylic ether **2a** in MeOH (mobile phase: 80:20 v/v MeOH–H_2O + 0.1% HOAc; flow rate: 0.8 mL/min; detection wavelength: 252 nm; temperature: 20 °C)

Next, photodeprotection of **2a** was performed in a 1-mm-wide quartz cell and monitored by UV–vis and fluorescence spectroscopy (Figure 4). As the reaction proceeded,

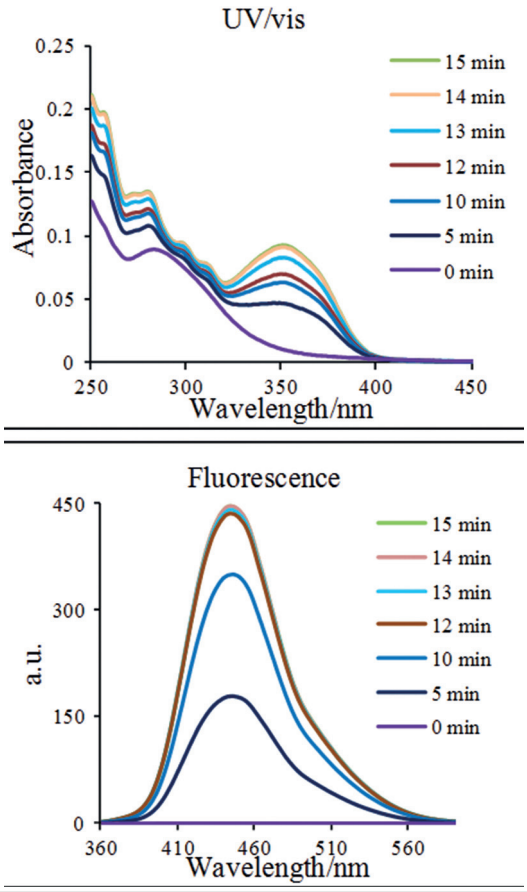
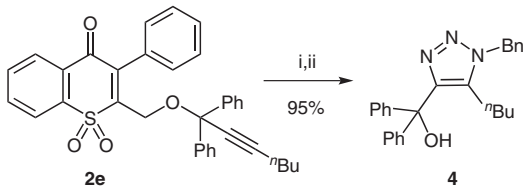


Figure 4 UV-vis and fluorescence spectra upon excitation at 350 nm of a 1.0×10^{-5} M methanolic solution of **2a**, recorded after 0, 5, 10, 12, 13, 14, and 15 min of irradiation

the absorption at around 350 nm increased, and a new fluorescence emission at 445 nm was observed.

The new absorption and emission peaks were attributed to the product **3**. At the same time, the mixture changed from nonfluorescent to highly fluorescent; therefore, the progress of the reaction can be monitored by means of fluorescence spectroscopy.

The protected products are promising substrates for the synthesis of 1,2,3-triazoles, which are frequently used as intermediates in chemical biology, ligand and material design, and pharmaceutical chemistry. Our strategy for triazole synthesis was based on the azide–alkyne cycloaddition reaction (click chemistry),[24] because of the unique ability of **PLPG 1**-protected products to release the corresponding propargylic alcohol photochemically. Propargyl ether **2e** was chosen as a starting material to release the desired propargylic alcohol **1e** through photodeprotection; subsequent azide–alkyne cycloaddition with benzyl azide gave the target triazole **4** as a single isomer[24] (Scheme 2). The one-pot reaction proceeded at room temperature with an excellent yield (95%). This method provides an additional route for the the preparation of triazoles in synthetic organic chemistry, and has potential applications in click chemistry.



Scheme 2 Application in azide–alkyne cycloaddition for the synthesis of a 1,2,3-triazole. *Reagents and conditions*: (i) *hv* (365 nm), CH_2Cl_2, r.t., 15 min; (ii) BnN_3 (1.5 equiv), $BF_3{\cdot}OEt_2$ (1.2 equiv), CH_2Cl_2, r.t., 5 min.

In summary, a novel photolabile protecting group for propargylic alcohols was developed. The photodeprotection reactions proceeded smoothly under photoirradiation to give the corresponding propargylic alcohols quantitatively within 15 minutes, as demonstrated by ^{1}H NMR spectra and HPLC. Because of its special thiochromenone structure, the photoproduct showed a high fluorescence quantum yield. This unique photochemical property makes it possible to monitor the reaction by fluorescence spectroscopy. A new strategy for triazole synthesis involving the use of the PLPG in a one-pot reaction was presented.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588915.

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(22) **2-{[(1,1-Dimethyl-3-phenylprop-2-yn-1-yl)oxy]methyl}-3-phenyl-4*H*-thiochromen-4-one 1,1-Dioxide (2a)**
Yellow oil; yield: 38.5 mg (87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (dd, *J* = 8.0, 0.8 Hz, 1 H), 8.12 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.87 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1 H), 7.75 (ddd, *J* = 8.0, 7.6, 1.2 Hz, 1 H), 7.43–7.38 (m, 3 H), 7.36–7.34 (m, 2 H), 7.30–7.27 (m, 5 H), 4.61 (s, 2 H), 1.53 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 147.3, 144.2, 141.0, 134.5, 132.9, 131.7, 131.4, 129.5, 129.33, 129.30, 128.8, 128.3, 128.1, 128.0, 123.2, 122.5, 89.8, 85.6, 72.0, 58.1, 28.5. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{27}H_{23}O_4S$: 443.1317; found: 443.1327. For **2b–f**, see Supporting Information.
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