



A family of stilbene-ethers as photolabile protecting groups for primary alcohols offers controlled deprotection based on choice of wavelength



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ABSTRACT

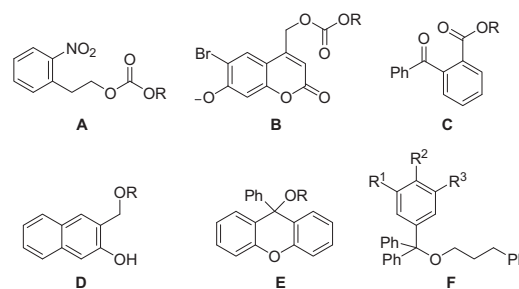
A novel stilbene-ether type of photolabile protecting group (PPG) for hydroxyl group has been developed. It contains a stable aryl ether group in the protected form and can be deprotected by acid-catalyzed photorearrangement under 300-nm irradiation. The selective deprotection has also been achieved by irradiation of the mixture of 4-alkoxystilbene and 2-(4-alkoxystyryl)furan at 365 nm.

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1. Introduction

Photolabile protecting groups (PPGs) have several merits to the conventional protecting groups. Their advantages include spatial and temporal controls and orthogonal reaction conditions to most of thermal reactions, so that PPGs are widely used in the areas of organic synthesis, biochemically caged compounds, and solid-phase synthesis.¹ Some PPGs have been developed for the protection of hydroxyl group, including 2-nitrobenzene derivative **A**,² coumarin-4-ylmethoxycarbonyl **B**,³ *o*-benzoylbenzoate ester **C**,⁴ 3-hydroxy-2-naphthalenemethanol **D**,⁵ 9-phenylxanthen-9-yl ether **E**,⁶ and trityl ether **F**⁷ (Scheme 1). In order to phototrigger deprotection reactions, these PPGs usually contain some acid- and base-sensitive functional groups, such as nitro, carbonate, ester, hydroxyl, and triphenyl ether groups.⁸ Therefore, to develop a new type of PPG that can be stable under most of acidic and basic conditions is an important issue.

Aryl alkyl ether is a stable functional group to most of acidic and basic reaction conditions, but it is seldom used as a protecting group. That is because decomposition of aryl alkyl ethers usually needs strong reagents,⁹ such as oxidants for methyl phenyl ether¹⁰ and Lewis acids for isopropyl aryl ether.¹¹ However, a unique

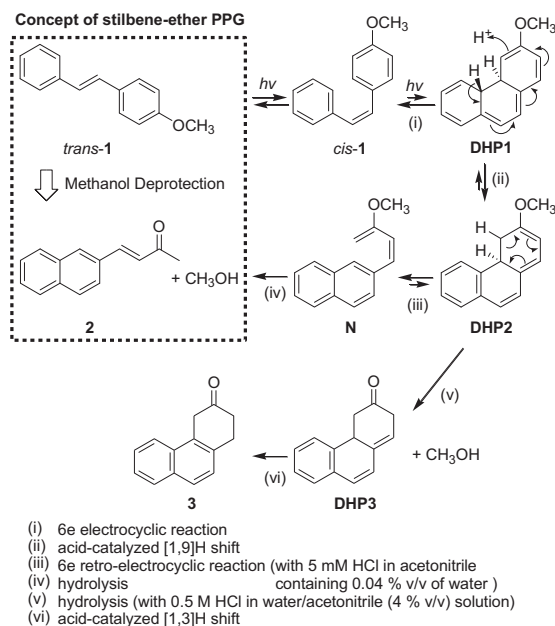


Scheme 1. Selected photolabile protecting groups of alcohols.

acid-catalyzed photorearrangement of stilbenyl ethers reported by Ho's group¹² has shown the ability to decompose aryl ethers under a mild condition (Scheme 2). One of the reported examples^{12c} was the irradiation of 4-methoxystilbene **1**. When **1** was irradiated with 5 mM of hydrochloric acid in acetonitrile ([water] is ca. 73.6 mM),¹³ 4-naphthan-2-yl-but-3-en-2-one **2** could be obtained. And when **1** was irradiated with 0.5 M of hydrochloric acid in water/acetonitrile ([water] is ca. 2.2 M)¹³ solution, 1,4-dihydro-2*H*-phenanthren-3-one **3** would be formed as the major product. The proposed mechanism for the formation of compounds **2** and **3** shows multiple steps, including photocyclization, acid-catalyzed [1,9] and [1,3] hydrogen shift, 6e retro-electrocyclic reaction, and hydrolysis. The aromatization (**DHP1** to **DHP2** and **DHP2** to **N**) and hydrolysis

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provide the driving force for this acid-catalyzed photorearrangement.



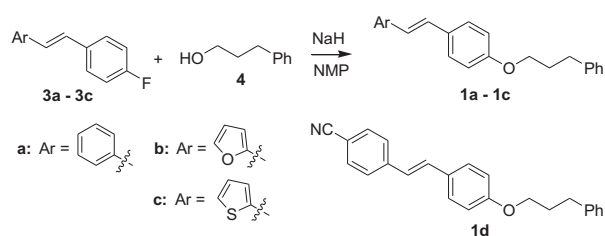
Scheme 2. Mechanism of acid-catalyzed photorearrangement of stilbenyl ethers and our concept of stilbene-ethers of PPG.

Our concept is to utilize stilbenyl ether as a protected form for alcohols and this acid-catalyzed photorearrangement as the deprotection step, which could change the aryl methyl ether group of compound **1** into the vinyl methyl ether group of intermediate **N**, and then release alcohol by hydrolysis of vinyl methyl ether (Scheme 2). Development of this stilbene-ether PPG contains several features: First, using aryl ether as a protecting group is very stable to most of thermal reaction conditions. Second, the deprotection condition is mild enough to keep the protected molecule from unwanted changes. Third, the necessity of catalytic acid for deprotection provides a safety-catch function.^{2a} Fourth, the selective deprotection may be achieved by different photoreactivities of stilbene-type compounds under selected wavelength irradiation. To the best of our knowledge, this is the first case using the photoreaction of stilbene-type compounds in the field of PPGs. Therefore, we would like to report this family of stilbene-ethers to be a new type of PPG.

2. Results and discussion

2.1. Protection of primary alcohol

The preparations of **1a–c** are outlined in Scheme 3. The precursors **3a–c** were first synthesized by the Wittig reaction of 4-fluorobenzyl bromide and the appropriate aldehydes. Afterward the nucleophilic aromatic substitution¹⁴ (S_NAr) of **3a–c** with 3-phenylpropanol **4** in presence of sodium hydride and *N*-methyl-2-pyrrolidone (NMP) afforded compounds **1a–c**, respectively. But compound **1d** could not be synthesized in the same manner. In order to prepare **1d**, an alternative synthetic method was offered by the Wittig reaction of 4-cyanobenzyl chloride and 4-(3-phenylpropoxy) benzaldehyde, which was synthesized from 4-hydroxybenzaldehyde and 3-phenyl-1-bromopropane. The synthetic yields of compounds **1a–d** are reported in Table 1. For the selection of irradiation wavelength, the absorption maxima of *trans* and *cis*-**1a–d** are also listed in Table 1.



Scheme 3. Syntheses of **1a–c** and the structure of **1d**.

Table 1
Protection yields and absorption maxima of **1a–d**

Entry	Compound	$\lambda_{\text{abs}}^{\text{max}}$ (<i>trans</i>) ^a	$\lambda_{\text{abs}}^{\text{max}}$ (<i>cis</i>) ^a	Yield (%)
1	1a	311 nm	290 nm	87 ^b
2	1b	321 nm	307 nm	64 ^b
3	1c	331 nm	298 nm	89 ^b
4	1d	337 nm	318 nm	66 ^c

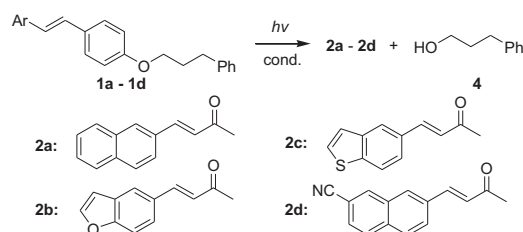
^a 2.5×10^{-5} M in acetonitrile.

^b The yields are determined after gravity chromatography purification twice.

^c The yield includes *cis*- and *trans*-**1d**.

2.2. Deprotection

The deprotection was carried out by irradiation of N_2 -purged solutions of **1a–d** at 300 nm ultraviolet light (Scheme 4), and the reaction conditions and the results are reported in Table 2. First, the irradiation of **1a** in a pure acetonitrile did not release alcohol **4** and only led to *trans*–*cis* isomerization (entry 1). When the irradiation of **1a** was took place in dichloromethane or acidic acetonitrile, the alcohol **4** would be released in moderate to good isolated yields (70–80%, entries 2–4). Deprotection of **1b** and **1c** also released alcohol **4** in good yields (74–88%, entries 5–8) after only 2-h and 4-h irradiation. Finally, irradiation of **1d** resulted in a poor result (55%, entry 9) after a prolonged irradiation time. The poor deprotection of compound **1d** may result from the substitution effect of cyano group on photocyclization reaction.¹⁵



Scheme 4. Deprotection of **1a–d**.

Table 2
Deprotection of **1a–d** by irradiation at 300 nm

Entry	Compound	Solvent ^a	$h\nu$ time (h)	Recovery of SM ^b (%)	Deprotection (%) ^c
1	1a	AN	6	88	0
2	1a	5 mM HCl/AN	6	27	70
3	1a	5 mM HCl/AN	10	8	76
4	1a	DCM	6	15	80
5	1b	5 mM HCl/AN	2	2	88
6	1b	DCM	2	0	81
7	1c	5 mM HCl/AN	4	9	74
8	1c	DCM	4	2	82
9	1d	5 mM HCl/AN	48	18	55

^a AN: CH_3CN , DCM: CH_2Cl_2 .

^b SM: starting material *cis/trans*-**1a–d**.

^c Isolated yield of released alcohol **4**.

It is worthy to mention that undehydrated dichloromethane could let this acid-catalyzed photorearrangement work well

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