



# A novel thiochromone-type photolabile protecting group for carbonyl compounds



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## ABSTRACT

A novel photolabile protecting group, thiochromone *S,S*-dioxide, possessing the 1,2-diol group for protection of ketones and aldehydes is described. Photodeprotection of the successfully protected carbonyl derivatives proceeded smoothly under photoirradiation filtered through Pyrex glass (>280 nm) using an ultrahigh-pressure mercury lamp to recover the corresponding carbonyl compounds and the starting protecting group.

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## 1. Introduction

Protecting groups are essential in organic synthesis, in order to achieve desired reactions by protecting reactive functional groups that are not desired in the reaction. However, most protected compounds are deprotected under acidic or basic conditions, or require a highly reactive reagent, which sometimes leads to an undesired reaction or decomposition of the substrates. In this context, much attention has been paid to photolabile protecting groups (PLPGs), which can be removed only by irradiation of light under neutral conditions without any additional reagents.<sup>1</sup> Thus, introducing PLPGs to substrates is a powerful method to perform desired reactions in organic synthesis. Moreover, since deprotection reactions of PLPGs proceed under irradiation with light, reaction scale can be reduced down to the nanoscale, so that the PLPGs can be applied in not only organic synthesis, but also in construction of DNA microarray,<sup>2</sup> or in caged compounds.<sup>3</sup> Especially, an application of PLPGs to caged compounds is now extensively studied in order to control biochemical reactions in a cell to investigate unknown biological phenomena or to remotely control cell functions, causing a demand for widely applicable and highly-efficient PLPGs.

Although a number of reports on PLPGs have already been published, relatively few PLPGs for ketones and aldehydes have been reported compared to those for alcohols, amines, carboxylic acid, and phosphates, even though there are many biological effectors, such as drugs possessing carbonyl moieties.<sup>4</sup> The first PLPG for carbonyl compounds was reported by Gravel et al., in which a diol derivative of a well-known PLPG *o*-nitrobenzyl group releases carbonyl compounds and  $\alpha$ -hydroxyketone under photoirradiation.<sup>4a</sup> Dore et al. reported a diol coumarin derivative as a PLPG for ketones and aldehydes, which photodeprotects carbonyl compound and regenerate starting PLPG.<sup>4b</sup> They both modified a linker of typical PLPGs to diol and protected ketones and aldehydes as an acetal moiety.

Inspired by their molecular designs, we designed a novel thiochromone PLPG **1d** possessing diol group as a linker, of which derivatives **1a–c** were developed in our laboratory and applied to the protection and deprotection for alcohols, amines, carboxylic acids, and phosphates (Fig. 1).<sup>5</sup> Herein, we report how this design was realized, leading to the development of the novel PLPG **1d** possessing the diol group as linker to connect with ketones and aldehydes.

## 2. Results and discussion

PLPG **1d** was prepared from compound **2**, a common starting material for our PLPGs (Scheme 1).<sup>5</sup> Introduction of methoxy

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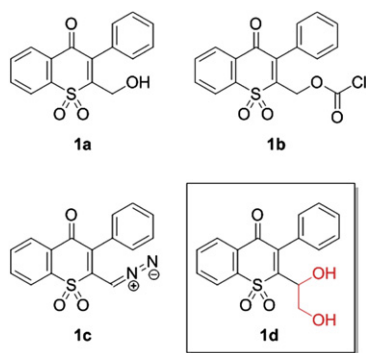
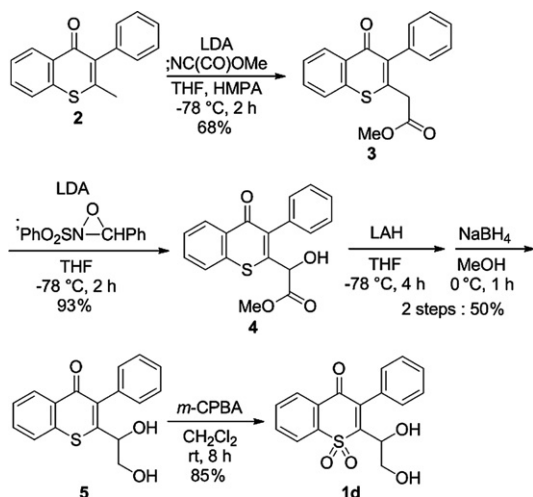


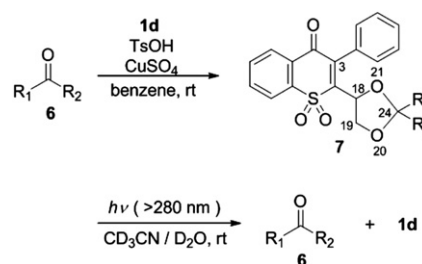
Fig. 1. Structures of new PLPGs.

Scheme 1. Synthetic route for PLPG **1d**.

carbonyl moiety to **2** by LDA and methyl cyanofornate afforded methyl ester **3** in 68% yield.  $\alpha$ -Hydroxylation of ester moiety in **3** using LDA and Davis reagent prepared by a previously reported procedure gave  $\alpha$ -hydroxy methyl ester **4** in 93%.<sup>6</sup> Reduction of ester moiety in **4** to alcohol was achieved in two steps: LAH reduction to give aldehyde intermediate as a crude product, followed by sodium borohydride reduction to give desired diol product **5** in 50% yield. Direct reduction of **4** with LAH or DIBALH did not work well to give complex mixtures including the desired diol **5**. The final step was carried out by oxidation of the sulfur atom of **5** with *m*-CPBA to give target diol PLPG **1d** in 85%.

The new PLPG was promising in protecting the carbonyl compounds and was further examined with various substrates. Protection reactions of the ketones **6a–e** and the aldehyde **6i–j** were straight forward, based on the reaction conditions reported by Wang et al.<sup>4e</sup> Treatment of carbonyl compounds **6** with 1.1 equiv of **1d** in the presence of 10 mol % of *p*-toluenesulfonic acid and 0.8 equiv of copper(II) sulfate in benzene at room temperature afforded the corresponding compounds **7** in high yield (Table 1, entries 1–5, 9, 10). However, protection reactions for ketones **6f–h** were not successful, supposedly due to their steric hindrance (entry 6).

Deprotection of all ketones and aldehydes proceeded smoothly under photoirradiation using a 500 W ultrahigh-pressure mercury lamp filtered through Pyrex glass (>280 nm) within 3 h (Table 1), except for aldehyde **6i** in which moderate photodecomposition of products was observed (entry 9). This decomposition would have happened because of the instability of the aldehyde **6i** under photoreaction conditions.

Table 1  
Protection and photodeprotection of carbonyl compounds **6**

Entry	Carbonyl compound <b>6</b>	Protection		Photodeprotection		
		Time (h)	Yield <sup>a</sup> (%)	Time (min)	Yield <sup>b</sup> (%)	
				<b>6</b>	<b>1d</b>	
1	<b>a</b>	8	95	180	91	90
2	<b>b</b>	24	88	180	99	94
3	<b>c</b>	8	70	180	70	93
4	<b>d</b>	36	80	160	75	92
5	<b>e</b>	15	85 <sup>c</sup>	60	89	89
6	<b>f</b>	55	20 <sup>c</sup>	100	99	99
7	<b>g</b>	8	11 <sup>c</sup>	120	99	89
8	<b>h</b>	44	N.R.	—	—	—
9	<b>i</b>	8	95 <sup>d</sup>	120	58	59
10	<b>j</b>	52	64 <sup>c</sup>	60	79	88

<sup>a</sup> Isolated yield.<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy.<sup>c</sup> Obtained as a diastereomeric mixture.<sup>d</sup> Obtained as a single diastereomer whose stereochemistry is not determined.

Progress of photodeprotection of acetone protected compound **7a** was monitored by <sup>1</sup>H NMR spectra (Fig. 2). Before irradiation, three peaks at 4.8 ppm (*H<sub>a</sub>*, dd, 1H), 4.3 ppm (*H<sub>b</sub>*, dd, 1H) and 4.1 ppm (*H<sub>c</sub>*, dd, 1H) derived from the linker methine and methylene of **7a** were observed. After 30 min irradiation, these peaks diminished and new peaks appeared instead. The peaks observed at 4.6 ppm (*H<sub>a'</sub>*, dt, 1H), 3.9 ppm (*H<sub>b'</sub>*, m, 1H), and 3.7 ppm (*H<sub>c'</sub>*, m, 1H) correspond to the PLPG **1d**. The peak at 2.1 ppm corresponds to acetone. Further irradiation for 120 min made the peaks of the substrate disappeared, while the peaks of the PLPG **1d** and the acetone got stronger, proving that the photodeprotection of **7a** proceeds to release both acetone and PLPG **1d** quantitatively under photoirradiation.

The deprotection mechanism was initially studied with TD-DFT calculations (B3LYP/6–31+g(d)) of the acetone protected compound **7a**, of which HOMO and LUMO maps suggested a charge

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