Synthesis and characterization of thiochromone *S*,*S*-dioxides as new photolabile protecting groups†

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3-Arylthiochromone derivatives were synthesized as new photolabile protecting groups, in which the photoreactivity was switchable based on oxidation of the sulfur atom (sulfide and sulfone); the protected substrates 9,14 released the corresponding alcohols, amines or carbonxylic acids almost quantitatively under UV-light in neutral condition and the photoproduct 10 showed high fluorescence intensity.

Protection and deprotection reactions are essential in the synthesis of multifunctional compounds. In many cases, these reactions are carried out under acidic or basic condition, or require highly reactive reagents, leading to the limitation of use of protecting groups in the synthetic processes.[1] From these viewpoints, much attention has been paid to photolabile protecting groups (PLPGs), which allow deprotection without additional reagents and in neutral conditions.[2] In addition, the recent advances in solid-phase synthesis and combinatorial chemistry caused intensive studies on this type of protection. PLPGs are also utilized for construction of DNA microarray[3] and for synthesis of peptides and caged compounds.[2a]

Chromone, quinolone and thiochromone derivatives have attracted attention for their unique photochemical properties, such as photoabsorption, photoreaction and photochromism.[4] However there is no report on them for PLPGs. In order to develop a new efficient PLPG, we especially focused on thiochromone **1** and the oxidized compound, thiochromone *S*,*S*-dioxide **2** (Chart 1). Compound **1** is easily converted to compound **2**, which may reveal difference in photochemical nature. Thus, we investigated the synthesis and application of **1** and **2** as new PLPGs for alcohols, amines and carboxylic acids.

2-Methyl-3-phenyl thiochromone **5**[5] was prepared by using a modified of the known procedure.[6,7] Condensation reaction of thiophenol with ethyl acetoacetate provided 2-methyl-thiochromone-4-one **3** (Scheme 1).[6] Iodination of **3** with CAN and I_2 followed by Suzuki–Miyaura coupling of the resulting iodide **4** with phenylboronic acid gave the desired compound **5**.[7] Allylic oxidation of **5** with SeO_2 and the subsequent reduction with $NaBH_4$ afforded 2-hydroxymethyl-3-phenyl thiochromone **1**. Furthermore oxidation of the sulfur atom of **1** with 2 equivalents of *m*-CPBA furnished thiochromone *S*,*S*-dioxide **2**.

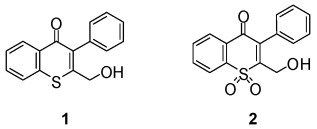
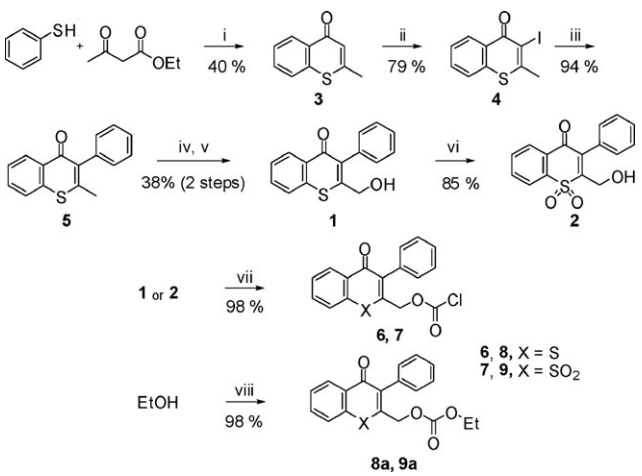


Chart 1 Thiochromone **1** and thiochromone *S*,*S*-dioxide **2**.

Chloroformate derivative **6** or **7** was obtained quantitatively by the treatment of **1** or **2** with phosgene solution prepared *in situ*, and Aliquat® 336. Protecting reaction of ethanol with the isolated **6** or **7** using pyridine proceeded to give **8a** or **9a**, respectively, in high yield.

The photodeprotection reactions were carried out in CD_3OD with an ultra-high pressure mercury lump filtered through Pyrex glass (>280 nm) at room temperature and monitored by ^{1}H-NMR spectroscopy (Scheme 2). Sulfide derivative **8a** was stable under irradiation and was recovered unchanged.[8] In stark contrast, sulfone derivative **9a** released EtOH quantitatively within 0.5 h. Thus the oxidative state of the sulfur atom plays a crucial role in photodeprotection.



Scheme 1 Synthesis of thiochromone derivatives. *Reagents and conditions*: (i) PPA (polyphosphoric acid), 100 °C; (ii) I_2, CAN, CH_3CN, 55 °C; (iii) $PhB(OH)_2$ (1.5 eq), $Pd(PPh_3)_2Cl_2$ (3.0 mol%), K_2CO_3 (3.0 eq), DMF–H_2O, 80 °C; (iv) SeO_2 (1.2 eq), chlorobenzene, reflux; (v) $NaBH_4$ (1.0 eq), MeOH, 0 °C; (vi) *m*-CPBA (2.1 eq), CH_3Cl, r.t.; (vii) phosgene solution (toluene), Aliquat® 336 (1.2 eq), r.t.; (viii) **6** or **7** (1.5 eq), pyridine, r.t.

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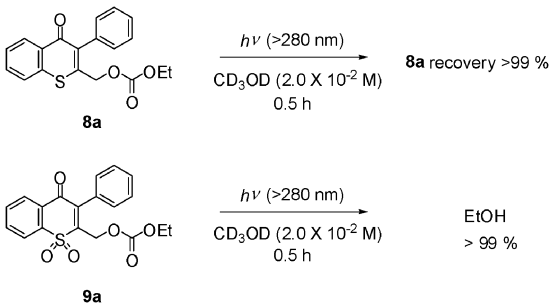
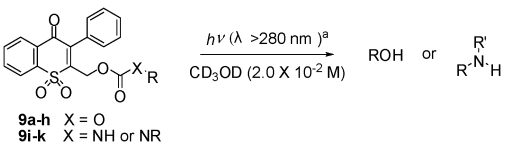
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for new compounds along with NMR spectra (^{1}H, ^{13}C). See DOI: 10.1039/b801860j

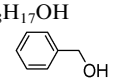
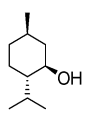
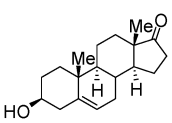
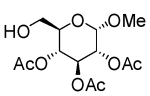
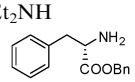


Scheme 2 Photoreaction of thiochromone derivatives.

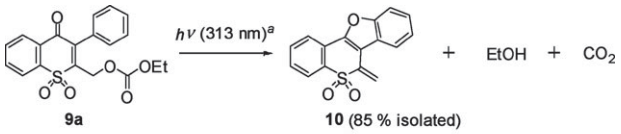
Next, the photodeprotection reactions were examined for various alcohols and amines using **7** (Table 1).[9] The reaction of protected primary alcohols **9a–c** proceeded smoothly to yield the corresponding alcohols (Table 1, entries 1–3). In the cases of secondary alcohols **9d, e**, prolonged time was required for consumption of substrates but the desired alcohols were released effectively (Table 1, entries 4, 5). Photoreactions of the protected chiral and highly functionalized alcohols **9f–h**

Table 1 Photodeprotection of **9**



Entry	Substrate	Alcohol or amine	Irradiation time/h	Yield (%)[b]
1	**9a**	EtOH	0.5	>99
2	**9b**	$C_8H_{17}OH$	0.5	>99
3	**9c**		0.5	>99
4	**9d**		1.0	97
5	**9e**		1.0	98
6	**9f**		1.0	>99 (98)[c]
7	**9g**		1.0	>99 (99)[c]
8	**9h**		0.5	>99 (99)[c]
9	**9i**	$C_4H_9NH_2$	1.0	97
10	**9j**	Et_2NH	1.0	98
11	**9k**		1.0	97

[a] The photoreactions were carried out at room temperature in CD_3OD by irradiation through a Pyrex filter (>280 nm) with an ultra-high-pressure mercury lamp. [b] Determined by ^{1}H-NMR spectroscopy. [c] Isolated yield in parentheses.



[a] Irradiation through UV monochromator at 313 nm in a quartz rectangular cell.

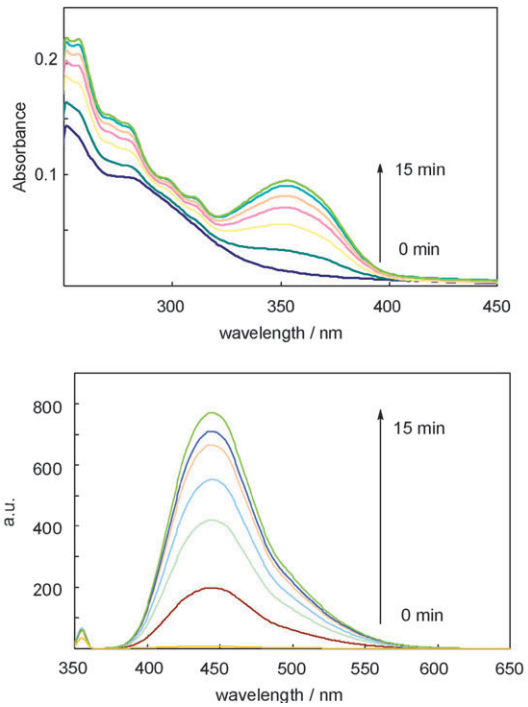
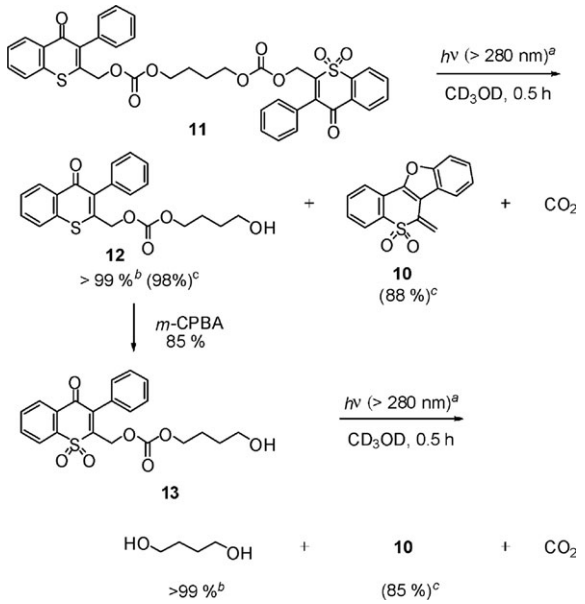


Fig. 1 UV-Vis and fluorescence spectra upon excitation at 365 nm of 1.0×10^{-5} M methanol solution of **9a** recorded after 0, 1, 3, 5, 7, 10, and 15 min of irradiation.

afforded menthol, steroid, and glucose analogues quantitatively without decomposition and changing stereochemistry (Table 1, entries 6–8). As for primary and secondary amines and peptide derivatives, the protection and photodeprotection proceeded effectively (Table 1, entries 9–11).[9] These results demonstrated the utility of **7** in the preparation of peptide compounds.

The photodeprotection reaction of **9a** was also monitored by UV-Vis and fluorescence spectroscopy (Fig. 1). As the reaction proceeded, the absorption at near 365 nm increased, and a new fluorescence emission at 440 nm was observed. After the photoreaction, a work-up of the reaction mixture gave the tetracyclic compound **10** as a yellow crystalline compound, whose structure was determined by NMR spectroscopy and HRMS analysis.[10] Thus the new absorption and emission peaks are attributed to the new product **10**. Irradiation at 350 nm took longer to complete photodeprotection compared with 313 nm, because of **10** bearing the strong absorbance at near 350 nm. Interestingly, **10** has 100 times stronger fluorescent intensity than the starting material **9a**, and the quantum yield for the emission is very high (about 0.85). Therefore monitoring of the reaction progress may be possible by fluorescence spectroscopy.[11]

Sulfide **8a** and sulfone **9a** reveal different photosensitivities as shown in Scheme 2. Thus, two OH groups of 1,4-butanediol

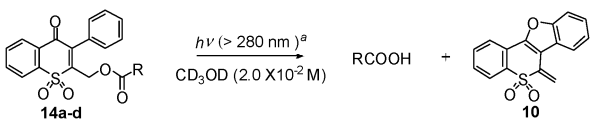


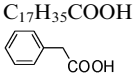
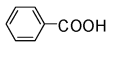
Scheme 3 Switching of photolabile ability. [a]The photoreactions were carried out at room temperature in CD_3OD by irradiation through a Pyrex filter (>280 nm) with an ultra-high-pressure mercury lamp. [b]Determined by ^{1}H-NMR spectroscopy. [c]Isolated yield in parentheses.

were masked separately with sulfone and sulfide derivatives to give **11** for selective deprotection (Scheme 3). When the photodeprotection reaction was carried out in the same conditions as above, the sulfone moiety was selectively removed to provide sulfide **12** in quantitative yield. The sulfide was easily converted to sulfone **13**, and the second photodeprotection of **13** proceeded smoothly to release 1,4-butandiol.

Thiochromone derivative is also a candidate as a photolabile protecting group for various carboxylic acid (Table 2).[12] Aliphatic and aromatic carboxylic acids were completely released by photo irradiation of **14a–d** within 1.0 h. In these reactions, compound **10** was also produced similar to the reaction of **9**, so photodeprotection can be confirmed by the observation of the fluorescence emission of **10** under black light.

Table 2 Photodeprotection of **14**



Entry	Substrate	RCOOH	Irradiation time/h	Yield (%)[b]
1	**14a**	$C_{11}H_{23}COOH$	1.0	>99
2	**14b**	$C_{17}H_{35}COOH$	1.0	>99
3	**14c**		1.0	>99
4	**14d**		1.0	>99

[a] The photoreactions were carried out at room temperature in CD_3OD by irradiation through a Pyrex filter (>280 nm) with an ultra-high-pressure mercury lamp. [b] Determined by ^{1}H-NMR spectroscopy.

In summary, we prepared novel photolabile protecting groups, thiochromone *S*,*S*-dioxide **2**, **7** for various alcohols, amines and carboxylic acids. The photodeprotection proceeded smoothly to release alcohols, amines or carboxylic acids almost quantitatively under UV light. The protected substrates were stable in dark conditions.[13] The applications of thiochromone type PLPGs to other functional groups as well as the elucidation of the reaction mechanism are under way.[14]

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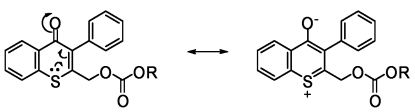
Notes and references

1 T. W. G. Green and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley-Interscience, John Wiley & Sons, Inc., 2007.
2 Recent reports and reviews: (*a*) G. Mayer and A. Heckel, *Angew. Chem., Int. Ed.*, 2006, **45**, 4900; (*b*) T. Igarashi, M. Shimokawa, M. Iwasaki, K. Nagata, M. Fujii and T. Sakurai, *Synlett*, 2007, **9**, 1436; (*c*) C. G. Bochet, *J. Chem. Soc., Perkin Trans. 1*, 2002, 125; (*d*) D. Dorman and G. Prestwich, *Trends Biotechnol.*, 2000, **18**, 64.
3 (*a*) S. P. A. Fodor, J. L. Read, M. C. Pirrung, L. Stryer, A. T. Lu and D. Solas, *Science*, 1991, **251**, 767; (*b*) G. H. Mcgall, A. D. Barone, M. Diggelmann, S. P. A. Fodor, E. Gentalen and N. Ngo, *J. Am. Chem. Soc.*, 1997, **119**, 5081; (*c*) M. Schena, *Microarray Analysis*, John Wiley & Sons, Inc., 2003.
4 (*a*) K. R. Huffman, M. Loy and E. F. Ullman, *J. Am. Chem. Soc.*, 1965, **87**, 5417; (*b*) V. Rossollin, V. Lokshin, A. Samat and R. Guglielmetti, *Tetrahedron*, 2003, **59**, 7725.
5 F. Bossert, *Tetrahedron Lett.*, 1968, **9**, 4375.
6 M. H. Holshouser, L. J. Loeffler and I. H. Hall, *J. Med. Chem.*, 1981, **24**, 853.
7 F. J. Zhang and Y. L. Li, *Synthesis*, 1993, 565.
8 The stability may be based on the intramolecular CT state, see: T. Patonay, W. Adam, A. Lévai, P. Kövér and M. Németh, *J. Org. Chem.*, 2001, **66**, 2275



9 Protected alcohols and amines (**9a–c**, **9h–k**) were provided in good yields (84–98%). In the case of secondary alcohols (**9d–g**) the protection yields were decreased (66–71%). Optimization of the protection is in progress; see ESI†.
10 **10**: ^{1}H-NMR ($CDCl_3$, TMS) (ppm) δ: 8.02 (1H, J = 7.9 Hz, d), 7.91 (1H, J = 7.9 Hz, d), 7.68 (1H, J = 7.9 Hz, d), 7.63 (1H, J = 7.9, 7.9 Hz, dd), 7.53 (1H, J = 7.9 Hz, d), 7.48 (1H, J = 7.9, 7.9 Hz, dd), 7.36 (1H, J = 7.9, 7.9 Hz, dd), 7.31 (1H, J = 7.9, 7.9 Hz, dd), 6.62 (1H, J = 1.8 Hz, d), 6.38 (1H, J = 1.8 Hz, d). ^{13}C-NMR ($CDCl_3$) 155.03, 146.92, 141.04, 136.30, 133.27, 129.46, 126.61, 125.77, 125.05, 124.49, 124.44, 123.93, 120.33, 119.63, 112.20, 111.54. IR ($CHCl_3$) 1309, 1223, 1212, 1207, 1155, 1129, 789, 781, 758. HRMS(EI) calcd. for $C_{16}H_{10}O_3S$ 282.0351; found: 282.0351.
11 H. Shiono, *Jpn. Pat.*, H11-29500, 1999.
12 Protected carboxylic acids **14a–d** were prepared by the condensation of carboxylic acid and **2** using diisopropyl carbodiimide and DMAP (73–81%); see ESI†.
13 No decomposition of **9a**, **9g**, **9i** and **14a** in $CDCl_3$ was observed for 3 days under room light.
14 The result that the photodeprotection was suppressed in the presence of O_2, suggests that the photoreaction proceeds through a triplet state of the substrate. However, the detail mechanism is not yet fully understood.