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Novel Photolabile Protecting Group for Carbonyl Compounds

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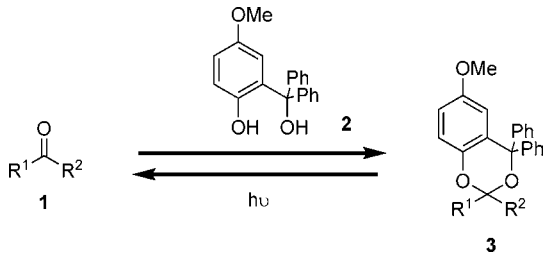
ABSTRACT



A novel type of photo-protecting group for carbonyl compounds is described. The protecting group is readily accessed in one step from commercially available material. Installation of the protecting group upon the carbonyl compounds is achieved in excellent yields. The carbonyl compounds in their protected form are remarkably stable under various conditions and can be released photochemically in high efficiency.

Photochemically labile protecting groups are appealing protective tools in organic synthesis and in life sciences in that the removal process can typically take place under neutral conditions without using any chemical reagents. From the synthetic chemists point of view, photochemical methods are valuable alternatives to the conventional approaches, which employ acids, bases, or reducing or oxidizing reagents. For biological and medical research, this approach provides an indispensable method for the introduction of biologically active compounds to the cell or tissue culture in a spatially and temporally controlled manner, which is of utmost significance to time-resolved biological studies and precisely controlled drug release. Photolabile groups that protect alcohols, amines, amides, carboxylic acids, and phosphates have been well documented.[1] However, there are few practically useful protecting groups for aldehydes and ketones.[2]

Carbonyl groups play key roles in organic chemistry and often need to be protected in a multistep synthesis against various reagents including reactive nucleophiles, reducing agents, and oxidants. Availability of a rich body of protective tools for carbonyls in the organic arsenal facilitates synthesis design. In addition, many carbonyl compounds have biological activities.[3,4] Photochemical release of caged carbonyl compounds is of interest to basic biological research and biomedical applications.

Efforts toward developing photolabile protecting groups for carbonyl compounds date back three decades, and progress has been made since.[2] Nevertheless, apparent

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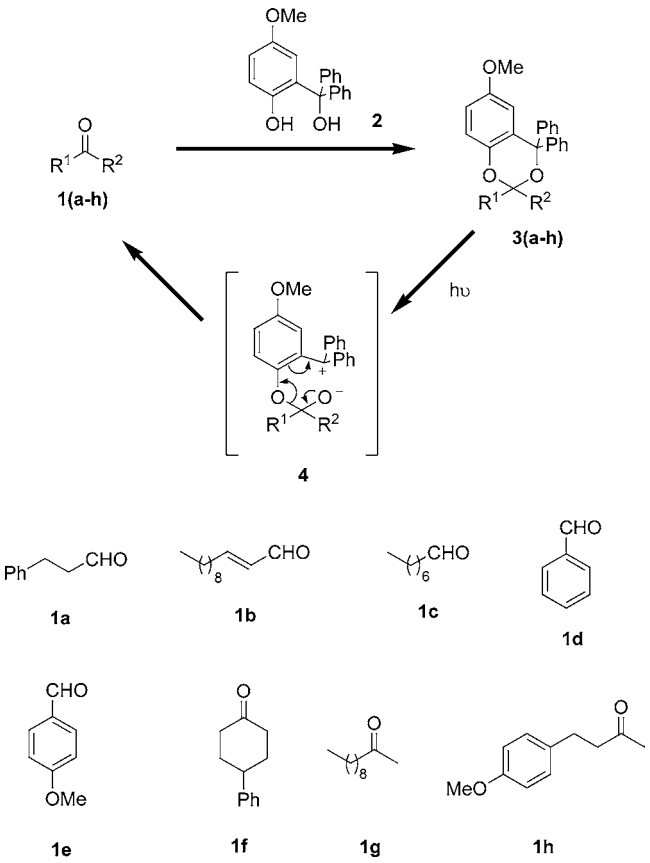
drawbacks hindered utilization of those early approaches in organic synthesis and biomedical research. For example, protecting groups based on well-established *ortho*-nitrobenzyl photochemistry have the inherent limitations of being sensitive to reactive organometallic reagents and reducing reagents, which restricts the scope of their application in organic synthesis. It also has been pointed out that their photochemical properties are not ideal for biological research.[5]

Here we report a novel photolabile protecting approach for carbonyl groups. Carbonyl compounds (**1a**−**h**) protected by 5-methoxysalicylic alcohol (**2**) in the form of cyclic ketals/acetals (**3a**−**h**) (Scheme 1) can be released upon irradiation,

Scheme 1. Protection of Carbonyls with 5-Methoxysalicylic Alcohol (**2**)



presumably via a zwitterionic intermediate **4**.

5-Methoxysalicylic alcohol (**2**) was readily prepared from the commercially available and inexpensive 5-methoxysalicylic acid by reacting with phenyl magnesium bromide. Protection of aldehydes **1a**−**e** was straightforward. Treatment of aldehydes with 1.5 equiv of **2** in the presence of 10 mol % of *p*TsOH in benzene at room temperature afforded the acetals in excellent yields (Table 1, entries 1−5). When the same procedure was applied to ketones, no significant yields could be achieved. Anhydrous $CuSO_4$ was required as a dehydrating reagent in the case of protecting 4-phenylcyclohexanone (**1f**) (Table 1, entry 6).[6] For linear ketones **1g** and **1h**, P_2O_5 worked best as the dehydrating reagent to provide high yields of protection (Table 1, entries 7 and 8).

Table 1. Protection and Photorelease of the Carbonyls

entry	carbonyl compounds	protection yield (%)	deprotection yield (%)	irradiation time (min)
1	**1a**	99[a]	90[e]	60
2	**1b**	91[a]	89 (Z/E = 1.4)[e]	40
3	**1c**	95[a]	85[f]	50
4	**1d**	>99[a]	74[e]	60
5	**1e**	99[a]	89[e]	60
6	**1f**	97[b]	80[g]	80
7	**1g**	93[c]	84[e]	80
8	**1h**	91[c]	86[g]	60

[a] **2** (0.3 mmol), *p*TsOH (0.02 mmol), and carbonyl compound (0.2 mmol) in 1.0 mL of benzene, 23 °C, 24 h. [b] **2** (0.3 mmol), *p*TsOH (0.02 mmol), carbonyl compound (0.2 mmol), and $CuSO_4$ (0.8 mmol) in 1.0 mL of benzene, 23 °C, 24 h. [c] **2** (0.3 mmol), *p*TsOH (0.02 mmol), carbonyl compound (0.2 mmol), and P_2O_5 (0.8 mmol) in 1.0 mL of benzene, 23 °C, 24 h. [d] Irradiated with a 450 W medium-pressure mercury lamp equipped with a Pyrex filter sleeve. [e] Isolated as the oxime derivatives. [f] Isolated as the semicarbazone derivative. [g] Isolated as the ketone without derivatization.

Photolysis of acetals **3a**−**e** was carried out in acetonitrile without excluding air. Photochemical release of aldehydes went smoothly.[7] Given the volatile nature of the carbonyl compounds tested, the released aldehydes were subjected to simple derivatization.[8] Oxime derivatives of aliphatic aldehydes **1a**,**b** and the semicarbazone derivative of octyl aldehyde (**1c**) were obtained in 90%, 89%, and 85% yield, respectively, after irradiation for 40−60 min and subsequent derivatization (Table 1, entries 1−3). Isomerization of the double bond in *trans*-2-dodecenal (**1b**) was observed during the irradiation. High yields of isolated oxime derivatives of aromatic aldehydes **1d**,**e** were also furnished after 60 min of irradiation and derivatization (Table 1, entries 4 and 5). It was noticed that the reaction media had an expected effect on the rate of photoreaction releasing aldehydes. For example, irradiation of **3a** for 30 min afforded a **1a**/**3a** ratio of 3.3:1 in C_6D_6 and a ratio of 5:1 in CD_3CN.[9]

Compared with acetals, photochemical release of ketones was slower under the same irradiation conditions. For

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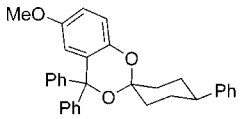
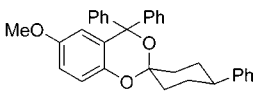
(6) Two stereoisomers of **3f** were obtained in a 2:1 ratio, favoring **3f(I)**. The structure of **3f(I)** is supported by single-crystal X-ray analysis.



3f(I)



3f(II)

(7) Under the photolysis conditions, no significant decomposition of the carbonyl compounds was detected.

(8) Acetals (**3a**−**h**) are stable under the derivatizing conditions. The isolated yields of the oximes and semicarbazone are consistent with the yields estimated from ^{1}H NMR of the underivatized small-scale runs in CD_3CN with an internal standard.[9]

(9) The runs in deuterium solvents were carried out in Pyrex NMR tubes, and the ratios were determined by integrations.

instance, irradiation of **3f** for 30 min led to a **1f**/**3f** ratio of 0.7:1.0 in C_6D_6 and a ratio of 1.3:1.0 in CD_3CN. The optimum value of 1.7:1.0 was reached when 10% (v/v) of water was used as the cosolvent of CD_3CN. Photolysis of **3f** in acetonitrile/water (9:1) for 80 min provided ketone **1f** in 80% isolated yield (Table 1, entry 6), along with 8% recovered **3f**. The oxime of **1g** and underivatized ketone **1h** were also isolated in 84% and 86% yield, respectively, after 80 min of irradiation of **3g** and **3h**.

We postulated that the photochemical reaction of **3** went via the zwitterionic intermediate **4**, bearing a triphenylmethyl cation-type of moiety (Scheme 1).[10] Therefore, the substituent groups at the benzylic position (C_α, Figure 1) should be

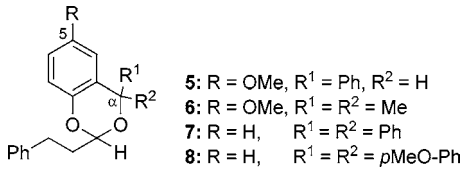


Figure 1. Structural variations of the protecting group.

crucial to the photoreaction efficiency. Indeed, irradiation of **5** (with one phenyl group at C_α, Figure 1) for 30 min led to a **1a**/**5** ratio of 2:1 in CD_3CN. The same irradiation conditions were applied to the acetal **6** (Figure 1, with two methyl groups at C_α), leading to a **1a**/**6** ratio of 0.06:1. Another factor that influenced the reaction outcomes is the methoxy group at C5 of the salicylic moiety. Without this methoxyl group, as in acetal **7** (Figure 1), irradiation for 30 min in CD_3CN resulted in a **1a**/**7** ratio of only 0.02:1. Interestingly, acetal **8** (Figure 1, with two 4-methoxyphenyl groups at C_α) is stable under the irradiation conditions (no **1a** was observed after 30 min of irradiation in CD_3CN). These observations suggest that the excited state *meta* effect could also play a role in the photoreaction.[11]

The acetals/ketals (**3a**−**h**) have remarkable dark stabilities under various chemical conditions. For example, neither refluxing in acetonitrile or in benzene for 24 h nor treatment with PhLi, $LiAlH_4$, *t*-BuOK, or DDQ led to detectable decomposition of **3a** (Table 2, entries 1−4). Under acidic conditions, **3a** was also quite stable (Table 2, entries 5−9) except when more than 10 equiv of *p*TsOH was used in MeCN at room temperature (entry 7). In this case, a considerable amount of **1a** (25%) was observed after 24 h. Notably, the typical conditions of cleaving 1,3-dioxanes and 1,3-dioxolanes (i.e., entry 9) did not decompose **3a**.[12] The acetals/ketals (**3a**−**h**) are also stable under laboratory lighting. As such, it is convenient to handle these compounds without special precautions.

Table 2. Stability of **3a** under Various Conditions

entry	reagent[a]	solvent	conditions	**3a** (%)[c]
1	PhLi[b]	THF	−78 to 23 °C, 6 h	100
2	$LiAlH_4$	C_6H_6	23 °C, 24 h	100
			reflux, 2 h	100
3	*t*-BuOK	MeCN	23 °C, 24 h	100
4	DDQ	MeCN	23 °C, 24 h	100
5	AcOH	MeCN	23 °C, 24 h	100
		C_6H_6	23 °C, 24 h	100
		C_6H_6	reflux, 2 h	94
6	TFA	MeCN	23 °C, 24 h	98
		C_6H_6	23 °C, 24 h	93
		C_6H_6	reflux, 2 h	89
7	*p*TsOH	MeCN	23 °C, 24 h	75
		C_6H_6	23 °C, 24 h	95
		C_6H_6	reflux, 2 h	92
8	HCl (37%)	MeCN	23 °C, 24 h	99
		C_6H_6	23 °C, 24 h	96
		C_6H_6	reflux, 2 h	93
9	HCl (1 N)[d]	THF	40 °C, 24 h	100

[a] **3a** (0.01 mmol) in 1.0 mL of MeCN or 0.5 mL of benzene treated with reagent (≥0.1 mmol). [b]**3a** (0.05 mmol) in 1.0 mL of dry THF treated with 0.4 mL of PhLi (2.0 M Bu_2O solution) at −78 °C. [c]Yields determined by ^1H NMR of the crude reaction mixture after workup. [d]**3a** (0.04 mmol) in 0.6 mL of THF with 0.2 mL of 1 N HCl.

In summary, we report a novel type of photo-protecting group for carbonyl compounds. The protecting group is readily accessed in one step from commercially available 5-methoxysalicylic acid. Installation of the protecting group to the carbonyl compounds was achieved in excellent yields with simple protocols. The carbonyl compounds in their protected form are remarkably stable under various conditions and were released photochemically in high efficiency. Furthermore, there is no sensitive functional group carried by the protecting group or introduced during the protecting step, which will facilitate its synthetic applications.

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Supporting Information Available: Experimental details and spectroscopic data for the products **2**, **3a**−**h**, and **5**−**8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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