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A chemoselective photolabile protecting group for aldehydes

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ABSTRACT

A new and high-efficiency photolabile protecting group (PLPG) for aldehydes is described. The PLPG was introduced to aldehydes by using a Lewis acid. Results showed that the PLPG can be released rapidly and smoothly under ultraviolet (UV) irradiation with high efficiency and low cost. This PLPG can easily synthesized and also be selectively protect aldehydes in the presence of ketones.

Photolabile protecting groups (PLPGs) can be removed by irradiation [1] and can release substrates in a spatially and temporally controlled manner. The releasing condition is mild, and no extra chemical reagent is not required [2]. PLPGs can be used to protect various chemical groups, such as alcohols [3], amines [4], and carboxylic acids [5]. Therefore, they are widely used in chemical synthesis and life science, such as synthesis of polypeptide [6] or DNA [7]. Many new PLPGs such as nitroaryl [8], coumarin-4-ylmethyl [9], arylmethyl [10], miscellaneous [11], and arylsulfonyl groups [12] have been developed and extensively used in many areas. However, only a few practically useful photolabile protecting groups for aldehydes, which are commonly used in modern organic synthesis, have been reported [16]. These are diferent from the traditional protecting groups protected aldehydes through an acetal moiety, and then are deprotected by reactions of acid catalysis [13], Lewis acid coordination [14] or redox [15].The PLPG o-nitrophenylethylene glycol (Npeg, Fig. 1) was first reported by Gravel [17] et al. in 1984. Npeg can protect aldehyde compounds and ketone compounds, which will later be released under UV irradiation via deprotection. However, Npeg still have deficiencies, such as long reaction time for deprotection and inability to protect aldehyde selectively. 2-(2-nitrophenyl) propan1-ol (Npp, Fig. 1), a new PLPG, was synthesized and used by Pfleiderer [9] et al. for protecting hydroxyl groups in a series of nucleosides nucleosides; Npp was also applied to the synthesis of cyclic peptide as PLPG for carboxylic groups in our previous studies [18], and the results of these studies indicated that Npp does not affect the stability of polypeptide. In this study, on the basis of Npeg and Npp, we further developed a new, simple, and efficient PLPG particularly for protecting aldehydes. 2-(2-nitrophenyl)-1,3-propanediol (Nppd), as a developed PLPG for protecting aldehydes, was prepared from 2-nitrotoluene, a cheap raw material, via only one step reaction (Scheme 1). Nppd has various advantages, such as simple synthesis with low cost, high efficiency and selectivity for protecting aldehydes without affecting ketones. In addtion, the protected products of aldehydes (acetals) were stable in the absence of light and can rapidly release original aldehydes under UV irradiation with high efficiency.

Some aldehydes (1a-h) and ketones (1i-k) were used to test Nppd's protecting efficiency (Scheme 2, Table 1). The protection of aldehydes by Nppd can be achieved by only a one-step reaction in a relatively mild condition. Particularly, 1 equivalent aldehyde and 2 equivalents of Nppd were dissolved in CH_2Cl_2. Then, 1 equivalent of Lewis acid $BF_3{\bullet}OEt_2$ was added as promoter, and anhydrous magnesium sulfate was added as dehydrating agent. The reaction was conducted at −15 for 90 min to generate the protected product (acetal). Results showed that the low temperature can promote the reaction. For example, the protection yield of 1b was 25% at room temperature, 37% at 0 , and 47% at −15 °C (Table 2). However, the protection yield of 1b in the 24 h reaction was nearly the same with that in the 90 min reaction (Table 3). It can be concluded that the protection yield cannot be increased only by extending the reaction time. Other promoters, such as

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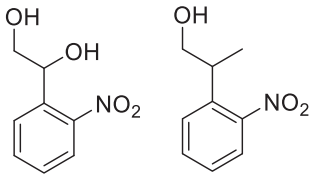
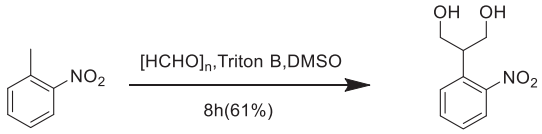
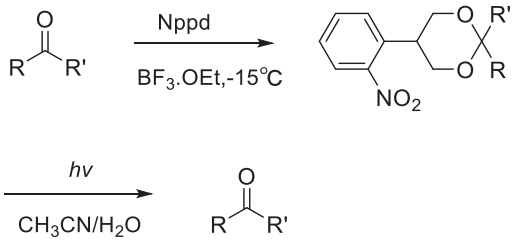


Fig. 1. Structure of Npeg (left) and Npp (right).



Scheme 1. Synthesis of Nppd.



Scheme 2. Protection of Carbonyls with Nppd.

Table 2
The protection yields of 1b under different reaction Time (90 min).

Reaction temperature( )	−15	0	25
Yield(%)	47	37	25

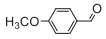
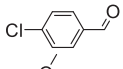
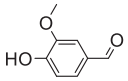
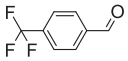
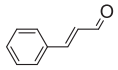
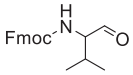
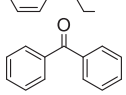
Table 3
The protection yields of 1b under different reaction Time (0).

Reaction time	90 min	24 h
Yield(%)	47	43

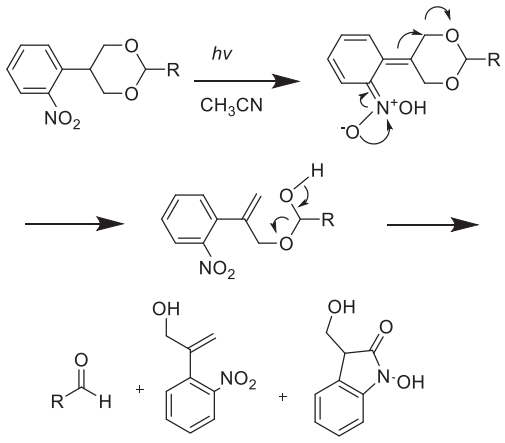
p-toluenesulfonic acid (TsOH), Pyridinium 4-toluenesulfonate (PPTS), and $FeCl_3$, were also used for protecting the aldehyde. Among them, BF_3•OEt_2 has showed a best result.

The reactivity of phenyl carbonyl groups vary depending on the substituents on the benzene ring. The electron-withdrawing substituents can enhance the reactivity while the electron-donating substituents reduce it, both of which will affect Nppd's protective ability. This conclusion has been proven by the production of 2a-c formed by 1a-c. Protective experiments on ketone groups were also studied and the results showed that the protective yields on cyclohexanone, phenylacetone, and diphenyl ketone were 0%, 4%, and 0%, respectively. Even if the $MgSO_4$ was replaced by a more effective dehydrating agent, such as P_2O_5, the ketone group still can't be protected by Nppd. Therefore, only the aldehyde group can be protected by Nppd even in the presence of the ketone group. Photodeprotection then released the corresponding aldehyde. Some aldehydes releasing reaction was performed under UV light at 365 nm in acetonitrile, instead of methanol reported by Wang [16] et al, because the protected product (acetal) has the good solubility in acetonitrile. It is noticed that the photodeprotection

Table 1
Protection and photorelease of the Aldehydes.

Entry	Carbonyl Compounds	Protection Yield[a] (%)	Deprotection Yield[b](%)	Irradiation Time (min)
1a		64	71[c]	120
2b		47	83[c]	60
3c		78	96[e]	60
4d		39	87[e]	60
5e		83	86[e]	120
6f		70	75[e]	75
7g		73	74[d]	80
8h		59	65[e]	90
9i		0	–	–
10j		4	–	–
11k		0	–	–

[a] Reaction conditions: 1 (1 mmol), Nppd (2 mmol), BF_3.OEt_2 (1 mmol), $MgSO_4$ (8.0 mmol) in 6 mL CH_2Cl_2, −15 °C, 90 min, isolated yield.
[b] Reaction conditions: Irradiated with a 250 W UV lamp (365 nm) equipped with a Pyrex filter sleeve, CH_3CN (0.05 M), isolated yield.
[c] Isolated as the oxime derivatives.
[d] Isolated as the semicarbazone derivative.
[e] Isolated as the aldehyde without derivatization.



Scheme 3. Possible photodeprotection mechanism.

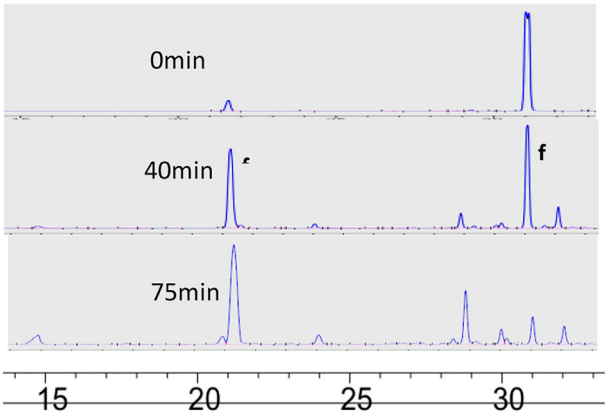


Fig. 3. HPLC traces recorded during irradiation of 2f.

reaction will not proceed without the presence of a certain amount of water. On this basis, a possible photodeprotection mechanism (Scheme 3) according to that of Npp [9] was infered herein. The photorelease of Nppd from the aldehyde's protected product (acetal) via a property-labile semiacetal formed from the acetal by a β-elimination mechanism. The semiacetal was decomposed immediately andyields were lower than the actual values due to their volatility. These aldehydes need to be processed by derivation after the deprotection to eliminate the volatility. For example, if 1a released from 2a after the deprotection is unprocessed by derivation, the releasing yield will fall to 13%.

Results of Nppd's application are illustrated in Table 1, which show that the Nppd can protect aldehydes with relatively high protection and deprotection yields. The protection yields on the aromatic aldehydes (1a, 1b, 1c, 1d, 1e), the unsaturated aldehyde (1f), the amino aldehyde protected by Fmoc (1h), and the aliphatic aldehyde (1g) were 64%, 47%, 78%, 39%, 83%, 70%, 73%, and 59%, respectively. In addition, their deprotection yields were 71%, 83%, 96%, 87%, 86%, 75%, 65%, and 74%. Amino aldehydes are widely used to synthesize medicine and can be served as precursors of synthetic antimicrobial drugs penicillin [19] or anticancer drug [20], and they also play an important role in synthesizing pseudopeptide. In the meanwhile, the amino groups or aldehyde groups of amino aldehydes are usually protected when they are used because of their chemical instability [21]. In this study, the amino aldehyde protected by Fmoc (1h) can be protected by the Nppd,

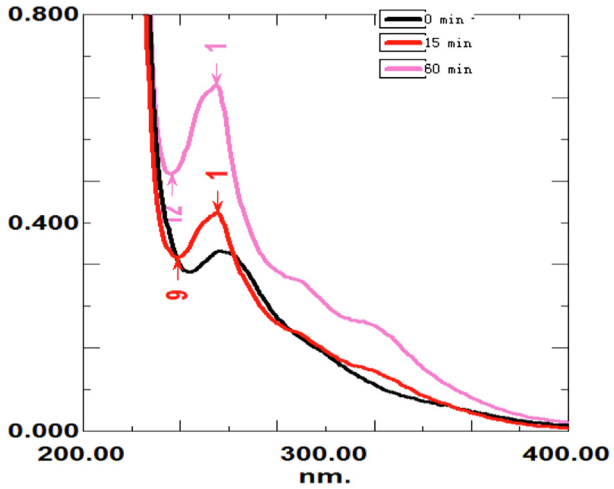


Fig. 2. UV spectra of 2c.

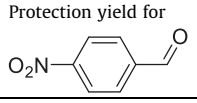
with protection yield of 59% and deprotection yield of 65%. Particularly, a certern amount of water (1 equivalent) has been added into the reaction mixture for every 15 min, to inhibit the thermal effects during the illumination, and to avoid side reaction of the amino aldehyde caused by excessive water.

1c was protected by Nppd to obtain 2c, and the process of deprotection was detected by UV spectrophotometer (Fig. 2). A new absorption peak appeared at the wavelength of 265 nm in the photolysis reaction and would increase gradually with the reaction time prolonging. This peak was the characteristic peak of 1c [22], indicating that the original compound 1c could be released rapidly at a constant speed from its protected compound 2c under UV at 365 nm.

Reversed-phase HPLC was used to investigate the photodeprotection progress of protected aldehydes. For example, 2f (0.02 M in CH_3CN) was investigated during irradiation at 365 nm (Fig. 3). The analysis was performed on Agilent 1100 apparatus equipped with a Agela Venusil ASB C18 column (5 μm, 4.6 mm × 250 mm) over a 10–70% gradient of acetonitrile: water with 0.1% TFA using a gradient elution in 30 min and flow rate of 1 mL/min. The wavelength for the detector was set at 220 nm, and the injection volume was 10 μL. Before irradiation, a peak with a retention time of 31.0 min, corresponding to 2f, was observed. During irradiation, this peak gradually disappeared, and a new peak (retention time 21.2 min, corresponding to 1f) appeared instead, proving that 2f released aldehyde under photoirradiation.

The performance of Nppd and Npeg in protecting efficiency, protecting selectivity, and deprotecting efficiency was compared (Table 4). The results shown in Table 2 indicated that Nppd's protecting efficiency for the carbonyls was lower than that of Npeg. Npeg formed five-membered cyclic acetals, which were easy to obtain, but the aldehyde group cannot be selectively protected by Npeg, and the releasing speed of aldehydes from the Nppd acetal is faster than that from the Npeg acetal. The deprotecting yield of Nppd (65%–96%) is nearly the same with Npeg (31%–90%). However, the reaction time for Nppd was only approximately

Table 4
Comparative protecting efficiency of Nppd and Npeg.

Protecting group	Protection yield for 	Protection yield for 
Nppd	0	78
Npeg	96	97

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33% of that for Npeg. Meanwhile, the amount of solvent for Nppd (15 mL CH_3CN) was just only 10% of that for Npeg (200 mL benzene). The speed of Nppd's releasing protected aldehydes is faster than that of Npeg, and the amount of solvent required is also less, and the solvent is more environmentally friendly.

Conclusion

Nppd, a new PLPG for aldehydes was designed and prepared from a cheap material, namely, 2-nitrotoluene, by a one-step reaction. The aldehydes can be protected by Nppd in mild condition and released rapidly and smoothly under the UV irradiation with high yields. This new PLPG can be used to protect aliphatic, aromatic, unsaturated, and amino aldehydes protected by Fmoc, and has a good application prospect in the field of organic synthesis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151709.

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