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Visible-Light-Induced Acetalization of Aldehydes with Alcohols

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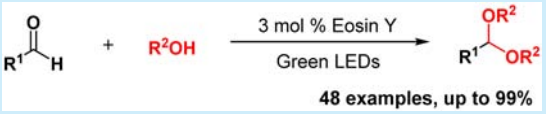
Supporting Information

ABSTRACT: In this work, we have achieved a simple and general method for acetalization of aldehydes by means of a photochemical reaction under low-energy visible light irradiation. A broad range of aromatic, heteroaromatic, and aliphatic aldehydes have been protected under neutral conditions in good to excellent yields using a catalytic amount of Eosin Y as the photocatalyst. Our visible light mediated acetalization strategies are successful for more challenging acid-sensitive aldehydes and sterically hindered aldehydes. Notably, this protocol is chemoselective to aldehydes, while ketones remain intact.

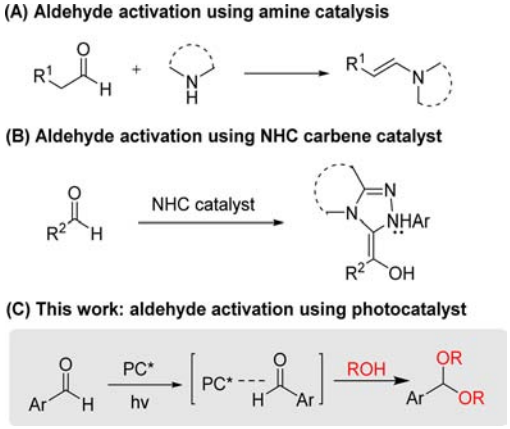


The development of practical synthetic strategies that fulfill green chemistry principles is a research priority for the chemical and pharmaceutical industries. Protection of carbonyl compounds such as aldehydes and ketones via acetal or ketal formation has been a common and powerful tool in multistep synthesis.[1] As a consequence, numerous endeavors have been devoted to the protection of carbonyl compounds.[2] Because the formation and hydrolysis of acetal are in equilibrium, typical procedures for acetalization always require the use of a corrosive acid catalyst, extended reaction times, or environmentally unfavorable solvents.[3] Therefore, it is highly desirable to develop an acetalization protocol that is mild, chemoselective, and cost-effective.

Over the years, various useful and unique organic reactions that are irradiated by visible light have been well-developed.[4] The transformations of aldehydes via photocatalysis have been widely studied through aldehyde activation. The amine is a commonly used catalyst for aldehyde activation in photocatalysis.[5] The in situ generated enamine intermediates can be used to enable the direct functionalization of carbonyls (Scheme 1A). Another method for aldehyde activation[6] is using NHC carbene as the catalyst to generate Breslow intermediates,[7] which can attack the iminium ions (Scheme 1B). These two aldehyde activation strategies require the combination of a photocatalyst with an amine catalyst or carbene catalyst to activate aldehydes. Herein, we have successfully achieved the aldehyde activation solely in the presence of a photocatalyst (Scheme 1C). This usage of low-energy visible light to initiate the acetalization reaction is more appealing. This protocol provides a simple and general way for acetalization of carbonyl compounds with a catalytic amount of Eosin Y as the photosensitizer.

We started our evaluation of visible-light-mediated aldehyde activation reaction parameters using 4-bromobenzaldehyde **1a** and methanol **2a** as model substrates (Table S1). The desired acetal product could be achieved in 99% yield in the presence of 3 mol % photocatalyst Eosin Y under a N_2 atmosphere.

Scheme 1. Models for Aldehyde Activation in Photocatalysis: (A) Aldehyde Activation Using Amine Catalysis; (B) Aldehyde Activation Using NHC Catalyst; (C) Acetalization of Aldehyde through Aldehyde Activation by Photocatalyst



Other tested photocatalysts such as $Acr^+-Mes\ ClO_4^-$, Methylene Blue, and $Ir(Fppy)_2(dtbbpy)(PF_6)$ catalyst could also promote this reaction and afford the product in high yield (Table S1, entries 2–4). However, the photocatalyst $Ru(bpy)_3(PF_6)_2$ did not promote this reaction. In the control experiments, no desired product was observed with neither the photocatalyst nor light indicating that both the photocatalyst and light are essential to this acetalization process (Table S1, entries 5, 6 and 7).

With the optimal conditions established, acetalization of various aldehydes with methanol has been examined. As illustrated in Scheme 2, we find that this new visible light mediated acetalization protocol allows direct protection of a

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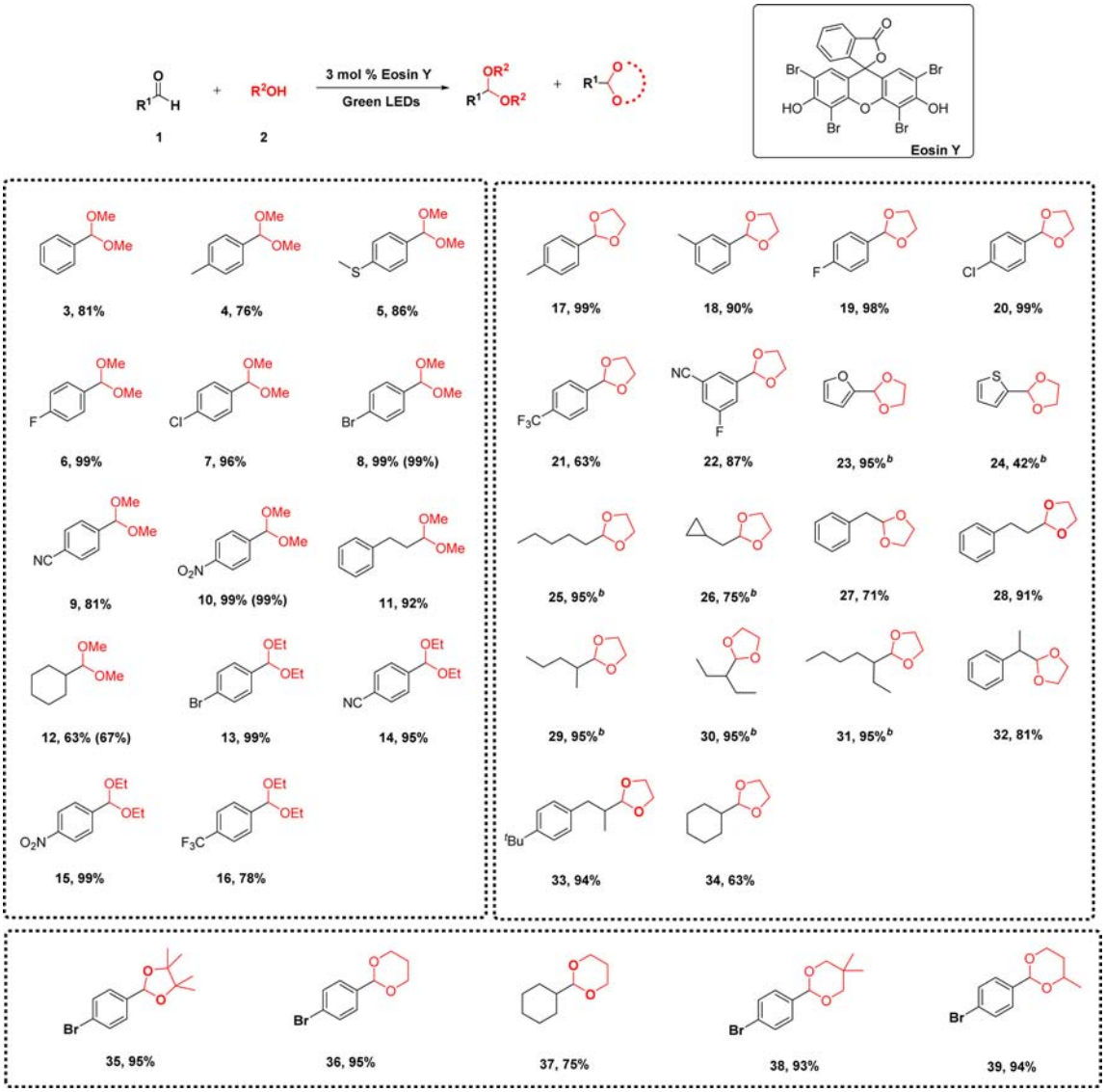
Scheme 2. General Substrate Scope for Protection of Aldehydes with Methanol, Ethanol or Diol Derivatives[a]



[a]Condition: **1** (0.5 mmol), Eosin Y (3 mol %) in a solvent (CH_3CN/ROH) under a nitrogen atmosphere irradiation using 3 W Green LEDs at room temperature for 12 h; yields refer to isolated products. The yield in parentheses is from when MeOH was used as the solvent. [b]Conversion yields determined by GC.

broad range of aromatic, heteroaromatic, and aliphatic aldehydes under neutral conditions using a catalytic amount of Eosin Y as the photocatalyst in good to excellent yields. The efficient formation of **3**−**10** illustrated that either electron-donating or -withdrawing substituents on the aryl ring were tolerated. This system was also compatible with a wide range of functional groups such as Me, SMe, Cl, Br, CN, NO_2, providing the possibility for further transformation. However, *para*-methoxybenzaldehyde could not afford the desired product. Besides aromatic substrates, the alkyl aldehydes such as 3-phenylpropanal and cyclohexanecarboxaldehyde worked well and transformed into the corresponding acetals in good yields (Scheme 2, **11** and **12**). This transformation could also be performed well just using MeOH as the solvent (the yield in the parentheses, **8**, **10**, and **12**). In addition, this system was also compatible with ethanol, which could react with several aldehydes to form target acetals in high yields (Scheme 2, **13**−**16**).

Moreover, this reaction was found to be not limited to methanol or ethanol as a protecting group, and different diol derivatives also delivered the acetals in high yields. Not only the electron-rich aldehydes but also electron-poor aldehydes afforded the 1,3-dioxolane derivatives with excellent yields (Scheme 2, **17**−**22**). Heterocyclic aldehydes such as 2-furaldehyde and 2-thenaldehyde readily underwent reaction to form acetal products (Scheme 2, **23** and **24**). Next, we explored the scope of aliphatic aldehydes and different diols as a protecting group. The scope of aliphatic aldehydes was also very broad (Scheme 2, **25**−**34**). The pinacol could also be converted into the corresponding acetal in a yield of 95% (Scheme 2, **35**). In particular, the 1,3-propanediol derivatives could also be suitable substrates, affording six-member ring acetals in high yields (Scheme 2, **36**−**39**). The acetal **4** was completely transformed into cyclic acetal **17** under the standard conditions using ethylene glycol as the cosolvent, indicating that this reaction was reversible.

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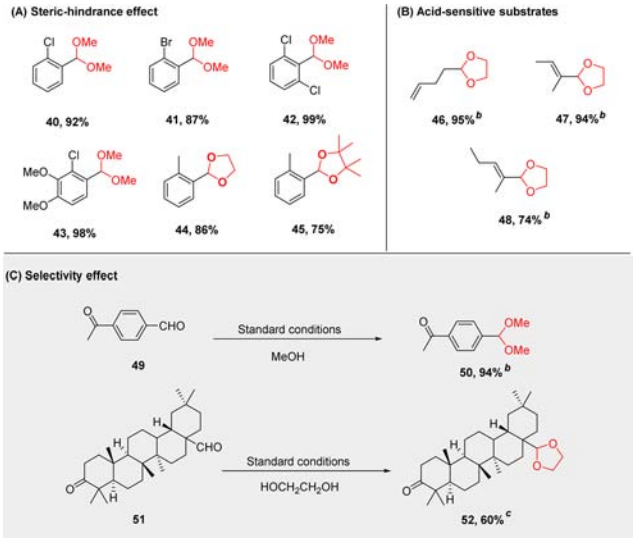
The steric hindrance of aldehyde protection usually causes lower yields, and as a consequence, more drastic reaction conditions are required. However, we found that *ortho*-substituted aldehydes could smoothly afford target acetal products under standard conditions (Scheme 3, **40**–**45**).

Scheme 3. Further Substrate Scope Investigation for the Protection of Aldehydes: (A) Steric Hindrance Effect Investigation; (B) Investigation of Acid-Sensitive Aldehydes; (C) Selectivity Effect Investigation[a]



[a]Standard conditions: aldehyde derivatives (0.5 mmol), Eosin Y (3 mol %) in a solvent (CH_3CN/ROH) under a nitrogen atmosphere with irradiation using 3 W Green LEDs at room temperature for 12 h. [b]Conversion yields determined by GC. [c]NMR yield.

Especially, 2,6-dichlorobenzaldehyde could be successfully transformed into the corresponding acetals in almost quantitative yield (Scheme 3, **42**). In the case of conventional acid-promoted protection reactions, the reaction of acid-sensitive aldehyde is a big challenge. Under these conditions, we found that substituted olefins were well tolerated in this transformation (Scheme 3, **46**–**48**). Moreover, we also investigated the chemoselectivity issue between aldehyde and ketone. Mixing benzaldehyde and acetophenone in one system permitted an excellent yield of the **3a** formation, while no conversation of acetophenone occurred. The 4-acetyl-benzaldehyde **49** was also tested in our system. The highly site-selective reaction of the aldehyde group formed the target product (Scheme 3, **50**). We found our system was also suitable for complicated molecular protection. When using molecule **51** as the substrate, the aldehyde group was successfully transformed into the acetal **52** in 60% yield, while the ketone group remained unreacted. Overall, these results reveal that our system exhibits high site selectivity and wide tolerance of functional groups for the protection of aldehydes.

Some mechanistic studies were also performed to gain insights into this process. As shown in Figure 1, no reaction occurred at the initial time in the absence of light. The transformation could progress smoothly after irradiation with visible light. Different from the common visible-light promoted reactions in which no further conversion occurred when the light source was removed, this reaction continued when the light was shut down. This result showed that the irradiation of visible light in this reaction is necessary. After irradiation for 5

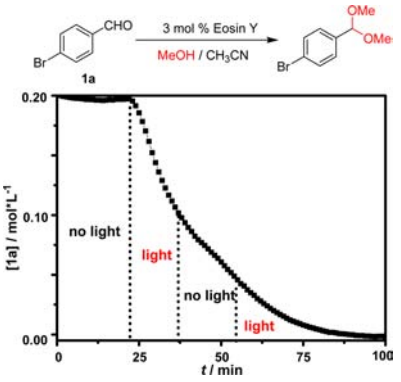


Figure 1. Profile of the reaction with the light off/on over time.

min and then placement in the dark monitored by in situ IR, we could also obtain our desired product in high yield, although it was less efficient compared to a sample that was irradiated the entire reaction time (Figure S1). When a catalytic amount of Na_2CO_3 was added into the reaction system, the reaction was completely inhibited. The most likely explanation for these results is the in situ photogenerated acidic species,[8] which then catalyzes the acetalization. Specifically, in an alcoholic solution, the photocatalyst EosinY behaves as photoacid and leads to protonated carbonyl components that are attacked by the nucleophilic alcohol.[9]

In addition, we also used *in situ* IR to carry out kinetic studies, which were monitored upon changing the concentration of 4-bromobenzaldehyde (**1a**), MeOH (**2a**) and photocatalyst, respectively (Figure 2). When different concen-

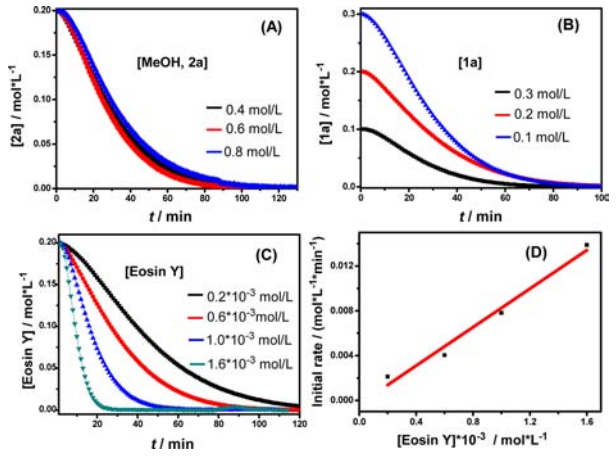


Figure 2. Kinetic studies of the visible-light mediated acetalization reaction using in situ IR.

trations of MeOH were used, the initial rate was almost invariant (Figure 2A), which revealed that the reaction rate was independent of the concentration of methanol. Then, further kinetic investigations were performed for the relationship between the reaction rate and the concentration of substrate (**1a**) (Figure 2B). It was found that the initial rate was related to the concentration of **1a**, and the plot of reaction rate against the concentration of **1a** revealed a first-order correlation with aldehyde concentration. As shown in Figure 2C the reaction rate was related to the concentration of the photocatalyst. A plot of reaction rate against the concentration of the photocatalyst in Figure 2D exhibited approximately a linear relationship, which suggested a first-order dependence on the

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photocatalyst. The above-mentioned results suggested the rate of this reaction was related to the concentration of aldehyde and photocatalyst.

In conclusion, we have developed a simple and general method for the acetalization of aldehydes by means of a photochemical reaction with Eosin Y as the photocatalyst. A variety of dimethyl acetals and cyclic acetals can be achieved in good yields under neutral conditions. The challenging acid-sensitive aldehydes and sterically hindered aldehydes are also well-tolerated. This system exhibits chemoselectivity for the aldehydes. Mechanistic insights indicate that visible light plays a vital role in this transformation. The detailed mechanism is currently under investigation in our laboratory and will be reported in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03403.

The experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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