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Photoorganocatalytic Synthesis of Acetals from Aldehydes

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A mild and green photoorganocatalytic protocol for the highly efficient acetalization of aldehydes has been developed. Utilizing thioxanthenone as the photocatalyst and cheap household lamps as the light source, a variety of aromatic and aliphatic aldehydes have been converted into acyclic and cyclic acetals in high yields. The reaction mechanism was extensively studied.

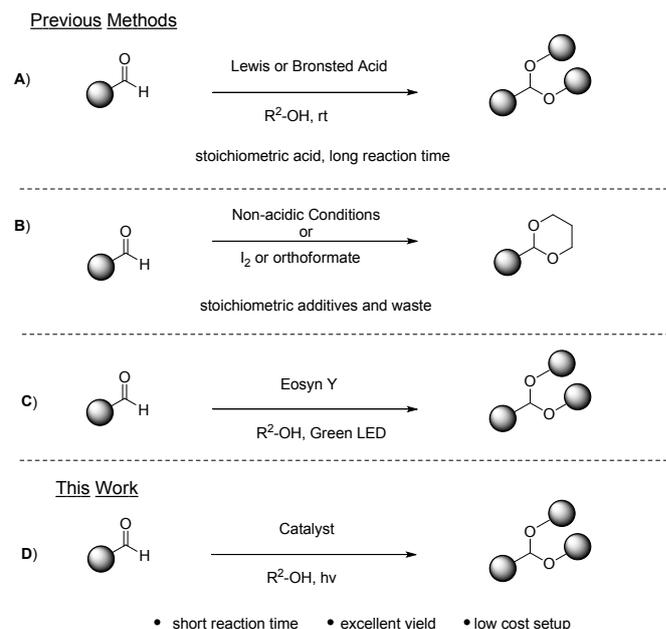
Introduction

The carbonyl moiety is among of the most popular and widely used functional groups in organic synthesis.¹ In some cases, its high reactivity can pose a puzzling obstacle that has to be overpowered, in order to achieve the desired transformations. This is usually accomplished via the protection of the carbonyl compounds into acetals. Except for this protecting character, acetals can be used as starting materials for new synthetic applications.² Apart from their synthetic interest, acetals are also employed as flavouring additives and aroma enhancers in cosmetic and food products³ or as anti-freezing additives in biodiesel fuels.⁴ Due to their versatile use, a variety of methodologies have been reported for the synthesis of acetals. The most common approach includes the use of strong mineral acids,⁵ transition-metal Lewis acids or organic acids⁶⁻⁸ (Scheme 1, **A**). The use of stoichiometric amount of acids and/or the use metals raise serious environmental concerns, clearly violating the principles of green chemistry.⁹

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To address this problem, alternative methods for the acetalization of



Scheme 1 Common synthetic pathways for the acetalization of aldehydes.

organic compounds have been developed. Acetals can be produced from carbonyl compounds utilizing basic¹⁰ or other non-acidic conditions employing iodine,¹¹ trialkyl orthoformates¹² or halohydrins¹³ (Scheme 1, **B**). Very recently,

a protocol for the synthesis of acetals, based on principles of photochemistry,¹⁴ has been developed¹⁵ (Scheme 1, C).

The authors proposed the use of an organic dye, Eosyn Y, with the use of green LED irradiation for the promotion of the reaction. Eosin Y, an organic dye bearing acidic groups, was employed in that work and the crucial question, that was not addressed, was whether the acidic nature of the catalyst, in conjunction with heat deriving from the LED irradiation, could contribute or be the main reason for product formation, in addition to the photochemical pathway.

Our laboratory has a multiannual experience in Photochemistry.¹⁶ Utilizing various photocatalysts, a variety of important and useful organic compounds were synthesized, studying exhaustively the mechanism of each photoreaction. Herein, we present a new, green, mild and fast photoorganocatalytic synthesis of acetals from aldehydes, utilizing thioxanthenone as the photoorganocatalyst and cheap and commercially-available household lamps as the irradiation source (Scheme 1, D). Based on our mechanistic studies and understanding of the reaction mechanism, a cheap and organic catalyst is employed and not an organic dye, which requires additional cost for removing it from industrial scales. Also, cheap household lamps are employed as the irradiation source and no heating, special apparatus or inert atmosphere are required. The reaction time is very short and the product can be obtained via solvent evaporation or distillation.

Results and discussion

We began our investigations with the conversion of 3-phenyl propanal **1a** (Table 1). A number of photoorganocatalysts were tested with thioxanthenone affording the highest yield (Table 1, entry 1-5). When phenylglyoxylic acid (among the best photoorganocatalysts that we had identified in other studies¹⁶) was employed as the photocatalyst, **2a** was synthesized quantitatively, however, this was due to the acidic character of phenylglyoxylic acid and not due to the photochemical reaction (Table 1, entry 1 vs 2). Thus, the acidic character of the photocatalyst must be taken into account, before concluding for its activity. Decreasing the catalyst loading to 10 mol% and the reaction time to 1.5 h, the desired acetal **2a** was

obtained in 95% yield (Table 1, entry 6).¹⁷ It must be noticed, that the product of the reaction is of enough purity and by just

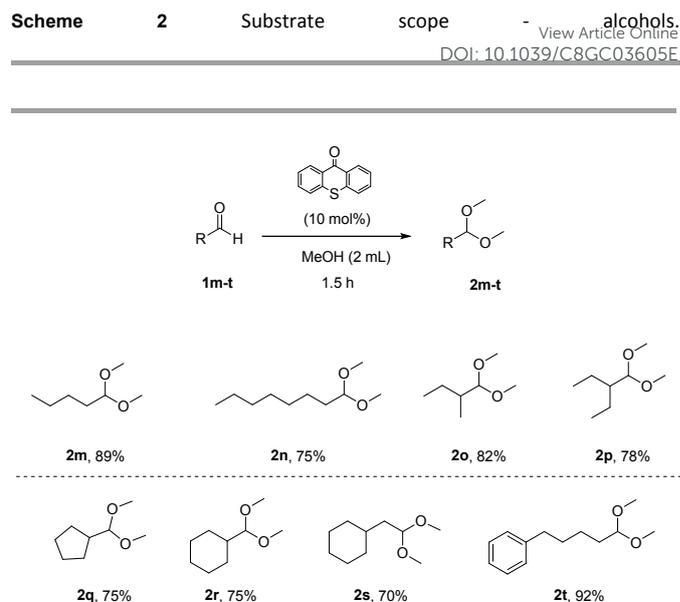
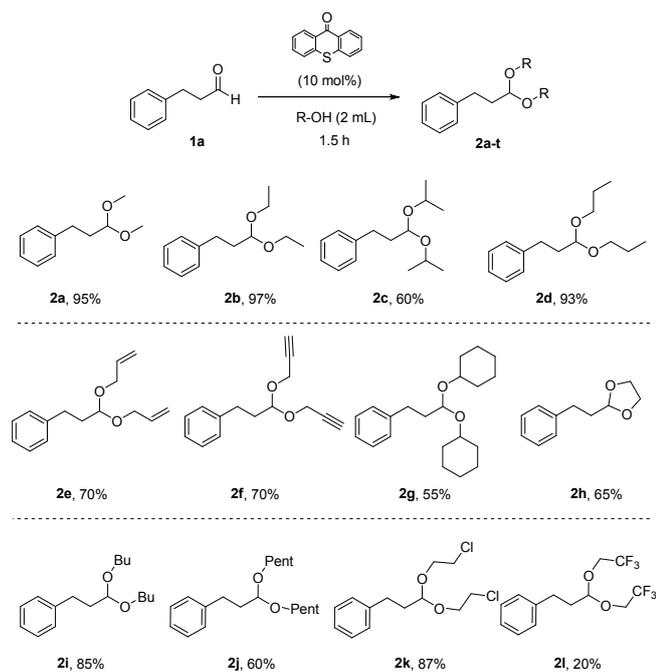
Table 1. Photoorganocatalytic synthesis of acetal **2a** from aldehyde **1a**.^{a)}

Entry	Catalyst Loading (mol%)	Catalyst	Time	Yield ^{b)} (%)
1	20		18	100
2 ^{c)}	20		18	90
3	20		18	22
4	20		18	90
5	20		18	95
6	10		1.5	95
7	5		18	75
8	2		18	62
9	-	-	18	5
10 ^{c)}	10		18	5
11 ^{d)}	10		18	5
12 ^{e)}	10		1.5	65

^{a)} All reactions were carried out with **1a** (0.50 mmol), catalyst (x mol%) and solvent (2 mL) under household bulb irradiation.^{b)} Isolated yield.^{c)} Reaction was kept in the dark. ^{d)} Reaction was kept under household bulb irradiation and the reaction tube was covered with foil. ^{e)} Reaction took place in methanol-acetonitrile mixture (1:1).

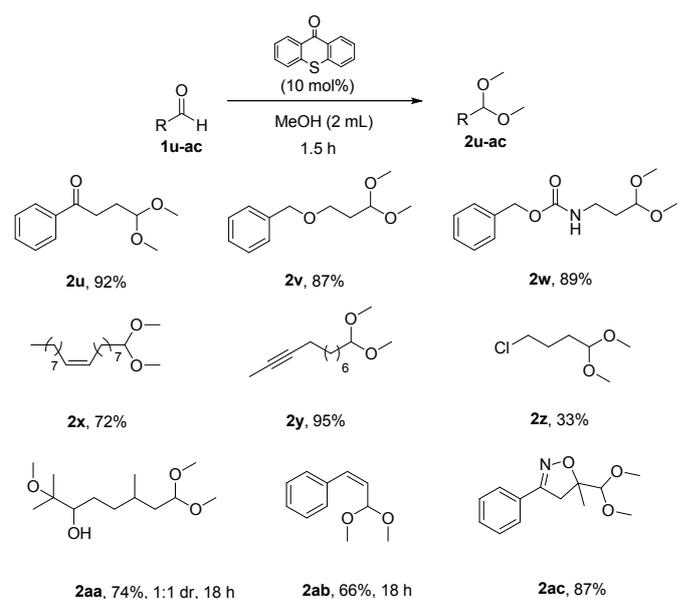
simple evaporation of the excess of methanol, no further purification is required. When the catalyst loading was decreased, the desired acetal **2a** was formed in lower yield (Table 1, entries 7 and 8). If the catalyst or visible light are omitted, no reaction took place (Table 1, entries 9 and 10 vs 1).¹⁷ When the reaction was covered with foil, under the optimized reaction conditions, the desired acetal was formed in a very low yield, verifying that heating from the lamps does not contribute to the reaction outcome (Table 1, entry 11). When a mixture of methanol and acetonitrile (other solvents have been tested as well) was used as solvent, the yield decreased (Table 1, entry 12).¹⁷

Having in hand the optimum reaction conditions, we turned our attention in exploring the substrate scope (Schemes 2-5). Utilizing as starting material 3-phenylpropanal (**1a**), a variety of alcohols were tested, providing the desired products in very good yields (Scheme 2). Primary alcohols, alcohols with functional groups, secondary alcohols or diols were applied successfully, affording acetals **2a-2l** in high yields (Scheme 2). As expected, secondary alcohols provided the product (**2c** and **2g**) in slightly lower yield, due to steric hindrance. Cyclic acetals, like **2h**, can be produced by our methodology. Next, we explored the scope of the aliphatic aldehydes with methanol (Scheme 3). It proved to be also very broad. Linear aliphatic aldehydes or branched aliphatic aldehydes led to the



desired acetals **2m-2p** in high yields. Aldehydes that contain cyclic or aromatic moieties led to acetals **2q-2t** in similarly high yields. In the case of aldehyde **1o**, a larger scale experiment (10 mmols) was attempted and the desired product **2o** was isolated by distillation (68% yield, bp **2o** 132-134° C, bp **1o** 92-94° C was not observed).

Addition of functional groups on the aldehyde did not affect the efficiency of the synthetic method and acetals **2u-2ac** were isolated in up to 95% yield (Scheme 4). It is worth noticing that



Scheme 4 Substrate scope for the synthesis of acetals with functional groups.

this method is selective, as it converts only aldehydes and ketones are left untouched (**2u**). Substrates with functional groups, as ether, amide, double or triple bond and halogen (low yield due to product volatility) gave the desired acetals in very good yields (**2v-2z**). It is important to mention that when substrate **1aa**, bearing an epoxide group, was employed, the epoxide ring was opened in the reaction conditions, leading to acetal **2aa** in 74% yield. When cinnamaldehyde was used as the substrate, the reaction conditions led to *Z*-acetal **2ab**. However, upon heating or standing, a ratio of almost 1:1 of *E*:*Z* product was observed. Utilizing as starting material an isoxazoline skeleton (**1ac**), the desired acetal **2ac** was isolated in 87% yield proving the general character of this method.

In an effort to expand the limits of the synthetic method a variety of aromatic aldehydes were also tested (Scheme 5). *Para*-, *meta*- and *ortho*-substituted aromatic aldehydes were utilized and the corresponding acetals were isolated in very good yields (**2ad-2ai**).

In order to study the reaction mechanism, a variety of tools were employed. Based on literature,¹⁸ the quantum yield (Φ) of the photocatalytic reaction was calculated: [$\Phi = 96$ ($\Phi > 1$)], which hints that a radical propagation mechanism is taking place.

Next, fluorescence quenching studies were performed (Figure 1). Increasing the added amount of pentanal, a decrease in the fluorescence of thioxanthenone was observed (Figure 1, **A**), while increasing the added amount of methanol, no changes in

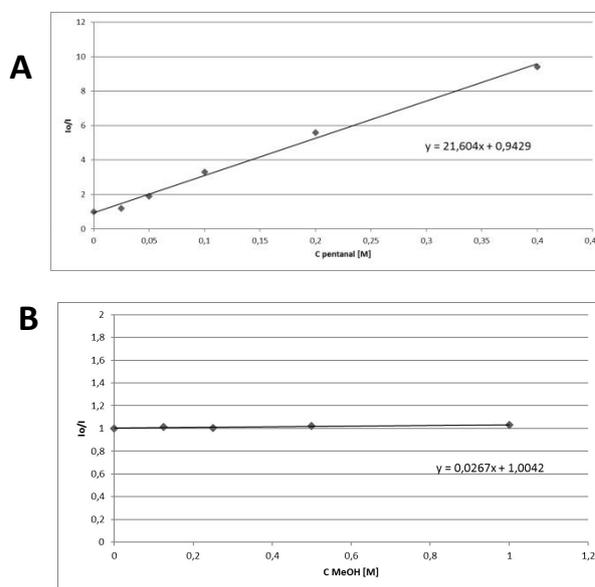
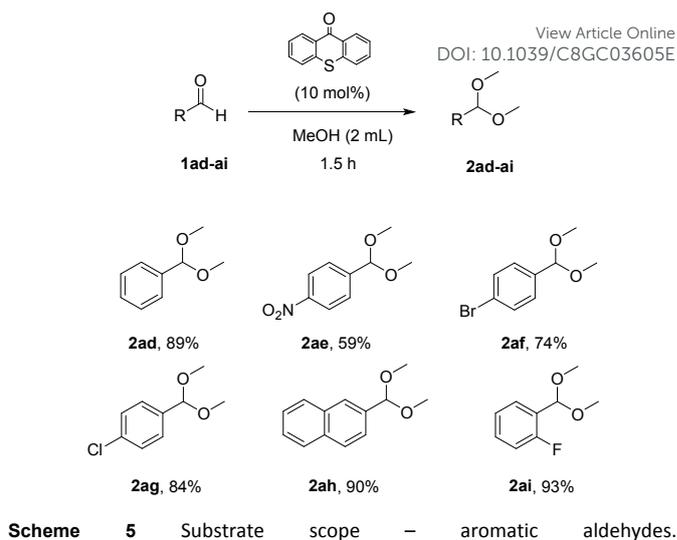


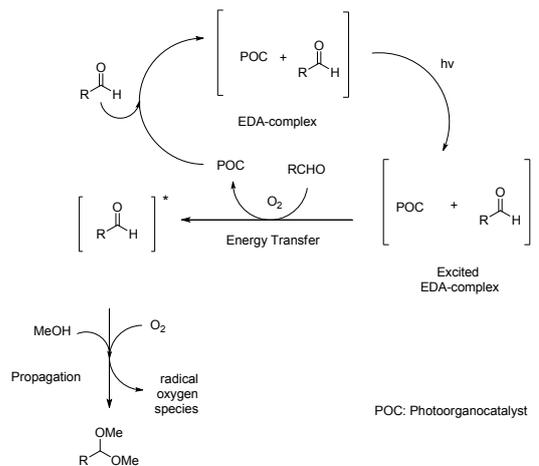
Figure 1. Stern-Volmer plots for the fluorescence quenching of thioxanthenone (1mM in MeCN) with **A.** pentanal, **B.** methanol.

the catalyst's fluorescence were seen (Figure 1, **B**). In an effort to further expand the applicability of this method, we employed benzyl mercaptan as a reagent and the corresponding thioacetal was obtained in 89% yield. Unfortunately, during the preparation of this manuscript, She, Wang and coworkers introduced a blue LED-mediated process.¹⁹ In that work, a single electron transfer to the thiol was proposed,¹⁹ while in the Eosin-catalyzed process, an energy transfer mechanism was proposed.¹⁵

Following literature, a variety of solvents were then studied and the quenching of the catalyst presented similar behaviour, so an energy transfer pathway is hinted.²⁰ This is in accordance with literature evidence that concur that an electron transfer event is highly unlikely to be happening [$E_{\text{ox,thiox}} = +1.69$ V, $E_{\text{red,thiox}} = -1.62$ V, $E_{\text{ox,PhCHO}} = +2.71$ V, $E_{\text{red,PhCHO}} = -1.93$ V].²¹

We then turned our attention in employing UV-Vis absorbance studies (Figure 2).¹⁷ Based on UV-Vis spectra, the absorption of thioxanthenone changes, after the addition of aldehyde (Figure 2). Thus, an EDA-complex is formed. The mixing of two compounds can lead to the formation of an aggregate, called electron donor-acceptor (EDA) complex. Though these complexes are known in literature since 1950s,²² it was not until recently, when Melchiorre and others have identified them as active photochemical species.²³ An EDA complex can

process, since the reaction under Argon led to 44% yield of the desired acetal.¹⁷ Utilizing all these data, the following



Scheme 5 Proposed reaction mechanism.

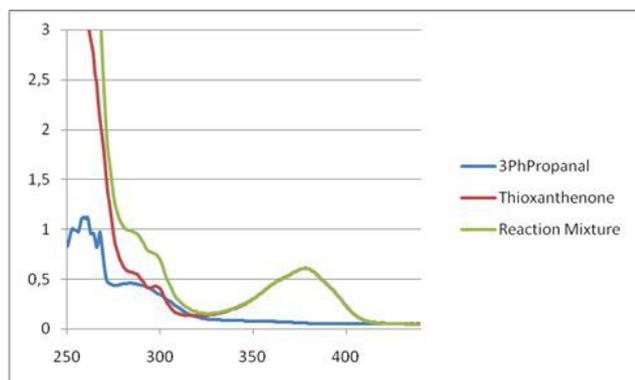


Figure 2 UV-Vis absorption spectra, recorded in a 1 cm path quartz cuvette, 3-phenylpropanal (**1a**) (3×10^{-4} M), thioxanthenone (2×10^{-5} M) and aldehyde with thioxanthenone in methanol.

be recognized by an increase in the UV-Vis absorbance, upon mixing the two reaction components. The indication that an EDA-complex is formed is also supported by $^{19}\text{F-NMR}$.¹⁷ Also, $^{13}\text{C-NMR}$, $^1\text{H-NMR}$ and $^{19}\text{F-NMR}$ studies were carried out.¹⁷

The crucial nature of the EDA-complex was highlighted, when a reaction with a cut-off filter (below 400 nm) was employed and the product was not formed.¹⁷ Furthermore, some additional control experiments were carried out. The addition of radical scavengers (Tempo, BHT) stopped the reaction, which means that besides the energy transfer, radicals are involved.¹⁷ The use of oxygen species quenchers proved that oxygen is involved in the process,¹⁷ only to accelerate the

mechanism can be proposed (Scheme 5). The addition of the aldehyde to the photoorganocatalyst leads to the formation of an EDA-complex, which upon irradiation activates the aldehyde via energy transfer, similar to the activation that a Lewis acid is performing, lowering the LUMO of the aldehyde and making it more prone to the upcoming nucleophilic attack of methanol, leading to the corresponding acetal. Then, the catalyst interacts with molecular oxygen and returns to its ground state, while the radical oxygen species, that are generated, lead to the propagation of radicals and ensure product formation.

Conclusions

In conclusion, a simple, cheap, green and efficient photoorganocatalytic protocol was developed, activating aldehydes for their reaction with alcohols leading to acetals. Bypassing the need for transition metal-complexes and stoichiometric acids, this method relies on a small organic molecule and cheap household lamps activating aldehydes via EDA-complexes, which can react readily with alcohols leading to acetals in high yields, that can be isolated either by solvent evaporation or distillation. Based on extensive mechanistic studies, a proposed mechanism is presented.

Experimental

General Procedure for the synthesis of acetals

In a glass vial with a screw cap containing thioxanthene-9-one (10.6 mg, 0.05 mmol) in alcohol (2 mL), aldehyde (0.50 mmol) was added. The vial was sealed with a screw cap and left stirring under household bulb irradiation (2 x 80W household lamps) for 1.5 h. The desired product was isolated either by solvent evaporation, distillation or after purification by column chromatography.

Acknowledgements

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