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Tandem Synthesis of Benzylidenemalononitrile Derivatives in/on Water under Visible Light

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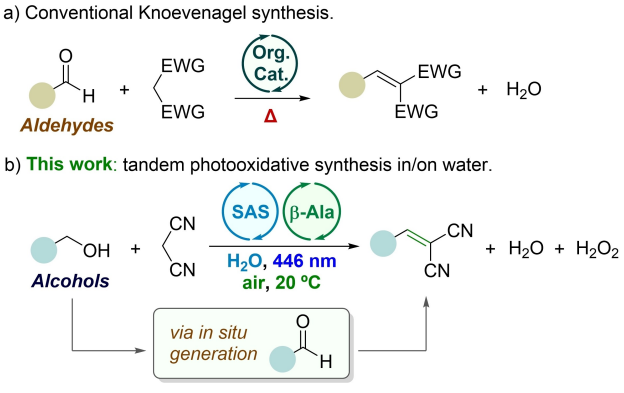
Tandem processes are valuable tools that allow to build molecular complexity while reducing waste production and the number of steps of synthetic routes. In this work, the in situ photooxidation of benzyl alcohols to the corresponding benzaldehydes is coupled with a Knoevenagel condensation for the preparation of benzylidenemalononitrile derivatives. In this rapid one-pot tandem process, sodium anthraquinone-1,5-disulfonate (SAS) and β-alanine are employed as safe and inexpensive catalysts, while air is used as a terminal oxidant. Moreover, using water as reaction medium results in most cases in the precipitation of the target products, thus facilitating their isolation.

Introduction

Currently, the chemical and pharmaceutical industries are experiencing a notorious shift in terms of sustainability, wherein reducing the energy input of reactions and restricting the use of hazardous chemicals have become first-order priorities.[1] In addition, shortening the length of synthetic routes by performing two or more steps in a single vessel can improve the overall efficiency of the process while circumventing intermediary purification steps and reducing waste production.[1c,2]

Due to their low cost, bench stability, and natural prevalence, alcohols are particularly attractive synthetic building blocks. In addition, their facile oxidation to the corresponding aldehydes enables the design of tandem oxidative processes (TOP), wherein their initial oxidation is coupled with an additional step.[3] While most of these processes rely on thermal conditions, the relatively low C–H bond dissociation energy (BDE) displayed by α-alkoxy positions can be easily exploited via photoinduced H-atom transfer (HAT).[4] Herein, equivalent aldehyde intermediates can be accessed under notably milder reaction conditions in the presence of a photoexcitable HAT agent and oxygen.[5] Accordingly, tandem photooxidative processes (TPP) constitute a more sustainable alternative to conventional TOP, allowing to build molecular complexity by using light. However, despite their potential applications, to date, these remain unexplored to a large extent. In addition to the design of tandem reactions, the replacement of hazardous organic solvents remains a major challenge. As a result, efforts are being made to prioritize the use of green solvents such as water.[1a,c,6] Unfortunately, this medium is often associated with solubility issues or revealed as incompatible with photocatalytic systems. To overcome these limitations, water-soluble photoexcitable HAT agents can be employed.[5a,7] For instance, sulfonated anthraquinones have been successfully implemented in TPP, as showcased by the Itoh group in their work on the photooxidative tandem condensation between benzyl alcohols and ketones in aqueous medium.[5a]

Benzylidenemalononitrile derivatives, also known as tyrphostins, display a broad range of biological properties.[8] In addition, these electron-poor olefins are regarded as versatile radical traps for the elucidation of reaction mechanisms and valuable substrates for Giese-type reactions.[9] Although a plethora of different reaction conditions have been reported so far,[10] their synthesis mainly relies on the classic Knoevenagel condensation, wherein an aldehyde and an active C–H methylene compound undergo a condensation reaction in the presence of an organocatalyst (Scheme 1a).[11] More recently, several tandem methodologies have been developed to access equivalent products from benzyl alcohols.[12] Inspired by these previous works,[5a,12] and the concept of TPP, we envisioned an alternative method to the classical reaction in alignment with the principles of green chemistry.[13] Herein, we hypothesized that benzyl alcohols could be employed as benzaldehyde precursors in designing a Knoevenagel cascade reaction in



Scheme 1. Synthesis of benzylidenemalononitrile derivatives. SAS: sodium anthraquinone-1,5-disulfonate. β-Ala: beta-alanine.

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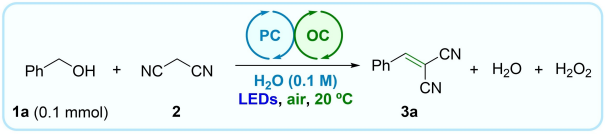
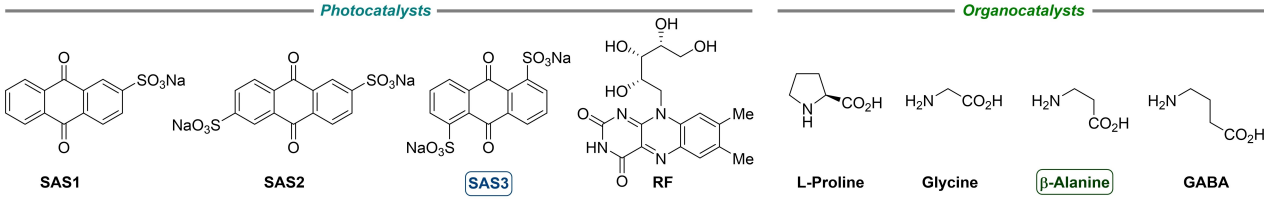
water, thus precluding organic solvents and replacing heat with light (Scheme 1b).

Results and Discussion

Taking a lead from Itoh's work,[5a] we set out to test the envisioned transformation with a dual catalytic system, involving sodium anthraquinone-2-sulfonate (**SAS1**), L-proline and water as solvent. Accordingly, due to their solubility in this medium, benzyl alcohol (**1a**) and malononitrile (**2**) were chosen as model substrates for the preparation of benzylidenemalononitrile (**3a**). At first, the reaction mixture was subjected to 405 nm (0.7 W) irradiation, under air (Table 1; entry 1). To our delight, after 2 h, the formation of a white precipitate was observed (Figure S4). Extraction of the reaction mixture with EtOAc and subsequent analysis via GC-FID revealed the formation of **3a** in low yield (39%) (Figure S6). In addition, the presence of unreacted starting materials (**1a** and **2**) and the formation of the postulated benzaldehyde intermediate was corroborated. Motivated by these promising results, we proceeded to optimize the system by surveying different water-soluble photocatalysts (Table 1; entries 2–4). While riboflavin (**RF**) proved compatible under blue light irradiation (entry 4), sulfonated anthraquinones delivered notably better results. In particular, sodium anthraquinone-1,5-disulfonate (**SAS3**) was revealed as the best choice, providing **3a** in 63% yield (entry 3). Next, the replacement of L-proline by piperidine, a base commonly used for Knoevenagel condensations,[10b] led to a significant drop in yield (entry 5). This might be attributed to the oxidation of the non-protonated amine by the excited state of the photocatalyst. In contrast, alternative amino acids such as glycine, β-alanine, or γ-aminobutyric acid (**GABA**) gave better results (entries 6–8). Accordingly, β-alanine was identified as the best option (**3a**, 65% yield) (entry 7). This safe and inexpensive naturally occurring amino acid has been previously reported for catalyzing condensation reactions even at mild temperatures.[14] The reaction yield was further improved up to 77% by increasing the number of equivalents of **2** from 1–1.5 (entry 10). In addition, alternative irradiation sources were examined, wherein 446 nm (0.7 W) LEDs delivered the best performance (81%) (entry 11). In contrast, when irradiating with 523 nm

Table 1. Optimization of reaction conditions.[a]



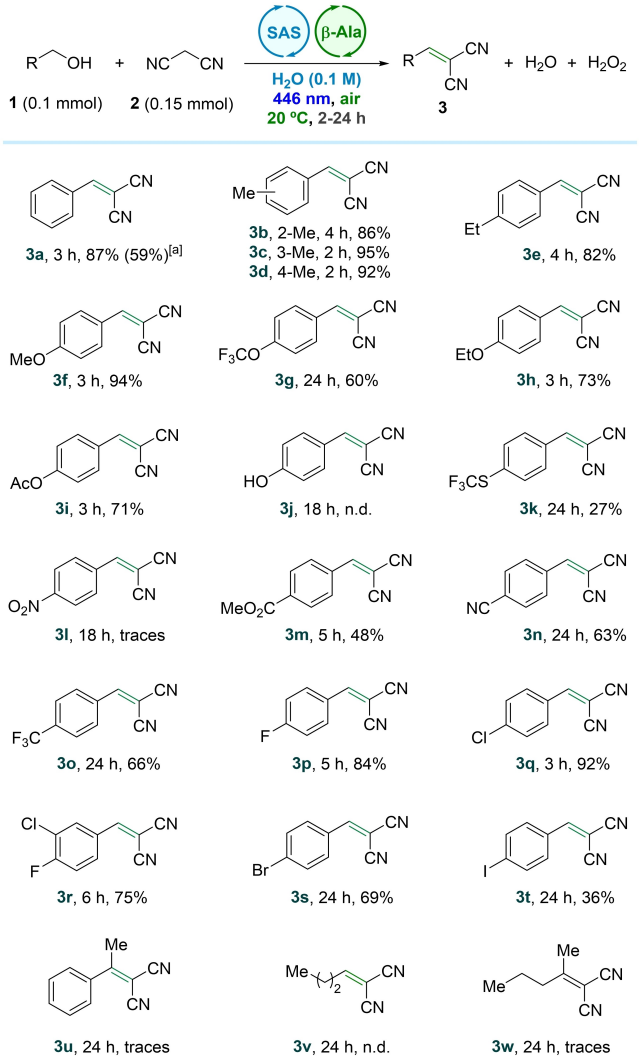


Entry	equiv. 2	PC (mol%)	OC (mol%)	t (h)	LEDs	Yield of 3a (%)[b]
1	1	SAS1 (10)	L-Proline (10)	2	405 nm (0.7 W)	39
2	1	SAS2 (10)	L-Proline (10)	2	405 nm (0.7 W)	58
3	1	SAS3 (10)	L-Proline (10)	2	405 nm (0.7 W)	63
4	1	RF (1)	L-Proline (10)	3	446 nm (0.7 W)	22
5	1	SAS3 (10)	Piperidine (10)	2	405 nm (0.7 W)	9
6	1	SAS3 (10)	Glycine (10)	2	405 nm (0.7 W)	50
7	1	SAS3 (10)	β-Alanine (10)	2	405 nm (0.7 W)	65
8	1	SAS3 (10)	GABA (10)	2	405 nm (0.7 W)	43
9	1.2	SAS3 (10)	β-Alanine (10)	2	405 nm (0.7 W)	71
10	1.5	SAS3 (10)	β-Alanine (10)	2	405 nm (0.7 W)	77
11	1.5	SAS3 (10)	β-Alanine (10)	2	446 nm (0.7 W)	81
12	1.5	SAS3 (10)	β-Alanine (10)	2	528 nm (0.2 W)	n.d.
13	1.5	SAS3 (10)	β-Alanine (5)	2	446 nm (0.7 W)	86
14	1.5	SAS3 (10)	β-Alanine (1)	2	446 nm (0.7 W)	68
15	1.5	SAS3 (5)	β-Alanine (5)	2	446 nm (0.7 W)	66
16	**1.5**	**SAS3 (10)**	**β-Alanine (5)**	**3**	**446 nm (0.7 W)**	**91**

[a] Reaction conditions: **1a** (0.1 mmol), **2**, photocatalyst, organocatalyst, H_2O (1 mL), LEDs (radiant power), air, 20 °C. [b] GC-FID yields determined using α,α,α-trifluorotoluene as internal standard upon extraction of the reaction mixture with EtOAc (1 mL).

(0.2 W) LEDs, **1a** remained unreacted (entry 12), as **SAS3** does not absorb in this region of the visible light spectrum (Figure S7). Afterward, the catalyst loadings were optimized (entries 13–15), wherein the loading of β-alanine could be successfully reduced to 5 mol% (entry 13). Regarding the photocatalyst, reducing its loading to 5 mol% led to a drop in yield (66%) (entry 15). As a result, a loading of 10 mol% of **SAS3** was maintained. Conducting the reaction for an additional hour led to excellent results (91%) (entry 16). Analysis of the reaction mixture via GC-FID (Figure S8) revealed complete consumption of **1a**, while only traces of benzaldehyde intermediate were detected. Lastly, the product was isolated via filtration of the reaction mixture, obtaining **3a** as a white solid in very good yield (87%). Lastly, the methodology was successfully scaled up using 8 mmol of **1a**, which resulted in the isolation of **3a** in acceptable yield (59%).

With the optimized conditions in hand, we explored the substrate scope of the transformation (Scheme 2). First, alkyl-substituted benzyl alcohols (**3b**–**3e**) were tested, wherein very

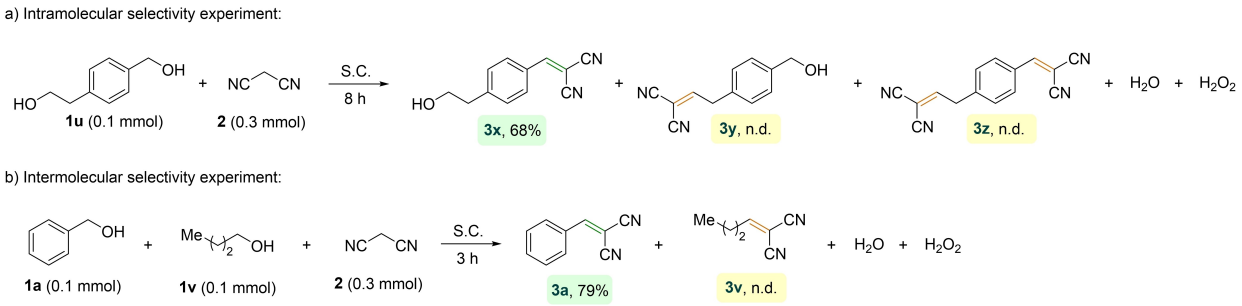


Scheme 2. Substrate scope. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol) **SAS3** (10 mol%), β-alanine (5 mol%), H_2O (1 mL), 446 nm (0.7 W), air, 20 °C. [a]Isolated yield of 8 mmol scale reaction after 7 h of irradiation at 24 °C.

good to excellent yields were achieved (82–95%). Interestingly, neither the relatively low BDE of the C–H bonds of the methyl group substituents nor their disposition had a significant impact on the reaction yield (**3b**–**3d**). However, in the case of *ortho*-methyl benzyl alcohol (**1b**) additional reaction time was required to achieve a similar yield to the *meta*- and *para*-substituted homologues (**1c** and **1d**), presumably due to increased steric hindrance. 4-Ethylbenzyl alcohol (**1e**) required longer reaction times, presumably due to its lower solubility in water. To our delight, product **3f**, also known as the drug tyrphostin A1,[8b] was successfully prepared in excellent yield (94%) from anisyl alcohol (**1f**). Similarly, 4-trifluoromethoxy- (**1g**), 4-ethoxy- (**1h**), and 4-acetoxy benzyl alcohol delivered satisfactory results (**3f**–**3h**). In contrast, the presence of an unprotected hydroxy group (**1j**) impeded reaction progress, as the starting material remained unreacted. According to a previous study, anthraquinone sulfonates can undergo rapid degradation under similar reaction conditions, in the presence of phenol derivatives.[15]

Next, the compatibility of different heteroatoms and functional groups was further explored. Herein, 4-(trifluoromethylthio)benzyl alcohol (**1k**) gave the corresponding product (**3k**) in poor yield. In addition, strong electron-withdrawing groups such as nitro (**1l**), ester (**1m**), cyano (**1n**), or trifluoromethyl (**1o**) were evaluated. However, only limited success was achieved, as these groups seemed to hinder the initial oxidation event of the alcohol. For instance, the nitro derivative (**3l**) could only be detected in trace amounts (Figure S9). Other halogenated starting materials (**1p**–**1t**) generally performed well in the tandem process, delivering the target products in moderate to excellent yields (36–92%). While fluoro- and chlorinated substrates (**1p**–**1r**) reacted in short reaction times, bromo- (**1s**) and iodo- (**1t**) substituents led to a significant reaction time increase accompanied by yield decrease. In the case of 4-iodobenzyl alcohol (**1t**), for instance, the formation of degradation products such as the corresponding benzoic acid was confirmed. Here, no correlation could be drawn between the electron-donating/withdrawing ability of the halogen atoms and the obtained yields. Subsequently, the methodology was tested on a secondary benzyl alcohol (**1u**) to give the corresponding ketone as a reactive intermediate. Although the formation of acetophenone was confirmed by GC-MS analysis, the aimed condensation product (**3u**) was only observed in trace amounts (Figure S10). This might be attributed to the lower electrophilicity, and higher steric hindrance displayed by acetophenone compared to benzaldehyde as a reactive intermediate. Lastly, two aliphatic alcohols were surveyed. While 1-pentanol (**1v**) remained unreacted, 2-pentanol (**1w**) delivered the aimed product (**3w**) in trace amounts (Figure S11). The scope was further explored with **1a** and different active C–H methylene compounds as nucleophiles (Scheme S6). Unfortunately, all alternatives to malononitrile failed.

Afterward, the selectivity of the methodology was investigated. Accordingly, an intramolecular competition experiment between an aliphatic and a benzylic alcohol was carried out (Scheme 3a). As a result, only the monofunctionalized product

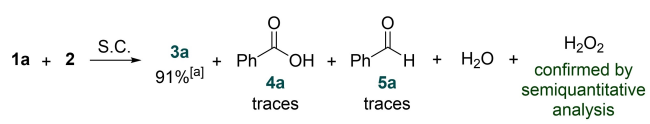


Scheme 3. Selective functionalization of benzyl alcohols over aliphatic alcohols. Standard conditions (S.C.): **SAS3** (10 mol%), β-alanine (5 mol%), H_2O (1 mL), 446 nm (0.7 W), air, 20 °C.

3x could be isolated in good yield (68%). The alternative monofunctionalized product **3y** (derived from the oxidation of the aliphatic alcohol) or the bifunctionalized product **3z** were not observed by GC-MS analysis (Figure S12). Additionally, an intermolecular competition experiment between benzyl alcohol and 1-pentanol was set (Scheme 3b), wherein **1a** delivered **3a** in very good yield (79%), while 1-pentanol remained unreacted (Figure S13).

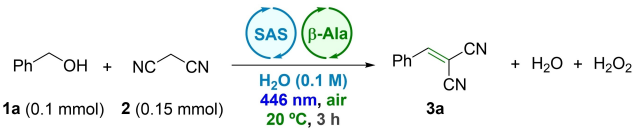
Next, we set out to unveil the reaction mechanism of the transformation by analyzing the reaction mixture of **3a** (Scheme 4). Herein, GC-MS analysis (Figure S14) revealed the presence of traces of benzaldehyde, thus supporting the postulated tandem process, wherein this species is generated in situ as a key intermediate. Furthermore, TLC analysis indicated the presence of benzoic acid as the sole side product, presumably derived from the overoxidation of the observed benzaldehyde intermediate. According to literature, aldehydes can readily oxidize to the corresponding acids upon exposure to air and light,[16] a process that might be accelerated in the presence of radical initiators such as HAT catalysts.[17] In addition, the presence of hydrogen peroxide as by-product was confirmed. Its concentration in the reaction mixture could be determined in the range of 2–5 mg/mL (0.06–0.15 M) employing semiquantitative peroxide test stripes (Figure S15).

A series of control experiments were carried out to get additional insight into the reaction mechanism (Table 2). When conducting the reaction in the absence of light (entries 2 and 3) or photocatalyst (entry 4), no product was observed. In contrast, the preclusion of β-alanine (entry 5) led to significant product formation (33%), however, in lower yield compared to the standard reaction conditions (91%). Herein, the reaction between benzaldehydes and malononitrile has been previously reported to proceed even without catalysts.[18] Furthermore, benzyl alcohol (**1a**) was subjected to the optimized conditions in the absence of **2** (entry 6) (Figure S16), which resulted in the



Scheme 4. Analysis of the reaction mixture of **3a**. S.C.: standard conditions. [a]GC-FID yield determined using α,α,α-trifluorotoluene as internal standard.

Table 2. Control experiments.



Entry	Deviation from conditions	Yield of 3a (%)[a]
1	–	91
2	No light	n.d.
3	No light; 60 °C	n.d.
4	No **SAS3**	n.d.
5	No β-alanine	33
6	No **2**	n.d.
7	Under N_2	9
8	Under N_2; 15 mol% **SAS3**	12
9	Under O_2 (1 atm.)	63
10	TEMPO (1 equiv.)	Traces

[a] GC-FID yields determined using α,α,α-trifluorotoluene as internal standard.

oxidation of **1a** to benzoic acid, as the aldehyde intermediate can undergo an additional oxidation step.[16,17] Conducting the reaction under nitrogen atmosphere led to product formation in almost stoichiometric amounts, referred to the photocatalyst loadings (entries 7 and 8). Under these conditions, no H_2O_2 generation was detected (Figure S17). This suggests that in the absence of oxygen, the reduced form of the photocatalyst cannot be regenerated due to the lack of a terminal oxidant. Instead, **SAS3** might be reduced to the corresponding hydroquinone (Scheme S7). Using an oxygen balloon instead of ambient air atmosphere (entry 9) led to a satisfactory yield of **3a** (63%), however inferior to the optimized conditions (91%). This might be attributed to the quenching of the photocatalyst in the presence of a significant excess of oxygen, as well as the undesired oxidation of the benzaldehyde to benzoic acid (as revealed by TLC-analysis). Lastly, the reaction was conducted in the presence of TEMPO as a radical scavenger (entry 10), which hampered reaction progress. Unfortunately, no radical trapping adduct could be isolated or detected.

In accordance with the performed mechanistic studies and previous reports,[5,7c,19] a plausible reaction mechanism was

proposed for the tandem photooxidative process (Scheme 5). At first, the alcohol starting material (**I**) engages with the photoexcited anthraquinone (**SAS***) via HAT to deliver a benzylic radical (**II**), which is postulated to further react with molecular oxygen to give a peroxy radical (**III**). This intermediate then reacts with the reduced form of the photocatalyst (**SASH•**) via HAT, regenerating its ground state (**SAS**) while giving the corresponding peroxide (**IV**), which, upon H_2O_2 release, forms benzaldehyde (**V**). This electrophilic intermediate can then undergo a condensation reaction with malononitrile (**VI**), catalyzed by β-alanine to give the corresponding benzylidenemalononitrile derivative (**VII**) and water.

Conclusions

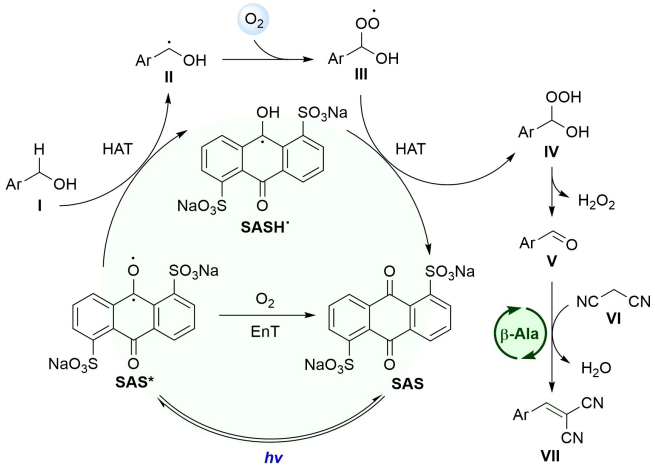
To summarize, we have developed a light-driven cascade reaction for the preparation of benzylidenemalononitrile derivatives using water as reaction medium. Herein, benzyl alcohols are employed as bench-stable starting materials and oxidized by air to benzaldehydes in a photooxidative process catalyzed by sodium anthraquinone-1,5-disulfonate. The in situ generated electrophilic intermediates are then reacted with malononitrile in the presence of β-alanine as a green and inexpensive organocatalyst. Due to the solubility in water of both catalysts, the reaction is carried out in this medium, which results in several cases in the direct precipitation of the final condensation products. Overall, the methodology is operationally simple, prioritizes the use of non-hazardous chemicals, and proceeds in short reaction times at room temperature.

Experimental Section

A 5 mL crimp-cap vial equipped with a stirring bar was loaded with the corresponding alcohol (0.1 mmol, 1.0 equiv.), malononitrile (10.1 mg, 0.15 mmol, 1.5 equiv.), β-alanine (0.5 mg, 5 μmol, 5 mol%), sodium anthraquinone-1,5-disulfonate (3.7 mg, 10 μmol, 10 mol%) and distilled water (1 mL). The vial was sealed, sonicated for 10 s, and its content was kept open to air via a needle. The resulting mixture was stirred under irradiation using a blue LED setup ($\lambda = 446$ nm, 0.7 W) at 20 °C. Depending on the product, different work-up procedures were followed:

-General Procedure **GP1a** (for compounds **3a**–**3f**, **3h**, **3l**, **3m**, **3n**, **3p**–**3s**): after 2–24 h, the reaction mixture was filtered under reduced pressure and the resulting solid washed with water (1 mL). The obtained solid was dissolved in $CHCl_3$ (5 mL), and the solvent was removed under reduced pressure to give the corresponding product. For product **3s**, further purification via column chromatography was required.

-General Procedure **GP1b** (for compounds **3g**, **3k**, **3o**, **3t**, **3x**): after 8–24 h, 100 mg of NaCl were added to the reaction mixture, and the product was extracted with EtOAc (3×1 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified via column chromatography.



Scheme 5. Proposed reaction mechanism.

Supporting Information Summary

The supporting information includes the general experimental procedures for the photoreactions, experimental procedures for the preparation of starting materials, characterization data of isolated compounds, and data related to the conducted mechanistic studies. The authors have cited additional references within the Supporting Information.[20–22]

Acknowledgements

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Conflict of Interests

The authors declare no conflict of interests.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Photooxidation · Water · Tandem · Benzylidenemalononitrile · Benzyl alcohol

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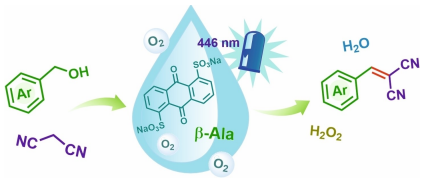
RESEARCH ARTICLE

Benzylidenemalononitrile derivatives are widely used as radical traps and as starting materials in Giese-type reactions. We report a tandem photo-oxidative process for the one-pot preparation of these products using water as reaction medium. In this cascade reaction, sodium anthraquinone-1,5-disulfonate is employed as a light-induced HAT catalyst, while β-alanine acts as a green and inexpensive organocatalyst. In most cases, the formed products precipitate and can be filtered, resulting in an operationally simple procedure.



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Tandem Synthesis of Benzylidenemalononitrile Derivatives in/on Water under Visible Light