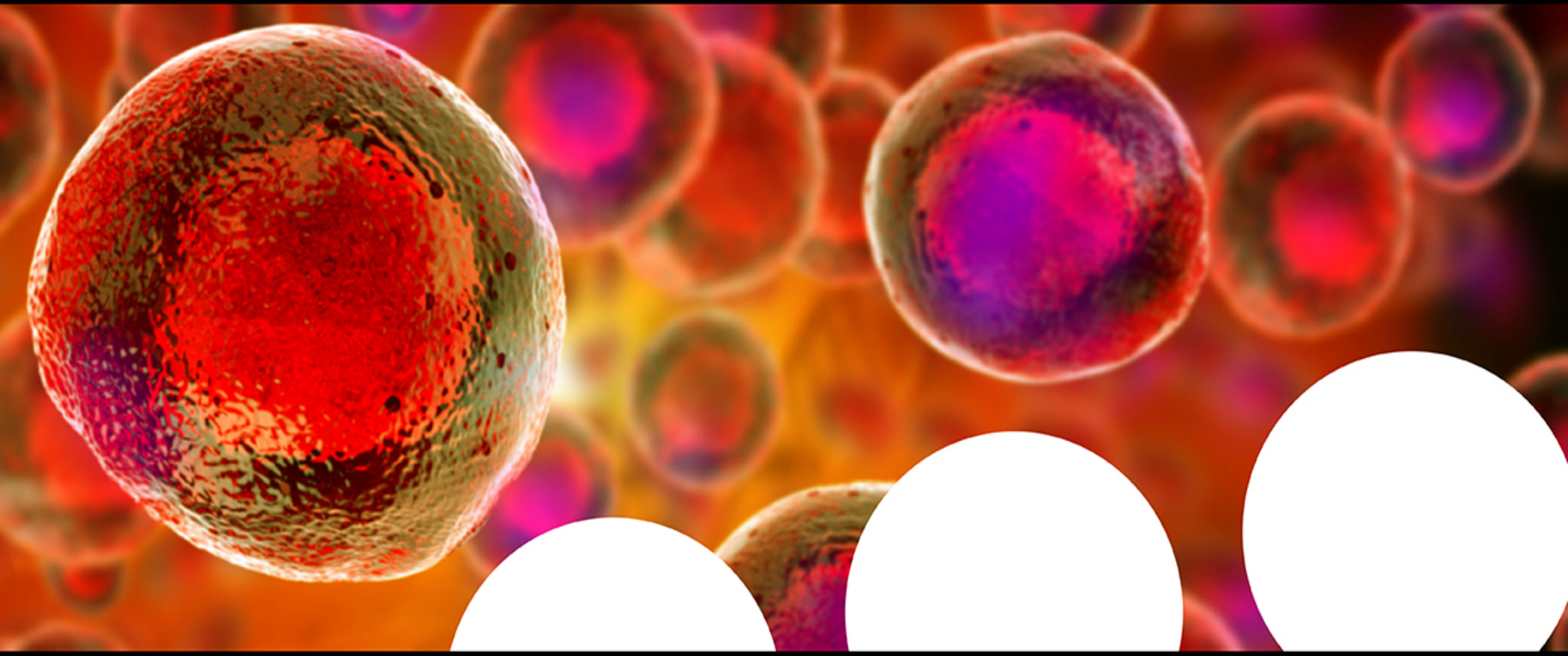

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Light-Induced Dealkylation of Benzamides in Aqueous Solution

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Abstract: The *N*-dealkylation reactions of benzamides occur naturally in living organisms but chemical methods remain poorly developed. So far, light-induced variants of these processes have been restricted to amides containing secondary *N*-alkyl groups or required pre-functionalization of the starting material. Here, we present a direct, controllable *N*-dealkylation of tertiary and secondary benzamides possessing primary alkyl substituents at *N*-atom. The developed strategy operates in aqueous environment under mild conditions involving either blue LEDs or sunlight irradiation. Preliminary mechanistic studies indicate two-step oxidation and the intermediacy of radicals at α-position to *N*-atom. Selectivity in *N*-dealkylation of homo- and heterosubstituted tertiary benzamides is also investigated.

Introduction

N-dealkylation is a vital process occurring in living organisms.[1–4] It is also one of the specific reactions of cytochrome P450, which is involved, *inter alia*, in the metabolism of *N*-containing drugs.[5–7] High activity of natural systems in *N*-dealkylation reactions has been successfully imitated in synthetic chemistry. In particular, the dealkylation of amines has been widely adapted,[8–10] giving access to many *N*-containing compounds, mostly via reaction with cyanogen bromide[11,12] or oxidation[13–15]. In contrast, the removal of *N*-alkyl groups from amides, which are ubiquitous both in nature and in agrochemicals or drug molecules, remains poorly developed.

There are chemical *N*-dealkylation methods that employ relatively harsh reaction conditions such as the use of alkali metals[16] or strong acids[17], but their scope is limited. Recently, milder reaction conditions for *N*-demethylation of *N*-methyl amides were developed by Wang, Zhang and co-workers who used copper-catalysis combined with *N*-fluorobenzenesulfonimide as the readily available single-electron transfer (SET) oxidant.[18] The issue of low reactivity of amides in dealkylation reactions have also been addressed by using electrochemical methods. In 1989 Hanzlik and co-workers performed anodic oxidation of *N*,*N*-dimethylamides in acetonitrile/water mixture to obtain *N*-methylamides.[19] Moreover, they were able to isolate *N*-methyl-*N*-(hydroxymethyl) derivative as a key intermediate, thus proving the oxidative mechanism. Jones and co-workers established an undivided, controlled current electrosynthetic procedure for the selective dealkylation of *N*,*N*-diethylbenzamides.[20]

Recently, light-induced processes gained traction as sustainable methods for exploring radical or radical-polar crossover reactions under mild conditions.[21] In the context of amide *N*-dealkylation, our group developed a photocatalytic, blue-light induced method for modification of *N*-alkylbenzamides in aqueous micellar solutions (Figure 1a).[22] This strategy, however, requires the presence of a halide substituent at *o*-position to the amide group, whose role is to make the molecule susceptible to reductive activation. A more direct approach was proposed by Lu and co-workers, who targeted secondary benzamides in the presence of oxone, catalytic amount of KBr and under white LEDs irradiation.[23] The method is suitable for *N*-dealkylation of substrates containing secondary alkyl groups, but in the presence of primary alkyl groups, imides form as major products.

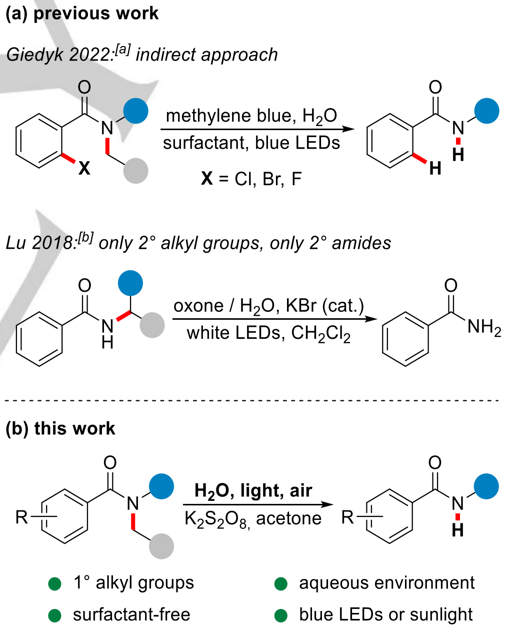


Figure 1. Light-induced strategies towards *N*-dealkylation of amides. [a] According to ref.[22] [b] According to ref.[23]

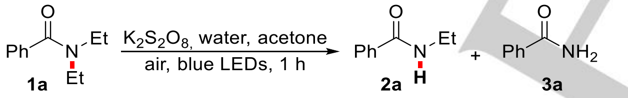
This article presents a direct, light-induced method for *N*-dealkylation of benzamides possessing primary alkyl substituents at *N*-atom (Figure 1b). The developed reactions proceed in aqueous environment under mild conditions, and do not require the presence of surfactants. Moreover, they prove efficient not only under blue LEDs irradiation but also under sunlight.

Results and Discussion

We started our investigations by using *N*,*N*-diethylbenzamide **1a** as a model and focusing on two key aspects of the studied reaction: the overall yield and the selectivity in terms of mono- versus di-dealkylation. The reaction parameters were optimized with respect to the oxidant, solvent system, time, ratio and concentration of reagents, allowing to obtain *N*-dealkylation products **2a**, **3a** in 72% combined yield and high preference for the monodealkylation (**2a** : **3a** ratio of 2.4 : 1; for full optimization studies see Supporting Information).

Control experiments showed that the addition of acetone improves the performance compared to the reaction in neat water,[24,25] presumably due to the higher solubility of benzamide **1a** (Table 1, entry 2). Interestingly, however, increasing the proportion of acetone in the mixture has a detrimental effect (entry 4). The use of acetate buffer (pH =5) improves the **2a** : **3a** ratio but this comes at the expense of the overall yield, which drops to 47% (entry 5). Similar results were observed for the reaction carried out with the addition of surfactants (entries 6, 8). The presence of oxidant is essential for this transformation to occur; potassium persulfate ($K_2S_2O_8$) proved to be the reagent of choice (entries 9-11). The irradiation with light is also necessary and blue LEDs cannot be replaced by green LEDs (entries 12, 13). The reaction is preferably carried out in a vial equipped with a needle that provides the access of air (entries 14-16). While the optimized conditions, which involve 1 h of stirring, lead mainly to the monodealkylation product **2a**, extending this time to 2 h worsens the **2a** : **3a** ratio (entries 3 vs 2, 7 vs 6). At the same time, the overall yield raises only moderately. Ultimately, reaction carried out for 13 h strongly favours didealkylation and formation of benzamide **3a** (entry 17).

Table 1. Controll experiments[a]



No.	Deviation from optimized conditions	Yield [%]	Ratio **2a** : **3a**
1	-	72	2.4 : 1
2	no acetone	56	6 : 1
3[b]	no acetone	67	2.4 : 1
4	in 1 : 1 water/acetone mixture	6	6 : 1
5	in acetate buffer pH = 5	47	15 : 1
6	in SDS_{aq} (33 mM)	52	6.4 : 1
7[b]	in SDS_{aq} (33 mM)	62	1.6 : 1
8	in TPGS 750M $_{aq}$ (33 mM)	53	5.6 : 1
9	no $K_2S_2O_8$	0	-
10	oxone instead of $K_2S_2O_8$	0	-
11	1,4-benzoquinone instead of $K_2S_2O_8$	34	6.6 : 1
12	no light	0	-
13	green LEDs	0	-
14	under O_2 atmosphere	3	31 : 1
15	under Ar atmosphere	52	2.7 : 1
16	closed flask	49	5.5 : 1
17	13 h instead of 1 h	68	1 : 8.2

[a] Optimized reaction conditions: substrate **1a** (0.1 mmol, 33 mM), $K_2S_2O_8$ (0.5 mmol, 165 mM), water (2.25 ml), acetone (0.75 ml), 35 °C, 451 nm, 1 h. Yields were calculated using GC analysis. *n*-Dodecane was used as internal standard.
[b] reaction carried out for 2 h instead of 1 h.

Exploring the scope of *N*,*N*-homosubstituted tertiary benzamides revealed a large influence of the substituents on the aromatic ring on the reactivity of the starting materials (Table 2). The presence of electron donating groups deactivates the substrate and prolonged reaction times were required to obtain products **2b** - **2e** in satisfactory yields. *p*-Fluoro-*N*-ethyl benzamide **2f** can be obtained in 40% yield after 3 h of irradiation, whereas electron-defficient *p*-cyano- and *p*-trifluoromethyl analogues **2g** and **2h** are formed from the corresponding substrates **1g** and **1h** in similar yields already after 0.5 h. In these cases, however, prolonging the reaction time does not lead to higher yields as the desired *N*-dealkylation is followed by further decomposition. Increasing the length of the alkyl chain at *N*-atom gradually worsens the reaction outcome, which is probably related to the lower solubility of benzamides **1i** and **1j**. On the contrary, benzamide **1k** bearing two *iso*-propyl groups can be efficiently dealkylated (64% of product **2k**), provided lower irradiation power and longer reaction time is used. We also examined benzamides **1l-1n** which are derivatives of cyclic amines. Pleasingly, they underwent the desired reaction giving *N*-benzoyl-amino acids **2l** and **2m** and *N*-benzoyl-amino ketone **2n** in satisfactory yields. The structures of products **2l-2n** additionally provide important mechanistic clues, showing that oxidation at α-position to the *N*-atom leads to a carbonyl compounds: aldehydes (prone to further oxidation) or ketones. It should be pointed out, that didealkylated benzamides remained major side products in each of the studied reactions.

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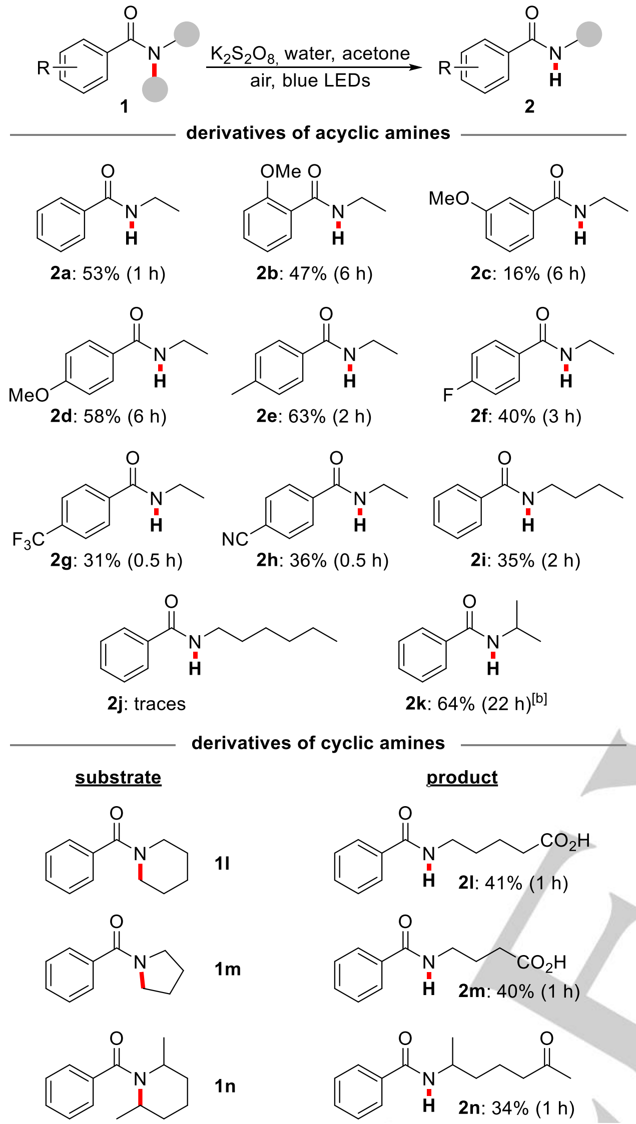
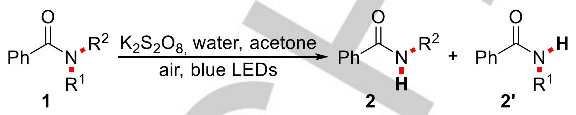
Table 2. *N*-dealkylation of tertiary homosubstituted amides [a]



[a] Optimized reaction conditions: substrate **1** (0.1 mmol, 33 mM), $K_2S_2O_8$ (0.5 mmol, 165 mM), water (2.25 ml), acetone (0.75 ml), 35 °C, 451 nm. Average isolated yields from 3 independent reactions are given. [b]1.5 W instead of 7 W.

To better determine the propensity of various alkyl substituents to undergo cleavage, we checked the scope of heterosubstituted benzamides (Table 3). In general, benzyl group is the easiest to be removed, which is in line with the stability of intermediate radicals that are expected to form at α-position to the *N*-atom (entries 1, 7). Surprisingly, however, primary alkyl groups are considerably more reactive then secondary ones (entries 2, 3). This unique feature renders the reactions of benzamides that have both types of groups very selective with ratios up to 53 : 1. Benzamide **1s** with two different primary alkyl groups can be transformed into the equimolar mixture of monoalkylated products **2s** and **2s'** with combined yield of 44% (entry 4). This further confirms that the aforementioned lower reactivity of homosubstituted substrate **2i** stems from the solubility issues, rather than the inherent properties of *n*-Bu substituent. The reactivity of benzamides **1t** and **1u** having *N*-aryl substituents depend on the electron density on the aromatic ring. While no dearylation was observed at all, removal of the accompanying *N*-methyl substituent was only possible with the substrate **1u**. Substrate **1t** remained completely non-reactive under the developed conditions.

Table 3. *N*-dealkylation of tertiary heterosubstituted amides [a]

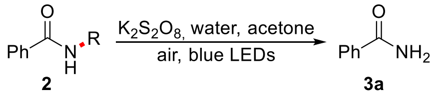


No.	R1	R2	Substrate	Time [h]	Yield 2+2' [%]	Ratio 2 : 2'
1	Me	Bn	**1o**	2	55	1 : 1.6
2	Me	Cy	**1p**	3	33	32 : 1
3	Me	*i*-Pr	**1r**	1	54	53 : 1
4	Et	*n*-Bu	**1s**	2	44	1 : 1
5	Me	(*p*-OMe)C_6H_4	**1t**	3	traces	-
6	Me	(*p*-CN)C_6H_4	**1u**	3	33	only **2**
7	*i*-Pr	Bn	**1w**	3	64	1 : 33

[a] Optimized reaction conditions: substrate **1** (0.1 mmol, 33 mM), $K_2S_2O_8$ (0.5 mmol, 165 mM), water (2.25 ml), acetone (0.75 ml), 35 °C, 451 nm. Average combined, isolated yields from 3 independent reactions are given.

After a slight modification of the water to acetone ratio, the strategy also proved successful for the *N*-dealkylation of secondary benzamides **2a**, **2i**, **2o** and **2x** (Table 4). They gave the desired product **3a** in moderate to very good yields of 32% – 78%. In these cases, corresponding imides that result from the formation of ketones at α-position to the *N*-atom, were the major by-products.

Table 4. Reaction of secondary amides [a]



No.	R	Substrate	Time [h]	Yield **3a** [%]
1	Et	**2a**	4	60
2	*n*-Bu	**2i**	6	78
3	Bn	**2o**	2	36
4	*i*-Bu	**2x**	2	32

[a] Reaction conditions: substrate **2** (0.1 mmol, 33 mM), $K_2S_2O_8$ (0.5 mmol, 165 mM), water (2 ml), acetone (1 ml), 35 °C, 451 nm. Average isolated yields from 3 independent reactions are given.

To understand how the reaction time affects the selectivity of *N*-dealkylation process, we monitored the conversion of model substrates **1a** and **2a** and the formation of the corresponding products. (Figure 2). The tertiary benzamide **1a** is rapidly consumed in just 2 h of irradiation, but concentration of the desired product **2a** only increases within the first hour. Later, a second *N*-dealkylation to benzamide **3a** dominates, along with hydrolysis to benzoic acid. The hydrolysis is due to the substantial change in the pH of the reaction, which decreases from neutral (pH = 7) to acidic (pH = 2) during the first hour of irradiation.[26] Further investigations using compound **2a** as a substrate confirmed that the *N*-dealkylation of secondary amides is slower compared to tertiary amides and it takes 3 h of irradiation to obtain 90% conversion. In this case, the concentration of the desired product **3a** reached its maximum (corresponding to 50% yield) after 4 h. We also traced the formation of another side product, imide **4a**. Contrary to previous reports,[23] under our conditions it forms in small amounts (15% yield), mainly during the first 2 h of irradiation.

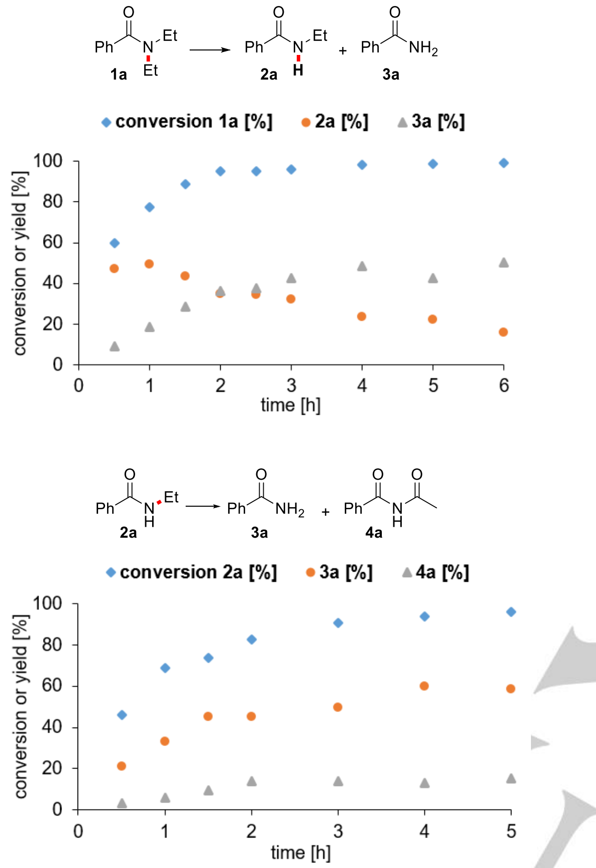


Figure 2. *N*-dealkylation of tertiary and secondary amides **1a** and **2a**: monitoring conversion of substrates and formation of products over time.

Since the control experiments (Table 1) clearly showed that light is indispensable for the reaction to occur, we carried out UV-Vis measurements to elucidate which reaction component is responsible for the light absorption (Figure 3). Although individual reaction components (substrate **1a** or $K_2S_2O_8$ in water/acetone mixture) absorb weakly in the blue light region, their mixture displays absorbance that is higher than the sum of individual ingredients. This indicates an interaction between substrate **1a** and the oxidant, that is in line with a solvent-caged effect proposed recently by Barnham and co-workers.[27] Moreover, the high absorbance at shorter wavelengths (<400 nm) prompted us to check if our reaction can be carried using natural source of energy. To our delight, stirring the mixture under sunlight for 2 hours afforded product **2e** in 44% isolated yield (Figure 4, for further details see Supporting Information).

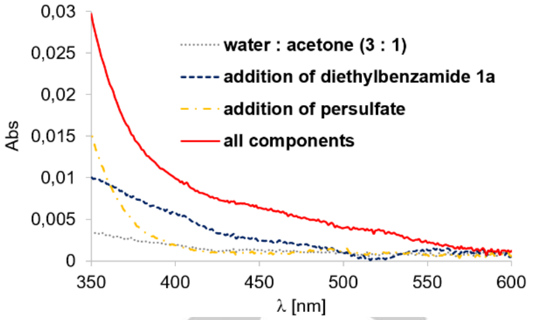


Figure 3. UV-Vis studies of mixtures containing various reaction components.

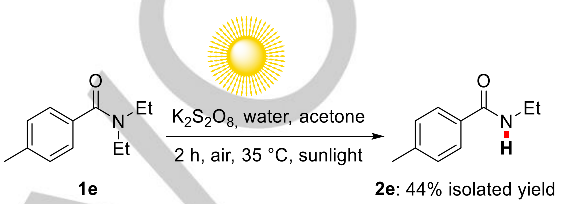


Figure 4. *N*-dealkylation of substrate **1e** under sunlight.

The involvement of carbon-radicals in the course of the reaction was confirmed by the reaction with TEMPO as a radical trap (Figure 5a). A corresponding adduct was unambiguously detected by HRMS method (m/z = 347.2705). Based on the aforementioned considerations, we propose a mechanism for developed *N*-dealkylation strategy (Figure 5b). Solvent-caged adduct of benzamide **A** derivative and persulfate anion $S_2O_8^{2-}$ undergoes light-induced excitation followed by hydrogen atom transfer (HAT), producing radical **B** and sulfate radical anion $SO_4^{\cdot-}$. A subsequent SET leads to cation **C**, which readily reacts with water. The resulting *N*-(1-hydroxyalkyl)-*N*-alkylbenzamide **D** is prone to the cleavage of *N*-hydroxyalkyl group and the formation of final product **E** and aldehyde **F**, which can undergo further oxidation to carboxylic acid.

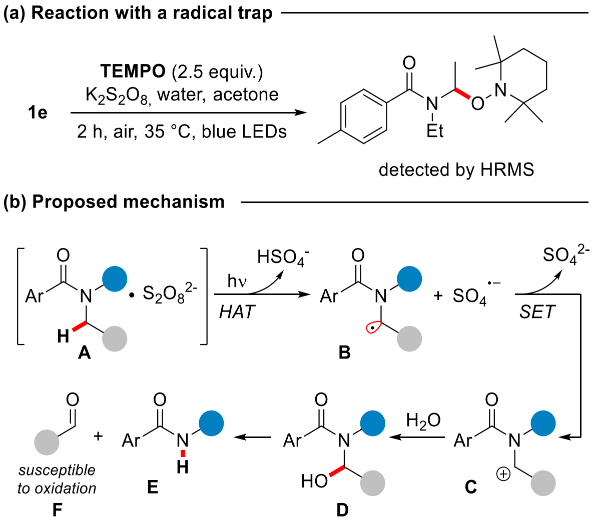


Figure 5. Mechanistic considerations.

Conclusion

In summary, we have developed a light-induced *N*-dealkylation of tertiary and secondary benzamides possessing primary alkyl substituents at *N*-atom. Our strategy is therefore complementary to existing methods that mainly target secondary *N*-alkyl groups. Its scope has been demonstrated in a range of functionalized starting materials, including derivatives of cyclic amines that lead to *N*-benzoyl-amino acids. Moreover, by operating in an aqueous environment and using light irradiation (blue LEDs or sunlight) as the source of energy, the developed strategy corresponds with the current need for sustainable methods of organic synthesis. We hope these findings will help changing the reputation of amides as unreactive starting materials and contribute to advancing their light-induced chemistry.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Acknowledgements

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Keywords: dealkylation • benzamides • photochemistry • aqueous solutions • light-induced

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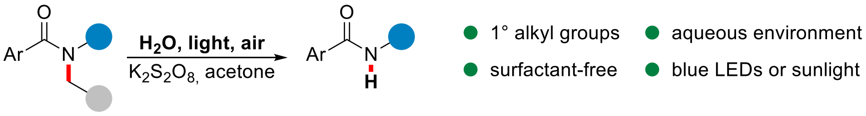

This article describes a controllable, light-induced *N*-dealkylation of tertiary and secondary benzamides having primary alkyl substituents at *N*-atom. The developed reactions take place in an aqueous environment under mild conditions and do not require the presence of surfactants. They can be carried out not only under irradiation with blue LEDs but also under sunlight.

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Author biographies

Martyna Cybularczyk-Cecotka graduated with a Master of Science in chemistry from the University of Warsaw, Faculty of Chemistry, Poland, in 2012. She completed her PhD studies at the University of Warsaw in 2018, working on dialkylindium alkoxides and aryloxides – their synthesis, reactivity towards *N*-heterocyclic carbenes and catalytic properties in *rac*-lactide polymerization. In 2019 she joined the newly formed group of Maciej Giedyk in the Institute of Organic Chemistry Polish Academy of Sciences, focusing on photocatalysis in water solutions. Her research interests focus on the synthetic aspects of green chemistry.

Agnieszka Kamińska obtained the title of Chemical Technology Engineer from the Faculty of Chemistry of the Warsaw University of Technology. She is currently pursuing a master's degree in medical chemistry and is investigating the potential applications of nanomaterials in teranostics.

Zuzanna Jopek graduated from Engineering studies in the field of Chemical Technology at the Faculty of Chemistry of the Warsaw University of Technology in 2021. She started Master studies at the Warsaw University of Technology, where she works on the development of new methods for the determination of compounds belonging to the vitamin E group and their oxidized derivatives.

Dr. Maciej Giedyk completed his PhD in 2016 under the supervision of Prof. Dorota Gryko, working on the catalytic properties of vitamin B_{12} derivatives. At the beginning of 2018, he took up a postdoctoral position in the group of Prof. Burkhard König at the University of Regensburg. In 2019, he was appointed an assistant professor at the Institute of Organic Chemistry, PAS. His research interests include the development of photocatalytic strategies, which utilize aqueous solutions as the reaction environment. In particular, he explores methods for converting stable and readily accessible starting materials through selective activation of strong chemical bonds.