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Authors: Elpida Skolia, Mary K. Apostolopoulou, Nikolaos F. Nikitas, and Christoforos G. Kokotos

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Photochemical Synthesis of Benzimidazoles from Diamines and Aldehydes

Elpida Skolia,[†[a]] Mary K. Apostolopoulou,[†[a]] Nikolaos F. Nikitas[a] and Christoforos G. Kokotos*[a]

Dedicated to Prof. Panagiota Moutevelis-Minakakis on the occasion of her retirement

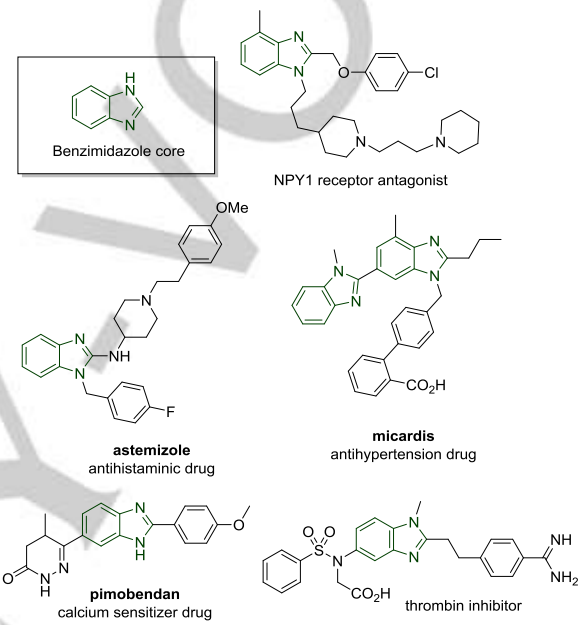
[a] E. Skolia, M. K. Apostolopoulou, N. F. Nikitas, Prof. Dr. C. G. Kokotos
Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece.
† denotes equal contribution
Corresponding author. E-mail: ckokotos@chem.uoa.gr homepage: http://www.chem.uoa.gr/?page_id=2898&lang=el

Abstract: An efficient, green, cheap and metal-free photochemical protocol for the synthesis of benzimidazoles has been developed. 2,2-Dimethoxy-2-phenylacetophenone was employed as the photoinitiator and CFL lamps were used as the light source, leading to the cyclization of substituted diamines with aldehydes and the corresponding benzimidazoles were obtained in good to high yields. Mechanistic studies were conducted, in order to determine a plausible mechanism for the reaction.

Introduction

Photochemistry, the use of visible light to promote organic reactions, exerts a powerful impact on the activation of molecules over the past few decades. Since 2008, photochemistry has experienced a research explosion, utilizing the term "photoredox catalysis".[1] Most photoredox methods utilize transition-metal complexes, which present good catalytic properties; however, they are usually potentially toxic and expensive. An alternative solution to metal complexes, as the field of photochemistry expands, is the use of small organic molecules as the photo-promoters.[2]

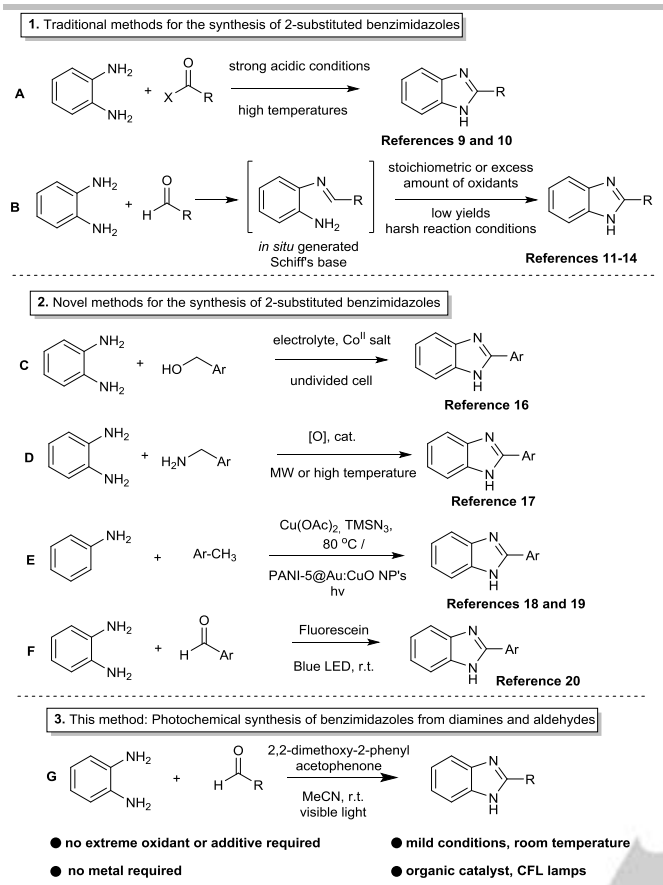
The introduction of novel, efficient and environmentally friendly reaction protocols for the synthesis of important organic intermediates or final products from readily available reagents constitutes a key challenge in organic synthesis. Heterocyclic compounds are frequently used in medicinal chemistry, due to their active role in biological systems. Benzimidazole is one of the oldest known nitrogen heterocycle, firstly synthesized by Hoebrecker and later by Ladenburg and Wundt in the 1870s.[3] The benzimidazole scaffold was firstly employed for its therapeutic potential at 1944 by Woolley, who was the first to introduce benzimidazoles as purine-substitutes to exhibit some biological responses.[4] Brink later identified 5,6-dimethylbenzimidazole as a degradation product of vitamin B_{12} and subsequently presented that its derivatives have activities similar to vitamin B_{12}.[5] All seven positions of the benzimidazole scaffold can be substituted, however, benzimidazole-based compounds that bear functional groups at the 2 position usually present interesting biological activities. Over the years, benzimidazole and its derivatives have evolved as important heterocyclic systems in the field of drugs and pharmaceuticals, due to their presence in bioactive compounds, which exhibit antiparasitic, anticonvulsant, analgesic, antihistaminic, antiulcer, antihypertensive, antiviral, anticancer, antifungal and anti-inflammatory action (Scheme 1).[6] Benzimidazoles derivatives can also act as ligands to transition metals[7] and are important intermediates in many organic reactions.[8] Organic chemistry is continuously seeking new methods for the synthesis of benzimidazole and its derivatives.



Scheme 1. Examples of biologically relevant benzimidazoles.

Two are the most general methods for the synthesis of 2-substituted benzimidazoles. Primarily, benzimidazoles are obtained via the coupling of 1,2-diaminobenzenes with carboxylic acids[9] or their derivatives,[10] under harsh dehydrating reaction conditions and high temperatures, utilizing strong acids, such as hydrochloric acid, polyphosphoric acid, boric acid, or p-toluenesulfonic acid. However, the use of milder reagents, particularly Lewis acids, inorganic clays or mineral acids, has improved the yield of this reaction (Scheme 2, **A**).[3d-3e,10] On the other hand, the synthesis of benzimidazoles can be achieved through the condensation of 1,2-diaminobenzenes with aldehydes via a two-step procedure that includes an *in situ*-generated Schiff's base and requires an oxidative reagent to generate the benzimidazole ring.[11] Various oxidative reagents have been employed for this purpose (Scheme 2, **B**).[12] Due to the ease of accessibility of a variety of aldehydes, the latter method has been extensively used.[13,14] These processes usually require stoichiometric or excess amount of oxidants to be used, produce toxic or environmentally problematic by-products, suffer from low yields, harsh reaction conditions, long reaction times, and use of metals and expensive reagents.[15] Therefore, the development of a cost-effective, safe and environment friendly protocol is desirable.

In recent years, greener catalytic processes for the synthesis of benzimidazoles have been developed, in order to



Scheme 2. Approaches for the synthesis of benzimidazoles.

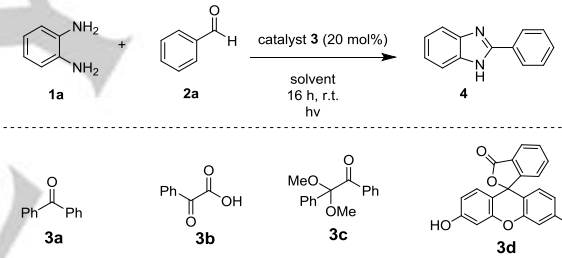
avoid the above mentioned problems. In 2015, Huang and coworkers presented an electrochemical method for the synthesis of benzimidazoles from alcohols and *o*-phenylene diamine, utilizing a Co^{II} salt as the catalyst (Scheme 2, **C**).[16] In 2017, Luo and coworkers synthesized benzimidazoles from primary amines with molecular oxygen as the oxidant (Scheme 2, **D**).[17] In a similar manner, an efficient copper-catalyzed strategy for the amination of methyl arenes using aniline, $TMSN_3$ and heating has been reported for the preparation of functionalized benzimidazoles,[18] while an oxidant-free copper-based photocatalytic system that utilizes Cu_2O-Fe_2O_3 nanoparticles (NPs) for the construction of C–N bonds was developed by Bhalla (Scheme 2, **E**).[19] Recently, Li and coworkers utilized an organic dye, fluorescein, as the photocatalyst to synthesize benzimidazoles via Blue LED irradiation (Scheme 2, **F**).[20] Photochemistry has provided interesting approaches for the synthesis of benzimidazoles from diamines and aldehydes, either employing tetrazines,[21] or heterogeneous photocatalytic systems.[22-26] Finally, a DMF-water (9:1) solvent system at 80 °C has been shown to promote the synthesis of benzimidazoles.[27] Limitations of these methods are the harsh reaction conditions, the catalyst preparation, the cost and effect on the environment and the limited substrate scope, especially when aldehydes bearing aliphatic chains are employed.

The use of *o*-phenylenediamine and aldehydes as substrates is one of the most effective methods for the synthesis of benzimidazoles, however, most current methods for their preparation exhibit difficulties and limitations. Thus, there is still need for an efficient, easy and green synthesis protocol. Our group works in the field of photochemistry[28] and has successfully synthesized different categories of compounds, utilizing a variety of photocatalysts and cheap household lamps as the irradiation source. Herein, we introduce an alternative, direct and metal-free protocol that requires light, for the synthesis of benzimidazoles from diamines and aldehydes. The initiator employed is a low-cost and commercially available compound that demonstrates high activity when irradiated. The reaction requires exceptionally mild conditions to proceed, as it occurs at room temperature under household bulb irradiation (Scheme 2, **G**). Cyclization of a variety of substituted aldehydes and diamines has been achieved and the corresponding products were afforded in good to high yields. This method is cheap and environmentally friendly, since it avoids the use of any expensive and toxic oxidants or catalysts, it is operationally simple and the starting reagents, as well as the visible light sources, are inexpensive and readily available.

Results and Discussion

We initiated our study utilizing *o*-phenylenediamine (**1a**) and benzaldehyde (**2a**) as the substrates. In the optimization of the reaction conditions, a variety of different irradiation sources, photocatalysts, solvents and stoichiometries were tested (Table

Table 1. Optimization of the reaction conditions for the photochemical reaction of **1a** with **2a**.



Entry	Catalyst	Solvent	CFL Yield (%)[a] / Blue LED Yield (%)[b]
1	**3a**	MeCN	68 / 70
2	**3b**	MeCN	78 / 59
3	**3c**	MeCN	89 (85)[c] / 70
4	**3d**[d]	MeCN	68 / 85
5	**3c**	CH_2Cl_2	53 / -
6	**3c**	EtOAc	42 / -
7	**3c**	MeOH	30 / -
8	**3c**	$CHCl_3$	60 / -

[a] All reactions were carried out with (**1a**) (0.30 mmol), (**2a**) (0.30 mmol), solvent (1.0 mL) and catalyst (20 mol%), under 2 x 85W household lamps (CFL) irradiation at room temperature for 16 h. Yields were determined by GC-MS. [b] The reaction was performed under Blue LED irradiation for 16 h. Yields were determined by GC-MS. [c] Yield of isolated product. [d] Catalyst loading: 5 mol%.

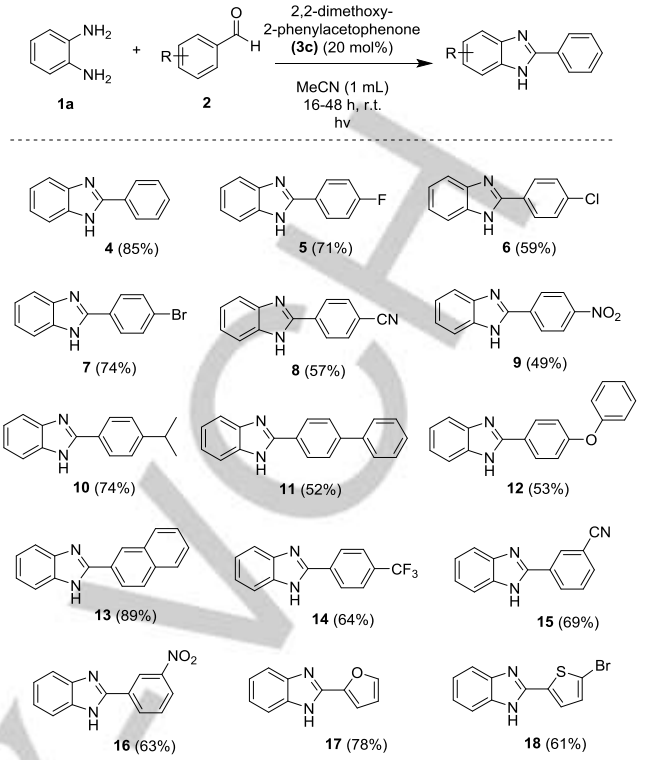
1). A number of photoorganocatalysts-photoinitiators and organic dyes were employed with 2,2-dimethoxy-2-phenylacetophenone (**3c**) providing the highest yields in CFL lamps, that comprise a cheaper and easier photochemical set-up (Table 1, entries 1-4). For comparison purposes, the previously described fluorescein catalyst was also employed (Table 1, entry 4).[20] The optimum solvent for the reaction proved to be MeCN (Table 1, entries 3 and 5-8).

Decreasing the amount of the catalyst loading or the solvent resulted in lower reaction yields and a further increase of them did not increase the yield (Table 2, entries 1-5). When either substrate was used in excess, the product was afforded in lower yields, due to formation of by-products, so a stoichiometric amount of both regents was preferred (Table 2, entries 6 and 7). We then studied the performance of the reaction with and without the catalyst, or without air or without light (Table 2, entries 8-10) and the results illustrated that in the absence of the photoinitiator, light or air, no reaction took place. Various reaction times were tested, with 16 h proving to be the optimum for this substrate.[29]

After establishing the optimum reaction conditions for the photochemical synthesis of benzimidazoles (Table 1, entry 3), we began exploring the substrate scope (Schemes 3 and 4). First, a variety of aldehydes were tested with *o*-phenylenediamine (Scheme 3). Aromatic aldehydes proved to be excellent substrates for the reaction, leading to the expected benzimidazoles in good to high yields. When benzaldehyde is employed, the yield of the product could reach 85% (Scheme 3, **4**). The reaction proceeded with both electron-rich and deficient aryl aldehydes, affording the corresponding products in good yields. It is important to highlight that the reaction tolerates the presence of a cyano- and a nitro-group, both in *meta*- and *para*-position (Scheme 3, **8**, **9** and **15**, **16**), halides including fluoro- (Scheme 3, **5**), chloro- (Scheme 3, **6**) and bromo- (Scheme 3, **7**), isopropyl- (Scheme 3, **10**), CF_3- (Scheme 3, **14**) and phenoxy-group (Scheme 3, **12**). Polyaromatic systems (Scheme 3, **11** and **13**), as well as heterocyclic substrates, though they required an increase in the reaction time (Scheme 3, **17** and **18**), proved to be good substrates for this methodology.

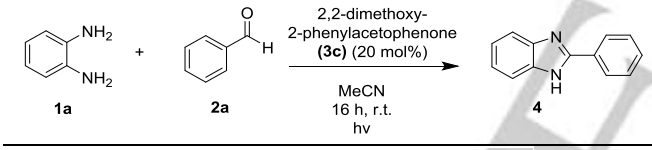
Moreover, in order to expand the substrate scope and search for the limits of our methodology, aliphatic aldehydes were also tested (Scheme 4). They proved to be suitable substrates when increasing the reaction time, leading to the expected products in moderate to good yields. This is not very usual in literature, since most literature precedents employ only aromatic aldehydes and not aliphatic aldehydes. Linear aldehydes both of smaller and larger chains reacted effectively (Scheme 4, **19**-**22**). Branched aliphatic aldehydes led to the desired product in good yields (Scheme 4, **23-27**). This protocol could be extended into different diamines which, when reacting with benzaldehyde, afforded benzimidazoles in moderate yields (Scheme 4, **28** and **29**).

In order to study the reaction mechanism, a variety of tools were employed. Quantum yield measurements provide a useful tool for identifying if photochemical reactions involve radical chains. Based on literature, a closed photocatalytic system lacking chain propagation exhibits a maximum theoretical quantum yield of $\Phi = 1$, which indicates that every photon absorbed by the photocatalyst produces one molecule of product. The chain processes, on the other hand, could



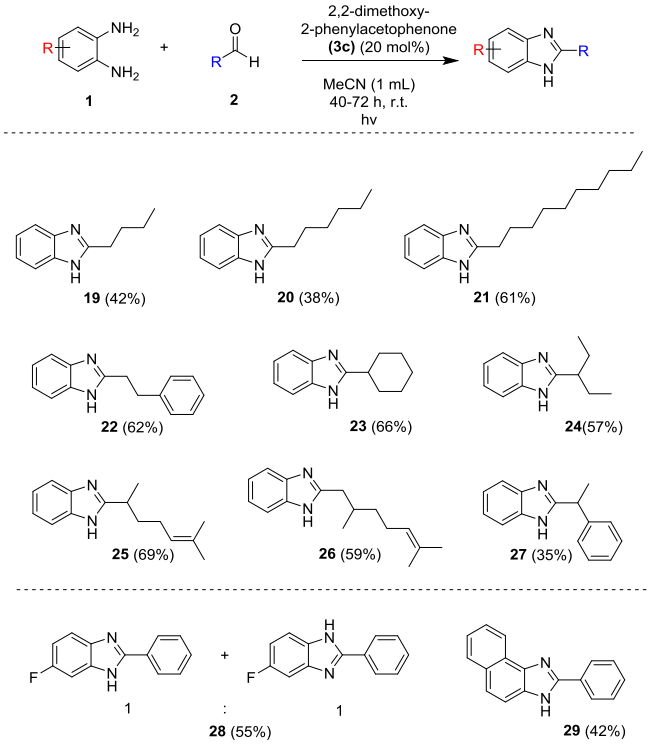
Scheme 3. Substrate scope for the synthesis of benzimidazoles from aromatic aldehydes.

Table 2. Final optimization of the reaction conditions for the photochemical reaction of **1a** with **2a**. [a]



Entry	Catalyst loading (mol %)	Solvent (mL)	**1a** (equiv.)	**2a** (equiv.)	Yield[b] (%)
1	10	1	1	1	46
2	20	1	1	1	89 (85)[c]
3	30	1	1	1	83
4	20	0.5	1	1	63
5	20	1.5	1	1	80
6	20	1	2	1	27
7	20	1	1	2	38
8	0	1	1	1	0
9[d]	20	1	1	1	0
10[e]	20	1	1	1	0

[a] All reactions were carried out with (**1a**) (0.30-0.60 mmol), (**2a**) (0.30-0.60 mmol), MeCN (0.5-1.5 mL) and 2,2-dimethoxy-2-phenyacetophenone (**3c**) (5-30 mol%), under household lamps irradiation at room temperature for 16 h. [b] Yields were determined by GC-MS. [c] Yield of isolated product. [d] Under Ar atmosphere. [e] The reaction was performed in the dark.



Scheme 4. Substrate scope for the synthesis of benzimidazoles from aliphatic aldehydes and diamines.

potentially provide multiple equivalents of product from each photon absorbed, therefore the quantum yield of a chain reaction is Φ >> 1.[30] The quantum yield of the photochemical reaction for the synthesis of 2-phenylbenzimidazole (**4**) was calculated (Φ = 7), indicating a chain propagation mechanism.

UV-Vis experiments were also performed to determine whether the reaction mechanism involves the formation of an EDA complex.[31,32] An electron donor-acceptor (EDA) complex is formed *in situ* by two structurally small molecules, one acting as electron donor (D) and the other acting as electron acceptor (A). Upon mixing of the two reagents, an EDA complex is formed, resulting usually in an increase in the UV absorbance. Upon mixing 2,2-dimethoxy-2-phenylacetophenone (**3c**), *o*-phenylenediamine (**1a**) and benzaldehyde (**2a**) in MeCN in couples or as the reaction mixture, no increase in the UV absorbance was observed. These results excluded the possibility of an EDA complex formation.

Next, ^{1}H-NMR mechanistic experiments were performed. *o*-Phenylenediamine (**1a**), benzaldehyde (**2a**), 2,2-dimethoxy-2-phenylacetophenone (**3c**) were employed in MeCN-d_3 and the reaction was monitored frequently through ^{1}H-NMR mechanistic experiments, after 1 h, 2 h, 3 h, 4 h, 6 h, 9 h, 12 h and 14 h of irradiation.[29] After 2 h of irradiation, peaks that can be attributed to benzaldehyde (**2a**), 2-benzylideneaminoaniline (**S1**), 2-phenyldihydrobenzimidazole (**S2**) and 2-phenylbenzimidazole (**4**) were observed. After 14 h of irradiation, peaks that can be attributed to 2-phenyldihydrobenzimidazole (**S2**) and 2-phenylbenzimidazole (**4**) were observed. These results suggest that benzaldehyde (**2a**) is fastly consumed to afford **S1**, which is the intermediate in the reaction mixture. Intramolecular cyclization affords **S2** and the photochemical oxidation occurs

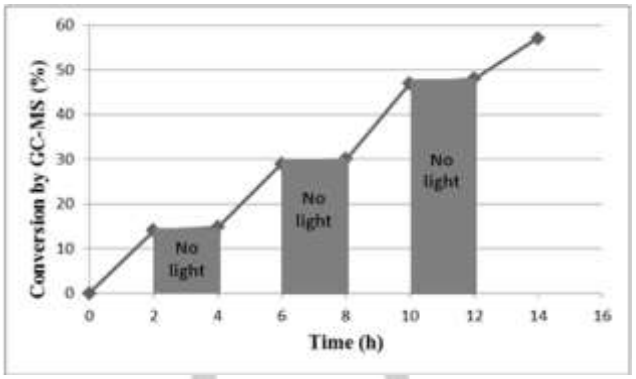


Figure 1. On-off mechanistic experiments.

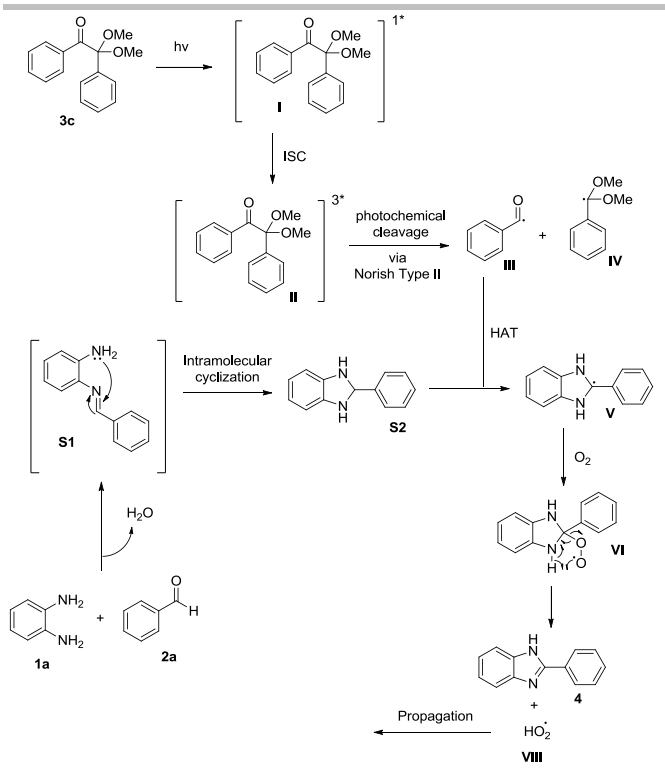
rapidly to afford 2-phenylbenzimidazole (**4**).[29]

Further mechanistic studies proved the radical nature of the reaction, since addition of TEMPO or BHT, two known radical scavengers, prevented the formation of the product.[29] Instead, when the reaction mixture with TEMPO and BHT was irradiated for 16 h, an adduct deriving from the benzoyl radical with TEMPO and with BHT respectively, as well as an adduct deriving from α,α-dimethoxybenzyl radical with TEMPO and BHT respectively, were observed by GC-MS, confirming the generation of the benzoyl and the α,α-dimethoxybenzyl radical from 2,2-dimethoxy-2-phenylacetophenone. ^{1}H-NMR mechanistic experiments of the reaction with BHT, also confirmed that in the presence of the radical scavenger the photochemical oxidation is inhibited. Finally, on-off experiments were carried out and proved that constant irradiation is necessary for the completion of the reaction. When the reaction mixture was irradiated for 2 h and then left stirring under dark for 2 h, the yield remained low (Figure 1).[29]

Utilizing the results of the experiments above, we can propose a plausible mechanism for the photochemical reaction of *o*-phenylenediamine (**1a**) and benzaldehyde (**2a**) to provide 2-phenylbenzimidazole (**4**) (Scheme 5). Firstly, **1a** and **2a** are fastly condensed to afford the imine intermediate **S1**. Subsequently, intramolecular cyclization affords **S2**.[20] Upon irradiation by light, 2,2-dimethoxy-2-phenylacetophenone (**3c**), that absorbs in the UV range (310-390 nm)[33] is excited to the singlet state **I**, followed by intersystem crossing that leads to triplet 2,2-dimethoxy-2-phenylacetophenone **II**. Through the triplet state, **II** undergoes photochemical α-cleavage via Norrish type I photo scission, to produce benzoyl radical **III** and α,α-dimethoxybenzyl radical **IV**, with **III** exhibiting usually higher reactivity.[33e] Either benzoyl radical **III** (more likely) or radical **IV** performs a hydrogen abstraction (HAT) with **S2** leading to radical intermediate **V**. Reaction with oxygen leads to intermediate **VI**, which via intramolecular shift leads to product **4** and **VII**, which propagates the reaction.

Conclusions

In conclusion, an efficient, green, metal-free and sustainable new protocol for the photochemical synthesis of benzimidazoles, by cyclization of diamines and aldehydes, was developed. The reaction takes place under mild conditions



Scheme 5. Proposed reaction mechanism.

including an organic photoinitiator and household bulb irradiation. A variety of substrates bearing different functionalities, which can be expanded to aliphatic aldehydes, as well, were tested successfully, leading to products in moderate to excellent yields. Mechanistic studies were performed in order to determine the reaction's mechanism. This novel approach employs cheap, green and sustainable materials, in order to synthesize more complex compounds.

Experimental Section

General Photochemical Procedure for the Synthesis of Benzimidazoles: In a glass vial containing diamine **1** (1 equiv., 0.30 mmol), aldehyde **2** (1 equiv., 0.30 mmol), 2,2-dimethoxy-2-phenylacetophenone (**3c**) (15 mg, 0.06 mmol, 20 mol%) and MeCN (1.0 mL) were added. The vial was sealed with a screw cap and left stirring under household bulb irradiation (2 x 85W household lamps) for 16-72 h. The desired product was purified by column chromatography (Pet. Ether / AcOEt : 7/3, CH_2Cl_2 / AcOEt : 9/1).

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Keywords: Aldehydes • Diamines • Benzimidazoles • HAT • Photochemistry • Green Chemistry

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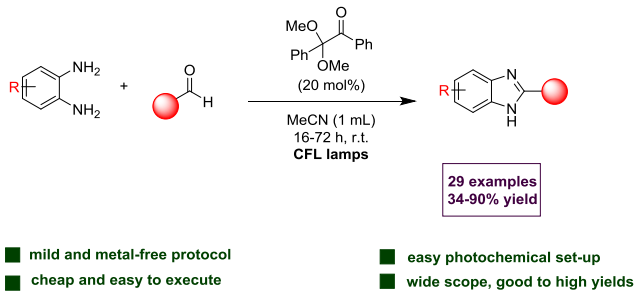

*Elpida Skolia, Mary K. Apostolopoulou, Nikolaos F. Nikitas and Christoforos G. Kokotos**

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Photochemical Synthesis of Benzimidazoles from Diamines and Aldehydes

Photochemistry. A green, facile, mild and metal-free protocol for the synthesis of benzimidazoles by cyclization of diamines and aldehydes was developed, using cheap household lamps as the light source and an organic molecule as the photoinitiator.

Institute and/or researcher Twitter usernames: @KokotosCG