Photocatalyzed Synthesis of 3-Substituted Phthalides: A Key Access to (+/-)-Herbaric Acid

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RESEARCH ARTICLE

Photocatalyzed Synthesis of 3-Substituted Phthalides. A Key Access to (±)-Herbaric acid

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Abstract: An efficient organophotocatalyzed protocol was developed for the preparation of 3-substituted phthalides. The presented transformation was performed under particularly mild conditions within 6h and was ultimately applied to a precursor of the herbaric acid.

Introduction

3-Substituted 3*H*-isobenzofuran-1-ones or phthalides are ubiquitous scaffold found in a good variety of relevant molecules.[1] They have proven to be useful versatile building blocks in organic synthesis and are widely occurring in natural substances exhibiting a broad range of biological activities. Representative examples include the *N*-Butylphthalide currently used for the treatment of cerebral ischemia,[2] the Catalpalactone exhibiting a particular antitermitic and cytotoxic activities,[3] the Spirolaxine, a potent anti-H. pylori agent,[4] the Vermistatin displaying cytotoxic effect against tumor cells[5] or the fungal metabolite Herbaric acid known for its antibacterial activity (Figure 1).[6] As such, the construction of this heterocycle core has attracted significant interest over the years.[7] Two main synthetic routes are dominant. The first is oriented towards the functionalization of unsubstituted phthalides while the second is based on the formation of the fused γ-lactone ring. Among the latter, which is the most investigated, the condensation of diverse nucleophiles with 2-carboxybenzaldehyde,[8] diverse transition metal-catalyzed cyclizations[9] and notably through C-H bond activation,[10] halogenolactonization,[11] organocatalyzed lactonization of 2-alkenylbenzaldehydes[12] have received a particular attention. These strategies usually required the use of toxic and non-abundant transition metal catalysts and/or high temperature.

Besides this, visible-light driven photocatalysis has proven to be particularly efficient in a wide range of organic transformations and can be a good alternative to more conventional catalysis.[13]

In the frame of this study, we ask ourselves whether a photocatalytic intramolecular oxa-Michael might be envisioned for the construction of the furanone moiety. In the literature, such transformation was realized in the presence of a large excess of strong acids[14] or at high temperature[15] and was interestingly observed as a side product under electrochemical conditions.[16]

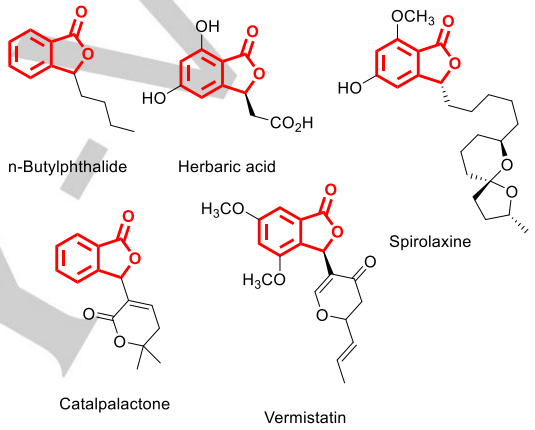


Figure 1. Representative phthalides.

Results and Discussion

The viability of our assumption was initially investigated on a model reaction with the methyl 2-carboxycinnamate **1a**. The first experiment was achieved in acetonitrile, in the presence of 2 mol% of (Ir[dF(CF$_3$)ppy]$_2$(dtbbpy))PF$_6$ (Ir) photocatalyst and 1 equivalent of K$_2$HPO$_4$ (Table 1, entry 1). After 16h of 11W blue LED light irradiation, we were delighted to observe the formation of the desired phthalide **2a** with 62% yield. Substituting the acetonitrile by the methanol led to a significant decrease in the yield (entry 2) while its replacement by the dimethyformamide has improved the yield to 77%. Next, a screening was conducted to identify the best photocatalyst (Figure 2). For this purpose, we evaluated the Ru(bpy)$_3$Cl$_2$ and three organophotocatalysts, the 9,10-dicyanoanthracene (DCA), the Fukuzumi acridinium (Mes-Acr$^+$) and the 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4-CzIPN) to initiate transformation (entries 4, 5, 6 and 7 respectively). From this survey, the 4-CzIPN was found to be as efficient as the iridium-based catalyst, yielding **2a** with 78% yield.

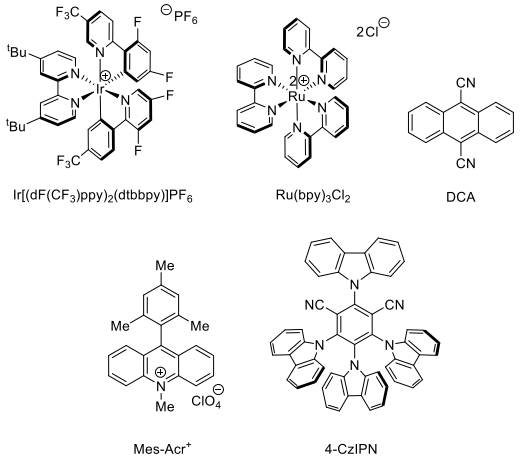
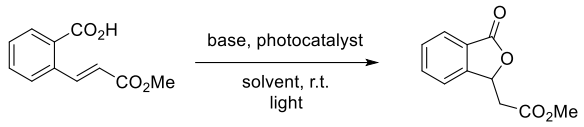


Figure 2. Photocatalysts evaluated

Table 1. Optimization of the reaction conditions[a]

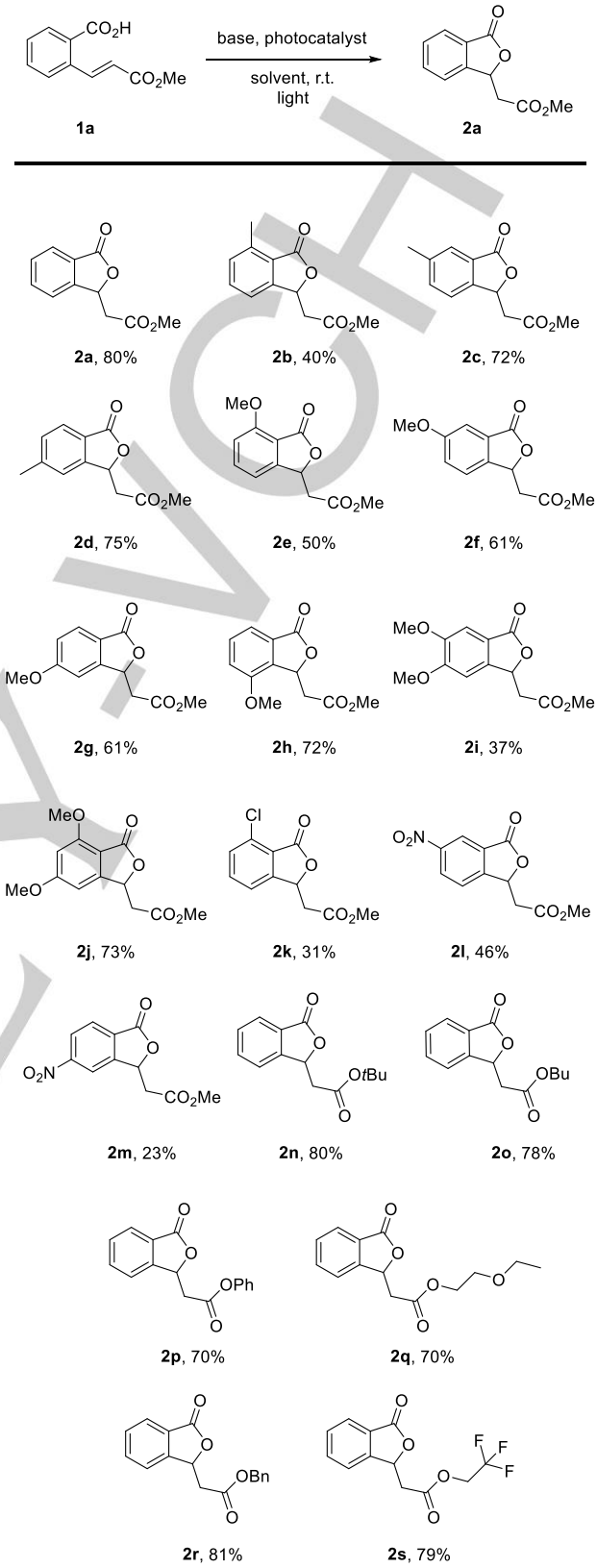


1a **2a**

Entry	Catalyst	Base	Solvent	Yield
1	Ir	K_2HPO_4	MeCN	62
2	Ir	K_2HPO_4	MeOH	36
3	Ir	K_2HPO_4	DMF	77
4	$Ru(bpy)_3Cl_2$	K_2HPO_4	DMF	50
5	DCA	K_2HPO_4	DMF	11
6	Mes-Acr$^+$	K_2HPO_4	DMF	0
7	4-CzIPN	K_2HPO_4	DMF	78
8[b]	4-CzIPN	K_2HPO_4	DMF	62
9	4-CzIPN	Cs_2CO_3	DMF	0
10	4-CzIPN	KH_2PO_4	DMF	Traces
11[c]	4-CzIPN	K_2HPO_4	DMF	81
12[d]	4-CzIPN	K_2HPO_4	DMF	63
13[c],[d]	4-CzIPN	K_2HPO_4	DMF	83 (80%)[e]
14[f]	4-CzIPN	K_2HPO_4	DMF	0
15	none	K_2HPO_4	DMF	0

[a] Reaction conditions: **1a** (0.25 mmol, 1 equiv.), base (1 equiv.), photocatalyst (2 mol%), solvent (1 mL), 11W blue LED irradiation, 16h reaction time, room temperature. [b] 2 mL DMF. [c] 34W Blue LED irradiation. [d] 6h reaction time. [e] Isolated yield. [f] No light.

For our further investigations, we chose the 4-CzIPN due to its ease of access and cost-effectiveness. Thereafter, we found that decreasing the concentration of reagents and photosensitizer or replacing the K_2HPO_4 by the Cs_2CO_3 or KH_2PO_4 led to drop down the yield of the reaction (Table 1, entries 8-10). Finally, the influence of the light source power was evaluated when irradiating the reactor with a 34W blue LED. This change turned out to have an impact on the kinetic of the transformation. Indeed, whilst with both blue light sources the yields are comparable after 16h of reaction time (entries 7 vs 11), the most powerful source allowed to reduce the reaction time to 6h (entries 12 vs 13). Furthermore, control experiments clearly confirm that the intramolecular cyclization requires light and photoinitiator (entries 14 and 15).



Scheme 1. Substrate scope of phthalides **2**

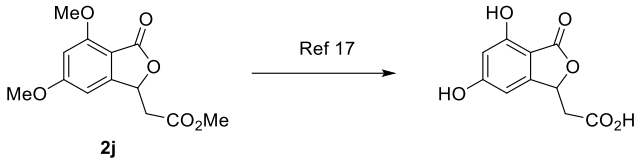
With the optimized conditions in hands, i.e. substrate (0.25 mmol), K_2HPO_4 (1 equiv.), 4-CzIPN (2 mol%), DMF (1 mL), 34W blue LED irradiation, room temperature and 6h reaction, the

scope of this photoredox transformation was investigated (Scheme 1). For this purpose, a good range of substrates possessing electron donating or withdrawing substituents in various positions of the aromatic moiety were selected.

Overall, the transformation was found to be extendable to a wide variety of compounds with yields ranging from 23 to 81%.

From a general overview, with few exceptions, the transformation appears to be more efficient with electron donating groups on the aromatic core (37-75% yields for **2b-j** vs 23-46% yields for **2k-m**). In addition, in the case of substrates monosubstituted on the aromatic moiety, any group on C7-position led to decrease significantly the yields of the phthalides (**2b** vs **2c**,**d**; **2e** vs **2f-g**). In addition, a variety of carboxylate ester derivatives successfully led to the phthalide adducts (70-81% yields for **2n-s**).

Among the isobenzofuranone synthesized, we were delighted to observe a good conversion and 73% yield for **2j**. Indeed, this latter could easily be converted into the (±)-herbaric acid by the means of already referenced methods (Scheme 1).[17]



2j

Scheme 1. Formal synthesis of racemic herbaric acid from **2j**.

Further studies were conducted to identify the type of mechanism involved in this transformation. First, the on/off experiments revealed the strict requirement of light for the reaction to proceed (Figure 3). Next, it was found that the presence of one equivalent of TEMPO partially hampered the reaction, thus suggesting the presence of free-radical intermediates (see supporting information).[18]

In addition, density functional theory (DFT) calculations were carried out in order to rationalize the non-reactivity in absence of photocatalyst. The calculated energy profile diagram revealed that the cyclization step from the carboxylate is much more energy demanding than from the carboxylate radical (Figure 4).

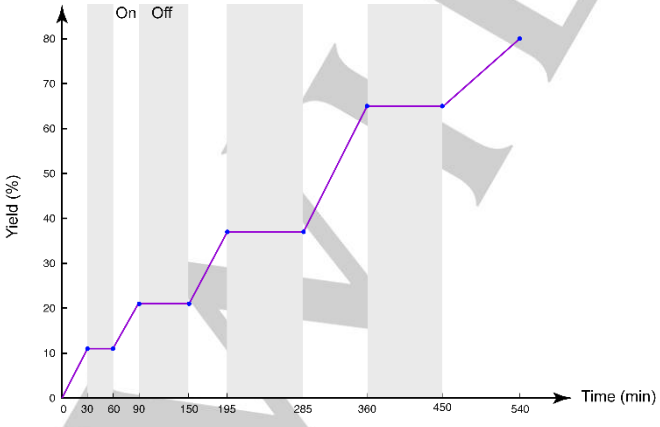


Figure 3. "Light on/off" intermittent experiment for formation of phthalide **2a**

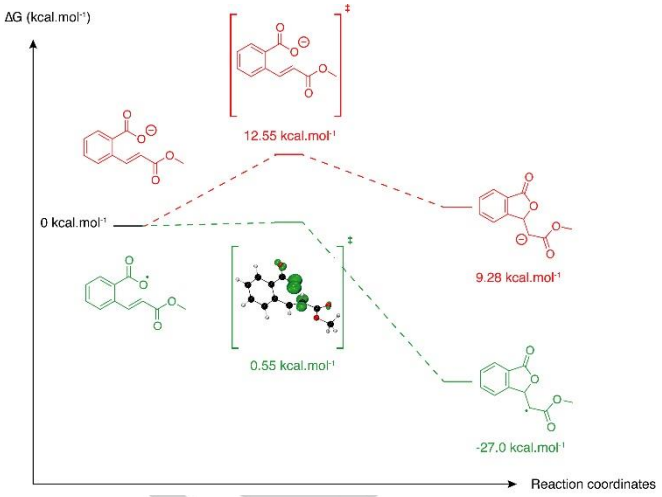
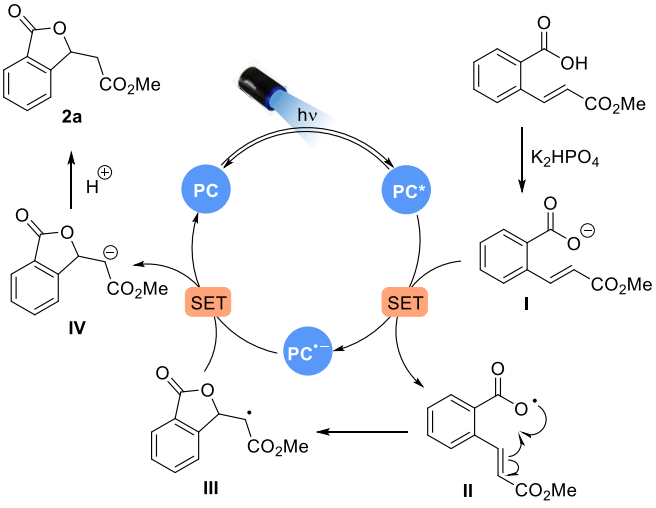


Figure 4. Energy diagram of the cyclization step.

Therefore, the mechanism envisioned of this photoinitiated intramolecular oxa-Michael addition is described in Scheme 2. Here, the catalytic cycle is initiated by single electron oxidation of the carboxylate **I** (formed after deprotonation of **1a**) which has an estimated oxidation potential of 1.35 V vs SCE[19] by the means of the excited state photocatalyst PC* ($E_{1/2Red}$ = 1.35 V vs SCE).[20] The formed carboxylate radical **II** can undergo an intramolecular radical Michael addition and therefore leads to the formation of the furanone moiety of the phthalide **III**. At this stage, the low rate constant for the decarboxylation of aroyloxy radical is crucial for this transformation to proceed.[21] The intermediate **III** is finally reduced by single electron transfer closing thus the catalytic cycle and leading to the formation of the phthalide **2a**. It is worth noticing that the mechanism which would start with the oxidation of the cinnamate unit to generate a cation radical is not favorable considering the higher oxidation potential of the cinnamate moiety (approximatively 1.8 V vs SCE).[22]



Scheme 2. Proposed mechanism.

Conclusion

In summary, we have developed a straightforward access to a variety of 3-susbtituted phthalides. During this investigation, we found that the reaction proceeds smoothly under mild conditions and light-driven irradiation in presence of an organophotocatalyst. Interestingly, we have proven that this method could allow the synthesis of the racemic herbaric acid.

Experimental Section

General information

Solvents, reagents and catalysts were used as received from commercial suppliers. Photocatalytic experiments were carried out in 10 mL Schlenck tubes and irradiation was performed using an Hepatochem device equipped with a 34W blue LED lamp. Thin layer chromatography (TLC) was carried out on aluminium-baked Macherey-Nagel silica gel 60. Flash column chromatography was performed over a Macherey-Nagel silica gel (230-400 mesh). NMR data were recorded on a Bruker Advance spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using tetramethylsilane (TMS) as internal standard and $CDCl_3$ or CD_3OD as solvent. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. For ^{1}H NMR: $CDCl_3$, δ = 7.26. Datas are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS were measured in REALCAT, Université de Lille. The experiments were performed on a Synapt G2Si (Waters) equipped with an ion mobility cell. The molecules were analyzed through direct infusion in sensitivity and positive mode with the following tune parameters: 3.00 kV as capillary voltage, 60 and 90 respectively set for the sampling cone and source offset. The source temperature was of 100 °C, with a desolvation temperature of 250 °C. The cone gas flow was set to 50 L/h, with a desolation gas flow of 600 L/h and the nebulizer set to 6.5 Bar. The mass range was set to 50 to 500 g/mol for the analysis.

General procedure for photocatalytic experiments

To a Schlenck tube were added 0.24 mmol of the previously synthetized Heck coupling compound, 1 eq K2HPO4 and 2 mol% 4CzIPN, dissolved in DMF (0.24 mol.L-1). The whole mixture was placed in an HEPATOCHEM photochemical reactor, using 34W Blue LEDs (450 nm). The mixture was stirred under irradiation for 6 hours. After evaporation of DMF, the product was isolated via flash chromatography, using ethyl acetate/petroleum ether as eluant.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

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

Keywords: intramolecular oxa-Michael cyclization, phthalides, photocatalysis, 4-CzIPN, (±)-herbaric acid

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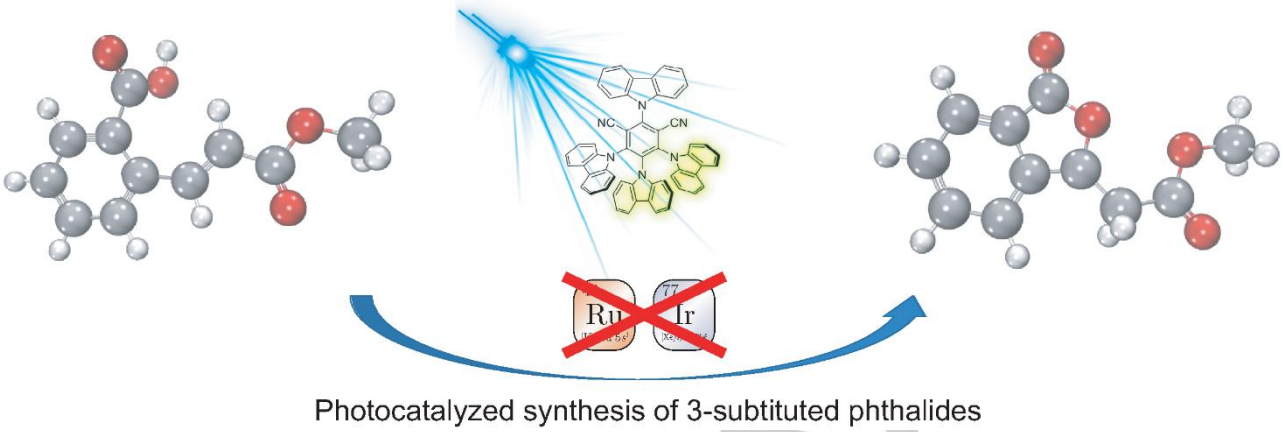

Photocatalyzed synthesis of 3-subtituted phthalides

Herein, we investigated a new organophotocatalyzed protocol enabling the preparation of 3-substituted phthalides. From this work, the 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) turned out to be a particularly efficient organophotocatalyst to promote lactone formation under visible-light irradiation within 6h. The methodology was extended to nineteen diversly substituted phthalides with yields ranging from 23 to 81%. Ultimately, it was found that this protocol could enable the formation of racemic herbaric acid.