

# Light-driven catalyst-free access to phthalazines: Merging two metal-free domino reactions in one-pot

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**ABSTRACT:** We report the development of an unprecedented metal-free four-step one-pot synthetic strategy to access high-value functionalized phthalazines using *o*-methyl benzophenones as starting compounds. Combination of a light-mediated enolization of *o*-methyl benzophenones/Diels-Alder reaction domino process with a subsequent deprotection/aromatization domino reaction in one-pot leads to sustainable and efficient organic synthesis. The tangible advantages, i.e. absence of catalysts or additives, utilization of commercially available and/or easily accessible substrates, mild reaction conditions, simplicity, and single work-up procedure, make this combined process highly appealing for the direct construction of various 1-aryl-phthalazines.

## Introduction

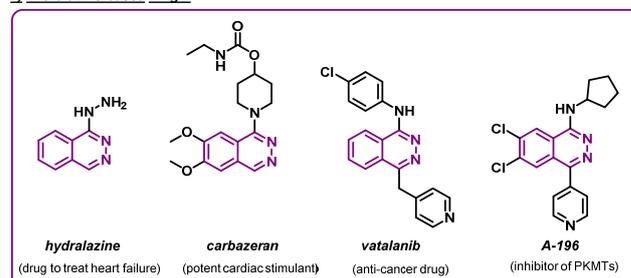
Among diverse *N*-heterocycles, phthalazines represent a valuable class of compounds and are important subunits of a broad variety of natural products with remarkable biological activities<sup>1-3</sup> and are ubiquitous in pharmaceuticals.<sup>4-6</sup> An impressive number of known drugs contain a phthalazine core, e.g., hydralazine (used to treat high blood pressure and heart failure),<sup>7</sup> carbazeran (potent cardiac stimulant)<sup>8</sup> and vatalanib (anti-cancer drug)<sup>9, 10</sup> and recently reported drug candidate A-196 (potent and selective inhibitor of protein lysine methyltransferases (PKMTs) (Figure 1a).<sup>11</sup>

Besides, phthalazine-based compounds are widely employed as catalysts<sup>12</sup> or ligands in a variety of transition metal complexes.<sup>13-16</sup> Apart from that, they act as key intermediates in organic synthesis. For instance, they can undergo a thermal rearrangement reaction towards corresponding quinazolines in high yield.<sup>17</sup>

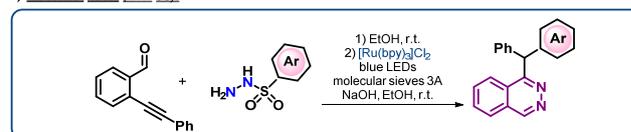
Commonly, phthalazine derivatives can be obtained by ring-closing reactions of either *o*-dicarbonyl compounds with hydrazine reagents,<sup>18, 19</sup> aromatic aldazines,<sup>20</sup> or arylhydrazines<sup>21</sup> maintained in liquid aluminum chloride or by refluxing in presence of zinc chloride. However, these and related methods<sup>22, 23</sup> require mostly toxic reagents and harsh reaction conditions. Therefore, development of new environmentally friendly and efficient methodologies for synthesis of substituted phthalazines is highly desirable.

Recently, domino and one-pot processes have attracted much attention, since they avoid a lengthy separation and purification process of intermediate products and, therefore, minimize chemical waste and save resources.<sup>24-28</sup>

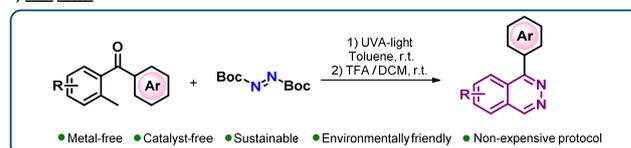
### a) Phthalazine-based drugs:



### b) Previous work (Ref. 35):



### c) This work:



**Figure 1.** a) Selected examples of phthalazine-based drugs. b) Previous photochemical protocol towards phthalazines.<sup>35</sup> c) Light-driven metal-free protocol developed in this work.

Especially photochemical domino and one-pot transformations have a high appeal, as light is an abundant, clean, and renewable reagent in chemistry.<sup>29-34</sup> Until the present, only a single example of photochemical synthesis of phthalazine derivatives was reported through [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub> catalyzed photoredox one-pot

process, combining a radical hydroamination reaction followed by a Smiles rearrangement (Figure 1b).<sup>35</sup>

While ruthenium metal-based complexes are very efficient photosensitizers and/or photoredox catalysts, this metal is expensive and not abundant. Therefore, a metal-free photochemical synthetic route towards phthalazine derivatives is highly desirable but has not been reported so far. Herein, we report a first example of a metal-free one-pot process (Figure 1c) involving light-induced photoenolization of *o*-methyl benzophenones as a key step towards new phthalazine derivatives. Specifically, we present a combined process, which joins a metal- and catalyst-free hetero-Diels-Alder reaction between long-wavelength UV-generated *o*-quinodimethanes and di-*tert*-butyl azodicarboxylate with a subsequent deprotection and aromatization (Figures 2 and 3). This facile four-step one-pot sequence, with only a single work-up procedure, results in new functionalized phthalazines with yields up to 66%.

## Results and Discussion

The photochemical enolization<sup>36</sup> of *o*-alkyl benzophenones towards transient substituted *o*-quinodimethanes or *o*-xylylenes is a remarkable and extensively investigated transformation.<sup>37</sup> The mechanism of this reaction, which was discovered by Cava and Napier in 1957<sup>38</sup> and later extended by Yang and Rivas,<sup>39</sup> has been comprehensively studied by flash photolysis,<sup>40</sup> ultrafast laser<sup>41, 42</sup> and supersonic jet spectroscopies,<sup>43</sup> paramagnetic resonance<sup>44, 45</sup> and time-resolved thermal lensing<sup>46</sup> techniques, as well as by isotope exchange and trapping studies.<sup>47-50</sup> Moreover, theoretical investigations have been carried out.<sup>51</sup> The photochemically generated *o*-quinodimethanes have been extensively used as dienes in the Diels-Alder cycloaddition in the synthesis of substituted achiral and chiral tetralines.<sup>52, 53</sup> The group of Melchiorre made a remarkable contribution to this field, not only by developing an asymmetric method and for obtaining chiral tetralines with high level of enantiocontrol, but also by exploring other reactions of photogenerated *o*-quinodimethanes.<sup>54, 55</sup>

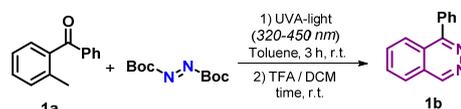
Until the present, photochemical metal-free synthesis of phthalazines via photogenerated *o*-quinodimethanes has failed.<sup>56</sup> While a tetrahydrophthalazine derivative was observed in reaction of diethyl azodicarboxylate with photodiene of *o*-methyl benzophenone, it could, however, not be converted into a phthalazine.<sup>56</sup> We envisaged that substitution of diethyl azodicarboxylate by di-*tert*-butyl azodicarboxylate as dienophiles in photochemically induced Diels-Alder reactions and subsequent hydrolysis of Boc groups could enable aromatization of tetrahydrophthalazine product intermediates towards phthalazines.

We initiated our study, using commercially available *o*-methyl benzophenone (**1a**) as a model substrate (Table 1). To our delight, the test reaction in presence of di-*tert*-butyl azodicarboxylate (2 equiv.) followed by a subsequent cleavage of *tert*-butyloxycarbonyl (Boc) in presence of trifluoroacetic acid (TFA) lead to formation of 1-phenylphthalazine in 20% yield (Table 1, Entry 1). Increasing amount of di-*tert*-butyl azodicarboxylate to 4 and 5 equiv. improved the yield to 51% and 54%, respectively (Table 1, Entries 2 and 4). However, increasing amount of di-*tert*-butyl azodicarboxylate to 6 equiv. resulted in 46% yield (Table 1, Entry 5). When the reaction was performed in more concentrated solution, it resulted in only 29% yield of desired product (Table 1, Entry 3). Carrying out the reaction in

more diluted solution led to shorter reaction time almost without loss of yield (Table 1, Entry 6). Next, we performed the reaction in degassed toluene using freeze-pump-thaw cycling as it was previously shown, that in aerated solutions, photogenerated *o*-xylylenes can be easily trapped by dissolved oxygen forming cyclic peroxides.<sup>57</sup> Indeed, conducting reaction in degassed toluene improved the yield to 59% (Table 1, Entry 7). Optimization of the amount of TFA necessary for removal of the Boc protecting groups and subsequent aromatization step let us further improve the yield to 66% (Table 1, Entry 8). It is worthwhile noting that calculated average yield of every individual step in this four-step *one-pot* transformation is up to 90%.

In absence of light at room temperature, no product formation was observed (Table 1, Entry 9). The same results were obtained by performing the reaction at 50 °C or by refluxing for 3 hours (Table 1, Entries 10 and 11). Notably, upon prolonged refluxing, the *o*-methyl-benzophenone remained unchanged, while di-*tert*-butyl azodicarboxylate was completely decomposed (Table 1, Entry 12). Thus, the presence of light proved to be crucial for the reaction.

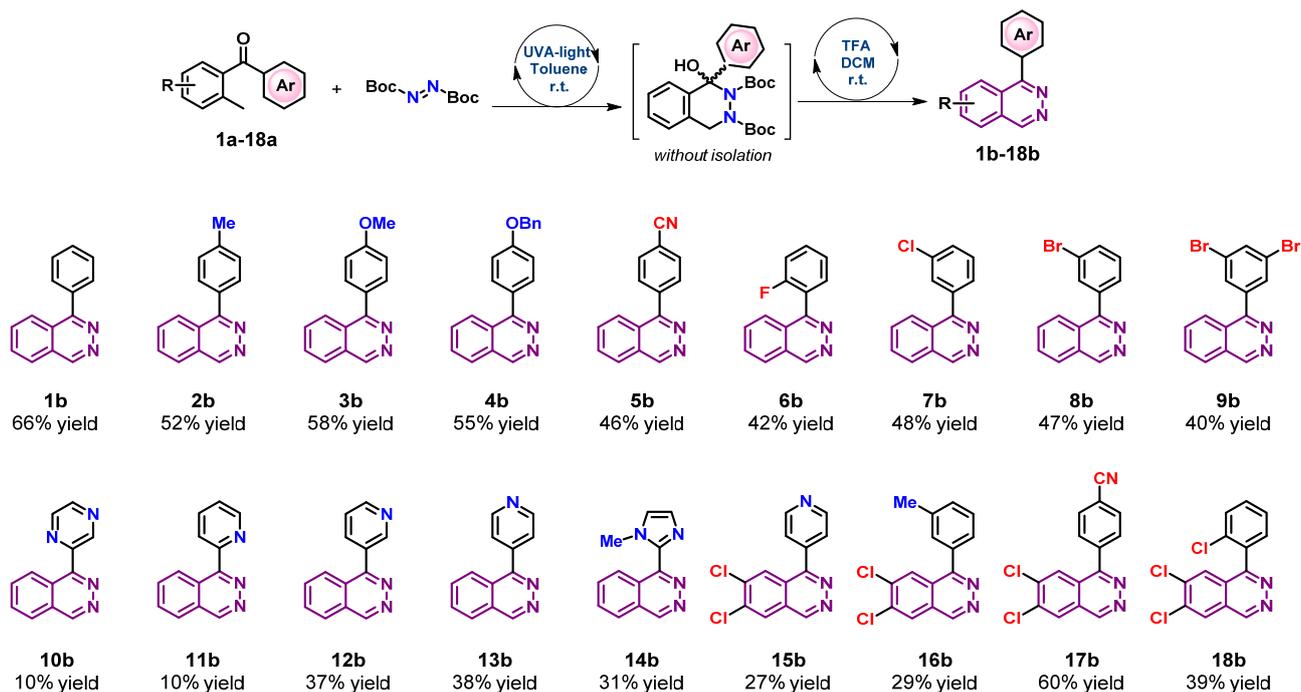
**Table 1.** Optimization of the reaction conditions.



Entry	DBAD, equiv	toluene, M <sup>[a]</sup>	time, h	Yield, %
1	2	0.1	2	20
2	4	0.1	7	51
3	4	0.2	7	29
4	5	0.1	4	54
5	6	0.1	8	46
6	5	0.05	3	49
7 <sup>[b]</sup>	5	0.05	3	59
8 <sup>[b,c]</sup>	<b>5</b>	<b>0.05</b>	<b>3</b>	<b>66</b>
9 <sup>[d]</sup>	5	0.05	3	n.r.
10 <sup>[e]</sup>	5	0.05	3	n.r.
11 <sup>[f]</sup>	5	0.05	3	n.r.
12 <sup>[f]</sup>	5	0.05	18	n.r.

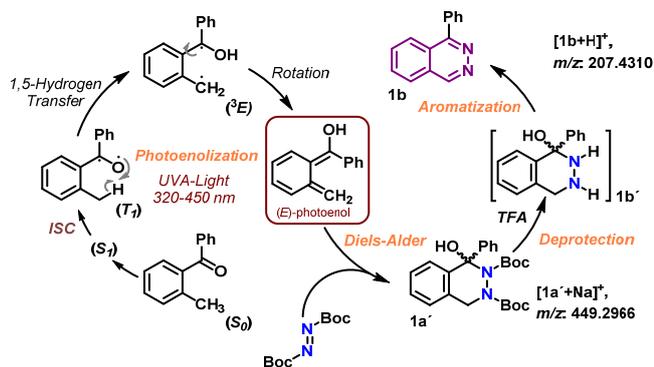
<sup>[a]</sup> With respect to **1a**. <sup>[b]</sup> Degassed toluene. <sup>[c]</sup> TFA-DCM=1:1 (4 mL). *Reactions in absence of light*; <sup>[d]</sup> at r.t.; <sup>[e]</sup> at 50 °C; <sup>[f]</sup> at reflux. DBAD = di-*tert*-butyl azodicarboxylate; n.r. = no reaction.

The scope of developed reaction was explored, using a set of *o*-methyl benzophenones **1a-18a**, and the results are summarized in Figure 2. First, influence of substituent at *para*-position of the phenyl ring of *o*-methyl benzophenone was examined. Several electron-donating groups (EDG), namely methyl, methoxy and benzyloxy, were well tolerated in the developed reaction and gave the corresponding phthalazines **2b**, **3b**, and **4b** with good yields of 52%, 58% and 55%, respectively. Substrates, bearing electron-withdrawing groups (EWG) in *para*-, *ortho*- and *meta*-positions, however, resulted in the desired 1-aryl-phthalazines in slightly lower yields (40-48% for products **5b-9b**).



**Figure 2.** Substrate scope of a new one-pot four-step reaction towards 1-aryl-phthalazines.

The reaction also allows to introduce N-heterocycles at the 1-position of the product (see compounds **10b-15b**). Notably, yields of *para*- and *meta*-substituted pyridines **12b** and **13b** are higher than for *ortho*-substituted pyridine **11b**. Electron-withdrawing substituents at the phthalazine core are also well tolerated: the products **15b-18b** are obtained with notable yields of 27%-60%. Nonetheless, presence of chlorine substituents at the benzene ring of the phthalazine core (cf. **15b** vs. **13b**) exhibits a significantly lower yield (of 27% and 38%, respectively). Surprisingly, *para*-cyano-substituted product is obtained in a much higher yield when chlorine substituents are present at the phthalazine moiety (**17b**, 60% yield), in comparison to product **5b** (46% yield) without those EWGs.



**Figure 3.** Proposed reaction mechanism of the light-driven metal-free one-pot reaction towards phthalazines.

According to the proposed mechanism for photoenolization, the singlet excited state ( $S_1$ ), delivered by the direct irradiation of

the substrate molecule in the ground state ( $S_0$ ), undergoes exclusive intersystem crossing ( $ISC$ ) to the relatively long-lived triplet state ( $T_1$ ) (Figure 3). Adiabatic H-atom transfer in the excited triplet ketone yields in triplet 1,4 biradical ( $^3E$ ). Due to free rotation of the ketyl group in the relaxed geometry of  $^3E$ , initially both the (*Z*)- and the (*E*)-photoenols are formed in about equal yield. However, the short-lived (*Z*)-dienol rapidly reverts to the starting ketone through efficient intramolecular 1,5-sigmatropic hydrogen shift. In contrast, (*E*)-photoenols are long-lived intermediates that can undergo reketonization to the starting material through a relatively slow solvent-mediated proton transfer. Once formed, the (*E*)-photoenol is trapped by di-*tert*-butyl azodicarboxylate forming tetrahydrophthalazin-1-ol **1a'**. Deprotection, accomplished with trifluoroacetic acid, initially delivers free tetrahydrophthalazin-1-ol **1b'**, which tends to release a molecule of water and hydrogen and aromatizes towards desired phthalazine **1b**.

## Conclusion

In summary, we developed a first light-driven metal-free route towards 1-aryl-phthalazines, starting from *o*-methyl benzophenone derivatives and di-*tert*-butyl azodicarboxylate. Various substituents such as alkyl, alkoxy, halogen, nitrile and N-heterocycles are tolerated, while the starting materials are commercially available or easily accessible. This environmentally benign one-pot four-step reaction proceeds under mild conditions and in absence of catalysts or additives.

## ACKNOWLEDGMENT

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