

# X-Ray Characterization of an EDA Complex which Drives the Photochemical Alkylation of Indoles\*\*

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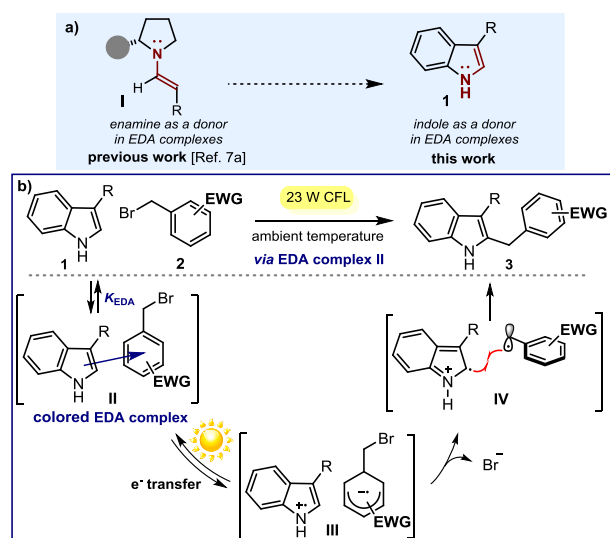
**Abstract:** Disclosed herein is a metal-free, photochemical strategy for the direct alkylation of indoles. The reaction, which occurs at ambient temperature, is driven by the photochemical activity of electron donor-acceptor (EDA) complexes, generated upon association of substituted 1*H*-indoles with electron-accepting benzyl and phenacyl bromides. Significant mechanistic insights are provided by the X-ray single-crystal analysis of an EDA complex relevant to the photo-alkylation and the determination of the quantum yield ( $\Phi$ ) of the process.

The appearance of strong color on bringing together two colorless or nearly colorless organic compounds is not an uncommon observation for a chemist. This phenomenon inspired Robert Mulliken to formulate, in 1952, the charge-transfer theory.<sup>[1,2]</sup> Accordingly, the association of an electron-rich substrate with an electron-accepting molecule can bring about the formation of a new molecular aggregation, called an electron donor-acceptor (EDA) complex.<sup>[3]</sup> EDA complexes are characterized by the appearance of a weak absorption band, the charge-transfer band, associated with an electron transfer (ET) from donor to acceptor. In many cases, the energy of this transition lies within the visible frequency range. Over the last six decades, the photo-physics of EDA complexes have been extensively studied,<sup>[3,4]</sup> while their use in synthetic chemistry has found limited applications.<sup>[5]</sup> As a common trait of these synthetic studies, the existence of EDA complexes as relevant reactive intermediates has generally been inferred from spectroscopic changes of the absorption spectra. In contrast, their isolation and structural characterization by X-ray single-crystal analysis, which provides more compelling mechanistic information, was possible in only a few cases.<sup>[6]</sup>

We report herein a metal-free, photochemical strategy which

enables the direct alkylation of 2- and 3-substituted 1*H*-indoles with electron-accepting benzyl and phenacyl bromides. The reactions occur at ambient temperature and under illumination of a readily available compact fluorescence light (CFL). The most significant results of our studies are the successful isolation and full characterization by X-ray single-crystal spectroscopic analysis of a visible-light-absorbing EDA complex, and the demonstration that its photochemical activity drives the alkylation process.

Our initial investigations were motivated by the desire to photo-generate open-shell reactive species under mild conditions.<sup>[7]</sup> Recently, we discovered that transiently generated electron-rich chiral enamines **I** can actively participate in the photo-excitation of substrates by inducing the formation of EDA complexes with alkyl halides **2** of high electron affinity (Figure 1a). Visible light irradiation of the colored EDA complex induced an electron transfer to occur, allowing easy access to radical species. This reactivity enabled the development of a metal-free, stereoselective  $\alpha$ -alkylation of carbonyl compounds.<sup>[7a,b]</sup> To further expand the synthetic potential of the EDA-complex activation strategy, we envisaged the possibility of using donor substrates other than enamines **I**. Given the electronic similarities with **I**, 1*H*-indoles **1** were considered as suitable donors, which could effectively form an EDA complex **II** upon association with alkyl halides **2** (Figure 1b). While precedents in the literature demonstrate the indole tendency toward EDA associations,<sup>[8]</sup> the potential of productively using the photo-activity of indole-based EDA complexes in synthetic chemistry has remained almost unexplored.<sup>[9]</sup>



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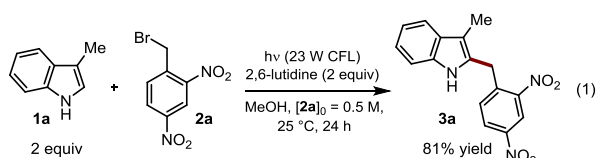
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**Figure 1.** a) Expanding the EDA-complex activation strategy to other donors. b) The alkylation of indoles driven by the photochemical activity of EDA complex II and our mechanistic proposal. EWG: electron withdrawing group;  $K_{EDA}$ : association constant for the formation of complex II.

We hypothesized that visible light irradiation of the transiently generated complex **II** might induce an electron transfer to occur, affording the contact radical pair **III**. The presence of bromine as a

suitable leaving group within the radical anion partner may trigger an irreversible and rapid fragmentation, productively rendering the bromide anion along with the positively charged intermediate **IV**, which brought two radicals in very close proximity. This condition could facilitate a radical combination within the solvent cage to afford the target indole alkylation product **3**. The indole nucleus is a privileged scaffold<sup>[10]</sup> found in numerous natural products and biologically active compounds, which makes the development of a photochemical indole alkylation strategy synthetically relevant.<sup>[11]</sup>

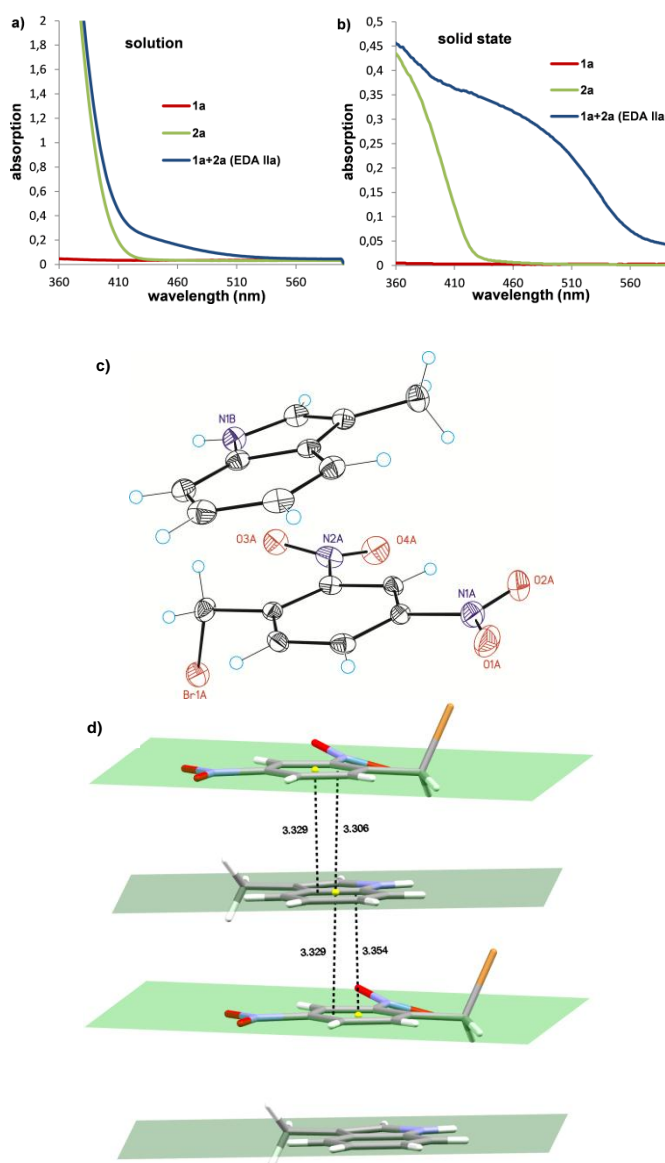
The feasibility of our plan was tested by reacting 3-methyl indole **1a** with 2,4-dinitrobenzyl bromide **2a** in MeOH under irradiation by a 23 W CFL lamp [Eq. (1)]. The reaction, conducted in the presence of 2,6-lutidine (2 equiv) so as to neutralize the acid generated during the process, afforded the C2-benzylated indole **3a** in 81% yield (optimization studies are detailed in Table S1 within the Supporting Information, SI). Control experiments, carried out by performing the reaction either in the dark or under an aerobic atmosphere,<sup>[12]</sup> did not provide any reactivity, testifying to the photochemical and radical nature of the transformation.



From the outset of our investigations, we noticed that a marked red color appeared immediately upon mixing a methanol solution of **1a** with the bromide **2a**. The optical absorption spectrum of the solution showed a bathochromic displacement above 430 nm, where neither substrate absorbs (Figure 2a). Adherence to the Mulliken correlation (see Figure S6 in the SI) further supported the formation of a colored EDA complex (**IIa**) in Figure 1b, where R = Me and EWG = 2,4-NO<sub>2</sub>). Using Job's method<sup>[13]</sup> of continuous variations, a molar donor/acceptor ratio of 1:1 in solution for **IIa** was readily established. Concomitantly, an association constant  $K_{EDA}$  of  $0.9 \pm 0.1 \text{ M}^{-1}$  in MeOH was determined by both spectrophotometric (using the Benesi-Hildebrand method)<sup>[14]</sup> and NMR analysis (using the Foster method,<sup>[15]</sup> see the SI for details). A most informative result came from the isolation of stable dark-orange crystals, suitable for an X-ray diffraction analysis,<sup>[16]</sup> grown by liquid diffusion of *n*-hexane into a dichloromethane solution of the EDA complex **IIa** at 0 °C and in the dark. X-ray structural determination<sup>[17]</sup> confirmed the formation of **IIa** as a face to face  $\pi$ - $\pi$  complex with a 1:1 donor-acceptor ratio (Figure 2c). The cofacially oriented indole and 2,4-dinitrobenzyl moieties afford infinite alternate stacks along the crystallographic *b*-axis. The average interplanar distance, measured between the centroids of the planar cores of the 2,4-dinitrobenzyl and the indole and the planes containing these planar nucleus, is 3.33 Å (Figure 2d). This interplanar spacing is significantly less than the van der Waals separation for aromatic molecules (3.40 Å),<sup>[18]</sup> which is consonant with intermolecular binding forces being at work in the solid state. Interestingly, the charge-transfer band in the solid-state optical absorption spectrum of the EDA complex **IIa** is well-resolved, and confirms the significant bathochromic shift with respect to the individual substrates (Figure 2b).

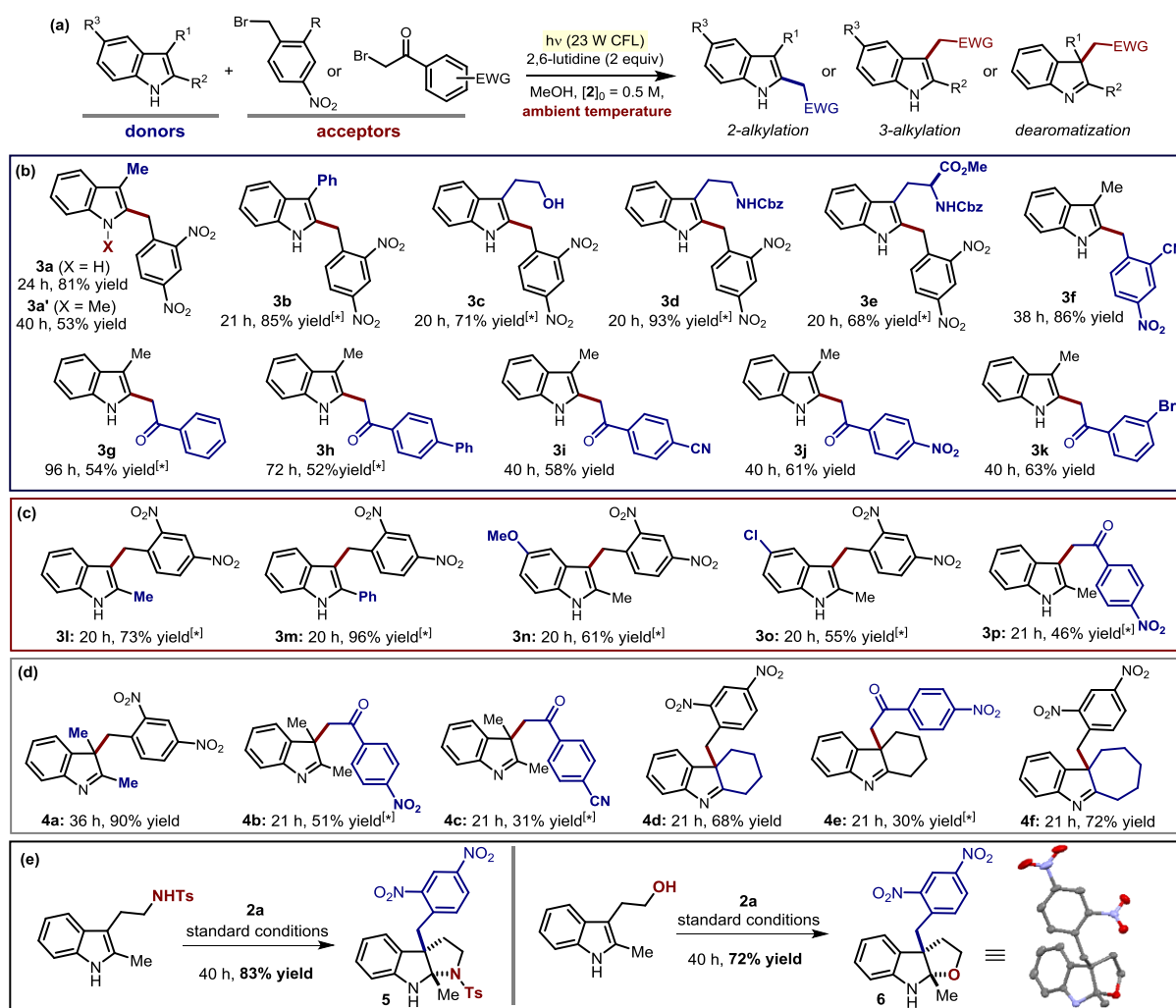
A series of experiments were performed to better elucidate the role of the EDA complex **IIa** in the model reaction.<sup>[19]</sup> Experiments with successive intervals of irradiation and dark periods resulted in total interruption of the reaction progress in the absence of light, and recuperation of reactivity upon further illumination. In addition, a 300 W xenon lamp, equipped with a cut-off filter at 450 nm, was used to select a wavelength that could only be absorbed by **IIa** (both **1a** and **2a** require higher energy photons for excitation, Figures 2a and 2b). The formation of the product **3a** with a comparable

reactivity indicated the photo-activity of the EDA complex **IIa** as solely responsible for the indole alkylation occurring. Finally, a quantum yield ( $\Phi$ ) of 0.2 was determined ( $\lambda = 450 \text{ nm}$ ), which is consonant with the mechanism proposed in Figure 1b, where a radical combination occurs within **IV** prior to diffusive separation of the radical pair out of the solvent cage.<sup>[20]</sup>



**Figure 2.** a) Optical absorption spectra recorded in MeOH in 1 cm path quartz cuvettes using a Shimadzu 2401PC UV-visible spectrophotometer. [**1a**] = [**2a**] = 0.1 M. b) Optical absorption spectrum of the EDA complex **IIa** in the crystalline state. c) ORTEP plot (50% probability) of EDA complex **IIa**.<sup>[17]</sup> d) Projection of the crystal structure along the *b* axis and distances used for calculating the average interplanar spacing (disorder has been omitted for clarity).

We then evaluated the synthetic potential of the photochemical alkylation strategy, conducting the reactions at ambient temperature and using household CFL bulbs as the light source (Figure 3a). As shown in Figure 3b, 3-substituted 1*H*-indoles, including naturally occurring *N*-Cbz (carboxybenzyl) protected tryptophan and tryptamine, were selectively benzylated by **2a** at the C2 position to afford products **3a-e** in good yields. *N*-methyl protected indole derivative was also a competent substrate (adduct **3a'**).



**Figure 3.** Evaluating the scope of the photochemical indole alkylation strategy. (a) General conditions: reactions performed on a 0.1 mmol scale using 2 equiv of 1-*H*-indoles and a 23 W CFL bulb. Results represent the average of two runs per substrate. (b) C2-selective alkylation: survey of the 3-substituted-1-*H*-indoles and alkyl bromides that can participate in the reaction. (c) C3-selective alkylation of 2-substituted-1-*H*-indoles. (d) Dearomatization-annulation strategy. <sup>[\*]</sup> Three commercially available 15 W black light CFL bulb ( $\lambda_{\text{max}} = 360$  nm) were used to illuminate the reaction vessel, since they provided slightly better yield (about 10% higher) than the use of 23 W CFL bulbs; for the emission spectra of the bulbs used in these experiments, see Figures S1 and S2 in the Supporting Information.

Moreover, we found that other bromide-containing acceptors productively combined with 1-*H* indoles to give photon-absorbing EDA associations. In addition to electron-deficient benzylic systems (product **3f**), a broad array of phenacyl bromides effectively participated in the C2-alkylation of **1a** (products **3g-k**). Importantly, 2-substituted 1-*H*-indoles, bearing a variety of substituents at 2 and 5 positions, underwent an effective photochemical C3-alkylation with both electron-poor benzylic and phenacyl bromides (products **3l-p**, Figure 3c). As a limitation of the method, the unsubstituted 1-*H*-indole reacted sluggishly with **2a** to afford a mixture of C3- and C2-alkylation products in a 1:1 ratio and in a low overall yield of 14% after 36 hours (results not shown).

We next examined the possibility of extending the photoalkylation to include 2,3-disubstituted-1-*H*-indoles, an approach which would provide a direct access to valuable indolenine products by means of a dearomatization pathway.<sup>[21]</sup> As detailed in Figure 3d, different substrates, including tetrahydrocarbazoles, successfully reacted with **2a** or phenacyl bromides, enabling the construction of products **4a-f** bearing a quaternary stereocenter. Gratifyingly, complete regio-selectivity was achieved, with the C3-alkylated adducts being exclusively produced. Notably, while few metal-mediated protocols exist for the C3-benzylation of 2,3-disubstituted-1-*H*-indoles,<sup>[22]</sup> this chemistry offers the first methodology for the direct construction of indolenines adorned with a phenacyl moiety at

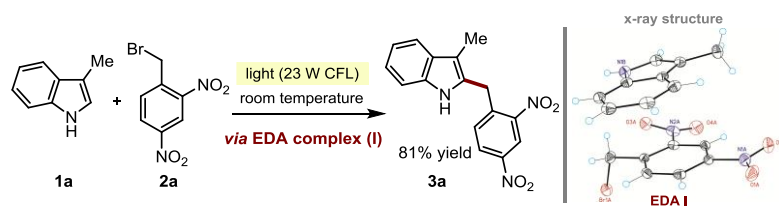
C3 (**4b-c** and **4e**). Of particular interest are the substrates with a pendant nucleophile, which cyclize onto the imine of **4** under the reaction conditions (Figure 3e). Specifically, *N*-tosyl (Ts) tryptamine and tryptophol participated in the reaction to afford the corresponding *cis*-fused pyrrolo- and furano-indolines **5** and **6**,<sup>[17]</sup> respectively, in high yields.

In summary, we have developed a straightforward method for the direct benzylation and phenacylation of substituted 1-*H*-indoles, which requires mild conditions in order to proceed. Evidence has been provided that the chemistry is driven by the photochemical activity of EDA complexes, easily formed upon mixing readily available indoles and electron-accepting benzylic or phenacyl bromides. The isolation and X-ray characterization of an EDA complex relevant to the photochemical alkylation accounted for additional mechanistic insights. This study establishes the potential of indoles to actively participate in the photo-excitation of substrates while promoting synthetically useful transformations. Further efforts are being carried out to investigate the potential of EDA-complex activation in synthetic organic chemistry.

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X-Ray Characterization of an EDA Complex which Drives the Photochemical Alkylation of Indoles



**Mutual aid.** The electron-rich indoles **1a** and the electron-accepting bromide **2a** readily aggregate to form a photo-active EDA complex **I**. Shining light on it, the alkylation product **3a** is formed with a high chemical yield. Herein, the synthetic consequences of this discovery along with the X-ray structure of the relevant EDA complex are discussed.