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

*Sandeep Kandukuri, Ana Bahamonde, Indranil Chatterjee, Igor D. Jurberg, Eduardo C. Escudero-Adán, and Paolo Melchiorre**

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, transiently generated upon association of substituted 1H-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 (Φ) 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.[1,2] 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.[3] 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,[3,4] while their use in synthetic chemistry has found limited applications.[5] 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.[6]

We report herein a metal-free, photochemical strategy which enables the direct alkylation of 2- and 3-substituted 1H-indoles with electron-accepting benzyl and phenacyl bromides. 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. The method, which occurs at ambient temperature and under illumination of a readily available compact fluorescence light (CFL), can be extended to include 2,3-disubstituted substrates: the resulting dearomatization processes afford valuable indolenine and pyrroloindoline products.

Our initial investigations were motivated by the desire to photo-generate open-shell reactive species under mild reaction conditions.[7] 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 α-alkylation of carbonyl compounds.[7a,b] 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** and its low ionization potential, 1H-indoles **1** were considered as suitable donors, which could effectively form an EDA complex **II** upon association with alkyl halides **2** (Figure 1b). While a large body of literature precedents demonstrates the indole tendency toward EDA associations,[8] the potential of productively using the photo-activity of indole-based EDA complexes in synthetic chemistry has remained almost unexplored.[9]
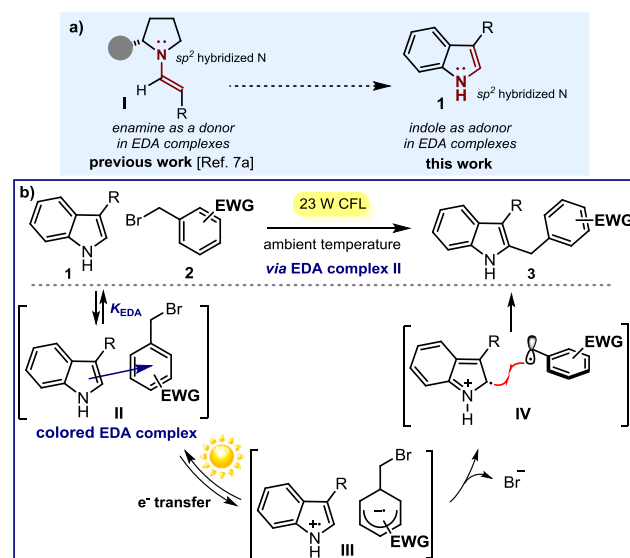
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Figure 1. a) Expanding the EDA-complex activation strategy to other donors. b) The alkylation of indoles driven by the photochemical activity of EDA complex **II** and our mechanistic proposal. EWG: electron withdrawing group; K_{EDA}: association 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[10] found in numerous natural products and biologically active compounds, which makes the development of a photochemical indole alkylation strategy synthetically relevant.[11]

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) 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,[12] did not provide any reactivity, testifying to the photochemical and radical nature of the transformation.
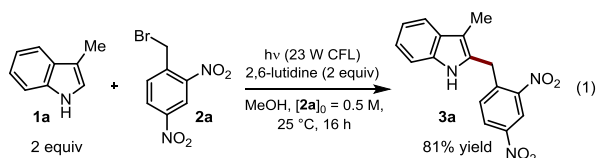
From the outset of our investigations, we noticed that a marked red color appeared immediately upon mixing a methanol solution of **1a** with the bromide **2a**. The optical absorption spectrum of the solution showed a bathochromic displacement above 430 nm, where neither substrate absorbs (Figure 2a). 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$_2$). Using Job's method[13] 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 ± 0.1 M^{-1} in MeOH was determined by both spectrophotometric (using the Benesi–Hildebrand method)[14] and NMR analysis (using the Foster method,[15] 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,[16] 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[17] confirmed the formation of **IIa** as a face to face π-π complex with a 1:1 donor-acceptor ratio (Figure 2c). The indole molecule may be considered planar, while the 2,4-dinitrobenzyl derivative in the complex is not, as a result of the behavior of the NO$_2$ moiety and the bromide. The benzene nucleus of **2a** is, however, planar. 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 3.33Å (Figure 2d). This interplanar spacing is considerably less than the van der Waals separation for aromatic molecules (3.40 Å),[18] which is consonant with intermolecular binding forces being at work in the solid state. Interestingly, the charge-transfer band in the solid-state 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.[19] 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**, albeit with a low yield of 17%, indicated the photo-activity of the EDA complex **IIa** as solely responsible for the indole alkylation occurring. Finally, a quantum yield (Φ) of 0.2 was determined (λ = 450 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.[20]
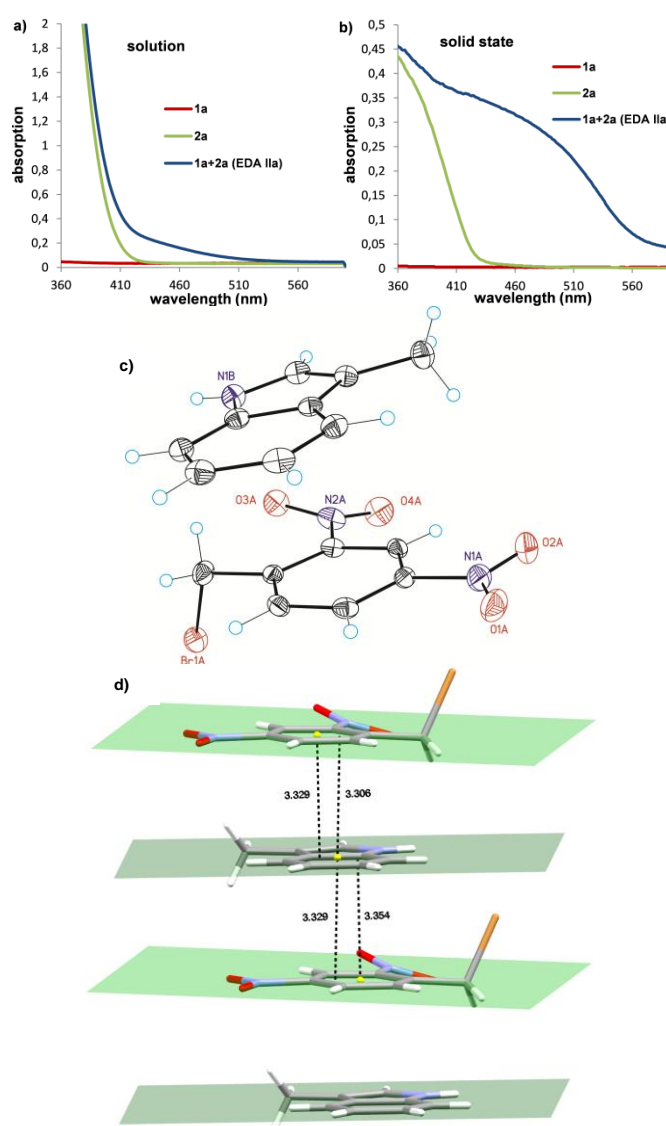

Figure 2. a) Optical absorption spectra recorded in MeOH in 1 cm path quartz cuvettes using a Shimadzu 2401PC UV-visible spectrophotometer. [**1a**] = [**2a**] = 0.1 M. b) Optical absorption spectrum of the EDA complex **IIa** in the crystalline state. c) ORTEP plot (50% probability) of EDA complex **IIa**.[17] 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. The reaction protocol is operationally simple,
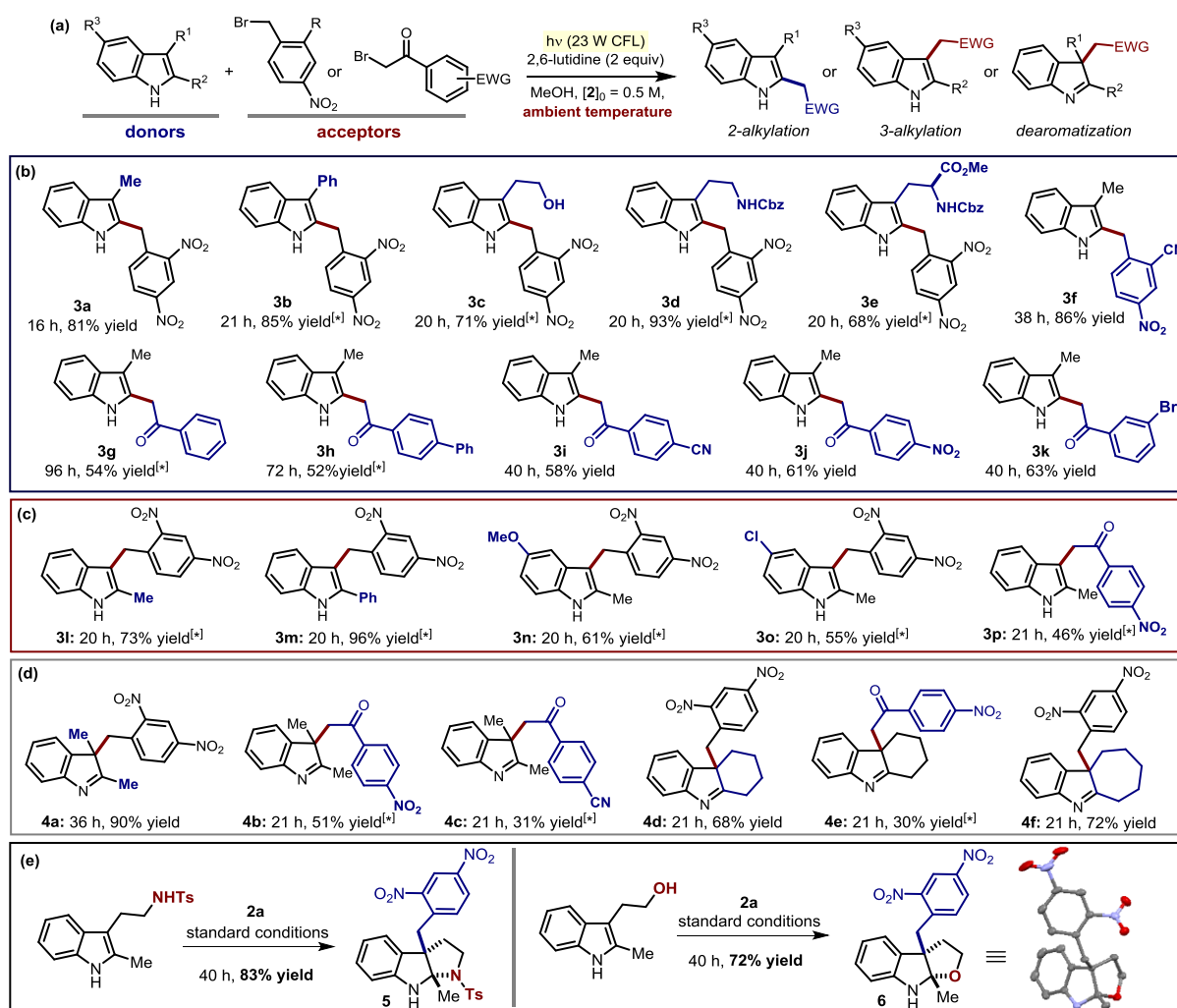
conducted at ambient temperature with readily available substrates, and using household CFL bulbs as the light source (Figure 3a).

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 1H-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-1H-indoles and alkyl bromides that can participate in the reaction. (**c**) C3-selective alkylation of 2-substituted-1H-indoles. (**d**) Dearomatization of 2,3-disubstituted-1H-indoles to give indolenines **4**. (**e**) Dearomatization-annulation strategy. [*] Three commercially available 15 W black light CFL bulb (λ_{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.

As shown in Figure 3b, 3-substituted 1H-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. 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 1H-indoles, bearing a variety of substituents at 2 and 5 positions, underwent an effective photochemical C3-alkylation with both electron-poor benzyl and phenacyl bromides (products **3l-p**, Figure 3c). As a limitation of the method, the unsubstituted 1H-indole reacted sluggishly with **2a** to afford a mixture of C3- and C2-alkylation products in a 1.1:1 ratio and in a low overall yield of 14% after 36 hours (results not shown).

We next examined the possibility of extending the photo-alkylation to include 2,3-disubstituted-1H-indoles, an approach which would provide a direct access to valuable indolenine products by means of a dearomatization pathway.[21] 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-1H-indoles,[22] 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 nicely participated in the reaction, affording the corresponding *cis*-fused pyrrolo- and furano-indolines **5** and **6**,[17] respectively, in high yields. These scaffolds are common motifs found in numerous natural products.[23] The fact that a sulfonamide and an alcohol were tolerated testifies to the high chemoselectivity of the reaction. Control experiments, performed for all the reactions in Figure 3, confirmed that the absence of light illumination completely suppressed the process.

In summary, we have developed a straightforward method for the direct benzylation and phenacylation of substituted 1H-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 benzyl or phenacyl bromides. In addition, 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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[12] Molecular oxygen can quench the excited EDA triplet state, thereby interrupting the ET process leading to the radical ion pair **III** (Figure 1b). The radical mechanism was further corroborated by the experiments conducted in the presence of TEMPO (1 equiv) or 2,6-di-*tert*-butyl-4-methylphenol (0.5 equiv), since the product **3a** was not detected after prolonged exposure to light.

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[19] While crystals of **IIa** could be safely stored for four months in the dark at 0 °C, irradiation from a 23 W CFL induced a fast yet unproductive degradation, as the alkylation product **3a** was not detected. The lack of reactivity in the crystalline state could be a consequence of either the absence of base (the model reaction in MeOH does not proceed at all without 2,6-lutidine), or an unproductive orientation of the substrates **1a** and **2a** in the solid state, as dictated by stabilizing packing interactions according to Mulliken's "Overlap and Orientation Principle", see: R. S. Mulliken, W. B. Pearson, in *Molecular Complexes*, Wiley Publishers: New York, 1969.

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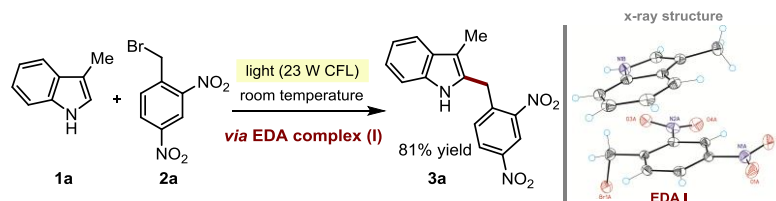
Mutual aid. The electron-rich indoles **1a** and the electron-accepting bromide **2a** readily aggregate to form a photo-active EDA complex **I**. Shining light on it, the alkylation product **3a** is formed with a high chemical yield. Herein, the synthetic consequences of this discovery along with the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