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How electrophilic are 3-nitroindoles? Mechanistic and Synthetic Investigations

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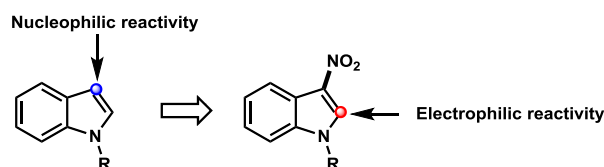
Kinetics of reactions of 3-nitroindoles with various nucleophiles have been investigated in DMSO at 20 °C. The electrophilicity of these compounds has been evaluated through the Mayr's free linear energy relationship $\log k_{20\text{ °C}} = s_N (E + N)$. It was found that 3-nitroindoles are electrophilic enough to react at room temperature, in the absence of any activator, with mild nucleophiles such as Danishefsky diene to furnish the corresponding dearomatized (4+2) cycloadducts in good yields.

Indoles are very important scaffolds that can be found in numerous natural products, many of which exhibit interesting biological activities.¹ They have also potential applications in various domains such as pharmacy, agrochemistry, and material science. It is therefore unsurprising that research in indole chemistry continues to grow exponentially.

From a reactivity standpoint, indoles are well recognized as moderate nucleophiles and their reactivity toward numerous electrophiles has widely been explored in organic synthesis especially in organocatalysis and transition metal catalysis.²

Recently, much attention has been paid to investigate the electrophilic reactivity of indoles.³ Indeed, it has been shown that incorporating a nitro group at the second or third positions of this heterocycle resulted in reducing its aromaticity, thus allowing facile addition of nucleophiles (Scheme 1). In this context, different research groups including some of us have contributed to exploit the "umpolung" reactivity of indoles and demonstrated that 3-nitroindoles, for instance, can be combined with different nucleophiles such as carbanions,⁴ amines,⁵ 1,3-dipoles,⁶ enriched dienophiles in tandem (4+2)/(3+2) cycloadditions⁷ or enamines in ene reactions for instance.⁸ Interestingly, Jorgensen et al. have very recently shown that 3-nitroindoles can react with 2,4-dienals in the presence of chiral secondary amine as an organocatalyst, leading to the formation of chiral dihydrocarbazole scaffolds in good yields and excellent enantioselectivities.⁹

Scheme 1. Nucleophilic and electrophilic reactivity of indoles.



Based on these seminal works, we reasoned that quantification of the electrophilicity of 3-nitroindoles would help not only to understand their unexpectedly high reactivity with nucleophiles for an aromatic compound but also to design new reactions. To this end, we selected to investigate the reactivity *N*-tosyl-3-nitroindoles **1** with various nucleophiles.

During the last decades, Mayr group has shown that numerous electrophile–nucleophile combinations can be described by the free linear relation (1). In this equation, while electrophiles are characterized with one parameter *E*, nucleophiles are described by two parameters, namely nucleophilicity (*N*) and specific nucleophilicity (*s_N*) (eq 1).

$$\log k (20\text{ °C}) = s_N (E + N) \quad (1)$$

The nucleophilicity/electrophilicity scales has been constructed by studying the reactions of benzhydrylium cations, which have been taken as reference electrophiles, with numerous nucleophiles, including σ^- , n^- , π^- nucleophiles. The validity of eq (1) is not restricted to cations and it has recently been shown that neutral electrophiles can also be described by the same equation. In this regard, the electrophilicity of Michael acceptors, nitrostyrenes, nitroarenes have been quantified.¹⁰

Based on this work, we began our kinetic investigations by studying the reactions of 3-nitroindole **1a** with carbanions **2** in DMSO at 20 °C (ajouter un schéma : Scheme 2). To satisfy pseudo-first order conditions, the reactions of **1a** with **2a** were performed using a large excess of the later, i.e. $[2a] \geq [1a]$.

As shown in Figure 1, the absorbance peak of **1a** at 345 nm completely disappeared after adding a large excess of the carbanion **2a** ($[2a] = M$). Additionally, we noticed the formation of a new absorbance peak at 437 nm, which was assigned to the formation of the σ -complex **3a**. Noteworthy, the same first-order kinetic constants (k_{obs}) were measured when kinetics of **1a** with **2a** were monitored at these two

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different wavelengths. This suggests that a unique species is formed during the process.

Plotting k_{obs} versus the concentration of **2a** led to a straight-line, where the slope gave the second-order rate constant (Figure 2).

By applying this kinetic methodology to the reactions of **1a** with the carbanions **2b–f**, the related second-order rate constants k_2 have been measured and are given in Table (1). Importantly, when $\log(k_2)/s_N$ were plotted against the nucleophilicity values (N) of **2**, a straight-line was obtained with a slope close to 1, in good agreement with the Mayr's free energy relationship (1) (Figure 3). This suggests that the reactivity of 3-nitroindole **1a** with nucleophiles can nicely be described by eq (1). The electrophilicity of **1a** was thus evaluated at -15.2 . Similarly, different 3-nitroindole derivatives **1b**, **1d** and **1f** were reacted with the carbanions **2a–d** and this allowed to evaluate their respective electrophilicities, from -12.8 for indole **1f** to -14.3 for indole **1b** (Figure 4). Expectedly, 3,6-dinitroindole **1f** is the most electrophilic of the series. N-Ts indole **1a** also proved more electrophilic than its carbamate counterpart **1b**, in line with the expected greater electron-withdrawing effect of the tosyl group compared to the ethoxycarbonyl one. This is however in contrast with some experimental observations, by us and others, in (formal) cycloaddition reactions.[ref] 3-Nitroindoles are thus highly electrophilic, compared to other nitroheteroaromatics (nitropyridine, -thiophene, -pyrazole, and -pyrrole for instance) .[CEJ, 2008, 14, 6108]

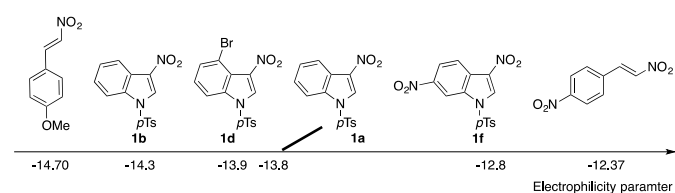


Figure 4. Compared electrophilicities of 3-nitroindoles and nitrostyrenes.

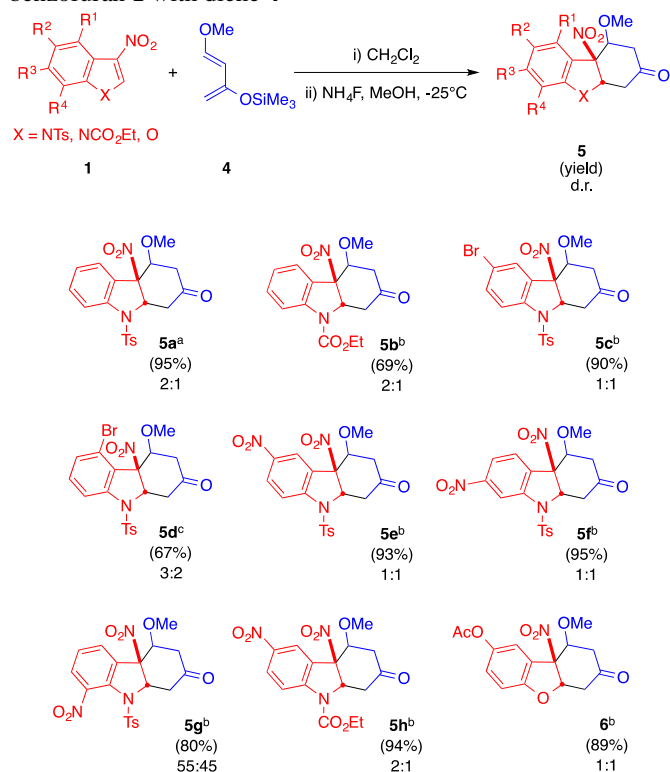
In light of these investigations and by using Mayr's rule of thumb, which suggests that a reaction of a nucleophile with an electrophile is possible when $E + N \geq -5$, one can anticipate **1a** to react with nucleophiles characterized by a $N \geq 10$. The reactivity limit of **1a**, at room temperature, is thus expected with mild nucleophiles such as sulfur ylides **4** or boronates **5** at 20°C . [rappel ref CEJ 2008]

3-nitroindoles used in cycloadditions.[ref]

Mayr rule not always applicable [JACS 2018, 140, 16758 Mayr]. With this in mind, we reacted **1** with diene **4** (1.2 equiv) in dichloromethane at room temperature and were pleased to observe a full conversion of the indole derivative within 24 hours. After smooth hydrolysis, the (4+2) cycloadduct **5a** was isolated as a 2:1 mixture of diastereomers in 95% yield and thus confirmed the unexpectedly high electrophilicity of nitroindole derivative **1a** (Table 2). Noteworthy, no rearomatization of the cycloadduct was noticed, showing that these conditions remain mild enough to avoid this potential subsequent

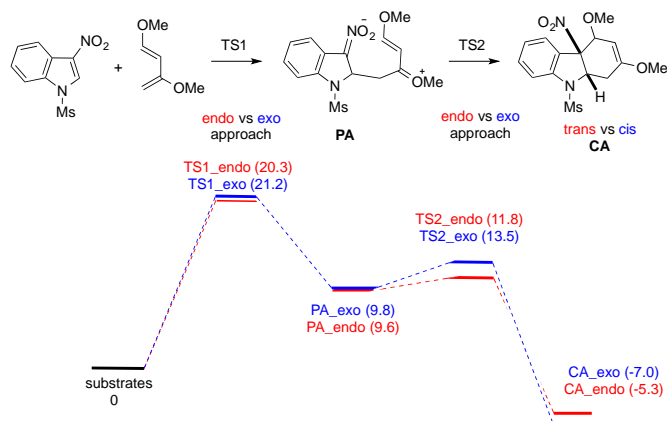
process.[rappel note] From a synthetic point of view, this result is important since it allows the dearomatization of **1a** through a (4+2) annulation process in reagentless conditions, at room temperature. The cycloadduct thereby obtained possesses a tetrasubstituted carbon center at the ring junction and point the finger at possible applications in the realm of indole-based alkaloids. Résultat sur plus grosse quantité ? We then examined the scope of this dearomatizing process with different 3-nitroindole derivatives. The ethyl carbamate protected indole proved slightly less reactive under these conditions and required a larger excess of diene **4** to furnish **5b** in a 69% yield (Table 2). This result is in line with the lower electrophilicity measured for this carbamate substrate. Bromo substituted indoles protected as sulfonylamides were then examined. The 5-bromo substituted substrate readily reacted to generate cycloadduct **5c** in a good 90% yield, but with a lower diastereoselectivity. The more sterically hindered 4-bromo indole proved less reactive and required heating at 42°C to complete the reaction. **5d** was isolated in a slightly lower 67% yield. Indoles bearing an additional nitro group on the 6-membered ring could also be dearomatized under these smooth conditions, and led to compounds **5e**, **5f** and **5g** in good yields and similar diastereoselectivities. With this supplementary electron-withdrawing group on the electrophilic substrate, the carbamate protected indole proved more reactive and furnished **5h** in a higher 94% yield (Table 2, compare **5b** and **5h**). This process proved also feasible with a different nitroaromatic compound that is nitrobenzofuran, which led to the hexahydrodibenzofuran **6** in a good yield.

Table 2. Reaction between heteroaromatic indoles and benzofuran **1** with diene **4**



^a using 1.2 equiv of **4** at r.t.. ^b using 2.4 equiv of **4** at r.t.. ^c using 2.4 equiv of **4** at reflux of CH₂Cl₂.

In order to evaluate the concerted or stepwise nature of the mechanism of this reaction, DFT calculations were effected at the M062X/6-31+G(d,p) level, considering a polarized continuum (SMD:DCM) to mimic the solvent effects.[ref] The calculations involved a N-mesyl-3-nitroindole derivative and 1,3-dimethoxybutadiene as realistic models of the reaction substrates. Two approaches (*endo* and *exo*) were considered and the calculations confirmed the stepwise mechanism of the cycloaddition process, involving the formation of a zwitterionic primary adduct in the first step and the cyclisation via a Michael addition to generate the cycloadduct in the second (Scheme X). Expectedly, the first nucleophilic addition step is the rate determining step. The differences between the *endo* and *exo* approaches is small ($\Delta\Delta G^\ddagger = 0.9$ kcal.mol⁻¹), in line with the experimental data (d.r. between 1:1 and 2:1).



Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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