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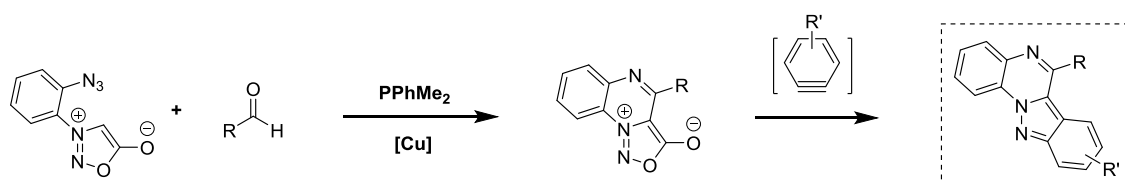
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# A sydnone-based route to access indazolo[2,3-a]quinoxaline derivatives

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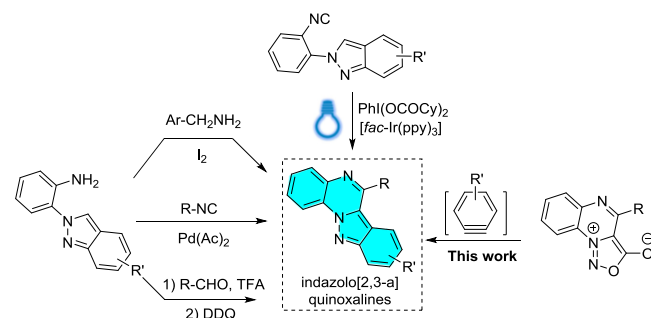
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**ABSTRACT:** A new synthetic route to indazolo[2,3-a]quinoxaline derivatives is described. The strategy is based on the 1,3-dipolar cycloaddition of arynes and quinoxaline-sydnone derivatives, as a key step. These polyaromatic sydnones were prepared through a copper-promoted intramolecular cyclisation of the C-4 position of sydnones on imines.

Planar polyaromatic quinoxaline derivatives, especially those fused with nitrogen-rich five-membered heterocycles are important pharmacophores displaying interesting biological properties, which received special attention from the pharmaceutical industry.<sup>1</sup> Among this family, indazolo[2,3-a]quinoxaline derivatives, bearing a fused pyrazine-pyrazole bicyclic aromatic core, represent an important class of anti-tumor drugs<sup>2</sup> due to their ability to intercalate between the base pairs of double-stranded DNA.<sup>3</sup> However, despite their pharmacological interest, only a few procedures for their preparation are described in the literature. To our knowledge, only two synthetic approaches to indazolo[2,3-a]quinoxalines have been reported to date to give access to these derivatives (Scheme 1).



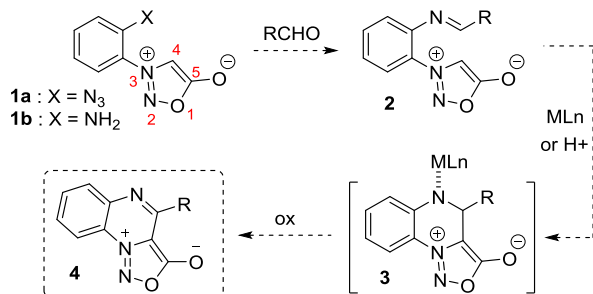
**Scheme 1.** Synthetic routes to indazolo[2,3-a]quinoxalines.

The first one involves a C3-functionalization of 2*H*-indazoles *via* three different ways: I<sub>2</sub>-mediated sp<sup>2</sup> C-H activation in presence of benzylamines,<sup>4</sup> Pd(II)-catalyzed isocyanide insertion<sup>5</sup> or intramolecular cyclisation of imine intermediates, followed by oxidation with DDQ.<sup>6</sup> The second is based on a visible-light induced radical coupling of *ortho*-substituted aryl-isocyanides and radicals generated from phenyliodine(III) dicarboxylate reagents, affording these polyaromatic structures in mild conditions (Scheme 1).<sup>7</sup>

Herein, we describe a novel synthetic method giving direct access to indazolo[2,3-a]quinoxaline derivatives from tricyclic sydnones. This strategy is complementary to the state of the art and might provide alternative solutions to medicinal chemistry programs.

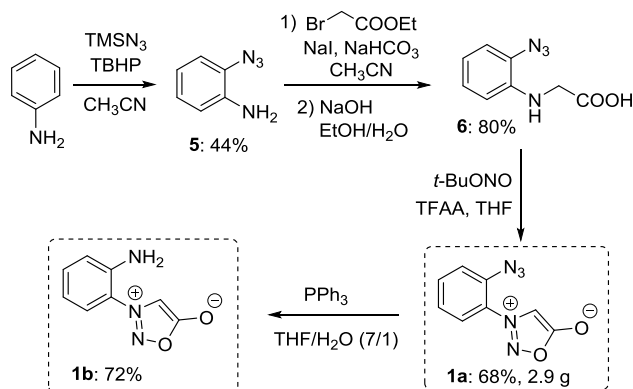
Polycyclic sydnones have been found interesting substrates to react with arynes to construct polyaromatic products through [3+2] cycloadditions.<sup>8</sup> We postulated that similar strategy would be possible for the construction of indazolo[2,3-a]quinoxalines from reaction of benzyne derivatives with tricyclic nitrogen-containing sydnones (Scheme 1). However, as such sydnone patterns have not been described, a suitable synthetic access was investigated. The C-4 position of sydnones is well-known to undergo facile C-H activation in cross-coupling reactions. Deshydrogenative Suzuki<sup>9</sup> and Heck<sup>10</sup> type reactions are notably described to functionalize sydnones by Pd-catalyzed C-H activation of the C-4 position. This position is also easily functionalisable by reaction with various electrophiles after abstraction of the proton in position C-4 with strong bases.<sup>11</sup> Based on these reports,

we hypothesized that access to **4** would be possible via intramolecular cyclisation of imines **2**, obtained either from azido-sydnone **1a** by Staudinger aza-Wittig reaction or from amino-sydnone **1b**. Under optimal conditions, **2** may react as an internal electrophile to form a new six-membered ring intermediate **3**, which should afford sydnone **4** upon oxidative rearomatization (Scheme 2).



**Scheme 2.** Proposed synthetic route to polycyclic sydnones **4**.

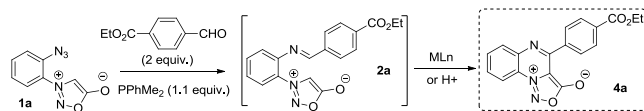
Azido-sydnone **1a** was easily obtained in 4 steps from aniline by slight adjustments from literature protocols.<sup>12</sup> Notably, the procedure was easily scaled-up, and 2.9 grams of **1a** could be isolated. Staudinger reaction with PPh<sub>3</sub> in mixture of THF/water afforded **1b** in a good yield (Scheme 3).



**Scheme 3.** Synthesis of sydnones **1a** and **1b** from aniline.

Having sydnones **1a** and **1b** in our hands, we tested our synthetic strategy with ethyl 4-formylbenzoate used as a model activated aldehyde. Unfortunately, all attempts to form imine derivatives from sydnone **1b** were unsuccessful. On the contrary, the Staudinger aza-Wittig reaction starting from azide **1a** was successful but very slow. Excess of aldehyde and the use of nucleophilic phosphines such as PhPMe<sub>2</sub> were necessary to form the expected imine **2a**. This imine was found not stable under purification conditions and was used *in situ* for the next cyclisation step. We therefore screened a series of one-pot conditions using PhPMe<sub>2</sub> for the first step and several Lewis or Brønsted acids to activate the imine function and favor the nucleophilic attack of the C-4 position of the sydnone leading to sydnone **4a** by intramolecular cyclisation (Table 1). Among the conditions explored, only Cu(OTf)<sub>2</sub> was

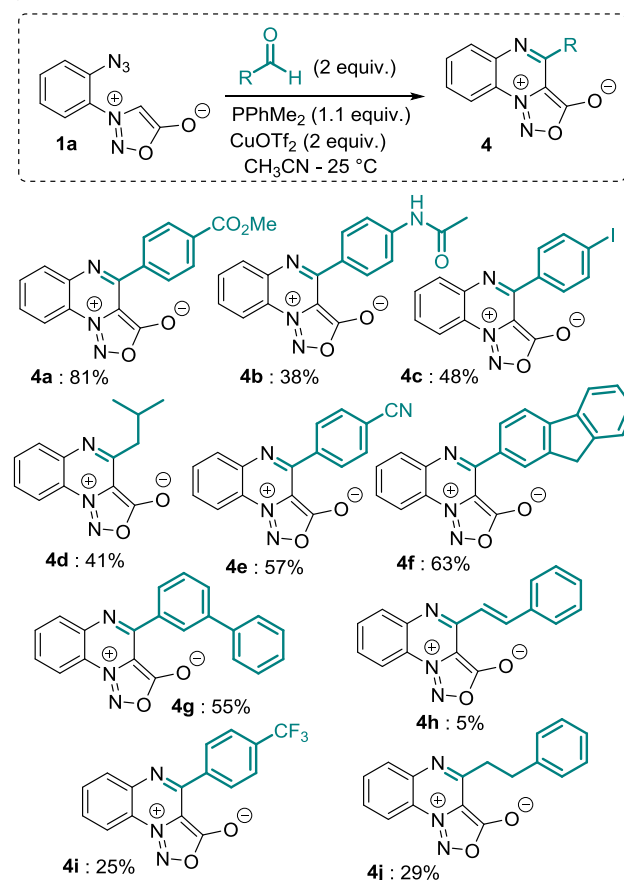
found efficient when used in excess (entries 7 and 8). Under optimized conditions, 2 equivalents of Cu(OTf)<sub>2</sub> at room temperature in acetonitrile allowed complete conversion of imine **2a** into sydnone **4a**, which was isolated in 81% yield. It is worth mentioning that during our investigations, no traces of the non-aromatic intermediate **3** was observed.



Entry	MLn or H <sup>+</sup>	Solvent	Time	T <sup>o</sup> C	<b>4a</b>
1	CH <sub>3</sub> SO <sub>3</sub> H - 2 equiv.	CH <sub>3</sub> CN	24 h	25 °C	22% <sup>a</sup>
2	AgOTf - 0.2 equiv.	CH <sub>3</sub> CN	24 h	25 °C	n.d.
3	Sc(OTf) <sub>3</sub> - 0.2 equiv.	CH <sub>3</sub> CN	24 h	25 °C	n.d.
4	Cu(OTf) <sub>2</sub> - 0.2 equiv.	CH <sub>3</sub> CN	24 h	25 °C	n.d.
6	Cu(OTf) <sub>2</sub> - 0.6 equiv.	CH <sub>3</sub> CN	24 h	25 °C	29% <sup>b</sup>
7	Cu(OTf) <sub>2</sub> - 1.1 equiv.	CH <sub>3</sub> CN	24 h	25 °C	68% <sup>b</sup>
8	Cu(OTf) <sub>2</sub> - 2 equiv.	CH <sub>3</sub> CN	14 h	25 °C	81% <sup>b</sup>

**Table 1.** Optimization of the reaction. <sup>a</sup> crude yields determined by LCMS. <sup>b</sup> isolated yields

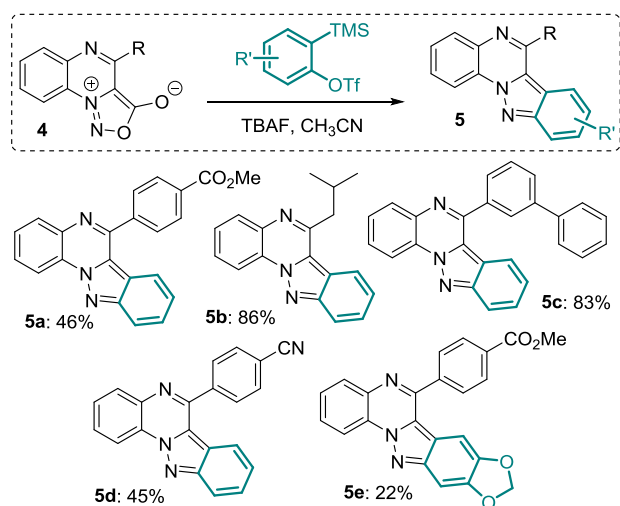
We then turned our attention to evaluating the scope in the construction of other tricyclic sydnones **4** by varying the structure of the aldehyde starting reactant (Scheme 4).



#### Scheme 4. Scope of the reaction.

Overall, this methodology demonstrated good functional-group tolerance, thus enabling preparation of a range of polycyclic sydnones in moderate to good yields starting from aromatic (both electron rich and poor) and aliphatic aldehydes (**4d**, **4j**). Vinyl aldehydes, in the contrary, were found not suitable substrates for this reaction. For example, only 5% yield of sydnone **4h** were obtained from cinnamaldehyde.

We were then interested in looking at the reactivity of these new sydnones as dipoles for cycloaddition reactions with alkynes. Sydnones are well-known to undergo efficient thermal cycloaddition reactions with terminal or di-substituted alkynes at elevated temperatures or under milder conditions through Cu-catalysis.<sup>13</sup> They are also known to react smoothly with strained alkynes such as cyclooctynes<sup>14</sup> and arynes.<sup>15</sup> Unfortunately, polyaromatic sydnones **4** were found inactive toward either terminal, activated di-substituted alkynes such as dimethyl acetylenedicarboxylate (DMAD) or cyclooctynes such as bicyclo-[6.1.0]-nonyne (BCN) and dibenzocyclooctynes (DBCO) even at elevated temperatures. We thus focused our attention to cycloaddition reactions with aryne derivatives starting from the Kobayashi precursor<sup>16</sup> in presence of TBAF and were pleased to observe a smooth reaction took place at room temperature, affording the desired indazolo[2,3-a]quinoxalines **5** in moderate to good yields (Scheme 5).



**Scheme 5. Synthesis of indazolo[2,3-a]quinoxalines **5** from sydnones **4**. See supporting information for experimental details.**

In conclusion, we have developed a new synthetic route to indazolo[2,3-a]quinoxaline derivatives based on the cycloaddition of arynes with polycyclic sydnones. These new sydnones were obtained in good yields upon intramolecular cyclisation of imines at the C-4 position of sydnones through Cu(II) assistance. We think this new synthetic route complete advantageously the only few methods actually available to construct these nitrogen-containing polyaromatic compounds that find several interesting biological properties.

#### ASSOCIATED CONTENT

##### Supporting Information

Synthetic procedure and Analytical data of all compounds

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##### Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

##### Notes

The authors declare no competing financial interest.

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