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Sydnone-based Approach to Hetero-helicenes Through 1,3-Dipolar-Cycloadditions

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Supporting Information Placeholder

ABSTRACT: The first approach to pyrazole containing helicenes via sydnone-aryne [3+2]-cycloaddition is described. An unprecedented regioselectivity in the cycloaddition step towards the more sterically hindered helical product was observed in presence of extended aromatic scaffolds. DFT calculations enabled to understand the origin of this unexpected selectivity.

Ortho-fused aromatic rings belong to a class of helical-shaped molecules named helicenes. 1 Since their discovery, these variegated aromatics have fascinated chemist practitioners due to their elegant architecture, inherent chirality and structural complexity. Helical structures are particularly interesting as they are found in many biomacromolecules inspiring chemists involved in the field of asymmetric catalysis,2 and their enhanced chiroptical properties have attracted much attention in material science.3 The presence of a heteroatom in the fused polycyclic system considerably alters the electronic structure and helps tuning various opto-electrical properties.4 In particular, nitrogen-containing helicenes, including pyridine,5 pyrrole,6 pyrazine7 and imidazolonium8,9 have attracted much attention. Despite the broad interest over this family of compounds, synthetic access still remains challenging and often requires cumbersome multistep approaches.3 Ideally, the desired helical motif would be assembled in the last step of the sequence, thus enabling divergent opportunities for structure diversity. Sydnones are azomethine imines, well-known for their 1,3-dipolar-cycloadditions with linear and strained alkenes, generating pyrazoles, a pharmaceutically and agrochemically relevant heterocyclic scaffold.9 We reasoned that properly designed prohelical sydnones 3, bearing ortho-extended aromatic substitutions, would be suitable partners with arynes bearing an extended aromatic core.10 After cycloaddition, the subsequent loss of carbon dioxide would deliver the desired pyrazole-containing helicenes, a family of heterohelicenes so far unreported (Figure 1).

We now describe a novel disconnection allowing a direct access to a range of unreported helical pyrazoles, based on a key sydnone-aryne cycloaddition. In the process, we discovered a unique example of selective cycloaddition involving these mesoionic betaines in favor of the sterically hindered helical product and determined the reasons behind such selectivity with analysis of DFT calculations.

Figure 1: Design of pyrazoles-based helicenes.

The implementation of this strategy relies on the prerequisite preparation of ortho-fused aromatic azomethine imine dipoles. N-methyl sydnone 1 was identified as key component to build up such ortho-aromatic structures. Readily available in two steps from commercial sarcosine, 1 provides a versatile handle for further derivatization. It was envisioned that metal catalyzed functionalization at the C4 position of the sydnone with 2-halobenzaldehyde would provide a key intermediate that might undergo intramolecular Knoevenagel condensation under basic conditions to give the desired product 3. Initial attempts showcased that the whole cascade could be performed in one single operation. Product 3a was first isolated in moderate yield together with the intermediate uncyclized aldehyde S3a.11 After some experimentation, it was found that in presence of catalytic amounts of Pd(OAc)2 and triphenylphosphine, with an excess of K2CO3 (4 equiv.), the desired mesoionic compound 3a could be obtained in 88% yield. Similarly, the tetracyclic ortho-sydnone 3b could be isolated in 66% yield starting from the corresponding 1-bromo-2-naphthaldehyde (Figure 2A).

With a reliable access to the prerequisite ortho-fused aromatic azomethine imines 3a and 3b secured, we turned our attention to the key 1,3-dipolar-cycloaddition between polycyclic sydnones and aryn precursors. The sydnone-aryne cycloaddition is a 50 year old transformation pioneered by Gotthardt, Huisgen, and Knorr and later by Kato and Tsuge in 1974,12 but only recently the synthetic potential of this transformation has been studied in detail.13 At first, we reacted sydnones 3a and 3b in presence of silyl triflate 4a (1.5 equiv.) and TBAF (1.5 equiv.) at room temperature. As expected, the desired products 5 and 6 were isolated in good yields, 77 and 70%, respectively (Figure 2C). It is worth mentioning that 5 and 6
Figure 2: A: One-pot synthesis of polycyclic sydnones 3a and 3b; B: aryne precursor; C: Synthesis of helical pyrazoles 5 and 6. D: Synthesis of helical pyrazoles 7a, 8a, 9a and 10a. Isomer ratio was measured by $^1$H-NMR of the crude mixture.

have been synthesized in only two steps from readily available N-methyl sydnone. The sequence could be extended to the ortho-fused 1,2-naphthylene precursor 4b (Figure 2D). In presence of tricyclic sydnone 3a the formation of the two possible cycloadducts, the desired hetero-[5]-helicene 7a and the S-shaped product 7b, was observed. As expected, no degree of selectivity was achieved and the cycloadducts were isolated in a 1:1 ratio and an overall 74% yield. The tetracyclic sydnone 3b gave a low degree of selectivity in favor of the sterically hindered hetero-[6]-helicene 8a (8a/8b, ratio 63/37). The $^1$H NMR analysis of the two regioisomers showed well-resolved signals, which could be clearly assigned with COSY and NOESY measurements. Intrigued by this unexpected result, we investigated the reactivity of ortho-sydnones 3a and 3b in presence of 3,4-phenanthrene precursor 4c (Figure 2D). This ortho-anualted aryne is particularly interesting because it should allow the formation of [6]- and [7]-helicenes. The reaction of 3a with 4c in presence of TBAF in THF delivered a crude mixture with a useful selectivity in favor of the helical product (crude $^1$H-NMR ratio 90:10). After purification, the two components of the reaction could be isolated in 79% and 6% yield. The 2D-NMR measurements determined the identity of the major compound as the desired [6]-helical pyrazole 9a. When 4c was reacted in presence of 3b, [7]-helicene 10a was isolated in 62% yield with high selectivity (10a:10b 96:4). Crystals of both isomers 10a and 10b were grown by slowly evaporating dichloromethane solutions and the structures were determined by single-crystal X-ray diffraction (Figure 3A).

The chiroptical properties of [7]-helicene 10a were subjected to a preliminary evaluation. Enantiomers of 10a were resolved from a racemic mixture using HPLC with a chiral-phase column. In Figure 3B are shown the circular dichrograms of the enantiopure samples, which exhibit both positive and negative Cotton effects at 235 and 357 nm. The spectra of the enantiomers are mirror images of each other. The measurements conducted in degassed dichloromethane for the set of enantiomers led to the observation of a mirror-image CPL signal (Figure 3C). The $g_{\text{max}}$ values are -0.001 and +0.001 at about the maximum emission wavelength for 10a. These values are of the same order of magnitude as those for other examples of organic CPL-active helicenes. These results confirm that the solution of [7]-helicene 10a in degassed dichloromethane exhibits active CPL signals, and also that the emitted light is polarized in opposite directions for the two enantiomeric forms for this helicene-like structure.

The selectivities observed for these sydnone-aryne cycloadditions were unexpected, given precedents in the literature. First, sydnones are known to be poorly regioselective in their cycloadditions with asymmetrical alkyne dipolarophiles. Moreover, the Houk-Garg distortion-based model to explain the preferred regioselectivity of attack of nucleophiles on strained alkynes, which is based on the difference in internal angles of the alkyne carbons, predicts...
low selectivity with 1,2-naphthylene or 3,4-phenanthryne, albeit in the observed direction. DFT optimizations of the two structures (M06-2X/6-31+G(d,p))\textsuperscript{11} reveal that the two aryne carbons have similar internal bond angles (Figure 4A).

In order to highlight whether the peculiar structure of sydnones 3a and 3b is responsible for the unusual selectivity, sydnone 3c was synthesized. As shown in Figure 4B, when N-phenyl sydnone 3c was reacted with 4c the opposite selectivity was observed (ratio 33:66 in favor of 11b).\textsuperscript{25} This result suggests that the origin of the selectivity might be related to the structure of the polycyclic sydnone itself.

To understand the origin of such a dichotomy, we calculated the free energy profiles for the reactions of 3a-3c with both 1,2-naphthylene and 3,4-phenanthryne, using the same DFT method described above. Profiles for the reaction of 3a with 3,4-phenanthryne to form 9a or 9b. Free energies (enthalpies) are in kcal/mol and were obtained at the M06-2X/6-311+G(2d,2p)/SMD (THF) // M06-2X/6-31+G(d,p) level of theory. D) Cycloaddition TSs leading to regioisomers 9a and 9b. M06-2X/6-311+G(2d,2p)/SMD (THF) // M06-2X/6-31+G(d,p). Free energies in kcal/mol.

The TSs leading to the two regioisomers for the representative reaction of 3a with 3,4-phenanthryne are shown in Figure 4D. The TSs for the other pairs of reactants can be found in the SI and display similar arrangements. First, the TS leading to the major helical isomer is more asynchronous, with the shorter forming bond being between the more nucleophilic terminus of the azomethine imine of the sydnone and the more electrophilic (linear) carbon of the aryne.\textsuperscript{26} Indeed, for the fused sydnones 3a and 3b, the nitrogen atom bears more HOMO character than the carbon, while for N-phenyl sydnone 3c, the opposite is found. Second, the forming bonds are fairly long, indicative of very early TSs, which are in accord with quantitatively reproduce the experimental selectivities, that is formation of the helical regioisomer is predicted to be favored for sydnones 3a and 3b, but unfavored for 3c.
the high exergonicity of the cycloaddition steps and the Hammond postulate. Third, the major TS seems to benefit from stabilizing C–H···π interactions (also called face-to-edge π–π interactions) between the polycyclic backbones of the reactants, while the minor TS does not.

Distortion/interaction analysis confirms this behavior: as the TSs are so early, the reactants are barely distorted from their ground-state geometries, and total distortion energies are, at most, 4.0 kcal/mol. As such, even though the helical regioisomer of the cycloadducts and pyrazoles is more sterically encumbered and always higher in energy than the S-shape isomer, this effect is not important in TS 1 since the reactants are still far from each other. Conversely, interaction energies range from −7.4 to −12.4 kcal/mol, and are greater for the helical vs the S-shape regioisomer. In fact, for the six systems studied, the activation energies correlate with interaction energies, but have no correlation with distortion energies. To confirm the stabilization offered by the dispersive aromatic-aromatic interactions, we computed the binding energies of aromatic dimers in the same geometries as the helical TSs. For the four combinations evaluated, the binding energies were between −0.4 to −1.9 kcal/mol, demonstrating the stabilization offered by the C–H···π interactions for the helical TSs, in addition to the more favorable primary orbital interactions. Thus, the TSs that benefit from the most interactions are also earlier, further lowering the cost to distort the reactants. These results indicate that with other very reactive partners, regioselective cycloadditions might be possible when interactions with polycyclic backbones are present. Indeed, when substituted sydnones 3d-3l were reacted with 4c similar values of regioselectivity (> 85/15) were observed in favor of the and the corresponding [6] and [7]-helicenes 12a 20a were isolated in 19 to 26% yields (Figure 5). While the presence of electro-neutral and withdrawing substituents on the sydnone does not affect the transformation, di-substituted electron-rich dipole 3h was poorly reactive and the desired [6]-helicene 16a was isolated in 18% yield. Derivative 20a with a the presence of a chloride substituent offered a useful handle for further functionalization. Under catalytic conditions, the products of Suzuki cross-coupling reaction 21a and 22a were isolated in 96 and 56% yield. This preliminary proof-of-concept showed the possibility to further functionalize this helical scaffold by means of metal catalysis and could be of interest for potential applications.

In summary, we have developed a method to access [4], [5], [6] and [7]-helicenes containing pyrazoles through sydnone 1,3-dipolar cycloadditions. This process involves the design and synthesis of ortho-substituted polyaromatic sydnones, which are more nucleophilic than conventional ones, and highlights the first example of regioselective cycloaddition of such mesoionic dipoles with arynes. Calculations showed that primary orbital interactions and C–H···π dispersive interactions control the regioselectivity of this transformation. This reaction will ultimately provide a modular access to substituted derivatives, and could be amenable to the synthesis of other helicenes families.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge via the Internet at http://pubs.acs.org.

Experimental procedures and computational details

NMR spectra for obtained compounds

Crystallographic data for compounds 10a (CCDC 1544556), 10b (CCDC 1872990), and 11b (CCDC 1544557).
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Notes
The authors declare no competing financial interests.

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REFERENCES


(11) See Supporting Informations for additional details.


In contrast to [6]-carbohelicenes, [6]-helicene 9a is not configurationally stable at room temperature. Calculated racemization energy barrier is 22.5 kcal/mol. Enantiomers of 9a were resolved by chiral-phase HPLC and a rapid racemization was observed. For additional information regarding the racemization barriers of other pyrazolohelicenes, see ref. 11. For a nice overview on carbohelicenes racemization, see: Barroso, J.; Cabellos, J. L.; Pan, S.; Murillo, F.; Zarate, Z.; Fernandez-Herrera, M. A.; Merino, G. Revisiting the racemization mechanism of helicenes. *Chem. Commun.* **2018**, *54*, 188-191.

The measured racemization barrier for pyrazolo[7]-helicene 10a was found to be 32.7 kcal/mol. This value is in agreement with the calculated racemization energy barrier for 10a: 31.6 kcal/mol. See ref 11 for details.

The degree of CPL is given by the luminescence dissymmetry ratio, \( g_{\text{ CPL}}(\lambda) = 2\Delta I/I = 2(I_R - I_L)/(I_R + I_L) \), where \( I_R \) and \( I_L \) refer, respectively, to the intensity of left and right circularly polarized emissions.


(23) Noteworthy, in presence of unsymmetric cyclooctynes, sydnones have been reported deliver a 1 to 1 mixture of regioisomers: Narayanam, M. K.; Liang, Y.; Houk, K. N.; Murphy, J. M. Discovery of new mutually orthogonal bioorthogonal cycloaddition pairs through computational screening. *Chem. Sci.* **2016**, *7*, 1257–1261.


(25) The nature of pyrazoles 11a and 11b was unambiguously established by NOE and X-ray crystallography (see SI for details).

(26) In all cases, the reactions are HOMO (sydnone) – LUMO (aryne) controlled. See Supporting Information for details.


(29) Unreacted sydnone 3b was preset in the reaction crude even after prolonged reaction time.