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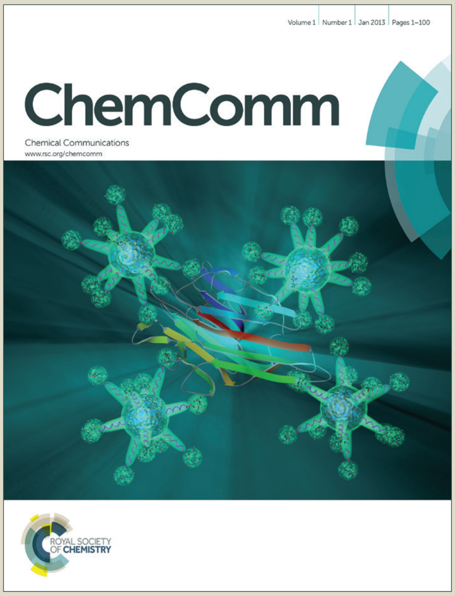

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Isoquinolino[4,3,2-*de*]phenanthridine: synthesis and its use in 1,3-dipolar cycloadditions to form nitrogen-containing polyaromatic hydrocarbons

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The synthesis of the novel azomethine ylide, isoquinolino[4,3,2-*de*]phenanthridine, and its use in 1,3-dipolar cycloaddition with various alkenes and alkynes to form the corresponding fused pyrrolidines and pyrroles is reported.

Cycloadditions between 1,3-dipoles and unsaturated dipolarophiles are an indispensable tool for the construction of 5-membered heterocyclic structures.[1] An especially impressive demonstration of their versatility and efficiency led to the concept of “click chemistry” using the Huisgen reaction.[2] Depending on the combination between 1,3-dipoles and dipolarophiles, a wide variety of heterocyclic rings can be synthesized. Among the various 1,3-dipoles, azomethine ylides are particularly useful intermediates to prepare pyrrolidines and pyrroles, which are important building blocks for many natural products and pharmaceuticals.[3] However, only few examples of 1,3-dipolar cycloaddition of azomethine ylides focus on the preparation of polyaromatic hydrocarbons (PAHs),[4] despite the increasing importance of nitrogen-containing PAHs.[5,6,7] Our research group focuses on isoquinolino[4,3,2-*de*]phenanthridine (**1**) as a novel class of azomethine ylide to generate pyrrolidines and dihydropyrroles containing a fused isoquinolino[4,3,2-*de*]phenanthridine structure, which in turn can be converted to the corresponding pyrroles upon oxidative dehydrogenation (Figure 1). Herein we report the synthesis of isoquinolino[4,3,2-*de*]phenanthridine (**1**) and its use in 1,3-dipolar cycloadditions with various alkenes and alkynes to form the corresponding pyrrolidines, 2,5-dihydropyrroles, and pyrroles.[8,9] The method presented is highly effective for the synthesis of fused 1,2,3,4,5-pentaarylpyrroles via reactions with diarylacetylenes. To the best of our knowledge, only few compounds with a fused 1,2,3,4,5-pentaarylpyrrole structure, such as 2,3-diaryl fused pyrroles (dibenzo[*e*,*g*]indole[10] and diacenaphtho[1,2-*b*:1',2'-*d*]pyrrole[11]), 3,4-diaryl fused pyrroles (dibenzo[*e*,*g*]isoindole[12,13] and acenaphtho[1,2-*c*]pyrrole[14]), and pyrrole-fused azacorronenes,[5b] have been reported.

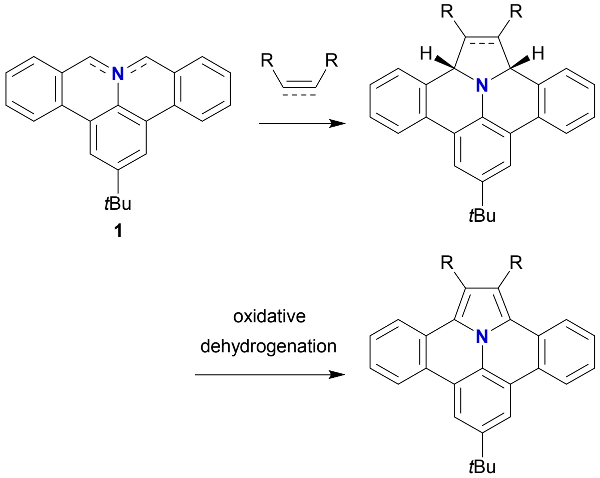
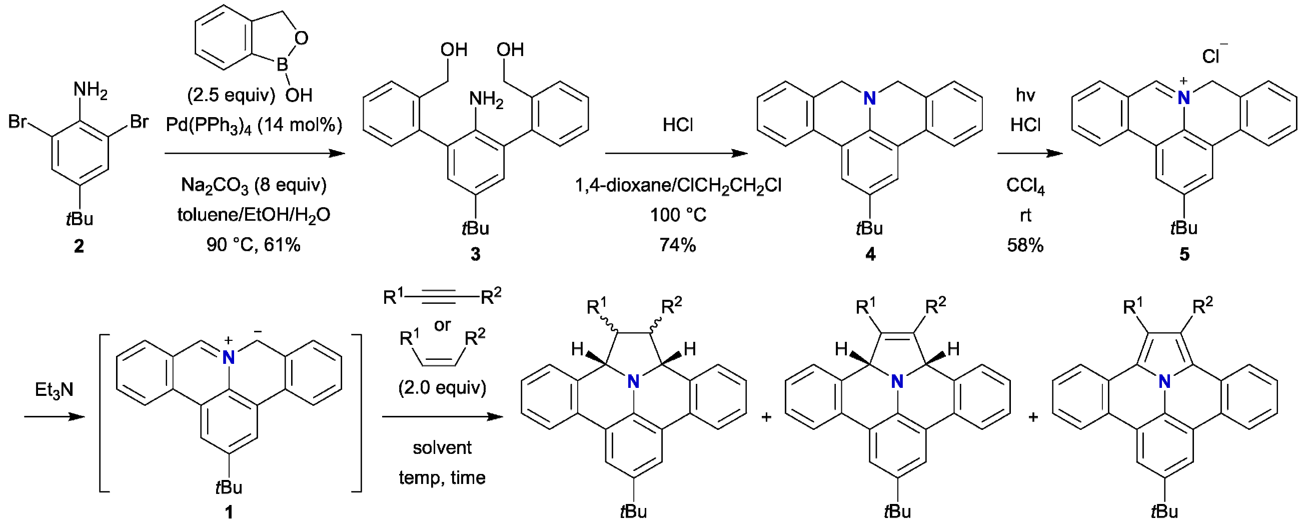


Figure 1. Structure of isoquinolino[4,3,2-*de*]phenanthridine **1** and its cycloaddition with dipolarophiles.

Scheme 1 illustrates the synthesis of isoquinolino[4,3,2-*de*]phenanthridine (**1**) starting from 2,6-dibromo-4-*tert*-butylaniline (**2**). Initially, a palladium-catalyzed Suzuki-Miyaura reaction of **2** with 1,3-dihydro-1-hydroxy-2,1-benzoxaborole generated 2,6-diarylaniline **3**.[15] A subsequent intramolecular cyclization of **3** by treatment with hydrogen chloride in 1,4-dioxane/1,2-dichloroethane at 100 °C afforded cyclized product **4** as a yellow crystalline powder in good yield (74%). When **4** was dissolved in carbon tetrachloride under exposure to irradiation of ambient light, the color of the reaction mixture changed from yellow to red, suggesting the

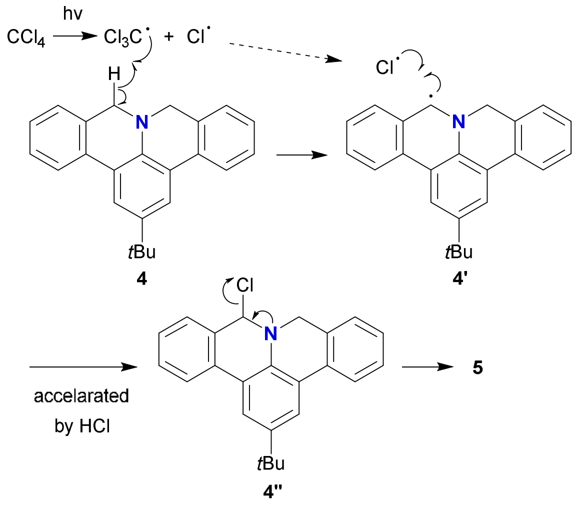
Scheme 1



R^1—≡—R^2				
$R^1 = R^2 = CO_2Me$	CH_2Cl_2, rt	**6a**: ---	**7a**: 60%	**8a**: 0%
$R^1 = R^2 = Ph$	toluene, 100 °C	**6b**: ---	**7b**: 0%	**8b**: 30%
$R^1 = R^2 = C_6H_4\text{-}4\text{-}CO_2Me$	toluene, 100 °C	**6c**: ---	**7c**: 0%	**8c**: 20%
R^1 R^2 (alkene)				
$R^1 = CO_2Me, R^2 = H$	CH_2Cl_2, rt	**6d**: 61% (*dr* = 53:47)	**7d**: 0%	**8d**: 0%
$R^1 = R^2 = –C(=O)NPhC(=O)–$	CH_2Cl_2, rt	**6e**: *endo*: 26%, *exo*: 22%	**7e**: 0%	**8e**: 0%

formation of radical species such as **4'** (Scheme 2). Since this reaction was not observed in the dark, the reaction might be initiated by a homolytic cleavage of a $Cl_3C–Cl$ bond.[16] Gradually **4** was converted to iminium chloride **5**, presumably through chlorinated intermediate **4''**. Conversion of **4** and **4'** into **5** was found to be accelerated by addition of hydrogen chloride, which led to a color change from red to yellow. Compound **5** exhibited characteristically unsymmetrical NMR resonances in chloroform-*d* with a distinctive iminium proton observed at 11.6 ppm. Subsequent deprotonation of compound **5** was accomplished by treatment with triethylamine under inert conditions to generate isoquinolino[4,3,2-*de*]phenanthridine **1** *in situ*.[17]

Scheme 2



In order to elucidate the properties of **1**, we performed density functional theory (DFT) calculations using the B3LYP hybrid functional at the 6-31G(d,p) basis set on model compound **1'**, in which the *t*-butyl group of **1** is replaced by a hydrogen (Figure 2). Compound **1'** can adopt a closed-shell zwitterionic structure as (**1'-C**) or an open-shell biradical structure as (**1'-O**). Our calculations revealed that **1'-C** is by 21.9 kcal/mol more stable than **1'-O**, indicating that **1** should exist as the azomethine ylide form (Figure 2a). Azomethine ylides are electron-rich species with high-lying HOMOs and LUMOs; accordingly, they preferentially react with electron-deficient dipolarophiles whereby the HOMO of the dipoles interacts with the LUMO of the dipolarophiles.[3d] The calculated HOMO of **1'-C** is predominantly located in both α-positions of the nitrogen atom, suggesting that **1** reacts with an unsaturated dipolarophile in these positions (Figure 2b).

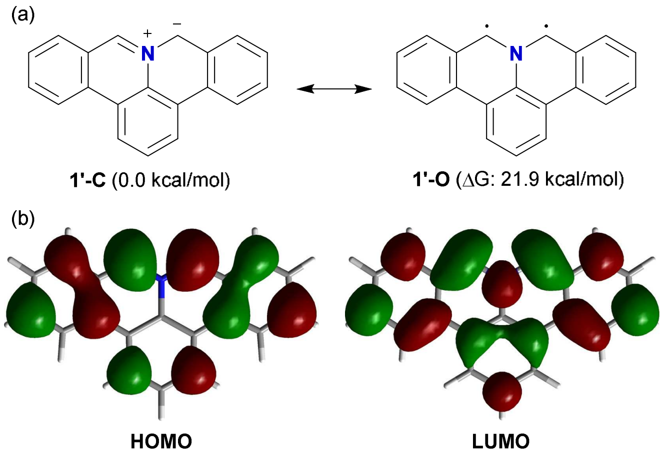


Figure 2. (a) DFT-calculated energy difference between the closed-shell zwitterionic state (**1'-C**) and open-shell biradical state (**1'-O**) at the B3LYP/6-31G(d,p) level of theory. (b) DFT-calculated HOMO and LUMO of **1'-C** using the same DFT parameters.

Indeed, we observed that azomethine ylide **1** underwent 1,3-dipolar cycloadditions, when it was generated *in situ* and concurrently treated with internal alkynes.[18] The reaction with dimethyl acetylenedicarboxylate (DMAD) at room temperature afforded 2,5-dihydropyrrole **7a** in 60% yield (Scheme 1). In the ^{1}H NMR spectrum, the benzylic proton of **7a** was observed at 5.28 ppm in chloroform-*d*. The cycloadditions with diarylacetylenes, Ar–C≡C–Ar (Ar = Ph or C_6H_4-4-CO_2Me), proceeded at a high temperature of 100 °C produced pyrroles **8b** and **8c** in 30 and 20% yields, respectively, via subsequent dehydrogenation of **7**.[9] All the compounds were characterized by ^{1}H and ^{13}C NMR spectroscopic analyses.

The solid-state structures of **7a**, **8b**, and **8c** were confirmed by single crystal X-ray crystallographic analysis (Figure 3). Suitable crystals were obtained by slowly evaporating dichloromethane solutions of these compounds. The top view of **7a** indicates that the three benzene rings and the 2,5-dihydropyrrole ring are not aligned in a coplanar fashion. The dihedral angles between the central benzene and the adjacent benzene rings are 23.7° (C14–C15–C17–C18) and −18.8° (C9–C10–C11–C12). In case of **8b** and **8c**, the three benzene rings and the pyrrole ring share a highly coplanar geometry with dihedral angles between the pyrrole moiety and the adjacent benzene rings of less than 3°. The C–N bond lengths and C1–N1–C4 angles in these pyrrole structures are consistent with those of previously reported fused 1,2,3,4,5-pentaarylpyrroles.[11,14]

Azomethine ylide **1** was found to react with electron-deficient alkenes. The reaction with methyl acrylate produced pyrrolidine **6d** in 61% yield as an inseparable mixture of *endo* and *exo* adducts (ca. 1:1). *N*-Phenylmaleimide also reacted with **1** to give pyrrolidine **6e** in moderate yield. The product was obtained as a mixture of diastereomers which could be separated by silica gel column chromatography to afford the *endo* isomer in 26% yield and the *exo* isomer in 22% yield. As fullerene C_{60} is known to be a good dipolarophile, the 1,3-dipolar cycloaddition of **1** with C_{60} was also investigated in order to form a hybrid of pyrrolidine and C_{60}.[19] The reaction of **1** with C_{60} at 40 °C afforded adduct **9**, which was successfully purified by preparative HPLC with a buckyprep® column, in 65% yield (Scheme 3). In the ^{1}H NMR spectrum of **9**, three singlet resonances were observed for the *t*-butyl group (1.46 ppm), for the benzylic protons (6.26 ppm), and the aromatic protons in *ortho* positions to the *t*-butyl group (7.74 ppm). Moreover, two doublet (7.95/7.73 ppm) and two triplet (7.52/7.40 ppm) resonances were observed for the aromatic protons of the peripherally fused benzo groups. The ^{13}C NMR spectrum of **9** shows 45 signals (32 signals for the C_{60} unit and 13 signals for the isoquinolino[4,3,2-*de*]phenanthridine unit), indicating that compound **9** is of C_s symmetry. The UV/vis spectrum of **9** showed a local-maximum signal at 433 nm, which is a characteristic band for 6:6 ring-bridged 58 π-electron fullerenes.[20] All the observed data are consistent with an addition of azomethine ylide **1** onto the 6:6 ring junction of C_{60}.

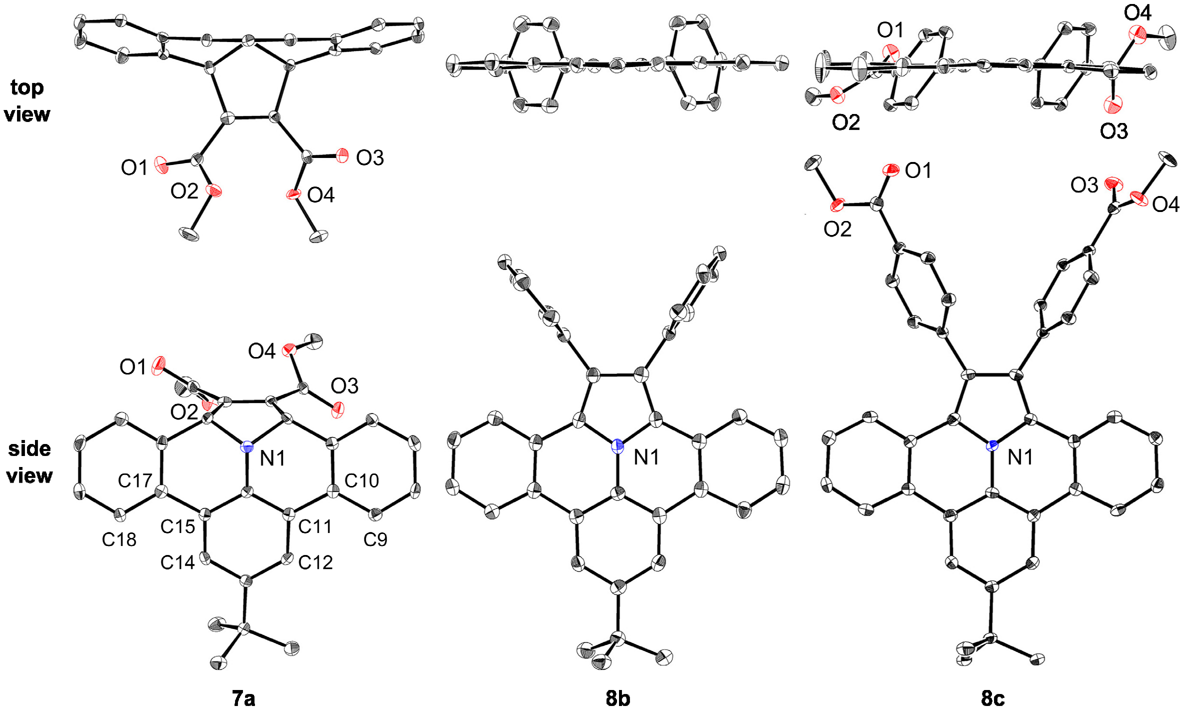
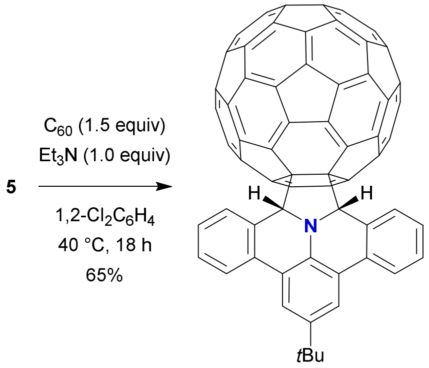


Figure 3. X-ray structures of **7a**, **8b**, and **8c**. Hydrogen atoms for all structures and *t*-butyl groups for top views are omitted for clarity.

Scheme 3



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Furthermore, we found that the cycloadditions were affected by the polarity of the solvent. The reaction of **1** in acetonitrile at 80 °C produced dimerized product **10** in 3.5% yield.[21] This homo coupling reaction of azomethine ylide **1** could potentially be applied to the synthesis of nitrogen-containing nanographene or graphene nanoribbons via subsequent oxidative cyclization and dehydrogenation.

In summary, we have developed a new method to synthesize the azomethine ylide, isoquinolino[4,3,2-*de*]phenanthridine **1**, that undergoes 1,3-dipolar cycloadditions with various alkenes and alkynes. This study presents a potentially useful method to form nitrogen-containing PAHs with fused pyrrole structures.

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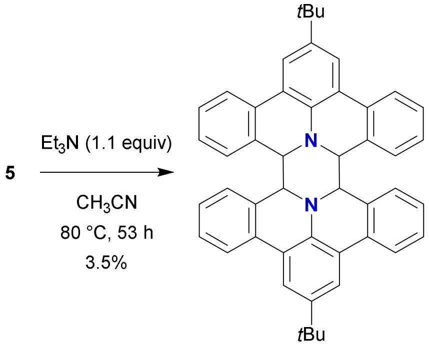
Scheme 4



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† Electronic Supplementary Information (ESI) available: Experimental details and analytical data, including X-ray crystallographic data for **7a**, **8b**, and **8c**. See DOI: 10.1039/c000000x/

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