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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. An especially impressive demonstration of their versatility and efficiency led to the concept of “click chemistry” using the Huisgen reaction. 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. However, only few examples of 1,3-dipolar cycloaddition of azomethine ylides focus on the preparation of polyaromatic hydrocarbons (PAHs), despite the increasing importance of nitrogen-containing PAHs. 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. The method presented is highly effective for the synthesis of fused 1,2,3,4,5-pentaarylpyrroles via reactions with diarylacetlenes. 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 and diacenaphtho[1,2-b:1′,2′-d]pyrrole), 3,4-diaryl fused pyrroles (dibenzo[e,g]isoindole and acenaphtho[1,2-c]pyrrole), and pyrrole-fused azacorronenes have been reported.

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-dianilinoline 3. 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...
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 ClC–Cl bond. 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-\(d_2\) 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.

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. The calculated HOMO of 1’-C is predominantly located in both \(\alpha\) positions of the nitrogen atom, suggesting that 1 reacts with an unsaturated dipolarophile in these positions (Figure 2b).
Indeed, we observed that azomethine ylide 1 underwent 1,3-dipolar cycloadditions, when it was generated in situ and concurrently treated with internal alkynes. 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$_6$H$_4$-4-CO$_2$Me), proceeded at a high temperature of 100 °C produced pyrroles 8b and 8c in 30 and 20% yields, respectively, via subsequent dehydrogenation of 7. 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.

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-Phenylimaleimide 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$_{60}$. 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$_5$ 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. All the observed data are consistent with an addition of azomethine ylide 1 onto the 6:6 ring junction of C$_{60}$.
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. 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-d]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

Notes and references


15 For related procedure, see: M. Albrecht, Synthesis, 2008, 2451.


18 A reaction with a terminal alkyne, phenylacetylene, under the same conditions afforded a complex mixture of products.


21 Feng and Müllen, et al. obtained dimer 10 in 51% yield by a reaction using tributylamine as a base and dimethylsulfoxide as a solvent at 190 °C. See reference 8.