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# Facile, Efficient, and Diastereoselective Synthesis of Heterohelicene-like Molecules

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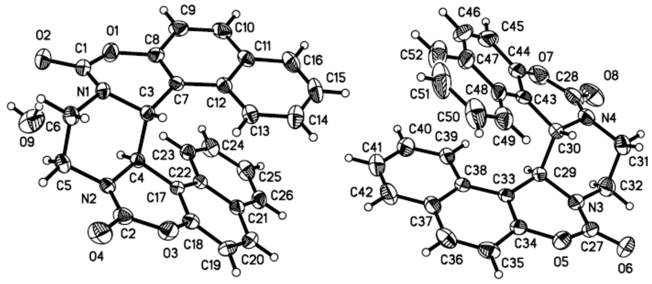
## ABSTRACT



**A concise and efficient route to new and interesting heterohelicene-like molecules has been developed through the one-pot, cascade reductive coupling reaction of *o*-hydroxydiimines or *o*-nitrodiimines and triphosgene in the presence of $TiCl_4$/Sm. Purification of the final products only required a single recrystallization leading to high purity. High diastereoselectivity was also achieved, and two structures of the final products were confirmed by X-ray diffraction analysis.**

Helicenes and helicene-like molecules have been regarded as an academic curiosity because they show nonplanar *ortho*-fused characteristics and exhibit the feature of helical chirality.[1] With the recent advances in this research area, helicenes and helicene-like molecules are considered to be potential candidates serving as liquid crystal molecules,[2] sensors,[3] and dyes.[3] They can also find applications in areas of asymmetric catalysis,[4] chiral molecular recognition,[5] and molecular machinery.[6]

Traditionally, helicenes have been synthesized via the oxidative photocyclization of bis(stilbene)s.[7,8] Several new synthetic methodologies have been developed in the past 10 years that include Diels–Alder cycloaddition,[9] [2 + 2 + 2]

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cycloisomerization,[10] carbenoid coupling,[11] radical tandem cyclization,[12] domino Friedel–Crafts type cyclization,[13] Pd-mediated techniques,[14] intramolecular McMurry reaction,[15] and olefin metathesis.[16] Some of them have high diastereo-[17] or regioselectivity.[18] Recently, Rajca et al. reported the synthesis of a novel oligothiophene, in which the thiophene rings are cross-conjugated and annelated into a helix.[19] However, among the numerous literatures, only a few of them describe the synthesis of heterohelicenes,[20] such as azahelicenes and oxa-helicenes, which suffer from some disadvantages such as drastic reaction conditions, unsatisfactory yields, long-reaction time, complex manipulation, and inaccessible starting materials. Thus, the development of new divergent and efficient synthetic strategies to heterohelicenes remains highly demanding and challenging. Herein, we report our preliminary results on the facile and efficient synthesis of new and interesting heterohelicene-like molecules in very good yields with excellent diastereoselectivities.

Starting material diimines, such as 6,6′-((1,1′)-(ethane-1,2-diylbis(azanylylidene))bis(methanylylidene)) bis(phenol) **3a**, are readily obtained from the reaction of salicylaldehyde **1a** with ethane-1,2-diamine **2a**. The intramolecular cascade reductive coupling reaction of **3a** together with triphosgene was examined in the presence of 4 equiv of $TiCl_4$/Sm as the promoter in THF under reflux for 2 h, which gave the desired dioxo-diaza[5]helicene-like **4a** in 88% yield after purification of the crude product through a single recrystallization. Having established the optimal reaction conditions, the substrate scope and limitations of the domino reductive coupling reaction were subsequently investigated. The representative results are summarized in Scheme 1. The diimines were easily reduced by a low-valent titanium reagent, so the main factor driving the reaction was the nucleophilicity of the hydroxy group of diimines. We found that the electronic properties of the substituents attached to the phenyl rings had more influence than the steric properties of the substituents on the reactivity.[21] Some dioxo-diaza[5]helicene-like compounds containing a hydroxy group, **4l**–**n**, were obtained in 85–86% yields by demethylation from their corresponding compounds containing a methoxy group in the presence of $BBr_3$.

Single crystals of compound **4c** were obtained and analyzed by X-ray structural analysis, as shown in Figure 1. The crystal belongs to the triclinic space group $P\overline{1}$(2). In the structure, the central piperazine ring shows a typical chair conformation, combining with the two *ortho*-fused lactonic rings and benzene rings to form the helicene-like conformation. The H2 and H10 are in a *trans* stereochemical configuration, while the interplanar angle between the terminal benzene rings is 34.5°.

In the present work, the use of $TiCl_4$/Sm as a potent reductive coupling combination has been successfully

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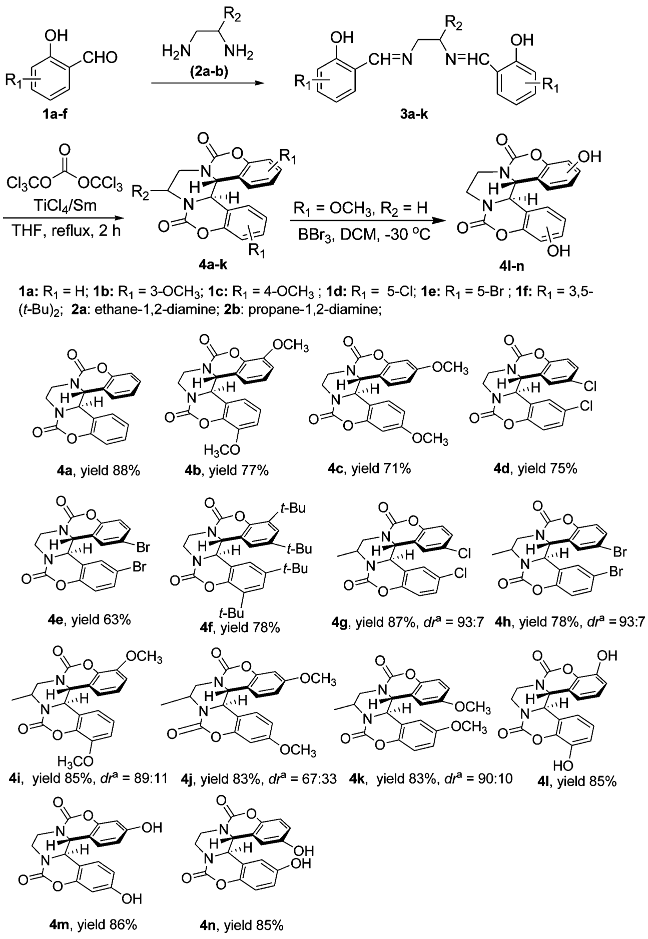
**Scheme 1.** Synthesis of Dioxo-diaza[5]helicene-like Compounds **4a**−**n**



[a] Determined by $^{1}$H NMR.

extended to assemble the structures of tetraaza[5]helicene-like compounds **7a**−**e** in which salicylaldehyde derivatives were replaced by *ortho*-nitrobenzaldehyde derivatives **5a**−**c**. Due to an additional reduction of the nitro group to the amino group, 8 equiv of $TiCl_4$/Sm relative to substrate **5** had to be used in this transformation. The tandem reductive coupling of **6a**−**d** and double cyclization with triphosgene were performed in THF under the above optimized reaction conditions.

The reaction can be completed within 3 h with the results summarized in Scheme 2. After purification of the final products through a single recrystallization, the desired tetraaza[5]helicene-like compounds **7a**−**d** were obtained in 73−89% yields with good to excellent diastereoselectivities, regardless of the variations in electronic and steric properties of the substituents attached to the phenyl rings of the *ortho*-nitrobenzaldehyde derivatives. The desired compound **7e** was also obtained in 83% yield by the demethylation from compound **7b**.

Because the steric hindrance did not show any obvious detrimental effect on the reactivity, this effective process was further applied to the synthesis of [7]-helicene-like molecules through the tandem reductive coupling reaction of triphosgene and diimines **9a**−**d** resulted from 2-hydroxy-1-naphthaldehyde **8a**−**b** with substituted ethane-1,2-diamines **2a**−**b** in the presence of 4 equiv of $TiCl_4$/Sm in THF under reflux for 2 h. As shown in Scheme 3, the desired dioxo-diaza[7]helicene-like compounds **10a**−**d** were obtained in very good chemical yields (75−89%) with excellent diastereoselectivities. Similarly, compound **10e** was obtained in 87% yield by demethylation from corresponding compound **10b**.

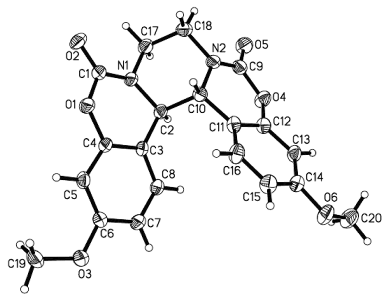
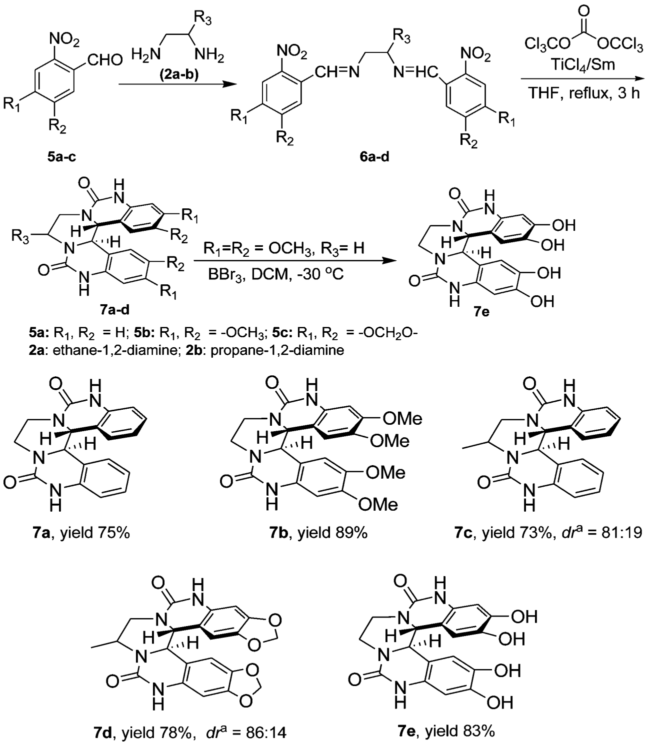


**Figure 1.** X-ray structure of compound **4c**.

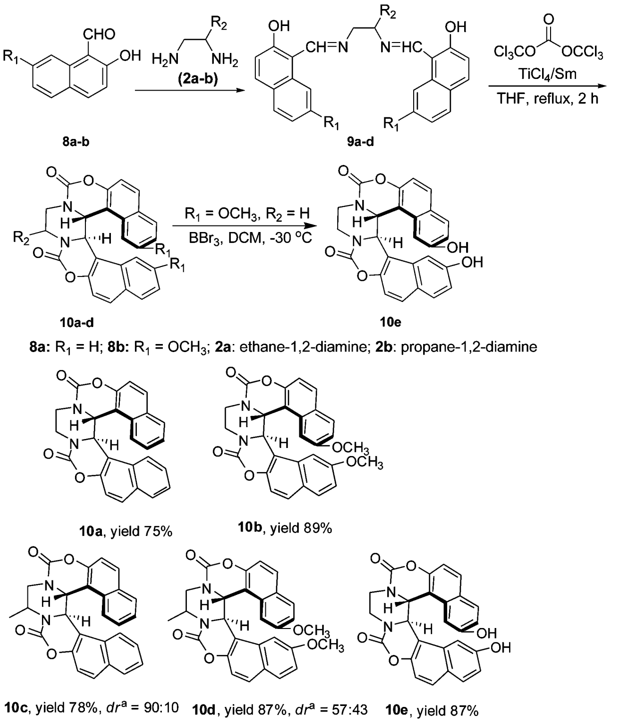
**Scheme 2.** Synthesis of Tetraaza[5]helicene-like Compounds **7a**−**e**



[a] Determined by $^{1}$H NMR.

To demonstrate the value of our developed synthetic method in the scaleable synthesis of heterohelicene-like compounds, a gram-scale synthesis of **10a** was

**Scheme 3.** Synthesis of Dioxo-diaza[7]helicene-like Molecules **10a–e**



[a] Determined by $^1$H NMR.

performed, resulting in 2.85 g with 68% yield and 96% purity.

The structure of **10a** was also confirmed by X-ray diffraction analysis. The molecular structure of product **10a** is shown in Figure 2. Similar to the case of **4c**, **10a** belongs to the triclinic space group $P\overline{1}(2)$. Due to the repulsion between the two terminal naphthalene rings, the two fused benzene rings in the naphthalene moiety in **10a** show a slight deviation from coplanarity. The average interplanar angles between the two benzene rings in the naphthalene moiety are 3.0° for (*P*)-**10a** and 2.9° for (*M*)-**10a**. The interplanar angles between the two terminal benzene rings are 31.9° for (*P*)-**10a** and 30.5° for (*M*)-**10a**.

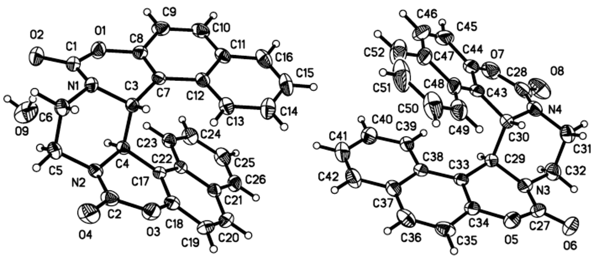


**Figure 2.** X-ray structure of compound **10a**.

During the synthesis, when ethane-1,2-diamine **2a** was chosen as the starting material, the resulting helicenes (such as **4a–f**, **7a–b**, and **10a–b**) clearly show a $C_2$ symmetric arrangement. $^1$H NMR spectra of those compounds exhibit a singlet for the two methenyl protons. When the ethane-1,2-diamine was replaced by propane-1,2-diamine **2b**, the helicenes bearing a methyl group at C-7 (such as **4g–k**, **7c–d**, and **10c–d**) led to the formation of a mixture of diastereoisomers[22] (see Supporting Information). Their $^1$H NMR spectra also show two doublets for the two methenyl protons because of the lack of $C_2$ symmetry. From the dr values of the above-mentioned compounds, we can presume that the diastereoselectivities are related to the number of helicenes and the position of the substituents attached to the phenyl rings.

In conclusion, a facile and efficient route has been developed for the synthesis of complex [5]- and [7]heterohelicene-like compounds by using *o*-hydroxydiimines or *o*-nitrodiimines and triphosgene in the presence of $TiCl_4$/Sm as the reductive coupling reagent. Purification of the final products only required a single recrystallization leading to high purity. Good chemical yields and a high diastereoselectivity have been achieved. Structures of the final products were confirmed by X-ray diffraction analysis. This novel synthetic method provides an easy access to heterohelicene-like molecules with remarkable structural complexity by taking advantage of readily available starting materials, operational simplicity, a short reaction time, high yields, and convenient purification. Further exploitation of this method and application of these products are underway.

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**Supporting Information Available.** Experimental procedures; characterization, crystallographic data, and CIF files for the products. This materials is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.

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