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Lewis Acid-Catalyzed One-Pot, Three-Component Route to Chiral 3,3′-Bipyrroles

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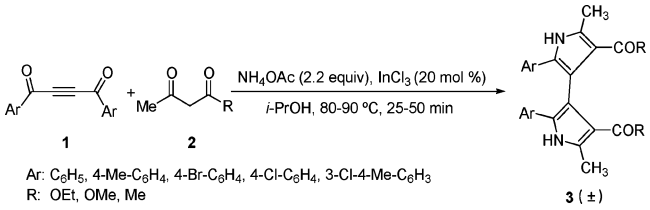
ABSTRACT



3,3′-Bipyrroles 3 could be synthesized using a double Michael addition reaction involving diaroyl acetylene 1 and the appropriate 1,3-dicarbonyls 2 using ammonium acetate as a nitrogen source. The axial chirality of bipyrrole was anticipated from the X-ray crystal structure and DFT calculations and confirmed by separating the racemates on a chiral column and subsequent CD spectra of the enantiomers. The absolute configuration of the enantiomers was achieved by theoretical CD spectra calculation using the ZINDO method.

Bipyrroles not only are key subunits in important natural products but also are known for their conducting properties. Polypyrroles are one of the most extensively studied[1] conducting polymers, since they possess numerous attractive features that are important to material science such as good redox properties, environmental stability, and high electrical conductivity. They have found applications as supercapacitors, electrochemical sensors, antistatic coatings, and drug delivery systems.[2] Bipyrroles are found as natural products belonging to the prodigiosin family,[3] and they are also known to exhibit a broad range of activity against bacteria, protozoa, and pathogenic fungi. They are capable of inducing apoptosis in many different human cancer cell lines with few side effects.[4]

A few halogenated bipyrroles have also been isolated from the blubber of marine mammals.[5] The commonly encoun-

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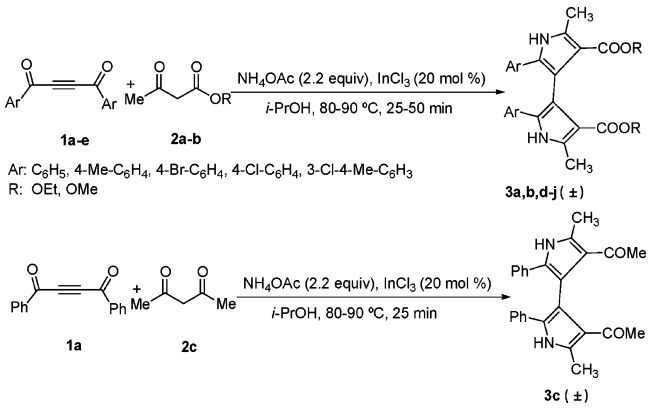
tered bipyrroles possess mainly the 2,2′-bipyrrole basic moiety. Hinz et al.[6] have synthesized 2,2′-bipyrrole using pyrolysis of 2-azido-5-(2-pyrrolyl)penta-2,4-dienoic esters. Apart from 2,2′-bipyrrole, Zaitsev et al.[7] have also prepared 2,3′-analogues of bipyrrole through the intermediacy of *O*-vinyloxime pyrroles. The first notable observation was made during the synthesis of CC-1065, a potent antitumor and antibiotic wherein 3,3′-bipyrrole was the building block.[8] The importance of the bipyrrole came to the fore recently when Wasserman et al.[9] synthesized the natural product isochrysohermidin, earlier isolated from *Mercurialis leiocarpa* in the *d,l* and *meso* form using singlet oxygen oxidation of the 3,3′-bipyrrole scaffold as the key step. Gleiter et al.[10] have reported palladium mediated synthesis of 3,3′-bipyrroles. Che et al.[11] have also synthesized highly luminescent functionalized bipyrroles. The synthesis by Peters et al.[12] of crown-ether functionalized bipyrroles having the property of conducting ions undoubtedly encouraged the organic chemist to explore this area of bipyrroles.

In our endeavor to synthesize some key nitrogen heterocycles, it was envisaged that dissymmetrical bipyrroles could be synthesized through a multicomponent synthetic approach involving double Michael addition followed by cyclization. In this reaction, diaroyl acetylene **1a**−**e**, *β*-keto esters **2a,b,** and ammonium acetate in the presence of a Lewis acid catalyst (Scheme 1) resulted in 3,3′-bipyrroles **3a**,**b**,**d**−**k** in good

Scheme 1. One-Pot Synthesis of 3,3′-Bipyrroles **3a**−**k**



yield (Table 1). Also, reaction of **1a** and acetyl acetone (**2c**) gave the expected bipyrrole **3c**, but reactions involving diaroyl acetylene **1b**−**e** and acetyl acetone (**2c**) gave an inseparable mixture of products. The reaction has been studied to obtain optimum conditions necessary for the product formation. Thus, the reaction was performed in the presence of various Lewis acids in isopropyl alcohol (IPA) at 80−90 °C. The Lewis acid catalysts used include $In(OTf)_3$, $InCl_3$, $ZnCl_2$, and $FeCl_3$ all of which promoted the reaction. $In(OTf)_3$ and $InCl_3$ in catalytic quantities (20 mol %) provided the best result in comparison to other Lewis acids investigated (see the Supporting Information). In the absence of the metal salts the desired product was not formed in good yield.

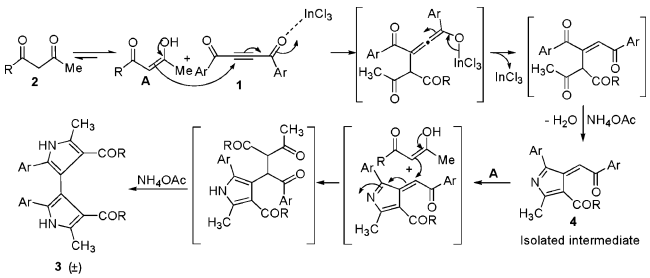
Table 1. Synthesis of Chiral 3,3′-Bipyrroles **3a**−**k**

entry	Ar	R	product	time (min)	yield (%)
a	C_6H_5	OEt	**3a**	45	76
b	C_6H_5	OMe	**3b**	30	72
c	C_6H_5	Me	**3c**	25	64
d	4-Me−C_6H_4	OEt	**3d**	40	70
e	4-Me−C_6H_4	OMe	**3e**	35	73
f	4-Br−C_6H_4	OEt	**3f**	50	61
g	4-Br−C_6H_4	OMe	**3g**	30	65
h	4-Cl−C_6H_4	OEt	**3h**	25	62
i	4-Cl−C_6H_4	OMe	**3i**	30	66
j	3-Cl-4-Me−C_6H_3	OEt	**3j**	35	64
k	3-Cl-4-Me−C_6H_3	OMe	**3k**	50	67

The reaction has also been studied using different solvents at 80−90 °C using $InCl_3$ as a catalyst. Among the solvents used only isopropyl alcohol (IPA) and methanol gave the desired product in reasonable yields with isopropyl alcohol (IPA) providing a better yield (see the Supporting Information). It is pertinent to mention here that when the same reaction was performed with a catalytic amount of saturated anhydrous HCl in IPA the reaction failed to proceed even after 4 h of refluxing.

In order to investigate the mechanistic pathway leading to the product during the reaction of dibenzoyl acetylene (**1a**) and ethyl acetoacetate (**2a**) in the presence of $InCl_3$ in IPA at 80−90 °C, the intermediate **4a** formed was isolated and characterized. It was possible to isolate **4** when the above reaction was stopped before completion. This intermediate **4** results from the Lewis acid assisted Michael addition of *β*-keto carbonyl **2** with diaroyl acetylene **1**, followed by ammonia addition and subsequent cyclization with loss of water.[13] **4** then undergoes Michael addition with another molecule of *β*-keto carbonyls **2** followed by a similar reaction sequence resulting in 3,3′-bipyrroles **3** (Scheme 2).

Scheme 2. Proposed Mechanism for Formation of 3,3′-Bipyrroles **3a**−**k**



The bipyrroles were expected to show atropisomerism, and as anticipated the X-ray crystal structure (Figure 1) of **3a**

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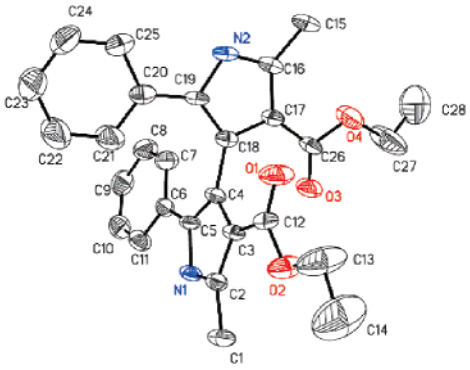

Figure 1. ORTEP diagram of 3,3′-bipyrrole **3a** (without hydrogen atoms for clarity).

revealed that the two-pyrrole rings are disposed with a C3−C4−C18−C17 torsion angle of 82.72 and a C5−C4−C18−C19 torsion angle of 87.90, which confirms that they are not in the same plane. This is further corroborated by the DFT calculations of **3c**. It was found (see the Supporting Information) that there are potentially ten diastereomeric conformers of **3c**. All reasonable transition structures linking these ten diastereomers were located computationally, and the recently generalized Winstein-Holness equation[14] was used to compute the activation energy for the racemization of **3c** (26.7 kcal/mol). This prompted us to attempt the resolution of **3a**. To date only three chiral bipyrroles, one with a 1,1′-attachment[15] and two with a 2,2′-linkage,[16,17] have been reported. Atropisomerism has also been observed in a poly-β-pyrrole.[18]

The racemic bipyrroles **3a** (Figure 2) and **3c** (Figure 3) were indeed separated by HPLC on a chiral OD-H column,

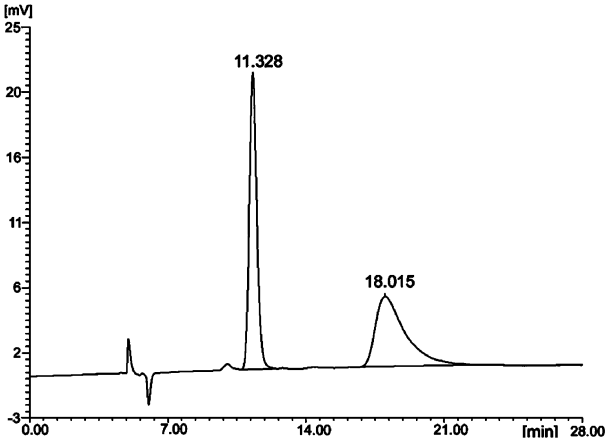

Figure 2. Chiral HPLC profile of **3a**.

and the CD spectra of the separated enantiomers confirm this (Figure 4). (+)-**3a** and (−)-**3a** represent the enantiomers with retention times of 11.328 and 18.015 min, respectively.

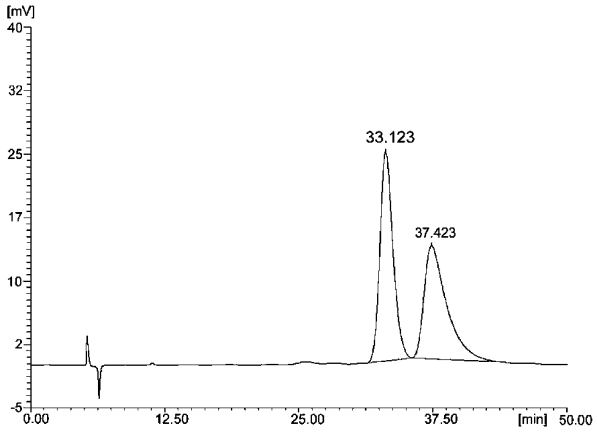

Figure 3. Chiral HPLC profile of **3c**.

The absolute configuration of the two enantiomers of **3a** follows from the theoretical CD spectra calculation using

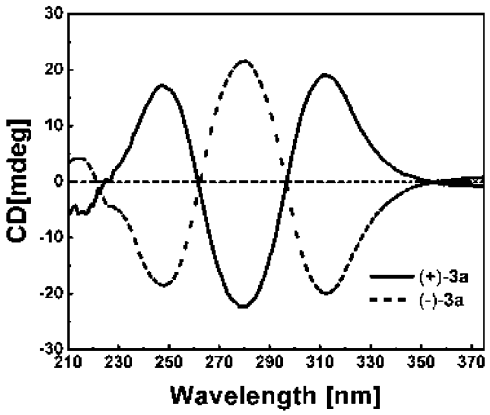

Figure 4. CD spectra of the two enantiomers of **3a**.

the ZINDO method. The calculations were performed for both the X-ray determined structure (not optimized) and the

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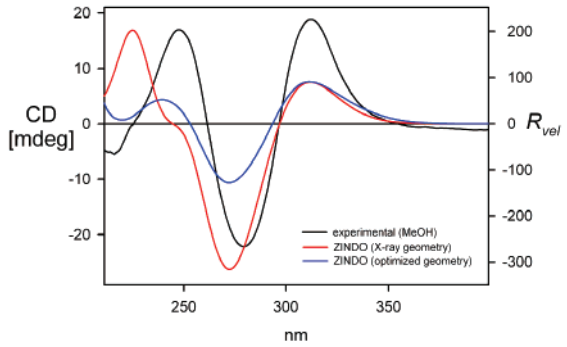

Figure 5. Comparison of experimental CD spectrum (in mdeg) of (+)-**3a** and ZINDO calculated CD spectra (R_{vel}) of **3a** with assumed *M*-helicity of the 3,3′-bipyrrole unit.

PM3 optimized structure. The structures differ in the magnitude of the 3,3′-bipyrrole dihedral angle (see the Supporting Information). However, the calculated CD spectra for the two structures with assumed *M*-helicity are qualitatively similar. Moreover, the experimental CD spectrum for (+)-**3a** agrees well with the calculated CD spectra (Figure 5). Therefore the absolute configurations of (+)-**3a** and (−)-**3a** are found to be *R* and *S*, respectively (Figure 6).

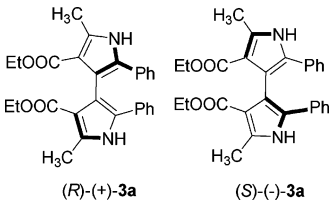

Figure 6. Absolute configuration of the two enantiomers of **3a**.

In summary, 3,3′-bipyrroles **3** could be synthesized using a very simple and efficient double Michael addition reaction. Reaction of a diaroyl acetylene **1** and the appropriate 1,3-dicarbonyl **2** with ammonium acetate as the nitrogen source results in pyrrole **4** which undergoes another Michael addition and nitrogen insertion for the bipyrrole formation. The atropisomers were separated on a chiral column and characterized. This work has necessitated further studies involving the application of the bipyrroles as chiral ligands and also screening of the compounds in vitro for anticancer activity. The importance of the electrochemical sensing property of the bipyrroles requires studies in this direction also.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, X-ray crystal structure coordinates and files in CIF format, DFT calculation data and theoretical CD spectra studies, and HPLC profiles of **3a** and **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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