

Synthesis of a Macrobicyclic Incorporating the Tris(pyrazolyl)methane Ligand

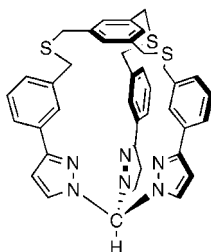
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ABSTRACT



Steric crowding of the 3-position of tris(pyrazolyl)borate and -methane ligands has produced tetrahedral metal complexes with controlled reactivity. As an alternative, we propose to incorporate the tris(pyrazolyl)methane chelate in a macrobicyclic structure in order to create a cavity with well-defined dimensions and shape. Acid-catalyzed equilibration of excess of the new pyrazole 3-(1*H*-pyrazol-3-yl)benzenemethanethiol acetate with $\text{HC}(3,5\text{-Me}_2\text{pz})_3$ followed by hydrolysis affords a functionalized tris(pyrazolyl)methane, which reacts with 1,3,5-tris(bromomethyl)-benzene in $\text{K}_2\text{CO}_3/\text{DMF}$ to give the title compound.

Tris(pyrazolyl)borate ($\text{Tp}^{\text{R,R'}}$) or scorpionate ligands^{1,2} are facially capping tridentate nitrogen donors that have been used in particular as models of the metal binding sites of several metalloenzymes including hemocyanin,³ blue copper proteins,⁴ and carbonic anhydrase (CA).⁵ Substitution of the pyrazole 3-position (R) by bulky groups in combination with

buttressing effects⁶ has been shown to enforce tetrahedral coordination geometry at the metal⁷ and allow for the control of the reactivity of the metal-bound species. In particular, the use of large, hydrophobic substituents such as *tert*-butyl in $\text{Tp}^{\text{tBu,Me}}$ or *p*-isopropylphenyl (*p*-cumenyl) in $\text{Tp}^{\text{Cum,Me}}$ has led to the isolation of stable yet highly nucleophilic TpZn-OH complexes. $\text{Tp}^{\text{tBu,Me}}\text{Zn-OH}$ successfully mimics the

(1) The notation $\text{Tp}^{\text{R,R'}}$ is equivalent to $\text{HB}(3\text{-R-5-R'}\text{pz})_3$, where pz is pyrazole. Analogous tris(pyrazolyl)methanes are noted $\text{Tpm}^{\text{R,R'}}$.

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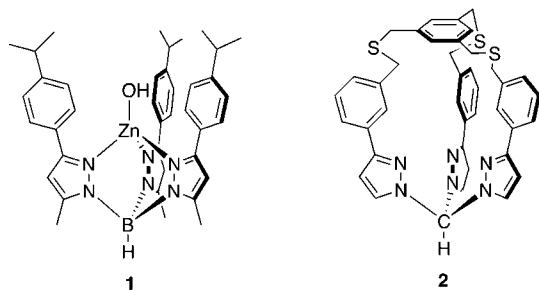


Figure 1. $\text{Tp}^{\text{Cum,Me}}\text{Zn}-\text{OH}$ (**1**)⁸ and macrobicyclic **2** incorporating the tris(pyrazolyl)methane chelate system.

active site of CA,⁵ and $\text{Tp}^{\text{Cum,Me}}\text{Zn}-\text{OH}$ (**1** of Figure 1) performs the hydrolysis of a range of small molecule substrates.⁸ The combination of Tp^{iPr_2} and bulky thiols has produced rare tetrahedral copper(II) complexes that closely mimic the spectroscopic characteristics of the blue copper proteins.^{4b,c} As a further example of the use of hindered homoscorpionates to control reactivity, copper(I) complexes of Tp^{Ms} (Ms is mesityl) have been shown to catalyze the cyclopropanation of olefins by ethyldiazoacetate with remarkable cis diastereoselectivity.⁹ Good enantiocontrol (85% ee) of the same reaction has been achieved with optically active C_3 -symmetric Tps that have been tailored from asymmetric pyrazoles.¹⁰

By contrast, tris(pyrazolyl)methane (Tpm) ligands,^{1,11} the neutral analogues of scorpionates, have received less attention. In a few instances, they have led to metal complexes with decreased stability,¹² as clearly demonstrated for Zn^{2+} , in particular.¹³

In this letter, we present the synthesis of a macrobicyclic incorporating the tris(pyrazolyl)methane ligand system (**2** of Figure 1) by closing a functionalized tris(pyrazolyl)methane derivative with a mesitylene cap. This approach is reminiscent of cyclophane chemistry.¹⁴ Macrobicyclic **2** is the first example of a new, general strategy for the control of the metal environment in complexes of Tpm ligands, and hopefully for improving their robustness.

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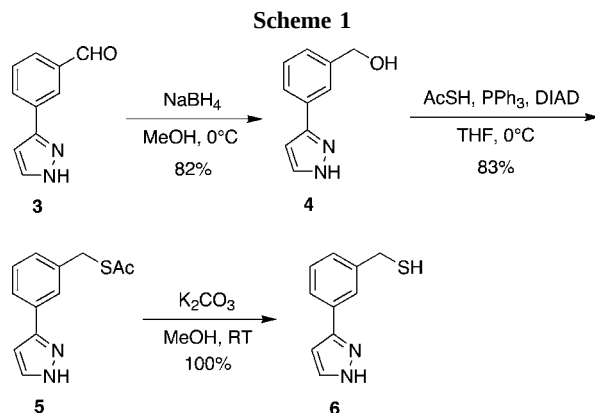
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The synthesis of **2** involves 3-(1*H*-pyrazol-3-yl)benzenemethanol **4**, a known compound¹⁵ prepared in this study by NaBH_4 reduction (MeOH, 0 °C) of the corresponding aldehyde **3**,¹⁶ in 82% yield (Scheme 1). Subsequent reaction



with thiolacetic acid in Mitsunobu reaction conditions (PPh_3 , DIAD, THF, 0 °C)¹⁷ afforded the benzenemethanethiol acetate derivative **5** in 83% yield after chromatography (25% EtOAc in heptane). The acetyl protecting group was removed by reaction of **5** with potassium carbonate in methanol at room temperature, followed by acidic workup, affording 3-(1*H*-pyrazol-3-yl)benzenemethanethiol **6** quantitatively.

Tris(pyrazolyl)methanes are classically prepared from chloroform by reaction with the appropriate pyrazolate that is either preformed^{11,18} or generated in situ (phase-transfer catalysis),¹⁹ i.e., basic reaction conditions that are not adapted to the use of either **5** or **6** as substrates. However, it was shown recently that acid-catalyzed equilibration of tris-(pyrazolyl)methane itself or Tpm^{Me_2} with pyrazoles allowed the preparation of various Tpm ligands.²⁰ Of particular interest for our study was the preparation of Tpm^{Ph} (**10**) in 67% yield by reaction of Tpm^{Me_2} (**7**) with 10 equiv of 3-phenyl-1*H*-pyrazole (**8**) in the presence of 1 equiv of TsOH in refluxing toluene (Scheme 2). The disubstituted product (**9**) was obtained in 33% yield.

Benzylthiol-substituted pyrazole **6** did not appreciably react under these conditions. By contrast the acetyl-protected derivative **5** afforded a complex mixture of hetero-tris(pyrazolyl)-methanes, due to the fact that the acetyl group had been cleaved in part. Column chromatography (silicagel, dichloromethane/heptane) allowed separation of the simple pyrazoles,

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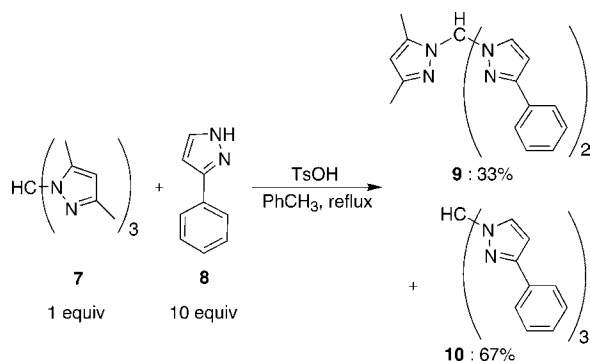
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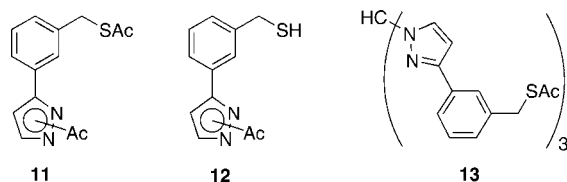
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Scheme 2. Synthesis of Tpm^{Ph} (Ref 20)



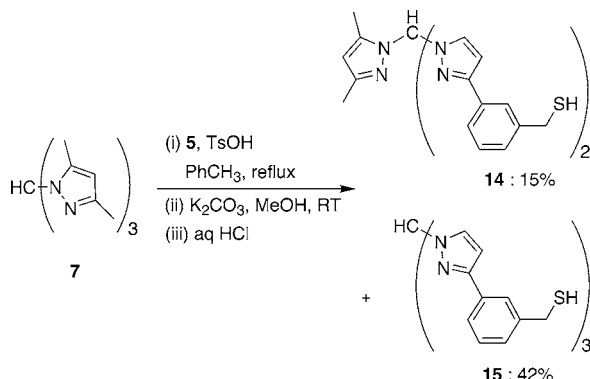
including those resulting from transacetylation, i.e., **11** (7.1%) and **12** (traces), from the Tpm mixture, from which pure tris(pyrazolyl)methane **13** could be isolated in 7.4% yield after crystallization (Scheme 3). In other experiments, the

Scheme 3



difficult separation of **13** was not attempted and the crude mixture of Tpm^s was directly reacted with potassium carbonate (DMF, MeOH) as described for **5**, affording a simple mixture of hetero-tris(pyrazolyl)methane **14** and homo-tris(pyrazolyl)methane **15** (Scheme 4). Column chro-

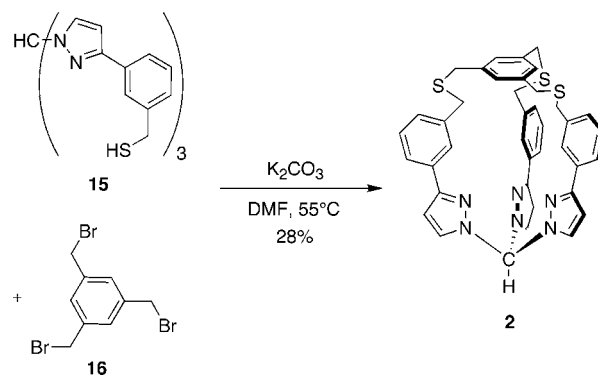
Scheme 4



matography (silicagel, 0.5–3% AcOEt in toluene) allowed separation of the target **15** (42% yield) from the disubstituted derivative **14** (15%), both obtained as colorless oils.

One-step capping of C₃-symmetric nucleophiles with 1,3,5-trisubstituted benzene electrophiles or vice-versa is a well-established method for making cage molecules,²¹ as a

Scheme 5



particular case of the tripod–tripode coupling strategy.²² Accordingly (Scheme 5), Tpm **15** was reacted with 1,3,5-tris(bromomethyl)benzene **16**²³ under high dilution conditions in DMF at 55 °C, using K₂CO₃ as the base. After chromatography (silicagel, CH₂Cl₂) and crystallization from CH₂Cl₂/heptane, macrobicyclic cage molecule **2** was obtained in 28% yield as colorless crystals.

Spectroscopic data fully support the closed structure of this C₃-symmetric compound. The MALDI-TOF spectrum shows the expected molecular peak at *m/z* 694.9. Methine resonances at 8.15 (¹H) and 81.9 ppm (¹³C) ppm are diagnostic NMR signals for the tris(pyrazolyl)methane chelate fragment. Successful and complete capping is confirmed by the presence of two close singlets at 3.63 and 3.60 ppm (¹H) and at 36.4 and 36.3 ppm (¹³C) for the benzylic methylene groups.²⁴

Following earlier work,²⁵ preliminary metal complexation studies with copper(I) have been undertaken. Handling of Corey–Pauling–Koltun (CPK) molecular models suggests that once the metal is chelated by the tris(pyrazolyl)methane fragment of the cage, only a limited space is left for a possible ancillary ligand. In particular, triatomic, end-on bound molecules such as CH₃CN are very likely to be excluded from the cavity.

We are currently exploring the complexation properties of macrobicyclic **2** and preparing other members of this

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new class of Tpm ligands. The results will be reported in due course.

Acknowledgment. This letter is dedicated to the memory of Jean-Marc Kern. We thank the Conseil Régional de Bourgogne for a fellowship to L.W.

Supporting Information Available: Copies of the ^1H NMR, ^{13}C NMR, FT-IR, and MALDI-TOF spectra of **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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