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

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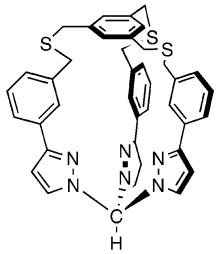
ABSTRACT



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 HC(3,5-Me_2pz)$_3$ followed by hydrolysis affords a functionalized tris(pyrazolyl)methane, which reacts with 1,3,5-tris(bromomethyl)-benzene in K_2CO_3/DMF to give the title compound.

Tris(pyrazolyl)borate ($Tp^{R,R'}$) 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 effects[6] has been shown to enforce tetrahedral coordination geometry at the metal[7] 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 $Tp^{tBu,Me}$ or *p*-isopropylphenyl (*p*-cumenyl) in $Tp^{Cum,Me}$ has led to the isolation of stable yet highly nucleophilic TpZn−OH complexes. $Tp^{tBu,Me}$Zn−OH successfully mimics the

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

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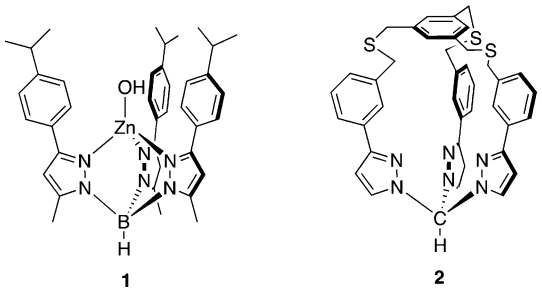


Figure 1. $Tp^{Cum,Me}Zn-OH$ (**1**)[8] and macrobicycle **2** incorporating the tris(pyrazolyl)methane chelate system.

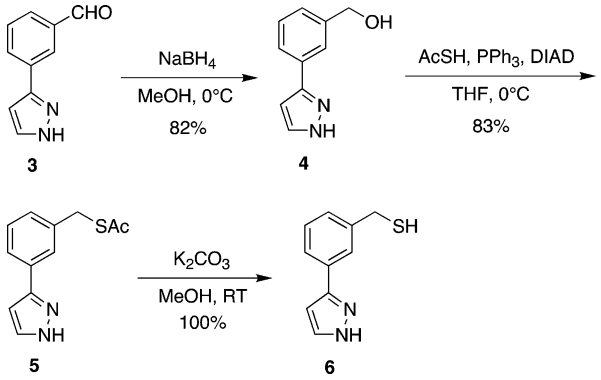
active site of CA,[5] and $Tp^{Cum,Me}Zn-OH$ (**1** of Figure 1) performs the hydrolysis of a range of small molecule substrates.[8] The combination of Tp^{iPr2} and bulky thiols has produced rare tetrahedral copper(II) complexes that closely mimic the spectroscopic characteristics of the blue copper 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 macrobicycle 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] Macrobicycle **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.

The synthesis of **2** involves 3-(1*H*-pyrazol-3-yl)benzenemethanol **4**, a known compound[15] prepared in this study by $NaBH_4$ reduction (MeOH, 0 °C) of the corresponding aldehyde **3**,[16] in 82% yield (Scheme 1). Subsequent reaction

Scheme 1



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^{Me2} 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^{Me2} (**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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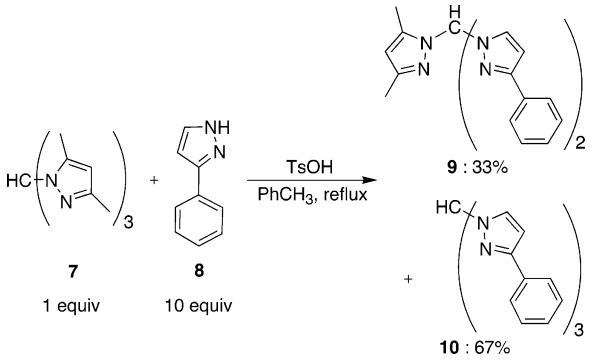
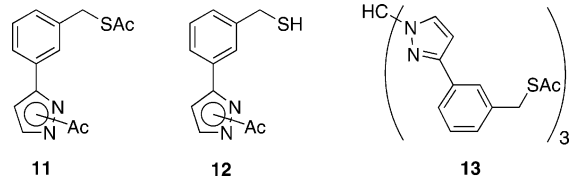
Scheme 2. Synthesis of Tpm^{Ph} (Ref 20)



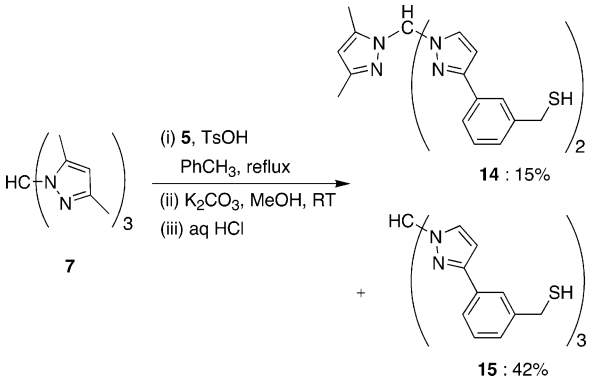
including those resulting from transacetylation, i.e., **11** (7.1%) and **12** (traces), from the Tpm mixture, from which pure tris(pyrazolyl)methane **13** could be isolated in 7.4% yield after crystallization (Scheme 3). In other experiments, the

Scheme 3



difficult separation of **13** was not attempted and the crude mixture of Tpms 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-

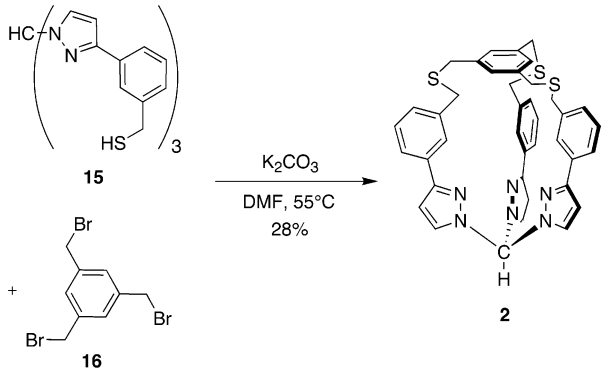
Scheme 4



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 C_3-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 tripode−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 K_2CO_3 as the base. After chromatography (silicagel, CH_2Cl_2) and crystallization from CH_2Cl_2/heptane, macrobicycle **2** was obtained in 28% yield as colorless crystals.

Spectroscopic data fully support the closed structure of this C_3-symmetric compound. The MALDI-TOF spectrum shows the expected molecular peak at *m*/*z* 694.9. Methine resonances at 8.15 (^{1}H) and 81.9 ppm (^{13}C) 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 (^{1}H) and at 36.4 and 36.3 ppm (^{13}C) 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, triaatomic, end-on bound molecules such as CH_3CN are very likely to be excluded from the cavity.

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

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(24) Data collected in $CDCl_3$ solution. In $(CD_3)_2CO$, the proton methine and methylene resonances are shifted, respectively, to 9.06 and 3.86 and 3.78 ppm (see Supporting Information).

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

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Supporting Information Available: Copies of the ^{1}H 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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