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The synthesis of symmetrical bis-1,2,5-thiadiazole ligands ☆

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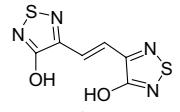
Abstract—We have been engaged in a search for coordination catalysts for the copolymerization of polar monomers (such as vinyl chloride and vinyl acetate) with ethylene. We have been investigating complexes of late transition metals with heterocyclic ligands. In this report we describe the synthesis of a symmetrical bis-thiadiazole. We have characterized one of the intermediates using single crystal X-ray diffraction. Several unsuccessful approaches toward **1** are also described, which shed light on some of the unique chemistry of thiadiazoles.

The ability to homopolymerize (or copolymerize with ethylene) commercially available polar vinyl monomers in a controlled fashion (i.e., producing tacticity) has been a goal of polymer scientists since the advent of Ziegler–Natta catalysts. Although there has been some success for acrylate copolymerizations,[1] there have been no reliable reports of the coordination polymerization of vinyl acetate or vinyl chloride, two of the least expensive polar monomers.

Jordan and our group have shown conclusively in several cases that known catalysts fail due to an elimination process, which occurs after insertion of the polar monomer.[2,3] The driving force for this elimination process is the strength of metal–oxygen (or metal–chlorine) bonds relative to metal–carbon bonds, particularly for early metals. This difference in energy is less for the late metals, and this has been the focus of the search for polar monomer catalysts.

However, late metals also form relatively strong olefin–metal π-complexes, which increases the insertion barrier and therefore slows the insertion rates. The key is to develop new complexes using late metals, which have a favorable balance of slow elimination chemistry and acceptable insertion rates for chain propagation.[3] The complexes that our models suggest may be useable catalysts have some common features: hard, anionic heteroatoms at 180°, delocalized charge in a conjugated ligand, and a soft π-interaction directly behind the active site.[4]

Two of the proposed ligand complexes, which fit this criteria are the bis-1,2,5-thiadiazole ligands **1** and **2**. In this report we describe the synthesis of a symmetrical bis-thiadiazole. Several unsuccessful approaches toward **1** are also described, which shed light on some of the unique chemistry of thiadiazoles.



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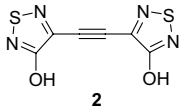

2

In our efforts to prepare such bis-thiadiazoles (**1** or **2**), numerous synthetic routes were investigated, which fall into two categories. Our first strategy was to form the thiadiazole rings after the carbon framework was

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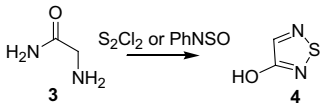
assembled. The second strategy, which ultimately proved to be successful, was to join two functionalized thiadiazoles. The former approach will be discussed first.

Our initial plan was to start with a symmetrical six-carbon backbone, and build the thiadiazole rings on the ends. One common synthetic method for 1,2,5-thiadiazoles is to treat an α-aminocarboxamide (**3**) with an electrophilic sulfur species such as S_2Cl_2 or PhNSO (Eq. 1).[5] Accordingly, we attempted to synthesize bis-α-aminocarboxamide (**5**), and expected to produce **6**, a saturated version of **1**. These methods were thwarted by a strong propensity for these molecules to cyclize. For example, in Scheme 1 the commercially available dibromide **7** was converted to diamine diester **8** via a bis-azide intermediate.[6] Attempts to convert diamine diester **8** to the bis-α-aminocarboxamide **5** using either aqueous or liquid ammonia under pressure led to the formation of piperidone **9**, and none of the desired product (**6**).[7] We used single crystal X-ray diffraction to conclusively identify piperidone **9**, which is shown in Figure 1. The structure is unexceptional.[8]



(1)

We turned our attention to approaches, which started with functionalized 1,2,5-thiadiazoles (**10a**,**b**). We reasoned that if a chlorinated thiadiazole would behave in a fashion similar to that of pyridine, we might be able to add an acetylenic nucleophile as shown in Eq. 2.

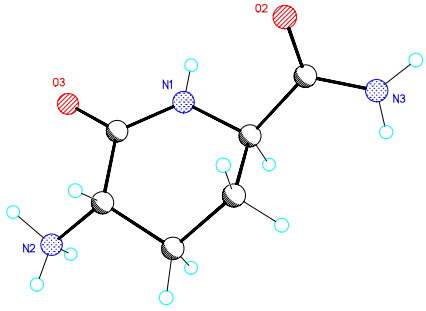
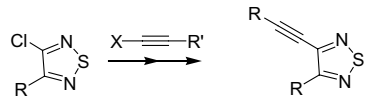


Figure 1. X-ray structure of lactam **9**.



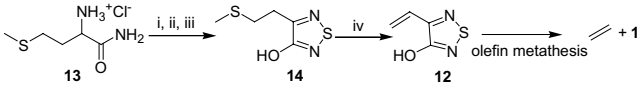
10a R = Cl
10b R = OH

11a R = Cl
11b R = OH

(2)

We investigated the reaction of a variety of acetylene nucleophiles (Na–C≡C–Na, Li–C≡C–$SiMe_3$, Li–C≡C–$SnMe_3$) with 3,4-dichlorothiadiazole (**10a**) and 3-chloro-4-hydroxythiadiazole (**10b**). Throughout this series of reactions, the starting material was consumed quickly, with no significant higher molecular weight products being formed. It has been reported in the literature that the reaction of Na–CC–$SiMe_3$ with 3,4-dichloro thiadiazole results in the formation of $S(C{\equiv}C{-}SiMe_3)_2$ and $Me_3SiC{\equiv}C{-}CN$.[9] We also investigated the use of $HC{\equiv}CCMe_2OH$ under phase-transfer conditions, which has been used successfully with 3-chlorothiophene and 2-chloropyridine.[10,11] However, the use of this procedure with 3,4-dichloro thiadiazole or 3-chloro-4-hydroxy-1,2,5-thiadiazole again formed a complex reaction mixture.

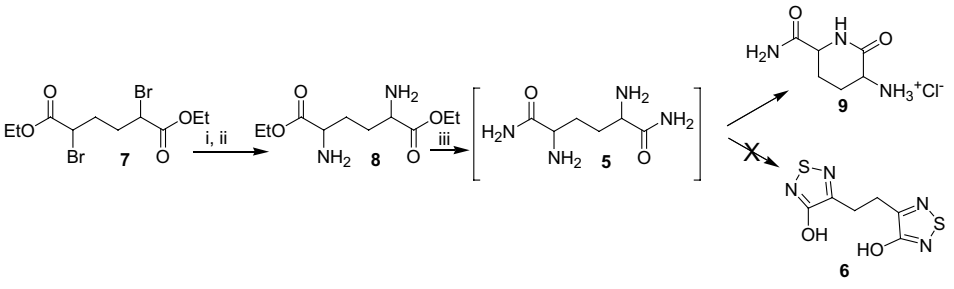
An alternative to this procedure was the implementation of an olefin metathesis methodology (Eq. 3). Specifically, we reasoned that the desired bis-thiadiazole **1** might be produced from olefin metathesis on vinyl-substituted thiadiazole **12**.



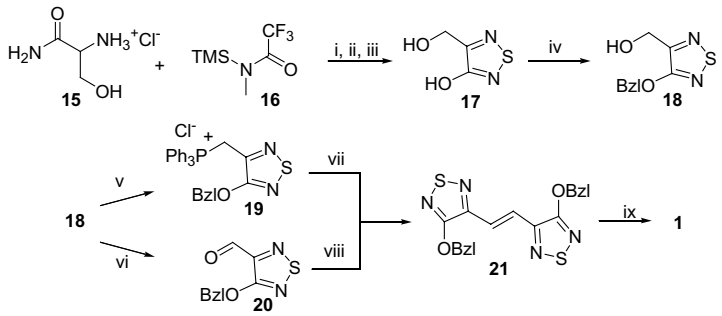
i) Hexane, 68°C ii) Pyridine, 90°C, distill off hexane
iii) Cool to 34°C, add PHNSO heat to 90°C for 16 h
iv) CH_3CO_3H, KOtBu, $CHCl_3$

(3)

The precursor (**12**) was prepared starting with the conversion of methionine amide **13** to the thiadiazole **14** using PhNSO. The published[12] procedure for conversion of **14** to the vinyl derivative **12** gave uneven results in our hands. We developed a one-pot procedure for preparing the vinyl derivative **12** from the thioether via oxidation, followed by treatment with base.[13] The crystalline olefin was isolated in good yield. Attempts to perform the olefin metathesis step with several different catalysts gave no reaction. Finally, attempted coupling of **14** with 3,4-dichloro-1,2,5-thiadiazole (**10a**) under



Scheme 1. Reagents and conditions: (i) NaN_3 EtOH, 76 °C, 17 h; (ii) EtOH, HCl, PtO, H_2; (iii) NH_3.



Scheme 2. Reagents and conditions: (i) MeCN, 1 h ambient temp; (ii) 0 °C, Et_3N; (iii) SO_2 in MeCN is added, warm to ambient temp; (iv) dioxane, HMPA, BzlCl, K_2CO_3, reflux for 3.5 h; (v) $CHCl_3$, $SOCl_2$, reflux for 1 h; (vi) CH_2Cl_2, 'Bobbitt's' reagent[16]; (vii) THF, −40 °, $K^+-N(TMS)_2$, warm to ambient; (viii) −40 °C, stir to ambient temp for 90 min; (ix) CH_2Cl_2, −78 °C, 1 M BBr_3.

Heck chemistry conditions did not form any coupled products.

Failure of this chemistry led us to investigate longer synthetic routes based on formation of the central olefin from 3-formyl-1,2,5-thiadiazole using Wittig or McMurray coupling methods. We hoped to prepare the formyl derivative by oxidation of known 3-hydroxy-4-hydroxymethyl-1,2,5-thiadiazole (**17**). A seldom-used method for formation of thiadiazole rings by treatment of α-aminocarboxamide **15** with a silylating agent (**16**) and SO_2 was used for the preparation of thiadiazole **17**.[14] This synthetic method is attractive since it does not involve potent electrophiles such as $SOCl_2$, S_2Cl_2 or SO_2Cl_2. Although the mechanism was not discussed, the amino acid is probably converted to a bis-trimethylsilyl derivative, which upon exposure to liquid SO_2 produces **17** (45%). This method for synthesis of thiadiazoles is not covered in any of the reviews, and we have not uncovered any other published examples (Scheme 2).[15]

The acidic hydroxyl group of thiadiazole **17** was protected as the benzyl ether **18**. The conversion of **18** to **20** required a mild oxidizing agent to avoid electrophilic attack on the thiadiazole ring. This was accomplished by using the heterogeneous oxidant, 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium perfluoroborate, which formed aldehyde **20** in >90% yield.[16]

A McMurray coupling reaction (Ti^{3+} under reductive conditions) of aldehyde **20** was initially attempted, but the desired olefin **21** was not detected. Upon workup, a strong mercaptan odor was observed, possibly indicating that the thiadiazole ring had been degraded under these reaction conditions. Next, our attention focused on Wittig chemistry. The phosphonium salt **19** was prepared from the hydroxymethyl derivative using standard techniques. Reaction of the ylide with the aldehyde formed the symmetrical olefin **21** in 89% yield. A single crystal X-ray structure analysis confirmed the geometry of the double bond (C6-C6A 1.33 A) to be *E*, depicting the thiadiazole rings disposed about the double bond at 180°. The formation of **21** with a *trans* configuration reflects the stability of the ylide, due to the carbanion-stabilizing thiadiazole ring substituent on the negatively charged carbon of the ylide. Such stable

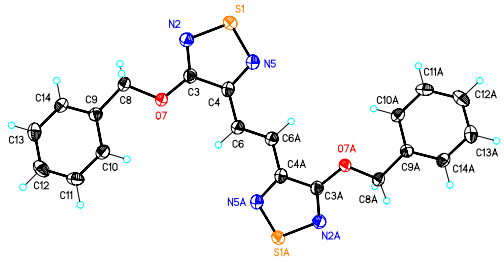


Figure 2. A single crystal X-ray structure analysis of **21**.

ylides are known to exclusively react with aldehydes to form *trans*-alkenes (Fig. 2).[17]

Final deprotection of the bis-benzyl derivative **21** was attempted several ways using nonhydrogenation debenzylation techniques. Initially, the use of excess BBr_3 at low temperatures did deprotect **21** to yield **1** in a matter of 2–3 h. However, the initial, isolated, crude product (**1**) was contaminated with boron impurities. Final purification of **1** was achieved by basification of an aqueous mixture of **1**, followed by filtration and subsequent reprecipitation of **1** via acidification with HCl. This deprotection sequence yielded **1** in >80%. With regard to some of the physical properties of **1**, it was found that the material had a very high melting/decomposition point (>300 °C) and was quite insoluble in most traditional solvents, with the exception of being marginally soluble in DMSO. Like phenol, the hydroxyl groups of this thiadiazole are quite acidic.

In conclusion, this work focused on the synthesis of **1**, which we were able to produce in four steps with an overall yield of 36%. The metal complexation of **1** is now being pursued, but the poor solubility of **1** has made the subsequent metalation of **1** challenging. Accordingly, we have been unable to test the validity of this ligand metal complex as a polar monomer catalyst.

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6. Select data for structural intermediates and products: (**8**) ^{1}H NMR (DMSO-d_6) δ 8.86 (br s, 4H), 4.21 (m, 4H), 3.99 (br s, 2H), 1.98 (m, 4H), 1.23 (t, 3H, $J = 7.1$ Hz). ^{13}C NMR (DMSO-d_6) 169.0, 61.9, 51.1, 25.8, 14.0 ppm. (**9**) ^{1}H NMR (DMSO-d_6) δ 8.4 (br s, 3H), 8.1 (s, 1H), 7.6 (s, 1H), 7.1 (s, 1H), 4.85 (m, 1H), 4.7 (1H, m), 2.2 (m, 2H), 1.7 (m, 2H). ^{13}C NMR (DMSO-d_6) 172.9, 167.4, 55.3, 48.7, 24.5 ppm. (**14**) ^{1}H NMR ($CDCl_3$) δ 10.4 (very br s, 1H), 3.1 (t, 2H, $J = 7$ Hz), 2.95 (t, 2H, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$) 162.7, 150.8, 31.3, 28.8, 15.4 ppm. (**12**) ^{1}H NMR ($CDCl_3$) δ 12.0 (br s, 1H), 6.90 (d of d, 1H, $J = 17.7$, 11.4 Hz), 6.45 (d, 1H, $J = 11.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 162.8, 147.3, 126.2, 122.1. (**17**) ^{13}C NMR ($CDCl_3$) δ 161.6, 150.4, 57.5. Anal. Calcd for $C_3H_4N_2O_2S$: C, 27.27, H, 3.03, N, 21.21. Found: C, 27.14, H, 3.23, N, 21.28. (**18**) Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.05, H, 4.50, N, 12.6. Found: C, 53.80, H, 4.52,N, 12.35. ^{1}H NMR ($CDCl_3$) δ 3.78 (br s, 1H), 4.75 (s, 2H), 5.46 (s, 2H), 7.40 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$) 59.1, 72.64, 128.70, 128.89, 129.01, 129.07, 135.96, 151.1, 162.1 ppm. (**19**) Anal. Calcd for $C_{28}H_{24}N_2OSPI$: C, 56.58, H, 4.04, N, 4.71. Found: C, 55.64, H, 4.08, N, 4.71. ^{13}C NMR ($CDCl_3$) 162.3, 140.0, 139.9, 134.8, 133.5, 133.3, 131.6, 131.1, 129.7, 118.4, 117.0, 71.8, 65.9 ppm. ^{31}P NMR ($CDCl_3$) 31.0 ppm. (**20**) mp 39–40.5 °C. Anal. Calcd for $C_{10}H_8N_2O_2S$: C, 54.55, H, 3.64, N, 12.72. Found: C, 54.33, H, 3.69, N, 12.71. ^{1}H NMR ($CDCl_3$) δ 5.55 (s, 2H), 7.40 (m, 5H), 10.11 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) 73.16, 128.58, 129.05, 129.08, 135.52, 145.17, 165.49, 182.21 ppm. (**21**) mp 138–140 °C. Anal. Calcd for $C_{20}H_{16}N_4S_2O_2$: C, 58.80, H, 3.95, N, 13.72. Found: C, 58.58, H, 3.97, N, 13.67. ^{1}H NMR ($CDCl_3$) δ 5.5 (s, 4H), 7.39 (m, 10H), 7.78 (s, 2H) ppm. ^{13}C NMR ($CDCl_3$) 72.88, 123.94, 128.53, 128.92, 129.05, 135.98, 146.54, 163.39 ppm. (**1**) mp 300–305 °C. ^{1}H NMR (DMSO) δ 7.7 (s, 2H), 13.3 (br s, 2H) ppm. ^{13}C NMR (d_6-DMSO) 123.96, 146.58, 163.94 ppm. HRMS (ES) *m/z* calcd for $C_7H_6N_4O_2S_2$: 227.9775 found 227.9776.
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13. Preparation of PhNSO: A 1 L 4-neck flask equipped with mechanical stirring, addition funnel, and condenser was charged with aniline (40.0 mL, 40.9 g, 0.439 mol) and 200 mL benzene. Nitrogen was flowed through a tee at the top of the condenser to a water bubbler to trap HCl gas. The addition funnel was charged with $SOCl_2$ (41.6 mL, density 1.631 g/mL, 67.9 g, 0.571 mol), which was added over a 15 min period. A solid formed during this addition. After addition, the reactor was gradually heated to 80 °C. The solid mostly dissolved to form a yellow solution. Pure product (55 g) was isolated by distillation at 200 °C.
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