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Synthesis of tris(pyrazolyl)methanes of unprecedented complexity and functionality

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Abstract—In this paper we show that simple tris(pyrazolyl)methane (Tpm) ligands can be equilibrated with substituted pyrazoles to form new 'mixed' tris(pyrazolyl)methanes. The product ratio depends on the nature of the starting tris(pyrazolyl)methane, the nature of the substituted pyrazole, and the relative amounts of these two reagents. The method has been used to easily synthesize several new asymmetric and functionalized Tpm ligands. © 2000 Elsevier Science Ltd. All rights reserved.

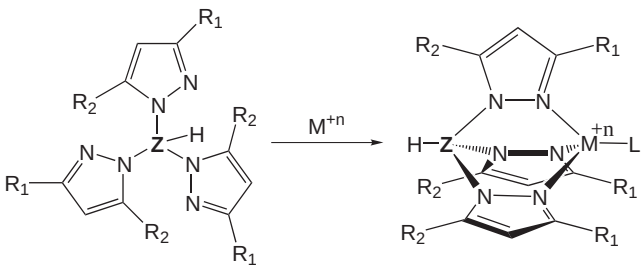
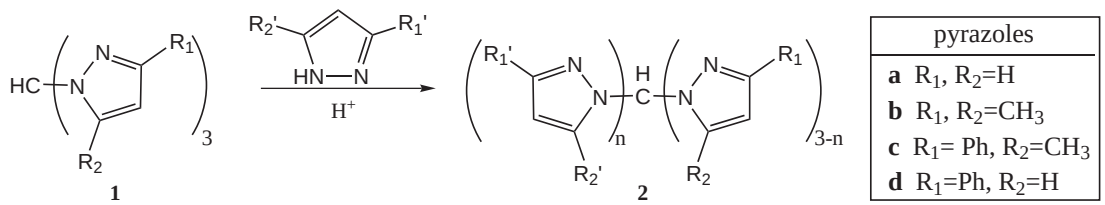


Figure 1. The tris(pyrazolyl)borates ($Z = B^-$) and -methanes ($Z = C$). R_1 and R_2 can be H, alkyl, or aryl.

The tris(pyrazolyl)borates (Tp) are a versatile class of nitrogen-donor ligands, first employed about 30 years ago, that are still receiving considerable attention today.[1] These anionic ligands consist of a tetrahedral boron bonded to 3 pyrazoles, with the remaining group on the boron usually being a hydride (Fig. 1, $Z = B^-$). More recently, the tris(pyrazolyl)methanes (Tpm) have been developed as ligands. (Fig. 1, $Z = C$).[2] The Tpm ligands contain a carbon in place of the boron and are therefore neutral analogues of the Tp ligands.

The most ordinary Tp and Tpm ligands (1st generation) are the unsubstituted parent ligands (Fig. 1, $R_1 = R_2 = H$) and the 3,5-dimethyl derivatives (Fig. 1, $R_1 = R_2 = CH_3$).[3] These simple ligands provide little steric hindrance and are capable of forming octahedral 2:1 ligand/metal complexes with a variety of metal ions.[4] However, introducing bulky substituents in the 3-position (2nd generation) produces sterically hindered ligands, which only reluctantly form (or are sometimes incapable of forming) 2:1 ligand/metal complexes.[5]

Previous syntheses of 3- and 5-substituted Tpm ligands produced a mixture of regioisomers, which were typically equilibrated under acidic conditions giving the most stable regioisomer.[6] We reasoned that under similar conditions, substitution of the pyrazoles with other nucleophiles would also be possible. In this paper we show that simple tris(pyrazolyl)methanes **1** can be equi-



Scheme 1.

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Table 1. The results of equilibrating **1a** and **1b** with various pyrazoles

Experiment	Starting compound	Pyrazole				Product distribution (%)		
			(R_1)	(R_2)	(equiv.)	$n=0$	$n=1$	$n=2$	$n=3$
1	**1a**	**b**	Me	Me	3	24	59	16	1
2			Me	Me	10	12	32	41	14
3		**c**	Ph	Me	1	67	29	4	0
4			Ph	Me	3	32	54	13	1
5			Ph	Me	10	10	47	35	8
6		**d**	Ph	H	3	14	37	35	14
7			Ph	H	10	3	15	41	41
8	**1b**	**c**	Ph	Me	1	27	46	23	4
9			Ph	Me	3	10	36	39	14
10			Ph	Me	10	~0	15	42	43
11		**d**	Ph	H	1	10	38	45	7
12			Ph	H	3	~0	17	56	27
13			Ph	H	10	~0	~0	33	67

librated with substituted pyrazoles (**a**–**d**) to form new 'mixed' tris(pyrazolyl)methanes **2** (Scheme 1). The composition of the product depends on the nature of the starting tris(pyrazolyl)methane, the nature of the substituted pyrazole, and the relative amount of these two reagents.

The results of our experiments are presented in Table 1. In a typical experiment, a mixture of the tris(pyrazolyl)methane (1 equiv.), the substituted pyrazole (1, 3 or 10 equiv.), and *p*-toluenesulfonic acid (1 equiv.) were mixed with toluene ([**1**] = 0.033 M) and the reaction was brought to reflux for 48 hours.[7] The reaction mixture was then worked up with $NaHCO_3$ (aq.), dried and evaporated. The ratio of the products was determined by the relative intensities of the ^{1}H NMR singlet from the methine C–H between 8.0 and 8.6 ppm. Small amounts (<5%) of regioisomers were noted in experiments 3–5.

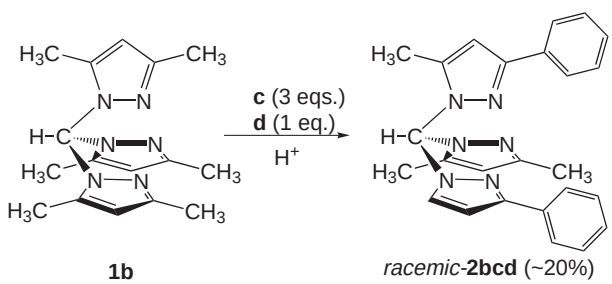
The chemical shifts of the individual compounds are shown in Table 2. Generally, the shift of the methine C–H was quite sensitive to the substitution and changed in a regular way with addition of each new pyrazole. The exception is the reaction of **1a** with **c** (experiments 3–5). The two tris(pyrazolyl)methanes **1a** and **1c** have very similar chemical shifts; however, it was still possible to resolve the ^{1}H NMR signals in this mixture. Also for the compounds shown it is possible to separate and purify the individual components of the mixture by flash chromatography.[8] In each case, the mixed components gave the expected ^{1}H NMR, ^{13}C NMR, and mass spectrum. To our knowledge, the mixed compounds (**2**) have never been described before.

Table 2. Chemical shifts of the methine C–H of **1** and **2**

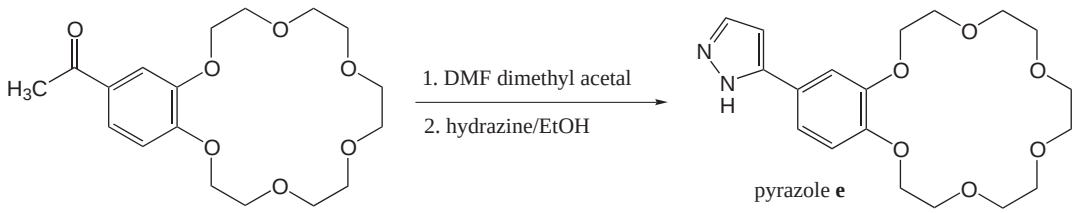
Reaction	^{1}H NMR chemical shift (δ)			
	$n=0$	$n=1$	$n=2$	$n=3$
1a+**b**	8.42 (**1a**)	8.27 (**2a$_2$b**)	8.19 (**2ab$_2$**)	8.07 (**1a**)
1a+**c**	8.42 (**1a**)	8.40 (**2a$_2$c**)	8.44 (**2ac$_2$**)	8.41 (**1c**)
1a+**d**	8.42 (**1a**)	8.45 (**2a$_2$d**)	8.47 (**2ad$_2$**)	8.50 (**1d**)
1b+**c**	8.07 (**1b**)	8.18 (**2b$_2$c**)	8.29 (**2ac$_2$**)	8.41 (**1c**)
1b+**d**	8.07 (**1b**)	8.21 (**2b$_2$d**)	8.36 (**2ad$_2$**)	8.50 (**1d**)

The results reveal that disubstituted **1b** is more reactive than unsubstituted **1a** towards substitution (exp. 3 versus 8). The increased lability of the 3,5-dimethylpyrazole groups in **1b** is undoubtedly due to steric hindrance arising from the substituent in the 5-position. Similarly, it is also apparent that a substituent in the 5-position (R_2) of the pyrazole hinders the incoming pyrazole (exp. 8 versus 11). By careful consideration of the reactivity of the starting tris(pyrazolyl)methane, the nature of the pyrazole, and the relative amount of each it is possible to maximize the yield of a particular product. For example, the monosubstitution product is favored when **1a** is equilibrated with 3 equiv. of 3,5-dimethylpyrazole (exp. 1), but with 10 equiv. the disubstituted product is favored. In the most favorable case (exp. 13) it was possible to favor the formation of the trisubstituted product, tris(3-phenylpyrazolyl)methane **1d**.

These results were then applied to the synthesis of a Tpm ligand containing 3 different pyrazoles. (Scheme 2). Equilibration of **1b** with **c** (3 equiv.) and **d** (1 equiv.)



Scheme 2.



Scheme 3.

leads to a mixture containing all ten possible Tpm ligands, with the desired *racemic*-**2bcd** being present at about 20% by NMR. Column chromatography lead to the isolation of the pure ligand.[9]

We next turned our attention to the synthesis of a functionalized Tpm ligand. Benzo-18-crown-6-substituted pyrazole **e** was synthesized from the 4-acetyl derivative as shown in Scheme 3.[10,11] Acid-catalyzed equilibration of this pyrazole (1 equiv.) with **1c** gave the expected mixture of the mono-, di-, and tri-substituted products, from which the monosubstituted compound **2c$_2$e** was isolated.[12]

In summary, a number of new ligands have been prepared and characterized by acid-catalyzed equilibration of simple Tpm ligands with pyrazoles. We are currently preparing metal complexes of the new 'mixed' ligands, as well as exploring the potentially interesting host–guest chemistry of metal complexes containing the crown ether pyrazole.

Acknowledgements

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7. The reaction progress was checked periodically by work-up of a small aliquot followed by NMR analysis. The composition of the mixture stopped changing within 24 hours in most cases, and in all cases 48 hours was sufficient to assure that equilibrium had been reached.
8. Typically, separation was achieved on silica gel by gradually increasing the amount of CH_3OH (0–5%) in CH_2Cl_2. The trisubstituted compounds elute with pure CH_2Cl_2, followed by the disubstituted compounds (1–2% CH_3OH) and then the monosubstitution products (4–5% CH_3OH).
9. Characterization of **2bcd**: ^{1}H NMR (300 MHz in $CDCl_3$) $\delta = 2.21$ (s, 3H), 2.23 (s, 3H), 2.29 (s, 3H), 5.90 (s, 1H), 6.43 (s, 1H), 6.60 (d, $J = 2.6$ Hz, 1H), 7.29–7.39 (m, 7H), 7.77 (d, $J = 8.1$ Hz, 2H), 7.81 (d, $J = 8.1$ Hz, 2H), 8.35 (s, 1H). ^{13}C NMR $\delta = 11.0$, 11.1, 13.8, 81.1, 103.7, 104.8, 108.0, 125.8, 126.0, 128.0, 128.2, 128.5, 128.6, 131.3, 132.7, 133.0, 141.3, 141.5, 149.7, 151.8, 153.3. EIMS m/z: 408 (10, M^+), 313 (30, $M^+ - \mathbf{b}$), 265 (30, $M^+ - \mathbf{d}$). 251 (100, $M^+ - \mathbf{c}$). EI-HRMS: calc. for $C_{25}H_{24}N_6$ 408.2062, found 408.2087.
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12. Characterization of **2c$_2$e**: ^{1}H NMR (500 MHz in $CDCl_3$) $\delta = 2.34$ (s, 6H), 3.68 (s, 4H), 3.71 (m, 4H), 3.76 (m, 4H), 3.93 (m, 4H), 4.18 (t, $J = 4.5$ Hz, 2H), 4.22 (t, $J = 4.7$ Hz, 2H), 6.44 (s, 3H), 6.53 (d, $J = 3.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 7.28–7.32 (m, 3H), 7.36–7.41 (m, 6H), 7.79 (d, $J = 7.8$ Hz, 4H), 8.45 (s, 1H). ^{13}C NMR $\delta = 11.3$, 68.8 (two peaks), 69.4 (two peaks), 70.6–70.7 (six peaks), 81.4, 103.4, 105.0, 111.2, 113.4, 119.0, 125.7, 126.1, 128.0, 128.5, 131.5, 132.9, 141.9, 148.9, 149.0, 151.8, 153.3.