Synthesis   Paper

Multigram Synthesis of Thallium Trispyrazolylborate Compounds

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MULTIGRAM SCALE!

$R^1 = R^2 = R^3 = Br$, Tp^{Br3}
$R^1 = R^2 = H; R^3 = 2,4,6-Me_3C_6H_2-$, Tp^{Ms}
$R^1 = R^3 = Me; R^2 = Br;$ $Tp^{*,Br}$

Abstract A multigram method for the preparation of thallium trispyrazolylborate complexes is described.

Since the first report about hydrotrispyrazolylborate ligands (Tp^x, Scheme 1) by Trofimenko in the mid-1960s,[1] their metal complexes have found important applications in different areas,[2-3] such as metallo-enzymes modelling,[4-5] dendritic and polymeric materials,[6] technomimetic molecules[7-8] and, especially, in catalysis.[9] This is probably the result of their versatility since the existence of three pyrazolyl substituents (R^1-R^3 in Scheme 1) provides an accessible manner to modify the steric and electronic properties of the ligand and, subsequently, the behavior around the metal center,[2-3] upon varying the R^1-R^3 substituents
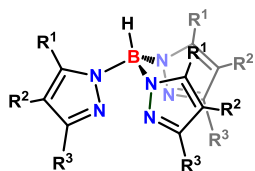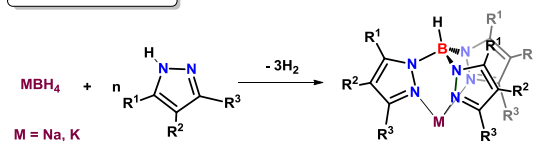

Scheme 1. Hydrotrispyrazolylborate ligands Tp^x

Many of the complexes containing a Tp^xM unit are currently prepared through transmetallation reactions using the thallium(I) derivatives $TlTp^x$, that have replaced the initial $NaTp^x$ or KTp^x salts. [2-3] This is the result of the higher solubility of the thallium complexes in organic solvents. The lattice energy of the thallium halide also helps in this exchange, particularly when compared with the potassium salt.[10] Those $TlTp^x$ compounds are commonly prepared in two steps (Scheme 2). Firstly, the synthesis of KTp^x or $NaTp^x$ by reaction of KBH_4 or $NaBH_4$ and the corresponding pyrazole is carried out following
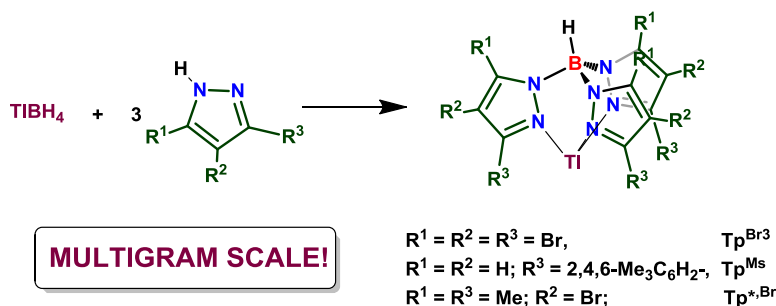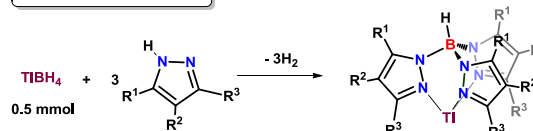
Trofimenko's original procedures.[1,2] Then those alkaline metal derivatives are reacted with $TlNO_3$.[11] The main drawbacks of this methodology are the need of an excess of pyrazol, which affect the isolation of KTp^x in the first step, and the low yield in the product and the separation of KNO_3 in the second step.

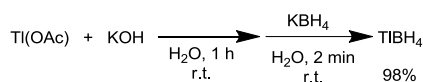**Scheme 2.** Synthetic routes toward hydrotrispyrazolylborate ligands Tp^x.

In 2008, Kitamura and coworkers described a straightforward synthetic method that overcomes those limitations based on the reaction of $TlBH_4$ and three equivalents of the pyrazole (Scheme 2).[12] The preparations described in that contribution were reported at a small scale (0.5 mmol). Given the importance of these ligands in organometallic and coordination chemistry, and their implication in homogeneous catalysis, we have focused in the development of a multigram synthetic protocol for three representative ligands providing either high steric pressure to the metal center (Tp^{Ms}, hydrotris(3-mesitylpyrazol-1-yl)borate),[13] low electronic donation (Tp^{Br3}, hydrotris(3,4,5-tribromopyrazol-1-yl)borate)[14] as well as the bromo-derivative of classical 3,5-dimethylpyrazolyl ($Tp^{*,Br}$, hydrotris(3,5-dimethyl-4-bromopyrazol-1-yl)borate).[15]

We have based our preparation on the method mentioned above by Kitamura and coworkers,[12] but with some modifications which have allowed to improve the overall yields of the TlTp^x synthesis on a large scale. It is worth mentioning that whilst in that report the TlTp*,Br was prepared from the TlBH$_4$ reagent, to the best of our knowledge no reports on the preparation of TlTp^{Br3} or TlTp^{Ms} from TlBH$_4$ are yet described.

$$Tl(OAc) \ + \ KOH \xrightarrow[\text{r.t.}]{H_2O, \ 1 \ h} \xrightarrow[\text{r.t.} \qquad 98\%]{KBH_4} TlBH_4$$

Scheme 3. Synthesis of TlBH$_4$.

In a first step, thallium borohydride was prepared at a ca. 100 mmol scale from using a mixture of thallium (I) acetate and potassium hydroxide in water at room temperature under air for one h. After complete hydrolysis of Tl(OAc) and subsequent formation of TlOH, potassium borohydride was added portionwise (five times) over a period of 1 min to the reaction mixture, with vigorous stirring. Upon additional 1 min of stirring the mixture was filtered, and the solid TlBH$_4$ was isolated, after washing and drying, in 98% yield.
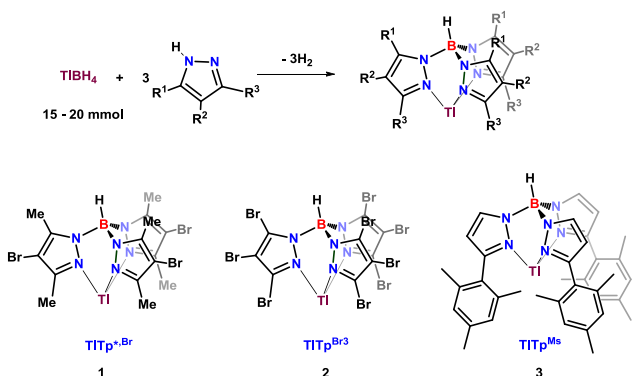
Scheme 4. Synthesis of the TlTp^x complexes **1**-**3**.

The TlTp^x complexes were synthesized by the reaction of thallium(I) borohydride with the corresponding pyrazole using the melted pyrazole as solvent (see Scheme 4). TlTp*,Br (**1**) was prepared upon heating at 180 °C for 4h. After the overall reaction time, the mixture was allowed reaching the room temperature before addition of chloroform to dissolve the product. Filtration through neutral alumina gave a clean solution that was evaporated, and the solid purified by sublimation to remove excess of pyrazole. Finally, 13.5 g of compound **1** (90% yield) were obtained. TlTp^{Br3} (**2**) required sequential heating, first 2 h at the pyrazole melting point (180 °C) followed by two additional h at 200 °C. Direct sublimation of the final solid to remove excess of pyrazole was the best procedure for purification, mainly due to the low solubility of compound **2** in most solvents. A 97% yield (14.6 g) was obtained. Finally, TlTp^{Ms} (**3**) was also prepared using a melting mixture of the pyrazole and TlBH$_4$, that was heated for 1 h at 180 °C and 3 h at 220 °C. With a similar workup to that

mentioned for **1**, compound **3** was obtained in 90% yield (13.5 g).

Some issues deserve special comments. First of all, we have learnt that a crucial aspect in these preparations is the purity of the initial pyrazole. The best results were always obtained using pyrazoles previously purified by sublimation. A ca. 20% improvement in the yield of the final thalium complex was observed when moving from starting pyrazoles purified by crystallization to those by sublimation. Secondly, we have found that the purification of compounds **1-3** by sublimation thus eliminating the excess of pyrazole is much more effective than crystallization. In spite of not being crystallized, compounds **1-3** are obtained with analytical purity by this procedure.

Safety is a major concern in these preparations, given the evolution of hydrogen gas at a somewhat elevated temperature. It is very important to maintain the stirring smoothly and constant, ensuring that hydrogen is not occluded in the melt. We suffered an explosion during one preparation due to the lack of stirring and probable accumulation of hydrogen inside the flask. Thus, the system must ensure hydrogen evacuation from the reaction mixture in a well ventilated hood.

In conclusion, we have developed a multigram synthesis of three hydrotrispyrazolylborate thalium compounds that display different steric and electronic features, making them accessible for their use in a large number of experiments.

All manipulations were carried out under an atmosphere of N$_2$ by using standard Schlenk techniques or glovebox techniques, unless otherwise specified. Solvents were dried by general methods, and degassed before use. 4-Bromo-3,5-dimethylpyrazole,[16] 3,4,5-tribromopyrazole[14] and 3-mesitylpyrazole[13] were prepared following reported procedures. The remaining reagents employed in this work were commercially available. Some precautions should be taken: (i) thallium compounds are very toxic; when handling these substances, avoid any contact with them; (ii) in the thallium hydrotrispyrazolylborate preparations, hydrogen gas is evolved and constitutes an explosion hazard, the reactions should be carried out in a hood, behind a shield, and with proper safeguards to avoid exposing the effluent gas to spark or flame; (iii) when working with thallium (I) borohydride, no traces of acid should be present in the filtrating plate or washing solvents. Under acidic conditions, exothermic decomposition of the metal borohydride takes place.

Procedures

Thallium borohydride

Thallium(I) acetate (25 g, 95 mmol) and potassium hydroxide (0.53 g, 9.5 mmol) were dissolved in 95 mL of distilled water and stirred at room temperature in open air for 1 h until complete hydrolysis. Then, potassium borohydride (10.26 g, 190 mmol) was added in 5 portions over a period of 1 min with vigorous stirring. After one additional min the mixture was passed through a filtrating plate and washed twice with methanol and twice with diethyl ether (ca 30-40 mL each time), both previously cooled at -20 °C. The resulting white solid was introduced in a Schlenk tube and dried under vacuum for 10 h, yielding 20.5 g of TlBH$_4$ as a loose white solid. Yield 98 %.

^{1}H NMR (DMF-d_7, 500 MHz) δ = 2.77 (1:1:1:1 *quartet*, J_{B-H} = 81 Hz, 4H).

^{11}B{^{1}H} NMR (DMF-d_7, 160 MHz) δ = -31.2 (*quint*, J_{B-H} = 81 Hz).

General Method for the Synthesis of the Thallium Hydrotrispyrazolylborate Compounds

The corresponding pyrazole and thallium(I) borohydride in the appropriate ratio (see below) were introduced in a 500 mL Schlenk tube. The tube was closed with a rubber septum and three vacuum-nitrogen

cycles were made. Then, the septum was replaced with a reflux condenser with a bubbler on top. Nitrogen flow was stopped and the solid mixture was slowly warmed, under stirring, using an oil bath with a temperature regulator until melting of pyrazole was observed. At this point, evolution of hydrogen should initiate. The mixture was heated at the corresponding temperature for the required time and then cooled to room temperature. During the reaction time, part of the unreacted pyrazole sublimed and deposited over the wall of the Schlenk tube. A heating gun was used to melt it and return it to the reaction mixture. The reaction mixture solidified during the cooling, and was dissolved in chloroform before filtration through neutral alumina. The alumina was washed with three additional portions of chloroform. The resulting solution was submitted to low pressure in a rotary evaporator to remove the solvent, affording a white solid that was further purified by sublimation to remove the remaining pyrazole. Yields strongly depended on the degree of purity of the starting pyrazole: higher yields were obtained in all cases when pyrazoles were purified by sublimation instead of recrystallization prior to be employed as reactants.

Thalium hydrotris(3,5-dimethyl-4-bromopyrazol-1-yl)borate, TlTp*,Br (1)

14 g (80 mmol) of 1-H-4-bromo-3,5-dimethylpyrazole and 4.4 g (20 mmol) of thallium (I) borohydride were used. Pyrazole melted at 170-175 °C and the reaction was heated at 180 °C during 4 h. Unreacted pyrazole was removed by sublimation (130 °C, 2 mbar), until no more pyrazole was collected. TlTp*,Br was obtained as a white solid in 90% yield (13.5 g of TlTp*,Br). In contrast, when the initial pyrazole was purified by recrystallization in petroleum ether the final yield into **1** decreased significantly (71 %, 10.6 g of TlTp*,Br).

^{1}H NMR (CDCl$_3$, 500 MHz) δ: 4.76 (broad signal, 1H), 2.37 (s, 9H), 2.27 (s, 9H).

^{11}B{^{1}H} NMR (CDCl$_3$, 160 MHz) δ: -7.08 (d, J_{B-H} = 96.6 Hz).

^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz) δ: 146.7 (d, J_{C-Tl} = 33.6 Hz), 143.0, 95.6 (d, J_{C-Tl} = 29.0 Hz), 12.5 (d, J_{C-Tl} = 95 Hz), 12.1.

Anal. Calcd. for C$_{15}$H$_{19}$BBr$_3$N$_6$Tl: C, 24.40; H, 2.59; N, 11.38. Found: C, 24.65; H, 2.58; N, 11.25.

Thalium hydrotris(3,4,5-tribromopyrazol-1-yl)borate, TlTp^{Br3} (2).

16.2 g of previously sublimed 1-H-3,4,5-tribromopyrazole (53.2 mmol) and 2.93 g of thallium borohydride (13.3 mmol) were used. The reaction was heated at the melting point of pyrazole (180-185 °C) during 2 h before the temperature was increased to 200 °C and the reaction mixture stirred during additional 2 h. After cooling to room temperature, the white solid obtained was directly purified by sublimation, thus removing the unreacted pyrazole (150 °C, 2 mbar). TlTp^{Br3} displays a very poor solubility in most common solvents, only DMSO dissolves it in significant degree. 14.6 g of TlTp^{Br3} were obtained as a white loose solid. Yield 97 %.

^{1}H NMR (CDCl$_3$, 500 MHz) δ: 5.40 (*broad signal*, 1H).

^{11}B{^{1}H} NMR (DMSO-d$_6$, 160 MHz) δ: -2.38.

^{13}C{^{1}H} NMR (DMSO-d$_6$, 125 MHz) δ (ppm): 127.0, 120.0, 97.5.

Anal. Calcd. for C$_9$HBBr$_9$N$_6$Tl: C, 9.59; H, 0.09; N, 7.45. Found: C, 9.91; H, 0.01; N, 7.40.

Thalium hydrotris(3-mesitylpyrazol-1-yl)borate, TlTp^{Ms} (3).

12.66 g (68 mmol) of 1-H-3-mesitylpyrazole and 4.27 g (19.4 mmol) of thallium (I) borohydride were employed, and the mixture was slowly heated to 180 °C. As the pyrazole melted (170-175 °C) the reaction turned grey and slowly cleared up with time. The mixture was heated at 180 °C for 1 h and then at 220 °C for 3 h, solidification being observed during this latter period. After that time, and upon cooling, 200 mL of CHCl$_3$ were added and the mixture was filtered through neutral alumina. The solution was taken to dryness and unreacted pyrazole was removed

by sublimation (160 °C, 1 mbar) to afford the desired compound. Yield (using pyrazole purified by recrystallization in toluene): 63 % (9.4 g). Yield (using pyrazole purified by sublimation as reactant): 90 % (13.5 g).

^{1}H NMR (CDCl$_3$, 500 MHz) δ: 7.82 (s, 3H), 6.83 (s, 6H), 6.1 (s, 3H), 4.72 (*broad*, 1H), 2.26 (s, 9H), 1.91 (s, 18H).

^{11}B{^{1}H} NMR (CDCl$_3$, 160 MHz) δ: -1.49.

^{13}C{^{1}H} NMR (CDCl$_3$, 125 MHz) δ: 150.6, 137.6, 137.5, 136.0, 131.2, 128.1, 105.0, 21.3, 20.5.

Anal. Calcd. for C$_{36}$H$_{40}$BN$_6$Tl: C, 56.01; H, 5.22; N, 10.89. Found: C, 55.04; H, 5.15; N, 10.66.

Funding Information

Supporting Information

NO (this text will be deleted prior to publication)

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