

**FORMATION OF A SIXTEEN-MEMBERED RING BY CONDENSATION OF *N,N'*-DIMESITYL-PROPANE-1,3-DIAMINE WITH TRIETHYL ORTHOFORMATE AND AMMONIUM TETRAFLUOROBORATE**

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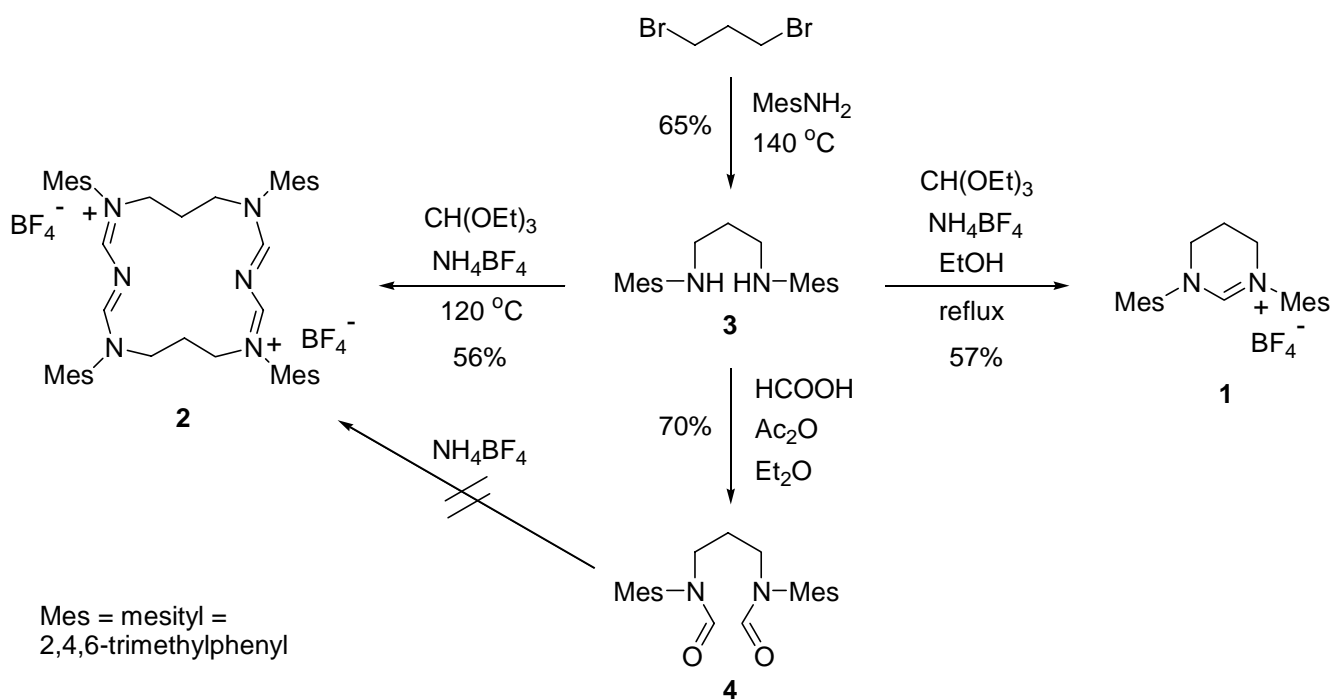
**Abstract** – Cyclocondensation of *N,N'*-dimesityl-propane-1,3-diamine with triethyl orthoformate and ammonium tetrafluoroborate gave as the major product macrocycle (**2**) under neat conditions and 1,3-dimesityl-3,4,5,6,-tetrahydropyrimidin-1-ium tetrafluoroborate with ethanol as the solvent. The structures of the two ring systems were confirmed by X-Ray diffraction analysis.

## INTRODUCTION

Bulky *N*-heterocyclic carbene ligands have had a major impact on the development of metal catalyzed transformations, particularly olefin metathesis and cross coupling reactions.<sup>1</sup> One of the most widely employed carbenes is 1,3-dimesitylimidazolidine-2-ylidene, which is obtained by deprotonation of commercially available 1,3-dimesityl-4,5-dihydroimidazol-1-ium tetrafluoroborate.<sup>2</sup> Very recently, the corresponding six-membered carbene, 1,3-dimesitylperhydropyrimidine-2-ylidene, was also prepared by deprotonation of 1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-1-ium tetrafluoroborate (**1**).<sup>3</sup> These cyclic amidinium tetrafluoroborates are usually prepared in one step by cyclocondensation of *N,N'*-dialkyl-alkane- $\alpha,\omega$ -diamines with triethyl orthoformate and ammonium tetrafluoroborate.<sup>4</sup> However, in the reported synthesis of **1** another three step procedure was employed using cyclization with formaldehyde followed by NBS oxidation and ion-exchange.<sup>3</sup> We were interested in cyclic amidinium salts in order to synthesize new olefin metathesis catalysts.<sup>5</sup> When we attempted to form **1** by the one step cyclocondensation method we obtained the sixteen-membered azacycle (**2**) as the major product (Scheme 1). This presents a new procedure for forming a large ring in good yield<sup>6,7</sup> and we decided to study the condensation reaction in further detail. Herein, we report optimized procedures for the preparation of **1** and **2**.

## RESULTS AND DISCUSSION

The starting material, *N,N'*-dimesityl-propane-1,3-diamine (**3**), was prepared by heating 1,3-dibromopropane with 4 equiv. of mesitylamine<sup>8</sup> (Scheme 1). In the first experiment, diamine (**3**) was treated at 120 °C with triethyl orthoformate and ammonium tetrafluoroborate in the absence of a solvent.<sup>4</sup> This resulted in a mixture of **1** and **2** in a 1:1 molar ratio together with some oligomeric material as determined from <sup>1</sup>H NMR spectroscopy. No other ring systems were observed in the condensation reaction. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of **1** and **2** were quite similar and the main difference was observed in the chemical shift and integration of the amidine protons. Eventually, the molecular composition and ring-size of both compounds were confirmed by MS spectrometry and X-Ray diffraction studies.



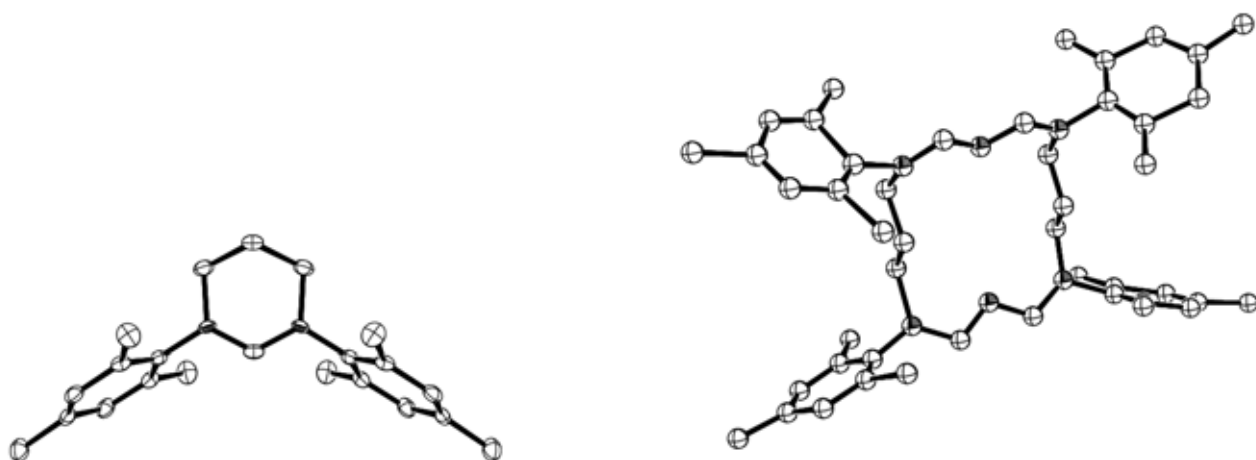
**Scheme 1**

It was soon discovered that the presence or absence of a solvent had a major influence on the distribution between **1** and **2**. Performing the reaction in the absence of a solvent favored the formation of **2** while diluting the mixture with a solvent benefited **1**. In fact, conducting the cyclocondensation under neat conditions at 120 °C in an open flask diminished the formation of the oligomeric material and **2** could now be isolated in 56% yield by crystallization from methanol (Scheme 1). Under these conditions the ethanol formed during the reaction evaporated from the mixture. This constitutes an unusually simple synthesis of a large ring without the use of high dilution or coordinating metals to direct the macrocyclization.

On the contrary, if ethanol was used as a solvent and the cyclocondensation performed at reflux, the ratio between **1** and **2** changed to 8:1. A slightly lower ratio was obtained with acetonitrile or ether as the solvent while acetic acid gave a complex mixture of products. Tetrafluoroborate (**1**) was isolated in 57% yield by direct crystallization from the experiment in ethanol (Scheme 1). Reaction in refluxing pyridine, on the other hand, yielded a mixture of **1** and some oligomers while none of **2** was formed under these conditions. After evaporation of the solvent and crystallization from ethanol tetrahydropyrimidine (**1**) was isolated in 54% yield from this experiment.

In an attempt to design an alternative synthetic route towards **2**, diamine (**3**) was formylated with a mixture of formic acid and acetic anhydride.<sup>9</sup> Bisformamide (**4**) crystallized in 70% yield from this reaction (Scheme 1). However, heating **4** with ammonium tetrafluoroborate and triethyl orthoformate only furnished a complex mixture of products while no reaction occurred in the absence of the orthoester. A complex mixture was also obtained when the formamides in **4** were first reacted with phosphorus oxychloride in dichloromethane and then subjected to the ammonium salt.<sup>10</sup> Hence, it did not seem feasible to convert **4** into **2** with ammonium tetrafluoroborate.

The structures of **1** and **2** were confirmed by single crystal X-Ray diffraction. Suitable crystals of **1** were obtained by crystallization from acetone. Good quality crystals of **2** were prepared by vapor diffusion of ether into a concentrated nitromethane solution of this compound. The X-Ray structures are shown in Figure 1.



**Figure 1.** X-Ray molecular structures of **1** and **2**

In conclusion, we have developed methods for cyclocondensation of *N,N'*-dimesityl-propane-1,3-diamine into the corresponding six- and sixteen-membered azacycles. In future cyclization reactions of propane-1,3-diamines care should be taken in order to distinguish these two ring systems from each other.

## EXPERIMENTAL

Thin-layer chromatography was performed on aluminum plates precoated with silica gel 60 and compounds were detected by UV light. NMR spectra were recorded on a Varian Mercury 300 spectrometer. Microanalyses and HRMS spectra were determined at the Department of Chemistry, University of Copenhagen.

***N,N'*-Dimesityl-propane-1,3-diamine (3).** A mixture of 1,3-dibromopropane (10 g, 49 mmol), mesitylamine (26.7 g, 197 mmol), and potassium iodide (45 mg, 0.27 mmol) was heated on an oil bath at 140 °C for 1 h. Cooled to rt to give a semisolid paste, which was suspended in 6 M aqueous NaOH (100 mL) and extracted with Et<sub>2</sub>O (2 × 100 mL). The combined organic phases were dried (NaOH) and concentrated. The resulting syrup was distilled to afford 10 g of **3** (65%), bp 190-205 °C/0.3mm. Crystallized on standing and could be further purified by recrystallization from EtOH (15 mL) to give 7.34 g (48%). *R<sub>f</sub>* 0.8 (EtOAc:hexane = 1:1). mp 43-43.5 °C. IR (KBr) 2912, 1483, 1434, 1231, 856 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.84 (s, 4H), 3.08 (t, *J* = 6.9 Hz, 4H), 2.82 (br s, 2H), 2.29 (s, 12H), 2.25 (s, 6H), 1.94 (quintet, *J* = 6.9 Hz, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 143.4, 131.0, 129.7, 47.5, 32.5, 20.8, 18.6. Anal. Calcd for C<sub>21</sub>H<sub>30</sub>N<sub>2</sub>: C, 81.24; H, 9.74; N, 9.02. Found: C, 80.78; H, 10.11; N, 9.09.

**1,3-Dimesityl-3,4,5,6-tetrahydropyrimidin-1-ium Tetrafluoroborate (1).** A suspension of diamine (**3**) (400 mg, 1.29 mmol), NH<sub>4</sub>BF<sub>4</sub> (135 mg, 1.29 mmol) and HC(OEt)<sub>3</sub> (0.429 mL, 2.58 mmol) in EtOH (5 mL) was heated to reflux under argon for 20 h, where after TLC revealed full conversion of the diamine. The mixture was cooled slowly to rt and white crystals precipitated. Cooled to 0 °C to complete the crystallization. Filtration gave 302 mg (57%) of **1**. IR (KBr) 1660, 1566, 1481, 1318, 1210, 1057 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.47 (s, 1H), 6.97 (s, 4H), 3.98 (t, *J* = 5.7 Hz, 4H), 2.58 (quintet, *J* = 5.7, 2H), 2.33 (s, 12H), 2.30 (s, 6H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 154.1, 140.7, 136.6, 134.5, 130.3, 46.6, 21.1, 19.5, 17.6. ESI HRMS Calcd for C<sub>22</sub>H<sub>29</sub>N<sub>2</sub> [M – BF<sub>4</sub>]<sup>+</sup> *m/z* 321.2331, found *m/z* 321.2354. Anal. Calcd for C<sub>22</sub>H<sub>29</sub>N<sub>2</sub>BF<sub>4</sub>: C, 64.72; H, 7.16; N, 6.86. Found: C, 64.57; H, 7.31; N, 6.79.

**1,5,9,13-Tetramesityl-3,5,11,13-tetraaza-1,9-diazoniacyclohexadeca-1,5,9,11-tetraene Bis-tetrafluoroborate (2).** Diamine (**3**) (0.5 g, 1.61 mmol), NH<sub>4</sub>BF<sub>4</sub> (185 mg, 1.76 mmol), and HC(OEt)<sub>3</sub> (1.25

mL, 7.5 mmol) were added to a 5 mL round-bottomed flask fitted with a magnetic stir bar. The flask was not sealed, but heated on an oil bath at 120 °C with a free flow of air above the flask to allow the EtOH formed to evaporate. After 30 min the product crystallized as a white powder with almost no liquid remaining. The product was dried in vacuo at 120 °C and recrystallized from MeOH (6 mL) to give 0.362 g (56%) of the macrocyclic salt (**2**). Further crystallization from the mother liquor resulted in mixtures of **1** and **2**. IR (KBr) 1611, 1562, 1333, 1224, 1083 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.34 (s, 4H), 6.94 (s, 8H), 4.08 (br s, 8H), 2.59-2.37 (m, 4H), 2.27 and 2.25 (two s, 36H). <sup>13</sup>C NMR (75 MHz, acetone-d<sub>6</sub>): δ 170.6, 140.6, 138.1, 135.2, 130.7, 50.9, 27.0, 20.9, 18.1. ESI HRMS Calcd for C<sub>46</sub>H<sub>60</sub>N<sub>6</sub>BF<sub>4</sub> [M – BF<sub>4</sub>]<sup>+</sup> *m/z* 783.4903, found *m/z* 783.4882; Calcd for C<sub>46</sub>H<sub>60</sub>N<sub>6</sub> [M – 2BF<sub>4</sub>]<sup>2+</sup> *m/z* 348.2434, found *m/z* 348.2422.

***N,N'*-Dimesityl-propane-1,3-diformamide (**4**)**. A solution of HCOOH (0.28 mL, 7.42 mmol) and Ac<sub>2</sub>O (0.74 mL, 7.84 mmol) was stirred at 60 °C for 90 min. The mixture was cooled in a water bath and diamine (**3**) (0.5 g, 1.61 mmol) was added in one portion resulting in a mild exothermic reaction. Cooled to rt followed by addition of Et<sub>2</sub>O (4 mL). The mixture was stirred for 15 h and then partitioned between Et<sub>2</sub>O and water. The organic phase was separated and washed with water, saturated aqueous NaHCO<sub>3</sub> solution, water, and brine. Dried over MgSO<sub>4</sub> and concentrated to give a white powder. Recrystallization from EtOAc (4 mL) yielded 0.415 g (70%) of **4**. *R<sub>f</sub>* 0.35 (EtOAc:hexane = 1:1). mp 146-147 °C. IR (KBr) 2924, 1672, 1657, 1485, 1362, 1295, 1113 cm<sup>-1</sup>. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.94 (s, 2H), 6.91 (s, 4H), 3.56 (t, *J* = 7.8 Hz, 4H), 2.29 (s, 6H), 2.11 (s, 12H), 1.81 (quintet, *J* = 7.8 Hz, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 163.6, 138.4, 136.5, 135.7, 129.8, 44.0, 26.7, 21.0, 18.3. Anal. Calcd for C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.07; H, 8.27; N, 7.55.

**X-Ray Crystallographic Analyses of **1** and **2****. The structures were solved by direct methods using SHELXS-97 and refined with SHELXL-97.

For **1**: All non hydrogen atoms were refined anisotropically. The fluorine atoms in the counterion were disordered and were split into six individual atoms with a total population of four. Crystals belong to the orthorhombic space group Pnma with *a* = 8.9957(15)Å, *b* = 15.504(2)Å, *c* = 15.024(3)Å. *V* = 2095.4(6)Å<sup>3</sup>. *Z* = 4, *d*<sub>calc</sub> = 1.294. Full-matrix least-squares refinement on *F*<sup>2</sup> led to final residuals *R*<sub>1</sub> = 0.0681 and *wR*<sub>2</sub> = 0.1368 for all 3024 reflections with *I* > 2σ(*I*).

For **2**: All non hydrogen atoms were refined isotropically and hydrogens were not included. The asymmetric unit contains six sixteen-membered rings and twelve tetrafluoroborates. The anions, however, are heavily disordered and not all could be located in the structure. Because of this, and the generally low intensity of the reflections the residuals are high. Crystals belong to the monoclinic space group Pn with *a* = 31.347(10)Å, *b* = 11.531(4)Å, *c* = 44.909(11)Å, β = 100.767(7). *V* = 15947.7Å<sup>3</sup>, *Z* = 12, *d*<sub>calc</sub> = 1.376.

Full-matrix least-squares refinement on  $F^2$  led to final residuals  $R1 = 0.1319$  and  $wR2 = 0.3761$  for all 25016 reflections with  $I > 2\sigma(I)$ .

## ACKNOWLEDGEMENT

We thank Professor Kurt Nielsen for his assistance with the X-Ray crystallographic studies and the Lundbeck Foundation for financial support.

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