

Honor's Cup Proposal

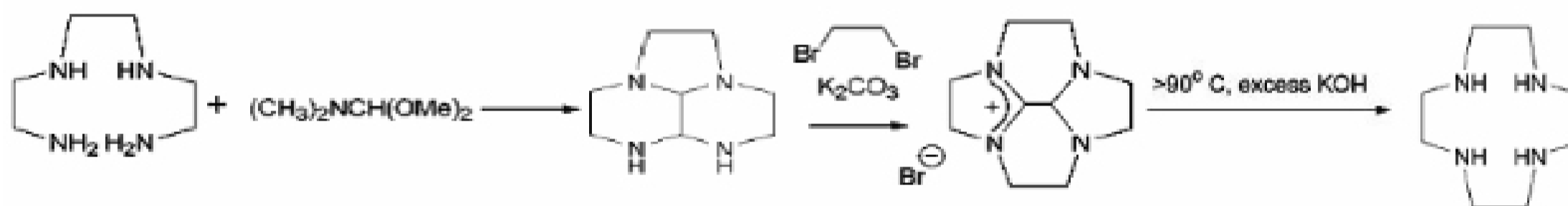
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Section: 270

Title: Synthesis of 1,4,7,10-Tetraazacyclododecane: Cyclen

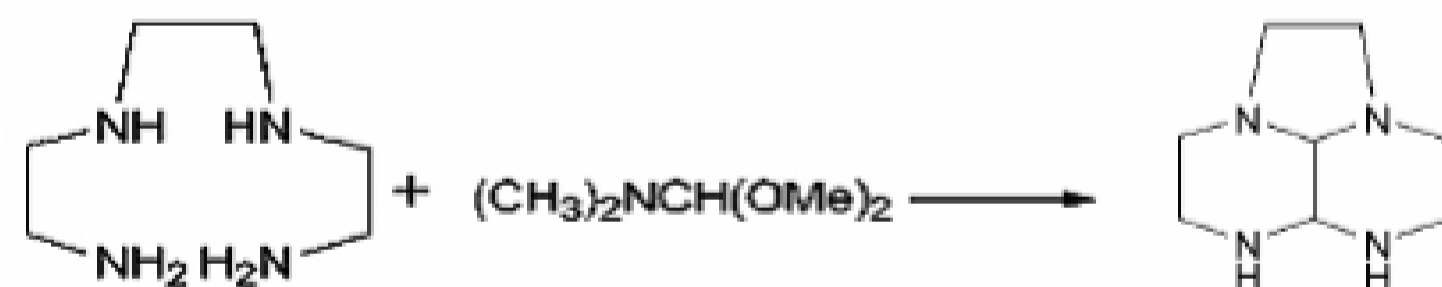
Introduction: The goal of this experiment is to produce 1,4,7,10-Tetraazacyclododecane using the starting materials triethylenetetramine, a liquid commonly used for epoxy curing agents, and *N,N*-Dimethylformamide dimethyl acetal, which is used in this experiment to form carbon-carbon bonds. Making this molecule is a topic of interest because it is quickly becoming a necessary intermediate for the synthesis of many different medicinal agents.

Overall Synthetic Reaction Scheme:



Steps:

Step 1:



Experimental:

First use a drying agent such as anhydrous $MgSO_4$ on excess TETA (5g or more) followed by a gravity filtration. To a stirred solution of linear TETA (2.884g, 0.0196 mol) was added *N,N*-dimethylformamide dimethyl acetal (5g, .039 mol). The solution was refluxed for 30 min. The reaction mixture was dried in vacuo. The resulting off-white solid was recrystallized from THF. The resulting white solid was filtered under a blanket of nitrogen and isolated in 85% yield (2.45g).

Note: The amounts that were used within the article for this step were divided by 34.674 in order to get the starting materials on a scale that involved neither of the beginning reagents being above 5g. Another alteration was the first step to dry the TETA, which is added in order to make more pure TETA. It is too expensive to buy the better grade of TETA so it is more practical to just remove the water using a drying agent instead.

Warnings (safety and environmental):

TETA: health hazard rating of 3, flammability of 1, and reactivity of 0. If it is combusted it can potentially release carbon monoxide, carbon dioxide, and nitrogen oxides into the air, but we do not plan to combust this material.

N,N-dimethylformamide dimethyl acetal: Highly flammable. Harmful by inhalation. Irritating to eyes and skin.

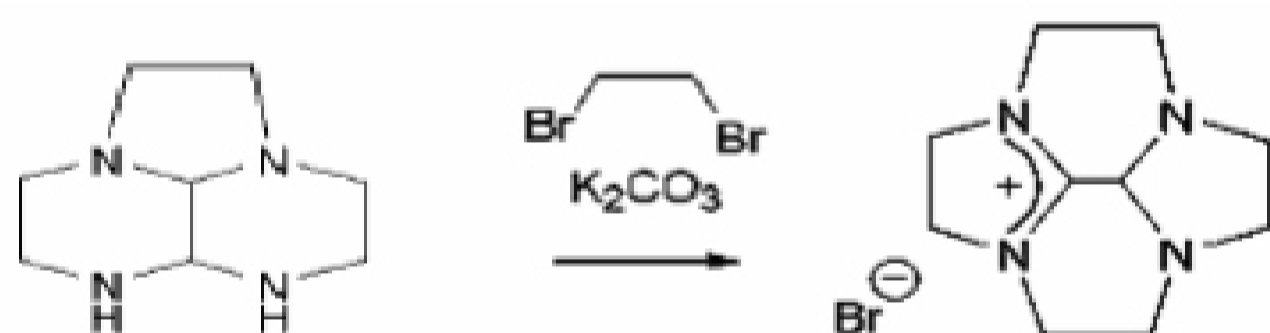
References:

Argese, M.; Brocchetta, M.; De Miranda, M.; Paoli, P.; Perego, F.; Rossi, P. *Tetrahedron* **2006**, *62*, 6855-6861.

Athey, P. S.; Kiefer, G. E. *J. Org. Chem.* **2002**, *67*, 4081-4085.

Chuburu, F.; Handel, H.; Le Baccon, M.; Tripiet, R. *Eur. J. Org. Chem.* **2003**, 1050-1055.

Step 2:



Experimental: A 500mL three-neck round-bottom flask equipped with a stirrer, a condenser, and a nitrogen inlet was charged within 69.2 mL of acetonitrile, the previously made product (2.45 g, 0.0147 mol), 1,2-dibromoethane (3.87 g, 0.0206 mol), and K₂CO₃ (1.53 g, 0.0113 mol). The mixture was heated to reflux while being stirred. After 3h at reflux, the K₂CO₃ was filtered and the filtrate was dried in vacuo. Typically, the salt was taken up in water without purification and carried on to the hydrolysis step. However, the pure salt form may be isolated by rinsing the crude solid with a minimal amount of cold acetonitrile, followed by filtration under nitrogen, which yielded a pale yellow solid weighing 1.73g for a yield of 70%.

Note: The amounts that were used within the article for this step were altered to use the entire previously made product at the start of this step. The paper used 58.8% of its first product in this step. The scalar of 34.674 was also carried through to this step.

Warnings (safety and environmental):

1,2-Dibromoethane: Can cause cancer - Group II (very hazardous), may cause harm to the unborn child, toxic by inhalation, in contact with skin, and if swallowed. Irritating to eyes, respiratory system and skin. May cause long-term adverse effects in the aquatic environment. If it is combusted it can potentially release carbon monoxide, carbon dioxide, and hydrogen bromide into the air, but we do not plan to combust this material.

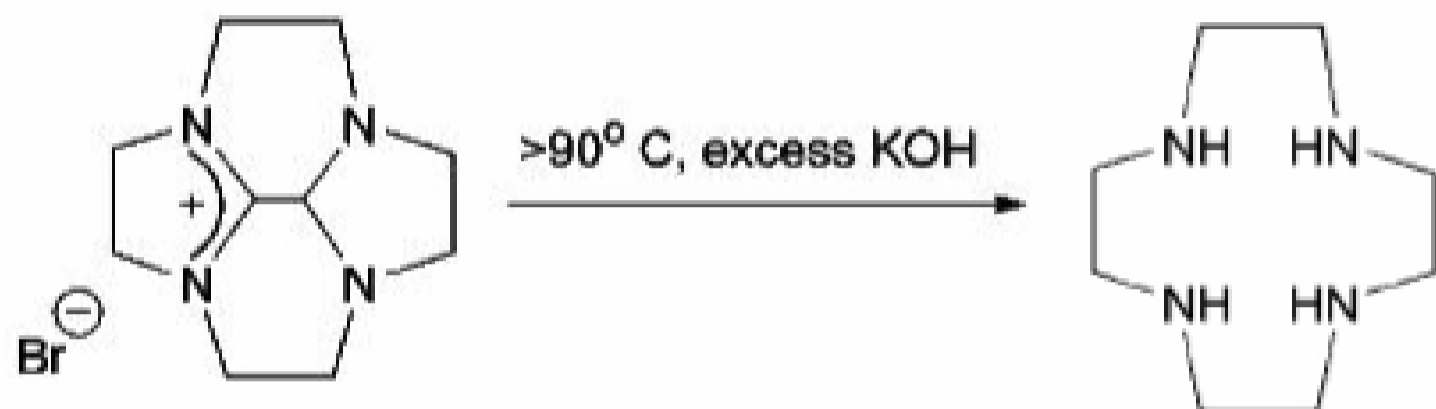
Anhydrous Potassium Carbonate: May seriously irritate respiratory system and eyes. Skin irritant.

References:

Athey, P. S.; Kiefer, G. E. *J. Org. Chem.* **2002**, *67*, 4081-4085.

Ramasubbu, A.; Wainwright, K. P.; *J. Chem. Soc., Chem. Commun.* **1982**, 277-278.

Step 3:



Experimental: The cyclized intermediate from the previous step (1.73g) was dissolved in water to give a total volume of 6.88 mL and added dropwise to a refluxing solution of 6.12mL of caustic (8 equiv, 1.97g). The caustic solution was heated for an additional 30 min after the addition of the previously made product. The aqueous caustic solution was gravity filtered while hot. The filtrate was then concentrated (in vacuo) until crystalline of cyclen was observed in the solution. After the mixture had cooled to ambient temperature, cyclen was filtered and the precipitation process was repeated until no further crystallization occurred. The final aqueous filtrate was dried in vacuo, and the remaining cyclen was removed by extractions of the solid residue with hot toluene. The overall yield of cyclen was 88% (1.522g).

Note: The amount made of the cyclized intermediate from the previous step was carried through to this step and ratios were applied to scale the original experimental to our smaller experiment size

Warning (safety and environmental):

Potassium Hydroxide: health hazard rating of 3, flammability of 0, and reactivity of 0.

References:

Argese, M.; Brocchetta, M.; De Miranda, M.; Paoli, P.; Perego, F.; Rossi, P. *Tetrahedron* **2006**, *62*, 6855-6861.

Athey, P. S.; Kiefer, G. E. *J. Org. Chem.* **2002**, *67*, 4081-4085.

Ramasubbu, A.; Wainwright, K. P.; *J. Chem. Soc., Chem. Commun.* **1982**, 277-278.

Costs:

70% technical grade triethylenetetramine: \$.08/g

95% purum *N,N*-Dimethylformamide dimethyl acetal: \$1.08/g

1,2-dibromoethane: \$.02/g

potassium hydroxide: \$.02/g

Anhydrous Potassium Carbonate: \$.06/g