

SYNTHESIS OF DIAZA-CROWN ETHERS ON SOLID SUPPORTS

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ABSTRACT. Diamines and diiodides derived from diethylene glycol or triethylene glycol are condensed on alumina coated with alkali fluorides in acetonitrile to form diaza-crown ethers in good yield. Comparison of the yields suggests that the contribution of the template effect, if any, is small, and the data reflect rather increasing basicity of the solid supports in passing from LiF to KF on alumina.

1. INTRODUCTION

Introduction of nitrogen atoms into macrocyclic structures is often associated with their protection and deprotection. Standard synthetic procedures for the preparation of diaza-crown ethers consist of the condensation of oligoethylene glycol bistosylates with respective diamines as their *p*-toluenesulphonyl [1] or ethoxycarbonyl [2] derivatives. So far, one example of alkali cation-promoted cyclization involving unprotected diamines has been published [3]. Comprehensive review concerning the synthesis of nitrogen-containing macrocycles has been reported by Gokel and co-workers [4].

Japanese chemists have demonstrated the utility of alumina coated with potassium fluoride as an efficient solid support in the synthesis of "all-oxygen" crown ethers [5]. Recently, we found this method useful in the preparation of diaza-crown ethers incorporating carbohydrates [6] and this observation inspired us to more systematic search in this direction.

2. MATERIALS AND METHODS

Neutral alumina /Merck 90, II-III grade of activity/ was

coated with LiF, NaF, and KF of analytical grade according to the method described by Japanese chemists [7]. *N,N'*-Dimethyl 1,5-diamino-3-oxa-pentane 1 was prepared from diglycolic acid via respective bisamide followed by reduction with lithium aluminum hydride in THF. Reduction of the *N,N'*-bisethoxycarbonyl-1,8-diamino-3,6-dioxaoctane with lithium aluminum hydride afforded *N,N'*-dimethyl 1,8-diamino-3,6-dioxaoctane 2. Diiodides 3 and 4 were obtained from the corresponding dichlorides [3]. All the solvents were of analytical grade.

Equimolar amounts of the diamine and diiodide were dissolved in acetonitrile and stirred for 72 h with five equivalents /calculated for alkali metal fluoride/ of the solid support /Figure 1/. The solution was filtered off, evaporated, and the residue was distilled in vacuum.

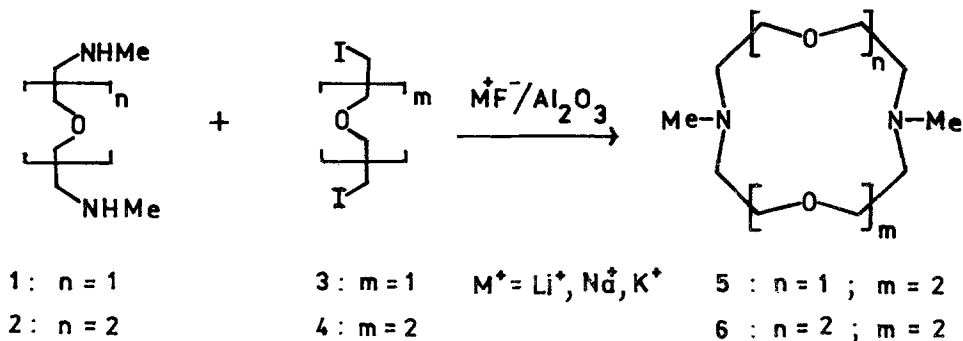


Figure 1. Condensation of diamines with diiodides leading to diaza-crown ethers.

All the reactions were monitored by TLC on alumina and the products were compared with authentic samples of [15]-N₂O₃ /5/ and [18]-N₂O₄ /6/.

3. RESULTS AND DISCUSSION

Combination of 1 and 3 provided exclusively the morpholinium quaternary salt instead of the desired diaza-12-crown-4. In all remaining cases, *N,N'*-dimethyl diaza-crown ethers were formed in good yield, although the yields depended on the metal fluoride used, as indicated in the Table.

The yield for 5 and 6 increases in passing from LiF to KF. This fact can be associated with increasing basicity of the solid supports not with an appreciable template effect for which the maximum yield should be observed when NaF on alumina was employed. Potassium fluoride on alumina turned out to be the most efficient in the synthesis of

TABLE: yields of diaza-crown ethers /%/

solid support	<u>5</u>	<u>6</u>
LiF/alumina	32	23
NaF/alumina	30	29
KF/alumina	48	55

diaza-crown ethers.

Easy work-up and good yield makes this method attractive for the synthesis of simple diaza-crown ethers.

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