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# Convenient Method for Preparation of Aza-Crown Ethers

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**Abstract:** A convenient method for the preparation of peraza crown ethers in a one-pot synthesis in the presence of  $KF/Al_2O_3$  is presented.

Keywords: Aza-crown compounds, cyclization reactions, solid-supported reagent

Macrocyclic ligands containing heteroatoms are complexing agents for ionic and neutral molecules. The aza-crown macrocycles play an important role in this field, as demonstrated by the fact that half of all synthetic macrocycles belong to this class. The special interest in the crown ether class is explained by a much stronger association of the nitrogen atoms as compared to the oxygen ones, due to a less electronegative force of nitrogen, which implies more availability of the electronic pair for complexation.

The peraza-crown macrocycles are the largest group of crown-ether compounds and provide binding sites for transition-metal and other heavymetal ions. These compounds can be obtained by two general methods, namely ring closure to form a bis Schiff base or ring closure to form carbon-nitrogen single bonds.<sup>[1]</sup> The reaction of a sulfonamide with a dihalide or a ditosilate ester belonging to the second method of general

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synthetic procedures is one of the most attractive ways to obtain this type of crown ether. This method allows the preparation of peraza-crowns of different sizes and number of nitrogen atoms.<sup>[2]</sup>

The Richman–Atkins process<sup>[2f,2g]</sup> has been used to prepare a large variety of peraza-crowns. The first step of this reaction consists in the preparation of bissulfonamide sodium salt under an inert atmosphere, followed by cyclization of this salt with sulfonate ester (especially ditosylate ester) leaving groups in a dipolar aprotic solvent (DMF), obviating the high-dilution technique of the Stetter and Ross procedure.<sup>[2a]</sup>

We tried to obtain the afore mentioned compounds in a one-pot synthesis, avoiding the preparation of bissulfonamide sodium salt under inert atmosphere. With that purpose in view, we achieved the reaction between bissulfonamide and ditosylate in the presence of the solid-supported reagent  $KF/Al_2O_3$  by taking advantage of its strongly basic nature,<sup>[3]</sup> according to Scheme 1.

The results of our experiments are shown in Table 1. A few solvents were tested (ethanol, a mixture of acetonitrile-THF, acetonitrile). The best yields were obtained in acetonitrile.



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Scheme 1.

Compound		Melting points (°C)		Desmustallization
	Yield (%)	Found	Lit.	solvent
1 2 3 4 5 6 7	75 70 57 80 61 62 50	222 208 210 234 296 204	$\begin{array}{c} 222 - 223^{[2g]} \\ 206^{[5]} \\ - \\ 234 - 236^{[2g]} \\ 294^{[4]} \\ 201^{[6]} \\ 183 - 184^{[2g]} \end{array}$	Ethanol Chloroform Ethanol Ethanol + chloroform Toluene Ethanol Ethanol

Table 1. Peraza-crown ethers obtained in the presence of the solid-supported reagent  $KF/Al_2O_3$ 

In conclusion,

- We succeeded in obtaining peraza crown ethers in a one-pot synthesis with good yields;
- The preparation of bissulfonamide sodium salts was eliminated and so the running of the reaction under an inert atmosphere as required by the Richman procedure was avoided; and
- Our method seems to be applicable to small- and medium-sized perazacrown ethers. The use of the solid-supported reagent KF/Al<sub>2</sub>O<sub>3</sub> in the case of peraza-crown ethers preparation is more advantageous than the synthesis of crown ethers from polyethylene glycol and polyethylene glycol ditosylates.<sup>[7]</sup>

# **EXPERIMENTAL**

## Materials

The melting points are uncorrected. The KF and basic  $Al_2O_3$  were obtained from Merck. Solvents were used as purchased. The RMN spectra were recorded on a Varian Gemini 300 spectrometer in CD<sub>3</sub>OD with tetramethylsilane as an internal reference. The K<sub>2</sub>O/Al<sub>2</sub>O<sub>3</sub> solid-supported reagent was prepared according to literature data.<sup>[8]</sup> The ditosyl derivatives of 1,2-ethyl and 1,3-propyl diol were prepared according to the literature data.<sup>[9]</sup> The tosylation of diethyltriamine and tetraethylpentaamine was achieved by using the method of Koyama and Yoshino.<sup>[10]</sup> The tosylation of amino diols were performed using the method of Bazzicalupi and coworkers.<sup>[11]</sup> N,N'-(Methyliminodiethylene)bisphthalimide was obtained by the procedure indicated by Searle and coworkers.<sup>[12]</sup>

# **Typical Procedure**

The N-tosyl polyamine (0.5 mmol), corresponding tosyl-diol or tosyl amino diol (0.5 mmol), and  $KF/Al_2O_3$  solid-supported reagent (2.5 g) were added to acetonitrile (20 mL), and the mixture was stirred and refluxed for 24 h. Then the reaction mixture was cooled, filtered from the solid support, and recrystallized from the suitable solvent (see Table 1).

**4-Methyl-1,7-ditosyl-1,4,7-triazacyclodecane** (3). Anal. calcd. for  $C_{22}H_{31}O_4N_3S_2$ : C, 56.96; H 6.71; N, 9.02 (456.6). Found: C, 57.10; H, 6.80; N, 9.20. H<sup>1</sup>NMR (300 MHz, CD<sub>3</sub>OD):  $\delta = 1.53$  (quintet, 2H), 2.27 (s, 3H N-Me), 2.35 (s, 6H, Me), 2.16 (t, 4H), 3.26 (t, overlap, 4H), 3.48 (t, overlap, 4H), 7.34 (d, 4H), 7.81 (d, 4H). <sup>13</sup>C NMR (300 MHz, CD<sub>3</sub>OD):  $\delta = 24.3$ , 26.8, 42.5, 43.1, 44.8, 54.4, 127.2, 129.4, 141.6, 146.7.

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