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Rapid and High Yield Detosylation of Linear and Macrocyclic p-Toluenesulfonamides

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RAPID AND HIGH YIELD DETOSYLATION OF LINEAR AND MACROCYCLIC p-TOLUENESULFONAMIDES

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Abstract: Rapid and high yield detosylation of linear and macrocyclic p-toluenesulfonamides were achieved by heating their approximately 50 % concentrated sulfuric acid solution at 170-180 °C for 5-8 min.

Macrocyclic p-toluenesulfonamides are the products of the ring closure step of the synthesis of polyazamacrocycles. Their detosylation can be achieved by several methods including electrochemical reduction[1], reduction with either sodium amalgam in buffered methanol[2-5] or lithium aluminium hydride[6-8], hydrolysis with HBr either in the presence[5,9-11] or absence[4,12] of phenol, but the simplest and most common procedure is heating these sulfonamides in approximately 10 % cc. sulfuric acid solutions at 100-110 °C for 1-3 days[5,13-15]. These conditions were inappropriate for **2a** and **4a** resulting in their partial or complete decomposition.

Results and discussion

After an accidental overheating of a sample of **4a** in cc. sulfuric acid at approx. 160 °C for 30 min, we observed complete detosylation. We found that, in contrast to earlier observations, at a temperature higher than approx.

140 °C splitting of the ether bond in macrocycle **2a** is significantly slower than detosylation of the nitrogens.

Equation 1

Detosylation of cyclic and open-chained p-toluene-sulfonamides. Conditions: cc H_2SO_4, 180 °C, 5-8 min.

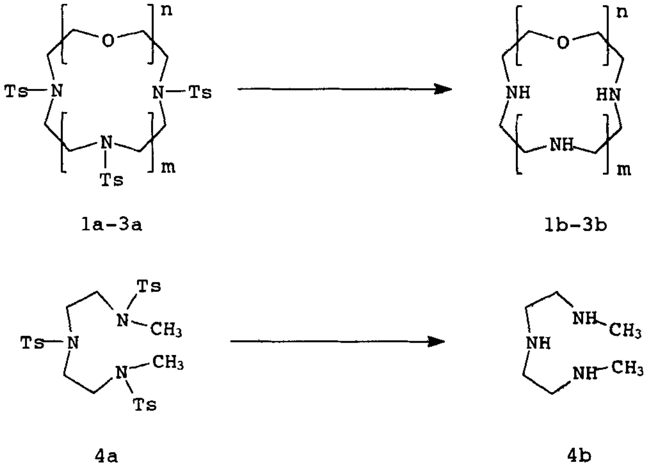

Table 1.

Composition and yields of compounds 1b-4b

Compound	m	n	Yield %[19]
1b	1	0	92
2b	1	1	52
3b	2	0	90
4b	n.a.	n.a.	90

Based upon this observation we developed an improved procedure that enables rapid and high-yield detosylation of p-toluene-sulfonamides of both polyaza and oxapolyaza type (**1a-4a**). It results in more cost-efficient production, significantly less toxic waste and environmental hazard. In continous mode, it can easily be scaled up to production.

Experimental

All chemicals were of reagent grade and used without further purification. p-Toluenesulfonamides were prepared according to standard procedures[14], the products were identical with authentic samples. Their purity was determined by ^{1}H NMR and thin layer chromatography.

Detosylation of 1,4,7-tritosyl-1,4,7-triazacyclononane (1a). A typical procedure. *Method A*

42.53 g of **1a** was dissolved *completely*[16] in 45 mL of concenctrated sulfuric acid at 60 °C and the clear solution was stirred and heated to 180 °C in 8 minutes. The resulting dark brown solution was allowed to cool below 80 °C on standing then cooled into ice. To this was added ether (500 ml) under very vigorous stirring. After addition the precipitate was decanted and washed thoroughly with ether (3x100 mL), re-dispersed into ether, filtered off and dried *in vacuo*[17]. Hot aqueous solution (20 mL) of this solid was filtered through a 0.45 micron membrane filter disc. The clear filtrate was brought to boiling and cc. hydrochloric acid (22 mL) was added dropwise. The hot solution was let to stand at room temperature overnight. Next day the crystalls were filtered off, washed with cold cc. hydrochloric acid (-10 °C, 8 mL), abs. ethanol (3x20 mL) and ether (2x30 mL) and dried to constant weight. The product **1b.3HCl** is a non-hygroscopic white solid (15.95 g, 92%, 98+% purity).

Method B: Continous mode

A 50% cc. sulfuric acid solution of **1a** was passed through a coiled glass tubular reactor immersed into a hot cc. sulfuric acid bath (Figure 1)[18]. The

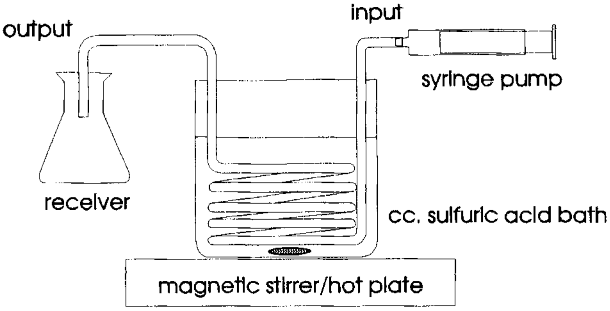

Figure 1.
Coiled glass tubular reactor for continous detosylation

outgoing hot reaction mixture is collected into a reciever flask immersed into cold sulfuric acid. The work-up procedure was identical with Method A.

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16 No solid residue is allowed in the solution.

17 This polyhydrosulfate is very hygroscopic.

18 Reactor inner diam.: 4 mm, effective volume: 15 ml, addition rate: approx. 2.5 mL/min. After addition the reactor was rinsed with cc. sulfuric acid (4 mL) and then purged with dry nitrogen gas.

19 Isolated yields, as perhydrochlorides.

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