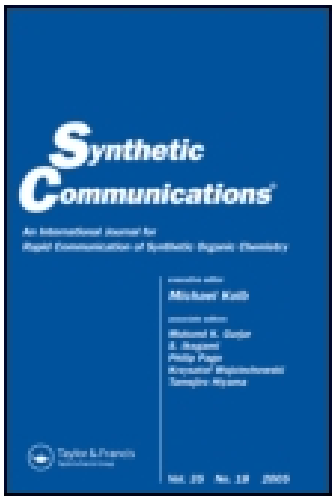


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

CONVENIENT SYNTHESIS OF MONO- AND DITOSYLATED 1,4,7-TRIAZACYCLONONANE

István Lázár [a] & Zsuzsanna Takács [a]
[a] Faculty of Natural Sciences, Department of Inorganic and Analytical Chemistry , Debrecen University , Debrecen-10, Pf. 21, 4010, Hungary
Published online: 16 Aug 2006.

To cite this article: István Lázár & Zsuzsanna Takács (2001) CONVENIENT SYNTHESIS OF MONO- AND DITOSYLATED 1,4,7-TRIAZACYCLONONANE, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:20, 3141-3144, DOI: 10.1081/SCC-100105889

To link to this article: http://dx.doi.org/10.1081/SCC-100105889

SYNTHETIC COMMUNICATIONS, 31(20), 3141–3144 (2001)

CONVENIENT SYNTHESIS OF MONO- AND DITOSYLATED 1,4,7-TRIAZACYCLONONANE

István Lázár* and Zsuzsanna Takács

Debrecen University, Faculty of Natural Sciences,
Department of Inorganic and Analytical Chemistry,
Debrecen-10, Pf. 21, 4010 Hungary

ABSTRACT

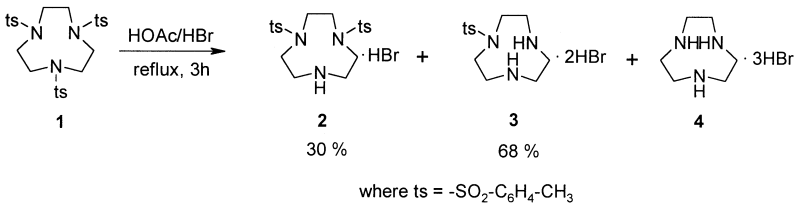
Mono- and ditosylated 1,4,7-triazacyclononane (**2**, **3**) were synthesized by rapid partial deprotection of 1,4,7-tritosyl-1,4,7-triazacyclononane (**1**) in vigorously stirred refluxing acetic acid–hydrobromic acid mixture.

Recently it has been discovered that a partially tosylated polyaza-macrocycle, 1-benzyl-4,7,10-tritosyl-1,4,7,10-tetraazacyclododecane, showed cytotoxic activity against human leukemic cells.[1] Our interest in detosylation of macrocyclic *p*-toluenesulfonamides[2] led us to the development of a simple method for the synthesis of partially tosylated triaza macrocycles, which can serve as starting materials for future developments and as new candidates for anticancer research. Regioselectively tosylated polyaza-macrocycles were prepared so far from free macrocyclic polyamines,[3] which, in turn,

*Corresponding author. E-mail: lazar@tigris.klte.hu

were synthesized from their pertosylated derivatives. Several methods have been developed[3–5] for detosylations, one of them is a simple but time-consuming hydrolysis with HBr/HOAc[6] mixture.

Our study of this process (see Scheme) revealed that the low solubility of **1** in HBr/HOAc mixture, its strong tendency to form a foam when boiling and poor efficiency of the magnetic stirbars all together resulted in too short contact time of **1** with the acid mixture, consequently it led to prolonged reaction times. We have found it possible to virtually stop the reaction sequence mostly at the monoprotected stage based upon the somewhat increased hydrolytic stability of **3** in the reaction mixture. Technically the crucial point for rapid partial detosylation was to provide high intensity stirring at the top of the reaction mixture for which an apparatus shown on Figure 1 was used. This process was found to be fairly advantageous not only for its rapidity and simplicity but also because it provided the target compounds **2** and **3** directly from **1** in one step, significantly cut the necessary amount of fine chemicals and reduced the volume of toxic waste.



Scheme. Partial detosylation of **1** to a mixture of **2** and **3**. (Isolated yields are given). The amount of **4** has been found negligible.

19.1 g (32.3 mmol) of **1**[7] was placed into a heart shaped three necked flask of 1–1.5 dm^3 volume and 256 cm^3 hydrobromic acid (48%) and 144 cm^3 glacial acetic acid was added. The mixture was brought to and kept in boiling under vigorous stirring untill dissolvation of **1**. This usually required 2–3 hours of time. Since longer reflux time favoured formation of **4** it was avoided.

The reaction mixture was cooled down, filtered if necessary and then evaporated on a rotary evaporator to dryness. The residue was taken up with 250 ml of water and let to stand overnight in ice. The precipitate was filtered off, washed twice with water and dried. This white solid proved to be pure **2**·HBr (4.98 g, 9.60 mmol, 30%). The filtrate was evaporated to dryness, the residue was taken up with absolute ethanol, filtered off, washed with ethanol and ether and dried to constant weight yielding

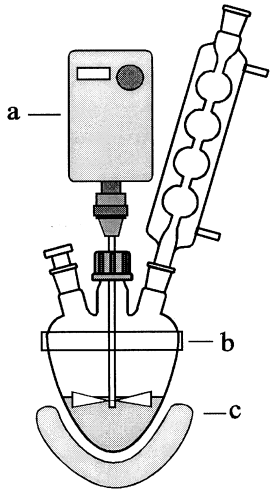


Figure 1. Apparatus for partial detosylation of **1**. (a) variable speed stirring motor, (b) flexible electric heating tape (optional), (c) variable temperature electric heating mantle.

3·2HBr (9.63 g, 21.6 mmol, 68%) as a beige solid. Free bases **2** and **3** were liberated from **2**·HBr and **3**·2HBr, respectively, by a strong base and extracted into chloroform from which the products were received after evaporation of the solvent as waxy white solids. Both **2** and **3** gave satisfactory elemental analysis and ^{1}H and ^{13}C NMR spectra.

ACKNOWLEDGMENT

Financial support from the Hungarian National Research Foundation (OTKA T-023810) and Bolyai Scholarship (BO/00452/99) is gratefully acknowledged.

REFERENCES

1. Hall, I.H.; Elkins, A.L.; Karthikeyan, S.; Spielvogel, B.F. Anticancer Research **1997**, *17*, 1195, Chem. Abstr. Vol. *127*, 377u.
2. Lazar, I. Synth. Commun. **1995**, *25*, 3181.

3. Helps, I.M.; Parker, D.; Chapman, J.; Ferguson, G. J. Chem. Soc. Chem. Commun. **1988**, 1094.
4. Searles, S.; Nukina, S. Chem. Rev. **1960**, 1077.
5. Hosseini, M.W.; Lehn, J.M. J. Amer. Chem. Soc. **1982**, *104*, 3525.
6. Martin, L.Y.; Sperati, C.R.; Busch, D.H. J. Amer. Chem. Soc. **1977**, *99*, 2968.
7. Richman, J.E.; Atkins, T.J. J. Amer. Chem. Soc. **1974**, *96*, 2268.

Received in the Netherlands December 20, 2000

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016