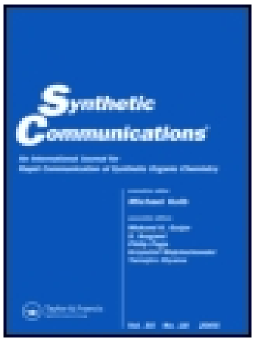

Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

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To cite this article: Vladimir S. Talanov & Richard A. Bartsch (1999) Improved Preparation of 24-Crown-8, Synthetic Communications, 29:20, 3555-3560, DOI: 10.1080/00397919908085989

To link to this article: http://dx.doi.org/10.1080/00397919908085989

SYNTHETIC COMMUNICATIONS, 29(20), 3555–3560 (1999)

IMPROVED PREPARATION OF 24-CROWN-8

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Abstract: An improved method for the preparation of 24-crown-8 is described. Cyclization at room temperature and purification of the crude product via an acetonitrile complex provides a much higher yield than those reported in the literature.

Because of their unique cation complexation properties, macrocyclic polyethers (crown ethers) find applications in many different scientific areas.[1] The preparation of crown ether compounds has attracted the attention of many synthetic organic chemists and a numerous preparative methods have been developed. Although a variety of crown ethers are now produced commercially or are available by straightforward synthetic routes, the preparation of the large-ring crown ether 24-crown-8 (1,4,7,10,13,16,19,22-octaoxacyclotetracosane) has remained problematic. Despite such synthetic difficulties, applications of 24-crown-8 as a diazonium salt stabilizer,[2,3] a complexing agent,[4,5] an extractant for radium ions[6] and other metal

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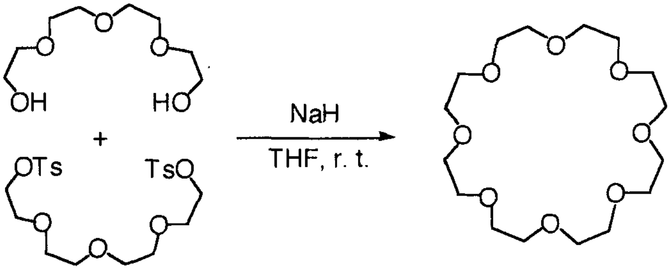
ions,[7] and a phase transfer catalyst,[4,8] as well as in inclusion gas chromatography,[9] have been reported. Also, its cavity size and that of the dibenzo analog, dibenzo-24-crown-8, are appropriate for pseudo-rotaxane formation.[10] An effective synthetic route to 24-crown-8 should facilitate the further development of these and other applications. Herein, we present an improved method for the preparation of 24-crown-8.

Reported methods for the synthesis of 24-crown-8 are characterized by low yields, cumbersome purification methods or sophisticated reactants. Reaction of tetraethylene glycol (TEG) with tosyl chloride and potassium hydroxide in dioxane at 65 °C gave a 23% gas chromatographic yield of 24-crown-8 in the product mixture.[11] Continuous extraction and partition chromatography gave an unspecified amount of the pure compound. When octaethylene glycol was reacted with tosyl chloride and potassium hydroxide in dioxane at 75 °C, Kugelrohr distillation of the crude product followed by further purification gave a 28% yield of 97% pure 24-crown-8.[12] Reaction of TEG with tetraethylene glycol ditosylate (TEGDT) in THF with potassium hydroxide as the base followed by an unspecified workup procedure gave a 7% yield of the crown ether.[7] Reaction of TEG and TEGDT with sodium hydride as the base in THF at reflux gave a crude product which was purified by column chromatography followed by Kugelrohr distillation to provide an 8% yield of 24-crown-8.[3]

When we performed the cyclization of TEG and TEGDT with sodium hydride in THF at 50 °C, considerable amounts of elimination side products were evident ($OCH{=}CH_2$ groups were identified by ^1H NMR spectroscopy in the crude product). By conducting the cyclization at room temperature (22-24 °C) for a longer time period, the competing elimination reaction was reduced substantially. Also, a lower reaction temperature should favor formation of the desired 24-crown-

8 compound over 48-crown-16, the 2+2 cyclization product.[13] After cyclization of TEG and TEGDT with sodium hydride in THF at room temperature, the NMR spectrum of the crude product mixture indicated a 55% yield of the desired 24-crown-8.



In the reported methods for 24-crown-8 synthesis, difficulties in purification of the crude product have led to substantial product losses. We have found that 24-crown-8 forms a solid complex with acetonitrile[14] which precipitates when an acetonitrile solution of the crown ether is cooled in a freezer. For the purification of 18-crown-6, formation of an acetonitrile complex is the preferred method.[15] Purification of 21-crown-7 by formation of acetonitrile[16] or nitromethane[12] complexes has also been reported. To the best of our knowledge, the use of an acetonitrile complex in the purification of 24-crown-8 has not been reported previously. It is interesting to note that we did not observe any precipitate formation under the same conditions for the larger ring-size crown ethers of 27-crown-9 and 30-crown-10.

Rapid filtration of the low-melting acetonitrile complex followed by its decomposition at 40-50 °C *in vacuo* provided a 39% yield of pure 24-crown-8. (To obtain a similar quality of 24-crown-8 from the crude product mixture, repeated column chromatography would have been required with a consequent reduction in yield.)

Thus a combination of room temperature cyclization to reduce the formation of side products and purification of the crude product by an acetonitrile complex allowed us to prepare pure 24-crown-8 in a yield which substantially surpasses those reported in the literature.

Experimental

THF was freshly distilled from sodium in the presence of benzophenone. Acetonitrile was dried over 4 Å molecular sieves. TEG was distilled *in vacuo*. TEGDT was obtained in 98% yield by the literature procedure[17] with improvements.[13] The ^1H and ^{13}C NMR spectra were measured with an IBM AF-200 spectrometer at 200.133 and 50.324 MHz, respectively.

24-Crown-8. To a magnetically stirred suspension of NaH (1.86 g, 77.5 mmol, washed with dry hexanes to remove the protecting mineral oil) in a 100 mL of dry THF in three-necked, 500-mL Morton flask under nitrogen at room temperature (22-24 °C), a solution of TEG (4.66 g, 24.0 mmol) and TEGDT (12.05 g, 24.0 mmol) in 380 mL of dry THF was added at a rate of 20 mL/h. After the addition was completed, the mixture was stirred at room temperature for 96 h. The unreacted sodium hydride was destroyed by careful addition of water (1 mL). Celite (5 g) was added and the mixture was filtered. The filtered solids were washed repeatedly with dichloromethane. The combined filtrate and washings were evaporated *in vacuo* and the residue was extracted with hot hexanes (2 X 150 mL). The combined extracts were evaporated and the resulting liquid was dissolved in acetonitrile. The solution was filtered, concentrated to a volume of 15 mL by evaporation *in vacuo* and placed in a freezer at -20 °C for 4 h. Crystals of the resultant acetonitrile complex which formed were filtered quickly, washed with cold acetonitrile and dried under oil pump vacuum at 40-50 °C to provide 2.50 g of 24-crown-8 ether as a colorless liquid. From the filtrate, another portion (0.77 g) of the desired compound was isolated similarly to give a total of 3.27 g (39 %) of 24-crown-8. ^{1}H NMR δ: (in $CDCl_3$) 3.683 (s); (in acetone-d_6) 3.595 (s). ^{13}C NMR ($CDCl_3$) δ: 70.71. IR (film): 1115 (C-O) cm^{-1}.

Acknowledgment

This research was supported by Robert A. Welch Foundation grant D-0775 to RAB.

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(Received in the USA 18 March 1999)