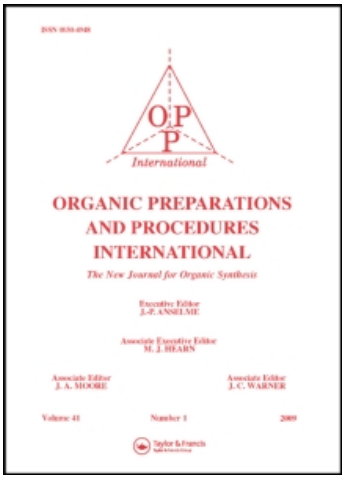


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS OF *N*- (4-AMINOPHENYL) MONOAZACROWN ETHERS

Wei Zeng[a]; Ying Du[a]; Hongbo Li[a]; Xiaoxia Lu[a]; Shengying Qm[a]
[a] Department of Chemistry, Sichuan University, Chengdu, P. R., CHINA

To cite this Article Zeng, Wei , Du, Ying , Li, Hongbo , Lu, Xiaoxia and Qm, Shengying(2003) 'SYNTHESIS OF *N*- (4-AMINOPHENYL) MONOAZACROWN ETHERS', Organic Preparations and Procedures International, 35: 2, 228 — 231
To link to this Article: DOI: 10.1080/00304940309355838
URL: http://dx.doi.org/10.1080/00304940309355838

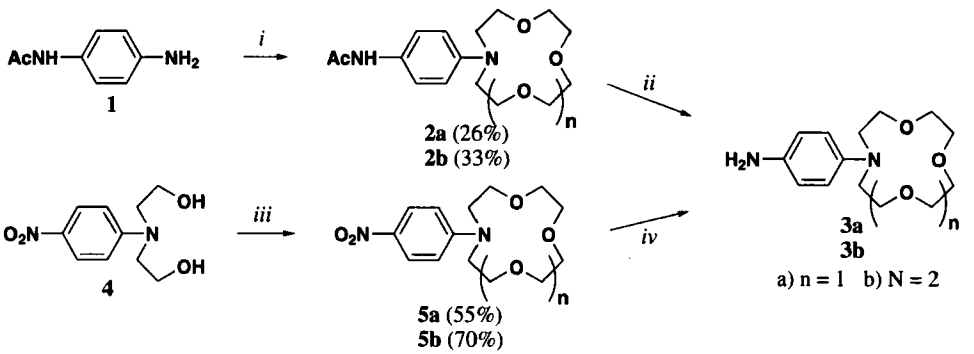
SYNTHESIS OF *N*- (4-AMINOPHENYL) MONOAZACROWN ETHERS

Submitted by (05/07/02)

Wei Zeng, Ying Du, Hongbo Li, Xiaoxia Lu and Shengying Qin*

Department of Chemistry, Sichuan University
Chengdu, 610064, P. R. CHINA
e-mail: qin-shengying @ 263.net

Crown ethers containing an amino group promise to be advantageous intermediates for the synthesis of chromogenic crown ethers, liquid crystal crown ethers and molecule acceptors.[1-4] Whereas monoaza–18–crown-6, monoaza- 15-crown-5, monoaza-12-crown-4, and their variously *N*-substituted derivatives have been known for many years,[5-8] new methods for their preparation continue to appear.[9,10] The preparation of *N*-(4-aminophenyl)monoazacrown ether **3b** has only been reported once *via* a three-step reaction from *N*-phenyldiethanolamine by cyclization, nitrosation, and reduction in an 9% overall yield.[1] We required a convenient synthesis of **3a** and **3b** for preparation of chromogenic monoazacrown ethers bearing picrylamino-type side arms; this paper herein describes two routes for the synthesis of *N*-(4-aminophenyl) monoaza-12-crown-4 (**3a**) and *N*-(4-aminophenyl)monoaza-15-crown-5 (**3b**) from readily available starting materials.



i) , CH_3CN, Na_2CO_3 *ii*) NaOH, H_2O, dioxane

iii) TSO OTS , NaH, THF *iv*) $SnCl_2 \cdot 2H_2O$, EtOAc

Compounds **3a** and **3b** were obtained from 4-aminoacetanilide in 21% and 28% overall yields, respectively. Arylamines **3a** and **3b** were also prepared in 49% and 60% yield, respectively, by aromatic nucleophilic substitution between 4-nitrochlorobenzene and diethanolamine. The second route exhibits many advantages such as higher overall yield, more convenient separation and purification compared to route 1.

EXPERIMENTAL SECTION

Mps were determined on a Yanaco MP-500 micro-melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet-1705X IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC-200MHz in $CDCl_3$ with tetramethylsilane, as the internal standard. Mass spectra were obtained on a Finnigan MAT 4510 spectrometer. Elemental analyses were performed on a Carlo Erbo-1160 elemental analyzer. Silica gel (60H for TLC, Qingdao, China) was used for flash column chromatography. 4-Aminoacetanilide (**1**), [11] 1,11-diiodo-3,6,9-trioxaundecane and 1,14-diiodo-3,6,9,12- tetraoxatetradecane,[8] 2,2'-[(4–nitrophenyl)imino]bisethanol (**4**),[12] diethyleneglycol and triethyleneglycol ditosylates[13] were synthesized according to publish procedures. THF and acetonitrile were distilled and dried prior to use; all other reagents were of analytical grade and were used without further purification.

***N*-(4-Acetoamidophenyl)monoaza-12-crown-4 (2a)**.- To a stirred solution of anhydrous acetonitrile (500 mL), 4-aminoacetanilide (**1**) (4.02 g, 26.8 mmol), 1,11-diiodo-3,6,9-trioxaundecane (11.93 g, 27.0 mmol), and anhydrous sodium carbonate (16.8 g, 158.5 mmol) were added in one portion under an atmosphere of nitrogen. The mixture was stirred at reflux for 48 h; after cooling to 25°, the solution was filtered, concentrated to dryness *in vacuo* to give a residue, which was extracted with ethyl acetate (2 x 20 mL). The combined extract was dried ($MgSO_4$) and removal of the solvent gave a crude product, which was purified by column chromatography (silica gel, EtOAc) to afford 2.06 g (26%) of **2a**, as white crystal, mp. 67-69°. ^{1}H NMR: δ 7.77 (s, 1H, NH), 7.28-6.78 (5H, m, Ar-H), 3.80-3.65 (12H, m, 3 x CH_2OCH_2), 3.55 (4H, 2 x NCH_2), 2.09 (s, 3H, CH_3); IR (KBr, film): 3290, 2901, 2880, 1650, 1598, 1525, 1126 cm^{-1}; MS (m/z): 308(M^+).

Anal. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.33; H, 7.79; N, 9.09. Found: C, 62.43; H, 7.88; N, 9.25

***N*-(4-Acetoamidophenyl)monoaza-15-crown-5 (2b)**, mp. 84-86°, was prepared (33%) using a method similar to that for **2a**. ^{1}H NMR: δ 7.77 (s, 1H, NH), 7.30-6.80 (5H, m, Ar-H), 3.81-3.65 (16H, m, 4 x CH_2OCH_2), 3.55 (4H, 2 x NCH_2), 2.09 (s, 3H, CH_3); IR (KBr, film): 3300, 2900, 2880, 1650, 1598, 1525, 1126cm^{-1}; MS (m/z): 352(M^+).

Anal. Calcd for $C_{18}H_{28}N_2O_5$: C, 61.36; H, 7.95; N, 7.95. Found: C, 61.58; H, 7.72; N, 8.03

***N*-(4-Aminophenyl)monoaza-12-crown-4 (3a)**.- To a solution of **2a** (2.0 g, 6.5 mmol) in dioxane (40 mL), was added aqueous sodium hydroxide (40 mL, 20%). The mixture was stirred at reflux for 4 h. After cooling to 25°, most of the solvent was distilled off and the resulting residue was extracted with hot $CHCl_3$ (2 x 20 mL). The combined extract was concentrated to dryness to give a crude product, which was purified by column chromatography (silica gel, MeOH) to afford 1.4 g (81%) of **3a**, as a slightly reddish oil. ^{1}H NMR: δ 6.62-6.53 (4H, m, Ar-H), 5.28 (2H, s, NH_2), 3.80-3.65 (12H, m, 3 x CH_2OCH_2), 3.60 (4H, m, 2 x NCH_2); IR (neat): 3300, 1601, 1158 cm^{-1}; MS (m/z): 266(M^+).

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.16; H, 8.27; N, 10.53. Found: C, 62.94; H, 8.38; N, 10.69

***N*-(4-Aminophenyl)monoaza-15-crown-5 (3b)**, mp. 44-45°, *lit.*[14] mp. 46°, was prepared (86%) using a method similar to that for **3a**. ^{1}H NMR: δ 6.62-6.53 (4H, m, Ar-H), 5.30 (2H, s, NH_2), 3.76-3.66 (16H, m, 4 x CH_2OCH_2), 3.61 (4H, m, 2 x NCH_2); MS (m/z): 310(M^+).

***N*-(4-Nitrophenyl)monoaza-12-crown-4 (5a)**.- A 1-L three-necked flask was purged with N_2 and NaH (1.86 g, 77.5 mmol) was added to the reaction vessel and washed with hexanes (4 x 50 mL). THF (300 mL) was then added to flask. This suspension was heated to reflux with vigorous stirring. A solution of **4** (16.95 g, 75 mmol) and diethylene glycol ditosylates (31.05 g, 75 mmol) in THF (300 mL) was added dropwise fine. Reflux was continued for 20 h. The mixture was cooled to 0° and carefully quenched with H_2O, and the solvent was evaporated *in vacuo*. The residue was dissolved in H_2O (400 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were concentrated to dryness to give a crude product, which was purified by column chromatography (silica gel, EtOAc) to afford 12.3 g (55%) of **5a**, as yellow crystal, mp. 114-116°. ^{1}H NMR: δ 6.73-6.70 (4H, m, Ar-H), 3.80-3.65 (12H, m, 3 x CH_2OCH_2), 3.60 (4H, m, 2 x NCH_2); IR (KBr, film): 1600, 1340, 1126 cm^{-1}; MS (m/z): 296(M^+).

Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.76; H, 6.76; N, 9.46. Found: C, 56.48; H, 6.85; N, 9.25

***N*-(4-Nitrophenyl)monoaza-15-crown-5 (5b)**, mp. 127-130°, *lit.*[14] mp. 127-130°, was prepared (70%) from triethyleneglycol ditosylates using a method similar to that for **5a**.

***N*-(4-Aminophenyl)monoaza-12-crown-4 (3a)**.- A mixture of **5a** (2.79 g, 9 mmol), $SnCl_2$·2HO (2.5 g, 11.06 mmol), EtOAc (10 mL), and conc. HCl (2.95 mL) was stirred at 40° for 40 min; subsequently, H_2O (20 mL) was added to the mixture and stirred at 40° for 1 h. The pH of the solution was adjusted to 8-9 with 40% NaOH, filtered and the filtrate was extracted with CH_2Cl_2 (3 x 30 mL), dried ($MgSO_4$), and evaporated *in vacuo* to give a crude product, which was purified by column chromatography (silica gel, MeOH) to give 2.13 g (89%) of **3a**, as a slightly reddish oil. ^{1}H NMR: δ 6.64-6.55 (4H, m, Ar-H), 5.30 (2H, s, NH_2), 3.84-3.65 (12H, m, 3 x CH_2OCH_2), 3.58 (4H, m, 2 x NCH_2); IR (neat): 3300, 1603, 1155 cm^{-1}; MS (m/z): 266(M^+).

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.16; H, 8.27; N, 10.53. Found: C, 63.25; H, 8.11; N, 10.61

***N*-(4-Aminophenyl)monoaza-15-crown-5 (3b)**, mp. 44-46°, *lit.*[14] mp. 46°, was prepared (85%) using a method similar to that for **3a**. ^{1}H NMR: δ 6.63-6.55 (4H, m, Ar-H), 5.30 (2H, s, NH_2), 3.74-3.63 (16H, m, 4 x CH_2OCH_2), 3.59 (4H, m, 2 x NCH_2); MS (m/z): 310(M^+).

REFERENCE

1. J. P. Dix and F. Vögtle, *Chem. Ber.*, **113**, 457 (1980).

2. S. Y. Qin, Z. F. Lu, J. Z. Li and X. M. Liu, *Youji Huaxue.*, **15**, 424 (1995); *Chem. Abst.*, **123**, 340081x (1997).

3. M. G. Xie and Q. Jiang, *Liq. Cryst.*, **21**, 461 (1996).

4. R. A. Bartsch and M. D. Eley, *Tetrahedron.*, **52**, 8979 (1996).

5. R. N. Greane, *Tetrahedron Lett.*, 1793 (**1972**).

6. G. W. Gokel and B. J. Grarcia, *Tetrahedron Lett.*, 317 (**1977**).

7. M. R. Johnson, I. O. Sutherland and F. F. Newton, *J. Chem. Soc. Perkin Trans I.*, 357 (**1979**).

8. M. J. Calrerley and J. Dale, *Acta Chem. Scand.*, **B36**, 241 (1982).

9. H. Maeda, Y. Nakatsuji and M. Okahara, *Chem. Commun.*, 471 (**1981**).

10. R. A. Schule, D. M. Dishong and G. W. Gokel, *Tetrahedron Lett.*, **22**, 2623 (1981).

11. C. M. Atkinson, C. W. Brown, J. Mcintyre and J. C. E. Simpson, *J. Chem. Soc.*, 2023 (**1954**).

12. M. Bil and S. Brunner, W. H. Fr. 1506945, **1967**; *Chem. Abst.*, **70**, 116216z (1969).

13. J. Dale and P. O. Kristiansew, *Acta Chem. Scand.*, **26**, 1471 (1972).

14. J. P. Dix and F. Vögtle, *Angew. Chem.*, **90**, 893 (1978).

****

SYNTHESIS OF α-HYDROXYTAMOXIFEN AND ITS 4-HYDROXY ANALOG

Submitted by (07/16/02)

M. R. Lashley,[†] C. W. Dicus,[†] K. Brown,[††,‡] M. H. Nantz *,[†]

[†] *Department of Chemistry, University of California, Davis CA 95616, USA*

[††] *Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, Livermore, CA 94551, USA*

e-mail: mhnantz@ucdavis.edu

Tamoxifen is an anti-estrogen prescribed for the treatment of estrogen receptor-positive (ER+) breast cancer[1] and approved in the US for use as a chemopreventive agent for women who have an increased risk of developing cancer.[2] Although tamoxifen is a widely used adjuvant drug therapy, it is known to cause human endometrial cancer[3] as well as liver cancer in rats.[4] These observations have prompted many efforts to determine whether tamoxifen-induced endometrial carcinogenesis involves a genotoxic or hormonal mechanism.[5] Recent studies on tamoxifen-