Macrocycle opening in crown ethers 3.* Transformation of 4'-nitrobenzocrown ethers into podands in the reaction with methylamine

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A method for the synthesis of nitrogen-containing podands from 4'-nitrobenzocrown ethers was developed. It involves nucleophilic regioselective cleavage of the macrocycle upon heating with MeNH₂.

Key words: 4'-nitrobenzocrown ethers, macrocycle opening, methylamine, podands.

The methods for the synthesis of open-chain analogs of crown compounds, podands,² are based on the condensation of two fragments. At the same time, the nucleophilic opening of the macrocycle of nitrobenzocrown ethers under the action of O-nucleophiles (RONa, NaOH)^{3,4} and formylbenzocrown compounds under the action of N-nucleophiles (RNH₂ and RNH₃⁺ X⁻)^{1,5} has been reported.

In this work we studied the synthesis of nitrogencontaining podands from 4'-nitrobenzocrown ethers. The starting 4'-nitrobenzocrown ethers (1a-c) and 4',4''(5'')-dinitrodibenzo-18-crown-6 ethers (1d,e)were obtained by the known procedures.⁶⁻⁸ We assumed that the nitro group in the *para*-position with respect to one of the two oxygen atoms of the benzocrown ethers would activate the nucleophilic regioselective opening of the macrocycle upon the action of methylamine.

It was shown that heating of 4'-nitrobenzocrown ethers 1a-c with an alcoholic solution of MeNH₂ results in the formation of podands (2a-c) in up to 98% yields (Scheme 1, Table 1). The presence of the strong electron-accepting nitro group allows one to carry out the reaction under significantly milder conditions and without additional activation of the macrocycle towards nucleophilic opening because of complexation with MeNH₃⁻Cl⁻, as was the case with formylbenzocrown ethers.⁵ Due to the high reactivity of compounds 1a-c, the yields of 2a-c almost do not depend on the macrocycle size.

The method found by us was also applied to compounds incorporating two reaction centers, 4', 4''(5'')dinitrodibenzo-18-crown-6 ethers (**1d**,e) (Scheme 2, Table 1), obtained by nitration of dibenzo-18-crown-6 ether as a difficultly separable mixture of two isomers.

*For Communication 2 see Ref. 1.

*High resolution mass spectroscopy data

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This reaction resulted in the formation of two podands $2d_{e}$ in 96 % overall yield. It can be seen from Table 2 that the formation of podand 2d proceeds substantially slower than that of 2e, which reached its maximum degree of transformation in ~70 h.

Table 1. Characteristics of podands 2a-e

Podanđ	Yield (%)	[M] ⁺ ,* <u>Found</u> Calculated	Molecular formula
2a	94	<u>300 13327</u> 300.13210	C ₁₃ H ₂₀ N ₂ O ₆
2b	98	<u>344.15705</u> 344.15831	$C_{15}H_{24}N_2O_7$
2c	92	<u>388.18566</u> 388.18452	$C_{17}H_{28}N_2O_8$
2d	44	_	$C_{11}H_{16}N_2O_5$
2e	52	-	C ₁₈ H ₂₂ N ₄ O ₇



1d





2d

Table 2. Reaction conditions for the macrocycle opening in crown ethers $1d_{e}$ upon the action of MeNH₂ at 100 °C and yields of podands $2d_{e}$

τ∕h	Υ (%) ^α (α (%))		$\frac{Y_{\Sigma}(\%)^{a}}{(\alpha_{\Sigma}(\%))}$	2d : 2e, mol/mol	
	2d	Ze	2d+2e		
20	25 (13)	56 (28)	81 (41)	t : 1.1	
20 ⁶	22 (14)	51 (33)	73 (47)	1 ; 1.1	
50	28 (19)	56 (40)	84 (59)	1 : 1.1	
70	29 (20)	67 (48)	96 (68)	1 : 1.2	
200¢	44 (42)	52 (51)	96 (93)	1 : 0.6	

Note: τ is reaction time, Y is yield, α is degree of transformation, Y_{Σ} is total yield, and α_{Σ} is total degree of transformation. ^{*a*} Calculated with respect to the reacted 1d +1e.

^b In the presence of a 10-fold molar excess of $MeNH_3^+$ Cl⁻. ^c The tube with the reaction mixture was shaken every 10 h.





This fact may result from the significantly lower solubility of *trans*-isomer 1d. During the reaction, the precipitate is gradually enriched with the *trans*-isomer and becomes completely composed of this isomer after 70 h; the complete transformation of 1d (the degree of transformation is 93 %) into podand 2d occurs only in 200 h.

When the reaction is carried out in the presence of $MeNH_3^+Cl^-$, the degree of transformation of the crown ethers 1d and 1e slightly increases, but the yield of compounds 2d,e decreases. This indicates the activation of the side reactions and the absence of the template effect of $MeNH_3^+$ upon opening of the 2d,e macrocycle, unlike in the reaction of formylbenzocrown compounds.^{1,5} The two electron-accepting nitro groups probably suppress completely the complexation of the crown ethers 1d and 1e with $MeNH_3^+$.

Chromatographic separation of the reaction mixture obtained after heating for 200 h afforded compounds 2d and 2e in a 1.7 molar ratio. This indicates an almost equal reactivity of both isomers, 1d and 1e, since the ratio of *cis*- and *trans*-isomers 1e: 1d was 1.13 (taking into account the non-reacted *trans*-isomer of 1d).

The structure of the compounds obtained was confirmed by spectral methods (Tables 1, 3, and 4) and by elemental analyses.

Podand	m/z (I _{rel} (%))*
2a	300 (100), 168 (84), 167 (34), 151 (29), 133 (33), 125 (22), 121 (32), 93 (25), 89 (93), 78 (20), 60 (30)
2b	344 (100), 313 (21), 256 (22), 238 (16), 212 (22), 168 (72), 167 (30), 151 (15), 122 (15), 121 (20), 89 (98)
2c	388 (38), 212 (50), 168 (70), 167 (33), 133 (26), 125 (35), 89 (100), 87 (25), 73 (71), 61 (56), 60 (67)
2d	256 (100), 168 (94), 167 (42), 150 (45), 148 (57), 138 (22), 122 (20), 121 (45), 93 (34), 88 (20), 78 (46)
2e	406 (45), 312 (64), 167 (100), 148 (69), 135 (58), 134 (86), 121 (65), 93 (58), 90 (50), 79 (47), 78 (83)

*The molecular ion peak and 10 most intense peaks are given.

Table 4. IR (vascline oil) and	¹ H NMR (CDCl ₃ —CCl ₄ , 1	1:1)	spectra of poda	inds 2a—e
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Poda	ind IR, v/cm ⁻¹	¹ Η NMR, δ (<i>J</i> /Hz)		
2a	3380 (NH. OH); 1540 (NO ₂)	2.69 (br.s. 1 H, OH); 2.97 (s, 3 H, MeN); 3.64–3.71 (m, 8 H, 4 CH ₂ O); 3.88 (m, 2 H, CH ₂ O); 4.24 (m, 2 H, CH ₂ O); 5.60 (br.s. 1 H, NH); 6.46 (d, 1 H, H-3, $J_{H-3,H-4} = 8.9$); 7.63 (d, 1 H, H-6, $J_{H-6,H-4} = 2.4$); 7.92 (dd, 1 H, H-4, $J_{H-4,H-3} = 8.9$; $J_{H-4,H-6} = 2.4$)		
2b	3360 (NH, OH); 1540 (NO ₂)	2.95 (s, 4 H. OH, MeN); 3.61–3.69 (m, 12 H, 6 CH ₂ O); 3.88 (m, 2 H, CH ₂ O); 4.22 (m, 2 H, CH ₂ O); 5.75 (br.s, 1 H, NH); 6.43 (d, 1 H, H-3, $J_{H-3,H-4} = 8.9$); 7.60 (d, 1 H, H-6, $J_{H-6,H-4} = 2.3$); 7.89 (dd, 1 H, H-4, $J_{H-4,H-3} = 8.9$; $J_{H-4,H-6} = 2.3$)		
2c	3360 (NH, OH); 1538 (NO ₂)	2.6 (br.s, 1 H, OH); 2.98 (s, 3 H, MeN); 3.60–3.69 (m, 16 H, 8 CH ₂ O); 3.88 (m, 2 H, CH ₂ O); 4.24 (m, 2 H, CH ₂ O); 5.43 (br.s, H, NH); 6.46 (d, 1 H, H-3, $J_{H-3,H-4} = 8.9$); 7.65 (d, 1 H, H-6, $J_{H-6,H-4} = 2.3$); 7.91 (dd, 1 H, H-4, $J_{H-4,H-3} = 8.9$: $J_{H-4,H-6} = 2.3$)		
2d	3320, 3420 (NH, OH); 1554 (NO ₂)	2.20 (br.s, 1 H, OH); 2.98 (d, 3 H, MeN, $J = 5.0$); 3.67 (m, 2 H, CH ₂ O); 3.74 (m, 2 H, CH ₂ O); 3.88 (m, 2 H, CH ₂ O); 4.24 (m, 2 H, CH ₂ O); 5.25 (m, 1 H, NH, $J = 5$); 6.47 (d, 1 H, H-3, $J = 9$); 7.64 (s, 1 H, H-6), 7.91 (d, 1 H, H-4, $J = 9$)		
2e	3412 (NH); 1530 (NO ₂)	2.91 (d, 6 H, 2 MeN, $J = 5.3$); 3.95 (m, 4 H, 2 CH ₂ O); 4.27 (m, 4 H, 2 CH ₂ O); 5.21 (br.q, 2 H, 2 NH, $J = 5.3$); 6.47 (d, 2 H, H-3, H-3', $J_{H-3,H-4} = J_{H-3',H-4'} = 8.9$); 7.66 (d, 2 H, H-6, H-6', $J_{H-6,H-4} = J_{H-6',H-4'} = 2.1$); 7.96 (dd, 2 H, H-4, H-4', $J_{H-4,H-3} = J_{H-4',H-3'} = 8.9$, $J_{H-4,H-6} = J_{H-4',H-6'} = 2.1$)		

Thus, we have developed a new method for the synthesis of nitrogen-containing podands based on the nucleophilic regioselective opening of the macrocycles of readily available nitro derivatives of benzocrown ethers upon the action of methylamine.

Reliable physicochemical methods or procedures based on differences in reactivity that allow one to estimate the content of *cis*- and *trans*-isomers in a mixture of 4', 4''(5'')-dinitrodibenzo-18-crown-6 ethers have not been described in the literature. It should be noted that the reaction studied can be regarded as the first promising method (for example, see Ref. 9) to estimate the quantitative content of the products of nitration of dibenzo-18-crown-6 ether.

Experimental

¹H NMR spectra were obtained on a Bruker AC-200p spectrometer using $CDCl_3$ -- CCl_4 (1 : 1) as a solvent and $SiMe_4$ as the internal standard. IR spectra were recorded on a Shimadzu IR-470 spectrophotometer in vaseline oil. Mass spectra were obtained on a Varian MAT-311A instrument at an ionization energy of 70 eV, using direct injection of samples into the ionization source. The reactions were monitored by TLC on DC-Alufolien Kieselgel 60 F₂₅₄ plates.

Synthesis of podands 2a-c (general procedure). A mixture of 4'-nitrobenzocrown ether 1a-c (0.5 mmol) and a 35 % solution of MeNH₂ in anhydrous EtOH (5 mL) was heated in a sealed tube at 100 °C for 20 h (water bath). The tube was then opened, the mixture was evaporated *in vacuo*, and the residue was purified by column chromatography on SiO_2 (Kieselgel 60, 0.063-0.100 mm, Merck, with CHCl₃ : MeCO₂Et : EtOH, 8 : 4 : 1, as the eluent). Podands **2a-c** were isolated as yellow oils.

Synthesis of podands 2d,e. A mixture of 4',4''(5'')dinitrodibenzo-18-crown-6 ethers (1d,e) (225 mg, 0.5 mmol) and 35% solution of MeNH₂ in anhydrous EtOH (5 mL) was heated in a sealed tube at 100 °C for 200 h (water bath). The tube was shaken every 10 h after cooling to ~20 °C. The tube was then opened, the mixture was evaporated in vacuo, and the residue was extracted with hot MeCO₂Et and filtered to afford 7 mg (0.016 mmol) of trans-isomer 1d insoluble in MeCO₂Et, m.p. 245-248 °C (cf. Ref. 10). The filtrate was concentrated, and the residue was purified by column chromatography on SiO₂ (Kieselgel 60, 0.063-0.200 mm, Merck, using MeCO₂Et as the eluent) to give 108 mg of 2d as orange crystals, m.p. 110-112 °C (from a 10 : 1 benzene-hexane mixture) and 103 mg of 2e as yellow crystals, m.p. 161-163 °C (from MeOH). Podand 2d. Found (%): C, 51.43; H, 6.20; N, 10.49, $C_{11}H_{16}N_2O_5$, Calculated (%): C, 51.54; H, 6.30; N, 10.94. Podand 2e. Found (%): C, 53.47; H, 5.47; N, 13.93. C₁₈H₂₂N₄O₇. Calculated (%): C, 53.20; H, 5.46; N, 13.79.

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