New One Step Synthesis of Crown Compounds Containing a 1,3,4-Thiadiazole Moiety

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Received November 21, 2003

New macrocyclic polyether compounds containing a 2,5-bis(2-hydroxyphenyl)-1,3,4-thiadiazole moiety have been prepared by a nucleophilic substitution reaction involving ethylene or polyethylene glycol ditosylate and a bisphenol, the 2,5-bis(2-hydroxyphenyl)-1,3,4-thiadiazole, with solid anhydrous carbonate as a base. The structures of the macrocycles obtained were firmly established by ^1H and ^{13}C nmr spectroscopy and their mass spectra.

J. Heterocyclic Chem., **41**, 419 (2004).

Introduction.

Since Pedersen reported the synthesis of crown ethers and their unique cation-complexing characteristics [1], there has been increasing interest in these compounds as complexing agents for various metal and organic cations. Various 1,3,4-thiadiazole derivatives exhibit a penchant for the formation of stable complexes with heavy- and transition-metal ions [2-7]. Over the past decades, efforts toward the synthesis of N-heterocyclic coronands and particulary macrocyclic polyether have been conducted [8-13]. A series of such compounds containing diaryl-1,3,4-oxadiazole has been reported recently [12]. In light of the general interest on the construction of synthetic macrocycles containing heterocyclic subunits as well as the limited examples of 1,3,4-thiadiazole inclusion in a macrocyclic framework [14-16], we report in the present paper, the syntheses of new 1,3,4-thiadiazoles containing macrocyclic polyethers. These macrocycles result from the heterocyclisation of 2,5-bis(2-hydroxyphenyl)-1,3,4-thiadiazole **1** [17] with ethylene or polyethyleneglycol ditosylate in non-protic polar solvents with excess alkali metal carbonates as a base. These new macrocyclic compounds are expected to show coordination behaviors toward cations, water and organic molecules such as amines or urea [8,18]. Some 2,5-disubstituted-1,3,4-thiadiazoles have been previously used as corrosion inhibitors [19-21]. The existing data show that most organic inhibitors act by adsorption on the metal surface [20] and it was discovered that corrosion inhibition may be enhanced by various chemicals additives such as salts of cations [22]. Macrocyclic derivatives with potential complexing properties are expected be useful for this purpose. The properties of these new compounds are under investigation.

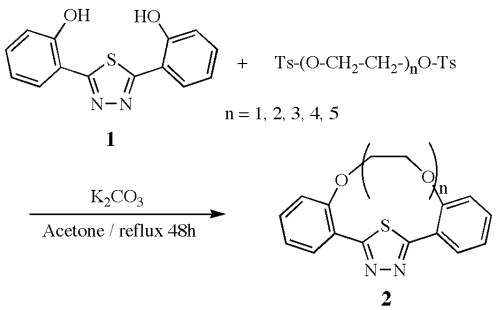
Results and Discussion.

Compounds 2a-e were prepared by a nucleophilic substitution reaction involving a glycol ditosylate with the bisphenol 1. The key step in the synthesis is the intramolecular reaction of the phenolate ion produced by the reaction of solid anhydrous potassium carbonate with the hydroxy group attached to the aromatic substituent of the thiadiazole. Desired compounds were isolated as pale yellow solids in 34-87 % yields (Table 1). The structure proposed for these new macrocyclic compounds are consistent with the data obtained from their ^1H, ^{13}C nmr spectra, MS and elemental analysis.

The synthesis of compound 2c was investigated using different bases (Na, K and Cs carbonates) and different solvents (acetone, acetronitrile and dimethylformamide). The results are given in Table 2. Similar results were obtained. However, slowly better yields were obtained using potassium carbonate indicating that there are no significant template effects during this reaction. Non-protic polar solvents are ordinary used for this reaction. Similar result were obtained using acetone, acetonitrile and dimethylformamide.

Structure of compounds 2a-e were assigned on the basis of their nmr and mass spectra. The ^1H nmr spectrum of 2a displayed a singlet at δ 4.29 ppm for the two bridging methylenes (5) and (6). The four methylenes (5), (6), (8) and (9) in compound 2b showed up as an A_2B_2 system, centered at δ 4.21 ppm. In compound 2c the four methylenes (5), (6), (11) and (12) appeared as an A_2B_2 system, centered at δ 4.19 ppm while (8) and (9) methylenes appeared as a singlet. The spectrum of 2d displayed two triplets for the four methylenes (5), (6), (14) and (15) centered respectively at δ 4.15 ppm for (6) and (14) and 4.38 ppm for (5) and (15) while the four methylenes (8), (9), (11) and (12) showed up as an A_2B_2 system centered at δ

Scheme 1



3.75 ppm. The spectrum of 2e displayed also two triplets for the four methylenes (5), (6), (17) and (18) centered respectively at δ 4.10 ppm for (6) and (17) and 4.42 ppm for (5) and (18), an A_2B_2 system centered at δ 3.71 ppm for the four methylenes (8), (9), (14) and (15) and a singlet at δ 3.66 ppm for the two methylenes (19) and (12).

Table 1

Analytical Data of Compounds **2a-e**

Compound No.	Yield %	Mp °C	Molecular Formula	Analysis (%) Found / Calcd. C	H	N	S
2a (n = 1)	87	144	$C_{16}H_{12}O_2N_2S$	64.93	4.22	9.31	10.78
				64.85	4.08	9.45	10.82
2b (n = 2)	55	210	$C_{18}H_{16}O_3N_2S$	63.63	4.65	8.31	9.26
				63.51	4.74	8.23	9.42
2c (n = 3)	86	180	$C_{20}H_{20}O_4N_2S$	62.61	5.17	7.37	8.26
				62.48	5.24	7.28	8.34
2d (n = 4)	62	150	$C_{22}H_{24}O_5N_2S$	61.76	5.57	6.68	7.29
				61.67	5.65	6.54	7.48
2e (n = 5)	34	140	$C_{24}H_{28}O_6N_2S$	61.12	5.89	5.97	6.85
				61.00	5.97	5.93	6.78

Table 2

Yields of Compound **2c** in Different Bases and Solvents

Solvent \ Base	Na_2CO_3	K_2CO_3	Cs_2CO_3
Acetone	73 %	86 %	70 %
Acetonitrile	79 %	84 %	73 %
Dimethylformamide	72 %	79 %	71 %

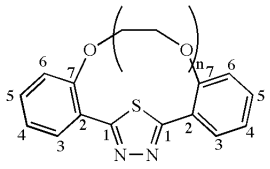
EXPERIMENTAL

Melting points were determined with on an IA 9000 series Electrothermal apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a Bruker F.T. AC 200 spectrometer (200 MHz for ^1H nmr and 60 MHz for ^{13}C nmr) using chloroform-d_1 ($CDCl_3$). Matrix assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOF-MS) are used to record the mass spectra of the macrocyclic polyether compounds. Elemental analyses were performed by the Elemental Analysis service of CNRS, Vernaison, France. All starting materials were of reagent grade and used as purchased. 2,5-Bis(2-hydroxyphenyl)-1,3,4-thiadiazole **1** was synthesized according to literature procedure [17].

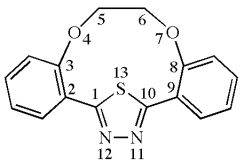
General Procedure for the Synthesis of Macrocycles **2a-e**.

A mixture of 2,5-bis(2-hydroxyphenyl)-1,3,4-thiadiazole **1** (1.5 g, 5.55 mmoles), anhydrous potassium carbonate (3.3 g, 24 mmoles) and ethylene or polyethylene glycol ditosylate (5.57 mmoles) in 150 ml of non-protic polar solvent (acetone, acetonitrile,…) was heated under reflux for 48 hours with vigorous stirring. The solvent was evaporated *in vacuo* and the solid residue was heated under reflux with 20 ml of a potassium hydroxide solution for 1 hour. After cooling, the crude product was collected by filtration, washed with water, recrystallized from ethanol and dried. Pale yellow solids were obtained. Yields using acetone, melting points and results of the elemental analysis (C, H, N, S) are given in Table 1.

The general formula of the parent macrocyclic compound with corresponding numbering scheme is given below. Localization of the methylene groups in the polyether macrocycle have been made using the IUPAC rules concerning the different bicyclic systems.



Numerotation used for the localization of aromatic carbon



Example of the numerotation used for the bicyclic systems (**2a**).

2,3,8,9-Dibenzo-4,7-dioxa-13-thia-11,12-diazabicyclo[8.2.1]-trideca-10,12-diene (**2a**).

This compound has ^1H nmr ($CDCl_3$): δ (ppm) 4.29 (s, 4H, CH_2 (5) and CH_2 (6)), 6.82 (d, J = 7.9 Hz, 2H, ArH), 7.08 (t, J = 7.3 Hz, 2H, ArH), 7.36 (t, J = 7.8 Hz, 2H, ArH), 8.33 (d, J = 8.0 Hz, 2H, ArH). ^{13}C nmr ($CDCl_3$): δ (ppm) 70.43 (CH_2 (5) and CH_2 (6)), 112.02 (C_6), 119.95 (C_4), 121.64 (C_2), 129.64 (C_3), 132.01 (C_5), 155.55 (C_7), 163.97 (C_1-thiadiazole). MALDI-TOFMS: *m/z* 297 (M +1).

2,3,11,12-Dibenzo-4,7,10-trioxa-16-thia-14,15-diazabicyclo-[11.2.1]hexadeca-13,15-diene (**2b**).

This compound has ^1H nmr ($CDCl_3$): δ (ppm) 4.08-4.04 (m, 4H, CH_2 (6) and CH_2 (8)), 4.37-4.33 (m, 4H, CH_2 (5) and CH_2 (9)), 7.13 (d, J = 8.6, 2H, ArH), 7.25 (t, J = 6.9 Hz, 2H, ArH), 7.44 (t, J = 7.9 Hz, 2H, ArH), 8.58 (d, J = 7.8, 2H, ArH). ^{13}C nmr ($CDCl_3$): δ (ppm) 69.71 (CH_2 (5) and CH_2 (9)), 70.71 (CH_2 (6)

and CH_2 (8)), 115.19 (C_6), 120.15 (C_4), 122.88 (C_2), 127.87 (C_3), 131.56 (C_5), 155.47 (C_7), 163.52 (C_1-thiadiazole). MALDI-TOFMS: *m/z* 341 (M +1).

2,3,14,15-Dibenzo-4,7,10,13-tretraoxa-19-thia-17,18-diazabicyclo[14.2.1]nonadeca-16,18-diene (**2c**).

This compound has ^{1}H nmr ($CDCl_3$): δ (ppm) 3.81 (s, 4H, CH_2 (8) and CH_2 (9)), 4.00-4.03 (m, 4H, CH_2 (6) and CH_2 (11)), 4.38-4.35 (m, 4H, CH_2 (5) and CH_2 (12)), 7.04 (d, J = 8.3 Hz, 2H, ArH), 7.17 (t, J = 7.6 Hz, 2H, ArH), 7.49 (t, J = 7.9 Hz, 2H, ArH), 8.67 (d, J = 7.9 Hz, 2H, ArH). ^{13}C nmr ($CDCl_3$): δ (ppm) 68.79 (CH_2 (5) and CH_2 (12)), 69.33 (CH_2 (8) and CH_2 (9)), 70.50 (CH_2 (6) and CH_2 (11)), 112.03 (C_6), 120.14 (C_4), 121.65 (C_2), 129.63 (C_3), 131.89 (C_5), 155.54 (C_7), 164.48 (C_1-thiadiazole). MALDI-TOFMS: *m/z* 385 (M +1).

2,3,17,18-Dibenzo-4,7,10,13,16-pentaoxa-22-thia-20,21-diazabicyclo[17.2.1] docosa-19,21-diene (**2d**).

This compound has ^{1}H nmr ($CDCl_3$): δ (ppm) 3.79-3.71 (m, 8H, CH_2 (8, 9, 11, and 12)), 4.15 (t, J = 5.7 Hz, 4H, CH_2 (6) and CH_2 (14)), 4.38 (t, J = 5.6 Hz, 4H, CH_2 (5) and CH_2 (15)), 7.08 (d, J = 8.3 Hz, 2H, ArH), 7.18 (t, J = 7.6 Hz, 2H, ArH), 7.50 (t, J = 7.8 Hz, 2H, ArH), 8.63 (d, J = 7.8 Hz, 2H, ArH). ^{13}C nmr ($CDCl_3$): δ (ppm) 68.67 (CH_2 (5) and CH_2 (15)), 69.67 (CH_2 (6) and CH_2 (14)), 71.13 (CH_2 (8) and CH_2 (12)), 72.05 (CH_2 (9) and CH_2 (11)), 112.63 (C_6), 117.98 (C_4), 122.13 (C_2), 130.01 (C_3), 133.56 (C_5), 155.81 (C_7), 164.05 (C_1-thiadiazole). MALDI-TOFMS: *m/z* 429 (M +1).

2,3,20,21-Dibenzo-4,7,10,13,16,19-hexaoxa-25-thia-23,24-diazabicyclo[20.2.1]pentacoza-21,24-diene (**2e**).

This compound has ^{1}H nmr ($CDCl_3$): δ (ppm) 3.66 (s, 4H, CH_2 (11) and CH_2 (12)), 3.72-3.70 (m, 4H, CH_2 (9) and CH_2 (14)), 3.78-3.76 (m, 4H, CH_2 (8) and CH_2 (15)), 4.10 (t, J = 5.4 Hz, 4H, CH_2 (6) and CH_2 (17)), 4.42 (t, J = 5.5 Hz, 4H, CH_2 (5) and CH_2 (18)), 7.11 (d, J = 8.3 Hz, 2H, ArH), 7.16 (t, J = 7.6 Hz, 2H, ArH), 7.48 (t, J = 7.9 Hz, 2H, ArH), 8.63 (d, J = 7.8 Hz, 2H, ArH). ^{13}C nmr ($CDCl_3$): δ (ppm) 68.77 (CH_2 (5) and CH_2 (18)), 69.58 (CH_2 (6) and CH_2 (17)), 71.07 (CH_2 (8) and CH_2 (15)), 71.11 (CH_2 (9, 11, 12 and 14), 112.92 (C_6), 118.94 (C_4), 121.99 (C_2), 129.48 (C_3), 132.84 (C_5), 155.74 (C_7), 163.68 (C_1-thiadiazole). MALDI-TOFMS: *m/z* 473 (M +1).

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