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Synthesis of Novel Bibrachial Lariat Ethers (BiBLEs) Containing [1,2,4]Triazolo[3,4-*b*][1,3,4]Thiadiazines

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ABSTRACT

A practical and regioselective method for the synthesis of *cis*-diastereomers of bibrachial lariat ethers (BiBLEs) bearing ester and amide groups is reported. The novel bibrachial lariat ethers (BiBLEs) 3a–d with neutral side chains were prepared by reaction of the corresponding aza-crown macrocycles 1a–b with ethyl chloroacetate and chloroacetamide.

KEYWORDS

macrocycle, bibrachial, lariat ethers, aza-crown, 1,3,4-thiadiazines.

1. Introduction

The first synthetic crown ether was discovered by Pederson.[1] Since then, various structural changes have been made to the basic crown ether skeleton in an attempt to enhance the selectivity of these rings and the capacity of complexation with metal ions. When hard and soft donor atoms were added into the structure of the macrocycles, it has been noted that the complexation properties were increased.[2,3] In addition, insertion of heterocyclic and aromatic compounds, have improved the complexation ability of the macrocyclic structures.[4,5] These changes may be due to increased number of cation complexing functional groups via their soft or hard donor atoms.[6]

Lariat ethers are macrocycles which have one or more side arms that contain electron-donating groups.[7,8] The donor groups in these side arms have been extensively used to enhance the stability of the lariat ether for cation compelaxation by giving three-dimensionality to the binding.[9] Lariat ethers may thus exhibit an enhanced complexation capacity for metal ions as compared with the parent macrocycles.[10] These valuable properties prompted us to synthesize a new series of 18–20 bibrachial lariat ethers (BiBLEs) containing 1,3,4-thiadiazine rings.

2. Experimental

2.1. General

All products were characterized using IR, ^{1}H NMR and ^{13}C NMR spectra as well as the mass spectral data. All yields refer to isolated products. IR spectra were performed on a galaxy series FT-IR 5000 spectrophotometer using KBr discs. NMR spectra were recorded on Brucker spectrophotometer (300 MHz) in DMSO-d_6 using TMS as an internal standard. Mass spectra were recorded on an Agilent Technologies (HP) 5973 Network mass selective detector under electron impact (EI).

2.2. General Procedure for the Synthesis of Compounds 3a–d

Sodium hydride (2.5 mmol) was added to a solution of compounds **1a–b**[13] (0.5 mmol) in absolute ethanol (10 mL) at room temperature. Salt formation was allowed to proceed at room temperature for 10 min and ethyl chloroacetate or chloroacetamide (1.1 mmol) was added and the solution stirred for 5 h at room temperature. After the completion of the reaction, the solvent was removed under vacuum and extracted with ethyl acetate. The organic layer was washed with water (3 × 10 mL), dried (Na_2SO_4), and evaporated under vacuum. The residue was crystallized from ethyl acetate and petroleum ether to give compounds **3a–d.**

Diethyl-8,12-dioxa-33,37-dithia-20,21,23,24,30,31,35,36-octa-azaheptacyclo(27.5.2.2^{19,22}.0^{2,7}.0^{13,18}.0^{21,25}.0^{32,36})octatriaconta-2,4,6,13(18),14,16,22,24,29,31-decaene-34,38-dicarboxylate (3a)

75% yield, IR: ν 3246 (NH stretch), 3060 (aromatic CH stretch), 2950 (aliphatic CH stretch), 1730 (C=O), 1610 (C=N), 1250 (Ar-O), 1160 (R-O) cm^{-1}; ^{1}H NMR: δ 7.35 (d, 2H, $H_{arom.}$ J = 5.0 Hz), 7.31 (s, 2H, 2 NH, D_2O exchange), 7.14 (d, 2H, $H_{arom.}$ J = 8.1 Hz), 7.02 (t, 2H, $H_{arom.}$ J = 7.0 Hz), 6.80 (d, 2H, $H_{arom.}$ J = 7.1 Hz), 4.61 (br, 4H, 2 × OCH_2), 4.44 (d, 2H, 2 N-CH, J = 7.9 Hz), 4.34 (d, 2H, 2 S-CH, J = 8.0 Hz), 3.96 (q, 4H, 2 × OCH_2, J = 7.0 Hz), 2.78 (br, 4H, 2 × CH_2), 2.00 (br, 2H, CH_2), 1.94 (br, 2H, CH_2), 0.99 (br, 6H, 2 × CH_3); ^{13}C NMR: δ 168.9, 156.7, 152.6, 141.2, 130.6, 128.1, 124.5, 121.4, 113.0, 66.5, 62.0, 44.2, 40.3, 27.7, 24.0, 22.0, 14.0; DEPT: δ 130.6 (CH), 128.1 (CH), 121.4 (CH), 113.0 (CH), 66.5 (CH_2), 62.0 (CH_2), 44.2 (CH), 40.3 (CH), 27.7 (CH_2), 24.0 (CH_2), 22.0 (CH_2), 14.0 (CH_3); MS (EI): m/z = 692 (M+), 677, 662, 647, 602, 278,146 (base peak), 120, 91; Anal. Calcd. for: $C_{32}H_{36}N_8O_6S_2$: C, 55.48; H, 5.24; N, 16.17; S, 9.26; Found: C, 55.22; H, 5.17; N, 15.96; S, 9.02.

Diethyl-8,13-dioxa-35,39-dithia-21,22,24,25,32,33,37,38-octa-azaheptacyclo(29.5.2.2^{20,23}.0^{2,7}.0^{14,19}.0^{22,26}.0^{34,38})tetraconta-2,4,6,14(19),15,17,23,25,31,33-decaene-36,40-dicarboxylate (3b)

70% yield, IR: ν 3260 (NH stretch), 3050 (aromatic CH stretch), 2930 (aliphatic CH stretch), 1732 (C=O), 1601 (C=N), 1246 (Ar-O), 1160 (R-O) cm^{-1}; ^{1}H NMR: δ 7.30 (d, 2H, $H_{arom.}$ J = 5.6 Hz) 7.28 (s, 2H, 2 × NH, D_2O exchange), 7.11 (d, 2H, $H_{arom.}$ J = 7.8 Hz), 7.03 (t, 2H, $H_{arom.}$ J = 7.1 Hz), 6.82 (d, 2H, $H_{arom.}$ J = 7.1 Hz), 4.58 (br, 4H, 2 × OCH_2), 4.40 (d, 2H, 2 N-CH, J = 8.0 Hz), 4.35 (d, 2H, 2 S-CH, J = 8.0 Hz), 3.88 (q, 4H, 2 × OCH_2, J = 7.1 Hz), 2.70 (br, 4H, 2 × CH_2), 1.90 (br, 4H, 2 × CH_2), 1.19 (br, 4H, 2 × CH_2), 1.04 (br, 6H, 2 × CH_3); ^{13}C NMR: δ 168.8, 156.1, 152.8, 141.5, 130.2, 128.0, 124.4, 121.0, 113.1, 65.9, 62.3, 44.0, 40.5, 25.2, 23.5, 23.0, 14.0; DEPT: δ 130.2 (CH), 128.0 (CH), 121.0 (CH), 113.1 (CH), 65.9 (CH_2), 62.3 (CH_2), 44.0 (CH), 40.5 (CH), 25.2 (CH_2), 23.5 (CH_2), 23.0 (CH_2), 14.0 (CH_3); MS (EI): m/z = 720 (M+), 705, 690, 675, 630, 292,146 (base peak), 120.91; Calcd. for: $C_{34}H_{40}N_8O_6S_2$: C, 56.65; H, 5.59; N, 15.54; S, 8.90; Found: C, 56.51; H, 5.50; N, 15.35; S, 8.73.

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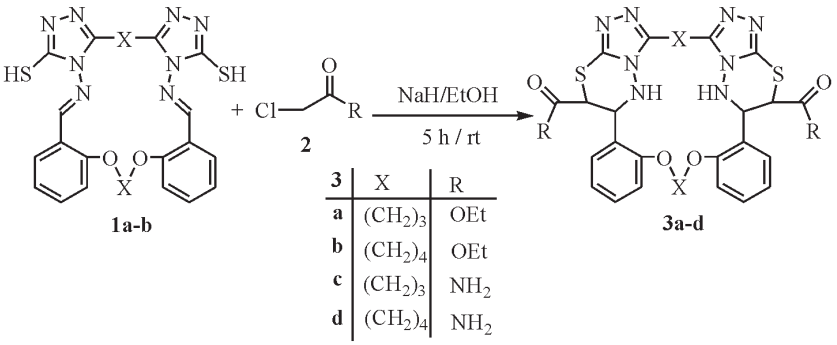


3	X	R
a	$(CH_2)_3$	OEt
b	$(CH_2)_4$	OEt
c	$(CH_2)_3$	NH_2
d	$(CH_2)_4$	NH_2

Scheme 1
Synthesis of compounds **3a–d.**

8,12-Dioxa-33,37-dithia-20,21,23,24,30,31,35,36-octaazaheptacyclo(27.5.2.2^{19,22}.0^{2,7}.0^{13,18}.0^{21,25}.0^{32,36})octatriaconta-2,4,6,13(18),14,16,22,24,29,31-decaene-34,38-dicarboxamide (3c)

65% yield, IR: ν 3310, 3185 (NH stretch), 3040 (aromatic CH stretch.), 1678 (C=O), 1255 (Ar-O), 1105 cm^{-1}; ^{1}H NMR: δ 7.80 (s, 2H, NH_2, D_2O exchange), 7.39 (d, 2H, $H_{arom.}$ J = 6.1 Hz), 7.34 (d, 2H, $H_{arom.}$ J = 7.0 Hz), 7.23 (s, 2H, 2 NH, D_2O exchange), 7.12 (d, 2H, $H_{arom.}$ J = 7.8 Hz), 7.01 (t, 2H, $H_{arom.}$ J = 6.5 Hz), 6.68 (s, 2H, NH_2, D_2O exchange), 4.52 (br, 2H, 2 × OCH_2), 4.44 (br, 2H, 2 × OCH_2), 4.40 (d, 2H, 2 N-CH, J = 7.8 Hz), 4.24 (d, 2H, 2 S-CH, J = 8.0 Hz), 2.80 (br, 4H, 2 × CH_2), 2.12 (br, 2H, CH_2), 1.96 (br, 2H, CH_2); ^{13}C NMR: δ 169.5, 156.7, 152.3, 142.1, 130.4, 127.8, 125.0, 121.0, 113.4, 66.4, 43.5, 40.1, 27.5, 24.0, 22.1; DEPT: δ 130.4 (CH), 127.8 (CH), 121.0 (CH), 113.4 (CH), 66.4 (CH_2), 43.5 (CH), 40.1 (CH), 27.5 (CH_2), 24.0 (CH_2), 22.1 (CH_2); MS (EI): m/z = 634 (M^+), 605, 576, 339, 278, 146, 119, 91, 57, 43 (base peak); $C_{28}H_{30}N_{10}O_4S_2$: C, 52.98; H, 4.76; N, 22.07; S, 10.10; Found: C, 52.72; H, 4.66; N, 21.88; S, 9.95. .

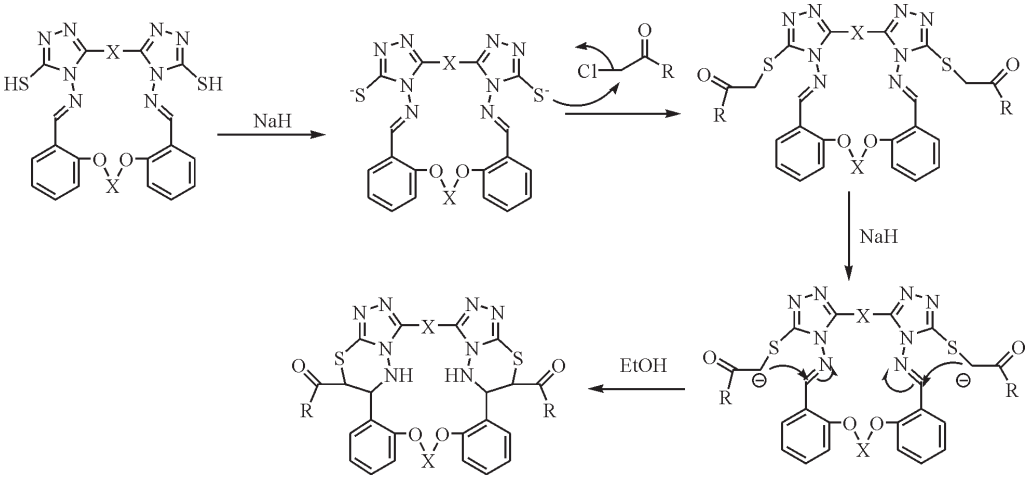
8,13-Dioxa-35,39-dithia-21,22,24,25,32,33,37,38-octaazaheptacyclo(29.5.2.2^{20,23}.0^{2,7}.0^{14,19}.0^{22,26}.0^{34,38})tetraconta-2,4,6,14(19),15,17,23,25,31,33-decaene-36,40-dicarboxamide (3d)

65% yield, IR: ν 3314, 3180 (NH stretch), 3060 (aromatic CH stretch.), 1682 (C=O), 1250 (Ar-O), 1110 cm^{-1}; ^{1}H NMR: δ 7.78 (s, 2H, NH_2, D_2O exchange), 7.41 (d, 2H, $H_{arom.}$ J = 6.1 Hz), 7.31 (d, 2H, $H_{arom.}$ J = 7.0 Hz), 7.25 (s, 2H, 2 × NH, D_2O exchange), 7.10 (d, 2H, $H_{arom.}$ J = 7.8 Hz), 6.99 (t, 2H, $H_{arom.}$ J = 6.5 Hz), 6.71 (s, 2H, NH_2, D_2O exchange), 4.48 (br, 2H, OCH_2), 4.37 (br, 2H, OCH_2), 4.38 (d, 2H, 2 N-CH, J = 7.8 Hz), 4.30 (d, 2H, 2 S-CH, J = 8.0 Hz), 2.75 (br, 4H, 2 × CH_2), 2.00 (br, 4H, 2 × CH_2), 1.23 (br, 4H, 2 × CH_2); ^{13}C NMR: δ 169.7, 156.6, 152.5, 142.1, 130.5, 127.8, 124.9, 121.1, 113.1, 66.1, 43.6, 40.0, 25.3, 25.1, 23.0; DEPT: δ 130.5 (CH), 127.8 (CH), 121.10 (CH), 113.1 (CH), 66.1 (CH_2), 43.6 (CH), 40.0 (CH), 25.3 (CH_2), 25.1 (CH_2), 23.0 (CH_2); MS (EI): m/z = 662 (M^+), 633, 604, 339, 292, 146, 119, 91, 57, 43 (base peak); Anal. Calcd. for: $C_{30}H_{34}N_{10}O_4S_2$: C, 54.36; H, 5.17; N, 21.13; S, 9.68; Found: C, 54.16; H, 5.09; N, 20.96; S, 9.55.

3. Results and Discussion

In continuation of our interest in developing the synthesis of new macrocycles and lariat ethers,[11–14] we report herein a simple and efficient method for the regioselective synthesis of novel bibrachial lariat ethers (BiBLEs) **3a–d**. In this paper we demonstrate a novel method to introduce 1,2,4-triazolo[3,4-*b*][1,3,4]-thiadiazines rings into macrocycles. Aza-crown ether compounds **1a–b** were prepared according to the published method.[13] The functionalities in these aza-crown ethers made them valuable key precursors for the formation of different fused heterocyclic compounds. The available macrocycles **1a–b** encouraged us to study their transformation into the lariat ethers containing ester or amide groups. Thus, the novel lariat compounds **3a–d** with neutral side arms were prepared by reaction of the corresponding aza-crown macrocycles **1a–b** with ethylchlroacetate and chloroacetamide. Stirring of compounds **1a–b** with ethyl chloroacetate or chloroacetamide in the presence of sodium hydride for 5 h afforded good yields of the corresponding novel bibrachial lariat ethers **3a–d** (Scheme 1).

The reaction proceeds *via* intramolecular cyclocondensation of the active methylene group with the imine group. A proposed mechanism for the reaction is outlined in Scheme 2.



Scheme 2
Postulated mechanism for bibrachial lariat ethers synthesis.

The expected compounds were obtained in good yields. The reaction of **1a–b** with ethyl chloroacetate and chloroacetamide in the presence sodium hydride was regioselective and afforded only the *cis* isomer after ring closure. The isolated compounds **3a–d** were obtained as *cis*-diastereomers. This fact was confirmed by ^{1}H NMR spectroscopy data. The stereochemistry of the products was determined from the coupling constant between the two vicinal methine protons. In the ^{1}H-NMR spectra of compounds **3a–d**, the coupling constant ($^3J_{N\text{-}CH,\ CH\text{-}S} \approx$ 7.8–8.0 Hz) is typical for the *cis* configuration.[11,14]

The IR, ^{1}H NMR and ^{13}C NMR spectra of **3a–d** confirmed the success of the cyclization by demonstrating the disappearance of the signals corresponding to the SH and CH=N protons and the appearance of signals assigned to the methine and NH protons. The infrared spectra of the aza-crown **1a–b** showed absorption bands at 2766 cm^{-1} due to SH groups which were absent in the IR spectra of compounds **3a–d.** Similarly, the ^{1}H NMR spectra of the compounds **1a–b** showed two characteristic absorptions (singlet at: δ 9.6 ppm) attributed to the CH=N groups, and another at δ 13.5 ppm, assigned to the SH, which disappeared after formation of compounds **3a–d**. In addition, absence of the ^{13}C NMR and DEPT spectroscopy signals due to the CH=N groups and appearance of the aliphatic carbon relative to the thiadiazine ring confirmed the formation of compounds **4a–d**.

4. Conclusion

In conclusion, a new series of bibrachial lariat ethers (BiBLEs) having pendant groups containing a strong donor group was prepared. These macrocycles can be used as promising polydentate ligands with three-dimensional binding character.

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