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Tetrahedron Letters 49 (2008) 723–726
Tetrahedron Letters

Sequential homo-coupling Diels–Alder/*retro* Diels–Alder reaction of 5,5′-bi-1,2,4-triazine-containing thiamacrocycles as a new route to thiacrown ethers incorporating a 2,2′-bipyridine subunit ☆

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Received 17 September 2007; revised 13 November 2007; accepted 22 November 2007

Abstract

A new route to thiacrown ethers **5a–d** and **6a–d** incorporating a 2,2′-bipyridine subunit is elaborated using, (1) homo-coupling of 1,2,4-triazine sulfides **3a–d** tethered to poly(ethylene glycol) chains with potassium cyanide and (2) Diels–Alder/*retro* Diels–Alder reaction with norbornadiene or 1-pyrrolidino-1-cyclopentene as the key steps.

Keywords: Diels–Alder/*retro* Diels–Alder reaction; 5,5′-Bi-1,2,4-triazine; Thiamacrocycles; 2,2′-Bipyridine; Thiacrown ethers

Aromatic biheterocycles have a wide range of applications in many areas of chemistry.[1] Of particular interest are 2,2′-bipyridines and their annulated derivatives which are employed as chelating ligands in the field of catalysis,[2] coordination and supramolecular chemistry,[3] metal-containing polymers,[4] molecular electronics and optoelectronic devices[5] and as photoactivated species by coordination to transition metals such as ruthenium(II) or rhenium(I).[6] They are also utilized as molecular hosts in bipyridine-containing macrocycles.[7] Besides the well-known complexation of metal ions,[8] the C_2-symmetric 2,2′-bipyridine crown ethers have been developed recently for the enantiomeric recognition of amino acid derivatives and chiral organic ammonium salts.[9] The study of similar interactions between sulfur analogues of such macrocycles and various inorganic or organic substrates is hampered by inefficient organic syntheses of thiacrown ethers containing sulfur atoms directly attached to the 2,2′-bipyridine rings.[10]

Our ongoing research on ring transformations of biheterocycles revealed that 5,5′-bi-1,2,4-triazines bearing alkylsulfanyl substituents on the triazine rings easily undergo Diels–Alder/*retro* Diels–Alder (DA–rDA) reaction with electron-rich dienophiles to give monocyclic or annulated 2,2′-bipyridine alkyl sulfides in good yields.[11–14] We now show that DA–rDA reactions of previously unknown 5,5′-bi-1,2,4-triazine-containing thiamacrocycles provide ready access to thiacrown ethers incorporating a 2,2′-bipyridine subunit within the macrocyclic framework. This approach evolved from the developments in 1,2,4-triazine cycloaddition chemistry[15] and from the reactivity of this heterocyclic ring system towards homo-coupling reactions in the presence of cyanide.[14] The important features of the strategy are summarized in Scheme 1, wherein 1,2,4-triazine sulfides **3a–d**, tethered to poly(ethylene glycol) chains were envisaged as key intermediates. Application of the homo-coupling procedure to **3a–d** by using potassium cyanide should provide 5,5′-bi-1,2,4-triazine-containing macrocycles **4a–d** which may be converted into the target molecules **5a–d** and **6a–d** via intermolecular DA–rDA reactions (Scheme 1).

1,2,4-Triazine sulfides **3a–d** were readily prepared via a two-step one-pot procedure, which involved the

☆ Part 41 in '1,2,4-Triazines in organic synthesis'. For part 40 see: Ławecka, J.; Bujnicki, B.; Drabowicz, J.; Rykowski A. *Tetrahedron Lett.* **2008**, *49*, 719–722.

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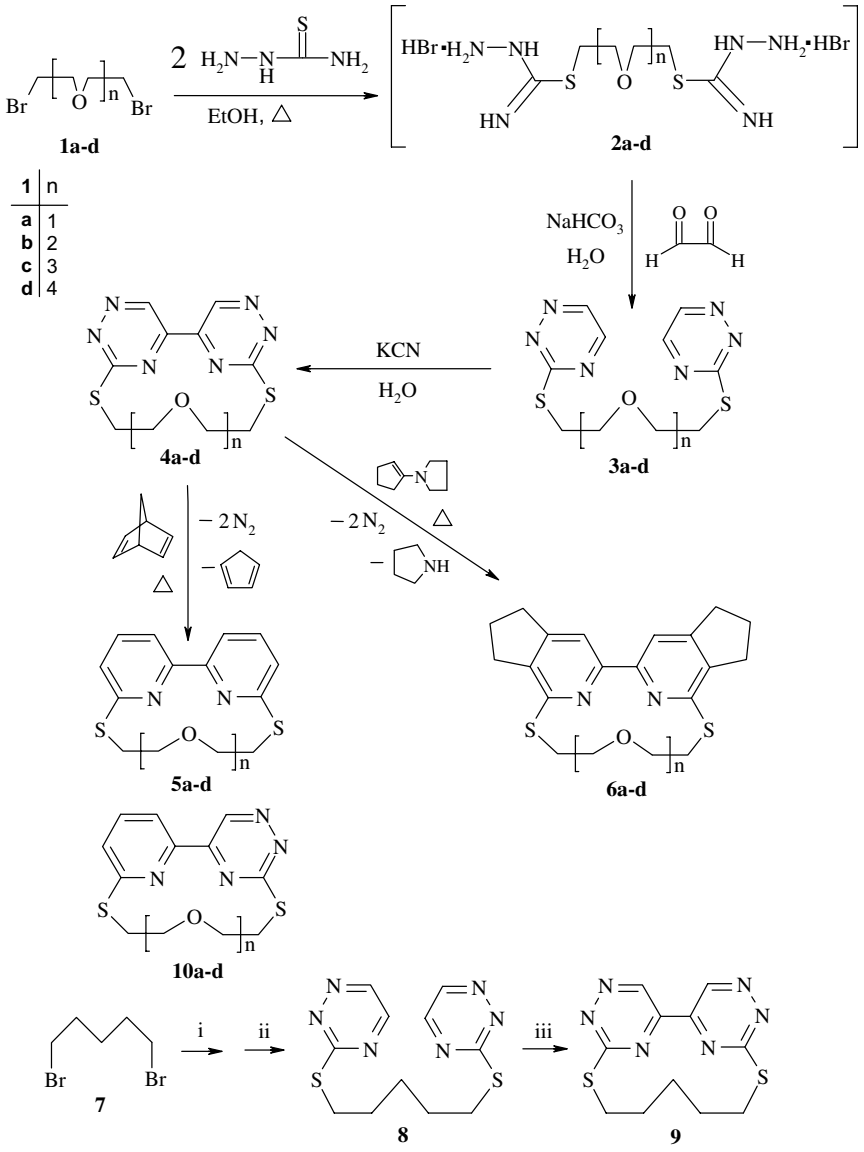
doi:10.1016/j.tetlet.2007.11.138



Scheme 1. Synthesis of 1,2,4-triazine bisulfides **3a–d**, **8**, 5,5′-bi-1,2,4-triazines **4a–d**, **9** and 2,2′-bipyridine-containing macrocycles, **5a–d** and **6a–d**. Reagents and conditions: (i) thiosemicarbazide, EtOH, reflux; (ii) 40% glyoxal, $NaHCO_3$, H_2O, rt; (iii) KCN, H_2O, rt.

S-alkylation of thiosemicarbazide with 0.5 equiv of the appropriate poly(ethylene glycol)dibromides **1a–d** to give the corresponding diquaternary salts **2a–d**, followed by the condensation of the latter with glyoxal in the presence of sodium bicarbonate. The 1,2,4-triazine sulfides **3a–d** were isolated in good yields after flash chromatography.[16] The synthesis of 2,2′-bipyridine thiacrown ethers **5a–d** or **6a–d** initially involved the preparation of precursors **4a–d** via intramolecular homo-coupling of the corresponding 1,2,4-sulfides **3a–d**. To establish optimal conditions for the cyclization process, the reaction of the easily available 1,5-bis(1,2,4-triazin-3-ylsulfanyl)pentane **8**[17] with potassium cyanide in water was investigated. To avoid unwanted intermolecular side reactions the process was carried out under high dilution conditions. After 24 h stirring at room temperature, the desired 5,5′-bi-1,2,4-triazine thiacrown ether **9** was formed in 62% yield, together with some unreacted starting material. In contrast, the reaction between **3a** and potassium cyanide was complete within 15 min (TLC) leading to cyclization product **4a**, exclusively. The reaction of 1,2,4-triazines **3b–d** and potassium cyanide under the same reaction conditions showed the generality of this process, since 5,5′-bi-1,2,4-triazine-containing thiamacrocycles **4b–d** were obtained as single products in good yields (see Table 1).[18] These results strongly suggest that the template effect of the potassium ion is effective in the case of 1,2,4-triazine sulfides **3a–d** tethered to poly(ethylene glycol) chains, and may not be operative for compound **8** without an oxygen in the tether.

The monocyclic or annulated 2,2′-bipyridine thiacrown ethers **5a–d** and **6a–d** were prepared by double Diels–Alder/*retro*-Diels–Alder [4+2]cycloaddition reactions of **4a–d** with norbornadiene or 1-pyrrolidine-1-cyclopentene. The highest yields of annulated derivatives **6a–d** were obtained when the reactions were carried out without solvent in freshly distilled enamine at 150 °C (see Table 1).[19]

Table 1
Reaction conditions, yields and mp of compounds **3a–d**, **4a–d**, **5a–d**, **6a–d**, **8** and **9**

Compound	Time [h]	Yield [%]	Mp [°C]
3a	20	38	57–58
3b	20	64	73–74
3c	20	55	48–49
3d	20	36	49–50
4a	15[a]	73	210–211
4b	15[a]	69	228–229
4c	12[a]	70	150–151
4d	10[a]	77	108–109
5a	86	63	132–133
5b	45	78	82–83
5c	40	70	106–107
5d	60	59	118–119
6a	17	64	270–271
6b	18	68	149–150
6c	14	67	121–122
6d	15	65	167–168
8	20	39	35–36
9	18	62	233–234

[a] Minutes.

The formation of monocyclic 2,2′-bipyridine thiacrown ethers **5a–d** via the reaction of **4a–d** with norbornadiene in boiling *p*-cymene needed more time for completion. When the reactions were followed by TLC, it was evident in all cases that an intermediate formed,[20] which was slowly converted into **5a–d**. Attempts to increase the cycloaddition yields failed even when long reaction times were used. However, when **4a–d** were reacted with norbornadiene in a sealed Carius tube at an elevated temperature under higher pressure, the only products were the corresponding symmetrical derivatives **5a–d** obtained in good yields.[21] Evidence for the structures of **5a–d** and their condensed analogues **6a–d** was obtained from ^{1}H and ^{13}C NMR, HRMS and elemental analysis.

In conclusion, we have demonstrated the first successful approach to 5,5′-bi-1,2,4-triazine thiamacrocycles possessing variable poly(ethylene glycol) units and their application to the synthesis of 2,2′-bipyridine thiacrown ethers via Diels–Alder/*retro* Diels–Alder reaction. Further studies on asymmetric oxidation of the latter and application of the obtained chiral sulfoxides as complexing agents are under investigation.

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16. *General procedure for the preparation of 1,2,4-triazine sulfides* **3a–d**, *and* **8**. Synthesis of compound **3b**: Typical procedure. A solution of 1.3 g (14.28 mmol) of thiosemicarbazide and 2.0 g (7.28 mmol) of 1,8-dibromo-3,6-dioxaoctane in absolute ethanol (40 ml) was stirred at reflux for 20 h. Ethanol was then evaporated and a solution of 40% 1.95 ml (13.44 mmol) of glyoxal and 1.128 g (13.44 mmol) of sodium bicarbonate in ice water (40 ml) was added to the brown residue containing hydrobromic salt **2b**. After stirring at room temperature for 30 min, methanol (55 ml) was added and the mixture was stirred at room temperature for 24 h. Methanol was evaporated in vacuo and the water layer was extracted with CH_2Cl_2 (5×10 ml). After evaporation of the solvent from the combined extracts, the remaining oily residue was purified by column chromatography on silica gel (Merck type 60, 230–400 mesh), using CH_2Cl_2–acetone (10:1) as eluent to give pure 1,8-bis(1,2,4-triazin-3-ylsulfanyl)-3,6-dioxaoctane **3b** (1.46 g, 64% yield) as a yellow solid. Mp 73–74 °C. ^{1}H NMR (200 MHz) ($CDCl_3$) δ (ppm): 3.48 (t, $J = 6.5$ Hz, 4H, CH_2), 3.68 (s, 4H, CH_2), 3.82 (t, $J = 6.5$ Hz, 4H, CH_2), 8.36 (d, $J = 2.4$ Hz, 2H, triazine hydrogen), 8.92 (d, $J = 2.2$ Hz, 2H, triazine hydrogen). ^{13}C NMR (50 MHz) ($CDCl_3$) δ (ppm): 30.1 (CH_2), 69.2 (CH_2), 70.3 (CH_2), 145.3, 148.1 and 173.8 (triazine carbon atoms). HRMS (EI): (M^+) calcd for $C_{12}H_{16}N_6O_2S_2$, 340.07762; found, 340.07684.
17. For the preparation of **8** see Ref. 16.
18. *General procedure for the preparation of 5,5′-bi-1,2,4-triazine-containing thiamacrocycles* **4a–d**. Synthesis of compound **4b**: Typical procedure. A suspension of 0.2 g (0.59 mmol) of **3b** in water (134 ml) was stirred at 40 °C until complete dissolution. After cooling to room temperature 0.137 g (2.12 mmol) of potassium cyanide was added as a solid and the resulting mixture was stirred for 15 min. The mixture was extracted with CH_2Cl_2 (5×50 ml). The combined extracts were dried over $MgSO_4$, then filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, using CH_2Cl_2–acetone (10:1) as eluent, to give pure 4,7-dioxa-1,10-dithia[10]3,3′-5,5′-bis(1,2,4-triazin-3-ylsulfanyl)cyclophane **4b** as a yellow solid. Mp 228–229 °C. ^{1}H NMR (200 MHz) ($CDCl_3$) δ (ppm): 3.43–3.51 (m, 4H, CH_2), 3.69 (s, 4H, CH_2), 3.81–3.89 (m, 4H, CH_2), 9.48 (s, 2H, triazine hydrogen). ^{13}C NMR (50 MHz) ($CDCl_3$) δ (ppm): 29.2 (CH_2), 69.2 (CH_2), 70.3 (CH_2), 141.9, 150.1 and 173.4 (triazine carbon atoms). Anal. Calcd for $C_{12}H_{14}N_6O_2S_2$: C, 42.59; H, 4.17; N, 24.83. Found: C, 42.70; H, 4.21; N, 24.80.
19. *General procedure for the preparation of thiacrown ethers* **6a–d** *incorporating an annulated 2,2′-bipyridine subunit*. Synthesis of compound **6b**: Typical procedure. 1.0 g (2.96 mmol) of compound **4b** was added to freshly distilled 2.43 g (17.75 mmol) of 1-pyrrolidine-1-cyclopentene. The mixture was heated at 150 °C for 18 h, then evaporated in vacuo. The residue was purified by column chromatography over silica gel using CH_2Cl_2–acetone (50:1) as eluent, to give pure **6b** (0.839 g, 68% yield) as a white solid. Mp 149–150 °C. Compound **6b**: ^{1}H NMR (200 MHz) ($CDCl_3$) δ (ppm): 2.14 (q, $J = 7.4$ Hz, 4H, CH_2), 2.83 (t, $J = 7.6$ Hz, 4H, CH_2), 2.95 (t, $J = 7.6$ Hz, 4H, CH_2), 3.59–3.68 (m, 8H, CH_2), 3.81–3.89 (m, 4H, CH_2), 7.36 (s, 2H, pyridine hydrogen). ^{13}C NMR (50 MHz) ($CDCl_3$) δ

(ppm): 24.1 (CH_2), 28.1 (CH_2), 30.1 (CH_2), 32.9 (CH_2), 70.3 (CH_2), 70.5 (CH_2), 114.5, 136.8, 153.4, 153.5, and 155.1 (pyridine carbon atoms). Anal. Calcd for $C_{22}H_{26}N_2O_2S_2$: C, 63.73; H, 6.32; N, 6.76. Found: C, 63.79; H, 6.28; N, 6.73.

20. The reaction of compounds **4a–d** with norbornadiene in boiling *p*-cymene gave the desired thiacrown ethers **5a–d** incorporating a 2,2′-bipyridine subunit in low yields (30–32%) accompanied by monoadducts **10a–d** (6–12% yields), see Scheme 1.
21. *General procedure for the preparation of thiacrown ethers* **5a–d**. Synthesis of compound **5b**: Typical procedure. A solution of norbornadiene (1.8 ml) in *p*-cymene (4 ml) was added to a Carius tube containing 0.2 g (0.59 mmol) of compound **4b**. The tube was tightly closed and the mixture was heated for 45 h at 140 °C (monitoring by TLC). The solvent was evaporated in vacuo and the product was purified by column chromatography on silica gel, using CH_2Cl_2–acetone (10:1) as eluent to give **5b** (0.154 g, 78% yield) as white solid. Mp 82–83 °C. ^{1}H NMR (200 MHz) ($CDCl_3$) δ (ppm): 3.61 (t, $J = 3.9$ Hz, 4H, CH_2), 3.68 (s, 4H, CH_2), 3.84 (t, $J = 4.0$ Hz, 4H, CH_2), 7.22 (d, $J = 7.6$ Hz, 2H, pyridine hydrogen), 7.46 (d, $J = 8.0$ Hz, 2H, pyridine hydrogen), 7.52–7.59 (m, 2H, pyridine hydrogen). ^{13}C NMR (50 MHz) ($CDCl_3$) δ (ppm): 28.7 (CH_2), 70.2 (CH_2), 70.6 (CH_2), 116.0, 122.5, 136.4, 156.2 and 158.6 (pyridine carbon atoms). Anal. Calcd for $C_{16}H_{18}N_2O_2S_2$: C, 57.46; H, 5.42; N, 8.38. Found: C, 57.44; H, 5.40; N, 8.32.