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S-Transalkylation/ring closing metathesis as a route to azathiamacrocycles incorporating 2,2′-bipyridine subunits☆

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Abstract—A new route to cyclophanes **6a**,**b** incorporating 2,2′-bipyridine subunits has been elaborated using as the key steps (1) *S*-transalkylation of 6,6′-bis(methylsulfanyl)-2,2′-bipyridines **2a**,**b** with ethyl bromoacetate resulting in the formation of 6,6′-bis[(ethoxycarbonyl)methylsulfanyl]-2,2′-bipyridines **3a**,**b** and (2) ring-closing metathesis of the corresponding alkenyl ethers **5a**,**b**.

The synthesis and properties of macrocycles incorporating the 2,2′-bipyridine subunit is an active area of research.[2] Such systems can serve as versatile chelating ligands binding various organic and inorganic substrates[3] and are used as building blocks for supramolecular chemistry.[4] Despite the vast knowledge on sulfur–metal interactions in coordination chemistry,[5] the use of *S*-based ligands derived from 2,2′-bipyridine appears to be still rather undeveloped. According to the literature, there is only one report of azathiacrown ethers containing sulfur atoms directly attached to the 2,2′-bipyridine rings.[6] However, the study of these interesting compounds with respect to their metal complexing ability has been hampered by inefficient chemical synthesis. We have recently elaborated a one-pot synthesis of annulated 2,2′-bipyridinium salts[7] **1** through tandem *S*-transalkylation/intramolecular ring closure of easily available 6,6′-bis(alkylsulfanyl)-2,2′-bipyridine[8] **2a** and its cycloalkeno derivatives[9] (Scheme 1). A facile *S*-transalkylation of the latter compounds with alkylating agents would afford a new route to azathiamacrocycles in which the 2,2′-bipyridine moiety is used as a subunit within the macrocyclic framework. The essential features of this strategy are summarized in the sequence depicted in Scheme 1, wherein bis(carboxylate)s **3a**,**b** were envisaged as key intermediates and the primary sub-goals of the project. Subsequent reduction of the carboethoxy groups in **3a**,**b** and treatment of the resulting alcohols **4a**,**b** with a halo alkene bearing a double bond at the terminus would provide the desired alkenyl ethers **5a**,**b**, which may be converted into the olefin cyclophanes **6a** and **6b** via ring closing metathesis (RCM).

When **2a** was treated with an excess of ethyl bromoacetate at 140 °C for 15 h the 6,6′bis[(ethoxycarbonyl)-methylsulfanyl]-2,2′-bipyridine **3a** was obtained in 91% yield.[10]

The formation of **3b** by reaction of **2b** with ethyl bromoacetate was less favourable and needed more time for completion. The reduction of the crude esters **3a**,**b** with lithium aluminium hydride in THF under reflux for 2 h led smoothly to the corresponding alcohols **4a**,**b**.[11] Reactions of the latter with allyl bromide in the presence of sodium hydride in DMF afforded alkenyl ethers **5a**,**b** exclusively.[12] Treatment of **5a**,**b** with ruthenium benzylidene complex $Cl_2(PCy_3)_2Ru{=}CHPh$ (Grubbs' catalyst I) (10 mol %) in a 0.01 M solution of methylene chloride under reflux resulted in the formation of the corresponding olefin cyclophanes **6a** and **6b**.[13] The ratio of the *E*/*Z* isomers in **6a** was 9:1 and in **6b** was 1:1.[14] The assignment of configuration at the double bond in the predominant isomers was made by analyzing ^{13}C satellites in their ^{1}H NMR spectra.[15] The vinyl protons were part

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☆ See Ref. 1.
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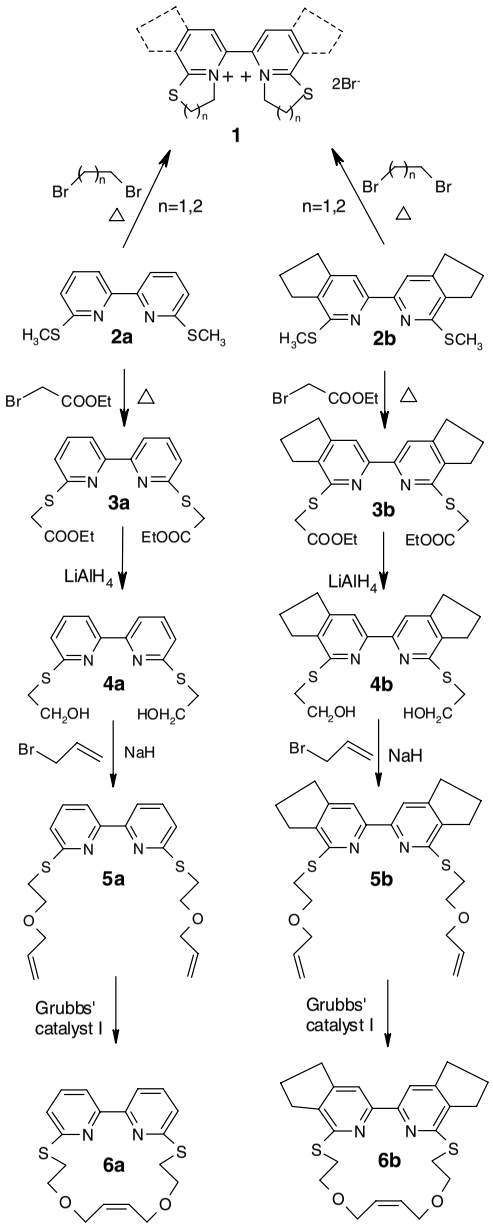

Scheme 1.

of an ABX spin system where X is an olefinic ^{13}C atom. Decoupling the protons in the allylic positions and long acquisition enabled observation of the vicinal coupling constant in the satellite spectra of **6a** and **6b**. These coupling constants (approximately 15 Hz) indicated a trans arrangement of the vinyl protons.

The yields, melting points, ^1H NMR spectra and elemental analysis of the compounds obtained are presented in Table 1.

In conclusion, the present work demonstrates the efficient application of a *S*-transalkylation/RCM route for the synthesis of 2,2′-bipyridine based cyclophanes, which have the potential of diverse application in supramolecular chemistry.

Table 1. Bipyridines **3a–6a** and annulated bipyridines **3b–6b** produced via Scheme 1

Compd	Procedure	Yield (%)	Mp (°C)	^1H NMR, spectra, δ	Formula	Calculated / Found (%)		
						C	H	N
3a	A	91	124	1.23 (t, $J = 7.1$, 6H), 4.00 (s, 4H), 4.17 (q, $J = 7.1$, 4H), 7.24 (d, $J = 8.1$, 2H), 7.65 (t, $J = 7.8$, 2H), 8.15 (d, $J = 7.27$, 2H)	$C_{18}H_{20}N_2O_4S_2$	55.08	5.14	7.14
						55.10	5.10	7.10
3b	A	73	196	1.25 (t, $J = 7.2$, 6H), 2.18 (quin, $J = 7.4$, 4H), 2.87 (t, $J = 7.4$, 4H), 2.98 (t, $J = 7.5$, 4H), 4.07 (s, 4H), 4.20 (q, $J = 7.1$, 4H), 8.04 (s, 2H)	$C_{24}H_{28}N_2O_4S_2$	60.99	5.97	5.93
						60.99	5.97	5.95
4a	B	84	67	3.45 (t, $J = 7.4$, 4H), 3.95 (t, $J = 7.3$, 4H), 7.25 (d, $J = 7.8$, 2H), 7.63 (t, $J = 7.7$, 2H), 7.95 (d, $J = 7.9$, 2H)	$C_{14}H_{16}N_2O_2S_2$	54.52	5.23	9.08
						54.53	5.20	9.11
4b	B	81	211	2.15 (quin, $J = 7.5$, 4H), 2.85 (t, $J = 7.5$, 4H), 2.99 (t, $J = 7.6$, 4H), 3.49 (t, $J = 5.5$, 4H), 3.99 (t, $J = 5.4$, 4H), 7.72 (s, 2H)	$C_{20}H_{24}N_2O_2S_2$	61.82	6.23	7.21
						61.54	6.23	7.18
5a	C	77	Oil	3.54 (t, $J = 5.9$, 4H), 3.76 (t, $J = 6.3$, 4H), 4.04 (dt, $J = 1.3$, 5.6, 4H), 5.15–5.32 (m, 4H), 5.81–6.05 (m, 2H), 7.21 (dd, $J = 0.9$, 7.9, 2H), 7.55 (t, $J = 7.9$, 2H), 8.05 (dd, $J = 0.9$, 7.7, 2H)	$C_{20}H_{24}N_2O_2S_2$	[a]		
5b	C	87	97	2.15 (quin, $J = 7.5$, 4H), 2.80 (t, $J = 7.5$, 4H), 2.95 (t, $J = 7.3$, 4H), 3.55 (t, $J = 6.9$, 4H), 3.70 (t, $J = 6.7$, 4H), 4.05 (d, $J = 5.6$, 4H), 5.25 (m, 4H), 5.85–6.05 (m, 2H), 8.05 (s, 2H)	$C_{26}H_{32}N_2O_2S_2$	66.63	6.88	5.98
						66.73	6.88	6.02
6a	D	40	79	3.65–3.70 (m, 4H), 3.55–3.60 (m, 4H), 4.80–5.00 (m, 4H), 4.98 (t, $J = 7.1$, 2H), 7.35 (dd, $J = 0.8$, 7.8, 2H), 7.65 (t, $J = 7.6$, 2H), 7.80 (dd, $J = 0.8$, 6.3, 2H)	$C_{18}H_{20}N_2O_2S_2$	59.97	5.59	7.77
						59.82	5.49	7.66
6b	D	71	220	2.10 (quin, $J = 7.3$, 4H), 2.60–3.00 (m, 8H), 3.30–3.80 (m, 12H), 5.60–5.90 (m, 2H), 7.90 (s, 2H)	$C_{24}H_{28}N_2O_2S_2$	65.42	6.41	6.36
						65.13	6.20	6.22

[a] HRMS EI: *m/z* calcd/found: 388.12792/388.12816.

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10. Procedure A: A stirred solution of **2a** or **2b** (6 mmol) in ethyl bromoacetate (5 ml) was heated under reflux for 15 h. After this time the reaction mixture was cooled and diethyl ether was added. The precipitates **3a**,**b** were filtered off and the crude products were purified by column chromatography using CH_2Cl_2 as the eluent. Analytically pure compounds, white solids, were recrystallized from methanol for **3a** and from a mixture of CH_2Cl_2/hexane for **3b**.
11. Procedure B: To a suspension of $LiAlH_4$ (0.28 mmol) was added **3a** or **3b** (0.2 mmol) in THF (6 ml). The reaction mixture was heated under reflux for 2–4 h under nitrogen. After cooling, THF saturated with water (2 ml), water (2 ml) and KOH 15% solution (1 ml) were added. The whole was extracted with THF (4×6 ml). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude products **4a**,**b** were purified by column chromatography using CH_2Cl_2/acetone (30:1) as eluent. Analytically pure compounds were recrystallized from a methanol/water mixture.
12. Procedure C: To a mixture of **4a**,**b** (1 mmol) and 60% NaH in mineral oil (6 mmol) in dry DMF (15 ml), allyl bromide (4 mmol) in DMF (5 ml) was added. The mixture was stirred at room temperature for 6 h. The reaction mixture was poured into ice/H_2O and acidified with AcOH. For **5a** the water layer was extracted with ether. The organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude product **5a** was purified by column chromatography using CH_2Cl_2/acetone (100:1) as the eluent. For **5b**: the precipitate was filtered off and recrystallized from ethanol to give **5b** as a white solid.
13. Procedure D: A solution of each of the substrates **5a**,**b** in CH_2Cl_2 ($c = 0.01$M) and Grubbs' catalyst I (10 mol %) was heated under reflux for 4–6 h. The solvent was removed in vacuo and the crude products were separated by column chromatography, using CH_2Cl_2/hexane (100:1) as the eluent. Analytically pure compounds **6a**,**b** were recrystallized from ethanol as white solids.
14. GC/MS: MS-QP550 mass detector (Shimadzu): column Zebron ZB-5, 30 M $\times$ 0.25 mm ID $\times$ 0.10 μM.
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