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Tetrahedron Letters 47 (2006) 1303–1306

Tetrahedron Letters

Synthesis of the first tris(crown formazan)

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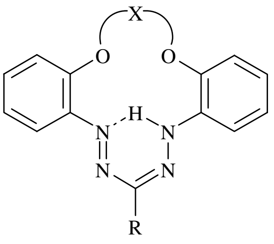
Received 22 September 2005; revised 2 December 2005; accepted 14 December 2005
Available online 9 January 2006

Abstract—A synthesis of tris(crown formazan) **2** from the corresponding hexakis(acetamidophenoxymethyl)benzene **11** by hydrolysis with an ethanolic solution containing hydrochloric acid followed by diazotization and subsequent coupling with cyanoacetic acid in pyridine containing $CuSO_4$ is described.

The chemistry and diverse applications of acyclic formazans as well as monocyclic crown-formazans have received much attention and are the subject of a large number of reviews.[1] Many macrocyclic formazans have been synthesized and their applications in selective metal extraction[2] and determination[3] were studied. Such applications depend mainly on the cavity size of the macrocyclic crown formazans as well as on the substituents in the macrocycle. In this respect we recently reported the synthesis of macrocyclic formazans **1** and studied their behavior in spectrophotometric determination of lithium as well as carriers in cesium ion selective electrodes.[4]

Moreover, interest has recently been directed towards the synthesis of multi-site crown compounds.[5] These multi-site molecular receptors are capable of binding two or more guest metal cations. In continuation of these studies we report here the first synthesis of the tris(crown formazan) **2**, which is expected to be useful analytically on account of its ability to bind more than one metal ion.



1

X, = $(CH_2)_3$, $(CH_2)_4$, $CH_2C(=CH_2)CH_2$, $CH_2CH(OH)CH_2$, $(CH_2)_2$-O-$(CH_2)_2$, R = H, Ph, CN, $ArSO_2$

Two strategies have been investigated for the synthesis of the target compound **2**. In the first strategy (Scheme 1) we studied the synthesis of crown formazan **3**, which should undergo cyclotrimerization upon heating with a catalytic amount of $CpCo(CO)_2$ to give the target compound **2**.[6]

For this purpose the bis(acetamido) derivative **6** was prepared in 70% yield as outlined in Scheme 2, by reacting the K-salt **5** (obtained upon treatment of acetamidophenol **4** with KOH) with 1,4-dibromo-2-butyne in boiling DMF. Compound **6** underwent acid hydrolysis upon treatment with an ethanolic solution containing hydrochloric acid to give an 85% yield of the corresponding bis(amine hydrochloride) **7**. Unfortunately, diazotization of **7** with $NaNO_2$ in hydrochloric acid followed by coupling with cyanoacetic acid in pyridine containing $CuSO_4$ did not yield the corresponding macrocyclic formazan **3**. The reaction instead gave a mixture of products that were difficult to separate and were not characterized.

It is also noteworthy that the macrocyclic formazan **9** could not be obtained by coupling of the corresponding bis(diazonium salt) **8**[7,8] with cyanoacetic acid (Scheme 3).

In search of an expedient pathway to prepare **2** our attention focused on compound **12** as a precursor, which should undergo diazotization and subsequent coupling

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Keywords: Alkylation; Diazotization; Coupling; Macrocyclic formazan.

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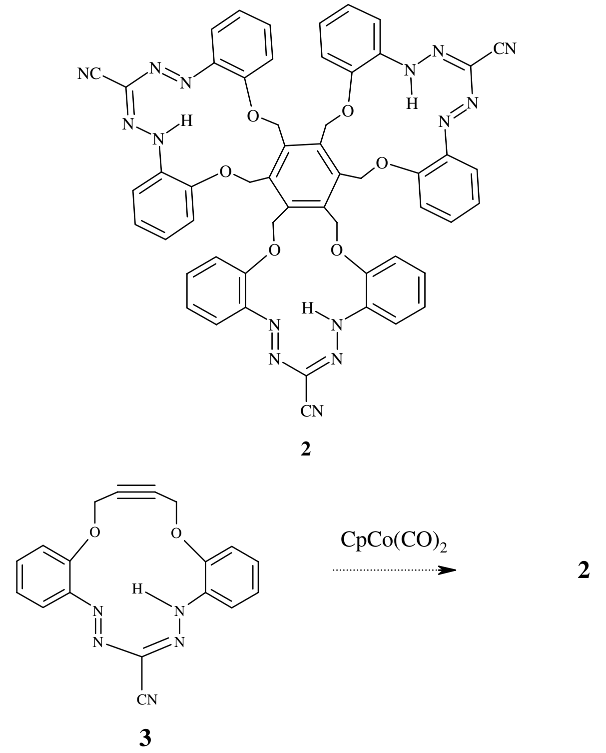
doi:10.1016/j.tetlet.2005.12.078

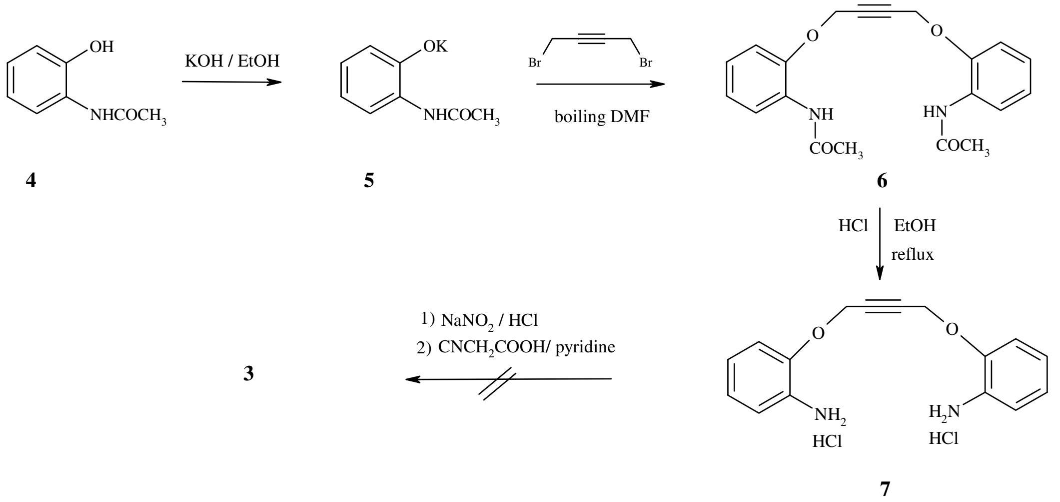


Scheme 1.

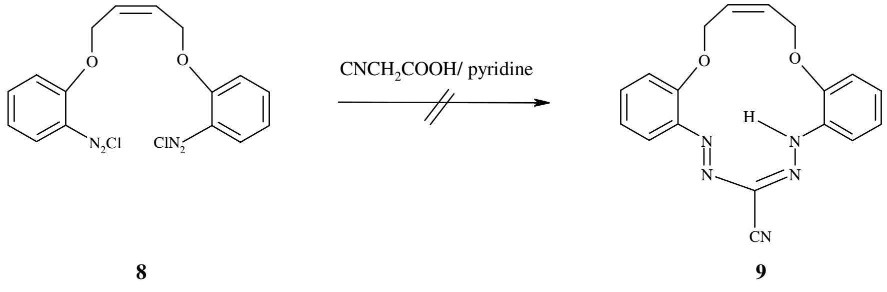
with cyanoacetic acid to furnish the target molecule **2** (Scheme 4). Thus, six-fold substitution of hexakis(bromomethyl)benzene **10**[9] with 6 equiv of the potassium salt **5** in refluxing DMF gave an 82% yield of the corresponding hexakis(acetamidophenoxymethyl)benzene **11** as colourless crystals. Treatment of the latter with an ethanolic solution containing hydrochloric acid gave the corresponding hexakis(amine hydrochloride) **12** in 78% yield. Diazotization with $NaNO_2$ in hydrochloric acid followed by coupling with cyanoacetic acid in pyridine containing $CuSO_4$ and subsequent purification gave the corresponding tris(crown formazan) **2** as deep red crystals in 10% yield.[10]

The structure of **2** was confirmed by IR, NMR and MS as well as elemental analysis. The symmetry of compound **2** is manifested by a singlet characteristic of the six equivalent OCH_2 groups in the ^1H NMR spectrum. The structure of compound **2** was further confirmed by comparison with those of the related crown formazans **13** and **14**.

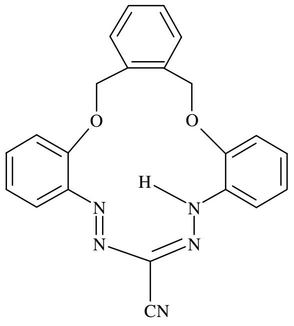
Compound **13** was synthesized as described[4c] by coupling of the corresponding bis(diazonium salt) with cyanoacetic acid in pyridine containing $CuSO_4$. Compound **14** was prepared as outlined in Scheme 5. Thus, reaction of the K-salt **5** with 1,3-bis(bromomethyl)benzene **15** in boiling DMF yielded 75% of the correspond-



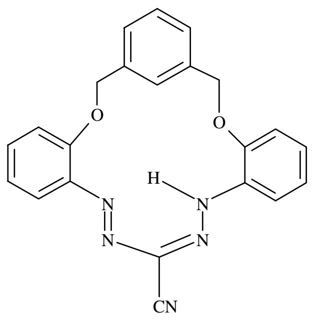
Scheme 2.



Scheme 3.



13



14

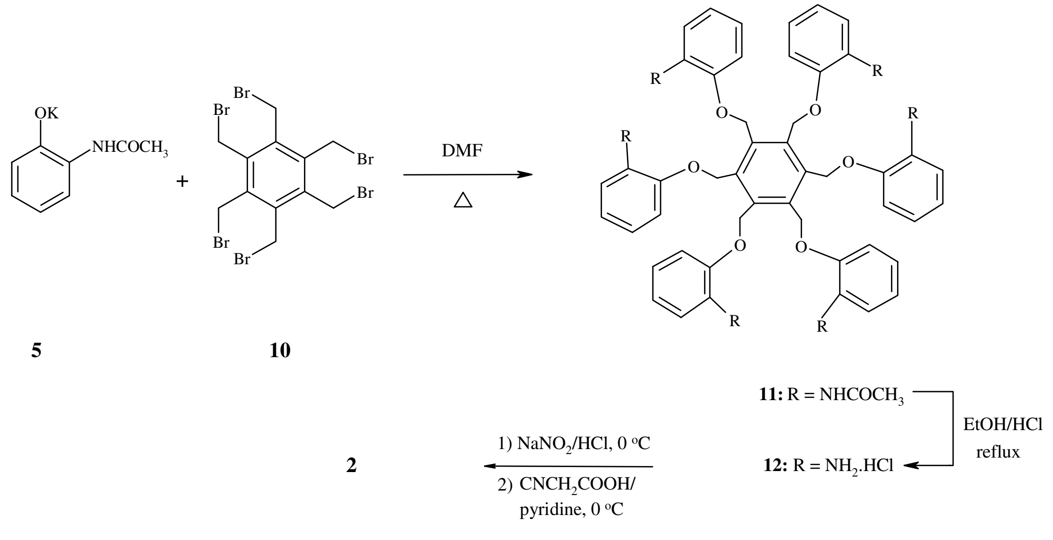
ing bis(acetamido) derivative **16**. The latter underwent acid hydrolysis upon treatment with an ethanolic solution containing hydrochloric acid to give the corresponding bis(amine hydrochloride) **17** in quantitative yield. Diazotization of **17** and subsequent coupling with cyanoacetic acid in pyridine afforded, after purification,[11] the macrocyclic formazan **14** as deep red crystals in 18% yield.

Comparison of the positions of the NH proton signals in the ^{1}H NMR spectra of the target compound **2** with those of crown formazans **13**[4c] and **14** confirmed the structure of **2**. Thus, compounds **2** and **13** were characterized by the presence of sharp signals for the NH protons in the downfield region at $\delta = 15.70$ and 16.0 ppm, respectively, which confirm the existence of an intramolecular hydrogen bond.[12]

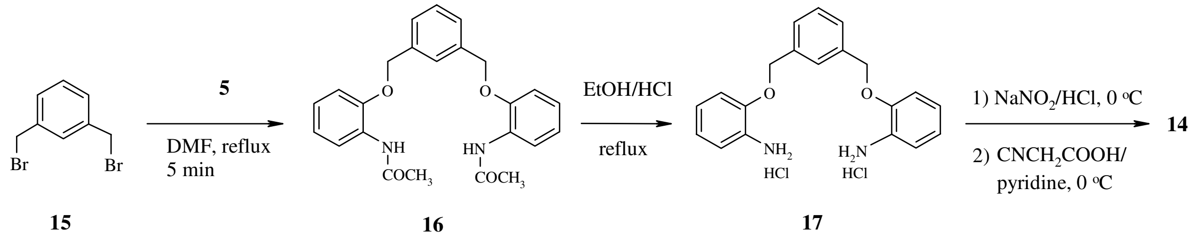
On the other hand the NH proton signal of the macrocyclic formazan **14** is at $\delta = 11.94$. This upfield shift of the NH proton indicates weakening of the intramolecular hydrogen bond, which can be attributed to the increase in size of the macrocycle **14** compared with that of **13**.

In conclusion, we have developed a simple method for the preparation of the tris(crown formazan) **2**. Full characterization of this compound is reported. Comparison of the structure of the latter with those of related crown formazans **13** and **14** is reported. Our current studies are directed towards extending the scope of this method to cover additional multi-site crown compounds with potential diverse applications in supramolecular chemistry. Studies on the cation binding properties of this new macrocycle are in progress.

Physical data for compounds **2**, **6**, **11**, **14** *and* **16**:[13] Compound **2**: mp >250 °C, MS (ESI): *m*/*z* (%) 1016 [(M+Na)$^+$, 32%], 413 (100); IR: 2230 (CN) cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.50 (s, 12H, OCH$_2$), 6.98–7.75 (m, 24H, ArH), 15.70 (s, 3H, NH) ppm. (Calcd for $C_{54}H_{39}N_{15}O_6$ (994.01): C, 65.25; H, 3.96; N, 21.14%. Found: C, 65.20; H, 4.20; N, 20.90%).



Scheme 4.



Scheme 5.

Compound **6**: colourless crystals (ethanol) mp 142–144 °C; IR: 3304 (NH) cm^{-1}, 1663 (CO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.19 (s, 6H, $NHCOCH_3$), 4.80 (s, 4H, OCH_2), 6.88–8.38 (m, 10H, ArH, NH) ppm. Compound **11**: colourless crystals (ethanol) mp 246–248 °C; IR: 3305 (NH) cm^{-1}, 1673 (CO); ^{1}H NMR (300 MHz, DMSO) δ 1.91 (s, 18H, $NHCOCH_3$), 5.28 (br s, 12H, OCH_2), 6.94–7.79 (m, 24H, ArH), 8.94 (s, 6H, NH) ppm. Compound **14**: mp >280 °C, MS (EI): *m/z* (%) 383 [M$^+$, 60%], 373 (73), 282 (100). IR: 3295 (NH) cm^{-1}, 2226 (CN). (Calcd for $C_{22}H_{17}N_5O_2$ (383.41): C, 68.92; H, 4.47; N, 18.27%. Found: C, 68.90; H, 4.60; N, 18.40%). ^{1}H NMR (300 MHz, DMSO) δ 5.20 (s, 4H, OCH_2), 6.85–7.90 (m, 12H, ArH), 11.94 (br s, 1H, NH) ppm. Compound **16**: colourless crystals (ethanol) mp 176–178 °C; IR: 3300 (NH) cm^{-1}, 1660 (CO); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (s, 6H, $NHCOCH_3$), 5.16 (s, 4H, OCH_2), 6.87–8.38 (m, 14H, ArH, NH) ppm.

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7. Compound **8** was obtained by first reacting **5** with 1,4-dibromo-2-butene in boiling DMF to give the corresponding bis(acetamido) derivative. The latter then underwent acid hydrolysis upon treatment with an ethanolic solution containing hydrochloric acid followed by diazotization with $NaNO_2$.
8. Compound **9** could only be obtained by ring closure metathesis (RCM) of 1,5-bis(2-allyloxyphenyl)-3-cyanoformazan using 2–7.5 mol % of Grubb's catalyst in refluxing CH_2Cl_2. Ibrahim, Y. A.; Behbehani, H.; Ibrahim, M. R.; Abrar, N. M. *Tetrahedron Lett.* **2002**, *43*, 6971–6974.
9. Hexakis(bromomethyl)benzene **10** was obtained by exhaustive bromomethylation of commercially available 1,3,5-trimethylbenzene followed by bromination following a literature procedure. Zavada, J.; Pankova, M.; Holy, P.; Tichy, M. *Synthesis* **1994**, 1132.
10. Typical experimental procedure for the synthesis of **2**: A solution of the hexakis(amine hydrochloride) **12** (1 mmol) in water (5 ml) and concd HCl (3 ml) was diazotized at -5 °C with a solution of sodium nitrite (0.23 g in 5 ml water) for 0.5 h. Stirring was continued for 1 h at -5 °C and then the reaction mixture was added dropwise with stirring to a solution containing cyanoacetic acid (3 mmol) in pyridine (150 ml), $CuSO_4 \cdot 5H_2O$ (0.5 g) and 20 ml water over a period of 1 h. The reaction mixture was then stored in a freezer overnight. A solid precipitated upon addition of concentrated hydrochloric acid, which was filtered and purified.[11]
11. Compounds **2** and **14** were purified on preparative TLC using silica gel (60 F_{254}) with CH_2Cl_2 as eluent ($R_f = 0.33$) for compound **2** and with a mixture of CH_2Cl_2:CH_3OH (40:1) as eluent ($R_f = 0.69$) for compound **14**.
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13. All new compounds described here gave correct elemental analyses.