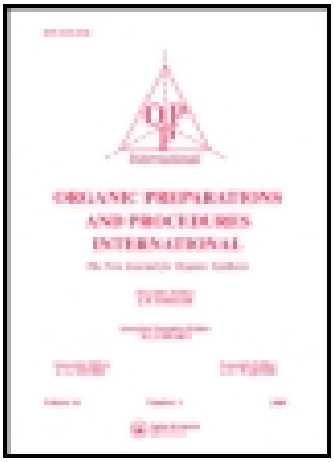

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SYNTHESIS OF N-(3-MERCAPTOPROPANOYL)-AZA-18-CROWN-6, N-(4-MERCAPTOBUTANOYL)-AZA-18-CROWN-6 AND THEIR DIMERS

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SYNTHESIS OF *N*-(3-MERCAPTOPROPANOYL)-AZA-18-CROWN-6, *N*-(4-MERCAPTOBUTANOYL)-AZA-18-CROWN-6 AND THEIR DIMERS

Sumitted by (01/04/99 Xinhao Yang, J. Justin Gooding, D. Brynn Hibbert and Naresh Kumar*

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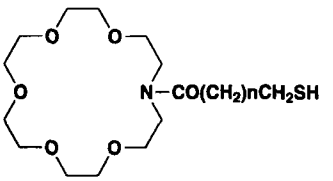
The characterisation of self-assembled monolayers (SAMs) and their application in electro-analytical chemistry such as inorganic sensors, organic and bioorganic sensors, has attracted a great deal of attention recently[1-3]. Thiol-based SAMs, derived from adsorption of functionalized alkane disulfides, sulfides or thiols on gold surfaces, are one of the most important and frequently used monolayers in electroanalytical applications[4,5]. We required **1** and **2** as a starting material for the preparation of SAMs for metal ion sensing applications.



1 n = 1

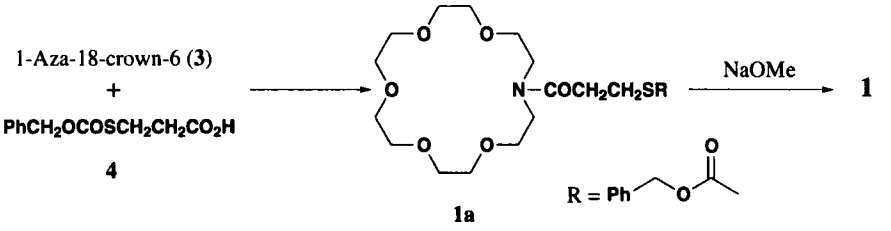
2 n = 2

Despite their simple structures, no syntheses of **1** and **2** have been described. It was envisaged that these compounds could be derived from the condensation of monoaza-18-crown-6 (**3**) with readily available 3-mercaptopropanoic acid and γ-thiobutyrolactone (**5**). Although synthesis of *N*-pyrrol-3-ylacetyl monoaza 18-crown-6 via *N,N'*-dicyclohexylcarbodiimide (DCC) mediated coupling of pyrrole-3-acetic acid and azacrown ether has been reported[6], this method could not be applied to synthesis of *N*-(meracptoalkanoyl) azacrown ethers **1** and **2**. Attempts to couple 3-mercaptopropanoic acid with monoaza-18-crown-6 in the presence of DCC led to a very messy reaction, while reaction of *S*-carbobenzyloxy-3-mercaptopropanoic acid (**4**)[7] gave very low yields of the desired product **1a** which could not be separated from the reaction mixture. Thus, the reaction of *S*-benzyloxycarbonyl-3-mercaptopropanoyl chloride with monoaza 18-crown-6 (**3**) followed by deprotection was investigated.

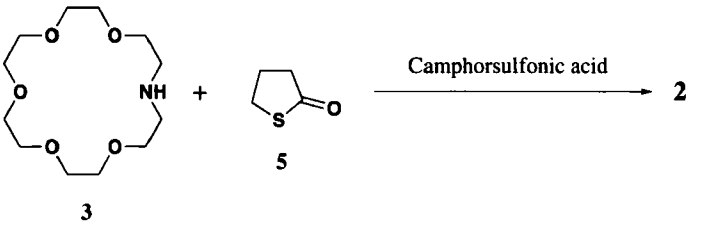
Monoaza-18-crown-6 (**3**) reacted smoothly with *S*-benzyloxycarbonyl-3-mercaptopropanoyl chloride, prepared from 3-mercaptopropanoic acid (**4**) and thionyl chloride, to give a good yield of *N*-(*S*-benzyloxycarbonyl-3-mercaptopropanoyl)-aza-18-crown-6 (**1a**). The best results were obtained when dry acetone in the presence of anhydrous sodium hydrogen carbonate was used as a solvent.

The ^{1}H NMR spectrum of **1a** showed the presence of two triplets at δ 2.74 and 3.10 corresponding to H2' and H1' respectively and infrared absorption at 1707 and 1637 cm^{-1} corresponding to the thioester and amide groups. Removal of the benzyloxycarbonyl group using sodium methoxide

gave the desired *N*-(3-mercaptopropanoyl)-aza-18-crown-6 (**1**) in good yields. The proton nmr spectrum of **1** showed a triplet at δ 1.69 corresponding to the SH group in addition to two triplets at δ 2.70 and 2.82 corresponding to H1' and H2' respectively.

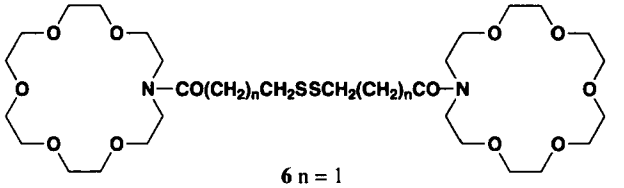


N-(4-mercaptobutanoyl)-aza-18-crown-6 (**2**) could be prepared by the reaction of 1-aza-18-crown-6 (**3**) with γ-thiobutyrolactone (**5**) in refluxing toluene containing catalytic amounts of camphorsulfonic acid. The proton nmr spectrum of **2** showed a triplet at δ 1.33 corresponding to the SH group in addition to three signals at δ 1.94, 2.51 and 2.60 corresponding to the mercaptobutyryl group. The infrared absorption for the amide group appeared at 1635 cm^{-1}.



While it was possible to assign all of the ^{13}C NMR chemical shifts for **1**, the ^{13}C nmr spectrum of **2** was found to be much more complex. Additional ^{13}C nmr signals were observed indicating a mixture of rotamers. These results are consistent with the ^{13}C nmr data reported for *N*-(4-mercaptobutanoyl)piperidine[8].

Both *N*-(3-mercaptopropanoyl)-aza-18-crown-6 (**1**) and *N*-(4-mercaptobutanoyl)-aza-18-crown-6 (**2**) are air sensitive. The mercapto compounds underwent rapid oxidative coupling to yield their respective disulfide dimers **6** and **7**. This was confirmed by the disappearance of signals corresponding to the SH groups at δ 1.69 and 1.33 respectively in their ^1H NMR spectra. The mass spectra



6 n = 1

7 n = 2

of the dimers showed the molecular ions at *m/z* 723 (100, M+Na) and 729 (100, MH^+) respectively. Therefore, these reactions were carried out under an inert atmosphere, and the products were stored under an atmosphere of argon.

In summary, this synthesis of **1** and **2** is short and can be adapted to the synthesis of other *N*-(mercaptoalkanoyl)-aza crown ethers.

EXPERIMENTAL SECTION

Mps are uncorrected and were determined using a Kofler hot stage micromelting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF 300 spectrometer. Infrared spectra were recorded with a Bomem Michelson Series FTIR. The electron impact and electrospray mass spectra were recorded on an VG Quattro mass spectrometer with source temperature of 200° and 70 eV ionising voltage. UV spectra were recorded on a Varian Cary 5 spectrophotometer. Microanalyses were performed by Dr H. P. Pham of the University of New South Wales. Column chromatography was carried using Merck silica gel 60H (Art, 7736).

***N*-(*S*-Benzyloxycarbonyl-3-mercaptopropionyl)-aza-18-crown-6 (1a).**- Thionyl chloride (1mL) was added to *S*-benzyloxycarbonyl-3-mercaptopropionic acid (**4**) (0.1g, 0.41 mmol). The mixture was heated with stirring at 50° for 10 min, cooled to room temperature and stirred further for another 15 min. Excess thionyl chloride was removed by evaporation under reduced pressure. Toluene (2 mL) was added to the residual oil, and the solution was evaporated under reduced pressure. This procedure was repeated with CH_2Cl_2 (2 mL), and the resulting acid chloride was dissolved in dry acetone (2 mL) and added dropwise at room temperature to a mixture of aza-18-crown-6 (**3**) (90 mg, 0.34 mmol) and Na_2CO_3 (127.2 mg, 1.2 mmol) in dry acetone (5 mL). The mixture was stirred under argon for 8 h followed by the addition of methanol (0.2 mL). The resulting suspension was stirred for 30 min, and the solvent was evaporated under reduced pressure. The oily residue was dissolved in dichloromethane (10 mL) and washed with aqueous HCl (1N, 5 mL), water (5 mL). The organic phase was dried, concentrated *in vacuo*, and chromatographed on an alumina column using dichloromethane/methanol (19:1) as the eluent. The fractions containing the *N*-(*S*-benzyloxycarbonyl-3-mercaptopropionyl)-azo-18-crown-6 were combined and evaporated to yield **1a** (0.16g, 78%) as a light yellow oil. IR (KBr): 2872, 1707, 1637, 1455, 1352, 1250, 1135, 751, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.74 (t, 2H, *J* = 7.2 Hz, H2'), 3.10 (t, 2H, *J* = 7.2 Hz, H1'), 3.59 (m, 24H, crown H), 5.17 (s, 2H, CH_2Ph), 7.30 (s, 5H, ArH). ^{13}C NMR ($CDCl_3$): δ 26.19 (C2'), 33.58 (C1'), 46.77 and 48.78 (NCH_2), 68.77, 68.91, 69.47, 69.8, 70.22, 70.41, 70.44, (O CH_2), 70.58 (CH_2), 70.78 (OCH_2), 128.28, 128.44, 128.56, (ArH), 135.22 (ArC), 171.16, 171.28 (CO). MS: *m/z* 486 (100, MH), 420 (10). UV-Vis λ_{max} (MeOH): 257 (ε = 898), 223 nm (3209).

Exact Mass Calcd for $C_{23}H_{36}NO_8S$: 486.216164 (MH). Found: 486.217765.

Anal. Calcd for $C_{23}H_{35}NO_8S$: C, 56.89; H, 7.27; N, 2.89. Found: C, 56.60; H, 7.54; N, 3.01

***N*-(3-Mercaptopropionyl)-aza-18-crown-6 (1) and its Dimer (6).**- Sodium methoxide (0.7 mL, 2 N) was added with stirring to a solution of *N*-(*S*-benzyloxycarbonyl-3-mercaptopropionyl)-aza-18-crown-6 (**1a**) (120 mg, 0.25 mmol) in absolute methanol (2 mL) under an atmosphere of argon. The mixture was stirred for 10 min, water (1.6 mL) was added and the mixture stirred for another 20 min. Solid carbon dioxide (excess) was added to the reaction mixture until the pH of the mixture was 8.0-8.5.

The solvent was removed by evaporation under reduced pressure, and the mixture was separated by chromatography on silica gel using initially ethyl acetate as the eluent to remove benzyl alcohol followed by ethanol to yield *N*-(3-mercaptopropionyl)-aza-18-crown-6 (**1**) (80mg, 86%). IR (KBr): 2870, 2554, 2357, 1632, 1454, 1352, 1295, 1250, 1116, 945, 838 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.69 (t, 1H, SH), 2.70 (t, 2H, *J* = 6.2 Hz, H1'), 2.82 (t, 2H, *J* = 6.2 Hz, H2'), 3.62 (m, 24H, crown H). ^{13}C NMR ($CDCl_3$): δ 20.29 (C2'), 37.22 (C3'), 46.95 and 48.96 (NCH_2), 69.51, 69.90, 70.40, 70.57, 70.80, 70.96 (OCH_2), 171.21 (CO). MS: *m/z* 352 (100, MH), 264 (10).

Exact Mass Calcd for $C_{15}H_{30}NO_6S$: 352.179385 (MH). Found: 352.178479.

Anal. Calcd for $C_{15}H_{29}NO_6S$: C, 51.26; H, 8.32; N, 3.99. Found: C, 51.06; H, 8.56; N, 3.91

On standing, *N*-(3-mercaptopropionyl)-aza-18-crown-6 (**1**), underwent aerial oxidation to yield **6**. IR (KBr): 2921, 2870, 2358, 1633, 1454, 1352, 1250, 1116, 940, 835 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.84 (t, 4H, *J* = 6.8 Hz, H1'), 2.94 (t, 4H, *J* = 6.8 Hz, H2'), 3.63 (m, 48H, crown H). ^{13}C NMR ($CDCl_3$): δ 32.98 (C2'), 33.57 (C3'), 46.90 and 48.99 (NCH_2), 69.57, 69.87, 70.38, 70.60, 70.68, 70.77, 70.90 (OCH_2), 171.37 (CO). MS: *m/z* 723 (100, M+Na), 701 (45, MH).

Exact Mass Calcd for $C_{30}H_{56}N_2O_{12}S_2Na$: 723.31655 (M+Na). Found: 723.30487.

Anal. Calcd for $C_{30}H_{56}N_2O_{12}S_2$: C, 51.41; H, 8.05; N, 4.00. Found: C, 51.70; H, 7.85; N, 3.72

***N*-(4-Mercaptobutanoyl)-azo-18-crown-6 (2) and its Dimer (7).**- A solution of γ-thiobutyrolactone (**5**) (100 mg, 0.46 mmol) in 3 mL of toluene, mono aza-18-crown-6 (**3**) (100 mg, 0.38 mmol), and camphorsulfonic acid (17.7 mg, 0.076 mmol) was heated at 100° for 8 h under an atmosphere of argon. The reaction mixed was diluted with toluene (5 mL), and washed with aqueous sodium bicarbonate and water. The organic phase was dried over anhydrous sodium sulfate, then concentrated *in vacuo*. The residual γ-thiobutyrolactone was removed under high vacuum to yield *N*-(4-mercaptobutanoyl)-aza-18-crown-6 **2** (0.1g, 74 %) as light yellow oil. IR (KBr): 2867, 2549, 1708, 1635, 1450, 1353, 1298, 1249, 1120, 1014, 943, 825, 629 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.33 (t, 1H, *J* = 8.2 Hz, SH), 1.94 (q, 2H, *J* = 7.2 Hz, H3'), 2.51 (t, 2H, *J* = 7.2 Hz, H2'), 2.60 (t, 2H, *J* = 7.2 Hz, H4'), 3.59-3.71 (m, 24H, crown H). ^{13}C NMR ($CDCl_3$): δ 24.25, 29.22, 31.11, 41.12, 48.90, 49.12 (CH_2), 69.46, 69.87, 70.18, 70.35, 70.57, 70.68, 70.82 (OCH_2), 172.29 (CO). MS: *m/z* 388 (100, M+Na), 366 (25, MH).

Exact Mass Calcd for $C_{16}H_{31}NO_6SNa$: 388.17641 (M+Na). Found: 388.17271.

Anal. Calcd for $C_{16}H_{31}NO_6S$: C, 52.58; H, 8.55; N, 3.83. Found: C, 52.40; H, 8.38; N, 3.57

On standing, *N*-(3-mercaptobutanoyl)-aza-18-crown-6 (**2**), underwent aerial oxidation to yield **7**. IR (KBr): 2870, 2359, 1633, 1471, 1353, 1117, 1014, 945, 836, 667 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.03 (q, 2H, *J* = 7.2 Hz, H3'), 2.47 (t, 2H, *J* = 7.2 Hz, H2'), 2.73 (t, 2H, *J* = 7.2 Hz, H4'), 3.60-3.68 (m, 24H, crown H). ^{13}C NMR ($CDCl_3$): δ 24.29 (C3'), 31.04 (C4'), 38.06 (C2'), 46.83 and 48.92 (NCH_2), 69.44, 69.82, 70.28, 70.56, 70.61, 70.69, 70.81 (O CH_2), 172.39 (CO). MS: *m/z* 729 (100, MH^+), 264 (10).

Exact Mass Calcd for $C_{32}H_{61}N_2O_{12}S_2$: 729.366595 (MH). Found: 729.366251.

Anal. Calcd for $C_{32}H_{60}N_2O_{12}S_2$: C, 52.72; H, 8.30; N, 3.84. Found: C, 52.90; H, 8.55; N, 3.76

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NEW N,N'-*bis*(SUBSTITUTED PHENYLAZO)PIPERAZINES AND THEIR CLEAVAGE REACTIONS IN ACETIC ACID

Submitted by (5/19/99)

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Piperazine derivatives have been are used as; anti-inflammatory,[1] andrenomedullary imaging agents,[2] as components in the amine-ketone photocoinitiation system,[3] calmodulin antagonist[4] and targeting agents for neuroblastoma.[5] In addition, the effects of these compounds have been studied in the area of cerebral circulation,[6] serotanin tyramine and benzylamine by porcine liver mitochondrial monoamine-oxidase[7] and on frog skeletal-muscle fibers.[8] The central thermo-regulatory,[9] antiarrhythmic,[10,11] electrophyssolagic and cardioprotective,[11] pharmacological,[12,13] agonist,[14] anxiolytic,[15] antagonistic,[16,17] and Ca-antagonistic activities[18] of some piperazine derivatives have also been investigated.