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Selective mono N-alkylations of cyclen in one step syntheses

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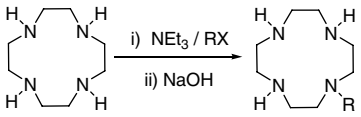
Abstract—In this Letter, we describe selective one step mono N-alkylations of cyclen (1,4,7,10-tetraazacyclododecane) using a range of functionalized alkyl halides. This 'easy to use' synthesis gives rise to mono-derivatives of cyclen from various alkyl halides or, when using alkyl dihalides, bis-cyclen derivatives, where the alkyl group links two cyclen macrocycles together. While the reaction conditions require the use of 1:4 stoichiometry (alkyl halide:cyclen), any unreacted cyclen can be recovered with an aqueous extraction and successfully reused. This procedure was found to be quite versatile, being particularly well-suited for cyclen targets bearing protected thiol groups, as well as α-chloroamide-derived chromophores; such cyclen pendant chromophores are employed as antennae for lanthanide luminescence probes and sensors.

Selective N-alkylation is an important step in the preparation of functionalized nitrogenous macrocycles such as cyclens or cyclams. To date, several synthetic routes have been reported for the selective mono N-alkylation of such frameworks. However, these usually involve multi-step syntheses, which often require the temporary protection of several of the amines in the cyclic framework prior to the selective alkylation. Examples of such synthetic strategies involve the use of common protecting groups such as *tert*-butyloxycarbonyl (Boc),[1] *p*-toluenesulfonyl (tosyl)[2] or the formyl[3] group in the 1, 4 and 7 positions of cyclen, followed by the alkylation of the remaining amino moiety and then deprotection. An alternative method often employed is the introduction of bulky substituents on three of the nitrogens of the macrocycle. Glyoxal[4] or transition metal carbonyls $M(CO)_6$,[5] such as $Mo(CO)_6$, are the most commonly used for this kind of protection. However, boron or phosphorus derivatives have also been used for this purpose.[6] Again, a final deprotection step is necessary to provide the desired mono N-alkylated product.

Direct alkylation of cyclen or cyclam has been much more rarely observed. Won and co-workers recently reported the preparation of various mono N-alkylated derivatives of such macrocycles.[7] However, both bis and tris-substitutions were often observed, which led to the need for purification by column chromatography, which is a real drawback in macrocyclic chemistry. Furthermore, the expensive cyclen, used in excess as the starting material, was not recovered. Hence, there exists a need for an improved strategy for the introduction of alkyl groups into such macrocycles in both high yields and in a versatile manner.

Here, we describe a general method for the mono N-alkylation of cyclen to obtain either mono-cyclen or bis-cyclen systems depending on the nature of the pendant arm. This improved synthesis involves the use of a four fold excess of cyclen, which can be alkylated using a variety of alkyl halides to give the mono product in high yield. While this method involves the use of excess cyclen, the unreacted macrocycle is easily removed during the work-up stage and can be recycled. In this Letter, we demonstrate the formation of several mono N-alkylated cyclen derivatives, which are obtained in high purity in moderate to good yields without the use of lengthy column chromatography (Scheme 1).



Scheme 1. The synthesis of mono N-alkylated systems, from cyclen. The cyclen moiety was reacted in 4:1 ratio with the alkyl halide RX, where X = Cl or Br.

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The synthesis involved the use of an alkyl halide (1 mmol), which was added to a solution of cyclen (4 mmol, 4 equiv) and triethylamine (1.2 mmol, 1.2 equiv) in one portion, in freshly distilled $CHCl_3$ (15 mL). The resulting solution was then refluxed gently for 15 h, under argon. After cooling to room temperature, the organic solution was washed three times with 5 mL of a 1 M sodium hydroxide solution to remove the excess of cyclen and then three times with water, dried ($MgSO_4$) and evaporated to yield colourless oils or white powders. The unreacted cyclen could be recycled by concentrating the above alkaline solution under reduced pressure and adjusting the pH of this concentrate to neutral pH using HCl (1 M). This gave a white precipitate, which when analyzed using ^{1}H NMR (600 MHz, $CDCl_3$) showed the presence of a single signal, a singlet, at 2.67 ppm, consistent with the chemical shifts of the methylene groups of the cyclen framework.

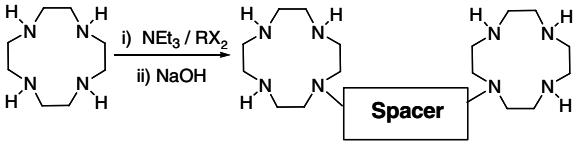
We first tested this simple method by making several mono-systems with various pendant arms (the resulting products obtained in this investigation are summarized in Table 1). Firstly, we used alkyl halides of several lengths, such as propyl, *n*-hexyl and *n*-dodecyl, **1a**–**c**, onto the cyclen framework. Such derivatives are particularly important for magnetic resonance imaging (MRI), since the Gd(III) complexes of such derivatives have been used in the past as lipophilic paramagnetic contrast agents.[8] These compounds were all formed successfully (e.g., cyclen mono N-alkylated compounds **1d**–**f**, Table 1), and obtained in moderate to good yields and in high purity, as demonstrated by ^{1}H NMR analysis, the ^{1}H NMR data matching that reported in the literature.[9] This was followed by the synthesis of several cyclen derivatives bearing a pendant chromophore. Examples include phenyl **2a**, naphthalene **3a** and acetamidoquinoline **4a**, since such groups are commonly used as antennae in sensitized lanthanide luminescence.[10] This gave compounds **2b**, **3b** and **4b**, respectively, in good yields. All characterizations were consistent with the literature data previously reported.[11] These results clearly demonstrate the versatility of this

Table 1. Alkylation of cyclen with alkyl bromide or chloride via Scheme 1

Entry	RX	Product	Yield (%)
1	$Cl(CH_2)_nCH_3$ **1a** $n = 11$ **1b** $n = 5$ **1c** $n = 2$	**1d** $n = 11$ **1e** $n = 5$ **1f** $n = 2$	69 75 38
2	**2a**	**2b**	63
3	**3a**	**3b**	59
4	**4a**	**4b**	60
5	$Br(CH_2)_{12}S$ **5a**	**5b**	68
6	**6a**	**6b**	59

simple method. Most importantly, it excludes the use of additional synthetic steps. We also investigated the formation of several mono-systems, functionalized with various alkyl halides, which had terminal acetyl protected thiol groups, as such groups could be employed to graft lanthanide ion complexes of such cyclen derivatives onto surfaces to give monolayers (SAMs) or Langmuir–Blodgett (LB) films.[12] A convenient way to attach those entities onto these surfaces is to chemically functionalize the pendant arms of the macrocycles with an electrophilic entity capable of adsorbing onto the surface, such as thiols.[13] Halides **5a** and **6a** were used with acetyl protected thiols, which can later be hydrolyzed to give the desired thiol functionalities.[14] Again here, the one step reaction worked well, and the corresponding cyclen derivatives **5b** and **6b** were synthesized in good yields as colourless oils.[15] We also investigated the synthesis of several bis-cyclen systems, where two mono N-alkylated cyclen macrocycles were linked together by an alkyl spacer, as demonstrated in Scheme 2. This was simply achieved by using alkyl dihalides. However, a twofold increase in cyclen was required; an 8:1 stoichiometry was used; again any unreacted cyclen was easily recovered.

Examples of the products of this modification are shown in Table 2. Compound **7b** has previously been reported as an important starting material for the formation of various transition metal ion complexes, and for the formation of bis-Gd(III) complexes for use as MRI contrast agents,[5,16] and as ribonuclease mimics for the hydrolysis of phosphodiesters.[17] Starting from the commercially available 1,4-bis(bromomethyl)benzene **7a** gave the desired bis-system **7b** as a white powder, in excellent yield. The incorporation of a di-sulfide bridge was also achieved using 1,2-bis(12-bromododecyl)disulfane, **8a**, and was made according to a reported procedure.[14a] The reaction of **8a** with 8 equiv of cyclen in chloroform in the presence of triethylamine afforded N-alkylated bis-system **8b** as a colourless sticky oil without the need for column chromatographic purification.[18]



Scheme 2. General reaction for the synthesis of mono N-alkylated cyclen bis-systems.

In summary, we have successfully improved the method for the mono N-alkylation of the cyclen framework, by using a 4:1 stoichiometry of cyclen to alkyl halides, in an 'easy to use' one step synthesis. We have also shown that the excess cyclen can be easily recovered at the work-up stage and subsequently recycled. We have also demonstrated that alkyl dihalides can be used to give corresponding bis-cyclens and that this method tolerates several important functional groups such as disulfide or protected thiol groups. We are currently exploring the use of this method further for the synthesis of both lanthanide-based ribonuclease mimics and in the synthesis of lanthanide-based luminescence devices.

Acknowledgements

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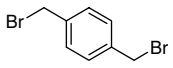
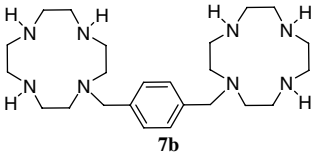
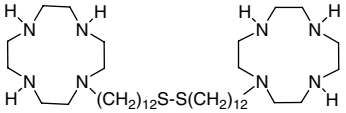
Table 2. Alkylation of cyclen with alkyl bromide via Scheme 2

Entry	RX	Product	Yield (%)
1	 **7a**	 **7b**	78
2	$Br(CH_2)_{12}S–S(CH_2)_{12}Br$ **8a**	 **8b**	70

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15. (a) Data for **5b**, Calcd for $C_{22}H_{47}N_4OS$ [M+H]: M = 415.3471. Found M = 415.3469. δ_H (400 MHz, $CDCl_3$): 2.84 (t, 2H, CH_2, $J = 7$ Hz), 2.77 (m, 4H, CH_2), 2.62 (m, 4H, CH_2), 2.55 (m, 4H, CH_2), 2.50 (m, 4H, CH_2), 2.38 (t, 2H, CH_2, $J = 7$ Hz), 2.30 (s, 3H, CH_3), 1.54 (qt, 2H, CH_2, $J = 7$ Hz), 1.44 (qt, 2H, CH_2, $J = 7$ Hz), 1.23 (m, 16H, CH_2). δ_C (100 MHz, $CDCl_3$) 195.43, 53.99, 50.99, 46.51, 45.57, 44.66, 30.11, 29.15, 29.11, 29.05, 29.03, 28.99, 28.95, 28.60, 28.58, 28.18, 26.93, 26.78; (b) Data for **6b**, Mass spectrum (MeOH, ES+): Expected M = 458.0. Found M = 417.3245 (M−Ac+H). δ_H (400 MHz, $CDCl_3$): 4.05 (t, 2H, CH_2, $J = 7$ Hz), 3.38 (s, 2H, CH_2), 2.82 (t, 2H, CH_2, $J = 7$ Hz), 2.76 (m, 8H, CH_2), 2.60 (m, 4H, CH_2), 2.56 (m, 4H, CH_2), 2.28 (s, 3H, CH_3), 1.58 (m, 2H, CH_2), 1.52 (m, 2H, CH_2), 1.22 (m, 14H, CH_2). δ_C (100 MHz, $CDCl_3$): 195.25, 171.04, 63.94, 61.18, 55.25, 51.12, 46.42, 45.64, 45.56, 45.48, 44.69, 32.52, 30.02, 28.89, 28.84, 28.81, 28.60, 28.50, 28.18, 27.99, 25.44, 25.30.
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18. *Experimental procedure and data for* **8b**: 1,2-Bis(12-bromododecyl)disulfane (100 mg; 0.18 mmol) was added to a solution of cyclen (247 mg; 1.43 mmol) and NEt_3 (0.06 mL; 0.43 mmol) in $CHCl_3$ (15 mL) and the resulting mixture was refluxed overnight. After cooling down, the crude mixture was diluted with 30 mL of $CHCl_3$ and then washed with NaOH 1 M (3×20 mL) and H_2O (2×20 mL), dried ($MgSO_4$) and evaporated under vacuum to afford a colourless oil (186 mg, 70%). Calcd for $C_{40}H_{87}N_8S_2 \cdot 0.5CHCl_3$: C, 60.58; H, 10.86; N, 13.95. Found: C, 60.68; H, 10.66; N. 13.96. Calcd for $C_{40}H_{87}N_8S_2$ [M+H]: M = 743.6523. Found M = 743.6495. δ_H (400 MHz, $CDCl_3$): 2.67 (br s, 8H, CH_2), 2.57 (t, 4H, CH_2, $J = 7$ Hz), 2.52 (br s, 8H, CH_2), 2.46 (br s, 8H, CH_2), 2.41 (br s, 8H, CH_2), 2.30 (m, 4H, CH_2), 1.56 (m, 4H, CH_2), 1.35 (m, 4H, CH_2), 1.27 (m, 4H, CH_2), 1.16 (m, 28H, CH_2). δ_C (100 MHz, $CDCl_3$) 54.0, 51.0, 46.5, 45.7, 45.6, 44.7, 38.6, 29.2, 29.1, 29.1, 29.0, 28.7, 28.7, 28.0, 27.0, 26.9, 26.8. ν(KBr)/cm^{-1}: 3290, 2923, 2852, 2808, 1642, 1491, 1464, 1352, 1201, 1149, 1043, 943, 721, 658.