A General Synthesis of 1,7-Disubstituted 1,4,7,10-Tetraazacyclododecanes

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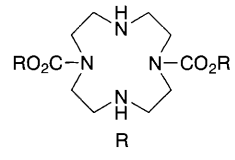
1,4,7,10-Tetraazacyclododecane reacts regioselectively in acid solution with several chloroformates to give 1,7-diprotected derivatives which could be alkylated and deprotected to afford 1,7-disubstituted 1,4,7,10-tetraazacyclododecanes.

Metal complexes of 1,4,7,10-tetraazacyclododecane and its derivatives are being widely used in diagnostic and therapeutic medicine, largely because of their favourable thermodynamic and kinetic stability.[1] In most derivatives which complex metal ions, the macrocycle has four identical coordinating pendant arms. Selective *N*-substitution of polyazamacrocycles presents an interesting synthetic challenge and only a few reports of partially substituted derivatives of 1,4,7,10-tetraazacyclododecane have appeared.[2–6] In search of new, tissue specific magnetic resonance imaging contrast agents we became interested in developing a versatile synthetic method which would afford 1,7-disubstituted 1,4,7,10-tetraazacyclododecanes conveniently and in high yields. Some time ago, we reported that sulfomethylation of this amine in aqueous solution afforded a 1,7-diprotected intermediate which could be converted to the diacetate, DO2A, in reasonable yields.[2] However, there were very few derivatives that could be synthesized using this approach so we began investigating other routes to such products.

One class of protective group that seemed appropriate for this purpose were the carbamates because of their low reactivity and ease of removal. This protective group is widely used in the peptide synthesis.[7] A careful review of the carbamate literature drew our attention to an early paper[8] that reported selective monoprotection of piperazine with ethyl chloroformate in acid solution with good yields. We have found that 1,4,7,10-tetraazacyclododecane also reacts with several chloroformates in acidic solution (pH *ca.* 2–3) to give high yields of the 1,7-diprotected derivatives (Table 1). Disubstitution takes place exclusively at the 1,7-positions and 1,4-substitution was not observed. The very high regioselectivity likely reflects the protonation sequence of the macrocycle, having two very basic (pK_as above 9) and two very acidic (pK_as below 2) nitrogens, so that microscopic protonation of two nitrogens favours positions as far apart as possible.[9]

Table 1 The isolated yields of 1,7-diprotected 1,4,7,10-tetraazacyclododecanes

Compound		Yield (%)
1	Methyl	93
2	Ethyl	98
3	Vinyl	90
4	Benzyl	88

The bis(carbamates), **1**–**4**, were isolated and characterized as free bases. Although the ^1H NMR spectra of these compounds are quite complicated due to hindered rotations about the N–CO_2R bonds, they were judged pure by elemental analysis and ^{13}C NMR. Compounds **1**, **2** and **4** were easily alkylated by a variety of reagents (Table 2) while the vinyl carbamate, **3**, was found to be too reactive for further derivatization. The methoxy- and ethoxycarbonyl groups were extremely resistant to acid hydrolysis but were cleaved in hot sodium or potassium hydroxide solution. The benyzloxycarbonyl group was stable in base but easily removed with hydrochloric acid. This protective group proved to be the most versatile because it could also be selectively removed by catalytic hydrogenation. This allowed the preparation of wide variety of 1,7-disubstituted tetraazacyclododecanes with chelating sidearms having either acid (**4a**,**c**) or ester (**4b**,**d**) functionalities. The ester derivatives (**4b**,**d**) provided a convenient entry to tetrasubstituted tetraazacyclododecane derivatives having two different pendant arms.

All compounds were characterized by analytical and spectroscopic methods.

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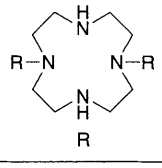
Table 2 Synthesis of 1,7-disubstituted 1,4,7,10-tetraazacyclododecanes

	Starting material	Reagents and conditions	End product 	Overall yield (%)	Entry
	1	i, $\overset{\nabla}{O}$, H_2O, 16 h; ii, NaOH, H_2O, reflux, 2 d	CH_2CH_2OH[a]	72	**1a**
	2	i, $(CH_2O)_x$, $P(OEt)_3$, 3 days; ii, KOH, H_2O, reflux, 3 d	$CH_2PO(OEt)OK$	69	**2a**
	4	i, $BrCH_2CO_2Bu^t$, Pr^i_2NEt, MeCN, 60 °C, 20 h; ii, HCl, H_2O, reflux, 1 d	CH_2CO_2H[a,b]	80	**4a**
	4	i, $BrCH_2CO_2Bu^t$, Pr^i_2NEt, MeCN, 60 °C, 20 h; ii, H_2, Pd on C, EtOH, 1 d	$CH_2CO_2Bu^t$	85	**4b**
	4	i, $(CH_2O)_x$, $P(OEt)_3$, 3 d; ii, HCl, H_2O, reflux, 1 d	$CH_2PO(OH)_2$[b]	68	**4c**
	4	i, $(CH_2O)_x$, $P(OEt)_3$, 3 d; ii, H_2, Pd on C, EtOH, 1 d	$CH_2PO(OEt)_2$	68	**4d**
	4	i, $\overset{\nabla}{N}Ts$, MeCN, reflux, 2 d; ii, CF_3SO_3H, reflux, 5 min,	$CH_2CH_2NH_2$	66	**4e**

[a] Previously reported[2,6]. [b] Isolated as hydrochloride salt.

Footnote

† **1**: ^{13}C NMR (50.10 MHz, $CDCl_3$) δ: 157.29 (*C*OO), 52.25 (*COOCH*$_3$), 50.82, 50.32, 50.03, 49.30, 48.89, 48.37, 48.10 (ring carbons). **2**: ^{13}C NMR ($CDCl_3$) δ: 156.77 (*C*OO), 60.84 (COO*CH*$_2$CH$_3$), 50.56, 50.12, 49.83, 49.33, 48.86, 48.34, 47.99 (ring carbons), 14.33 (COOCH$_2$*C*H$_3$). **3**: ^{13}C NMR ($CDCl_3$) δ: 154.05 (*C*OO), 142.39, 142.33 (COO*C*H=CH$_2$), 95.55, 95.35 (COOCH=*C*H$_2$), 51.23, 50.85, 50.59, 50.44, 49.56, 49.15, 48.25, 47.84 (ring carbons). **4**: ^{13}C NMR ($CDCl_3$) δ: 156.59 (*C*OO), 136.55, 128.31, 127.78, 127.67 (aromatic carbons), 66.86 (C$_6$H$_5$*C*H$_2$), 50.94, 50.59, 50.53, 50.06, 49.42, 48.95, 48.34, 48.04 (ring carbons). **1a**: ^{13}C NMR (D_2O) δ: 60.97 (HO*C*H$_2$CH$_2$N), 56.82 (HOCH$_2$*C*H$_2$N), 52.38 (CH$_2$N*C*H$_2$CH$_2$NH), 44.99 (CH$_2$NCH$_2$*C*H$_2$NH). **2a**: ^{13}C NMR (D_2O) δ: 61.97 (d, J_{CP} = 5.86 Hz, PO*C*H$_2$CH$_3$), 52.66, (d, J_{CP} = 4.40 Hz, PCH$_2$N*C*H$_2$CH$_2$NH), 52.01, (d, J_{CP} = 143.56 Hz, P*C*H$_2$N), 45.37 (PCH$_2$NCH$_2$*C*H$_2$NH), 17.76 (d, J_{CP} = 5.85 Hz, POCH$_2$*C*H$_3$). ^{31}P NMR (202.40 MHz, D_2O, rel. to external H_3PO_4) δ: 22.19. **4a**: ^{13}C NMR (D_2O) δ: 176.50 (*C*O$_2$H), 55.36 (*C*H$_2$CO$_2$H), 50.78 (CH$_2$N*C*H$_2$CH$_2$NH), 44.32 (CH$_2$NCH$_2$*C*H$_2$NH). **4b**: ^{13}C NMR ($CDCl_3$) δ: 170.85 (*C*OOBu^t), 80.83 (*C*Me$_3$), 56.96 (*C*H$_2$COOBu^t), 51.93 (CH$_2$N*C*H$_2$CH$_2$NH), 45.82 (CH$_2$NCH$_2$*C*H$_2$NH), 28.00 (C*Me*$_3$). **4c**: ^{13}C NMR (D_2O) δ: 52.47 (d, J_{CP} = 161.14 Hz, P*C*H$_2$N), 52.34 (d, J_{CP} = 7.32 Hz, PCH$_2$N*C*H$_2$CH$_2$NH), 44.35 (PCH$_2$NCH$_2$*C*H$_2$NH). ^{31}P NMR (D_2O) δ: 22.27. **4d**: ^{13}C NMR ($CDCl_3$) δ: 61.39 (d, J_{CP} = 7.32 Hz, PO*C*H$_2$CH$_3$), 52.42 (d, J_{PC} = 4.39 Hz, PCH$_2$N*C*H$_2$CH$_2$NH), 50.59 (d, J_{CP} = 146.48 Hz, P*C*H$_2$N), 45.21 (PCH$_2$NCH$_2$*C*H$_2$NH), 16.42 (d, J_{CP} = 4.39 Hz, POCH$_2$*C*H$_3$). ^{31}P NMR ($CDCl_3$) δ: 26.55. **4e**: ^{13}C NMR ($CDCl_3$) δ: 58.18 (N*C*H$_2$CH$_2$NH$_2$), 52.43 (CH$_2$N*C*H$_2$CH$_2$NH), 45.36 (CH$_2$NCH$_2$*C*H$_2$NH), 40.07 (NCH$_2$*C*H$_2$NH$_2$).

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