ω-Mono *N*-Alkylation of Linear Tetraamines through the Reaction of Aldehydes and Ketones on their Tricarbonyl Chromium, Molybdenum or Tungsten Complexes

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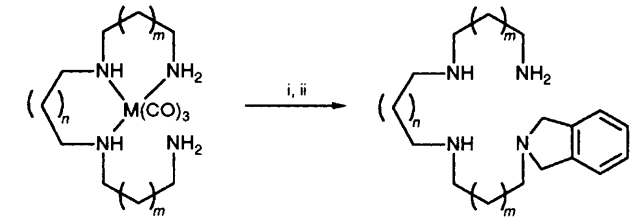
The reductive amination of carbonyl compounds by the non-coordinated amino function of the *fac*-$LM(CO)_3$ tridentate complexes of 1,4,7,10-tetraazadecane, 1,5,8,12-tetraazadodecane and 1,5,9,13-tetraazatridecane has been selectively achieved giving rise to ω-mono *N*-functionalized linear tetraamines.

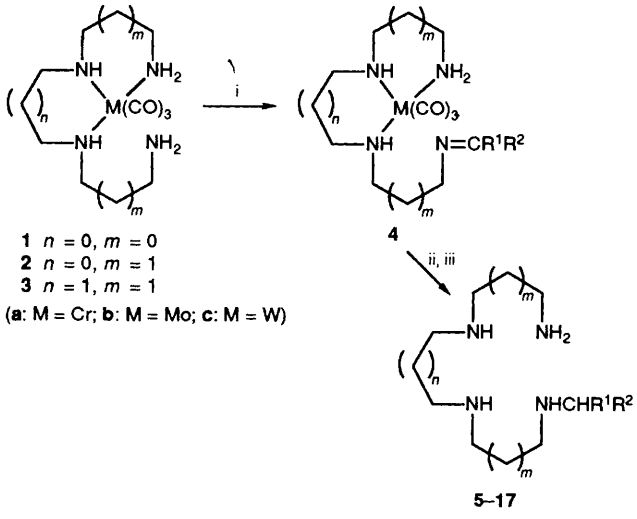
Linear polyamines have been studied widely because of their important role in many biological processes.[1] Although many are now available, there is still a need to modify them in order to reach specific properties.[2] This is generally achieved by the use of the classical techniques of organic *N*-protecting groups.[2] We previously disclosed the advantages of three new methods of monofunctionalization of cyclic tetraamines, all involving the concept of temporary triprotection, keeping one nitrogen atom free for a further *N*-alkylation.[3] The selected triprotecting agents were tris(dimethylamino)borane,[4] tris-(dimethylamino) phosphine[5] or hexacarbonylchromium;[6] this last method was adopted recently by others for the synthesis of neutral Gd^{3+}–DOTA (DOTA = 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid) analogues.[7]

Although the regioselective *N*-alkylkation of linear tetraamines could be achieved *via* the reaction of their tricar-



1a $n = 0, m = 0$, M = Cr
2a $n = 0, m = 1$, M = Cr

Scheme 1 *Reagents and conditions*: i, *o*-$BrCH_2C_6H_4CH_2Br$; ii, aerial oxidation, pH 1, H_3O^+



1 $n = 0, m = 0$
2 $n = 0, m = 1$
3 $n = 1, m = 1$
(**a**: M = Cr; **b**: M = Mo; **c**: M = W)

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5–17

Scheme 2 *Reagents and conditions*: i, $R^1R^2C{=}O$, DMF, 100 °C; ii, $NaBH_4$, room temp.; iii, aerial oxidation, pH 1, H_3O^+

bonylchromium complexes **1a**, **2b** with *o*-dibromoxylene (a bis-alkylation occurred selectively on the primary nitrogen atom) (Scheme 1), the extension of the concept of triprotection to the regiospecific ω-mono *N*-alkylation raised several problems: attempts to monoalkylate chromium and molybdenum tricarbonyl complexes **1a**, **2a** and **2b** with benzyl bromide were disappointing, giving rise to mixtures.

We report here that, by a proper choice of the complexing group 6 metal carbonyl, and a further reaction of aldehydes and ketones on the triprotected tetraamines, mono *N*-functionalized tetraamines can be obtained in good yields with rigorous regioselectivity (Scheme 2).

A preliminary study of the complexation modes of several linear tetraamines with group 6 metal carbonyls showed that a *fac*-tridentate complexation was observed with tetraamines having two and/or three carbon atoms chains, and that it is also dependent on the nature of the metal carbonyl used.† Selected data for complexes **1b**, **2b**, **2c**, **3c**, obtained unequivocally from the corresponding tetraamines,‡ are gathered in Table 1. Three distinct resonances are observed in the ^{13}C NMR spectra for the three carbon monoxide ligands; this is in agreement with a $LM(CO)_3$ complex bearing a dissymmetrically coordinated ligand L. IR data are also consistent with a local C_{3v} symmetry although a supplementary band is observed around 1685 cm^{-1}, for the complexes **2b**, **2c** and **3c** having the non-coordinated nitrogen at the end of a three-carbon chain. This band, which may be due to an interaction of the non-coordinated amino group with the $M(CO)_3$ moiety of the complexes, disappears after reaction with benzaldehyde; **4b**, obtained from **2b** ($m = 1$, $n = 0$, $R^1 = H$, $R^2 = C_6H_5$), was isolated and showed the expected spectral data.§ Further reactions of complexes **1**, **2** and **3** with aldehydes or ketones to give imines proceeded most conveniently within 2 h in dimethylformamide (DMF) at 100 °C. An *in situ* reduction into amine with sodium borohydride, followed by a final oxidation in air gave rise to the mono *N*-alkylated tetraamines.

The following run is typical: to the complex **2b** (1.0 mmol) in dry and degassed DMF (10 ml) an excess of dry $MgSO_4$, and benzaldehyde (1.0 mmol) were added. The mixture was heated with stirring under a nitrogen atmosphere at 100 °C for 2 h and then cooled to room temp.; sodium borohydride (1 mmol) was added and allowed to react overnight. The solvent was removed *in vacuo* and the residue taken up in degassed 10% aqueous HCl. The resulting acidic mixture (pH 1) was oxidized in air until no more CO evolved, and then washed with dichloromethane (2 × 25 ml). The pH was raised to 14 with NaOH pellets with cooling. After extraction with dichloromethane (2 × 25 ml). The pH was raised to 14 with NaOH pellets with cooling. After extraction with dichloromethane (2 × 25 ml), drying and evaporation, the oily residue was found to be pure **6**.

As shown in Table 2, this procedure was applied success-

Table 1 IR and ^{13}C NMR data for the $M(CO)_3$ moiety of the $LM(CO)_3$ complexes **1b**, **2b** and **3c**

$LM(CO)_3$	Yield (%)	IR[a] (v/cm^{-1})	^{13}C NMR[b] δC=O
1b	90	1895s 1755vs	229.4 228.6 227.5[c]
2b	95	1875s 1750vs 1684s	228.4 228.0 227.0[c]
3c	37	1875s 1755–1690(broad vs)	223.7[d] 222.5[e] 221.9[c,f]
2c	57	1885s 1755vs 1695s	225.0[g] 223.8[h] 222.9[c,i]

[a] In Nujol. [b] 75.47 MHz, CD_3SOCD_3. [c] 1:1:1 intensity. [d] J_{cw} 186.6 Hz. [e] J_{cw} 185.5 Hz. [f] J_{cw} 187.6 Hz. [g] J_{cw} 185.8 Hz. [h] J_{cw} 184.4 Hz. [i] J_{cw} 185.3 Hz.

Table 2 ω-mono *N*-alkylation of linear tetraamines

Starting $LM(CO)_3$	R^1	R^2	Product	Yield (%)	*m/z* (%) M^+
1a	H	Ph	**5**	65	237[b](1)
1b				75	
2a				85	
2b	H	Ph	**6**	95	[c]
2c				57	
3c	H	Ph	**7**	46	278(1)
1a	H	$PhCH_2$	**8**	76	250(2)
1b				60	
2a	H	$PhCH_2$	**9**	70	279[b](1)
2b				72	
3c	H	$PhCH_2$	**10**	62	293[b](1)
2b	H	Fc[a]	**11**	71	372(2)
2b	H	4-MeC_6H_4	**12**	83	279[b](1)
2b	H	2,4-$(MeO)_2C_6H_3$	**13**	80	325[b](1)
2b	H	n-C_9H_{19}	**14**	61	[c]
2b	H	$(Ph)_2CH$	**15**	62	[c]
2b	C_6H_5	Et	**16**	50	292(0.5)
2b	Bu^n	Me	**17**	45	[c]

[a] Fc = ferrocenyl. [b] $(M + 1)^+$. [c] Not detected.

† To be published elsewhere.

‡ Complexes **1–3** were prepared as previously described for the chromium complexes **1a**, **2a**. Complex **2c** was obtained after 7 h of heating.

§ **4b** $\nu_{(CO)}$/cm^{-1}: 1886s, 1752vs; ^{13}C NMR (CD_3CN) δ: 229.7, 228.7, 227.5 (*CO*); 162.3 (*CH*=N); 137.4, 131.7, 129.7, 128.8 (C_6H_5); 60.6, 56.0, 53.3, 51.9, 47.1, 46.5, (*C*α-N); 31.3, 25.8 (*C*β-N).

fully to the reductive amination of aromatic, aliphatic aldehydes and ketones.

All the mono *N*-alkylated tetraamines gave satisfactory IR, ^1H and ^{13}C NMR¶ and mass spectral data.

¶ *Selected data*: ^{13}C NMR, **5** ($CDCl_3$) δ 140.2, 128.3, 128.0, 126.8 (C_6H_5); 53.7 ($CH_2C_6H_5$); 51.7, 49.1, 49.03, 48.97, 48.5, 41.3, (Cα-N). **11** (C_6D_6) 88.1 (C_5H_4 *ipso*); 68.8 (C_5H_5); 68.6, 67.8 (C_5H_4); 50.0, 49.9, 49.3, 48.8, 48.5, 48.1, 40.6 (Cα-N); 33.8, 30.7 (Cβ-N). **12** (C_6D_6) 138.6, 136.1, 129.2, 128.4 (C_6H_4); 54.2 ($CH_2C_6H_4$); 50.1, 49.8, 48.7, 48.3, 48.0, 40.6 (Cα-N); 33.2, 30.8 (Cβ-N); 21.1 (CH_3). **13** (C_6D_6) 160.4, 158.9, 130.4, 121.7, 104.0, 98.9 (C_6H_3); 55.0, 54.9 (CH_3O); 49.7, 49.6, 48.7, 48.6, 48.0, 47.9, 40.2 (Cα-N); 32.4, 30.5 (Cβ-N). **14** ($CDCl_3$) 49.64, 49.59, 48.9, 47.92, 47.88, 47.3, 39.8 [Cα-N); 32.7, 31.5, 29.63, 29.60, 29.5, 29.22, 29.18 (2C), 28.9, 27.0, 22.3 [Cβ-N + $(CH_2)_8$]; 13.7 (CH_3). **15** ($CDCl_3$) 142.6, 128.3, 127.6, 126.1 (C_6H_5); 54.1 [$CH(C_6H_5)_2$]; 50.7, 48.9, 48.8, 47.8, 47.7, 47.2, 39.7 (Cα-N); 33.1, 29.6 (Cβ-N); **16** (CD_2Cl_2) 144.6, 128.5, 127.7, 127.1 (C_6H_5); 65.5 (CH); 49.0, 48.8, 48.5, 48.1, 46.5, 40.6 (Cα-N); 31.7, 31.2, 29.7 (Cβ-N + CH_2CH_3); 10.9 (CH_3). **17** (C_6D_6) 53.6 (CH); 49.9 (2C), 48.9, 48.1, 46.1, 40.6, 37.3 (Cα-N); 33.6, 31.2 (Cβ-N); 28.6, 23.4, 20.7, 14.4 ($CH_3CH_2CH_2$ + CH_3).

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