

# One Pot Symmetrical and Dissymmetrical Regiospecific $\omega, \omega'$ -Bis Mono N-Alkylation of Linear Tetraamines via their Chromium, Molybdenum or Tungsten Tricarbonyl Complexes

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*Abstract* : Dissymmetric  $\omega, \omega'$ -N-dialkylated linear tetraamines have been obtained after the successive reactions of two aldehydes and subsequent reduction and removal of the  $M(\text{CO})_3$  protection.

There is currently great interest in the biological activity<sup>1</sup> of synthetic analogs of spermine since they have proven, especially  $\omega, \omega'$ -terminally dialkylated analogs, to be the most potent antineoplastic polyamine derivatives<sup>2</sup>.












Since direct alkylation of tetraamines by alkylating agents gives mixtures, unless a procedure involving the tedious use of N-protecting organic groups is adopted<sup>3</sup>, there is an obvious need for an easy to run and regiospecific procedure of mono and/or dialkylation, starting from the tetraamine itself.

In a previous paper<sup>4</sup>, we described the  $\omega$ -mono N-alkylation of linear tetraamines L through the reductive amination of aldehydes and ketones by their tridentate fac-LM(CO)<sub>3</sub> complexes 1, 2 or 3 (M = Cr, Mo, W), (Scheme I, path a).

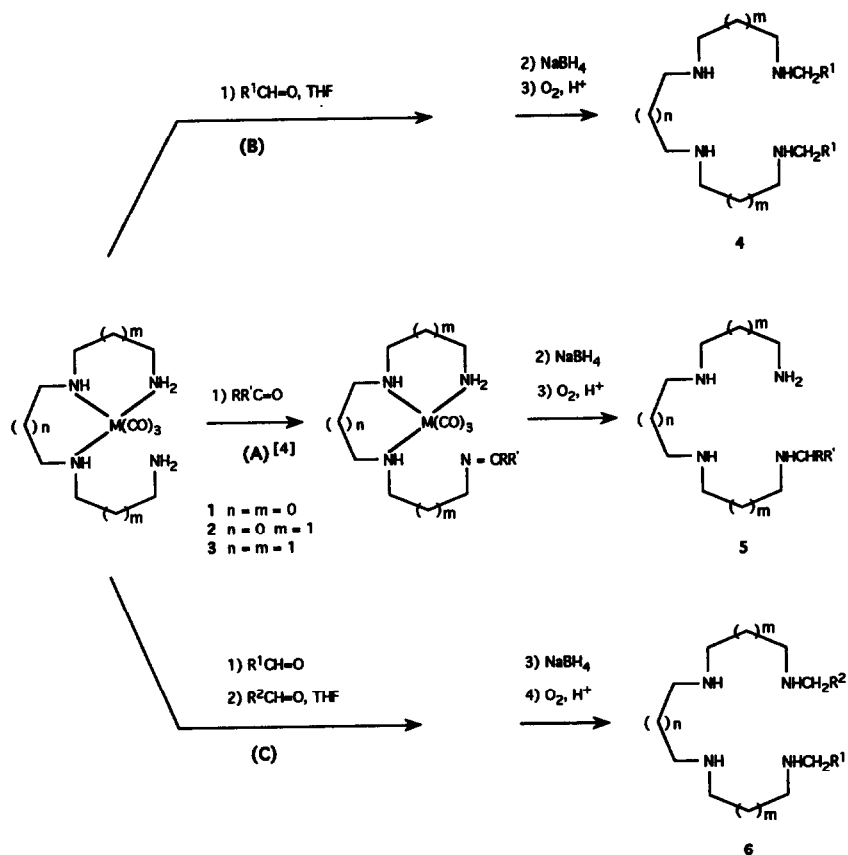
During this work, we observed that heteroaromatic aldehydes, containing an oxygen or sulfur atom, when submitted to this stoichiometric methodology, led to symmetrical  $\omega, \omega'$ -bis mono N-alkylated derivatives, in about 45% yield, instead of the expected  $\omega$ -mono N-alkylated compound (Scheme I, path b). Yields could be raised up to 80%, with the same regioselectivity, when 2 equivalents of RCH=O were used, meaning that the second  $\omega'$ -primary amino function, bound to the metal in the starting LM(CO)<sub>3</sub> structure of the complex, became reactive again (Table I, entries 2, 5, 6, 7).

These results of a general scope with heteroaromatic aldehydes led us to examine the influence of the heteroatom in this reaction. Therefore, in the presence of THF as a heteroatom

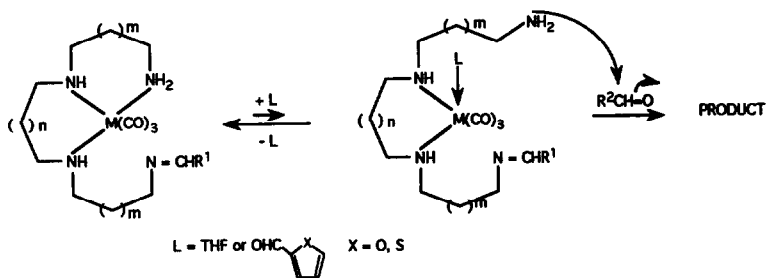
Table I :  $\omega, \omega'$ -bis mono N-alkylation of linear tetraamines 4 or 6.

Entry	LM(CO) <sub>3</sub>		M	R <sup>1</sup>	R <sup>2</sup>	4 or 6		
	m	n				Yield [%]	<sup>1</sup> H[a] $\delta$ (ppm)	m/z [M+1] <sup>+</sup>
1	0	0	Cr	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	83	3,78	[d]
2	0	0	Cr			61	3,77	306[e]
3	0	0	Cr	C <sub>6</sub> H <sub>5</sub>		76	3,78 3,76	317
4	1	0	Mo	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	79	3,77	[d]
5	1	0	Mo			68	3,76	[d]
6	1	0	Mo			75	3,63	[d]
7	1	0	Mo			72	3,97	[d]
8	1	0	Cr	n-C <sub>5</sub> H <sub>11</sub>	n-C <sub>5</sub> H <sub>11</sub>	74	[c]	315
9	1	0	Mo	C <sub>6</sub> H <sub>5</sub>		84	3,76 3,74	345
10	1	0	Mo	C <sub>6</sub> H <sub>5</sub>	Fc [b]	71	3,78 3,50	[d]
11	1	0	Mo	C <sub>6</sub> H <sub>5</sub>	n-C <sub>5</sub> H <sub>11</sub>	75	3,78 [c]	[d]
12	1	1	W	C <sub>6</sub> H <sub>5</sub>		59	3,78 3,76	358

[ a ] : signals of the -NCH<sub>2</sub>R<sup>1</sup> or -NCH<sub>2</sub>R<sup>2</sup> groups (in CDCl<sub>3</sub>)[ b ] : Fc = Ferrocenyl ; [ c ] : masked ; [ d ] : not detected ; [ e ] : [ M<sup>+</sup> ]



SCHEME I



SCHEME II

source, aliphatic and simple aromatic aldehydes were found to yield actually  $\omega, \omega'$ -bis mono N-alkylated tetraamines (Table I, entries 4, 8) as sole detected polyaminesderivatives.

Based on these results, we now report a one pot synthesis of  $\omega, \omega'$ -dissymmetrically N-disubstituted tetraamines (Scheme I, path c).

On reaction with benzaldehyde, complexes 1, 2 and 3 yield, according to Scheme I, an intermediate imine<sup>4</sup> which on subsequent in situ treatment, either directly with an heteroaromatic aldehyde (Table I, entries 3, 9, 12), or with an alkyl or a simple aromatic aldehyde in the presence of THF (Table I, entries 10, 11), lead after usual work up<sup>4</sup>, to dissymmetrically  $\omega, \omega'$ -dialkylated tetraamines.

All the attempts to isolate and characterise the bis imine expected from the reaction of furaldehyde (entry 5) with 2 (M = Mo) failed. However, an IR spectrum could be recorded and showed the two expected bands [ $\nu_{\text{CO}} = 1895(\text{s}), 1764(\text{vs}) \text{ cm}^{-1}$ ] for a fac-LM(CO)<sub>3</sub> complex with a local C<sub>3v</sub> symmetry, suggesting that the three CO ligands are still present after reaction of the two aldehydes.

So it is likely that, in the presence of THF or heteroaromatic aldehydes, the tridentate intermediate imine exists in equilibrium with a small amount of a species in which the second primary amino function is selectively liberated, allowing the second aldehyde to react (Scheme II).

Experimental procedure :

To the complex LM(CO)<sub>3</sub><sup>4</sup> (1,0 mmole) in dry and degassed N, N-dimethylformamide (10 ml) an excess of dry MgSO<sub>4</sub> and the first aldehyde R<sup>1</sup>CH=O (1,0 mmole) were added. The mixture was heated and stirred under a nitrogen atmosphere at 100°C for 2 hours ; a THF solution (2 ml) of the second aldehyde R<sup>2</sup>CH=O (1,0 mmole), was then added and heating was continued at 100°C for 2 hours (heteroaromatic aldehydes were added neat). After cooling at room temperature, sodium borohydride (1 mmole) 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 x 25 ml). The pH was raised to 14 with NaOH pellets with cooling ; extraction with dichloromethane (2 x 25 ml), drying and evaporation gave then the  $\omega, \omega'$ -dialkylated tetraamine.

All the bis mono N-alkylated tetraamines gave satisfactory IR, <sup>1</sup>H and <sup>13</sup>C NMR and mass spectral data.

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