Note

N^1,N^7-expeditious dialkylation of cyclen (1,4,7,10-tetraazacyclododecane). An astonishing reactivity of cyclen tricarbonyl molybdenum and chromium complexes

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Abstract

After reaction with alkyl iodides and subsequent oxidative removal of the $M(CO)_3$ triprotection, molybdenum and chromium *fac*-$LM(CO)_3$ complexes of cyclen (L) unexpectedly lead to N^1,N^7-dialkylated cyclen derivatives.

Key words: Molybdenum complexes; Chromium complexes; Carbonyl complexes; Tetraazamacrocycle complexes

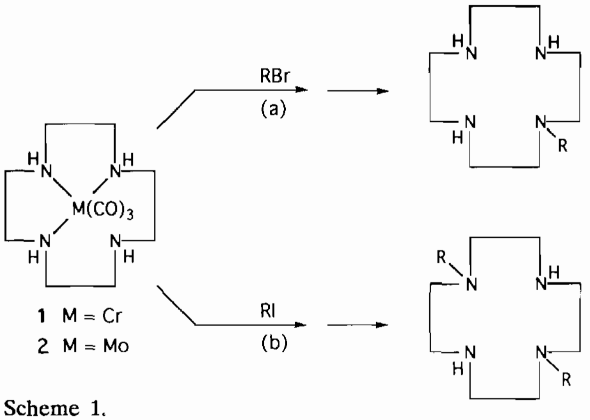
The problem of the selective alkylation of tetraazamacrocycles (to give them specific properties [1]) is still a challenge for which several solutions have been given very recently. Among them is the temporary tricomplexation with Group 6 metal carbonyls [2, 3]. This methodology raises several questions: will the reaction with $M(CO)_6$ give a tricomplexed ligand with an uncomplexed nitrogen atom whatever the ring size? Furthermore, if this condition is satisfied, will we observe a monoalkylation on the uncomplexed nitrogen atom? The first issue has been studied and the ring size conditions giving rise to a tricomplexation will be addressed elsewhere.

We report here some new results of this methodology, on the example of cyclen, which are an attempt at answering the second question, and also are a new methodology for the regiospecific N,N″-dialkylation of tetraazamacrocycles.

The chemistry of cyclen (1,4,7,10-tetraazacyclododecane) derivatives is strongly limited by the difficulties encountered during their synthesis; for instance *N*^{1},*N*^{7}-dimethyl-1,4,7,10-tetraazacyclododecane has been prepared through a multistep, time consuming synthesis, involving the classical n-tosyl protection/deprotection sequence [4].

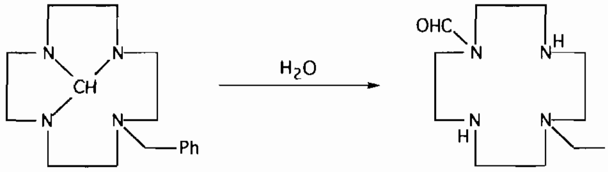
As a major improvement of the synthesis of N^1,N^7-dialkylated cyclen derivatives we now report a direct method starting from the macrocycle itself via its chromium and molybdenum *fac*-$LM(CO)_3$ complexes.

In a previous communication [2], we described the mono N-alkylation of tetraazamacrocyclic compounds through the reaction of their *fac*-$LM(CO)_3$ chromium complexes with alkyl bromides (Scheme 1, path (a)).



Scheme 1.

This very selective procedure of mono N-alkylation, relying on the temporary triprotection [2, 3, 5] of tetraamines by the $M(CO)_3$ moiety, unexpectedly failed when applied to the reaction of these *fac*-$LM(CO)_3$ complexes with alkyl iodides (Scheme 1, path (b)): after oxidative removal of the protection, as sole detected product, were obtained the N^1,N^7-disubstituted derivatives as established by comparison with the literature data of *N*^{1},*N*^{7}-dimethyl cyclen [4]. Therefore, the simple replacement of an alkyl bromide by an alkyl iodide in this reaction dramatically modifies the results. Such a N^1,N^7-difunctionalization of cyclen has already been reported by others [6] as the result of its tricyclic orthoamide hydrolysis (eqn. (1)), however the reasons for this very high regioselectivity have not been explained.



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As shown in Table 1, a series of alkyl iodides has been submitted to this new procedure, allowing the straightforward preparation of four N^1,N^7-dialkylated cyclen derivatives.

The following procedure is typical.

Complex **2** [2] (1.0 mmol) is dissolved in dry and degassed *N,N*-dimethylformamide (20 ml); dry Na_2CO_3 (5.0 mmol) and the appropriate alkyl iodide (see Table 1 for the stoichiometry) are added and allowed to react with stirring under a nitrogen atmosphere for 48 h at room temperature. The solution is then filtered under nitrogen, the solvent removed *in vacuo* and the residue taken up in 10% aqueous degassed HCl. The resulting mixture is oxidized in air until no more CO evolves. This acidic solution is washed with dichloromethane (2×25 ml), then made alkaline (pH 14) with NaOH pellets with cooling; extraction with dichloromethane (2×50 ml), drying and subsequent removal of the solvent finally give the N^1,N^7-dialkylated cyclen derivatives.

All the N^1,N^7-dialkylated cyclen derivatives gave satisfactory ^1H and ^{13}C NMR and mass spectral data (^{13}C data are reported in Table 2).

TABLE 1. Stoichiometry and yield for each alkyl iodide

R(I)	*x* (stoichiometry)	N^1,N^7-dialkylated cyclen yield (%)
Me	2	67
Et	2	70
n-Pr	3	77
Benzyl	3	55

TABLE 2. ^{13}C NMR data ($CDCl_3$; 75.47 MHz) for N^1,N^7-dialkylated cyclen

R	δ (ppm)
Me	54.0; 44.6 (CH_2 α-N); 43.8 (CH_3)
Et	50.9; 48.4; 45.3 (CH_2 α-N); 12.1 (CH_3)
n-Pr	57.0; 51.6; 45.9 (CH_2 α-N); 20.2 (CH_2 β-N); 11.4 (CH_3)
Benzyl	138.8; 128.7; 128.0; 126.9 (C_6H_5); 59.7; 51.3; 45.0 (CH_2 α-N)

This new highly selective procedure, in which the total synthesis of the macrocycle itself is not required, is the most efficient method of cyclen dialkylation.

As the reaction of alkyl bromides with *fac*-$LM(CO)_3$ has been shown to proceed via a S_N2 mechanism at the free nitrogen atom [7], it is very likely that the second alkylation which occurs with alkyl iodides, is under the control of the metal itself; the participation of the metal is currently under investigation. A further paper to be published elsewhere will be devoted to the 'bromide'/'iodide' sequence which allows the N^1,N^7-dissymmetrical dialkylation of cyclen.

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