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GENERAL ROUTE FOR THE SYNTHESIS OF MONO N-ALKYLATED DERIVATIVES OF TETRAAZAMACROCYCLES

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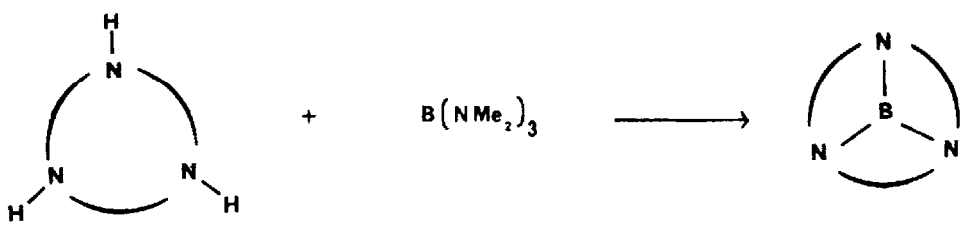
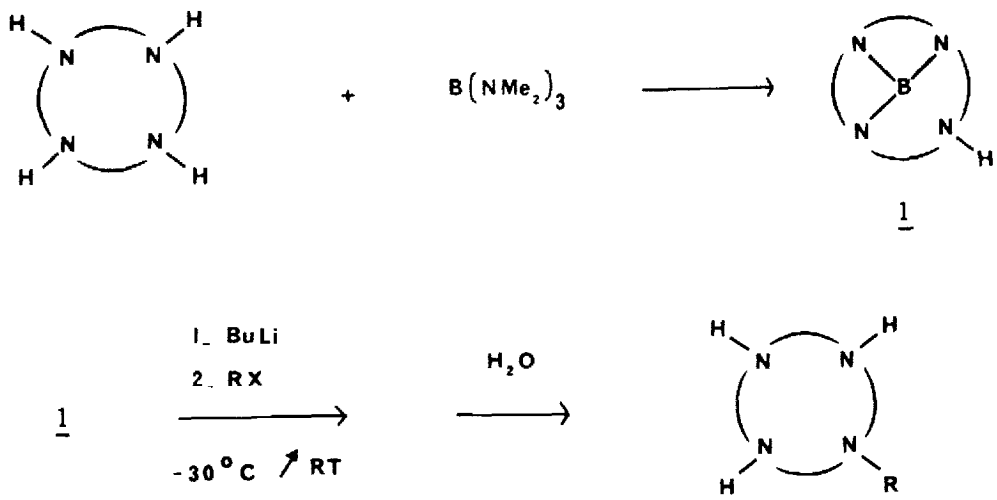
Abstract : The selective synthesis of mono N-substituted derivatives of tetraazamacrocycles can be achieved using a new boron triprotection easily removed after alkylation.

Recently many tetraazamacrocycles and their metal complexes have been prepared and characterized An ever increasing number of applications have been reported for these metal-complexing ligands which contain an additional functional groups As the presence of a single substituent on one nitrogen atom does not alter their binding abilities, mono-N-alkylated polyazacrowns bearing for instance a lipophilic side-chain or an exocyclic reactive function have been designed as possible metal extractants or catalysts (1-3) Beside the known methods of mono N-alkylation, which generally require the total synthesis of the macrocycle itself or a multistep tritosyl protection-deprotection process (4), several authors described the direct introduction of some selected functionalized side chains, based on the use of a large excess of the polyazacrown *versus* the electrophile (5) Owing to the high price of these cyclic polyamines, the need for a simple method is evident

We now report a general and stoichiometric method for the synthesis of mono N-substituted derivatives of cyclam, cyclen and some other tetraazamacrocycles which was achieved by the use of tris(dimethylamino)borane as a key reagent The synthesis of boron-nitrogen heterocycles by transaminating triazacycloalkanes with tris(dimethylamino)-borane has been previously reported (6).



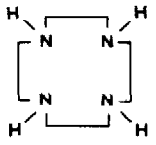
Applied to tetraazamacrocycles, this reaction leads to new tetraazaboracycloalkanes 1, in which three nitrogen atoms are temporarily blocked, keeping the fourth nitrogen atom free for a further selective monoalkylation as depicted on the following scheme



The following procedure was typical the tetraazamacrocycle (cyclam, 1 mmol) was refluxed with tris(dimethylamino) borane (1 mmol) in dry toluene (20 ml) After the end of the reaction, detected by titrating the evolved dimethylamine (2-3 hours), the solvent was evaporated and replaced by dry THF (20 ml). After cooling at -30°C, *n*-butyllithium (1 mmol) was added and allowed to react for 15 minutes. The alkylating reagent (1 mmol) was added and the mixture was stirred at room temperature for about 2 hours water was then added in order to remove the boron moiety. The pH was raised to 14 with 4N NaOH, the solvent removed under reduced pressure and the residue extracted with CH_2Cl_2. Drying over $MgSO_4$, filtration and evaporation of the solvent yield an oily residue which was found to be the monoalkylated tetraazamacrocycle (yield 80-95 %) This crude material does not need further purification

The boron intermediates such as 1 are extremely moisture-sensitive ; however, the mass spectrum (7) and the ^{13}C NMR spectrum (8) could be recorded for the boron-cyclam intermediate and were fully consistent with the proposed structure 1 , the molecular ion which is also the base peak and the ten expected NMR signals (for 1) were observed

Various selected alkylating reagents and tetraazamacrocycles have been submitted to this procedure, (Table I)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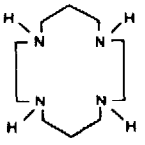
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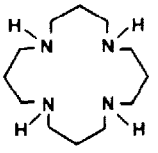
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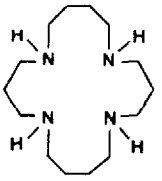
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Table I : Alkylation of tetraazaboracycloalkane

Macrocycle	Alkylating agent	Product (yield)
Cyclen	$PhCH_2Br$	Cyclen N-CH_2Ph (50%)
Cyclam	$PhCH_2Br$	Cyclam N-CH_2Ph (95%)
	CH_2=CH-CH_2Br	Cyclam N-CH_2CH=CH_2(85%)
	CH_3OTs	Cyclam N-CH_3 (80%)
	Cl-CH_2-Ferrocenyl	Cyclam N-CH_2Fc (80%)
	Cl-CH_2- 	Cyclam N-CH_2-  (95 %)
3333	$PhCH_2Br$	3333 N-CH_2Ph (80%)
3434	$PhCH_2Br$	3434 N-CH_2Ph (70%)

All the mono N-alkylated tetraazamacrocycles gave satisfactory spectral data. This easy to run one-pot process involving the versatile boron intermediate constitutes a powerful method of stoichiometric preparation of mono N-functionalized tetraazamacrocycles. The mild conditions of deprotection allow the introduction of sensitive groups such as polymerisable moieties. Further studies and extensions are under active investigation.

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7 1 m/e(%) : 208(100), 178(16), 164(58), 151(97) ; 146(65), 109(18), 95(19), 81(20), 67(34)

8 1 ^{13}C NMR 75.47 MHz (toluene-d8) 57.4, 56.8, 55.5 ; 55.0, 54.0 ; 52.7 ; 50.8 ; 50.0 ($CH_2\alpha$-N), 35.9, 33.2 ($\underline{C}H_2$ β-N)

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