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A NEW POLYAMINE SYNTHESIS.

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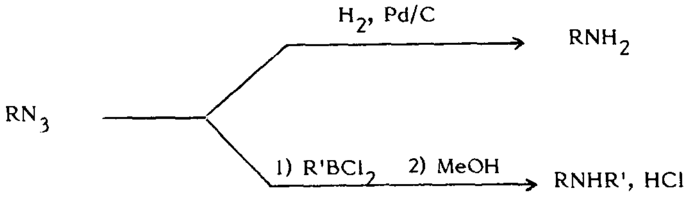
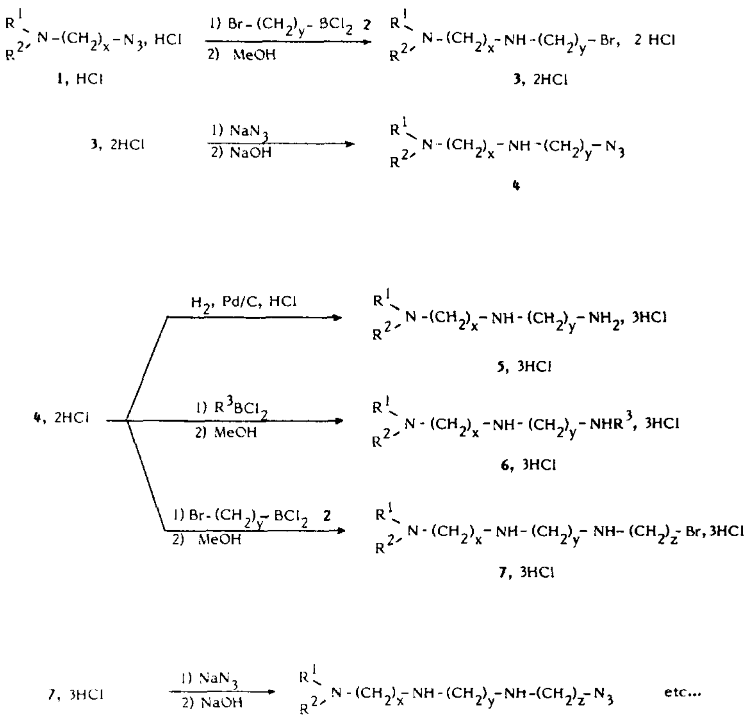
Summary - A new flexible method for the step by step construction of polyamines based on the reaction of dichloroboranes with azides is reported.

In recent years, a great deal of attention has been focused on polyamines largely because of their biological properties and the prominent role they play in proliferative processes(1). Examination of the literature revealed only a limited number of methods available for the preparation of these compounds essentially based on the selective modification of preexisting polyamines (i.e. putrescine, spermidine, spermine...)(2) or on the complete elaboration of their skeleton using a nitrile functionality as a CH_2-NH_2 precursor (3).

The azido group is an usual primary amine genitor (4) to which surprisingly little attention has been devoted in the field of polyamines (5,6,7). Furthermore, as Brown et al. reported in 1971, azides may also easily lead to secondary amines via their reductive alkylation with boranes (8).



In an earlier paper, we studied the chemoselectivity of the reaction of dichloroboranes with functionalized azides (9). These results led us to envision the sequence depicted in the following scheme for the stepwise building of polyamines.



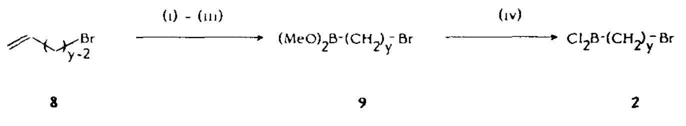
The ω-amino azides **1** were easily prepared from the corresponding commercially available halides, except for **1e** (R^1 = CH_3CO, R^2 = H, x = 3) which was obtained by acylation of **1c** (table I).

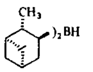
Table I - Synthesis of ω-amino azides **1** (10)

Azide	R^1	R^2	x	Yield (%)(a)	Azide	R^1	R^2	x	Yield (%)(a)
1a	H	H	2	77	**1d**	Me	Me	3	77
1b	Me	H	2	73	**1e**	CH_3CO	H	3	89 (b)
1c	H	H	3	80					

(a) Isolated yields. (b) From **1c**.

Dichloroboranes **2** (y = 3 or 4) were accessible from the corresponding dimethylboronates which were prepared by hydroboration of allyl- or butenyl bromides according to the following scheme :



y = 3 i)  then CH_3CHO (11) ii) H_2O iii) MeOH (12) iv) BCl_3

9(13) : b.p.$_{0.1}$ = 30-35°C, yield (from **8**) = 68 %. **2** : b.p.$_{15}$ = 35-40°C yield (from **9**) = 78 %

y = 4 i) $HBBr_2 : SMe_2$ ii) H_2O(14) iii) MeOH(12) iv) BCl_3

9 : b.p.$_{0.1}$ = 35-38°C, yield (from **8**) = 75 % . **2** : b.p.$_{15}$ = 40-43°C , yield (from **9**) = 85 %

The hydrochlorides **1**, HCl are reductively alkylated by reaction with the dichloroboranes **2** (1.5 eq., CH_2Cl_2 or C_6H_6, r.t.) giving after methanolysis the diamino derivatives **3**, 2HCl. Nucleophilic substitution of bromide with NaN_3 in boiling water followed by basification with NaOH and extraction allowed the isolation of the azides **4**. These compounds may be hydrogenated or again alkylated with a selected dichloroborane leading respectively to the triamines **5**, **6** or **7**, isolated as their trishydrochlorides (table II).

Table II - Synthesis of some di- and triamines (10)

1,HCl ⟶ **3**,HCl

Diamines	R^1	R^2	x	y	Yield(%)(a)
3a, HCl	Me	H	2	3	71
3b, HCl	H	H	3	3	79
3c, HCl	CH_3CO	H	3	3	71

3,HCl ⟶ **4**

Diamines	R^1	R^2	x	y	Yield(%)(a)
4a	Me	H	2	3	65
4b	H	H	3	3	70
4c	CH_3CO	H	3	3	83

4, 2HCl ⟶ **5** or **6**, 3HCl

Triamines	R^1	R^2	R^3	x	y	Yield(%)(a)
5a, 3HCl	Me	H	H	2	3	89
5b, 3HCl	H	H	H	3	3	90

Triamines	R^1	R^2	R^3	x	y	Yield(%)(a)
5c, 3HCl	CH_3CO	H	H	3	3	91
6a, 3HCl	H	H	n-Hex	3	3	75

(a) Isolated yields calculated from the starting hydrochlorides **1**, HCl or **4**, 2HCl.

The sequence **1**, HCl → **3**, 2HCl → **4**, 2HCl → **5**, **6** or **7**, 3HCl establishes the principle of a flexible synthesis of di- and triamines. It may easily be extended to the tetramines and, as illustrated below, thermine tetrahydrochloride(15) was prepared using this methodology.

$$H_2N-(CH_2)_3-N_3,\ HCl \xrightarrow[2)\ MeOH]{1)\ Br-(CH_2)_3-BCl_2} H_2N-(CH_2)_3-NH-(CH_2)_3-Br,\ 2HCl$$

1c **3b** (yield = 79 %)

$$\mathbf{3b},\ 2HCl \xrightarrow[2)\ NaOH]{1)\ NaN_3} H_2N-(CH_2)_3-NH-(CH_2)_3-N_3$$

4b (yield = 70 %)

$$\mathbf{4b},\ 2HCl \xrightarrow[3)\ NaN_3\quad 4)\ NaOH\quad 5)\ H_2,\ Pd/C,\ HCl]{1)\ Br-(CH_2)_3-BCl_2\quad 2)\ MeOH} H_2N-(CH_2)_3-NH-(CH_2)_3-NH-(CH_2)_3-NH_2,\ 4HCl$$

thermine, 4HCl
(yield = 55 % from **4b**, 2HCl)

This approach, which does not involve any protective step, provides an easy access to polyamines. Only few examples have been described in this preliminary communication, but the obtention of regio- and stereo specifically substituted azides **1** and dichloroboranes **2** will allow the synthesis of a great number of di-, tri- or tetraamines. More details on our investigations in this field will be published in a near future.

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(10) All new compounds gave satisfactory elemental analyses and the proposed structures were consistent with the spectral data.

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(13) **9** may be also obtained from allyl bromide and $HBBr_2$: SMe_2 followed by methanolysis in a 20 % yield.

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(15) Thermine, 4HCl : F = 275-280°C (lit. (16) = 280°C (decomp.). ^1H NMR (D_2O) : 1.87-2.37 (m, 6H) ; 3.03-3.35 (m, 12H). ^{13}C NMR (D_2O) : 25.4 ; 26.6 ; 39.5 ; 47.3 ; 47.6. Analysis : calcd. for $C_9H_{24}N_4$, 4HCl : C, 32.34 ; H, 8.38 ; N, 16.76 ; found : C, 32.32 ; H, 8.34 ; N, 16.99.

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