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Solid-phase combinatorial synthesis of polyamine derivatives using aminoalcohol building blocks

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Abstract—A systematic study of nucleophilic displacement of mesyl groups using benzylamine was carried out on Multipin Synphase™ supports. The optimal conditions were applied for the combinatorial synthesis of polyamine derivatives from commercially available aminoalcohols and amines. © 2001 Published by Elsevier Science Ltd.

Polyamines (PA) are low molecular weight naturally occurring polycationic molecules. Synthetic analogues and derivatives are potential therapeutic agents in biological disorders such as cancer and parasitic diseases. They can also be ion-channel blockers or vectors in gene delivery. For these reasons, they have attracted considerable attention in organic chemistry.[1]

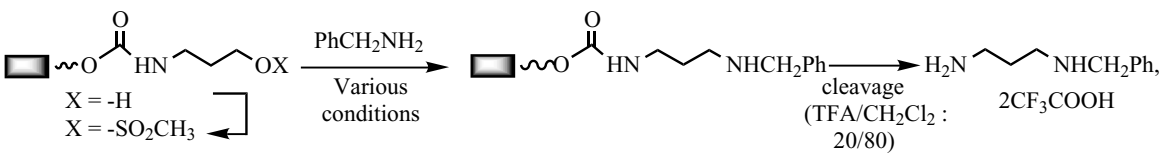
The solid-phase synthetic pathway to these compounds may involve the selective functionalization or protection from commercially available PA.[2] However, a greater diversity can be obtained through the assembly of the PA skeleton from suitable amino building blocks using alkylation of amines or sulphonamides,[3] reductive alkylation[4] and acylation followed by reduction.[5] In spite of certain flexibility these reactions often require the preparation of variable building blocks.

We report here the optimisation and the combinatorial exploitation of a rapid and versatile synthetic pathway to diverse PA from commercially available linear aminoalcohols. Their hydroxyle group may undergo simple reaction with methanesulfonyl chloride then displacement by an excess of primary amine, secondary amines or by a second aminoalcohol leading to a variable PA chain.

SynPhase™ 'Lanterns' (Mimotopes Pty Ltd) were chosen because they offer synthesis characteristics and functionality comparable to Wang resin. Their easy and fast handling facilitates combinatorial synthesis of milligram scale individualised compounds (35 μmol per support) using the 'split-pool' technique.

The 3-aminopropan-1-ol and benzylamine were used as model building blocks for the optimisation sequence (Scheme 1).

The first steps of the method used commercial and low cost reagents. The anchorage of the first aminoalcohol was achieved via an acidic labile carbamate linker.[6] The best conditions for the subsequent mesylation were easily determined and consisted of the use of methane sulfonyl chloride (1.1 M, rt, 30 mn) in anhydrous pyridin. In contrast, the third step—nucleophilic substitution by an amino group—was supposed to be used either with readily available synthons or with hardly accessible amines. For this reason, we were very inter-



Scheme 1.

Keywords: polyamines; combinatorial synthesis; solid-phase synthesis.

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ested in an optimal reaction for many concentrations of the amine.

Multiple attempts varied benzylamine concentration (0.1, 0.25, 0.5, 0.75 and 1 M corresponding to 1.7–17 equiv.) in DMSO (0.6 mL), duration (ranging from 0.5 to 48 h) and temperature (rt, 50 and 80°C). After cleavage, the ^{1}H NMR spectra of the crude compound in D_2O in the presence of 4-nitrophenol (35 μmol) as an internal standard were then realised. The integration ratio of the desired compound to the internal standard allowed an evaluation of the yield and the purity of the *N*-benzylpropanediamine.

For each concentration a mathematical study allowed Eq. (1) to be formulated: yield $= K(1–10^{at})$ (K: maximal yield, a: reaction rate, t: time).[7] Thus, optimal conditions could be defined: 1 M concentration of benzylamine at 50°C for 6 h in anhydrous DMSO. The concentration of benzylamine not only increased the reaction rate but also influenced its completion. Whereas the maximal yield did not exceed 70% at 0.5 M, it reached 90% at 1 M. The duration of reaction did not compensate low concentrations showing a limit of this synthetic pathway.

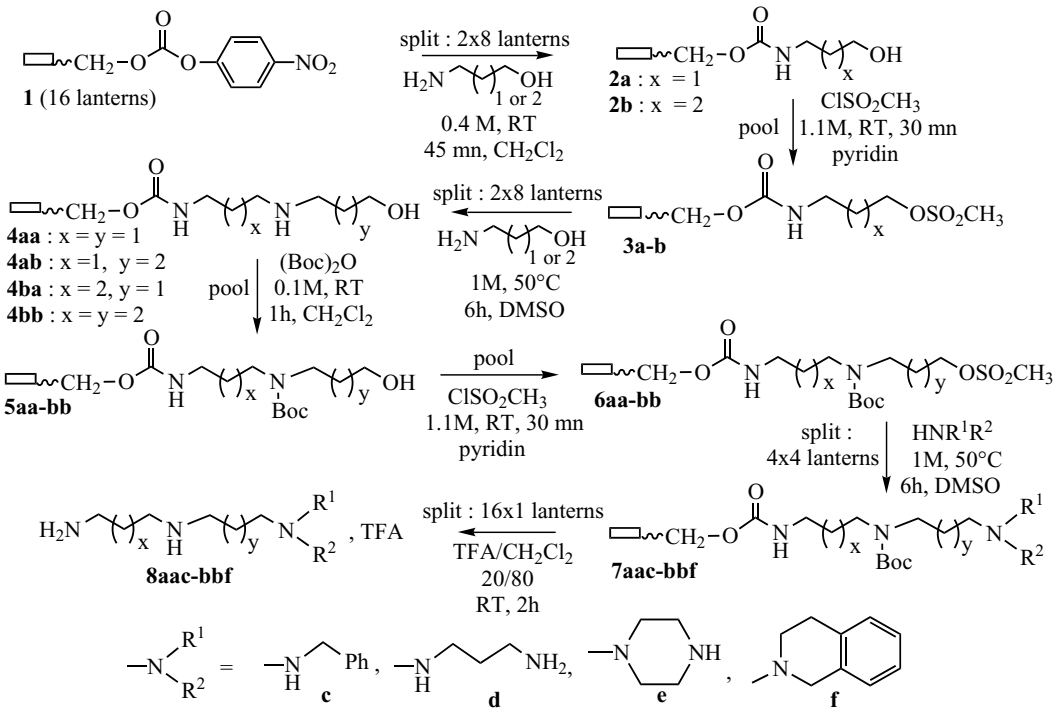
We transposed these findings to the synthesis of a small combinatorial library of 16 individualised PA starting from commercially available aminoalcohols and amines[8] (Scheme 2).

Sixteen SynPhase supports **1** were divided in two pools and reacted, respectively, with 3-aminopropan-1-ol and 4-aminobutan-1-ol. The supports (**2a**–**b**) were pooled for the mesylation then divided again and reacted with the same aminoalcohols following the optimal conditions for the nucleophilic substitution (1 M, 50°C, 6 h) leading to **4aa**–**bb**. They were pooled again for the protection of the secondary amine allowing the mesylation of hydroxyle group. The resulting supports **6** were finally shared in four pools and reacted with secondary or primary amines. Their separated cleavage in acidic conditions provided the individualised compounds **8**.

These spermidine, homospermidine and norspermidine derivatives **8** were analysed using various techniques. The ^{1}H NMR spectra were recorded in the presence of an internal standard, as described above. This analysis confirmed the obtaining of the expected crude compounds **8** in good yield (50–85%) and purity (>90%).[8] The HPLC,[9] MS[10] and paper electrophoresis[11] analyses supported this valuation and demonstrated the presence of residual starting materials such as aminoalcohols or mesylated aminoalcohols due to incomplete nucleophilic substitution. The substitution could also occur with two neighbouring mesyl groups resulting in the weak production of bis-alkylated products.

Fig. 1 represents the ^{1}H NMR spectrum in D_2O and the HPLC chromatogram of the crude N^8-benzylspermidine (trifluoroacetate salt) **8abc**, whose analytical data are given in notes.[12] The yield and purity levels of this compound are representative of the other derivatives **8** of the series.

In conclusion, we have developed a simple and efficient method for the small scale combinatorial synthesis of PA derivatives from diverse and commercially available aminoalcohols and amines. The purity of the crude products is compatible with direct screening of their biological activity. Our investigations proceed with the extension of the procedure to obtain tetramine deriva-



Scheme 2.

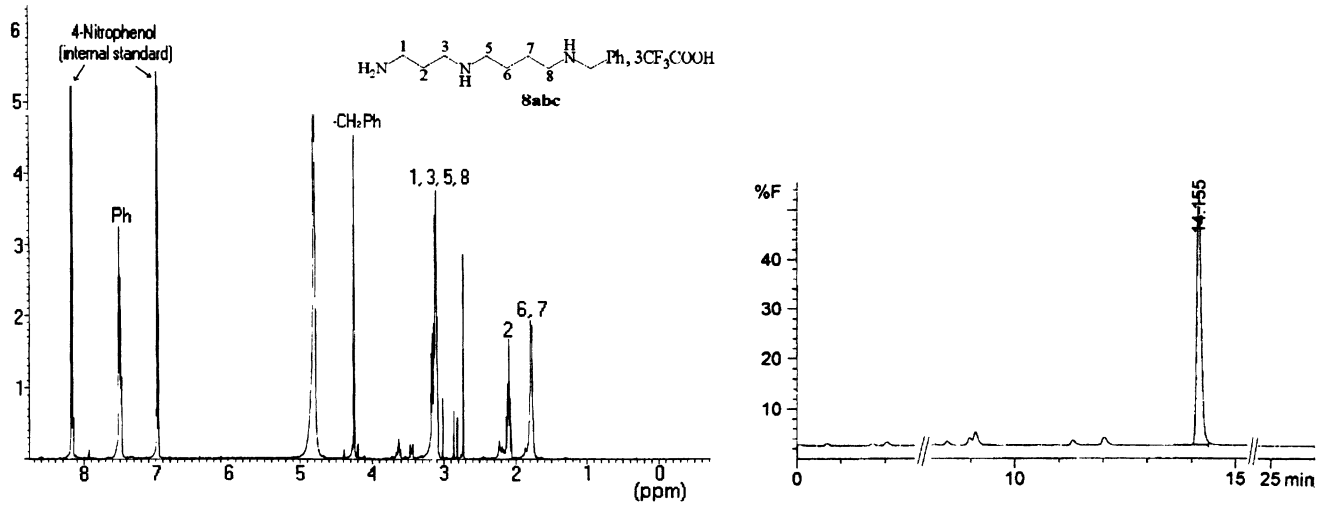


Figure 1.

tives and with its possible transposition to Wang resin to produce larger quantities (100 mg scale).

Acknowledgements

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7. At a benzylamine concentration of 1 M, $K=91$, $a=0.25$, at 0.5 M, $K=70$, $a=0.136$, at 0.25 M, $K=65$, $a=0.075$ determined by linear regression on semi-logarithmic scale.
8. **Experimental procedure for the preparation of 8**: Sixteen SynPhase™ Lanterns (Code SPPS, D series, Linker HMP, 35 μmol) were reacted at room temperature in a solution of 4-methylmorpholine (0.22 mol L^{-1}) and 4-nitrophenylchloroformate (0.22 mol L^{-1}) in CH_2Cl_2 (25 mL). After 45 min the lanterns **1** were washed four times with CH_2Cl_2 then shared in two pools and left to react for 2 h at room temperature in solutions of aminoalcohol (0.4 mol L^{-1}) in CH_2Cl_2 (15 mL). The lanterns were then pooled and washed successively in CH_2Cl_2, DMF (×4), H_2O (×2), DMF (×1), THF (×1), and CH_2Cl_2 (×2) (general procedure of washing) leading to **2**. They were then reacted for 30 min at room temperature in a solution of methane sulfonyle chloride (1.1 mol L^{-1}) in pyridin (25 mL) and washed according to the general procedure. These lanterns **3** were suitably divided in two pools and reacted for 6 h at 50°C with aminoalcohols (1 mol L^{-1}) in DMSO (15 mL) and then washed under the same conditions. The lanterns **4** were suspended at room temperature in a solution of $(Boc)_2O$ (0.1 mol L^{-1}) in CH_2Cl_2 (25 mL). After 1 h, they were washed and treated with methane sulfonyl chloride under the conditions described above for the preparation of **2**. These lanterns **6** were divided in four pools and reacted at 50°C for 6 h with various amines (1 mol L^{-1}) in DMSO (5 mL) and washed according to the general procedure. The cleavage occurred in a solution of trifluoroacetic acid in CH_2Cl_2 (20/80) (2 mL) containing the internal standard (35 μmol). After 2 h, the samples were evaporated to dryness to provide the crude compounds **8** (purity >90%, yields: **8aac**: 65%, **8abc**: 68%, **8bac**: 75%, **8bbc**: 66%, **8aad–bbd**: 50%, **8aae**: 59%, **8abe**: 52%, **8bae–bbe**: 50%, **8aaf–abf**: 75%, **8baf**: 73%, **8bbf**: 85%).
9. The HPLC analyses were performed on a Hewlett–Packard Agilent 1100 apparatus equipped with a Nucleosyl 100-5 C18 AB column. The samples were dissolved in water and eluted with a gradient of CH_3CN in aqueous CH_3COOK and octane sulfonate. Amine containing

molecules were revealed through a post column orthophthalaldehyde (OPA) derivatization. (Seiler, N.; Knödgen, B. *J. Chromatogr*. **1980**, *221*, 227–235.)

10. High resolution mass spectra were recorded on a VARIAN MAT 311 apparatus using FAB ionisation. The compounds **8aad**–**bbd** were ionised using ES technique.
11. High-voltage paper electrophoresis were performed on a PHEROGRAPH model 64 using 3 MM paper with a 3% HCOOH solution as eluent.
12. The NMR spectra were recorded on a Bruker DMX 500 WB apparatus at 500 MHz. **8abc** N^8-Benzylspermidine trifluoroacetate. ^{1}H NMR (D_2O, internal standard: 4-nitrophenol), δ (ppm): 1.78 (m, 4H, H-6,7), 2.10 (m, 2H, H-2), 3.14 (m, 8H, H-1,3,5,8), 4.25 (s, 2H, $\underline{CH_2}$Ph), 7.5 (m, 5H, H-Ph). MS (FAB): $(M+H)^+$ theor.: 236.2127, found: 236.2126.