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Lipophilic Propanediamines : New Building Blocks for Combinatorial Chemistry

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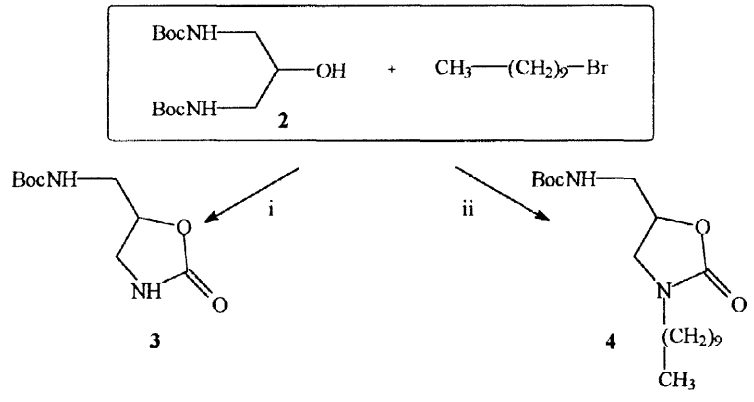
Abstract : Combinatorial chemists need building block libraries where molecular diversity is taken into account. For this purpose, we describe the synthesis of a library of 2-alkyl and 2-alkoxypropanediamines for which a large scale of lipophilicity is investigated. © 1998 Published by Elsevier Science Ltd. All rights reserved.

The molecular diversity of the libraries in combinatorial chemistry[1] is introduced, at each step of the synthetic scheme, by building blocks. These often being commercially available reactants. When the general structure of a lead molecule is known, a thorough investigation of the space of the descriptors implicated in the biological activity is necessary for SAR studies. So, a focused library has to be built to optimise the lead. Among existing libraries of building blocks, 1,3-propanediamines have been poorly studied (especially 2-alkyl[2] and 2-alkoxy compounds), but are very interesting as scaffolds in synthesis, including the formation of (thio)ureas or guanidines.

2-alkoxypropanediamines were obtained by O-alkylation of the nitrogen protected 1,3-diaminopropan-2-ol. Ramalingam et al.[3] describe the synthesis of the N,N'-di-*t*-butyloxycarbonyl-2-methoxy-1,3-diaminopropane (54 % yield) from N,N'-di-*t*-butyloxycarbonyl-1,3-diaminopropan-2-ol by reaction with methyl iodide in THF in presence of sodium hydride. We observed that the same reaction with a longer alkyl halide such as 1-bromodecane led to the formation of the oxazolidinone **3**[4] (scheme 1). Such cyclisation also occurred with 1-iododecane. Using DMF instead of THF, we obtained the oxazolidinone more quickly (1 h in DMF, 15 h in THF). Interestingly in this solvent, the *t*-butoxide anion formed in the mixture and pulled out the NH proton of the oxazolidinone to give N-alkylated derivative **4**[4].



***Scheme 1** : (i) NaH, THF, 15 h, r.t., 89%, (ii) NaH, DMF, 1 h, r.t., 67%.*

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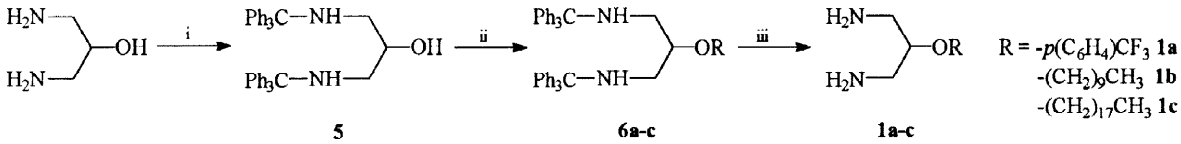
Similar to previous results[5], we observed that the oxazolidinone was formed in the reaction mixture in DMF or THF independent of the presence of any halide. This result confirms that the formation of the oxazolidinone is faster than the O-alkylation. To overcome this cyclisation and form the decyloxycompound, two solutions were attempted. In the first, we replaced the bromine atom of the electrophilic reagent with a better leaving group, whilst in the second the protecting group of the amino functions was changed. In the first case, the trifluoromethylester group was chosen as leaving group. Decanol was allowed to react with trifluoromethylsulfonic anhydride to give the sulfonic ester with a quantitative yield[6]. Then, the reaction with **2** afforded exclusively the corresponding 2-decyloxy-di-*t*-butyloxycarbonyl-1,3-diaminopropane with a 70% yield. The drawback of this synthesis is the high cost of trifluoromethylsulfonic anhydride since several grams of each diamine have to be produced. The second procedure used a trityl[7] as the amino protecting group. Introduction of this protection on 1,3-diaminopropan-2-ol was carried out with triphenylmethylchloride and triethylamine in DMA at r.t.. The alcohol function was finally alkylated with the corresponding akylhalide and NaH in DMF at room temperature. Salts of the diamines[8] were obtained after deprotection with CH_2Cl_2/TFA (scheme 2).



***Scheme 2** : (i) Ph_3CCl, Et_3N, DMA, 15h, rt, 60% ; (ii) R-Br, NaH, DMA, 51-78% ; (iii) a) TFA, CH_2Cl_2, b) NaOH 56-82%.*

In summary, a new method has been developed for lipophilic alkoxypropanediamines synthesis. The solid phase strategy is in progress for using these new scaffolds in combinatorial chemistry.

References and notes

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2. Four 2-alkyl-1,3-propanediamines **1d-g**[8] (phenethyl, hexyl, decyl, octadecyl) were synthesised[3].
3. Ramalingam, K. ; Raju, N. ; Nanjappan, P. ; Nowotnik, D.P. *Tetrahedron*, **1995**, *51*, 2875-2894.
4. NMR data of the oxazolidinones in $CDCl_3$: 4-(N-*t*-butyloxycarbonyl-aminomethyl)oxazolidin-2-one **3** : ^1H (100 MHz) : 1.32 (s, 9H, CH_3 Boc); 3.31-3.53 (m, 4H, CH_2); 4.61 (m, 1H, CH); 5.37 (t, 1H, NHBoc); 6.62 (ls, 1H, $NH_{cyc.}$) ppm. ^{13}C (25 MHz): 28.1 ($\underline{C}H_3$ Boc); 42.9*($\underline{C}H_2$-NHBoc); 43.2*(CH_2 cycl.); 75.6 (CH); 79.8 ($\underline{C}(CH_3)_3$); 156.2*(C=O Boc); 159.9* (C=O cycl.) ppm. 4-(N-*t*-butyloxycarbonyl-aminomethyl)-N-decyl-oxazolidin-2-one **4** : ^1H (100 MHz) : 0.81 (t, 3H, CH_3, J=5,7 Hz) ; 1.20 (m, 16H, CH_2) ; 1.37 (s, 9H, $\underline{C}H_3$ Boc) ; 3.09-3.51 (m, 6H, CH_2-NH) ; 4.54 (m, 1H, CH) ; 5.00 (ls, 1H, NHBoc) ppm. ^{13}C (25 MHz): 14.1 (CH_3) ; 22.6 (CH_2-CH_3) ; 26.6 ; 27 .2 ; 29.2 ; 29.5 ; 31.8 (CH_2) ; 28.3 (CH_3 Boc) ; 43.4 ; 44.1 ; 46.6 (CH_2-N) ; 72.2 (CH) ; 79.9 ($C(CH_3)_3$) ; 156.2 *(C=O Boc); 159.9* (C=O cycl.) ppm.
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7. Nakajima, K.; Takai, F.; Tanaka, T.; Okawa, K. *Bull. Chem. Soc. Jpn.*, **1978**, *51*, 1577.
8. NMR data of the diamines were almost measured in CD_3OD : **1a** : FAB + : M+1 : 235 ;^1H (360 MHz) 3.10 (m, 2H, CH_2NH) ; 4.8 (m, 1H, CH) ; 7.12 (d, H, o-Ph, A_2B_2, J= 8.8 Hz) ; 7.51 (d, 2H, m-Ph, A_2B_2, J= 8.8 Hz) ppm. ^{13}C (25 MHz) : 40.8 (CH_2N) ; 72.0 (CH) ; 117.4 (o-Ph) ; 112.3 ;123.9 (CF_3) ; 128.2 ;128.3 (m-Ph, $\underline{C}CF_3$) ; 160.2 (C-O) ppm. **1b** : FAB+ : M+1 : 231 ;^{13}C (25 MHz) 14.4 (CH_3) ; 23.7 ($\underline{CH_2}CH_3$) ; 26.8 ;30.6 ; 33.0 (CH_2) ; 40.8 (CH_2N) ; 71.8 (CH_2O) ; 73.5 (CH) ppm. **1c** : FAB+ : M+1 : 343 ; ^{13}C (25 MHz) 14.7 (CH_3) ; 23.7 ($\underline{CH_2}CH_3$) ; 26.7 ;30.8 ; 33.1 (CH_2) ; 40.7 (CH_2N) ; 71.7 (CH_2O) ; 73.2 (CH) ppm. **1d** : FAB+ : M+1 : 343 ; ^{13}C (25 MHz) 14.7 (CH_3) ; 23.7 ($\underline{CH_2}CH_3$) ; 26.7 ;30.8 ; 33.1 (CH_2) ; 40.7 (CH_2N) ; 71.7 (CH_2O) ; 73.2 (CH) ppm. **1e** : FAB+ : M+1 : 179 ; ^{13}C (DMSO, 25 MHz) : 29.9 ($\underline{CH_2}CH$) ; 31.5 ($\underline{CH_2}Ph$) ; 39.3 (CH_2N) ; 125.2 (p-Ph) ; 128.2 (o,m-Ph) ; 141.7 (i-Ph) ppm. **1f** : FAB+ : M+1 : 159 ; ^{13}C (25 MHz) 14.2 (CH_3) ; 23.2 ($\underline{CH_2}CH_3$) ; 27.7 ; 29.9 ; 32.2 (CH_2) ; 36.1 (CH) ; 41.3 (CH_2N) ppm. **1g** : FAB+ : M+1 : 215 ; ^{13}C (25 MHz) 14.4 (CH_3) ; 23.7 ($\underline{CH_2}CH_3$) ; 27.1 ; 29.9 ; 30.4 ; 30.7 ; 33.0 (CH_2) ; 36.9 (CH) ; 41.4 (CH_2N) ppm. **1i** : FAB+ : M+1 : 328 : ^{13}C ($CDCl_3$-CD_3OD, 25 MHz) 12.6 (CH_3) ; 21.7 ($\underline{CH_2}CH_3$) ; 25.9 ; 27.8 ; 28.4 ; 28.7 ; 31.0 (CH_2) ; 37.5 (CH) ; 42.6 (CH_2N) ppm.