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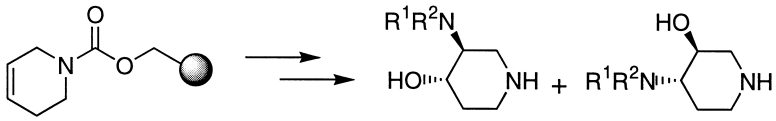

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Efficient Solid-Phase Synthesis of β-Aminosubstituted Piperidinols

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The solid-phase synthesis of a β-aminosubstituted piperidinol library starting from 1,2,3,6-tetrahydropyridine is described. The synthetic strategy involves formation of the 3,4-epoxypiperidine Wang resin **4** and subsequent ring opening with primary and secondary amines. The epoxide ring-opening was efficiently promoted by lithium perchlorate in acetonitrile. The progress of the reaction sequences leading to the epoxide resin **4** was monitored by ATR FTIR on single resin bead and HRMAS NMR techniques. This methodology is considered to be suitable for the generation of arrays of compounds.

Introduction

Solid-phase organic synthesis is emerging as a powerful technique to rapidly generate combinatorial libraries of small molecules useful in medicinal chemistry projects.[1−3] Substituted piperidines are found both in natural and synthetic products that exhibit, for example, antibiotic,[4] antipsychotic,[5] and analgesic[6] activities. Due to their broad biological activities, piperidine derivatives represent attractive targets for the elaboration of solid-phase synthesis methodology and the production of combinatorial libraries. We report herein the synthesis of polymer-bound 3,4-epoxypiperidine **4** from 1,2,3,6-tetrahydropyridine and its use to generate β-aminosubstituted piperidinol library **5**−**8**. This work also provides us with a case study to investigate and monitor the solid-phase preparation of oxiranes, which are important intermediates in organic synthesis.

The nitrogen atom of piperidine offers a convenient site of attachment onto a polymeric support. From the several linkers used for the solid-phase immobilization of amines,[7−11] the linkage equivalent to the benzyloxycarbonyl protecting group[7] shows several advantages for our synthetic strategy. The carbamate bond provides an efficient protection of the nitrogen atom against oxidation and alkylation reactions. The amines are liberated from the resin with trifluoroacetic acid (TFA) or by hydrogenation.[7] Reduction of the carbamate bond with lithium aluminum hydride furnish *N*-methylamines.[12]

Results and Discussion

The epoxide resin **4** was synthesized in a three-step procedure starting from Wang resin **1** (Scheme 1). The progress of the reactions was monitored by attenuated total reflection (ATR) FTIR[13−15] on single beads and high-resolution magic angle spinning (HRMAS) NMR[16−24] (Figure 2). In the first step, *p*-nitrophenyl carbonate Wang resin (**2**)[7,12,25] was prepared by the addition of *p*-nitrophenyl chloroformate to high loading Wang polystyrene resin **1** in the presence of pyridine in CH_2Cl_2. Reaction of **2** with 1,2,3,6-tetrahydropyridine in *N*,*N*-dimethylacetamide (DMA) in the presence of *N*-diisopropylethylamine (DIPEA) afforded the carbamate **3**. ATR FTIR of **3** showed a carbamate stretching frequency at 1696 cm^{-1} and a signal at 1654 cm^{-1} corresponding either to the double bond of **3** or to the amide bond of DMA (Figure 1C). The carbonate stretching frequency at 1761 cm^{-1} was completely absent, suggesting complete reaction had occurred. The ^1H MAS NMR of **3** (Figure 2C) showed the protons of the double bond at 5.58, 5.64, and 5.78 ppm. Only a few examples of the formation of epoxides on a solid support have been described.[26−29] Oxidation of **3** to epoxide resin **4** was performed with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2. As shown

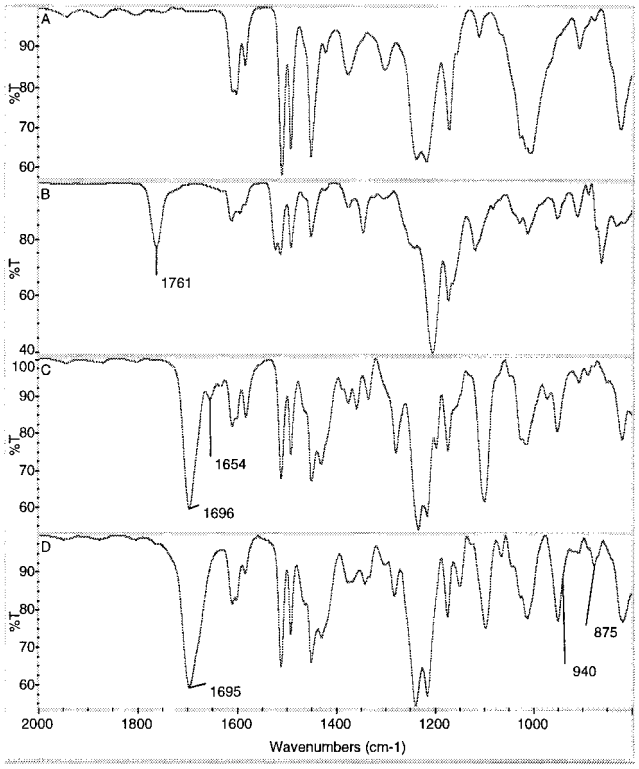

Figure 1. ATR FTIR spectra on single bead of resin **1** (A), **2** (B), **3** (C), and **4** (D).

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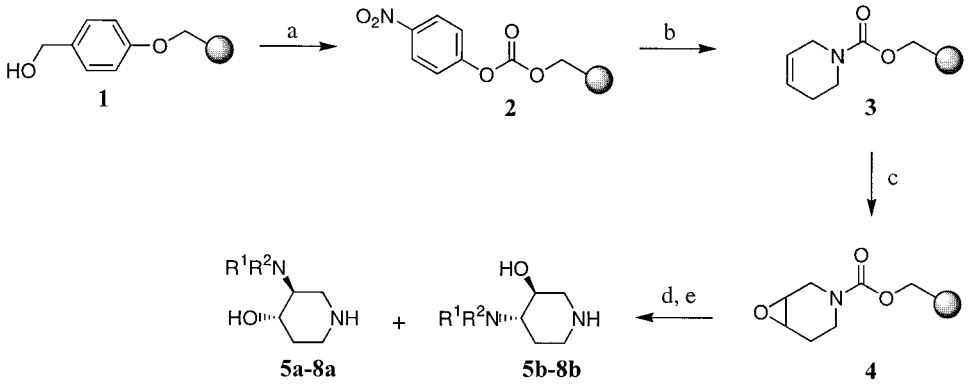
Scheme 1[a]



[a] Reagents and conditions: *p*-nitrophenylchloroformate, pyridine, CH_2Cl_2; (b) 1,2,3,6-tetrahydropyridine, DIPEA, DMA; (c) *m*-CPBA, CH_2Cl_2; (d) 2 equiv $LiClO_4$, 4 equiv R^1R^2NH, acetonitrile, 85 °C; (e) TFA:CH_2Cl_2 1:1.

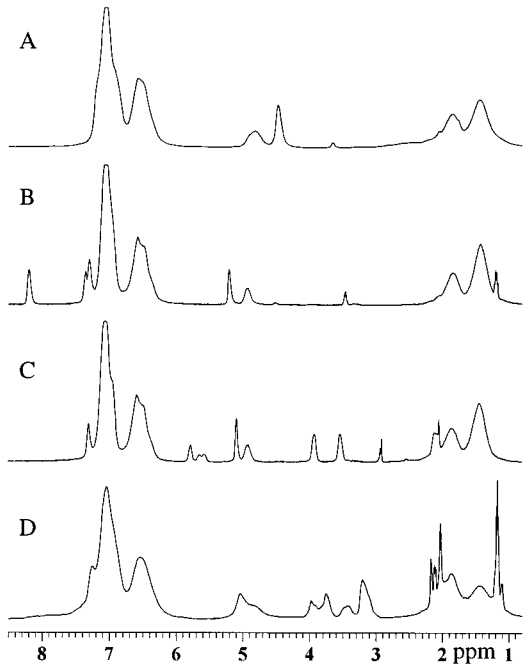
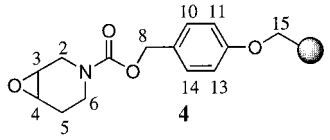


Figure 2. ^{1}H MAS NMR spectra of resins **1** (A), **2** (B), **3** (C), and **4** (D).

in Figure 2D, the epoxidation reaction was complete on the basis of the disappearance of the NMR signals corresponding to the protons of the double bond of **3**, and the appearance of the oxirane proton signals at 3.11 and 3.23 ppm. TOCSY[30], HSQC,[31] and ROESY[32] HRMAS experiments were required to confirm the structure of **4** and to assign all resonances (Table 1). Although not conclusive, the FTIR spectrum of **4** indicated disappearance of the signal at 1654 cm^{-1} and modifications between 800 and 950 cm^{-1} (Figure 1D), where the epoxide stretching frequencies are expected.

The ring-opening of epoxide resin **4** by amines was examined using either lithium perchlorate[33,34] or ytterbium-(III) trifluoromethansulfonate[35] as activating agents. The reaction promoted by lithium perchlorate furnished products in higher yields and purity, and it was more conveniently carried out. Different reaction temperatures and stoichiometries of reagents were examined. Optimal reaction conditions involved the reaction of epoxide resin **4** with 2 equiv of lithium perchlorate and 4 equiv of an amine in acetonitrile at 85 °C.[36] To achieve complete conversion for a broad range

Table 1. ^{1}H MAS NMR Data of Resins **1**, **2**, **3**, and **4**[a]

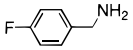
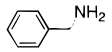
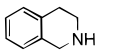
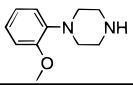


4

	2	3	4	5	6	8	10, 14	11, 13	15
1						4.47	6.90	6.90−7.20	4.81
2	7.29	8.19		8.19	7.29	5.20	6.90	7.35	4.93
3	3.79	5.58 5.64	5.78	2.05	3.54	5.10	6.90	7.30	4.93
4	4.00	3.11	3.23	2.06 2.13	3.19 3.51	5.05	6.90	7.29	4.93

[a] Chemical shifts in ppm relative to TMS. For the structure verification and signal assignment of **4** it was necessary to perform 2D HRMAS experiments (TOCSY, ROESY, and HSQC).

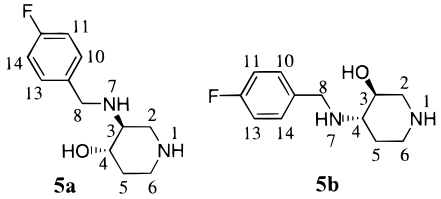
Table 2

Entry	Amine	Compound C-3 : C-4	Ratio[a]	Purity[b]	Yield[c]
1		**5a** : **5b**	44 : 56	95	53
2		**6a** : **6b**	44 : 56	90	69
3		**7a** : **7b**	44 : 56	90	78
4		**8a** : **8b**	44 : 56	90	75

[a] Regioisomer ratio was determined by ^{1}H NMR and 2D NMR experiments. [b] Purity in % was determined by ^{1}H NMR. [c] Yield in % of the trifluoroacetate salts was calculated from initial loading of epoxide resin **4** (1.12 mmol/g).

of amines, the reaction was performed at 85 °C and the reaction time was 24 h for secondary amines and 48 h for primary amines. Anilines were not investigated under these conditions. A larger excess of lithium perchlorate and increased reaction times led to the formation of impurities. When performed without lithium perchlorate or run in stronger coordinating solvents such as tetrahydrofuran or DMA, the reaction was strongly slowed or did not proceed.[34] Cleavage from the resin with 50% TFA/CH_2Cl_2 afforded the trifluoroacetate salts of compounds **5**−**8** (Table 2). Both regioisomers were obtained in an approximately 1:1 ratio as determined by ^{1}H NMR. HSQC and ROESY experiments

Table 3. ^{1}H NMR Data of Compounds **5a** and **5b**[a]



5a **5b**

	1[b]	2	3	4	5	6	7[b]	8	10, 14	11, 13
5a	9.00	3.01 (ax)	3.08	3.84	1.60 (ax)	2.92 (ax)	9.12	4.30	7.60	7.30
	9.12	3.71 (eq)			2.08 (eq)	3.31 (eq)	9.33			
5b	9.00	2.79 (ax)	3.91	3.11	1.76 (ax)	2.92 (ax)	9.12	4.28	7.60	7.30
	9.12	3.33 (eq)			2.32 (eq)	3.35 (eq)	9.33			

[a] Chemical shifts in ppm relative to TMS. Structure verification and signal assignments were performed by ^{1}H NMR, HSQC, and 2D ROESY spectra of the bistrifluoroacetate salts. [b] Assignment within the same column may be interchanged.

for compounds **5** demonstrated that the stereoselectivity of the aminolysis reactions was anti (Table 3).

Summary

In summary, we have developed an expedient solid-phase strategy to generate β-aminosubstituted piperidinol libraries. This methodology is suitable for the parallel synthesis of compound arrays. The combination of ATR FTIR on single bead and HRMAS NMR techniques is particularly useful for monitoring the reaction sequences discussed here. The resin bound epoxide represents an attractive starting material, and further epoxide ring-opening reactions with other classes of nucleophiles will be described in due course.

Experimental Section

All chemicals were purchased from Fluka AG and Aldrich. TFA was peptide synthesis grade. Solvents were purified before use or purchased in absolute quality. The polysterene Wang resin (1.7 mmol/g, 1% cross-linking, 200−250 micrometers, batch# Wang017) was from Polymer Laboratories, Shropshire, U.K. ATR/FTIR: Nicolet-860 FT-IR spectrometer with an IR-microscope NICPLAN; resolution 4 cm^{-1}, 200 or 500 co-added scans, MCT detector, characteristic bands in cm^{-1}. ESIMS: PE Sciex API 300; *m/z* (rel.). NMR spectra: Bruker DRX 400 spectrometer, at 400 MHz ^{1}H frequency; in DMSO-d_6 or $CDCl_3$; TMS as internal standard; HRMAS spectra were collected with a 4 mm HRMAS probe at MAS of 4000 Hz; samples on beads were swollen in $CDCl_3$.

***p*-Nitrophenyl Carbonate Wang Resin (2).** Wang resin **1** (25 g, 42.5 mmol) was swollen in dry CH_2Cl_2 under Ar for 30 min. After filtration of the solvent, a solution of *p*-nitrophenyl chloroformate (42.7 g, 212.5 mmol) in dry CH_2Cl_2 (100 mL) was added, followed by slow addition of a solution of dry pyridine (32 mL, 425 mmol) in dry CH_2Cl_2 (100 mL). The suspension was shaken for 48 h at room temperature under Ar. The carbonate resin **2** was washed on a semiautomated shaking-vessel machine with dioxane:methanol 1:1 (1 × 5 min and 5 × 2 min), dioxane:dichloroethane 1:1 (1 × 5 min and 5 × 2 min), isopropyl alcohol (2 × 2 min) and DMA (2 × 2 min). A sample of **2** was washed with CH_2Cl_2 (4 × 2 min) and dried under high vacuum: 86% conversion based on elemental analysis. HRMAS ^{1}H NMR (400 MHz, $CDCl_3$): see Table 1. FTIR: ν = 1770s, 1520s, 1350s, 1205s. Anal. found: N, 1.61.

2,3,6-Trihydropyridine Carbamate Wang Resin (3). Resin **2** was suspended in dry DMA, and 1,2,3,6-tetrahydropyridine (7.8 mL, 85 mmol) and DIPEA (36.3 mL, 212.5 mmol) were successively added. After the mixture was shaken for 72 h at room temperature, the solvent was filtered off and the resin was washed on a semiautomated shaking-vessel machine with DMA (4 × 4 min), isopropyl alcohol (4 × 2 min), dioxane:dichloroethane 1:1 (4 × 2 min), isopropyl alcohol (4 × 2 min) and CH_2Cl_2 (4 × 2 min). Drying under high vacuum afforded the carbamate resin **3** (29.8 g): 95% conversion based on elemental analysis. MAS ^{1}H NMR (400 MHz, $CDCl_3$): see Table 1. FTIR: ν = 1697s, 1234s, 1216s. Anal. found: N, 1.68.

3,4-Epoxypiperidine Carbamate Wang Resin (4). Carbamate resin **3** (27 g, 32.4 mmol) and 70% *m*-CPBA (24 g, 97.2 mmol, from Lancaster) in CH_2Cl_2 (200 mL) were shaken for 6 h at room temperature. The suspension was filtered off, washed on a semiautomated shaking-vessel machine with DMA (3 × 5 min), isopropyl alcohol (4 × 4 min), DMA (3 × 5 min), and isopropyl alcohol (5 × 4 min), and dried under high vacuum. This afforded 28.5 g of **4**: 95% conversion based on elemental analysis. MAS ^{1}H NMR (400 MHz, $CDCl_3$): see Table 1. FTIR: ν = 1698s, 1615m, 1512m, 1239s. Anal. found: N, 1.57.

General Procedure for Opening of Epoxide 4. (3*RS*,4*RS*)-3-(4-Fluorobenzylamino)piperidine-4-ol (5a) and (3*RS*,4*RS*)-4-(4-Fluorobenzylamino)piperidine-3-ol (5b). Epoxide resin **4** (130 mg, 0.15 mmol) was placed in a glass reaction vessel. Acetonitrile (2 mL), a solution of $LiClO_4$ in acetonitrile (1 M, 0.3 mL, 0.3 mmol), and 4-fluorobenzylamine (0.075 mL, 0.6 mmol) were added successively. The glass reactor was sealed, and the reaction mixture was heated at 85 °C for 48 h. The resin was filtered and washed with dioxane:H_2O 1:1 (3 × 3 mL), dioxane (1 × 3 mL), isopropyl alcohol (3 × 3 mL), DMA (3 × 3 mL), isopropyl alcohol (3 × 3 mL), and dichloroethane (6 × 3 mL). A solution of TFA:CH_2Cl_2 1:1 (4 mL) was added, and the suspension was shaken for 3 h. The solution and one subsequent wash with TFA:CH_2Cl_2 1:1 (2 mL) were collected and combined. The solvent was removed to afford the trifluoroacetate salts of **5a** and **5b** as a yellowish oil (38 mg). ESIMS ($[M + H]^+$): 225.2 (100). ^{1}H NMR (400 MHz, DMSO-d_6): **5a** δ = 9.33 (br s, 1H);

9.12 (br s, 1H); 9.00 (br s, 1H); 7.60 (d, $J = 2.1$, 2H); 7.30 (d, $J = 2.2$, 2H); 4.30 (s, 2H); 3.84 (m, 1H); 3.71 (m, 1H); 3.31 (m, 1H); 3.08 (m, 1H); 2.92 (m, 2H); 2.08 (m, 1H); 1.60 (m, 1H). **5b** $\delta = 9.33$ (br s, 1H); 9.12 (br s, 1H); 9.00 (br s, 1H); 7.60 (d, $J = 2.1$, 2H); 7.30 (d, $J = 2.2$, 2H); 4.28 (s, 2H); 3.91 (m, 1H); 3.32 (m, 2H); 3.11 (m, 1H); 2.92 (m, 1H); 2.79 (m, 1H); 2.32 (m, 1H); 1.76 (m, 1H).

(3*RS*,4*RS*)-3-Benzylamino-piperidine-4-ol (6a) and (3*RS*,4*RS*)-4-Benzylamino-piperidine-3-ol (6b). The title compounds were prepared according to the general procedure, using benzylamine (0.064 mL, 0.6 mmol) and affording 28 mg of a yellowish oil. ESIMS ($[M+H]^+$): 207.2 (100). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.45$ (br s, 1H); 9.27 (br s, 1H); 9.17 (br s, 2H); 7.52−7.55 (m, 4H); 7.40−7.47 (m, 6H); 4.32 (s, 2H); 4.29 (s, 2H); 3.89−3.98 (m, 2H); 3.71−3.74 (m, 1H); 3.29−3.37 (m, 3H); 3.08−3.13 (m, 2H); 2.91−3.00 (m, 3H); 2.75−2.81 (m, 1H); 2.31−2.35 (m, 1H); 2.06−2.09 (m, 1H); 1.74−1.79 (m, 1H); 1.58−1.64 (m, 1H).

(3*RS*,4*RS*)-3-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-piperidine-4-ol (7a) and (3*RS*,4*RS*)-4-(1,2,3,4-Tetrahydroisoquinolin-2-yl)-piperidine-3-ol (7b). The title compounds were prepared according to the general procedure, using 1,2,3,4-tetrahydroisoquinoline (0.079 mL, 0.6 mmol) and heating at 85 °C for 24 h, thus affording 42 mg of a yellowish oil. ESIMS ($[M + H]^+$): 233.2 (100). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.70$ (br s, 1H); 9.49 (br s, 1H); 9.36 (br s, 1H); 9.23 (br s, 1H); 7.19−7.23 (m, 8H); 4.51−4.60 (m, 4H); 4.20−4.23 (s, 2H); 3.53−3.62 (m, 6H); 3.43−3.46 (m, 2H); 2.78−3.35 (m, 10H); 2.21−2.27 (m, 1H); 1.95−2.07 (m, 1H); 1.68−1.77 (m, 1H).

(3*RS*,4*RS*)-3-(4-(2-Methoxyphenyl)piperazin-1-yl)-piperidine-4-ol (8a) and (3*RS*,4*RS*)-4-(4-(2-Methoxyphenyl)-piperazin-1-yl)-piperidine-3-ol (8b). The title compounds were prepared according to the general procedure, using 1-(2-methoxyphenyl)piperazine (0.079 mL, 0.6 mmol) and heating at 85 °C for 24 h, thus affording 58 mg of a brownish oil. ESIMS ($[M + H]^+$): 291.4 (100). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 9.54$ (br s, 1H); 9.17 (br s, 1H); 8.98 (br s, 2H); 7.01−7.04 (m, 4H); 6.89−7.00 (m, 4H); 4.06−4.11 (m, 2H); 3.80 (s, 6H); 3.69−3.71 (m, 1H); 3.12−3.55 (m, 14H); 2.80−3.02 (m, 3H); 2.27−2.32 (m, 1H); 2.09−2.13 (m, 1H); 1.89−1.95 (m, 1H); 1.65−1.72 (m, 1H).

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Supporting Information Available. ^{1}H NMR, HSQC, and 2D ROESY of compound **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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