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Synthesis of amino alcohols on solid support via sulfonium-ion mediated Darzens reaction

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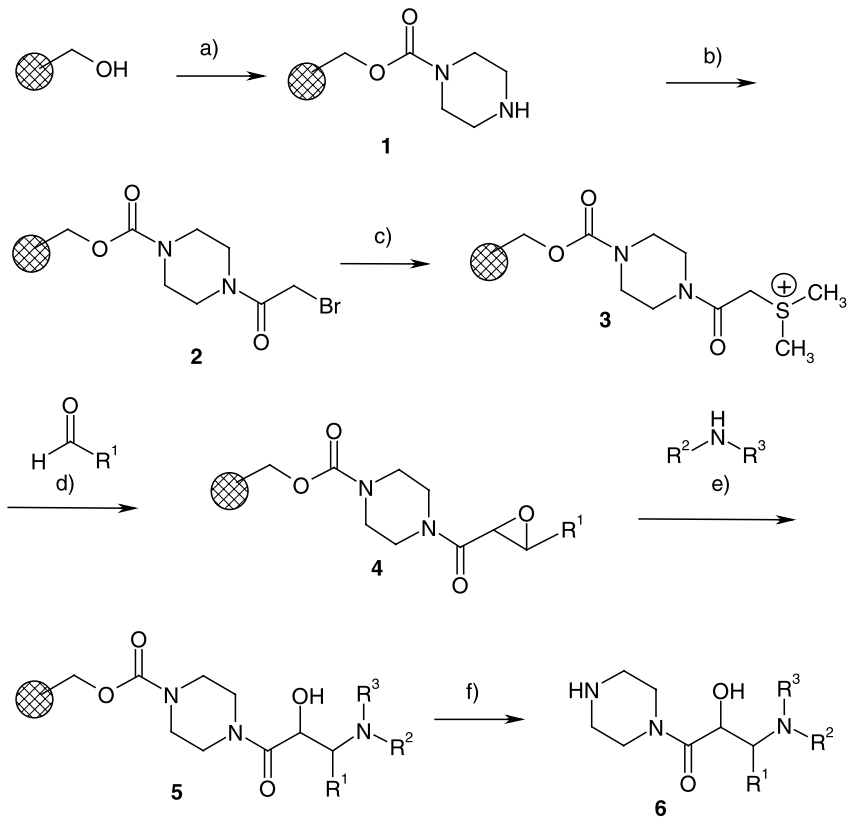
Abstract—Epoxides were synthesized on a solid support via an immobilized sulfonium salt, which is generated from a bromoacetic amide. Subsequent ring opening with amines leads to a single diastereoisomer of an amino alcohol, which can be cleaved from the solid support.

The need for high efficiency in industrial chemical research has, in recent years, led to the development of methods for parallel synthesis of analogous compounds.[1] In this context, solid-phase synthesis has



Scheme 1. *Reagents*: (a) i $ClC(=O)OC_6H_4$-*p*-NO_2, py, CH_2Cl_2, ii piperazine, DMF; (b) bromoacetic acid, DIC, CH_2Cl_2; (c) dimethyl sulfide, heptanone; (d) DBU, DMSO, 70°C; (e) DMSO, 70°C; (f) TFA, CH_2Cl_2.

Keywords: amino alcohols; Darzens reaction; epoxides; solid-phase synthesis; sulfonium salts.

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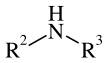
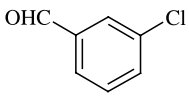
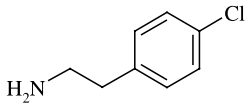
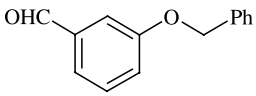
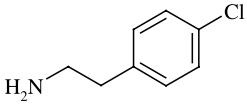
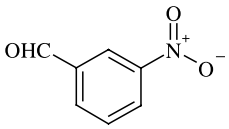
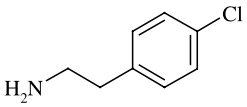
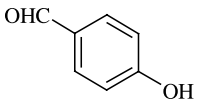
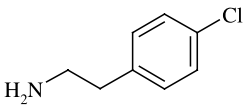
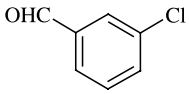
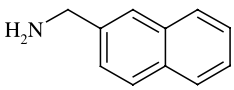
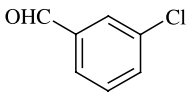
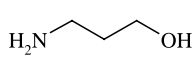
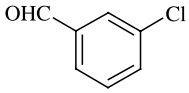
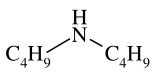
gained a lot of interest, since it is most advantageous in multi-step syntheses. Even though many reactions are already possible on the solid-phase,[2] new, robust immobilized reactions will enhance the scope of possible structures that can be produced by automated parallel synthesis. Of special interest are those reactions that can be used for the synthesis of small compounds with high polarity, because these compounds are particularly suitable as lead compounds for drug candidates.[3]

We were interested in using solid-phase bound bromoacetic amides, as shown in Scheme 1, as they are easily accessible starting materials. The synthesis started with the immobilized piperazine **1**, which was attached to a polystyrene-Wang-resin via a carbamate linker[4] and acylated with bromoacetic acid leading to the bromoacetic amide **2**. The following bromo-sulfur exchange reaction gave the sulfonium salt **3**.[5] In this reaction, 3-heptanone was used as a solvent, because it proved to be a good substitute for the low boiling acetone, which can be problematic in automated synthesizers. A reaction with an aromatic aldehyde in the presence of DBU furnished the epoxides **4**. The final ring opening with an amine[6] provided the immobilized amino alcohols **5**, which was cleaved from the solid support by treatment with 50% trifluoroacetic acid in dichloromethane. We isolated amino alcohols **6** as the only major product.[5,7,8] The purities of the crude products were determined by ELS.[9,10]

The results for a number of representative aldehydes and amines are given in Table 1. Both electron deficient and electron rich aldehydes gave good results. Primary amines worked well in the epoxide-ring opening reac-

Table 1. ELS purities of **6a–g**

entry			purity (%)[a]
6a			67
6b			77
6c			50
6d			0
6e			76
6f			17
6g			40

[a] purity of the crude product, determined by ELS

tion, whereas secondary amines gave low purities. Free hydroxyl groups on either the aldehyde or the amine disturbed the course of the reaction.

For analytical reasons, compound **6b** was isolated after HPLC purification as a single diastereomer of one regioisomer. The structure of the purified material was confirmed to be **6b** by NMR analysis, including 1D ^{1}H and ^{13}C NMR and 2D COSY, TOCSY, HSQC and HMBC experiments. Direct and long-range $^{1}H,^{13}C$-connectivities observed in the HSQC and HMBC experiments served to assign the proton bearing carbon atoms and to confirm the molecular framework involving quaternary and hetero atoms. In Fig. 1, diagnostic long-range correlations are depicted by arrows, and the characteristic ^{13}C chemical shifts for the oxygen and nitrogen bearing carbon atoms are given. In analogy to reactions in solution, where it is known that resonance-stabilized sulfonium ylids react with aromatic aldehydes giving rise to *trans*-epoxides,[7] we assume that the racemic (*R**,*R**)-diastereomer of amino alcohol **6b** was isolated after inversion during the ring-opening reaction with the amine.

When bromoacetic amide **2** was treated directly with DBU and 3-chlorobenzaldehyde, as in the standard protocol of the Darzens reaction,[11] and then subsequently reacted with 4-chlorophenethylamine, a complex mixture of products was isolated. This indicates that the sulfonium salt **3** is indeed formed during the course of the earlier reactions, and is a key-intermediate.

In conclusion, we have developed an easy method for the synthesis of amino alcohols via a sulfonium salt mediated Darzens reaction on a solid support. The synthesis was designed such that it should be directly compatible with automated synthesizers.

Typical procedure:

3-(3-(Benzyloxy)phenyl)-3-[2-(4-chlorophenyl)ethylamino]-2-hydroxy-1-(piperazin-1-yl)propan-1-one (**6b**)

Step 1:
A solution of bromoacetic acid (83 mg, 0.6 mmol) in CH_2Cl_2 (1 mL) was added to the piperazine-carbamate-Wang-polystyrene resin[4] (loading: 1.07 mmol/g, 37 mg, 0.04 mmol). A solution of diisopropylcarbodiimide (0.044 mL, 0.28 mmol) in CH_2Cl_2 was added. The reaction vessel was shaken for 16 h, the solvent removed and the resin washed with DMF (3×2 mL) and CH_2Cl_2 (3×2 mL).

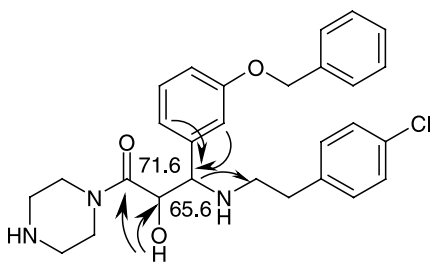


Figure 1. Diagnostic long-range $^{1}H,^{13}C$-connectivities and ^{13}C chemical shifts observed for **6b**.

Step 2:
The resin was suspended in heptanone (1.5 mL) for 20 min. The solvent was removed. A solution of dimethylsulfide (0.059 mL, 0.8 mmol) in heptanone (1.5 mL) was added to the resin. The reaction vessel was shaken for 16 h at room temperature, the solvent removed and the resin was washed with DMF (3×2 mL) and CH_2Cl_2 (3×2 mL).

Step 3:
The 3-chlorobenzaldehyde (84 mg, 0.6 mmol) in DMSO (1 mL) was added to the resin. A solution of DBU (0.036 mL, 0.24 mmol) in DMSO (0.5 mL) was added. The reaction mixture was shaken at room temperature for 16 h, the solvent removed and the resin washed with DMF (3×2 mL) and CH_2Cl_2 (3×2 mL).

Step 4:
A solution of the 4-chlorophenethylamine (125 mg, 0.80 mmol) in DMSO (1.5 mL) was added to the resin. The reaction vessel was shaken at 80°C for 16 h. The reaction vessel was cooled to room temperature. The solvent was removed and the resin washed with DMF (3×2 mL), CH_2Cl_2 (3×2 mL), MeOH (3×2 mL), isopropanol (3×2 mL), and *tert*-butyl methyl ether (3×2 mL).

Step 5:
A mixture of trifluoroacetic acid (1 mL) and CH_2Cl_2 (1 mL) was added to the resin. The reaction vessel was shaken for 20 min. The filtrate was collected and the resin was washed with CH_2Cl_2 (1 mL). The filtrates were combined, the solvent removed in vacuo and the crude product was analyzed by LC-MS/ELS.

MS ($C_{28}H_{32}ClN_3O_3$): calcd for $[M+H]^+$: 494; found: 494. ^{1}H NMR (400 MHz, DMSO-d_6, free base): δ 2.25 (br, 2H, N*H*); 2.50 (m, 3H); 2.80 (m, 3H); 3.35 (m, 6H); 3.75 (d, 1H, $J=5$ Hz; ArC*H*NH); 4.45 (t, 1H, $J=6$ Hz; C*H*OH); 4.70 (d, 1H; $J=7$ Hz; O*H*); 5.05 (AB, 2H; $J=13$ Hz; OCH_2Ph); 6.85 (t, 2H; $J=7$ Hz); 6.95 (s, 1H); 7.15 (m, 3H); 7.25–7.50 (m, 7H). ^{13}C NMR (100 MHz, DMSO-d_6, free base): δ 35.90, 43.70, 46.23, 46.67, 47.12, 48.99, 65.63, 69.96, 71.64, 113.96, 115.41, 121.87, 128.55, 128.63, 128.87, 129.24, 129.49, 131.23, 131.28, 138.05, 140.33, 143.08, 159.00, 171.21.

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