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# Solid-phase synthesis of arylalkanolamines†

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**Abstract**—A versatile method for the solid-phase synthesis of differentially substituted arylalkanolamines has been developed using immobilized carbamates. The method has been successfully used for the synthesis of arylethanolamines and arylpropanolamines in high yields and purities. © 2001 Elsevier Science Ltd. All rights reserved.

The ability to synthesize large numbers of molecules using the combinatorial approach requires the development of methods to measure the diversity of such collections of compounds. While large diverse libraries remain a valuable source of novel lead molecules, the overall efficiency of utilizing such compound collections is usually lower than that for rationally designed, directed or pharmacophore based libraries.[1] In continuation of our interest in pharmacophore based libraries,[2] we targeted the solid-phase synthesis of arylalkanolamines as they are a class of therapeutically important compounds. These prototypes are associated with a wide range of biological activities ranging from hypertension, asthma, obesity, diabetes, NMDA antagonism, anxiety and depression.

Solid-phase syntheses of alkanolamines and arylalkanolamines have been reported in the literature.[3,4] Purandre and Poss[4] synthesized arylalkanolamines in three steps, comprising reductive alkylation of resin bound amines, alkylation of secondary amines with structurally diverse chloroacetophenones and chloropropiophenones and, finally, reduction of the resulting ketones to alcohols. However, side reactions such as incomplete alkylation of the resin and partial quaternary salt formation, were encountered during their solid-phase synthesis.

In this paper we present a versatile solid-phase synthesis of arylalkanolamines **6**, in particular, arylethanolamines and arylpropanolamines, from resin bound carbamates in high yields. We designed our strategy in a manner so as to have at least two components that can be independently and readily varied (Scheme 1) for introducing diversity. Our solid-phase synthesis of arylalkanolamines commences with the preparation of immobilized carbamates **2** from Wang resin and isocyanates **1** in the presence of an organic base.[5] Alternatively, carbamates **2** can be generated using carbonyldiimidazole[6,7] or 4-nitrophenyl chloroformate[8,9] and amines, but the isocyanate method resulted in higher loading and was also less cumbersome to use. Next, the immobilized carbamates **2** were reacted with phenacyl bromides **3** to afford *N*-alkylated carbamates **4** in quantitative yields. These reactions were efficiently performed in DMF by activation of the NH group with NaH followed by addition of the phenacyl bromides and heating at 80°C for 12 h. The ketone was cleaved from the resin and characterized by NMR.[10] The resulting immobilized ketones **4** were then smoothly reduced to the alcohols **5** using sodium borohydride in a THF–alcohol mixture. The cleavage of the final products from the resin **5** with 50% TFA–DCM afforded the arylalkanolamines **6** as enantiomeric mixtures in high yield ranging from 75 to 95% and purities from 85 to 93%. Further, to investigate the scope and limitation of our strategy, we synthesized a library of 12 compounds using four isocyanates, two bromoacetophenones and one 3-chloropropiophenone. The compounds were obtained in good yields with purities ranging from 85 to 93% (Table 1 and Ref. 10). The compounds were characterized using HPLC, FAB MS and NMR.[10]

In summary, we have developed a versatile approach for the solid-phase synthesis of arylalkanolamines from polymer bound carbamates. It can be successfully used for the generation of libraries of arylalkanolamines.

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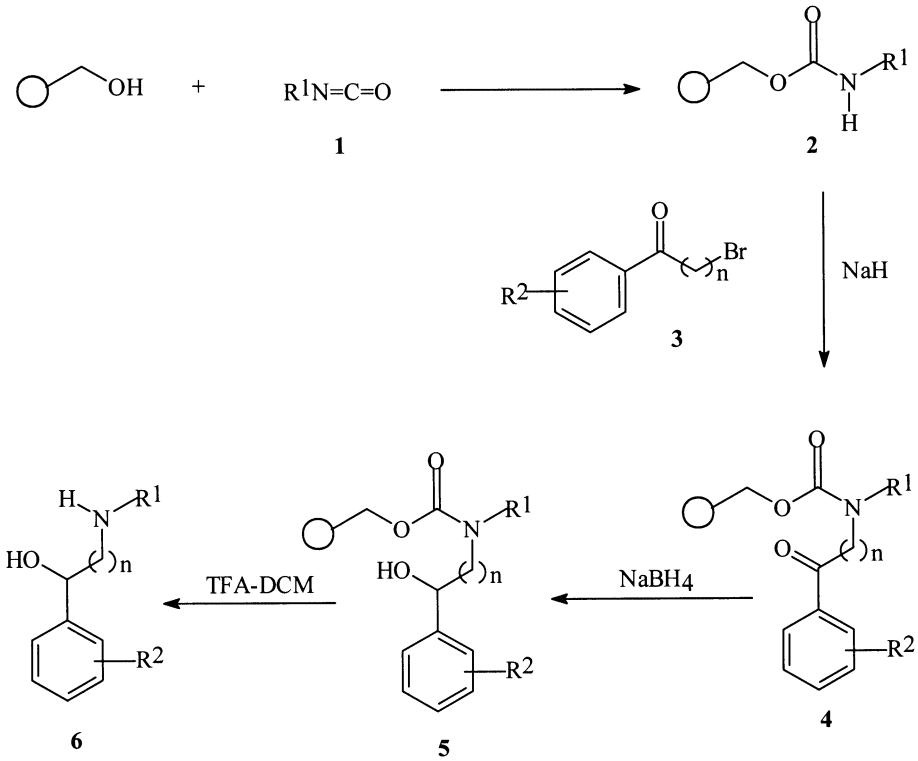


**Scheme 1.** $n=1$, arylethanolamine and $n=2$, arylpropanolamine.

**Table 1.** Structures, yields and purity of the library compounds

| Compound | $R^1$ | $R^2$ | $n$ | Isolated yield (%) | HPLC purity (%)[a] |
|---|---|---|---|---|---|
| **1** | *o*-Tolyl | H | 1 | 82 | 89 |
| **2** | *p*-Tolyl | H | 1 | 92 | 88 |
| **3** | 3-Chloro-4-methylphenyl | H | 1 | 81 | 90 |
| **4** | Benzyl | H | 1 | 78 | 86 |
| **5** | *o*-Tolyl | 4-Br | 1 | 75 | 87 |
| **6** | *p*-Tolyl | 4-Br | 1 | 75 | 90 |
| **7** | 3-Chloro-4-methylphenyl | 4-Br | 1 | 81 | 86 |
| **8** | Benzyl | H | 2 | 79 | 85 |
| **9** | *o*-Tolyl | H | 2 | 88 | 90 |
| **10** | *p*-Tolyl | H | 2 | 85 | 89 |
| **11** | 3-Chloro-4-methylphenyl | H | 2 | 82 | 93 |

[a] Whatmann C18 reversed-phase column (250×4.6 mm, 10 μm) with a linear gradient 10–98% $CH_3CN$ in water over 45 min, flow rate 0.5 ml/min, and UV detection at 254 nm.

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5. General experimental procedure for **6**: To a suspension of Wang resin (100 mg, 0.07 mmol) in toluene was added the benzylisocyanate (5 equiv., 0.35 mmol) and $Et_3N$ (10 equiv., 0.7 mmol). After shaking at 100°C for 16 h, the solvent was drained and the resin washed with DMF (5×3 min), DMF:$H_2O$ (1:1; 5×3 min), MeOH (5×3 min), DCM (5×3 min) and dried in vacuo to give **2**. Next, the carbamate **2** was treated with NaH (60% in oil, 5 equiv., 0.35 mmol) in DMF at rt for 1.5 h, followed by addition of phenacyl bromide (10 equiv., 0.7 mmol) in DMF. After shaking at 80°C for 16 h the resin was successively washed with DMF (3×2 min), MeOH (3×2 min), DCM (3×2 min) and finally dried in vacuo to give **4**. Thereupon resin **4** was treated with sodium borohydride (10 equiv., 0.7 mmol) in a mixture of THF–ethanol (1.2 ml, 1:1) for 12 h. The resin was successively washed with THF (3×2 min), DMF (3×2 min), MeOH (3×2 min), DCM (3×2 min) and dried in vacuo to give resin **5**. Finally resin **5**

was cleaved with a mixture of TFA–DCM (4 ml, 1:1) for 2 h and the resulting mixture was filtered and evaporated to dryness in vacuo. The residue was freeze dried by dissolving in *t*-BuOH–water (4:1) to give compound **6** as the trifluoroacetate salt in 85% overall yield.

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10. 2-(Benzylamino)-1-(4-bromophenyl)ethan-1-ol: FAB MS 307 (M+H); HPLC purity 95%; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.8 (brs, 1H, OH), 2.96 (brs, 1H, NH), 3.18 (m, 2H, $CH_2$), 4.02 (s, 2H, $CH_2$), 4.32 (q, 1H, $J=7.2$ Hz, CH), 6.86 (d, 2H, $J=8.7$ Hz, Ar-H), 7.36–7.42 (m, 5H, Ar-H), 7.89 (d, 2H, $J=8.4$ Hz, Ar-H); RP-HPLC: $t_R=$ 15.6 min on a Whatmann C18 reversed-phase column (250×4.6 mm, 10 μm) with a linear gradient 10–98% $CH_3CN$ in water (v/v) over 45 min, flow rate 0.5 ml/min, and UV detection at 254 nm.

2-(Benzylamino)-1-(4-bromophenyl)ethan-1-one: FAB MS 305 (M+H); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 4.03 (s, 2H, $CH_2$), 5.47 (s, 2H, $CH_2$), 6.89 (d, 2H, $J=8.4$ Hz, Ar-H), 7.38–7.44 (m, 5H, Ar-H), 7.85 (d, 2H, $J=8.4$ Hz, Ar-H); RP-HPLC: $t_R=23.6$ min on a Whatmann C18 reversed-phase column (250×4.6 mm, 10 μm) with a linear gradient 10–98% $CH_3CN$ in water over 45 min, flow rate 0.5 ml/min, and UV detection at 254 nm.