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Solid Phase Synthesis of Unsymmetrical Secondary Amines- Application to the Synthesis of Arylethanolamines and Arylpropanolamines

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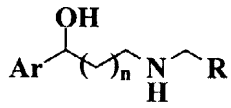
Abstract: A novel and simple solid phase synthesis of unsymmetrical secondary amines was developed. The general methodology was applied to the synthesis of arylethanolamines and arylpropanolamines.

Combinatorial chemistry has attracted widespread attention in recent years.[1] Significant progress has been made in the development of solid phase and solution phase methodologies for the synthesis of large numbers of compounds. In this connection, several methods for attaching primary amines and secondary amines to a polymeric resin support have been previously reported.[2] However, none of these methods allow for the stepwise introduction of two substituents that can lead to differentially unsymmetrical secondary amines. Also, many therapeutically important arylethanolamines and arylpropanolamines (**Figure 1**) contain unsymmetrical secondary amines.[3] These chemotypes have a wide range of activities, including α, β-adrenoreceptor and monamine reuptake binding affinities. Regulation of these sites have been sought in the treatment of high blood pressure, asthma, diabetes, anxiety, depression etc. In spite of possessing these therapeutically important activities, these compound classes have eluded the attention of combinatorial chemists. We report herein a simple solid phase synthetic approach to prepare differentially substituted secondary amines and in particular, arylethanolamines and arylpropanolamines (**Figure 1**).



Arylethanolamine (**A**) n = 0
Arylpropanolamine (**B**) n = 1

Figure 1

An effort was initiated to establish a general method for the synthesis of unsymmetrical secondary amines (**Scheme 1**). Thus, Fmoc deprotection of commercially available Fmoc-Knorr resin (0.8 mmol/g obtained from Advanced ChemTech) (**1**) with piperidine-DMF (1:1) followed by reductive alkylation of the resin with 4-fluorobenzaldehyde gave the corresponding alkylated Knorr resin (**2**).[4] During this reaction, dialkylation was not observed as cleavage (1:1-TFA:CH_2Cl_2) of the product resin provided only the benzyl amine and none of the corresponding dibenzyl amine. Alkylation of the resin bound secondary amine with benzyl bromide was then attempted under various conditions. The reaction was complete in DMF-acetone (1:1) as solvent at room temperature in presence of 3.0 equivalents of alkylating agent and afforded resin (**3**). The resulting resin was

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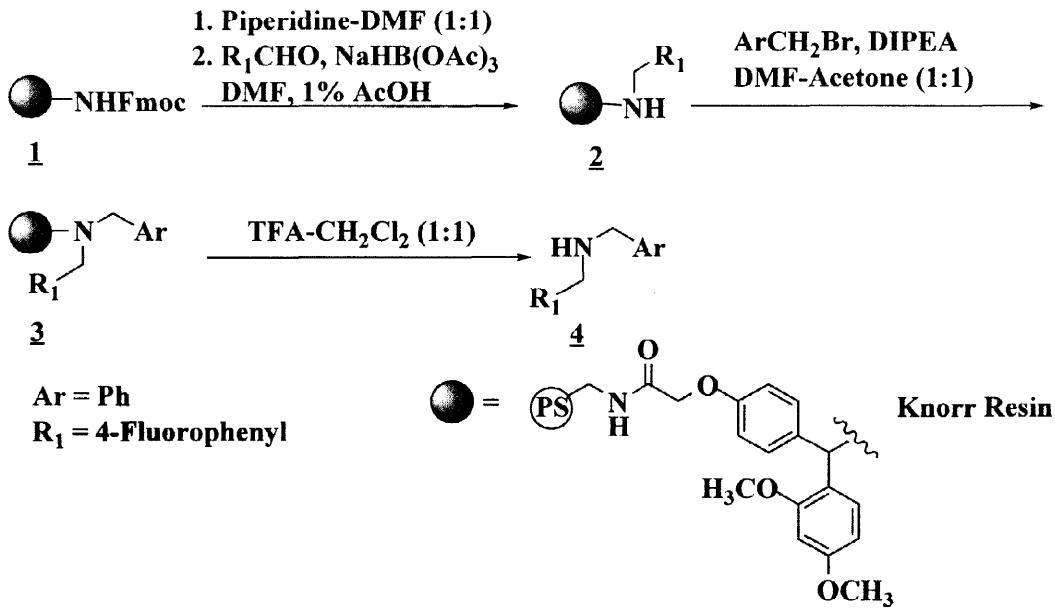
then subjected to acidolysis (TFA-dichloromethane; 1:1) to furnish the trifluoroacetate salt of amine (**4**) in 66% overall yield and 95% purity.

Scheme 1



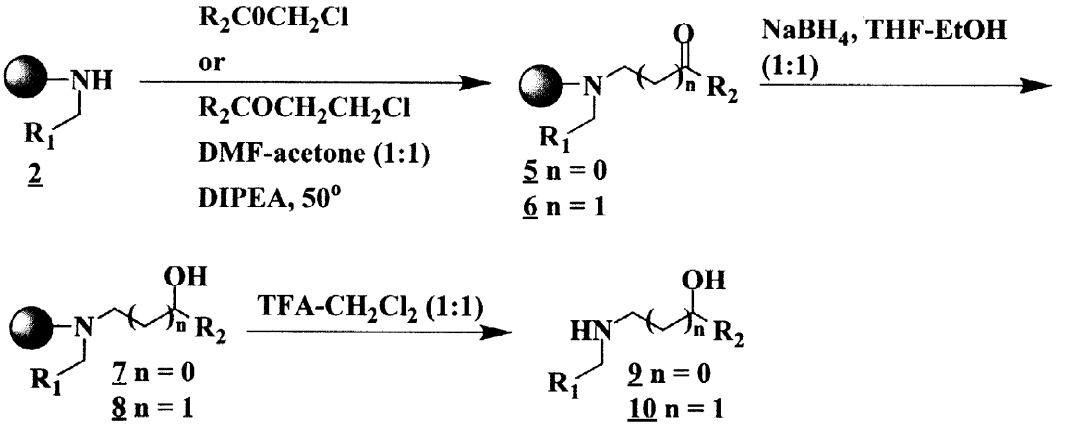
Having established an efficient protocol for the synthesis of unsymmetrical secondary amines, we next investigated the synthesis of aryethanolamines and arylpropanolamines. It was envisaged that these targets could be readily obtained by alkylation of a resin bound secondary amine with either β-haloacetophenones or γ-halopropionophenones followed by ketone reduction and final cleavage from the resin (**Scheme 2**).

Alkylation of the resin bound secondary amine (2) with 2-chloroacetophenone and 3-chloropropionophenone was attempted using the conditions utilized for benzyl halides. However, the reaction was incomplete when carried out at room temperature even in presence of a large excess of alkylating agent. Furthermore, alkylation with the more activated 2-bromoacetophenone resulted in partial quaternary salt formation. Ultimately, the reaction was successfully carried out using 3 equivalents of alkylating agent at 50°C in DMF-acetone (1:1) as solvent. The resulting ketones (5 and 6) were reduced using sodium borohydride to give the corresponding resin bound alcohols (7 and 8). This reaction was monitored by disappearance of the 1685 cm^{-1} band in the FT-IR spectrum of the resin. Cleavage of the product from the solid support was carried out using TFA-methylene chloride (1:1) to afford the final products **9** and **10** with 96% and 92% purity, respectively. The overall yield (for the 3 steps) was 45% and 56%, respectively. [5, 6]

Next, the parallel synthesis of 24 compounds from four benzaldehydes, three 2-chloroacetophenones and three 3-chloropropionophenones was carried out. The results of this synthetic run are as presented in the **Table**. In general, the reaction sequence worked extremely well with the 2-chloroacetophenones. The average yield and purity was 56% and 93%, respectively. In the case of the 3-chloropropionophenones, the yield and purity of the products derived from simple 3-chloropropionophenone and 4'-fluoro-(3-chloro)-propionophenone were comparable to that obtained from the corresponding 2-chloroacetophenones. However,

the products (20 and 32) obtained from 4'-bromo-(3-chloro)-propionophenone required purification by preparative HPLC. The main impurities in these samples were the corresponding benzyl amines derived from incomplete alkylation of the resin (2).

Scheme 2



Table

Compound #	R_1	R_2	n	% Yield	% Purity
9, 10	4-fluorophenyl	phenyl	0, 1	45[a], 56[b]	96[a], 92[b]
11, 12	4-fluorophenyl	4-fluorophenyl	0, 1	58[a], 63[b]	94[a], 91[b]
13	4-fluorophenyl	3-methoxyphenyl	0	62	98
14	4-fluorophenyl	4-bromophenyl	1	39	98
15, 16	2-chloro-4-fluorophenyl	phenyl	0, 1	73[a], 64[b]	96[a], 93[b]
17, 18	2-chloro-4-fluorophenyl	4-fluorophenyl	0, 1	66[a], 57[b]	89[a], 97[b]
19	2-chloro-4-fluorophenyl	3-methoxyphenyl	0	59	94
20	2-chloro-4-fluorophenyl	4-bromophenyl	1	43*	95[c]
21, 22	2-cyanophenyl	phenyl	0, 1	69[a], 63[b]	90[a], 89[b]
23, 24	2-cyanophenyl	4-fluorophenyl	0, 1	62[a], 54[b]	93[a], 94[b]
25	2-cyanophenyl	3-methoxyphenyl	0	61	97
26	2-cyanophenyl	4-bromophenyl	1	32*	97[c]
27, 28	2-bromo-5-methoxyphenyl	phenyl	0, 1	59[a], 65[b]	89[a], 91[b]
29, 30	2-bromo-5-methoxyphenyl	4-fluorophenyl	0, 1	61[a], 58[b]	97[a], 90[b]
31	2-bromo-5-methoxyphenyl	3-methoxyphenyl	0	72	93
32	2-bromo-5-methoxyphenyl	4-bromophenyl	1	30*	98[c]

[a] and [b] denote n = 0 and n =1 respectively. * and [c] denote yield and purity obtained after preparative HPLC.

In summary, an efficient and simple solid phase method for the preparation of unsymmetrical secondary amines has been developed. Further exploitation of this methodology for the synthesis of other biologically relevant compounds is in progress.

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5. General Experimental Procedure for **9**: A suspension of commercially available Fmoc-Knorr resin (150 mg, 0.132 mmol) in DMF-piperidine (1:1) was vortexed for 30 minutes. The solvent was drained and the resin was washed with DMF (3 X 5 mL) and then resuspended in a mixture of DMF-trimethyl orthoformate (5 mL, 1:1). 4-Fluorobenzaldehyde (20 mg, 0.16 mmol) and acetic acid (10 μL) were added and the resin was allowed to vortex for 1 hour. Sodium triacetoxyborohydride (41 mg, 0.2 mmol) was added and the resulting suspension was vortexed overnight. The resin was successively washed with DMF (3 X 5 mL), dichloromethane (3 X 5 mL) and finally with methanol to afford resin **2**. 2-Chloroacetophenone (60 mg, 0.4 mmol) was added to resin **2** suspended in a mixture of DMF-acetone (8 mL, 1:1). The reaction mixture was heated at 45°C for 10 hours. Thereupon the resin was washed with DMF (3 X 5 mL) and THF (2 X 5 mL) to afford resin **5**. Sodium borohydride (10 mg, 0.26 mmol) was added to resin **5** previously swollen in a mixture of THF-ethanol (8 mL, 1:1) and the mixture was vortexed for 4 hours. The resin was successively washed with THF (2 X 5 mL), 10% acetic acid solution in THF (3 X 5 mL), THF (2 X 5 mL) and finally methanol (2 X 5 mL), to give resin **7**. Resin **7** was shaken in a mixture of TFA-dichloromethane (5 mL, 1:1) for 3 hours and the resulting solution was filtered and concentrated to give a pale brown colored residue. The residue was reconstituted in methanol and concentrated to give compound **9** as the trifluoroacetate salt (21.3 mg) in 45% overall yield (from Knorr resin).
6. All compounds were analyzed by EIMS and HPLC coupled with a UV detector. Additionally, compounds **9** and **10** were also analyzed by ^{1}H and ^{13}C NMR.