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Liquid Phase Synthesis of Arylamines and its application to the Benzimidazolone *via* Nucleophilic Aryl Substitution

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Abstract

A method for soluble, inexpensive polymer-supported synthesis of aryl amines and benzimidazolone on the basis of nucleophilic aryl substitution (S_NAr) is described. This method involves a direct coupling reaction between resin bound aryl fluoride and amines at ambient temperature. The products are isolated in quantitative yields and excellent purity by simple precipitation and washing. This liquid phase method proves to be a useful tool for constructing combinatorial arylamine and benzimidazolone libraries.

Keywords: combinatorial chemistry, acylation, piperazine, liquid-phase synthesis

Combinatorial organic synthesis on solid support [1-3] has been regarded as an important tool for chemists to synthesize a large number of pharmaceutically interesting compounds. In combination with high throughput screening, this technology may dramatically accelerate drug lead discovery. While most of the libraries thus established have been synthesized on solid support, liquid-phase combinatorial synthesis (LPCS) provides an interesting approach, where molecules are prepared on a liquid, soluble polymer-poly(ethylene glycol) [4-5]. This polymer support, in contrast to an insoluble matrix, is soluble in many organic solvents and has a strong tendency for precipitation in particular solvent. Upon reaction, the product remains covalently bound to the support, and purification can be accomplished after precipitation simply by filtering and washing away the unreacted low-molecule-weight, solution-phase reagents. Therefore, general difficulties in solid phase reactions such as lower reactivity and characterization of polymer bound intermediate products could be alleviated by the use of organic-soluble polymer support.

The aryl amine moiety is frequently found as a key structural element in compounds possessing broad biological activity [6]. Therefore, a general method for the rapid multiple synthesis of these molecules would be of great value in developing combinatorial approaches for drug discovery and lead optimization. A recent report described the solid phase preparation of aryl amines *via* displacement of aromatic bromides by various amines [7-8]. However, this method required drastic conditions of elevated temperature (e.g. refluxing toluene) to obtain a clean and complete reaction. Herein, we wish to report a promising liquid-phase approach that aryl amine libraries can be synthesized on soluble polymer support in quantitative yield and excellent chemical purity (Table 1).

When applied to scaffold analog synthesis, this approach requires the polymer building block **3** to be soluble under conditions of S_NAr reaction and to be insoluble during the workup of reaction mixtures while other impurities are soluble. The solubility of the reactants and polymer support allows reaction kinetics

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control similar to those observed in solution chemistry. Our liquid phase method then retains two crucial advantages of solid phase synthesis, *i.e.* addition of excess reagents and simple product purification.

Scheme 1.

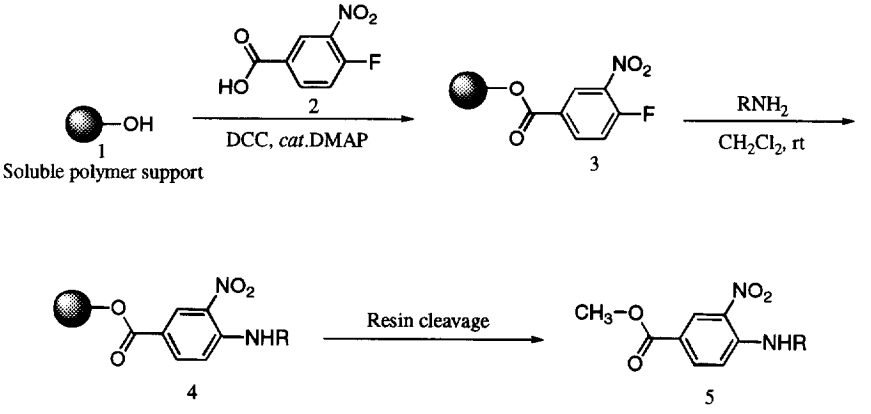
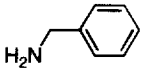
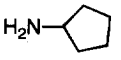
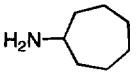
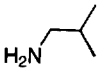
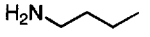
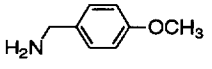
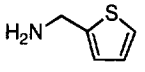


Table 1. Coupling of Soluble Polymer Bound Aryl Fluoride and Primary Amines

Entry	RNH_2	Observed MS[a]	Crude yield[b] (%)	Crude purity[c] (%)
5a		287	99	92
5b		265	99	96
5c		293	99	95
5d		253	99	98
5e		253	99	97
5f		239	99	92
5g		317	99	97
5h		293	99	96

a. Confirmed by electron spray mass spectrometer (MH^+).
b. Determined from weight of crude sample.
c. Purity determined by HPLC analysis of crude products. Products show satisfactory ^1H NMR and MS data.

The basic synthetic route is outlined in Scheme 1. The resin bound activated aryl fluoride **3** was prepared from MeO-PEG **1** (MW: 5000), 4-fluoro-3-nitrobenzoic acid **2** and N,N'-dicyclohexylcarbodiimide (DCC) *via* ester linkage [4]. The resulting polymer-supported aryl fluoride **3** was then allowed to react with a variety of primary amines at ambient temperature [4]. After the reactions were completed, the PEG-bound products (**4a~4h**) were precipitated by the addition of an ice-cold solution of *t*-butyl methyl ether and after drying the products were ready for the next cleavage step. No attempts were taken to optimize the reaction conditions and all reagents were used directly without further purification. Table 1 shows a representative selection of compounds synthesized[1]. Treatment of polymer bound aryl amines with catalytic amount of KCN in methanol resulted in a very efficient cleavage from polymer support to provide the desired molecules (**5a~5h**) in quantitative yield. Each crude product was then analyzed by HPLC and gave excellent purity (92~98%).

It is worthy to note that, in contrast to the various restrictions on the analysis of reaction development in solid-phase synthesis, liquid phase synthesis allows routine analytical methods (UV, IR, NMR, TLC) to monitor reaction progress without following cleave-&-analyze technique. This non-destructive method to monitor reaction progress makes LPCS method even more valuable.

In order to further explore the versatility of this methodology and increase the diversity of molecules, benzimidazol-2-one-5-methyl ester was synthesized (Scheme 2). The first point of diversity was employed by the S_NAr reaction of isobutylamine to the polymer bound o-fluoronitrobenzene **3**. Reduction of **4d** was achieved smoothly to **6** by treatment of Tin(II) chloride dihydrate. Cyclization to the benzimidazolone with trichlorophosgene gave **7** in high yield. To create a second point of diversity, the cyclized product **7** was deprotected with sodium hydride followed by quenching with methyl iodide to give the completely functionalized benzimidazolone **8**. Liberation of alkylated product **9** from the polymer was proceeded completely under mild conditions (1 % KCN /methanol). The desired compound **9** was obtained in six steps in 90 % crude yield and 80 % crude purity determined by HPLC [9]. This methodology is greatly suitable for

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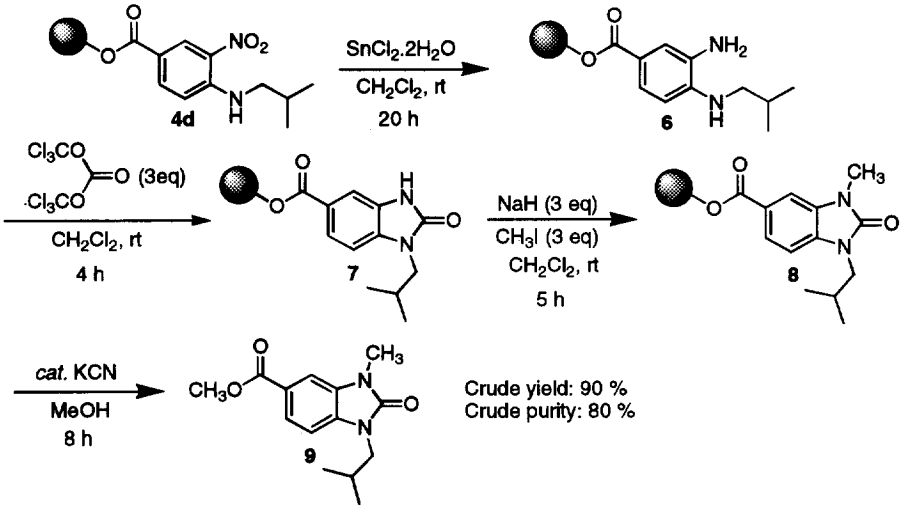
[1] In a typical procedure for the synthesis of **5g** is as follow: PEG supported aryl fluoride **3** (258.4 mg, 5.0×10^{-2} mmol) and 4-Methoxy-benzylamine (8.2 mg, 6×10^{-2} mmol) were stirred in 5 mL CH_2Cl_2 for 18 h. After completion, the solution was concentrated by rotary evaporation and reaction mixture was precipitated by slow addition of cold diethyl ether with stirring. Polymer bound product was then filtered under aspirator pressure using a fritted funnel and washed several times with cold ether. The crude PEG product was redissolved, precipitated twice and dried *in vacuo* for the next sequence. The transesterification of substituted product in KCN/methanol is representative for the cleavage procedure: 313 mg of **4g** was dissolved in 5 mL 1% KCN/CH_3OH and stirred at room temperature for overnight. The solution was evaporated under vacuum to remove methanol and PEG product was dissolved in 4 mL methylene chloride, precipitated into icy cold ether. The polymer was filtered and the combined filtrate was dried to give crude product **5g** as a bright yellow solid (15.6 mg, 99 %); The crude purity of this compound was determined to be 97 % by the HPLC analysis (250x4.6 mm Sphereclone 5μ Si, gradient elution 50 % ethyl acetate/hexane, 1 mL/min.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (d, J = 1.9 Hz, 1 H), 8.63 (bs, 1 H), 8.02 (dd, J = 9.0, 1.9 Hz, 1 H), 7.27 (d, J = 8.5 Hz, 2 H), 6.92 (d, J = 8.5 Hz, 2 H), 6.88 (d, J = 9.0 Hz, 1 H), 4.53 (d, J = 5.4 Hz, 2 H), 3.90 (s, 3 H), 3.82 (s, 3 H); ^{13}C NMR($CDCl_3$) δ 165.7, 159.5, 147.6, 136.5, 131.7, 129.6, 128.7, 128.5, 117.7, 114.6, 114.1, 55.5, 52.3, 47.0. IR (neat) 3397,1734,1622,1521. HRMS: calcd. for $C_{16}H_{16}N_2O_5$ 316.1060, found 316.1054.

automated process because all the synthetic steps can be carried out in methylene chloride at ambient temperature.

Scheme 2. Liquid phase synthesis of benzimidazolone



In summary, a novel liquid-phase combinatorial synthesis of aryl amine libraries and benzimidazolone has been developed. This methodology should decrease the difficulties of adapting established solution-phase precedents to polymer supported reactions since reactions can be carried out in homogeneous solution. All three reactions involved (linker attachment, S_NAr reaction, and resin cleavage) are highly efficient in giving the desired compounds in high yields and excellent purity by simple precipitation and washing. Although the aromatic fragment must contain a nitro group in the *ortho* position for S_NAr reaction, it is useful for subsequent transformation to benzimidazolone (Scheme 2). This method of synthesis is versatile and produces compounds with known pharmacophoric scaffolds, and which are thus ideally suited for combinatorial library generation. Further exploration of this technology is ongoing and will be reported in later papers.

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References

[1] Terrett NK, Gardener M, Gordon DW, Kobylecki, R. Tetrahedron 1995;30:8135-8173.
[2] Myers PL, Greene JW, Teig SL. Today's Chemist at Work 1997;6:46-53.
[3] Borman S, Chemical & Engineering News 1998; April 6:47-67.
[4] Pan PC, Sun CM. Tetrahedron Lett. 1998;39:9505-9508.
[5] Gravert DJ, Janda, K. Chem Rev. 1997;97: 489-509.
[6] Broekkamp CL, Leysen D, Peeters BWMM, Pinder RM. J. Med. Chem. 1995; 38:4615-4633.
[7] Willoughby CA, Chapman KT. Tetrahedron Lett. 1996;37:7181-7184.
[8] Ward YD, Vittorio F. Tetrahedron Lett. 1996;37:6993-6996.
[9] Physical data for benzimidazol-2-one-5-methyl ester is as follow: **9**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.4, 1.1 Hz, 1 H), 7.67 (d, J = 1.1, Hz, 1 H), 7.00 (d, J = 8.4 Hz, 1 H), 3.93 (s, 3 H), 3.71 (d, J = 7.2 Hz, 2 H), 3.50 (s, 3 H), 2.21 (m, 1H), 0.97 (d, J = 6.6 Hz, 6 H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 167.4, 155.1, 133.9, 130.0, 124.0, 123.3, 108.8, 107.4, 52.3, 49.1, 28.2, 27.5, 20.3. IR (neat) 2981, 1699, 1508. HRMS: calcd. for $C_{14}H_{18}N_2O_3$ 262.1318, found 262.1318.