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Solid Phase Synthesis of Aryl and Heteroaryl Amines Using the Curtius Rearrangement

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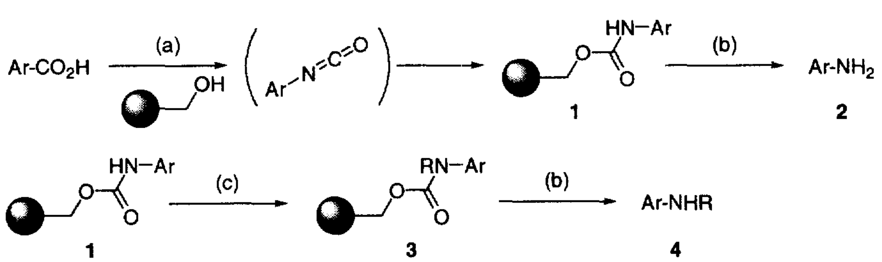
Abstract: An efficient method for the solid phase synthesis of secondary aryl amines and heteroaryl amines was developed. The key step was the formation of aryl or heteroaryl carbamates using the Curtius rearrangement of aryl carboxylic acids with Wang resin as a trapping hydroxyl group. N-alkylation reactions of resin-bound carbamates under the Mitsunobu condition or using sodium hydride gave secondary aryl or heteroaryl amines in good yields. The developed method can be applied in the preparation of libraries containing aryl and heteroaryl amine structures as a pharmacophore.

Solid phase synthetic technologies have been widely developed and are now very important, especially in the pharmaceutical industry. Since biologically active compounds often possess aryl and heteroaryl amines as the essential pharmacophore, the construction of such amine libraries are useful for the discovery of lead compounds for new drugs. In solution phase, a carbamate group is often utilized for *N*-protection,[1)] however, direct introduction of *N*-carbamate to aryl or heteroaryl amines often results in a low yield, which is largely due to the poor nucleophilicity of the aryl amines compared to alkyl or allyl amines. For this reason, aryl and heteroaryl carbamates are prepared in solution phase chemistry from the corresponding carboxylic acids via the Curtius rearrangement, followed by trapping of the isocyanate intermediate with alcohols.[4)] Also in solid phase chemistry, reaction of aryl amines with *p*-nitrophenylcarbonate resin does not give carbamates in good yields. Actually coupling 4,6-dimethyl-2-aminopyridine to *p*-nitrophenylcarbonate resin using potassium bis(trimethylsilyl)amide as a base according to the previously published method in solution phase[3)] resulted in a 40% yield despite using a 3-fold excess of the amine and a long reaction time (20 hours). Recently, H.-P. Buchstaller described the coupling reaction of phenylisocyanate and Wang resin to obtain the corresponding



Reagents: (a) Wang resin, diphenylphosphoryl azide, triethylamine, toluene, 100°C; (b) 50% trifluoroacetic acid/dichloromethane; (c) (1)NaH, DMF (2) R–X, 80°C.

Scheme 1

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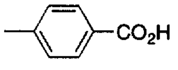
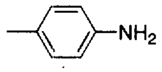
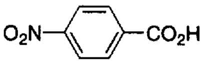
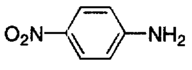
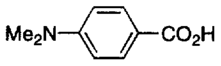
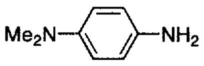
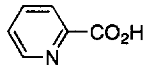
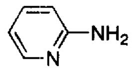
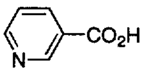
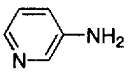
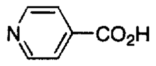
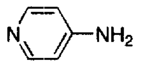
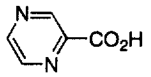
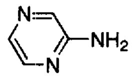
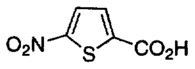
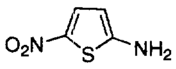
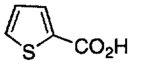
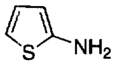
resin-bound aniline with carbamate bond, but the number of easily available phenylisocyanate derivatives is limited. Thus, we applied the Curtius rearrangement in solid phase synthesis to prepare combinatorial libraries with more structural diversity. Here we report an efficient synthesis of aryl and heteroaryl amine libraries via the Curtius rearrangement followed by *N*-alkylation under the Mitsunobu condition as well as a condition using NaH as a base (**Scheme 1**).

The Curtius rearrangement of a range of aryl and heteroaryl carboxylic acids in the presence of commercial polystyrene Wang resin as a trapping hydroxyl group was carried out (3-fold excess of carboxylic acid / 5-fold

Table 1.

Entry	Starting Carboxylic Acid	Product	Yield(%)[a]	Purity(%)[b]
1			>95	83
2			>95	94
3			>95	84
4			>95	91
5			>95	82
6			>95	83
7			90	86
8[c]			>95	90
9[c]			>95	85

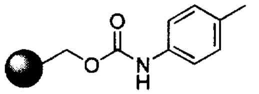
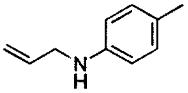
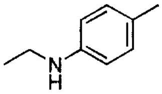
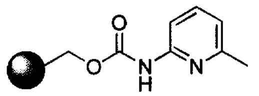
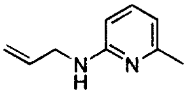
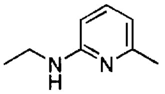
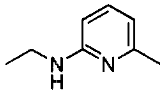
a) Yield based on the TFA salt relative to a theoretical loading of 1.2 mmol/g.
b) Purity determined by HPLC and ^{1}H NMR.
c) These reactions were carried out at 80 ßC.

excess of diphenylphosphorylazide / 10-fold excess of triethylamine / toluene / 100 °C / 16 h).[5] The formation of carbamate **1** was monitored by IR spectroscopy ($\nu_{C=O}$:1730 cm^{-1}). After cleavage of the product from resin by 50% TFA in dichloromethane, the objective aryl and heteroaryl amines **2** were given in good yields with high purity. This procedure worked well on benzoic acids with an electron-withdrawing substituent (entry 2) and an electron-donating substituent (entry 3). Also, the reaction proceeded smoothly in the case of pyridine carboxylic acid derivatives, with nitrogen at any position in the pyridine ring (entries 4-6). Other heteroaryl carboxylic acids gave excellent results (entries 7-9), as shown in Table 1.

Next, the *N*-alkylation of resin-bound carbamates was tested. The results of all of the alkylation reactions are shown in Table 2. *N*-(4-methylphenyl)carbamate (entries 1, 2) and *N*-(6-methyl-2-pyridyl)carbamate (entries 3, 4) were alkylated completely under standard conditions (5-fold excess of NaH /10-fold excess of ethyl iodide and allyl bromide as alkylating agents / DMF / 80 °C / 15 h).[5] The reactions were monitored by IR spectroscopy by the shift of carbamate absorbances from 1730 cm^{-1} to 1705 cm^{-1} after alkylation. The carbamate resin was treated with NaH in DMF for 1.5 h at room temperature, followed by alkylation with allyl bromide and ethyl iodide in DMF at 80 °C for 15 h, and cleavage from the resin. The reaction proceeded completely, and excellent yields and high purity of the mono -*N*-alkyl aryl and pyridyl amines were obtained.

We also applied the Mitsunobu reaction to the resin-bound *N*-(6-methyl-2-pyridyl)carbamate system[6,7] (ethanol / *N,N,N',N'*-tetramethylazodicaboxamide (TMAD) / tributylphosphine / THF / 60 °C / 15 h) to obtain the ethyl adduct in almost the same yield as that obtained using the ethyl iodide method (entry 5).

Table 2.

Entry	Starting Carbamate	Product	Yield(%)[a]	Purity(%)[b]
1			77	91
2			93	94
3			>95	93
4			>95	84
5			>95	90

a) Yield based on the TFA salt relative to a theoretical loading of 1.2 mmol/g.
b) Purity determined by HPLC and ^{1}H-NMR.

In summary, an efficient and convenient method for preparing aryl and heteroaryl amines starting from carboxylic acids via the Curtius rearrangement in solid phase has been developed. Also, alkylation of the resultant carbamate resin gave various mono alkylated aryl amines in excellent yields and purities. This method is applicable to not only benzoic acids but also to pyridine carboxylic acids.

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5. General procedure: A mixture of Wang resin (1.0 g, 1.2 mmol; loading 1.2 mmol/g), carboxylic acid (3.6 mmol), diphenylphosphoryl azide (1.3 ml, 6 mmol) and triethylamine (1.67 ml, 12 mmol) in toluene (10 ml) was heated at 100 °C for 16 h. The resin was washed successively with DMF (4 x 15 ml), DMF-H_2O (1:1) (4 x 15 ml), MeOH (4 x 15 ml), and CH_2Cl_2 (4 x 15 ml). The resin was dried under high vacuum for 10 h. The resin (30 mg, 0.036 mmol) and NaH (60% in oil, 7.2 mg, 0.18 mmol) were shaken in DMF (0.5 ml) for 1.5 h. Then alkylating agent (0.36 mmol) was added and the mixture was heated at 80 °C for 16 h. The resin was washed successively with DMF (3 x 3 ml), MeOH (3 x 3 ml), and CH_2Cl_2 (3 x 3 ml). The product resin was shaken with 50% TFA-CH_2Cl_2 for 5 min, filtered, washed, and evaporated to dryness to leave aryl amine, which was analyzed by HPLC, LC-MS and ^1H NMR.
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