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Curtius Degradation in Solid-Phase Synthesis

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Abstract: An optimized and broadly applicable procedure for the solid-phase synthesis of primary amines and carbamates *via* Curtius-degradation of carboxylic acids has been developed. The targeted primary amines and carbamates were obtained in excellent purity and high overall yields.

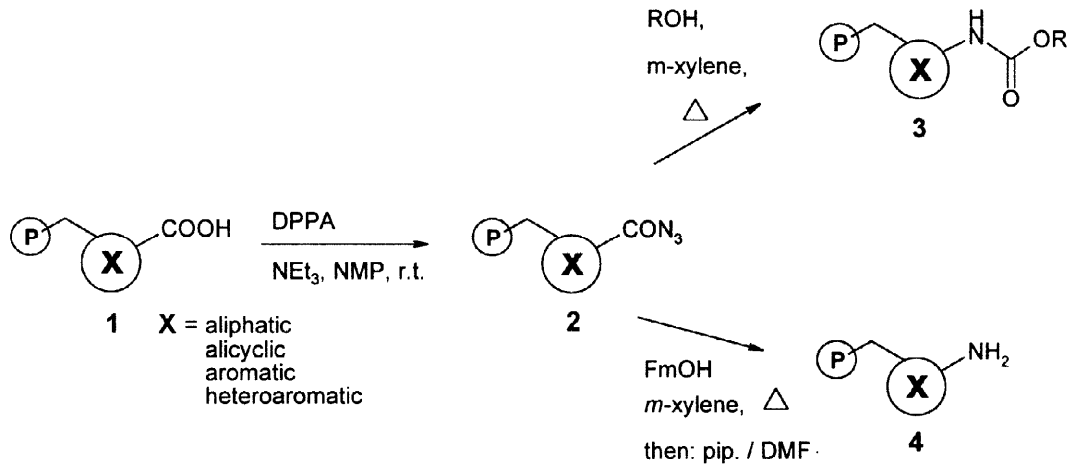
Keywords: Curtius reaction; solid-phase synthesis; rearrangement; degradation

In recent years, efficient methods for the rapid synthesis of a large number of chemical entities have been developed. Using split-and-mix synthesis or high-throughput, parallel solid phase (or solution phase) methods, the production of more than 1000 compounds / week has become a laboratory routine in many industrial combinatorial chemistry groups.[1]

More recently, the synthesis of information-based libraries has gained considerable interest.[2-4] In contrast to random libraries which contain "diverse" molecules[5] for high throughput screening, information-based libraries consist of derivatives of a small molecule lead molecule. Alternatively, information-based libraries may be directed towards a specific group of biological target molecules,[2,3] or address a specific, 3-dimensional protein epitope.[4a] Even more so than the production of a large number of compounds, the design and synthesis of directed, pharmacophore-based libraries relies on the availability of broadly applicable, reliable organic transformations where synthetic success is predictable.

As an example of a synthetic transformation which eventually should facilitate the incorporation of either "diverse" or "similar" building blocks representing the desired pharmacophoric elements, we have investigated the Curtius-degradation of carboxylic acids on a polystyrene support, yielding carbamates and primary amines.

Scheme 1



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The chemistry involved is outlined in Scheme 1. After transformation of a resin-bound carboxylic acid into the corresponding azide using diphenylphosphoryl azide, the resin-bound azides were decomposed in a controlled manner to provide the corresponding carbamates. When 9-fluorenemethanol is chosen as the alcoholic reagent, the Fmoc-protected amines as convenient precursors of free primary amines[6] are obtained.

As can be extracted from Table 1 (Fmoc-protected amines) and Table 2 (other derivatives), the described transformation works reliably for a wide variety of structurally different, aromatic or aliphatic carboxylic acids. Moreover, it appears that the success of the synthetic transformation is essentially independent of the chemical structure of the substrate molecule, and the nature of the linkage to the solid support (Table 1, entries 1, 3 and 4).

Table 1

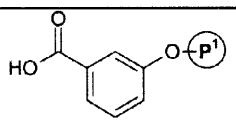
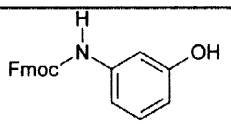
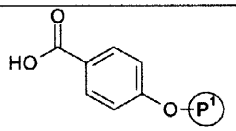
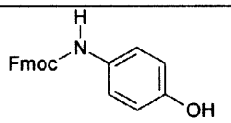
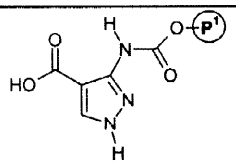
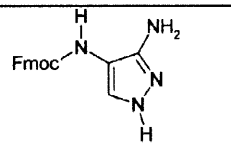
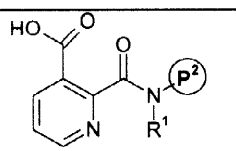
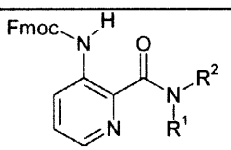
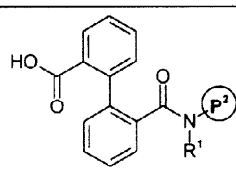
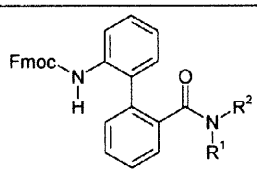
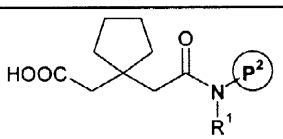
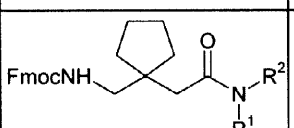
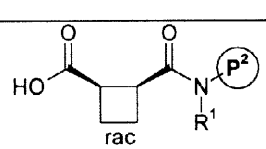
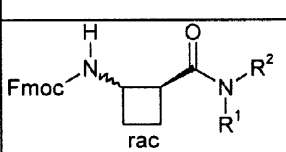
entry	starting material	product	purity[a]	yield[b]
1			> 90 %	34 %
2			> 90 %	75 %
3			85 %	49 %
4			> 90%	75%
5			80 %	68%
6			> 90%	78%
7			> 90 %[c]	70 %

Table 2

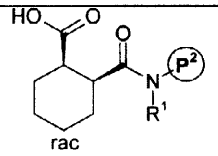
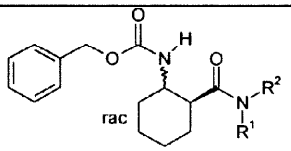
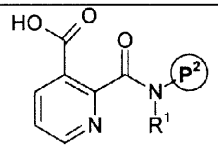
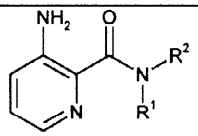
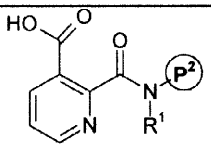
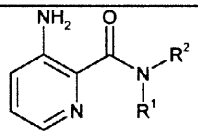
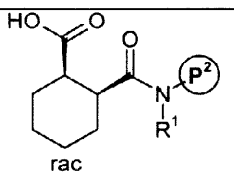
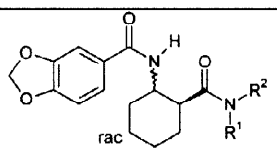
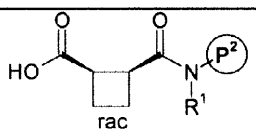
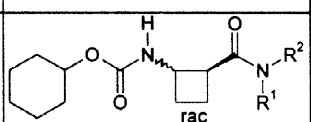
entry	starting material	product	purity[a]	yield[b]
8			> 90 %[c]	85 %
9		 *via* N-Fmoc-derivative	> 90 %	60 %
10		 *via* "direct" degradation	< 5 %	n.d.
11		 *via* N-Fmoc-derivative	> 90 %[c]	78 %
12			> 90 %[c]	86 %

Table 1, Table 2: Curtius Degradation of Polystyrene-Supported Carboxylic Acids

$\mathbf{P^1}$ = Wang resin; $\mathbf{P^2}$ = 3-methylphenylcarboxamide on Rink resin; R^1 = methylcyclopropyl; R^2 = 3-methylphenylcarboxamide. For the synthesis of the resin-bound substrate molecules, see experimental section. a) Purities were determined by ^{1}H NMR. b) Overall yields were determined by weight of the cleaved and dried reaction products. c) as a 1 : 1 mixture of the two diastereomers.

In our hands, attempts towards a "direct" Curtius degradation of resin-bound azides to primary amines on a polystyrene support in the presence of water and presence or absence of weak acids like acetic acid or pyridinium *p*-toluenesulfonate gave impure products, containing between 0 and 10 % of the desired free amine (see entry 10). Since the "indirect" procedure *via* the N-Fmoc protected amine, followed by subsequent deprotection using 20% piperidine in DMF, is superior with respect to reliability, yields and purities (see entries 9, 11), we strongly recommend the synthetic route via the Fmoc-protected amines.

In summary, we have developed and validated the Curtius degradation of carboxylic acids on a polystyrene support, yielding carbamates and / or primary amines. The transformation works reliably in good overall yields for a wide variety of carboxylic acids, largely independent of the specific chemical structure of the resin-bound substrate molecule. We believe that these features will make the Curtius degradation a valuable

and reliable chemical transformation for the parallel solid-phase synthesis of diverse random libraries, as well as directed small molecule libraries.

Experimental:

a) A solution of the corresponding dicarboxylic acid anhydride[7] (1.25 mmol) in NMP (0.80 mL) was added to 250 mg (approx. 0.25 mmol) of the corresponding amine on polystyrene resin, and the mixture was heated to 60°C for 2 h. The intermediate **1** on resin was washed with three portions of 5 mL NMP. b) The free carboxylate on resin **1** (250 mg, approx. 0.25 mmol) was agitated for 90 min at room temperature with a mixture of NMP (3.0 mL), triethylamine (525 µL, 3.75 mmol) and diphenylphosphoryl azide (540 µL, 2.5 mmol). The azide **2** was washed with NMP (3 x 5 mL) and *m*-xylene (3 x 5 mL) c) A solution of 9-fluorenemethanol (1.0 mmol) in *m*-xylene (1.2 mL) was added to the azide **2** on polystyrene resin (100 mg, mmol), and the mixture was heated to 90°C for 16 h. The resulting carbamate **3** was washed with *m*-xylene (2 x 3.5 mL), methanol (2 x 3.5 mL) and dichloromethane (3 x 3.5 mL), and cleaved from resin by exposure to 1.5 mL of a 50% solution of TFA in dichloromethane. The resin was drained, the filtrate containing the reaction product was collected, and the solvents were evaporated. All crude products were characterized by HPLC/MS and ^{1}H NMR; in addition, selected samples were purified and characterized by HRMS and / or combustion analysis.

Synthesis of the resin-bound substrate molecules: 1. Entries 1 and 2:[3a] a) Wang-resin (0.25 mmol), dichloromethane (1.2 mL), diethylisopropylamine (1.2 mL), methanesulfonylcloride (125 µL) in dichloromethane (0.8 mL), 30 min at 0°C, then 45 min at r.t.; b) methyl-4-hydroxybenzoate (1.2 mmol, entry 1) or ethyl-3-hydroxybenzoate (1.2 mmol, entry 2), potassium-*tert.*-butoxide (1.0 mmol), DMSO (2.5 mL), 80°C, 2 h; c) ester hydrolysis as described in ref. 8.

2. Entry 3: a) Wang-resin (0.25 mmol), 4-nitrophenylchloroformate (1.16 mmol), pyridine (275µL), dichloromethane (2.5 mL), 4 h at r.t.;[9] b) Ethyl-3-amino-4-pyrazolecarboxylate (0.80 mmol), diethylisopropylamine (0.80 mmol), dioxane (2.5 mL), 2 h at 60°C, then 2 h at 80°C; c) ester hydrolysis as described in ref. 8.

3. Entries 4 to 12: a) Rink resin (0.25 mmol), DeFmoc as described in ref. 8; b) 3-(chloromethyl)benzoic acid (1.25 mmol), diisopropylcarbodiimide (1.25 mmol), THF (8.0 mL), r.t., 3 h;[10] c) 2.0 M (aminomethyl)cyclopropane in DMSO (7.0 mL), 60°C, 16 h.

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7. Entry 4, 9, 10: pyridine-2,3-dicarboxylic acid anhydride; entry 5: diphenic anhydride; entry 6: 3,3-tetramethyleneglutaric anhydride; entry 7, 12: cis-1,2-cyclobutanecarboxylic anhydride; entry 8, 11: cis-1,2-cyclohexanecarboxylic anhydride.

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