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Solid Phase Urea Synthesis: An Efficient and Direct Conversion of Fmoc-Protected Amines to Ureas

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Abstract: An efficient "one-pot" conversion of Fmoc-protected amino acids to the ureas in the solid phase is described. This methodology uses $MeSiCl_3$ in the presence of Et_3N to cleave Fmoc-protected amines directly to their isocyanates. This transformation has been demonstrated on some Fmoc-protected amino acids. Trapping of the resin-bound isocyanate by the addition of amines generates the desired amino acid ureas in high HPLC purities.

The generation of urea-containing combinatorial libraries plays an important role in the search for potential drug candidates. Ureas represent a class of peptidomimetics that have improved pharmacokinetic (bioavailability and metabolic stability) properties compared to peptides. Therefore, an efficient and practical method for the solid phase synthesis (SPS) of ureas is of considerable interest. As urea synthesis by the reaction of resin-bound amines with isocyanates is limited to readily available isocyanates, the general method of choice has been to transform resin-bound amines to an activated carbamate, which may undergo subsequent amination to produce the desired urea. Phenyl carbamates[1] and *p*-nitrophenyl carbamates[2] have been reported as activated intermediates for the formation of ureas. In these cases, urea synthesis requires a three-step sequence involving nitrogen deprotection, carbamoylation with the phenyl chloroformate, and amination. Benzotriazole ureas have also been used as activated intermediates for urea synthesis.[3] More recently, a new resin was prepared that produces ureas by thermolytic cleavage of oxime-carbamates.[4]

The ability to directly transform an Fmoc-protected amine to its isocyanate would be valuable as the reactivity of isocyanates makes them ideal functionalities for the combinatorial SPS of ureas. However, the real advantage of this transformation over existing methods for urea SPS would be in the elimination of both the amine deprotection and activation steps, thereby allowing the use of a "one pot" reaction. We recently reported the use of chlorosilanes to selectively cleave carbamates directly to their isocyanates in solution.[5] Realizing its utility for solid phase urea synthesis, we evaluated its applicability in the cleavage of Fmoc-protected amines on Wang resin. We now report an efficient solid phase synthesis of ureas in a "one-pot" reaction directly from Fmoc-protected amines and demonstrate this on a selection of Fmoc-protected amino acids (Scheme 1). It is worth noting that it is a valuable alternative to the use of phosgene in the solution phase synthesis of amino acid ester isocyanates reported by Nowick and coworkers.[6]

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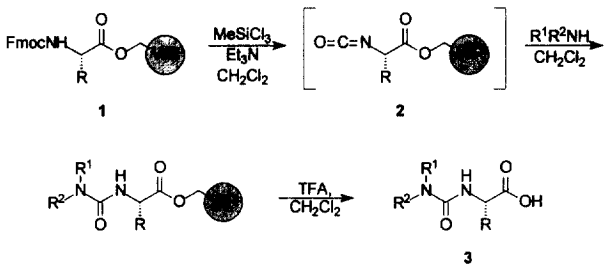
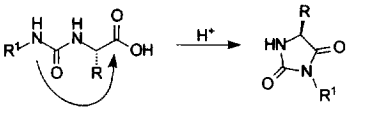


Scheme 1. Solid phase synthesis of ureas from Fmoc-protected amino acids.

The direct activation of Fmoc-protected amino acids **1a-g** to their isocyanates was accomplished by treatment with $MeSiCl_3$ (10 eq) and Et_3N (20 eq) in CH_2Cl_2 at room temperature. Although Fmoc cleavage is typically complete within 10 h, a standard reaction time of 24 h was used in this study. The resin-bound isocyanates that were formed *in situ* were then treated with amines to produce, upon cleavage, the desired ureas **3a-g** in high HPLC purities (Table 1).[7] The products were all fully characterized by LC-MS, HRFABMS, ^1H and COSY NMR experiments. We believe that the ureas are enantiomerically pure, as similar chemistry for hydantoin synthesis showed that the reaction conditions preclude racemization.[8]

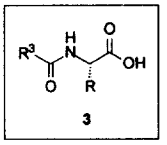
We found that di-substituted ureas formed by trapping the resin-bound isocyanates with primary amines were susceptible to hydantoin formation by intramolecular cyclization after cleavage of the urea from the resin (Scheme 2). Amino acid urea cyclization has been utilized in the synthesis of hydantoin libraries.[9] In several cases, some degree of this cyclization could not be avoided as it appeared to be facilitated by the presence of acid (used for cleavage) and often contributed towards lowering the observed HPLC purities. Therefore, it is not surprising that the ureas formed in the highest purities were **3d** and **3g**, where a secondary amine was used to trap the isocyanates. In these cases, cyclization to the hydantoin is impossible.



Scheme 2. Cyclization of amino acid ureas to hydantoins.

Interestingly, the treatment of isocyanate **2e** with 4-fluoro-2-nitroaniline failed to produce the desired urea, whereas urea **3c** was formed from isocyanate **2c** and 4-fluoro-3-nitroaniline. With the highly electron withdrawing nitro substituent at the ortho position, the aniline is not nucleophilic enough to produce the desired urea.[10] It is also worth noting that the cleavage of Fmoc-protected dipeptides results in cyclization to the corresponding hydantoins.[8] In addition, Fmoc-protected tripeptides show partial cyclization to hydantoins. Given that the possibility for side reactions is substrate-dependent, we believe that the methodology is convenient for generating ureas or other similar derivatives in the absence of other isocyanate-reactive functionalities within the molecule.

Table 1. Urea amino acids **3a-g** generated from **1a-g**.



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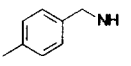
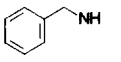
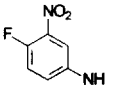
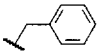
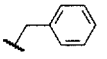
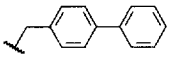
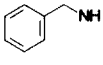
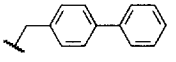
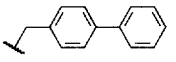
Urea	R^3 Group	R	HPLC purity [a] (%)	$(M+H)^+$ (calculated)	$(M+H)^+$ [b] (found)
3a			76	265.1552	265.1552
3b			79	265.1552	265.1552
3c			88	348.0996	348.0995
3d			92	277.1552	277.1553
3e			88	341.1865	341.1865
3f			88	375.1709	375.1708
3g			90	369.2178	369.2178

[a] HPLC % purities of the crude cleavage solutions were estimated at $\lambda = 214$ nm.[7]

[b] HRFABMS found for $(M+H)^+$ are reported.

^{1}H NMR (DMSO-d_6):

3a: δ 12.50 (br. s, 1H), 7.16-7.07 (m, 4H), 6.43 (t, 1H, $J = 6.0$ Hz), 6.14 (d, 1H, $J = 9.2$ Hz), 4.16 (d, 2H, $J = 5.7$ Hz), 4.06 (dd, 1H, $J =$ 9.1, 4.9 Hz), 2.27 (s, 3H), 2.01 (septd, 1H, $J = 6.8$, 5.0 Hz), 0.88 (d, 3H, $J = 6.8$ Hz), 0.83 (d, 3H, $J = 6.9$Hz).

3b: δ 12.51 (br. s, 1H), 7.31 (t, 2H, J = 7.6 Hz), 7.25-7.20 (m, 3H), 6.48 (ABX, 1H, $J_{AX} = 6.0$, $J_{BX} = 6.0$, $J_{AB} = 15.1$ Hz, $\nu_A = 2109.2$, $\nu_B = 2099.6$, $\nu_X = 3239.1$ Hz), 6.17 (d, 1H, $J = 8.8$ Hz), 4.21 (ABX, 2H, as above), 4.11 (dd, 1H, $J = 9.1$, 5.0 Hz), 1.74 (m, 1H), 1.38 (m, 1H), 1.13 (m, 1H), 0.86 (t, 3H, $J = 7.4$ Hz), 0.86 (d, 3H, $J = 6.8$ Hz).

3c: δ 12.89 (br. s, 1H), 9.18 (s, 1H), 8.35 (dd, 1H, $J = 6.7$ ($J_{H\text{-}F}$), 2.7 Hz), 7.56 (ddd, 1H, $J = 9.1$, 3.9 ($J_{H\text{-}F}$), 2.7 Hz), 7.45 (dd, 1H, $J =$ 11.2 ($J_{H\text{-}F}$), 9.1 Hz), 7.30 (m, 2H), 7.23 (m, 3H), 6.52 (d, 1H, $J = 7.9$ Hz), 4.46 (td, 1H, $J = 7.8$, 5.1 Hz), 3.10 (dd, 1H, $J = 13.8$, 4.9 Hz), 2..98 (dd, 1H, $J = 13.8$, 7.8 Hz).

3d: δ 12.44 (br. s, 1H), 7.28-7.16 (m, 5H), 6.55 (d, 1H, $J = 8.3$ Hz), 4.21 (ddd, 1H, $J = 10.4$, 8.0, 4.5 Hz), 3.21 (m, 4H), 3.01 (dd, 1H, J = 13.5, 4.5 Hz), 2.92 (dd, 1H, $J = 13.6$, 10.5 Hz), 1.49 (m, 2H), 1.34 (m, 4H).

3e: 12.67 (br. s, 1H), 7.64 (m, 2H), 7.58 (AA'BB', 2H, $J_{AA'} = J_{BB'} = 2.5$ Hz, $J_{AB} = J_{A'B'} = 8.3$ Hz, $\nu_A = \nu_{A'} = 3030.3$ Hz, $\nu_B = \nu_{B'} =$ 2905.4 Hz), 7.45 (t, 2H, $J = 7.6$ Hz), 7.35 (td, 1H, $J = 7.3$, 1.4 Hz), 7.26 (AA'BB', 2H, as above), 6.14 (t, 1H, $J = 5.8$ Hz), 6.04 (d, 1H, $J = 8.3$ Hz), 4.40 (td, 1H, $J = 8.0$, 5.3 Hz), 3.04 (dd, 1H, $J = 13.9$, 5.2 Hz), 2.91 (dd, 1H, $J = 13.6$, 7.7 Hz), 2.79 (t, 2H, $J = 6.3$ Hz), 1.57 (non, 1H, $J = 6.7$ Hz), 0.80 (d, 3H, $J = 6.7$ Hz), 0.80 (d, 3H, $J = 6.7$ Hz).

3f: δ 12.71 (br. s, 1H), 7.66-7.63 (m, 2H), 7.58 (AA'BB', 2H, $J_{AA'} = J_{BB'} = 2.0$ Hz, $J_{AB} = J_{A'B'} = 8.2$ Hz, $\nu_A = \nu_{A'} = 3032.4$ Hz, $\nu_B = \nu_{B'}$ = 2910.4 Hz), 7.46 (t, 2H, $J = 7.6$ Hz), 7.35 (tt, 1H, $J = 7.4$, 1.4 Hz), 7.28 (AA'BB', 2H, as above), 7.30-7.25 (m, 2H), 7.22-7.18 (m, 3H), 6.57 (t, 1H, $J = 6.2$ Hz), 6.22 (d, 1H, $J = 8.6$ Hz), 4.43 (td, 1H, $J = 8.0$, 5.2 Hz), 4.18 (d, 2H, $J = 6.0$ Hz), 3.07 (dd, 1H, $J =$ 13.8, 5.2 Hz), 2.93 (dd, 1H, $J = 13.8$, 8.0 Hz).

3g: δ 12.51 (br. s, 1H), 7.64-7.61 (m, 2H), 7.56 (AA'BB', 2H, $J_{AA'} = J_{BB'} = 2.0$ Hz, $J_{AB} = J_{A'B'} = 8.2$ Hz, $\nu_A = \nu_{A'} = 3776.0$ Hz, $\nu_B = \nu_{B'}$ = 3666.0 Hz), 7.45 (t, 2H, $J = 7.8$ Hz), 7.36-7.32 (m, 1H), 7.34 (AA'BB', 2H, as above), 6.18 (d, 1H, $J = 8.3$ Hz), 4.30 (ddd, 1H, J = 10.0, 8.3, 4.7 Hz), 3.15-3.06 (m, 3H), 3.03-2.96 (m, 3H), 1.35 (m, 4H), 0.75 (t, 6H, $J = 7.5$ Hz).

In conclusion, we have demonstrated that $MeSiCl_3$ with Et_3N may be used to generate ureas in high HPLC purities from Fmoc-protected amino acids on Wang resin. We believe that this methodology may be extended to other Fmoc-compatible acid-labile resins and is suitable for the generation of urea combinatorial libraries.

Typical procedure for conversion of Fmoc-protected dipeptides to hydantoins. To a solution of Fmoc-aa-Wang resin (0.090 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (251 μL, 1.801 mmol (20 eq)) and $MeSiCl_3$ (106 μL, 0.903 mmol (10 eq)). The resulting solution was shaken at rt for 24 h. The solution was then drained off, and shaken in a 10 % solution of the amine in CH_2Cl_2 for 30 min. The resin was filtered and washed successively with CH_2Cl_2, DMF, CH_3CN and CH_2Cl_2.

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(7) The HPLC purities of the crude cleavage solutions are reported rather than isolated chemical yields as we feel that the HPLC traces provide a better indication of the utility of the reaction as a solid phase synthetic methodology. HPLC conditions: 5-95% CH_3CN in H_2O + 0.1% TFA; linear gradient over 6 min, flow rate: 2 mL/min, Haisil 100 C_{18} 3μm column (50 x 4.6 mm); the purity was estimated on analytical traces at $\lambda = 214$ nm.

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(10)Hutchins and Chapman (ref. 2) showed that p-nitrophenylaniline was unable to undergo nucleophilic attack of p-nitrophenylcarbamates.