Pergamon

Tetrahedron Letters 40 (1999) 2493–2496

TETRAHEDRON LETTERS

Solid Phase Hydantoin Synthesis: An Efficient and Direct Conversion of Fmoc-Protected Dipeptides to Hydantoins

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Received 14 December 1998; accepted 25 January 1999

Abstract: An efficient and direct conversion of Fmoc-protected dipeptides to hydantoins 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. Internal cyclization of the amide on the isocyanate follows to produce the hydantoins in high purity and with no indication of racemization.

The solid phase synthesis (SPS) of hydantoins is of interest for the generation of combinatorial libraries of chemically diverse small organic compounds.[1] DeWitt and coworkers have reported the synthesis of hydantoins by N-cyclization and simultaneous cleavage of urea amino acids attached to the solid support by an ester linkage.[2] A similar cyclization / cleavage strategy for the synthesis of hydantoins, reported by Dressman and coworkers, utilizes a carbamate linker to attach amino acids by their N-termini to a hydroxymethyl polystyrene resin.[3] Hydantoin syntheses from dipeptides have been reported by Patel[4] and Houghten.[5] In both cases the terminal amine is activated to the isocyanate required for intramolecular cyclization, either by reaction with phosgene,[5] or by prior formation of the phenyl carbamate.[4] We recently reported the use of chlorosilanes to selectively cleave carbamates directly to their isocyanates in solution.[6] Realizing the potential of this transformation for the generation of peptidomimetics, and given the commercial availability of Fmoc-protected amino acids and their utility for SPS, we investigated the cleavage of Fmoc-protected amines to the isocyanates on Wang resin. We now report the solid phase synthesis of hydantoins in one step directly from Fmoc-protected dipeptides (Scheme 1).

Selected resin-bound dipeptides **1a-g** were cleaved to the isocyanates by treatment with $MeSiCl_3$ (20 eq) and Et_3N (40 eq) in $CHCl_3$. Mild heating at 70 °C for 24 h drives the cyclization reactions to completion affording, upon cleavage, the hydantoins **3a-g** in high HPLC purities (Table 1). Although a range of aprotic solvents may be employed, the lack of precipitation of by-product $Et_3N{\cdot}HCl$ in chloroform led to its choice as the general reaction solvent for this study. Interestingly, the use of DMF as the solvent failed to produce any desired product. A survey of chlorosilanes for the cleavage of Fmoc-protected amines showed that while $PhSiCl_3$ and $MeSiCl_3$ produced similar results, cleavage with $HSiCl_3$, Me_2SiCl_2 and Me_3SiCl was unsuccessful for reasons that remain unclear.

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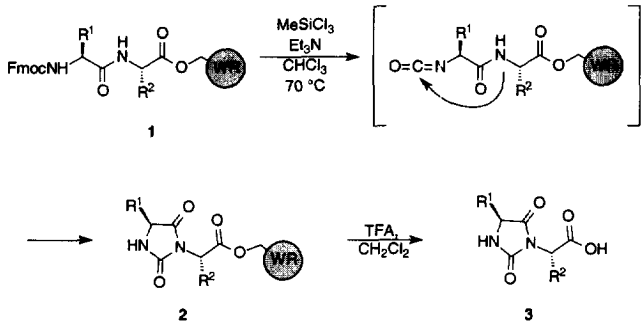
PII: S0040-4039(99)00243-9



Scheme 1. Solid phase synthesis of hydantoins from Fmoc-protected dipeptides

The products were fully characterized by LC-MS, HRFABMS, ^{1}H and COSY NMR experiments.[7] Figure 1 illustrates a typical crude HPLC trace of a hydantoin.[8] In all cases, the hydantoins formed were diastereomerically pure, as judged by ^{1}H NMR, demonstrating that, as expected, no racemization had occurred during the course of the reaction. All reactions proceeded to the hydantoins in excellent purities, with the exception of **3g,** which had several baseline impurities. We speculate that the cyclization of **3g** was hindered by the greater conformational flexibility of the peptide, given the lack of a bulkier substituent at R^2. Therefore, the uncyclized isocyanate may have been present after 24 h thereby generating some impurities during the resin wash.

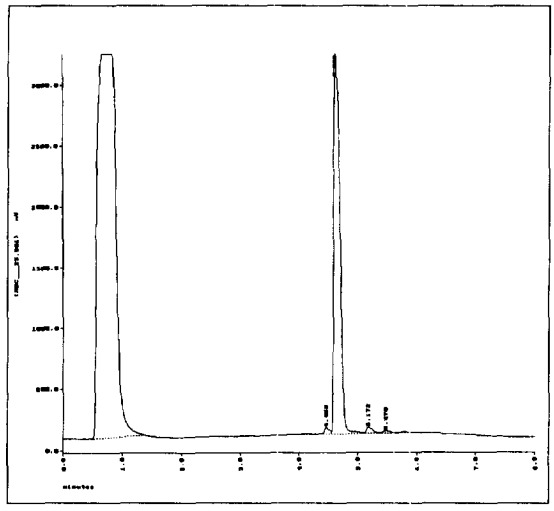
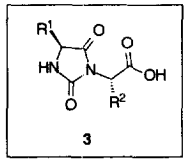


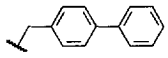
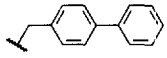
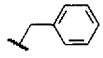
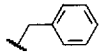
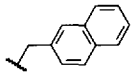
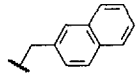
Figure 1 Crude HPLC of hydantoin **3f** after cleavage from resin.[8]

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

Table 1. Hydantoins **3a-g** generated from dipeptides **1a-g**.



3

Entry	R^1	R^2	HPLC purity [a] (%)	$(M+H)^+$ (calculated)	$(M+H)^{+}$ [b] (found)
3a			92	381.1814	381.1813
3b	CH_3		91	339.1345	339.1345
3c			98	305.1501	305.1501
3d			96	291.1345	291.1345
3e			96	355.1658	355.1660
3f			98	355.1658	355.1660
3g		H	73	215.1032	215.1032

[a] HPLC % purities of the crude cleavage solutions were estimated at $\lambda = 214$ nm[8]
[b] HRFABMS found for $(M+H)^+$ are reported.

Typical procedure for conversion of Fmoc-protected dipeptides to hydantoins. To a solution of Fmoc-Leu-Phe-Wang resin (0.060 mmol) in $CHCl_3$ (2 mL) was added Et_3N (335 μL, 2.403 mmol (40 eq)) and $MeSiCl_3$ (141 μL, 1.205 mmol (20 eq)). The resulting solution was shaken at 70 °C for 24 h. The resin was then filtered and washed successively with CH_2Cl_2, DMF, CH_3CN and CH_2Cl_2.

Acknowledgement

We gratefully acknowledge NIH, PRF, American Heart Association, UIUC Research Board, and Critical Research Initiatives Program for financial support. We extend special thanks to Dr. Mary Beth Carter (Biogen Inc., Cambridge MA) for useful discussions during the course of this investigation.

References and Notes

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(7) Selected ^{1}H NMR data for **3c**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (br. s, 1H), 8.26 (s, 1H), 7.26-7.11 (m, 5H), 4.79 (AB<u>X</u>, 1H, J_{AX} = 4.5, J_{BX} = 12.0, J_{AB} = 13.9 Hz, ν_A = 1324.7, ν_B = 1304.5, ν_X = 1917.2 Hz), 3.95 (ddd, 1H, J = 9.4, 4.4, 1.0 Hz), 3.29 (<u>AB</u>X, see above), 1.57 (dseptd, J = 9.5, 6.6, 4.4 Hz), 1.17 (ddd, 1H, J = 13.7, 9.4, 4.4 Hz), 0.94 (ddd, 1H, J = 13.7, 9.5, 4.4 Hz), 0.78 (d, 6H, J = 6.6 Hz).

(8) 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 λ = 214 nm.