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Solid phase synthesis of 1,3-disubstituted succinimides

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Abstract

The solid phase synthesis of *N*-substituted succinimides is described. The strategy used is based on the intramolecular cyclization of a dipeptide containing aspartic acid in the second position promoted by diphenylphosphorylazide (DPPA) and triethylamine. Large numbers of succinimides can be prepared using different, commercially available building blocks.

The screening of combinatorial libraries of heterocycles and small organic molecules has led to the discovery of new, biologically active compounds.[1] Solid phase synthesis is the standard technique for the generation of libraries,[2] not only for individual compounds but also for mixtures. In our laboratory, we have focused on the development of new strategies for the synthesis of heterocyclic compounds using amino acids and small peptides as starting materials.[3]

Succinimides are an important class of heterocyclic compounds with numerous applications in different fields.[4] In medicine, they have been used for the treatment of arthritis, tuberculosis, convulsion and epilepsy. They are considered as bioisosteres of hydantoins,[5] a heterocycle widely exploited in the synthesis of combinatorial libraries.[6,3c] In organic synthesis they have been used as valuable reagents and intermediates for the synthesis of natural and unnatural compounds.[7] Recently, succinimide-based pseudopeptides have been shown to stabilize β-turn conformations.[8] It has also been shown that they can be used as irreversible protease inhibitors.[9]

Only two approaches for the solid phase synthesis of succinimides have been reported to date.[10] We present here an efficient strategy for the synthesis of 1,3-disubstituted succinimides. The synthesis was carried out using the 'tea-bag' methodology,[11] and is illustrated in Scheme 1. Following Fmoc deprotection, the resin-bound free amino acid is coupled to aspartic acid ^{t}Bu ester using standard Fmoc chemistry. The deprotection of the ester with 95% TFA, followed by the activation of the generated carboxylic acid using diphenylphosphorylazide and Et_3N,[12] led to the resin-bound succinimide **1**. Following cleavage of the Fmoc protecting group, the generated amine was acylated with a wide range of carboxylic acids. Cleavage of the resin with hydrogen fluoride, followed by extraction and lyophilization,[13] affords the desired succinimide **2** in good yield and high purity (Table 1).

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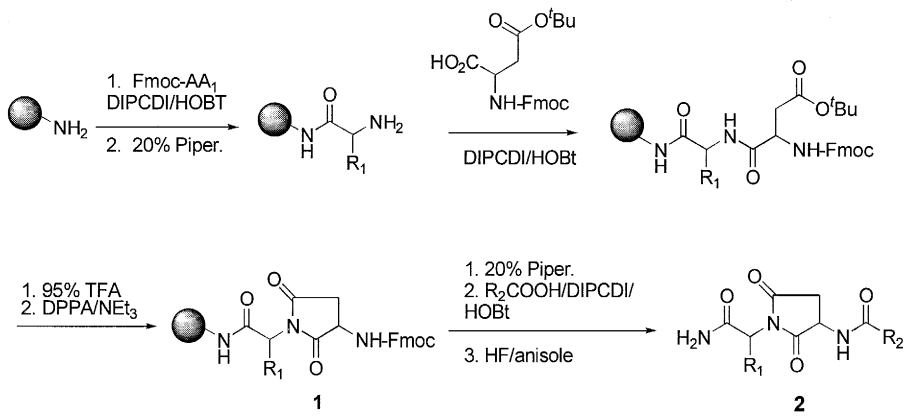
Table 1
Individual succinimides synthesized

Compound #	R_1	R_2	Mass expected	Mass found	Yield
1a*	$PhCH_2$		261.28	226.0	>95%
1b*	$CH_2CH(CH_3)_2$		227.26	228.0	>95%
1c*	CH_3		185.18	186.1	>95%
2a	$PhCH_2$	CH_3	303.21	304.0	>95%
2b	$PhCH_2$	Ph	365.38	366.2	>95%
2c	$PhCH_2$	$PhCH_2$	379.41	380.3	85.4%
2d	$CH_2CH(CH_3)_2$	CH_3	269.30	270.0	>95%
2e	$CH_2CH(CH_3)_2$	Ph	331.37	332.4	88.8%
2f	$CH_2CH(CH_3)_2$	$PhCH_2$	345.39	346.1	92.6%
2g	CH_3	CH_3	227.22	227.9	>95%
2h	CH_3	Ph	289.22	290.0	82.3%
2i	CH_3	$PhCH_2$	303.31	304.0	>95%

* Characterized following Fmoc deprotection and HF cleavage from the resin.



Scheme 1. Solid phase synthesis of 1,3-disubstituted succinimides

Twelve compounds were synthesized using four amino acids and three carboxylic acids (Table 1). All individual compounds were obtained in good yield and purity, and were characterized by LC-MS.[14] Fig. 1 illustrates a typical LC-MS spectra for compound **2f** obtained from leucine and phenylacetic acid, which is representative of the purity obtained for all compounds. The screening results will be reported elsewhere.

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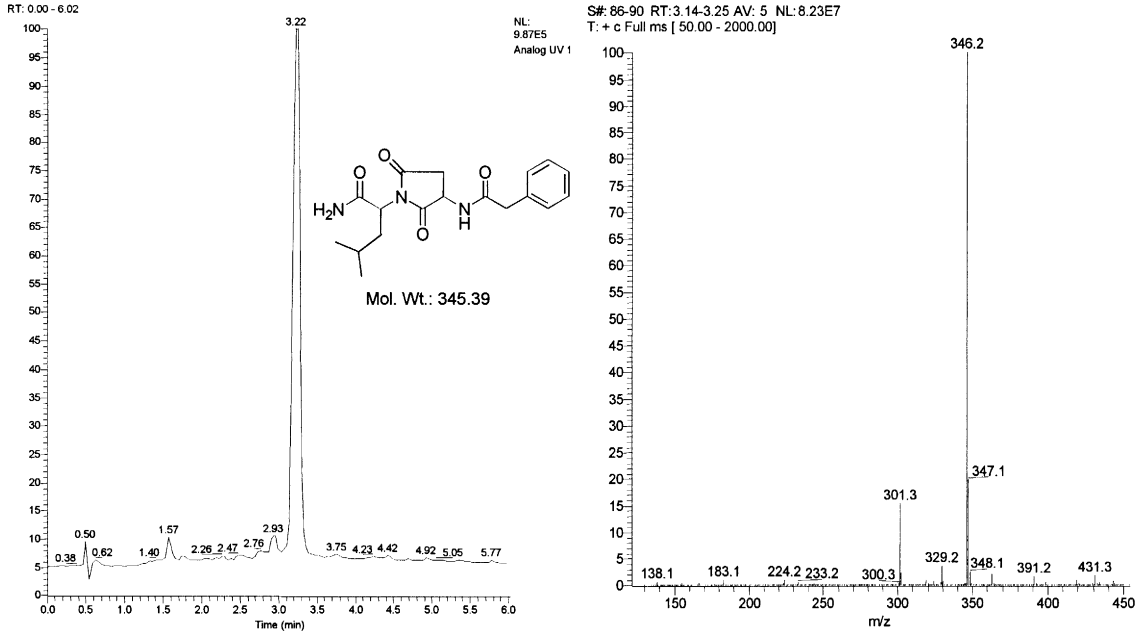

Fig. 1. LC-MS of succinimide **2f**

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13. Typical procedure for the synthesis of individual succinimides: 50 mg of *p*-methylbenzhydrylamine (MBHA) resin (1 meq/g, 100–200 mesh) was contained within a sealed polypropylene mesh packet.[11] Following neutralization of the resin with 5% diisopropylethylamine (DIPEA) in dichloromethane (DCM) and washing with DCM, the first Fmoc amino acid (6 equiv.) was coupled using hydroxybenzotriazole (HOBT, 6 equiv.) and diisopropylcarbodiimide (DIPCDI, 6 equiv.) in dimethylformamide (DMF). Removal of the Fmoc group was achieved using 20% piperidine in DMF. The ^{t}Bu ester of the aspartic acid was coupled using the same procedure. Deprotection of the ester with 95% TFA in DCM generates the free carboxylic acid. The cyclization takes place by heating the resin-bound dipeptide at 70°C overnight using a sixfold excess of DPPA and Et_3N in THF. The Fmoc group was removed and the amine acylated with a carboxylic acid (10 equiv.) in the presence of DIPCDI (10 equiv.) and HOBt (10 equiv.) in DMF. The resin was cleaved with anhydrous HF and anisole (95:5) at 0°C for 1.5 h. The product was extracted with acetic acid (95%) and lyophilized to yield the desired succinimide. AcOH is a good solvent for lyophilizing hydrophobic compounds, since it can be lyophilized at both dilute and high concentrations.
14. The parent compound **1a** was also characterized by NMR spectroscopy. Both ^{1}H NMR and ^{13}C NMR (in DMSO-d_6) show pairs of peaks due to the existence of conformational isomers.