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Microwave-Enhanced Solid-Phase Synthesis of *N,N′*-Linked Aliphatic Oligoureas and Related Hybrids

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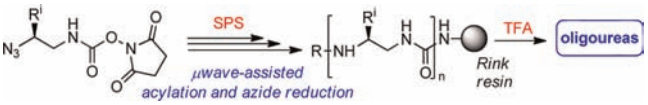
ABSTRACT



A practical and efficient microwave-assisted solid-phase method for the synthesis of *N,N′*-linked oligoureas and related amide/urea hybrid oligomers, featuring the use of succinimidyl (2-azido-2-substituted ethyl) carbamate monomers, is reported. The rate enhancement of urea formation under microwave irradiation combined with the mild conditions of the phosphine-based azide reduction makes this approach very effective for routine synthesis of oligoureas and possibly for library production.

Since its introduction by Merrifield, solid-phase synthesis (SPS) has revolutionized the fields of peptide and protein chemistry.[1] This technology has facilitated the development of foldamers, i.e., artificial folded architectures,[2] by giving access to oligomers of ever-increasing size and complexity and by allowing the preparation of libraries. Aliphatic *N,N′*-linked oligoureas[3] **A** (Figure 1) are a class of nonpeptidic helical foldamers that show promise for biological applications (e.g., as α-peptide mimetics).[4,5] Several SPS methodologies to access aliphatic oligoureas have been described. All are based on a sequential coupling of activated monomers derived from monoprotected ethylenediamine derivatives[6] such as succinimyl carbamates **1** developed by our laboratory.[7] Although these monomers have proven useful to access short oligoureas in reasonable yields and purities, they still suffer some drawbacks: long coupling times (2 × 120 min) and a large excess of monomers (at least double couplings of 3 equiv) are typically needed. Microwave irradiation has been shown to alleviate some of the hurdles inherent with SPS (e.g., slow reaction rates associated with folding and chain aggregation) and to significantly accelerate the assembly of α-peptides[8] and oligoamide foldamers (peptoids,[9] β-peptides,[10] and aromatic oligoamides[11]).

Herein we describe our efforts to improve SPS of aliphatic oligoureas with the assistance of microwave irradiation. Preliminary investigations were conducted

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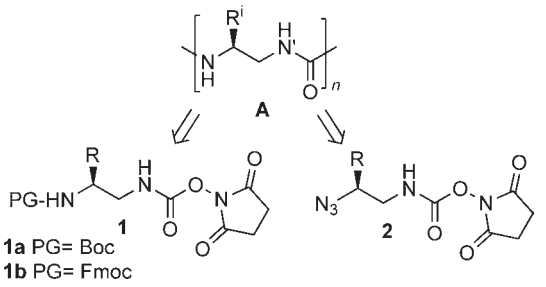

Figure 1. Schematic representation of oligoureas **A** and formulas of activated monomers **1** and azide monomer **2**.

using monomers **1a** and **1b** starting from 4-methylbenzhydrylamine (MBHA)[12] and Rink amide polystyrene (PS) resins, respectively. It rapidly became apparent that microwave irradiation was not compatible with Fmoc chemistry, leading to degradation of *N*-Fmoc protected monomers **1b** and uncontrolled oligomerization on resin. Conversely, excellent results were obtained when *N*-Boc-protected monomers **1a** were used with microwave irradiation. Under optimized conditions (70 °C, 25 W, dimethylformamide (DMF)), the coupling times and excess monomers (1.5 equiv of **1a**, 10 min, double coupling) were significantly reduced at no cost for overall purity and yield (see the Supporting Information for details). However, while the Boc strategy is more robust, final HF cleavage from the resin is impractical for routine use and library production. In search of an alternative to the Fmoc protecting group that would allow the use of standard TFA-labile type resins, we decided to reinvestigate the use of azides as masked amines for SPS of oligoureas.

Early work by Schultz and collaborators reported the SPS of short 3-mers using 4-nitrophenyl (2-azido-1-substituted ethyl) carbamates derived from *N*-Boc-protected α-amino acids as activated monomers, the azide reduction being performed in the presence of a tin reagent.[6a,13] Concurrently, Meldal et al. reported a solid-phase peptide synthesis (SPPS) approach based on the use of α-azido acids and employing dithiothreitol (DTT) as azide-reducing agent.[14] More recently, the Staudinger reduction[15] with trimethylphosphine (PMe_3) was successfully applied to SPPS,[16] peptide nucleic acids (PNAs),[17] and peptoids.[18] On the basis of these promising precedents, succinimidyl (2-azido-2-substituted ethyl) carbamates **2** (Figure 1) were selected as new monomers for the microwave-assisted SPS of oligoureas.

Two synthetic routes were developed as outlined in Scheme 1, depending on the nature of the side chain of starting *N*-protected β-amino alcohols **3**.[19] Route A involves the conversion of unprotected β-amino alcohol **4** to its corresponding azide **5** following the method of Wong[20] with imidazole-1-sulfonyl azide hydrochloride as the diazo-transfer reagent.[21] Next, phthalimide intermediate **6** was formed by substituting alcohol **5** under Mitsunobu conditions.[6b,22] However, because of the high volatility of azido alcohols **5d**–**e** (R = *i*-Bu, Me, respectively), preference was given to pathway B in which *N*-Boc-β-amino alcohols **3d**–**e** are first converted to their phthalimide **8d**–**e** again under Mitsunobu conditions. Removal of phthalimide with hydrazine hydrate[23] afforded 2-azido-2-substituted ethylamines **7** which were directly converted to activated carbamates **2a**–**f** in good overall yields (see Table 1) by treatment with *N*,*N*′-disuccinimidyl carbonate (DSC). Notably, route B was also found to be more efficient in the preparation of carbamate **2f** with indole side chain (Table 1).

With activated monomers **2a**–**f** in hand, we then explored the coupling/azide reduction cycle on solid support under microwave assistance. Tetraurea **9** was chosen as a first model to optimize reaction conditions and screen methods for reducing azides to amines (Table 2). Synthesis was performed on a hydrophilic solid support (NovaPEG Rink amide resin) compatible with a variety of solvents including aqueous solvent systems typically used for the mild reduction of azides during Staudinger reaction.[16,17] The poly(ethylene glycol) (PEG) matrix is known to exhibit high swelling properties in water and to diminish the risk of chain aggregation.[24] On-resin urea formation was performed with monomer **2a** by using microwave irradiation conditions optimized for coupling Boc monomers **1a**. Three conditions for on-resin azide reduction were tested in parallel. Because azide reduction is known to proceed slowly,[6a] and in some cases to require heating, we also contemplated using microwave irradiation for this step.

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(12) We previously found that the urea linkage formed by coupling **1a** to MBHA resin does not resist standard conditions for Boc cleavage.[4b] To circumvent this problem, oligoureas in Boc chemistry are prepared with a terminal amide group by attaching an isosteric γ^4-amino acid to the MBHA resin.

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Scheme 1. General Synthetic Procedure for the Preparation of Azido Carbamates **2** Depending on the Nature of the Residue Side Chain

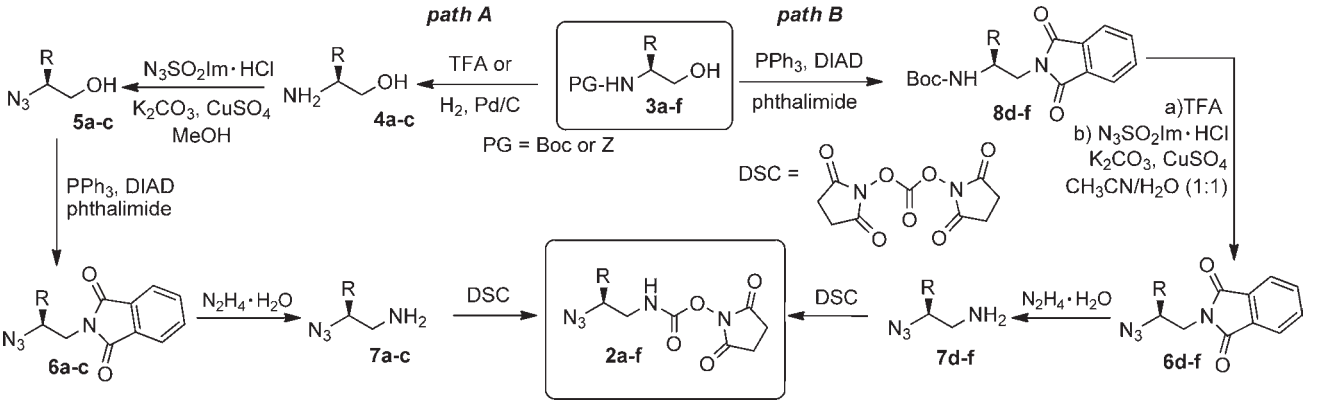
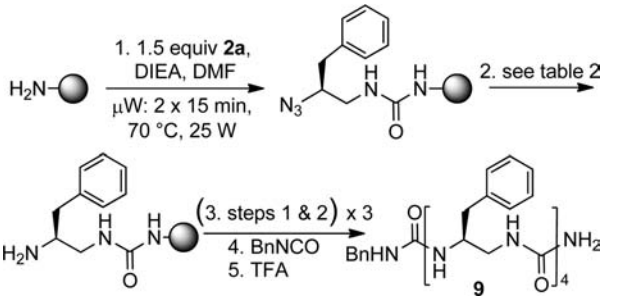


Table 1. Succinimidyl (2-Azido-2-substituted ethyl) Carbamates **2a**–**f** Prepared According to Scheme 1

compounds	side chain (R)	route[a]	yield[b] (%)	HPLC t_R[c]
2a	Bn	A	36	7.25
2b	*p*-*t*-Bu$OC_6H_4CH_2$	A	34	8.25
2c	Boc$NH(CH_2)_3$	A	33	6.88
2d	*i*-Bu	B	43	7.25
2e	Me	B	27	4.83
2f	1*H*-indol-3-yl-CH_2	B	34	7.09

[a] See Scheme 1. [b] The yield given corresponds to the overall yield. [c] RP-HPLC system: linear gradient 10 to 100% of B in 10 min with A (0.1% TFA in H_2O) and B (0.1% TFA in CH_3CN), UV detection 200 nm.

Table 2. Microwave-Assisted SPS of Urea-Based Tetramer **9** and Azide Reduction Conditions Screened on Solid Support



entry	azide reducing agent	conditions	purity[c] (%)
1	$SnCl_2$, PhSH, Et_3N	THF, 25 W, 50 °C[a]	40
2	DTT, DIEA	DMF, 25 W, 70 °C[b]	34
3	PMe_3	dioxane/H_2O, 25 W, 70 °C[b]	73

[a] 2 × 10 min. [b] 2 × 30 min. [c] Purity of crude **9** analyzed by RP-HPLC: linear gradient 50–100% of B in 10 min (UV detection 200 nm). DIEA: diisopropylethylamine. TFA: trifluoroacetic acid.

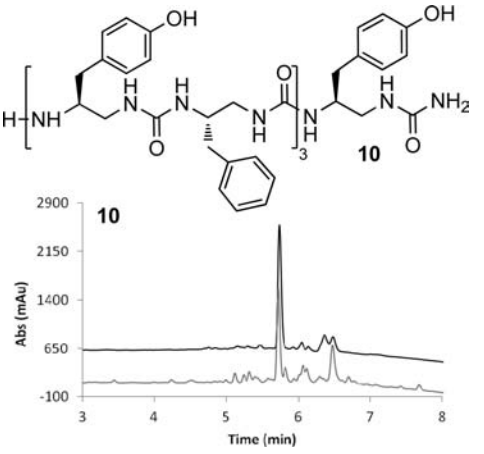
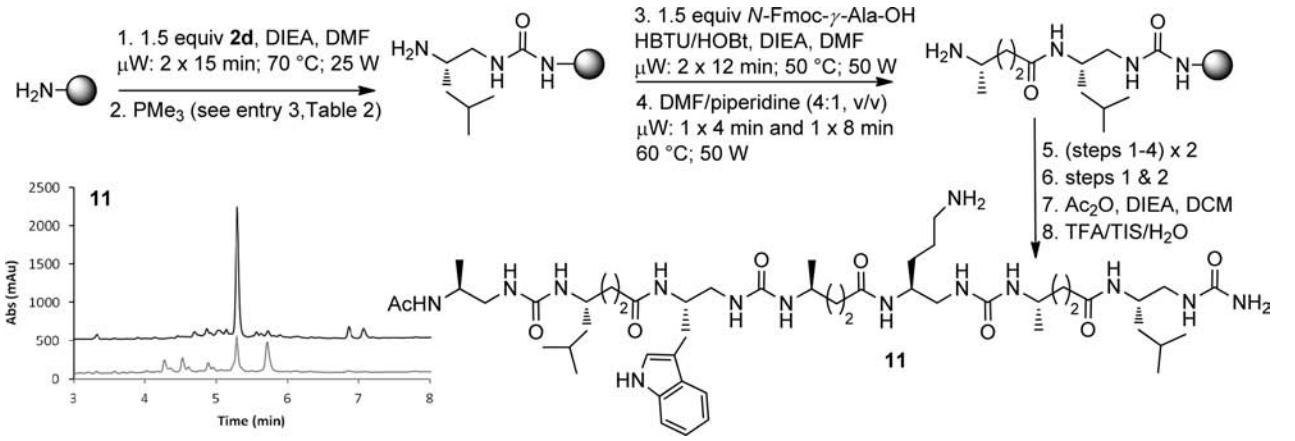


Figure 2. RP-HPLC profiles (UV detection at 200 nm) of **10** prepared by Fmoc strategy using monomers **1b** (gray trace, purity 32%) and by microwave-assisted azide strategy (black trace, purity 70%). HPLC conditions: see the footnote in Table 1.

As outlined in Table 2, the best results were obtained when conversion of azides into amines was performed with PMe_3 (10 equiv) in a mixture of dioxane/water (70:30) under microwave irradiation (70 °C, 25 W, 2 × 30 min). These microwave-SPS conditions provided oligourea **9** in 73% purity (based on RP-HPLC) and good recovery yield (86%). In comparison, the purity of crude product after cleavage was much lower when $SnCl_2$/PhSH/Et_3N was employed. The same observation was made when DTT was used, with the presence of many side products resulting from incomplete azide reductions.

These optimized conditions for azide reduction using the Staudinger reaction with microwave irradiation were further tested for the preparation of longer oligomers (e.g., heptaurea **10**). Oligourea **10** was obtained in 70% purity (based on RP-HPLC) and fair yield (57%) after TFA cleavage and precipitation of the cleaved product with

Scheme 2. Microwave-Assisted SPS of Oligourea Hybrid **11** Using Azide Monomers **2**[a]



[a] Insets: RP-HPLC chromatograms (UV detection at 220 nm) of **11** prepared using the azide strategy (black trace, purity 86%) and by using standard *N*-Fmoc monomers **1b**[7a] (gray trace, purity 30%). HPLC conditions: see the footnote in Table 1.

methyl *tert*-butyl ether (Figure 2). This result confirms the possibility to perform multiple successive azide reductions on solid support (up to seven for **10**) without compromising the final purity of the oligoureas.

For comparison, we also prepared **10** using standard Fmoc chemistry (monomer **1b** without microwave assistance) starting from the same NovaPEG resin. The mass recovery of crude product based on resin loading was 71%.[7a] The RP-HPLC purity of the cleaved material was only 32%, highlighting the overall superiority of the azide strategy combined with microwave irradiation (Figure 2). Furthermore, the total time to assemble **10** was considerably reduced under microwave assistance (11 h versus at least 30 h using Fmoc chemistry).

To further demonstrate the general applicability of this methodology, we evaluated the SPS of heterogeneous foldamer backbones made of alternating urea and amide linkages (e.g., **11**). The microwave-assisted SPS of heptamer **11** is detailed in Scheme 2. γ-Amino acids were inserted in the chain as their *N*-Fmoc-protected derivatives in the presence of HBTU/HOBt as coupling reagents with assistance of microwave irradiation. We also examined the synthesis of **11** using standard Fmoc chemistry without application of microwave irradiation (see the Supporting Information for details).[7a] Mass recovery of crude **11** based on resin loading, following TFA cleavage and lyophilization, was similar in both cases (46% for the Fmoc strategy, 50% for the azide strategy). However, purity based on HPLC analysis of crude **11** was only 30% when the synthesis was performed using *N*-Fmoc-protected monomers **1b** (Scheme 2). Analysis of byproducts revealed truncated sequences lacking urea linkages. In contrast, the combined use of azido monomers **2** and microwave irradiation resulted in a marked improvement. The deletion impurities were completely eliminated and oligomer **11** was recovered in high purity (86%) as judged by HPLC analysis of the crude product (Scheme 2).

In conclusion, we have developed the synthesis of succinimidyl (2-azido-2-substituted ethyl) carbamate monomers and have validated the clear benefits of their combined use with microwave irradiation on solid support to quickly access urea-based foldamers. Under microwave assistance, the azide reduction using PMe_3 was highly reproducible and efficient, leading to the preparation of oligoureas and related hybrids in high purity and good yields. This improved procedure is likely to facilitate the preparation of libraries of urea-based foldamers for biological evaluation as well as the construction of larger and more sophisticated foldamer architectures.

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Supporting Information Available. Experimental procedures and characterization data for **2**–**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.