Pergamon

Tetrahedron Letters 39 (1998) 6613–6616

TETRAHEDRON LETTERS

An Efficient Synthesis of *N,N'*-Linked Oligoureas

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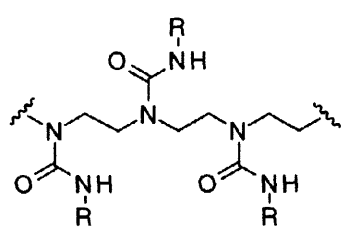
Received 17 April 1998; accepted 24 June 1998

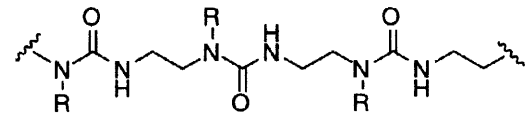
Abstract: This paper reports an efficient synthesis of *N*-alkyl-*N,N'*-linked oligoureas [-NR-CO-NH-CH_2CH_2-]$_n$, which involves the repetition of three steps: (1) main-chain extension by ring-opening of *N*-(2-nitrobenzenesulfonyl)-2-imidazolidone (**1**) by a secondary amine RR'NH to afford sulfonamide RR'N-CO-NH-CH_2CH_2-NH-SO_2Ar (2) side-chain attachment by *N*-alkylation of the sulfonamide with alkyl halide R"X, and (3) removal of the sulfonyl group to give a new secondary amine RR'N-CO-NH-CH_2CH_2-NHR"). A tetraurea was prepared in 10 steps and 58% overall yield by this method.

Unnatural oligomers are synthetic compounds designed to mimic peptides and other biopolymers.[1-3] Within the past decade, these compounds have emerged as important research targets in drug discovery and other areas. Oligoureas are a particularly attractive class of unnatural oligomers, because the urea group has interesting biological and hydrogen-bonding properties, and because the urea linkage is readily formed by the reaction of amines with isocyanates or related compounds. For the past several years, we have studied the synthesis and hydrogen-bonding properties of *N,N*-linked oligoureas [-N(CONHR)-$(CH_2)_m$-]$_n$, and have shown that these compounds adopt intramolecularly hydrogen-bonded structures.[4-6] Other researchers have been active in the synthesis and study of *N,N'*-linked oligoureas [-NH-CO-NH-CH_2CHR-]$_n$. Burgess and coworkers first introduced these compounds in 1995 and described their solid-phase synthesis in 1997.[7,8] Schultz and coworkers reported an alternative synthesis of these compounds[9] and described the solution-phase synthesis of oligomeric cyclic ureas.[10] Recently, Liskamp and coworkers introduced *N*-alkyl-*N,N'*-linked oligoureas [-NR-CO-NH-CH_2CH_2-]$_n$, and described their efforts toward the synthesis of these compounds.[11]

As part of our research program aimed at developing conformationally defined oligoureas (viz. foldamers),[12] we are also investigating *N*-alkyl-*N,N'*-linked oligoureas. To study the folding properties of these compounds, we needed to prepare oligureas bearing different *N*-alkyl groups. Accordingly, we sought a synthetic route that allowed for the easy introduction of *N*-alkyl groups and could be adapted to the solid phase to permit rapid syntheses. Here, we describe the development of such a synthetic route and demonstrate its efficacy in a solution-phase synthesis.



N,N-linked oligourea



N,N'-linked oligourea

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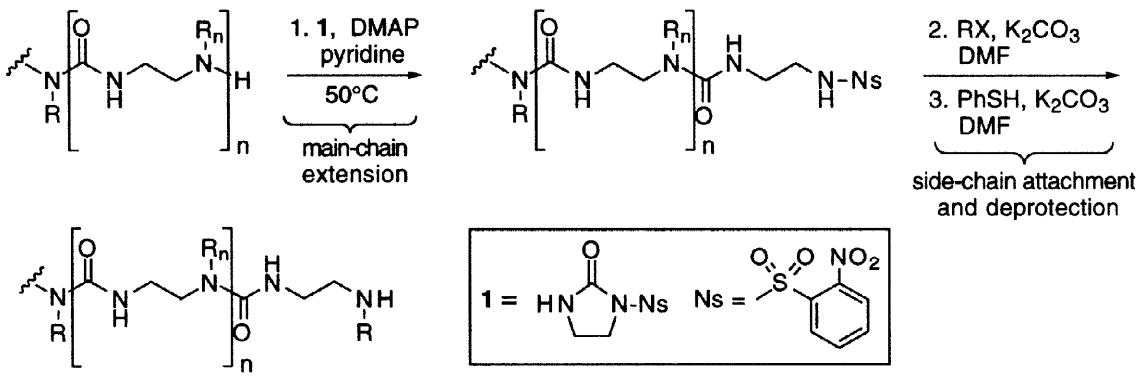
PII: S0040-4039(98)01396-3

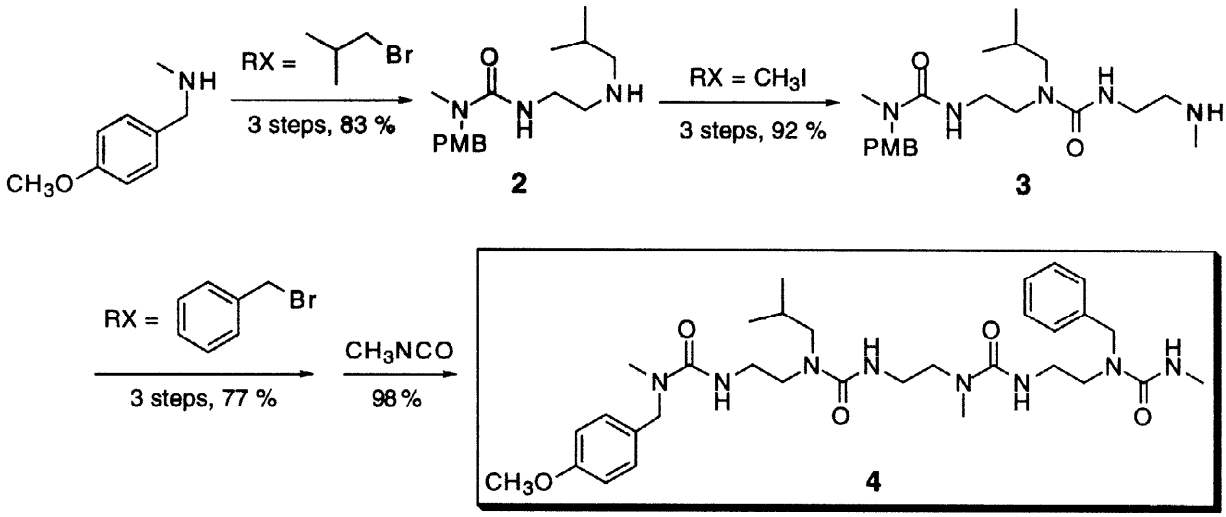
Our synthesis of *N*-alkyl-*N,N'*-linked oligoureas is iterative, involving the repetition of three steps: (1) main-chain extension, (2) side-chain attachment, and (3) deprotection (Scheme 1). The oligomer main chain is *extended* by ring-opening of *N*-(2-nitrobenzenesulfonyl)-2-imidazolidone (**1**) by a secondary amine.[13] The side chain is *attached* to the resulting sulfonamide by Fukuyama's procedure for *N*-alkylation.[14,15] The 2-nitrobenzenesulfonyl (Ns) group is then *removed* to reveal a secondary amine,[16] which is used in the next iteration of the sequence. The key features of our synthetic approach are that all chemical transformations are high yielding and that only two types of building blocks are used: (1) imidazolidone **1**, which forms the main chain and (2) commercially available alkyl halides, which form the side chains.



Scheme 1. Three-step reaction sequence for constructing *N*-alkyl-*N,N'*-linked oligoureas.

We discovered imidazolidone **1** and its reaction with secondary amines while attempting to prepare isocyanate Ns-NH-CH_2CH_2-NCO as a building block for *N,N'*-linked oligoureas. When we treated *N*-(2-nitrobenzenesulfonyl)ethylenediamine hydrochloride (Ns-NH-CH_2CH_2-NH_2•HCl) with phosgene in a biphasic mixture of $CHCl_3$ and aqueous $NaHCO_3$, we did not observe the anticipated isocyanate.[17] Instead, cyclic compound **1** formed. Upon treatment with diethylamine, **1** reacted to afford the ring-opening product Et_2N-CO-NH-CH_2CH_2-NH-Ns. High yields of this ring-opening product were obtained when the reaction was performed in pyridine at 50 °C in the presence of DMAP. Under these conditions, imidazolidone **1** reacts cleanly with a variety of secondary amines RR'NH to form ureas RR'N-CO-NH-CH_2CH_2-NH-Ns. Accordingly, **1** constitutes a useful building block for constructing *N,N'*-linked oligoureas bearing *N*-alkyl groups; while the ring-opening reaction extends the main chain, the Ns group activates the terminal amine for side-chain attachment by Fukuyama's *N*-alkylation method. Imidazolidone **1** is readily prepared in multigram quantities from *N*-Boc-ethylenediamine[18] and can be stored indefinitely at room temperature without decomposition.[19]

To demonstrate the merits of the three-step sequence shown in Scheme 1, we synthesized tetraurea **4** by repeating the sequence three times (Scheme 2). In the first iteration, 4-methoxy-*N*-methylbenzylamine[20] was treated with imidazolidone **1**, the resulting sulfonamide was *N*-alkylated with isobutyl bromide, and the Ns group was removed to afford amine **2** in 83% yield. In the next iteration, methyl iodide was used as the alkylating agent, generating amine **3** in 92% yield. A third iteration, using benzyl bromide, gave a secondary amine (not shown) in 77% yield. Reaction of this amine with methyl isocyanate gave tetraurea **4** in 98% yield.[21] The overall yield for the ten-step synthesis of **4** was 58%, making the average yield of each step 95%.



Scheme 2. Synthesis of an *N,N'*-linked tetraurea bearing different *N*-alkyl groups. All yields are for isolated and purified products.

The iterative application of the three-step sequence provides an efficient synthesis of *N*-alkyl-*N,N'*-linked oligoureas. All steps are high yielding, easy to perform, and lead to clean conversion to product; because these characteristics are essential to solid-support chemistry, this method should be highly adaptable to the solid phase. Although the solid-phase synthesis is currently underway, the solution-phase synthesis is remarkably easy and represents a significant improvement over the previous approach to *N*-alkyl-*N,N'*-linked oligoureas.[11] In the previous approach, discrete monomers have to be prepared to achieve a sequence of different side-chains, and a total of six steps are required to add each unique residue to the growing oligomer - three to synthesize the monomer and three to install the monomer. The method described here requires only three steps to add each unique residue.

The *N*-alkyl-*N,N'*-linked oligoureas produced by this method should be valuable in future studies requiring oligomers that resemble peptides and (pending our structural studies) may adopt stable secondary structures. Liskamp termed these compounds *ureapeptoids*, by their analogy to *N*-alkyl oligoglycines, which are called *peptoids*.[22] One of the attractive aspects of peptoids is that they can be easily prepared by a *submonomer* approach, in which two types of building blocks are used to construct each residue.[23] The synthetic method we have devised provides an analogous submonomer approach to ureapeptoids.

ACKNOWLEDGMENTS. This work was supported by the National Institutes of Health (GM-49076), the National Science Foundation (CHE-9553262), the Camille and Henry Dreyfus Foundation, and the Alfred P. Sloan Foundation. MEW thanks the National Institutes of Health for support in the form of a postdoctoral fellowship (1 F32 GM19022-01).

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13. *Main-Chain Extension:* A 0.4 M solution of the secondary amine RR'NH, 1.2 equiv of **1**, and 0.5 equiv of DMAP in dry pyridine was stirred at 50 °C under N_2 for 4-6 h. The solvent was removed by rotary evaporation, the residue was dissolved in CH_2Cl_2, and the resulting solution was washed with 0.5 M aq HCl and dried over Na_2SO_4. The solvent was removed to afford the crude sulfonamide RR'N-CO-NH-CH_2CH_2-NH-Ns, which was purified by column chromatography on silica gel.
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15. *Alkylation:*[14] A 0.4 M solution of the sulfonamide RR'N-CO-NH-CH_2CH_2-NH-Ns in DMF was stirred with 2 equiv of anhyd K_2CO_3 and 2-5 equiv of alkyl halide R"X for 1 h - 5 d. The solvent was removed by rotary evaporation, and the residue was dissolved in CH_2Cl_2. The resulting solution was washed with water, dried over Na_2SO_4, and concentrated to afford the crude alkyated product RR'N-CO-NH-CH_2CH_2-NR"-Ns, which was purified by column chromatography on silica gel.
16. *Removal of the Ns Group:*[14] A 0.2 M solution of the sulfonamide RR'N-CO-NH-CH_2CH_2-NR"-Ns in DMF containing 3 equiv of anhyd K_2CO_3 was deoxygenated by evacuating and purging with N_2 three times. Thiophenol (1.5 equiv) was added, and the reaction mixture was stirred for 3-6 h. The solvent was removed by rotary evaporation, the residue was dissolved in CH_2Cl_2, and the resulting solution was washed with 1 M aq $NaHCO_3$ and dried over Na_2SO_4. The solvent was removed to afford the crude secondary amine RR'N-CO-NH-CH_2CH_2-NHR", which was purified by column chromatography on silica gel.
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19. *Preparation of Imidazolidone 1*: *N*-Boc-ethylenediamine[18] and 1.5 equiv of 2-nitrobenzenesulfonyl chloride were stirred in a 1:1 mixture of CH_2Cl_2 and saturated $NaHCO_3$ for 6 h. The layers were separated, and the organic phase was washed three times with 1 M aq $NaHCO_3$. The organic phase was concentrated by rotary evaporation, and the residue was purified by column chromatograpy on silica gel (1:1 EtOAc-hexanes) to give Boc-NH-CH_2CH_2-NH-Ns in 94% yield. The Boc group was removed by bubbling HCl into a methanolic solution of Boc-NH-CH_2CH_2-NH-Ns. The solvent was removed by rotary evaporation, and the residue was recrystallized from methanol to give HCl•NH_2-CH_2CH_2-NH-Ns in 92% yield. A rapidly stirring solution of HCl•NH_2-CH_2CH_2-NH-Ns in a 1:1 mixture of $CHCl_3$ and saturated aq $NaHCO_3$ was treated with 2 equiv of phosgene (1.93 M solution in toluene, Fluka; CAUTION: toxic, use only in a fumehood), and the solution was stirred for 20 min at room temperature. The layers were separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic fractions were dried over Na_2SO_4 and concentrated to give a white solid, which was recrystallized from EtOAc-isooctane to afford imidazolidone **1** in 99% yield as a fluffy white solid: mp 148-149 °C; IR (KBr pellet) 3282, 1741, 1533, 1361, 1261, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46-8.44 (m, 1 H), 7.78-7.71 (m, 3 H), 5.19 (br s, 1 H), 4.20 (appar t, *J* = 7.7 Hz, 2 H), 3.60 (appar t, *J* = 7.7 Hz, 2 H); ^{13}C NMR (100 MHz, D_6-DMSO) δ 154.3, 147.4, 135.5, 132.4, 132.0, 130.7, 124.4, 44.2, 37.2; HRMS (CI, NH_3) *m/z* $(M + H)^+$ $C_9H_{10}N_3O_5S$ calcd 272.0341, obsd 272.0338.
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21. All intermediates gave satisfactory spectra. Data for tetraurea **4**: IR (KBr pellet) 3343, 1630, 1535, 1513, 1386, 1247, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (appar t, *J* = 7.2 Hz, 2 H), 7.25-7.22 (m, 3 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 6.84 (d, *J* = 7.8 Hz, 2 H), 6.52 (br s, 1 H), 6.34 (br s, 1 H), 6.00 (br s, 1 H), 5.59 (br s, 1 H), 4.49 (s, 2 H), 4.39 (s, 2 H), 3.78 (s, 3 H), 3.33-3.26 (m, 10 H), 3.16 (appar q, *J* = 6.4 Hz, 2 H), 2.99 (d, *J* = 7.6 Hz, 2 H), 2.89 (s, 3 H), 2.81 (d, *J* = 4.4 Hz, 3 H), 2.79 (s, 3 H), 1.86 (appar sept, *J* = 6.8 Hz, 1 H), 0.87 (d, *J* = 6.8 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 159.6, 159.3, 158.9, 158.8, 138.3, 129.7, 128.6, 128.5, 127.2, 127.1, 113.9, 55.2, 55.0, 51.3, 50.6, 48.1, 47.2, 46.3, 40.2, 39.9, 39.7, 34.6, 33.8, 27.9, 27.7, 19.9; HRMS (FAB) *m/z* $(M + H)^+$ $C_{32}H_{51}N_8O_5$: calcd 627.3982, obsd 627.3975.
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