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An activated building block for the introduction of the histidine side chain in aliphatic oligourea foldamers

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Dedicated to Professor Dieter Seebach on the occasion of his 75th birthday

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ABSTRACT

A new *N*-Boc-protected monomer for the synthesis of oligourea foldamers containing the (1*H*-imidazolyl-4yl)methyl side chain of histidine, has been prepared in seven steps from Trt-His(τ-Trt)-OMe. This protecting group combination on histidine was found to be critical to ensure efficient access to the requisite activated building block. This new derivative, suitable for solid phase synthesis, expands the current arsenal of building blocks with proteinogenic side chains useful for the design of peptidomimetic oligourea foldamers.

1. Introduction

Histidine, with its (1*H*-imidazolyl-4yl)methyl side chain is a remarkable amino acid in many ways. Besides its intrinsic basicity, crucial to the catalytic properties of many enzymes, the ability of the imidazole ring to bind and coordinate metal ions is widely used to stabilize tertiary folds and helical structures[1] (e.g., zinc fingers with Cys_2His_2 tetrahedral Zn(II) site[2]). Not surprisingly, His residues have been incorporated in a variety of α-peptide sequences and structural motifs (single α-helices,[3] α-helical bundles,[4] helix-loop-helix,[5] ββα tertiary folds[6]) designed de novo to mimic protein metal binding sites and/or active sites for catalysis. With the aim to reproduce the microenvironment of enzyme catalytic pockets, Reymond and co-workers have developed artificial catalytic architectures based on His-rich peptide dendrimers.[7] Using a biomimetic approach, Miller and co-workers engineered small synthetic peptides, containing a π-methylated imidazole moiety, as effective organocatalysts for various asymmetric transformations.[8] Furthermore, His-rich α-peptide sequences have also found interesting biotechnological and biological applications. This includes His-tags for protein purification,[9] metal-dependent cell-penetrating peptides for drug-delivery purposes[10] and cationic amphipathic peptides for gene transfer.[11]

Synthetic foldamers (i.e., non-natural oligomers that fold into well-defined structures), owing to their structural predictability and large contact areas, represent privileged scaffolds to orient recognition motifs in space and interact with a variety of targets (metals, small molecules, biopolymers).[12] Thus, sets of building blocks equivalent to α-amino acids, i.e., bearing requisite information for folding and diversity in side chains are of particular interest in the context of foldamer-based recognition. However, examples of peptidomimetic foldamers with His-type side chains at their surface are scarce. This can be ascribed in part to synthetic difficulties created by the basic and nucleophilic 1*H*-imidazole ring. The preparation of *N*-Fmoc-protected β^3- and β^2-amino acid homologues of histidine (in eight and ten steps, respectively) by Seebach and co-workers,[13] and their incorporation in β-peptide

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foldamers for metal binding studies is noteworthy in this regard.[14] Similarly, peptoids (oligomers of *N*-alkyl glycines) containing thiol and imidazole side chains at defined position have been designed that fold into two-helix bundles upon zinc addition.[15]

Aliphatic oligoureas bearing proteinaceous side chains (**A**) are a class of non-peptide helical foldamers with potential to mimic bioactive peptide helices and interact with bio(macro)molecules (Fig. 1).[16] These aza analogues of γ^4-peptides form well-defined 2.5 helical structures stabilized by three-centred H-bonds in solution[17] and solid state.[18] Aliphatic oligoureas are accessible by stepwise synthesis using suitably protected activated building blocks derived from ethylene diamine precursors (Fig. 1)[19,20] or by condensation of activated oligomeric segments.[18a] We have previously reported the synthesis and use of *N*-*tert*-butoxycarbonyl (Boc)[19a] and *N*-fluorenylmethoxy-carbonyl (Fmoc) monomers[19b] of type **B** with side chains of Ala, Val, Leu, Pro, Phe, Tyr, Trp and Lys. *N*-Fmoc-protected building blocks were initially developed to allow the rapid synthesis of oligoureas on solid support (Rink-amide resin).[17,19b,21] Later, we found that monomers protected with a Boc group were much more effective, consistently giving oligoureas in higher yields and purities following cleavage from the resin (4-methylbenzhydrylamine (MBHA) resin).[22] With the aim to expand our arsenal of proteinogenic building blocks and to append histidine-type side chains at the surface of oligourea helices, we have now investigated the synthesis of a requisite *N*-Boc-protected building block starting from histidine. Because of the nucleophilic character of the 1*H*-imidazole ring, a judicious combination of *N*(α) and *N*(τ) protecting groups on histidine turned out to be crucial for the successful formation of His-type monomers **2** and subsequent use for solid phase oligourea synthesis.

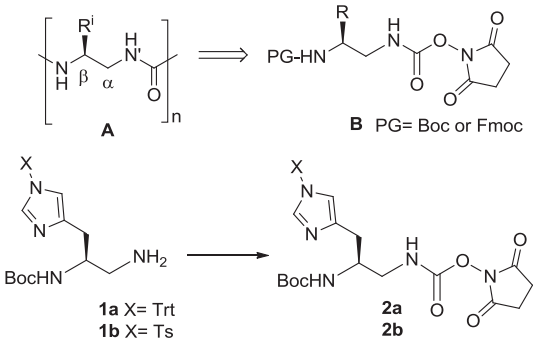


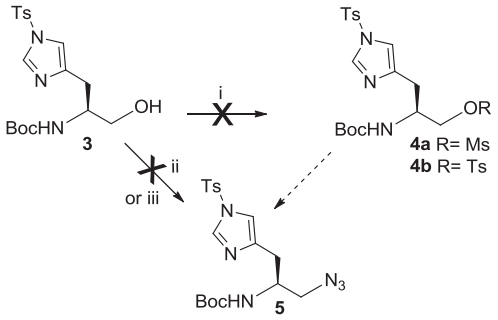
Fig. 1. Schematic representation of aliphatic oligoureas of type **A** and corresponding monomeric **B**-type units. Formulae of targeted His-type activated monomers **2a** and **2b** and corresponding *N*-Boc-protected ethylene diamine precursors **1a** and **1b**.

2. Results and discussion

Succinimidyl {2-{[(*tert*-butoxy)carbonyl]amino}-2-X-ethyl}-carbamate building blocks **B** bearing proteinogenic side chains have been prepared either via a Curtius rearrangement of their corresponding *N*-protected β^3-amino acids and subsequent trapping of the isocyanate with *N*-hydroxy succinimide[19] or by activation of the corresponding *N*-protected ethylene diamine derivatives with *N*,*N*′-disuccinimidyl carbonate (DSC).[18a] Several syntheses of *N*-Boc-protected derivatives of β^3-homohistidine have been reported, including Boc-β^3hHis(Trt)-OH via the Arndt–Eistert homologation of Boc-His(Tos)-OH by Seebach and co-workers[13] and Boc-β^3hHis(-Boc)-OH via the Kolbe nitrile synthesis of the beta amino alcohol derived from Mts-His(Mts)-OH by Wyatt and co-workers.[23] Although these derivatives could eventually serve as precursors in the synthesis of building block **2**, the approach involving the preparation of a Boc-protected ethylene diamine precursor **1** was preferred (Fig. 1).

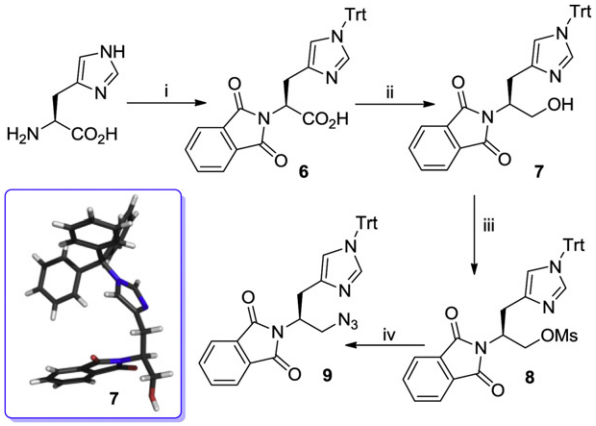
2.1. Synthesis of *N*-Boc-protected His-type activated monomers 2a and 2b

We initially investigated the synthesis of monoprotected diamine **1b** from Boc-α-His(Ts)-OH. Reduction of Boc-α-His(Ts)-OH into its corresponding histidinol using conditions developed by Rodriguez and co-workers[24] afforded alcohol **3** in modest yield (32%). Attempts to activate alcohol **3** as its mesylate **4a** or tosylate **4b** did not yield any isolable products. Moreover, the direct conversion of alcohol **3** into azide **5** under Mitsunobu conditions using hydrazoic acid[25] or diphenyl phosphorazidate (DPPA)[26] as an alternative failed. Furthermore, Thompson's procedure using DPPA/1,8-diazabicycloundec-7-ene (DBU) in toluene was also unsuccessful (Scheme 1).[27]



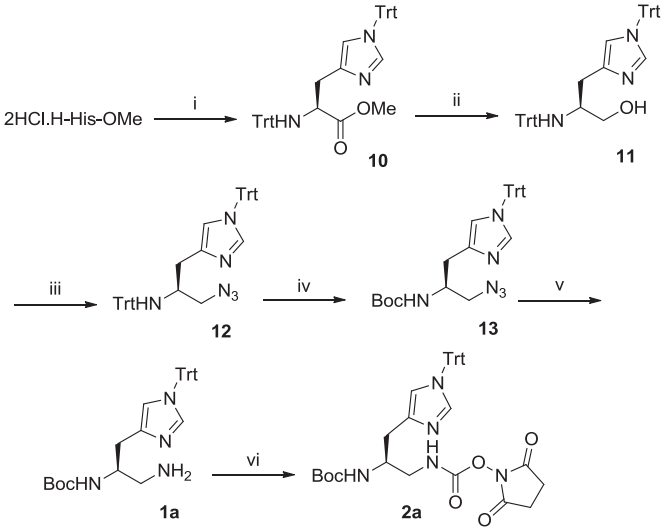
Scheme 1. Synthetic strategy first envisioned for the preparation of azide **5**. (i) MsCl or TsCl, Et_3N, CH_2Cl_2, 0 °C; (ii) DIAD, PPh_3, HN_3, THF, 0 °C, (iii) DPPA, DBU, NaN_3, toluene.

At this point, as previously suggested by Wyatt in his work on homologation of histidine,[23] we suspected that the nucleophilicity of the Boc-protected α-amine was sufficient to cause an intramolecular attack of the activated alcohols **4** resulting in the degradation of the reaction intermediates. In order to suppress the reactivity of the histidine α-amino function, we decided to temporarily convert it into a phthalimide group (Scheme 2).[20b] Surprisingly, attempts to form the alcohol by reduction of the acid function when using a *N*(α)-phthaloyl, *N*(τ)-Ts protection combination did not yield any isolable product. This reduction was only achieved when a trityl group (Trt) was installed on τ-nitrogen and under the conditions of McGeary[28] to furnish alcohol **7** with a moderate yield of 46% (Scheme 2). Several routes to convert **7** into azide **9** were next investigated, but the formation of azide **9** was only achieved by reaction of mesylate **8** with sodium azide, albeit in very low yield (9%).



Scheme 2. (i) (a) *N*-Carbethoxyphthalimide, Na_2CO_3; (b) Trt-Cl, Et_3N, 83% over the two steps. (ii) (a) BOP, DIEA, DMF, 0 °C, (b) $NaBH_4$, 46%; (iii) MsCl, Et_3N, DCM, 0 °C, 100%; (iv) NaN_3, DMF, 80 °C, 9%. Inset: X-ray crystal structure of compound **7** (CCDC 844330). See Supplementary data for details.

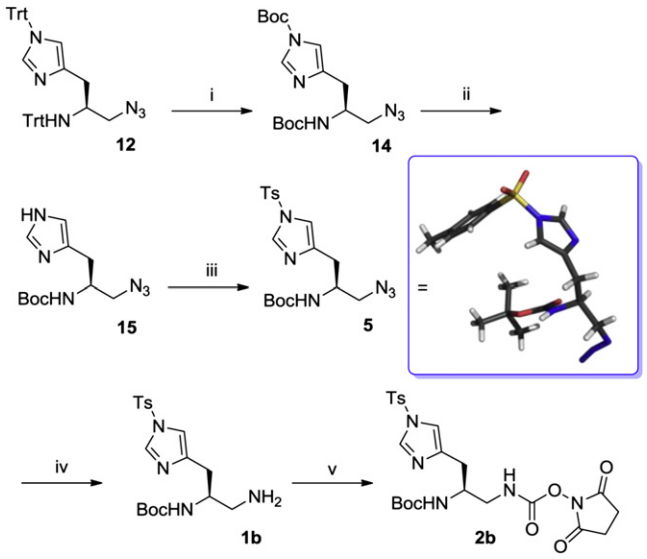
At this stage, we decided to reconsider our protecting group strategy to access ethylene diamine **1** and we envisioned the introduction of a temporary *N*(α)-Trt protecting group on histidine. The *N*(α)-Trt group, which creates strong steric hindrance, was expected to prevent intramolecular nucleophilic attack of any activated intermediate. Previous studies with dityrityl histidine and related dityrityl histamine derivatives have shown that the amino-trityl is much more acid labile than the imino-trityl and that selective *N*-detritylation is possible.[29] Accordingly, we thus decided to keep the *N*(τ)-Trt protection on the imidazole ring and exploit the possibility for a selective *N*-Trt deprotection following azide formation. Thus, 2HCl·H-His-OMe was treated with Trt-Cl in the presence of triethylamine (Et_3N) to afford Trt-His(τ-Trt)-OMe **10** in quantitative yield (Scheme 3).[30] Reduction of the methyl ester with $LiAlH_4$ furnished alcohol **11** in high yield.[31] Several conditions for the transformation of alcohol **11** into the corresponding azide were screened. It was gratifying to find that in the presence of DPPA and NaN_3 alcohol **11** was converted to azide **12** in 75% yield. As anticipated, deprotection of **12** at the primary amine function occurred selectively upon exposure to a 2% TFA solution in a mixture of MeOH/DCE. The resulting TFA salt was immediately treated with $(Boc)_2O$ in the presence of Et_3N to furnish *N*-Boc-protected **13** in good yield. Reduction of the azide function of **13** by hydrogenation in presence of 5% $Pd/BaSO_4$ afforded the *N*-Boc-protected ethylene diamine **1a**, which was transformed without further purification to succinimidyl carbamate **2a** after treatment with DSC in 68% over the two steps (Scheme 3).



Scheme 3. (i) Trt-Cl, Et_3N, CH_3CN; (ii) $LiALH_4$, THF, 0 °C, 93% over the two steps; (iii) DPPA, DBU, NaN_3, DMF, 75%; (iv) (a) DCE, MeOH, TFA, (b) $(Boc)_2O$, Et_3N, 76%; (v) H_2, $Pd/BaSO_4$, EtOAc; (vi) DSC, CH_2Cl_2, 68% over the two steps.

In this way, the synthesis of the *N*-Boc-protected succinimidyl carbamate **2a** equipped with a *N*(τ)-Trt protection on imidazole ring was achieved in seven steps with an overall yield of 36%, starting from commercially available 2HCl·H-His-OMe (Scheme 3).

However, the sensitivity of the *N*(τ)-Trt group under the acidic conditions required for Boc deprotection during chain extension, is likely to be a limitation to the use of monomer **2a** for oligourea synthesis. For this reason, we explored the possibility to convert azide precursor **12** into the potentially more useful monomer **2b** bearing a *N*(τ)-Ts protection. By analogy to Boc-His(τ-Tos)-OH, which is commonly used in peptide synthesis, the *N*(τ)-Ts protection in **2b** is expected to be fully stable under the coupling and Boc deprotection conditions during oligourea main chain elongation and to be removed during final HF cleavage of the resin. Dityrityl-compound **12** was first converted into its diBoc-protected version **14** by treatment with HCl and subsequent reaction with Boc_2O and DMAP (Scheme 4). Then, the *N*(τ)-Boc protection was selectively removed by basic solvolysis with aqueous K_2CO_3 in MeOH to give monoprotected derivative **15**.[32,33] Tosylation of **15** under standard conditions furnished key azide **5** in quantitative yield. The structure of **5** was unambiguously characterized by X-ray diffraction analysis (CCDC 844331) (Scheme 4). It is worth mentioning that **5**, which was not accessible from Boc-His(Tos)-OH (Scheme 1), was here obtained in good overall yield. Interestingly, these results highlight the practical utility of the temporary *N*(α)-Trt protection to prevent nucleophilic intramolecular attacks and other side reactions on activated intermediates as postulated above.[23] Azide **5** was next reduced to amine **1b** by catalytic hydrogenation using 5% $Pd/BaSO_4$ and **1b** was finally converted to the corresponding succinimidyl carbamate **2b** in 88% yield over the last two steps (Scheme 4).



Scheme 4. (i) (a) Aqueous 6 M HCl, THF, 70 °C, (b) $(Boc)_2O$, Et_3N, DMAP, CH_3CN/H_2O, 0 °C, 65%; (ii) K_2CO_3, $MeOH/H_2O$, 98%; (iii) TsCl, Et_3N, DMAP, DCM, 0 °C, 92%; (iv) H_2, $Pd/BaSO_4$, EtOAc; (v) DSC, CH_2Cl_2, 86% over the two steps. Inset: X-ray crystal structure of key azide **5**. See Supplementary data for details.

In this second synthetic route featuring a selective *N*(τ)-Boc deprotection, His-derived carbamate **2b** was obtained with an overall yield of 51% starting from dityrityl azide **12** and in 33% from commercially available 2HCl·H-His-OMe. Consequently, the original strategy developed for the preparation of monomer **2a** starting from Trt-His(τ-Trt)-OMe was successfully extended to access monomer **2b**. The utility of monomers **2a** and **2b** for the synthesis on solid support of His-side chain-containing oligoureas was then tested.

2.2. Solid phase synthesis of oligoureas containing histidine-type units

To enable comparison of building blocks **2a** and **2b** and facilitate the analysis of the resulting imidazole-containing oligoureas, a model sequence containing only one His-like unit was prepared. Oligourea **16** was designed based on an antimicrobial amphiphilic oligourea sequence[21,22] by introduction of a His-type unit at the penultimate position (Fig. 2). The general procedure for oligourea synthesis on solid support is outlined in Scheme 5. The assembly of the chain was performed manually starting from an MBHA resin (100 μmol scale) by sequential coupling of activated *N*-Boc-protected monomers **B** (3 equiv, 2×90 min) in the presence of diisopropylethylamine (DIEA) following a reported procedure (Scheme

5).[22] Completion of the coupling steps was monitored by a chloranil test,[34] which compared to the Kaiser test[35] proved to be more accurate in determining the efficiency of the acylation steps.

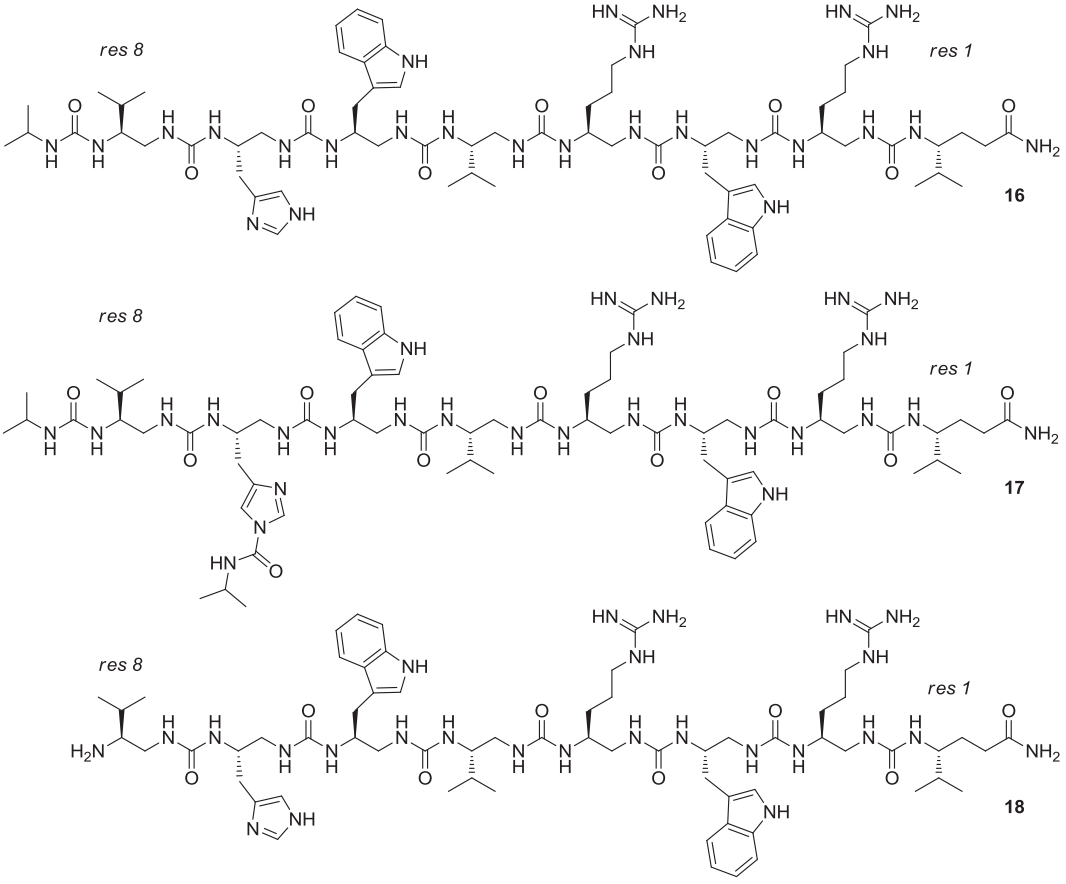
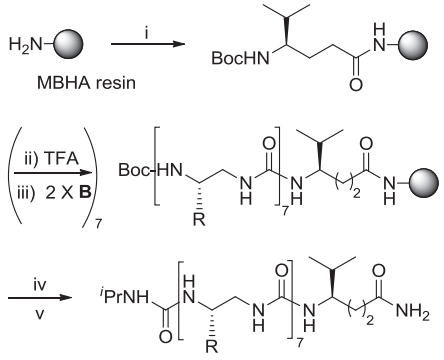


Fig. 2. Imidazole-containing oligoureas **16**–**18** synthesized by SPS. Residue numbering starts from γ^4-Val residue.



Scheme 5. General procedure for SPS of oligoureas. (i) Boc-γ^4-Val-OH, BOP, DIEA, DMF. (ii) Removal of the Boc protection: TFA, 2×5 min (iii) monomer **B**, DIEA, DMF, 2×3 h (iv) (a) TFA, 2×5 min; (b) isopropylisocyanate, DIEA, DMF. (v) HF, 10% *p*-cresol, 0 °C, 1 h.

The benzhydrylamine (BHA) and MBHA resins have been originally developed for the synthesis of amidated peptides using the Boc strategy.[36] However, the urea linkage formed by coupling a Boc-protected monomer of type **B** to the amino group of an MBHA or BHA resin is more acid labile than the corresponding amide linkage and is not sufficiently stable to resist the acid treatment of subsequent Boc deprotection rounds.[22] To solve this problem and prevent unwanted cleavage of the urea bond connected to the resin, an amide bond is introduced first by coupling a *N*-Boc-protected γ^4-amino acid to the amino group of the MBHA resin (Scheme 5). It was shown previously that this isosteric replacement at the terminus has no consequence on the helix forming propensity of the resulting urea oligomer.

Whereas elongation of the chain starting from the γ^4-Val residue up to the second Trp-like residue proceeded smoothly, the condensation of His-type monomer **2a**, turned out to be more difficult than expected. The chloranil test indicated incomplete acylation even after prolonged coupling time. This difficulty may be attributable to the bulkiness of the Trt group at the τ-position of the imidazole ring, although the related trityl-protected histidine derivative Fmoc-His(τ-Trt)-OH is commonly used in solid phase peptide synthesis (SPPS). Alternatively, we cannot exclude that helical folding of the oligourea during chain elongation may also diminish the efficiency of this coupling step.[37,38] Following Boc deprotection and simultaneous removal of the *N*(τ)-Trt protection upon TFA treatment, the last residue (Val-type) and the terminal capping motif (isopropylurea) were successively incorporated in the growing chain and the resin was finally cleaved with HF. Reverse phase HPLC (RP-HPLC) coupled to electrospray ionization mass spectrometry (ESI-MS) of the cleaved product indicated the presence of two main compounds in a 3:2 ratio: the first one corresponding to the deletion oligomer missing the His-type unit, the second one, with a molecular mass of 86 Da higher than the desired oligomer **16**, resulting from acylation of the imidazole group by isopropylisocyanate during the last step of the SPS (**17**, Fig. 2). In contrast, over-acylation of the imidazole side chain by the Val-type monomer was not observed, suggesting that succinimidyl carbamates **B** are not reactive enough to react with the free imidazole group. It is noteworthy that in aqueous acidic medium, purified

oligomer **17** was found to undergo partial deacylation at the imidazole ring to give the target oligourea **16** (see Supplementary data for details). Nevertheless, these observations underscore that unprotected imidazole side chains in oligoureas are not compatible with the use of isocyanates for the final capping step. The synthesis of an oligomer uncapped at its terminus was thus undertaken. Oligourea **18** (see Fig. 2) was obtained after HF cleavage, again as a mixture with its deleted form (i.e., missing the His-type unit), in a 1:1 ratio and was finally isolated after purification by preparative RP-HPLC in 9% yield.

Finally, the solid phase synthesis of *N*-capped oligourea **16** was repeated using monomer **2b**. In contrast to what was observed with **2a**, on resin urea bond formation with **2b** was found to proceed to completion after the second coupling step (based on chloranil test). Thus, the benefits of a *N*(τ)-Ts protection are twofold: first, it is less hindered and as a result, promotes a better insertion of His-type units within the oligourea backbone, and second, it remains in place under Boc deprotection conditions. After Boc removal, and introduction of the last residue, the chain was terminated by treatment of the resin with isopropylisocyanate and the resin was cleaved by HF. RP-HPLC analysis of the crude product revealed the formation of a major compound (46% purity) whose identity was confirmed by ESI-MS to be 8-mer **16** (see Supplementary data for details). Oligourea **16** was purified by RP-HPLC and recovered in an overall yield of 13% based on resin loading. The homogeneity of oligoureas **16** and **18** was finally assessed by C_{18} RP-HPLC (>99%) and their structures were confirmed by ESI-MS and ^{1}H NMR analyses. All together, these results demonstrate the superiority of monomer **2b** over **2a** and its practical utility for the preparation of oligourea foldamers containing His-type units.

2.3. ^{1}H NMR conformational studies

NMR analysis was used to determine the helix forming propensities of oligoureas **16** and **18** in solution. ^{1}H NMR spectra were recorded in CD_3OH at a concentration of 6 mM. Spin systems were unambiguously resolved using a combination of COSY and TOCSY 2D experiments (for nomenclature of the main chain protons, see formula **A** in Fig. 1).[17] Sequence-specific assignment of all resonances in the ^{1}H NMR was achieved by a ROESY experiment and was deduced from the strong N′H(*i*+1),NH(*i*) NOE connectivities within each urea bond. The helical character of **16** and **18** was qualitatively inferred from the large vicinal coupling constants between NHs and βCH(R) protons, and the strong differentiation between vicinal coupling constants of main chain diastereotopic methylene protons (αCH$_2$) (Fig. 3 and Supplementary data).

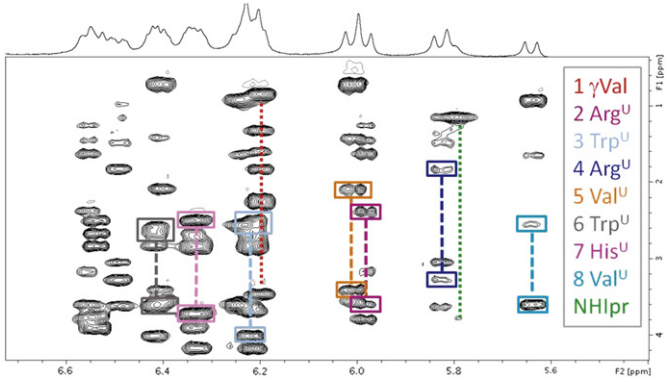


Fig. 3. Fingerprint NH/CH and N′H/CH region of the TOCSY experiment of oligomer **16**, recorded in CD_3OH (400 MHz). For clarity reasons, a three letter code analogous to that of standard α-amino acids with a U letter in superscript is used to identify all residues in the sequence. Red and green dashed lines highlight the fingerprints of γ^4-Val residue and isopropyl group, respectively.

The NH/CH fingerprint region of the TOCSY spectrum of **16** is shown in Fig. 3 and pairs of main chain diastereotopic CH_2 protons are indicated for all residues. We previously reported that the chemical shift difference (Δδ) between main chain diastereotopic CH_2 protons is a useful descriptor of the conformational homogeneity of helical *N*,*N*′-linked oligoureas.[17,22,37] The diastereotopicity values measured for **16** and **18** are collected in Fig. 4. In both cases, Δδ values for residues 2–6 are equal or larger than 1 ppm, which is consistent with a helical folding. However, the amino terminal residue (P8) and the penultimate His-type residue (P7) in **18** are characterized by no and weak diastereotopicity of their methylene protons, respectively, which suggests helix fraying in this part of the structure. In agreement with previous studies on oligoureas,[17,37] capping the amino group with isopropylisocyanate was found to reinforce the 2.5 helical population as evidenced by the significant increase of Δδ values for the last two residues of **16**.

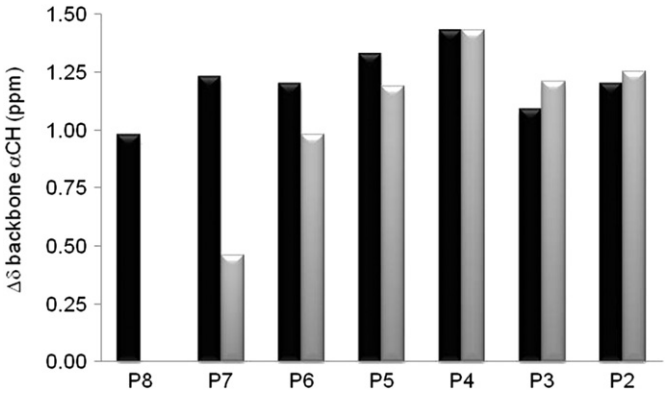


Fig. 4. Chemical shift difference (Δδ) between geminal αCH protons in oligoureas **16** (black bars) and **18** (grey bars) for residues 1–8 as determined by ^{1}H NMR in CD_3OH.

2.4. Circular dichroism (CD) study

Circular dichroism is a useful and complementary technique to study the folding propensity of aliphatic oligoureas. Far-UV CD spectra of oligomers **16** and **18** were first recorded in trifluoroethanol (TFE) at a concentration of 0.2 mM. As expected, CD measurements revealed that in TFE, **16** retains a stable 2.5 helical structure with a typical signature presenting an intense maximum at 203 nm. The per residue molar ellipticity (PRME) value is comparable to that previously found for oligoureas of similar length.[17a,22] In contrast, the slight change observed in the shape of the CD spectrum of uncapped **18** together with the significant decrease in the intensity of the CD maximum confirmed helix destabilization observed by NMR (Fig. 5a). Overall, these results emphasize the critical role played by the capping motif in stabilizing 2.5 helical oligoureas in solution.

Next, to gain information about the influence of the imidazole side chain protonation state on the helicity of **16**, we recorded CD spectra in aqueous buffers within pH range from 5 to 7.6 (Fig. 5). It is noteworthy that the CD signature characteristic of the canonical 2.5 helical structure observed in TFE is maintained in aqueous environment at pH 7. However, the significantly lower PRME value at λ=203 nm indicates partial destabilization relative to TFE.[39] Furthermore, the CD signature was hardly affected by pH variations between 5 and 7.6 thus suggesting that the protonation state of the imidazole side chain has no influence on 2.5 helix folding propensity in water (Fig. 5b).

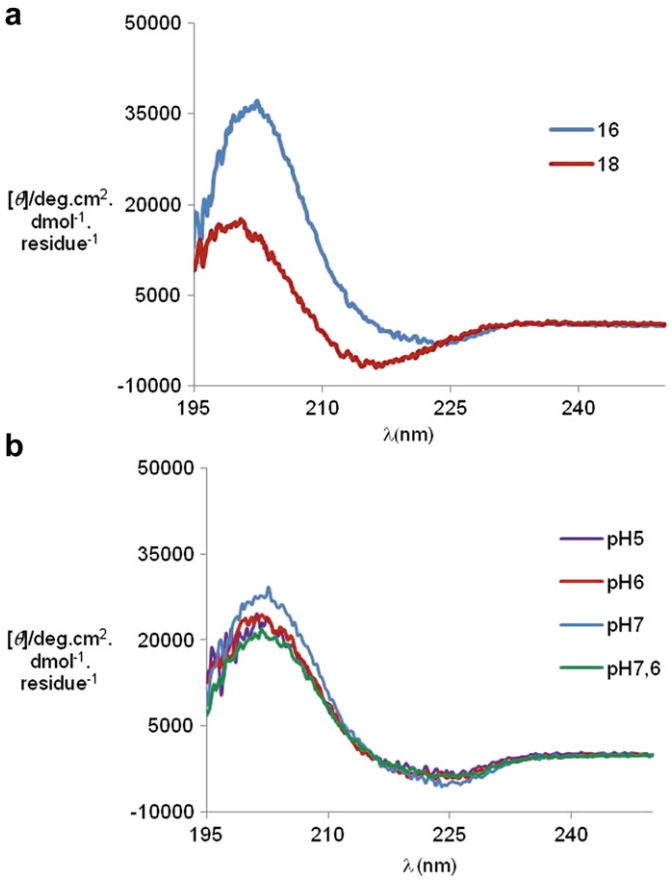


Fig. 5. (a) Far-UV CD spectra of **16** and **18** recorded at 0.2 mM in TFE. (b) Far-UV CD spectra of **16** recorded at 0.2 mM in aqueous buffers at different pH values (10 mM sodium acetate and phosphate buffers). Data are expressed in term of molar ellipticity per residue ([θ] in deg cm^2 dmol^{-1}).

3. Conclusion

An efficient synthesis of activated succinimidyl carbamate of type **B** (PG=Boc) with (1*H*-imidazol-4-yl)-methyl side chain (**2a** and **2b**) has been developed starting from histidine. After several unsuccessful attempts, we found that the protecting group scheme on histidine was critical to access key monoprotected diamine precursors (**1a** and **1b**). Only when starting from Trt-His(τ-Trt)-OMe, could *N*-Boc-protected diamines **1** be obtained in satisfactory yields. Activated building blocks **2a** and **2b** were finally obtained in 36% and 33% overall yield, respectively, starting from commercially available 2HCl·H-His-OMe. The utility of **2b** and its superiority over **2a** for the SPS of aliphatic oligourea foldamers incorporating His-type units has been demonstrated. The preparation of 8-*mer* oligourea **16** containing one imidazole side chain was successfully achieved in good overall yield and purity when employing **2b**. Conformational analyses by ^{1}H NMR spectroscopy and CD confirmed helical folding of **16** in both TFE and aqueous environment. Access to new oligourea sequences with His-type blocks at selected positions is likely to be useful for the design of more sophisticated foldamer architectures and will certainly contribute to expand the scope of their possible applications (e.g., metal ion recognition and/or catalysis).

4. Experimental section

4.1. General methods

Commercially available reagents were used throughout without purification. Boc-γ^4-Val-OH and MBHA resin (1 mmol/g) were purchased from PolyPeptide Laboratories France. Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexa-fluorophosphate (BOP) was purchased from Iris company. All organic solvents were of analytical quality and Milli-Q (Millipore) water was used for RP-HPLC analyses and purifications. Activated monomers used for solid phase synthesis were prepared using a previously reported procedure.[21] Oligourea synthesis was performed manually in a syringe (vide infra). Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck) with detection by UV light and charring with 1% ninhydrin in ethanol followed by heating. Flash column chromatography was carried out on silica gel (40–63 μm, Merck). Melting points were measured in open capillary tubes and are uncorrected. Optical rotations were determined on a Jasco P-2000 polarimeter and are given as $[\alpha]_D^{25}$ (concentration in g/100 mL solvent). IR spectra were recorded with a Bruker IFS55 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on two different NMR spectrometers: (1) an Avance II NMR spectrometer (Bruker Biospin) with a vertical 7.05 T narrow-bore/ultrashield magnet operating at 300 MHz for ^{1}H observation and 75 MHz for ^{13}C observation by means of a 5-mm direct BBO 1H/19F_XBB_H probe with Z gradient capabilities; (2) a DPX-400 NMR spectrometer (Bruker Biospin) with a vertical 9.4 T narrow-bore/ultrashield magnet operating at 400 MHz for ^{1}H observation by means of a 5-mm direct QNP ^{1}H/^{13}C/^{31}P/^{19}F probe with gradient capabilities. Chemical shifts are reported in parts per million (ppm) relative to the ^{1}H residual signal of the deuterated solvent used. ^{1}H NMR splitting patterns with observed first-order coupling are designated as singlet (s), doublet (d), triplet (t), or quartet (q). Coupling constants (*J*) are reported in hertz. CD spectra were recorded on a J-815 Jasco CD spectrometer. RP-HPLC analyses were performed on a Dionex U3000SD using a Macherey–Nagel Nucleodur column (4.6×100 mm, 3 μm) at a flow rate of 1 mL min^{-1}. The mobile phase was composed of 0.1% (v/v) TFA/H_2O (Solvent A) and 0.1%TFA/CH_3CN (Solvent B). Semi-preparative purifications of oligoureas were performed on a Gilson GX-281 system using a Macherey–Nagel Nucleodur column (20×250 mm, 5 μm) at a flow rate of 20 mL min^{-1}. The mobile phase was similar as for the analytic system, unless otherwise notified. A gradient elution (0–20 min: 80%–40% A) was applied at a flow rate of 20 mL min^{-1}. Column effluent was monitored by UV detection at 214 and 254 nm. ESI-MS analyses were carried out on a ThermoElectron LCQ Advantage spectrometer equipped with an ion trap mass analyzer and coupled with a ThermoElectron Surveyor HPLC system.

4.2. Synthesis of building blocks 2a and 2b

*4.2.1. (S)-Methyl 3-(1-trityl-1H-imidazol-4-yl)-2-(tritylamino)propanoate (**10**).* To a stirred suspension of 2HCl·H-His-OMe (15 g, 61.98 mmol) in CH_3CN (600 mL) at 0 °C, Et_3N (43.31 ml, 309.92 mmol) was added and after 5 min Trt-Cl (43.07 g, 154.96 mmol) was added slowly portion wise. The reaction mixture was allowed to stir at room temperature overnight. The CH_3CN was concentrated under reduced pressure and the residue was dissolved in CH_2Cl_2 (500 mL), washed with aqueous saturated solution of $NaHCO_3$ (100 mL), water (100 mL) and with brine (100 mL), dried over $MgSO_4$ and concentrated under high vacuum to afford **10** (40.47 g, quantitative yield) as a yellow solid, which was used for next step without characterization.

*4.2.2. (S)-3-(1-Trityl-1H-imidazol-4-yl)-2-(tritylamino)propan-1-ol (**11**).* To a stirred suspension of $LiAlH_4$ (9.39 g, 247.90 mmol) in dry THF (100 ml) at 0 °C, compound **10** (40.47 g, 61.97 mmol) dissolved in dry THF (300 ml) was added slowly and the reaction mixture was allowed to stir a room temperature for 2 h. The reaction mixture was carefully quenched with aqueous saturated solution of Na_2SO_4, diluted with EtOAc (400 mL), and filtered over Celite bed. The

filtrate was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated under vacuum. After purification on silica gel eluting with 5% EtOAc in cyclohexane to EtOAc/CH_2Cl_2 (1:1, v/v), alcohol **11** was isolated as a solid (36.1 g, 93%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.00 (d, J=6.1, 14.4 Hz, 2H), 2.45 (d, J=14.4 Hz, 1H), 2.88–3.14 (m, 2H), 3.55 (d, J=11.1 Hz, 1H), 6.35 (s, 1H), 7.08–7.44 (m, 25H), 7.55 (d, J=6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 31.8, 52.5, 65.8, 71.0, 75.2, 120.4, 126.2, 127.8, 128.1, 128.7, 129.7, 137.7, 138.1, 142.3, 147.2.

*4.2.3. (S)-1-Azido-N-trityl-3-(1-trityl-1H-imidazol-4-yl)propan-2-amine (**12**).* To a stirred solution of alcohol **11** (36.1 g, 55.54 mmol) in DMF (180 ml) at 65 °C, were successively added DPPA (17.85 mL, 83.30 mmol), DBU (11.74 mL, 83.30 mmol) and after 5 h NaN_3 (1.81 g, 27.769 mmol). Stirring was maintained at the same temperature for 12 h after which time the reaction mixture was cooled down to room temperature, then diluted with EtOAc (360 mL) and washed with saturated solution of $NaHCO_3$ (100 mL), water (2×100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. After purification on silica gel eluting with 6% EtOAc in cyclohexane azide **12** was obtained as an off white solid (28.1 g, 75%). Mp 67–69 °C; $[\alpha]_D^{25}$ +11.6 (c 1.0, $CHCl_3$); IR (neat): 3030, 2098, 1490, 1446, 1185, 1130, 1056, 1033, 902 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22 (dd, J=7.2, 14.4 Hz, 1H) 2.37 (d, J=7.3 Hz, 1H), 2.48 (dd, J=4.6, 14.4 Hz, 1H), 2.71 (dd, J=6.3, 11.8 Hz, 1H), 3.01–2.89 (m, 1H), 3.08 (dd, J=3.3, 11.8 Hz, 1H), 6.41 (d, J=1.2 Hz, 1H), 7.43–7.04 (m, 25H), 7.58–7.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.2, 52.2, 54.3, 71.1, 75.2, 77.2, 120.0, 125.6, 127.9, 128.0, 128.7, 129.8 137.7, 138.4, 142.3, 146.7; HRMS(ESI):m/z calculated for $C_{44}H_{38}N_6$ $[M+H]^+$ 651.3236, found 651.3242.

*4.2.4. (S)-tert-Butyl 1-azido-3-(1-trityl-1H-imidazol-4-yl)propan-2-ylcarbamate (**13**).* Azide **12** (6.1 g, 9.38 mmol) was dissolved in a $C_2H_4Cl_2$/MeOH/TFA (188:8:4, v/v/v) solution mixture (200 mL). The reaction mixture was stirred between 0 and 10 °C for 10 min, then basified with Et_3N, then treated with $(Boc)_2O$ (2.15 ml, 9.38 mmol) and allowed to stir at room temperature for 20 min. The reaction mixture was washed with saturated aqueous solution of $NaHCO_3$ (50 mL), with molar aqueous solution of $KHSO_4$ (50 mL), water (50 mL) and with brine (50 mL), dried over $MgSO_4$, and concentrated under vacuum., After purification on silica gel eluting with 10–20% of EtOAc in cyclohexane, azide **13** was isolated as an off white solid (3.65 g, 76%). Mp 47–50 °C; $[\alpha]_D^{25}$ −6.9 (c 1.0, $CHCl_3$); IR (neat): 3025, 2099, 1706, 1494, 1446, 1365, 1242, 1167, 1036 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.75 (d, J=5.7 Hz, 2H), 3.28 (dd, J=6.8, 12.1 Hz, 1H), 3.48 (dd, J=5.3, 12.1 Hz, 1H), 4.05–3.90 (m, 1H), 5.92 (d, 1H, J=5.7 Hz), 6.74 (s, 1H), 7.18–7.08 (m, 6H), 7.44–7.32 (m, 9H), 7.66 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.9, 28.3 (3), 29.3, 50.2, 53.4, 75.9, 79.3, 120.1, 128.2 (2), 128.3 (4), 129.6 (4), 135.9, 137.9, 141.8 (3), 155.4; HRMS(ESI): m/z calculated for $C_{30}H_{33}N_6O_2$ $[M+H]^+$ 509.2665, found 509.2657.

*4.2.5. (S)-tert-Butyl 1-amino-3-(1-trityl-1H-imidazol-4-yl)propan-2-ylcarbamate (**1a**).* To a stirred solution of **13** (3.61 g, 0.39 mmol) in EtOAc (72 mL) at room temperature, 5% Pd on $BaSO_4$ (400 mg) was added and the reaction mixture was stirred under H_2 gas atmosphere for 20 h. The reaction mixture was filtered over Millipore filter paper, the filtrate was concentrated under reduced pressure and dried under high vacuum line to afford amine **1a** (3.41 g, quantitative yield) as a pale yellow liquid, which was used for next step without characterization.

*4.2.6. Carbamate (**2a**).* To a stirred suspension of *N*,*N*′-disuccinimidyl carbonate (2.174 g, 8.50 mmol) in CH_2Cl_2 (10 mL), a solution of amine **1a** in CH_2Cl_2 (20 mL) was added dropwise (3.41 g, 7.07 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then filtered off, the filtrate was washed with an aqueous molar solution of $KHSO_4$ (3×5 mL), the organic layer was dried over $MgSO_4$ and concentrated under vacuum, and **2a** was obtained after recrystallization using CH_2Cl_2/petroleum ether solvent mixture (3.21 g, 68%). Mp 124–127 °C; IR (neat): 3402, 1770, 1749, 1730, 1501, 1481, 1178, 1163, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H), 2.75 (s, 4H), 3.23–3.02 (m, 2H), 3.48–3.39 (m, 2H), 4.07–3.92 (m, 1H), 6.24 (d, J=8.0 Hz, 1H), 6.79 (s, 1H), 7.20–7.06 (m, 6H), 7.50–7.34 (m, 9H), 7.75–7.64 (m, 1H), 8.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5, 27.1, 28.3, 44.7, 50.3, 78.2, 79.1, 120.7, 128.6, 128.9, 129.8, 132.5, 135.7, 140.3, 152.8, 155.9, 170.4; HRMS(ESI): m/z calculated for $C_{35}H_{38}N_5O_6$ $[M+H]^+$, 624.2822 found 624.2819.

*4.2.7. (S)-tert-Butyl 4-(3-azido-2-(tert-butoxycarbonylamino)-propyl)-1H-imidazole-1-carboxylate (**14**).* To a stirred solution of azide **12** (2.28 g, 3.507 mmol) in THF (10 mL) at room temperature, a solution of aqueous 6 N HCl (10 mL) was added and stirring was maintained at 70 °C for 4 h. After completion of the reaction, the THF was removed under reduced pressure, and water (10 ml) was added. The aqueous phase was washed with CH_2Cl_2 (2×5 mL). The aqueous layer was concentrated then co-evaporated with EtOH under reduced pressure and dried under high vacuum line to furnish hydrochloride salt, which was directly suspended in CH_3CN (20 mL) at 0 °C. Et_3N (0.487 mL, 3.51 mmol), DMAP (0.042 g, 0.35 mmol) followed by Boc_2O (1.77 mL, 7.72 mmol) and of water (0.5 mL) were successively added and the reaction mixture was allowed to stir at room temperature overnight. Acetonitrile was concentrated under vacuum and the crude was dissolved in EtOAc (40 mL), the organic layer was washed with water (5 mL), brine (5 mL), and dried with $MgSO_4$ and concentrated under reduced pressure. After silica gel purification eluting with 15% EtOAc in cyclohexane compound **14** was obtained (0.832 g, 65%) as a white solid. Mp 81–83 °C; $[\alpha]_D^{25}$ +2.4 (c 1.0, $CHCl_3$); IR (neat): 3421, 2951, 2092, 1748, 1720, 1532, 1505, 1396, 1384, 1261, 1250, 1164 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 9H) 1.50 (s, 9H), 2.70 (d, J=6.0 Hz, 2H), 3.30 (dd, J=5.1, 12.1 Hz, 1H), 3.33 (dd, J=5.1, 12.1 Hz, 1H), 3.98–3.82 (m, 1H), 5.52 (d, J=7.5 Hz, 1H), 7.09 (s, 1H), 7.91 (d, J=1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.7, 28.2, 29.8, 49.9, 53.2, 79.2, 85.4, 114.6, 136.7, 139.1, 146.9, 155.0; HRMS(ESI): m/z calculated for $C_{16}H_{27}N_6O4$ $[M+H]^+$, 367.2094 found 367.2093.

*4.2.8. (S)-tert-Butyl-1-azido-3-(1H-imidazol-4-yl)propan-2-ylcarbamate (**15**).* To a stirred solution of compound **14** (0.400 g, 1.09 mmol) in MeOH (4 mL) at 0 °C, K_2CO_3 (0.075 g, 0.55 mmol) and water (0.1 mL) were added and the reaction was allowed to stir at room temperature for 1 h. MeOH was removed under reduced pressure, and the crude was dissolved in EtOAc (20 mL). The organic layer was washed with water (5 mL), brine (5 mL), dried with $MgSO_4$ and concentrated under reduced pressure to afford after drying under high vacuum line compound **15** (0.285 g, 98%) as an off white solid. Mp 86–87 °C; $[\alpha]_D^{25}$ −9.5 (c 1.0, $CHCl_3$); IR (neat): 3392, 2980, 2089, 1710, 1530, 1504, 1391, 1251, 1130 cm^{-1}, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (s, 9H), 2.86 (d, J=6.3 Hz, 2H), 3.30 (dd, J=6.1, 12.1 Hz, 1H), 3.42 (dd, J=4.9, 12.2 Hz, 1H), 4.10–3.90 (m, 1H), 5.56 (d, 1H), 6.87 (s, J=8.5 Hz, 1H), 7.62 (d, J=1.0 Hz, 1H), 10.33 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 29.4, 50.2, 53.3, 79.8, 116.0, 134.0, 135.2, 155.5; HRMS(ESI): m/z calculated for $C_{11}H_{19}N_6O_2$ $[M+H]^+$, 267.1569 found 267.1571.

*4.2.9. (S)-tert-Butyl-1-azido-3-(1-tosyl-1H-imidazol-4-yl)propan-2-ylcarbamate (**5**).* To a stirred solution of **15** (0.285 g, 1.071 mmol) in CH_2Cl_2 (5 ml) at 0 °C, Et_3N (0.178 ml, 1.285 mmol), followed by tosyl chloride (0.224 g, 1.18 mmol) and DMAP (0.013 g, 0.11 mmol) were added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then diluted with CH_2Cl_2

(15 mL), washed with molar aqueous solution of $KHSO_4$ (5 mL), water (5 mL), brine (5 mL) dried with $MgSO_4$, and concentrated under reduced pressure. After silica gel purification eluting with 15% EtOAc in cyclohexane compound **5** was obtained as white solid (0.412 g, 92%). Mp 104–106 °C; $[\alpha]_D^{25}$ −2.0 (*c* 1.0, $CHCl_3$); IR (neat): 3438, 2096, 1709, 1512, 1392, 1287, 1260, 1141, 1089 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.43 (s, 3H), 2.75 (d, *J*=5.5 Hz, 2H), 3.25 (dd, 1H, *J*=6.1, 12.2 Hz), 3.38 (dd, 1H, *J*=4.8, 12.2 Hz), 4.05–3.89 (m, 1H), 5.30 (d, *J*=6.8 Hz, 1H), 7.05 (d, *J*=1.0 Hz, 1H), 7.35 (d, *J*=8.2 Hz, 2H), 7.83 (d, *J*=8.5 Hz, 2H), 7.93 (d, 1H, *J*=1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 28.3, 29.9, 49.6, 53.2, 79.6, 114.8, 127.3, 130.8, 134.8, 136.4, 140.7, 146.3, 155.1; HRMS(ESI): *m*/*z* calculated for $C_{18}H_{25}N_6O_4S$ $[M+H]^+$, 421.1658 found 421.1660.

*4.2.10. (S)-tert-Butyl 1-amino-3-(1-tosyl-1H-imidazol-4-yl)propan-2-ylcarbamate (**1b**).* To a stirred solution of azide **5** (0.150 g, 0.36 mmol) in EtOAc (20 ml) at room temperature 5% Pd on $BaSO_4$ (0.050 g) was added and the reaction was stirred under H_2 gas atmosphere for 20 h. The reaction mixture was filtered over Millipore filter paper, the filtrate was evaporated and dried under high vacuum to afford compound **1b** (0.140 g, quantitative yield) as a pale yellow liquid, which was directly used for next step without characterization.

*4.2.11. Carbamate (**2b**).* To a stirred suspension of DSC (0.109 g, 0.43 mmol) in CH_2Cl_2 (5 mL), a solution of amine **1b** (0.140 g, 0.355 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C and left to react at room temperature for 3 h. The reaction mixture was filtered off, the filtrate was washed with molar aqueous solution of $KHSO_4$ (2×5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Compound **2b** was isolated after recrystallization with a mixture of CH_2Cl_2 and petroleum ether as a white solid (0.165 g, 86%). Mp 74–76 °C; IR (neat): 3342, 1762, 1752, 1720, 1540, 1506, 1410, 1390, 1180, 1174, 1142, 1091 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 9H), 2.45 (s, 3H), 2.77 (d, *J*=5.7 Hz, 2H), 2.82 (s, 4H), 3.39–3.17 (m, 2H), 4.06–3.88 (m, 1H), 5.48 (d, *J*=7.2 Hz, 1H), 6.82 (br s, 1H), 7.30 (s, 1H), 7.38 (d, *J*=8.3 Hz, 2H), 7.83 (d, *J*=8.3 Hz, 2H), 7.97 (d, *J*=1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.7, 25.5, 28.3, 29.9, 45.4, 49.9, 77.3, 79.8, 115.2, 127.4, 130.5, 134.7, 136.5, 140.3, 146.4, 152.0, 156.0, 170.0; HRMS(ESI): *m*/*z* calculated for $C_{23}H_{30}N_5O_8S$ $[M+H]^+$, 536.1815 found 536.1805.

4.3. General procedure for solid phase synthesis of urea oligomers 18–20

Oligomers **16**–**18** were synthesized manually using Boc chemistry on a 100 μmol scale starting from MBHA resin. The first coupling step was performed with a solution of Boc-γ^4-Val-OH (1.5 equiv) in DMF, with BOP (1.5 equiv) and DIEA (3 equiv) and the resin was shaken for 30 min. This step was performed twice and completion of the coupling was monitored by a Kaiser test. For each following coupling step, a solution of succinimidyl carbamate (3 equiv) and DIEA (6 equiv) in DMF was added on the resin, shaking was maintained for 120 min. A double coupling was performed systematically. The coupling solution was then filtered off and the resin was washed with DMF (5×1 min). Completion of couplings was monitored with the chloranil test. Boc protecting group was removed using TFA (5 and 10 min). TFA was removed by filtration and the resin was washed with CH_2Cl_2 (3×1 min) and with DMF (3×1 min). End capping of the terminal amine with isopropylisocyanate (3 equiv) was performed in DMF, in the presence of DIEA (5 equiv) and the resin was shaken for 30 min. Finally, the resin was washed with CH_2Cl_2 and dried under nitrogen. τ-Tosyl protection on imidazole side chain was removed prior HF cleavage by using two times a solution of 10 equiv of hydroxybenzotriazole (HOBt) in DMF for 15 min. Other side chain deprotections and cleavage of the oligomers from the resin were performed simultaneously by treatment with HF (containing 10% *p*-cresol as a scavenger) for 60 min at 0 °C. The crude oligoureas were finally purified by RP-HPLC and lyophilized.

Oligomer **16**: Purity of crude product 46%. Yield after purification 19 mg, 13%; white powder; RP-HPLC t_R 7.71 min (linear gradient, 20–60% B, 10 min); MS (ESI) *m*/*z* 1453.7 $[M+H]^+$.

Oligomer **17**: Purity of crude product 31%. Yield after purification 3.5 mg, 5%; white powder; RP-HPLC t_R 8.34 min (linear gradient, 20–60% B, 10 min); MS (ESI) *m*/*z* 1538.7 $[M+H]^+$.

Oligomer **18**: Purity of crude product 19%. Yield after purification 11 mg, 8%; white powder; RP-HPLC t_R 5.21 min (linear gradient, 20–60% B, 10 min); MS (ESI) *m*/*z* 1367.5 $[M+H]^+$.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.11.066. These data include MOL files and InChiKeys of the most important compounds described in this article.

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39. In contrast, the PMRE value measured at 203 nm for **18** does not change much between TFE and aqueous environment (pH 7), suggesting that in the case of uncapped oligoureas, TFE is as much destabilizing as water (see Fig. S22 in Supplementary data).