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Synthesis of Hetero-Bifunctional, End-Capped Oligo-EDOT Derivatives

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SUMMARY

Conjugated oligomers of 3,4-ethylenedioxythiophene (EDOT) are attractive materials for tissue engineering applications, and as model systems for studying the properties of the widely used polymer PEDOT. We report here the facile synthesis of a series of keto-acid end-capped oligo-EDOT derivatives (n = 2-7) through a combination of a novel end capping strategy and iterative direct arylation chain extension. Importantly, these structures not only represent the longest oligo-EDOTs reported to date, but are also bench stable in contrast to previous reports on such oligomers. The constructs reported here can undergo subsequent derivatization for integration into higher order architectures, such as those required for tissue engineering applications. The synthesis of hetero-bifunctional constructs, as well as those containing mixed monomer units is also reported, allowing further structural complexity to be installed in a controlled manner. Finally, we describe the optical and electrochemical properties of these oligomers and demonstrate the importance of the keto-acid end-group in determining their characteristics.

The Bigger Picture

The production of materials that can aid the repair, regrowth, or replacement of damaged tissue is a key challenge in tissue engineering. In this context, conjugated polymers have been proposed as attractive materials for the engineering of electroactive tissues such as the heart. While there has been much progress in the field, the use of conjugated polymers is still hindered by their high heterogeneity, stiffness, poor solubility, and lack of chemical functionality. There is therefore a pressing need to produce new routes to produce constructs such as those reported here, which offer homogeneity, stability, ease of synthesis and most importantly flexibility of design. This flexibility allows the incorporation of conjugated structures into the higher order biomaterial architectures required for tissue engineering, as well as tunable solubility and material properties. It is anticipated that this report will open the doors to an exciting new chapter in the use of EDOT in biology.

INTRODUCTION

Conjugated polymers (CPs) are promising materials for tissue engineering applications.[1–4] However further developments are required in order to allow their full potential to be realised in the biomedical field. While initial investigation have shown CPs to be able to modulate cellular growth,[5] migration[6] and differentiation,[7,8] as well as protein adhesion and conformation,[9] difficulties remain as a consequence of their poor material characteristics, difficult processing and lack of biodegradability.[1,2,10] Further, the production of constructs bearing reactive functionalities for integration into more complex scaffold architectures remains challenging.[2]

In order to address these issues there is increasing interest in the use of oligomers rather than polymeric systems. While often being more synthetically complex,[11] oligomers offer the benefits of a defined molecular structure, improved solubility, tunability and additional chemical functionality.[2,12] Oligomers may also act as mono-disperse model systems for studying the electronic and optical properties of the parent polymer, for which such investigations may be hindered.[13]

Poly(3,4-ethylenedioxythiophene) (PEDOT) is a particularly attractive material for tissue engineering due to its high conductivity, and electrical and chemical stability when doped with polymeric ionomers such as polystyrene sulfonate (PSS).[14,15] While the synthesis of thiophene based-oligomers has been widely reported,[11,16–19] those of EDOT (**1**, Scheme 1) have generated comparatively little interest, largely due to the poor oxidative stability and low solubility of the oligomers.[20,21] Mesityl,[22] phenyl,[21] *n*-hexyl[23] and trimethylsilyl[24] capping groups have all been reported, with longer oligomers reported to be unstable in solution, very poorly soluble and difficult to purify, limiting their utility. Indeed, there remains only a single report on the synthesis of a pentameric species with no synthetic details reported[24] (Figure 1A). Further, the end-caps utilised offer no opportunities for further chemical derivatization and subsequent incorporation into more complex structures.

Here, we report the facile synthesis and characterisation of bench stable oligo-EDOT derivatives, up to n = 7, produced via a novel keto-acid end capping strategy and iterative C-H activation chemistry. Importantly, this allows the production of hetero-bifunctional constructs with a wide range of functional handles for further modification (Figure 1B). These motifs allow further integration into more challenging substrates such as those required for tissue engineering applications.

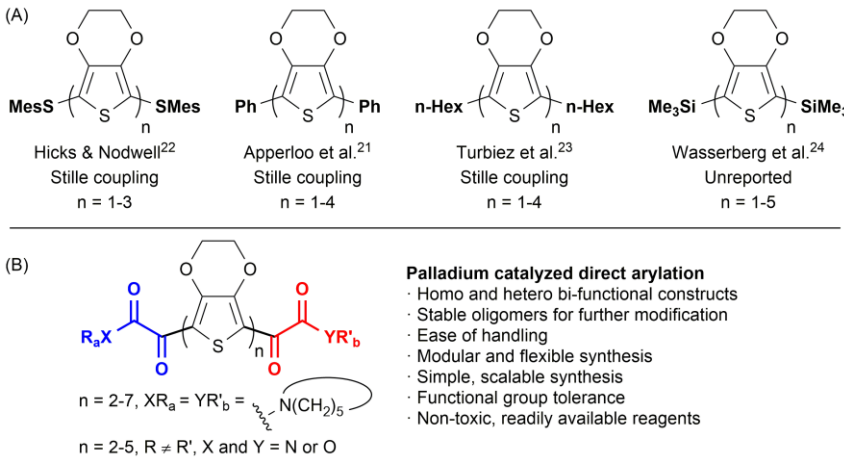


Figure 1. Previous EDOT-end caps and concept of this report
(A) Previous reports of the synthesis of EDOT-oligomers.
(B) Keto-acid capped oligomers presented in this work, synthesised by direct arylation.

RESULTS AND DISCUSSION

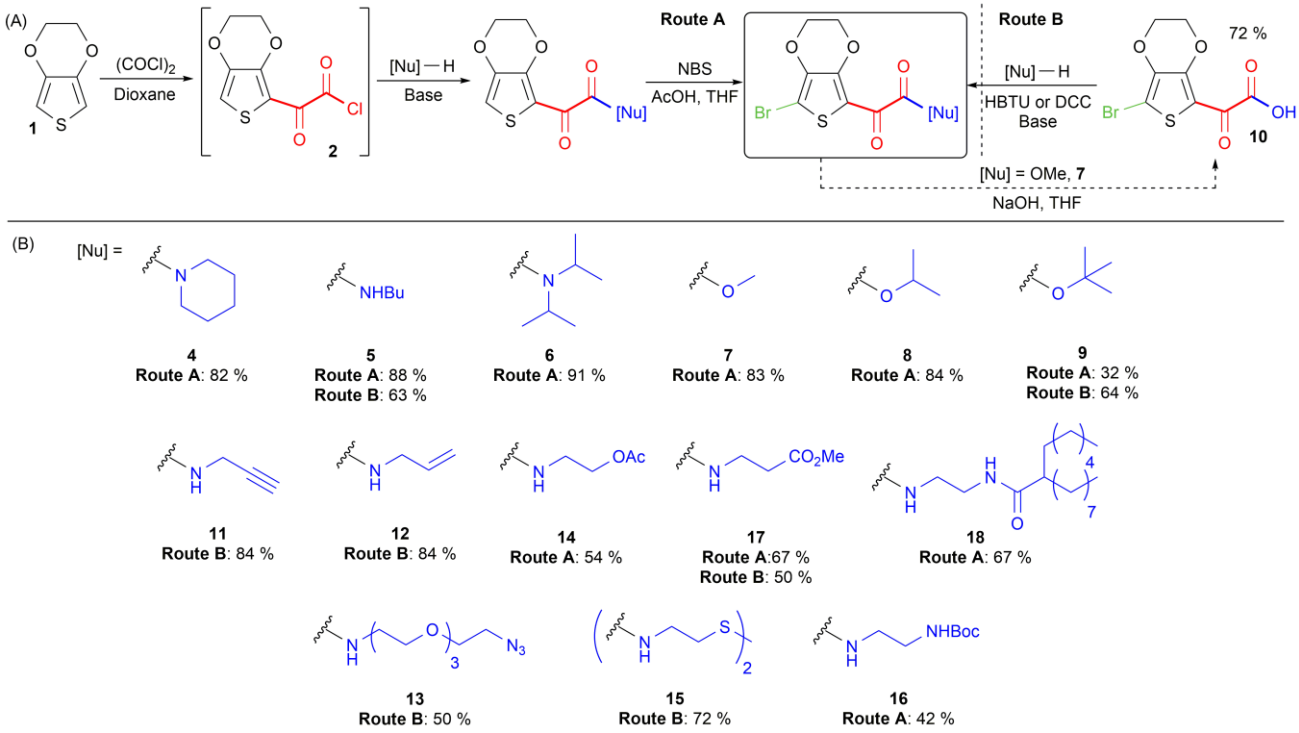
Oligomer synthesis

Our initial designs were inspired by reports of thiophene glyoxylation with oxalyl chloride.[25] We reasoned that the intermediate glyoxylyl chloride **2** could be reacted in situ with a range of nucleophiles to generate α-functionalised EDOT derivatives (Scheme 1). Importantly, the choice of nucleophile would have little influence on aromatic stability allowing for a range of diverse constructs to be produced. After treatment of EDOT with 1 equiv. of oxalyl chloride the intermediate chloride **2** reacted smoothly with piperidine to generate the tertiary keto-amide **3** in good yield. Subsequent bromination with *N*-bromosuccinimide yielded the di-functional monomer **4** on a multi-gram scale.[22]

A range of functionalised monomers could be produced by this method, including secondary amines (**5**), hindered tertiary amines (**6**), esters (**7**, **8**, **9**) and monomers bearing functional groups for further modifications. Further, hydrolysis of brominated-EDOT methyl ester **7** and subsequent amide or ester coupling allowed the synthesis of a range of di-functional monomers from a common intermediate **10** (Scheme 1-Route B). As such, monomers containing orthogonal reactive groups for further conjugation such as alkynes (**11**), alkenes (**12**), azides (**13**), and protected alcohols (**14**), thiols (**15**) and amines (**16**) could all be produced in good yields in a simple fashion.[26]

Next, we investigated the chain extension of brominated monomer **4** to form dimer **19**. The most popular strategies for undertaking such reactions utilise Kumada,[27] Negishi[28] or Stille[29] couplings. However, problems such as poor functional group

tolerance, monomer instability, and high reagent toxicity result in significant limitations, particularly for use in biological applications.[22,30,31] As such, we chose to investigate the use of direct arylation which has emerged in recent years as a powerful tool for constructing conjugated systems.[32,33] Pleasingly, **4** was found to be partially converted to **19** in the presence of 1.5 equiv. of EDOT **1** in *N,N*-dimethylformamide (DMF) at 130 °C for 1 hr (Scheme 2A). Importantly, the reaction was catalysed by a readily available combination of $Pd(OAc)_2$, pivalic acid, and potassium carbonate, thus negating the need for expensive or air-sensitive catalysts and ligands, or the use of specialist techniques.[34]



Scheme 1. EDOT glyoxylation and functionalisation

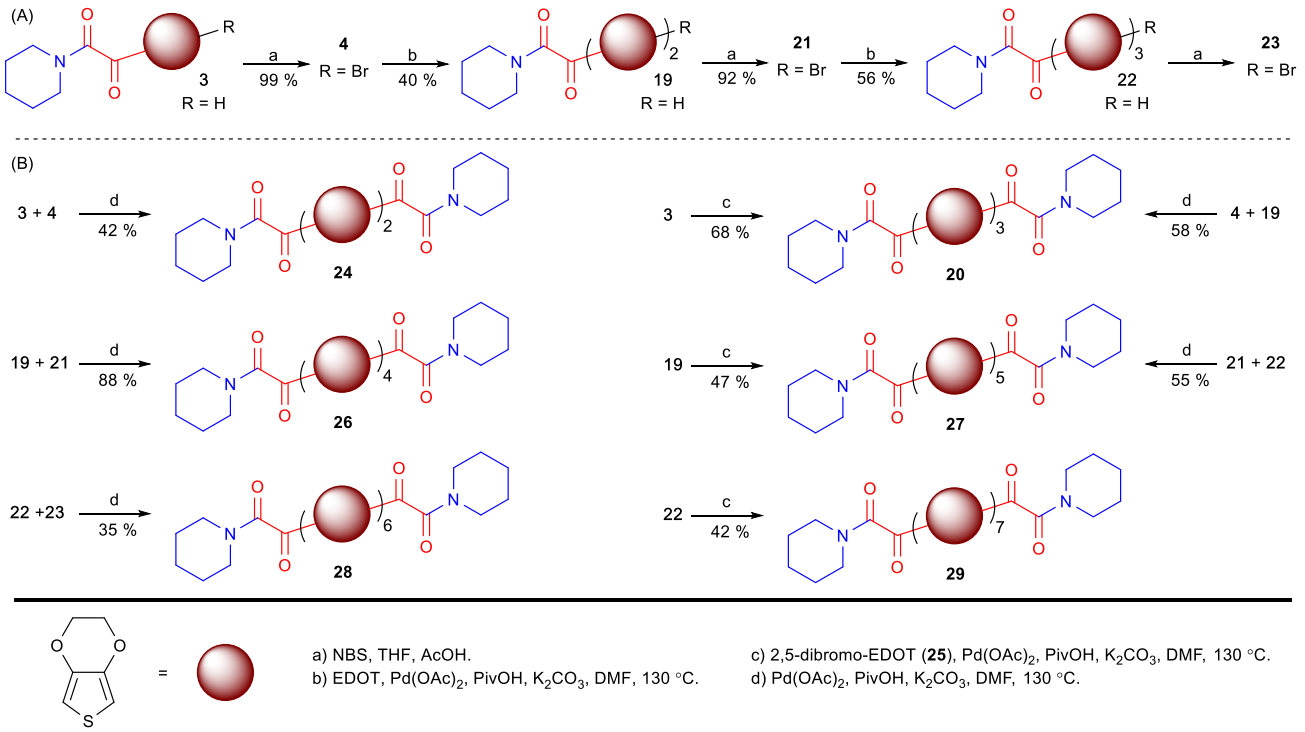
(A) Treatment of EDOT with oxalyl chloride and subsequent treatment with the desired nucleophile generates functional end-capped derivatives which can then undergo bromination (Route A). Alternatively, amide or ester coupling can be undertaken from a common intermediate **10** to obtain the desired monomers (Route B).

(B) Functionalised brominated-monomers synthesised.

Investigating the reaction further, yields were found to be increased significantly through the use of 4 equiv. of EDOT, the excess of which could be readily re-isolated through column chromatography. At lower loadings, a significant amount of the symmetrical di-capped trimer **20** was produced due to further reaction of **19** with **4**. While small amounts of this side-product were still produced at higher EDOT loadings, yields were significantly lowered and separation was readily achieved. Further iterations of bromination and direct arylation allowed the production of brominated dimer **21** and trimer **22** on a gram scale, both of which were found to be bench-stable. Bromination to form brominated trimer **23** was also found to be possible, although its low solubility and stability prevented its characterisation and required its immediate use once prepared, as will be discussed later.

With these mono-capped building blocks in hand, we investigated the synthesis of di-capped oligomers (Scheme 2B). By heating a mixture of brominated and non-brominated monomers **4** and **3** (1.1 equiv.), under the same conditions required for chain extension, di-capped dimer **24** was cleanly produced. Similarly, trimer **20** was produced from **4** and dimer **19**. Alternatively, **20** could be produced by reacting 2 equiv. of either monomer **3** or brominated monomer **4** with 2,5-dibromo-EDOT **25** or EDOT **1** respectively, in an optimised version of the previously discussed chain extension side reaction.

By suitable choice of starting materials, di-capped oligomers (n = 2-5, **24**, **20**, **26**, **27**) were all readily produced and easily isolated by column chromatography. Extending the scope further to the use of brominated trimer **23**, used immediately without purification, allowed the synthesis of hexamer **28**, while coupling of trimer **22** with 2,5-dibromo-EDOT **25** allowed the synthesis of heptamer **29**, the first time the synthesis of EDOT-oligomers of such lengths have been reported. Oligomers up to n = 6 were found to be bench and air stable and therefore could be easily handled, purified, and analysed, with no change in structure being observed by UV-Vis or ^{1}H NMR spectroscopy after 2 months storage at room temperature. Heptamer **29** was produced with reduced purity (~ 80 % as judged by ^{1}H NMR) but retained stability. While oligomers of n = 2-5 were also found to be stable in solution, after long periods in chlorinated solvents (> 2 weeks) hexamer **28** and heptamer **29** were found to undergo partial degradation as indicated by a broadened UV-Vis absorption.



Scheme 2. Synthesis of piperidine-end capped homo-bifunctional EDOT oligomers
(A) Chain extension of mono-functional (n = 1-3) piperidine capped oligomers.
(B) Convergent coupling to generate bifunctional piperidine end-capped constructs (n = 2-7).

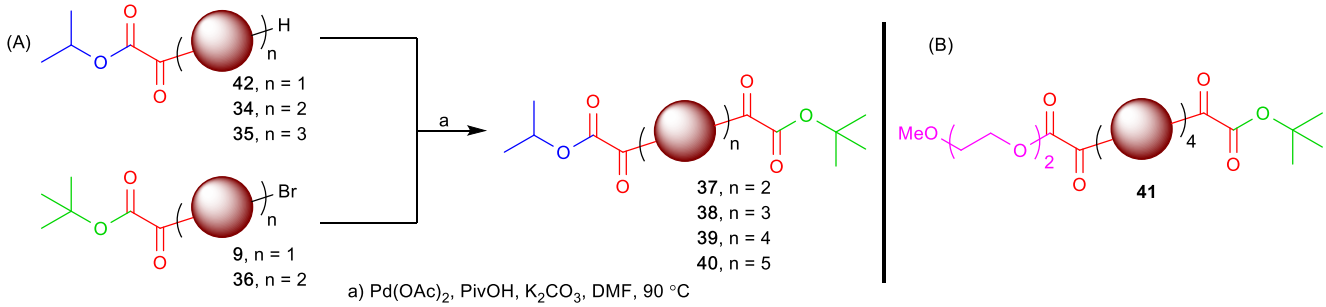
Oligomer solubility was found to decrease with increasing chain length and aggregation in solution became significant at longer lengths, yet it remained high enough to allow manipulation in solution and the use of typical synthetic techniques such as phase extraction and column chromatography. Oligomers of n = 2-5 were soluble at concentrations of > 20 mM in dichloromethane (DCM), hexamer **28** at concentrations > 5 mM, while heptamer **29** could be solubilised at concentrations of up to 0.5 mM. It is important to note that solubility is strongly influenced by the choice of end-group, and can be readily improved by the introduction of a flexible solubilising linker to the functional group of interest, as will be discussed later. Finally, oligomers **20** and **26** were analysed by inductively coupled plasma mass spectrometry (ICP-MS) to determine the levels of residual palladium present. As for other heavy metals, palladium contamination in pharmaceuticals and biomedical devices is tightly regulated due to the potential for toxic side effects. Palladium contamination was found to be at a low level of 7.4 ± 0.5 ppm for trimer **20** and 1.2 ± 0.5 ppm for tetramer **26**. While it is difficult to make a direct comparison between a substrate intended for applications in tissue engineering and an active pharmaceutical ingredient (API), it is useful to note that these low levels of contamination are below the 10 ppm limit set by the ICH and USP for acceptable levels of palladium in APIs.[35] Furthermore, since no extensive effort was taken to

remove palladium from the samples it is likely that these levels could be reduced further. For example the use of palladium chelators during purification or the use of heterogeneous catalysts would be expected to lead to a significant reduction in contamination in any structures intended for biological applications.[36–38]

While the ability to create symmetrical oligo-EDOTs with non-functional end-groups is a useful tool for modelling the properties of PEDOT, the true utility of the method described above for the synthesis of di-piperidine capped oligomers is in the synthesis of hetero-bifunctional constructs, which can be selectively derivatised at both ends allowing their integration into more complex architectures. In order to demonstrate this, we first synthesised a series of unsymmetrical oligomers, capped with a piperidine motif at one terminus and diisopropylamine at the other (see SI Scheme S1). By coupling differently terminated oligomers as described above, oligomers of n = 2-5 (**30**-**33**) were produced in a limited number of steps.

During these experiments, a number of observations were made. Firstly, although a temperature of 130 °C was required for the chain extension and oligomer synthesis with brominated-piperidine based species, for diisopropyl-functionalised oligomers 90 °C was found to be sufficient to give complete conversion within 1 hr of reaction, leading to cleaner reaction products. Indeed, for all other end-capping groups investigated during this work, 90 °C was high enough to facilitate reaction.[39] Secondly, while couplings generally proceeded cleanly, the amount of side-products produced increased with increasing oligomer length. The major side-product was found to result from the instability of the brominated species, resulting in partial dehalogenation and subsequent homo-coupling, and to a lesser extent homo-coupling of the non-brominated reaction partner. Such side reactions have been extensively studied,[40] and are also known to occur during Stille and Suzuki polymerisations.[41] While outside the scope of this work (which focuses on the use of unoptimised, simple and cheap catalyst systems), it is likely that such products could be minimised through judicious choice of both metal and ligand.[42]

In order to create functional oligomers primed for further reaction and derivatization, we considered that a number of common reactive handles would not be amenable to the chain extension and bromination procedures described above.[43] It would therefore be advantageous to be able to install functionality at a late stage after oligomer synthesis. As such, we investigated the use of orthogonal ester protecting groups in order to provide latent functionality. Initial attempts to react methyl ester **7** with an excess of EDOT **1** led not only to chain extension but also a significant amount (~ 40 %) of ester cleavage (see SI Scheme S2). However, by switching to *iso*-propyl ester **8** clean conversion to dimer **34** was observed at 90 °C, followed by subsequent bromination and extension to yield trimer **35** (reaction at 130 °C as described for piperidine-oligomers led to complete ester cleavage). Similarly, the orthogonally protected *tert*-butyl ester **9** could undergo iterative chain extension and bromination to yield brominated dimer **36**.



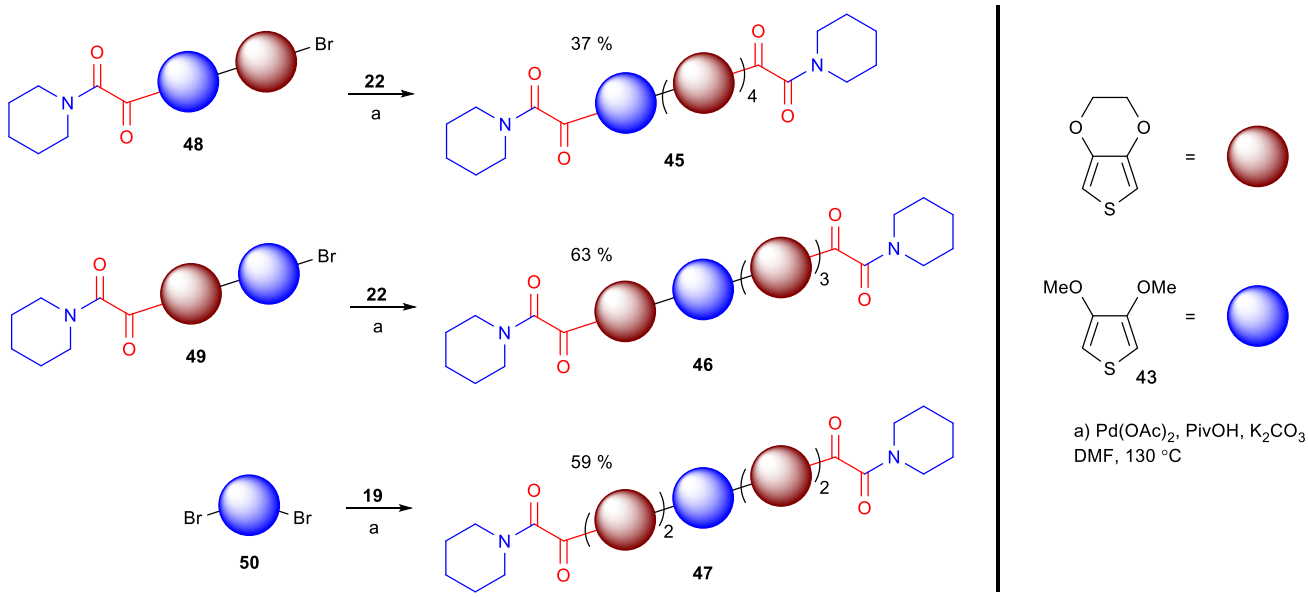
Scheme 3. Synthesis of orthogonal-ester functionalised hetero-bifunctional oligomers
(A) Synthesis of unsymmetrical, orthogonally protected oligo-EDOT diesters **37**-**40** with *iso*-propyl and *tert*-butyl end groups.
(B) Triethylene glycol ester capped tetra-EDOT **41** with improved solubility.

With these substrates in hand we were able to synthesise di-capped, orthogonally protected oligomers **37**-**40** with n = 2-5 in a short number of steps, in good yields (Scheme 3a, see SI Scheme S2 for full details). While the synthesis of tetramer **39** and pentamer **40** was confirmed by mass spectrometry, the propensity of the constructs to aggregate in solution prevented analysis by NMR. As an alternative, constructs possessing a solubility enhancing triethylene glycol chain could also be

produced as discussed above (**41**, Scheme 3b). Here, the significant difference in end-group polarity greatly aided purification, offering a potential means to enhance purity during particularly difficult separations. This representative example demonstrates an important advantage of the synthesis reported in this work - since the choice of end-group is an important determinant in the material properties of the synthesised constructs, factors such as the solubility of the material can be altered to reflect the desired application simply by choosing an appropriate end-cap.

Amide coupling following sequential ester deprotection, first in the presence of trifluoroacetic acid to remove the *tert*-butyl group, then sodium hydroxide to cleave the *iso*-propyl ester, allowed the subsequent synthesis of unsymmetrical constructs bearing reactive functionality for further modification (see SI Scheme S3). Due to the mild amide or ester forming conditions required, this method is applicable to the late-stage hetero-functionalisation of the oligomers reported with a wide-range of reactive or functional groups, such as those shown in Scheme 1. The potential applications of this methodology are diverse. The ability to create hetero-bifunctional oligomers of a tunable length, bearing handles for further modification, allows the modular synthesis of more complex structures. For example, the integration of such constructs into biologically active scaffolds[2] or the production of amphiphilic, self-assembling morphologies[44,45] offers exciting possibilities in the fields of both the material and bio-medical sciences.

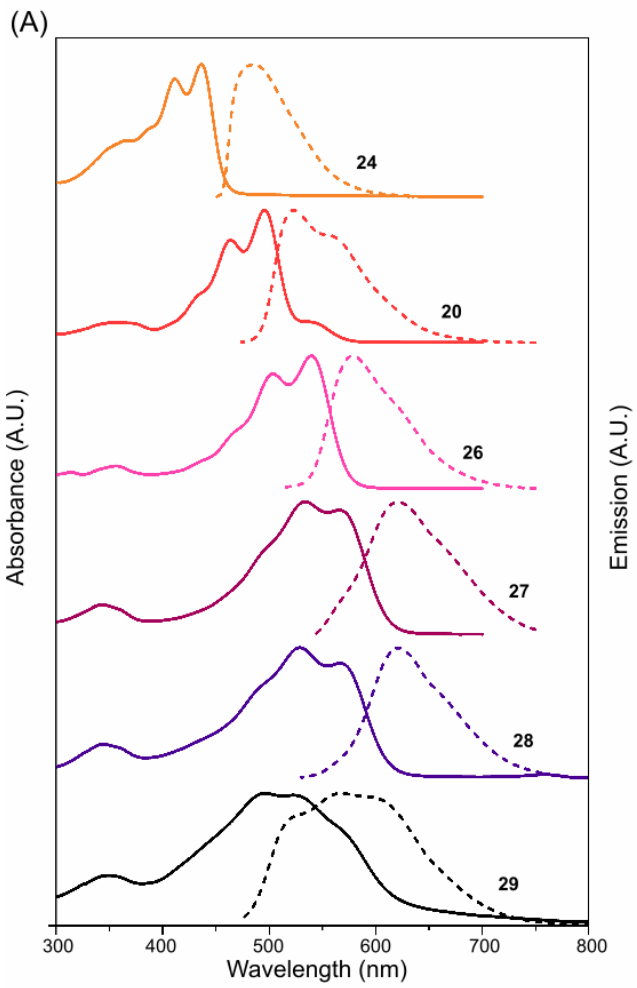
Finally, we wished to investigate the application of our methodology to the synthesis of mixed-oligomers, composed of different monomer units which may possess interesting properties. In particular, we considered the rigidity of EDOT-oligomers, which are known to lead to highly planar structures with enhanced π-conjugation.[23] We reasoned that by disrupting planarity in a controlled fashion, the properties of the resultant material could be tuned. Structurally related dialkoxythiophene monomers such as dimethoxythiophene (DMT, **43**) and 3,4-propylenedioxythiophene (ProDOT, **44**) were found to be suitable substrates for our glyoxylation and chain extension procedures. We therefore introduced a single DMT moiety in an EDOT-pentameric structure, in order to create three structural isomers **45**, **46** and **47** (Scheme 4, see SI Scheme S4 for full details). The simple manner in which such compounds can be created allows the rapid construction of a library of dialkoxythiophene-based constructs, in order to investigate the effects of structure, substituents and isomerisation on the chemical and electrical properties of CPs.

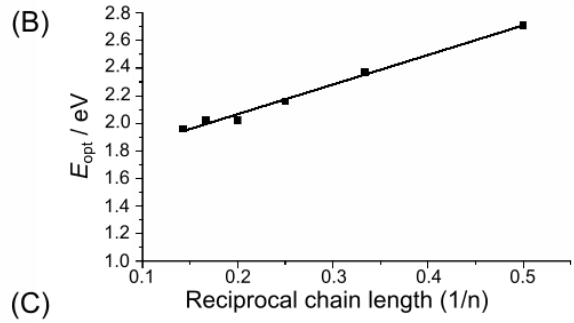


Scheme 4. Synthesis of dimethoxythiophene containing isomers
Pentameric EDOT-oligomers were synthesised containing a single DMT unit, to generate the structural isomers, **45**, **46**, and **47**.

Oligomer characterisation

Solutions of the di-piperidine capped oligomers described above (**24**, **20**, **26**-**29**) in DCM were analysed by UV-Vis and fluorescence spectroscopy. Within the range investigated the optical properties of the materials were found to be independent of concentration, indicating that aggregation was not occurring. As expected, a gradual red-shift in the onset of absorbance was observed with increasing chain length (Figure 2), though a blue-shift in absorbance maxima for heptamer **29** was observed likely due to the presence of impurities in the sample. Furthermore, the spectra possessed well-defined vibronic structures, a widely reported feature of EDOT oligomers not shared by unsubstituted thiophene structures.[21,23,46] When compared to the parent C-H capped oligomers biEDOT **51** and terEDOT **52**, mono-piperidine capped dimer **19** and trimer **22** displayed a large red-shift in absorbance (see SI Figure 1). This effect was even more pronounced for the di-capped oligomers **24** and **20**. A red shift in absorbance of > 100 nm indicated that conjugation of the thiophene core with the keto-acid end-group, to create an acceptor (A)-donor (D)-acceptor triad, played a major role in influencing the properties of the synthesised oligomers leading to a significant narrowing of the optical gap (E_{opt}).[47,48]





(C)

Entry	Compound	End-group	Monomer	Length	E_{opt}
1	**24**	Piperidine	EDOT	2	2.71 eV
2	**20**	Piperidine	EDOT	3	2.37 eV
3	**26**	Piperidine	EDOT	4	2.16 eV
4	**27**	Piperidine	EDOT	5	2.02 eV
5	**28**	Piperidine	EDOT	6	2.02 eV
6	**29**	Piperidine	EDOT	7	1.96 eV
7	**53**	-N*i*Pr$_2$	EDOT	5	2.02 eV
8	**54**	-NHBu	EDOT	5	1.92 eV
9	**55**	-O*i*Pr	EDOT	3	2.30 eV
10	**56**	-O*i*Pr	EDOT	5	1.88 eV
11	**45**	Piperidine	DMT/EDOT	5	2.03 eV
12	**46**	Piperidine	DMT/EDOT	5	2.06 eV
13	**47**	Piperidine	DMT/EDOT	5	2.08 eV
14	**57**	Piperidine	DMT	5	2.14 eV
15	**58**	Piperidine	ProDOT	5	2.09 eV

Figure 2. Oligomer optical characterisation
(A) Normalised UV-Vis (solid line) and fluorescence (dashed line) spectra of di-piperidine capped oligomers **24**, **20** and **26**-**29**.
(B) Correlation of inverse chain length and E_{opt} for oligomers **24**, **20** and **26**-**29**.
(C) Summary of E_{opt} for a series of di-functionalised oligomers.

When compared to previously reported EDOT end-capped oligomers, absorption was strongly red-shifted relative to the corresponding mesityl, phenyl, hexyl and

trimethylsilyl structures highlighted in Figure 1.[21–24] The remarkably low energy E_{opt} of the structures reported here is likely due to the lowering in energy of the lowest unoccupied molecular orbital (LUMO) as a result of the electron withdrawing nature of the keto-acid moiety, as discussed later. Oligomer capping with primary amines to yield secondary amides was found to result in a further lowering of E_{opt} (Figure 2C, entry 8). This effect was enhanced through capping with more electron poor ester groups, resulting in an E_{opt} as low as 1.88 eV for the *iso*-propyl ester di-capped pentamer **56** (Figure 2C, entry 10).

The constrained 6-membered ring of EDOT is known to result in favourable attractive intramolecular S-O interactions between repeating units.[23,49] This effect is reduced upon the introduction of the more structurally flexible methoxy units of DMT. Therefore, as predicted the introduction of a single DMT residue into an EDOT pentamer led to an increase in E_{opt} due to disruption of the highly planar EDOT repeating structure. This effect was found to be position dependent, with the longest continuous EDOT chain determining the degree of disruption. When compared to the pentaEDOT oligomer **27**, DMT containing isomer **45** (4 continuous residues) exhibited a ΔE_{opt} = +0.013 eV, while isomer **47** (2 continuous residues) possessed an increased ΔE_{opt} = +0.057 eV (Figure 2C, entries 11-13). This widening of the optical gap was further enhanced in an oligomer consisting of end-capped penta-DMT **57** (ΔE_{opt} = +0.122 eV), or the analogous penta-ProDOT oligomer **58** (ΔE_{opt} = + 0.44 eV) (Figure 2C, entries 14 and 15). These results support our hypothesis that the oligomer properties can be tuned through the suitable choice and positioning of alternative monomer units.

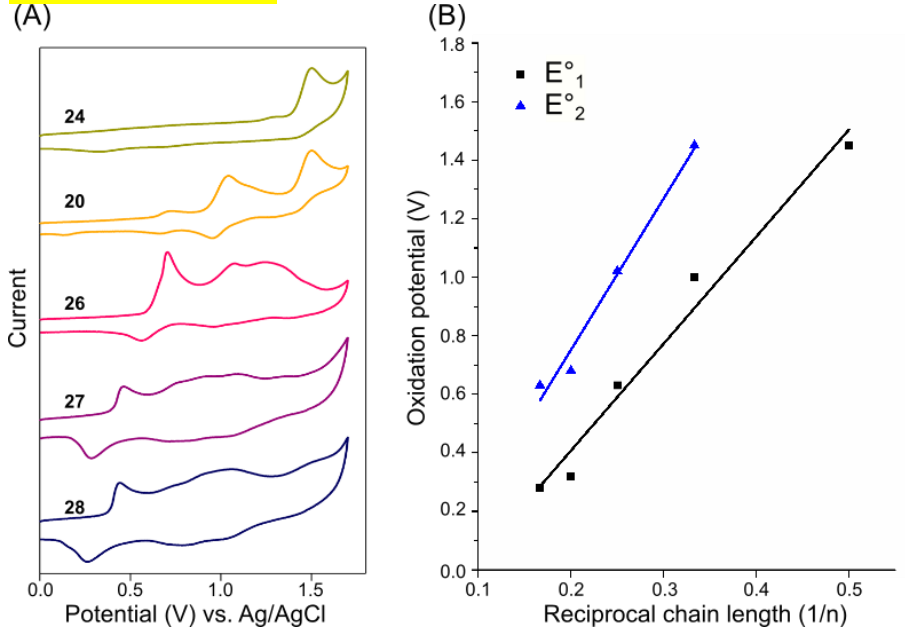


Figure 3. Cyclic voltammetry characterisation

(A) Cyclic voltammograms of piperidine capped oligomers **24**, **20** and **26**-**28**. CVs were recorded at a scan rate of 100 mV s^{-1} with oligomer concentrations of 1 mM in DCM containing 0.1 M Bu_4NPF_6.

(B) Correlation of inverse chain length and 1st/2nd oxidation potentials for oligomers **24**, **20** and **26**-**28**.

Next, we investigated the solution electrochemical properties of selected oligomers by cyclic voltammetry. Di-piperidine capped oligomers **24**, **20** and **26**-**28** (n = 2-6) were all investigated. However, due to the low solubility of EDOT-heptamer **29** and its reduced purity, weak signal intensity was observed during measurements and therefore this structure was not further investigated. Cyclic voltammograms (CVs) demonstrate a decrease in the first oxidation potential with increasing chain length, supporting the results obtained by UV-Vis spectroscopy (Figure 3A). Linear correlations were found between the first and second oxidation potentials, and the inverse chain length (Figure 3B). The oxidation of oligomers **24**, **20,** and **26** (n = 2-4) were electrochemically quasi-reversible, with pentamer **27** and hexamer **28** displaying improved electrochemical reversibility (Figure 3). Furthermore, CVs of penta-DMT **57** and penta-ProDOT **58** allowed comparison to penta-EDOT **27** (see SI

Figure 2). As was seen for the optical gap, the first oxidation potential was found to follow the trend EDOT < ProDOT < DMT. These results further support the higher effective conjugation of EDOT oligomers, and a degree of planarity disruption induced by the high torsional strain of DMT based structures.[50] The ease with which the oxidation potentials can be tuned, both through alteration of oligomer length and monomer composition, offers intriguing possibilities for applications not only in tissue engineering, but also in creating sensitive and selective organic bioelectronics.[51,52]
Finally, we undertook computational density functional theory (DFT) calculations to further probe the influence of the keto-acid end-groups on oligomer properties.[53] The trends observed in the calculated HOMO-LUMO gaps during these studies reproduced the structural and length dependencies observed during experimental measurements. Initial calculations on carboxy-terminated EDOT pentamer **59** validated our hypothesis that the keto-acid end-group played an important role in extending π-conjugation (Figure 4). This was particularly true for the LUMO, with the electron-withdrawing nature of the end-group leading to a large orbital localisation across the ketone group. Partial distribution of the LUMO across the terminal carboxyl indicated that the choice of an ester or amide linkage may influence the electrical properties of oligomeric constructs. Thus, the presence of a more electron-deficient ester group would be expected to lead to a lowering of the LUMO level when compared to an analogous amide substrate, leading to a decreased HOMO-LUMO gap (see SI Figure 3). This supports our experimental observation of a decreased E_{opt} for *iso*-propyl ester di-capped oligomers when compared to amide-capped structures.

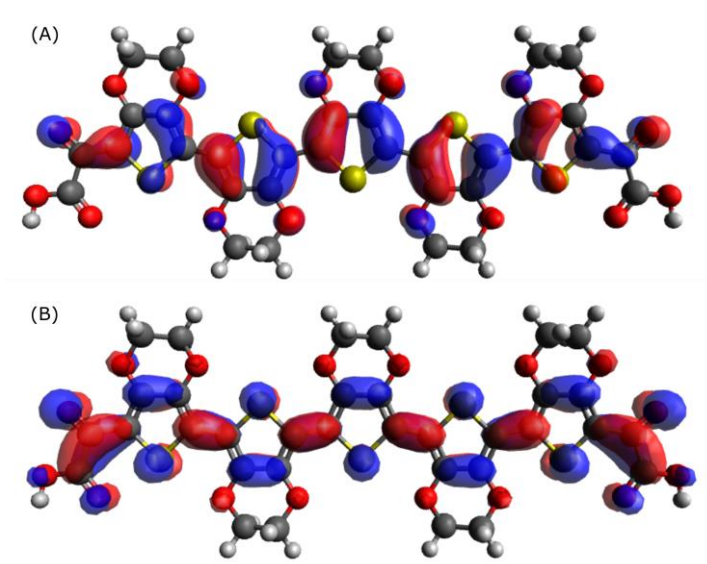


Figure 4. DFT orbital projections
(A) HOMO orbital distribution of carboxy-capped pentamer **59**.
(B) LUMO orbital distribution.

DFT also provided rationale for the increase in E_{opt} observed for tertiary amide capped structures. In order to accommodate the steric bulk of both the piperidine and diisopropylamine substituents, the dicarbonyl groups were found to be significantly disrupted from the antiperiplanar orientation observed for other substituents. This led to dihedral angles of as little as 131 ° for diisopropyl capped dimer **60** and 142 ° for piperidine capped dimer **24** (see SI Figure 4). As a result conjugation was partially disrupted leading to an increase in the HOMO-LUMO gap, supporting the observed increase in E_{opt}. Replacement of EDOT with DMT or ProDOT offered 2 different mechanisms through which disruption of the expected planar configuration could potentially occur. In the case of DMT, the high torsional strain of consecutive units was found to lead to a slight twisting of the backbone for longer oligomer structures, therefore decreasing effective conjugation. In contrast, calculations predicted a slight deflection of the alkoxy-substituents in the ProDOT structure (174 ° vs. 180 ° dihedral angle in EDOT and DMT) in order to

accommodate an expanded 7-membered ring. The resultant cumulative decrease in electron-donation from these substituents may explain the slight increase in E_{opt} observed for the ProDOT derivatives described above.

Conclusion

We have developed a novel end-capping strategy which allows the rapid installation of keto-amides and keto-esters at the end of oligomeric-EDOT chains. The resultant materials retain solubility and are bench stable, in contrast to previous reports of oligo-EDOT derivatives. These developments allow us to report, for the first time, the synthesis of hexa- and hepta-meric EDOT constructs. Furthermore, the use of iterative chain extension allows the construction of hetero-bifunctional constructs, bearing orthogonally reactive handles for further modification. Characterisation of the structures produced demonstrated the important role played by the keto-acid end-group in determining oligomer properties. The remarkably low optical gap observed for the oligomeric structures was attributed to the important role played by the extended conjugated system, and particularly lowering of the LUMO energy as demonstrated by DFT calculations. Notably, through suitable choice of oligomer length, end-group, and monomer composition, the optical, electronic, and physical properties of a construct can be readily tuned, both across a wide range and with fine control. This ability to undertake a flexible and modular approach to structural design creates intriguing opportunities in the synthesis of novel materials. Work to explore the full possibilities of this powerful methodology is currently ongoing in our group for the integration of tunable conjugated materials into tissue engineering scaffolds.

EXPERIMENTAL PROCDURES

General method for EDOT glyoxylation

Oxalyl chloride (850 µL, 10 mmol) was added drop-wise to a solution of EDOT (1.05 mL, 10 mmol) in dioxane (30 mL). The mixture was heated to 100 ºC for 1 hr then allowed to cool to room temperature. The requisite amine (15 mmol) and base (50 mmol) were then added and the mixture stirred for 3 hrs. After this time the mixture was diluted with DCM (150 mL), washed with water (100 mL), and the organics dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography and pure fractions were concentrated *in vacuo*.

General method for monomer bromination

EDOT derivative (5 mmol) was dissolved in a mixture of THF (5 mL) and acetic acid (3 mL). If solubility was poor a further 25 mL of THF was added. The mixture was placed in the dark and *N*-bromosuccinimide (6 mmol) was added. After stirring for 2 hrs the mixture was either precipitated in water (150 mL), causing precipitation of the product which could be collected by filtration, or diluted with DCM (150 mL) and washed with sat. $NaHCO_3$ (3 x 100 mL), dried with $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography was then undertaken if required, though the products were usually sufficiently pure for further use.

General method for chain extension

Brominated monomer (1 mmol), pivalic acid (0.5 mmol), palladium (II) acetate (0.05 mmol) and potassium carbonate (10 mmol) were charged under nitrogen. Dry DMF (2 mL) and EDOT (4 mmol) were then added and the mixture heated to 90 ºC for 2 hrs. After cooling to rt the mixture was diluted with DCM (50 mL) and washed with water (2 x 50 mL) and brine (50 mL). The organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography and pure fractions were concentrated *in vacuo*.

General method for oligomer synthesis

Brominated oligomer (1 mmol), hydrogen-capped oligomer (1.2 mmol), pivalic acid (0.5 mmol), palladium (II) acetate (0.05 mmol) and potassium carbonate (10 mmol) were charged under nitrogen. Dry DMF (2 mL) was added and the mixture heated to 90 ºC for 2 hrs. After cooling to rt the mixture was diluted with DCM (50 mL) and washed with water (2 x 50 mL) and brine (50 mL). The organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography and pure fractions were concentrated *in vacuo*.

SUPPLEMENTAL INFORMATION

Supplemental Information includes 4 supplemental figures, 1 supplemental table, 4 supplemental schemes, full experimental details and characterisation, and NMR spectra of all novel compounds. Also included is a table detailing all compound labels and structures.

AUTHOR CONTRIBUTIONS

C.D.S. performed all experiments and wrote the manuscript. M.B performed CV measurements. A.A. performed UV-Vis measurements. C.D.S., M.B., A.A., and C.B.N. analysed and interpreted data. C.D.S., D.M., and M.M.S. developed the ideas. All authors commented on the manuscript. M.M.S. supervised the project.

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