Rationalisation of Patterns of Competing Reactivity by X-ray Structure Determination: Reaction of Isomeric (Benzyloxythienyl)oxazolines with a Base

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Abstract: Three isomeric (benzyloxythienyl)oxazolines 9, 11 and 13 have been prepared and are found, upon treatment with a strong base, to undergo either Wittig rearrangement or intramolecular attack of the benzylic anion on the oxazoline function to give products derived from cleavage of the initially formed 3-aminothienofuran products. This pattern of reactivity is directly linked to the distance between the two reactive groups as determined by X-ray diffraction, with the greatest distance in 11 leading to exclusive Wittig rearrangement, the shortest distance in 13 giving exclusively cyclisation-derived products, and the intermediate distance in 9 leading to both processes being observed. The corresponding N-butyl amides were also obtained in two cases and one of these undergoes efficient Wittig rearrangement leading to a thieno[2,3-c]pyrrolole product.

Keywords: oxazoline; Wittig rearrangement; thiophene; thieno[2,3-c]pyrrole; X-ray structure

1. Introduction

Some time ago we described the reaction of 2-(2-benzyloxyphenyl)oxazoline 1 with a strong base to give either the 3-aminobenzofuran product 2 resulting from intramolecular nucleophilic ring-opening of the oxazoline by the benzylic anion, or the oxazoline 3 in which the benzyloxy group has undergone a Wittig rearrangement (Scheme 1) [1]. Heterocycle formation by cyclisation of an aryloxy carbocation onto an ortho functional group is rather uncommon but formation of 3-aminobenzofurans by the so-called Gewald reaction of benzonitriles provides one example [2]. Similarly, although the Wittig rearrangement has been known for almost a century [3], it is not commonly used in synthesis and a recent review shows rather limited developments over the last 20 years [4]. While the aminobenzofuran formation could be optimised by using 3.3 equiv. of Schlosser’s base (n-BuLi/t-BuOK) and applied to a number of substituted examples [1], the Wittig rearrangement process was not so favourable and, under optimal conditions of 2.2 equiv. n-butyllithium (n-BuLi) in THF, an isolated yield of just 29% was obtained. As will shortly be reported elsewhere, the N-butyl amide group is a more effective promoter of the Wittig rearrangement and treating compound 4 with 3.3 equiv. n-BuLi in THF gives almost entirely the rearranged product 5, conveniently isolated as the phthalide 6 after acetic-mediated cyclisation in 90% yield. However in the latter study, simply changing to the N,N-diisopropyl amide 7 and treating with 2.2 equiv. n-BuLi in toluene again resulted in cyclisation to give the 3-aminobenzofuran 8. It is clear from these studies that there is a delicate balance between Wittig rearrangement of the benzyloxy group without affecting the adjacent activating group, and interaction of the two groups with the formation of a furan ring.
In contrast to the symmetrical benzene ring, the different adjacent positions on a heterocycle such as thiophene are not equivalent and so a more interesting pattern of reactivity can be expected, which would also lead to some unusual and novel heterocyclic products. In this paper, we report the synthesis, characterisation and reactivity upon treatment with a strong base, of the three isomeric (benzyloxythienyl)oxazolines 9, 11 and 13 (Scheme 2) as well as the corresponding (benzyloxythienyl)-N-butylcarboxamides 10, 12 and 14. As well as examining the pattern of reactivity we were interested to discover whether there was any correlation between this and the distance between the two adjacent groups as determined by X-ray diffraction.

2. Results

2.1. Synthesis of 3-Benzylxoy-2-thienyl Systems 9 and 10

O-Benzylolation of the commercially available methyl ester 15 followed by ester hydrolysis of 16 gave the carboxylic acid 17 (Scheme 3). This was readily converted into the corresponding acid chloride which was reacted immediately with 2-amino-2-methylpropan-1-ol to give the hydroxy amide 18, which was cyclised using thionyl chloride to give the target oxazoline 9 in good overall yield. Alternatively, treating acid 17 with thionyl chloride followed by an excess of butylamine gave the target amide 10 also in high yield.

Scheme 1. Competition between Wittig rearrangement and cyclisation in benzene-based systems.

Scheme 2. The six isomeric thiophene compounds targeted for reactivity studies.

Scheme 3.
unusual morpholine-containing thiophenone as compared to extra oxygen atom.

Scheme 3. Synthesis of 3-benzyloxy-2-thienyl compounds 9 and 10.

2.2. Reaction 3-Benzyloxy-2-thienyl Systems 9 and 10 with Base

When compound 9 was subjected to the same conditions used to convert 1 into 2, a mixture of two products was formed which were separated by preparative thin-layer chromatography (TLC) on alumina and identified as the expected Wittig rearrangement product 19, formed in 8% yield, and a second more major product (43%) which was initially thought to be the expected cyclisation product 21 (Scheme 4). However certain features of the spectra were not consistent with this, notably the non-equivalence of the two methyl groups and CH$_2$O hydrogens which suggested the presence of a stereogenic centre. After further evidence from $^{13}$C and 2D NMR studies suggested the presence of a 2-alkylidenethiophen-3(2H)-one structure, and the HRMS result showed the presence of an extra oxygen atom as compared to 21, the actual structure was finally confirmed as the unusual morpholine-containing thiophenone 20 by X-ray diffraction.

Scheme 4. Reaction of oxazoline 9 with n-BuLi/1-BuOK.

The molecular structure of 20 features two independent molecules in the unit cell in addition to one molecule each of CH$_2$Cl$_2$ and acetone. The two molecules are actually enantiomers and they both take up half chair conformations with the ring oxygen out of the plane, the NH in the plane and one methyl axial and one equatorial (Figure 1). Where they differ is that one has phenyl axial and OH equatorial while for the other it is the opposite way round.

In the crystal, there is hydrogen bonding both intramolecularly between the NH and C=O and intermolecularly between C=O and OH; in terms of the Etter–Bernstein graph-set descriptors [5] $C^1_1$(7) [S(6)]. The intermolecular interaction involves the two enantiomeric molecules alternating and the pattern is shown schematically in Figure 2 with parameters in Table 1.
Once the structure of 20 was clear, its formation could be rationalised as shown in Scheme 4 by initial cyclisation of 9 to give the thieno[3,2-b]furan product 21 and hydrolysis of this on the alumina with opening of the furan ring to give 22, which in its thiophen-3-one tautomeric form can be oxidised by air to form the favourable fully conjugated enedione structure 24, which then cyclises to form the cyclic hemiketal 20. It should be noted that compound 20 was found to be quite unstable and although it was isolated in small amount with sufficient purity for identification, further attempts at purification resulted in decomposition. As described in a recent review [6], thiophene-based o-quinomethane analogues have a rich and varied chemistry, however, the formation of such a structure by hydrolysis then oxidation of a thieno[3,2-b]furan is unprecedented.

We now turned to the N-butyl amide 10 and found a much simpler pattern of reactivity. Treatment of 10 with n-BuLi under the standard conditions developed in the benzene series, resulted in exclusive Wittig rearrangement to give secondary alcohol 25 which could be characterised spectroscopically but was converted for isolation into the stable thieno[2,3-c]pyrrolone product 26 by treatment with p-toluenesulfonic acid in boiling toluene (Scheme 5) [7]. This method was also used to obtain stable cyclic products in the benzene-based systems, however, note that while 5 and analogues cyclise to lactones 6 with loss of butylamine, here we have a loss of water to form the lactam in excellent yield. The synthesis and chemistry of thieno[c]pyrrolones and their dihydro analogues has been recently reviewed [8].

Since such fused-ring heterocycles are rather uncommon we took the chance to determine the X-ray structure of compound 26 (Scheme 5). Only one previous X-ray structure of a compound with this ring system appears to have been published, that of the compound with butyl replaced by quinolin-8-yl [9], but the molecular dimensions are very similar. Interestingly the tert-butyl amide 27 isomeric with 25 has been prepared by ortho-directed metalation of N-tert-butylthiophene-2-carboxamide with n-BuLi followed by reaction with benzaldehyde [10].
2.3. Synthesis of 2-Benzyl氧-3-thienyl Systems 11 and 12

Entry to this system was gained by starting with the 3-thienyloxazoline 28 and introducing oxygen functionality at the 2-position by lithiation and treatment with bis(trimethylsilyl) peroxide (Scheme 6). As we have described in detail elsewhere [11], the resulting product had the 3-(oxazolin-2-ylidene)thiophen-2-one structure 29 which exhibited an interesting and varied pattern of reactivity. However, for the present purpose, it could be cleanly O-benzylated in moderate yield to give the desired compound 11.

As described below, attempted application of a similar method to the formation of the amide 12 failed since lithiation of the corresponding N-butyl amide 32 followed by treatment with bis(trimethylsilyl) peroxide instead gave the silyl compound 33.

2.4. Reaction of 2-Benzyl氧-3-thienyl Systems 11 and 12 with Base

Treatment of oxazoline 11 with n-BuLi under the standard conditions developed for ring closure of 1 to give 2 gave exclusively the Wittig rearrangement product 30 in good yield (Scheme 7).

Although attempts to prepare the amide 12 by lithiation and bis(trimethylsilyl) peroxide treatment failed, instead giving the new silane 33 (Scheme 8), the expected Wittig rearrangement product from 12, compound 34, was prepared by lithiation and benzaldehyde treatment of 32. It was not isolated, however, the reaction product was directly treated with p-toluenesulfonic acid giving the thieno[2,3-c]pyrrole [8] product 35 isomeric with 26 together with a low yield of the oxidation product 36. This last product showed extra signals in the $^{13}$C NMR spectrum due to amide rotamers (Supplementary Materials).
2.5. Synthesis of 4-Benzylthoxo-3-thienyl Systems 13 and 14

Synthesis of the required compounds in this series was more challenging since suitably substituted thiophene starting materials are not commercially available. Instead, we had to resort to a ring-synthesis of a thiophene with the desired functionality in place. This started from the sulfide-containing diester 37 prepared by conjugate addition of methyl thioglycolate to methyl acrylate [12], which underwent base-induced ring closure [13] to give compound 38 in low yield (Scheme 9). Aromatisation of this was achieved using sulfuryl chloride [14] to give the thiophene ester 39. Conversion of this into the required benzyl ether 41 proved to be more difficult than expected. Simple alkylation using benzyl bromide and either potassium carbonate or sodium hydride resulted in polymerisation and reaction with phenyldiazomethane [15] also failed.

Following a literature report that reaction of the 4-acetoxy compound 40 with ethanol and sulfuric acid gave the 4-ethoxy compound [15], this compound was prepared by reaction of 38 with isopropenyl acetate followed by sulfuryl chloride, but the treatment of this with benzyl alcohol and sulfuric acid again resulted in polymerisation. Access to 41 was finally achieved, albeit in low yield, by resorting to treatment with benzyl bromide in the presence of silver oxide in a process reminiscent of the Purdie–Irvine method for methylation of sugars developed in St Andrews over 100 years ago [16]. With the key intermediate 41 in hand, the remaining synthetic steps proceeded without incident: hydrolysis gave the acid 42 which was converted into its acid chloride and then reacted
either with 2-amino-2-methylpropan-1-ol to give amide 43 which was cyclised with thionyl chloride to oxazoline 13, or with butylamine to directly afford the amide 14.

2.6. Reaction of 4-Benzoyloxy-3-thienyl Systems 13 and 14 with Base

Treatment of oxazoline 13 with 3.3 equiv. of Schlosser’s base gave largely unretracted starting material, however, increasing this to 4.4 equiv. did give a reaction and after chromatographic purification, the 4-benzoyloxy-3-thienyl amide 45 was isolated in moderate yield (Scheme 10). This is evidently formed by air oxidation of the expected cyclisation product, the 3-aminothieno[3,4-b]furan 44. As shown in our previous work [1], such ring-fused 3-aminofuran products are susceptible to oxidative ring-cleavage.

![Scheme 10. Base-induced cyclisation and oxidative ring opening of 13.](image)

The reaction of the corresponding N-butyl amide 14 with n-BuLi under the conditions required for Wittig rearrangement gave largely unreacted starting material and the only new products isolated in low yield after chromatographic purification (Scheme 11) were the 2,3,4-trisubstituted thiophene 46 together with the debenzylated compound 47 which was found to exist in solution as a mixture with the thiophen-3(2H)-one tautomer 47a (see Section 3). It seems likely that the products have resulted from the intermolecular reaction between two carbanions derived from 14 but in view of their very low yield this process was not investigated further. Products 45, 46 and 47 which were isolated in low amounts following one or two stages of chromatography were found to decompose upon attempted further purification.

![Scheme 11. Reaction of amide 14 with strong base.](image)

To summarise the reactivity of the isomeric systems, oxazoline 11 underwent exclusive Wittig rearrangement and oxazoline 13 gave products derived from cyclisation, while for 9 Wittig rearrangement was observed as a minor process with the major product derived from cyclisation. The N-butyl amides gave a less complete picture with 10 undergoing exclusive Wittig rearrangement in high yield, 12 not being available for investigation (although its expected Wittig rearrangement product was obtained by other means), and 14 remaining largely unreacted under the conditions. In the case of the three isomeric oxazolines, each compound was obtained as good quality crystals suitable for X-ray diffraction and so it was decided to determine their molecular structures to examine whether there might be a direct link between the distance between the benzoyloxy and oxazoline groups and the observed reactivity. All three compounds gave structures with the monoclinic P2₁/c space group and these are shown in a similar orientation in Figure 3.

For the intramolecular cyclisation to compete with Wittig rearrangement, the key distance is that between benzoyloxy carbionion carbon and C-2 of the oxazoline. Since the benzoyloxy groups have rotated to place this carbon pointing away from the oxazoline in each case, the benzoyloxy oxygen is taken as a reference point and it can be seen that the molecular geometry correlates well with the observed reactivity. Thus, for 11, the benzoyloxy group is too far away (3.046(1) Å) for cyclisation and we observe exclusively
a Wittig rearrangement, for 13 the benzyloxy group is much closer (2.945(1) Å) and only products derived from cyclisation are observed, while in 9 we have an intermediate situation (3.006(3) Å) and mainly cyclisation-derived products are observed but with a little Wittig rearrangement.

![Figure 3. Molecular structures of 9, 11 and 13 showing angles (°) and benzyloxy O to oxazoline C(2) distance (Å).](image)

3. Experimental

3.1. General Experimental Details

NMR spectra were recorded on solutions in CDCl$_3$ unless otherwise stated using Bruker instruments and chemical shifts are given in ppm to high frequency from Me$_4$Si with coupling constants $J$ in Hz. IR spectra were recorded using the ATR technique on a Shimadzu IRAffinity 1S instrument. The ionisation method used for high-resolution mass spectra is noted in each case. Column chromatography was carried out using silica gel of 40–63 mm particle size and preparative TLC was carried out using 1.0 mm layers of Merck alumina 60G containing 0.5% Woelm fluorescent green indicator on glass plates. Melting points were recorded on a Gallenkamp 50W melting point apparatus or a Reichert hot-stage microscope.

3.2. Preparation and Reactions of 3-Benzzyloxy-2-thienyl Systems

3.2.1. Methyl 3-(Benzyloxy)thiophene-2-carboxylate 16

A literature procedure [17] was modified as follows: benzyl bromide (11.9 cm$^3$, 17.11 g, 0.100 mol) was added to a stirred mixture of methyl 3-hydroxythiophene-2-carboxylate 15 (15.85 g, 0.100 mol) and potassium carbonate (27.60 g, 0.200 mol) in acetone (50 cm$^3$) and the reaction mixture was heated at reflux for 18 h. After cooling to rt, the inorganic salts were removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (150 cm$^3$) and washed with water (100 cm$^3$) before being dried and evaporated. The crude residue was recrystallised (aq. MeOH) to give 16 (18.94 g, 76%) as pale yellow crystals; mp 69–72 °C; (lit. [17] 66–67 °C); $R_f$ (Merck alumina 60G) 0.51; $R_f$ (alumina 60G containing 0.5% Woelm fluorescent green indicator on glass plates) 0.54; IR (KBr) 3422, 3090, 2920, 1720, 1621, 1547, 1380, 1230 cm$^{-1}$; $^1$H NMR spectral data were in accordance with those previously reported [17].

3.2.2. 3-(Benzyloxy)thiophene-2-carboxylic Acid 17

Following a literature procedure [17], a mixture of methyl 3-(benzyloxy)thiophene-2-carboxylate 16 (18.40 g, 74.1 mmol) and sodium hydroxide (5.99 g, 0.150 mol) in water (18.94 g, 76%) was heated at reflux for 2.5 h. After cooling to rt, the aqueous layer was washed with CH$_2$Cl$_2$ (2 × 50 cm$^3$) before being acidified to pH 1 by the addition of 2 M HCl. The resultant suspension was extracted with CH$_2$Cl$_2$ (2 × 100 cm$^3$) and the combined organic
layers were dried and evaporated. The crude residue was recrystallised (aq. MeOH) to give 17 (15.07 g, 87%) as tan-coloured crystals; mp 122–125 °C; (lit. [17] 125–126 °C); δH (400 MHz, CD2SOCD2) 12.49 (1H, br s, CO2H), 7.74 (1H, d, J 5.6, 5-H), 7.48–7.45 (2H, m, Ph), 7.41–7.37 (2H, m, Ph), 7.35–7.30 (1H, m, Ph), 7.14 (1H, d, J 5.6, 4-H) and 5.25 (2H, s, CH2); δC (100 MHz, CD2SOCD2): 162.4 (C), 160.1 (C), 136.8 (C), 128.4 (2CH), 127.9 (CH), 127.3 (2CH), 118.5 (Ar CH), 110.5 (C) and 72.4 (CH2). The 1H NMR spectral data were in accordance with those previously reported [17]. 13C NMR data are reported for the first time.

3.2.3. 3-(Benzyloxy)-N-(1-hydroxy-2-methylpropan-2-yl)thiophene-2-carboxamide 18

Oxalyl chloride (3.0 cm3, 34.8 mmol) was added dropwise to a solution of 3-(benzyloxy)thiophene-2-carboxylic acid 17 (4.00 g, 17.1 mmol) and in Et2O (25 cm3) and the mixture was stirred for 18 h. Evaporation gave 3-(benzyloxy)thiophene-2-carbonyl chloride as a brown oil which was used without further purification.

A solution of 3-(benzyloxy)thiophene-2-carbonyl chloride (assuming 17.1 mmol) in CH2Cl2 (40 cm3) was added dropwise to a solution of 2-amino-2-methylpropan-1-ol (3.10 g, 34.8 mmol) in CH2Cl2 (40 cm3) stirred at 0 °C. After the addition, the mixture was allowed to warm to rt and stirred for 18 h before being poured into water. The organic layer was separated and the aqueous layer was extracted with CH2Cl2 (30 cm3). The combined organic layers were washed successively with 2M HCl, 2M NaOH and water before being dried and evaporated to give 18 (5.14 g, 99%) as a pale yellow solid which was used without further purification; mp 122–125 °C; νmax/cm−1 3358, 3065, 2968, 1626, 1531, 1425, 1240, 1057, 777, 704 and 600; δH (500 MHz) 7.43–7.40 (6H, m, NH and Ph), 7.41 (1H, d, J 5.5, 5-H), 6.93 (1H, d, J 5.5, 4-H), 5.18 (2H, s, OCH2Ph), 3.58 (2H, s, CH2OH) and 1.19 (6H, s, CH3); δC (125 MHz) 162.5 (C), 157.3 (C), 136.8 (C), 128.4 (2CH), 127.9 (CH), 127.3 (2CH), 118.5 (CH), 116.2 (CH), 74.1 (CH2), 70.9 (CH2), 56.3 (CH2), and 24.8 (2CH3); HRMS (ESI+): found 306.1150. C16H20NO3S (M + H) requires 306.1158.

3.2.4. 2-(3-(Benzyloxy)thiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole 9

Thionyl chloride (1.4 cm3, 22.8 g, 19.2 mmol) was added to a solution of 3-(benzyloxy)-N-(1-hydroxy-2-methylpropan-2-yl)thiophene-2-carboxamide 18 (4.71 g, 15.4 mmol) in CH2Cl2 (50 cm3) and the mixture was stirred at room temperature for 18 h. The mixture was washed with 2M NaOH and water before being dried and evaporated to give 9 (4.01 g, 90%) as a pale brown oil which solidified on standing as a tan-coloured solid; mp 65–68 °C; νmax/cm−1 3308, 2965, 1632, 1545, 1260, 1251, 1209, 1026, 766 and 745; δH (500 MHz) 7.45–7.42 (2H, m, Ph), 7.37–7.33 (2H, m, Ph), 7.31–7.27 (1H, m, Ph), 7.24 (1H, d, J 5.5, 5-H), 6.78 (1H, d, J 5.5, 4-H), 5.24 (2H, s, OCH2Ph), 4.09 (2H, s, OCH2), and 1.38 (6H, s, CH3) δC (125 MHz) 157.6 (C), 157.3 (C), 136.8 (C), 128.4 (2CH), 127.8 (2CH), 126.9 (2CH), 118.1 (CH), 108.9 (C), 79.2 (CH2), 73.4 (CH2), 67.1 (CH2), and 28.3 (2CH3); HRMS (ESI+): found 288.1047. C16H18NO2S (M + H) requires 288.1053.

3.2.5. 3-(Benzyloxy)-N-butylthiophene-2-carboxamide 10

Thionyl chloride (2.5 cm3, 43.4 g, 34.3 mmol) was added to a suspension of 3-(benzyloxy)thiophene-2-carboxylic acid 17 (4.00 g, 17.1 mmol) in toluene (30 cm3) and the mixture was heated under reflux for 3 h. After cooling to room temperature, the mixture was evaporated to give 3-(benzyloxy)thiophene-2-carbonyl chloride as a brown oil which was used without further purification.

A solution of 3-(benzyloxy)thiophene-2-carbonyl chloride (assuming 17.1 mmol) in toluene (30 cm3) was added dropwise to a solution of n-butylamine (5.1 cm3, 3.77 g, 51.6 mmol) in toluene (10 cm3) stirred at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to room temperature over 1 h before being poured into water. The organic layer was separated and washed with 2M NaOH and brine, dried and evaporated to give, after purification by column chromatography (SiO2, Et2O/hexane 7:3), at Rf 0.65, 10 (4.49 g, 91%) as an orange oil; νmax/cm−1 3364, 2961, 1628, 1558, 1435, 1364,
1310, 1074, 976, 773 and 606; δ\text{H} (500 MHz) 7.43–7.38 (5H, m, Ph), 7.36 (1H, d, J 5.5, 5-H), 7.19 (1H, br s, NH), 6.89 (1H, d, J 5.5, 4-H), 5.19 (2H, s, OCH\text{2}), 3.36 (2H, td, J 7.0, 5.5, NCH\text{2}), 1.47–1.41 (2H, m, NCH\text{2}CH\text{2}), 1.28–1.20 (2H, m, CH\text{2}CH\text{3}) and 0.85 (3H, t, J 7.5, CH\text{3}); δ\text{C} (125 MHz) 161.7 (C), 154.9 (C), 153.6 (C), 128.4 (2CH), 128.76 (CH), 128.5 (CH), 127.7 (2CH), 118.1 (C), 116.2 (CH), 73.9 (OCH\text{2}), 38.9 (NCH\text{2}), 31.5 (CH\text{2}), 20.0 (CH\text{2}) and 13.7 (CH\text{3}); HRMS (ESI\text{*}): found 312.1017. C\text{16}\text{H}_{15}\text{NaNO\text{2}S} (M + Na) requires 312.1029.

3.2.6. (2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)thiophen-3-yl)(phenyl)methanol 19 and (E)-2-(2-Hydroxy-5,5-dimethyl-2-phenylmorpholin-3-ylidene)thiophen-3(2H)-one 20

Under a nitrogen atmosphere, n-butyllithium (2.5 M in hexanes, 0.66 mmol) was added to a stirred mixture of 2-(3-(benzyloxy)thiophen-2-yl)-4,4-dimethyl-4,5-dihydrooxazole 9 (0.1440 g, 0.50 mmol) and potassium tert-butoxide (0.1850 g, 1.65 mmol) in dry THF (5 cm\text{3}). The mixture was stirred at rt for 2 h before being quenched by the addition of saturated aq. NH\text{4}Cl and extracted with Et\text{2}O (3 × 10 cm\text{3}). The combined extracts were dried and evaporated to give, after purification by preparative TLC (Al\text{2}O\text{3}, Et\text{2}O/hexane 7:3), at R\text{f} 0.65, 19 (12 mg, 8%) as an orange oil; δ\text{H} (400 MHz) 7.42–7.38 (2H, m, Ph), 7.34–7.30 (3H, m, ArH and Ph), 7.28–7.23 (1H, m, Ph), 6.71 (1H, d, J 5.2, ArH), 6.02 (1H, s, CHO\text{H}), 4.11 and 4.09 (2H, AB pattern, J 8.2, CH\text{2}), 1.40 (3H, s, CH\text{3}) and 1.27 (3H, s, CH\text{3}); δ\text{C} (125 MHz) 158.6 (C), 150.4 (C), 142.8 (C), 130.1 (CH), 128.2 (CH), 128.0 (2CH), 127.1 (CH), 126.5 (2CH), 124.7 (C), 79.5 (CH\text{2}), 70.9 (CHO\text{H}), 68.1 (CM\text{E}\text{2}), 28.3 (CH\text{3}) and 28.1 (CH\text{3}). The \text{1}H NMR spectral data were consistent with those previously reported [18]. 13C NMR data are reported for the first time.

This was followed by a second fraction, at R\text{f} 0.15, to give 20 (64.5 mg, 42%) in slightly impure form as brown crystals; mp 103–105 °C; ν\text{max}/cm\text{–1} 1582, 1537, 1449, 1317, 1260, 1221, 1067, 768, 698 and 669; δ\text{H} (400 MHz, CD\text{3}CO\text{CD}\text{3}) 7.65–7.62 (2H, m, Ph), 7.52 (1H, d, J 5.6, 5-H), 7.40–7.35 (3H, m, Ph), 6.32 (1H, d, J 5.6, 4-H), 4.12 and 3.69 (2H, AB pattern, J 11.6, CH\text{2}), 3.06 (2H, br s, OH and NH), 1.53 (3H, s, CH\text{3}) and 1.39 (3H, s, CH\text{3}); δ\text{C} (125 MHz, CD\text{3}CO\text{CD}\text{3}) 182.1 (C=O), 162.7 (C), 141.5 (C), 138.5 (CH\text{3}), 129.5 (CH\text{3}), 128.6 (2CH), 127.6 (2CH), 122.1 (CH), 103.5 (C), 95.0 (C), 68.3 (CH\text{2}), 51.4 (CM\text{E}\text{2}), 26.8 (CH\text{3}) and 26.5 (CH\text{3}); HRMS (NSI\text{*}): found 304.1004. C\text{16}\text{H}_{16}\text{NaNO\text{2}S} (M + H) requires 304.1002.

3.2.7. N-Butyl-3-(hydroxy(phenyl)methyl)thiophene-2-carboxamide 25 and 5-Butyl-4-phenyl-4,5-dihydro-6\text{H}-thieno[2,3-c]pyrrolo-6-one 26

Under a nitrogen atmosphere, n-butyllithium (2.5 M in hexanes, 6.6 cm\text{3}, 16.5 mmol) was added dropwise to a stirred solution of 3-(benzyloxy)-N-butylthiophene-2-carboxamide 10 (1.45 g, 5.01 mmol) in dry THF (50 cm\text{3}). After stirring at room temperature for 2 h, the reaction mixture was quenched by the addition of saturated aq. NH\text{4}Cl and extracted with Et\text{2}O (3 × 30 cm\text{3}). The combined organic extracts were washed with NaOH and water before being dried and evaporated to give 25 as a pale brown oil which was used without further purification; ν\text{max}/cm\text{–1} 3256, 3086, 2957, 2930, 1612, 1545, 1450, 1302, 1026, 698 and 669; δ\text{H} (400 MHz) 7.37–7.29 (4H, m, Ph), 7.27–7.23 (1H, m, Ph), 7.21 (1H, d, J 5.0, 5-H), 6.96 (1H, t, J 5.6, NH\text{H}), 6.71 (1H, d, J 5.0, 4-H), 6.02 (1H, s, CHO\text{H}), 5.87 (1H, br s, OH), 3.30 (2H, td, J 7.2, 5.6, NCH\text{2}), 1.52–1.45 (2H, m, NCH\text{2}CH\text{2}), 1.35–1.26 (2H, m, CH\text{2}CH\text{3}) and 0.89 (3H, t, J 7.2, CH\text{3}); δ\text{C} (75 MHz) 163.1 (C=O), 147.8 (C), 142.3 (C), 133.4 (C), 130.4 (CH), 128.2 (2CH), 127.3 (CH), 126.7 (2CH), 126.2 (2CH), 70.9 (CHO\text{H}), 39.9 (NCH\text{2}), 31.3 (CH\text{2}), 20.0 (CH\text{2}) and 13.7 (CH\text{3}); HRMS (ESI\text{*}): found 312.1023. C\text{16}\text{H}_{15}\text{NaNO\text{2}S} (M + Na) requires 312.1029.

A mixture of N-butyl-3-(hydroxy(phenyl)methyl)thiophene-2-carboxamide 25 (assuming 5.01 mmol and p-toluenesulfonic acid monohydrate (1.90 g, 9.99 mmol) in toluene (50 cm\text{3}) was heated at reflux for 1 h. After cooling to room temperature, the reaction mixture was washed with water (50 cm\text{3}), 2 M NaOH (50 cm\text{3}) and brine (50 cm\text{3}) before being dried and evaporated. The crude residue was purified by filtration through a silica plug (Et\text{2}O) to give 26 (1.26 g, 93%) as a tan-coloured solid; mp 90–93 °C; ν\text{max}/cm\text{–1} 2955, 1668, 1441, 1398, 1310, 1069, 781, 743, 698 and 637; δ\text{H} (400 MHz) 7.55 (1H, d, J 4.8, 5-H), 7.38–7.32 (3H, m, Ph), 7.16–7.13 (2H, m, Ph), 6.79 (1H, d, J 4.8, 4-H), 5.39 (1H, s, CH\text{Ph}), 3.84
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3.3. Preparation and Reactions of 2-Benzoyloxy-3-thienyl Systems

3.3.1. Attempted Cyclisation of 2-(2-(Benzyloxy)thiophen-3-yl)-4,4-dimethyl-4,5-dihydrooxazole 11

Under a nitrogen atmosphere, n-butyllithium (2.5 M in hexanes, 0.66 cm³, 1.65 mmol) was added to a stirred mixture of 2-(2-benzyloxythiophen-3-yl)-4,4-dimethyl-4,5-dihydrooxazole 1 [11] (0.1437 g, 0.50 mmol) and potassium tert-butoxide (0.1875 g, 1.67 mmol) in dry THF (5 cm³). The mixture was stirred at rt for 2 h before being quenched by the addition of saturated aq. NH₄Cl and extracted with Et₂O (3 x 10 cm³). The combined extracts were dried and evaporated to give, after purification by preparative TLC (Al₂O₃, Et₂O/hexane 1:1), at Rf 0.32 (3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)thiophen-2-yl)(phenyl)methanol 30 (96.7 mg, 67%) as an orange oil; νmax/cm⁻¹ 3177, 2965, 1636, 1535, 1452, 1288, 1194, 1148, 974 and 698; δ (J) 8.14 (500 MHz) 8.04 (1H, br s, OH), 7.49 (2H, d, J 7.0, Ph), 7.36-7.28 (4H, m, ArH and Ph), 7.06 (1H, d, J 5.0, ArH), 6.10 (1H, s, CHOH), 4.09 and 4.06 (2H, AB pattern, J 15.3 Hz, CH₂), 3.87 (3H, s, CH₃) and 1.28 (3H, s, CH₃); δ (C) (125 MHz) 159.6 (C), 153.7 (C), 141.8 (C), 128.6 (CH), 127.9 (2CH), 127.7 (CH), 126.8 (2CH), 125.5 (C), 123.2 (CH), 79.0 (CH₂), 69.5 (CHOH), 67.3 (4ry, CHr), 28.5 (CH₂) and 28.1 (CH₃); HRMS (NSI⁺): found 288.1052. C₁₆H₁₈NOS (M + H) requires 288.1053. The organic layer was separated and washed with 2M NaOH and brine, dried and evaporated to give, after recrystallisation with Et₂O/hexane 3:2) to give, at Rf 0.33 (3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)thiophen-2-yl)(phenyl)methanol 31 (2.52 g, 19.7 mmol) in CH₂Cl₂ (30 cm³) and the mixture was stirred for 18 h. Evaporation gave thiophen-3-carboxyl chloride as a pale-yellow solid which was used immediately without further purification.

A solution of thiophen-3-carboxyl chloride (assuming 19.7 mmol) in toluene (30 cm³) was added dropwise to a solution of n-butylamine (5.8 cm³, 4.29 g, 58.7 mmol) in toluene (30 cm³) stirred at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to rt over 1 h before being poured into water. The organic layer was separated and washed with 2M NaOH and brine, dried and evaporated to give, after recrystallisation (EtOAc/hexane), 32 (2.54 g, 70%) as colourless crystals; mp 66-68 °C; (lit. [19] 53-55 °C); νmax/cm⁻¹ 3253, 3085, 2921, 1617, 1555, 1301, 1220, 1127, 881, 831, 741 and 707; δ (J) (500 MHz) 7.84 (1H, dd, J 3.0, 1.5, ArH), 7.37 (1H, dd, J 5.0, 1.5, ArH), 7.33 (1H, dd, J 5.0, 3.0, ArH), 6.02 (1H, br s, NH), 3.43 (2H, td, J 7.0, 6.0, NCH₂), 1.62-1.56 (2H, m, NCH₂CH₂), 1.44-1.37 (2H, m, CH₂CH₂) and 0.95 (3H, t, J 7.5, CH₃). The ¹H NMR spectral data were in accordance with those previously reported [19]. IR data are reported for the first time.

3.3.2. N-Butylthiophene-3-carboxamide 32

Oxalyl chloride (2.0 cm³, 3.00 g, 23.6 mmol) was added to a solution of thiophene-3-carboxylic acid 31 (2.52 g, 19.7 mmol) in CH₂Cl₂ (30 cm³) and the mixture was stirred for 18 h. Evaporation gave thiophene-3-carboxyl chloride as a pale-yellow solid which was used immediately without further purification.

A solution of thiophene-3-carboxyl chloride (assuming 19.7 mmol) in toluene (30 cm³) was added dropwise to a solution of n-butylamine (5.8 cm³, 4.29 g, 58.7 mmol) in toluene (30 cm³) stirred at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to rt over 1 h before being poured into water. The organic layer was separated and washed with 2M NaOH and brine, dried and evaporated to give, after recrystallisation (EtOAc/hexane), 32 (2.54 g, 70%) as colourless crystals; mp 66-68 °C; (lit. [19] 53-55 °C); νmax/cm⁻¹ 3253, 3085, 2921, 1617, 1555, 1301, 1220, 1127, 881, 831, 741 and 707; δ (J) (500 MHz) 7.84 (1H, dd, J 3.0, 1.5, ArH), 7.37 (1H, dd, J 5.0, 1.5, ArH), 7.33 (1H, dd, J 5.0, 3.0, ArH), 6.02 (1H, br s, NH), 3.43 (2H, td, J 7.0, 6.0, NCH₂), 1.62-1.56 (2H, m, NCH₂CH₂), 1.44-1.37 (2H, m, CH₂CH₂) and 0.95 (3H, t, J 7.5, CH₃). The ¹H NMR spectral data were in accordance with those previously reported [19]. IR data are reported for the first time.

3.3.3. N-Butyl-2-(trimethylsilyl)thiophene-3-carboxamide 33

Under a nitrogen atmosphere, n-butyllithium (2.5 M in hexane, 5.2 cm³, 13.0 mmol) was added dropwise to a stirred −78 °C solution of N-butylthiophene-3-carboxamide 32 (1.10 g, 6.00 mmol) in dry THF (30 cm³). After stirring at −78 °C for 5 min, the reaction mixture was allowed to warm to rt for 1 h, before being cooled to −78 °C and treated with bis(trimethylsilyl) peroxide (1.28 g, 7.18 mmol). The reaction mixture was allowed to warm to rt over 1 h before being poured into sat. aq. NH₄Cl (100 cm³) and extracted with Et₂O (3 x 50 cm³). The combined organic extracts were dried and evaporated and the crude residue was purified by column chromatography (SiO₂, Et₂O/hexane 3:2) to give, at Rf 0.33 (0.32 g, 21%) as tan-coloured crystals; mp 86-89 °C; νmax/cm⁻¹ 3285, 2957, 1620, 1558, 1402, 1296, 1240, 1005, 833, 746, 704 and 604; δ (J) (500 MHz) 7.50 (1H, d, J 5.0, ArH), 7.29 (1H, d, J 5.0, ArH), 5.94 (1H, br s, NH), 3.41 (2H, td, J 7.0, 6.0, NCH₂), 1.61-1.55 (2H, m, NCH₂CH₂), 1.43-1.36 (2H, m, CH₂CH₃), 0.94 (3H, t, J 7.5, CH₂CH₃) and
0.39 (9H, s, SiMe₃); δ_C (125 MHz) 164.6 (C=O), 145.7 (C), 143.0 (C), 130.2 (CH), 126.9 (CH), 39.6 (NCH₃), 31.7 (CH₂), 20.1 (CH₂), 13.8 (CH₃) and 0.0 (SiMe₃); HRMS (NSI⁺): found 256.1184. C₁₂H₂₂NOSSi (M + H) requires 256.1186.

3.3.4. 5-Butyl-6-phenyl-5,6-dihydro-4H-thieno[2,3-c]pyrrol-4-one 35 and 2-Benzoyl-N-butyliophene-3-carboxamide 36

Under a nitrogen atmosphere, n-butyllithium (2.5 M in hexane, 4.2 cm³, 10.5 mmol) was added dropwise to a stirred −78 °C solution of N-butyliophene-3-carboxamide 32 (0.9158 g, 5.00 mmol) in dry THF (50 cm³). After stirring at −78 °C for 5 min, the reaction mixture was allowed to warm to rt for 1 h before benzaldehyde (0.57 cm³, 6.0 g, 5.61 mmol) was added and stirring was continued for 18 h. The reaction mixture was poured into sat. aq. NH₄Cl (100 cm³) and extracted with Et₂O (3 × 50 cm³) and the combined organic layers were dried and evaporated.

The residue was dissolved in toluene (100 cm³) and treated with p-toluenesulfonic acid monohydrate (1.90 g, 9.99 mmol) before being heated at reflux for 1 h. After cooling to rt, the reaction mixture was washed with water (50 cm³), 2 M NaOH (50 cm³) and brine (50 cm³) before being dried and evaporated. The crude residue was purified by column chromatography (

3.4. Preparation and Reactions of 4-Benzoyloxy-3-thienyl Systems

3.4.1. Methyl 3-((2-Methoxy-2-oxoethyl)thio)propanoate 37

Following a literature procedure [12], methyl acrylate (18.37 g, 0.213 mol) was added dropwise to a stirred mixture of methyl thioglycolate (21.18 g, 0.200 mol) and piperidine (0.2 cm³, 0.17 g, 2.02 mmol). Once approximately half of the methyl acrylate had been added, further piperidine (0.2 cm³, 0.17 g, 2.02 mmol) was added. Once the addition was complete, the reaction mixture was heated at reflux for 1 h. After cooling to rt, the reaction mixture was diluted with Et₂O (150 cm³) and washed with water (5 × 50 cm³) before being dried and evaporated to give 37 (37.12 g, 97%) as a pale yellow oil; mp 96–98 °C, ν_max(C=O) 172.0 (C=O), 170.7 (C=O), 52.4 (CH₃), 51.8 (CH₃), 34.1 (CH₂), 33.4 (CH₂) and 27.5 (CH₂). The ¹H NMR spectral data were in accordance with those previously reported [11]. ¹³C NMR data are reported for the first time.

3.4.2. Methyl 4-Oxotetrahydrothiophene-3-carboxylate 38

Following a literature procedure [13], sodium methoxide was prepared by the addition of sodium (12.51 g, 0.544 mol) in small portions to methanol (90 cm³). Once the sodium had fully dissolved, a solution of methyl 3-(2-methoxy-2-oxoethyl)thio)propanoate 37
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(37.12 g, 0.193 mol) in methanol (30 cm³) was added dropwise and the reaction mixture was heated at reflux for 1 h. After cooling to rt, the reaction mixture was poured into a mixture of crushed ice (400 g) and conc. HCl (100 cm³) before being extracted with CH₂Cl₂ (2 × 300 cm³). The combined organic layers were washed with sat. aq. NaHCO₃ (250 cm³) before being dried and evaporated. The crude residue was purified by distillation to give 38 (11.69 g, 38%) as a colourless oil which partially crystallised on standing; bp 103 °C/4.9 Torr; (lit. [20] 109 °C/4 Torr).

3.4.3. Methyl 4-Hydroxythiophene-3-carboxylate 39

Following a literature procedure [14], sulfuryl chloride (9.7 cm³, 16.15 g, 0.120 mol) was added dropwise to a stirred 0 °C solution of methyl 4-oxotetrahydrothiophene-3-carboxylate 973 (17.41 g, 0.109 mol) in CH₂Cl₂ (110 cm³) over a period of 1 h. The reaction mixture was stirred at 0 °C for 30 min before being washed with sat. aq. NaHCO₃ (150 cm³) and water (3 × 50 cm³). The organic layer was dried and evaporated to give after filtration through a silica plug (Et₂O/hexane 1:1) to give, at Rf 0.90, 983 (5.47 g, 27%) as a red oil; νmax/cm⁻¹ 3113, 2949, 1726, 1449, 1265, 1082, 770 and 698; δH (300 MHz) 8.07 (1H, d, J 3.5, ArH), 6.98 (1H, d, J 3.6, ArH), 6.39 (1H, d, J 3.6, ArH) and 3.92 (3H, s, CH₃); δC (125 MHz) 162.2 (C=O), 156.1 (C–O), 131.0 (CH), 119.0 (C), 100.0 (CH) and 51.8 (CH₂). The ¹H NMR spectral data were in accordance with those previously reported [15]. ¹³C NMR data are reported for the first time.

3.4.4. Methyl 4-Acetoxythiophene-3-carboxylate 40

Following a literature procedure [15], a mixture of methyl 4-oxotetrahydrothiophene-3-carboxylate 38 (30.80 g, 0.192 mol) and p-toluenesulfonic acid monohydrate (0.19 g, 1.00 mmol) in isopropenyl acetate (70 cm³) was heated at reflux for 18 h. After cooling to rt, the reaction mixture was concentrated in vacuo to give methyl 4-acetoxy-2,5-dihydrothiophene-3-carboxylate as a dark brown oil which was used without further purification.

Following a literature procedure [15], sulfuryl chloride (19.5 cm³, 32.47 g, 0.241 mol) was added dropwise to a stirred −25 °C solution of methyl 4-acetoxy-2,5-dihydrothiophene-3-carboxylate (assumingly 0.192 mol) in CH₂Cl₂ (80 cm³) over a period of 1 h. The reaction mixture was allowed to warm to rt for 18 h before being evaporated to give 40 (19.10 g, 50%) as a dark brown oil which was used without further purification; δH (500 MHz) 8.07 (1H, d, J 3.8, ArH), 6.98 (1H, d, J 3.8, ArH), 3.83 (3H, s, OCH₃) and 2.33 (3H, s, COCH₃). The ¹H NMR spectral data were in accordance with those previously reported [15].

3.4.5. Silver(I) Oxide

A solution of sodium hydroxide (14.61 g, 0.365 mol) in water (440 cm³) was added dropwise to a stirred solution of silver nitrate (60.00 g, 0.353 mol) in water (110 cm³). Once the addition was complete, the precipitate was collected by filtration and washed with water until the washings were neutral before being dried and evaporated. The crude residue was purified by distillation to give 38 (11.69 g, 38%) as a colourless oil which partially crystallised on standing; bp 103 °C/4.9 Torr; (lit. [20] 109 °C/4 Torr).

3.4.6. Methyl 4-(Benzylxoy)thiophene-3-carboxylate 41

A mixture of methyl 4-hydroxythiophene-3-carboxylate 39 (12.91 g, 81.6 mmol), silver(I) oxide (28.40 g, 0.123 mol) and benzyl bromide (10.7 cm³, 15.39 g, 90.0 mmol) in CH₂Cl₂ (500 cm³) was heated at reflux for 3 d. After cooling to rt, the reaction mixture was filtered and evaporated and the crude residue was purified by column chromatography (SiO₂, Et₂O/hexane 1:1) to give, at Rf 0.90, 983 (5.47 g, 27%) as a red oil; νmax/cm⁻¹ 3113, 2949, 1726, 1449, 1265, 1082, 770 and 698; δH (500 MHz) 8.01 (1H, d, J 3.5, ArH), 7.48 (2H, d, J 7.5, Ph), 7.38 (2H, t, J 7.5, Ph), 7.31 (1H, t, J 7.5, Ph), 6.31 (1H, d, J 3.5, ArH), 5.13 (2H, s, CH₂) and 3.86 (3H, s, CH₃); δC (125 MHz) 162.2 (C=O), 156.1 (C–O), 131.0 (CH), 128.5 (2CH), 127.8 (CH), 126.8 (2CH), 123.7 (C), 99.9 (CH), 72.3 (CH₂) and 51.6 (CH₃); HRMS (ESI⁺): found 271.0393. C₁₃H₁₂NaO₃S (M + Na) requires 271.0399.
3.4.7. 4-(Benzylxyloxy)thiophene-3-carboxylic Acid 42

A mixture of methyl 4-(benzylxyloxy)thiophene-3-carboxylate 41 (5.17 g, 20.8 mmol) and sodium hydroxide (1.74 g, 43.5 mmol) in water (45 cm³) was heated at reflux for 18 h. After cooling to rt, the reaction mixture was washed with CH₂Cl₂ (30 cm³) before being adjusted to pH 1 by the addition of 2 M HCl and extracted with CH₂Cl₂ (2 × 50 cm³). The combined organic extracts were dried and evaporated to give, after recrystallisation (PhMe), 42 (3.08 g, 63%) as brown crystals; mp 101–105 °C; νmax/cm⁻¹: 3123, 1667, 1537, 1447, 1285, 1196, 1088, 880 and 764; δH (500 MHz) 9.96 (1H, br s, CO₂H), 8.21 (1H, d, J 3.5, ArH), 7.45–7.37 (5H, m, Ph), 6.48 (1H, d, J 3.5, ArH) and 5.20 (2H, s, CH₂); δC (125 MHz) 164.7 (C=O), 155.0 (C–O), 135.5 (C), 135.2 (CH), 128.6 (2CH), 128.3 (CH), 127.2 (2CH), 122.7 (C), 100.3 (CH) and 72.9 (CH₂); HRMS (ESI⁺): found 257.0239. C₁₂H₁₀NaO₃S (M + Na) requires 257.0243.

3.4.8. 4-(Benzylxyloxy)-N-(1-hydroxy-2-methylpropan-2-yl)thiophene-3-carboxamide 43

Thionyl chloride (0.31 cm³, 0.51 g, 4.25 mmol) was added to a suspension of 4-(benzylxyloxy)thiophene-3-carboxylic acid 42 (0.50 g, 2.13 mmol) in toluene (5 cm³) and the mixture was heated under reflux for 3 h. After cooling to rt, the mixture was evaporated to give 4-(benzylxyloxy)thiophene-3-carbonyl chloride as a red oil which was used immediately without further purification.

A solution of 4-(benzylxyloxy)thiophene-3-carbonyl chloride (assuming 2.13 mmol) in CH₂Cl₂ (30 cm³) was added dropwise to a solution of 2-amino-2-methylpropan-1-ol (0.41 g, 4.60 mmol) in CH₂Cl₂ (10 cm³) stirred at 0 °C. After the addition, the mixture was allowed to warm to rt and stirred for 18 h before being poured into water. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (2 × 20 cm³). The combined organic layers were washed successively with 2M HCl, 2M NaOH and water before being dried and evaporated to give 43 (0.60 g, 92%) as a pale-yellow solid which was used without further purification; mp 90–92 °C; νmax/cm⁻¹: 3366, 2970, 1628, 1560, 1435, 1364, 1310, 1074, 976 and 606; δH (400 MHz) 8.07 (1H, d, J 3.6, ArH), 7.65 (1H, br s, NH), 7.46–7.37 (5H, m, Ph), 6.46 (1H, d, J 3.6, ArH), 5.22 (1H, br s, OH), 5.08 (2H, s, OCH₂Ph), 3.57 (2H, s, CH₂OH) and 1.16 (6H, s, CH₃); δC (100 MHz) 162.1 (C=O), 153.1 (C–O), 135.1 (C), 131.9 (CH), 128.8 (CH), 128.7 (2CH), 128.1 (2CH), 126.6 (C), 99.7 (CH), 73.2 (CH₂), 70.7 (CH₂), 56.0 (CM_e) and 24.5 (2CH₃); HRMS (ESI⁺): found 306.1150. C₁₆H₂₀NO₃S (M + H) requires 306.1158.

3.4.9. 2-(4-(Benzylxyloxy)thiophen-3-yl)-4,4-dimethyl-4,5-dihydrooxazole 13

Thionyl chloride (0.15 cm³, 0.24 g, 2.06 mmol) was added to a solution of 4-(benzylxyloxy)-N-(1-hydroxy-2-methylpropan-2-yl)thiophene-3-carboxamide 43 (0.50 g, 1.64 mmol) in CH₂Cl₂ (20 cm³) and the mixture was stirred at rt for 18 h. The mixture was washed with 2M NaOH and water before being dried and evaporated to give, after purification by column chromatography (SiO₂, Et₂O/hexane 3:2), at Rf 0.40, 13 (0.41 g, 87%) as a pale yellow solid; mp 77–80 °C; νmax/cm⁻¹: 2965, 1651, 1535, 1449, 1371, 1211, 1194, 1042, 733 and 698; δH (400 MHz) 7.79 (1H, d, J 3.6, ArH), 7.47 (2H, d, J 7.6, Ph), 7.36 (2H, t, J 7.4, Ph), 7.29 (1H, t, J 7.2, Ph), 6.30 (1H, d, J 3.6, ArH), 5.16 (2H, s, OCH₂Ph), 4.05 (2H, s, OCH₂) and 1.39 (6H, s, CH₃); δC (100 MHz) 157.2 (C), 155.3 (C), 136.9 (C), 129.1 (CH), 128.4 (2CH), 127.6 (CH), 126.7 (2CH), 121.6 (C), 100.3 (CH), 78.5 (OCH₂), 72.4 (OCH₂), 67.5 (CM_e) and 28.4 (2CH₃); HRMS (ESI⁺): found 288.1047. C₁₆H₁₈NO₃S (M + H) requires 288.1053.

3.4.10. 4-((1-Hydroxy-2-methylpropan-2-yl)carbamoyl)thiophen-3-yl Benzoate 45

Under a nitrogen atmosphere, n-butyllithium (2.5 M in hexanes, 0.88 cm³, 2.20 mmol) was added to a stirred mixture of 2-(4-(benzylxyloxy)thiophen-3-yl)-4,4-dimethyl-4,5-dihydrooxazole 13 (0.1443 g, 0.50 mmol) and potassium tert-butoxide (0.2587 g, 2.21 mmol) in dry THF (5 cm³). The mixture was stirred at rt for 2 h before being quenched by the addition of saturated aq. NH₄Cl and extracted with Et₂O (3 × 10 cm³). The combined extracts were dried and evaporated to give, after purification by preparative TLC (Al₂O₃,
Et₂O/hexane 1:1), at Rf 0.35, 45 (55.8 mg, 35%) in slightly impure form as a brown oil; νmax/cm⁻¹ 3335, 2972, 1744, 1638, 1545, 1450, 1246, 1177, 1047, 908, 766 and 700; δH (400 MHz) 8.19–8.16 (2H, m, Ph), 7.99 (1H, d, J 3.6, ArH), 7.71–7.67 (1H, m, Ph), 7.55 (2H, t, J 7.8, Ph), 7.34 (1H, d, J 3.6, ArH), 6.61 (1H, br s, NH), 4.58 (1H, br s, OH), 3.59 (2H, s, CH₂) and 1.24 (6H, s, CH₃); δC (125 MHz) 163.7 (CO), 162.2 (CO), 143.2 (CO), 134.4 (CH), 130.0 (CH₂), 129.9 (CH), 129.3 (C), 128.9 (2CH), 128.4 (C), 113.7 (CH), 69.9 (OCH₂) and 24.6 (2CH₃); HRMS (ESI⁺): found 320.0953. C₁₆H₁₈NO₃S (M + H) requires 320.0951.

### 3.4.11. 4-(Benzyloxy)-N-butylthiophene-3-carboxamide 14

Thionyl chloride (1.0 cm³, 1.63 g, 13.7 mmol) was added to a suspension of 4-(benzyloxy)thiophene-3-carboxylic acid 42 (1.50 g, 6.40 mmol) in toluene (15 cm³) and the mixture was heated under reflux for 3 h. After cooling to rt, the mixture was evaporated to give 4-(benzyloxy)thiophene-3-carboxyl chloride as a red oil which was used immediately without further purification.

A solution of 4-(benzyloxy)thiophene-3-carboxyl chloride (assuming 6.40 mmol) in toluene (30 cm³) was added dropwise to a solution of n-butylamine (1.9 cm³, 1.41 g, 19.2 mmol) in toluene (10 cm³) stirred at 0 °C. Once the addition was complete, the reaction mixture was allowed to warm to rt over 1 h before being poured into water. The organic layer was separated and washed with 2M NaOH and brine, dried and evaporated to give, after purification by column chromatography (SiO₂, Et₂O/hexane 3:2), at Rf 0.50, 14 (1.24 g, 67%) as a tan-coloured solid; mp 51–53 °C; νmax/cm⁻¹ 3385, 3111, 2970, 1630, 1545, 1364, 1265, 1184, 1074, 988, 714 and 579; δH (400 MHz) 8.10 (1H, d, J 3.6, ArH), 7.45–7.37 (6H, m, NH and Ph), 6.43 (1H, d, J 3.6, ArH), 5.10 (2H, s, OCH₂), 3.34 (2H, t, J 6.8, 5.6, NCH₂), 1.45–1.38 (2H, m, NCH₂CH₃), 1.25–1.15 (2H, m, NCH₂CH₃) and 0.81 (3H, t, J 7.2, CH₃); δC (100 MHz) 161.5 (C=O), 153.5 (C–O), 135.5 (C), 131.5 (CH), 128.8 (2CH), 128.7 (2CH), 127.9 (2CH), 127.1 (C), 99.5 (CH), 73.1 (OCH₂), 38.7 (NCH₂), 31.3 (CH₂), 20.0 (CH₂) and 13.7 (CH₃); HRMS (ESI⁺): found 290.1207. C₁₆H₂₀NO₃S (M + H) requires 290.1209.

### 3.4.12. Attempted [1,2]-Wittig Rearrangement of 4-(Benzyloxy)-N-butylthiophene-3-carboxamide 14

Under a nitrogen atmosphere, n-butyllithium (2.5 M, 2.7 cm³, 6.75 mmol) was added dropwise to a stirred solution of 4-(benzyloxy)-N-butylthiophene-3-carboxamide 14 (0.5787 g, 2.00 mmol) in dry THF (20 cm³). After stirring at rt for 2 h, the reaction mixture was quenched by the addition of saturated aq. NH₄Cl and extracted with Et₂O (3 × 30 cm³). The combined organic extracts were washed with NaOH and water before being dried and evaporated to give, after purification by column chromatography (SiO₂, Et₂O/hexane 3:2), at Rf 0.65, 4-(benzyloxy)-N-butyl-2-(hydroxy(phenyl)methyl)thiophene-3-carboxamide 46 (27.8 mg, 4%) in slightly impure form as a tan-coloured solid; mp 74–76 °C; νmax/cm⁻¹ 3335, 3111, 2970, 1630, 1545, 1364, 1265, 1184, 1074, 988, 714 and 579; δH (400 MHz) 7.73 (1H, t, J 5.0, NH), 7.52–7.48 (2H, m, Ph), 7.44–7.30 (8H, m, Ph), 6.77 (1H, br s, OH), 6.26 (1H, s, ArH), 6.21 (1H, s, CHOH), 5.04 (2H, s, OCH₂), 3.41–3.25 (2H, m, NCH₂), 1.42–1.35 (2H, m, NCH₂CH₂), 1.21–1.12 (2H, m, NCH₂CH₂) and 0.80 (3H, t, J 7.2, CH₃); δC (100 MHz) 163.6 (C=O), 155.9 (C), 154.3 (C), 140.9 (C), 135.2 (C), 128.8 (3CH), 128.03 (2CH), 128.01 (2CH), 127.97 (CH), 127.3 (2CH), 121.9 (C), 97.5 (CH), 73.0 (OCH₂), 70.8 (CHOH), 39.0 (NCH₂), 31.0 (CH₂), 19.9 (CH₂) and 13.7 (CH₃); HRMS (ESI⁺): found 418.1439. C₂₁H₂₅NO₃S (M + Na) requires 418.1447.

This was followed by a second fraction at Rf 0.50 which was further purified by preparative TLC (SiO₂, CH₂Cl₂) to give, at Rf 0.35 N-butyl-4-hydroxythiophene-3-carboxamide 47 (30.9 mg, 8%) in slightly impure form as a brown oil; νmax/cm⁻¹ 3337, 2957, 2930, 1634, 1557, 1441, 1273, 739 and 698; ¹H NMR revealed a 3:2 mixture of enol and keto tautomers; δH (500 MHz, enol tautomer 47) 10.36 (1H, br s, OH), 7.54 (1H, d, J 3.3, ArH), 6.36 (1H, d, J 3.3, ArH), 6.35 (1H, br s, NH), 3.41 (2H, t, J 7.3, 6.0, NCH₂), 1.62–1.51 (2H, m, NCH₂CH₂), 1.44–1.33 (2H, m, NCH₂CH₂) and 0.95 (3H, t, J 7.5, CH₃); δC (125 MHz, enol tautomer 47) 165.1 (C=O), 156.1 (C–O), 124.6 (CH), 121.7 (C), 100.1 (CH), 39.1 (NCH₂), 31.6 (CH₂), 20.08 (CH₂) and 13.7 (CH₃); δH (500 MHz, keto tautomer 47a) 9.33 (1H, s, CH), 8.06 (1H, br
s, NH), 3.89 (2H, s, SCH₂), 3.36 (2H, td, J 7.0, 6.0, NCH₂), 1.62–1.51 (2H, m, NCH₂CH₂), 1.44–1.33 (2H, m, CH₂CH₃) and 0.93 (3H, t, J 7.3, CH₃); δC (125 MHz, keto tautomer 47a) 199.9 (C=O), 174.7 (CH), 159.9 (CONH), 128.2 (C), 42.7 (SCH₂), 38.7 (NCH₂), 31.5 (CH₂), 20.11 (CH₂) and 13.7 (CH₃); HRMS (NSI⁺): found 200.0740. C₇H₁₄NO₂S (M + H) requires 200.0740.

3.5. X-ray Structure Determination

Data have been deposited at the Cambridge Crystallographic Data Centre as CCDC 2111424 (9), 2111425 (20), 2111426 (11), 2111427 (26) and 2111428 (13). The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures. In all cases, data were collected on a Rigaku XtaLAB 200 diffractometer using graphite monochromated Mo-Kα radiation, λ = 0.71075 Å and the structures were solved by direct methods and refined by full-matrix least-squares against F2 (SHELXL Version 2014/7 [21]).

Compound 20

Slow evaporation of an acetone/CH₂Cl₂ solution gave tan-coloured crystals suitable for X-ray structure determination. Crystal data for 20: 2C₁₆H₁₇NO₃S·CH₂Cl₂·Me₂CO, M = 749.76, yellow prism, crystal dimensions 0.10 × 0.10 × 0.10 mm, monoclinic, space group P2₁/n, a = 17.4520, b = 9.9840, c = 21.1050 Å, β = 92.3760°, V = 3674.1899 Å³, Z = 4, Dc = 1.355 Mg m⁻³, T = 93 K, R = 0.0929, Rw = 0.2464 for 4473 reflections with I > 2σ(I) and 458 variables.

Compound 26

Slow evaporation of a CH₂Cl₂ solution gave crystals suitable for X-ray structure determination. Crystal data for 26: C₁₆H₁₇NOS, M = 271.38, colourless needle, crystal dimensions 0.12 × 0.02 × 0.02 mm, monoclinic, space group P2₁, a = 8.237(3), b = 5.717(2), c = 15.097(6) Å, β = 90.539(10)°, V = 710.9(5) Å³, Z = 2, Dc = 1.268 Mg m⁻³, T = 93 K, R = 0.0481, Rw = 0.1086 for 2072 reflections with I > 2σ(I) and 172 variables.

Compound 9

Slow evaporation of an MeCN solution gave crystals suitable for X-ray structure determination. Crystal data for 9: C₁₆H₁₇NO₂S, M = 287.38, colourless plate, crystal dimensions 0.10 × 0.10 × 0.01 mm, monoclinic, space group P2₁/c, a = 15.9970(19), b = 7.5839(6), c = 12.4523(15) Å, β = 111.010(14)°, V = 1410.3(3) Å³, Z = 4, Dc = 1.353 Mg m⁻³, T = 93 K, R = 0.0584, Rw = 0.1406 for 2462 reflections with I > 2σ(I) and 181 variables.

Compound 11

Slow evaporation of a CH₂Cl₂ solution gave crystals suitable for X-ray structure determination. Crystal data for 11: C₁₆H₁₇NO₂S, M = 287.38, colourless prism, crystal dimensions 0.12 × 0.10 × 0.06 mm, monoclinic, space group P2₁/c, a = 14.8176(4), b = 8.72450(17), c = 11.9720(3) Å, β = 113.314(3)°, V = 1421.32(7) Å³, Z = 4, Dc = 1.343 Mg m⁻³, T = 93 K, R = 0.0274, Rw = 0.0730 for 2906 reflections with I > 2σ(I) and 181 variables.

Compound 13

Slow evaporation of a toluene solution gave crystals suitable for X-ray structure determination. Crystal data for 13: C₁₆H₁₇NO₂S, M = 287.38, colourless plate, crystal dimensions 0.20 × 0.20 × 0.01 mm, monoclinic, space group P2₁/c, a = 15.6319(4), b = 8.7152(3), c = 10.7572(3) Å, β = 93.909(3)°, V = 1462.10(7) Å³, Z = 4, Dc = 1.305 Mg m⁻³, T = 296 K, R = 0.0333, Rw = 0.0888 for 2781 reflections with I > 2σ(I) and 181 variables.

4. Conclusions

The three isomeric thienyloxazolines showed a varied and interesting pattern of reactivity with two of them undergoing Wittig rearrangement and two giving products derived from ring cleavage of an intermediate 3-aminothienofuran. One of the corresponding thienyl amides also underwent Wittig rearrangement and cyclisation of the product, as well as an isomeric one obtained by other means, gave two isomeric thienopyrrolones. The pattern of reactivity in the oxazoline series correlates well with the molecular geometry in the solid state as determined by X-ray diffraction, and the use of this method to
explain patterns of competing reactivity between closely similar molecules may be useful more generally.

**Supplementary Materials:** The following are available online, Figures S1–S41: NMR spectra of new compounds. CIF and check-CIF files for X-ray structures of 9, 11, 13, 20 and 26.

**Author Contributions:** A.D.H. performed the experiments; A.M.Z.S. collected the X-ray data and solved the structures; R.A.A. designed the experiments, analysed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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