The Journal of Organic Chemistry

Subscriber access provided by Brought to you by ST ANDREWS UNIVERSITY LIBRARY

Note

Synthesis, Structure and Unusual Reactivity of a Stable 3-(Oxazolidin-2-ylidene)thiophen-2-one

R. Alan Aitken, Andrew D. Harper, and Alexandra M. Z. Slawin

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01309 • Publication Date (Web): 15 Jul 2016

Downloaded from http://pubs.acs.org on July 27, 2016

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Synthesis, Structure and Unusual Reactivity of a Stable 3-(Oxazolidin-2-ylidene)thiophen-2-one

R. Alan Aitken[1]*, Andrew D. Harper and Alexandra M. Z. Slawin

EaStCHEM School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, U.K.

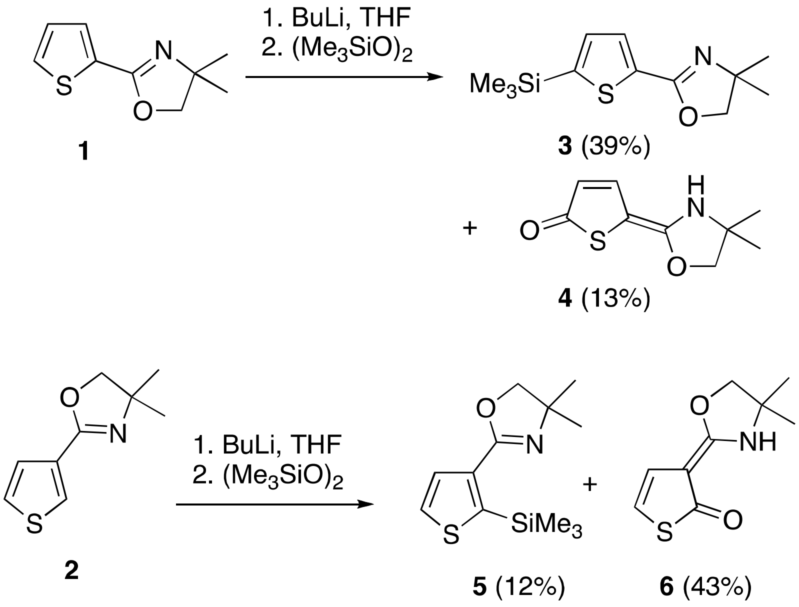
raa@st-and.ac.uk

[1] ISHC Member

Treatment of 2- and 3-thienyloxazolines with butyllithium and bis(trimethylsilyl) peroxide results in ring hydroxylation to give products which exist mainly as the oxazolidinylidenethiophenones. The 3-oxazolidinylidenethiophen-2-one is a rare example of a stable heterocyclic *ortho*-quinone methide analog which shows a varied pattern of reactivity, including both *C*- and *O*-alkylation, Michael addition via C-5 to an acetylenic ester, tetrachlorobenzannulation across positions 4 and 5, and formation of a hexacyclic fused-ring product with *N*-phenyltriazolinedione. Crystal structures of the products are dominated by inter- and intramolecular NH to CO hydrogen bonding.

The existence of simple hydroxythiophenes primarily in non-aromatic thiophenone tautomeric forms is well known and was demonstrated for 2-hydroxythiophene when it was first prepared using IR and UV spectra as well as chemical properties.[1] A short time later, the advent of NMR spectroscopy allowed quantification of the different tautomers for 2-hydroxythiophene and methylated derivatives.[2,3] The main route to hydroxythiophenes in these early studies was oxidation of metallated thiophenes, either treatment of a Grignard reagent with oxygen gas,[1] or conversion of a thienyllithium into the corresponding boronic acid followed by reaction with H_2O_2.[2,3] The 4,5-dihydrooxazole or 2-oxazoline is arguably the most important heterocyclic *ortho*-directing group,[4] and particularly the readily available 4,4-dimethyl-2-oxazolin-2-yl group been used to direct *ortho*-lithiation and subsequent functionalization in a wide range of aromatic and heteroaromatic systems.[5] Although the 2-thienyloxazoline **1** is well known[6–9] and its lithiation and reaction with a range of electrophiles at positions 3 or 5 has been reported, these do not include reactions resulting in ring hydroxylation. The isomeric 3-thienyloxazoline **2** has only been mentioned in three papers,[10–12] and its chemistry is limited to lithiation and reaction with three aromatic aldehydes. In this paper we describe the lithiation and ring hydroxylation of both **1** and **2** to give, in each case, a stable crystalline product which exists exclusively in a single oxazolidinylidenethiophenone tautomeric form as shown by NMR and X-ray diffraction. The latter product shows versatile chemical behavior resulting from the transposition of functional groups present, with appropriate reagents allowing reaction to be observed at any of the four thiophene carbon atoms.

Based on literature precedent, lithiation of 2-thienyloxazoline **1** could result in functionalization either at position 3 or 5, and furthermore the chosen hydroxylating agent bis(trimethylsilyl) peroxide, which adds the readily hydrolyzed OTMS group to most aryllithium systems, instead results in exclusive addition of just TMS to 2-thienyllithium.[13] In agreement with this pattern, treatment of **1** with butyllithium in THF followed by the peroxide gave mainly the 5-trimethylsilyl compound **3** but this was accompanied by a second minor product, separable by chromatography, which proved to be the thiophenone tautomeric form **4** corresponding to the 5-hydroxy-2-thienyloxazoline (Scheme 1).



1

3 (39%)

4 (13%)

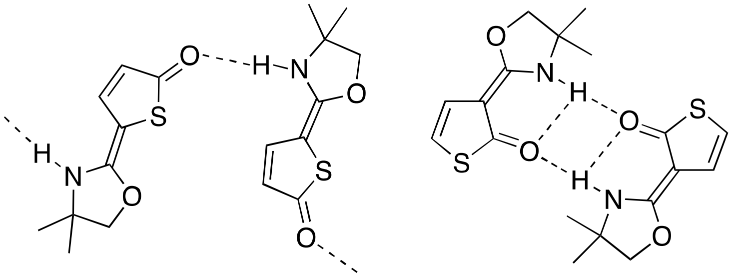
2

5 (12%)

6 (43%)

SCHEME 1

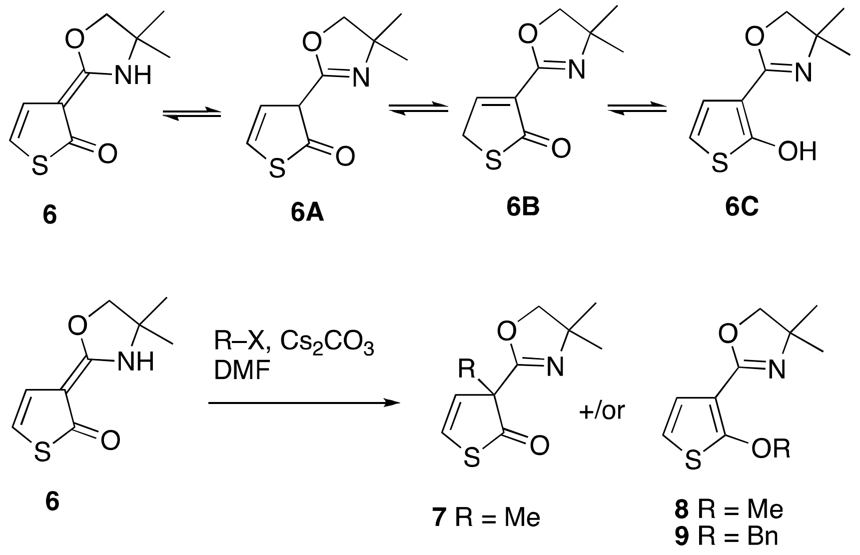
When the 3-thienyloxazoline **2** was subjected to the same reaction, the corresponding 2-functionalized products **5** and **6** were formed but the ratio was now reversed with the more interesting thiophenone **6** isolated in moderate yield on a preparative scale. The existence of compounds **4** and **6** in solution as the thiophenone forms shown was clear from the ^{13}C NMR data including signals for a ketone C=O (δ 196.0 for **4,** 192.4 for **6**) and highly polarized "push-pull" thiophenone to oxazolidine C=C double bond (δ 161.6, 91.2 for **4**, 164.1, 93.9 for **6**). In addition, while compound **6** was well behaved in $CDCl_3$, the isomer **4** was only soluble in CD_3OD or CD_3SOCD_3 and gave very broad signals for the thiophenone part of the molecule in both ^{1}H and ^{13}C spectra. This indicated a dynamic process at work, perhaps related to hydrogen bonding, and since both compounds were crystalline, this was further probed by single crystal X-ray diffraction (see Supporting Information). This confirmed that, in the solid state also, **4** and **6** have the molecular structures shown in Scheme 1, and also gave clear evidence for hydrogen bonding as shown in Scheme 2, with **4** forming intermolecular NH to CO hydrogen bonded chains while **6** exists as pairs of molecules with both inter and intramolecular NH to CO interactions. There are only very few previous X-ray structures of alkylidenethiophenones[14] and, in the 3-alkylidenethiophen-2-one series of **6** for example, none of the three previous structures[15–17] are of the aminoalkylidene type that would allow hydrogen bonding.



SCHEME 2: Hydrogen bonding patterns in the crystal structures of **4** and **6**

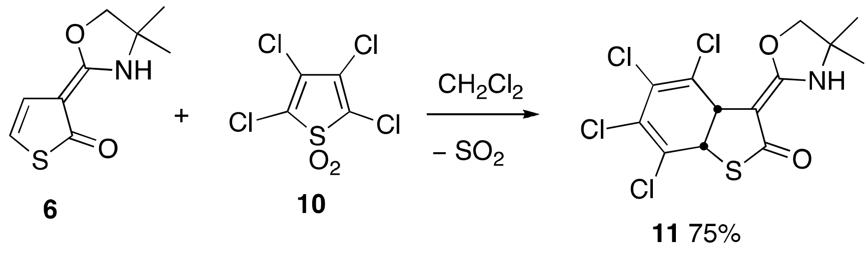
Such hydrogen bonding interactions have been detected before by NMR methods in various 3-aminoalkylidenethiophen-2-one systems,[18–20] and theoretical studies to evaluate the relative energies of the various tautomeric forms have also been reported.[21–23]

Although there are various general routes to 3-alkylidenethiophen-2-ones,[24] their chemistry has not been thoroughly investigated. This is surprising given that they are heterocyclic analogs of the *o*-quinone methides which have recently emerged as highly versatile and useful synthetic intermediates.[25–30] The presence of an enamine function as in **6** raises the additional complication of different possible tautomeric forms and we were interested to examine whether, although **6** exists overwhelmingly as such both in solution and the solid state, it might react to give products formally derived from one or more of the alternative forms **6A**, **6B** and **6C** (Scheme 3).



SCHEME 3

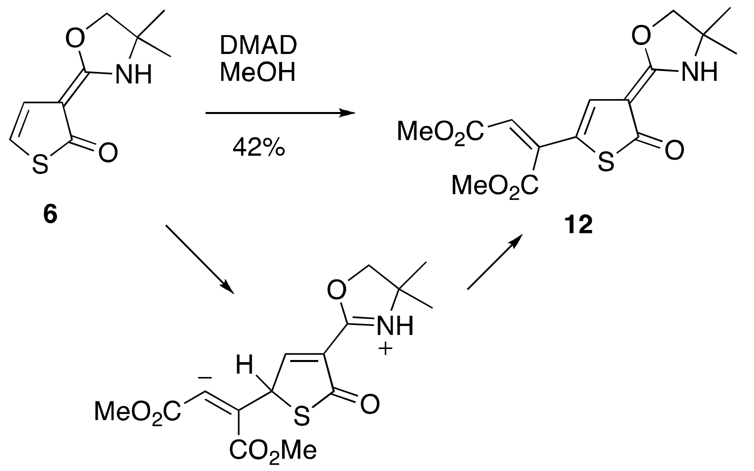
Alkylation using methyl iodide in DMF in the presence of cesium carbonate gave two isomeric products in almost equal amount, which were separated chromatographically and characterized as **7** and **8**. In contrast, reaction with dimethyl sulfate under comparable conditions gave exclusively the *O*-methyl product **8**. Similar treatment of **6** with either benzyl mesylate or benzyl bromide gave only the *O*-benzyl product **9** in around 50% yield. Hard-soft principles are clearly directing the alkylation to give products corresponding to **6A** and **6C**. Although there are a few examples of 3-alkylidenethiophen-2-ones acting as dienes in the Diels Alder reaction,[24] we are not aware of any examples where they act as the dienophile. Tetrachlorothiophene *S,S*-dioxide **10**, a readily available crystalline diene that reacts with a wide range of double bond types,[31] was found to add readily to **6** with subsequent loss of SO_2 to afford the tetrachlorobenzothiophenone **11** in good yield (Scheme 4).



SCHEME 4

The structure of this very high-melting solid was confirmed by X-ray diffraction (see Supporting Information), which also revealed a pattern of paired molecules with both inter- and intramolecular NH to CO hydrogen bonding, much as was observed with **6**.

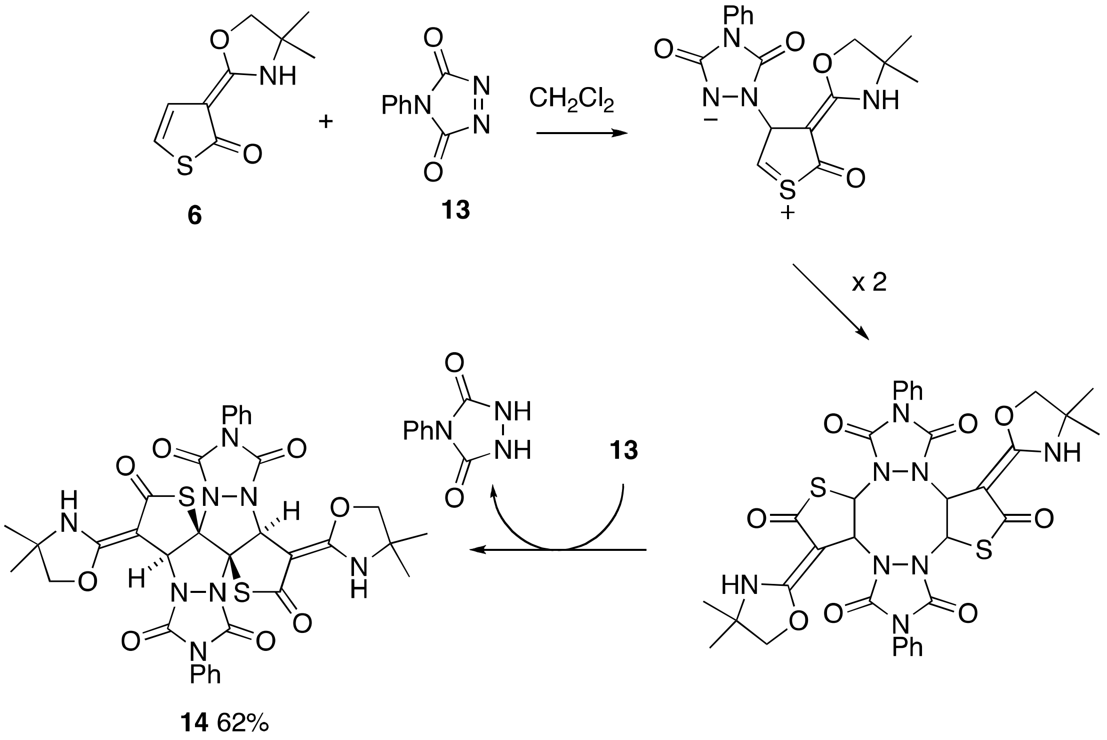
Yet another mode of reactivity was found with dimethyl acetylenedicarboxylate (DMAD) which reacted with **6** in methanol to afford the adduct **12** in moderate yield (Scheme 5). This apparently arises from attack of **6** as a vinylogous enamine to give the intermediate shown followed by proton transfer, and overall results in 5-functionalization corresponding to form **6B**. A similar mode of reactivity resulting in Michael addition via C-5 was proposed to account for the unexpected dimerization of 3-aminoalkylidenethiophen-2-ones.[32]



SCHEME 5

Finally, compound **6** was found to react readily with *N*-phenyltriazolinedione **13** to give a colorless solid, shown by HRMS to have a formula corresponding to (2 × **6** + 2 × **13** – 2H) which was also supported by NMR. The structure and stereochemistry of **14** was only revealed by X-ray diffraction of a crystal obtained by recrystallization from acetonitrile (see Supporting Information). In this case the crystal structure features chains of bifunctional molecules linked by the same type of strong inter- and intramolecular hydrogen bonding already seen for **6** and **11**.

We believe this reaction involves initial interaction of **6** and **13** to form a sulfonium imide (Scheme 6) which then dimerizes to form an eight-membered ring. Transannular dehydrogenation of the dimer by a further molecule of **13** with loss of the two S–CH–N hydrogens gives the hexacyclic core of **14**. Because of the symmetry involved there are six possible stereoisomers of **14** arising from the four stereogenic centres but simple MM2 calculations show that the observed isomer is predicted to be by far the most thermodynamically stable. Further studies on the reactivity of this remarkable compound are now in progress.



SCHEME 6

Experimental Section

General Experimental Details: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ unless otherwise stated with internal TMS as reference. IR spectra were recorded using the ATR technique. HRMS measurements were made either using ES or ASAP ionization both with TOF analyzer, or NSI with an ion trap analyzer.

Bis(trimethylsilyl)peroxide,[13] benzyl methanesulfonate,[32] 4-phenyl-1,2,4-triazoline-3,5-dione,[33] and tetrachlorothiophene *S,S*-dioxide[31] were prepared by published methods. Thiophene-3-carboxylic acid was prepared by Ag_2O oxidation of thiophene-3-carbaldehyde.[34] 4,4-Dimethyl-2-(2-thienyl)-4,5-dihydrooxazole (**1**)[9] and 4,4-dimethyl-2-(3-thienyl)-4,5-dihydrooxazole (**2**)[11] were prepared by literature methods.

(*E*)-5-(4,4-Dimethyloxazolidin-2-ylidene)thiophen-2(5*H*)-one (4): Under a nitrogen atmosphere, a 2.5 M solution of *n*-butyllithium in hexanes (2.9 mL, 7.25 mmol) was added dropwise to a solution of oxazoline **1** (1.18 g, 6.51 mmol) in dry THF (30 mL) stirred at –78°C. After stirring at –78 °C for 1 h, bis(trimethylsilyl) peroxide (1.36 g, 7.62 mmol) was added and the reaction mixture was allowed to warm to rt over 18 h. The resultant solution was poured into saturated aq. NH_4Cl (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were dried and evaporated. Purification by column chromatography (SiO_2, gradient elution, Et_2O to 9:1 EtOAc:MeOH) gave first a 3:2 mixture of **4,4-dimethyl-2-(5-trimethylsilyl-2-thienyl)-4,5-dihydrooxazole (3)** and unreacted starting material (1.01 g) as an orange gum. Re-chromatography of this (SiO_2, Et_2O/hexane 3:7) gave at R_f 0.60 pure **3** as pale yellow crystals, mp 65–68 °C (0.65 g, 39%); IR 1645 cm^{-1}; ^1H NMR (500 MHz) δ 7.61 (d, J = 3.5 Hz, 1H), 7.17 (d, J = 3.5 Hz, 1H), 4.07 (s, 2H), 1.36 (s, 6H), 0.32 (s, 9H); ^{13}C NMR (125 MHz) δ 157.4 (C), 145.4 (C), 134.9 (C), 133.7 (CH), 130.6 (CH), 79.0 (CH_2), 67.5 (C), 28.0 (CH_3), –0.6 (CH_3); HRMS (NSI^+) m/z: [$M+H^+$] Calcd for $C_{12}H_{20}NOSSi$ 254.1029; Found 254.1030.

This was followed by a second fraction which was recrystallized (PhMe) to give the title product (0.17 g, 13%) as brown crystals, mp 168–172 °C (dec.); IR 2978, 1622 cm^{-1}; ^1H NMR (500

MHz) δ (CD_3OD) 7.77 (d, $J = 5.0$ Hz, 1H), 5.73 (br s, 1H), 4.42 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (125 MHz) δ (CD_3OD) 196.0 (C), 161.6 (C), 144.2 (br s, CH), 112.2 (br s, CH), 91.2 (C), 82.2 (CH_2), 61.2 (C), 26.6 (CH_3); HRMS (NSI^+) m/z: [$M+H^+$] Calcd for $C_9H_{12}NO_2S$ 198.0583; Found 198.0580. Slow evaporation of a methanol solution gave crystals suitable for X-ray structure determination (CCDC No. 1481946)

(*E*)-3-(4,4-Dimethyloxazolidin-2-ylidene)thiophen-2(3*H*)-one (6): (small scale reaction) Under a nitrogen atmosphere, a 2.5 M solution of *n*-butyllithium in hexanes (0.40 mL, 1.0 mmol) was added to a solution of oxazoline **2** (0.181 g, 1.0 mmol) in dry THF (10 cm^3) stirred at –78 °C. After stirring at –78 °C for 1 h, bis(trimethylsilyl) peroxide (0.222 g, 1.24 mmol) was added and the reaction mixture was allowed to warm to rt over 18 h. The mixture was poured into saturated aq. NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried and evaporated and the residue was purified by preparative TLC (SiO_2, Et_2O/hexane 4:1) to give at R_f 0.90:

4,4-Dimethyl-2-(2-trimethylsilyl-3-thienyl)-4,5-dihydrooxazole (5) as a pale yellow oil **(**30.6 mg, 12%); IR 1717, 1643 cm^{-1}; ^1H NMR (500 MHz) δ 7.63 (d, $J = 5.0$ Hz, 1H), 7.47 (d, $J = 5.0$ Hz, 1H), 4.05 (s, 2H), 1.37 (s, 6H), 0.37 (s, 9H); ^{13}C NMR (125 MHz) δ 159.4 (C), 144.0 (C), 135.8 (C), 130.6 (CH), 129.5 (CH), 78.7 (CH_2), 67.5 (C), 28.4 (CH_3), 0.2 (CH_3); *m/z* (ES^+) 254.10 ($M+H^+$, 100%). HRMS (ES^+) m/z: [$M+H^+$] Calcd for $C_{12}H_{20}NOSSi$ 254.1029; Found 254.1021.

and at R_f 0.35:

the title compound **6** (28.2 mg, 14%) as orange crystals, mp 193–197 °C (dec.); IR 3248, 1622 cm^{-1}; ^1H NMR (400 MHz) δ 6.57 (d, $J = 6.8$ Hz, 1H), 6.05 (d, $J = 6.8$ Hz, 1H), 4.31 (s, 2H), 1.49 (s, 6H); ^{13}C NMR (100 MHz) 192.4 (C), 164.1 (C), 118.2 (CH), 108.1 (CH), 93.9 (C), 80.1

(CH_2), 59.3 (C), 27.1 (CH_3); *m/z* 614.14 ($3M+Na^+$, 4%), 417.09 ($2M+Na^+$, 41%), 220.04 ($M+Na^+$, 100%) and 198.06 ($M+H^+$, 15%). HRMS (ES^+) m/z: [$M+Na^+$] Calcd for $C_9H_{11}NNaO_2S$ 220.0403; Found 220.0395.

(*E*)-3-(4,4-Dimethyloxazolidin-2-ylidene)thiophen-2(3*H*)-one (6): (larger scale reaction) A 2.5 M solution of *n*-butyllithium in hexanes (11.0 mL, 27.5 mmol) was added dropwise to a solution of oxazoline **2** (4.53 g, 25.0 mmol) in dry THF (125 mL) stirred at –78 °C. After stirring at –78 °C for 5 min, the reaction mixture was allowed to warm to rt over 1 h then bis(trimethylsilyl) peroxide (5.35 g, 30.0 mmol) was added. After stirring at rt for 18 h, the reaction mixture was poured into saturated aq NH_4Cl (250 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried and evaporated. Recrystallization (EtOAc-hexane) gave the title compound (2.13 g, 43%) as orange crystals suitable for X-ray structure determination (CCDC No. 1481945)

Reaction of 6 with MeI

Methyl iodide (70 μL, 0.160 g, 1.12 mmol) was added to a stirred mixture of thiophenone **6** (0.197 g, 1.0mmol) and cesium carbonate (0.98 g, 3.01 mmol) in DMF (10 mL). The reaction mixture was stirred at rt for 18 h before being poured into water (100 mL) and extracted with CH_2Cl_2 (50 mL) and Et_2O (3 × 50 mL). The combined organic layers were washed with brine (×5) before being dried and evaporated. Filtration through a silica plug (Et_2O) followed by purification using preparative TLC (SiO_2, EtOAc/hexane 1:1) gave at R_f 0.50:

3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-methylthiophen-2(3*H*)-one (7) as a yellow oil (9.8 mg, 5%); IR 1736, 1684 cm^{-1}; ^1H NMR (400 MHz) δ 6.70 (d, $J = 7.6$ Hz, 1H), 5.95 (d, $J = 7.6$ Hz, 1H), 3.96 and 3.95 (AB pattern, $J = 8.4$ Hz, 2H), 1.57 (s, 3H), 1.29 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (125 MHz) δ 204.9 (C), 162.2 (C), 127.9 (CH), 123.5 (CH), 79.7 (CH_2), 67.2 (C), 59.2

(C), 28.2 (CH_3), 28.1 (CH_3), 20.9 (CH_3); HRMS (NSI^+) m/z: [$M+H^+$] Calcd for $C_{10}H_{14}NO_2S$ 212.0740; Found 212.0740.

and at R_f 0.40:

2-(2-Methoxy-3-thienyl)-4,4-dimethyl-4,5-dihydrooxazole (8) (17.5 mg, 8%) as a light brown solid, mp 105–108 °C; IR 1649 cm^{-1}; ^{1}H NMR (400 MHz) *δ* 7.17 (d, *J* = 6.0 Hz, 1H), 6.53 (d, *J* = 6.0 Hz, 1H), 4.04 (s, 3H), 4.03 (s, 2H), 1.36 (s, 6H); ^{13}C NMR (125 MHz) *δ* 167.9 (C), 158.0 (C), 126.9 (CH), 110.0 (CH), 108.3 (C), 78.5 (CH_2), 66.9 (C), 62.1 (CH_3), 28.4 (CH_3); HRMS ($ASAP^+$) m/z: [$M+H^+$] Calcd for $C_{10}H_{14}NO_2S$ 212.0740; Found 212.0739.

Reaction of 6 with Me_2SO_4

Dimethyl sulfate (0.10 cm^3, 0.133 g, 1.06 mmol) was added to a stirred mixture of thiophenone **6** (0.197 g, 1.00 mmol) and cesium carbonate (0.98 g, 3.01 mmol) in DMF (10 mL). The reaction mixture was stirred at rt for 18 h before being poured into water (100 mL) and extracted with CH_2Cl_2 (30 mL) and Et_2O (3 × 30 mL). The combined organic layers were washed with brine (×5), before being dried and evaporated. Filtration through a silica plug (EtOAc) gave **8** (66 mg, 31%) as a brown solid; spectroscopic data as above.

2-(2-Benzyloxy-3-thienyl)-4,4-dimethyl-4,5-dihydrooxazole (9): (with $PhCH_2OMs$) Benzyl methanesulfonate (0.77 g, 4.13 mmol) was added to a stirred mixture of thiophenone **6** (0.80 g, 4.06 mmol) and cesium carbonate (4.02 g, 12.3 mmol) in DMF (40 mL). The reaction mixture was stirred at rt for 3 d before being poured into water (150 mL) and extracted with CH_2Cl_2 (50 mL) and Et_2O (3 × 50 mL). The combined organic layers were washed with brine (×5) before being dried and evaporated. The crude residue was purified by column chromatography (SiO_2, Et_2O/hexane, 3:2) to give the title compound (0.62 g, 53%) as an orange oil; IR (ATR) 1636 cm^{-1}; ^{1}H NMR (500 MHz) *δ* 7.47–7.45 (m, 2H), 7.39–7.32 (m, 3H), 7.15 (d, *J* = 6.0 Hz, 1H), 6.55

(d, *J* = 6.0 Hz, 1H), 5.23 (s, 2H), 4.05 (s, 2H), 1.36 (s, 6H); ^{13}C NMR (125 MHz) *δ* 166.1 (C), 158.1 (C), 135.6 (C), 128.5 (2CH), 128.4 (CH), 127.8 (2CH), 126.4 (CH), 112.0 (CH), 111.2 (C), 78.7 (CH$_2$), 77.5 (CH$_2$), 66.8 (C), 28.5 (CH$_3$); HRMS (NSI$^+$) m/z: [M+H$^+$] Calcd for $C_{16}H_{18}NO_2S$ 288.1053; Found 288.1051.

2-(2-Benzyloxy-3-thienyl)-4,4-dimethyl-4,5-dihydrooxazole (9): (with PhCH$_2$Br) Benzyl bromide (120 μL, 0.173 g, 1.01 mmol) was added to a stirred mixture of thiophenone **6** (0.197 g, 1.0 mmol) and cesium carbonate (0.98 g, 3.01 mmol) in DMF (10 mL). The reaction mixture was stirred at rt for 3 d before being worked up as above to give the title compound (0.142 g, 49%) as an orange oil; spectroscopic data as above.

(*E*)-4,5,6,7-Tetrachloro-3-(4,4-dimethyloxazolidin-2-ylidene)-3a,7a-dihydrobenzo[*b*]thiophen-2(3*H*)-one (11): Tetrachlorothiophene *S,S*-dioxide (**10**; 0.254 g, 1.00 mmol) was added to a stirred solution of thiophenone **6** (0.198 g, 1.00 mmol) in CH$_2$Cl$_2$ (10 mL) and the reaction mixture was stirred at rt for 18 h. The precipitate was collected by filtration and washed with CH$_2$Cl$_2$ to give the title product (0.29 g, 75%) as a colourless solid, mp 307–310 °C (dec.); IR 3267, 1643 cm^{-1}; ^{1}H NMR (700 MHz) *δ* (CD$_3$SOCD$_3$) 9.04 (s, 1H), 5.13 (d, *J* = 8.4 Hz, 1H), 4.49 (d, *J* = 8.4 Hz, 1H), 4.21 (s, 2H), 1.35 (s, 3H) and 1.31 (s, 3H); ^{13}C NMR (175 MHz) *δ* (CD$_3$SOCD$_3$) 185.8 (C), 162.3 (C), 135.8 (C), 127.7 (C), 124.7 (C), 121.9 (C), 80.8 (C), 78.9 (CH$_2$), 59.3 (C), 51.9 (CH), 46.2 (CH), 25.9 (CH$_3$), 25.7 (CH$_3$); HRMS (NSI$^+$) m/z: [M+Na$^+$] Calcd for $C_{13}H_{11}{}^{35}Cl_4NO_2SNa$ 407.9157; Found 407.9157. Recrystallization (EtOH-MeCN) of a small sample gave crystals which were suitable for X-ray structure determination (CCDC No. 1481947).

Dimethyl 2-((*E*)-4-(4,4-dimethyloxazolidin-2-ylidene)-5-oxo-4,5-dihydrothiophen-2-yl)maleate (12): A mixture of dimethyl acetylenedicarboxylate (130 μL, 150 mg, 1.06 mmol) and thiophenone **6** (198 mg, 1.01 mmol) in methanol (10 mL) was heated at reflux for 2 days. The reaction mixture was evaporated and the residue was purified by repeated column chromatography (gradient elution, 9:1 Et_2O:hexane to EtOAc) to give the title product (144 mg, 42%) as yellow crystals, mp 145–147 °C (dec.); IR 3221, 1719, 1632 cm^{-1}; ^1H NMR (500 MHz) δ 9.42 (br s, 1H), 6.82 (s, 1H), 5.67 (s, 1H), 4.36 (s, 2H), 3.95 (s, 3H), 3.73 (s, 3H), 1.52 (s, 6H); ^{13}C NMR (125 MHz) δ 189.8 (C), 167.5 (C), 166.0 (C), 164.2 (C), 144.1 (C), 125.6 (CH), 118.8 (C), 110.5 (CH), 97.2 (C), 80.5 (CH_2), 60.0 (C), 52.9 (CH_3), 51.7 (CH_3), 27.1 (CH_3); HRMS (NSI^+) m/z: [$M+H^+$] Calcd for $C_{15}H_{18}NO_6S$ 340.0849; Found 340.0851.

The acyclic trisubstituted double bond geometry was determined to be (*E*) by the EXSIDE-HSQC technique which gave values of $^3J_{CH}$ = 14 Hz for $MeO_2C–C\underline{H}=C(\underline{C}O_2Me)CS$ and $^3J_{CH}$ = 7 Hz for $MeO_2C–C\underline{H}=C(CO_2Me)\underline{C}S$.

(1*E*,3a*S,8a*R**,*9E*,11a*S**,16a*R**)-1,9-Bis(4,4-dimethyloxazolidin-2-ylidene)-6,14-diphenyltetrahydro-2*H*,5*H*,10*H*,13*H*-thieno[2'',3'':4',5'][1,2,4]triazolo[1'',2'':1',2']pyrazolo[4',3':3,4]thieno[2',3':4,5]pyrazolo[1,2-*a*][1,2,4]triazole-2,5,7,10,13,15(6*H*,14*H*)-hexaone (14):** To a stirred solution of thiophenone **6** (98.5 mg, 0.50 mmol) in dichloromethane (5 mL) was added 4-phenyl-1,2,4-triazoline-3,5-dione (**13**; 87.4 mg, 0.50 mmol). The reaction mixture was stirred at rt for 24 h then the precipitated solid was collected by filtration and washed with Et_2O and CH_2Cl_2 to give the title product (76.0 mg, 62%) as a colourless solid, mp 237–240 °C (dec.); IR 3298, 1713, 1634, cm^{-1}; ^1H NMR (500 MHz) δ (CD_3COCD_3) 7.57–7.55 (m, 4H), 7.52–7.48 (m, 4H), 7.42–7.39 (m, 2H), 6.59 (s, 2H), 4.51 (s, 4H), 1.57 (s, 12H); ^{13}C NMR (125 MHz) δ (CD_3COCD_3) 187.9 (C), 164.4 (C), 153.4 (C), 152.0 (C), 132.9 (C), 129.6 (4CH), 128.7 (2CH), 126.8 (4CH), 117.4 (C), 115.5 (CH), 92.0 (C), 81.1 (CH_2), 60.8 (C), 26.6 (CH_3); HRMS (NSI^+) m/z: [$M+H^+$] Calcd for $C_{34}H_{31}N_8O_8S_2$

743.1701; Found 743.1717. Recrystallization (MeCN) of a small sample gave colourless crystals from which the structure and stereochemistry was determined by X-ray crystallography (CCDC No. 1481948).

Acknowledgment. We thank EPSRC (UK) for a DTA studentship (Grant EP/L505079/1) and the EPSRC UK National Mass Spectrometry Facility at Swansea University.

Supporting Information Available: Copies of NMR spectra for all new compounds and X-ray structural details for compounds **4**, **6**, **11** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hurd, C. D.; Kreuz, K. L. *J. Am. Chem. Soc.* **1950**, *72*, 5543–5546.

(2) Gronowitz, S.; Hoffman, R. A. *Arkiv Kemi* **1960**, *15*, 499–512.

(3) Hörnfeldt, A.-B.; Gronowitz, S. *Acta Chem. Scand.* **1962**, *16*, 789–791.

(4) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306–312.

(5) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837–860.

(6) DellaVecchia, L.; Vlattas, I. *J. Org. Chem.* **1977**, *42*, 2649–2650.

(7) Ribéreau, P.; Queguiner, G. *Tetrahedron* **1984**, *40*, 2107–2115.

(8) Carpenter, A. J.; Chadwick, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 173–181.

(9) Schöning, A.; Debaerdemeker, T.; Zander, M.; Friedrichsen, W. *Chem. Ber.* **1989**, *122*, 1119–1131.

(10) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 693–696.

(11) Iwao, M.; Lee, M. L.; Castle R. N. *J. Heterocycl. Chem.* **1980**, *17*, 1259–1264.

(12) Pratap, R.; Lee, M. L.; Castle, R. N. *J. Heterocycl. Chem.* **1981**, *18*, 1457–1459.

(13) Taddei, M.; Ricci, A. *Synthesis* **1986**, 633–635.

(14) Halvorsen, H.; Hope, H.; Skramstad, J. *Synth. Commun.* **2007**, *37*, 1167–1177.

(15) Zhang, Y.; Hörnfeldt, A.-B.; Gronowitz, S.; Stalhandske, C. *Acta Chem. Scand.* **1994**, *48*, 843–849.

(16) Evans, N. R.; White, A. J. P. *Org. Biomol. Chem.* **2013**, *11*, 3871–3879.

(17) Fukazawa, A.; Adachi, M.; Nakakura, K.; Saito, S.; Yamaguchi, S. *Chem. Commun.* **2013**, *49*, 7117–7119.

(18) Bogdanov, V. S.; Kalik, M. A.; Gol'farb, Ya. L. *Bull. Acad. Sci. USSR, Chem. Ser.* **1970**, *19*, 2278–2278.

(19) Negrebetskii, V. V.; Bogdanov, V. S.; Kessenikh, A. V. *J. Struct. Chem. USSR* **1971**, *12*, 649–651.

(20) Bogdanov, V. S.; Kalik, M. A.; Zhidomirov, G. M.; Chuvylkin, N. D.; Gol'farb, Ya. L. *J. Org. Chem. USSR (Engl. Transl.)* **1971**, *7*, 2025–2031.

(21) Minkin, V. I.; Kosobutski, V. A.; Simkin, B. Ya.; Zhdanov, Yu. A. *J. Mol. Struct.* **1975**, *24*, 237–248.

(22) Simkin, B. Ya.; Bren', V. A.; Minkin, V. I. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 1581–1593.

(23) Kvitko, I. Ya. *J. Org. Chem. USSR (Engl. Transl.)* **1979**, *15*, 2341–2345.

(24) see for example, Pedersen, E. B.; Lawesson, S.-O. *Tetrahedron* **1970**, *26*, 2959–2974.

(25) Van de Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367–5405.

(26) Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210–9215.

(27) Willis, N. J.; Bray, C. D. *Chem. Eur. J.* **2012**, *18*, 9160–9173.

(28) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.-L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655–3664.

(29) Caruana, L.; Fochi, M.; Bernardi, L. *Molecules* **2015**, *20*, 11733–11764.

(30) Wang, Z; Sun, J. *Synthesis* **2015**, *47*, 3629–3644.

(31) Raasch, M. S. *J. Org. Chem.* **1980**, *45*, 856–867.

(32) Walter, H.; Rothen, H. P.; Winkler, T. *J. Prakt. Chem.* **2000**, *342*, 75–79.

(32) Culshaw, P. N.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1201–1208.

(33) Bausch, M. J.; David, B. *J. Org. Chem.* **1992**, *57*, 1118–1124.

(34) Campaigne, E.; LeSuer, W. M. *Org. Synth.* **1953**, *33*, 94–95.

(Graphical Abstract)