Chemical and spectroscopic properties of the 3-hydroxythiophene [thiophen-3(2*H*)-one] system†

Gordon A. Hunter and Hamish McNab*

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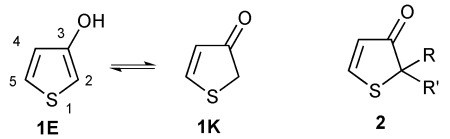
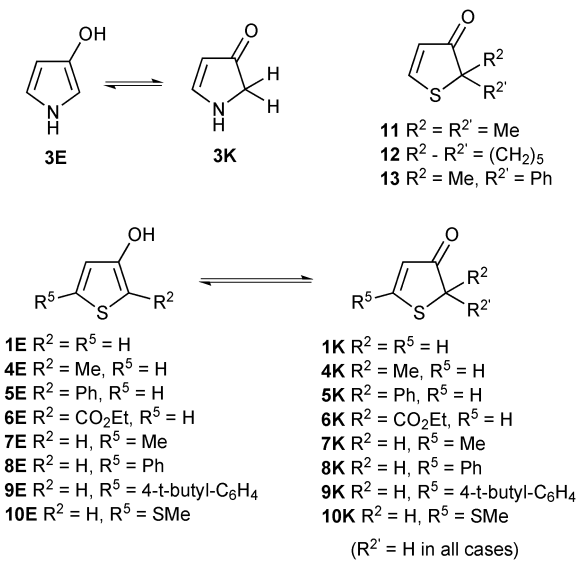
3-Hydroxythiophene **1** spontaneously dimerises to 4,5-dihydro-5-(3-hydroxythien-2-yl)thiophen-3(2*H*)-one **14**. 3-Hydroxythiophenes **1E** and **4–10E** exist in solvent-dependent equilibrium with their thiophen-3(2*H*)-one **1K** and **4–10K** tautomers; the amount of hydroxy tautomer is greater than in the case of the corresponding 3-hydroxypyrroles. 3-Hydroxythiophenes are much less reactive to electrophiles than corresponding 3-hydroxypyrroles, but the 5-methylsulfanyl derivative **10** reacts at the 2-position with methoxymethylene Meldrum's acid and undergoes Vilsmeier formylation. The enolates derived from 3-hydroxythiophenes by treatment with base can be *O*-alkylated and *O*-acylated with high regioselectivity. 2,2-Disubstituted thiophen-3(2*H*)-ones undergo equilibrium conjugate addition with nucleophiles, but the resulting adducts could not be isolated.

Introduction

The thiophene system is one of the most fundamental heterocyclic entities and the hydroxy-substituent is similarly central to organic chemistry as a whole. A comprehensive review of hydroxythiophene systems was published nearly 25 years ago, but at that stage 3-hydroxythiophene **1** and its simple mono-substituted derivatives were thought to be too unstable to be investigated.[1] However, flash vacuum pyrolysis (FVP) of 5-thioalkylmethylene derivatives of Meldrum's acid[2] provides a convenient route to the parent compound (as a mixture of enol **1E** and keto **1K** forms) and a range of 2-substituted and 5-substituted 3-hydroxythiophenes [thiophen-3(2*H*)-ones]. Products were isolated at low temperatures in the absence of reagents and therefore can be rapidly transferred from the FVP trap to the bench for reactivity studies. The more stable 2,2-disubstituted thiophen-3(2*H*)-ones **2**, locked in the keto form, are also available by the FVP strategy. Very little work on the properties of simple 3-hydroxythiophenes has been published since the mid-1980s,[1] though X-ray crystal structures,[3] EPR spectra,[4] S-oxidation[5] and alkylation of various derivatives[6] have been reported. There is considerable patent activity in the use of 5-trifluoromethyl derivatives as herbicides.[7]



In the work described in this paper, we present an overview of the chemistry of 3-hydroxythiophene **1** and some simple mono-substituted derivatives, ranging from general stability, tautomerism and NMR spectroscopic parameters to typical reactions with electrophiles and nucleophiles. Corresponding information for *N*-substituted 3-hydroxypyrroles[8] [1*H*-pyrrol-3(2*H*)-ones] has been published (tautomerism,[9] NMR spectra,[10] reactions with electrophiles,[11] and reactions with nucleophiles[11a]) and we have recently reported data for the parent 1*H*-pyrrol-3(2*H*)-one[12] (3-hydroxypyrrole) **3** thus allowing comparison between two closely related, highly reactive, fundamental heterocyclic systems.



Results and discussion

This paper will focus on the 3-hydroxythiophene [thiophen-3(2*H*)-ones] **1** and **4–10** and the thiophen-3(2*H*)-ones **11–13**, all of which were made by the FVP strategy previously reported.[2]

General stability

Most 3-hydroxythiophenes prepared by FVP are reasonably stable compounds that can be stored at −20 °C almost

School of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, UK. E-mail: H.McNab@ed.ac.uk; Fax: + 44 (0)131 650 4743; Tel: + 44 (0)131 650 4718

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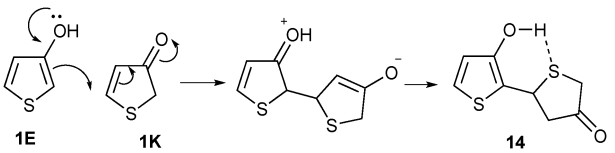
indefinitely, though the 2-methyl derivative is an exception. It is thought to form a dimer[13] though we were unable to confirm this observation. Instead, we found that the parent compound **1** dimerises spontaneously at room temperature or below, either as the neat material or in solution, over a period of a few days. The ^{1}H NMR spectrum of the product showed two adjacent 'thiophene' protons at δ_H 7.01 and 6.62, and two sets of geminally coupled aliphatic protons [δ_H 3.51 and 3.37 (^2J 17.7 Hz): 2.96 (dd) and 2.83 (dd) (^2J 17.8 Hz)]. The ^{13}C NMR spectrum showed the presence of one carbonyl group (δ_C 212.69). These data are consistent with the conjugate addition product **14**, formed by the 3-hydroxythiophene acting as the donor and the thiophen-3(2*H*)-one acting as the acceptor (Scheme 1). Coincidentally, analogous dimerisation by Michael addition under basic conditions is shown by 2-hydroxythiophene and some of its derivatives.[14]

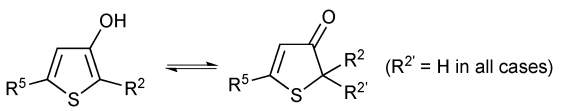
Tautomerism[15]

As found previously for the 3-hydroxypyrrole system,[9,16] most 3-hydroxythiophenes **1E** and **4–10E** exist in solution in equilibrium with their thiophen-3(2*H*)-one tautomers **1K** and **4–10K**. The amount of the keto tautomer is greatest in non-polar solvents (Table 1) and the amount of the hydroxy tautomer is generally greater than for the corresponding 1-substituted 3-hydroxypyrrole system (*cf.* ref. 9). For example, the keto–enol ratio for 3-hydroxythiophene **1** is 74 : 26 in $CDCl_3$ and <1 : 99 in d_6-acetone; the corresponding values for 1-*tert*-butyl-3-hydroxypyrrole in the same solvents are 90 : 10 and 25 : 75, respectively.[9]



Scheme 1

Table 1 Effect of solvent on the keto : enol ratio of selected 3-hydroxythiophenes **1**



R^2	R^5	Solvent	Keto : enol ratio
H	H	$CDCl_3$	74 : 26
H	H	CD_3CN	8 : 92
H	H	d_8-THF	<1 : 99
H	H	d_6-Acetone	<1 : 99
H	H	CD_3OD	<1 : 99
H	H	d_6-DMSO	<1 : 99
Me	H	$CDCl_3$	33 : 67
Me	H	d_6-DMSO	3 : 97
Ph	H	$CDCl_3$	<1 : 99
CO_2Et	H	$CDCl_3$	<1 : 99
H	Me	$CDCl_3$	>99 : 1
H	Me	d_6-DMSO	<1 : 99
H	Ph	$CDCl_3$	>99 : 1
H	Ph	d_6-DMSO	<1 : 99
H	SMe	$CDCl_3$	>99 : 1
H	SMe	d_6-DMSO	72 : 28

Previously, it was thought that, of the three possible monomethyl derivatives, only the 2-substituted compound **4** was stable enough for measurement of tautomeric equilibrium composition.[13] Our result for **4** (keto : enol 33 : 67 in chloroform) is in reasonable agreement with the published data (keto : enol 20 : 80, in CS_2 solution). The 5-methyl derivative **7** shows a much increased level of keto tautomer (keto : enol >99 : 1 in chloroform).

As previously reported,[17] substituents in the 2-position that can conjugate to the hydroxy-group (*e.g.* Ph, CO_2Et) increase the amount of enol tautomer. On the other hand, electron donating substituents in the 5-position that can conjugate to the enone unit increase the amount of keto form; thus the keto form of the 5-methylsulfanyl compound **10K** dominates, even in d_6-DMSO solution.

3-Hydroxythiophenes—^{1}H and ^{13}C NMR spectra

^{1}H NMR spectroscopic data for a range of 3-hydroxythiophenes (mostly 2,5-disubstituted) have been collated.[1] Tables of ^{1}H and ^{13}C NMR data for the 3-hydroxythiophene tautomer of a range of mono-substituted derivatives are provided in the ESI† and data for 3-hydroxythiophene **1E** itself are shown in Fig. 1.

The parameters are clearly those of a highly electron rich heteroaromatic system, with δ_H in the range 6.29–7.10 and δ_C in the range 98.0–124.4. However, the corresponding figures of 3-hydroxypyrrole[12] **3E** are δ_H 5.61–6.43 and δ_C 98.19–114.99. Whereas the 2-position is the site of lowest chemical shift in the 3-hydroxythiophenes it is the 4-position that has the lowest chemical shift in the 3-hydroxypyrrole series. The proton–proton coupling constant $^3J_{4,5}$ of **1E** (5.1 Hz) is much larger than for 3-hydroxypyrrole **3E**[12] (2.7 Hz). As commonly found for thiophenes in general,[18] the magnitude of $^1J_{CH}$ is *ca.* 15–20 Hz larger for the positions adjacent to the heteroatom, than for the 4-position.

3-Alkoxythiophenes and 3-acetoxythiophenes (see below) have generally similar parameters to their 3-hydroxy analogues (ESI†), though the acetoxy compound **21** shows significant deshielding at H-2 and C-2 with respect to the other compounds.

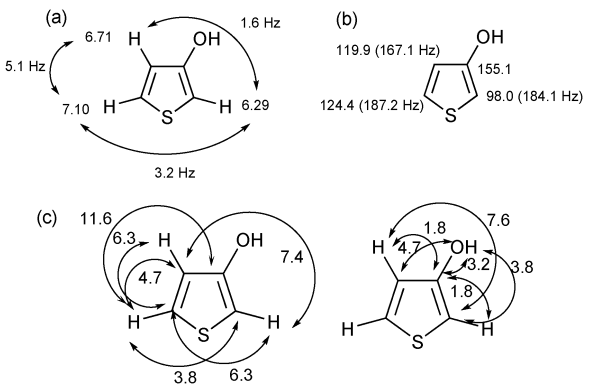


Fig. 1 (a) ^{1}H NMR parameters of **1E** in $CDCl_3$ solution; (b) ^{13}C NMR chemical shifts and one-bond ^{1}H–^{13}C coupling constants (in parentheses) of **1E**; (c) long range ^{1}H–^{13}C coupling constants of **1E** (in Hz).

Thiophen-3(2*H*)-ones—^{1}H and ^{13}C NMR spectra

Tables of ^{1}H and ^{13}C NMR data for the thiophen-3(2*H*)-one tautomer of a range of derivatives are provided in the ESI†, augmenting some previously reported data.[1] Parameters for thiophen-3(2*H*)-one **1K** itself are shown in Fig. 2.

In the ^{1}H NMR spectrum a widely spaced doublet, typical of a push–pull conjugated system, is observed for H-4 (δ_H 6.22, $^3J_{4,5}$ 5.7 Hz) and H-5 (δ_H 8.16) and these effects are also reflected in the ^{13}C NMR spectrum (C-4, δ_C 123.4; C-5 δ_C 164.9). Corresponding parameters for the 1*H*-1-*tert*-butylpyrrol-3(2*H*)-one are H-4, δ_H 5.09 $^3J_{4,5}$ 3.4 Hz; H-5, δ_H 7.93; C-4 δ_C 99.13; C-5 δ_C 162.58. The major differences between the two systems are the chemical shifts of the 4-position, which show the increased electron density in the enamine substructure of the pyrrolone *vis-à-vis* the enol thioether substructure of the thiophenones. The three bond coupling constant $^3J_{4,5}$ is also much larger in the thiophenone than the pyrrolone. Similar differences have been noted in open-chain aminopropenals and alkylsulfanylpropenals.[19]

Reactions with electrophiles at carbon and oxygen

Thiophen-3(2*H*)-ones are smoothly *O*-protonated by TFA, causing deshielding of all protons in the ^{1}H NMR spectrum. Data for the parent compound are presented in Fig. 3. Maximum deshielding relative to the neutral thiophenone (0.68 ppm) is observed at H-5; by comparison, the deshielding observed in the 1*H*-1-*tert*-butylpyrrol-3(2*H*)-one ranges between 0.69 and 0.90 ppm.[20] This suggests that the thiophenone is less basic than the pyrrolone and that equilibrium protonation in TFA is less complete in the thiophenone case.

In DTFA, 2,2-disubstituted pyrrolones underwent deuterium exchange at the 4-position only; 2,2-unsubstituted examples underwent exchange at the 4-position and, more slowly, at the 2-position, but not at the 5-position.[19] The thiophenones **11–13** showed very different behaviour. No exchange occurred in these 2,2-disubstituted examples, even after many weeks at room temperature. This reflects the low reactivity towards electrophiles of the thioenol ether *vis-à-vis* enamine substructures. In contrast, the parent thiophenone **1** underwent exchange at all three sites, in the order 2 > 5 > 4. Taken together with the result for **11–13**, it appears that exchange occurs *via* the hydroxythiophene form only.

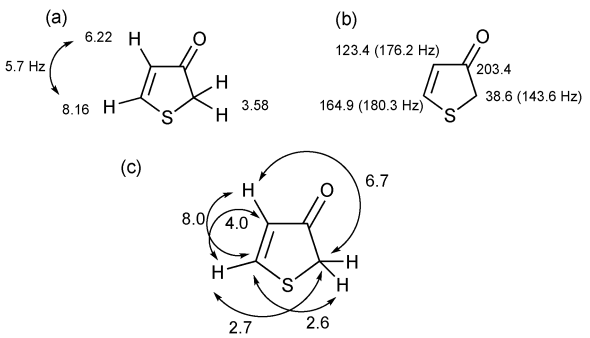


Fig. 2 (a) ^{1}H NMR parameters of **1K** in $CDCl_3$ solution; (b) ^{13}C NMR chemical shifts and one-bond ^{1}H–^{13}C coupling constants (in parentheses) of **1K**; (c) long range ^{1}H–^{13}C coupling constants of **1K** (in Hz); couplings from C-3 were too complex for assignment.

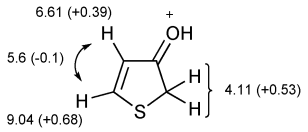
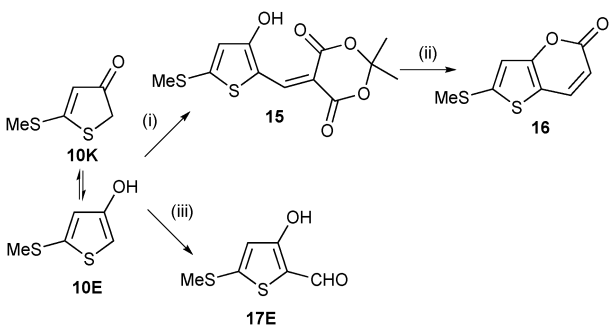


Fig. 3 ^{1}H NMR parameters of **1** in TFA (difference from unprotonated species shown in parentheses).

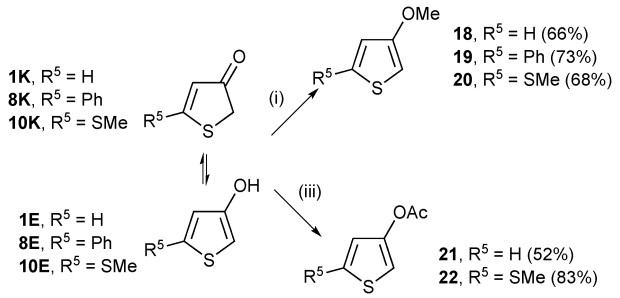
Both 3-hydroxypyrroles and 2,2-disubstituted 1*H*-pyrrol-3(2*H*)-ones react readily with methoxymethylene Meldrum's acid to give substitution products under mild conditions.[11c] Under the same conditions, reaction of the parent thiophenone **1** led only to decomposition and that of the 2,2-disubstituted thiophenone **11** also failed. Reaction of the more electron-rich 5-methylsulfanyl derivative **10** was successful, but slow; owing to its insolubility, it was not possible to assign regiochemistry of the product by NMR spectroscopy. FVP of this compound at 650 °C provided a fused pyrone (50%); irradiation of the *S*-methyl group in an NOE experiment caused enhancement of a singlet, confirming the product to be 2-methylsulfanyl-thieno[3,2-*b*]pyran-5-one **16**. Hence the original reaction with methoxymethylene Meldrum's acid must have taken place at the 2-position, *via* the hydroxythiophene form **10E** to give **15** (Scheme 2). Similarly, Vilsmeier formylation of **10** gave the 2-carboxaldehyde **17E** (60%). Simple 3-hydroxythiophenes can therefore react in the 2-position with certain electrophiles, but they are much less reactive than the corresponding 3-hydroxypyrrole and many attempted reactions resulted only in decomposition; similar problems have been encountered by earlier workers in the field.[21]

It is known that the ambident anions derived from 3-hydroxypyrroles[22] and 3-hydroxythiophenes[6,23] can be *C*-alkylated or *O*-alkylated. Conditions for totally regioselective *O*-alkylation of the enolate derived from *N*-substituted 1*H*-pyrrol-3(2*H*)-ones were developed utilising a hard base (sodium hydride) and alkylating agent (alkyl tosylate) and a highly polar aprotic solvent [*N*,*N*′-dimethylimidazolidinone (DMI)]. These conditions were successfully applied to regioselective *O*-alkylation of thiophen-3(2*H*)-ones[24] [and, indeed, a furan-3(2*H*)-one (ESI†)] to provide **18–20** (66–73%) though longer reaction times are required than for the hydroxypyrroles (Scheme 3).

As previously reported,[25] acylation of 3-hydroxythiophenes had no regiochemical issues, giving the *O*-acylated products **21–22** exclusively when acetyl chloride and triethylamine were used in THF (Scheme 3).



Scheme 2 *Reagents and conditions*: (i) methoxymethylene Meldrum's acid, CH_3CN, 48 h; (ii) FVP, 650 °C, 0.001 Torr; (iii) DMF/$POCl_3$, 1 h.



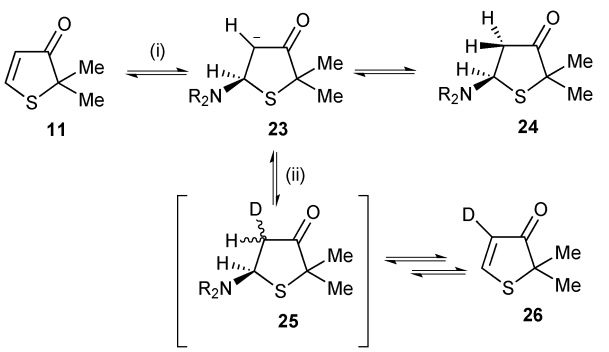
Scheme 3 *Reagents and conditions*: (i) NaH, MeOTs, DMI, 24 h; (ii) AcCl, Et_3N, THF.

Reactions with nucleophiles

3-Hydroxypyrroles do not react with nucleophiles, though when fixed in the 1*H*-pyrrol-3(2*H*)-one form, deuterium exchange of the 5-proton of 4-halogeno derivatives takes place under strongly basic conditions.[11a] In view of the spontaneous dimerisation of 3-hydroxythiophene (Scheme 1) it was expected that other thiophen-3(2*H*)-ones should be able to act as Michael acceptors in reactions with nucleophiles, as found for thiophen-2(5*H*)-ones.[26]

In practice, treatment of 2,2-dimethylthiophen-3(2*H*)-one **11** with morpholine gave evidence of 50–60% conjugate addition, with *in situ* formation of **24** in a range of deuterated solvents (acetonitrile, DMSO, benzene, acetone, and chloroform). The amount of conjugate addition could be increased to *ca.* 80% by using a five-fold excess of secondary amine. However, all attempts to isolate the conjugate addition product failed, which suggests that **11** and **24** exist in equilibrium. There is some evidence for this when d_4-methanol was used as solvent. Although the adduct **25** could not be detected, deuterium exchange at the 4-position *via* the enolate **23** was observed after a few hours (Scheme 4). When d_6-acetone was used as solvent, evidence of deuterium exchange was observed with signals characteristic of both **25** and **26** present after 9 days.

Only the deuterium exchange product **26** was observed when a primary amine was used in place of morpholine (*tert*-butylamine, 90% exchange after 9 days; aniline, 15% exchange after 9 days). Thiophenol provided *ca.* 50% conjugate addition, but only in the presence of triethylamine.



Scheme 4 *Reagents and conditions*: (i) morpholine/solvent; (ii) morpholine/d_4-methanol.

Conclusions

In this paper, we have reported the first systematic study of the properties of 3-hydroxythiophene **1** and some of its simple mono-substituted derivatives. Although 3-hydroxythiophene itself dimerises spontaneously by a conjugate addition process, when freshly prepared it can be protonated in TFA and can undergo deuterium exchange at all positions in DTFA. It exists as a solvent-dependent mixture of keto and enol tautomers, with a higher proportion of enol **1E** than comparable 3-hydroxypyrroles. It can be *O*-alkylated and *O*-acylated under appropriate basic conditions with high selectivity. Compared with 3-hydroxypyrroles, the corresponding thiophenes are much less reactive towards electrophiles, and this is reflected in the more shielded positions of the ring resonances in both ^1H and ^{13}C NMR spectra. These properties of 3-hydroxythiophenes have been exploited in the synthesis of thiophene analogues of the prodigiosin series of natural products.[24]

Experimental

^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, for solutions in [^2H]chloroform, used as supplied, unless otherwise stated. Residual solvent peaks were used for calibration. Spectra were recorded at the ambient temperature of the probe (297 K), at typical concentrations of 30 mg per 0.5 cm^3 and at a resolution of 0.27 Hz per data point. Coupling constants are quoted in Hz. Mass spectra were recorded under electron impact conditions.

Stability of thiophen-3(2*H*)-ones

The majority of thiophen-3(2*H*)-one derivatives had lengthy shelf-lives when stored at −20 °C. However the neat unsubstituted thiophen-3(2*H*)-one **1** dimerised slowly and reasonably cleanly, even at −20 °C, to provide a single product. In chloroform solution at room temperature the dimer was formed faster but with significant decomposition.

When the neat material was stored at −5 °C for 7 days, analysis by ^1H NMR spectroscopy showed that the crude product was mostly the dimer with very little evidence of other decomposition. This crude material was purified by dry flash chromatography (silica, using ethyl acetate and *n*-hexane as eluent) to give 4,5-dihydro-5-(3-hydroxythien-2-yl)thiophen-3(2*H*)-one **14** (60%; contains *ca.* 5% **1**) bp 170 °C (0.2 Torr) (decomp.) (found: M^+ 199.9968. $C_8H_8S_2O_2$ requires M, 199.9966); δ_H 7.01 (1H, d, ^3J 5.4), 6.62 (1H, d, ^3J 5.4), 4.91 (1H, t, ^3J 7.4), 3.51 (1H, d, ^2J 17.7), 3.37 (1H, d, ^2J 17. 7), 2.96 (1H, dd, ^2J 17.8, ^3J 7.4), and 2.83 (1H, dd, ^2J 17.8, ^3J 7.4); δ_C 212.69 (quat), 150.38 (quat), 122.30, 120.46, 117.29 (quat), 47.34, 39.41 and 37.80; *m*/*z* 200 (M^+, 57%), 153 (53), 126 (100), 125 (20), 100 (25), 97 (61), 72 (24) and 71 (31).

In contrast to previous reports,[13] 2-methylthiophen-3(2*H*)-one **4** was found to undergo decomposition at −20 °C and had a limited shelf-life.

Protonation of thiophen-3(2*H*)-ones

These experiments were carried out by *in situ* observation using NMR spectroscopy. The appropriate thiophen-3(2*H*)-one (25–50 mg) was dissolved in trifluoroacetic acid and

spectra were obtained using an external D_2O lock. The deuterium exchange of the protonated substrate was observed using [^{2}H]trifluoroacetic acid.

2,2-Dimethyl-5-(3-hydroxy-5-methylsulfanyl-2-thienylmethylene)-1,3-dioxane-4,6-dione 15

A solution of freshly prepared 2,2-dimethyl-5-methoxymethylene-l,3-dioxane-4,6-dione (0.93 g, 5 mmol) in acetonitrile (10 cm^3) was added to a stirred solution of 5-methylsulfanylthiophen-3(2*H*)-one **10** (0.73 g, 5 mmol) in acetonitrile (15 cm^3). The resulting solution was stirred for 48 h at room temperature. The product was obtained as a precipitate which was filtered, dried and recrystallised from acetonitrile to give 2,2-dimethyl-5-(3-hydroxy-5-methylsulfanyl-2-thienylmethylene)-1,3-dioxane-4,6-dione **15** (0.98 g, 65%), mp 168–170 °C (from acetonitrile) (found: C, 48.0; H, 4.05%. $C_{12}H_{12}O_5S_2$ requires C, 48.0; H, 4.0%); δ_H ([$^2H_6$]DMSO) (OH undetected) 8.50 (1H, s), 6.71 (1H, s), 2.70 (3H, s) and 1.65 (6H, s); δ_C 170.50 (2 quat), 163.80 (quat), 162.92 (quat), 140.69, 113.70, 113.23 (quat), 103.25 (quat), 95.59 (quat), 26.57 (2 CH_3) and 16.06 (CH_3); *m*/*z* 300 (M^+, 23%), 242 (100), 198 (31), 170 (96), 155 (71), 98 (39), 85 (61), 72 (24), 70 (28) and 69 (58).

The analogous reactions involving thiophen-3(2*H*)-one **1** and the 2,2-dimethyl-derivative **11** resulted only in decomposition.

2-Methylsulfanylthieno[3,2-*b*]pyran-5-one 16

FVP of **15** using the following parameters: furnace temperature T_f 650 °C, inlet temperature T_i 180 °C, pressure 0.001 Torr, time of pyrolysis 2 h, gave 2-methylsulfanylthieno[3,2-*b*]-pyran-5-one **16** (50%) mp 100–102 °C (from cyclohexane) (found: C, 48.2; H, 3.0%. $C_8H_6O_2S_2$ requires C, 48.5; H, 3.05%); δ_H 7.56 (1H, dd, ^3J 9.6 and ^5J 0.6), 6.87 (1H, d, ^5J 0.6), 6.14 (1H, d, ^3J 9.6) and 2.58 (3H, s); δ_C 161.10 (quat), 155.90 (quat), 146.25 (quat), 137.39, 116.69, 115.74 (quat), 109.73 and 19.36; *m*/*z* 198 (M^+, 100%), 170 (87), 155 (88), 98 (56), 85 (69), 70 (50), 69 (56) and 57 (20).

3-Hydroxy-5-methylsulfanylthiophene-2-carboxaldehyde 17

Phosphoryl chloride (2 cm^3) was dissolved in DMF (10 cm^3) at room temperature with stirring. A solution of 5-methylsulfanylthiophen-3(2*H*)-one **10** (140 mg, 1 mmol) in DMF (10 cm^3) was added in portions at room temperature with rapid stirring. After the addition was complete, the reaction was stirred at room temperature for a further 1 h. The reaction mixture was poured onto crushed ice and hydrolysed with sodium hydroxide solution (2 M; 25 cm^3). After the ice had melted, the resulting solution was acidified (2 M HC1) to pH 6–7 and extracted with ether (3 × 50 cm^3). The combined organic layers were washed with water (2 × 50 cm^3) and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a solid that was recrystallised to give 3-hydroxy-5-methylsulfanylthiophene-2-carboxaldehyde **17** (100 mg, 60%) mp 118–120 °C (decomp.) (from cyclohexane) (found: M^+ 173.9809. $C_6H_6O_2S_2$ requires M 173.9807); δ_H 9.40 (1H, s), 8.86 (1H, br s), 6.54 (1H, s) and 1.24 (3H, s); δ_C 183.06, 166.72 (quat), 155.26 (quat), 115.95, 114.24 (quat) and 17.68; *m*/*z* 174 (M^+, 90%), 173 (46), 103 (32), 85 (79), 74 (63), 73 (34), 72 (34), 69 (67), 57 (34) and 45 (100).

Alkylation

The general conditions developed for the regioselective *O*-alkylation of the pyrrol-3(2*H*)-ones were also found to be applicable to the corresponding thiophen-3(2*H*)-ones,[6,21,23] though a longer reaction time was required (12 h at room temperature rather than 1 h for the pyrrolones). Thus, a solution of the hydroxythiophene (2 mmol) in dimethylimidazolidinone (5 cm^3) was added under nitrogen to a stirred suspension of sodium hydride (80% dispersion in oil, 0.288 g, *ca.* 6 mmol) in dimethylimidazolidinone (20 cm^3). A solution of methyl *p*-toluenesulfonate (0.372 g, 2 mmol) in dimethylimidazolidinone (4 cm^3) was added dropwise and the resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched with ethanol/water (40 cm^3, 1 : 1) and extracted with ether (3 × 50 cm^3). The combined organic layers were back-extracted with water (5 × 100 cm^3), dried ($MgSO_4$) and the solvent removed under reduced pressure. The following 3-alkoxythiophenes were prepared:

3-Methoxythiophene **18** (66%) bp 65–67 °C (0.1 Torr) [lit.,[27] 81–82 °C (65 Torr)] δ_H 7.20 (1H, dd, ^3J 5.2 and ^4J 3.1), 6.79 (1H, dd, ^3J 5.2 and ^4J 1.6), 6.28 (1H, dd, ^4J 1.6 and 3.1) and 3.82 (3H, s); δ_C 158.70 (quat), 124.67, 119.16, 96.53 and 57.21.

3-Methoxy-5-phenylthiophene **19** (73%) bp 112–114 °C (0.2 Torr) [lit.,[28] 141–142 °C (3 Torr)]; δ_H 7.61–7.29 (5H, m), 7.01 (1H, d, ^4J 1.7), 6.22 (1H, d, ^4J 1.7) and 3.83 (3H, s); δ_C 158.58 (quat), 142.83 (quat), 134.26 (quat), 128.74, 127.64, 125.31, 115.25, 96.31 and 57.03; *m*/*z* 190 (M^+, 17%), 178 (27), 147 (5), 114 (6) and 69 (100).

3-Methoxy-5-methylsulfanylthiophene **20** (68%) bp 71–73 °C (0.2 Torr) (found: C, 45.1; H, 4.95%. $C_6H_8OS_2$ requires C, 45.0; H, 5.0%); δ_H 6.71 (1H, d, ^4J 1.7), 6.17 (1H, d, ^4J 1.7), 3.74 (3H, s) and 2.45 (3H, s); δ_C 157.60 (quat), 136.58 (quat), 122.07, 98.65, 56.88 and 21.17; *m*/*z* 160 (M^+, 100%), 146 (45), 145 (36), 85 (30) and 69 (14).

Acylation

The appropriate thiophen-3(2*H*)-one (1 mmol) was dissolved in THF (3 cm^3). Triethylamine (1.1 mmol) was added with stirring followed by a solution of acetyl chloride (5 mmol) in THF (3 cm^3). The reaction mixture was stirred at room temperature for 1 h before being quenched with a mixture of ethanol (10 cm^3) and water (20 cm^3). The aqueous solution was extracted with dichloromethane (3 × 15 cm^3), the combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. The following 3-acetoxythiophenes were prepared, the precursor thiophen-3(2*H*)-one is indicated in brackets.

3-Acetoxythiophene **21** [thiophen-3(2*H*)-one] (52%) bp 68–69 °C (0.2 Torr) (found: C, 50.6; H, 4.35%. $C_6H_6O_2S$ requires C, 50.7; H, 4.25%); δ_H 7.23 (1H, dd, ^3J 5.3 and ^4J 3.4), 7.09 (1H, dd, ^4J 1.4 and 3.4), 6.90 (1H, dd, ^3J 5.3 and ^4J 1.4) and 2.26 (3H, s); δ_C 168.38 (quat), 146.91 (quat), 124.03, 121.16, 110.71 and 20.85; *m*/*z* 142 (M^+, 26%), 100 (100), 71 (41) and 70 (13).

3-Acetoxy-5-methylsulfanylthiophene **22** [(5-methylsulfanylthiophen-3(2*H*)-one] (83%) bp 100 °C (0.2 Torr) (found: C, 44.7; H, 4.25%. $C_7H_8O_2S_2$ requires C, 44.7; H, 4.25%); δ_H 6.96 (1H, d, ^4J 1.6), 6.83 (1H, d, ^4J 1.6), 2.41 (3H, s) and 2.16

(3H, s); δ_C 168.06 (quat), 145.88 (quat), 136.20 (quat), 124.18, 112.87, 21.32 and 20.69; *m*/*z* 188 (M^+, 22%), 146 (100), 131 (42), 103 (18) and 85 (10).

Reaction of thiophenones with nucleophiles

2,2-Dimethylthiophen-3(2*H*)-one **11** (64 mg, 0.5 mmol) was dissolved in a deuterated solvent and its ^{1}H NMR spectrum monitored in the presence of various amines (1–5 equiv.). After a period of between 10 min to 4 h, equilibrium conjugate addition was attained and the products were characterised by the signals at around δ_H 4.8 (^3J 8.4 and 3.4 Hz), 3.2 (^2J 17.7 and ^3J 8.4 Hz) and 2.7 (^2J 17.7 and ^3J 3.4 Hz).

A similar experiment involving thiophenol (1 equiv.) in deuterated chloroform showed no reaction. However in the presence of triethylamine (1 equiv.) equilibrium conjugate addition was observed in less than 10 min. The product was again characterised by the definitive peaks in the ^{1}H NMR spectrum.

When attempts were made to isolate the addition products by 'flash evaporation' of the solvent under reduced pressure, only mixtures of starting materials and product could be obtained. Identical experiments carried out with the 5-methylsulfanylthiophen-3(2*H*)-one **10** showed no reaction with any combination of solvent or amine even at elevated temperatures (79 °C).

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