JOC Article

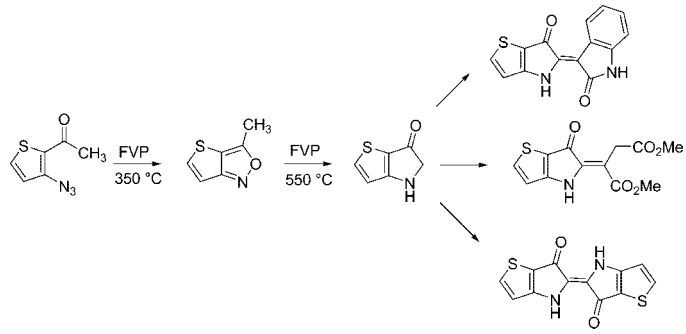
Synthesis and Chemistry of 4,5-Dihydrothieno[3,2-*b*]pyrrol-6-one—A Heteroindoxyl

Alexander P. Gaywood and Hamish McNab*

School of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, United Kingdom

H.McNab@ed.ac.uk

Received March 6, 2009

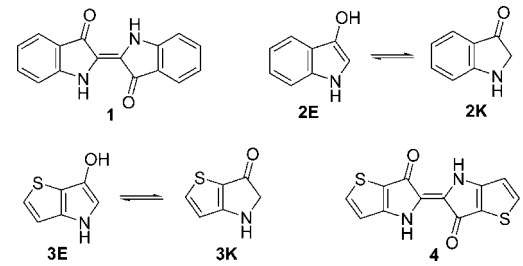


Flash vacuum pyrolysis (FVP) of 2-acetyl-3-azidothiophene gives 3-methylthieno[3,2-*c*]isoxazole as the major product at a furnace temperature of 350 °C whereas at temperatures above 550 °C the new heteroindoxyl 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one is exclusively formed. The heteroindoxyl exists predominantly as the keto tautomer. It is *O*-protonated by TFA, *N*-acetylated by acetic anhydride, *N*-nitrosated by nitrous acid, and provides an *N*-methylene Meldrum's acid derivative on treatment with methoxymethylene Meldrum's acid. Reactions of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one with diazonium salts, with isatin, and with dimethyl acetylenedicarboxylate take place at the methylene position to provide a hydrazone, an indirubin analogue, and a succinate derivative, respectively. Oxidation of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one gives a heteroindigotin, which shows a hypsochromic shift in the UV spectrum, relative to indigotin itself.

Introduction

Indigotin **1** is the major chemical constituent of indigo, which has been used as a dyestuff for at least 4000 years.[1,2] The reduced monomeric unit of indigotin, 3-hydroxyindole **2E** [indol-3(2*H*)-one **2K**] (or indoxyl), is much less studied owing to its easy oxidative dimerization to indigotin **1**. There are few examples of indigotin structures in which the benzene ring has been replaced by an aromatic heterocycle[3] and none in which that heterocycle is a thiophene unit. Equally, there are no simple examples of corresponding heteroindoxyls, though some *N*-functionalized derivatives have been claimed in a patent[4] and some related thieno-isatin analogues are known.[5]

In this paper, we report the first successful synthesis of a parent heteroindoxyl, 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3**, which was made by a nitrene insertion strategy under flash vacuum pyrolysis (FVP) conditions. The chemical properties of the heteroindoxyl are also discussed, including its oxidative dimerization to the new heteroindigotin **4**, by analogy with the known chemistry of indoxyl **2** and of monocylic 3-hydroxypyrroles [1*H*-pyrrol-3(2*H*)-ones].



(1) (a) Gordon, P. F.; Gregory, P. *Organic Chemistry in Colour*; Springer-Verlag: Berlin, 1983. (b) Christie, R. M. *Colour Chemistry*; Royal Society of Chemistry: Cambridge, 2001.

(2) Ferreira, E. S. B.; Hulme, A. N.; McNab, H.; Quye, A. *Chem. Soc. Rev.* **2004**, *33*, 329–336.

(3) (a) Kägi, H. *Helv. Chim. Acta* **1942**, *35*, 1471–1480. (b) Sucharda, E. *Ber. Dtsch. Chem. Ges.* **1925**, *58*, 1724–1727. (c) Lüttke, W.; Hunsdiecker, D. *Chem. Ber.* **1966**, *99*, 2146–2153.

10.1021/jo900496u CCC: $40.75
Published on Web 04/29/2009

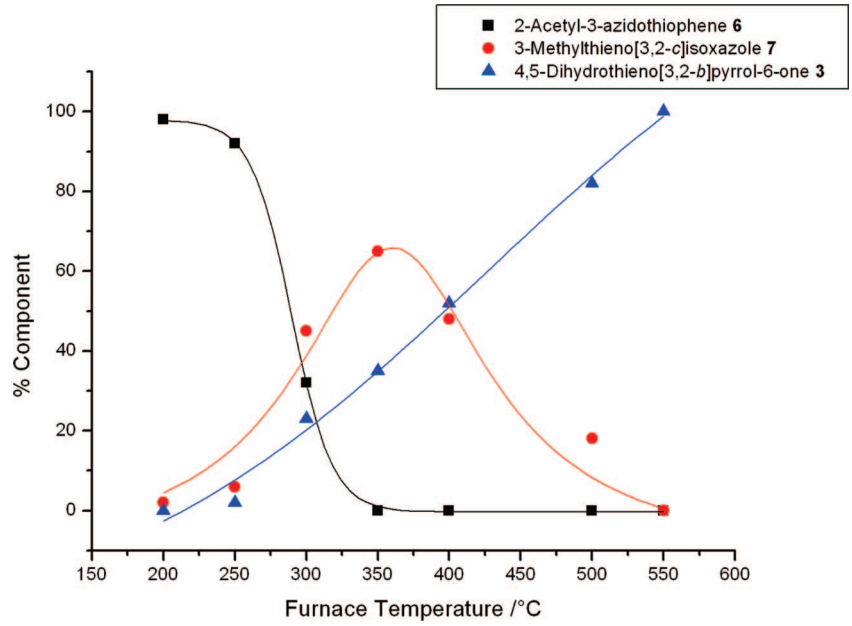
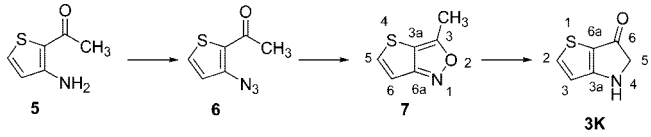
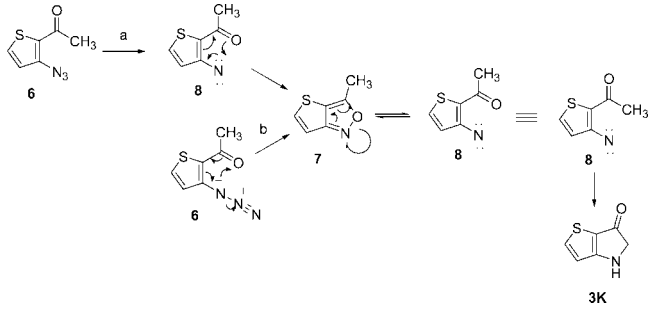


FIGURE 1. Temperature profile of the FVP of 2-acetyl-3-azidothiophene **6**.

SCHEME 1



SCHEME 2



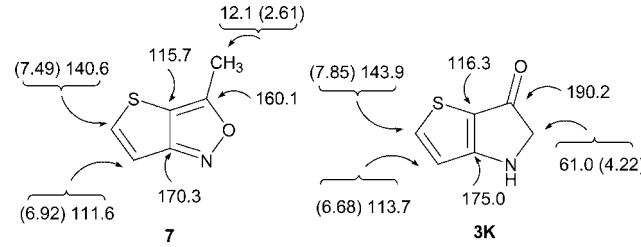


FIGURE 2. ^{13}C NMR and ^{1}H NMR (in parentheses) chemical shifts of **3K** and **7**.

Results and Discussion

The starting material, 2-acetyl-3-azidothiophene **6**, was made from 2-acetyl-3-aminothiophene[6] **5** by diazotization and reaction with sodium azide (Scheme 1).[7]

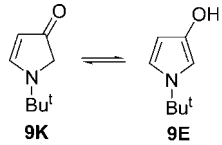
Pyrolysis of **6** in solution has been previously reported, and led to a 5% yield of a poorly characterized product which was tentatively identified as 3-methylthieno[3,2-*c*]isoxazole **7.**[7] In contrast, under FVP conditions, the temperature profile (Figure 1) shows the formation of two distinct products over different temperature regimes. Onset of decomposition of the azide **6** began at 250 °C and was complete by 350 °C. At furnace temperatures below *ca.* 400 °C, 3-methylthieno[3,2-*c*]isoxazole **7** was the major product (a 350 °C pyrolysis gave **7** in 51% isolated yield after chromatography) whereas at temperatures of 550 °C and above, the new heteroindoxyl 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** was formed exclusively (61% isolated yield at 550 °C).

Two possible mechanisms can be drawn for the formation of the thienoisoxazole **7** (Scheme 2). First, FVP of the azide **6** may give the nitrene **8** which is quenched by the adjacent keto group to provide **7** as the kinetic product (route a). At higher temperatures a CH insertion reaction of **8** would provide **3** as the thermodynamic product. Alternatively, anchimeric assistance of the N_2 loss by the ketone function of **6** may provide **7** directly without the involvement of free nitrene intermediates (route b). Although the evidence is not unequivocal, we favor route b, since there is some rate acceleration in the FVP of *o*-azidoketones by comparison with non-*ortho*-substituted model compounds.[8] Formation of the heteroindoxyl **3** at higher temperatures can then occur by reversible electrocyclic ring-opening of **7** to the nitrene **8**, which provides **3** by CH insertion (Scheme 2).

The mp and ^{1}H NMR spectrum obtained for the thienoisoxazole **7** correspond with data that had been tentatively assigned to this compound (Figure 2).[7] Although the ^{1}H NMR spectra of **6** and **7** show similar features, their ^{13}C NMR and mass spectra are very different; in particular **7** shows a dramatic shielding of the methyl group [δ_C (**7**) 12.1 *c.f.* δ_C (**6**) 29.1]. Few other examples of 5,6-unsubstituted thieno[3,2-*c*]isoxazoles are known.[7,9]

(4) Glenn, R. W.; Lim, M. U.S. Pat. Appl. Publ. US 2006042025, 2006.
(5) Shvedov, V. I.; Vasil'eva, V. K.; Kharizomenova, I. A.; Grinev, A. N. *Khim. Geterotsikl. Soedin* **1975**, 767–769; *Chem. Abstr.* **1975**, *83*, 193123.
(6) Huddleston, P. R.; Barker, J. M. *Synth. Commun.* **1979**, *9*, 731–734.
(7) Dyall, L. K.; Suffolk, P. M.; Dehaen, W.; L'abbe, G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2115–2119.
(8) Gaywood, A. P. PhD. thesis, The University of Edinburgh, 2006.

The new heteroindoxyl **3K** showed CH_2 resonances at δ_H ($C[^2H]Cl_3$) 4.22 and δ_C ($C[^2H]Cl_3$) 61.0 (*c.f.* corresponding signals for indoxyl **2K** at δ_H 3.89 and δ_C 54.1, respectively) and the characteristic methyl signal of **7** was absent (Figure 2). The heteroindoxyl **3** is relatively stable and can be handled at the bench without special precautions. However, substantial decomposition was evident after a few days in solution in DMSO. Because of potential oxidative dimerization to the heteroindigotin **4**, it was normally used for reactivity studies immediately after preparation.



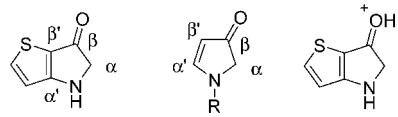
9K **9E**

Indoxyl **2**[8,10] and simple 1*H*-pyrrol-3(2*H*)-ones[11] (e.g., **9**) are known to exist preferentially as the enols **2E** and **9E,** respectively, when dissolved in hydrogen-bond acceptor solvents such as DMSO. Relative to these systems, the heteroindoxyl **3** shows increased preference for the keto form **3K** (Supporting Information); the hydroxy tautomer **3E** is detected at low level (20%) only in DMSO solution [δ_H(**3E**) 10.30 (1H, br, s), 8.49 (1H, s), 7.13 (1H, d), 6.92 (1H, d) and 6.51 (1H, s)]. The fusion of two electron-rich π-systems in **3E** may contribute to its relative destabilization.

Reactions of the heteroindoxyl **3** with mild electrophiles may be expected to take place at the oxygen atom, at the nitrogen atom or (*via* the enol) at the CH_2 group of the pyrrolone ring. The regioselectivity of such reactions can depend on a number of factors, including HSAB effects, the predominant tautomeric form, rate of tautomer interconversions etc. In practice, although reactions take place with high selectivity, examples of all three modes have been observed in the specific cases described below.

The enaminone conjugated system of 1*H*-pyrrol-3(2*H*)-ones is smoothly *O*-protonated in acid solution, supported experimentally by the X-ray crystal structure of a picrate salt.[12] Such protonation results in well-defined shifts of signals in ^{13}C NMR spectra.[12] Heteroindoxyl **3** is stable in TFA solution and the key changes in the ^{13}C NMR spectra in this medium are shown in Table 1, by comparison with corresponding pyrrolone (**9** and **10**) species. The labeling schemes shown are used for ease of comparison. The pattern of shielding and deshielding observed on protonation of **3** [significant deshielding at C(α′), significant shielding at C(β) and little change at C(β′)] mirrors the situation in both pyrrolone models **9** and **10**, which suggests that the *O*-protonated species **11** contributes significantly to the equilibrium.[12]

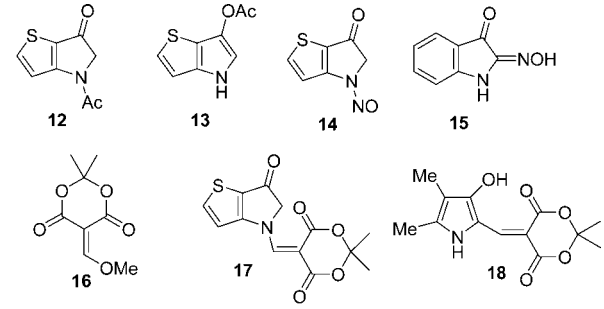
TABLE 1. Change in ^{13}C Chemical Shifts between Neutral and Protonated Forms of 4,5-Dihydrothieno[3,2-*b*]pyrrol-6-one 3 and Pyrrolones 9 and 10[12]



3 **9**, R = Bu^t **11**
10, R = Ph

position	**3**	**9**[12]	**10**[12]
C(α′)	+7.3	+7.5	+10.6
C(β)	−12.7	−11.9	−10.2
C(β′)	−0.5	+1.7	−1.5

Reaction of **3** with neat acetic anhydride gave a 98% yield of the *N*-acyl product **12**; the regiochemistry of the acylation was confirmed by the continued presence of a CH_2 group at δ_H 4.56 in the ^1H NMR spectrum of the product. No acetoxy compound **13** could be detected. Indoxyl **2** behaves similarly under the same conditions.[13] Treatment of **3** with aqueous nitrous acid gave exclusively the *N*-nitroso-compound **14**, (56%), though nitrosation of indoxyl **2** itself is known to provide the oxime **15**.[13] The presence of only small amounts of enol tautomer **3E**, coupled with the potential irreversibility of *N*-nitrosation, may rationalize the change in regioselectivity. Treatment of **3** with the weak electrophile, methoxymethylene Meldrum's acid (MMMA) **16** also takes place at N(4) to provide the *N*-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-ylidene)methylenated product **17** (37%). The same regioselectivity is observed for the corresponding reaction of indoxyl **2**,[8] though the reaction of an *N*-unsubstituted pyrrolone with MMMA, took place instead at the methylene group to give **18**.[14] The presence of the fused rings in **2** and **3** clearly influence regioselectivity. Attempted FVP of **17** was unsuccessful owing to its involatility.



12 **13** **14** **15**
16 **17** **18**

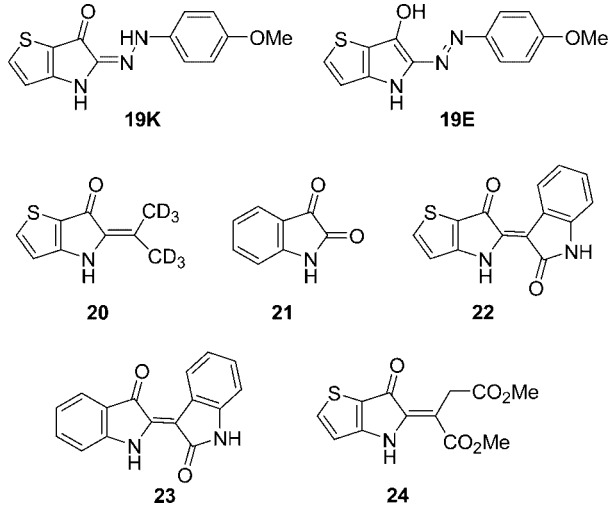
Despite the relative lack of enol tautomer **3E**, some electrophiles react preferentially at the CH_2 (5-position). Deuterium exchange at this site takes place in neutral media, presumably via traces of the enol form **3E**. Competitive exchange of the corresponding protons of **3** and indoxyl **2** was studied semiquantitatively in [$^2H_4$]methanol solution, by the method described in the Supporting Information. In this way, any self-catalysis of the exchange process would be experienced equally by both compounds. In the event, both compounds reacted at a similar rate with $t_{1/2}$ ca. 3 h. Because the amount of enol tautomer in **3** is significantly less than in **2**, it follows that either the rate of tautomerization or the rate of deuterium exchange of the thiophene species **3** is likely to be faster than that of indoxyl **2** itself.

Azo-coupling reactions take place at C(5) to provide hydrazones (e.g., **19K**) (25%). In the 1*H*-pyrrol-3(2*H*)-one series, in which analogous azo-coupling products have been shown by X-ray crystallography to adopt the hydrazone tautomer, the ^{13}C NMR chemical shift of the C═O function is in the range δ_C 178−180[15] and similar values are found for corresponding

(9) (a) Paulmier, C. *C.R. Acad. Sci. Ser. IIc: Chim.* **1975**, 319–321. (b) Gronowitz, S.; Westerlund, C.; Hornfeldt, A. B. *Chem. Scripta* **1976**, *10*, 165–72.
(10) Capon, B.; Kwok, F. *J. Am. Chem. Soc.* **1989**, *111*, 5346–5356.
(11) Blake, A. J.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1455–1458.
(12) Blake, A. J.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1463–1468.
(13) Étienne, A. *Bull. Soc. Chim. Fr.* **1948**, 651–658.
(14) Derbyshire, P. A.; Hunter, G. A.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2017–2025.
(15) Blake, A. J.; McNab, H.; Monahan, L. C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 701–704.

derivatives of indoxyl **2**.[8] The corresponding signal for **19** occurs at δ_C 171.40; the observed shielding of 8−10 ppm relative to its structural analogues may suggest that, although the hydrazone **19K** predominates, the azo-tautomer **19E** may contribute to the equilibrium.

The methylene group of **3** can participate in aldol reactions; condensation takes place spontaneously in [$^2H_6$]acetone in the absence of any added catalysts to give the alkene **20**. In the presence of Hünig's base, condensation of **3** with isatin **21** provides an indirubin analogue (20%) as a single isomer, thought to be the *Z*-isomer **22** by analogy with the indirubin structure **23**. Compound **22** shows λ_{max} 521 nm (ε 7200 L mol^{-1} cm^{-1}), (methanol), displaying a hypsochromic shift of 19 nm compared with the spectrum of indirubin **23** itself.[16]



4,5-Dihydrothieno[3,2-*b*]pyrrol-6-one **3** undergoes a Michael reaction with DMAD, to give dimethyl 2-[6-oxo-4,6-dihydrothieno[3,2-*b*]pyrrol-(5Z)-ylidene]-succinate **24** (30%) as a single isomer. Reactions of 1-substituted pyrrol-3(2*H*)ones with DMAD can also take place at the corresponding (2-)position, though the tautomeric nature of the product is different.[17] The structure of **24** was confirmed by X-ray crystallography (Supporting Information) which defines the *Z*-nature of the geometry around the alkene function, presumably assisted by hydrogen-bonding from the N−H to the carbonyl of the ester function O(9) [e.g., O9A···H8, 2.14 Å; O9A···N8, 2.691(3) Å]. This structure also shows the geometry of a heteroindoxyl unit for the first time; it is planar about the core fused ring system (e.g., mean deviation from planarity 0.0211 Å; maximum deviation 0.035 Å at C5) and the bond angles between the two fused 5-membered rings [135.3(3)° and 139.3(2)°] are characteristically ≫120°.

Finally, oxidative dimerization of **3** using potassium ferricyanide in a pH 7 phosphate buffer[18] gave the heteroindigotin **4** (53%), assumed to be the *E*-isomer shown. Due to its very low solubility, this compound could be characterized only by mass spectrometry and UV spectroscopy. It had λ_{max} 577 nm (DMSO) and 570 nm (DMF) showing a hypsochromic shift of 44 nm relative to indigotin **1** itself [λ_{max} 621 nm (DMSO)[19]]. The effect of substituents on the colors of indigoids has been the subject of much theoretical analysis,[20] with hypsochromic shifts observed for electron-donating substituents located at the 6(6′)-positions. Bathochromic shifts are observed for corresponding substituents at the 5(5′)-positions. With respect to electronic absorption spectra, it therefore follows that the electron-rich fused thiophene rings in **4** are behaving as 6(6′)-indigotin substituents.

In conclusion, we have synthesized the first heteroindoxyl **3**, by a pyrolytic strategy in which the final step is a nitrene insertion. The heteroindoxyl **3** reacts readily with a number of electrophilic reagents, but in some cases these reactions show different regiochemistry from that of analogues such as indoxyl and 3-hydroxypyrroles. The indigotin analogue **4** can be made from **3** under radical-coupling conditions. The thermal behavior of azidoacetyl compounds, providing fused isoxazoles at low temperatures and indoxyl analogues at high temperatures, has some generality, and further examples will be reported in future publications.

Experimental Section

Flash Vacuum Pyrolysis (FVP) Experiments. The precursor was volatilized under rotary pump vacuum (pumping speed 100 dm^3 min^{-1}) through an empty, electrically heated silica tube (35 × 2.5 cm) and the products were collected in a U-tube, cooled with liquid nitrogen, situated at the exit point of the furnace. For the azide precursor described below, a metal sublimation oven was used and the scale was limited to a maximum of a few hundred mg. We experienced no problems with pyrolyses of the azide reported here but clearly every precaution must be taken in handing such potentially explosive materials. The pressure was measured by a Pirani gauge situated between the product trap and the pump. Upon completion of the pyrolysis, the trap was allowed to warm to room temperature under a nitrogen atmosphere. The entire pyrolysate was dissolved in solvent and removed from the trap. The precursor, pyrolysis conditions [quantity of precursor, furnace temperature (T_f), inlet temperature (T_i), initial pressure (P_i) and pyrolysis time (t)] and products are quoted.

FVP of 2-Acetyl-3-azidothiophene 6. CAUTION Azides are potentially explosive—see precautions outlined in the previous paragraph. FVP of 2-acetyl-3-azidothiophene **6** (135 mg, 0.81 mmol; T_f 350 °C; T_i 55 °C; P_i 2.8 × 10^{-2} Torr; t 7 min) gave a product which was dissolved in dichloromethane and purified by dry flash chromatography on silica (eluted with 25% hexane in ethyl acetate) to yield 3-methylthieno[3,2-*c*]isoxazole **7** (57 mg, 51%); mp 50−52 °C (lit.,[7] 56−57 °C); δ_H (360 MHz) 2.61 (3H, s, CH_3), 6.92 [1H, d, $J_{6,5}$ 5.1, H(6)], 7.49 [1H, d, $J_{5,6}$ 5.1, H(5)]; δ_C (90 MHz) 12.1 (CH_3), 111.6 [C(6)], 115.7 [quat, C(3a)], 140.6 [C(5)], 160.1 [quat, C(3)] and 170.3 [quat, C(6a)]; *m*/*z* 139 (M$^+$, 100%), 126 (62), 111 (50), 110 (28), 97 (17) and 70 (40).

FVP of 2-acetyl-3-azidothiophene **6** (115 mg, 0.68 mmol; T_f 550 °C; T_i 55 °C; P_i 3.8 × 10^{-2} Torr; t 9 min) yielded 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3K** (58 mg, 61%); mp 120−123 °C; (Found: M$^+$ 139.0092. C_6H_5NOS requires M 139.0092); δ_H (360 MHz) 4.22 (2H, s, CH_2), 4.89 (1H, br s, NH), 6.68 [1H, d, $J_{3,2}$ 5.1, H(3)] and 7.85 [1H, d, $J_{2,3}$ 5.1, H(2)]; δ_C (90 MHz) 61.0 [CH_2, C(5)], 113.7 [C(3)], 116.3 [quat, C(6a)], 143.9 [C(2)], 175.0 [quat, C(3a)] and 190.2 [quat, C(6)]; *m*/*z* 139 (M$^+$, 100%), 111 (68), 110 (79), 84 (61), 70 (31) and 67 (48). In [$^2H_6$]DMSO solution the enol form **3E** made up *ca.* 20% of the tautomeric mixture δ_H(**3E**, [$^2H_6$]DMSO) 6.51 (1H, s), 6.92 (1H, d), 7.13 (1H, d), 8.49 (1H, s) and 10.30 (1H, br, s) and δ_H(**3K**, [$^2H_6$]DMSO) 4.20 (2H, s), 6.86 (1H, d), 7.38 (1H, br. s) and 8.25 (1H, d).

(16) Guengerich, F. P.; Sorrells, J. L.; Schmitt, S.; Krauser, J. A.; Aryal, P.; Meijer, L. *J. Med. Chem.* **2004**, *47*, 3236–3241.
(17) Hunter, G. A. PhD thesis, The University of Edinburgh, 1990.
(18) Pfeiffer, G.; Bauer, H. *Liebigs Ann. Chem.* **1980**, 564–589.
(19) Gompper, R.; Hartmann, K.; Kellner, R.; Polborn, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 464–467.
(20) Reference 1a, pp 211−219.

4-Acetyl-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one 12. Acetic anhydride (2 cm^3) was added to 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** (35 mg, 0.25 mmol) and the mixture was gently heated using a hot air blower for 5 min. The solvent was removed under reduced pressure to yield 4-acetyl-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **12** (44 mg, 98%); mp 126−128 °C; (Found: M^+ 181.0196, $C_8H_7NO_2S$ requires *M* 181.0198); δ_H 2.25 (3H, s, CH_3), 4.56 (2H, s, CH_2), 7.69 (1H, d, *J* 5.0, thiophene-H) and 7.94 (1H, d, *J* 5.0, thiophene-H); δ_C 22.3 (CH_3), 61.1 (CH_2), 118.2, 123.0 (quat), 143.1, 164.9 (quat), 165.3 (quat) and 184.5 (quat); *m*/*z* 181 (M^+, 41%), 135 (100), 138 (39), 111 (70), 110 (52) and 69 (21).

4-Nitroso-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one 14. A solution of sodium nitrite (135 mg, 1.73 mmol) in water (0.6 cm^3) was added to a solution of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** (143 mg, 1.04 mmol) in water (40 cm^3) containing acetic acid (0.2 cm^3). The mixture was stirred at room temperature for 1 h. The resulting precipitate was collected, added to dichloromethane (5 cm^3) and filtered. The filtrate was concentrated to provide 4-nitroso-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **14** (74 mg, 43%). Another crop of almost pure product (23 mg) was obtained by extraction of the initial aqueous filtrate with dichloromethane (3 × 75 cm^3 portions). These combined organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure (overall yield 56%); mp 135−138 °C; (Found: M^+ 167.9991, $C_6H_4N_2O_2S$ requires *M* 167.9994); δ_H 4.79 (2H, s, CH_2), 7.83 (1H, d, *J* 5.1, thiophene-H) and 8.58 (1H, d, *J* 5.1, thiophene-H); δ_C 58.4 (CH_2), 113.7, 123.9 (quat), 145.5, 161.2 (quat) and 182.0 (quat); *m*/*z* 168 (M^+, 8%), 139 (34), 138 (100), 111 (12), 110 (41) and 83 (14).

2,2-Dimethyl-5-(6-oxo-5,6-dihydrothieno[3,2-*b*]pyrrol-4-ylmethylene)-1,3-dioxane-4,6-dione 17. 5-Methoxymethylene Meldrum's acid **16** (144 mg, 0.81 mmol) was added to a suspension of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** (120 mg, 0.86 mmol) in acetonitrile (7 cm^3) and the mixture was stirred at room temperature for 24 h. The solution was then filtered through Celite, the solvent concentrated to 0.5 cm^3 under vacuum and the precipitate was collected to yield 2,2-dimethyl-5-(6-oxo-5,6-dihydrothieno[3,2-*b*]pyrrol-4-ylmethylene)-1,3-dioxane-4,6-dione **17** (87 mg, 37%); mp 204−206 °C (from acetone); (Found: C; 52.9; H 4.0; N 4.85. $C_{13}H_{11}NO_5S$ requires C 53.25; H 3.75; N 4.75); δ_H 1.77 (6H, s, 2 × CH_3), 5.10 (2H, s, CH_2), 7.28 [1H, d, $J_{3,2}$ 5.2, H(3)], 8.09 [1H, d, $J_{2,3}$ 5.2, H(2)] and 8.47 (1H, s, alkene); δ_C 26.9 (2 × CH_3), 65.6 (CH_2), 90.2 (quat), 104.0 (quat), 112.8, 124.8 (quat), 143.9, 147.5, 159.5 (quat), 164.5 (quat), 165.8 (quat) and 183.7 (quat); *m*/*z* 293 (M^+, 17%), 235 (100), 191 (25), 167 (68) and 135 (47).

5-[(4-Methoxyphenyl)hydrazono]-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one 19. A saturated solution of sodium nitrite (125 mg, 1.58 mmol) in water was added dropwise to a solution of *p*-anisidine (123 mg, 1 mmol) in conc. hydrochloric acid (5 cm^3) at 0 °C. The mixture was stirred for 15 min. A solution of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** (139 mg, 1 mmol) in methanol (20 cm^3) was added dropwise, and the solution was stirred for a further 30 min. The resulting precipitate was collected and washed with water to yield 5-[(4-methoxyphenyl)-hydrazono]-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **19** (69 mg, 25%); mp 173−175 °C; (Found: M^+ 273.0572, $C_{13}H_{11}N_3O_2S$ requires *M* 273.0572); δ_H ([$^2H_6$]DMSO) 3.73 (3H, s, MeO), 6.92 (2H, d, *J* 8.9, 2 × Ar−H), 7.00 (1H, d, *J* 5.0, thiophene-H), 7.19 (2H, d, *J* 8.9, 2 × Ar−H), 8.16 (1H, d, *J* 5.0, thiophene-H) and 10.49 (1H, br s); δ_C ([$^2H_6$]DMSO) 55.1 (CH_3), 113.8, 114.2 (2 × CH), 114.5 (2 × CH), 137.1 (quat), 137.6 (quat), 141.5, 154.0 (quat), 160.3 (quat) and 171.7 (quat) (one quat overlapping); *m*/*z* 273 (M^+, 66%), 123 (57), 122 (87), 108 (78), 91 (100) and 84 (60).

5-[$^2H_6$]Isopropylidene-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one 20. A solution of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** in [$^2H_6$]acetone was allowed to stand at room temperature for 24 h. New peaks were observed at δ_H ([$^2H_6$]acetone) 6.76 (1H, d, *J* 5.3) and 7.90 (1H, d, *J* 5.3). Removal of solvent provided a compound whose mass spectrum showed a dominant ion at *m*/*z* 185, corresponding to 5-([$^2H_6$]isopropylidene)-4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **20.**

3-[6-Oxo-4,6-dihydrothieno[3,2-b]pyrrol-(5*Z*)-ylidene]-1,3-dihydro-indol-2-one 22. Solid 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** (83 mg, 0.60 mmol) followed by *N*,*N*-disopropylethylamine (*ca.* 0.1 cm^3) was added to a solution of isatin **21** (87 mg, 0.59 mmol) in methanol and the solution was stirred at room temperature for 5 h. The solution was concentrated to 5 cm^3 under vacuum, and the resulting precipitate was collected and washed with methanol to provide 3-[6-oxo-4,6-dihydrothieno[3,2-*b*]pyrrol-(5*Z*)-ylidene]-1,3-dihydro-indol-2-one **22** (32 mg, 20%); mp >330 °C; (Found: M^+ 268.0305, $C_{14}H_8N_2O_2S$ requires 268.0306); λ_{max} (Methanol) 521 nm (ε 7200 mol^{-1} cm^{-1}); δ_H ([$^2H_6$]-DMSO) 6.92 (1H, m, Ar−H), 7.00−7.06 (2H, m, 1 × Ar−H and 1 × thiophene-H), 7.29 (1H, m, Ar−H), 8.28 (1H, d, *J* 7.2), 8.84 (1H, m, Ar−H), 10.89 (1H, s, NH) and 10.93 (1H, s, NH); δ_C ([$^2H_6$]DMSO) 110.0, 110.3 (quat), 113.0 (quat), 115.6, 121.3 (quat), 121.8, 126.0, 130.3, 141.8 (quat), 144.0 (quat), 144.9, 166.5 (quat), 171.0 (quat) and 179.0 (quat); *m*/*z* 268 (M^+, 100%), 240 (50), 191 (46), 147 (32), 119 (39) and 92 (36).

Dimethyl 2-[6-Oxo-4,6-dihydrothieno[3,2-*b*]pyrrol-(5*Z*)-ylidene]succinate 24. A solution of DMAD (60 mg, 0.42 mmol) in DMSO (0.5 cm^3) was added to a solution of 4,5-dihydrothieno[3,2-*b*]pyrrol-6-one **3** (66 mg, 0.42 mmol) in DMSO (1.5 cm^3) and the mixture was stirred at room temperature for 1 h. Water (3 cm^3) was added and the mixture was stored overnight at −20 °C. The resulting precipitate was collected and washed with water to yield dimethyl 2-[6-oxo-4,6-dihydrothieno[3,2-*b*]pyrrol-(5*Z*)-ylidene]succinate **24** (35 mg, 30%); mp 194−196 °C; (Found: M^+ 281.0361, $C_{12}H_{11}NO_5S$ requires *M* 281.0358); δ_H 3.71 (3H, s, CO_2Me), 3.82 (3H, s, CO_2Me), 4.11 (2H, s, CH_2), 6.67 [1H, d, $J_{3,2}$ 5.0, H(3)], 7.83 [1H, d, $J_{2,3}$ 5.0, H(2)] and 9.33 (1H, br s, NH); δ_C 29.4 (CH_2), 51.9 (CH_3), 52.3 (CH_3), 107.3 (quat), 112.6, 114.7 (quat), 143.4, 146.8 (quat), 164.4 (quat), 168.8 (quat), 171.6 (quat) and 178.3 (quat); *m*/*z* 281 (M^+, 22%), 249 (30), 217 (20), 136 (18), 101 (39) and 78 (100).

4H,4′H-[5,5′]Bi[thieno[3,2-*b*]pyrrolylidene]-6,6′-dione 4. 4,5-Dihydrothieno[3,2-*b*]pyrrol-6-one **3** (40 mg, 0.3 mmol) was dissolved in a mixture of phosphate buffer (pH 7, 11 cm^3) and methanol (2 cm^3), and heated to 50 °C, under a nitrogen atmosphere. A solution of potassium ferricyanide (292 mg, 0.96 mmol) in water (2 cm^3) was added dropwise over 10 min, and the mixture was stirred for a further 30 min, keeping the temperature at 50 °C. The mixture was allowed to cool, stored overnight at −20 °C, and the resulting precipitate was collected and washed with water to give 4*H*,4′*H*-[5,5′]bi[thieno[3,2-*b*]pyrrolylidene]-6,6′-dione **4** as a purple solid (21 mg, 53%); (Found: M^+ 273.9871, $C_{12}H_6N_2O_2S_2$ requires *M* 273.9871); λ_{max} (DMSO) 577 nm; *m*/*z* 274 (M^+, 17%), 191 (51), 139 (60), 126 (54), 112 (55), 110 (57), 69 (36) and 54 (100). No NMR or extinction coefficient data could be obtained due to the extreme insolubility of the compound.

Acknowledgment. We are most grateful to the EPSRC (UK) and The University of Edinburgh for a Research Studentship (for A.P.G.), to Ms Kirsty Stefaniuk for preliminary experiments and to Dr. S. A. Moggach and Professor S. Parsons for the X-ray crystal structure.

Supporting Information Available: Full experimental details for synthesis and FVP of **6**, solvent dependence of keto:enol tautomer ratio for **3**, **2** and **9**, conditions for attempted FVP of **17**, competitive deuterium exchange of methylene signals of **2** and **3**, effect of *O*-protonation on NMR spectra of **3**, ^1H and ^{13}C NMR spectra of **3**, **7**, **12**, **14**, **17**, **19**, **22** and **24**, ORTEP plot and selected bond lengths [Å] and angles [deg] for **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900496U