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Synthesis and structural characterization of 3-thienyl alkyl imides

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Abstract—Five new thiophene imides having the structures $C_4H_3SC(O)N(H)C(O)R$ (where R=Me, Et, Pr, *t*-Bu, **1**–**4**) and $C_4H_3SCH_2C(O)N(H)C(O)CH_3$ **5** have been prepared. Control over the orientation of the carbonyl groups was achieved by the introduction of a bulky group in the terminal position of the side chain, and molecular modeling calculations indicated that the energy difference between the *ct* and *tt* conformations is small. The acidity of **1**–**4** decreases from Me to *t*-Bu, and, although **1**–**4** will not undergo oxidative polymerization, the introduction of a single spacer CH_2 group allows **5** to polymerize.

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1. Introduction

Compounds incorporating the thiophene ring are of great interest because of the potent pharmaceutical properties that this moiety confers.[1] Recent reports have dealt with the applications of thiophene-containing substances as antitumor agents, antithrombotic drugs, and in the treatment of benign prostatic hyperplasia.[2] Other proposed uses are as antidepressants, calcium channel blockers, and smooth muscle relaxants.[3] The hydrogen-bonding ability and metal-complexation capability of the imide group in diacetamide[4] suggested that incorporation of this function in thiophene-containing monomers could produce a new series of compounds with the potential for hydrogen-bonding interactions of pharmaceutical importance. In addition, the imide function could potentially act as a chelating group similar to the thenoyltrifluoroacetone ligand and sequester metals which confer fluorescent properties on the complex such that it could be used as a taggant.[5] Finally, variants of these compounds can form the basis for a set of poly(3-substituted)thiophenes[6] having chelating abilities which render them potential candidates for the reversible binding of metals and hydrogen-bonding interactions suiting them for use as molecular recognition agents. In this work, we report the successful synthesis of a series of new 3-substituted thiophenes containing an imide moiety, –C(O)NHC(O)– **1**–**5** and their structural characterization. A structure search (STN) revealed that only one thiophene compound containing the non-cyclic imide structure had been prepared in an investigation of benzodiazepine receptor ligands[7] although recently several thiophenes attached to cyclic imides have been reported.[8] The synthesis and NMR spectra of 2-thienylpyrrolylurea, which contains the –C(O)N(H)C(O)N(H)– group, have been reported and the compound shows antiviral activity.[9] Here we report a general preparation for 3-thienyl imides and the first crystallographic data for compounds of this type.

2. Results and discussion

2.1. Synthesis

The acid-catalyzed acylation of primary amides with anhydrides has been reported as a general method for the preparation of acyclic imides with an alkyl or phenyl group attached to the imide moiety.[10] This method was adapted to the synthesis of compounds **1**–**4** from 3-thenamide and the corresponding alkyl anhydride in the presence of a catalytic amount of concentrated sulfuric acid (Scheme 1). 3-Thiopheneacetamide and acetic anhydride also gave **5** in good yield (Scheme 2); however, two side-products (*m*/*z*, 267, M^+) were obtained in small amounts and were identified as the 2-acetyl- and 5-acetyl-substituted products which can be distinguished from each other by their proton coupling constants (2-substituted, J_{4-5}=4.80 Hz, 5-substituted, J_{2-4}=0.90 Hz[11]). It appears that the α-positions (2-, 5-) become more reactive towards electrophilic attack owing to the electron-donating effect of the CH_2 spacers. **1** was also prepared in low yield by the reaction of 3-thiophenecarboxylic acid with acetyl isocyanate, but the polarities of the product and 3-thiophenecarboxylic acid are similar making their separation difficult.

The molecular structures of *N*-acyl-3-thenamides and their analogues were determined from their ^1H and ^{13}C NMR spectra. Assignments were made employing HCCOSY

Keywords: thiophene; thienyl-; alkylimide; synthesis; crystal structure; electrochemistry; conformation.

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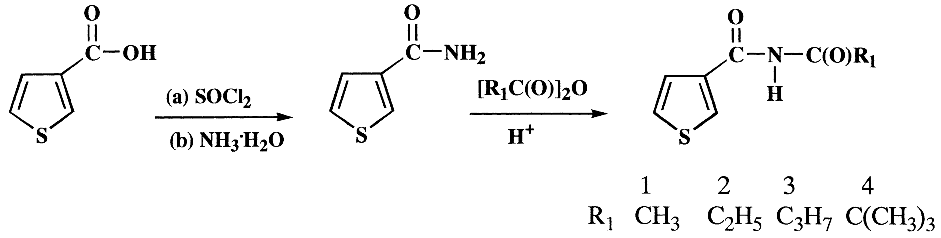


Scheme 1. Synthesis of 3-thienyl alkyl imides.

spectra and by analogy with the spectra of 3-thiophene carboxylic acid and 3-thiophene acetic acid as well as those of other derivatives.[11] Coupling constants (J_{H-H}) in the range characteristic of 3-substituted thiophenes were observed (J_{2-4}=0.9–1.9 Hz, J_{2-5}=2.6–3.5 Hz and J_{4-5}=4.6–5.4 Hz). The ^{13}C NMR spectral data showed two carbonyl carbon resonances with chemical shifts in the range of 160 ppm (next to ring) and 180 ppm (acyl), as well as those characteristic of ring and alkyl carbon atoms.

Infrared spectra of **1–5** showed the presence of a broad N–H band (ν_{N-H}, 3300–3200 cm^{-1}) at lower frequency than that for the free imide in dilute solution; this is indicative of substantial hydrogen bonding normally observed in imides.[12,13] Two C═O vibrations (ν_{COas}, 1740–1700 and ν_{COs}, 1678–1600 cm^{-1}) were observed; the relatively lower carbonyl stretching frequency in compounds **1–4** may result from a conjugation effect of the thiophene ring on the attached carbonyl group as well as hydrogen-bonding. The carbonyl vibrations are similar to those reported for *N*-acyl-benzamide.[4] The IR spectrum of **5** shows a sharp intense absorption at 1731 cm^{-1} along with a shoulder at 1693 cm^{-1}. The fact that a lowering is also observed for the carbonyl bands in **5**, for which conjugation with the ring is largely absent, is also consistent with hydrogen bonding involving the carbonyl group. The band for **1–5** in the range of 762–746 cm^{-1} is the ring hydrogen out-of-plane deformation unique to 3-substituted thiophenes.[14]

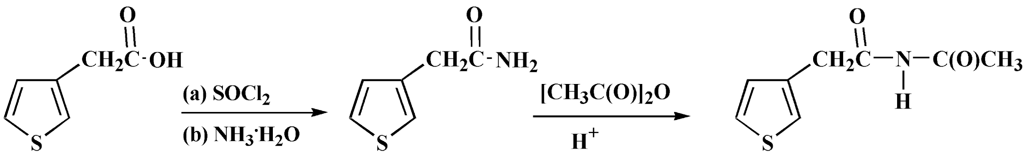
UV–visible spectra of **1–5** in MeCN showed two broad peaks with high molar absorptivities, one in the range of 200–215 nm (ε=4.2) attributed to the allowed $\pi\rightarrow\pi^*$ transition of the imide carbonyl group and one in the range of 230–250 nm (ε=3.6–4.1) attributed to a combination of the $\pi_2\rightarrow\pi_4^*$ and $\pi_3\rightarrow\pi_5^*$ transitions of the thiophene ring.[11,15] A red shift of the $\pi\rightarrow\pi^*$ transition of the imide/carbonyl moeity was observed when the imide group was connected directly to the ring by removing the methylene spacer, for example, 203 nm in **5** and 213 nm in **1**. This could be the result of extended π-interactions over the thiophene ring and imide group in compounds having the imide group directly attached to the ring.

GC–MS analyses were carried out to provide additional information for structural determination. Peaks for the molecule-ion (M$^+$) were obtained at m/z values that were consistent with their calculated molecular mass values. The new compounds **1–5** exhibited intense peaks at m/z values equal to the fragment resulting from the cleavage of the group β to the thiophene ring (m/z=111 for $C_4H_3SC(O)^+$) as is observed for 3-substituted thiophenes generally.[11] The ion at m/z=127 ($C_4H_3SC(O)NH_2^+$) results from the loss of the acyl side chain accompanied by hydrogen addition. The formation of these ions is more favorable when the acyl group bears a longer alkyl chain, as in the cases of propionyl and butyryl **3**, **4**. Fragments resulting from cleavage of the alkyl side chain were observed in all cases. The most intense peak for **5** is at m/z=124 ($C_4H_3SCHC(O)^+$) which results from the loss of an acetamide moiety from the molecule ion. A peak at m/z=97 ($C_4H_3SCH_2^+$) for **5**, resulting from the cleavage of a group β to the thiophene ring, was observed with moderately strong intensity.

2.2. X-Ray crystal structure study

A single crystal X-ray structure determination was carried out for **1–4** in order to gain information about the conformations of the imide groups, the orientation of the carbonyl group to the ring, and the extent of intra- and intermolecular hydrogen-bonding. A search of the Cambridge Structural Database (Version 5.24, Nov., 2002) indicated that no structural data containing the thiophene imide structure had been deposited.

2.2.1. Crystal structures of *N*-acyl-3-thenamides 1–4. In these molecules, the atoms of the thiophene ring were found to be approximately planar. The extent of conjugation of the thiophene ring to the attached carbonyl group was evident by the shorter C3–C6 bond length, 1.473(4)–1.482(4) Å. The relative orientation of the thiophene ring to the carbonyl group correlates with the attached imide group. Thiophene ring disorder about the C3–C6 bond axis was observed in **1** and **2** with the major orientation shown in Figure 1. The *S*,*O-trans* orientation is preferred for **1** (0.58) and **2** (0.90). The *S*,*O-trans* orientation is the only form observed for **3**



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Scheme 2. Synthesis of *N*-acetyl-3-thiopheneacetamide.

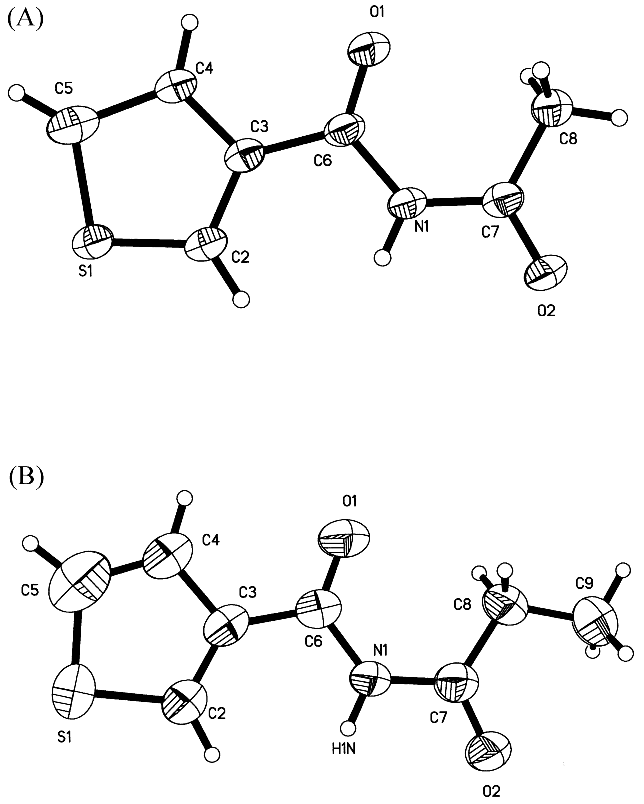

Figure 1. Perspective drawings of major orientation of crystalline solids (A) **1** and (B) **2** with non-hydrogen atoms represented by thermal vibration ellipsoids drawn to encompass 50% of their electron density.

and **4** in which two types of crystallographically independent molecules were observed in the lattice, as shown in Figure 2a and b, respectively. The thiophene ring planes are nearly coplanar with respect to the carbonyl plane in these compounds, having torsion angles of 2.5 to 9.2°. This is attributed to the conjugative effect of the thiophene ring. A slight increase of torsion angle was observed on going from the methyl to the *t*-butyl group at the end of the imide structure probably owing to the increased steric effect of the substituent group.

The ordered imide structure (–CO–NH–CO–) adopts the *ct* conformation in crystalline solids **1**, **2** and **3**, in which the two carbonyl groups are *cis* and *trans*, respectively to the NH function, and they are almost in the same plane as indicated by the C–N–C–O torsion angles of 2.3(3) and 179.52(18)°; 5.7(7) and −178.5(4)°, and 2.4(4) and −178.4(2)°, respectively. The N–C bond lengths in compounds **1**, **2** and **3** were in the range of 1.381–1.396 Å for the C–N bonds indicating the extended conjugation in the imide structure. This conformational adaptation is commonly observed in diacetamide and some *N*-acylbenzamides.[4] Significantly, compound **4** crystallizes in the *tt* conformation in which the two carbonyl groups were trans to the NH function, and the two carbonyl groups are slightly twisted with respect to each other. The C–N–C–O torsion angles in two crystallographically independent molecules were different: one was 7.8(6) and 3.2(6)° and the other was 7.4 and 22.1°. This conformation is similar to that observed in *N*-isobutyrylbenzamide.[16] The N–C bond lengths in compound **4** were quite different in the two molecules: 1.377 and 1.376 Å in molecule A, 1.401 and 1.397 Å in molecule B. Better conjugation in the imide structure for molecule A was due to the greater planarity of the two carbonyl groups. The *tt* conformation of the imide group resembles the orientation of the two carbonyl groups in metal acetylacetonates which exist in the *tt* conformation. Thus, the successful synthesis of a thiophene imide in the *tt* conformation, **4**, provides a route to thiophene-containing metal chelating ligands via steric control at the carbonyl carbon.

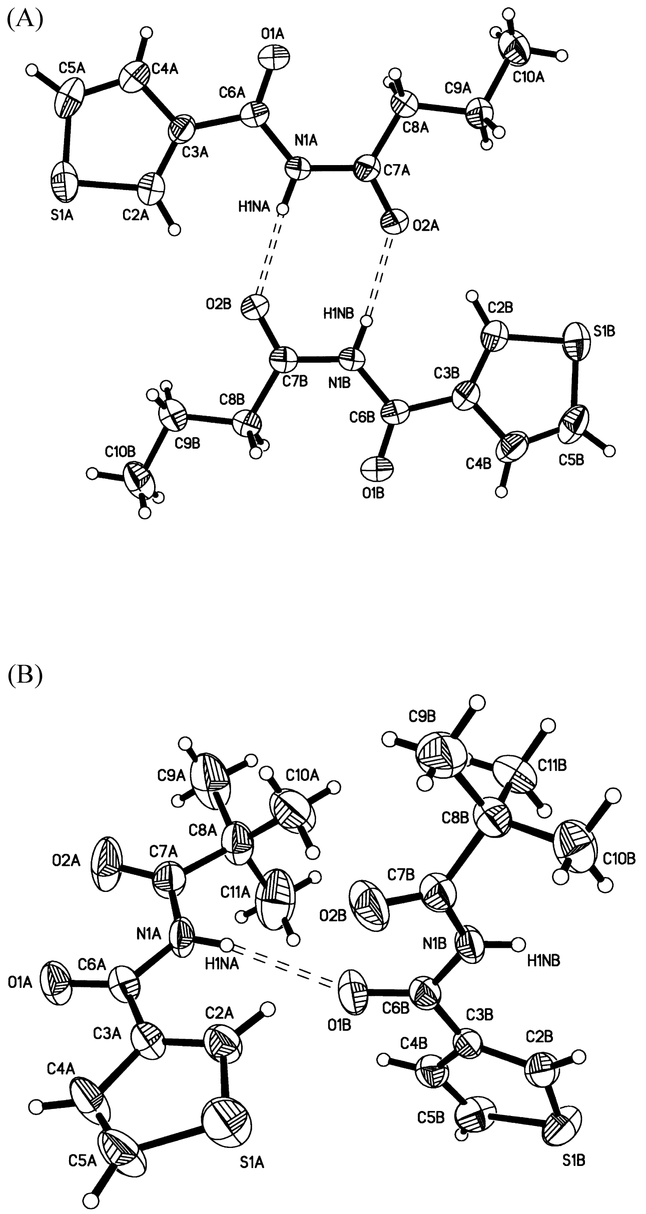

Figure 2. Perspective drawings of crystallographically independent molecules in crystalline solid (a) **3** and (b) **4** with non-hydrogen atoms represented by thermal vibration ellipsoids drawn to encompass 50% of their electron density. Hydrogen-bonding interactions are shown as dashed bonds.

The hydrogen-bonding interactions lead to dimers in compounds **1**–**3** through pairing of the N–H group to the oxygen atom of the carbonyl group in the adjacent molecule (Fig. 2a) while hydrogen-bonding leads to a chain structure in **4** (Fig. 2b). Only the carbonyl group bonded to the alkyl group was involved in the hydrogen-bonding as indicated by a slight increase in the C7–O2 bond length (0.005–0.012 Å) compared to that of C6–O1. The molecules were positioned with the thiophene ring at opposite sides of the hydrogen bonds favored by the minimum steric interactions in the molecules. Table 1 shows a comparison of hydrogen-bonding interactions in compounds **1–4**. A slight increase of the hydrogen-bond strength going from compounds **1** to **3** was observed as indicated by decrease of the N···O distances: 3.045(2) Å in **1**, 2.947(4) Å in **2**, and 2.947(3) and 2.925(3) Å in **3**.

2.3. Molecular modelling

Since **4** showed a preference for the *tt* conformation and **1–3** for the *ct* conformation, ab initio molecular modeling calculations were carried out for compounds **1–4** to see whether the ground state energies were significantly different. Since the *S,O-trans* conformers have been found to be preferred from the X-ray structure results in this work and from other reports on 3-substituted thiophenes,[17] the calculations were based on this conformation. These calculations were performed using the density functional B3LYP method with a 6-311G** basis set for both the *ct* and *tt* conformations of the imide structure. (Calculations using the Hartree–Fock method with a 3-21G(*) basis set gave energy differences which varied over a much wider range in a seemingly random fashion.) Although the results of the calculation indicated the *ct* conformer has a lower energy compared to the corresponding *tt* conformer, the differences were small ranging from 7 to 11 kJ mol^{-1}. Such small energy differences imply that both forms can exist depending on the external environment (for example, the gas phase and the hydrogen-bonded solid state). The experimental data for diacetamide also showed that it could exist in both conformational forms depending on its environmental conditions despite the lower calculated energy level for its *ct* conformation.[4,18]

2.4. Electrochemistry

The redox properties of the new 3-substituted thiophenes, compounds **1–5**, were characterized by an examination of the reduction behavior of the imide group which acts as an N–H acid and the oxidation potentials of the thiophene moiety. Previous results from electrochemical studies of the reduction of acids in polar aprotic solvents such as acetonitrile and DMSO, have shown a trend of cathodic peak-shift for diminishing acid strengths, and, with few exceptions, the ranking of the acid strengths has been reported to stay the same in acetonitrile, DMSO or water.[19,20] Results for the reduction of **1–5** along with that for 3-thiophenecarboxylic acid (**3-TA**) and 3-thiopheneacetic acid (**3-TAA**) for comparison are summarized in Table 2. Cyclic voltammograms for compound **1** which are representative of this class of imides are shown in Figure 3. When glassy carbon was used as the working electrode, no reduction wave was observed in accordance with the fact that Pt is catalytic for hydrogen reduction and reduction of the imides probably involves direct discharge of hydrogen on the platinum surface.[21] The large negative potentials indicate a very low degree of acid dissociation in acetonitrile which is also consistent with direct discharge on the electrode surface[21], although a process involving adsorbed hydrogen[22] cannot be ruled out. ΔE_ps in the range of 0.34–0.84 V and i^a_p/i^a_ps less than 1 indicated that these processes were irreversible.

Table 2. Cyclic voltammetric data for the reduction of monomers on a Pt electrode (d=1 mm) in acetonitrile, scan rate: 0.100 V s^{-1} (vs SCE)

Compound	$E^c_{p/2}$ (V)	E^c_p (V)[a]	E^a_p (V)[a]	$\Delta E = E^a_p - E^c_p$
1	−1.33	−1.51	−0.74	0.77
2	−1.39	−1.56	−0.83	0.73
3	−1.41	−1.59	−0.82	0.77
4	−1.39	−1.60	−0.80	0.80
5	−1.42	−1.60	−0.88	0.72
3-TA	−0.76	−1.02	−0.66	0.36
3-TAA	−0.75	−1.00	−0.66	0.34

[a] The maximum deviation was calculated to be ±0.02 V.

Values of $E^c_{p/2}$ for the moderately strong imide acid, $HN(C(O)CF_3)_2$, **TFAI**, −0.32 V,[13] and the weaker acid, **3-TA**, −0.76 V, indicate that the order of acidity in acetonitrile parallels that in water (pK_a: 2.00 and ca. 4.00, respectively). The similar $E^c_{p/2}$ values obtained for **3-TA** (−0.76 V) and **3-TAA** (−0.75 V) indicated that these two possess similar acid strengths in acetonitrile which is also consistent with their similar pK_a values obtained in aqueous solution, 3.92–4.10 for **3-TA** and 4.07 for **3-TAA**.[23,24] These data allow an ordering of the acid strengths according to **TFAI**≫(**3-TA**∼**3-TAA**)≫**1**>**2**, **3**, **4**≥**5** which is consistent with the decrease in the electron-withdrawing effect of the substituents. Introduction of a CH_2 spacer group between the imide function and the thiophene ring further decreased the acidity.

Compounds **1–5** were also subjected to electrochemical

Table 1. Comparison of hydrogen-bonding interactions in crystalline solids **1–4**[a]

Compound	Donor[b] atom D	Acceptor atom A	Distance D···A[c] (Å)	Distance H···A[c] (Å)	Angle D–H···A[c] (°)	Angle H–D···A[c] (°)	Angle[d] (°) H···A···X[c]
1	N_1–H_{1N}	O_2	3.045(2)	2.21(2)	162(2)	13(1)	140.1(5)C_7
2	N_1–H_{1N}	O_2	2.947(4)	2.09(3)	170(3)	7(2)	139.7(8)C_7
3	N_{1A}–H_{1NA}	O_{2B}	2.947(3)	2.08(3)	171(3)	6(2)	135.1(7)C_{7B}
	N_{1B}–H_{1NB}	O_{2A}	2.925(3)	2.10(3)	170(2)	7(2)	137.1(7)C_{7A}
4	N_{1A}–H_{1NA}	O_{2B}	3.089(4)	2.31(3)	165(3)	11(2)	159.3(8)C_{6B}
	N_{1B}–H_{1NB}	O_{2A}	3.027(4)	2.20(4)	169(3)	8(2)	151.1(9)C_{6A}

[a] Atoms are labeled in agreement with Figure 1 for each compound.
[b] The hydrogen atom involved in the interaction is also indicated.
[c] The numbers in parentheses are the estimated standard deviations in the last significant digit.
[d] The symbol X is used to denote those atoms which are covalently bonded to the acceptor oxygen atom.

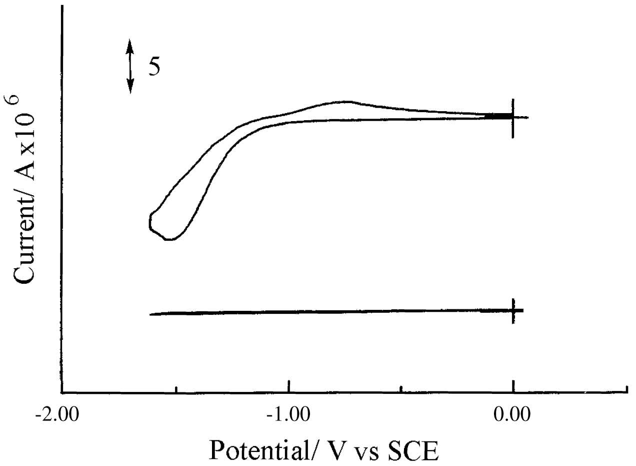

Figure 3. Cyclic voltammograms for reduction of **1**, 5 mM, 0.1 M TBAPF$_6$/acetonitrile, vs Ag wire, v=0.100 Vs^{-1}: Pt (d=1 mm, top), glassy carbon (d=1 mm, bottom).

Table 3. Cyclic voltammetric data for the oxidation of thiophene monomers measured from 5 mM monomer in 0.1 M TBAPF$_6$/acetonitrile solutions on (A) Pt and (B) glassy carbon electrode, scan rate: 0.100 V s^{-1} (vs SCE)

Compound	A[a]		B[a]	
	$E^a_{p/2}$ (V)	E^a_p (V)	$E^a_{p/2}$ (V)	E^a_p (V)
1	2.35	2.57	2.14	2.26
2	2.31	2.55	2.02	2.14
3	2.32	2.56	2.02	2.13
4	2.24	2.47	2.01	2.12
5	2.02	2.20	1.91	2.07
3-TA	2.34	2.59	2.15	2.26
3-TAA	2.01	2.19	1.89	2.00

[a] The average standard deviation is ±0.01 V.

oxidation to determine whether polymerization would occur. Figure 4a is representative of CVs for **1**–**4**; an oxidation peak for the thiophene ring was observed on the forward scan but no reverse peak was observed nor was growth of a polymeric film detected over a number of cycles. CV data are listed in Table 3. Clearly, the electron-withdrawing effect of the carbonyl group adjacent to the ring raises the oxidation potential of the thiophene ring to a value at which the radical-cation produced becomes reactive enough to attack the solvent, which is in large excess, and minimal oligomerization/polymerization occurs.[25] However, increasing the electron-donating power of the substituents at the position on the imide function opposed to the ring apparently influences the oxidation potential of the thiophene such that a decrease from **1** to **4** is observed. In the case of compounds **2**–**4**, a reddish stream was observed to diffuse away from the electrode during attempted electropolymerization indicating the possible formation of readily reducible oligomers. Using a catalytic amount of 2,2′-bithiophene[26,27] or coating the electrode with poly(3-methylthiophene) prior to the experiment[27] did not produce a film.

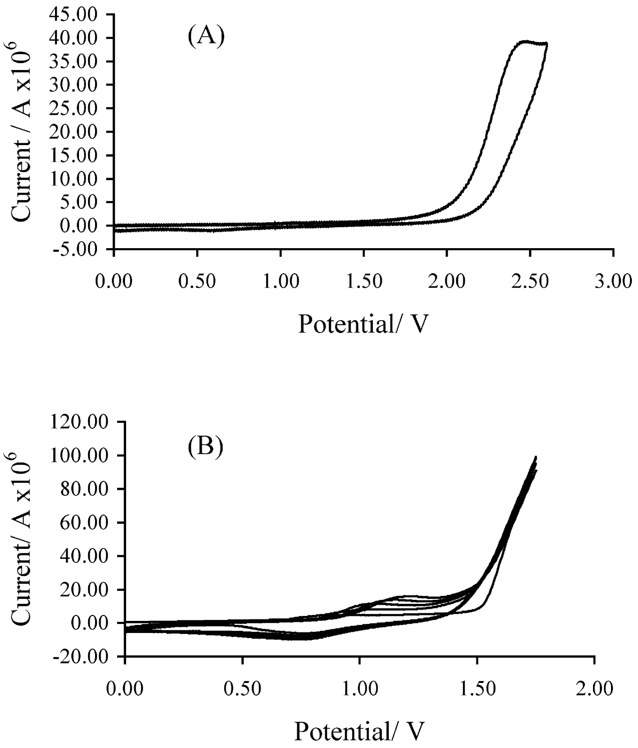

Figure 4. Cyclic voltammograms for oxidation of **4** and **5** vs SCE, v=0.100 Vs^{-1}: (a) **4**, 5 mM, 0.1 M TBAPF$_6$/acetonitrile, Pt (d=1 mm), (b) **5**, 0.1 M, 0.1 M TBAPF$_6$/nitrobenzene, Pt (d=1.25 mm).

In the case of **5**, the CH$_2$ spacer lowers the oxidation potential enough for electropolymerization to occur from TBAPF$_6$/nitrobenzene, Figure 4b. A nucleation loop was observed and growth of the polymer was monitored by the increased polymer redox currents upon repetitive cycling.[28] The onset potential for the polymerization was set lower than the initial peak potential to minimize overoxidation of the polymer.[29] However, ΔE_p for the redox waves associated with the polymer increased dramatically after each scan and the growth rate began to decrease after a few scans; in addition, a blue stream of oxidized oligomer was observed to diffuse away from the electrode and only thin films, which could not be removed from the electrode, were produced. The thin film of **P5**, after being rinsed with MeCN, was cycled in monomer-free 0.1 M TBAPF$_6$/MeCN solution. A linear dependence of i^c_p and i^a_p on the scan rate was observed which is characteristic of redox-active species anchored on the electrode surface.[30]

Current–time transients for the deposition of **P5** on a Pt

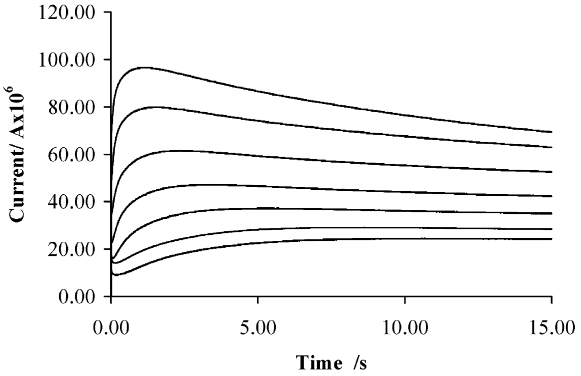

Figure 5. Current-time transients for potential steps for 0.1 M compound **5** in 0.1 M TBAPF$_6$/nitrobenzene on Pt (d=1.25 mm). Curves 1 to 7 corrrespond to potential steps (vs Ag wire) to 1.525, 1.550, 1.575, 1.600, 1.650, 1.700 and 1.750 V, respectively.

electrode from 0.1 M **5** in 0.1 M $TBAPF_6$/nitrobenzene by potential step are shown in Figure 5. After an initial spike, the current falls to a minimum after an induction period and then increases until it reaches a current plateau. The induction time decreases as the applied potential is increased. The use of a 0.2 M monomer solution gave similar current–time response patterns. These features, along with the cross-over observed from CV, are similar to those reported for conducting polymers for which the deposition process involves nucleation followed by continuous three-dimensional growth (steady-state values at long times).[31–33]

A reflectance IR spectrum was taken of a film of **P5** on a Pt electrode using Pt as a background. Although the absorptions were not strong owing to the thinness of the film, an N–H stretching mode near 3300 cm^{-1}, carbonyl stretching modes near 1700 cm^{-1}, and a band at 830 cm^{-1} which is characteristic of 2,3,5,-substituted thiophenes could be discerned.[34] This indicated that the monomeric structure remained intact after electropolymerization. A scanning electron micrograph of polymer **P5** on a Pt electrode shows features similar to those reported for other 3-substituted thiophenes and consistent with a hemispherical three-dimensional growth pattern originating from nuclei on the electrode. EDAX measurements indicated the presence of carbon, oxygen, fluorine, sulfur and phosphorus atoms (from PF_6^- in the electrode after doping). Nitrogen was obscured due to the closely spaced intense carbon and oxygen peaks.

A polymer-coated ITO electrode was scanned to potentials at which it was either fully oxidized or reduced for UV measurements. The oxidized **P5** film changed color from dark blue to red–brown immediately after reaching open circuit. The reduced film gave a broad absorption band with λ_{max} at around 425 nm ($\pi \rightarrow \pi^*$) while, upon the addition of a small amount of $NOBF_4$, this band shifted to give a broader peak with λ_{max} centered near 740 nm (oxidized state, polaron–bipolaron carrier absorptions). These results are consistent with those observed for 3-(carboxylalkyl)thiophene polymers.[35]

3. Conclusions

Acid-catalyzed acylation of amides by anhydrides was successfully extended to the synthesis of new *N*-acyl-3-thenamides and their analogues, compounds **1–5** in yields of 60% or higher. *N*-Acyl-3-thenamides **1–4** exhibit the preferred *S*,*O*-*trans* conformation in the solid state. The conformational orientation for the imide group depends on the alkyl group attached. A *ct* conformer, having a slightly lower calculated equilibrium energy, was found for compounds **1–3**. Compound **4** adopts the *tt* conformation which makes it potentially useful as a chelating agent, since it is similar in structure to acetylacetonates. The hydrogen-bonding character of the imide group is retained in these molecules. Compounds **1–3** form dimers through a pair of hydrogen-bonding interactions that suggest their use in hydrogen-bond directed molecular recognition studies.

N-Acetyl-3-thiopheneacetamide **5** undergoes oxidative electropolymerization to give the corresponding new polymer film **P5** which contains the imide functional group and exhibits electrochromic behavior, dark blue in the oxidized state and brown in the neutral form. A change in the absorption wavelength from 425 to 740 nm was observed when **P5** was oxidized from the neutral state. The metal complexation ability and the hydrogen-bonding capability of the imide moiety on the polymer chain are of interest for future investigation.

N-Acyl-3-thenamides, **1–4**, did not undergo oxidative electropolymerization under the conditions studied. The formation of short-chain species could be qualitatively observed from the cyclic voltammetric studies. An effect of the electron-donating group on the ring through the imide group was indicated.

4. Experimental

4.1. Materials and instrumentation

The following compounds were obtained commercially: MeCN (99%), 2,2′-bithiophene (97%), butyric anhydride (99%), trimethylacetic anhydride (97%), (Sigma-Aldrich), 3-thiopheneacetic acid (98%), thionyl chloride (99.5+%), nitrobenzene (99.0+%), acetic anhydride (97%+), acetyl chloride (Acros Organics), 3-thiophene-carboxylic acid (Lancaster and Fluorochem. Ltd.), $TBAPF_6$, KOCN, (Fluka), propionic anhydride, and deuterated solvents (Cambridge Isotope Labs, Inc.). 3-Acetyl isocyanate, 3-thenoyl chloride, 3-thenamide, and 3-thiopheneacetamide were prepared by literature methods.[36–38]

NMR spectra were obtained on a Bruker AV300 MHz FT NMR spectrometer. Chemical shifts in the ^1H and ^{13}C NMR spectra are relative to TMS. Resonances were assigned from HCCOSY NMR spectra. IR spectra were obtained from thin films, spots on an IR card (3M, type 61), gases (10-cm cell, KBr window) or solids (KBr pellet) using a Mattson Instruments 4020 Galaxy series II FT-IR spectrophotometer. Reflectance IR spectra were taken with a SPECAC Specular Reflectance attachment unit. UV–visible spectra were recorded from 10^{-5}–10^{-4} M samples in acetonitrile on an HP 8453 or 8452A diode array spectrophotometer. EI-MS at 70 eV were obtained on an HP 5890 series II GC coupled to an HP 5958A mass spectrometer. Elemental analyses were carried out by Atlantic Microlabs, Inc. SEM and EDAX measurements were carried using a Phillips 515 SEM equipped with PV9800 EDAX attachment.

4.2. Electrochemistry

A Pine model AFRDE4 Bi-Potentiostat with a LINSEIS LY 16100-II recorder or a model AFCBP 1 Bi-Potentiostat with a PC were employed for electrochemical experiments using a single compartment cell with a platinum, glassy carbon, or ITO (Donnely Corp.) as the working electrode. A Pt plate served as the counter electrode and a Ag wire as a pseudoreference electrode; this was referred periodically to the SCE. The cell was cleaned with conc. HNO_3, rinsed with deionized water and dried for 12 h at 130°C prior to use. Before each measurement, the working electrode (Pt or

GC) was polished using 1.0, 0.3, and 0.05 μm α-alumina paste (Buehler), rinsed with deionized water, dried, and treated with dry acetonitrile in an ultrasonic bath for 1 min. Freshly distilled acetonitrile (over CaH_2) or nitrobenzene (electronic grade) was used as the solvent. $TBAPF_6$ was employed as the supporting electrolyte (0.1 M). The electrolyte and sample solutions were purged with dry N_2 for 10 min and a stream of dry N_2 was maintained over the solutions during the experiments. Freshly recrystallized 2,2′-bithiophene and freshly distilled 3-methylthiophene were used for catalytic and sequential composite polymerization experiments, respectively.

4.3. X-Ray crystallography

X-Ray crystallographic data consisting of independent absorption-corrected reflections having (2Θ(Mo K$\bar{\alpha}\alpha$) <48.3 to $55.0°$) (the equivalent of 0.7 to 1.0 limiting (Cu K$\bar{\alpha}$) spheres) using ω scans and graphite-monochromated (Mo K$\bar{\alpha}$) radiation were collected on a computer-controlled Bruker AXS P4 autodiffractometer. The structure was solved by 'Direct Methods', and the parameters were refined by the counter-weighted full-matrix least-squares on F^2 method and a structural model with anisotropic temperature factors for all non-hydrogen atoms. The hydrogen atom bonded to nitrogen was located from a difference Fourier map and refined as an independent isotropic atom. The remaining hydrogen atoms were included in the structure factor calculations as idealized atoms (assuming sp^2- or sp^3-hybridization of the carbon atom and C–H bond length of 0.93–0.97 Å) 'riding' on their respective carbon atoms. The isotropic thermal parameters of these hydrogen atoms were fixed at values of 1.2 (non-methyl) and 1.5 (methyl) times the equivalent isotropic thermal parameters of the carbon atoms to which they are covalently bonded. Data collection and reduction were obtained using standard versions of Siemens/Bruker software for the diffraction system. Structure determination and refinement were performed using the SHELXTL-PC (version 5.10) interactive software package (G. Sheldrick, Bruker AXS, Madison). CCDC 21613-216133 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB21EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

4.4. Molecular modeling

Molecular modeling studies were carried out using the PC Spartan *Plus* program, version 2.0 (Wavefunction Inc.). Initial minimization of structures was performed with the Merck Molecular Mechanics Force Field. Density functional calculations (B3LYP with a 6-311G** basis set) were carried out using PC Spartan '02. The total energy differences between the *ct* and *tt* conformations were (compound, ΔE kJ mol^{-1}): **1**, 11; **2**, 7; **3**, 8, **4**, 11. The Hartree–Fock method with a smaller basis set (HF/3-21G*) gave inconsistent results.

4.5. Synthesis

4.5.1. *N*-Acetyl-3-thenamide 1. The general procedure is illustrated by that for **1**. 3-Thenamide (8.0 mmol) was placed into a dry two-neck 25-mL flask equipped with a condenser, an addition funnel and a stir bar. A mixture of acetic anhydride (8.8 mmol) and concentrated sulfuric acid (0.88 mmol, 10 mol%) was added to the reaction flask under a nitrogen atmosphere. The reaction mixture was heated to reflux for 2 h. The resulting dark brown reaction mixture was cooled, then quenched with ice water. Dichloromethane was used to extract the mixture several times. The organic layer was combined and washed with dilute $NaHCO_3$ followed by several portions of distilled water. The mixture was dried with $MgSO_4$ and filtered. A light brown solid was obtained after solvent removal. Further purification by flash chromatography (40% ethyl acetate and 60% hexanes) gave the desired pale yellow compound (69%), mp 127–129°C. ^{1}H NMR (300 MHz, δ in ppm, $CDCl_3$): 9.24 (b, 1H), N*H*; 8.19 (dd, 1H, J_{24}=1.4 Hz, J_{25}=2.9 Hz), H_2; 7.55 (dd, 1H, J_{45}=5.1 Hz) H_4; 7.37 (dd, 1H), H_5; 2.58 (s, 3H), C*H*$_3$. ^{13}C NMR (75.5 MHz, δ in ppm, $CDCl_3$): 174.7, *C*(O)CH$_3$; 160.7, *C*(O)NH; 135.8, C_3; 131.3, C_2; 127.3, C_4; 127.0, C_5; 25.8, *C*H$_3$. FT-IR (KBr, cm^{-1}): 3287 m, 3097 m, 1707 s, 1670 s, 746 s. UV–visible (λ in nm (log ε)): 213 (4.31), 245 (4.07). MS (EI, 70 eV) (*m*/*z*, fragment, %): 169, $C_7H_7NO_2S^+$(parent, M$^+$), 47; 111, $C_4H_3SC(O)^+$, 100; 43, $C(O)CH_3^+$, 25. Analysis calculated for $C_7H_7NO_2S$ (F.W. 169.20): C, 49.69%; H, 4.18%; N, 8.27%. Found: C, 49.73%; H, 4.37%; N, 8.11%.

A second method, utilizing the reaction of 3-thiophenecarboxylic acid and acetyl isocyanate in dry MeCN, produced about 57% of the amount of CO_2 expected from the stoichiometric equation, but only 13% of pure **1** was isolated.

4.5.2. *N*-Propionyl-3-thenamide 2. The reaction of 3-thenamide (6.0 mmol) and propionic anhydride (6.6 mmol) catalyzed by concentrated sulfuric acid (0.6 mmol, 10 mol%) was carried out following the general procedure above to give **2** as a white crystalline solid. Yield: 71%. Mp 135.5–137°C. ^{1}H NMR (300 MHz, δ in ppm, $CDCl_3$): 9.29 (b, 1H), N*H*; 8.22 (dd, 1H, J_{24}=1.3 Hz; J_{25}=2.9 Hz), H_2; 7.58 (dd, 1H, J_{45}=5.1 Hz), H_4; 7.39 (dd, 1H), H_5; 3.03 (q, 2H, J=7.3 Hz), C*H*$_2$; 1.21 (t, 3H), C*H*$_3$. ^{13}C NMR (75.5 MHz, δ in ppm, $CDCl_3$): 178.0, *C*(O)CH$_2$CH$_3$; 160.9, *C*(O)NH; 136.3, C_3; 131.4, C_2; 127.2, C_5; 127.1, C_4; 31.4, *C*H$_2$; 8.4, *C*H$_3$. FT-IR (KBr, cm^{-1}): 3258 m, 3098 m, 2973 w, 2938 w, 1707 s, 1678 s, 748 m. UV–visible (λ in nm (log ε)): 213 (4.28), 245 (4.05). MS (EI, 70 eV) (*m*/*z*, fragment, %): 183, $C_8H_9NO_2S^+$(parent, M$^+$), 47; 111, $C_4H_3SC(O)^+$, 100; 57, $C_2HS^+/C_2H_5C(O)^+$, 32. Analysis calculated for $C_8H_9NO_2S$ (F.W. 183.22): C, 52.44%; H, 4.96%; N, 7.64%. Found: C, 52.43%; H, 4.98%; N, 7.61%.

4.5.3. *N*-Butyryl-3-thenamide 3. The reaction of 3-thenamide (2 mmol) with butyric anhydride (2.2 mmol) in the presence of concentrated sulfuric acid (0.2 mmol, 10 mol%) gave **3** as a white crystalline solid with a melting point of 102.5–104°C. Yield: 66%. ^{1}H NMR (300 MHz, δ in ppm, $CDCl_3$): 9.02 (b, 1H), N*H*; 8.17 (dd, 1H, J_{24}=1.3 Hz, J_{25}=2.9 Hz), H_2; 7.48 (dd, 1H, J_{45}=5.1 Hz), H_4; 7.39 (dd, 1H), H_5; 2.98 (t, 2H, J=7.3 Hz), C(O)C*H*$_2$CH$_2$; 1.74 (m, 2H), C(O)CH$_2$C*H*$_2$; 1.03 (t, 3H,

J=7.4 Hz), CH_3. ^{13}C NMR (75 MHz, δ in ppm, $CDCl_3$): 176.7, C(O)CH_2; 160.6, C(O)NH; 136.1, C_3; 131.1, C_2; 127.2, C_5; 126.8, C_4; 39.5, C(O)CH_2CH_2; 17.6, C(O)CH_2CH_2; 13.7, CH_3. FT-IR (KBr, cm^{-1}): 3258 s, 3166 m, 3122 m, 3098 s, 2959 s, 2929 w, 2872 w, 1703 s, 1680 s 748 s. UV–visible (λ in nm (log ε)): 213(4.25), 245(4.03). MS (EI, 70eV) (m/z, fragment, %): 197, $C_9H_{11}NO_2S^+$(parent, M^+), 23; 182, M−CH_3, 10; 169, M−C_2H_4, 15; 128, $C_4H_3SC(O)NH_3^+$, 27; 111, $C_4H_3SC(O)^+$, 100; 43, $C_3H_7^+$, 46. Analysis calculated for $C_9H_{11}NO_2S$ (F.W. 197.26): C, 54.80%; H, 5.63%; N, 7.10%. Found: C, 54.84%; H, 5.58%; N, 7.00%.

4.5.4. *N*-Trimethylacetyl-3-thenamide 4. The reaction of 3-thenamide (6 mmol) with trimethylacetic anhydride (6.6 mmol) and concentrated sulfuric acid (0.6 mmol, 10 mol%) gave **4** as a white crystalline solid. Yield: 53. Mp 114.5–116.5°C. ^1H NMR (300 MHz, δ in ppm, $CDCl_3$): 8.40 (b, 1H), NH; 7.99 (dd, 1H, J_{24}=1.2 Hz, J_{25}=3.0 Hz), H_2; 7.41 (dd, 1H, J_{45}=5.1 Hz), H_4; 7.37 (dd, 1H), H_5; 1.30 (s, 3H), CH_3. ^{13}C NMR (75 MHz, δ in ppm, $CDCl_3$): 175.9, C(O)C; 161.0, C(O)NH; 136.4, C_3; 131.2, C_2; 126.8, C_4; 126.7, C_5; 40.5, C(O)C; 27.1, CH_3. FT-IR (KBr, cm^{-1}): 3346 m, 3303 s, 3121 w, 3091 s, 2972 m, 2932 w, 2909 w, 1728 s, 1672 s 769 m. UV–visible (λ in nm (log ε)): 214(4.17), 244(sh, 3.97). MS (EI, 70 eV) (m/z, fragment, %): 211, $C_{10}H_{13}NO_2S^+$(parent, M^+), 20; 111, $C_4H_3SC(O)^+$, 100; 57, $C_2HS^+/(CH_3)_3C^+$,18. Analysis calculated for $C_{10}H_{13}NO_2S$ (F.W. 211.31): C, 56.84%; H, 6.12%; N, 6.63%. Found: C, 56.95%; H, 6.12%; N, 6.55%.

4.5.5. *N*-Acetyl-3-thiopheneacetamide 5. 3-Thiopheneacetamide was prepared by the reaction of 3-thiopheneacetic acid with cold ammonia; a different synthetic method has been reported for this compound.[39] The procedure described above for **1** was followed for **5** using 3-thiopheneacetamide as the reactant; a mixture of 50% ethyl acetate/50% hexane was employed for flash chromatography. The product, **5**, was a white solid, mp 101–103°C (63%). ^1H NMR (300 MHz, δ in ppm, $CDCl_3$): 8.60 (b, 1H), –NH; 7.34 (dd, J_{25}=3.0 Hz, J_{45}=5.4 Hz, 1H), H_5; 7.18 (dd, J_{24}=1.0 Hz, 1H), H_2; 7.02 (dd, 1H), H_4; 3.84(s, 2H), CH_2; 2.38 (s, 3H), CH_3. ^{13}C NMR (75.5 MHz, δ in ppm; $CDCl_3$): 172.3, -C(O)CH_3; 170.8, CH_2C(O); 132.9, C_3, 128.5, C_4 126.9, C_5; 124.1, C_2; 39.0, CH_2, 25.3, CH_3. FT-IR (KBr, cm^{-1}): 3265 m, 3173 m, 3091 w, 3015 w, 2934 w, 2893 w, 1731 s, 1693 m, 767 m. UV–visible (λ_{max} in nm (log ε)): 203 (4.24), 233 (3.80). MS (EI, 70 eV) (m/z, fragment, %): 183, $C_8H_9NO_2S^+$(parent, M^+), 19; 124, $M^+-CH_3C(O)NH_2$, 100; 97, $C_4H_3SCH_2^+$, 50; 96, $M^+-CH_3C(O)NH_2-CO$, 16; 43, $C(O)CH_3^+$, 47; Analysis calculated for $C_8H_9NO_2S$ (F.W. 183.23): C, 52.44%; H, 4.96%; N, 7.64%. Found: C, 52.51%; H, 4.89%; N, 7.60%.

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