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# Synthesis of 3-Heteroalkyl-2-*N*-organylaminothiophenes. The First Proof for Amino-imino Tautomerism of *N*-Monosubstituted Aminothiophenes

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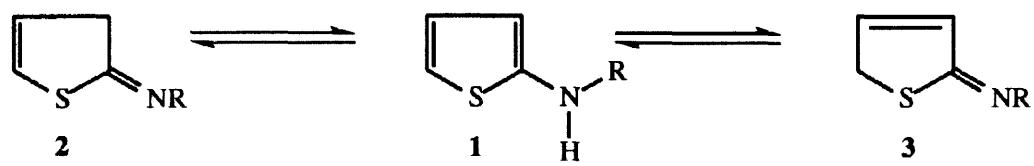
***Abstract:*** The compounds 2-*N*-methylamino-3-methoxythiophene and 2-*N*-phenylamino-3-methoxythiophene obtained in fair to good yields in a novel one-pot synthesis from methyl or phenyl isothiocyanate and 1-lithiomethoxyallene have been shown to be in equilibrium with the imino tautomers. The analogous 3-methylthio derivatives obtained by a similar procedure from 1-lithiomethylthioallene exist exclusively in the amino form. 

2-Aminothiophenes **1** can, in principle, occur in equilibrium with the tautomeric forms **2** and **3**. The most simple representative, 2-aminothiophene, and a few *N*-alkyl derivatives are known for a long time[1,2].




**2** **1** **3**

**Scheme 1**

Since the chemical behaviour of these unstable compounds deviated in many respects from that of the aryl amines, it was first thought that they preferably exist in the imino form **2**. In 1960[3] it was proved by NMR spectroscopy that the parent aminothiophene occurs exclusively in the amino form **1**. This was confirmed later by more detailed investigations[4-6]. Several other 2-*N*-substituted thiophenes have been synthesized[7], but in none of the cases amino-imino tautomerism has been mentioned. The strong preference for the amino tautomers may be explained by assuming that the –M-effect of the electron-withdrawing substituents present compensates the +M-effect of the amino group, which stabilizes the amino form. On the other hand, one would

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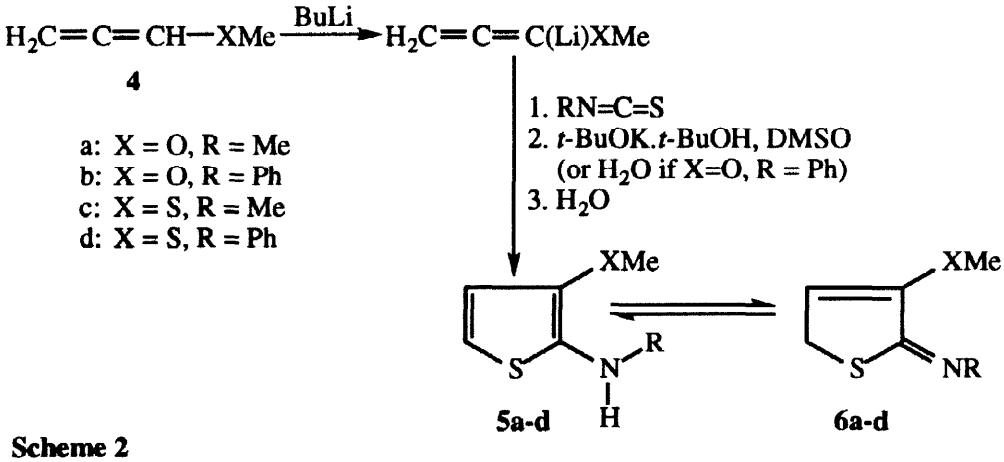
expect that the presence of electron-donating substituents ($OCH_3$, $SCH_3$) at suitable positions of the ring could stabilize the imino tautomers.

We here wish to report a facile one-pot procedure giving access to a number of hitherto unavailable 3-substituted 2-*N*-organylaminothiophenes. This enabled us to synthesize relevant representatives for investigating the tautomerism.

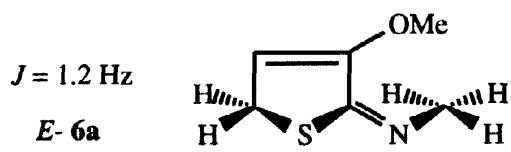



**Scheme 2**

The tautomeric equilibrium between **5** and **6** was studied in detail by $^1H$ NMR and $^{13}C$ NMR spectroscopy for **5a** and **5b**, using $CCl_4$, 1 : 1 mixtures of $CCl_4$ and $CDCl_3$, pure $CDCl_3$ or $(CD_3)_2C{=}O$ as solvents. The NMR spectra of **5c** and **5d** showed only signals, assignable to the amino structures.

In a 1 : 1 mixture of $CCl_4$ and $CDCl_3$ **5a** is in equilibrium with its tautomer **6a**: ratio ~ 1 :7. The NMR sub-spectrum of the amino form **5a** is similar to that of the corresponding 2-*N,N*-dimethylamino-3-methoxythiophene, obtained by adding excess of methyl iodide instead of water, after the treatment with *t*-BuOH, *t*-BuOK and DMSO[8] (see experimental part). It consists of the AB system of the thiophene protons H-4 and H-5 in the region of 6.3-6.7 ppm ($J$ = 5.7 Hz), two singlets for the MeN and MeO protons at 2.83 and 3.74 ppm, respectively, and a broad singlet of the NH group at 3.85 ppm. In the sub-spectrum of **6a**, the CH= proton appears as a triplet at 5.71 ppm ($J_{CH_2}$ = 3.18 Hz). Therefore, the $CH_2$ group should appear as a doublet. Actually it looks like a double doublet at 3.74 ppm, due to an unexpected long-range interaction ($J_{6(CH_2,\ MeN=)}$ = 1.2 Hz). Hence, the $CH_3N{=}$ signal is splitted in a triplet (3.23 ppm). The MeO group appears as a singlet at 3.77 ppm.

Theoretically, the imine **6a** can exist in a *E*- or *Z*-form. However, in the NMR spectra only one of them is seen. From the well-known W-effect[9] it is possible to assume that the *E*-configuration is more probable owing to better conditions for the spin information transfer.




The assumption is supported by AM-1 calculation ($\Delta\Delta H.O.F._{E,Z}$ = ~1.5 Kcal/mol) and the $^{13}C$ NMR spectrum simulation (C-2, ppm: Found: 163.6, Calc.: 160.7 ±7.8 (*E*), 150.3 ±4.3 (*Z*)[10].

Replacement of the solvent ($CDCl_3/CCl_4$ 1 : 1 mixture) by the more polar $CDCl_3$ slightly shifts the tautomeric equilibrium toward the imino form (**5a** : **6a** = 1 : 15), which is explained by its higher polarity, as compared with that of the amino form. In neat $CCl_4$, however, the population of the NH tautomer increases (**5a** : **6a** = 1 : 1).

In the case of **5b** the amino form predominates in neat $CDCl_3$ (**5b** : **6b** = 10 : 7). One might assume that replacement of $CDCl_3$ by the more polar acetone-$d_6$ would favour the more polar imine **6b**. Actually, a strong shift to the amino form is observed (**5b** : **6b** = 33 : 1), which is explained by specific solvatation with the formation of hydrogen bonds (for a similar effect in 3-hydroxypyrroles see[11]).

The tautomerization rate **5a** → **6a** is very fast. For example, after dilution of a solution of **5a** in $CDCl_3$ with $CCl_4$ (or vice versa) an immediately repeated recording of the NMR spectrum (requiring no longer than 5 minutes) showed the same equilibrium ratio of **5a** and **6a** as mentioned above. This high mobility may be the consequence of a significant basicity of the amino form **5a**. Equilibriation between **5b** and **6b** was found to occur much more slowly.

Summarizing, we can state that the 3-methoxy-substituted derivatives **5a** and **5b** are the first examples of tautomeric systems in the 2-thiopheneamine series.

## EXPERIMENTAL PART

To a solution of 0.10 mol of *n*-BuLi in 65 ml of hexane and 70 ml of THF was added at –90 °C 0.11 mol of the allenic ether or sulfide **4**. After an additional period of 15 min (at –90 to –70°C) 0.10 mol of methyl isothiocyanate or 0.07 mol of phenyl isothiocyanate was added over 5 min at –80 °C. The solution was stirred for an additional 15 min at –70 °C in the case of methyl isothiocyanate or 1 h at –80 °C in the case of phenyl isothiocyanate, then 0.10 mol of *t*-butylalcohol and a solution of 0.10 mol of potassium *tert*-butoxide in 50 ml of DMSO were successively added at –40 °C. In the case X = O, R = Ph, however, no *t*-BuOH, *t*-BuOK and DMSO were added, but the temperature of the reaction mixture was allowed to reach 0 °C and was subsequently treated with 250 ml of water. In the other cases the reaction mixture was stirred for ~15 min at 25-30 °C. After the addition of water and extraction with ether, the combined organic solutions were washed with saturated aqueous ammonium chloride, dried over potassium carbonate. The solvent was removed under reduced pressure followed by distillation of the remaining liquid through a short Vigreux column.

The following compounds were obtained (microanalyses were satisfactory):

**5a+6a**, b.p. 60 °C/0.7 mm Hg, $n^{20}_D$ 1.565, yield 36 %. Mass-spectrum, m/z (I, %): 143 (93.8, $M^{+\bullet}$), 128 (100, $M^{+\bullet}$ –Me), 101 (83), 42 (49).

**5a** $^1$H NMR-spectrum (300 MHz, $CDCl_3$): δ = 2.83 (s, 3 H, NMe), 3.74 (s, 3 H, OMe), 3.85 (Br.s, 1 H, NH), 6.3-6.7 (dd, *J* = 5.7 Hz, 2 H, H-4,5). $^{13}$C NMR-spectrum (75 MHz, $CDCl_3$): δ = 34.89 (MeNH), 58.31 (MeO), 106.79 (C-5), 116.47 (C-4), 136.27 (C-3), 139.50 (C-2).

**6a** $^1$H NMR-spectrum (300 MHz, $CDCl_3$): δ = 3.23 (t, 3 H, MeN=), 3.74 (dd, $J_{6(CH_2,\ MeN)}$ = 1,2 Hz, 2 H, $CH_2$), 3.77 (s, 3 H, OMe), 5.71 (t, $J_{CH_2}$ = 3.18 Hz, 1 H, CH=). $^{13}$C NMR-spectrum (75 MHz, $CDCl_3$): δ = 30.02 (C-5), 42.71 (MeN=), 56.82 (MeO), 106.69 (C-4), 156.10 (C-3), 163.58 (C-2).

**5b+6b**, b.p. 140 °C/0.6 mm Hg, $n^{20}_D$ 1.633, yield 79 %. Mass-spectrum, m/z (I, %): 205 (78.4, $M^{+\bullet}$),

190 (100, $M^{+\bullet}$ –Me), 104 (50.4), 77 (44.3, Ph).

**5b** $^1$H NMR-spectrum (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H, MeO), 5.17 (br.s, 1 H, NH), 6.70 (d, $J_3$ = 6.0 Hz, 1 H, H-4), 6.66 (m, 2 H, *o*-Ph), 6.81 (d, 1 H, H-5), 7.08 (m, 2 H, *m*-Ph), 7.25 (m, 1 H, *p*-Ph); $^1$H NMR-spectrum (300 MHz, acetone-$d_6$): δ = 3.75 (s, 3 H, MeO), 6.63 (br.s, 1 H, NH), 6.68 (m, 1 H, *p*-Ph), 6.75 (m, 2 H, *o*-Ph), 6.86 (d, 1 H, H-4), 7.02 (d, 1 H, H-5), 7.11 (m, 2 H, *m*-Ph). $^{13}$C NMR-spectrum (75 MHz, acetone-$d_6$): δ = 58.98, 114.44, 118.36, 119.08, 119.15, 125.18, 129.89, 148.63, 151.65.

**6b** $^1$H NMR-spectrum (300 MHz, $CDCl_3$): δ = 3.67 (d, $J_4$ = 3.3 Hz, 2 H, $CH_2$), 3.76 (s, 3 H, MeO), 5.79 (t, 1 H, H-4), 6.7-7.05 (m, 5 H, Ph). $^{13}$C NMR-spectrum (75 MHz, acetone-$d_6$): δ = 31.56, 58.19, 111.87, 120.8, 123.83, 125.18, 127.75, 130.10, 153.27.

**5c**, b.p. 70 °C/0.5 mm Hg, $n^{20}_D$ 1.608, yield 72 %. $^1$H NMR-spectrum (300 MHz, $CDCl_3$): δ = 2.19 (s, 3 H, SMe), 2.94 (s, 3 H, NMe), 4.72 (br.s, 1 H, NH), 6.41 (d, 1 H, H-4), 6.82 (d, 1 H, H-5). $^{13}$C NMR-spectrum (75 MHz, $CDCl_3$): δ = 19.36, 34.46, 107.37, 128.98, 131.30, 158.10.

**5d**, b.p. 150 °C/0.5 mm Hg, $n^{20}_D$ 1.677, yield 49 %. $^1$H NMR-spectrum (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, SMe), 6.51 (br.s, 1 H, NH), 6.78 (d, 1H, H-4), 6.97 (d, $J_{4,5}$ = 5.77 Hz, 1 H, H-5), 6.98 (m, 1 H, *p*-Ph), 7.12 (m, 2 H, *o*-Ph), 7.33 (m, 2 H, *m*-Ph). $^{13}$C NMR-spectrum (75 MHz, $CDCl_3$): δ = 19.10 (SMe), 113.19 (C-5), 115.58 (C-2, Ph), 116.26 (C-3), 120.79 (C-4, Ph), 129.18 (C-4), 129.37 (C-3, Ph), 143.52 (C-2), 145.76 (C-1, Ph). Mass-spectrum, m/z (I, %): 221 (91, $M^{+\bullet}$), 206 (45, $M^{+\bullet}$ –Me), 173 (100, $M^{+\bullet}$ –MeSH), 77 (34, Ph).

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