A novel transformation of 2-acetylthiophene and its halogen derivatives under Vilsmeier reaction conditions

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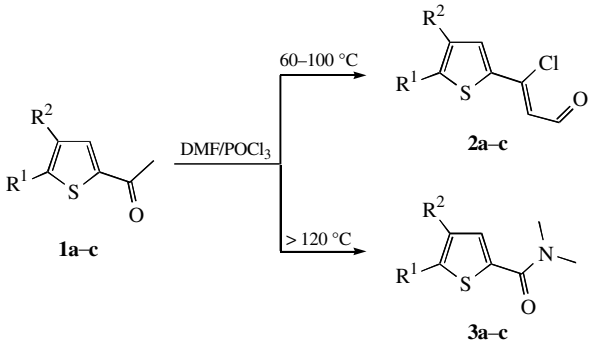
Under conditions of the Vilsmeier reaction either β-chloro-β-(2-thienyl)acrylic aldehydes or *N*,*N*-dimethyl-2-thiophenecarboxamides can be synthesised from 2-acetylthiophenes depending on the reaction temperature and time.

The Vilsmeier reaction is a general procedure for introducing an aldehyde group into activated aromatic rings.[1–3] This method has been widely used for the synthesis of various aldehyde derivatives of benzene, thiophene, furan, pyrrole *etc.*, *via* a complex derived from DMF and $POCl_3$, $SOCl_2$ or $COCl_2$. The Vilsmeier complex is also used as a halogenating and dehydrating agent.[4–6] In particular, the dehydration of N-monosubstituted formamides by DMF–$POCl_3$ is a simple procedure for the synthesis of isonitriles.[4] Specific transformations under the action of Vilsmeier's reagent are known, *e.g.*, the synthesis of previously unknown amidomercaptals from the 2-thienyl sulfides or alkanethiols.[5,6] Interesting synthetic possibilities are offered by the joint action of Vilsmeier's reagent and hydride reductants.[7]

In addition to the electrophilic formylation of aromatic compounds, Vilsmeier's reagent has been also widely used in reactions with carbonyl compounds.[8] Arnold and Zemlicka[9,10] found that the reaction of Vilsmeier's reagent with ketones containing methyl or methylene groups adjacent to the carbonyl group affords substituted β-chloroacrylaldehydes. The reaction can be used for the preparation of β-chloroacrylaldehydes from ketones including aryl alkyl ketones.[8] The reaction proceeds on the addition of a ketone to Vilsmeier's reagent at 5–10 °C followed by heating the reaction mixture at 60 to 100 °C up to the complete transformation into β-chloroacrylaldehyde.

However, we found that 2-acetylthiophenes **1a–c** heated with Vilsmeier's reagent above 120 °C afforded *N*,*N*-dimethylthiophene-2-carboxamides **3a–c** rather than expected β-chloroacrylaldehydes **2a–c** (Scheme 1).†



1–3: **a** $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = Br$
1c, **2c** $R^1 = R^2 = Br$
3c $R^1 = Cl$, $R^2 = Br$

Scheme 1

The structures of amides **3a–c** were found from spectroscopic data and the results of elemental analyses,‡ in the case of **3a** the characteristics were compared with published data. The structure of amide **3b** was found by spectrometric techniques, elemental analysis and through its independent synthesis from known 4-bromothiophene-2-carboxylic acid.[15] As to the replacement of bromine by a chlorine atom on the interaction of 2-acetyl-4,5-dibromothiophene **1c** with Vilsmeier's reagent, the preparation of 5-chlorothiophene-2-carbaldehyde by the reaction of 2-bromothiophene with *N*-methylformanilide and $POCl_3$ at 100 °C should be mentioned.[16] Note that there is a weak parent peak (*m*/*z* 313) of *N*,*N*-dimethyl-4,5-dibromothiophene-2-carboxamide in the mass spectrum of unpurified amide **3c**.

The mechanism of this novel transformation remains unclear. The reaction likely involves many steps (Scheme 2) and includes the formation of intermediate **6**, which is analogous to key compounds yielding β-chloroacrylaldehydes.[8] The formation of β-chloroacrylaldehydes from acetylthiophenes and Vilsmeier's reagent at 60–100 °C was described.[8,17,18] In particular, 3-chloro-3-(2-thienyl)propenal was obtained in 11% yield by treatment of 2-acetylthiophene with Vilsmeier's reagent at 60 °C.[17] The formation of both 3-chloro-3-(2-thienyl)propenal and *N*,*N*-dimethylthiophene-2-carboxamide in the ratio ~1:1 on the heating of 2-acetylthiophene with Vilsmeier's reagent for 1 h instead of 3 h§ may indirectly indicate that β-chloroacrylaldehydes are inter-

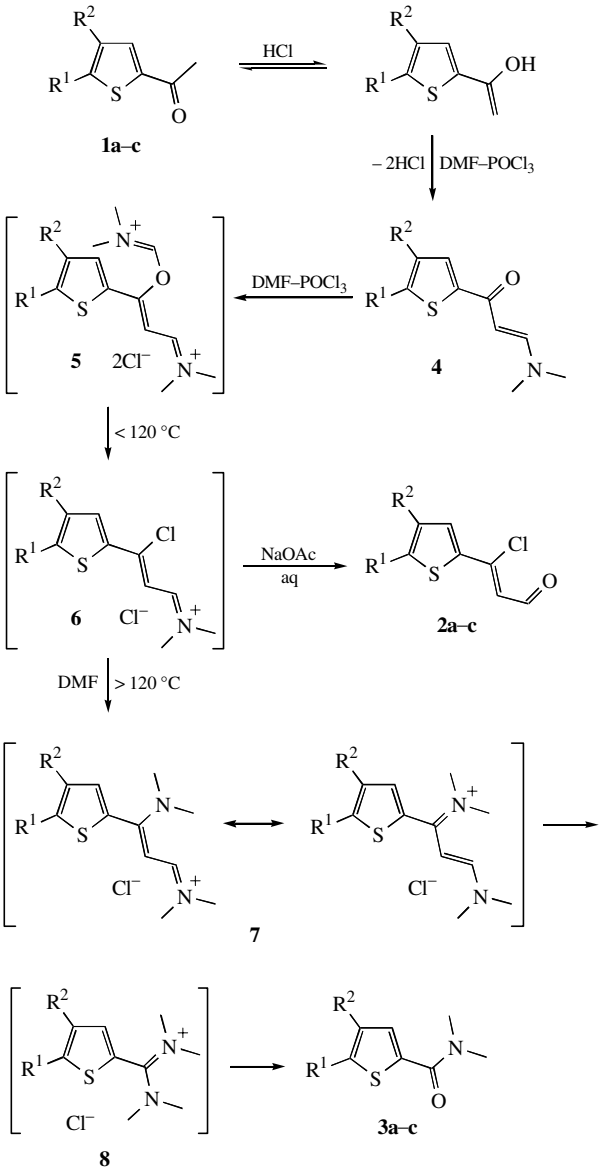
† *Preparation of* N,N-*dimethylthiophene-2-carboxamides* **3a–c** *(general procedure).* Phosphorus oxychloride (2.5 ml, 4.1 g, 0.027 mol) was added dropwise to DMF (8.5 ml, 8.2 g, 0.11 mol) cooled to 0–10 °C. The mixture was kept for 15 min at this temperature, then for 15 min at 45–50 °C and cooled again to 0–10 °C; a starting 2-acetylthiophene (0.024 mol) was added. (2-Acetylthiophene was purchased from Aldrich, 2-acetyl-4-bromothiophene **1b** and 2-acetyl-4,5-dibromothiophene **1c** were prepared according to the published procedure.[11]) The reaction mixture was gradually heated to 120–130 °C and kept at this temperature for 2.5–3 h. After cooling, CH_2Cl_2 (50 ml) was added, and the organic layer was washed successively with concentrated AcONa and $NaHCO_3$ solutions and finally with water. The residue after evaporation of the extract was recrystallised from a suitable solvent.

‡ N,N-*Dimethylthiophene-2-carboxamide* **3a**: yield 41%, mp 44–45 °C (from light petroleum, lit.,[12] mp 44–45 °C). ^{1}H NMR [200 MHz, $(CD_3)_2CO$] δ: 3.18 (br. s, 6H, Me_2N), 7.09 (dd, 1H, 4-H), 7.43 (dd, 1H, 3-H), 7.62 (dd, 1H, 5-H); J_{45} 4.8 Hz, J_{34} 3.7 Hz, J_{35} 1.1 Hz (*cf.* ref. 13). MS (EI, 70 eV), *m*/*z* (%): 155 (46) $[M]^+$, 111 (100) $[M – NMe_2]^+$.

N,N-*Dimethyl-4-bromothiophene-2-carboxamide* **3b**: yield 39%, mp 98–100 °C (from heptane). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.21 (br. s, 6H, Me_2N), 7.25 (s, 1H, 5-H), 7.38 (s, 1H, 3-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 30.85 (Me), 109.12 (C–Br), 126.36 [C(3)], 131.12 [C(5)], 139.21 [C(2)], 162.80 (C=O). MS (EI, 70 eV), *m*/*z* (%): 235 (59) $[M]^+$, 191 (99) $[M – NMe_2]^+$. Found (%): C, 36.41; H, 3.83; Br, 33.78; S, 13.55; N, 6.24. Calc. for C_7H_8BrNOS (%): C, 35.91; H, 3.44; Br, 34.13; S, 13.7; N, 5.98.

N,N-*Dimethyl-4-bromo-5-chlorothiophene-2-carboxamide* **3c**: yield 47%, mp 75–76 °C (from heptane). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.19 (br. s, 6H, Me_2N), 7.13 (s, 1H, 3-H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 34.74 (Me), 35.37 (Me), 98.92 (C–Cl), 107.48 (C–Br), 128.34 [C(3)], 133.96 [C(2)], 159.35 (C=O). MS (EI, 70 eV), *m*/*z* (%): 271 (11) $[M]^+$, 269 (38) $[M]^+$, 267 (24) $[M]^+$, 227 (24) $[M – NMe_2]^+$, 225 (78) $[M – NMe_2]^+$, 223 (64) $[M – NMe_2]^+$. Found (%): C, 31.32; H, 2.52; Br, 30.32; Cl, 13.46; S, 12.17; N, 4.39. Calc. for $C_7H_7BrClNOS$ (%): C, 31.22; H, 2.60; Br, 29.74; Cl, 13.19; S, 11.89; N, 5.24. Found (by the Schöniger[14] method) (%): S, 10.81. Calc. for $C_7H_7BrClNOS$ (%): S, 11.89.

§ On the interaction of 2-acetylthiophene **1a** with Vilsmeier's reagent at 100–120 °C for 1 h, the residue (2.06 g of a yellow oil) obtained after evaporation of the solvent was chromatographed on silica gel (light petroleum–EtOAc, 2.5:1, as an eluent) to give two substances. After recrystallization from light petroleum the following compounds were obtained: 3-chloro-3-(2-thienyl)propenal **2a**, 0.75 g (yield 21%), mp 54–55 °C (lit.,[17] 55–57 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.55 (d, 1H, C=CH, *J* 3.6 Hz), 7.08 (dd, 1H, 4-H, J_{45} 4.8 Hz, J_{34} 3.7 Hz), 7.51 (dd, 1H, 5-H, J_{35} 1.2 Hz), 7.61 (m, 1H, 3-H), 10.08 (d, 1H, CH=O, *J* 6.05 Hz). Amide **3a**, 0.92 g (yield 25%), identical to the above substance mp and ^{1}H NMR spectrum.



Scheme 2

mediates in the formation of the carboxamides. However, compound **3** cannot be obtained from aldehyde **2** under these conditions: the heating of 3-chloro-3-(2-thienyl)propenal under Vilsmeier reaction conditions leads to decomposition and tar formation. On the assumption that aldehydes **2** are formed from intermediates **6** on the treatment of the reaction mixture, the transformation of compounds **6** into amides **3** can be considered as a process including the formation of enamines **7** by the interaction of DMF (in an excess of DMF) with **6** like the synthesis of *N*,*N*-dimethylcarboxamides from DMF and acyl chlorides at 140–150 °C.[19] Since intermediate **7** is a vinylog of amidines, a further transformation into *N*,*N*-dimethylamide **3** may be similar to the formation of amides from amidines on hydrolysis. It is also similar to the acidic cleavage of β-dicarbonyl compounds. The transformation **7** → **3** is likely to proceed *via* amidinium salt **8**.

In conclusion, we found a new transformation under Vilsmeier reaction conditions, which is promising for the one-step preparation of *N*,*N*-dimethylthiophenecarboxamides from 2-acetylthiophenes. The heating of acetylthiophenes with Vilsmeier's reagent can lead to both β-chloro-β-(2-thienyl)acrylaldehydes and *N*,*N*-dimethylthiophene-2-carboxamides depending on the heating temperature and reaction time. Vilsmeier's reagent can also be used as a transhalogenating agent.

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