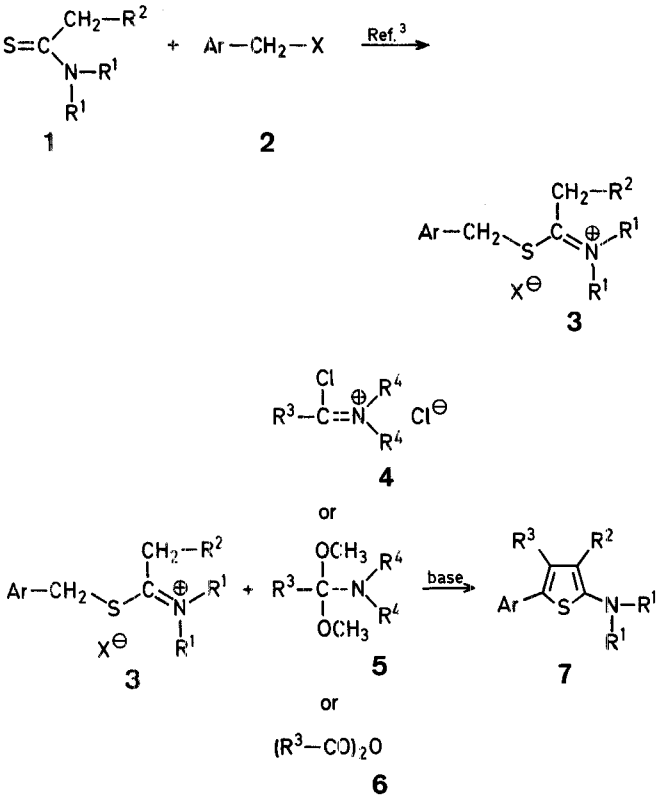
Formylation Products of Thioamides; Part 11[1]. A Novel Route to Substituted 2-Aminothiophenes by the Reaction of *S*-Alkylated Thioamides with Carboxylic Acid Derivatives

Jürgen LIEBSCHER*, Kersten FEIST

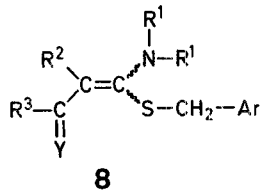
Sektion Chemie, Humboldt-Universität zu Berlin, DDR-1040 Berlin, Hessische Str. 1–2, German Democratic Republic

Recently, we reported on the iminoformylation of *N,N*-disubstituted thioacetamides **1** with formamide chlorides **4** (R^3 = H) to give 3-aminopropenethioamides[2]. We now report on the reaction of *S*-benzyl-substituted mercaptomethyleniminium salts **3** with formamide chlorides **4** (R^3 = H) or other acid derivatives, such as substituted formamide acetals **5** (R^3 = H) or acid anhydrides **6**, which affords a novel synthesis of thiophenes **7**.



Ar = 4-O_2N—C_6H_4, 4-NC—C_6H_5
X = Br

The mercaptomethyleniminium salts **3** were conveniently prepared[3] by *S*-alkylation of thioacetamides **1**. The reaction of these salts **3** with the acid derivatives **4**, **5**, or **6**, mostly in the presence of triethylamine, yields substituted 2-aminothiophenes **7**[4]. If no triethylamine is used in the reaction of **3** with formamide chlorides **4** (R^3 = H), intermediate ketene-*S,N*-aminals **8** [R^3 = H; Y = $^{\oplus}N(CH_3)_2$] can be isolated and separately cyclised[5] in a basic medium.



8

The above observation implicates the following mechanism for the transformation of **3** to **7**. The acid derivative **4**, **5**, or **6** attacks the R^2-substituted methylene group of the mercaptomethyleniminium salts **3** yielding a corresponding acyl- or imidoylketene-*S,N*-aminal **8** [Y=O or $^{\oplus}N(CH_3)_2$]. Subsequent base-catalysed intramolecular condensation of **8** affords the thiophenes **7** while H_2Y is eliminated.

In the case of the reaction of compound **3** [R^2 = 4-H_3C—C_6H_4; Ar = 4-O_2N—C_6H_4; $N(R^1)_2$ = morpholino] with acetic anhydride **6** (R^3 = CH_3) in the presence of triethylamine, however, no thiophene **7** but the corresponding open-chain acylketene-*S,N*-aminal **8a** (Table) was obtained, which could not be cyclised by further treatment with triethylamine, pyridine, phosphoryl chloride, polyphosphoric acid, or sodium ethoxide.

Table. Substituted 2-Aminothiophenes **7** and Ketene-*S,N*-aminals **8** prepared

Substrate **3** (X = Br) R^2	Ar	Substrate **4**, **5**, or **6** R^3	R^4	R^4	Product[a]	Yield [%] (Method)	m.p. [°C] (solvent)	Molecular Formula[b] or Lit m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
H	4-O_2N—C_6H_6	H	CH_3	CH_3	**7a**	76 (A)	161–162° (acetone)	$C_{14}H_{14}N_2O_3S$ (290.3)	1505, 1335	3.1 (m, 4H); 3.7 (m, 4H); 5.99 (d, 1H, J = 4 Hz); 7.10 (d, 1H, J = 4 Hz); 7.36 (d, 2H, J = 8 Hz); 8.0 (d, 2H, J = 8 Hz)
H	4-NC—C_6H_4	H	CH_3	CH_3	**7b**	52 (A)	186–187° (acetone)	$C_{15}H_{14}N_2OS$ (270.4)	2210	–
H	4-O_2N—C_6H_4	CH_3	–	–	**7c**	65 (C)	142° (CH_3CN)	$C_{15}H_{16}N_2O_3S$ (304.4)	1500, 1330	2.25 (s, 3H); 3.1 (m, 4H); 3.8 (m, 4H); 5.90 (s, 1H); 7.41 (d, 2H, J = 8 Hz); 8.12 (d, 2H, J = 8 Hz)
CH_3	4-O_2N—C_6H_4	H	CH_3	CH_3	**7d**	64 (A)	161–162° (CH_3CN)	$C_{15}H_{16}N_2O_3S$ (304.4)	1505, 1340	2.06 (s, 3H); 2.9 (m, 4H); 3.7 (m, 4H); 7.05 (s, 1H); 7.42 (d, 2H, J = 9 Hz); 8.05 (d, 2H, J = 9 Hz)
C_6H_5	4-O_2N—C_6H_4	H	CH_3	CH_3	**7e**	79 (A)	187–188° (C_2H_5OH)	185°[5]	1505, 1330	–
		H	—$(CH_2)_2$—O—$(CH_2)_2$—		**7e**	62 (B)				
4-H_3C—C_6H_4	4-O_2N—C_6H_4	H	CH_3	CH_3	**7f**	42 (A)	237–238° (CH_3CN)	$C_{21}H_{20}N_2O_3S$ (380.5)	1510, 1340	–
4-H_3C—C_6H_4	4-O_2N—C_6H_4	H	CH_3	CH_3	**7g**	61 (A)[c]	147–148° (acetone/CH_3CN)	$C_{22}H_{22}N_2O_2S$ (378.5)	1510, 1345	–
4-H_3C—C_6H_4	4-O_2N—C_6H_4	CF_3	–	–	**7h**	46 (D)	128–130° (CH_3OH)	$C_{22}H_{19}F_3N_2O_3S$ (448.5)	1520, 1350	2.30 (s, 3H); 2.7 (m, 4H); 3.5 (m, 4H); 7.10 (s, 4H); 7.49 (d, 2H, J = 8 Hz); 8.12 (d, 2H, J = 8 Hz)
4-H_3CO—C_6H_4	4-O_2N—C_6H_4	H	CH_3	CH_3	**7i**	48 (A)	245° (CH_3CN)	$C_{21}H_{20}N_2O_4S$ (396.5)	1515, 1340	–
4-H_3C—C_6H_4	4-O_2N—C_6H_4	CH_3	–	–	**8a**[d]	81 (C)	151–152° (C_2H_5OH)	$C_{22}H_{24}N_2O_4S$ (412.5)	1700, 1510, 1330	2.20 (s, 6H); 2.6 (m, 4H); 3.1 (m, 4H); 3.98 (s, 2H); 7.02 (s, 4H); 7.26 (d, 2H, J = 9 Hz); 8.01 (d, 2H, J = 9 Hz)
C_6H_5	4-O_2N—C_6H_4	H	CH_3	CH_3	**8b**[e]	71 (A)[f]	194–195° (CH_3COOH)	195°[5]	1505, 1350	–

[a] R^1—R^1 in **7a–f**, **h**, **i** and **8a**, **b** = —$(CH_2)_2$—O—$(CH_2)_2$—; R^1—R^1 in **7g** = —$(CH_2)_5$—.

[b] Satisfactory microanalyses obtained: C, ±0.36; H, ±0.42; N, ±0.36; S, ±0.36.

[c] The mixture is not refluxed but heated at 100 °C.

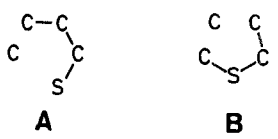
[d] Y = O; M.S.: m/e = 412 (M^+, 16%); 369 (100%); 337 (21%); 105 (26%).

[e] Y = $N^{\oplus}(CH_3)_2$ $ClO_4^{\ominus}$.

[f] In the absence of triethylamine. Product **8b** was cyclised to **7c** in 98% yield.

In the latter case, the acyl group of **8a** is split off and a corresponding deprotonated **3** is formed. Probably the cyclisation of the acylketene-*S,N*-aminal **8a** fails for configurational reasons. For a successful application of the mercaptomethyleniminium salts **3** in the synthesis of thiophenes **7**, a sufficiently strong electron-withdrawing Ar substituent, such as 4-O_2N—C_6H_4 or 4-NC—C_6H_4, is necessary. 4-Chlorophenyl substituted **3** (Ar = 4-Cl—C_6H_4) remained unchanged when treated with **4**, **5**, or **6** under the conditions applied in the examples mentioned above. Also, mercaptomethyleniminium salts **3** possessing a carbonyl group in place of Ar do not seem to be suitable reactands since they are reported to undergo a smooth intramolecular cyclisation to give 2-aminothiophenes different from **7**[6].

The substituted 2-aminothiophenes **7** (Table) are orange-coloured, stable crystalline compounds which are formed in satisfactory or good yields. Their structures are confirmed by spectroscopic data and microanalyses. 4-Unsubstituted 2-aminothiophenes **7** (see **7e**, Table) can also be prepared starting from thioamides **1** by an independent synthesis following a reversed reaction sequence, first by iminoformylation[2,7] and secondly by alkylation[5] according to type **A**. As far as we know, the present formation of the thiophenes **7** from substituted mercaptomethyleniminium salts **3** and acid derivatives **4**, **5**, or **6** is the first example of a synthesis of the thiophene ring following type **B**. This synthesis of substituted 2-aminothiophenes ist thus a useful alternative to known procedures[5,8–11] of type **A**.



A **B**

Substituted Mercaptomethyleniminium Salts 3; General Procedure:
A mixture of thioamide **1** (0.03 mol), substituted benzyl halide **2** (0.03 mol), and chloroform (20 ml) is refluxed for 30 min. If the product does not crystallise from the reaction mixture, some ether is added. The product is filtered by suction, washed with ether, and is used without further purification; yield: 80–90%.

Substituted 2-Aminothiophenes 7 and Acylketene-*S,N*-aminal 8a; General Procedures:

Method A (from **4**): A solution of dimethylformamide chloride **4**[R^3 = H, R^4 = CH_3; prepared by the dropwise addition of phosphoryl chloride (1.53 g, 10 mmol) to dimethylformamide (14 ml)] is combined with the substituted mercaptomethyleniminium salt **3** (10 mmol). After addition of triethylamine (8.5 ml), the mixture is refluxed for 30 min. The cold reaction mixture is poured into ice/water (50 ml). The product is filtered by suction and recrystallised.

Method B (from **5**): A mixture of mercaptomethyleniminium salt **3** (10 mmol), ethanol (10 ml) and formamide acetal **5** [R^3 = H,N(R^4)$_2$ = morpholino; 20 mmol] is refluxed for 25 min. The product is filtered by suction and recrystallised.

Method C (from **6**, R^3 = CH_3): Triethylamine (12 ml) is added to a suspension of the mercaptomethyleniminium salt **3** (10 mmol) in acetic anhydride (**6**, R^3 = CH_3; 20 ml). The mixture is refluxed for 1 h. The cold reaction mixture is poured into water (50 ml). After the excess of acetic anhydride has been hydrolysed the product crystallises. It is filtered by suction and recrystallised.

Methode D (from **6**, R^3 = CF_3): Trifluoroacetic anhydride (**6**, R^3 = CF_3; 4.2 g, 20 mmol) is added to a suspension of the mercaptomethyleniminium salt **3** (10 mmol) in tetrachloromethane (10 ml). After addition of triethylamine (8.5 ml), the mixture is refluxed for 30 min. The solvent is evaporated and the residue is poured into water (50 ml). After 1 h, the organic layer is separated. The product crystallises when methanol (few drops) is added. The product is filtered by suction and recrystallised.

Received: July 30, 1984

[1] Part 10: Knoll, A., Liebscher, J., *Khim Geterotsikl. Soedin.*, in press.
[2] Liebscher, J., Abegaz, B., *Synthesis* **1982**, 769.
[3] Kantlehner W., in: *Advances in Organic Chemistry*, Vol. 9, part 2, *Iminium Salts in Organic Chemistry*, Böhme, H., Viehe, H.G., Eds., Wiley-Interscience, New York, 1976, p. 279ff. and references cited therein.
[4] Liebscher, J., Feist, K., applied for *DDR-Patent* (11.1.1984).
[5] Liebscher, J., Abegaz, B., Areda, A., *J. Prakt. Chem.* **1983**, *325*, 168.
[6] Hartmann, H., Mayer, R., *Z. Chem.* **1966**, *6*, 28.
[7] Bredereck, H., Simchen, G., Funke, B., *Chem. Ber.* **1971**, *104*, 2709.
[8] Smutny, E.J., *J. Am. Chem. Soc.* **1969**, *91*, 208.
[9] Rajappa, S., Advani, B.G., *Indian J. Chem.* **1971**, *9*, 759.
[10] Gompper, R., Kutter, E., *Angew. Chem.* **1962**, *74*, 251.
[11] Ben Mansour, N., Rudorf, W.D., Augustin, M., *Z. Chem.* **1981**, *21*, 69.