CONVERSION OF THIOACETAMIDES, ACETAMIDES, AND ACETONITRILES INTO TRIMETHINIUM SALTS UNDER VILSMEIER CONDITIONS*

Jürgen Liebscher[a]**, Alexander KNOLL[a], Horst HARTMANN[b] and Sabine ANDERS[b]

[a] *Department of Chemistry, Humboldt University Berlin, 1040 Berlin, G.D.R. and*

[b] *Department of Chemistry, Technical University Dresden, 8027 Dresden, G.D.R.*

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Thioacetamides and N-(3-aminothioacryloyl)formamidines can be transformed to trimethinium salts by the reaction with formamide chlorides. The same products are formed by a modified Vilsmeier–Haack–Arnold reaction of acetamides or acetonitriles. The latter transformations can also be performed in two steps by the isolation of intermediate 2-aza-3-chlorpentamethinium salts.

Trimethinium salts *III* can conveniently be prepared by the reaction of substituted acetic acids *I* with formamide chlorides *II* (Scheme 1, refs[1–5]). In this reaction twofold iminoformylation of the CH_2 group of compound *I* takes place while CO_2 is formally eliminated by C—C bond scission. Our investigations of bisiminoformylation of carboxylic acid derivatives have shown that the C-skeleton of unsubstituted thioacetamides *IV* (X = S) is maintained in the reactions with formamide acetals[6]. Hence N-(3-aminothioacryloyl)formamidines *V* are formed. Further investigations in the synthesis of compounds *V* have dealt with the possibility to substitute the formamide acetals by formamide chlorides *II*. The latter compounds were already employed in the C- (ref.[7]) and N-monoiminoformylation (ref.[8]) of thioamides.

Our results concerning the reaction of N-unsubstituted thioamides *IV* (X = S) with excess formamide chlorides *II* show that surprisingly, no azapentamethine compounds *V* are obtained but trimethinium salts *III*. The same products *III* appear when formamide chlorides *II* are reacted with N-(3-aminothioacryloyl)formamidines *V* which can be assumed as intermediates in the transformation of thioacetamides *IV* (X = S) to trimethinium salts *III*.

Further investigations with formamide chlorides *II* have shown[9] that not only thioacetamides *IV* (X = S) but also acetamides *IV* (X = O) or acetonitriles *VI* can serve as starting materials in the synthesis of trimethinium salts *III* (Table I). These transformations can be performed either in a direct way (method *A*, *C*) or by a two-

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** The author to whom correspondence should be addressed.

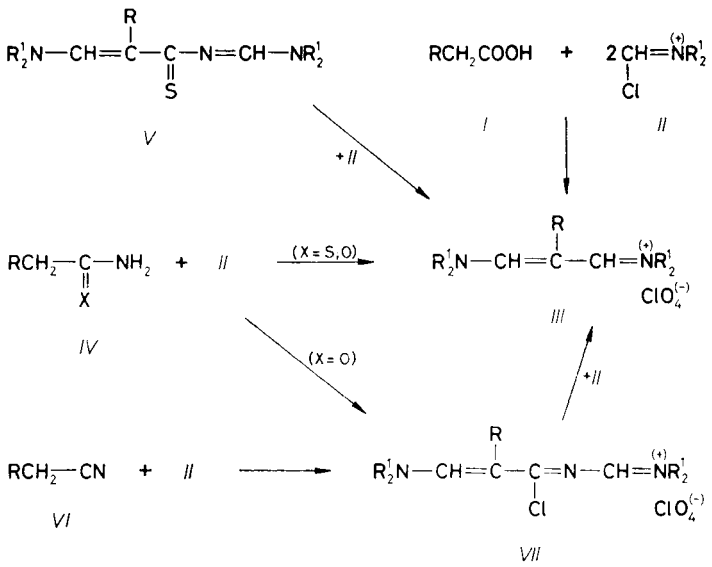
TABLE I

Trimethinium perchlorates *III*

No. R	NR_2^1	Yield %	Method	M.p., °C (Solvent)	Formula M_r	Calculated/found		
						% C	% H	% N
IIIa	$N(C_2H_4)_2O$	10	*D*	260–262	$C_{17}H_{23}ClN_2O_6$	52·78	5·99	7·24
C_6H_5		82	*A*[a]	(ethanol)	386·8	52·46	5·72	6·96
IIIb[b]	$N(CH_2)_4$	96	*A*[a]	219–221	$C_{17}H_{23}ClN_2O_4$	57·53	6·55	7·90
C_6H_5				(n-propanol)	354·9	57·51	6·23	7·66
IIIc	$N(CH_3)_2$	61	*A*[a]	200–203[c]	$C_{13}H_{19}ClN_2O_4$	—	—	—
C_6H_5		36	*A*[d]	(n-propanol)	302·8			
IIId	$N(CH_2)_5$	82	*B*	245–248	$C_{19}H_{27}ClN_2O_4$	59·59	7·12	7·32
C_6H_5				(acetic acid)	382·9	59·92	7·24	7·33
IIIe[e]	$N(CH_3)_2$	59	*C*	238–240	$C_{15}H_{23}ClN_2O_4$	54·47	7·01	8·47
$3,5(CH_3)_2C_6H_3$				(acetic acid)	330·8	54·34	7·17	8·16

[a] X = S in *IV*. [b] ^{1}H NMR ($CDCl_3$) δ, ppm: 1·75 (m, 8 H); 2·56 (m, 4 H); 3·75 (m, 4 H); 7·28 (m, 5 H); 7·88 (s, 2 H). [c] Ref.[1] m.p. 200–201°C. [d] X = O in *IV*. [e] UV (CH_2Cl_2) λ_{max}, nm (log ε): 253 (3·68); 283 sh (3·76); 320 (4·64). IR (KBr pellets) ν, cm^{-1}: 1 605 (C=N); 655, 1 110 (ClO_4).

-step procedure. In the latter case acetamides *IV* (X = O) or acetonitriles *VI* are reacted in the presence of HCl with formamide chlorides *II* giving rise to the known formation[10] of 2-aza-3-chloropentamethinium salts *VII*. The isolated salts *VII* are changed to trimethinium salts *III* by treatment with formamide chlorides *II* at higher temperatures (method *D*).

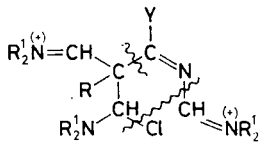


SCHEME 1

It is worth mentioning that trimethinium salts possessing different terminal amino groups could not be obtained either from N-(3-aminothioacryloyl)formamidines *V* or from 2-aza-3-chloropentamethinium salts *VII*. The dipyrrolidino-substituted thioacryloyl formamidine *V* (R = C_6H_5; NR^1_2 = pyrrolidino) gives *e.g.* a 1 : 1 mixture of the two symmetrically substituted trimethinium salts *III* (R = C_6H_5; NR^1_2 = pyrrolidino and R = C_6H_5; NR^1_2 = morpholino) on treatment with morpholinium compound *II* (NR^1_2 = morpholino). The same result is obtained in the reaction of compound *V* (R = C_6H_5; NR^1_2 = morpholino) with the chloromethylenpyrrolidinium salt *II* (NR^1_2 = pyrrolidino).

The transformation of azapentamethine system *V* or *VII* to trimethinium salts *III* can be interpreted by an electrophilic attack of formamide chlorides *II* at the enamine C-atom carrying substituent R. A similar attack was observed in the reaction of acetonitrile *VI* (R = H) with formamide chlorides *II* (ref.[10]). In this reaction, the expected bisiminoformylation products *VII* (R = H) suffer further iminoformylation at position *IV* and a dication *VII* (R = $\overset{+}{C}H{=}\overset{+}{N}R^1_2$) is formed while the original

C-skeleton is retained. Azapentamethine compounds *V* or *VII* with R ≠ H do not possess a proton that can be substituted. Hence the stabilisation of the adduct *VIII* formed after the attack of the formamide chloride *II* at the enamine C-atom can only take place by C—C-bond cleavage. Possibly the stabilisation process follows a fragmentation pattern like is shown in *VIII*, giving rise to trimethinium salts *III* while formamide chloride *II* and cyanogen chloride or HSCN are eliminated. One can expect that these byproducts are not stable under the conditions employed. Hence, attempts to isolate these compounds have failed.



VIII, Y = Cl; $SCH{=}\overset{(+)}{N}R_2^1$; SH

Our results show that in principle the known synthesis of trimethinium salts *III* by the Vilsmeier–Haack–Arnold reaction of carboxylic acids can be extended to acid derivatives such as thioamides, acetamides or acetonitriles.

EXPERIMENTAL

Method A. The solution of formamide chloride *II*, prepared by dropwise addition of 5·4 g (0·035 mol) of $POCl_3$ to 0·05 mol of formamide $HCONR_2^1$, is combined with 0·01 mol of substituted thioacetamide *IV* (X = S) or acetamide *IV* (X = O). The mixture is heated to 90—100°C for 2 hours. The cold reaction mixture is dissolved in a solution of 1 ml of 70% $HClO_4$ in 20 ml of glacial acetic acid. After the addition of ether, the product *III* precipitates. It is filtered by suction and recrystallized in the presence of some charcoal.

Method B. Following the method *A*, a solution of formamide chloride *II* is prepared from 0·02 mol of $POCl_3$ and 0·05 mol of formamide $HCONR_2^1$ and combined with 0·01 mol of N-(3-aminothioacryloyl)formamidine *V*. The mixture is kept at room temperature for 1 hour and then heated on a boiling water bath for 5 hours. The cold reaction mixture is dissolved in a solution of 1 ml of 70% $HClO_4$ in 30 ml of methanol. After the addition of some ether, the product *III* is filtered by suction and recrystallized.

Method C. Under cooling (temperature below 25°C) and stirring 0·022 mol of $POCl_3$ are added to a solution of 0·02 mol of nitrile *VI* in 0·05 mol of formamide $HCONR_2^1$. The mixture is saturated with HCl gas at 0°C for 1 hour and then heated to 110—120°C for 4 hours. The cold reaction mixture is dissolved in 30 ml of ethanol. After the addition of 2 ml of 70% $HClO_4$ (cooling) and of the ether, the product *III* precipitates. It is filtered by suction and recrystallized.

Method D. Three drops of $POCl_3$ are added to a solution of 0·01 mol of 2-aza-3-chloropentamethinium salt *VII* in 5 ml of formamide $HCONR_2^1$. The mixture is heated to 115—120°C for 2 hours. After cooling, the reaction mixture is dissolved in 30 ml of ethanol and diluted with ether. The product *III* is filtered by suction and recrystallized.

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