REACTIONS OF AROMATIC AND HETEROAROMATIC COMPOUNDS CONTAINING ELECTRON-ACCEPTOR SUBSTITUENTS.

XXIII.* NEW METHOD FOR THE CHLOROMETHYLATION OF CARBONYL COMPOUNDS OF THE THIOPHENE AND BENZENE SERIES

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A method was developed for the preparation of 4-chloromethyl-2-acylthiophenes and m-(chloromethyl)acylbenzenes in up to 65% yields by the action of paraformaldehyde and anhydrous aluminum chloride on the corresponding carbonyl compounds. The reaction mechanism is discussed.

In our previous communications we showed that the conversion of 2-acetothienone, 2-formylthiophene, and acetophenone to complexes involving the carbonyl group and aluminum chloride substantially changes the specificity of chloromethylation. Thus 2-formylthiophene and 2-acetothienone are converted to a mixture of 4- and 5-chloromethyl-substituted compounds under normal chloromethylation conditions (the Blanc reaction), i.e., by the action of paraformaldehyde and HCl in the presence of $ZnCl_2$ [2, 3]. Acetophenone is chloromethylated in the side chain under similar conditions and also by the action of monochloromethyl ether in the presence of various catalysts [4, 5]. On the other hand, when $AlCl_3$ is present, the action of mono- and α,α'-bis(chloromethyl) ethers leads to 4-chloromethyl-2-acylthiophenes and m-chloromethylacetophenone [6-8].

It is inconvenient to use chloromethyl ethers, since, on the one hand, they are harder to obtain than paraformaldehyde or formalin and, on the other, they have carcinogenic activity [9]. The present research was undertaken in order to search for a method for the selective chloromethylation of carbonyl compounds of the thiophene and benzene series with the formation of 4- and, respectively, m-substituted compounds by the use of agents that do not have the disadvantages of chloromethyl ethers. We were able to solve this problem by the action of paraformaldehyde and excess $AlCl_3$ on the indicated ketones. This method [10, 11] is extremely simple: the carbonyl compound is added to a suspension of anhydrous aluminum chloride in dry chloroform, CCl_4, or methylene chloride, paraformaldehyde is added to the cooled (to 3-5°C) mixture, and the resulting mixture is stirred at room temperature for 3 h. The 4-chloromethyl-2-acylthiophenes and m-chloromethylacylbenzenes are obtained in up to 60-65% yields based on the carbonyl compound. Isomeric chloromethylation products were not detected. It should be noted that the proposed method makes the passage of hydrogen chloride into the mixture unnecessary, since the aluminum chloride is used not only to tie up the carbonyl compound in a complex and as a catalyst for the process but also serves as a source of chlorine for the formation of the chloromethyl group; a special experiment showed that passage of HCl into the mixture does not lead to an increase in the yield of 4-chloromethyl-2-acetothienone.

The quantitative ratios of the reagents depend on the activity of the substrate. In particular, the chloromethylation of 2-acetothienone and 2-propiothienone proceeds smoothly in the case of equimolar amounts of ketone and paraformaldehyde. A 30% excess of paraformaldehyde is necessary in the case of 2-formylthiophene. On the other hand, a 2.5-fold amount of paraformaldehyde and more than 3 moles of $AlCl_3$ (as against 2.0-2.5 moles in the case of thiophene compounds) are required for the chloromethylation of acetophenone and propiophenone.

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*See [1] for communication XXII.

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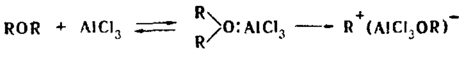
TABLE 1. Chloromethylation of Carbonyl Compounds of the Thiophene and Benzene Series

Starting compounds and amounts, g (mole)			Products	Yield, %	bp, °C (mm)	Literature data
carbonyl compound	$AlCl_3$	paraformaldehyde				
2-Acetothienone 12,6 (0,10)	28,0 (0,21)	3,1 (0,1)	4-Chloromethyl-2-acetothienone	62,5	88—89 (0,1)	8
2-Formylthiophene 10,8 (0,1)	33,6 (0,25)	3,75 (0,125)	4-Chloromethyl-2-formylthiophene	62,0	80—81 (0,3)	8
2-Propiothienone 2,1 (0,015)	5,0 (0,037)	0,9 (0,017)	4-Chloromethyl-2-propiothienone	39,0	104—105 (0,15)	—[a]
Acetophenone 12,0 (0,1)	48,0 (0,36)	7,6 (0,25)	m-Chloromethylacetophenone	63,0	85—86 (0,08)	7
Propiophenone 2,7 (0,02)	9,6 (0,072)	1,5 (0,05)	m-Chloromethylpropiophenone	44,0[b]	93—94 (0,15)	—[c]

a) Found: C 50.7; H 4.8; Cl 18.7; S 16.9%. C_8H_9ClOS. Calculated: C 50.9; H 4.8; Cl 18.8; S 17.0%. PMR spectrum (in CCl_4): 1.11 (3H, t, CH_3, J = 7 Hz), 2.81 (2H, q, CH_2, J = 7 Hz), 4.51 (2H, s, CH_2Cl), 7.51 (1H, d, J = 1.5 Hz, H^3), and 7.62 ppm (1H, d, J = 1.5 Hz, H^5). b) Unchanged propiophenone (34%) was isolated, and the yield of product based on the converted propiophenone was 66%. c) The compound had n_D^{22} 1.5475. Found: C 66.2; H 6.2; Cl 18.6%. $C_{10}H_{11}ClO$. Calculated: C 65.8; H 6.1; Cl 19.4%. PMR spectrum (in CCl_4): 1.08 (3H, t, CH_3, J = 7 Hz), 2.82 (2H, q, CH_2, J = 7 Hz), 4.50 (2H, s, CH_2Cl), 7.32 (2H, m, p- and m-H), and 7.75 ppm (2H, m, o-H).

The method herein described is evidently applicable only to compounds that contain electron-acceptor substituents and, in any case, are stable with respect to the action of $AlCl_3$ and the resulting chloromethyl-substituted product. In particular, an attempt to carry out the chloromethylation of thiophene with paraformaldehyde and $AlCl_3$ (in methylene chloride at —30°C) led to profound resinification. It is also known that the reaction of benzene and its homologs with paraformaldehyde and $AlCl_3$ leads to complex mixtures of products, from which diarylmethanes and compounds of the anthracene series were isolated but in which chloromethyl-substituted compounds were not detected [12, 13].

In the reaction of aluminum chloride with paraformaldehyde the latter may undergo depolymerization to formaldehyde; in addition, the formation of larger fragments, including fragments containing chlorine and arising as a result of cleavage of C—O bonds, is possible. In particular, one of the possible products is α,α'-bis(chloromethyl) ether. In this case, in accordance with the data in [7, 8], probable intermediates are substituted benzyl ether $ArCH_2OCH_2Cl$ and $(ArCH_2)_2O$, which are subsequently converted to $ArCH_2Cl$. In the reaction with 2-acetothienone we obtained the corresponding "dibenzyl" ether, which is, in fact, unstable in the presence of $AlCl_3$ and is converted to 4-chloromethyl-2-acetothienone; however, this transformation does not go to completion under conditions close to those used in this research for chloromethylation by the action of paraformaldehyde and $AlCl_3$. We therefore imagine that the mechanism of the process under consideration is similar to the mechanism of alkylation with ethers in the presence of Lewis acids (for example, see [14]); the first step will be the formation of a complex, which may be the source of a carbonium ion:

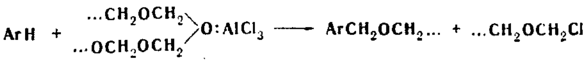


$$ROR + AlCl_3 \rightleftharpoons {}^{R}_{R}\!\!>\!O{:}AlCl_3 \longrightarrow \overset{+}{R}(AlCl_3OR)^-$$

The "acetal" structure of paraformaldehyde should facilitate cleavage of the C—O bonds, and the resulting cation is stabilized due to delocalization of the positive charge:

$$....CH_2\overset{+}{O}CH_2 \longleftrightarrow ....CH_2\overset{+}{O}{=}CH_2$$

The intermediate of the $ArCH_2$—O—CH_2—O... type that is formed during the reaction should be easily cleaved by aluminum chloride to give the chloromethyl-substituted compound:



$$ArH + \begin{matrix}...CH_2OCH_2\\ ...OCH_2OCH_2\end{matrix}\!\!>\!O{:}AlCl_3 \longrightarrow ArCH_2OCH_2... + ...CH_2OCH_2Cl$$

$$ArCH_2OCH_2... \xrightarrow{AlCl_3} ArCH_2Cl$$

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 or $CDCl_3$ were recorded with a Varian DA-60-IL radiospectrometer (60 MHz) with tetramethylsilane as the internal standard. Chloromethylation was carried out by a single method. The amounts of reagents and data on the reaction products are presented in Table 1. The carbonyl compound was added at no higher than 40°C to an efficiently stirred suspension of anhydrous aluminum chloride in dry chloroform (25-30 ml per 0.1 mole of carbonyl compound), after which paraformaldehyde was added to the resulting complex at 3-5°C, and the mixture was stirred at this temperature for 10 min and at room temperature for 3 h. It was then poured over ice, and the aqueous mixture was extracted with chloroform. The extract was washed successively with water, $NaHCO_3$ solution, and water, and dried over $MgSO_4$. The solvent was removed by distillation, and the product was isolated by vacuum distillation.

Reaction of Bis(5-acetyl-3-thenyl) Ether with Aluminum Chloride. Bis(5-acetyl-3-thenyl) ether was obtained by refluxing 4-hydroxymethyl-2-acetothienone [15] in benzene in the presence of calcined $ZnCl_2$; a product with mp 112-114°C (from alcohol) was obtained in 20% yield. PMR spectrum (in $CDCl_3$): 2.46 (3H, s, CH_3), 4.47 (2H, s, CH_2), 7.56 (1H, d, H^5), and 7.43 ppm (1H, d, H^3, $J_{35} = 1.5$ Hz). Found: C 57.4; H 4.9; S 21.6%. $C_{14}H_{14}O_3S_2$. Calculated: C 57.1; H 4.8; S 22.0%. When a solution of this ether in $CHCl_3$ was stirred with $AlCl_3$ (3.5 moles per mole of the ether) for 5 h at 20°, it was converted to 4-chloromethyl-2-acetothienone. The ratio of the starting ether and the chloromethyl-substituted product was ~1:1 (according to the PMR data).

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