REACTIONS OF AROMATIC AND HETEROAROMATIC COMPOUNDS CARRYING ELECTRON ACCEPTOR SUBSTITUENTS

COMMUNICATION 1. INFLUENCE OF THE SOLVENT ON THE BROMINATION OF ACETOPHENONE IN THE PRESENCE OF AN EXCESS OF ALUMINUM CHLORIDE*

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As is well known, in the halogenation of aromatic and heteroaromatic ketones, the halogen is inserted into the side chain; this process is accelerated when small quantities of aluminum chloride are added. In 1956 Pearson and Pope described a method of bromination of acetophenone without a solvent in the presence of excess aluminum chloride [2]; under these conditions phenacyl bromide practically is not formed, while m-bromoacetophenone is obtained in a 60% yield. Later the method of halogenation without a solvent in excess aluminum chloride was successfully used for chlorination and bromination of a number of aromatic aldehydes and ketones [3], as well as derivatives of aromatic acids [4], anilines [5], pyridine and picolines [6], isoquinoline and quinoline [7] in the ring. Pearson and co-workers ascribed a steric effect to the excess aluminum chloride, which they call the swamping catalyst effect. These researchers considered the observance of three conditions necessary for successful halogenation [3]: 1) the ketone is entirely bound in a complex with $AlCl_3$ before the addition of bromine; 2) no solvent is used; 3) the complex should be a liquid, to enable mixing of the mass during the addition of bromine to be carried out.

Discarding the original hypotheses of these authors, with respect to the structure and reactivity of complexes of aromatic carbonyl compounds with aluminum chloride [3], we should assume that in such complexes the aromatic ring is deactivated to an even greater degree than in a carbonyl compound not bonded to a Lewis acid. This fact was later recognized by Pearson himself [4]. It is quite evident that the very possibility of insertion of a halogen into such a deactivated ring is due to the fact that the excess aluminum chloride polarizes the halogen molecule; in the limiting case apparently a cation of the halogen arises:

$$AlX_3 + X_2 \rightarrow X^+(AlX_4)^- \rightarrow X^+ + AlX^-_4$$

The absence of halogenation products of the side chain can be explained by suppression of enolization of the ketone, since the latter is bound in a complex

$$ArCOR + AlCl_3 \rightleftarrows ArCOR \cdot AlCl_3$$

Maintaining the viewpoint outlined in his later studies, to explain the halogenation of the deactivated aromatic ring, Pearson, nonetheless, does not give up his previously introduced concept of the so-called swamping catalyst effect, the sense of which he essentially did not interpret. On the basis of the meaning of the word swamping, it may be assumed that the author is attributing some sort of significance to the consistency of the medium. From this standpoint there was no basis for renouncing the use of a solvent which, just like excess aluminum chloride, would permit the reaction to be conducted in homogeneous medium.

*For a preliminary communication, see [1].

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A substance inert under the reaction conditions, capable of dissolving complexes of $AlCl_3$ with carbonyl compounds without appreciable dissociation and, moreover, forming no strong complexes with the excess aluminum chloride that might prevent the activation of the halogen, could be used as such a solvent. Naturally, there is some sort of limit for the amount of the solvent, since too large an excess of the latter is capable of causing dissociation of complexes. As for the amount of the excess aluminum chloride, any convenient small amount of it over the equimolar amount should in principle send the process in the required direction; however, the optimum amount, ensuring a sufficient reaction rate and preventing appreciable dissociation of the complex of $AlCl_3$ with the carbonyl compound, should be determined experimentally.

Actually, we found that in the bromination of acetophenone in chloroform, the same results are obtained as under the conditions described by Pearson, moreover, there is no need to use too large amounts of aluminum chloride; in bromination in chloroform, a yield of m-bromoacetophenone of ~60% is reached not only when 2.5 moles of $AlCl_3$ per mole of the ketone is used, as is recommended in [2], but also with 1.5 moles of $AlCl_3$ per mole of the ketone. Further reducing the amount of aluminum chloride leads to a certain slowdown of the bromination and an increase in the formation of phenacyl bromide, which becomes the basic reaction product when aluminum chloride is used in amounts close to equimolar.* In the bromination of acetophenone in dichloroethane, the yield of m-bromoacetophenone reaches 80-85%. Methylene chloride, carbon tetrachloride, and carbon disulfide can also be used as solvents. At the same time, products of bromination of acetophenone in the ring cannot be obtained in nitrobenzene, which is explained by the low activity of the catalyst (the excess $AlCl_3$ is bound into a complex with nitrobenzene). Saturated hydrocarbons are unsuitable for conducting the reaction, since the complex of acetophenone with aluminum chloride does not dissolve in them at all.

The concepts outlined above on the mechanism of the bromination of aliphatic–aromatic ketones in the presence of excess aluminum chloride are in good agreement with our observations of the interaction of acetophenone with N-bromosuccinimide. It is known [9] that this agent under normal conditions reacts according to a radical-chain mechanism, and bromine attacks the side chain in the α-position to the multiple bond or aromatic ring. In the presence of Lewis acids there is a heterolytic decomposition of the N–Br bond of N-bromosuccinimide, which becomes a source of Br^+; activation of the process requires not a catalytic, but an equivalent amount of the Lewis acid. It was found that N-bromosuccinimide, taken in an equimolar ratio with acetone and aluminum chloride, is incapable of brominating acetophenone in the ring. Only at a ratio $AlCl_3$: acetophenone : N-bromosuccinimide equal to 2.2 : 1 : 1, i.e., when the amount of $AlCl_3$ is sufficient for the formation of complexes both with acetophenone and with N-bromosuccinimide, is m-bromoacetophenone obtained.

The reaction products, obtained according to Pearson and under the conditions that we used, contained a small, difficultly removed impurity (0.5-2.5%) of the initial acetophenone and 0.5-1% (sometimes more) (see the experimental section) of phenacyl bromide. The acetophenone impurity was determined quantitatively by gas–liquid chromatography, while the impurity of ω-bromoketone was determined argentometrically after mineralization of the halogen by the action of NaOH in alcohol; phenacyl bromide can also be determined chromatographically, but the accuracy of such a determination is very low.

The formation of phenacyl bromide in the presence of excess aluminum chloride can be attributed to the low equilibrium concentration of the free ketone, which is capable of being brominated in the side chain in its enol form. On the contrary, the possibility remains that the complex of the ketone with $AlCl_3$ is directly subjected to bromination in the side chain, if there is a mechanism of such a reaction not associated with enolization. Recently a similar mechanism was proposed for the case of bromination of aliphatic ketones in the presence of bases [10]. It is interesting in connection with this to note that excess aluminum chloride does not entirely suppress the bromination of aliphatic ketones. As we have shown, methyl ethyl ketone and pinacoline are brominated in the presence of excess aluminum chloride without a solvent, although with difficulty, in the α-position to the carbonyl group.

Thus, in the case of aliphatic–aromatic ketones, complex formation does not entirely suppress but sharply reduces the rate of bromination of the side chain, so that bromination in the ring becomes the basic process. It is understood that the dissociation of the complex, achievable, for example, on account of an increase in the amount or replacement of the solvent, creates more favorable conditions for the bromination of the side chain. Thus, when the volume of chloroform is increased from 50 to 300 ml per 0.1 mole

*Unfortunately, we did not note this circumstance in the articles [1, 8].

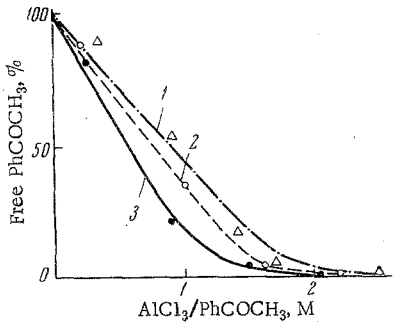

Fig. 1. Amount (%) of free acetone in solutions containing various relative amounts of aluminum chloride: 1) solution in CH_2Cl_2; 2) solution in $CHCl_3$; 3) solution in CH_2ClCH_2Cl.

of acetophenone, the bromination product represents almost pure phenacyl bromide. A comparison of the results of the bromination of acetophenone in various solvents shows that there is a parallelism between the amount of phenacyl bromide formed and the degree of dissociation of the complex of the ketone with aluminum chloride in this solvent. For example, the product obtained by bromination in methylene chloride (ratio $AlCl_3$: acetophenone = 1.5 : 1) contains ~14% phenacyl bromide, and only at a ratio $AlCl_3$: acetophenone equal to 2.5 : 1 can m-bromoacetophenone containing only 1% phenacyl bromide be obtained. And yet, in chloroform, ~99% m-bromoacetophenone is already obtained at a ratio $AlCl_3$: acetophenone equal to 1.5 : 1. Special experiments with the aid of the IR spectra established the fact that the degree of dissociation of the complex of aluminum chloride with acetophenone in methylene chloride is higher than in chloroform or dichloroethane (Fig. 1).*

Summarizing our results, we can state that there is no significant difference in the nature of the process occurring in the solvent or without it, and, consequently, there is no specific swamping catalyst effect. The only role of a large excess of aluminum chloride, in our opinion, is reduced to the fact that the mass formed in this case, in contrast to the 1 : 1 complex or close to it, has a comparatively low melting point, as a result of which there is no longer any need for a solvent. Nonetheless, in halogenation, and, possibly, other reactions of electrophilic substitution of aromatic compounds bearing negative substituents, there are no reasons to give up the use of a solvent, replacing it with excess aluminum chloride. The use of a solvent permits not only a reduction of the required amount of aluminum chloride, but also a substantial simplification of the treatment of the mixture; in work without a solvent, by the end of halogenation the reaction mass frequently is solidified. However, the practical expediency of conducting certain reactions of electrophilic substitution, especially if they require rigorous conditions (see [11]) in excess aluminum chloride without a solvent cannot be excluded. Investigations along this line are being continued, and we hope to report our new results soon.

EXPERIMENTAL

Bromination of Acetophenone. A solution of 12 g acetophenone (0.15 mole $AlCl_3$ per 0.1 mole of the ketone) in 50 ml anhydrous $CHCl_3$ was slowly added with vigorous mixing to 20 g of anhydrous aluminum chloride; a spontaneous temperature rise of the mixture was observed in this case, and the aluminum chloride dissolved. To the solution obtained, 16 g of bromine was added dropwise at room temperature. After the evolution of hydrogen bromide ceased, the mixture was boiled for 2 h and then left for 16 h at 20°. The dark brown mass was poured out onto ice with 30 ml of hydrochloric acid, the organic layer removed, and the aqueous layer extracted with chloroform. The combined extract was washed with water, with solutions of soda, sodium hyposulfite, and again with water, and dried over $MgSO_4$. After the chloroform was distilled off, the residue was redistilled under vacuum. The following fractions were isolated: I) 90-113° (8 mm); n_D^{20} 1.5624; 1.4 g; II) 113-115° (8 mm); n_D^{20} 1.5764 10 g; III) 115-123° (8 mm); n_D^{20} 1.5777; 1.9 g. Fraction I, according to the data of gas – liquid chromatography,† contained approximately equal amounts of acetophenone and m-bromoacetophenone; fractions II and III contained m-bromoacetophenone with an impurity of 1.6% acetophenone, 0.6% phenacyl bromide,‡ and traces of dibromoacetophenone.

*To determine free acetophenone in solutions containing acetophenone and $AlCl_3$ in various ratios, we used the bands C = O ~ 1685 cm^{-1} and C = O bonded at $AlCl_3$, ~1550 cm^{-1} (the positions of both bands depend on the solvent used); accuracy of determination 10% rel. The investigated solvents had a concentration with respect to acetophenone of ~0.3 M. The IR spectra were obtained on a DS-301 spectrophotometer by B. V. Lopatin, to whom the authors would like to express their sincere gratitude.

† Chromatographic analyses were conducted on an LKhM-4 chromatograph (Special Design Office of the Institute of Organic Chemistry, Academy of Sciences of the USSR) with a thermal conductivity detector, carrier gas helium, gas velocity 30 ml/min, stainless steel column 2 m long and 4 mm in diameter, 15% polyethylene glycol succinate on Chromosorb W, temperature 170°C.

‡ To determine phenacyl bromide, a weighed sample of the bromination product (~0.5 g) was dissolved in 20 ml of alcohol, 3 ml of a 1 N solution of NaOH was added, and the mixture was left overnight at 20°. The solution was acidified with nitric acid, and the halogen determined by titration according to Volhard.

Yield of m-bromoacetophenone 11.9 g (60%). * The oxime had mp 98.7-100.2° (from aqueous alcohol). According to the data of [2], the oxime of m-bromoacetophenone has mp 100-101°.

In the case of bromination under similar conditions, but using 0.25 M $AlCl_3$, the yield of m-bromoacetophenone was 57%, the content of phenacyl bromide 0.7%.

Bromination according to the method cited above in dichloroethane (ratio $AlCl_3$: acetophenone, 1.5 : 1) yielded m-bromoacetophenone with a yield of 84.5%. If the reaction is conducted in dichloroethane without boiling (3.5 h at 40° and 18 h at 20°), the yield of m-bromoacetophenone is practically unchanged (86%), and the content of phenacyl bromide is ~2%.

The bromination of acetophenone in methylene chloride with 1.5 M $AlCl_3$ gives a monobromo derivative with a yield of 36.5%, and the content of phenacyl bromide in it reaches 14%. Only when 2.5 moles of $AlCl_3$ per mole of acetophenone is used does bromination in methylene chloride give a yield of 61% of m-bromoacetophenone, containing ~1% phenacyl bromide.

In carbon tetrachloride (1.5 mole $AlCl_3$ per mole of the ketone), the yield of m-bromoacetophenone is 40%, and its content of phenacyl bromide is ~3.5%.

In carbon disulfide (ratio $AlCl_3$: acetophenone = 1.5:1), m-bromoacetophenone containing 9.5% phenacyl bromide was obtained with a yield of 26%.

In bromination in nitrobenzene, a product containing 93-94% phenacyl bromide was obtained with a yield of 51%.

The bromination of acetophenone in an increased amount of chloroform (150 ml per 0.05 mole of the ketone in the presence of 0.075 mole $AlCl_3$) gives practically pure phenacyl bromide with a yield of 55%.

In the bromination of acetophenone with N-bromosuccinimide in the presence of 2.2 moles $AlCl_3$ per mole of acetophenone and one mole of N-bromosuccinimide, m-bromoacetophenone containing ~5% phenacyl bromide was obtained with a yield of ~40%.

Bromination of Pinacoline. To 66.5 g of $AlCl_3$, 20 g of pinacoline was added with mixing. The temperature of the mixture rose to 70°. Then 32 g of bromine was added at room temperature to the liquid mass formed, the mixture was heated on a boiling water bath for 3 h, then poured out onto a mixture of ice with hydrochloric acid. The heavy dark brown oil that separated was extracted with ether, the extract washed with a solution of sodium hyposulfite, then with water, and dried. Redistillation yielded 6.7 g (18.7% of the pinacoline taken) monobromopinacoline, bp 81-83° (20 mm); n_D^{20} 1.4632; n_D^{25} 1.4617; d_4^{20} 1.3202. Found: C 40.14; 40.06; H 6.00; 6.02; Br 45.07; 44.76%. $C_6H_{11}BrO$. Calculated: C 40.24; H 6.19; Br 44.62%. According to the data of [12]: bp 59° (4 mm); n_D^{25} 1.4659; d_4^{20} 1.333. In addition to the monobromide, we isolated 4.3 g (8.3%) dibromopinacoline, mp 73-74° (from alcohol). According to the data of [13]: mp 74-75.5°.

Bromination of Methyl Ethyl Ketone. To 133 g $AlCl_3$ we added 28.8 g methyl ethyl ketone with mixing at a rate such that the temperature of the mixture did not exceed 75°. A 64 g portion of bromine was added at room temperature, and the mixture was heated on a boiling water bath for 6 h, after which it was poured out onto ice with hydrochloric acid. The product was extracted with ether, the extract washed with a solution of sodium hyposulfite and with water, and dried over magnesium sulfate. Redistillation yielded 6.7 g (10.9%) 3-bromo-2-butanone, bp 135-139°, n_D^{20} 1.4607, from which acetylmethylcarbinol benzoate was isolated, bp 131-133° (7 mm); n_D^{20} 1.5097. According to the data of [14]: 3-bromo-2-butanone, bp 136°, n_D^{20} 1.4571; acetylmethylcarbinol benzoate, bp 136-137° (8 mm), n_D^{19} 1.5082. In addition, a fraction with bp 66-73° (7 mm) was isolated; n_D^{20} 1.5270; 5.24 g; representing 3,3-dibromo-2-butanone; yield 5.6%. The sample for analysis had bp 89° (21 mm); n_D^{20} 1.5255; d_4^{20} 1.9548. Found: C 21.05; 21.16; H 2.75; 2.85; Br 69.57; 69.47%; MR 36.07. $C_4H_6Br_2O$. Calculated: C 20.90; H 2.62; Br 69.52%; MR 36.21. According to the data of [15]: bp 80-83° (10 mm); 194-195°; d_{20}^{20} 1.9729.

CONCLUSIONS

1. The bromination of a complex of acetophenone with aluminum chloride with the formation of m-bromoacetophenone, contrary to the literature data, can be carried out successfully in a suitable solvent (dichloroethane, chloroform), and the excess of aluminum oxide sufficient for the reaction can be reduced to 0.5 mole, instead of 1.5 moles in work without a solvent.

*In the reproduction of the method of [2], the yield of m-bromoacetophenone was 68%, the content of phenacyl bromide in the product 4.7%.

2. The dissociation of the complex observed when the dilution is increased or the solvent is replaced, leads to the formation of phenacyl bromide, the product of bromination of the side chain.

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