BENZOYLATION OF DEACTIVATED COMPOUNDS OF THE THIOPHENE AND FURAN SERIES WITH PHENYLDICHLOROCARBENIUM TETRACHLOROALUMINATE*

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The reactions of benzo trichloride with methyl and ethyl esters and nitriles of 2-thiophenecarboxylic and 2-furan carboxylic acids, with 2-acetylthiophene, 2-acetylfuran, and 2-thiophenaldehyde in the presence of an excess of anhydrous aluminum chloride have been studied. The phenyldichloromethyl group enters into position 4 of the thiophene and position 5 of the furan ring and on treating the reaction mixture with water is converted to benzoyl group.

Keywords: 2-acetylthiophene, 2-acetylfuran, benzotrichloride, thiophene- and furan-2-carbonitriles, 2-thiophenaldehyde, 2-thiophene- and 2-furan carboxylic acid esters, benzylation with phenyldichlorocarbenium tetrachloroaluminate.

The incomplete hydrolysis of trichloromethylarenes (TCMA) is used in industry to obtain the corresponding aromatic acid chlorides. In addition the Friedel–Crafts reaction between TCMA and arenes or heterenes with subsequent hydrolysis of the resulting diaryl dichloromethanes or aryl(heteryl)dichloromethanes may serve as a preparative route for the synthesis of diaryl and aryl(heteryl) ketones. Our attention was drawn to the report [1] on phenyldichlorocarbenium tetrachloroaluminate [PhCCl₃]⁺AlCl₄⁻ (1) as an effective reagent for obtaining substituted benzophenones possessing high stability (the complex was conserved unchanged for two weeks at 25°C). It was concluded by the authors of [1] on the basis of ¹³C NMR spectra that the phenyldichlorocarbenium carbocation has a substantially larger positive charge compared with the charge on the carbonyl carbon atom in the complex of benzoyl chloride with aluminum chloride PhCOCl·AlCl₃. This also causes the complex 1 to be more reactive as an electrophile.

The use of benzotrichloride in the presence of AlCl₃ enables the corresponding ketones to be obtained at room temperature in high yield from various aromatic compounds, including anisole, naphthalene, thiophene, chlorobenzene, bromobenzene, and α-dichlorobenzene [2]. The benzylation of acetanilide was studied in particular detail and is linked with the development of new methods of synthesis of 3,4-diaminobenzophenone as a key intermediate for obtaining the antihelmintic drug mebendazole [3]. The action of benzotrichloride in the presence of three-fold molar amount of aluminum chloride in 1,2-dichloroethane leads to 4-acetylaminobenzophenone in 72-98% yield. It is essential to note that acetanilide is not benzyolated by benzoyl chloride in the presence of AlCl₃. Only the initial acetanilide and benzoic acid were isolated from the reaction mixture [1].

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Consideration of the fairly wide range of aromatic compounds giving benzylation products under the action of complex 1 [2], shows that there are 11o compounds amongst them with strong electron-withdrawing substituents possessing a –I–M effect. However our preliminary experiments showed that even methyl benzoate reacts with benzotrichloride in the presence of AlCl₃, although the yield of products was low. The problem of the present work is the investigation of the benzylation with complex 1 of carbonyl compounds of furan 2a-d and thiophene 3a-d and also the corresponding nitriles 4 and 5. The choice of subject was caused by the possibility of comparison with known data on their acylation by the traditional agents, the acid chlorides.

The benzylation of 2-furancarboxylic acid methyl ester (2a) was described for the first time in 1964 by Galust'yan and Tsukervanik [4]. The reaction was carried out by the action of benzoyl chloride in the presence of ferric chloride (in catalytic amount) in CCl₄ at 80-90°C for 5-8 h. Later, the reaction of ester 2a in benzene with X-substituted benzoyl chlorides catalyzed by ferric chloride was studied (X = H, NO₂, CH₃, Cl, CH₂O) [5]. A high yield of keto ester 6a (as described in [4]) was no reached: it was only 41%.

The acetylation of methyl ester 2a directed to position 5 by the action of acetic anhydride in the presence of FeCl₃, or SnCl₂, has been described [6]. The reaction however may be complicated by substitution in the acetyl group. On acylating the ethyl ester 2b with acetic anhydride in benzene in the presence of SnCl₂, 5-acetoacetyl-2-ethylfuranoate was formed and not 5-acetyl-2-ethylfuranoate [7]. Acetylation of 2-acetyl-furan (2c) with acetic anhydride directed to the side-chain, though the yield of 2-acetoacetyl-furan was only 4.6% [8]. The reaction of 2-acetyl-furan with acetyl chloride in the presence of aluminum chloride does not proceed even in the absence of solvent at 115°C and a large portion of the starting ketone was recovered unchanged [9]. Such a result is explained by deactivation of the furan ring, primarily position 5, by the modified substituting agent MeCO-AlCl₃. Furfurol (2d) is acetylated unexpectedly readily [9]: 5-acetylfurfurol was formed in 45% yield by the action of 2 mole of acetyl chloride and 2.5 mole of AlCl₃ in chloroform even at a temperature of 50°C. This is probably caused by the conversion of furfurol into the corresponding chloroacetate under the reaction conditions [9].

The thiophene analogs of the keto esters of type 6, as far as we know, are not described in the literature, however acylation of ketones of thiophene series has been studied in comparative detail. In particular, under the usual conditions (using solvent) the presence of an alkyl group is a necessary condition for introducing a second acyl group into the thiophene nucleus [10]. Acetylation of 2-acetyltiophene (3b) was successfully carried out by the action of acetyl chloride in the presence of an excess of aluminum chloride at 100°C without solvent. In this way 2,4-diacetyltiophene was obtained in a yield of 50-70% on the reacted ketone, and contained about 5% contamination by the 2.5-isomer [11]. Benzylation of ketone 3b under the same conditions was complicated by overacylation so that a mixture of products was formed containing 2-benzyltiophene, diacetyl-, acetylbenzoyl-, and dibenzoyltiophene [12]. It is essential to emphasize that on acylating 2-acetyltiophenes diketones are formed preferentially with acyl residues in positions 2 and 4 of the thiophene ring [11.12]. Such an orientation is caused by the fact that complexes of monoacyl tiophenes with aluminum chloride react. These contain the very strong meta orientant, the modified acyl grouping RCO·AlCl₃, which proved to be capable of overcoming the α-orienting effect of the hetero atom. In the case of the furan analogs complexation at the acyl substituent fails to overcome the more powerful orienting effect of the oxygen atom [13].

We have found that the esters of 2-furancarboxylic acid 2a,b and of 2-thiophencarboxylic acid 3a,b, in the presence of an excess of AlCl₃, without solvent or in such solvents as 1,2-dichloroethane, chloroform, or dichloromethane, react with benzotrichloride. After the usual processing the esters of 5-benzylfuran-2-carboxylic acid 6a,b and 4-benzyltiophene-2-carboxylic acid 7a,b were obtained in 50-75% yield. The corresponding acids 8 and 9 were obtained by the alkaline hydrolysis of these esters. In difference to benzotrichloride, benzoyl chloride under the same conditions gave practically no reaction with ester 2b, which is additional confirmation of the higher reactivity of phenyldichlorocarbenium tetrachloroaluminate 1 compared with the PhCOCl·AlCl₃, complex.

Undoubtedly the direct reaction products are not keto esters 6, 7 but the corresponding dichloro compounds, viz.: the esters of 5-(α,α-dichlorobenzyl)furan-2-carboxylic acid 10a,b and 4-(α,α-dichlorobenzyl)-thiophene-2-carboxylic acid 11a,b. As a rule they are partially conserved on treating the reaction mixtures with water and are detected by 'H NMR spectrum, mass spectrum, and elemental analysis results. The ratio keto ester : dichloride depends seemingly on the nature of the latter but changes from experiment to experiment so