

Aroylation of 2- and 3-acetylthiophenes using benzoyl chloride, benzotrichloride, and their substituted derivatives

Leonid I. Belen'kii,* Galina P. Gromova, Anton V. Kolotaev, and Sergei I. Luiksaar

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prospect, 47, 119991 Moscow, Russia
E-mail: libel@cacr.ioc.ac.ru

Dedicated to Professor Mikhail G. Voronkov on the occasion of his 80th birthday
(received 01 Jun 01; accepted 08 Jan 02; published on the web 16 Jan 02)

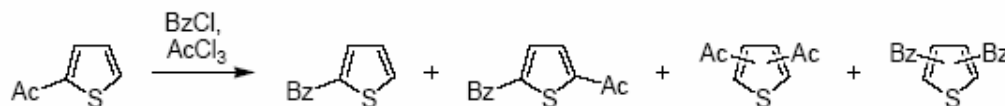
Abstract

Aryldichlorocarbenium tetrachloroaluminates are shown to be preferable reagents for the aroylation of 2-acetylthiophene, while the usual $\text{ArCOCl} \cdot \text{AlCl}_3$ complexes give better results in aroylation of 3-acetylthiophene. Scope and limitations of both aroylation procedures are discussed.

Keywords: Aryldichlorocarbenium tetrachloroaluminates, complexes of aroyl chlorides with AlCl_3 , 2-acetylthiophene, 3-acetylthiophene, aroylation

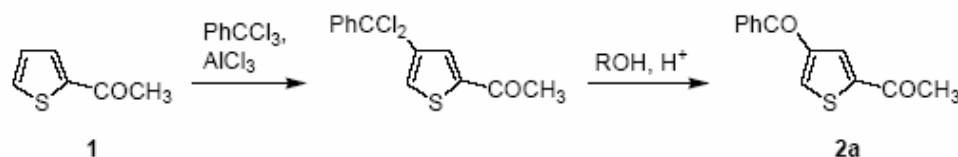
Introduction

Previously, the effect of complex formation with Lewis and Brønsted acids on the reactivity of carbonyl compounds of thiophene derivatives and, especially, on the orientation of the electrophilic attack at the thiophene ring has been studied by our group extensively (see reviews^{1,2}). It has been shown that in such complexes the reactivity of carbonyl compounds is suppressed and the orientation is changed: electrophiles do not enter the free α' -position as usual, but preferentially or even exclusively attack position 4 that upon complex formation is deactivated to the lesser extent. In particular, 2-acylthiophenes are acylated with acetyl and chloroacetyl chlorides in the presence of excess anhydrous aluminum chloride without a solvent at ca 100 °C affording 2,4-diacylthiophenes with an admixture (6–8%) of the 2,5-isomer in 50–70% total yield with respect to the consumed ketone.^{3,4} The reaction of 2-acetylthiophene (**1**) with benzoyl chloride under the conditions mentioned is complicated by transacylation, and therefore, results in a mixture of products containing 2-benzoylthiophene (yield ca 30%) as well as diacetyl-, acetylbenzoyl- (13% of the total products) and dibenzoylthiophenes (Scheme 1).⁴

**Scheme 1**

Acylation of 3-acylthiophenes with acyl chlorides proceeds more smoothly affording the corresponding 2,4-diacylthiophenes in 70–80% yields without 2,5-isomer.⁴

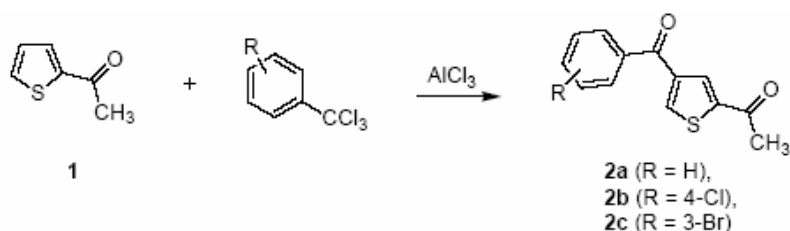
Recently, we have shown that the undesirable transacylation reaction accompanying the benzoylation of 2-acylthiophenes can be suppressed by replacing the PhCOCl·AlCl₃ complex by phenyldichlorocarbenium tetrachloroaluminate [PhCCl₂]⁺ AlCl₄[−]; actually, this complex is an alkylating and not an acylating agent: the corresponding substituted arylhetaryldichloromethanes are the primary products.⁵ Thus, 2-acetylthiophene (**1**) and benzotrichloride with an excess of aluminum chloride (to form **1**·AlCl₃ and [PhCCl₂]⁺[AlCl₄][−] complexes) gave, at a reaction temperature of ca. 80 °C and after treatment of the reaction mixture with an acidic, aqueous alcohol solution, 2-acetyl-4-benzoylthiophene (**2a**) without admixture of the 2,5-isomer (as indicated by ¹H NMR; Scheme 2).⁵

**Scheme 2**

The goal of the present work was the comparison of trichloromethylarenes and aroyl chlorides in the preparation of 2,4-diacylthiophenes. As starting materials for the generation of the aryldichlorocarbenium tetrachloroaluminates both benzotrichloride and some substituted benzotrichloride derivatives were employed; substituted benzoyl chlorides were used as well. 2-Acetylthiophene (**1**) and 3-acetylthiophene (**3**) were the substrates selected for studying the scope and the limitations of reactions mentioned.

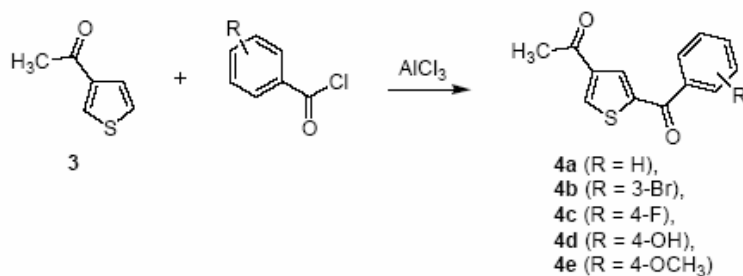
Results and Discussion

Taking into account the side reactions encountered by using benzoyl chloride with AlCl₃ in the benzoylation of 2-acetylthiophene (**1**),⁴ aryldichlorocarbenium tetrachloro-aluminates can be suggested as the preferable reagents for the aroylation of **1**. Particularly, we have shown⁵ that in the presence of aluminum chloride, benzotrichloride reacts with 2-acetylthiophene selectively and at lower temperature than benzoyl chloride to give diketone **2a** in a much higher yield (50%⁵ instead of 13%⁴).

**Scheme 3**

In this work, 2-acetylthiophene (**1**) is shown to react with 4-chlorobenzotrichloride at 70–85 °C giving 2-acetyl-4-(4-chlorobenzoyl)thiophene (**2b**) in 39% yield. With 3-bromobenzotrichloride at 95–100 °C, the yield of 2-acetyl-4-(3-bromobenzoyl)thiophene (**2c**) is 32% (Scheme 3). Our attempts to carry out similar acylation reactions using 2,4-dimethyl- and 2-chlorobenzotrichlorides failed. Polymer formation took place, and part of the starting compounds was recovered, probably due to steric hindrance of the ArCCl₂⁺ group and an *ortho* substituent.

Unexpectedly, the yield of 4-acetyl-2-benzoylthiophene (**4a**) from the reaction of benzotrichloride and 3-acetylthiophene (**3**) was lower than described⁴ for the reaction with benzoyl chloride (47% as compared to 76%). Considering the yields mentioned and the evidence, that the employment of acid chlorides does not require an additional hydrolysis step of the resulting arylhetaryldichloromethanes, there is no obvious advantage of using substituted benzotrichlorides in aroylation reactions of 3-acetylthiophene (**3**). Reactions of the latter with substituted benzoyl chlorides proceeded more smoothly than in the case of 2-acetylthiophene (**1**) and give 4-acetyl-2-aryltiophenes (**4b,c**) in rather high yields. Thus, 3-acetylthiophene reacted with 3-bromobenzoyl chloride at 98–100 °C and with 4-fluoro-benzoyl chloride at 80–90 °C affording 4-acetyl-2-(3-bromobenzoyl)thiophene (**4b**) and 4-acetyl-2-(4-fluorobenzoyl)thiophene (**4c**) in 65% and 46% yields, respectively (Scheme 4).

**Scheme 4**

However, not all tested aroyl chlorides were sufficiently stable under the acylation conditions applied. Thus, we could not obtain any product from the reaction with 4-(trifluoromethyl)benzoyl chloride. In the case of 4-methoxybenzoyl chloride the main product was the demethylated 4-acetyl-2-(4-hydroxybenzoyl)thiophene (**4d**). 4-Acetyl-2-(4-methoxybenzoyl)thiophene (**4e**) could be obtained in low yield (15%) only after methylation with dimethyl sulfate of the primarily formed reaction mixture of **4d** and **4e** (Scheme 4).

In summary, aryldichlorocarbenium tetrachloroaluminates have been shown to be preferable

reagents for the arylation of 2-acetylthiophene, whereas the usual $\text{ArCOCl} \cdot \text{AlCl}_3$ complexes give better results in arylation of 3-acetylthiophene.

Experimental Section

General Procedures. ^1H NMR spectra of CDCl_3 solutions were recorded with a Bruker AC-200 instrument (200 MHz).

The purity of the products was checked by TLC on Silufol UV-254 using petroleum ether/ethyl acetate mixtures (3:1 for **2b**, 2:1 for **4e**, 5:1 in all other cases) as eluents. Light petroleum ether refers to the fraction of boiling range 40–60 °C, petroleum ether refers to the fraction of boiling range 60–80 °C. All starting materials, ketones, benzotrichloride, and the aryl chlorides, were commercially available reagents (Aldrich, Merck). 2,4-Dimethylbenzotrichloride was prepared by trichloromethylation of *m*-xylene;⁶ 3-bromobenzotrichloride was obtained from 3-bromobenzotrifluoride with AlCl_3 and AcCl according to a known procedure;⁷ 2-chlorobenzotrichloride and 4-chlorobenzotrichloride were prepared by side-chain chlorination of 2- and 4-chlorotoluene, respectively, following literature procedures.⁸

2-Acetyl-4-(4-chlorobenzoyl)thiophene (2b). To the mixture of **1** (5 g, 4.3 mL, 39.7 mmol) and AlCl_3 (15.88 g, 119.0 mmol) was added dropwise with stirring 4-chlorobenzotrichloride (9.13 g, 6.1 mL, 39.7 mmol). The mixture was stirred at 70–85 °C for 15 min until the evolution of hydrogen chloride ceased, and after cooling it was poured onto ice. The aqueous layer was extracted with chloroform, the extract was washed with water until neutral, dried over MgSO_4 , and the solvent was evaporated. The residue, a dark brown liquid (13.15 g), was dissolved in ethanol (50 mL) containing H_2SO_4 (0.5 mL), and the solution was refluxed for 3.5 h. After cooling the solution, the crude semisolid precipitate (5.34 g) was filtered off. The filtrate was partially evaporated, diluted with chloroform, and the resulting solution was washed with water, then with an aqueous solution of Na_2CO_3 followed by water, and dried over MgSO_4 . Upon evaporation of the solvent the residual oil (4.95 g) was boiled with petroleum ether and gave after recrystallization from light petroleum ether colorless crystals of the diketone **2b** (4.09 g, 39%); mp 126–127 °C. ^1H NMR: δ 2.62 (3H, s, Me), 7.50 (2H, m, *m*-H), 8.10 and 7.76 (2H, m, *o*-H), 7.84 (1H, d, 3-H), 8.13 (1H, d, 5-H). Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{ClO}_2\text{S}$: C, 58.98; H, 3.43; Cl, 13.39; S 12.11. Found: C, 58.93; H, 3.59; Cl, 13.12; S, 11.86.

2-Acetyl-4-(3-bromobenzoyl)thiophene (2c). To AlCl_3 (16 g, 120 mmol) was added in portions while cooling with cold water **1** (5 g, 40 mmol). To the liquid complex formed, 3-bromobenzotrichloride (10.9 g, 40 mmol) was added dropwise with stirring. The reaction mixture was heated at 95–100 °C for 20 min and worked-up as described before. After evaporation of chloroform extract the oily residue was dissolved in *i*-PrOH (100 mL); conc. H_2SO_4 (0.5 mL) was added, and the solution was refluxed for 1 h. The hot solution was decanted from a resinous lower layer. Upon cooling the solution, the separated diketone crystals were

filtered off and washed with cold *i*-PrOH affording colorless crystals **2c** (5.2 g, 35%); mp 152–153 °C (*i*-PrOH). ¹H NMR: δ 2.63 (3H, s, Me), 7.41 (1H, m, *m*-H), 7.74 (1H, m, *p*-H), 7.77 and 8.12 (2H, m, *o*-H), 7.97 (1H, d, 3-H), 8.17 (1H, d, 5-H). Anal. Calcd. for C₁₃H₉BrO₂S: C, 50.50; H, 2.93; Br, 25.84; S, 10.37. Found: C, 50.57; H, 2.99; Br, 24.42; S, 9.80.

4-Acetyl-2-benzoylthiophene (4a). To AlCl₃ (23.7 g, 178 mmol) was added **3** (7.5 g, 59 mmol). Upon addition of benzotrichloride (11.6 g, 8.4 mL, 59 mmol) the temperature of the mixture rose to 47 °C, and subsequently, the reaction temperature was maintained in the range 90–93 °C for 30 min. After the HCl evolution has ceased, the reaction mixture was cooled, chloroform (60 mL) was added, and the mixture was poured onto ice. The organic layer was separated, and the aqueous layer was extracted with chloroform. The combined extracts were evaporated, dissolved in ethanol (90 mL), and after addition of H₂SO₄ (1.5 mL) the solution was refluxed for 2 h. The treatment of the ethanolic solution as described above gave diketone **4a** (6.41 g, 47%) as colorless crystals; mp 92–93 °C (lit.⁴ 92–93 °C). ¹H NMR: δ 2.56 (3H, s, Me), 7.51 (2H, m, *m*-H), 7.62 (1H, m, *p*-H), 7.83 (2H, m, *o*-H), 8.01 (1H, d, 3-H), 8.37 (1H, d, 5-H).

4-Acetyl-2-(3-bromobenzoyl)thiophene (4b). To the stirred mixture of **3** (2.0 g, 15.8 mmol) and AlCl₃ (6.32 g, 47.4 mmol), 3-bromobenzoyl chloride (2.1 mL, 3.47 g, 15.8 mmol) was added. The evolution of hydrogen chloride started at 57 °C, and at 72 °C the temperature rose to 98 °C with concomitant vigorous HCl evolution. The reaction at 98–100 °C was completed within 12 min. After the HCl evolution had ceased, the reaction mixture was cooled, chloroform (20 mL) was added, and the mixture was poured onto ice. The organic layer was separated, and the aqueous layer was extracted with chloroform. The combined extracts were dried over MgSO₄, the solvent was evaporated, and a crude product (5 g) was obtained. Recrystallization from ethanol gave colorless crystals of diketone **4b** (3.2 g, 65%); mp 101–102 °C. An analytical sample **4b** was prepared, mp 103–105 °C (ethanol). ¹H NMR: δ 2.56 (3H, s, Me), 7.40 (1H, m, *m*-H), 7.77 (2H, m, *p*-H and *o*-H), 7.99 (1H, m, *o*-H), 7.99 (1H, d, 3-H), 8.36 (1H, d, 5-H). Anal. Calcd. for C₁₃H₉BrO₂S: C, 50.50; H, 2.93; Br, 25.84; S, 10.37. Found: C, 50.51; H, 3.05; Br, 25.25; S, 10.13.

4-Acetyl-2-(4-fluorobenzoyl)thiophene (4c). To AlCl₃ (9.6 g, 72 mmol), **3** (3.0 g, 24 mmol) was added in portions. Upon stirring and cooling a liquid complex was formed. The cooling water bath was removed, and 4-fluorobenzoyl chloride (2.83 mL, 3.81 g, 24 mmol) was added dropwise. Heating the mixture to 40 °C induced the evolution of HCl. The reaction was carried out for 35 min at 80–90 °C. After removal of the heating bath, the mixture became viscous. Dichloromethane (50 mL) was added, and the resulting solution was poured onto ice. The organic layer was separated, washed with water several times until neutral, and dried over CaCl₂. The solvent was evaporated, and the crystalline residue was recrystallized from light petroleum ether affording colorless crystals of diketone **4c** (4.3 g, 46%); mp 114–115 °C. ¹H NMR: δ 2.55 (3H, s, Me), 7.22 (2H, m, *m*-H), 7.91 (2H, m, *o*-H), 8.00 (1H, d, 3-H), 8.35 (1H, d, 5-H). Anal. Calcd. for C₁₃H₉FO₂S: C, 62.89; H, 3.65. Found: C, 62.91; H, 3.66.

Reaction of 3-acetylthiophene (3) with 4-methoxybenzoyl chloride. To the complex obtained from AlCl₃ (4.74 g, 35.6 mmol) and **3** (1.0 g, 7.9 mmol), 4-methoxybenzoyl chloride (1.755 g,

10.3 mmol) was added in portions at 56–78 °C within 25 min. A vigorous HCl evolution took place, and the mixture solidified. Dichloromethane (20 mL) was added to the mixture, and the resulting solution was treated with water. The organic layer was washed with water and dried over MgSO₄. After removal of the solvent, a mixture (2 g) was obtained, containing **3** (¹H NMR and TLC), 3-acetyl-5-(4-hydroxybenzoyl)thiophene (**4d**), and 3-acetyl-5-(4-methoxybenzoyl)thiophene (**4e**). The mixture was refluxed in a solution of NaOH (0.35 g, 8.7 mmol) in water (3.5 mL) together with Me₂SO₄ (0.554 g, 4.4 mmol) for 3 h. The reaction mixture was extracted with ether, and after removal of the solvent, the product was obtained as viscous oil (1.0 g). Column chromatography (silica gel, petroleum ether/ethyl acetate 5:1 → 2:1 as eluent) gave three fractions: Fraction 1 contained starting material **3** (0.31 g); fraction 2 (0.48 g) was a mixture of the methoxy-substituted diketone **4e** with the hydroxy-substituted diketone **4d**; fraction 3 was mainly the hydroxy-substituted diketone **4d** (0.12 g).

4-Acetyl-2-(4-methoxybenzoyl)thiophene (4e). Repeated column chromatography of fraction 2 followed by crystallization from *i*-PrOH and petroleum ether afforded pure **4e** (0.3 g, 15%) as colorless crystals; mp 102–103 °C. ¹H NMR: δ 2.53 (3H, s, Me), 3.89 (3H, s, MeO), 6.98 (2H, m, *m*-H), 7.89 (2H, m, *o*-H), 7.98 (1H, d, 3-H), 8.30 (1H, d, 5-H). Anal. Calcd. for C₁₄H₁₂O₃S: C, 64.60; H, 4.65; S, 12.32. Found: C, 65.13; H, 4.87; S, 11.56.

4-Acetyl-2-(4-hydroxybenzoyl)thiophene (4d). Fraction 3, colorless crystals (mp 150 °C) was contaminated (¹H NMR) with ca 8% of diketone **4e**. **4d**: ¹H NMR: δ: 2.58 (3H, s, Me), 1.25 (1H, br s, HO), 6.96 (2H, m, *m*-H), 7.86 (2H, m, *o*-H), 7.92 (1H, d, 3-H), 8.35 (1H, d, 5-H). The IR of this fraction exhibits a strong broad band at 3300 (ν_{OH}) and a narrow band at 1670 cm⁻¹ (ν_{CO}).

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