The significance of the acylation reaction of amines is presented in the literature references. The products of the reaction are important intermediates in obtaining practically useful compounds. It has been shown that the most common methods of acylfunctionalization of amines are acetylation, trifluoroacetylation, and formylation, usually acid anhydrides or chlorides are used as acylating reagents in these reactions in the presence of highly toxic and expensive catalysts. The authors have developed an approach to the synthesis of a number of N-acylated amino-9,10-anthraquinones, which is based on the use of a new acylation system consisting of a strong organic acid and ammonium thiocyanate. It has been determined that 1-amino-9,10-anthraquinone and its derivatives in the presence of the two-fold excess of ammonium thiocyanate can be acetylated only by formic and trifluoroacetic acids. 2-Amino-9,10-anthraquinone additionally can be acetylated by mercaptoacetic and acetic acids. The scheme of the reaction discovered has been proposed, it involves in situ generation of ammonium acetate from carboxylic acid and ammonium thiocyanate, which serves as the acylating reagent.

N-ACYLATION OF AMINO-9,10-ANTHRACINOINES BY THE SYSTEM OF STRONG CARBOXYLIC ACID – AMMONIUM THIOCYANATE

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Key words: amino-9,10-anthraquinones; carboxylic acids; ammonium thiocyanate; ammonium acetate; acylation
Acylation of amines is one of the most common methods of their structural modifications, and it is widely used in organic synthesis and medicinal chemistry. N-Acyl residues are important protective groups, and the corresponding amides are effective intermediates in various chemical transformations aimed to obtain practically useful compounds. In the process of acylfunctionalization of amines the most generally used methods are: acetylation [1], trifluoroacetylation [2] and formylation [3-5]. The commonly used acylating reagents are acetic acid anhydride and chloride in the presence of highly toxic and expensive catalysts [6-9], trifluoroacetic acid anhydride and other highly electrophilic derivatives of trifluoroacetic acid [10-13], complexes of formic acid with carbodiimides [14, 15] or Lewis acids [16]. Thus, the search for environmentally benign and technologically convenient methods of acylation of amines by carboxylic acids with catalytic addition of cheap reagents is a topic of great interest [17-19].

N-Acylamino-9,10-anthraquinones became the subject of increased attention of researchers in recent years because of identification of 1-acetamide-9,10-anthraquinone as a new mutagenetic metabolite of 1-aminoanthracene [20]. 2-Trifluoroacetamide-9,10-anthraquinone was used as a selective colorimetric sensor for a cyanide anion in aqueous solutions [21]. The synthesis of N-acylamino-9,10-anthraquinones was carried out via the reaction with acetic [20, 22, 23], trifluoroacetic [21] acid anhydrides, and acetyl chloride [24].

We have shown that for this purpose a new acylating system consisting of a strong carboxylic acid and ammonium thiocyanate could be successfully used. It was found that the structure of aminosubstrate and carboxylic acid affected the acylation reactions of N-acylamino-9,10-anthraquinones 2a-l on examples of reactions of 1- and 2-amino-9,10-anthraquinones (AQ-NH₂) 1a-f with formic, acetic, mercaptoacetic, and trifluoroacetic acids in the presence of the two-fold excess of ammonium thiocyanate (Table). It was determined that 1-amino-9,10-anthraquinone 1a and its derivatives 1b-d were acylated only by formic and trifluoroacetic acids in the presence of ammonium thiocyanate. In the case of diaminoo-9,10-anthraquinones 1c,d both amino groups took part in the reaction. 2-Amino-9,10-anthraquinone 1e underwent only trifluoroacylation, and isomeric 1-amino-2-chloro-9,10-anthraquinone was not acylated by any of the acids tested.

The regularities found well correlate with the electronic parameters of amino-9,10-anthraquinones, as well as with acidity of carboxylic acids. Thus, less basic 1-amino-9,10-anthraquinones 1a-d gave the corresponding amides 2a-g only with relatively strong trifluoroacetic (pKa = 0.23) and formic (pKa = 3.73) acids. At the same time more basic 2-amino-9,10-anthraquinone 1e gave amides not only with such strong acids as trifluoroacetic and formic acids, but with weaker mercaptoacetic (pKa = 3.83) and acetic (pKa = 4.76) acids. However, acylation did not proceed with propanoic or butanoic acids. The result of the reaction is quite unexpected because the system of inorganic (organic) acid and ammonium thiocyanate is normally used to generate in situ thiocyanic acid, which is a thiocarbamoyl reagent for weak bases [25]. Therefore, in the case of amino-9,10-anthraquinones 1 formation of antraquinoylthioureas was expected. In fact, an alternative reaction – acylation of amino-9,10-anthraquinones by ammonium carboxylate resulted from the reaction of ammonium thiocyanate with strong organic acids took place (Scheme). These results are consistent with the data published
# Table

**Products of N-acylation of amino-9,10-anthraquinones 1a-f by the system of strong carboxylic acid – ammonium thiocyanate**

|   | AQNH₂ | Acid      | Time of reaction, h | AQNH(C(O)R) |
|---|-------|-----------|---------------------|--------------|
| 1a|       | HC(O)OH   | 6                   |              |
| 1b|       | F₃CC(O)OH | 1                   |              |
| 1c|       | HC(O)OH   | 6                   |              |
| 1d| F₃CC(O)OH | 1         | 2e                  |              |
| 1  | 2          | 3  | 4          |
|----|------------|----|------------|
| 1d | HC(O)OH    | 6  | 2f         |
|    | F<sub>3</sub>CC(O)OH | 1  | 2g         |
| 1e | AcOH       | 3  | 2h         |
|    | HSCH<sub>2</sub>C(O)OH | 6  | 2i         |
|    | HC(O)OH    | 6  | 2j         |
|    | F<sub>3</sub>CC(O)OH | 1  | 2k         |
| 1f | F<sub>3</sub>CC(O)OH | 1  | 2l         |
in work [26] on direct acetylation of anilines with ammonium acetate in acetic acid, as well as the experimental data on the absence of reactions when instead of thiocyanate ammonium, thiocyanate potassium or ammonium chloride were used, and direct conversion of 2-amino-9,10-anthraquinone 1e to amide 2h in the reaction with the excess of ammonium acetate in acetic acid.

The composition and structure of amides 2a-l synthesized were confirmed by elemental analysis data, mass spectrometry, and 1H, 19F NMR spectroscopy.

Herein, the new preparative, high yielding method for the synthesis of N-acylated amino-9,10-anthraquinones was introduced.

**Experimental Part**

1H NMR spectra of the compounds synthesized were obtained on a Bruker Avance DRX-500 spectrometer, the internal standard was TMS. 19F NMR spectra were obtained on Varian VXR-300 spectrometer, the internal standard was CFCl3. Chromatographic spectra were obtained on a Agilent 1100/DAD/HSD/VLG 119,562 device.

The general method of acylation of amino-9,10-anthraquinone 1a-f to 30 ml of the corresponding carboxylic acid (0.001 Mol) of amino-9,10-anthraquinone 1a-f, 0.152 g (0.002 Mol) of ammonium acetate in acetic acid. To 30 ml of the corresponding carboxylic acid (0.001 Mol) of amino-9,10-anthraquinone 1e, 0.223 g (0.001 Mol) of 2-amino-9,10-anthraquinone, 0.152 g (0.002 Mol) of ammonium acetate and 0.223 g (0.001 Mol) of 2-amino-9,10-anthraquinone 1e, 0.152 g (0.002 Mol) of ammonium acetate and heat when boiling for 3 h. Cool the reaction mixture, dilute with the 4-fold excess of water, filter the precipitate, wash with water and dry.

N-(9,10-Dioxyo-9,10-dihydroanthracen-1-yl)diformamide 2a. Yield – 91%. M.p. – 210-212°C. 1H NMR, δ, ppm.: 8.08-8.17 m (3H, CHar); 7.87-7.91 m (3H, CHar); 8.64 m (1H, CHar); 8.96 br.s (1H, COH); 11.89 br.s (1H, NH). [M+1] + 252. Found, %: C 71.71; H 3.61; N 5.58. C15H9NO3. Calculated, %: C 71.71; H 3.61; N 5.58.

N-(9,10-Dioxyo-9,10-dihydroanthracen-1-yl)trifluoroacetamide 2b. Yield – 95%. M.p. – 182-183°C. 1H NMR, δ, ppm.: 7.95-8.24 m (6H, CHar); 8.74 d (1H, J=7.7 Hz, CHar); 13.17 s (1H, NH). 19F NMR, δ, ppm.: -75.55 (CF3). [M+1] + 319. Found, %: C 60.31; H 2.43; N 4.31. C16H10F3NO3. Calculated, %: C 60.20; H 2.53; N 4.39.

N-(9,10-Dioxyo-9,10-dihydroanthracen-1-yl)trifluoroacetamide 2c. Yield – 92%. M.p. – 287-289°C. 1H NMR, δ, ppm.: 7.77-7.87 m (2H, CHar); 3.04 s (1H, SH); 3.95 m (2H, CH2); 8.04-8.12 m (4H, CHar); 11.85 s (1H, NH); 13.03 s (1H, OH). 19F NMR, δ, ppm.: -75.40 (CF3). [M+1] + 383. Found, %: C 56.17; H 2.17; N 5.92. C16H16F3NO3. Calculated, %: C 56.61; H 2.22; N 3.86.

N,N'-(9,10-Dioxyo-9,10-dihydroanthraencn-1,4-diyldiformamide 2d. Yield – 87%. M.p. – 290-292°C.

N,N'-(9,10-Dioxyo-9,10-dihydroanthracene-1,4-diyldiformamide 2f. Yield – 85%. M.p. > 330°C. 1H NMR, δ, ppm.: 7.86-7.95 m (4H, CHar); 8.67 m (2H, CHar); 8.91 br.s (2H, COH); 11.84 br.s (2H, NH). [M+1] + 295. Found, %: C 50.35; H 1.81; N 6.58. C16H10F3NO3. Calculated, %: C 50.25; H 3.45; N 9.51.

N,N'-(9,10-Dioxyo-9,10-dihydroanthracene-1,5-diyldiformamide 2i. Yield – 89%. M.p. – 242-243°C. 1H NMR, δ, ppm.: 7.67-7.86 m (4H, CHar); 8.62-8.64 m (2H, CHar); 12.25 br.s (2H, NH). 19F NMR, δ, ppm.: -75.43 (2CF3). [M+1] + 431. Found, %: C 50.34; H 1.79; N 6.54. C16H11F3NO3. Calculated, %: C 50.25; H 1.87; N 6.51.

N,N'-(9,10-Dioxyo-9,10-dihydroanthracene-1,5-diyldiformamide 2j. Yield – 89%. M.p. – 232-233°C. 1H NMR, δ, ppm.: 3.04 s (1H, SH); 3.81 m (2H, CHar); 7.81-7.87 m (3H, CHar); 8.12 m (3H, CHar); 8.35 s (1H, CHar); 10.70 s (1H, NH). [M+1] + 297. Found, %: C 64.74; H 3.59; N 4.82. C16H16F3NO3. Calculated, %: C 64.63; H 3.73; N 4.71.

N,N'-(9,10-Dioxyo-9,10-dihydroanthracene-2-yl)trifluoroacetamide 2h. Method A: see the general procedure, yield – 88%. Method B: to 30 ml of acetic acid add 0.223 g (0.001 Mol) of 2-amino-9,10-anthraquinone 1e, 0.152 g (0.002 Mol) of ammonium acetate and heat when boiling for 3 h. Cool the reaction mixture, dilute with the 4-fold excess of water, filter the precipitate, wash with water and dry. Yield – 87%. M.p. – 258-260°C. 1H NMR, δ, ppm.: 7.8 m (2H, CHar); 8.04-8.15 m (4H, CHar); 8.39 s (1H, CHar); 10.57 s (1H, NH). [M+1] + 252. Found, %: C 72.54; H 4.01; N 5.32. C16H16F3NO3. Calculated, %: C 72.45; H 4.18; N 5.28.

N,N'-(9,10-Dioxyo-9,10-dihydroanthracene-2-yl)mercaptooacetamide 2i. Yield – 89%. M.p. – 232-233°C. 1H NMR, δ, ppm.: 3.04 s (1H, SH); 3.81 m (2H, CHar); 7.81-7.87 m (3H, CHar); 8.12 m (3H, CHar); 8.35 s (1H, CHar); 10.70 s (1H, NH). [M+1] + 297. Found, %: C 64.74; H 3.59; N 4.82. C16H16F3NO3S. Calculated, %: C 64.63; H 3.73; N 4.71.

N,N'-(9,10-Dioxyo-9,10-dihydroanthracene-2-yl)trifluoroacetamide 2j. Yield – 93%. M.p. – 282-283°C. 1H NMR, δ, ppm.: 7.84-7.87 m (2H, CHar); 7.96-7.99 m (1H, CHar); 8.08-8.11 m (3H, CHar); 8.36 s (1H, COH); 8.41 s (1H, CHar); 10.79 s (1H, NH). [M+1] + 252. Found, %: C 71.56; H 3.67; N 5.50. C16H16F3NO3S. Calculated, %: C 71.71; H 3.61; N 5.58.

N,N'-(9,10-Dioxyo-9,10-dihydroanthracene-2-yl)trifluoroacetamide 2k. Yield – 96%. M.p. – 216-217°C. 1H NMR, δ, ppm.: 8.13-8.36 m (4H, CHar); 8.75-8.81 m (3H, CHar); 13.01 s (1H, NH). 19F NMR, δ, ppm.: -75.61 (CF3). [M+1] + 319. Found, %: C 60.32; H 2.48; N 4.29. C16H16F3NO3S. Calculated, %: C 60.20; H 2.53; N 4.39.
**N-(3-Chloro-9,10-dioxo-9,10-dihydroanthracen-2-yl)-2,2,2-trifluoroacetamide 2l.** Yield – 90%. M.p. > 330°C. \(^1H\) NMR, δ, ppm.: 7.90-8.25 m (6H, CH\(_{ar}\)); 11.69 br.s (1H, NH). \(^19\)F NMR, δ, ppm.: -75.16 с, (CF\(_3\)).

\([M+1]^+ 354.\) Found, %: C 54.27; H 2.10; Cl 10.12; N 3.91. C\(_{16}\)H\(_7\)Cl\(_3\)F\(_3\)NO\(_3\). Calculated, %: C 54.34; H 2.00; Cl 10.02; N 3.96.

**Conclusions**

The effective method for the synthesis of \(N\)-formyl(acetyl-, mercaptoacetyl- and trifluoroacetyl)amino-9,10-anthraquinones based on the interaction of amino-9,10-anthraquinones with the corresponding carboxylic acids in the presence of the excess ammonium thiocyanate has been developed.

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