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N-ACYLATION OF AMINO-9,10-ANTHRAQUINONES 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

The significance of the acylation reaction of amines is presented in the literary reference information. The products of the reaction of the corresponding amides 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*-АЦИЛЮВАННЯ АМІНО-9,10-АНТРАХІНОНІВ СИСТЕМОЮ СИЛЬНА КАРБОНОВА КИСЛОТА – ТІОЦІАНАТ АМОНІЮ**

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Ключові слова: *аміно-9,10-антрахінони; карбонові кислоти; тіоціанат амонію; ацетат амонію; ацилювання*
Наведена інформативна літературна довідка синтетичної значимості реакції ацилювання амінів, продукти якої відповідні аміди є важливими інтермедіатами при отриманні значного масиву практично корисних сполук. На основі аналізу літературних джерел виявлено, що в процесах ацилфункціоналізації амінів найпоширенішими є методи ацетилювання, трифтороацетилювання та формілювання, в яких, як правило, в ролі ацилюючих реагентів використовуються ангідриди або хлороангідриди кислот у присутності високотоксичних і дорогих каталізаторів. Авторами розроблено підхід до синтезу низки N-ацильованих аміно-9,10-антрахінонів, який грунтується на застосуванні нової ацилюючої системи сильна органічна кислота – тіоціанат амонію. На прикладах взаємодії аміно-9,10-антрахінонів із форміатною, ацетатною, тіоацетатною та трифтороацетатною кислотами в присутності двократного надлишку тіоціанату амонію з'ясовано вплив структури аміносубстрату та карбонової кислоти на перебіг реакції ацилювання і утворення антрахіноліламідів. Встановлено, що 1-аміно-9,10-антрахінон та його заміщені аналоги в присутності тіоціанату амонію схильні до ацилювання тільки форміатною та трифтороацетатною кислотами, натомість 2-аміно-9,10-антрахінон окрім форміатної та трифтороацетатної кислот утворює аміди під дією ацетатної та тіоацетатної кислот. Запропонована схема знайденої реакції, яка передбачає in situ генерування із карбонової кислоти та тіоціанату амонію ацетату амонію, який власне і виконує роль ацилюючого реагента.

***N*-АЦИЛИРОВАНИЕ АМИНО-9,10-АНТРАХИНОНОВ СИСТЕМОЙ СИЛЬНАЯ КАРБОНОВАЯ КИСЛОТА – ТИОЦИАНАТ АММОНИЯ**

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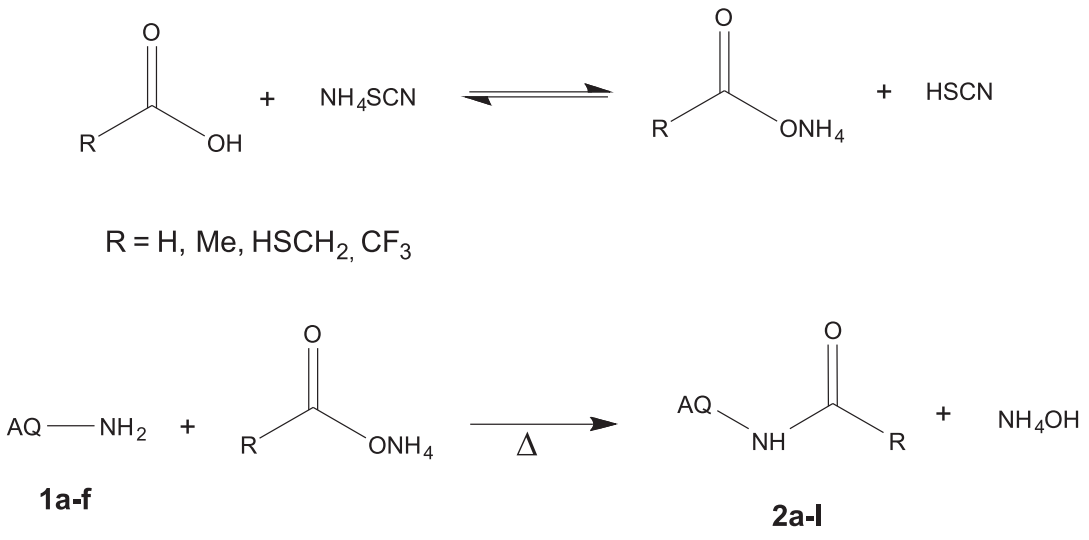
Ключевые слова: *амино-9,10-антрахиноны; карбоновые кислоты; тиоцианат аммония; ацилирование*
Приведена информативная литературная справка синтетической значимости реакции ацилирования аминов, продукты которой соответствующие амиды являются важными интермедиатами при получении значительного массива практически полезных соединений. На основе анализа литературных источников установлено, что в процессах ацилфункционализации аминов наиболее распространены методы ацетилирования, трифтор- ацетилирования и формилирования, в которых, как правило, в роли ацилирующих реагентов используются ангидриды или хлорангидриды кислот в присутствии высокотоксичных и дорогих катализаторов. Авторами разработан подход к синтезу ряда N-ацилированных амино-9,10-антрахинонов, основанный на применении новой ацилирующей системы сильная органическая кислота – тиоцианат аммония. На примерах взаимодействия амино-9,10-антрахинонов с муравьиной, уксусной, тиоуксусной и трифторуксусной кислотами в присутствии двухкратного избытка тиоцианата аммония выяснено влияние структуры аминосубстратов и карбоновой кислоты на протекание реакции ацилирования и образования антрахинолиламидов. Установлено, что 1-амино-9,10-антрахинон и его замещенные аналоги в присутствии тиоцианата аммония подвержены ацилированию только муравьиной и трифторуксусной кислотами, в то время как 2-амино-9,10-антрахинон кроме муравьиной и трифторуксусной кислот образует амиды под действием уксусной и тиоуксусной кислот. Предложена схема найденной реакции, которая предусматривает in situ генерирование с карбоновой кислоты и тиоцианата аммония ацетата аммония, который собственно и выполняет роль ацилирующего реагента.

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-NH_2) **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 diamino-9,10-anthraquinones **1c,d** both amino groups took part in the reaction. 2-Amino-9,10-anthraquinone **1e** reacted not only with strong formic and trifluoroacetic acids, but it also gave amides with mercaptoacetic and acetic acids. On the contrary, 2-amino-3-chloro-9,10-anthraquinone **1f** 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



Scheme

Table

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

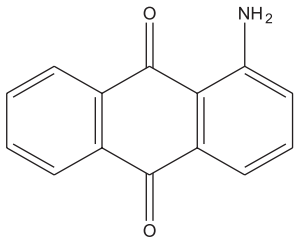
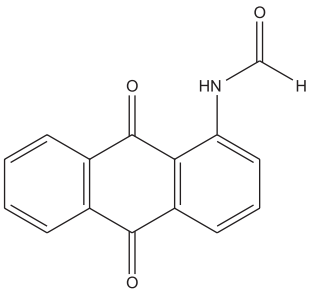
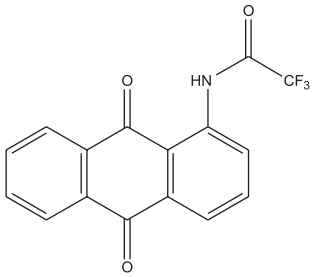
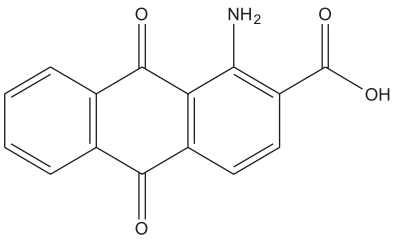
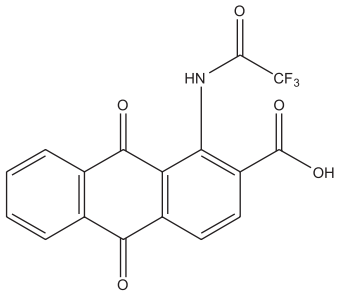
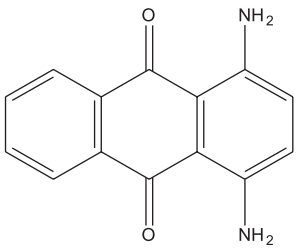
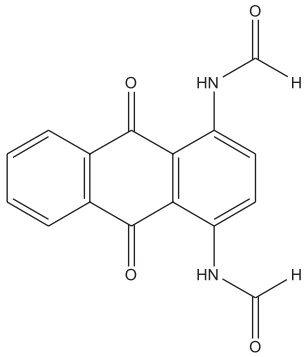
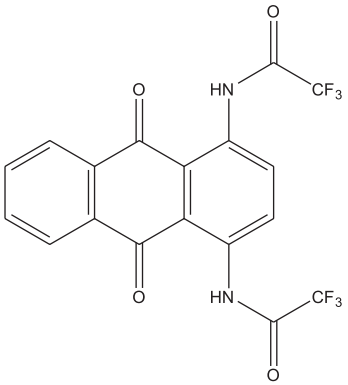
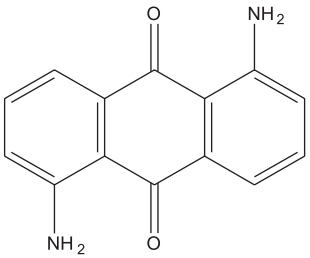
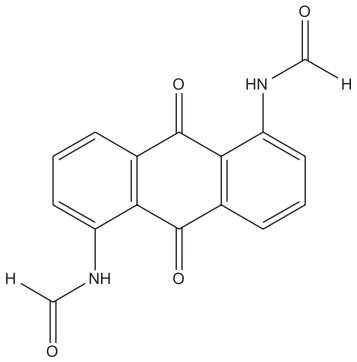
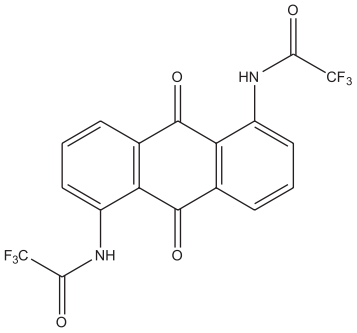
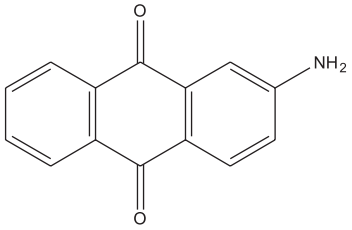
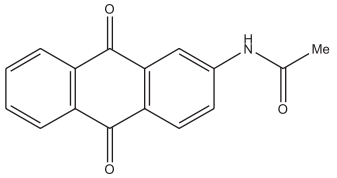
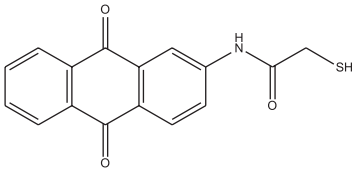
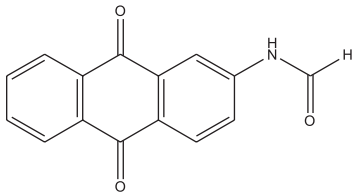
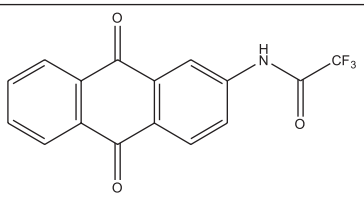
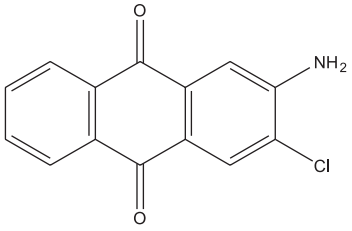
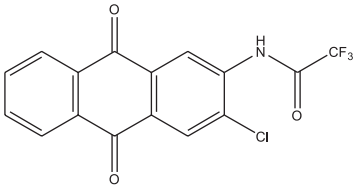
$AQNH_2$		Acid	Time of reaction, h	AQNHC(O)R	
1		2	3	4	
1a		HC(O)OH	6	2a	
		$F_3CC(O)OH$	1	2b	
1b		$F_3CC(O)OH$	1	2c	
1c		HC(O)OH	6	2d	
		$F_3CC(O)OH$	1	2e	

Table continued

1		2	3	4	
1d		HC(O)OH	6	2f	
		$F_3CC(O)OH$	1	2g	
1e		AcOH	3	2h	
		$HSCH_2C(O)OH$	6	2i	
		HC(O)OH	6	2j	
		$F_3CC(O)OH$	1	2k	
1f		$F_3CC(O)OH$	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 ^{1}H, ^{19}F NMR spectroscopy.

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

Experimental Part

^{1}H NMR spectra of the compounds synthesized were obtained on a Bruker Avance DRX-500 spectrometer, the internal standard was TMS. ^{19}F NMR spectra were registered on a Varian VXR-300 spectrometer, the internal standard was $CFCl_3$. Chromato-mass spectra were obtained on a Aligent 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 add (0.001 Mol) of amino-9,10-anthraquinone **1a-f**, 0.152 g (0.002 Mol) of ammonium thiocyanate (in the case of compounds **1a,b,f**) or 0.304 g (0.004 Mol) of ammonium thiocyanate (in the case of compounds **1c,d**), and heat when boiling for 1-6 h. Cool the reaction mixture, dilute with the 4-fold excess of water, filter the precipitate, wash with water and dry.

***N*-(9,10-Dioxo-9,10-dihydroanthracen-1-yl)formamide 2a**. Yield – 91%. M.p. – 210-212°C. ^{1}H NMR, δ, ppm.: 8.08-8.17 m (3H, CH_{ar}); 7.87-7.91 m (3H, CH_{ar}); 8.64 м (1H, CH_{ar}); 8.96 br.s (1H, COH); 11.89 br.s (1H, NH). $[M+1]^+$ 252. Found, %: C 71.59; H 3.69; N 5.47. $C_{15}H_9NO_3$. Calculated, %: C 71.71; H 3.61; N 5.58.

***N*-(9,10-Dioxo-9,10-dihydroanthracen-1-yl)-2,2,2-trifluoroacetamide 2b**. Yield – 95%. M.p. – 182-183°C. ^{1}H NMR, δ, ppm.: 7.95-8.24 m (6H, CH_{ar}); 8.74 d (1H, *J*=7.7 Hz, CH_{ar}); 13.17 s (1H, NH). ^{19}F NMR, δ, ppm.: -75.55 (CF_3). $[M+1]^+$ 319. Found, %: C 60.31; H 2.43; N 4.31. $C_{16}H_8F_3NO_3$. Calculated, %: C 60.20; H 2.53; N 4.39.

9,10-Dioxo-1-(2,2,2-trifluoroacetamido)-9,10-dihydroanthracene-2-carboxylic acid 2c. Yield – 92%. M.p. – 287-289°C. ^{1}H NMR, δ, ppm.: 7.77-7.87 m (2H, CH_{ar}); 8.04-8.12 m (4H, CH_{ar}); 11.85 s (1H, NH); 13.03 s (1H, OH). ^{19}F NMR, δ, ppm.: -75.40 (CF_3). $[M+1]^+$ 364. Found, %: C 56.17; H 2.17; N 3.92. $C_{17}H_8F_3NO_5$. Calculated, %: C 56.21; H 2.22; N 3.86.

***N,N'*-(9,10-Dioxo-9,10-dihydroanthracene-1,4-diyl)diformamide 2d**. Yield – 87%. M.p. – 290-292°C. ^{1}H NMR, δ, ppm.: 7.86-8.12 m (5H, CH_{ar}); 8.57 m (1H, CH_{ar}); 8.87 br.s (2H, COH); 12.01 br.s (2H, NH). $[M+1]^+$ 295. Found, %: C 65.40; H 3.36; N 9.57. $C_{16}H_{10}N_2O_4$. Calculated, %: C 65.32; H 3.45; N 9.51.

***N,N'*-(9,10-Dioxo-9,10-dihydroanthracene-1,4-diyl)bis(2,2,2-trifluoroacetamide) 2e**. Yield – 81%. M.p. – 260-261°C. ^{1}H NMR, δ, ppm.: 7.87 m (2H, CH_{ar}); 8.01 m (2H, CH_{ar}); 8.62 m (2H, CH_{ar}); 13.10 br.s (2H, NH). ^{19}F NMR, δ, ppm.: -75.42 (c, $2CF_3$). $[M+1]^+$ 431 Found, %: C 50.35; H 1.81; N 6.58. $C_{18}H_8F_6N_2O_4$. Calculated, %: C 50.25; H 1.87; N 6.51.

***N,N'*-(9,10-Dioxo-9,10-dihydroanthracene-1,5-diyl)diformamide 2f**. Yield – 85%. M.p. > 330°C. ^{1}H NMR, δ, ppm.: 7.86-7.95 m (4H, CH_{ar}); 8.67 m (2H, CH_{ar}); 8.91 br.s (2H, COH); 11.84 br.s (2H, NH). $[M+1]^+$ 295. Found, %: C 65.41; H 3.32; N 9.60. $C_{16}H_{10}N_2O_4$. Calculated, %: C 65.32; H 3.45; N 9.51.

***N,N'*-(9,10-Dioxo-9,10-dihydroanthracene-1,5-diyl)bis(2,2,2-trifluoroacetamide) 2g**. Yield – 79%. M.p. – 242-243°C. ^{1}H NMR, δ, ppm.: 7.67-7.86 m (4H, CH_{ar}); 8.62-8.64 m (2H, CH_{ar}); 12.25 br.s (2H, NH). ^{19}F NMR, δ, ppm.: -75.43 (c, $2CF_3$). $[M+1]^+$ 431. Found, %: C 50.34; H 1.79; N 6.54. $C_{18}H_8F_6N_2O_4$. Calculated, %: C 50.25; H 1.87; N 6.51.

***N*-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)acetamide 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. ^{1}H NMR, δ, ppm.: 2.12 s (3H, CH_3); 7.88 m (2H, CH_{ar}); 8.04-8.15 m (4H, CH_{ar}); 8.39 s (1H, CH_{ar}); 10.57 s (1H, NH). $[M+1]^+$ 264. Found, %: C 72.54; H 4.01; N 5.32. $C_{16}H_{11}NO_3$. Calculated, %: C 72.45; H 4.18; N 5.28.

***N*-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)-2-mercaptoacetamide 2i**. Yield – 89%. M.p. – 232-233°C. ^{1}H NMR, δ, ppm.: 3.04 s (1H, SH); 3.81 m (2H, CH_2); 7.81-7.87 m (3H, CH_{ar}); 8.12 m (3H, CH_{ar}); 8.35 s (1H, CH_{ar}); 10.70 s (1H, NH).: $[M+1]^+$ 297. Found, %: C 64.74; H 3.59; N 4.82; $C_{16}H_{11}NO_3S$. Calculated, %: C 64.63; H 3.73; N 4.71.

***N*-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)formamide 2j**. Yield – 93%. M.p. – 282-283°C. ^{1}H NMR, δ, ppm.: 7.84-7.87 m (2H, CH_{ar}); 7.96-7.99 m (1H, CH_{ar}); 8.08-8.11 m (3H, CH_{ar}); 8.36 s (1H, COH); 8.41 s (1H, CH_{ar});10.79 s (1H, NH). $[M+1]^+$ 252. Found, %: C 71.56; H 3.67; N 5.50. $C_{15}H_9NO_3$. Calculated, %: C 71.71; H 3.61; N 5.58.

***N*-(9,10-Dioxo-9,10-dihydroanthracen-2-yl)-2,2,2-trifluoroacetamide 2k**. Yield – 96%. M.p. – 216-217°C. ^{1}H NMR, δ, ppm.: 8.13-8.36 m (4H, CH_{ar}); 8.75-7.81 m (3H, CH_{ar}); 13.01 s (1H, NH). ^{19}F NMR, δ, ppm.: -75.61 c (CF_3). $[M+1]^+$ 319. Found, %: C 60.32; H 2.48; N 4.29. $C_{16}H_8F_3NO_3$. 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. ^{1}H NMR, δ, ppm.: 7.90-8.25 m (6H, CH_{ar}); 11.69 br.s (1H, NH). ^{19}F NMR, δ, ppm.: -75.16 c, (CF_3). $[M+1]^+$ 354. Found, %: C 54.27; H 2.10; Cl 10.12; N 3.91. $C_{16}H_7ClF_3NO_3$. 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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