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REACTIONS OF N-CHLORACETYLATION OF TOLUIDINE ISOMERS

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Abstract

The results of the study of reactions of N-chloroacetylation of toluidine isomers are presented in the article. Methods for purification of reaction products have been developed. Structure of the obtained compounds has been confirmed by means of 1H and 13C NMR spectroscopy.

Keyword: *N-chloroacetylation, chloroacetyl chloride, o-, m-, p-toluidine, 2-chloro-N-tolyl acetamide, acetonitrile, acetone, ethylacetates*

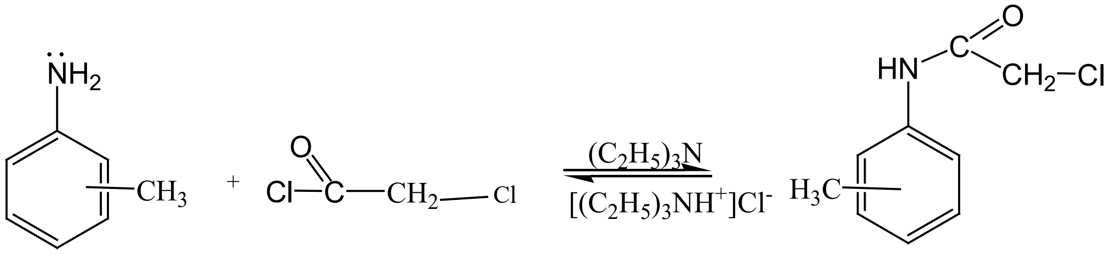
Introduction

Many biologically active substances have been synthesized on the basis of chloracetylation reactions of amino compounds and are widely used in medicine today. Currently, the study of the structure of amide bonds between amino acids reveals new methods for the synthesis of new peptides and proteins, which are an integral part of biology and medicine. It is known that more than 50% of all medicinal substances contain amide bonds. Amide bonds are formed by N-acylation reactions. Acid chloride anhydrides are one of the most widely used N-acylating agents for the formation of amide bonds and are used industrially throughout the world. When chloroacetyl chloride is used as an acylating agent, the reactions proceed under mild conditions and allow obtaining chloroacetyl products in high yields. Because, on the one hand, most of the compounds containing chloroacetyl group have high biological activity, on the other hand, chloroacetyl chloride is a strong acylating agent. The reason is that due to the negative inductive effect of the chlorine atom in chloroacetyl chloride, the carbon atom in the carbonyl group has an additional positive charge and facilitates the progress of the nucleophilic substitution reaction. N-aryl 2-chloroacetamides are used as herbicides, antimicrobials, antifungals, disinfectants (Manuri Brahmayyaa, Shing-Yi Suena, Shenghong A. Dai, 2017. P. 1–2). In addition, carbonic acid amides and their derivatives are used in medicine as antidepressants. Currently, paracetamol, phenacetin and filament are widely used in modern medicine. The main active fragment of these drugs is acrylamides of aromatic carboxylic acids. Expanding research work, new amides, including p-toluidine glycolate and

2-hydroxy-N-(4-methyl) phenylacetamide, are synthesized based on N-hydroxyacetylation of p-toluidine (Joris Hulsbosch, Laurens Claes, Dirk E. D eVos. 2018. P. 1646–1650; Koula, D.O.U.K.A.N.I., Nacera, G.A.C.E.M. and Hayat, B.E.N.L.A.R.B.I.. 2014. P. 1–16). It is known from the literature that acylation reactions of aromatic amines with halogen anhydrides are carried out at low temperatures, otherwise, due to the release of a large amount of heat in the reaction mixture, the mixture of oxidation and polymerization products sinks to the bottom of the vessel in the form of resin, the reason for which is explained by the easy access of the amino group to acylation reactions. Therefore, reagents for N-chloroacetylation reactions of aniline were obtained in the same molar ratio and carried out at a temperature below –20 C (Yusufov M.S., Abdushukurov A.K., 2020. P. 74–75; Yusufov M.S., Abdushukurov A.K., Akhmedova N.B., Yazilova G.M., 2018. P. 159–161). Currently, benzimidazole and benzoxazole derivatives are of great interest to pharmaceutical experts, since they are inhibitors of fructose-1,6-bisphosphatases in the condensation reactions of benzoxazoles with benzenesulfonamide, in which they have good pharmacokinetic activity (Lai C., Rebecca J., Daly M., Fry E., Hutchins C., Abad-Zapatero C., P. 1807–1810), and they are also inhibitors of amyloxygenases is considered (Neochoritis C., Zarganes-Tzitzikas T., Tsoleridis C., Stephanidou-Stephanatou J., Kontogiorgis C., Hadjipavlou-Litina D., Choli-Papadopoulou T., P. 297–306). In addition, many member derivatives of benzimidazole exhibit antibacterial and antimicrobial activity. Their use as a substrate of diazonium salts, a derivative of aminophenylbenzoxazole, increases the anti-inflammatory properties of the drugs (Carella A., Centore R., Sirigu A., Tuzi A., Quatela A., Schutzmann S., Casalboni M. 2004. P. 1948–1954). Experiments carried out in this field in our country and abroad show that it is possible to recommend synthesis of new organic substances and intermediate compounds with high biological activity based on reactions of chloroacetylation of aromatic hydrocarbons, as well as for use in the national economy and medicine.

Results and discussion:

To achieve these goals, chloroacetylation reactions of toluidine isomers were studied. In the literature, it was found that N-acyl products are formed when there are 1:1 molar ratios of reagents (Yusufov M.S., Abdushukurov A.K., 2020. P. 236–237).



The results of the reactions are presented in the table below.

Table 1. *Effect of solvent and time on reactions of chloroacetyl chloride with toluidine isomers to obtain 2-chloro-N-o-, m-, p-tolylacetamides:*

Name of reagents	Mole ratios of reagents	Temperature, °C	Duration of reaction, hours	Solvent	Yeild, %	Product T(liquid)	Rf
Chloro acetyl chloride: o-toluidine: TEA	1:1:1	2–5	6	Acetonitrile	83	106	0.65
				Benzene	78		
Chloroacetyl chloride: m-toluidine: TEA	1:1:1	–2–5	6	Acetonitrile	85	183	0.62
				Benzene	79		
Chloroacetyl chloride: p-toluidine: TEA	1:1:1	–2–5	6	Acetonitrile	88	175	0,73
				Benzene	79		

Toluidine isomers are more nucleophilic than aniline because the presence of an electron-donating (CH_3) substituent on the aromatic ring increases the nucleophilicity of the amino group on the aromatic ring and the chloroacetylation reaction proceeds better. In order to synthesize biologically active substances, N-chloroacetylation reactions of toluidine isomers were carried out under different conditions, and this reaction proceeds as follows.

Table 2. *Results obtained under ultrasonic conditions of chloroacetyl chloride with toluidine isomers:*

Name of reagents	Mole ratios of reagents	Temperature,°C	Dura tion of reaction, hours	Solvent	Yeild, %	Product T(liquid)	Rf
Chloro acetyl chloride: o-toluidine: TEA	1:1:1	−2–5	1	Acetonitrile	88	106	0,65
				Benzene	86		
Chloroacetyl chloride: m-toluidine: TEA	1:1:1	−2–5	1	Acetonitrile	90	183	0,62
				Benzene	85		
Chloroacetyl chloride: p-toluidine: TEA	1:1:1	−2–5	1	Acetonitrile	91	175	0,73
				Benzene	87		

Polar and non-polar solvents were used for the reaction, and in order to reduce the duration of the reaction, it was carried out in an ultrasonic device and optimal conditions were selected.

Experimental part: 0.0214 g (0.0001 mol) of o-toluidine and 0.0338 ml (0.0001 mol) of triethylamine were placed in a round bottomed flask and dissolved in 10 ml of acetonitrile. In the second bowl, 0.02712 g (0.0001 mol) of chloroacetyl chloride was also dissolved in 5 ml of acetonitrile. Then, the reaction mixture in the first bowl was added dropwise to the reaction mixture in the second bowl while cooling (−2–5 °C) and stirring. Cooling stopped. The reaction was stirred at room temperature for 6 h. The formation of new substance in the reaction was monitored by chromatography every hour. A hexane: ethyl acetate ratio of 10:1 was used for this purpose. The solvent was evaporated in a rotary evaporator and the resulting reaction mixture was recrystallized from an organic solvent.

In order to reduce the duration of the reaction and increase the yield of the reaction, without changing the mole ratio, the solutions were added dropwise while stirring at −2–5 °C and carried out in an ultrasonic device at room temperature. The reaction product was monitored every 15 minutes by thin layer chromatography (TLC) for the formation of the N-acyl product. The duration of the reaction was 1 hour. Reactions carried out in an ultrasonic device were chosen as optimal conditions. Acetonitrile and benzene were chosen as solvents for the reactions.

The advantage of this method over the above method is the difference in time, and it is possible to obtain a product with a high yield in a short period of time.

I. Synthesis of 2-Chloro-N-(o-tolyl)-acetamide: The obtained 2-chloro-N-o-tolylacetamide amide melting point and Rf values were determined. Yield 3.07 g (85%). mp 105–106^{0}C., Rf=0,65 1H and 13C NMR were recorded on a JNM-ECZ400R spectrometer (JEOL, Japan) at an operating frequency of 400 MHz for 1H in CD_3OD solutions.d 2.24 (s, 3H, CH3), 4.17 (s, 2H, CH2), 6.95 (d, 2H, H-Ar), 6.85 (d, 2H, H-Ar), 9.9 (s, 1H, NH); 13C NMR spektrum (CD_3OD) 400 MHz 163.86, 135.1, 134.2, 129.7, 120.3, 42.66, 21.0; IR spectra were recorded on an FT-IR/NIR Spectrum 3 spectrometer (Perkin Elmer, Switzerland) using an ATR system. (KBr) ν/cm^{-1}, 3254- (NH), 3134, 3089 (CHAr.), 2953 (CH_2Alip.), 1671 (C=O), 1552 (C=CAr.), 1253 (C–Cl), 864 (CHAr.), 505 (C–CAr.),

II. Synthesis of 2-Chloro-N-(m-tolyl)-acetamide: The obtained 2-chloro-N-m-tolylacetamide amide melting point and Rf values were determined. mp 183–185 °C, Yield 2.88 g. (83%). Rf=0,62. 1H and 13C NMR were recorded on a JNM-ECZ400R spectrometer (JEOL, Japan) at an operating frequency of 400 MHz for 1H in CD_3OD solutions.d 2.19 (s, 3H, CH3), 6.35 (s, 2H, CH2), 6.68 (d, 2H, H-Ar), 10.41 (s, 1H, NH); 13C NMR spektrum (CD_3OD) 400 MHz 162.84, 135.1, 134.2, 129.7, 120.3, 42.66, 21.0; IR spectra were recorded on an FT-IR/NIR Spectrum 3 spectrometer (Perkin Elmer, Switzerland) using an ATR system. (KBr) ν/cm^{-1}, 3253 (NH), 3134, 3091 (CHAr.), 2853 (CHAlip.), 1674 (C=O), 1616 (C=CAr.), 1252 (C–Cl), 864 (CHAr.), 505 (C–CAr.).

III. Synthesis of 2-chloro-N-(p-tolyl)-acetamide. The obtained 2-chloro-N-p-tolylacetamide amide melting point and Rf values were determined. mp 174–175 °C; Yield –3.17 g (88%) Rf=0,73 1H and 13C NMR were recorded on a JNM-ECZ400R spectrometer (JEOL, Japan) at an operating frequency of 400 MHz for 1H in CD3OD solutions.d 2.33 (s, 3H, CH3), 4.17 (s, 2H, CH2), 7.15 (d, 2H, H-Ar), 7.42 (d, 2H, H-Ar), 8.21 (s, 1H, NH); 13C NMR (50 MHz), 163.86, 135.1, 134.2, 129.7, 120.3, 42.66, 21.0; IR spectra were recorded on an FT-IR/NIR Spectrum 3 spectrometer (Perkin Elmer, Switzerland) using an ATR system. (KBr) ν/cm^{-1} 3307, 3203 (NH), 3134, 3089 (CHAr.), 2953 (CHAlip.), 1674 (C=O), 1552 (C=CAr.), 1292, 1252 (C––Cl), 748 (NH), 505 (C–CAr.).

Conclusion

2-chloro-N-(o-tolyl)-acetamide, 2-chloro-N-(m-tolyl)-acetamide, 2-chloro-N-(p-tolyl)-acetamide synthesized from toluidine isomers as chloroacetylation products. The effect of solvent and time on the reaction yield was investigated and the optimum conditions were found. Methods of purification of the obtained substances were determined. The structure of the substances was confirmed by IR and PMR sectors.

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