engineering proceedings

MDPI

Proceeding Paper

Synthesis of Hexamethylenetetramine Mono- and Di(P-Methoxyphenylacetochloride) †

Ruzimurod Jurayev Sattorovich [1,*], Azimjon Choriev Uralivich [2] and Bekzod Eshqulov Ravshan ugli [3]

[1] Department of "Chemical Engineering and Quality Management", Shakhrisabz Branch of Tashkent Institute of Chemical Technology, 20, Shahrisabz Str., Shakhrisabz 181306, Uzbekistan
[2] Department of "Organic Chemistry", Karshi State University, 17, Kuchabog Str., Karshi 180103, Uzbekistan; azimjon-organik@mail.ru
[3] Faculty of Chemical Technology, Shakhrisabz Branch of Tashkent Institute of Chemical Technology, 20, Shahrisabz Str., Shakhrisabz 181306, Uzbekistan; bekzodeshqulov49@gmail.com
* Correspondence: jurayevorganikqdu-1992@mail.ru
† Presented at the 3rd International Electronic Conference on Processes—Green and Sustainable Process Engineering and Process Systems Engineering (ECP 2024), 29–31 May 2024; Available online: https://sciforum.net/event/ECP2024.

Abstract: In this study, hexamethylenetetramine mono- and di(p-methoxyphenylacetochloride) synthesis is presented in a clear and effective manner. Under mild conditions, p-methoxyphenylacetyl chloride and hexamethylenetetramine undergo a synthesis reaction. By adjusting the reactant and reaction conditions, the mono- and di-substituted products were produced selectively. The reaction of 4-methoxyphenylchloroacetate with various amines is a nucleophilic exchange reaction, and it was found that these reactions can proceed under normal conditions at the liquefaction temperature of the solvent. Before carrying out these reactions, the properties of amines were studied briefly. It can be found that the activity of the hydrogen attached to the nitrogen atom of amines depends on the nature of the group attached to the nitrogen. This relationship was expressed by Menshutkin's kinetic equation and Arrinius' equations. In addition, it became known that the reactions can be carried out easily due to the activity of the electrons that are not involved in the bond. To study the reactivity of tertiary amines, uratropin was chosen and its 4-methoxyphenylchloroacetate was reacted at 1:1 and 1:2 ratios, and the products were isolated. When the spectra of the obtained substances were analyzed, it was proven that a new substance was formed with the presence of an absorption region characteristic of the N-substituted amine group.

Keywords: 4-methoxyphenylchloroacetate; uratropin; nucleophilic exchange reaction; Menshutkin's kinetic equation and Arrinius' equations; IR spectrum

check for updates

Citation: Sattorovich, R.J.; Uralivich, A.C.; Ravshan ugli, B.E. Synthesis of Hexamethylenetetramine Mono- and Di(P-Methoxyphenylacetochloride). *Eng. Proc.* **2024**, *67*, 53. https://doi.org/10.3390/engproc2024067053

Academic Editor: Juan Francisco García Martín

Published: 26 September 2024

Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Because of its versatility and reactivity, hexamethylenetetramine (HMT), a heterocyclic amine with a highly symmetrical structure, is essential to organic synthesis. Its capacity to function as a source of formaldehyde is one of its most noteworthy characteristics, which makes it a useful substance in a variety of industrial and medicinal applications. Because of the wide range of derivatives that can be produced, the interaction of HMT with organochlorine compounds—which are composed of chlorine atoms bound to organic frameworks—has garnered a lot of attention [1].

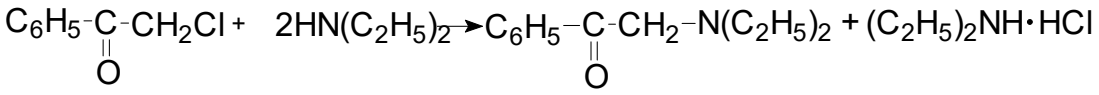
Quaternary ammonium salts, acyl derivatives, and halogenated alcohols are produced by the reactions of HMT with organochlorine chemicals. These derivatives are used to make explosives, specialty polymers, disinfectants, herbicides, and medicines. For example, acyl derivatives have the potential to be exploited as drug synthesis intermediates, and quaternary ammonium salts generated from HMT are used as disinfectants. Furthermore,

materials science makes use of organochlorine compounds changed by HMT, mainly in the creation of flame retardants and high-performance resins [2–4].

The goal of this work is to synthesize new molecules by reacting HMT with different organochlorine chemicals, with a particular focus on comprehending the structural and functional characteristics of these compounds. The aim is to contribute to the expanding field of organochlorine chemistry and investigate the possible uses of these derivatives in sectors like materials science, agriculture, and pharmaceuticals [5,6].

Chemists have discovered that amino compounds, alcohols, phenolates, and carboxylic acids react favorably with haloketones in nucleophilic substitution processes. They discovered that the hydrogen in the amino group can be replaced by a phenacyl group in these processes.

X. Morle and I. Roth [7,8] carried out the reaction of phenacyl chloride and diethylamine.



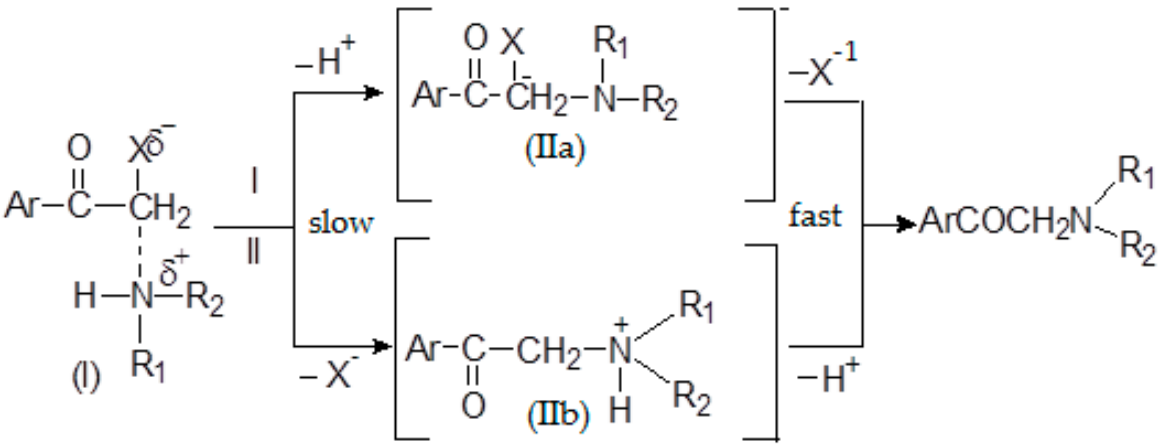
In an ether environment at 20 °C, the following combinations of phenacyl chloride and diethylamine, piperidine, and morpholine showed faster reactions than the others: diethylamine (4 days), 65% yield; piperidine (2 days), 76% yield; and morpholine (1 day), 73% yield.

By reacting piperidine with phenacyl chloride at 20 °C, X. Morle produced N-phenacylpiperidine with an 80% yield.

The type of groups in the aromatic ring affects how the nucleophilic substitution process proceeds. The aromatic ring's electron-acceptor groups [9] promote the development of nucleophilic exchange reactions or the activation of halogen. Groups that donate electrons slow down the nucleophilic substitution process.

However, the authors were still able to obtain a high reaction yield in the presence of groups within the ring that had distinct electron interactions: Ar=C_6H_5- (98%), p-CH_3-C_6H_4- (83%), p-Cl-C_6H_4- (98%), p-Br-C_6H_4- (95%), p-CH_3O-C_6H_4- (98%), m-O_2N-C_6H_4- (98%), p-O_2N-C_6H_4- (98%), p-C_6H_4-C_6H_4- (91%), and α-$C_{10}H_7$-(77%).

The nucleophilic exchange of aniline, primary, and secondary amines with phenacylbromide in nitrobenzene at 25 °C was conducted by the authors [10], who discovered that the reaction could happen in two phases and in two directions. The neutral complex loses a proton in the first direction, resulting in the formation of the negatively charged intermediate product (IIa). Halogen is bound to carbon in the intermediate product before being released into the primary product. In the second pathway, halogen becomes the major product by taking a proton out of the ensuing positively charged complex (IIb) after it has first been separated from the neutral complex:



The characteristics of the chloroacetylation of different phenols and the modification of the resultant chemical were examined in our earlier scientific publications [11–13]. This work is continued in this article. How hexamethylenetetramine and the chloroacetyl product of p-methoxyphen interacted was studied [14,15].

Hexamethylenetetramine is relatively stable and possesses a symmetrical structure similar to that of adamantane, despite the strong reactiveness of the dihetero-substituted methylene groups. Several physicochemical techniques have been used to show that the four nitrogen atoms are chemically and sterically equivalent [16,17].

The hexamethylenetetramine molecule loses its symmetry upon protonation of one nitrogen atom, which may lead to a variety of fragmentation processes that are catalyzed by acids. Two, three, or more carbon–nitrogen subunits may develop depending on the circumstances, or the reagent may function as a source of ammonia and formaldehyde. As a result, the reagent can be utilized to add functional groups to appropriate molecules or to synthesize heterocyclic or alicyclic structures. Moreover, hexamethylenetetramine forms molecular complexes with phenols, naphthols, and alkyl or aryl halides, as well as complex salts with metal ions and organic and inorganic acids. Under different circumstances, these complexes can break down to produce amines, aldehydes, or heterocyclic compounds [18].

2. Experimental

Silufol—254 plates were subjected to thin-layer chromatography (TLC) in order to ascertain the reaction products' composition. In the mobile phase system of methyl alcohol and chloroform (1:10), TLC was utilized to assess the purity of the chemical compounds produced during the process as well as the evolution of the reaction. Aluminum plates covered with silica gel (silica gel 60 F254) purchased from Merck, India, were used as the stationary phase in the TLC process. The products' FT-IR spectra were obtained on a Specord IR-71 spectrophotometer using the KBr pellet technique. TMS was used as the internal standard for the 1H NMR recordings, and chemical shift values were expressed in a ppm scale using a Bruker (Germany) 400 MHz NMR apparatus. The uncorrected melting points of the synthesized compounds were measured using the open capillary technique and an Mvtec melting point apparatus [19–21].

2.1. Synthesis of Hexamethylenetetramine p-Methoxyphenylacetatochloride

A total of 2 g of p-methoxyphenylchloroacetate and 1.4 g of hexamethylenetetramine were placed in a 100 mL flask equipped with a reflux condenser. The reaction mixture was dissolved in 10 mL of chloroform. Then, the flask was heated. The reaction occurs rapidly when heated. The reaction mixture was stirred for 1 h. Then, heating was stopped and cooled to room temperature. The reaction mixture was quenched. As a result, the reaction product precipitated in a solid state, and chloroform, which was used as a solvent, was separated by decantation into a separate container. As a result, the solid residue left at the bottom of the vessel was collected in a petri dish and dried under vacuum conditions. The resulting solid residue had a liquefaction temperature of 110 °C. Product yield was 2.9 g, 86%.

2.2. Synthesis of Hexamethylenetetramine Di(p-Methoxyphenylacetatochloride)

A reflux condenser was fitted to a 100 mL round-bottom flask, and uratropin and p-methoxyphenyl chloroacetate were added in a 1:2 mol ratio. Here, 15 ML of ethyl alcohol were used to dissolve 0.98 g (0.005 mol) of uratropin and 2.005 g (0.01 mol) of p-methoxyphenyl chloroacetate, which were then combined in a flask. For three hours, the reaction mixture was agitated. After the reaction, the reaction mixture was poured into a furfur cup, and the solvent was evaporated under normal conditions. The reaction mixture was cooled to room temperature. Then, it was extracted in chloroform and washed 3 times with distilled water. The reaction product dissolved in chloroform during extraction and was dried with calcium chloride for 1 day (24 h) and filtered after 1 day. Chloroform was distilled off under normal conditions. Hexamethylemtetramine

di(p-methoxyphenylacetatochloride) was the end product that was isolated as a result. Using thin-layer paper chromatography (silica gel 60 F254; methyl alcohol and chloroform (1:10)), an Rf = 0.56452 was achieved as evidence that the product was created. There was a 78% yield.

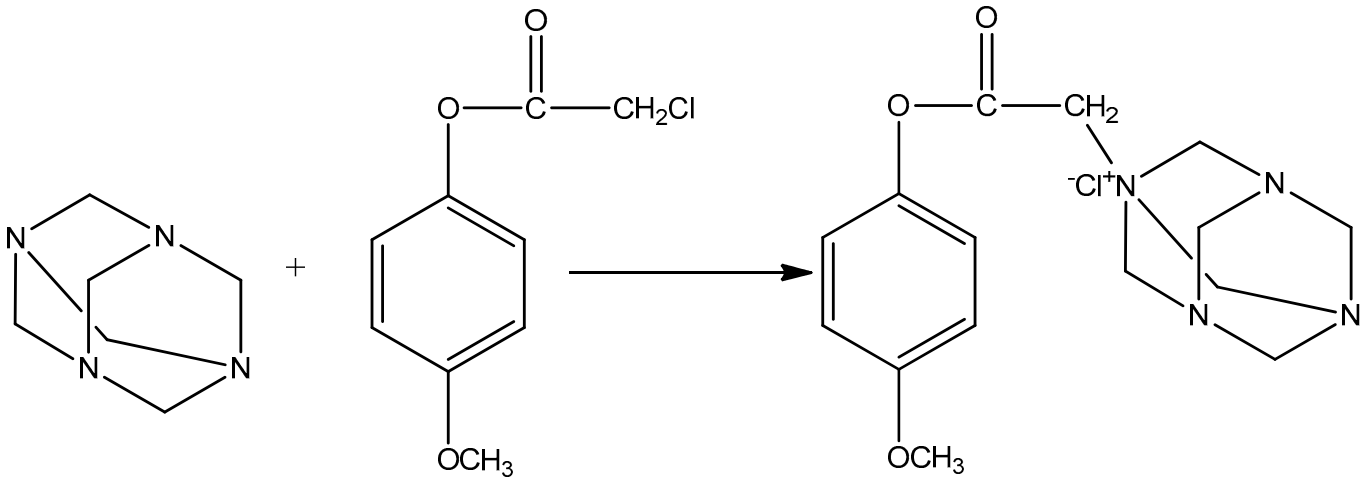
3. Results and Discussion

An amino group can simply replace the halogen atom in the phenyl ethers of α-haloacids because it is more mobile than in halogenoalkanes. The halogen atom's reactivity is greatly influenced by the electron-acceptor carbonyl group in α-halogen ketones, which also helps the halogen ketone react with amines and ammonia.

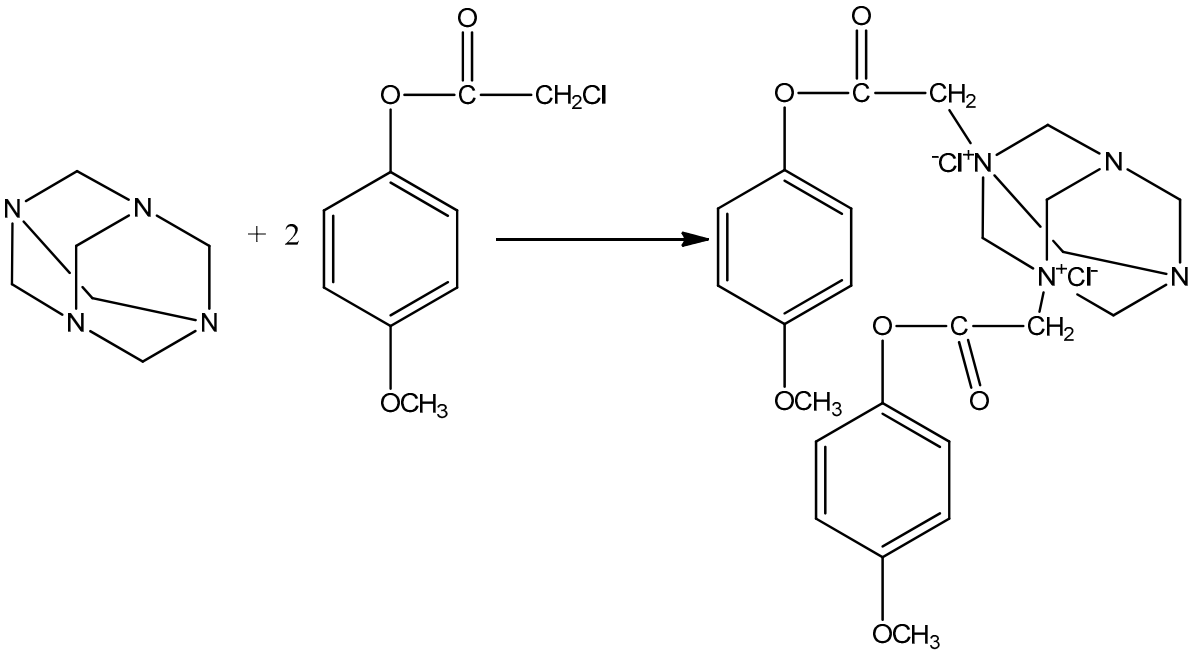
The type of the halogens as well as the atoms and groups of atoms to which the carbon atom attached determine whether a halogen atom is exchanged for an amino group.

It is well recognized from the literature that amino compounds with alkoxy, phenoxy, and acid residues in their molecules exhibit distinct biological activities. Therefore, nucleophilic exchange reactions between p-methoxyphenylchloroacetate, hexamethylenetetramine, and urea were performed in order to generate novel molecules.

In the synthesis of p-methoxyphenylacetate hexamethylenetetramine chloride (1-(2-(4-methoxyphenoxy)-2-oxoethyl)-1,3,5,7-tetraazaadamantan-1-ium chloride), p-methoxyphenylchloroacetate, hexamethylenetetramine, and heptane were used as a solvent. In this case, the reaction went very fast and continued for 3 h, and due to the fact that the starting materials were taken in a 1:1 mol ratio, the quaternary salt-p-methoxyphenylacetate hexamethylenetetramine chloride was obtained with an 86% yield as a reaction product. The resulting quaternary salt has a liquefaction temperature of 110 °C, and due to its hygroscopicity, it liquefied when left in the open air. The reaction proceeded according to the following scheme:



Synthesis of hexamethylenetetramine di(p-methoxyphenylacetatochloride) (1,3-bis(2-(4-methoxyphenoxy)-2-oxoethyl)-1,3,5,7-tetraazaadamantane-1,3-diium chloride); we performed the aforementioned reaction with a 2:1 ratio (p-methoxyphenylchloroacetate:hexamethylenetetramine) because the results were satisfactory, and the procedure proceeded smoothly (it took 4 h).



To confirm that the materials created during the synthesis process were indeed created, physicochemical techniques were applied. The original working substances and the compounds that were produced as a result of the reaction's IR spectra were acquired. The resulting compounds' structures were validated by the spectrum data.

Due to the presence of a benzene ring in the IR spectrum of substances resulting from nucleophilic exchange reactions of p-methoxyphenylchloroacetate with various amines, particularly secondary, tertiary, and quaternary amines, the valence vibration of the C-H bond in the aromatic system (νC-$H_{arom.}$) was 2900–3100 cm^{-1} in the weak region, the valence vibration of the C=C bond of the aromatic ring was 1500–1600 cm^{-1} in the middle region, and the deformation vibration of the C-H bond (δC-$H_{arom.}$) was 900 cm^{-1}. Light absorption was observed in the weak region of 700 cm^{-1}. In the transition region of 1500–1600 cm^{-1}, absorption lines appeared due to the vibration of the aromatic ring skeleton.

Absorption lines can be clearly seen in the intensity region of 1790–1720 cm^{-1} of the valence vibration of the carbonyl group of the synthesized substances (νC=O). Valence vibrations of the ether bond (νC-O-C) were 1240–1190 cm^{-1}, and absorption lines with intensity in the middle region were formed. Two adjacent CH groups in the aromatic ring (1,4-substitutions) gave a vibrational line in the weak region of 1125–1090 cm^{-1}.

Deformation vibration of the C-H bond in the methylene group (δC-H) was observed in the intensive region of 1480–1490 cm^{-1}. In the obtained compounds, the valence vibration range of the C-Cl bond was not determined in the monochloro-substituted alkyl and aryl halides, and the valence vibration characteristic of the C-N group was formed in all of the resulting substances in the average absorption range of 1250–1180 cm^{-1}. In the IR spectrum of the compound formed with tertiary amines, the observation of the absorption region of 1440–1400 cm^{-1}, characteristic of the $–N^{+}$-CH_2- group, confirmed the presence of new substances.

IR spectrum data of p-methoxyphenylchloroacetate (Figure 1): 3452.17 cm^{-1} in the strong–medium-intensity absorption region, with valence vibrations characteristic of an acetyl group at 3112.37, 3072.9, and 3011.65 cm^{-1}. The valence vibration characteristics of the C-H group in the aromatic ring in the medium–weak intensity absorption region were 1598.03, 1509.24, 1455.96, 1465.40, 1441.33, and 1410.82 cm^{-1}. The specific valence vibrations in the aromatic ring in the moderate–weak absorption region of the C=C group were 947.85, 922.51, 826.57, 769.65, 769.83, and 709.45. The deformational vibration characteristics of the C=O group in the absorption region was 1759.51 cm^{-1}. The valence vibration characteristic

of the C-O group in the medium–weak absorption region was 1054.80 cm^{-1}. In the average absorption region of 522.68 cm^{-1}, a vibration characteristic of the C-Cl group was observed.

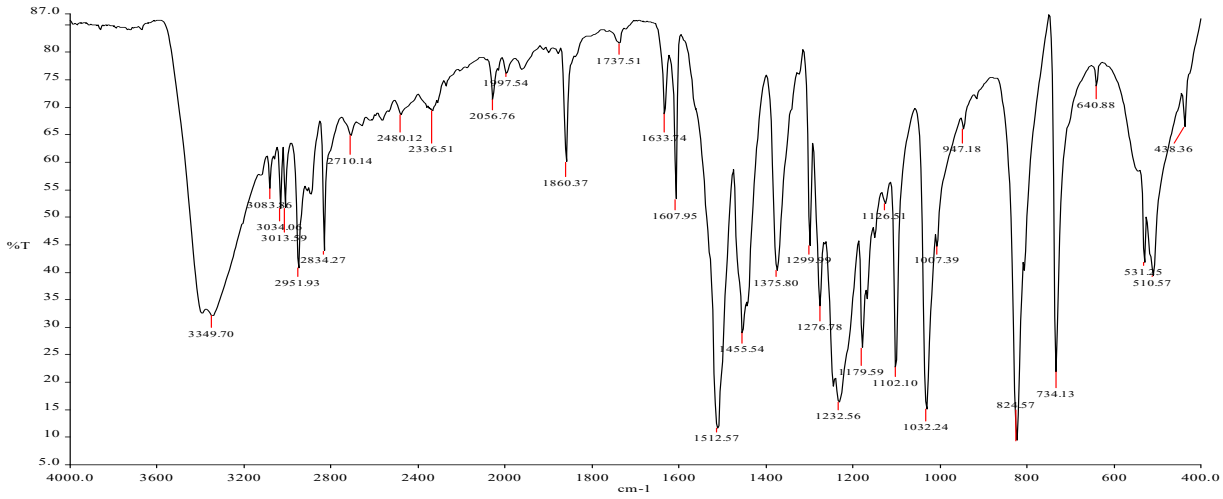


Figure 1. IR spectrum of p-methoxyphenylchloroacetate.

IR spectrum data of p-methoxyphenylacetate hexamethylenetetramine chloride (Figure 2): In the weak absorption region, valence vibration characteristics of the C-H group in the aromatic ring were 3195.51 and 3003.38 cm^{-1}. The asymmetric valence vibrations characteristic of the CH_2 group in the weak absorption region was 2953.51 cm^{-1}. The vibration of the C=O group characteristic of acid properties in the very strong absorption region was 1766.16 cm^{-1}. Deformation vibrations typical of the CH_2-N^+ group were in the absorption region of 1441.70 cm^{-1}. The average weak absorption region vibrations specific to the C-O group of acetals were 1143.07 and 1101.95 cm^{-1}. Valence vibrations characteristic of the C-N group of $ArNR_2$ or $(RCH_2)_3N$ were observed in the absorption region of 1183.14 cm^{-1}.

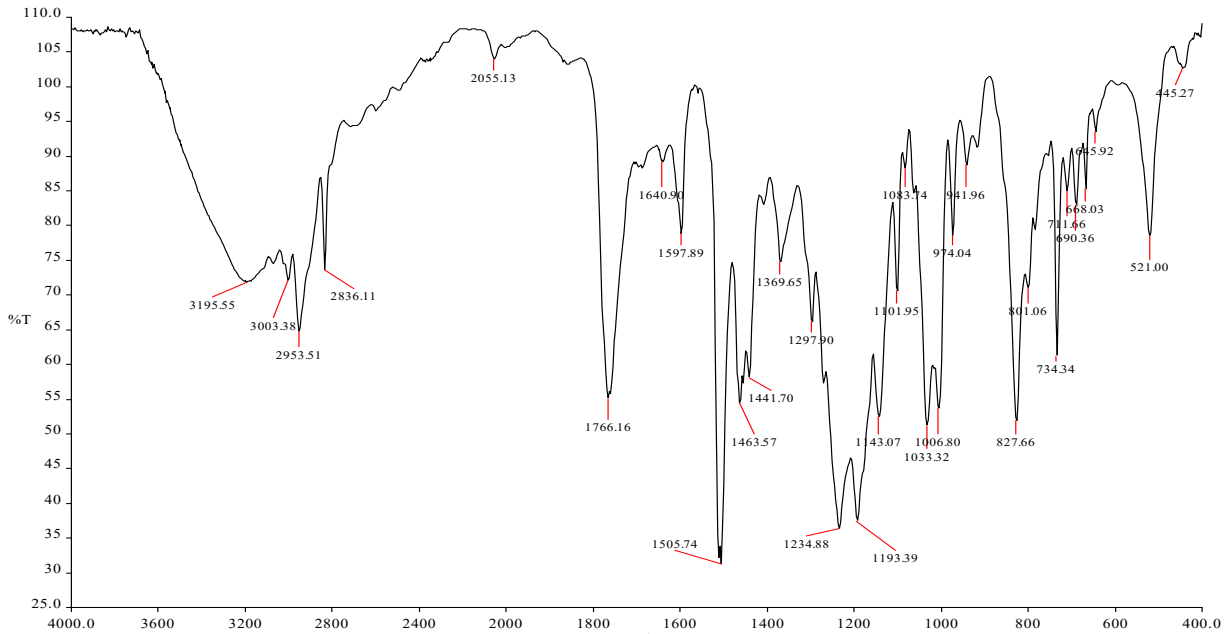


Figure 2. IR spectrum of p-methoxyphenylacetate hexamethylenetetramine chloride.

The ^{13}C NMR spectrum data of p-methoxyphenylacetate hexamethylenetetramine chloride (Figure 3): This spectrum shows that the carbonyl (C=O) group of the acetate

may be represented by the peak at 173 ppm. The methoxy group (-OCH_3) is most likely represented by the peak at 55.97 ppm. The aromatic carbons in the phenyl ring may be responsible for the peaks that range from 115 to 150 ppm. Peaks at 30–40 ppm are indicative of alkyl carbons, which might be the methylene group (-CH_2) of the acetate or the hexamethylenetetramine carbons.

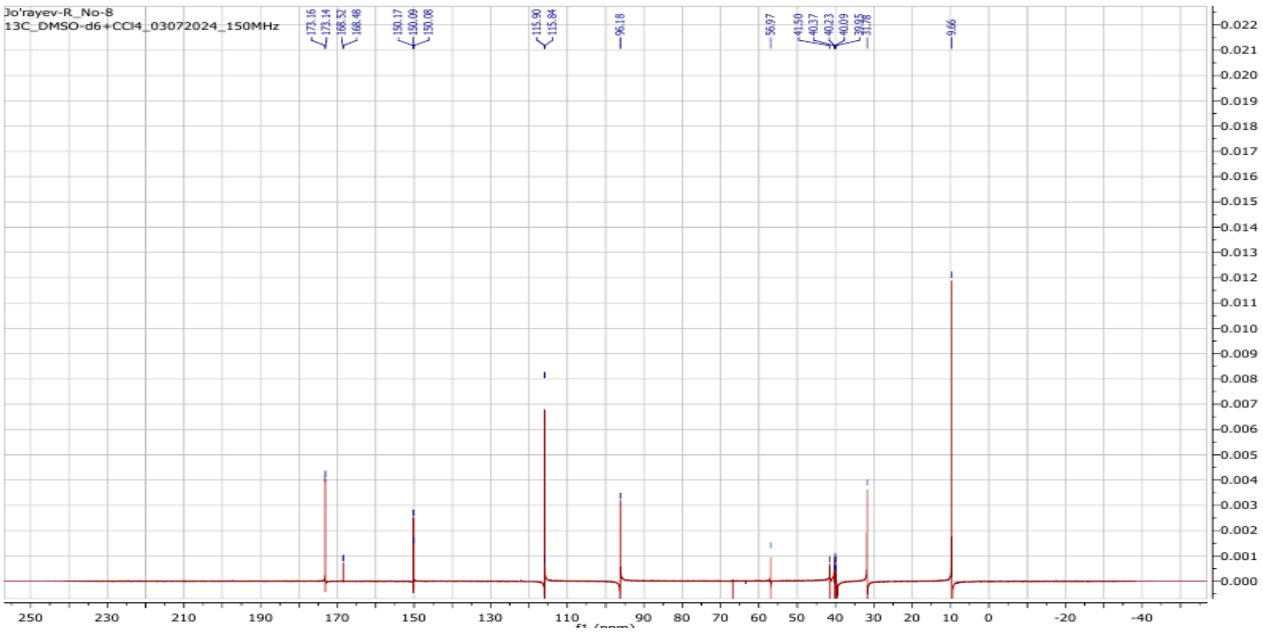


Figure 3. ^{13}C NMR spectrum of p-methoxyphenylacetate hexamethylenetetramine chloride.

The ^{1}H NMR spectrum of p-methoxyphenylacetate hexamethylenetetramine chloride (Figure 4): The methoxy group (-OCH_3) is the source of the signal at about 3.7 ppm. The aromatic protons would be represented by peaks at 7–8 ppm. The peak attributed to the acetate's methylene (-CH_2) group is around 2–3 ppm. Any extra peaks at 1–4 ppm might be the result of protons in the structure of hexamethylenetetramine.

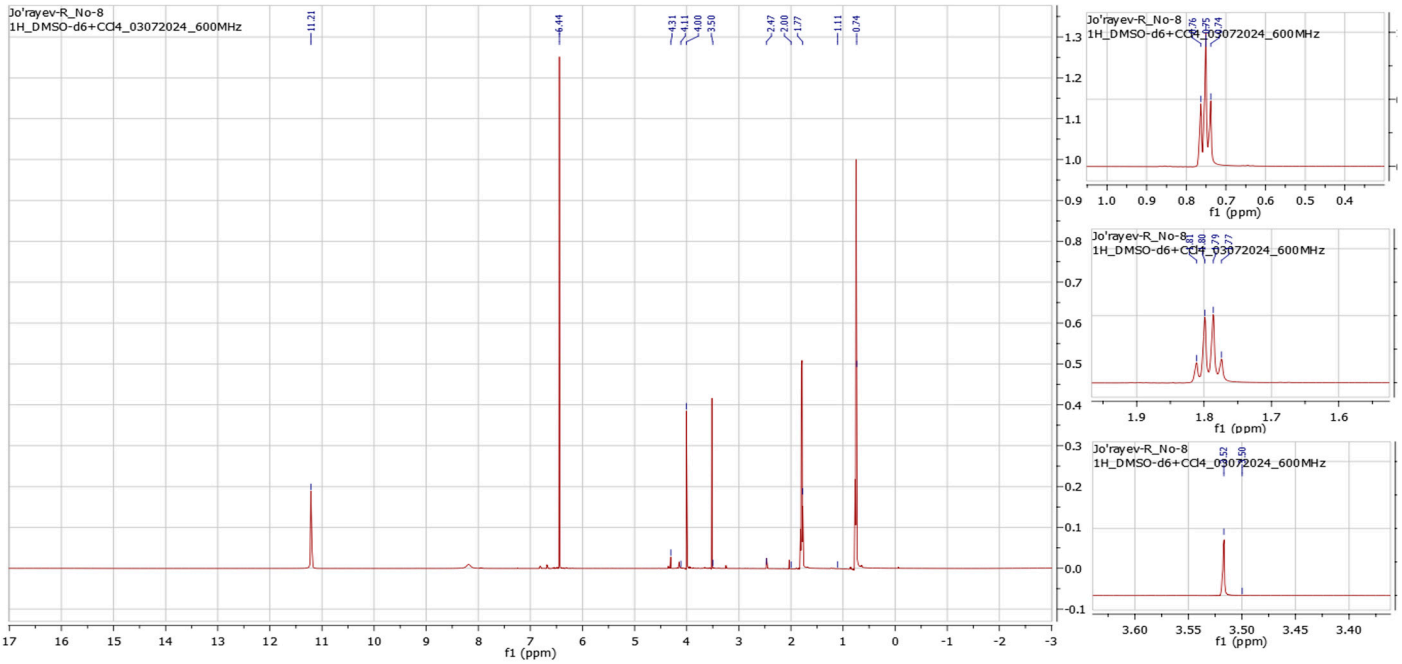


Figure 4. ^{1}H NMR spectrum of p-methoxyphenylacetate hexamethylenetetramine chloride.

4. Conclusions

The reaction of 4-methoxyphenylchloroacetate with various amines is a nucleophilic exchange reaction, and it was found that these reactions proceed under normal conditions at the liquidus temperature of the solvent. To study the reactivity of tertiary amines, uratropin was chosen and its 4-methoxyphenylchloroacetate was reacted with 1:1 and 1:2 ratios, and the products were isolated. When the spectra of the obtained substances were analyzed, it was proved that a new substance was formed with the presence of an absorption region characteristic of the N-substituted amine group.

Author Contributions: Conceptualization, R.J.S.; writing—original draft preparation, R.J.S. and B.E.R.u.; visualization, R.J.S. and A.C.U.; writing—review and editing, R.J.S. and A.C.U.; supervision, A.C.U. and B.E.R.u. contributed equally to this paper. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the Agency of innovative development under the Ministry of Higher Education, Science and Innovation of the Republic of Uzbekistan (Contract No. 65).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: The authors wish to acknowledge the Shahrisabz branch of the Tashkent Institute of Chemical Technology, Shahrisabz, Uzbekistan, and the Karshi State University, Karshi, Uzbekistan.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Mohrle, N.; Roth, I. On the specificity of the TTC reaction. *Arch. Pharm.* **1963**, *12*, 811–819.
2. Morle, N. Preparation of hydroxylactams by mercury (II)-ADTA dehydrogenation. *Arch. Pharm.* **1965**, *298*, 658–663.
3. Raisner, M.; Adlerova, E.; Protiva. Analgesic solution of tetrisine. *Collect. Czechoslov. Chem. Commun.* **1963**, *28*, 1031–1043.
4. Hevnsch, W.; Stumme, W. Reaction of α-chloroacetophenone with n-butylamine. *Chem. Berichte* **1950**, *89*, 2844–2849.
5. Flavio, M. Synthesis of ω-phenacylamino compounds of pharmaceutical interest. *Chimica* **1961**, *37*, 402–404.
6. Sych, E.D.; Moreyko, O.V. Azolocyanine from 35-di-arylthiazolium salts. *Chem. Heterocycl. Compd.* **1970**, *8*, 1034–1036.
7. Maksym, P.; Tarnacka, M.; Bielas, R.; Hachuła, B.; Zajac, A.; Szpecht, A.; Smiglak, M.; Kaminski, K.; Paluch, M. Structure-Property Relationships of Tailored Imidazolium- and Pyrrolidinium-Based Poly(Ionic Liquid)s. Solid-like vs. Gel-like Systems. *Polymer* **2020**, *192*, 122262. [CrossRef]
8. Binks, F.C.; Cavalli, G.; Henningsen, M.; Howlin, B.J.; Hamerton, I. Examining the Kinetics of the Thermal Polymerisation Behaviour of Epoxy Resins Initiated with a Series of 1-Ethyl-3-Methylimidazolium Based Ionic Liquids. *Thermochim. Acta* **2018**, *663*, 19–26. [CrossRef]
9. Shevchuk, M.I.; Dombrovsky, A.V. Preparation of α-monobromomethylaryl ketones by bromination of methylaryl ketones in dioxane. *J. Gen. Chem.* **1963**, *33*, 1135–1136. (In Russian)
10. Litvinenko, L.M.; Perelman, L.A.; Popov, A.F. Deuterium kinetic isotope effect in the reaction of aniline with phenacyl bromide. *J. Org. Chem.* **1972**, *8*, 572–574. (In Russian)
11. Choriev, A.U.; Jurayev, R.S.; Abdushukurov, A.K.; Abdullayev, M.G. Synthesis of 2-Izopropyl-5-methylphenylcarboxymethylen Tartrate. *Eng. Proc.* **2023**, *37*, 57. [CrossRef]
12. Jurayev, R.S.; Choriev, A.U.; Qaxxorov, N.T. The Photometric Determination of Iron(III) with 2-Napthylcarboxymethylene Citrate. *Eng. Proc.* **2023**, *48*, 49. [CrossRef]
13. Jurayev, R.S.; Choriev, A.U.; Qaxxorov, N.T. Effect and Spectroscopic Analysis of Solutions in Trychloratsetylpyrogallol Synthesis. *Chem. Proc.* **2023**, *14*, 80. [CrossRef]
14. Smith, M.B. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 7th ed.; Wiley: Hoboken, NJ, USA, 2013.
15. Carruthers, W.; Coldham, I. *Modern Methods of Organic Synthesis*; Cambridge University Press: Cambridge, UK, 2006.
16. Andersen, A.F. The Crystal Structure of Nickel Acetylacetonate. *Acta Crystallogr.* **1957**, *10*, 107.
17. Veska, L.N.; Cruickshank, D.W.J. The Crystal Structure of Trigonal Selenium. *Acta Crystallogr.* **1961**, *14*, 1092.
18. Ferdeghini, C.; Guazzelli, L.; Pomelli, C.S.; Ciccioli, A.; Brunetti, B.; Mezzetta, A.; Vecchio Ciprioti, S. Synthesis, Thermal Behavior and Kinetic Study of N-Morpholinium Dicationic Ionic Liquids by Thermogravimetry. *J. Mol. Liq.* **2021**, *332*, 115662. [CrossRef]
19. Field, L.D.; Sternhell, S.; Kalman, J.R. *Organic Structures from Spectra*, 3rd ed.; Wiley: New York, NY, USA, 2003.

20. Harwood, L.M.; Claridge, T.D.W. *Introduction to Organic Spectroscopy*; OUP: Oxford, UK, 1996.
21. Silverstein, R.M.; Webster, F.X.; Kiemle, D.J. *Spectrometric Identification of Organic Compounds*; Wiley: New York, NY, USA, 2005.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.