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# SYNTHESIS OF PYRIDINE- AND PIPERIDINE-CONTAINING POLYCYCLIC COMPOUNDS BASED ON 2,6-DINITROHALOGENBENZENES

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*4-chloro-3-nitrobenzoic acid, N-(2,6-dinitroaryl)pyridinium salts, N-(2,6-dinitroaryl)piperidines, nitration, pyridine quaternisation*

***Abstract.*** *This article deals with the study of the nitration of 4-chloro-3-nitrobenzoic acid. The substrate is highly deactivated for $S_EAr$ reactions and therefore strict conditions are required (anhydrous $KNO_3$ in concentrated $H_2SO_4$ at 165 °C for 10 hours). We have developed methods for the transformation of 4-chloro-3,5-dinitrobenzoic acid and its ester into new polycyclic systems containing pyridine or piperidine fragments by quaternization and reduction reactions.*

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## Introduction

2,6-Dinitrohalogenbenzenes are valuable products of organic synthesis as they are used in the preparation of biologically active substances [1-13].

In order to form these compounds, 2,6-dinitrohalogenbenzenes are reacted with heterocyclic fragments or transformed into part of a condensed heterocyclic system. Nitrogen-containing heterocycles are the most important structural components of drugs [14, 15] and piperidine and pyridine are two most common ones [16, 17].

At the same time the synthesis of 2,6-dinitrohalogenbenzenes is difficult because the conventional way of synthesizing nitrohalogenarenes via nitration is unsuitable because of the *meta*-orienting effect of the $NO_2$ group, which leads to isomeric 2,4-dinitroarenes. It increases the cost of substances and prevents the production of a wide range of useful compounds based on them.

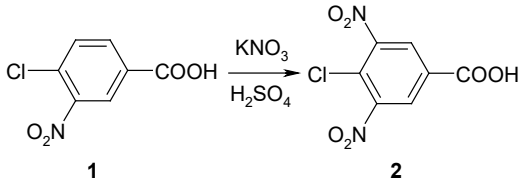
In order to avoid the mentioned problem, it is necessary to block the fourth position of the aroma ring. The carboxylic group is suitable due to several reasons: 1) in 4-halogen-3-nitrobenzoic acid, it orients the entry of the second $NO_2$-group to the desired position, 2) it is able

to undergo chemical transformation to form carboxylic acid derivatives (e.g. esters) and 3) it can be detached during decarboxylation.

The aim of this paper is to develop methods for the transformation of 4-chloro-3-nitrobenzoic acid into 2,6-dinitrohalogenarenes, followed by the introduction of a nitrogen-containing heterocyclic fragment into them.

**Main body**

At the first stage of our research we tested the methodology for the nitration of 4-chloro-3-nitrobenzoic acid (**1**). We considered the deactivating effect of the $NO_2$- and COOH-groups and used anhydrous potassium nitrate on concentrated sulphuric acid:




**1** **2**

Initially we performed the nitration at 120 °C for 5 h at a ratio of substrate to nitrating agent = 1 to 1.2. After the synthesis we cooled the reaction mass and poured it into ice. We filtered off the yellowish precipitation under vacuum, washed it with water and dried in the desiccator. We sampled from the dry residue and analyzed the ratio of the starting **1** to the reaction product 4-chloro-3,5-dinitrobenzoic acid (**2**) by integrating the signals in the $^1$H NMR spectra. The results are presented in Table 1.

**Table 1**. The conversion of 4-chloro-3-nitrobenzoic acid (**1**) to 4-chloro-3,5-dinitrobenzoic acid (**2**) by nitration with potassium nitrate in sulphuric acid

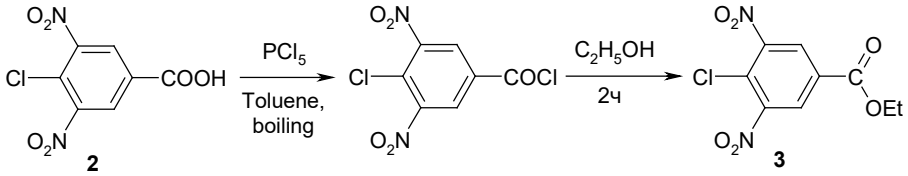
| No. of experiment | Temperature, °C | Reaction time, h | Ratio **1** to **2** |
|---|---|---|---|
| 1 | 120 | 5 | 3 |
| 2 | 140 | 5 | 1.6 |
| 3 | 140 | 8 | 0.38 |
| 4 | 130 | 10 | 0.27 |
| 5 | 140 | 10 | 0.20 |
| 6 | 150 | 10 | 0.15 |
| 7 | 160 | 10 | 0.04 |
| 8 | 165 | 10 | 0.01 |
| 9 | 170 | 7[a] | - |

[a]the reaction mass turned black, so we stopped the experiment.

However, a large part of the substrate remained unreacted (experiment 1). This indicated the low reactivity of acid **1** in $S_EAr$ reactions. Therefore, we changed the temperature and time of the nitration process in order to obtain the desired product.

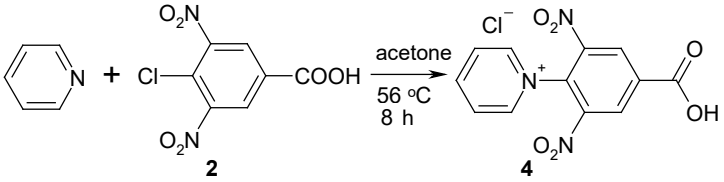
We found that the minimum content of the initial compound was observed during the nitration process for 10 hours at 165 °C and a twofold excess of $KNO_3$ (experiment 8). The product yield was 68%. This low amount of product seems to be caused by destructive oxidation processes in a hot sulphuric acid. A further increase of the temperature of synthesis led to blackening and resinification of the reaction mass (experiment 9).

We then functionalised 4-chloro-3,5-dinitrobenzoic acid (**2**) in a nucleophilic substitution reaction at the acyl carbon atom to give ester **3**:




For this purpose we first converted the substrate to chlorohydride by the action of phosphorus pentachloride. We did not isolate the product, but added dehydrated ethanol directly to the flask and stirred for 2 hours, after which we evaporated the excess alcohol. When cooled, the desired ethyl 4-chloro-3,5-dinitrobenzoate (**3**) crystallised in 82% yield.

Following this we conducted experiments on the formation of quaternary pyridinium salts from **2** and **3** by the pyridine quaternisation reaction:




The process in the case of acid **2** we conducted in a solution of dehydrated acetone under heating and stirring. As the reaction proceeded, particles of the acetone insoluble pyridinium salt **4** appeared in the flask. We cooled the solution after 8 hours and filtered off the yellow precipitate, washed with fresh acetone and dried in the fume cupboard. The yield of N-(4-carboxy-2,6-dinitrophenyl)pyridinium chloride was 80%. The $^1$H NMR spectrum of the product is shown in the Fig. 1.

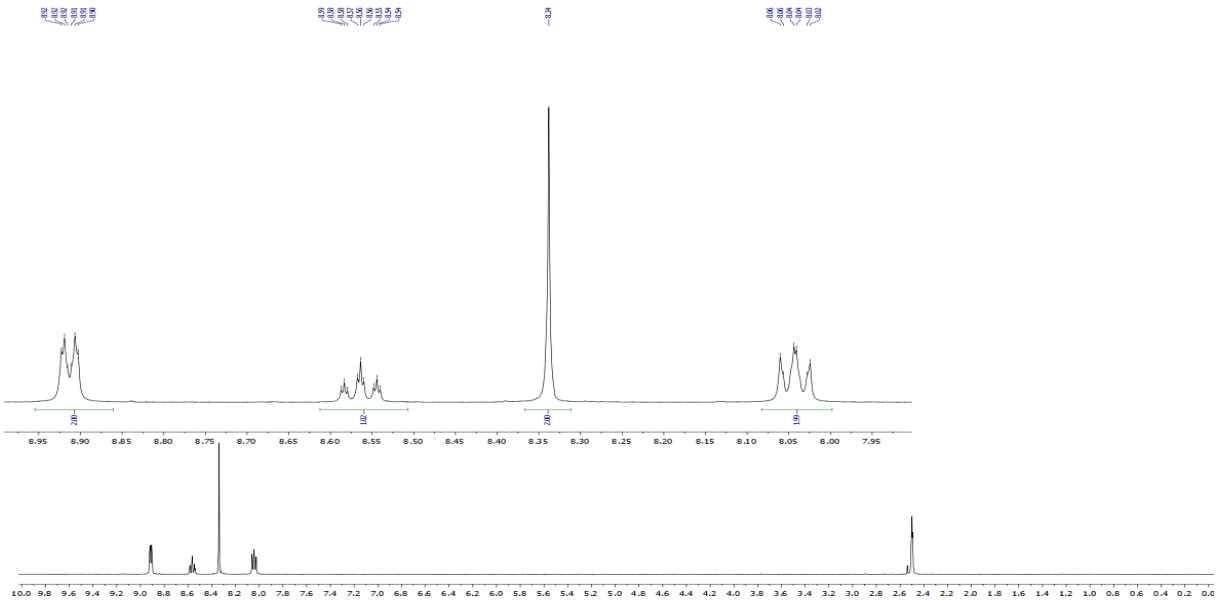
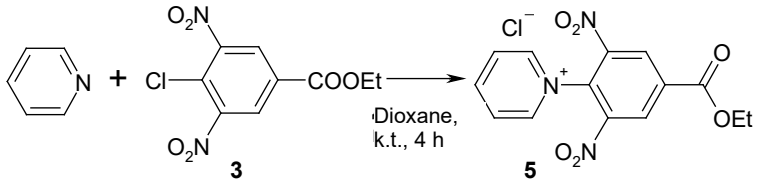


**Fig. 1.** $^1$H NMR spectrum of N-(4-carboxy-2,6-dinitrophenyl)pyridinium chloride (Bruker DRX400, SF=400 MHz, solvent and internal standard DMSO-$d_6$)

The spectrum had 5 signals: 4 in the aromatic region from protons of the phenyl and pyridine fragment and one singlet in the very high frequency region at 11.14 m.p. from the hydrogen atom of the COOH group. All peaks shifted to the weak field region towards benzene due to the strong electron acceptor effect of the functional groups and the endocyclic nitrogen atom carrying the full formal positive charge. Due to its effect on α-carbons, their protons were strongly de-screened and gave doublet of triplets at 8.91 ppm. At slightly lower frequencies the triplet of triplets from hydrogen at the γ-carbon of the pyridinium fragment was located. At 8.34 ppm we observed a singlet from two equivalent hydrogen atoms of the benzene ring having an $NO_2$ at the *ortho*- and *para*-position and a COOH-group at the *ortho*-position. Finally, the strongest field of all signals yielded a peak as a triplet of doublets from the hydrogen β-carbons of pyridine (8.04 ppm).

The quaternisation reaction of pyridine with ethyl 4-chloro-3,5-dinitrobenzoate in acetone under heating resulted as a mixture of hardly separable products. When the process was conducted at room temperature, we were also unable to isolate the desired compound in its pure form. Only a change of solvent to dioxane resulted in N-(4-ethoxycarbonyl-2,6-dinitrophenyl)pyridinium chloride (**5**):




For the compound a $^1$H NMR spectrum was recorded (Fig. 2), where in contrast to compound **4** a peak from the proton of the carboxylic group was absent. We observed an anomaly - the number of signals from protons of the benzene ring and ethyl group was doubled, while the intensity of the two sets was the same, but the second set was shifted relative to the first: the shift was 0.3 ppm for the peaks of the phenyl fragment and $CH_2$-alkyl chain and 0.15 ppm for the $CH_3$-alkyl chain.

This unusual increase in the number of peaks is probably due to the formation of two spatial isomers of N-(4-ethoxycarbonyl-2,6-dinitrophenyl)pyridinium chloride (**5**), which differ by the mutual arrangement of the pyridine and benzene fragments with respect to each other. Their rotation around a simple bond is inhibited by the presence of two nitro groups, which can help anchor the molecules in a particular conformation.

To confirm the resulting structure of N-(4-ethoxycarbonyl-2,6-dinitrophenyl)pyridinium chloride we obtained its mass spectrum with electron impact ionization. We observed a very low intensity of the molecular ion peak (*m/z* 318), indicating a low stability of the quaternary salt during hard ionization. The pyridine fragment with *m/z* 79, the reference peak, was detached from the molecular ion. The resulting cation with *m/z* 239 lost the alkyl chain and a dinitrobenzoic acid radical with *m/z* 211 was formed when the $C_2H_5$ was broken off. The remaining fragmentation ions were of low intensity.

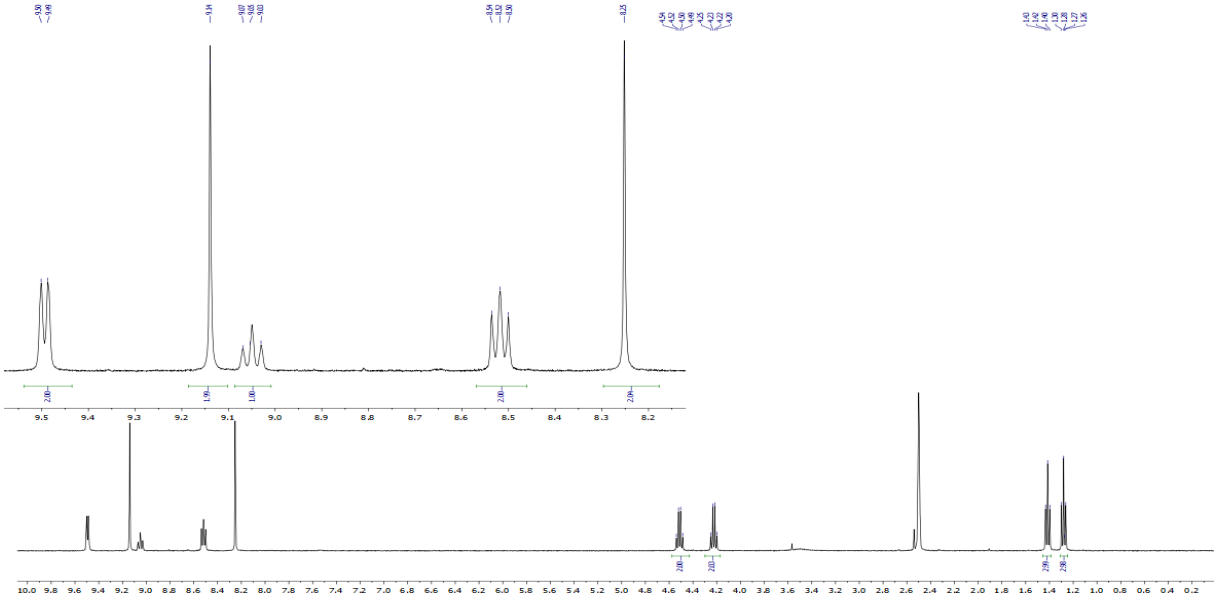
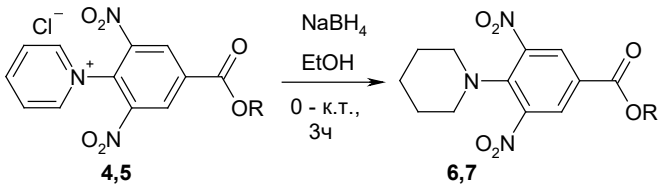


**Fig. 2.** [1]H NMR spectrum of N-(4-ethoxycarbonyl-2,6-dinitrophenyl)pyridinium chloride (Bruker DRX400, SF=400 MHz, solvent and internal standard DMSO-$d_6$)

It is important to note that both pyridinium salts **4** and **5** are not described in the literature (we searched the Reaxys database), that is, they were synthesized for the first time in this work.

We further proposed to perform the reduction of the pyridine cycle on substances **4** and **5** in order to obtain piperidine derivatives. We did this with sodium borohydride in spirit:




**4,5** **6,7**

where in **4,6** R=H, **5,7** R=Et

We conducted the reaction in ethanol at 0 °C for one hour and then at room temperature for another two hours. We took a fourfold excess of $NaBH_4$. This made it possible to synthesize substances **6** and **7** in yields of 77% and 72%.

The compounds were characterized by [1]H NMR spectroscopy. On the proton spectrum of 3,5-dinitro-4-(piperidine-1-yl)benzoic acid, 4 signals were observed (Fig. 3). Two multiplet peaks at 1.55 ppm with an integral intensity of 6 and at 2.98 ppm with an integral intensity of 4 belong to the hydrogen atoms of the piperidine fragment. The signal at 2.98 ppm was obviously given by hydrogen atoms at two α-carbons of the cycle shifted towards the higher frequencies due to the inductive effect of the endocyclic nitrogen atom. In the aromatic region of the spectrum, one singlet at 8.40 ppm was observed from two benzene hydrogen. The H atom of the carboxyl group appeared in the weakest field at 13.70 ppm.

In the [1]H NMR -spectrum of ethyl-3,5-dinitro-4-(piperidine-1-yl)benzoate (**7**) (Fig. 4) in contrast to compound **6** two additional peaks from the ethyl group were present: triplet at 1.32 ppm and quartet at 4.34 ppm. The signals of the finishing fragment and the heterocycle had approximately the same chemical shift values.

Both substances **6** and **7** have only been described in one paper [18] and their NMR spectra have been recorded for the first time.

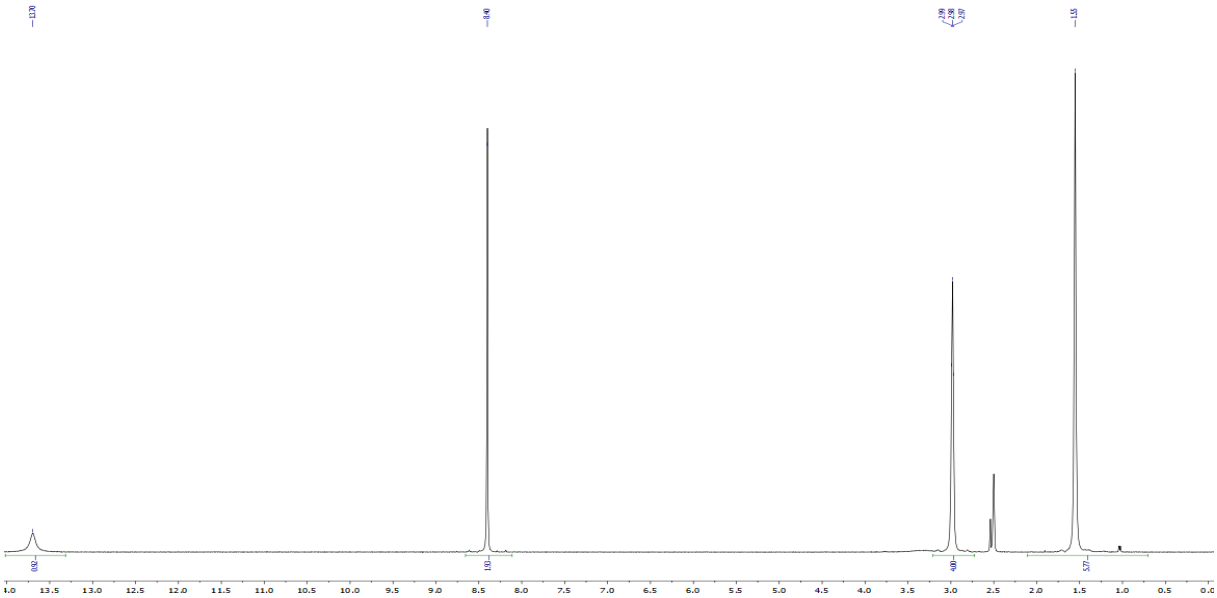


**Fig. 3.** $^1$H NMR spectrum of 3,5-dinitro-4-(piperidine-1-yl)benzoic acid (Bruker DRX400, SF=400 MHz, solvent and internal standard DMSO-$d_6$)

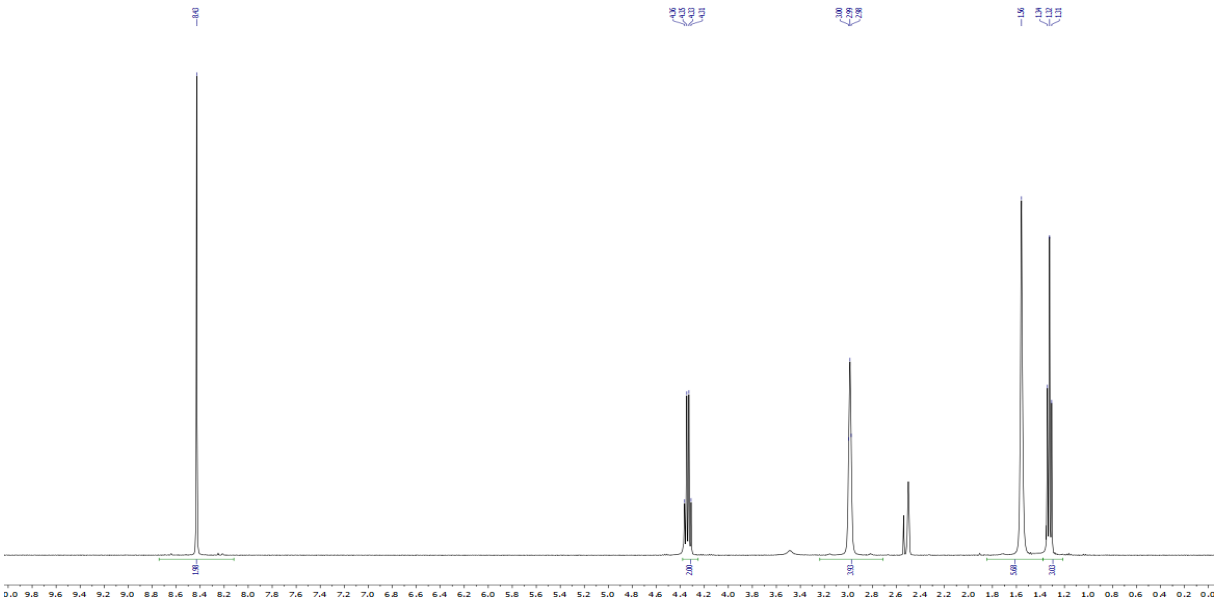


**Fig. 4.** $^1$H NMR spectrum of ethyl 3,5-dinitro-4-(piperidine-1-yl)benzoate (Bruker DRX400, SF=400 MHz, solvent and internal standard DMSO-$d_6$)

As a result of the conducted research we worked out methods, firstly, to prepare 2,6-dinitrohalogenbenzenes, containing carboxylic or ester groups, secondly, to synthesize polyfunctional molecules, containing pyridine or piperidine fragment, on the basis of 2,6-dinitrohalogenbenzenes.

The N-(2,6-dinitrophenyl)piperidines and N-(2,6-dinitrophenyl)pyridinium salts synthesized in this study are interesting as substrates for a possible intramolecular reductive heterocyclization to form 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazoles or pyrido[1,2-*a*]benzimidazoles with high biological activity.

**Experimental part**

We determined the melting points on a PolyTherm A device at a heating rate of 3 °C/min and did not adjust. NMR spectra were recorded on a Bruker DRX-400 for DMSO-$d_6$ solutions. The remaining solvent proton signals in $^1$H NMR (δ 2.50 ppm) were used as the reference for the chemical shift counts. Mass spectra were recorded on a FINNIGAN MAT instrument. INCOS 50, electron flux energy 70 eV.

**Method for the synthesis of compound 2**

In a three-neck flask 4.00 g (19.85 mmol) of 4-chloro-3-nitrobenzoic acid was added and 15 mL of concentrated $H_2SO_4$ was poured. The substrate was dissolved by stirring and heating to 80 °C. Afterwards a solution of 4.01 g (39.66 mmol) of potassium nitrate in 15 mL of concentrated $H_2SO_4$ was added for 10 min. At the end of the addition of the reactant, the flask was heated to 165 °C and the solution stirred for 10 hours. Then the reaction mixture was cooled down to room temperature and poured into ice. The precipitate was filtered off under vacuum and washed with plenty of water to pH = 7. The precipitate was dried in the fume cupboard at 70 °C.

4-chloro-3,5-dinitrobenzoic acid (**2**). The yield is 3.35 g (68%). $T_{melt}$ = 159–162 °C. Spectrum $^1$H NMR (DMSO-$d_6$, 400 MHz) δ, ppm.: 8.76 s (2H, H$^2$, H$^6$), 13.98 s (COO<u>H</u>).

**Method for the esterification of 4-chloro-3,5-dinitrobenzoic acid**

In a three-necked flask 10.04 g (40.73 mmol) of 4-chloro-3,5-dinitrobenzoic acid was added and 50 mL toluene was added. It was heated until dissolved under stirring and 8.90 g (42.77 mmol) phosphorus pentachloride ($PCl_5$) was added in portions. After the gas (HCl) release was finished, the solution was heated to boiling and evaporated to ~10 mL. Then 20 ml of absolute ethanol was added to the flask. The resulting solution was stirred for 2 hours. The precipitate was filtered off under vacuum and washed with absolute alcohol. The precipitate was dried in the fume cupboard at 70 °C.

Ethyl 4-chloro-3,5-dinitrobenzoate (**3**). The yield is 9.20 g (82%). $T_{melt.}$ = 81–83 °C. Spectrum $^1$H NMR (DMSOO-$d_6$, 400 MHz) δ, ppm: 1.36 t (3H, $CH_3$, $J$ 7.1 Hz), 4.40 qu (2H, $CH_2$, $J$ 7.1 Hz), 8.81 s (2H, H$^2$, H$^6$).

**Method for the preparation of quaternary pyridinium salts from 4-chloro-3,5-dinitrobenzoic acid and its ester**

In a three-necked flask 2.00 g (8.11 mmol) of 4-chloro-3,5-dinitrobenzoic acid was added, 10 mL acetone and 1.3 mL (16.2 mmol) pyridine were added. The reaction mass was heated under stirring to 56 °C and the reaction was conducted for 8 hours. The solution was cooled down to room temperature and the precipitate was filtered off under vacuum and washed with dehydrated acetone. The precipitate was dried in the fume cupboard at 70 °C.

N-(4-carboxy-2,6-dinitrophenyl)pyridinium chloride (**4**). The yield is 2.13 g (80%). $T_{melt}$ = 174.5–178.5 °C. Spectrum $^1$H NMR (DMSO-$d_6$, 400 MHz) δ, ppm: 8.04 td (2H, H$^3$, H$^5$, $J$ 6.6, 1.6 Hz), 8.34 s (2H, H$^{3'}$, H$^{5'}$), 8.56 tt (1H, H$^4$, $J$ 7.8, 1.6 Hz), 8.91 dt (2H, H$^2$, H$^6$, $J$ 5.0, 1.6 Hz), 11.14 s (COOH).

In a three-necked flask 2.00 g (7.3 mmol) of ethyl 4-chloro-3,5-dinitrobenzoate was added and 10 mL of dioxane was added. After dissolution of the substrate, 0.8 mL (9.9 mmol) of pyridine was added and stirred for 4 hours at room temperature. The precipitate was filtered off under vacuum and washed with absolute alcohol. The precipitate was dried in the fume cupboard at 70 °C.

N-(4-ethoxycarbonyl-2,6-dinitrophenyl)pyridinium chloride (**5**). The yield is 2.03 g (79%). $T_{melt}$ = 215.5–219.5 °C. Spectrum $^1$H NMR (DMSO-$d_6$, 400 MHz) δ, ppm: 1.28 t (3H, $CH_3$, *J* 7.1 Hz), 1.42 t (3H, $CH_3$, *J* 7.1 Hz), 4.22 qu (2H, $CH_2$, *J* 7.1 Hz), 4.52 qu (2H, $CH_2$, *J* 7.1 Hz), 8.25 s (2H, 2H, $H^{3'}$, $H^{5'}$), 8.52 t (2H, $H^3$, $H^5$, *J* 7.8), 9.05 t (1H, $H^4$, *J* 7.8 Hz), 9.14 s (2H, $H^{3'}$, $H^{5'}$), 9.49 d (2H, $H^2$, $H^6$, *J* 5.6 Hz).

**Method for the reduction of the quaternary salts of pyridinium**

N-(4-ethoxycarbonyl-2,6-dinitrophenyl)pyridinium chloride or N-(4-carboxy-2,6-dinitrophenyl)pyridinium chloride (24 mmol) was dissolved in 20 ml $C_2H_5ON$, then 3.65 g sodium borohydride (96 mmol) was added in portions at 0 °C. The mixture was continued to stir at 0 °C for 1 h and then at room temperature for 2 h. The solvent was evaporated at reduced pressure, then 5 ml water was added. The mixture was extracted with $CHCl_3$ (3×10 mL). The combined organic phases were dried over $Na_2SO_4$ and evaporated. The remaining product was purified by recrystallisation in isopropyl alcohol to obtain the desired products.

3,5-Dinitro-4-(piperidine-1-yl)benzoic acid (**6**). The yield is 77%. $T_{melt}$ = 226–228.5 °C. Spectrum $^1$H NMR (DMSO-$d_6$, 400 MHz) δ,ppm: 1.55 m (6H, piperidine), 2.98 m (4H, piperidine), 8.40 s (2H, $H^{2,6}$), 13.70 s (1H, COOH).

Ethyl 3,5-dinitro-4-(piperidine-1-yl)benzoate (**7**)**.** The yield is 72%. $T_{melt}$ = 88–92.5 °C. Spectrum $^1$H NMR (DMSO-$d_6$, 400 MHz) δ, ppm: 1.32 t (3H, $CH_3$, *J* 7.1 Hz), 1.56 m (6H, piperidine), 2.99 m (4H, piperidine), 4.34 qu (2H, $CH_2$, *J* 7.1 Hz), 8.43 s (2H, $H^{2,6}$).

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**References**

1. **Rehman, A., Hussain, M., Rehman, Z., Ali, S., Rauf, A., Nasim, F.H. & Helliwell, M.** (2011) Self-assembled pentagonal bipyramidal and skew trapezoidal organotin(IV) complexes of substituted benzoic acids: Their antibacterial, antifungal, cytotoxic, insecticidal and urease inhibition activities, *Inorg. Chim. Acta,* 370, pp. 27-35. DOI: 10.1016/j.ica.2011.01.007 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0020169311000144
2. **Gautam, N., Goyal, K., Saini, O., Kumar, A. & Gautam, D.C.** (2011) Synthesis and biological activity of substituted 3-fluoro/3-trifluoromethyl 10H-phenothiazines, its ribofuranosides and sulfones, *J. Fluor. Chem*., 132, pp. 420-426. DOI: 10.1016/j.jfluchem.2011.04.012 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0022113911001230
3. **Remes, C., Paun, A., Zarafu, I., Tudose, M., Caproiu, M.T., Ionita, G., Bleotu, C., Matei, L. & Ionita, P.** (2012) Chemical and biological evaluation of some new antipyrine derivatives with particular properties, *Bioorg. Chem*., 41-42, pp. 6-12. DOI: 10.1016/j.bioorg.2011.12.003 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0045206811001064?via%3Dihub

4. **Jangid, D.K., Guleria, A., Gautam, D.C., Yadav, H., Mathur, M. & Swami, A.K.** (2019) Antimicrobial studies, synthesis and characterization of novel 1-nitro-10H-phenothiazine bearing sulfone/nucleoside moieties, *Nucleosides, Nucleotides and Nucleic Acids,* 38, pp. 533-549. DOI: 10.1080/15257770.2019.1576879 [online]. Available at: https://www.tandfonline.com/doi/abs/10.1080/15257770.2019.1576879
5. **Al-Hiari, M., Qaisi, A.M., El-Abadelah, M.M. & Voelter, W.** (2006) Synthesis and Antibacterial Activity of Some Substituted 3-(Aryl)- and 3-(Heteroaryl)indoles, *Monatshefte für Chemie*, 137, pp. 243–248. DOI: 10.1007/s00706-005-0424-6 [online]. Available at: https://link.springer.com/article/10.1007/s00706-005-0424-6
6. **Gautam, N., Gupta, S., Ajmera, N. & Gautam, D.C.** (2012) Synthesis, Characterization, and Biological Evaluation of 10H-Phenothiazines, Their Sulfones and Ribofuranosides, *J. Heterocycl. Chem*., 49, pp. 710-715. DOI: https: 10.1002/jhet.771 [online]. Available at: https://onlinelibrary.wiley.com/doi/full/10.1002/jhet.771
7. **Zhang, B., Pang, L., Nautiyal, M., Graef, S.D., Gadakh, B., Lescrinier, E., Rozenski, J., Strelkov, S.V., Weeks, S.D. & Aerschot, A.V.** (2020) Synthesis and Biological Evaluation of 1,3-Dideazapurine-Like 7-Amino-5-HydroxymethylBenzimidazole Ribonucleoside Analogues as Aminoacyl-tRNA Synthetase Inhibitors, *Molecules,* 25, pp. 1-24. DOI: 10.3390/molecules25204751 [online]. Available at: https://www.mdpi.com/1420-3049/25/20/4751
8. **Sykes, B.M., Atwell, G.J., Hogg, A., Wilson, W.R., O'Connor, C.J. & Denny, W.A.** (1999) N-Substituted 2-(2,6-Dinitrophenylamino)propanamides: Novel Prodrugs That Release a Primary Amine via Nitroreduction and Intramolecular Cyclization, *J. Med. Chem*., 42, pp. 346-355. DOI: 10.1021/jm960783s [online]. Available at: https://pubs.acs.org/doi/10.1021/jm960783s
9. **Baguley, T.D., Nairn, A.C., Lombroso, P.J. & Ellman, J.A.** (2015) Synthesis of benzopentathiepin analogs and their evaluation as inhibitors of the phosphatase STEP, *Bioorg. Med. Chem. Lett*., 25, pp. 1044-1046**.** DOI: 10.1016/j.bmcl.2015.01.020 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0960894X15000323?via%3Dihub
10. **Molteni, V., He, X., Nabakka, J., Yang, K., Kreusch, A., Gordon, P., Bursulaya, B., Warner, I., Shin, T., Biorac, T., Ryder, N.S., Goldberg, R., Doughtyc, J. & He, Y.** (2004) Identification of novel potent bicyclic peptide deformylase inhibitors, *Bioorg. Med. Chem. Lett*., 14, pp. 1477–1481. DOI: 10.1016/j.bmcl.2004.01.014 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0960894X04000502?via%3Dihub
11. **Kojima, T., Mochizuki,M., Takai, T., Hoashi, Y., Morimoto, S., Seto, M., Nakamura, M., Kobayashi, K., Sako, Y., Tanaka, M., Kanzaki, N., Kosugi, Y., Yano, T. & Aso, K.** (2018) Discovery of 1,2,3,4-tetrahydropyrimido[1,2-*a*]benzimidazoles as novel class of corticotropin releasing factor 1 receptor antagonists, *Bioorg. Med. Chem*., 26, pp. 2229-2250. DOI: 10.1016/j.bmc.2018.01.020 [online]. Available at: https://www.sciencedirect.com/science/article/pii/S0968089617323374?via%3Dihub
12. **Mochizuki, M., Kori, M., Kobayashi, K., Yano, T., Sako, Y., Tanaka, M., Kanzaki, N., Gyorkos, A.C., Corrette, C.P., Cho, S.Y., Pratt, S.A. & Aso, K.** (2016) Design and synthesis of benzimidazoles as novel corticotropin-releasing factor 1 receptor antagonists, *J. Med. Chem*., 59(6), pp. 2551–2566. DOI: 10.1021/acs.jmedchem.5b01715 [online]. Available at: https://pubs.acs.org/doi/10.1021/acs.jmedchem.5b01715
13. **Zheng, Z., Bhatia, P., Daanen, J., Kolasa, T., Patel, M., Latshaw, S., Kouhen, O.F.E., Chang, R., Uchic, M.E., Miller, L. , Nakane, M., Lehto, S.G., Honore, M.P., Moreland, R.B., Brioni, J.D. & Stewart, A.O.** (2005) Structure-Activity Relationship of Triazafluorenone Derivatives as Potent and Selective mGluR1 Antagonists, *J. Med. Chem.,* 48, pp. 7374-7388. DOI: 10.1021/jm0504407 [online]. Available at: https://pubs.acs.org/doi/10.1021/jm0504407
14. **Filimonov, S.I., Makarova, E.S., Chirkova, J.V. & Kabanova, M.V.** (2022) Diastereomeric composition of the reaction of the formation of hexahydro-5h-chromeno[4,3-*d*]pyrimidin-5-ones, *From Chemistry Towards Technology Step-By-Step,* 3(1), pp. 131-138. DOI: 10.52957/27821900_2022_01_131 [online]. Available at: http://chemintech.ru/index.php/tor/2022tom3no1.
15. **Kotov, A.D., Kunichkina, A.S. & Peoskurina, I.K.** (2022) Transformation of 5-halogen-3-aryl-2,1-benzisoxazoles into quinazolines, *From Chemistry Towards Technology Step-By-Step,* 2(4), pp. 81-84. DOI: 10.52957/27821900_2021_04_81 [online]. Available at: http://chemintech.ru/index.php/tor/2021-2-4
16. **Begunov, R.S. & Sokolov, A.A.** (2022) One-pot Reduction and Halogenation of N-(2,4-dinitrophenyl)piperidine, *From chemistry towards technology. Step-by-step,* 3(2), pp. 92-97. DOI: 10.52957/27821900_2022_02_92 [online]. Available at: http://chemintech.ru/index.php/tor/2022tom3no2.

17. **Vitaku, E., Smith, D.T., Njardarson, J.T.** (2014) Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals, *J. Med. Chem.,* 57( 24), pp. 10257-10274. DOI: 10.1021/jm501100b [online]. Available at: https://pubs.acs.org/doi/10.1021/jm501100b
18. **Van Duin, H**. (1954) The separation and identification of normal aliphatic alcohols, *Recueil des Travaux Chimiques des Pays-Bas*., 73, pp. 68-77. DOI: 10.1002/recl.19540730111 [online]. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/recl.19540730111.

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