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Synthesis of Nitrogen-Functionalized N-aryl-2-formylpyrroles by the Yuryev Reaction

Darya S. Volkova*[a], Evgeniy V. Root[a, b], Alexey A. Kukushkin[a], Anna V. Ignatyuk[b] and George A. Suboch[a]

[a]*Reshetnev Siberian State University of Science and Technology Krasnoyarsk, Russian Federation*

[b]*Krasnoyarsk State Medical University named after Prof. V.F. Voino-Yasenetsky Krasnoyarsk, Russian Federation*

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Abstract. The Yuryev reaction was modified by replacing ammonia with aniline derivatives containing electron acceptors in the aromatic core: 2,4-dinitroaniline, p-nitrozoaniline, 4-aminoazobenzene. Under mild conditions of the reaction of furfural with p-aminoazobenzene and p-nitrozoaniline, a more stable intermediate compound, the Stenhouse salt, is formed, therefore, more stringent conditions were used to obtain the target nitrogen-functional N-aryl-2-formylpyrroles. As a result of mastering two techniques, 1-(2,4-dinitrophenyl)-2-formylpyrrol, 1-(4-nitrosophenyl)-2-formylpyrrol, 1-{4-[(E)-phenylazo]-phenyl}-2-formylpyrrol, potentially showing useful biological activity, were synthesized.

Keywords: formylpyrroles, furfural, Yuryev reaction, N-substituted pyrroles, nitrogen-containing substituents, pyrrolal-2, PASS-online.

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* Corresponding author E-mail address: 2198vds@gmail.co

Синтез азотфункционализированных N-арил-2-формилпирролов по реакции Юрьева

Д. С. Волкова[a]*, Е. В. Роот[a, б], А. А. Кукушкин[a], А. В. Игнатюк[б], Г. А. Субоч[a]
[a]Сибирский государственный университет науки и технологий им. академика М. Ф. Решетнева Российская Федерация, Красноярск
[б]ФГБОУ ВО КрасГМУ им. проф. В. Ф. Войно-Ясенецкого Минздрава России Российская Федерация, Красноярск

Аннотация. Проведена модификация реакции Юрьева путем замены аммиака на анилин-производные, содержащие в ароматическом ядре электроноакцепторы: 2,4-динитроанилин, п-нитрозоанилин, 4-аминоазобензол. В мягких условиях реакции фурфурола с п-аминоазобензолом и п-нитрозоанилином образуется более устойчивое промежуточное соединение – соль Стенхауза, поэтому для получения целевых азотфункционированных N-арил-2-формилпирролов применялись более жесткие условия. В результате освоения двух методик синтезированы 1-(2,4-динитрофенил)-2-формилпиррол, 1-(4-нитрозофенил)-2-формилпиррол, 1-{4-[(E)-фенилазо]-фенил}-2-формилпиррол, потенциально проявляющие полезную биологическую активность.

Ключевые слова: формилпирролы, фурфурол, реакция Юрьева, N-замещенные пирролы, азотсодержащие заместители, пирролаль-2, PASS-online.

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Introduction

The heteroatom substitution reactions discovered by Yu. K. Yuryev are a convenient method for the synthesis of a wide variety of thiophene, pyrrole and furan derivatives. The conversion of furan and its derivatives into pyrrole can be modified by replacing ammonia with various amines. N-substituted pyrroles are obtained in this way [1–3].

Among furan derivatives, available furfural is distinguished, which is widely used to produce various furan derivatives and other heterocyclic compounds [4–6].

The production of 1-(4-nitrophenyl)-pyrrole-2 from furfural and p-nitroaniline using ethanol as a solvent is known [7, 8]. Later, a technique was proposed that differs in the conditions of the reaction [9]. According to the authors, both methods provide a quantitative yield of the product, but the isolation stage is significantly problematic.

Under similar synthesis conditions, with the ratio of pyrrole-amino-acid reagents (1:2:1), the best results were for anilines having acceptor substituents in the aromatic core [10]. The authors of [11] have shown that when furforol interacts with aromatic amines, Stenhouse salts are formed as intermediates, which, when hydrochloric acid is added, leads to the closure of the pyrrole cycle and the formation of the final product of the reaction – 1-arylpyrrolal-2.

Many pyrrole derivatives have useful biological activity and are part of medicines it is known. Therefore, taking into account the practical significance of pyrrole derivatives in the pharmaceutical industry [12], the purpose of this research is to expand the preparative capabilities of the Yuryev reaction by introducing electron acceptor substituents into the arylpyrrole molecule and predicting the beneficial biological activity of the compounds obtained.

Results and discussion

The modification of the Yuryev reaction is characterized by the simplicity of synthesis, relatively high yields and availability of reagents such as furfural and anilines, therefore, for the synthesis of new N-aryl-2-formylpyrroles, the replacement of a heteroatom in the furfural core was chosen when interacting with various aniline derivatives.

Furfural is of interest to researchers by the presence of an active carbonyl group in the core, which suggests the possibility of further modification of compounds [13]. Azomethines based on N-aryl-2-formylpyrroles can be formed with aromatic amines. The carbonyl group in PFA migrates to position 3, forming isomers of N-arylated formylpyrroles. Condensation reactions on the carbonyl group with aniline derivatives are known: 2,4-dinitroaniline, p-nitrozoaniline, 4-aminoazobenzene [7, 9].

The study of new furfural transformations is assumed according to the scheme (Fig. 1):

To study the possibility of synthesis of nitrogen-functionalized N-aryl-2-formylpyrroles, aromatic amines containing groups (–NO_2, –NO, –N=N–Ph) were used (Table 1).

The reaction was monitored using TLC (hexane-ethyl acetate 3:1). It was possible to isolate a new product with a yield of 14 % only in the synthesis of 1-(2,4-dinitrophenyl)-2-formylpyrrol in preliminary experiments The structure of the compound obtained for the first time was proved by mass spectrometry: the peak of the molecular ion corresponding to the molar mass of 1-(2,4-dinitrophenyl)-2-formylpyrol (m/z 261) was determined. The small yield is probably due to the presence of the ortho-effect of the nitro group of the initial 2,4-dinitroaniline [14–16].

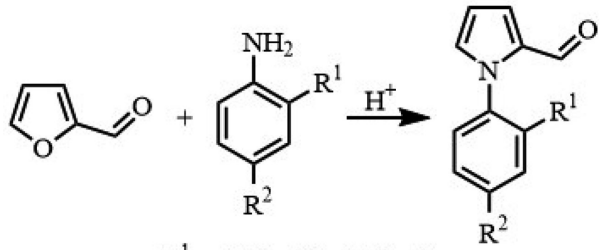

Fig. 1 Condensation of furfural with substituted aromatic amines

In the studied conditions, according to the method [8], with p-aminoazobenzene and p--nitrozoaniline, the target N-aryl-2-formylpyrroles could not be isolated, most likely this is due to the formation of a more stable Stenhouse salt, the hydrolysis of which to N-aryl-2-formylpyrroles does not take place under mild conditions [11]. The Stenhouse salt is an intermediate of all the condensation reactions of furan and aniline derivatives, only in the case of the interaction of furfural with p-aminoazobenzene and p-nitrozoaniline it turns out to be stable enough for these reactions to end with its formation.

Further studies of the condensation of furfural with 4-nitrosoaniline and 4-aminoazobenzene were carried out under more stringent conditions (Fig. 2) [11].

The reaction was monitored using TLC (hexane-ethyl acetate 2:1), the formation of target N-aryl-2-formylpyrroles was observed in all cases. The structure of the new substances was proved by mass spectrometry methods, in which the peaks of molecular ions of compounds corresponding to molar masses (m/z 200) and (m/z 275) were determined.

The yields of synthesized substances by two methods are presented in Table 1.

The main ways of fragmentation of 1-(2,4-dinitrophenyl)-pyrrole are associated with the loss of one hydrogen atom, followed by the elimination by the F_2 ion of substituents $-NO_2$ and then the CO molecule (ions F_2 и F_5) (Fig. 3). Cleavage of the aryl residue from the F_1 ion is also observed (F_4). An independent pathway of fragmentation of the M^+ ion is the loss of the substituent $-NO_2$ (ion F_3). Rearrangement ions of M-NO, characteristic of nitroarenes, are completely absent, as well as ions (M-H-CO), the intensity of peaks of which is very high in the mass spectra of formylindoles.

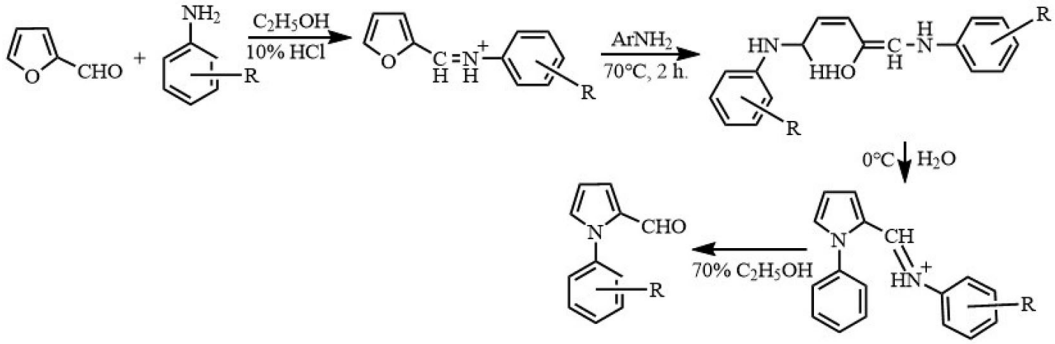

Fig. 2. Formation of N-aryl-2-formylpyrroles through Stenhouse salt

Table 1. Comparison of reaction yields by two methods

Substances	Yield by methods, (%)	
	A (10% HCl, 70°C, 2 h.)	B (2N HCl, 70°C, 5 h., PhH)
1-(2,4-dinitrophenyl)-2-formylpyrrol	14	-
1-(4-nitrosophenyl)-2-formylpyrrol	6	17
1-{4-[(E)-phenylazo]-phenyl}-2-formylpyrrol	7	20

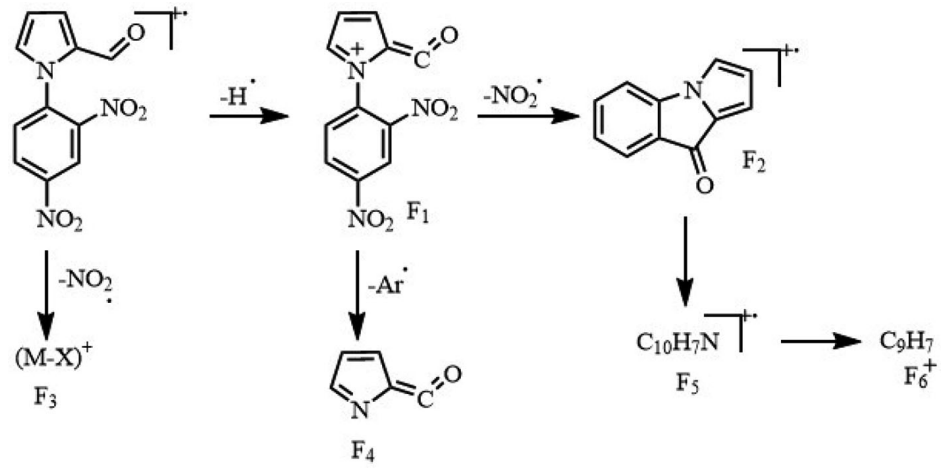

Fig. 3 Fragmentation of 1-(2,4-dinitrophenyl)-2-formylpyrrol

Thus, the mass spectra confirm the structure of the resulting N-(2,4-dinitrophenyl)-2-formylpyrrol.

The PASS-online program made it possible to predict the biological activity of a number of synthesized N-aryl-2-formylpyrroles as an inhibitor of monodehydroascorbate reductase (NADH), botrolysin and an APOA1 expression enhancer. Therefore, the synthesized compounds can be used in the agrochemical industry to produce a plant growth stimulant, in the pharmaceutical industry – to normalize the metabolism in the human body.

Experimental

The purity and individuality of the synthesized compounds were proved by thin-layer chromatography using silica gel plates (Sorbfil ПТСХ-П-А, layer thickness 80–100 microns, grain size 8–12 microns) in the hexane-ethanol system (4:1), manifestation in UV light.

The mass spectra were obtained using a high-performance liquid chromatograph with a Shimadzu LC/MS-2020 mass-selective detector, the mobile phase is methyl alcohol.

1-(2,4-dinitrophenyl)-2-formylpyrrol. A. When heated in a water bath, 0.26 g (5 mmol) of 2,4-dinitroaniline was dissolved in 11.1 ml of ethyl alcohol. After complete dissolution, 0.22 ml (2.7 mmol) of furfural and 0.1 ml of 10 % hydrochloric acid solution were added. Then 10.8 ml of water was poured in small portions and kept at a temperature of 70 °C for 2 hours with constant stirring. After cooling the reaction mass, the orange precipitate was filtered out, washed on a filter with a 70 % alcohol solution. Yield = 14 %, 0.09 g, 0.3 mmol. Signals in the mass spectrum, m/z (I,%): 261 (4,44) [M^+], 260 (0,55), 233 (0,75), 218 (0,5), 217 (4,34), 206 (63), 195 (21), 188 (0,53), 141 (6,56), 127 (21,01), 94 (1,38).

1-(4-nitrosophenyl)-2-formylpyrrol. A. When heated in a water bath, 0.078 g (0.6 mmol) of p--nitroaniline was dissolved in 1.2 ml of ethyl alcohol. After complete dissolution, 0.03 ml (0.3 mmol) of furfural and 0.01 ml of 10 % hydrochloric acid solution were added. Next, 1.2 ml of water was poured in small portions and kept at a temperature of 70 °C for 2 hours with constant stirring. After cooling the reaction mass, the precipitate was filtered out, washed on a filter with a 70 % alcohol solution. Yield = 6 %, 0.003 g, 0,018 mmol.

B. When heated in a water bath, 0.075 g (0.8 mmol) of p-nitroaniline was dissolved in 2 ml of ethyl alcohol. After complete dissolution, 0.03 ml (0.3 mmol) of furfural and 0.015 ml of 2H hydrochloric acid solution were added. Darkening of the solution was observed. Next, 2 ml of water was poured in small portions and kept under heating for 5 hours with constant stirring. At the end of the reaction, the oil layer was separated, the aqueous layer was extracted with benzene. The combined extracts were thoroughly washed with 10 % hydrochloric acid solution and water. The benzene solution was evaporated on a rotary evaporator, the resulting beige oil product was passed through a layer of silica gel to separate from the resin. Control over the course of the reaction and analysis of the resulting substance was carried out by TLC. Hexane and ethyl acetate (3:1) were used as the eluent. Yield = 17 %, 0.01 g, 0.05 mmol.

1-{4-[(E)-phenylazo]-phenyl}-2-formylpyrrol. A. When heated in a water bath, 1 g (5.1 mmol) of p-aminoazobenzene is dissolved in 10.4 ml of ethyl alcohol. After complete dissolution, 0.21 ml (2.5 mmol) of furfural and 0.09 ml of 10 % hydrochloric acid solution were added. Then 10.4 ml of water was poured in small portions and kept at a temperature of 70 °C for 2 hours with constant stirring. After cooling the reaction mass, the precipitate was filtered out, washed on a filter with a 70 % alcohol solution. Yield = 7 %, 0.048 g, 0.2 mmol.

B. When heated in a water bath, 0.9 g (5 mmol) of p-aminoazobenzene was dissolved in 7 ml of ethyl alcohol. After complete dissolution, 0.28 ml (2.5 mmol) of furfural and 0.2 ml of 2h hydrochloric acid solution were added. Darkening of the solution was observed. Next, 7 ml of water was poured in small portions and kept under heating for 5 hours with constant stirring. At the end of the reaction, the oil layer was separated, the aqueous layer was extracted with benzene. The combined extracts were thoroughly washed with 10 % hydrochloric acid solution and water. The benzene solution was evaporated on a rotary evaporator, the resulting dark orange oil product was passed through a layer of silica gel to separate from the resin. Control over the course of the reaction and analysis of the resulting substance was carried out by TLC. Hexane and ethyl acetate (2:1) were used as the eluent. Yield = 20 %, 0.138 g, 0.5 mmol.

Conclusion

For the first time, furfural was condensed with 2,4-dinitroaniline, 4-nitrozoaniline and 4-aminoazobenzene under the conditions of the Yuryev reaction, which made it possible to expand the preparative capabilities of the reaction and synthesize a number of new, previously unknown 1-aryl-2-formylpyrroles. This method of obtaining pyrrole derivatives is characterized by simplicity of synthesis and relatively high yields.

The effect of the following substituents has been established: -NO, -NO_2, –N=N-Ph, on the reaction of replacing the heteroatom in the furfural nucleus by comparing inductive effects, effects on the nucleophilicity of the amino group, as a reaction center. The reaction conditions for anilines containing these groups in their core have been experimentally selected.

The synthesis of aniline derivatives took place under harsh conditions, which is why the yields decreased. We have suggested that strong electron acceptors stabilize the resulting intermediate compound, the Stenhouse salt, whose hydrolysis does not occur under mild conditions.

1-(4-nitrophenyl)-2-formylpyrrol can be obtained from furfural and p-nitroaniline under mild conditions with a yield of 70 %. However, in the case of 1-(2,4-dinitrophenyl)-2-formylpyrrol, it was

not possible to achieve relatively high reaction yields, which can be explained by the presence of the ortho-effect of the nitro group of the initial 2,4-dinitroaniline.

The mass spectra of the obtained 1-(2,4-dinitrophenyl)-2-formylpyrrol were taken, proving the presence of the target product in the mixture of substances.

Based on the PASS-online of the synthesized compounds, 1-(2,4-dinitrophenyl)-2-formylpyrrol showed the greatest useful biological activity.

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