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SYNTHESIS OF N-SUBSTITUTED HETEROCYCLES IN A SEALED MONOWAVE 50 REACTOR

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Abstract. *The paper examines the process of aromatic nucleophilic substitution in 2-chloronitrobenzene and 2,4-dichloro-1,5-dinitrobenzene in a Monowave 50 synthesis reactor. The authors identify accelerated reactions of substrates with azaheterocyclic compounds (pyridine or indole) in hermetically sealed vessels.*

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Introduction

Nitrogen-containing heterocycles are useful structural elements for the synthesis of biologically active molecules. Thus, aromatic nucleophilic substitution of the halogen atom in 2-chloronitrobenzene for azacyclic fragments with further functionalisation causes formation ofthe products with antiviral [1], anticancer [2], and antifungal activity [3]. Similar S_NAr reactions in 2,4-dichloro-1,5-dinitrobenzene allow us to obtain substances with proton pump inhibiting activity (to suppress gastric acid secretion) [4], anticancer [5], antibacterial [6], antitubercular [7-9], antiviral [10], KCNQ ion channel stimulating activity (for the treatment of epilepsy and a number of other diseases) [11].

One of the tasks of modern chemistry is reducing of necessary substances synthesis time and increasing the synthesis productivity. One of the ways to accelerate S_NAr reactions is to conduct them in the presence of excess pressure in the reaction medium [12-15].

The purpose of this study is developing a methodology for aromatic nucleophilic substitution of 2-chloronitrobenzene and 2,4-dichloro-1,5-dinitrobenzene with nitrogen-containing heterocycles under hermetically sealed autoclave reactor conditions.

Main body

We used Monowave 50 to perform the S_NAr reactions (Figure 1). It is a robust and safe laboratory reactor for synthesis in sealed vessels at temperatures up to 250 °C and pressures

up to 20 bar [16]. The reactor utilises conductive heating of a sealed glass vessel through a stainless steel heating jacket and online monitoring of temperature and pressure in addition to magnetic stirring. The reactor allows the synthesis conducting several times faster than traditional units with heating plates and stirrers.

We used pyridine as a model nucleophile. This azaheterocyclic fragment is often present in synthesised compounds [17-18], and the resulting pyridinium salts act as substrates for intramolecular cyclisation to form condensed systems [19-20].

We put pyridine and 2-chloronitrobenzene (**1**) into a borosilicate glass vial, added a solvent - dehydrated acetone; sealed the vial with a silicone cap with a gasket, placed it in the reactor and closed the lid. Then we turned on stirring and heated to 60 °C for 2 hours. However, it was not possible to obtain the product under these conditions. Therefore, we performed a series of experiments for the synthesis of 1-(2-nitrophenyl)pyridinium chloride (2) by varying the temperature from 80 °C with a step of 20 °C. In this case, increasing the temperature above the boiling point of the solvent created an increase in pressure inside the reactor. The synthesis at 160 °C for 2 hours and pressures from 8 (beginning of the experiment) to 18 atmospheres (end of the experiment) resulted in the separation of a precipitate from the reaction mass, which was filtered and dried. We recorded a ^{1}H NMR spectrum and a high-resolution mass spectrum, matching the expected spectral characteristics of the product. The similar S_NAr reaction in an open round bottom flask at pyridine boiling (115 °C) required more than 24 hours to obtain a comparable yield to the process in Monowave 50.

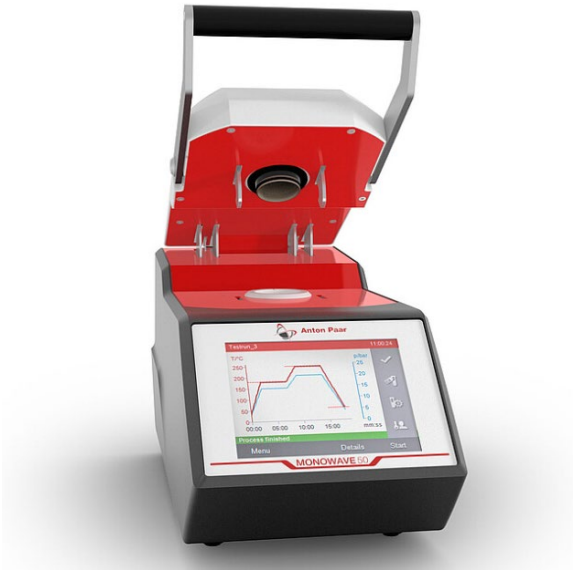
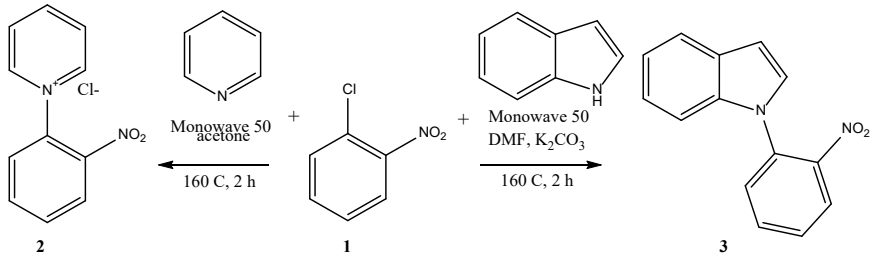


Fig. 1. Monowave 50 reactor (front view)

Another nucleophile used was indole. It is known as a versatile heterocyclic building block due to its multiple pharmacological activities, and is often used in the creation of drug products candidates [21-22]. DMFA was used as solvent and potassium carbonate as base for the reaction of substance **1** with indole.

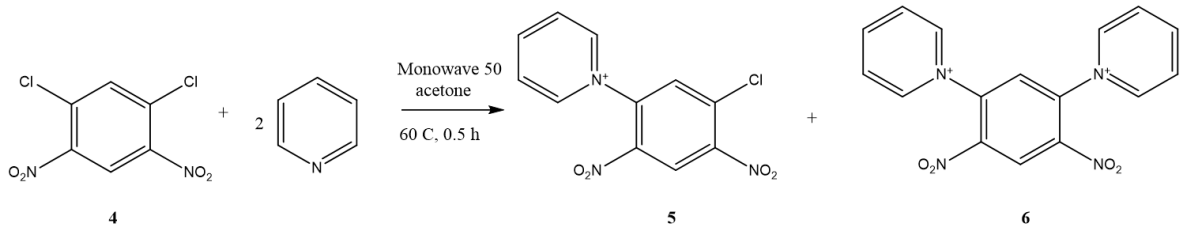


2 **1** **3**

S_NAr process at 160 °C for 2 h and pressure from 2 (start of experiment) to 5 atmospheres (end of experiment) resulted in a reaction mixture, which was poured into water

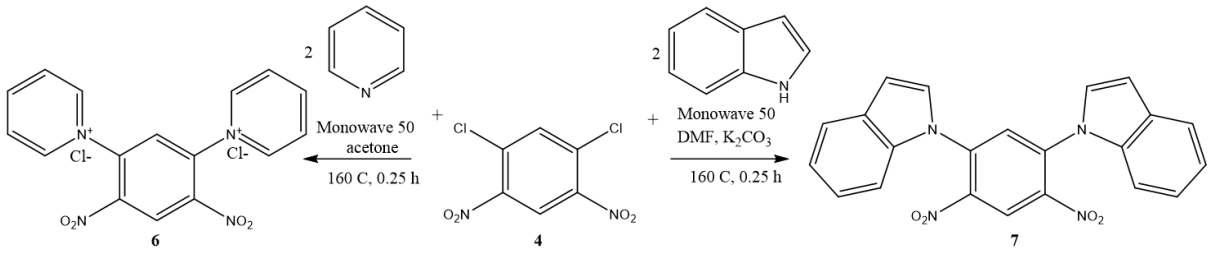
and 1-(2-nitrophenyl)-1*H*-indole (**3**) was obtained by filtration. In comparison, no target substance was formed in the experiment in an open three-neck flask during the same time and after 2 hours only the starting indole and halogennitroarene were isolated.

We next conducted the substitution reaction in 2,4-dichloro-1,5-dinitrobenzene (**4**), a much more active substrate due to the presence of two activating groups. An attempt to substitute both halogen atoms for the pyridine moiety at 60 °C in acetone for 30 min yielded a mixture of substances consisting of 1-(5-chloro-2,4-dinitrophenyl)pyridinium chloride (**5**) and the expected 1,1'-(4,6-dinitro-1,3-phenylene)-bis(pyridinium) dichloride (**6**).



4 **5** **6**

We studied the influence of temperature and reaction time on the products composition. As a result, pure compound **5** can be obtained when the experiment was conducted no higher than 30 °C, stirring the reaction mixture for 1.5 hours. The synthesis of compound **6** required heating up to 160 °C (pressure in the reactor was from 7 to 18 atm), which reduced the required time to 15 minutes. These temperature and time were also suitable for the substitution of both halogen atoms of substance **4** for indole fragments. In this case, as in the example of 2-chloronitrobenzene, the solvent was DMFA and the base was potassium carbonate.



6 **4** **7**

Hence, we have developed methods of S_NAr reactions in activated arenes in a sealed Monowave 50 reactor for the preparation of substances containing pyridine or indole fragments. The advantages of the proposed synthesis method include short process time, minimised solvent consumption, and energy saving due to short reaction times.

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 solutions. The residual solvent proton signals in ^{1}H NMR (DMSO δ2.50 ppm or chloroform δ7.26 ppm) spectra were used as a reference for counting chemical shifts. We recorded high resolution mass spectra on a "Bruker micrOTOF II" (Bruker Daltonics), electrospray ionisation (ESI), mass scanning range (*m/z* 50) 3000 Da, syringe injection. We used MeCN or MeOH as solvent and the solution flow rate was 3 μl/min. The interface temperature was 180 °C, the spray gas was nitrogen (4.0 l/min).

Methodology for the synthesis of 1-(2-nitrophenyl)pyridinium chloride

We put 0.33 g (2.1 mmol) of 2-chloronitrobenzene, 0.18 ml (2.2 mmol) of pyridine, 6 ml of dehydrated acetone, and a magnetic anchor into a 10 ml glass vial; sealed the vial with a silicone cap, and placed it in a Monowave 50 reactor. Then we closed the lid of the unit. The mixture was stirred with a magnetic stirrer (400 rpm) and heated in AFAP mode (heating at maximum speed) up to 160 °C. When the set temperature was reached, the mixture was incubated for 120 minutes. Next, we cooled the reactor to 30 °C, opened the lid and took out the vial. We removed the cap from it, took out the magnetic anchor, filtered the precipitate under vacuum, washed it with dehydrated acetone and dried it in a desiccator.

1-(2-nitrophenyl)pyridinium chloride (**2**). Yield 0,44 g (89%). $T_{melt.}$ = 247–251 °C. NMR spectrum ^{1}H (DMSO-d_6, δ, ppm., *J*/Hz): 8.06 (ddd, *J* 8.6 Hz, 7.0 Hz, 1.8 Hz, 1H, $H^{4'}$), 8.09-8.18 (m, 2H, $H^{5',6'}$), 8.41 (t, *J* 8.6 Hz, 2H, $H^{3,5}$), 8.55 (dd, *J* 8.3 Hz, 1.4 Hz, 1H, $H^{3'}$), 8.93 (td, *J* 7.9 Hz, 1.5 Hz, 1H, H^4), 9.43 (d, *J* 6.0 Hz, 2H, $H^{2,6}$). HRMS: *m/z* calculated $C_{11}H_9N_2O_2^+$ 201.0659 $[M]^+$, found: 201.0651.

Methods for the synthesis of 1-(2-nitrophenyl)-1*H*-indole

We put 0.33 g (2.1 mmol) of 2-chloronitrobenzene, 0.26 g (2.2 mmol) of indole, 0.46 g (3.3 mmol) of potassium carbonate, 6 ml of DMFA and a magnetic anchor into a 10 ml glass vial; sealed the vial with a silicone cap, and placed it in a Monowave 50 reactor. Then we closed the lid of the unit. The mixture was stirred with a magnetic stirrer (400 rpm) and heated in AFAP mode (heating at maximum speed) up to 160 °C. When the set temperature was reached, the mixture was incubated for 120 minutes. Next, we cooled the reactor to 30 °C, opened the lid, and took out the vial. We removed the cap from it, took out the magnetic anchor, poured the contents into a beaker with 30 ml of water. Then we filtered the precipitate under vacuum, washed with water and dried in a desiccator.

1-(2-Nitrophenyl)-1*H*-indole (**3**). Yield 0.43 g (86%). $T_{melt.}$ = 83–86 °C [23]. NMR spectrum ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 6.74 (dd, *J* 3.2, 0.8 Hz, 1H), 7.12-7.22 (m, 4H), 7.55-7.62 (m, 2H), 7.67-7.71 (m, 1H), 7.74 (dt, *J* 7.8, 1.2 Hz, 1H), 8.04 (dd, *J* 8.2,1.2 Hz, 1H). HRMS: *m/z* calculated $C_{14}H_{11}N_2O_2^+$ 239.0821 $[M+H]^+$, found: 239.0821.

Methods for the synthesis of 1-(5-chloro-2,4-dinitrophenyl)pyridinium chloride and 1,1'-(4,6-dinitro-1,3-phenylene)-bis(pyridinium) dichloride

We put 0.5 g (2.1 mmol) of 2,4-dichloro-1,5-dinitrobenzene, 0.18 ml (2.2 mmol) of pyridine (for synthesis **5**) or 0.36 ml (4.4 mmol) of pyridine (for synthesis **6**), 6 ml of dehydrated acetone, and a magnetic anchor into a 10 ml glass vial; sealed the vial with a silicone cap, and placed it in a Monowave 50 reactor. Then we closed the lid of the unit. Next, we turned on stirring with a magnetic stirrer (400 rpm) and heating in AFAP mode to 30 °C (for synthesis **6**) or 160 °C (for synthesis **7**). When the target temperature was reached, the mixture was incubated for 90 minutes (for synthesis **6**) or 15 minutes (for synthesis **7**). Next, we cooled the reactor to 30 °C, opened the lid and took out the vial. We removed the cap from it, took out the magnetic anchor, filtered the precipitate under vacuum, washed it with dehydrated acetone and dried it in a desiccator.

Chloride of 1-(5-chloro-2,4-dinitrophenyl)pyridinium (**5**). Yield 0.52 g (79%). $T_{melt.}$ = 162–164 °C. NMR spectrum ^{1}H (DMSO-d_6, δ, ppm, *J*/Hz): 8.44 (t, *J* 8.5 Hz, 2H, $H^{3',5'}$),

8.85 (s, 1H, H^6), 8.96 (t, *J* 8.5 Hz, 1H, $H^{4'}$), 9.32 (s, 1H, H^3), 9.38 (d, *J* 6.0 Hz, 2H, $H^{2',6'}$). HRMS: *m/z* calculated $C_{11}H_7N_3O_4^+$ 280.0120 $[M]^+$, found: 280.0111.

Dichloride of 1,1'-(4,6-dinitro-1,3-phenylene)-bis(pyridinium) (**6**). Yield 0.75 g (90%). T_{melt} > 300 °C. ^{1}H NMR spectrum (DMSO-d_6, δ, ppm, *J*/Hz): 8.52 (t, *J* 8.5 Hz, 4H, $H^{3',5',3'',5''}$), 9.02 (t, *J* 8.5 Hz, 2H, $H^{4',4''}$), 9.24 (s, 1H, H^6), 9.44 (s, 1H, H^3), 9.66 (d, *J* 5.5 Hz, 4H, $H^{2',6',2'',6''}$). HRMS: *m/z* calculated $C_{16}H_{12}N_4O_4^{2+}$ 324.0853 $[M]^+$, found: 324.0841.

Methodology for the synthesis of 1,1'-(4,6-dinitro-1,3-phenylene)bis(1H-indole)

We put 0.5 g (2.1 mmol) of 2,4-dichloro-1,5-dinitrobenzene, 0.52 g (4.4 mmol) of indole, 0.92 g (6.6 mmol) of potassium carbonate, 6 ml of DMFA, and a magnetic anchor into a 10-ml glass vial; sealed the vial with a silicone cap and placed it in a Monowave 50 reactor. Then we closed the lid of the unit. The mixture was stirred with a magnetic stirrer (400 rpm) and heated in AFAP mode (heating at maximum speed) up to 160 °C. When the set temperature was reached, the mixture was incubated for 15 minutes. Next, we cooled the reactor to 30 °C, opened the lid, and took out the vial. We removed the cap from it, took out the magnetic anchor and poured the contents into a beaker with 30 ml of water. Then we filtered the precipitate under vacuum, washed with water and dried in a desiccator.

1,1'-(4,6-Dinitro-1,3-phenylene)bis(1H-indole) (**7**). Yield 0.65 g (78%). $T_{melt.}$ = 124-128 °C. NMR spectrum ^{1}H (DMSO-d_6, δ, ppm, *J*/Гц): 6.72 (d, *J* 8.2 Hz, 2H), 7.20 (m, 4H), 7.55 (m, 4H), 7.84 (s, 1H), 8.28 (d, *J* 7.8 Hz, 2H), 8.95 (s, 1H). HRMS: *m/z* calculated $C_{22}H_{15}N_4O_4^+$ 399.1094 $[M+H]^+$, found: 399.1083.

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