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## Multicomponent Synthesis of Novel Unsymmetric 6-Aryl Substituted 5-Nitropyridines

We have previously studied a multicomponent reaction for the synthesis of unsymmetrical 5-nitro-1,4-dihydropyridines using unsubstituted 2-nitroacetophenone, 1,3-dicarbonyl compounds, and various aldehydes such as formaldehyde, acetaldehyde, and furfural. This paper reports the use of unsymmetrical 3-acetyl-5-nitro-1,4-dihydropyridines containing aryl substituents at the 6-position in a multicomponent synthesis reaction. The starting aryl-substituted nitroacetophenones were prepared by two methods. The first method involved the two-step Katritzky method, which is described in the literature. This method consists of preparing N-acylbenzotriazoles from the corresponding substituted derivatives of benzoic acid and 1,2,3-benzotriazole in the presence of thionyl chloride. This is followed by C-acylation of nitromethane in supernatron medium (t-BuOK – DMSO). A number of 2-nitroacetophenone derivatives were prepared from more commercially available aromatic aldehydes by the Henry reaction with nitromethane followed by oxidation of the resulting secondary nitroalcohols. The multicomponent reaction of 6-aryl-substituted 5-nitro-1,4-dihydropyridines and their subsequent aromatization into 5-nitropyridines allowed us to reduce the overall reaction time by more than 40 times and to increase the total yield of 5-nitro-6-arylpyridines by an average of twofold compared to the method described in the literature. Furthermore, the 3-acetyl-5-nitropyridines we have obtained are significant intermediates in the synthesis of novel, more complex heterocyclic systems with potential biological activity. These systems include  $\delta$ -carbolines and epoxybenzoxocyno[4,3-b]pyridines, which are currently of great interest for the study of their properties.

**Keywords:** green chemistry, multicomponent reaction, substituted 2-nitroacetophenones, pyridine derivatives, 5(3)-nitro-1,4-dihydropyridines, 5(3)-nitropyridines, 3-acetyl-5-nitropyridines, heterocyclic compounds.

### Introduction

During the 1980s and 1990s, pharmaceuticals containing 1,4-dihydropyridine were developed and proved to be effective. These pharmaceuticals are now known as “Dihydropyridine calcium channel blockers” and are used as L-type calcium channel blockers [1]. They are commonly used to treat cardiovascular diseases such as hypertension, angina pectoris, arrhythmias, and for the prevention of heart disease. The drugs work by blocking the entry of calcium into the cells of the heart and blood vessels, causing them to relax and dilate [2].

Dihydropyridine calcium channel blockers primarily lower blood pressure by causing relaxation of the smooth muscle in the walls of blood vessels. In contrast, certain L-type calcium channel blockers, such as those from the phenylalkylamine class like verapamil, exert a notable impact on the heart [3-4].

An example of the use of compounds from the 1,4-dihydropyridine class in pharmacology is nifedipine. It was patented in 1967 and is listed in the World Health Organization's Essential Medicines List. As of 2021, this medication was the 128th most frequently prescribed drug in the United States, with over 4 million prescriptions [5-7].

Ongoing research continues to explore novel methods for synthesizing and discovering effective medications based on 1,4-dihydropyridine (1,4-DHP) and its derivatives (Fig.).

For instance, over 20 years ago, the neuroprotective drug cerebrocrast 4 was discovered in the search for more effective drugs for high blood pressure.

Cerebrocrast exhibits a high affinity for DHP-receptors and is recognized for enhancing cognitive abilities. It functions as a nootropic agent, improving cognitive functions and memory, while also providing neuroprotective benefits by tackling age-related, hypoxic, and alcohol-induced neuronal disorders [8].

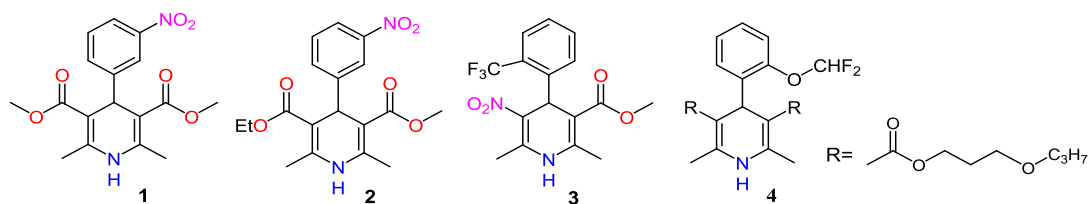
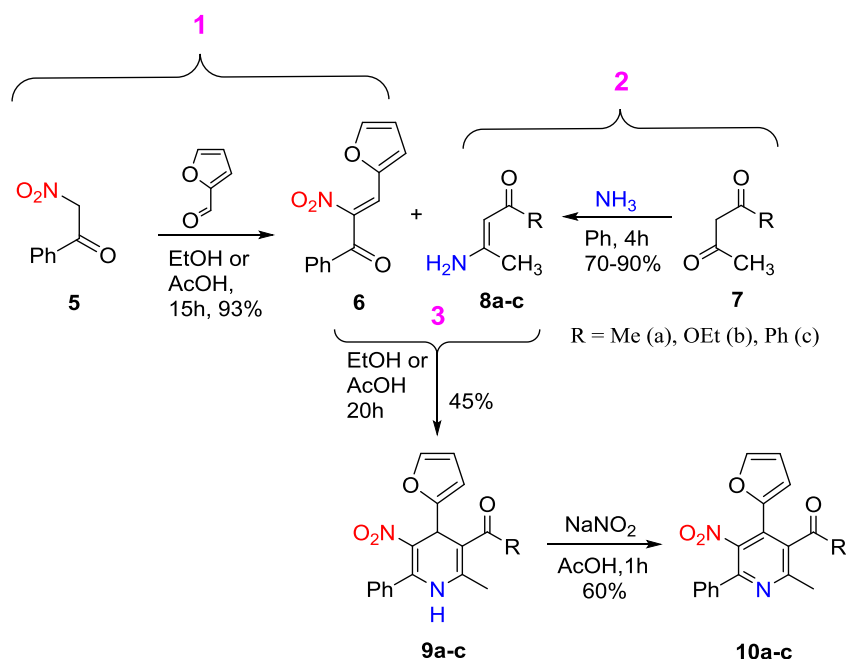


Figure. The structural formulas of bioactive 1,4-DHPs

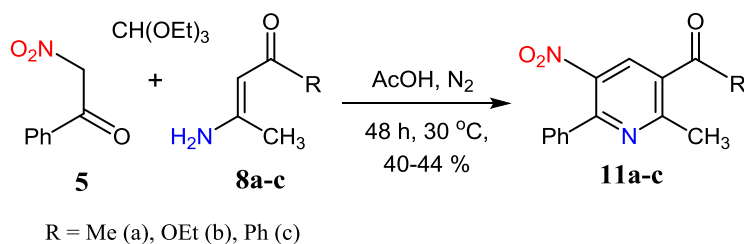
The synthesis of symmetrical derivatives of 1,4-dihydropyridine of types **1** and **2** using the Hantzsch method with a double equivalent of the dicarbonyl compound is straightforward and yields are consistently high. However, the one-step synthesis of unsymmetrical derivatives of 1,4-dihydropyridine of type **3** using the Hantzsch method is challenging. This is mainly due to the different reactivity of the carbonyl compounds used, which leads to a mixture of different products, including symmetrical 1,4-dihydropyridines.

The synthesis of unsymmetrical 5-nitropyridines of type **10a-c** involves the reaction of enamines  $\beta$ -dicarbonyl compound and nitrochalcone, followed by oxidation of the obtained 1,4-dihydropyridines **9a-c** (Scheme 1) [9]. This method of preparation requires the synthesis of starting enamines [11] and nitrochalcone [10], high time and energy costs, and 1,4-dihydropyridines **9a-c** are formed with relatively low overall yields.



Scheme 1. Three step synthesis of 4-substituted 5-nitro-6-phenylpyridines

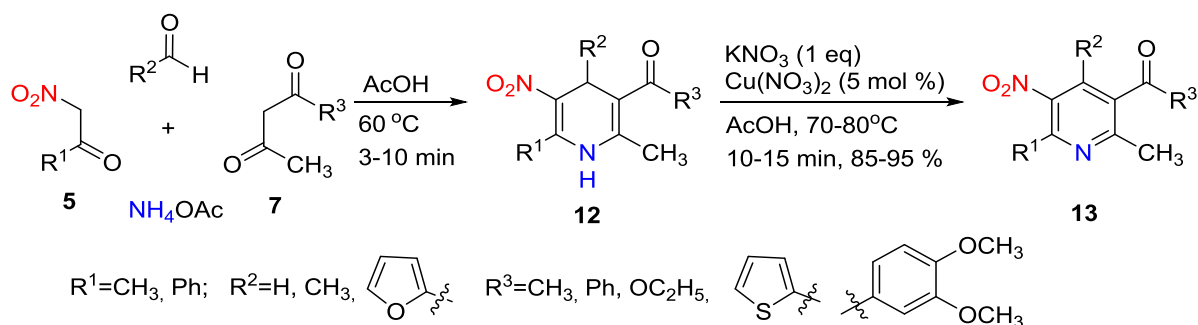
A one-step, three-component method for the preparation of 4-substituted 5-nitro-6-phenylpyridines **11a-c**, which are prepared from nitroacetophenone **5**, enamine  $\beta$ -dicarbonyl compounds **8a-c** and triethylorthoformate [12-13], is also reported in the literature (Scheme 2).



Scheme 2. A one-step method for the preparation of 4-substituted 5-nitro-6-phenylpyridines

This method, in comparison with the classical method, proceeds in one stage and does not require oxidative aromatization. However, in our opinion, this method has a number of disadvantages, namely high duration of all reactions (from 50 to 122 hours), long heating time, use of inert gas, use of more expensive triethylorthoformate, relatively low overall reaction yield, as well as an additional stage of preliminary preparation of  $\beta$ -dicarbonyl compounds **8a-c** with enamine.

In [14–16], we successfully applied and extensively tested the methodology for the four-component synthesis of **12-c** type 1,4-DHP. Nitroacetophenone (or nitroacetone) **5**, the corresponding  $\beta$ -dicarbonyl compound **7** in equivalent molar amounts, an excess of ammonium acetate and an aldehyde (formaldehyde, furfural, acetaldehyde) or its sources (urotropine, acetal) were used for the reaction (Scheme 3).



Scheme 3. Synthesis of 4-unsubstituted and 4-substituted 5-nitro-6-phenylpyridines

Therefore, our proposed method for the synthesis of 4-unsubstituted and 4-substituted 5-nitro-6-phenyl-1,4-dihydropyridines and their subsequent conversion into pyridines enabled us to reduce the overall reaction time and increase the overall combined yield of 5-nitro-6-phenylpyridines by almost twofold compared to established methods in the literature.

### Experimental

#### Materials

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Magritek spin solve 80 carbon ultra (81 and 20 MHz, respectively) instruments using DMSO- $d_6$  and  $\text{CDCl}_3$  the internal standard, with residual solvent signals (2.49 and 39.9 ppm for  $^1\text{H}$  and  $^{13}\text{C}$  nuclei in DMSO- $d_6$ ; 7.25 and 77.0 ppm for  $^1\text{H}$  and  $^{13}\text{C}$  nuclei in  $\text{CDCl}_3$ ).

The physicochemical and spectral characteristics of compounds **19a-c** were in agreement with the literature data [13].

**6-aryl-5-nitro-1,4-dihydropyridines 18a-f (general method).** To previously dissolved substituted nitroacetophenone (5 mmol) in glacial acetic acid (4–5 mL), 0.18 g (1.3 mmol) of urotropine, 1.16 g (15 mmol) of ammonium acetate and 0.50 g (5 mmol) of acetylacetone were added. The reaction mixture was stirred at 60 °C for 3–10 min. The reaction mixture with crystalline precipitate was cooled to 0–5 °C, filtered, washed first with 50 % aqueous 2-propanol solution, then with water. The product was recrystallized from 2-propanol.

**1-(2-methyl-5-nitro-6-(p-tolyl)-1,4-dihydropyridin-3-yl)ethan-1-one (18a).** Yield 0.530 g (39 %), orange crystals, mp 157–159 °C.

$^1\text{H}$  NMR (81 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.16 (s, 3 H,  $\text{CH}_3$ ); 2.24 (s, 3 H,  $\text{CH}_3$ ); 2.37 (s, 3 H,  $\text{CH}_3$ ); 3.69 (s, 2 H,  $\text{CH}_2$ ); 7.26 (br. s, 4 H, H-2,3,5,6 Ar); 9.15 (s, 1 H, NH).  $^{13}\text{C}$  NMR (20 MHz, DMSO- $d_6$ )  $\delta$  ppm: 18.0; 20.9; 27.2; 30.2; 111.0; 122.4; 127.6; 128.8; 131.0; 138.9; 143.4; 147.7; 197.0.

**1-(6-(4-bromophenyl)-2-methyl-5-nitro-1,4-dihydropyridin-3-yl)ethan-1-one (18b).** Yield 0.826 g (60 %), red crystals, mp 166–167 °C.

$^1\text{H}$  NMR (81 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.15 (s, 3H,  $\text{CH}_3$ ); 2.25 (s, 3H,  $\text{CH}_3$ ); 3.70 (s, 2 H,  $\text{CH}_2$ ); 7.33 (d,  $J$ = 8.30 Hz, 2 H, H-2,6 Ar); 7.68 (d,  $J$ =8.30 Hz, 2 H, H-3,5 Ar); 9.23 (br. s., 1 H, NH).  $^{13}\text{C}$  NMR (20 MHz, DMSO- $d_6$ )  $\delta$  ppm: 18.0; 27.0; 30.2; 111.1; 122.6; 122.8; 129.9 (2 C); 131.3 (2 C); 133.3; 143.2; 146.5; 197.0.

**1-(6-(4-methoxyphenyl)-2-methyl-5-nitro-1,4-dihydropyridin-3-yl)ethan-1-one (18c).** Yield 0.547 g (38 %), orange crystals, mp 264–266 °C.

$^1\text{H}$  NMR (81 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.23 (s, 3 H,  $\text{CH}_3$ ); 2.29 (s, 3 H,  $\text{CH}_3$ ); 3.77 (s, 2 H,  $\text{CH}_2$ ); 3.88 (s, 3 H,  $\text{OCH}_3$ ); 7.00 (d,  $J$ =8.60 Hz, 2 H, H-3,5 Ar); 7.32 (d,  $J$ =8.60 Hz, 2 H, H-2,6 Ar), 9.03 (br. s., 1 H,

NH).  $^{13}\text{C}$  NMR (20 MHz, DMSO- $d_6$ )  $\delta$  ppm: 18.0; 27.1; 30.2; 55.7; 110.8; 111.3; 120.4; 123.2; 123.8; 128.5; 130.6; 143.6; 144.4; 156.2; 197.0.

**1-(6-(4-fluorophenyl)-2-methyl-5-nitro-1,4-dihydropyridin-3-yl)ethan-1-one (18d).** Yield 0.856 g (62 %), orange crystals, mp 178–179 °C.

$^1\text{H}$  NMR (81 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.16 (s, 3 H,  $\text{CH}_3$ ); 2.25 (s, 3 H,  $\text{CH}_3$ ); 3.70 (s, 2 H,  $\text{CH}_2$ ); 7.18–7.54 (m, 4 H, H-2,3,5,6 Ar); 9.22 (br. s., 1 H, NH).  $^{13}\text{C}$  NMR (20 MHz, DMSO- $d_6$ )  $\delta$  ppm: 18.5; 27.7; 30.7; 111.6; 115.3; 116.4; 123.3; 130.5; 130.9 (2 C); 143.8; 147.2; 169.2; 197.6.

**1-(6-(2-methoxyphenyl)-2-methyl-5-nitro-1,4-dihydropyridin-3-yl)ethan-1-one (18e).** Yield 0.706 g (49 %), orange crystals, mp 156–157 °C.

$^1\text{H}$  NMR (81 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.14 (s, 3 H,  $\text{CH}_3$ ); 2.24 (s, 3 H,  $\text{CH}_3$ ); 3.69 (br. s., 2 H,  $\text{CH}_2$ ); 3.76 (s, 3 H,  $\text{OCH}_3$ ); 7.02–7.44 (m, 4 H, H-3,4,5,6 Ar); 9.15 (s, 1 H, NH).  $^{13}\text{C}$  NMR (20 MHz, DMSO- $d_6$ )  $\delta$  ppm: 18.0; 27.1; 30.2; 55.7; 110.8; 111.3; 120.4; 123.2; 123.8; 128.5; 130.6; 143.6; 144.4; 156.2; 197.0.

**1-(6-(3,4-dimethoxyphenyl)-2-methyl-5-nitro-1,4-dihydropyridin-3-yl)ethan-1-one (18f).** Yield 0.429 g (27 %), orange crystals, mp 217–219 °C.

$^1\text{H}$  NMR (81 MHz, DMSO- $d_6$ )  $\delta$  ppm: 2.16 (s, 3 H,  $\text{CH}_3$ ); 2.24 (s, 3 H,  $\text{CH}_3$ ); 3.68 (s, 2 H,  $\text{CH}_2$ ); 3.75 (s, 3 H,  $\text{OCH}_3$ ); 3.80 (s, 3 H,  $\text{OCH}_3$ ); 6.78 — 7.09 (m, 3 H, H-2,5,6 Ar); 9.13 (s, 1 H, NH).  $^{13}\text{C}$  NMR (20 MHz, DMSO- $d_6$ )  $\delta$  ppm: 18.0; 27.2; 30.2; 55.6; 55.7; 110.9; 111.5; 111.7; 120.5; 122.1; 125.1; 143.5; 147.5; 148.5; 149.8; 196.9.

**6-aryl-5-nitropyridines 19a-f (general method).** To a mixture of 1,4-dihydropyridine (0.2 mmol) in glacial acetic acid (1 mL) cooled to 0 °C, a solution of 0.03 g  $\text{CrO}_3$  (0.3 mmol) in  $\text{H}_2\text{O}$  (0.5 mL) was added dropwise at such a rate that the temperature of the reaction mixture did not exceed 10 °C. After addition of the  $\text{CrO}_3$  solution, stirring was continued for 2 hours, and then the mixture was poured into an ice-water mixture (20 mL) and neutralized with aqueous ammonia. The crystals were filtered and recrystallized from ethanol.

**1-(2-methyl-5-nitro-6-(p-tolyl)pyridin-3-yl)ethan-1-one (19a).** Yield 0.481 g (89 %), white crystals, mp 97–98 °C. (lit. mp — 98–99 °C) [18].

$^1\text{H}$  NMR (81 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.42 (s, 3H,  $\text{CH}_3$ ); 2.67 (s, 3H,  $\text{CH}_3$ ); 2.88 (s, 3H,  $\text{CH}_3$ ); 7.28 (d,  $J=7.10$  Hz, 2H, H-3,5 Ar); 7.52 (d,  $J=7.10$  Hz, 2H, H-2,6 Ar); 8.42 (s, 1H Py).  $^{13}\text{C}$  NMR (20 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 21.2; 25.2; 29.3; 128.1; 129.1; 130.9; 133.3; 135.2; 137.6; 143.3; 152.7; 161.9; 197.5.

**1-(6-(4-bromophenyl)-2-methyl-5-nitropyridin-3-yl)ethan-1-one (19b).** Yield 0.516 g (77 %), light yellow crystals, mp 146–147 °C. (lit. mp — 148–149 °C) [18].

$^1\text{H}$  NMR (81 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.69 (s, 3H,  $\text{CH}_3$ ); 2.88 (s, 3H,  $\text{CH}_3$ ); 7.46 (d,  $J=8.40$  Hz, 2 H, H-3,5 Ar); 7.63 (d,  $J=8.30$  Hz, 2 H, H-2,6 Ar); 8.47 (s, 1H, H-4 Py).  $^{13}\text{C}$  NMR (20 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 25.2; 29.3; 125.1; 129.9; 130.9; 132.0; 133.3; 134.6; 143.2; 152.7; 162.0; 197.4.

**1-(6-(4-methoxyphenyl)-2-methyl-5-nitropyridin-3-yl)ethan-1-one (19c).** Yield 0.378 g (66 %), white crystals, mp 103–104 °C. (lit. mp — 101–102 °C) [18].

$^1\text{H}$  NMR (81 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.64 (s, 3H,  $\text{CH}_3$ ); 2.86 (s, 3H,  $\text{CH}_3$ ); 3.85 (s, 3H,  $\text{OCH}_3$ ); 7.00 (d,  $J=8.60$  Hz, 2 H, H-3,5 Ar); 7.32 (d,  $J=8.60$  Hz, 2 H, H-2,6 Ar); 8.39 (s, 1H, H-4 Py).  $^{13}\text{C}$  NMR (20 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 25.3; 29.1; 55.4; 114.3; 121.6; 127.8; 129.8; 130.2; 133.4; 143.0; 153.1; 161.6; 197.5.

**1-(6-(4-fluorophenyl)-2-methyl-5-nitropyridin-3-yl)ethan-1-one (19d).** Yield 0.499 g (91 %), light yellow crystals, mp 119–120 °C.

$^1\text{H}$  NMR (81 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.76 (s, 3 H,  $\text{CH}_3$ ); 2.96 (s, 3 H,  $\text{CH}_3$ ); 7.13–7.34 (m, 2 H, H-3,5 Ar); 7.60–7.77 (m, 2 H, H-2,6 Ar); 8.54 (s, 1 H, H-4 Py).  $^{13}\text{C}$  NMR (20 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 25.2; 29.2; 115.4; 116.5; 130.3; 130.8; 131.8; 133.4; 135.0; 143.3; 152.6; 157.9; 161.9; 170.3; 197.5.

**1-(6-(2-methoxyphenyl)-2-methyl-5-nitropyridin-3-yl)ethan-1-one (19e).** Yield 0.418 g (73 %), white crystals, mp 144–145 °C.

$^1\text{H}$  NMR (81 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.76 (s, 3 H,  $\text{CH}_3$ ); 2.96 (s, 3 H,  $\text{CH}_3$ ); 3.79 (s, 3 H,  $\text{OCH}_3$ ); 6.98 (d,  $J=8.01$  Hz, 1 H, H-3 Ar); 7.13–7.64 (m, 2 H, H-4,5 Ar); 7.80 (d,  $J=7.17$  Hz, 1 H, H-6 Ar); 8.58 (s, 1 H, H-4 Py).  $^{13}\text{C}$  NMR (20 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 25.2; 29.2; 55.0; 110.6; 121.5; 125.6; 130.3; 130.8; 131.8; 132.7; 144.3; 151.4; 156.4; 162.0; 219.8.

**1-(6-(3,4-dimethoxyphenyl)-2-methyl-5-nitropyridin-3-yl)ethan-1-one (19f).** Yield 0.600 g (95 %), white crystals, mp 127–128 °C.

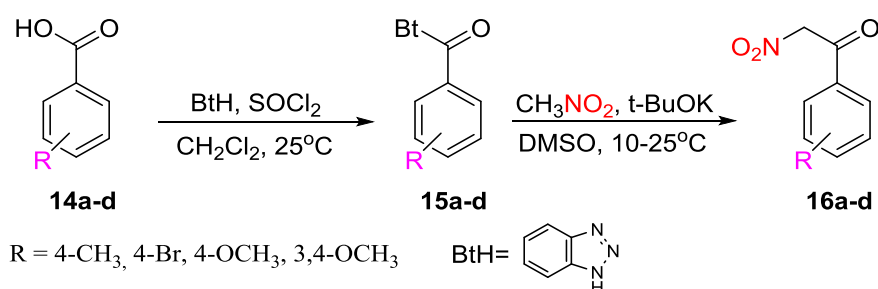
$^1\text{H}$  NMR (81 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm: 2.79 (s, 3 H,  $\text{CH}_3$ ); 3.01 (s, 3 H,  $\text{CH}_3$ ); 4.06 (s, 6 H,  $\text{OCH}_3$ ); 7.05 (d,  $J=8.80$ , 1 H, H-5 Ar); 7.33 (d,  $J=8.80$ , 1 H, H-6 Ar); 7.35 (s, 1 H, H-2 Ar); 8.51 (s, 1 H, H-4 Py).  $^{13}\text{C}$  NMR

(20 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 25.3; 29.1; 56.0 (2 C); 111.1; 111.4; 121.7; 127.8; 129.9; 133.3; 143.2; 149.2; 151.2; 153.0; 161.6; 197.4.

### Results and Discussion

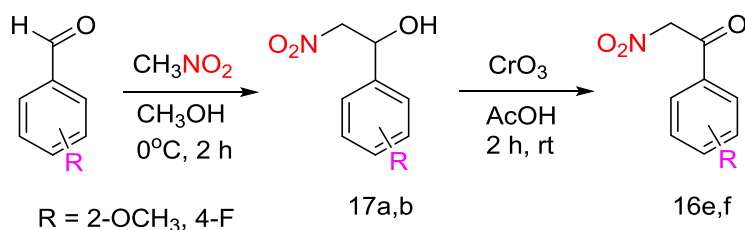
The previously described syntheses were based on the use of only unsubstituted 2-nitroacetophenone or nitroacetone in multicomponent reactions. In order to extend the possibilities of using this multicomponent reaction to synthesize new unsymmetrical derivatives of 5-nitropyridines containing an aryl substituent at the sixth position, it was necessary to synthesize aryl-substituted nitroacetophenones. For the preparation of aryl-substituted nitroketones, the Katritzky method [17-18], which is carried out in two stages, is widely used (Scheme 4).

In the first stage, the corresponding N-acylbenzotriazoles **15a-d** are prepared by interaction of commercially available substituted benzoic acid derivatives **14a-d** with 1,2,3-benzotriazole in the presence of thionyl chloride. Further, the required nitroacetophenones **16a-d** were prepared by C-acylation of nitromethane with the obtained N-acylbenzotriazoles **15a-d**. The reaction was carried out in superbase (t-BuOK – DMSO), with the benzotriazole acting as a good leaving group.



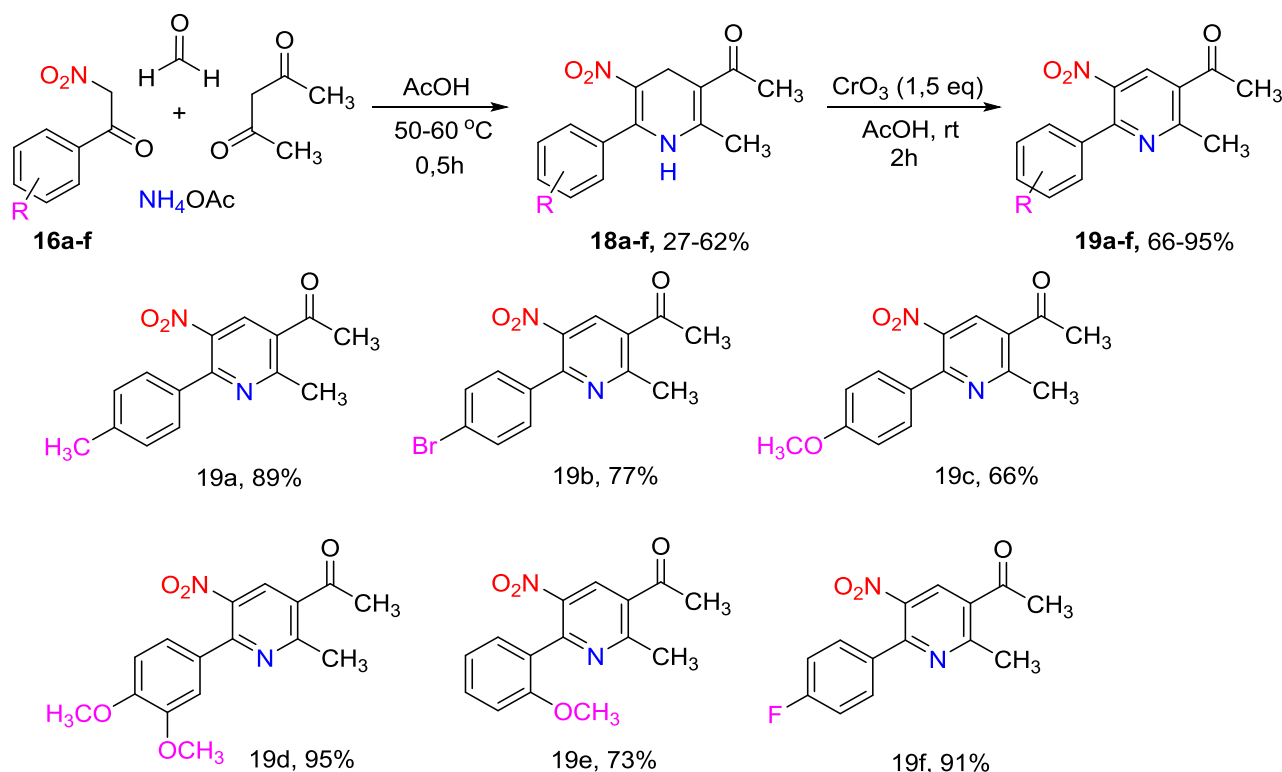
Scheme 4. Synthesis of aryl-substituted nitroketones by the Katritzky method

Nitroacetophenones **16e, f** were prepared from more readily available aromatic aldehydes by the Henry reaction with nitromethane, followed by oxidation of the resulting secondary nitroalcohols **17a, b** [19] (Scheme 5). During the reaction, in addition to hydroxynitro compounds, nitroalkenes were formed in small amounts (up to 20 % according to GC-MS data), i.e. products of elimination of a water molecule from the nitro alcohols formed in the first stage. The purification of the obtained target nitro alcohols was carried out by column chromatography on silica gel (hexane/ethyl acetate) according to the provided method [19].



Scheme 5. Synthesis of aryl-substituted nitroketones by the Henry reaction

The prepared aryl-substituted nitroketones were then incorporated into a multicomponent reaction for the synthesis of unsymmetrical 4-substituted 3-acetyl-5-nitro-1,4-dihydropyridines **18a-f** according to the method described in [14] (Scheme 6). However, experimental syntheses showed that the aryl-substituted nitroketones used are rather poorly soluble in acetic acid, the solvent we use, which ultimately leads to their insufficient involvement in the reaction and, as a consequence, the formation of a significant amount of symmetrical side 3,5-diacetyl-1,4-dihydropyridine. To avoid unwanted side processes, we first predissolved the nitroacetophenones in acetic acid, and then added excess ammonium acetate and urotropine, and finally acetylacetone.



Scheme 6. Synthesis of 4-unsubstituted 3-acetyl-5-nitro-6-arylpyridines

It was found that the yields of the corresponding 3-acetyl-5-nitro-6-aryl-1,4-dihydropyridines **18a-f** are also related to the presence of electronic effects of the substituent in the aromatic ring. Thus, the donor substituents slightly reduce the yield of the target product due to a decrease in the partial positive charge on the carbon atom of the carbonyl group and, accordingly, lead to a decrease in the CH-acidity of the methylene group of nitroketones, which is the main reaction center in the Knoevenagel reaction.

The oxidation of 5-nitro-6-aryl-1,4-dihydropyridines to the corresponding 5-nitro-6-arylpyridines **19a-f** was carried out according to the standard method with chromium oxide (VI) in acetic acid solution at room temperature. The oxidation proceeded quite smoothly and in high yields (from 66 to 95 %) (Scheme 6).

### Conclusions

Thus, we have extended the possible scope of application of the multicomponent reaction in the synthesis of six new 6-aryl-substituted 3-acetyl-5-nitro-1,4-dihydropyridines, not previously described in the literature, whose oxidation afforded the corresponding 5-nitropyridines.

The multicomponent reaction of 6-aryl-substituted 5-nitro-1,4-dihydropyridines and their subsequent aromatization to pyridines allowed the overall reaction time to be reduced by more than 40-fold and the overall yield of the target 5-nitro-6-arylpyridines to be almost doubled on average compared to the method reported in the literature [12-13].

In conclusion, the new 3-acetyl-5-nitro-6-arylpyridines **19a-f** synthesized by us can be of great interest as intermediate synthons in the synthesis of more complex heterocyclic systems. For example, 3-(5-nitropyridines have proved to be good precursors in the synthesis of synthetic analogs of the alkaloid chindoline and other structural analogs of substituted  $\delta$ -carboline obtained by the Cadogan reaction [20-21]. The presence of 3-acetyl and 2-methyl groups in the structure of 5-nitro-6-arylpyridines **19a-f** simultaneously suggests their potential use as important synthons and in the synthesis of epoxybenzoxocino[4,3-b]pyridine derivatives [22-24], which are structural analogs of natural integrastatins.

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### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. **CRedit**: **Ilya Ivanovich Kulakov** investigation, formal analysis, data curation and writing—original draft preparation; **Semyon Yuryevich Chikunov** investigation, formal analysis; **Andrey Vladimirovich Elyshev** supervision, project administration, funding acquisition; **Ivan Vyacheslavovich Kulakov** conceptualization, methodology, validation, writing—review and editing and supervision.

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### Conflicts of Interest

The authors declare no conflict of interest.

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