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Multicomponent synthesis of 4-unsubstituted 5-nitropyridine derivatives

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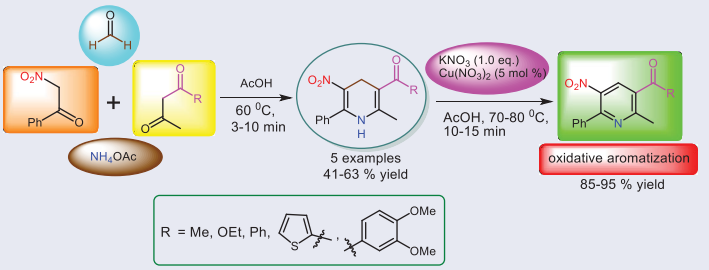
ABSTRACT

Multicomponent reaction of 2-nitroacetophenone, urotropine (or paraformaldehyde), β-dicarbonyl compound and ammonium acetate afforded five new 4-unsubstituted 5-nitro-6-phenyl-1,4-dihydropyridine derivatives, oxidation of which provided the corresponding 5-nitro-6-phenylpyridines. The proposed approach for the synthesis of 4-unsubstituted 5-nitro-6-phenyl-1,4-dihydropyridines and their subsequent aromatization into pyridines made it possible to reduce the total reaction time by more than 200 times and the overall yield of 5-nitro-6-phenylpyridine by 2 times compared with the known methods.

GRAPHICAL ABSTRACT



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Introduction

Currently, multicomponent reactions (MCR),[1,2] are one of the modern trends of organic chemistry. They not only correspond to the general concept of green chemistry as one of the promising areas of the future chemistry[3] but also meet the criteria of environmental friendliness, atom and step efficiency, which brings them close to perfect syntheses.

Multicomponent reactions make it possible to synthesize a large number of various heterocyclic compounds in one step and with good yields, including the symmetric 1,4-dihydropyridines (1,4-DHP) by the Hantzsch reaction.[4] However, the synthesis of non-symmetric 1,4-DHP through to the classical by the Hantzsch method is associated with significant difficulties in the preparation and isolation of an individual reaction

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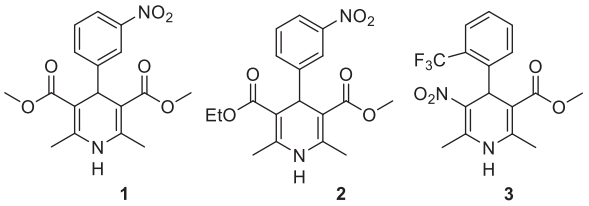


Figure 1. Biologically active 1,4-dihydropyridines.

product due to the different reactivity of the used carbonyl compounds.[5] There are only few examples on the synthesis of non-symmetric 1,4-DHP by this method.[6] In this regard, research in this area is an urgent task.

Note some 1,4-DHP derivatives are used as antihypertensive drugs (for example, nifedipine **1**, nitrendipine **2**, etc.), which are calcium channel blockers.[7] A distinctive feature of these compounds is the presence of a 3-nitrophenyl fragment in the position 4 of the dihydropyridine ring.[8] Similar properties were found in 5-nitro-1,4-dihydropyridines **3**,[9] that also increase the relevance of research related to the development of new synthesis methods and the search for new effective drugs in the series of 5-nitro-1,4-dihydropyridine derivatives (Figure 1).

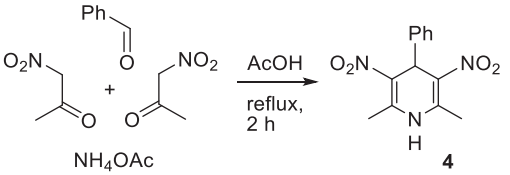
Thus, an example of multicomponent synthesis of symmetric 3,5-dinitro-1,4-DHP **4** has been reported in Vigante et al.[10] (Scheme 1).

However, there are no examples of the synthesis of unsymmetrical 3(5)-nitro-1,4-DHP according to the scheme similar to the above. Generally, non-symmetric 5-nitro-1,4-DHP can be synthesized by the reaction of the corresponding nitrochalcone **6** and enamines of β-dicarbonyl compounds **8** (Scheme 2).[11] This method requires preliminary synthesis of nitrochalcone **6**[12] and enamines **8**,[13] as well as a lot of time and energy. Moreover, the overall yield of the target 5-nitro-1,4-DHP **9** is low. Further oxidation of 5-nitro-1,4-DHP **9** with sodium nitrite in glacial acetic acid furnished the corresponding 5-nitropyridine **10**.[11]

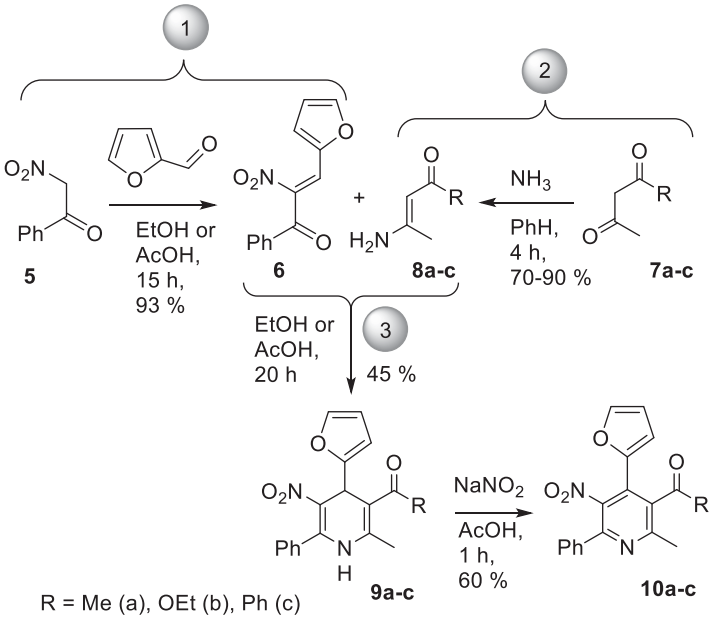
In addition, functionally substituted 1,4-DHPs are important intermediates in the classical method for preparation of pyridines, including 3- or 5-nitropyridines, which in turn are excellent precursors in the synthesis of unavailable 3- or 5-aminopyridines. So, for example, there is a three-component one-step method for producing 4-unsubstituted 5-nitro-6-phenylpyridines **11a–c** starting from nitroacetophenone **5**, enamines **8a–c** and triethyl orthoformate[14,15] (Scheme 3). The obtained pyridines **11** turned out to be good precursors in the synthesis of alkaloid quindoline, its structural analogues and substituted δ-carbolines.[16]

In our opinion, this method also has significant drawbacks compared to the classical method of obtaining pyridines through the intermediate stage of 1,4-DHP formation: the total duration of all reactions is from 50[14] to 122 h,[15] including prolonged heating at 30 and 80 °C, the use of inert gas, the additional stage of the preliminary preparation of β-dicarbonyl compounds enamines **8a–c**, the use of more expensive triethyl orthoformate, as well as a relatively low total reaction yield. At the same time, unfortunately, analysis of literature data showed that despite the ease of synthesis of 1,4-DHPs there are no data on the methods for producing 4-unsubstituted 5-nitro-6-phenylpyridines **11a–c** by oxidation of the corresponding 1,4-DHPs.

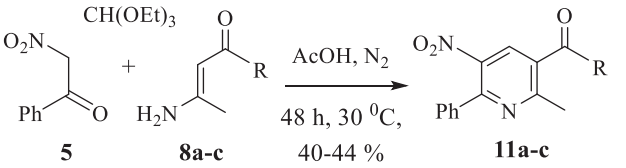
Recently,[17] we have reported the four-component synthesis of 1,4-DHPs **9a–c** based on the reaction of 2-nitroacetophenone **5**[18] with equimolar amounts of β-dicarbonyl



Scheme 1. Synthesis of symmetric 3,5-dinitro-1,4- dihydropyridines.



Scheme 2. Three step synthesis of 4-substituted 5-nitro-6-phenylpyridines.

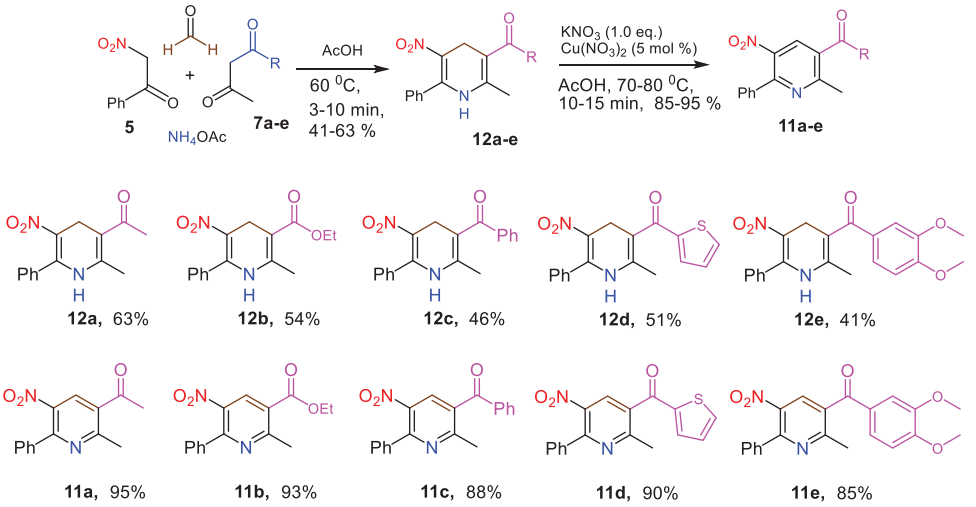


Scheme 3. Synthesis of 4-unsubstituted 5-nitro-6-phenylpyridines.

compounds **7a–c** and furfural in the presence of an excess of ammonium acetate. The optimal conditions for oxidation of the obtained 1,4-DHPs **9a–c** with potassium nitrate in the presence of catalytic amounts of copper(II) nitrate to the corresponding pyridines **10a–c** with yields of up to 85% have been also shown. Compared to the method reported in,[11] the preparation of pyridines **10a–c** through the multicomponent synthesis of 1,4-DHPs and their subsequent oxidation allowed us to reduce the number of stages from 4 to 2, increase the total pyridine yield from 24% to 38% and significantly reduce the total reaction time from 40 to 1 h.[17]

Results and discussion

Therefore, it was of interest to study the possibility of obtaining in this way non-symmetric 4-unsubstituted 5-nitro-6-phenylpyridines **11a–c** by the classical method, i.e., through the



Scheme 4. Synthesis of 4-unsubstituted 5-nitro-6-phenylpyridines.

stage of multicomponent synthesis of intermediate 1,4-DHPs and their further aromatization into pyridines.

The four-component reactions were performed using equimolar amounts of nitroacetophenone **5**, the corresponding *β*-dicarbonyl compound **7a–e**, formaldehyde, and an excess of ammonium acetate (Scheme 4).

Various sources of formaldehyde (formalin, urotropine and paraformaldehyde) were used. Acetic acid, which dissolves all 4 components, was used as a solvent. To select optimal conditions, the synthesis of compound **12a** was used as the model reaction. The formaldehyde source, reaction temperature, an excess of acetylacetone **7a** and ammonium acetate, as well as the solvent were varied. Acetates or chlorides of Cu^{2+}, Ni^{2+}, Zn^{2+}, Mn^{2+} (10–20 mol%) were screened as possible reaction catalysts.

The best results were obtained when the reaction was performed at 60–70 °C and using urotropine (or paraformaldehyde) as a formaldehyde source. At a lower temperature (<60°C), the reaction time increased, and at a higher temperature (>70°C) a significant grinding of the reaction mixture occurred, which made it difficult to isolate the reaction product and reduced its yield. The use of formalin immediately led to the resinification of the reaction mixture, probably due to its uncontrolled excess. An excess of diketone **7a** or urotropine led to the additional formation of a certain amount of symmetric 3,5-diacetyl-2,6-dimethyl-1,4-DHP. It should be noted that the reaction progress was monitored both by TLC and visually by the precipitation of a red-orange fine-crystalline precipitate. The crystalline product was filtered off, dried and analyzed. By ^{1}H NMR data, it did not require further purification. Isolation of an additional amount of compound **12a** from the mother liquor proved to be very laborious and added only 2–3% to the total yield; therefore, it was neglected.

When changing acetic acid with other solvents (benzene, 2-propanol, ethanol, DFA), the desired product **12a** did not precipitate from the reaction mixture, which significantly complicated its isolation and reduced yields to 15–20%. The best yields (up to 63%) and reaction time (3–6 min) were obtained using 3(or 5)-fold excess of ammonium acetate and about 10-fold molar excess of the solvent. The use of a smaller

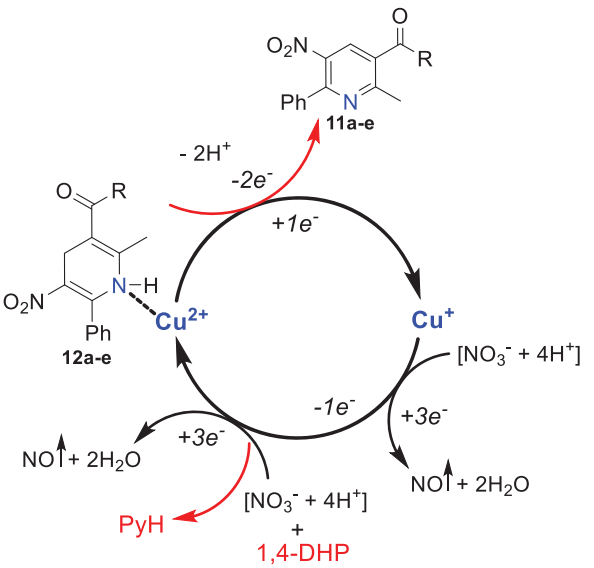
amount of the solvent made it difficult to dissolve the starting components, whereas a large dilution did not lead to complete precipitation of the reaction product. The use of acetates or chlorides of the above metals as possible reaction catalysts did not practically affect the increase in yield and the reaction rate (Table 1).

The resulting 5-nitro-1,4-dihydropyridines **12a–e** were further oxidized to 5-nitropyridines **11a–e** by procedure developed by us previously[17] using potassium nitrate instead of toxic sodium nitrite in the presence of 5 mol% of copper(II) nitrate (or acetate) in acetic acid, which also led to high yields (up to 95%) and the purity of the corresponding

Table 1. Optimization of synthesis methods on the example of compound **12a**.

Entry	Catalyst (mol %)	Solvent	Eq. $AcONH_4$	Eq. AcOH	Temp. (°C)	Reaction time (min)[a]	Yield (%)
1.	–	AcOH	5	20	40	15	45
2.	–	AcOH	5	20	70	–	43
3.	–	AcOH	5	20	80	–	20
4.	–	EtOH	5	–	60	–	18
5.	–	DFA	5	–	60	–	22
6.	–	$AcOH/H_2O$, 1:1	5	10	60	–	20
7.	–	AcOH/ EtOH, 1:1	5	10	60	–	25
8.	–	AcOH	5	20	60	5	51
9.	–	AcOH	2	20	60	–	32
10.	–	AcOH	3	20	60	5,5	47
11.	–	AcOH	5	10	60	1,5	63
12.	–	AcOH	3	10	60	2,5	63
13.	$Cu(AcO)_2 \cdot H_2O$ (10)	AcOH	3	20	60	7	49
14.	$Cu(AcO)_2 \cdot H_2O$ (10)	AcOH	3	10	60	3,5	56
15.	$Cu(AcO)_2 \cdot H_2O$ (20)	AcOH	3	20	60	6	59
16.	$ZnCl_2$ (10)	AcOH	3	20	60	4	46
17.	$ZnCl_2$ (10)	AcOH	3	10	60	2	61
18.	$ZnCl_2$ (20)	AcOH	3	10	60	4	58
19.	$Mn(AcO)_2$ $4H_2O$ (10)	AcOH	3	20	60	2	53
20.	$Mn(AcO)_2$ $4H_2O$ (10)	AcOH	3	10	60	1,5	59
21.	$Mn(AcO)_2$ $4H_2O$ (20)	AcOH	3	20	60	8	52

[a] The time of precipitation of the reaction product from the reaction mixture.



Scheme 5. Proposed oxidation mechanism of 5-nitro-1,4-dihydropyridines **12a–e** to 5-nitropyridines **11a–e**.

Table 2. Comparison of the methods for the synthesis of compound **12a**.

Reaction parameters	Method MCR	Literature method[14]
Step number	2	2
Overall yield, %	63	31
Overall reaction time, h	0.25	52

pyridines. Although the oxidation only with potassium nitrate, without copper catalysis, provides the desired product, it significantly increases the reaction time (almost 3 times) and reduces the yield to 70–80%. In this regard, we suggested that copper(II) cations coordinated with nitrogen atom of 1,4-DHP significantly accelerate the electron transfer in corresponding redox reaction, reducing to Cu(I). Then nitrate ions easily oxidize Cu(I) to Cu(II), and the oxidation process of 1,4-DHP repeats again (Scheme 5).

A comparative analysis of the synthesis method developed by us (method MCR) and those described earlier[14] is given in Table 2.

Conclusions

In summary, we developed a simple, universal, economic, and efficient method for the synthesis of 4-unsubstituted 5-nitro-6-phenylpyridines, which in many respects satisfies the principles of green chemistry and significantly exceeds the method described in the literature in terms of overall yield and reaction time. The obtained positive results will allow relatively quickly synthesizing the libraries of such derivatives for subsequent modifications.

Experimental

IR spectra were recorded on an Infralum FT-801 spectrometer for KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX400 instrument (400 and 100 MHz, respectively) using DMSO-d_6 (compound **12d,e**) or $CDCl_3$ (remaining compounds) the internal standard was TMS or residual solvent signals (7.25 and 77.0 ppm in the case of $CDCl_3$ for 1H and 13 C nuclei, respectively, and 39.9 ppm for ^{13}C nuclei in DMSO-d_6). The MALDI TOF (matrix-assisted laser desorption/ionization) mass-spectra were obtained on a Ultraflex-II mass spectrometer (Bruker Daltonics) in a positive ion mode using reflection mode (20 mV target voltage) with 4-hydroxybenzoic acid (and sodium 4-hydroxybenzoate) matrix. Elemental analysis was performed on a Carlo Erba 1106 CHN instrument. Melting points were determined using a Koffler hot bench. Monitoring of the reaction course and the purity of the products was carried out by TLC on Sorbfil plates and visualized using iodine vapor or UV light.

The physicochemical and spectral characteristics of compounds **12a–c** matched the literature data.[14]

Preparation of 5-nitro-6-phenyl-1,4-dihydropyridine derivatives 12a–e (general method)

A mixture of 2-nitroacetophenone (**5**) (0.83 g, 5.0 mmol), hexamethylenetetramine (0.18 g, 1.25 mmol), the appropriate β-dicarbonyl compound **7a–e** (5.0 mmol), and ammonium acetate (1.16 g, 15.0 mmol) in glacial acetic acid (3 ml) was stirred at 60 °C

for 3–10 min. The reaction mixture containing crystalline precipitate that formed after the completion of reaction was cooled to 0–5°C, filtered, washed first with 40% aqueous solution of ethanol, and dried. Recrystallized from 2-propanol (or ethanol).

Preparation of 5-nitro-6-phenylpyridine derivatives 11a–e (general method)

A mixture of 1,4-dihydropyridine **12a–e** (10.0 mmol), potassium nitrate (1.01 g, 10.0 mmol), and copper(II) nitrate trihydrate (121 mg, 0.5 mmol) in glacial acetic acid (20 ml) was stirred at 70 °C for 10–15 min (control by TLC). When the reaction was complete, the solution was cooled, poured into ice–water mixture (100 ml), and salted out using NaCl. The obtained precipitate was filtered off, washed with water, and dried. The filtrate was additionally extracted with ethyl acetate (2 × 10 ml). The extract was dried over Na_2SO_4, and the solvent was removed by distillation. The crystals isolated from the extract were combined with the precipitate and recrystallized from hexane (or ethanol).

Full experimental details, ^1H and ^{13}C NMR spectra can be found via the "Supplementary Content" section of this article's webpage.

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