CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201806172

Link to VoR: http://dx.doi.org/10.1002/chem.201806172

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Mild nitration of pyrazolin-5-ones by a combination of $Fe(NO_3)_3$ and $NaNO_2$. Discovery of a new easily available class of fungicides – 4-nitropyrazolin-5-ones

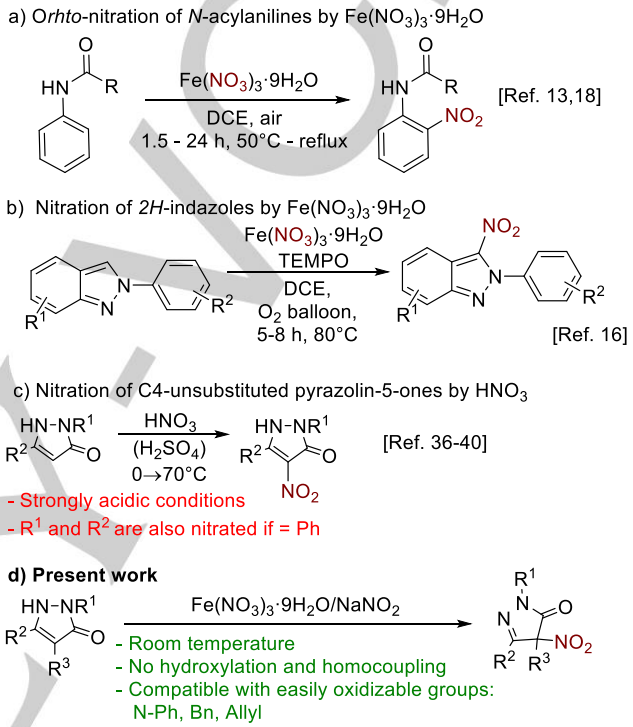
Igor B. Krylov,[a,b] Alexander S. Budnikov,[a,b,c] Elena R. Lopat'eva,[a,c] Gennady I. Nikishin,[a] Alexander O. Terent'ev*[a,b,c]

Abstract: 4-Nitropyrazolin-5-ones were synthesized by nitration of pyrazolin-5-ones at room temperature employing the $Fe(NO_3)_3/NaNO_2$ system. The method demonstrated selectivity towards position 4 of pyrazolin-5-ones even in the presence of NPh and allyl substituents, which are sensitive to nitration. It was shown that other systems containing Fe(III) and nitrites, namely $Fe(NO_3)_3$/*t*-BuONO, $Fe(ClO_4)_3/NaNO_2$, and $Fe(ClO_4)_3$/*t*-BuONO are also effective. Presumably, Fe(III) ions oxidized nitrite ($NaNO_2$ or *t*-BuONO) with the formation of NO_2 free radicals that served as the nitrating agent for pyrazolin-5-ones. The synthesized 4-nitropyrazolin-5-ones were discovered to be a new class of fungicides. Their *in vitro* activity against phytopathogenic fungi was comparable or even superior to commercial fungicides (fluconazole, clotrimazole, triadimefon, kresoxim-methyl). Reported results represent a promising starting point for the development of a new type of plant protection agents that are easily synthesized from widely available reagents.

Introduction

Nitro compounds are widely used as reagents in the synthesis of fine chemicals, drugs, explosives, fuels etc. Nitrogen dioxide (NO_2) is one of the most simple and effective nitrating agents,[1] but it is not convenient in operation and storage due to its volatility, toxicity and corrosive properties. Therefore, in recent years great efforts were made to develop systems for the generation of NO_2 *in situ*.[2-33] Nitrates and nitrites, such as $(NH_4)_2Ce(NO_3)_6$,[2] $Cu(NO_3)_2$,[3-5] $AgNO_3$,[6] $Mg(NO_3)_2$,[7] $Fe(NO_3)_3$•$9H_2O$,[8-19] *t*-BuONO,[20-25] $NaNO_2$,[26-29] and $AgNO_2$,[30-32] are available and convenient nitrating agents and precursors of NO_2. $Fe(NO_3)_3$•$9H_2O$ has found the widest application in nitration reactions due to its low toxicity, availability and low decomposition temperature with release of NO_2.[8-19,33]

Recently, Chandrasekharam and Gao reported the *ortho*-nitration of *N*-acylanilines by $Fe(NO_3)_3$•$9H_2O$[13,18] (Scheme 1a). Sharada's group achieved the nitration of 2*H*-indazoles by the $Fe(NO_3)_3$•$9H_2O$/TEMPO system[16] (Scheme 1b). However, in both cases elevated temperatures are necessary for iron (III) nitrate activation.



Scheme 1. Present work in the context of published results on arene nitration by $Fe(NO_3)_3$ and nitration of pyrazolin-5-ones

The introduction of the nitro group into pyrazolin-5-ones has not been extensively studied. Preparation of 4-nitropyrazolin-5-ones by oxidation of the corresponding 4-oximinopyrazolin-5-ones by ozone[34] or by nitration of pyrazolin-5-ones with isoamyl nitrite[35] were reported. However, in these studies, nitro derivatives were not fully characterized, and the yields of the products were not given. In most cases, nitration of pyrazolin-5-ones was carried out using nitric acid or HNO_3/H_2SO_4 mixture under heating (Scheme 1c).[36-40] Disadvantages of these procedures are harsh acidic conditions and low selectivity. Thus, in the case of phenyl-substituted pyrazolin-5-ones, nitration of both phenyl and pyrazolone rings occurred.[38]

One of the main problems of selective oxidative functionalization of pyrazolin-5-ones, especially 4-substituted derivatives, is their tendency to undergo hydroxylation[41,42] and oxidative dimerization.[41,43-45] These processes easily proceed even under the action of molecular oxygen at room

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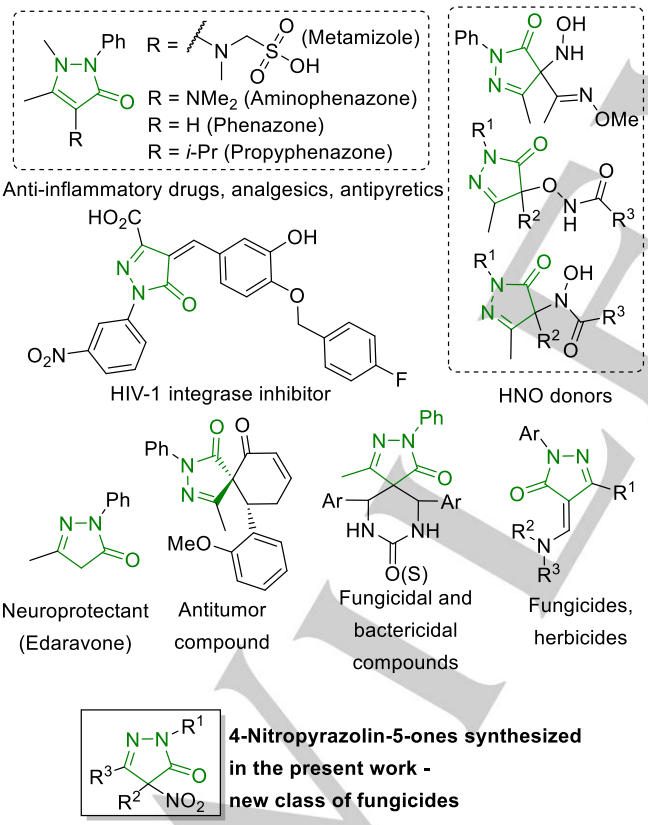
temperature.[45] In addition, oxidative destruction of the pyrazolin-5-one ring is also known.[46,47] Among the recent works devoted to the functionalization of pyrazolin-5-ones by the attack of electrophiles[48-55] or radicals[56-58] at the position 4 of heterocycle, only one involved creation of C-N bond, in which azodicarboxylates were used as N-electrophiles.[52]

In the present work, we proposed a $Fe(NO_3)_3/NaNO_2$ nitrating system, which made it possible to synthesize 4-nitropyrazolin-5-ones having a substituent at C-4 under ambient conditions (Scheme 1d). The method is tolerant to easily oxidizable functional groups, such as allyl, benzyl, and N-phenyl and avoids typical oxidative processes of pyrazolin-5-ones: hydroxylation[41,42] and oxidative dimerization.[41,43-45] It should be noted that previously reported procedures (Scheme 1c) were described only for 4-unsubstituted pyrazolin-5-ones.

The choice of pyrazolin-5-ones as substrates for nitration in the present study is associated with a wide range of their biological activities (Scheme 2). These include anti-inflammatory and analgesic, antitumor,[59] antimicrobial,[60,61] hypoglycemic,[62] antitubercular,[63] herbicidal[64-66] and fungicidal,[64,67-71] p38 inhibiting,[72] HIV integrase inhibiting,[73] 4-phosphodiesterase inhibiting,[74,75] and HNO-donor properties.[76,77]



Scheme 2. Examples of bioactive compounds and drugs with pyrazolin-5-one heterocycle.

Although some pyrazolin-5-ones of quite complicated structure were reported to possess fungicidal activity,[64,67-71], such properties are not intrinsic or typical for the pyrazolin-5-one scaffold. Instead, these compounds are widely recognized as anti-inflammatory and analgesic drugs. In the present work, high fungicidal activity of the synthesized 4-nitropyrazolin-5-ones was discovered. It should be emphasized that 4-nitropyrazolin-5-ones represent a new class of potent and readily accessible fungicides. The long-term demand for the search of new types of fungicides for agriculture and medicine[78,79] is due to the development of fungal resistance against widely used compounds.[80-83] Currently, only six families of agrochemical fungicides classified by mode of action dominate around 80% of the world market.[82] The most important fungicide families are demethylation inhibitors (DMIs, e.g. triazoles), "multisite/chemical reactives" such as dithiocarbamates, Qo-site inhibitors of complex III such as strobilurin derivatives, and succinate-dehydrogenase inhibitors (SDHIs).[82] It is known that compounds with different modes of action are desirable for the minimization of the risk of resistance development. The other side of the described issue of deficiency in the fungicide arsenal is the fact that an alarmingly high number of molecules used in crop protection are either structurally or pharmacologically related to drugs utilized in medicine.[84] Overuse of compounds with a common mode of action extends risk of resistance development in pathogenic fungi.

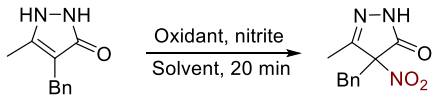
To sum up, the present paper consists of two parts: (1) the development of Fe(III) salt / nitrite system for room temperature nitration of pyrazolin-5-ones, and (2) the discovery of 4-nitropyrazolin-5-ones as a new potent class of fungicides.

Results and Discussion

At the first stage of the present study, the nitration conditions were optimized using 4-benzyl-3-methylpyrazolin-5-one **1a** as a model substrate. The influence of nitrating system composition, solvent, and temperature on the yield of nitropyrazolin-5-one **2a** was studied (Table 1).

Runs 1-3 showed that $Fe(NO_3)_3 \cdot 9H_2O$ is an effective reagent for nitration of pyrazolin-5-one **1a** at 60-80°C, but at room temperature 4-nitropyrazolin-5-one **2a** was obtained in only 33% yield (run 4). Apparently, the elevated temperature was necessary for the decomposition of $Fe(NO_3)_3 \cdot 9H_2O$ with the release of the active nitrating agent NO_2.[8-19,33] The introduction of $NaNO_2$ into the reaction allowed the room temperature nitration of pyrazolin-5-one **1a** with high yields (runs 5-7). The optimal ratio of reagents was pyrazolin-5-one: $Fe(NO_3)_3 \cdot 9H_2O$: $NaNO_2$ = 1:2:1 (run 5). When the amount of $NaNO_2$ was doubled, the yield of **2a** decreased from 83% (run 5) to 62% (run 6). Increasing the amount of $Fe(NO_3)_3$ (run 7) did not lead to a significant increase of yield of **2a** in comparison to run 5. In runs 5, 8-11, the influence of the solvent on the yield of **2a** was studied, the best result was obtained in MeCN (run 5, yield 83%).

Table 1. Optimization of the reaction conditions for nitration of **1a**[a].



1a **2a**

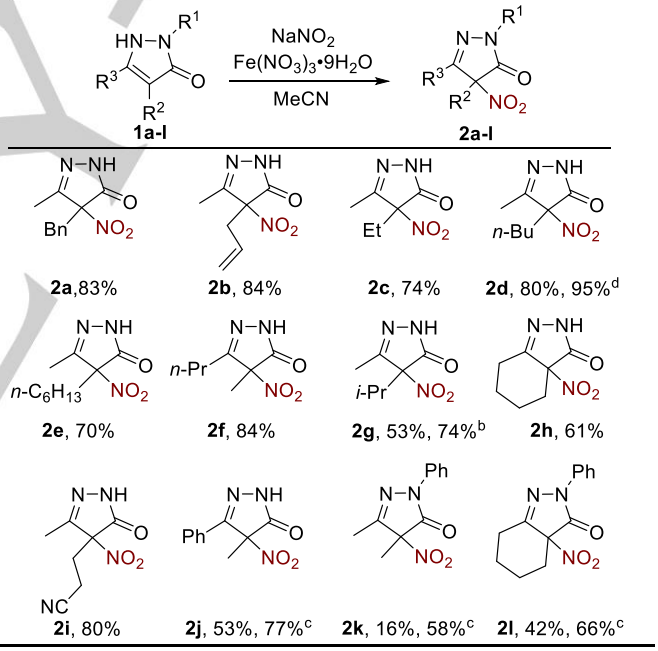
Run	Oxidant (molar ratio oxidant / **1a**)	Nitrite (molar ratio nitrite / **1a**)	Solvent	T (°C)	Yield[b], %
1	$Fe(NO_3)_3•9H_2O$ (2)	-	MeCN	60	74
2	$Fe(NO_3)_3•9H_2O$ (2)	-	MeCN	80	67
3	$Fe(NO_3)_3•9H_2O$ (1)	-	MeCN	60	51
4	$Fe(NO_3)_3•9H_2O$ (2)	-	MeCN	RT	33
5	**$Fe(NO_3)_3•9H_2O$ (2)**	**$NaNO_2$ (1)**	**MeCN**	**RT**	**83**
6	$Fe(NO_3)_3•9H_2O$ (2)	$NaNO_2$ (2)	MeCN	RT	62
7	$Fe(NO_3)_3•9H_2O$ (4)	$NaNO_2$ (2)	MeCN	RT	87
8	$Fe(NO_3)_3•9H_2O$ (2)	$NaNO_2$ (1)	AcOH	RT	52
9	$Fe(NO_3)_3•9H_2O$ (2)	$NaNO_2$ (1)	MeOH	RT	<5
10	$Fe(NO_3)_3•9H_2O$ (2)	$NaNO_2$ (1)	TFE	RT	26
11	$Fe(NO_3)_3•9H_2O$ (2)	$NaNO_2$ (1)	$C_2H_4Cl_2$	RT	33
12[c]	$Fe(NO_3)_3•9H_2O$ (2)	$NaNO_2$ (1)	MeCN	RT	52
13	$Fe(NO_3)_3•9H_2O$ (2)	*t*-BuONO (1)	MeCN	RT	74
14	$Fe(ClO_4)_3•nH_2O$ (2)	*t*-BuONO (1)	MeCN	RT	81
15	$Fe(ClO_4)_3•nH_2O$ (2)	$NaNO_2$ (1)	MeCN	RT	84
16	$(NH_4)_2Ce(NO_3)_6$ (2)	$NaNO_2$ (1)	MeCN	RT	7
17	$Cu(NO_3)_2•2.5H_2O$ (2)	$NaNO_2$ (1)	MeCN	RT	22
18	$Co(NO_3)_2•6H_2O$ (2)	$NaNO_2$ (1)	MeCN	RT	10
19	$Pb(NO_3)_2$ (2)	$NaNO_2$ (1)	MeCN	RT	<5

[a] General reaction conditions: oxidant (1-4 mmol, 404-1616 mg) was added over 5-10 seconds to a stirred mixture of 4-benzyl-3-methylpyrazolin-5-one **1a** (1 mmol, 188 mg), solvent (5 mL) and $NaNO_2$ or *t*-BuONO (0-2 mmol, 0-138 mg) at given temperature; stirring was continued at the same temperature for 20 min. [b] Isolated yield. [c] Before the addition of iron (III) nitrate, 10 mol% of TEMPO (15 mg, 0.1 mmol) was added.

In protic solvents (AcOH, MeOH, TFE, runs 8-10) the yield did not exceed 52%. A possible reason was interaction of the solvents and H_2O with NO_2, the plausible nitrating reagent generated *in situ*. In the nonpolar solvent $C_2H_4Cl_2$, which was widely used previously for nitration by $Fe(NO_3)_3•9H_2O$,[9,11-13,16,17] **2a** was obtained in low yield (33%, run 11), which can be explained by the low solubility of the reagents at room temperature. In a number of studies on $Fe(NO_3)_3•9H_2O$ mediated nitration,[11,12,16] 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) was an effective additive to increase the yields of nitro derivatives. In run 12 with addition of 10 mol% TEMPO, the yield of product **2a** decreased in comparison to run 5. In runs 13-15, components of nitration systems were varied. Combinations $NaNO_2/Fe(NO_3)_3$, *t*-BuONO/$Fe(NO_3)_3$, *t*-BuONO/$Fe(ClO_4)_3$, and $NaNO_2/Fe(ClO_4)_3$ showed comparable efficiency, yields were in the range 74 - 84%. Thus, both the salt $NaNO_2$ and the organic nitrite *t*-BuONO can be used. The replacement of iron (III) nitrate with perchlorate (runs 5 and 15, 13 and 14) did not lead to significant changes in the yield **2a**, or led to its increase. The effectiveness of $Fe(ClO_4)_3$ indicates that the nitrate ions are not obligatory for nitration when $NaNO_2$ or *t*-BuONO are present in the reaction mixture. Fe^{3+} ions and nitrites play the key role. In runs 16-19, replacement of iron salts with nitrates of other metals resulted in low yields of **2a**, which did not exceed 22%.

With the optimized conditions in hand (Table 1, run 5), we tested the scope of the developed nitration procedure (Table 2).

Table 2. The synthesis of nitropyrazolin-5-ones **2a-l** by the nitration of pyrazolin-5-ones **1a-l**[a].



[a] General reaction conditions: $Fe(NO_3)_3•9H_2O$ (2 mmol, 808 mg) was added over 5-10 seconds to a stirred mixture of pyrazolin-5-one **1** (1 mmol), MeCN (5 mL) and $NaNO_2$ (1 mmol, 69 mg) at room temperature; stirring was continued for 20 min. [b] The amounts of $NaNO_2$ and $Fe(NO_3)_3•9H_2O$ were doubled: $NaNO_2$ (2 mmol, 138 mg) $Fe(NO_3)_3•9H_2O$ (4 mmol, 1616 mg). [c] Order of addition of reagents was changed: $Fe(NO_3)_3•9H_2O$ (2 mmol, 808 mg) was added over 5-10 seconds to a stirred mixture of $NaNO_2$ (1 mmol, 69 mg) and MeCN (5 mL), after 5 min, pyrazolin-5-one was added over 5-15 seconds, stirring was continued for 20 min [d] The synthesis was scaled up to 1.08 g (7 mmol) of pyrazolin-5-one **1d** and afforded 1.33 g (6.68 mmol) **2d**.

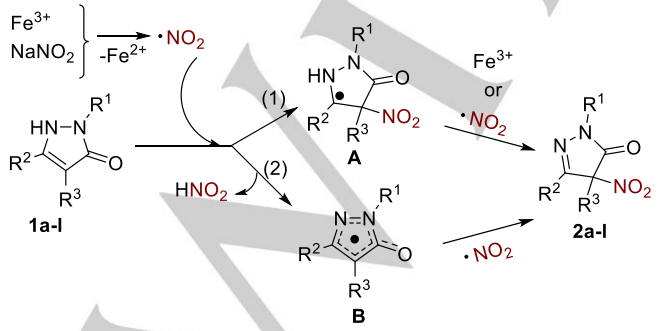
4-Nitropyrazolin-5-ones with various substituents were successfully synthesized, including benzyl and allyl (**2a,b**), alkyl (**2c-g**), condensed cyclohexyl (**2h,l**), 2-cyanoethyl (**2i**), and phenyl (**2j-l**). Under the general reaction conditions (pyrazolin-5-

one: $Fe(NO_3)_3•9H_2O$: $NaNO_2$ = 1:2:1, RT, 20 min) pyrazolin-5-ones **1a-f,h,i** were nitrated smoothly to give 4-nitropyrazolin-5-ones **2a-f,h,i** in 61-84% yield. It should be noted that allyl moiety was well tolerated under reaction conditions, affording the corresponding nitrated product **2b** in 84% yield, despite that NO_2 can react with C=C double bond.[85-88] A relatively low yield of nitro derivative **2g** (53%) was obtained in the case of pyrazolin-5-one containing the isopropyl substituent at position C4, which can be explained by the steric hindrance at the reaction center. Doubling the excess of $NaNO_2$ and $Fe(NO_3)_3•9H_2O$ allowed to increase the yield of **2g** to 74%, (table 2, note b).

In the case of the general reaction procedure $Fe(NO_3)_3$ was added to the mixture of $NaNO_2$ and pyrazolin-5-one (referred to as "standard order of addition"), so Fe^{3+} ions could react with $NaNO_2$ or pyrazolin-5-one. Employing this procedure moderate to low yields were obtained for pyrazolin-5-ones containing Ph-substituent at positions N1 or C3 (products **2j-l**, 16-53%). We proposed that oxidation of these pyrazolin-5-ones by Fe^{3+} occurred faster[57] than generation of NO_2 from nitrite ion. To minimize side oxidation of **1j-l** by $Fe(NO_3)_3$, a series of experiments were conducted, where $Fe(NO_3)_3$ was allowed to react with $NaNO_2$ first, and only then pyrazolin-5-ones **1j-l** were added to the reaction mixture (such procedure is referred below as "inverse order of addition"). In this case the yields of the target nitropyrazolin-5-ones **2j-l** increased to 58-77% (note c).

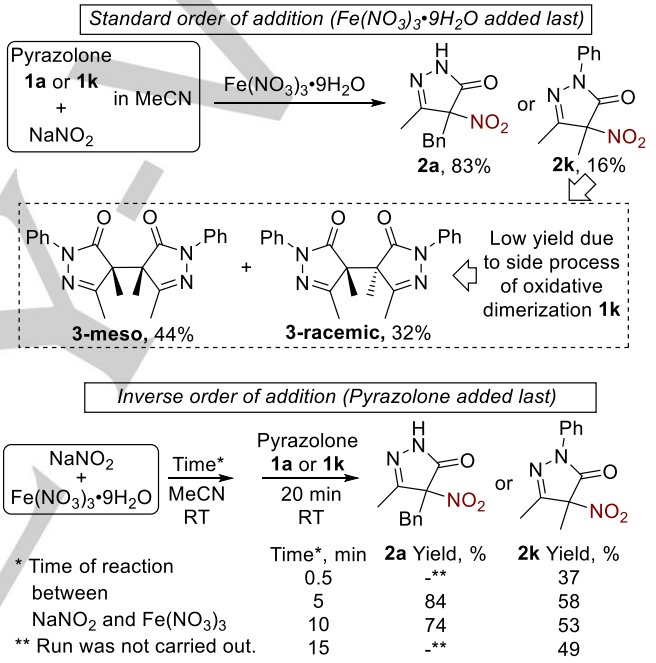
In the gram-scale synthesis 95% (1.33 g) isolated yield of **2d** was achieved, which indicates good scalability of the developed protocol (Table 2, note d).

The plausible reaction pathway is shown in Scheme 3. First, NO_2 is generated by the oxidation of the nitrite ion by Fe^{3+}.[26-29] Then two sequences are possible: (1) the attack of NO_2 on pyrazolin-5-one **1a-l** with formation of radical **A** followed by its oxidation by Fe^{3+} or NO_2, and (2) the abstraction of hydrogen atom from the pyrazolin-5-one **1a-l** by NO_2 with formation of radical **B** followed by its coupling with the second NO_2 molecule. Addition of free radicals to the pyrazolin-5-ones *via* intermediates **A** or **B** is supported by the previously reported reaction between pyrazolin-5-ones and N-oxyl radicals.[57] Both hydrogen atom abstraction reactions[87-90] and reactions of addition to double C=C bonds[85-88] are typical for NO_2. For the iron (III) nitrate mediated nitration reactions, the NO_2 free radical was previously suggested to be the active nitration agent.[8-19,33]



Scheme 3. Possible pathway of the radical nitration of pyrazolin-5-ones by Fe^{3+} / $NaNO_2$ combination.

As was mentioned before in the comments to table 2, the standard order of addition of reagents implied addition of $Fe(NO_3)_3•9H_2O$ to the mixture of $NaNO_2$, pyrazolin-5-one, and MeCN. Changed order of addition of reagents was used to increase the yield of products **2j-l** and implied addition of pyrazolin-5-one to the mixture of $Fe(NO_3)_3•9H_2O$, $NaNO_2$ and MeCN. In this order of addition, $Fe(NO_3)_3$ was allowed to react with $NaNO_2$ before pyrazolin-5-one was added. In the case of the standard order of addition of reagents, Fe(III) can react simultaneously with $NaNO_2$ and pyrazolin-5-one, which was undesirable for pyrazolin-5-ones that are easily undergo side oxidation processes under action of Fe(III).[57] Scheme 4 shows the isolated yields of the target nitropyrazolin-5-ones **2a** and **2k** depending on the order of addition of reagents.



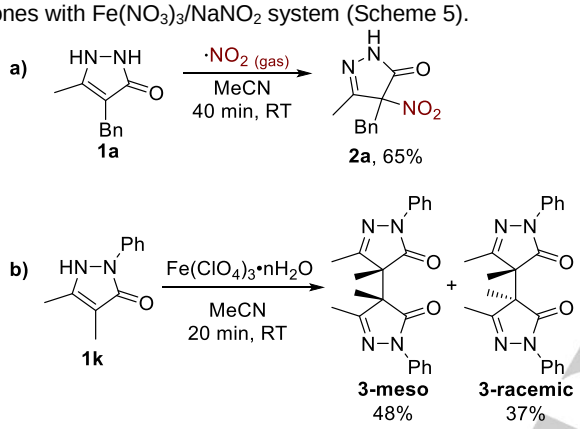
Scheme 4. Influence of the order of addition of reagents on the yields of nitropyrazolin-5-ones **2a** and **2k**

In the case of pyrazolin-5-one **1a**, a change in the order of addition of reagents did not lead to significant changes in yield **2a** (83% for the standard procedure and 74-84% for the inverse order of addition). When reaction time between $Fe(NO_3)_3•9H_2O$ and $NaNO_2$ in the inverse order of addition was increased from 5 to 10 min the **2a** yield slightly decreased (84% and 74%, respectively) which can be attributed to the decomposition of the generated NO_2 over a period of 10 min.

In the case of pyrazolin-5-one **1k**, the inverse order of addition of reagents significantly increased the yield of **2k** compared to the standard order of addition. Under standard conditions, the formation of **2k** (yield 16%) was accompanied by oxidative dimerization of **1k** (diastereomeric dimers **3-meso** and **3-racemic** were isolated in yields of 44% and 32%, respectively).

The use of the inverse order of addition of reagents allowed to avoid oxidative dimerization and afforded **2k** in 37-58% yield. The optimal reaction time between $Fe(NO_3)_3$•$9H_2O$ and $NaNO_2$ was 5 min (the yield of **2k** 58%). In the case of longer reaction times between $NaNO_2$ and $Fe(NO_3)_3$ the yield of **2k** decreased (53% for 10 min, 49% for 15 min), apparently, for the same reason as in case of experiment with **2a**, due to gradual decomposition of the nitration agent (NO_2). Shorter time (0.5 min) of interaction between $Fe(NO_3)_3$•$9H_2O$ and $NaNO_2$ gave a 37% yield of **2k** that was average between yield using the standard order of addition (16%) and the yield with optimal time of 5 min (58%), which can be attributed to the incomplete reaction between $Fe(NO_3)_3$•$9H_2O$ and $NaNO_2$ after 0.5 min.

Control experiments were conducted to support the plausible roles of Fe^{3+} ions and NO_2 in the reaction of pyrazolin-5-ones with $Fe(NO_3)_3$/$NaNO_2$ system (Scheme 5).



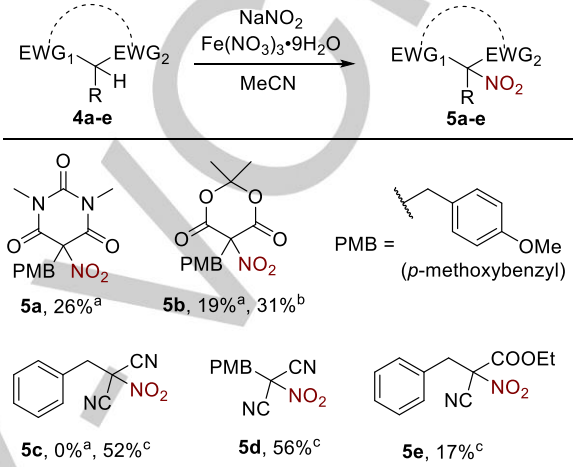
Scheme 5. Control experiments: a) nitration of **1a** by NO_2 as single reagent, b) oxidative dimerization of **1k** by iron (III) perchlorate

The possibility of nitration of pyrazolin-5-ones by NO_2 was confirmed by the experiment in which solution of pyrazolin-5-one **1a** in MeCN was treated with NO_2 gas yielding the desired nitro-pyrazolin-5-one **2a** (Scheme 5a).

As was mentioned above, a low yield of **2k** in the case of a standard order of addition of reagents was explained by the side oxidation reactions of **1k** under the action of Fe^{3+}. This hypothesis was confirmed by the experiment in which pyrazolin-5-one **1k** was treated by $Fe(ClO_4)_3$ in the absence of nitrating agents (Scheme 5b). Oxidative dimerization of pyrazolin-5-one **1k** with formation of two diastereomeric products **3** was observed.

At the next stage of our study, the applicability of the proposed system for the nitration of various CH acids was investigated. The prerequisite for this experiments was that deprotonated or tautomeric forms of CH-acids contained conjugated π-systems that could be attacked by NO_2 similarly to pyrazolin-5-one π-system.[57,91-93] Indeed, a series of nitro derivatives of CH-acids **4a-e** were synthesized using the developed $Fe(NO_3)_3$/$NaNO_2$ system (Table 3). Under standard conditions (substrate: $Fe(NO_3)_3$•$9H_2O$: $NaNO_2$ = 1: 2: 1, RT, 20 min) barbituric acid **4a** and Meldrum's acid **4b** give the corresponding nitration products **5a** and **5b** with low yields; for product **5b**, it was slightly increased by raising the temperature to 80 °C, extending the reaction time to 40 min and doubling the amounts of $Fe(NO_3)_3$ and $NaNO_2$.

Table 3. The synthesis of nitro derivatives **5a-e** by the nitration of substituted barbituric acid **4a**, substituted Meldrum's acid **4b**, substituted malononitriles **4c,d** and cyanoacetic ester **4e** [a].



[a] Standard conditions: $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added over 5-10 seconds to a stirred mixture of CH-acid **4a-e** (1 mmol), MeCN (5 mL) and $NaNO_2$ (1 mmol, 69 mg) at room temperature; stirring was continued for 20 min. [b] The amounts of $NaNO_2$ and $Fe(NO_3)_3$•$9H_2O$ were doubled: $NaNO_2$ (2 mmol, 138 mg) $Fe(NO_3)_3$•$9H_2O$ (4 mmol, 1616 mg), the temperature was increased to 80 °C, reaction time was 40 min [c] $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added over 5-10 seconds to a stirred mixture of substituted malononitrile **4c,d** or cyanoacetic ester **4e** (1 mmol), MeCN (5 mL) and $NaNO_2$ (1 mmol, 69 mg) at 80°C; stirring was continued at the same temperature for 20 min.

In the case of malononitrile **4c** the reaction did not proceed at standard room temperature conditions; 89% of **4c** was recovered. However, nitration of malononitriles **4c,d** and cyanoacetic ester derivative **4e** was successfully conducted at 80°C, nitro products **5c-e** were obtained in 17-56% yields (Table 3).

In vitro fungicidal activity of the synthesized nitrocompounds

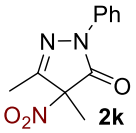
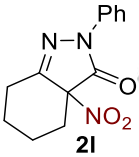
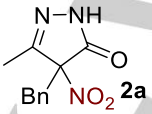
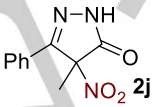
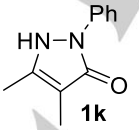
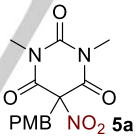
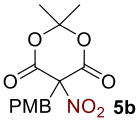
In the second part of our research, the synthesized 4-nitropyrazolin-5-ones **2** were discovered as a new class of fungicides. Phytopathogenic fungi against which synthesized compounds were tested are a dangerous threat to crop production (affected agricultural plants include cereals, rice, maize, apple, potato etc.). In agriculture and medicine, new types of fungicides are always demanded to struggle the fungal resistance development. There are hundreds of available commercial fungicidal substances, but currently only six modes of action are used in products that dominate around 80% of the fungicide market.[82] New classes of active fungicidal compounds are necessary to guarantee safe crop production and maintain

the activity of known effective fungicides by resistance management.[94,95] It should be noted that compounds tested in the present study are structurally not related to the compounds with known fungicidal activity and thus their fungicidal activity was not predictable. Indeed, fungicidal activity is not intrinsic for the pyrazolin-5-one structural fragment and nitro groups are rarely present in the structures of commercial fungicides. The rare examples of fungicidal compounds containing NO_2 group are dinitrophenol fungicides.[96] There are dozens of nitro-containing drugs, including antimicrobial and anti-parasitic ones. Almost all of them are nitroarenes or nitroheteroarenes and they are characterized by a C(sp^2)-NO_2 fragment. The problems in the application of these classes of bioactive molecules include the potential lack of selectivity, as well as genotoxic, mutagenic and carcinogenic properties.[97] The obvious distinguishing structural feature of compounds **2a-l** compared to known nitro-containing biocides is the *tert*-C(sp^3)-NO_2 fragment. Such principal structural difference allows supposing that the toxicity issues characteristic of nitroarenes and nitroheteroarenes may not be inherent to 4-nitropyrazolin-5-ones **2a-l**.

The nitropyrazolin-5-ones **2a,j,k,l** and nitro derivatives of barbituric and Meldrum's acids **5a** and **5b** were tested according to a standard procedure[98] against six phytopathogenic fungi from different taxonomic classes: *V.i. - Venturia inaequalis*, *R.s. - Rhizoctonia solani*, *F.o. - Fusarium oxysporum*, *F.m. - Fusarium moniliforme*, *B.s. - Bipolaris sorokiniana*, *S.s. – Sclerotinia sclerotiorum* (Table 4). The inhibition of the mycelium growth in the potato-sucrose agar containing tested compounds (30 mg/L) served as measure of fungicidal activity. Widely known fungicidal compounds fluconazole, clotrimazole, triadimefon, and kresoxim-methyl were used as a reference compounds. IC_{50} values of the selected compounds (**2k**, triadimefon, and kresoxim-methyl) are given in parentheses.

Nitropyrazolin-5-ones **2k** and **2l** containing a phenyl substituent at the nitrogen atom N-1 showed a pronounced fungicidal activity with respect to all tested species of phytopathogenic fungi. Nitropyrazolin-5-one **2k** surpassed commercial fungicidal active substances used as standards. Figure 1 shows petri dishes where almost complete mycelial growth inhibition for compound **2k** was observed. Nitropyrazolin-5-ones **2a** and **2j** with unsubstituted amide nitrogen are significantly inferior in activity compared to the **2k** and **2l**, which can be explained by the insufficient lipophilicity of **2a** and **2j**.[81,99] It should be noted that the starting pyrazolin-5-one **1k** without nitro group exhibits only a slight mycelial growth inhibition, which confirms the key role of the nitro group in pyrazolin-5-one in the manifested fungicidal activity. Nitro derivatives **5a,b** of barbituric and Meldum's acids did not show pronounced fungicidal activity. Thus, after initial tests 4-nitropyrazolin-5-ones were identified as a new promising class fungicidal compounds against phytopathogenic fungi that cause serious damage[100-102] in the cultivation of crops.

Table 4. Fungicidal activity of the synthesized compounds **2a,j,k,l** and **5a,b** and starting pyrazoline-5-one **1k**.

Compound	Mycelium growth inhibition [a], %; IC_{50}, mg/L in parentheses					
	V. i.	R. s.	F. o.	F. m.	B. s.	S. s.
 **2k**	100 (2.7)	100 (8.8)	90 (3.3)	100 (5.8)	100 (5.0)	81 (11)
 **2l**	100	89	50	69	94	50
 **2a**	44	76	34	50	46	15
 **2j**	14	11	11	5	36	6
 **1k**	22	30	11	10	39	14
 **5a**	22	7	6	3	21	8
 **5b**	37	27	15	9	34	7
Fluconazole	45	45	72	31	79	58
Clotrimazole	49	95	94	99	99	91
Triadimefon	47 (>30)	53 (27)	80 (10)	67 (15)	70 (4.0)	56 (18)
Kresoxim-methyl	96 (1.1)	87 (0.019)	65 (0.65)	72 (1.4)	56 (19)	41 (>30)

[a] Mycelium growth inhibition values were measured at 30 mg/L concentrations of the tested compounds in the nutrient medium

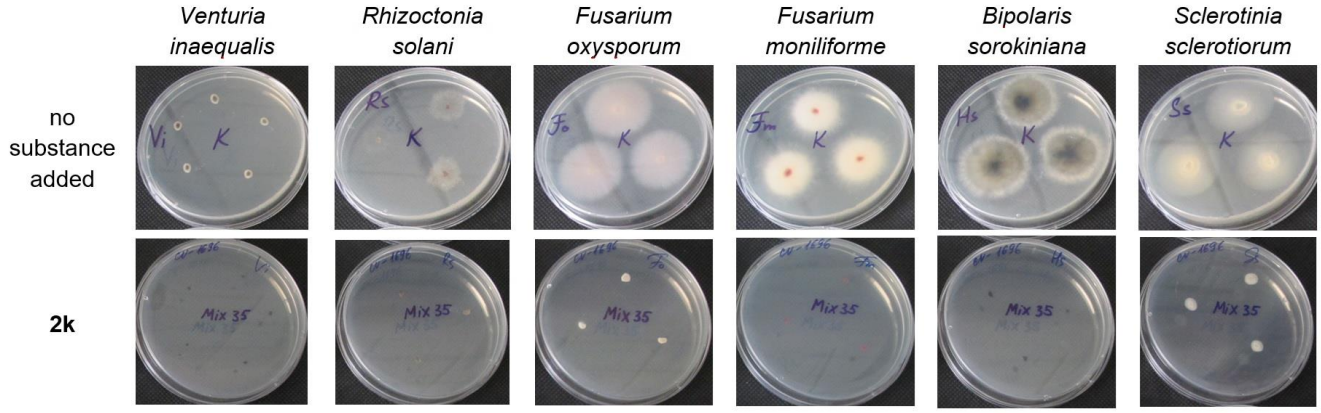
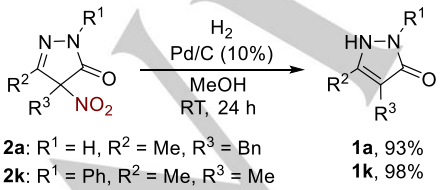


Figure 1. Photo demonstrating almost complete mycelial growth inhibition by compound **2k** in concentration 30 mg/L

Reactivity of nitro group in 4-nitropyrazolin-5-ones 2a,k under reductive conditions

One of the main ways of metabolism of the nitro group in living organisms is the reduction, which includes the formation of radical species, nitroso compounds (R-N=O) and hydroxylamines (RNHOH).[97,103,104] Therefore, 4-nitropyrazolin-5-ones can be considered as compounds that may be metabolically- and structurally-related to the reported HNO donors.[76,77] The key structural feature of the mentioned compounds responsible for the demonstrated activity is easily cleavable C-N bond at C4 position of pyrazolin-5-one. Taking into account the connection of high antifungal activity of 4-nitropyrazolin-5-ones with the presence of nitro group in the pyrazolin-5-one heterocycle, initial experiments on chemical reactivity of synthesized 4-nitro-pyrazolin-5-ones under reductive conditions were made.

The reactivity of the nitro group in synthesized 4-nitropyrazolin-5-ones is significantly different from that of the nitro group in the majority of organic compounds. It is well known that hydrogenation over a Pd/C catalyst is a reliable reduction method of nitro group to amino group in high yields.[105-107] However, hydrogenation of 4-nitropyrazolin-5-ones **2a** and **2k** over standard Pd/C (10%) catalyst at RT and atmospheric pressure of H_2 resulted in C-N bond cleavage and formation of unsubstituted pyrazolin-5-ones **1a** and **1k** (Scheme 6).



Scheme 6. The Pd/C catalyzed reduction of 4-nitropyrazolin-5-ones **2a,k** by molecular hydrogen

The cleavage of the *tert*-C(sp^3)-N bond of 4-nitropyrazolin-5-ones under the reductive conditions may play a significant role in their metabolism, and hence, toxicity issues associated with the formation of nitrogen containing products of reduction[97] may not be of relevance.

Conclusions

The system $Fe(NO_3)_3/NaNO_2$ was proposed for room temperature nitration of pyrazolin-5-ones. The developed method is compatible with functional groups that are sensitive to nitration conditions, such as N-phenyl, benzyl, and allyl. The $Fe(NO_3)_3/NaNO_2$ system allows to avoid side oxidation processes, that are typical for pyrazolin-5-ones, such as oxidative dimerization and hydroxylation. 1-Phenyl-4-nitropyrazolin-5-ones showed excellent fungicidal activity *in vitro* against phytopathogenic fungi. It should be noted that synthesized compounds are structurally not related to known classes of fungicidal substances (such as azoles, strobilurins, SDHIs, dinitrophenols) and discovery of their high fungicidal activity was not predictable. These compounds were identified as a promising starting point for development of novel and easily available class of fungicides.

Experimental Section

In all experiments RT stands for 22-25 °C. Iron(III) perchlorate hydrate reagent grade ($Fe(ClO_4)_3•nH_2O$, Alfa Aesar, anhydrous basis purity ca. 65%), $Fe(NO_3)_3•9H_2O$ 99+%, $(NH_4)_2Ce(NO_3)_6$ 99%, $Pb(NO_3)_2$ 99%, $Cu(NO_3)_2•2.5H_2O$ 98%, $Co(NO_3)_2•6H_2O$ 99+%, $NaNO_2$ 99%, *t*-BuONO 90%, 2,2,6,6-Tetramethylpiperidinooxy (TEMPO) 98%, $N_2H_4•H_2O$ (64% hydrazine), phenylhydrazine 98% were used as is from commercial sources. CH_2Cl_2, $C_2H_4Cl_2$, and MeOH were distilled prior to use. MeCN and EtOAc were distilled over P_2O_5. Glacial acetic acid was used as is from commercial sources. Preparation of the starting pyrazolin-5-ones is described in the ESI.

Experimental details for Table 1 (Optimization of the reaction conditions for nitration of 1a)

Oxidant ($Fe(NO_3)_3•9H_2O$, $Fe(ClO_4)_3•nH_2O$, $(NH_4)_2Ce(NO_3)_6$, $Cu(NO_3)_2•2.5H_2O$, $Co(NO_3)_2•6H_2O$, $Pb(NO_3)_2$, 1-4 mmol, 404-1616 mg) was added for 5-10 seconds to a stirred mixture of 4-benzyl-3-methylpyrazolin-5-one **1a** (1 mmol, 188 mg), solvent (5 mL) and nitrite

($NaNO_2$ or *t*-BuONO, 0-2 mmol, 0-138 mg) at given temperature; stirring was continued at the same temperature for 20 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and 3% aqueous solution of HCl (30 mL) and shaken. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), then all organic extracts were combined. Organic extracts were washed with water (2 × 20 mL), dried over $MgSO_4$, and rotary evaporated under water-jet vacuum. Nitration product **2a** was isolated by column chromatography on silica gel using the EtOAc/CH_2Cl_2 = 1/20 eluent.

4-Benzyl-3-methyl-4-nitro-1H-pyrazolin-5-one, 2a: yellow powder; mp = 84-85 °C dec.; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.53 (bs, 1H, NH), 7.35-7.26 (m, 3H, meta,para-Ph), 7.23-7.14 (m, 2H, ortho-Ph), 3.79 (d, *J* = 13.5 Hz, 1H, CH_2), 3.62 (d, *J* = 13.5 Hz, 1H, CH_2), 2.16 (s, 3H, CH_3); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 167.8 (O=C-NH), 153.8 (C=N), 129.9 (C_{Ar}), 129.8 (ortho-CH_{Ar}), 129.2 (meta-CH_{Ar}), 128.6 (para-CH_{Ar}), 93.2 (C-NO_2), 37.7 (CH_2), 14.4 (CH_3); ^{15}N NMR (40.56 MHz, $CDCl_3$): δ = -4.5 (NO_2), -54.9 (C=N), -207.0 (O=C-NH); FT-IR (KBr): ν_{max} = 3238, 1733, 1564, 1352, 1312, 1271, 773, 757, 711, 699, 604 cm^{-1}; HR-MS (ESI): m/z = 256.0698, calcd. for $C_{11}H_{11}N_3O_3$+Na^+: 256.0693; elemental analysis calcd. (%) for $C_{11}H_{11}N_3O_3$: C 56.65, H 4.75, N 18.02; found: C 56.47, H 4.58, N 17.77.

Experimental details for Table 2 (The synthesis of 4-nitropyrazolin-5-ones 2-l by the nitration of pyrazolin-5-ones 1a-l)

General procedure: $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added for 5-10 seconds to a stirred mixture of pyrazolin-5-one **1** (1 mmol), MeCN (5 mL) and $NaNO_2$ (1 mmol, 69 mg) at room temperature; stirring was continued at room temperature for 20 min. Products **2a, 2d-h** were isolated as described above in experimental details for Table 1. Products **2k,l** were isolated analogously, but CH_2Cl_2 was used as eluent for column chromatography. In the case of products **2b**, **2c**, **2i, 2j** reaction mixture was diluted with EtOAc (10 mL) and a solution prepared from brine (20 mL), H_2O (14 mL) and concentrated HCl (2 mL), and shaken. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL) and washed with brine (20 mL). Nitration products **2b, 2c, 2i, 2j** were isolated by column chromatography on silica gel using the EtOAc/CH_2Cl_2 = 1/20 eluent.

Procedure b for synthesis 2g (experiment according to note b): $Fe(NO_3)_3$•$9H_2O$ (4 mmol, 1616 mg) was added for 5-10 seconds to a stirred mixture of pyrazolin-5-one **1g** (1 mmol, 140 mg), MeCN (5 mL) and $NaNO_2$ (2 mmol, 138 mg) at room temperature; stirring was continued at room temperature for 20 min. Nitration product was isolated as described above in experimental details for Table 1.

Procedure c (experiments in Table 2 with note c): $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added over 5-10 seconds to a stirred mixture of $NaNO_2$ (1 mmol, 69 mg) and MeCN (5 mL) at room temperature; after 5 min pyrazolin-5-one **1j-l** (1 mmol, 174-214 mg) was added over 5-15 seconds. Stirring was continued at room temperature for 20 min. Nitration products **2j-l** were isolated as described above in general procedure.

Scaled up synthesis of 2d (according to note d): $Fe(NO_3)_3$•$9H_2O$ (14 mmol, 5.656 g) was added over 5-10 seconds to a stirred mixture of pyrazolin-5-one **1d** (7 mmol, 1.08 g), MeCN (35 mL) and $NaNO_2$ (7 mmol, 483 mg) at room temperature; stirring was continued at room temperature for 20 min. The reaction mixture was diluted with EtOAc (70 mL) and a solution prepared from of brine (105 mL), H_2O (70 mL) and concentrated HCl (10 mL), and shaken. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 70 mL), then all organic extracts were combined. Organic extracts were washed with brine (140 mL), dried over $MgSO_4$, and rotary evaporated under water-jet vacuum. Nitration product **2d** was isolated by column chromatography on silica gel using the EtOAc/CH_2Cl_2 = 1/20 eluent.

4-Allyl-3-methyl-4-nitro-1H-pyrazolin-5-one, 2b: slightly brown viscous gum; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.92 (bs, 1H), 5.59-5.20 (m, 3H), 3.18 (dd, *J* = 13.7, 6.8 Hz, 1H), 3.04 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 167.7, 154.0, 126.2, 123.4, 91.8, 36.1, 14.0; FT-IR (KBr): ν_{max} = 3528, 1730, 1557, 1422, 1404, 1384, 1350, 1305, 1264, 942, 818, 761, 746, 694, 611, 548 cm^{-1}; elemental analysis calcd. (%) for $C_7H_9N_3O_3$: C 45.90, H 4.95, N 22.94; found: C 45.98, H 4.90, N 22.98.

4-Ethyl-3-methyl-4-nitro-1H-pyrazolin-5-one, 2c: yellow powder; mp = 64-66 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 9.01 (bs, 1H), 2.51 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.28 (dq, *J* = 14.9, 7.5 Hz, 1H), 2.09 (s, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 168.0, 154.2, 93.5, 25.1, 13.7, 6.8; FT-IR (KBr): ν_{max} = 3323, 3259, 1742, 1717, 1561, 1546, 1358, 821, 663, 582 cm^{-1}; HR-MS (ESI): m/z = 194.0530, calcd. for $C_6H_9N_3O_3$+Na^+: 194.0536.

4-Butyl-3-methyl-4-nitro-1H-pyrazolin-5-one, 2d: slightly brown viscous gum; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.70 (bs, 1H), 2.55-2.38 (m, 1H), 2.31-2.15 (m, 1H), 2.08 (s, 3H), 1.47-1.30 (m, 2H), 1.30-1.01 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 168.0, 154.4, 92.9, 31.3, 24.4, 22.5, 13.75, 13.71; FT-IR (KBr): ν_{max} = 3279, 2963, 2935, 2875, 1739, 1556, 1432, 1383, 1352, 1251, 819, 760 cm^{-1}; HR-MS (ESI): m/z = 222.0842, calcd. for $C_8H_{13}N_3O_3$+Na^+: 222.0849.

4-Hexyl-3-methyl-4-nitro-1H-pyrazolin-5-one, 2e: amber viscous gum; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.98 (bs, 1H), 2.45 (td, *J* = 12.8, 4.8 Hz, 1H), 2.21 (td, *J* = 12.8, 4.8 Hz, 1H), 2.08 (s, 3H), 1.46-1.02 (m, 8H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ =168.2, 154.5, 93.0, 31.5, 31.3, 29.0, 22.5, 22.2, 14.1, 13.7; FT-IR (thin layer): ν_{max} = 3278, 2958, 2931, 2861, 1737, 1557, 1381, 1349, 819, 760 cm^{-1}; elemental analysis calcd. (%) for $C_{10}H_{17}N_3O_3$: C 52.85, H 7.54, N 18.49; found: C 53.13, H 7.78, N 18.06.

4-Methyl-4-nitro-3-propyl-1H-pyrazolin-5-one, 2f: yellow powder; mp = 67-69 °C dec.; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 9.05 (bs, 1H), 2.38-2.25 (m, 2H), 1.84 (s, 3H), 1.76-1.57 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 169.1, 158.5, 89.6, 29.5, 18.4, 17.5, 13.7; FT-IR (KBr): ν_{max} = 3300, 1736, 1711, 1568, 1560, 1384, 667 cm^{-1}; HR-MS (ESI): m/z = 208.0696, calcd. for $C_7H_{11}N_3O_3$+Na^+: 208.0693.

4-Isopropyl-3-methyl-4-nitro-1H-pyrazolin-5-one, 2g: slightly yellow powder; mp = 80-81 °C dec.; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 8.74 (bs, 1H), 3.01-2.85 (m, 1H), 2.13 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 167.3, 153.8, 95.9, 32.8, 16.2, 14.9, 14.5; FT-IR (KBr): ν_{max} = 3285, 1726, 1555, 1471, 1436, 1397, 1377, 1356, 1342, 1265, 822, 757, 727, 680, 565 cm^{-1}; elemental analysis calcd. (%) for $C_7H_{11}N_3O_3$: C 45.40, H 5.99, N 22.69; found: C 45.64, H 6.16, N 22.60.

3a-Nitro-2,3a,4,5,6,7-hexahydro-3H-indazol-3-one, 2h: white powder. mp = 127-128 °C dec.; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 9.21 (bs, 1H), 3.18-3.01 (m, 1H), 2.85-2.68 (m, 1H), 2.50-2.29 (m, 1H), 2.21-2.06 (m, 1H), 1.97-1.82 (m, 1H), 1.81-1.64 (m, 1H), 1.62-1.38 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 168.1, 158.1, 89.1, 33.6, 27.5, 21.0; FT-IR (KBr): ν_{max} = 3336, 1721, 1557, 1351, 1339, 1325, 829 cm^{-1}; elemental analysis calcd. (%) for $C_7H_9N_3O_3$: C 45.90, H 4.95, N 22.94; found: C 45.87, H 4.83, N 22.87.

3-(3-Methyl-4-nitro-5-oxo-4,5-dihydro-1H-pyrazol-4-yl)propanenitrile, 2i: slightly yellow powder; mp = 105-107 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6): δ = 12.10 (bs, 1H), 2.78-2.65 (m, 2H), 2.65-54 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (75.47 MHz, DMSO-d_6): δ = 167.1, 153.0, 118.5, 91.5, 25.7, 13.4, 10.6; FT-IR (KBr): ν_{max} = 3249, 2263, 1735, 1556, 1345, 1256, 826, 674, 604, 552 cm^{-1}; elemental analysis calcd. (%) for $C_7H_8N_4O_3$: C 42.86, H 4.11, N 28.56; found: C 42.93, H 4.08, N 28.39.

4-Methyl-4-nitro-3-phenyl-1H-pyrazolin-5-one, 2j: white powder; mp = 138-140 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 9.14 (bs, 1H), 7.70-7.55 (m, 2H), 7.54-7.37 (m, 3H), 2.07 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ =169.3, 154.7, 131.6, 129.5, 128.2, 126.0, 88.9, 19.3; FT-IR (KBr): ν_{max} = 3242, 1727, 1550, 1385, 769, 758, 693, 651 cm^{-1}; elemental analysis calcd. (%) for $C_{10}H_9N_3O_3$: C 54.79, H 4.14, N 19.17; found: C 54.78, H 4.12, N 19.16.

3,4-Dimethyl-4-nitro-1-phenylpyrazolin-5-one, 2k: slightly yellow crystals; mp = 40-41 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.94-7.84 (m, 2H), 7.51-7.39 (m, 2H), 7.32-7.22 (m, 1H), 2.22 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 164.6, 154.7, 137.0, 129.2, 126.2, 119.0, 91.8, 17.8, 13.3; FT-IR (thin layer): ν_{max} = 1731, 1597, 1558, 1501, 1383, 1368, 1294, 1147, 759, 691 cm^{-1}; HR-MS (ESI): m/z = 256.0697, calcd. for $C_{11}H_{11}N_3O_3$+Na$^+$: 256.0693.

3a-Nitro-2-phenyl-2,3a,4,5,6,7-hexahydro-3H-indazol-3-one, 2l: amber powder; mp = 86-87 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.1 Hz, 2H), 7.50-7.38 (m, 2H), 7.31-7.21 (m, 1H), 3.26-3.12 (m, 1H), 2.97-2.83 (m, 1H), 2.59-2.42 (m, 1H), 2.30-2.10 (m, 1H), 2.04-1.74 (m, 2H), 1.70-1.48 (m, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 164.0, 157.5, 137.1, 129.1, 126.1, 119.0, 91.3, 33.9, 27.54, 27.47, 21.0; FT-IR (KBr): ν_{max} = 1726, 1557, 1500, 1385; elemental analysis calcd. (%) for $C_{13}H_{13}N_3O_3$: C 60.23, H 5.05, N 16.21; found: C 60.27, H 5.18, N 16.08.

Reaction conditions for Scheme 4.

Standard order of addition. $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added over 5-10 seconds to a stirred mixture of pyrazolin-5-one **1k** (1 mmol, 188 mg), MeCN (5 mL) and $NaNO_2$ (1 mmol, 69 mg) at room temperature; stirring was continued at room temperature for 20 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and 3% solution of HCl (30 mL) and shaken. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), then all organic extracts were combined. Organic extracts were washed with water (2 × 20 mL), dried over $MgSO_4$, and rotary evaporated under water-jet vacuum. Column chromatography on silica gel using the CH_2Cl_2 as eluent gave 4,5-dimethyl-4-nitro-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **2k** (38 mg, 0.163 mmol, 16%), meso-4,4',5,5'-tetramethyl-2,2'-diphenyl-2,2',4,4'-tetrahydro-3H,3'H-[4,4'-bipyrazole]-3,3'-dione **3-meso** (82 mg, 0.219 mmol, 44%) and racemic-4,4',5,5'-tetramethyl-2,2'-diphenyl-2,2',4,4'-tetrahydro-3H,3'H-[4,4'-bipyrazole]-3,3'-dione **3-racemic** (60 mg, 0.160 mmol, 32%).

Meso-3,3',4,4'-tetramethyl-1,1'-diphenyl-[4,4'-bipyrazol]-5,5'-dione, 3-meso: white powder; mp = 161-162 °C (Lit.[45] mp = 163-164 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 4H), 7.49-7.34 (m, 4H), 7.22 (t, *J* = 7.3 Hz, 2H), 1.93 (s, 6H), 1.73 (s, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 173.1, 161.9, 137.6, 129.2, 125.7, 119.1, 54.5, 14.7, 14.6; HR-MS (ESI): *m/z* = 397.1637, calcd. for $C_{22}H_{22}N_4O_2$+Na$^+$: 397.1635; elemental analysis calcd. (%) for $C_{22}H_{22}N_4O_2$: C 70.57, H 5.92, N 14.96; found: C 70.52, H 5.95, N 14.91.

Racemic-3,3',4,4'-tetramethyl-1,1'-diphenyl-[4,4'-bipyrazol]-5,5'-dione, 3-racemic: slightly yellow powder; mp = 141-142 °C (Lit.[45] mp = 140-141 °C); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.9 Hz, 4H), 7.45-7.31 (m, 4H), 7.18 (t, *J* = 7.3 Hz, 2H), 2.19 (s, 6H), 1.60 (s, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 173.1, 159.8, 137.7, 129.0, 125.4, 119.3, 55.7, 16.0, 15.4; HR-MS (ESI): *m/z* = 397.1634, calcd. for $C_{22}H_{22}N_4O_2$+Na$^+$: 397.1635; elemental analysis calcd. (%) for $C_{22}H_{22}N_4O_2$: C 70.57, H 5.92, N 14.96; found: C 70.63, H 5.94, N 14.91.

Inverse order of addition of reagents. $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added for 5-10 seconds to a stirred mixture of $NaNO_2$ (1 mmol, 69 mg) and MeCN (5 mL); stirring was continued at room temperature for 0.5-15 min and then pyrazolin-5-one **1a** or **1k** (1 mmol, 188 mg) was added over 5-15 seconds; stirring was continued at room temperature for 20 min. Nitration products **2a** or **2k** were isolated as described above for standard order of addition.

Experimental details for Scheme 5.

a) Nitration of 4-benzyl-3-methylpyrazolin-5-one 1a with gaseous NO_2. Mixture of 4-benzyl-3-methylpyrazolin-5-one **1a** (1 mmol, 188 mg) and MeCN (5 mL) at room temperature was treated with gaseous NO_2 that was generated by thermal decomposition of three portions of finely powdered $Pb(NO_3)_2$ (4 g, 12 mmol per each portion). A second and a third portions of $Pb(NO_3)_2$ were added when emission of brown gas from the previous portion had ceased. Decomposition of $Pb(NO_3)_2$ was performed in the glass flask. Each portion was heated about 10 minutes. After the third portion was added, the hose connecting the flask where $Pb(NO_3)_2$ was decomposed with the flask containing pyrazolin-5-one and MeCN was disconnected and stirring of reaction mixture was continued at room temperature for another 10 minutes. Thus, the total reaction time was 40 min. The nitration product **2a** was isolated as described above in experimental details for Table 1.

b) The reaction of 3,4-dimethyl-1-phenylpyrazolin-5-one 1k with iron (III) perchlorate: $Fe(ClO_4)_3$•nH_2O (817 mg, 1.5 mmol) was successively added to a stirred at room temperature mixture of 3,4-dimethyl-1-phenylpyrazolin-5-one **1k** (282 mg, 1.5 mmol) and MeCN (5 mL); stirring was continued at room temperature for 20 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (25 mL) and shaken. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and all organic extracts were combined. Organic extracts were washed with water (2 × 20 mL), dried over $MgSO_4$, and rotary evaporated under water-jet vacuum. Meso-4,4',5,5'-Tetramethyl-2,2'-diphenyl-2,2',4,4'-tetrahydro-3H,3'H-[4,4'-bipyrazole]-3,3'-dione **3-meso** (135 mg, 0.361 mmol, 48%) and racemic-4,4',5,5'-Tetramethyl-2,2'-diphenyl-2,2',4,4'-tetrahydro-3H,3'H-[4,4'-bipyrazole]-3,3'-dione **3-racemic** (104 mg, 0.278 mmol, 37%) were isolated by column chromatography on silica gel using the EtOAc/benzene eluent; the volume part of EtOAc was gradually increased from 0 to 10%.

Experimental details for Table 3 (The synthesis of nitroderivatives 5a-e by the nitration of substituted barbituric acid 4a, substituted Meldrum acid 4b, substituted malononitriles 4c,d and cyanoacetic ester 4e)

Procedure a for the synthesis of nitroderivatives 5a-c. $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added for 5-10 seconds to a stirred mixture of **4a-c** (1 mmol, 156-276 mg), MeCN (5 mL) and $NaNO_2$ (1 mmol, 69 mg) at room temperature; stirring was continued at room temperature for 20 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and 3% aqueous solution of HCl (30 mL) and shaken. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and all organic extracts were combined. Organic extracts were washed with water (2 × 20 mL), dried over $MgSO_4$, and rotary evaporated

under water-jet vacuum. Nitration products **5a-b** were isolated by column chromatography on silica gel using the PE/CH_2Cl_2 = 1/10 eluent. Experiment with 2-benzylmalononitrile **4c** gave the starting compound (139 mg, 0.890 mmol, 89%) after evaporation step.

5-(4-Methoxybenzyl)-1,3-dimethyl-5-nitropyrimidine-2,4,6(1H,3H,5H)-trione, 5a: slightly yellow powder; mp = 102-103 °C dec.; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 2H), 3.77 (s, 3H), 3.19 (s, 6H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 162.5, 160.2, 148.9, 130.6, 121.0, 114.7, 92.8, 55.4, 41.9, 29.2; FT-IR (KBr): ν_{max} = 1696, 1570, 1515, 1445, 1379, 1351, 1299, 1257, 1242 cm^{-1}; elemental analysis calcd. (%) for $C_{14}H_{15}N_3O_6$: C 52.34, H 4.71, N 13.08; found: C 52.43, H 4.80, N 12.91.

5-(4-Methoxybenzyl)-2,2-dimethyl-5-nitro-1,3-dioxane-4,6-dione, 5b: slightly yellow powder; mp = 119-120 °C dec.; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.88 (s, 2H), 3.78 (s, 3H), 1.82 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 160.2, 160.0, 131.6, 120.5, 114.9, 109.2, 90.8, 55.5, 41.7, 29.8, 27.9; FT-IR (KBr): ν_{max} = 1785, 1752, 1576, 1515, 1365, 1316, 1307, 1288, 1258, 1178 cm^{-1}; elemental analysis calcd. (%) for $C_{14}H_{15}NO_7$: C 54.37, H 4.89, N 4.53; found: C 54.29, H 4.89, N 4.55.

Procedure b for synthesis 5b (according to note b): $Fe(NO_3)_3$•$9H_2O$ (4 mmol, 1616 mg) was added for 5-10 seconds to a stirred at 80 °C mixture of 5-(4-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione **4b** (1 mmol, 264 mg), MeCN (5 mL) and $NaNO_2$ (2 mmol, 138 mg) stirring was continued at 80 °C for 40 min. Nitration product **5b** was isolated as described above for the synthesis of **5a-b** according to procedure a.

The synthesis of nitroderivatives 5c-e by the nitration of substituted malononitriles 4c,d and cyanoacetic ester 4e (according to note c). $Fe(NO_3)_3$•$9H_2O$ (2 mmol, 808 mg) was added for 5-10 seconds to a stirred at 80 °C mixture of compound **4c-e** (1 mmol, 156-203 mg), MeCN (5 mL) and $NaNO_2$ (1 mmol, 69 mg); stirring was continued at 80 °C for 20 min. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and 3% aqueous solution of HCl (30 mL) and shaken. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and all organic extracts were combined. Organic extracts were washed with water (2 × 20 mL), dried over $MgSO_4$, and rotary evaporated under water-jet vacuum. Nitration products **5c-e** were isolated by column chromatography on silica gel using the EtOAc/PE = 3/10 eluent.

2-Benzyl-2-nitromalononitrile, 5c: white powder; mp = 98-99 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.58-7.41 (m, 3H), 7.41-7.32 (m, 2H), 3.86 (s, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 130.5, 130.2, 129.8, 127.6, 108.2, 78.9, 45.1; FT-IR (KBr): ν_{max} = 1593, 1347, 1310, 717, 704, 698 cm^{-1}; elemental analysis calcd. (%) for $C_{10}H_7N_3O_2$: C 59.70, H 3.51, N 20.89; found: C 59.60, H 3.35, N 20.53.

2-(4-Methoxybenzyl)-2-nitromalononitrile, 5d: white powder; mp = 93-94 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 8.6 Hz, 2H), 3.85 (s, 3H), 3.84 (s, 2H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 161.3, 131.5, 119.4, 115.2, 108.3, 79.0, 55.5, 44.8; FT-IR (KBr): ν_{max} = 1594, 1519, 1271, 1177, 1024, 839, 803 cm^{-1}; elemental analysis calcd. (%) for $C_{11}H_9N_3O_3$: C 57.14, H 3.92, N 18.17; found: C 57.44, H 4.01, N 17.96.

Ethyl 2-cyano-2-nitro-3-phenylpropanoate, 5e: slightly yellow powder; mp = 34 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.42-7.34 (m, 3H), 7.34-7.27 (m, 2H), 4.49-4.32 (m, 2H), 3.84 (d, *J* = 14.4 Hz, 1H), 3.73 (d, *J* = 14.4 Hz, 1H), 1.34 (t, *J* = 7. Hz, 3H); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 159.3, 130.1, 129.9, 129.30, 129.27, 111.0, 90.1, 65.9, 41.3, 13.8; FT-IR (KBr): ν_{max} = 1758, 1576, 1262, 1015, 851, 700 cm^{-1}; elemental analysis calcd. (%) for $C_{12}H_{12}N_2O_4$: C 58.06; H 4.87; N 11.29; found: C 58.12; H 4.87; N 11.25.

Reaction conditions for Scheme 6.

Pd/C catalyst (10%, 40 mg) was added to a solution of 4-nitropyrazolin-5-one **2a** or **2k** (1 mmol, 233 mg) in MeOH (5 mL) and hydrogenation was carried at RT and atmospheric pressure of H_2 for 24 h. Reaction mixture was filtered through celite, and the filtrate was rotary evaporated under water-jet vacuum. Evaporation gave 4-benzyl-3-methylpyrazolin-5-one **1a** (175 mg, 0.931 mmol, 93%) or 3,4-dimethyl-1-phehylpyrazolin-5-one **1k** (184 mg, 0.980 mmol, 98%), respectively.

Experimental detail for fungicidal activity testing (Table 4)

Tests of fungicidal activity were carried out according to a standard procedure[98] against six phytopathogenic fungi from different taxonomic classes: *V.i. - Venturia inaequalis*, *R.s. - Rhizoctonia solani*, *F.o. - Fusarium oxysporum*, *F.m. - Fusarium moniliforme*, *B.s. - Bipolaris sorokiniana*, *S.s. – Sclerotinia sclerotiorum*. Test substances preliminarily dissolved in acetone (concentration 3 mg/mL) were introduced into liquid sugar-potato agar having a temperature of 50-55 ° C, so that the final concentration of the substance in the nutrient medium was 30 mg/L (0.9 mL of solution in acetone per 90 mL agar). After thorough mixing, the agar was poured over sterile Petri dishes and, after cooling to room temperature, the pieces of mycelium from the peripheral growth zone of the mycelium of a three to five-day culture of the fungus were transferred to them with a needle. The control is a colony grown in the same nutrient medium without the addition of the active substance. 72 hours after inoculation, the diameters of the formed fungal colonies were measured. The indicator of fungicidal activity is suppression of mycelium growth in comparison with the control, calculated as $((D_c - D_s) / D_c) * 100\%$, where D_c - diameter of colony of fungus in control medium, D_s - colony diameter in medium with the tested substance added. In order to estimate IC_{50} values, series of test solutions of compounds in acetone were prepared by serial dilution by a factor of 3 (3 mg/mL, 1 mg/mL, 0.333 mg/mL, 0.111 mg/mL, 0.0370 mg/mL, 0.0123 mg/mL, 0.00412 mg/mL, 0.00137 mg/mL, 0.000457 mg/mL). Prepared solutions were tested for the fungicidal activity according to the standard procedure described above.

Acknowledgements

This work was supported by the Russian Science Foundation (Grant 17-73-10405).

Keywords: nitration • pyrazolin-5-ones • fungicidal compounds • crop protection • nitrogen dioxide

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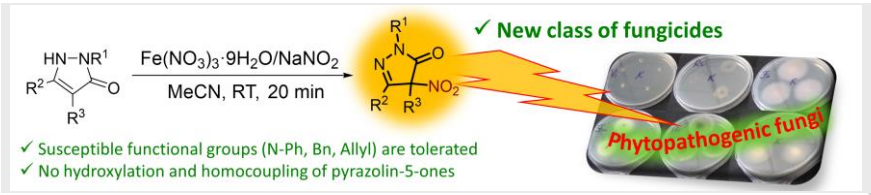

A new class of potent and structurally simple fungicides was discovered along with an original method for their preparation. The *in vitro* activity of the synthesized 4-nitropyrazolin-5-ones against phytopathogenic fungi is comparable or superior to commercial fungicides (fluconazole, clotrimazole, triadimefon, kresoxim-methyl).

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Mild nitration of pyrazolin-5-ones by a combination of $Fe(NO_3)_3$ and $NaNO_2$. Discovery of a new easily available class of fungicides – 4-nitropyrazolin-5-ones