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Dinitropyrazoles †

A A Zaitsev, I L Dalinger, S A Shevelev

Contents

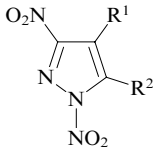
I.	Introduction	589
II.	1,3- Dinitropyrazoles and 1,5- dinitropyrazoles	589
III.	1,4-Dinitropyrazoles	593
IV.	3,4-Dinitropyrazoles and 4,5-dinitropyrazoles	602
V.	3,5-Dinitropyrazoles	611

Abstract. The syntheses, properties and applications of dinitropyrazoles are systematically reviewed. The bibliography includes 163 references.

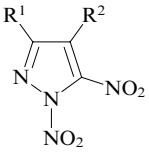
I. Introduction

Many nitro derivatives of pyrazole are of great practical value. They find applications as energetic materials, intermediates for the synthesis of a wide range of pharmaceutical and agrochemical products, ingredients of modern dyes and phosphors, materials for non-linear optics and condensation monomers. Of particular interest are dinitropyrazoles, which allow the multipurpose functionalisation of the pyrazole ring.

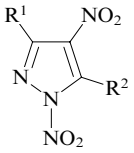
Theoretically, the existence of six isomeric dinitropyrazoles is possible: 1,3- (**A**), 1,5- (**B**), 1,4- (**C**), 3,4-(**D**), 4,5- (**E**) and 3,5-dinitropyrazoles (**F**). For the convenience of presentation, 1,3- and 1,5-dinitropyrazoles (due to the similarity of their properties and methods of synthesis as well as due to paucity of the latter) are discussed in one section; this applies to 3,4- and 4,5-dinitropyrazoles for the same reasons.



A (1,3)



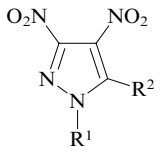
B (1,5)



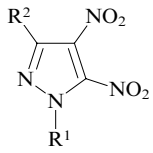
C (1,4)

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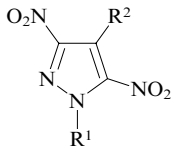
Received 15 December 2008
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D (3,4)



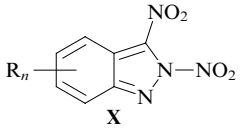
E (4,5)



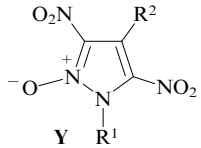
F (3,5)

R^1, R^2 = H, Alk, Ar, Het, AlkC(O), ArC(O), Hal, CN, *etc.*

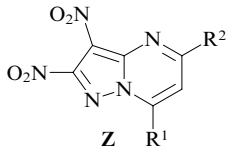
The review also addresses a few 2,3-dinitroindazoles (**X**, formally corresponding to the **B** type), 3,5-dinitropyrazole 2-oxides (**Y**) and any fused systems containing a dinitropyrazole fragment (for instance, of the **Z** type).



X



Y



Z

R, R^1, R^2 = H, Alk, Ar, Hal, NO_2, *etc.*

To date, information on dinitropyrazoles has been very sparse, there was no systematic survey covering these compounds. At the same time, reviews and monographs can be mentioned that contain some data on dinitropyrazoles.[1 – 14]

II. 1,3- Dinitropyrazoles and 1,5- dinitropyrazoles

It is well known that many 3- and 5-substituted NH-pyrazoles exist in solution as mixtures of unseparable tauto-

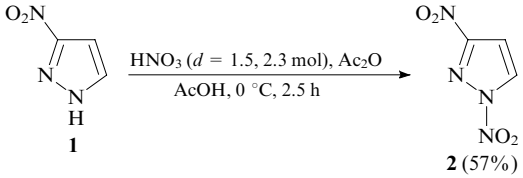
† The review is dedicated to the 75th anniversary of the N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences.

mers.[1–5] As the barrier of transition of one tautomer to another is fairly low, some of their properties are averaged. Accordingly, the H(3) and H(5) hydrogen atoms in the ^{1}H NMR spectra and the C(3) and C(5) carbon atoms in the ^{13}C NMR spectra are indistinguishable. Very often, in different chemical transformations 3(5)-substituted pyrazoles react as mixtures of tautomers, yielding mixtures of 1,3- and 1,5-derivatives. Moreover, the positions 3 and 5 of the pyrazole ring often possess very similar reactivities, at least the difference between them is considerably lesser than that between any of these positions and the position 4 of the pyrazole ring.[1–5] In addition, both 1,3- and 1,5-dinitropyrazoles are few in number; the latter are known only in the indazole series (2,3-dinitroindazoles). Therefore, these compounds, as already mentioned in the Introduction, are reasonable to consider in one section.

1. Synthesis of 1,3- and 1,5- dinitropyrazoles

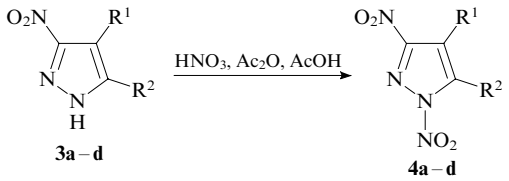
The only method of synthesis of 1,3- and 1,5-dinitropyrazoles is the N-nitration of the corresponding 3(5)-nitropyrazoles (including 3-nitroindazoles). Various reagents can be used to this end.

For the first time, a representative of the 1,3-dinitropyrazole series was obtained [15] in the early 1970s by nitration of 3(5)-nitropyrazole (**1**) with acetyl nitrate in acetic acid by a procedure developed [16] for the N-nitration of pyrazoles as far back as 1955. The reaction results only in the nitration product **2** to which the structure of 1,3- rather than 1,5-dinitro-derivative was ascribed based on ^{1}H NMR spectra.‡



(Hereinafter, d is the density in g cm^{-3}, the amount in moles is given per mole of the original pyrazole.) Later the structure of compound **2** was confirmed [19,20] by ^{15}N NMR spectroscopy.§ The fact that the thermal rearrangement of this pyrazole proceeds to form only one dinitro derivative in high yield (for details, see Section II.2) is also indirect evidence for the structure of this pyrazole.

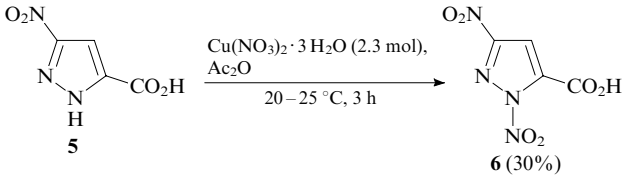
By analogy to compound **2**, the corresponding dinitropyrazoles were obtained [19,21] **4a–d** from substituted nitropyrazoles **3a–d**. The structures of compounds **4a**,**b** were established [19,20] by ^{15}N NMR spectroscopy.¶ The structures of compounds **4c**,**d** was postulated by the authors by analogy to the pyrazole **4a**.



R^1 = H, R^2 = Me (**a**); R^1 = CN, R^2 = H (**b**); R^1 = Cl, R^2 = Me (**c**); R^1 = Br, R^2 = Me (**d**).

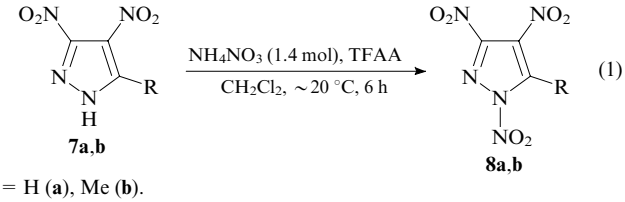
Compound **4**	Yield (%)	Ref.
a	50–80	19–21
b	50–80	19, 20
c	79	21
d	92	21

The nitration of 3(5)-nitropyrazole-5(3)-carboxylic acid (**5**) was performed [22] with a system copper nitrate–acetic anhydride.



The structure of 1,3-dinitropyrazole-5-carboxylic acid (**6**) obtained was postulated on the basis of an empirical observations that electrophilic attacks of 3(5)-nitropyrazole occur, as a rule, either exclusively or predominantly at the nitrogen atom the most remote from the nitro group.

For the synthesis of trinitropyrazoles **8** from dinitropyrazoles **7**, the so-called trifluoroacetyl nitrate, *i.e.*, a mixture of ammonium nitrate and trifluoroacetic anhydride (TFAA) [23,24] was used.



(1)

R = H (**a**), Me (**b**).

The authors of this study note that trinitropyrazoles can also be obtained using acetyl nitrate in acetic acid, but the synthesis of stable patterns of pyrazoles **8a**,**b** requires aprotic conditions.

Trinitropyrazoles are relatively stable substances, they do not decompose at 0–5 °C for at least 3–4 months. The structures of trinitropyrazoles **8a**,**b** were determined [19] with the help of ^{13}C and ^{15}N NMR spectroscopy.†

In the nitration of 6-chloroindazole (**9**) with acetyl nitrate a mixture of nitro- (**10**) and dinitroindazoles (**11**) is produced.[25] The amount of the dinitration products is low: the yield of a mixture of isomers **11a** and **11b** is only 2%.

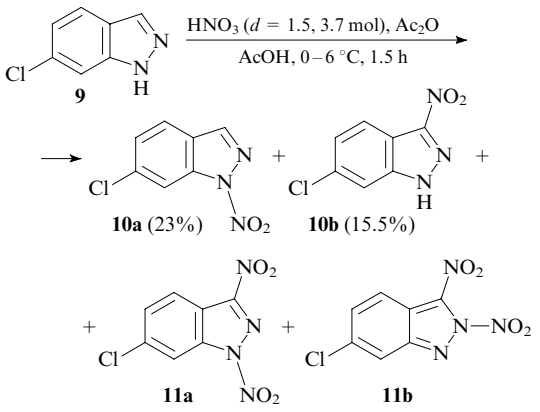
‡ According to the literature data,[17,18] the value of the coupling constant $^3J_{H(4),H(5)}$ is 2.2–3.0 Hz, and $^3J_{H(3),H(4)}$ is 1.3–2.0 Hz; the observed value ^3J = 2.8 Hz for compound **2** points to the location of the NO_2 group at the C(3) atom of the pyrazole ring.

§ For example, in the ^{15}N NMR spectrum of compound **2** the coupling constant $^2J_{N,H}$ = 2.5 Hz can be observed only for the N(1) nitrogen atom (δ −113.10), which is only possible if it is the position 5 of the pyrazole ring that is unsubstituted.

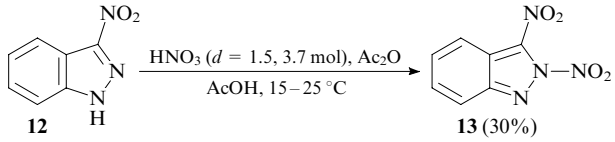
¶ In the ^{15}N NMR spectrum, the coupling constants ^{1}H–^{15}N $^3J_{N,Me}$ = 2.1 Hz (for pyrazole **4a**) and $^2J_{N,H}$ = 1.9 Hz (in the case of **4b**) can be observed only for the N(1) nitrogen atom (δ −113.96 for **4a** and −113.38 for **4b**), which is only possible if the corresponding substituent (Me, H) is located in the position 5 of the ring.

† Thus, it follows directly from ^{15}N NMR spectra that one of the nitro groups is located in the position 3 of the pyrazole ring: both compounds exhibit coupling constants of the N(1) nitrogen atom with the corresponding hydrogen atoms [$^2J_{N(1),H(5)}$ = 3.0 Hz for the signal for N(1) (δ −117.01) in the case of **8a** and $^3J_{N(1),Me}$ = 2.2 Hz for the signal for N(1) (δ −118.83) in the case of **8b**].[19]

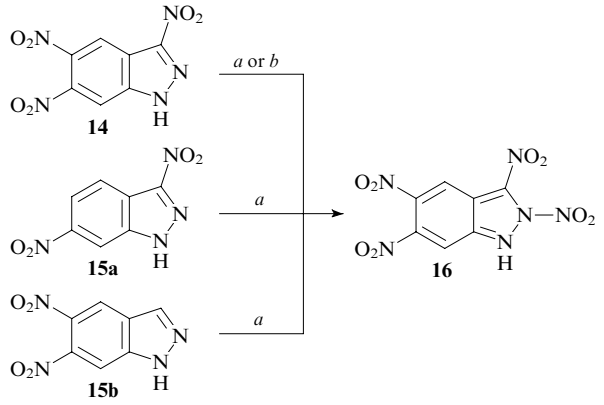
Furthermore, these dinitroindazoles were neither isolated as individual substances, nor characterised by spectroscopy. Data from elemental analysis served as the only proof.



It was reported [26] that the nitration of 3-nitroindazole (**12**) with acetyl nitrate afforded 2,3-dinitroindazole (**13**) in 30% yield. However, the possible formation of isomeric 1,3-dinitroindazole in this reaction and the arguments for the position of the NO_2 group at the N(2) nitrogen atom are not discussed.



It was established [27] that on treatment with a sulfuric–nitric acid mixture, trinitroindazole **14** and isomeric dinitroindazoles **15a**,**b** yield 2,3,5,6-tetrainitroindazole (**16**).



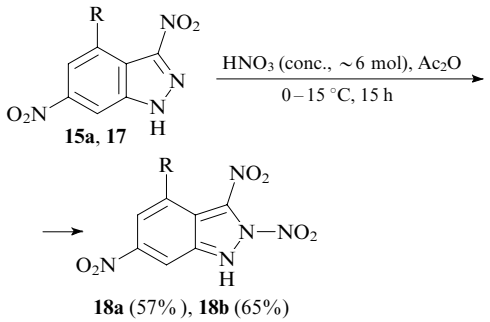
(*a*) HNO_3 (conc., ~25–30 mol), H_2SO_4 (conc.), 80 °C, 3–4 h (yield 82%–84%); (*b*) HNO_3 (conc., ~6 mol), Ac_2O, 0–15 °C, 15 h (yield 58%).

It should be noted that the formation of *N*-nitroazoles on treatment with a nitrating mixture is very uncommon, and in the pyrazole and indazole series this is perhaps a unique instance.

Even the authors themselves, in their first work [28] on this subject, erroneously assigned the structure of 3,5,6,7-tetranitroindazole to compound **16**. Thus compound **16** does not decompose on boiling in organic solvents (PhMe, CCl_4, C_2Cl_6, $ClCH_2CH_2Cl$), and no evolution of nitrogen oxides is observed. Upon the addition of D_2O to a solution of compound **16** in DMSO-d_6, one of the signals in the ^1H NMR spectrum disappears. This signal was assigned to the NH-proton of the indazole ring. Studies of the spectra of compound **16** in DMSO-d_6 and $(CD_3)_2CO$ with addition of variable amount of water showed [27] that upon the addition of D_2O, chemical shifts changed and the signals for H(4) and H(7) in the spectrum coalesce. Subsequently, it was found that compound **16** can also be prepared under classical conditions, *i.e.*, by the nitration of indazole **14** with acetyl nitrate. In the IR spectrum of compound **16**, bands at 1660 and 1290 cm^{-1} are observed, which clearly indicates the presence of an $N-NO_2$ group (see Table 1 of the electronic supplement; http://www.turpion.org/journal/rc).

The presence of an *N*-nitro group is also confirmed by the denitration of this compound (see Section II.2). The position of the nitro group at the nitrogen atom is also evidenced by the value of the dipole moment of compound **16** (2.19 D in dioxane at 25 °C), which virtually coincides with the calculated values of 2.24 D (Ref. 27) and 2.22 D (Ref. 29). The calculated dipole moments for other isomeric tetranitroindazoles fall into the range of 4–10 D. Low solubility of compound **16** in the nitrating mixture and, therefore, its exit from the reaction sphere as soon as it is formed can be a possible reason for its synthesis under such non-typical conditions.

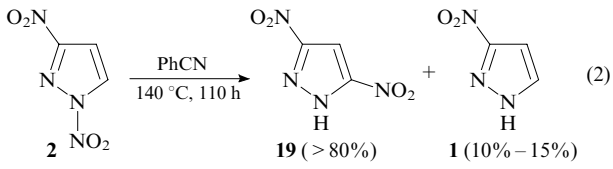
The nitration of indazoles **15a**, **17** with acetyl nitrate yielded 2,3,6-trinitroindazole (**18a**) and 2,3,4,6- tetranitroindazole (**18b**), respectively.[27] The position of the nitro group at the N(2) atom of the indazole was postulated by the authors by analogy with compound **16**.



R = H (**15a**, **18a**), NO_2 (**17**, **18b**).

2. Properties of 1,3- and 1,5-dinitropyrazoles

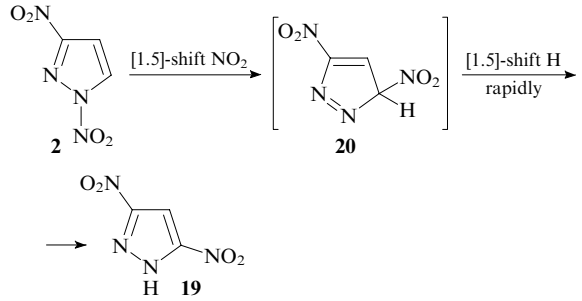
The thermal rearrangement, which is characteristic of *N*-nitropyrazoles,[15] also occurs in the case of 1,3-dinitropyrazoles. Thus the thermolysis of the simplest dinitropyrazole **2** in benzonitrile leads to 3,5-dinitropyrazole (**19**)[15] in high yield. The reaction is accompanied by the formation of an insignificant amount of denitration product **1**.



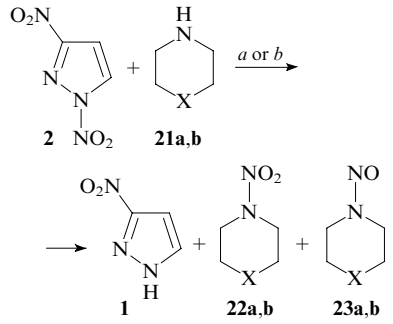
(2)

The kinetics of the rearrangement of compound **2** in nitrobenzene was investigated.[30] It was establshed that in

the temperature range 160–200 °C the reaction is first-order ($k_{150°C} = 3 \times 10^{-5}$ s^{-1}). The experimentally determined activation parameters are as follows: $\Delta H^{\neq} =$ 37 kcal mol^{-1}, $\Delta S^{\neq} = 2$ cal mol^{-1} K^{-1}. Such a low enthalpy of activation as compared to an estimated value of the energy of the bond N–NO$_2$ (45–50 kcal mol^{-1}) together with the data on the rearrangements of other *N*-nitropyrazoles (the lack of a kinetic isotope effect H/D, low sensitivity of the activation parameters to the nature of the solvent, the absence of by-products of radical reactions) suggest that the key step of the rearrangement is a concerted intramolecular [1,5]-sigmatropic shift of the NO$_2$ group. The intermediate 3,5-dinitro-3*H*-pyrazole (**20**) undergoes fast aromatisation to form 1*H*-pyrazole **19**.



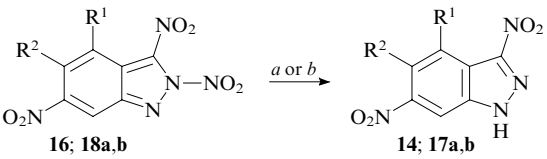
It was also found [31] that treatment of dinitropyrazole **2** with secondary amines [piperidine (**21a**) and morpholine (**21b**)] brings about denitration of the N–NO$_2$ group, which is characteristic of *N*-nitropyrazoles, to afford 3(5)-nitropyrazole (**1**) and 1-nitropiperidine (**22a**) and 4-nitromorpholine (**22b**), respectively, and also minor amounts of 1-nitrosopiperidine (**23a**) and 4-nitrosomorpholine (**23b**). It should be noted that the addition of compounds preventing the nitrosation of amines [CO(NH$_2$)$_2$, K$_2$CO$_3$, MgCO$_3$] to the reaction mixture does not affect the formation of compounds **23a**,**b**.



(3)

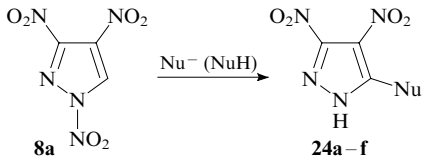
X = CH$_2$ (**a**), O (**b**); X = O: **1** (84%), **22b** (84%), **23b** (14%);
(*a*) for X = CH$_2$: MeCN, 20 °C, 5 days or reflux, 45 min;
(*b*) for X = O: EtOH, 25 °C, very long or reflux, 16 h.

It was demonstrated [27] that the denitration of dinitroindazoles **16**, **18a**,**b** can be carried out both on refluxing with solutions of acids (H$_2$SO$_4$, HCl, HBr, HNO$_3$, HOAc), *i.e.*, under classical conditions of acid-induced denitration, and also on treatment with reductants, for example, sodium iodide. In the former case, the NO$_2$ group is eliminated as a nitronium ion (to form nitric acid), and in the latter case, it is eliminated as the nitrite ion.



(*a*) H_3O^+ (–HNO$_3$), 100 °C, 4–5 h;
(*b*) 1) NaI, Me$_2$CO, 15–20 °C, 1 h; 2) HCl, H$_2$O (–HNO$_2$, – I$_2$).

It was establshed [10,23,24] that on treatment of trinitropyrazole **8a** (as a solution in Et$_2$O) with various O-, C- and N-nucleophiles, *cine*-subsitution of the *N*-nitro group occurs, which is characteristic of 1,4-dinitropyrazoles (see Section III.2), and the substitution products **24a**–**f** are formed.



(4)

Compound **24**	Nu	Reaction conditions	Yield (%)
a	OMe	–	–
b	OEt	KOH, EtOH, ~20 °C, 10 min	71 [a]
c	CN	KCN, EtOH, ~20 °C, 30 min	85
d	N_3	NaN$_3$, EtOH, ~20 °C	95
e	CH(CO$_2$Et)$_2$	EtONa, CH$_2$(CO$_2$Et)$_2$, EtOH, 20 °C, 1 h	78
f	pz [b]	Hpz, MeCN, ~20 °C, 7 h	71

[a] As the ammonium salt; [b] Hpz is pyrazole.

In a joint study by two research groups, [21] data on the biological activity of dinitropyrazoles **4a**,**c**,**d**, and also other nitropyrazoles have been obtained. It was establshed that all of them possess the ability to substantially increase the ocular blood flow (experiments on rabbits) and restore the function of retina (experiments on rats) disordered as a result of ischemia. Such an effect of compounds **4a**,**c**,**d** is associated with the ability of *N*-nitropyrazoles to generate nitrogen(II) oxide [32] which acts as a regulator of the vasodilatory process.[33] Liberation of NO from nitropyrazoles **4a**,**c**,**d** in cell cultures of the rabbit lacrimal gland was detected.[34] Afterwards, a potential possibility of using these dinitropyrazoles for the treatment or prevention of macular degeneration was mentioned also in a patent.[35]

1,3-Dinitropyrazoles are low-melting (M_p < 100 °C) or oily substances; the melting points of 2,3-dinitroindazoles are higher (130–200 °C).

The IR spectra of 1,3-dinitropyrazoles and 2,3-dinitroindazoles display characteristic absorption bands at 1620–1680 and 1264–1290 cm^{-1}, which correspond to the antisymmetric and symmetric vibrations of the NNO$_2$ group, and also absorption bands at 1525–1580 and 1320–1380 cm^{-1}, which correspond to the antisymmetric and symmetric vibrations of the CNO$_2$ group.

In the ^{1}H NMR spectra of 1,3-dinitropyrazoles, the signals for the H(4) and H(5) atoms appear in the ranges δ 7.17–7.40 and 8.45–9.08, respectively, and depend on the

chemical environment of these atoms. The signals for the protons of Me groups in the ^{1}H NMR spectra of 5-methyl-1,3-dinitropyrazoles are observed at δ 2.71–2.80.

In the ^{13}C NMR spectra, 1,3-dinitropyrazoles exhibit signals for the C(3), C(4) and C(5) atoms in the ranges δ 144.75–153.92, 92.70–128.35 and 128.25–143.75, respectively; the precise value of a chemical shift depends on the chemical environment of these atoms. The signals for the protons of Me groups in the ^{13}C NMR spectra of 5-methyl-1,3-dinitropyrazoles fall into the interval δ 12.97–14.28.

In the ^{15}N NMR spectra of 1,3-dinitropyrazoles, the chemical shifts of the N(1), N(2), (N)NO_2 and [C(3)]NO_2 nitrogen atoms appear in the ranges δ from −113.10 to −118.83; from −91.65 to −98.58; from −59.78 to −68.65 and from −24.20 to −31.02, respectively.

Data on the properties of 1,3-dinitropyrazoles are presented in Table 1 of the electronic supplement.

III. 1,4-Dinitropyrazoles

The known 1,4-dinitropyrazoles are much more numerous than the corresponding 1,3-dinitro derivatives, and their chemistry is more diverse.

1. Synthesis of 1,4-dinitropyrazoles

Like 1,3-derivatives, 1,4-dinitropyrazoles are formed as a result of N-nitration of pyrazoles, however, the range of the reactants used is wider; in addition, in this case there is a possibility of the intoduction of two nitro groups simultaneously into the pyrazole ring.

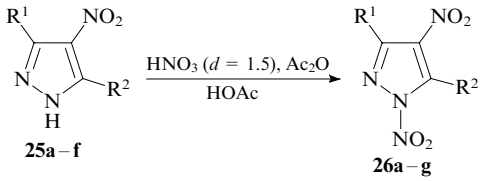
The first 1,4-dinitropyrazoles were synthesised[16] as early as 1955 by the nitration of 4-nitropyrazoles **25a–c** (Table 1).[16] A detailed study[31] of the nitration products of

Table 1. The conditions of nitration of compounds **24a–f** and the yields of reaction products.

Product	Ratio HNO_3 : **24** (mol)	T/°C	Time of reaction /h	Yield (%)	Ref.
26a	1.1	20	1	traces	16
	3.2	0	0.5	81	15
26b	1.1	20	1	34	16
26b + **26g**	2.5	< 25	—	88 (60)[a] + 7	31
26c	1.1	20	1	59	16
26d	3.2	0	1.5	97	15
26e	2.5	20	5	90	36
26f	2.33	< 15	3–4	72	37

[a] The nitration of 3-methyl-4-nitropyrazole by this method[31] produces a mixture of isomers **26b** and **26g** in two portions: pure **26b** and a mixture of **26b** and **26g**; the overall yield of isomer **26b** is 88%; the yield of the pure product **26b** in the frist portion is 60%.

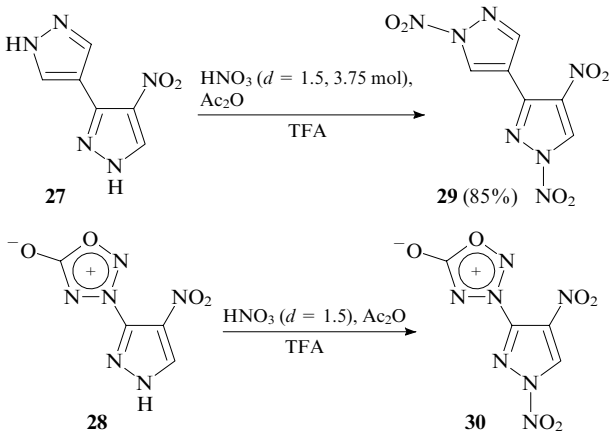
pyrazole **25b** led to the detection of a minor nitration product, *viz*., compound **26g**. Based on ^{1}H NMR spectra, compound **26b** was identified as 3-methyl-1,4-dinitropyrazole, while compound **26g** was identified as isomeric 5-methyl-1,4-dinitropyrazole.‡ The structure of the 3-Ph-isomer was also ascribed[15] to dinitropyrazole **26d**.§ The position of subsituents in compounds **26e** and **26f** has not been discussed.[36, 37]



25a–f **26a–g**

$R^1 = R^2 = H$ (**a**); R^1 = Me: $R^2 = H$ (**b**), Me (**c**); R^1 = Ph, $R^2 = H$ (**d**); $R^1 = CO_2Pr^i$: $R^2 = H$ (**e**), Me (**f**); $R^1 = H$, R^2 = Me (**g**).

Instead of acetic acid, trifluoroacetic acid (TFA) can also be used as a solvent. Upon the nitration of 4-nitro-3,4′-bipyrazole (**27**) and 3-(4-nitropyrazol-3-yl)-1,2,3,4-oxatriazol-3-ium-5-olate (**28**), the corresponding 1,4-dinitro derivatives **29** and **30** were synthesised[38, 39]. The 3,4′-assembly of pyrazole rings in compound **29** was proved by ^{15}N NMR spectroscopy.¶ The position of subsituents in dinitropyrazole **30** was not the matter of determination and was postulated by analogy with compound **28**.



27 **29** (85%) **28** **30**

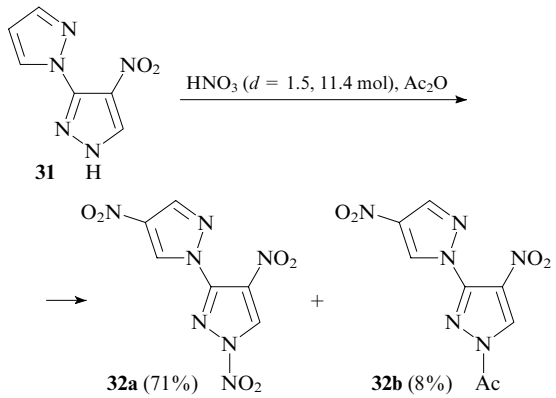
In a number of cases, the 'classical' nitration with acetyl nitrate (a mixture of HNO_3 and Ac_2O in AcOH)[41] affords no nitration products. Thus it was established that 4′-nitro-

‡ The ^{1}H NMR spectrum of compound **26b** (in $CDCl_3$) contains signals for the Me group at δ 2.73 and for an aromatic proton at δ 9.13, whereas in the spectrum of compound **26g** these signals appear at δ 3.12 and 8.12, respectively, *i.e.*, owing to the low-field effect of the adjacent *N*-nitro group, δ(CH) is larger for the 3-Me-isomer, while δ(Me) is larger for the 5-Me-isomer.

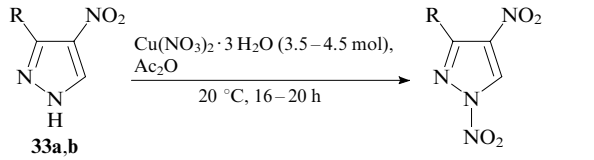
§ Indeed, the δ(CH) value for the proton of the pyrazole ring in the ^{1}H NMR spectrum of compound **26d** (in $CDCl_3$) is 9.10, which is very close to the value of 9.13 observed for compound **26b**.

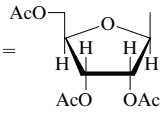
¶ In the ^{15}N NMR spectrum with selective polarisation transfer $^1H \rightarrow {}^{15}N$, a signal for the N(1) nitrogen atom with δ −113.58 and $^2J_{N(1),H(5)} = 1.6$ Hz is observed. Since the coupling constant $^3J_{N(2),H(5)} < 1$ Hz, no signal for the N(2) nitrogen atom appears. In the case of 5,4′-assembly of the rings, two signals would appear in the $^1H \rightarrow {}^{15}N$ polarisation transfer spectrum for N(1) and N(2), with the coupling constants 10–14 Hz.[40]

1,3′-bipyrazole (**31**) gives derivative **32a** (as a mixture with acetyl derivative **32b**) only in the absence of acetic acid. The arrangement of subsituents in bipyrazole **32a** was not discussed.

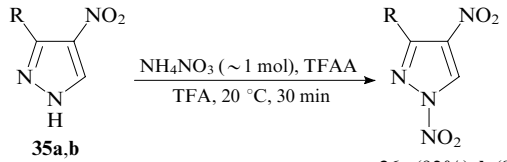


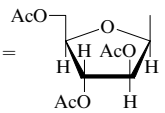
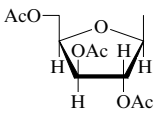
For the synthesis of 1,4-dinitro-3-(2,3,5-tri-*O*-acetyl-*β*-D-ribofuranosyl)pyrazole (**34a**) and 3-[(*S*)-2,3-diacetoxypropyl]-1,4-dinitropyrazole (**34b**) from nitropyrazoles **33a**,**b**, copper nitrate trihydrate [42–44] was used. The structure of 3-R-derivative was ascribed [43] to compound **34a** on the ground of the chemical shift of the proton of the pyrazole ring (δ = 9.11) in the ^{1}H NMR spectrum of compound **34a** and the difference $\Delta(\delta)$ = 0.9 with that in the starting pyrazole **33a**. In subsequent works of this research group, the issue of the structures of other 1,4-dinitropyrazoles was not considered.



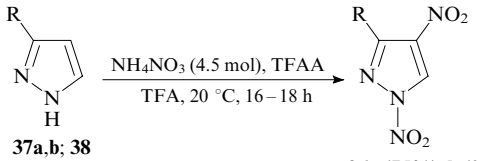
R =  (**a**), (*S*)-$CH_2CH(OAc)CH_2OAc$ (**b**).

The system ammonium nitrate–trifluoroacetic anhydride in trifluoroacetic acid was employed [45,46] for the *N*-nitration of nitropyrazoles **35a**,**b** to compounds **36a**,**b**.



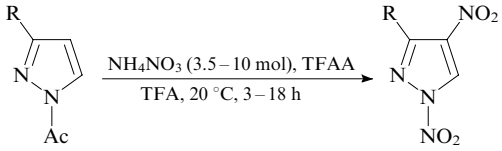
R =  (**a**),  (**b**).

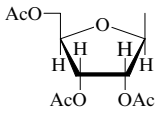
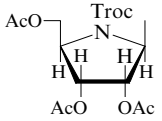
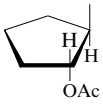
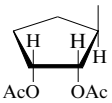
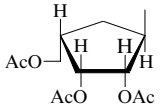
Further investigations showed [47] that 1,4-unsubstituted pyrazoles are nitrated to the corresponding 1,4-dinitro derivatives in the system NH_4NO_3–TFAA in TFA in a single synthetic step. In this way, compounds **26a**,**b** and **34b** were prepared from pyrazoles **37a**,**b** and **38**, respectively. It is of note that the presence of trifluoroacetic acid is essential for the preparation of dinitropyrazoles; in the absence of the acid, the system NH_4NO_3–TFAA nitrates 3(5)-methylpyrazole (**37b**) only to 1-nitro derivative.



R = H (**37a**, **26a**), Me (**37b**, **26b**), (*S*)-$CH_2CH(OAc)CH_2OAc$ (**38**, **34b**).

In subsequent studies on nitration with this system it was shown [48] that not only NH-pyrazoles, but also *N*-acetylpyrazoles can be used; under the nitration conditions, the Ac group in pyrazole **39** is readily replaced by NO_2. This method was used by other research groups for the synthesis of compounds **41a**–**d**.[49–52] from *N*-acetylpyrazoles **40a**–**d**.

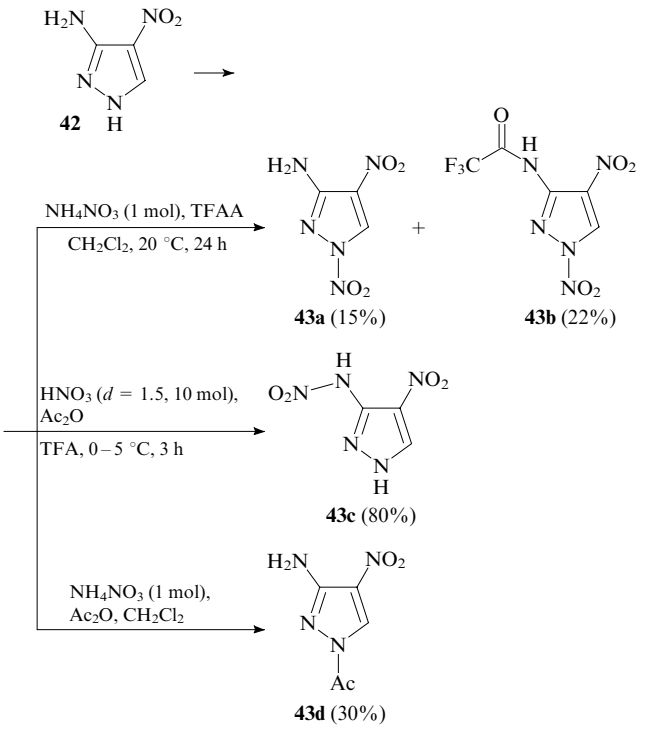


Starting compound	Product	R	Product yield (%)
39	**34a**		95
40a	**41a**		~100
40b	**41b**		~100
40c	**41c**		99
40d	**41d**		98

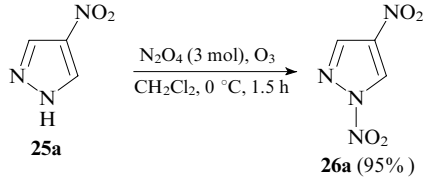
Troc is 2,2,2-trichloroethoxycarbonyl.

It is only in the system NH_4NO_3–TFAA in CH_2Cl_2 (aprotic conditions) that 3(5)-amino-4-nitropyrazole (**42**) can be converted in the corresponding 3-amino-1,4-dinitropyrazole (**43a**) (together with the amino group trifluoroacetylation product **43b**).[53] Upon the addition of small amounts of TFA, *N*-trifluoroacetyl-3-amino-1,4-dinitropyrazole (**43b**) is formed almost exclusively. The replacement of trifluoroacetic anhydride by acetic anhydride in the abovementioned system results in 1-acetyl-3-amino-4-nitropyrazole (**43d**). No *N*-nitration of the pyrazole ring of compound **42** occurs with the systems $Cu(NO_3)_2 \cdot 3\,H_2O$–Ac_2O, $AgNO_3$–AcCl, NO_2BF_4–CH_2Cl_2, its trimethylsilyl derivative is neither N-nitrated with NO_2BF_4 in CH_2Cl_2. The system HNO_3–Ac_2O in TFA gives only the amino group nitration product **43c**. It is known that 3-aminopyrazoles are protonated at the nitrogen atom of the heterocycle;[54]

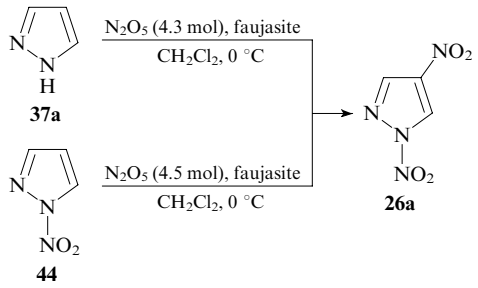
apparently, it is this feature that determines the direction of the reaction under acidic conditions. The position of the NH_2 and $CF_3C(O)NH$ groups at the C(3) carbon atom of the pyrazole ring in compounds **43a** and **43b** follows from the chemical shifts of the unsubstituted carbon atoms (CH) in the ^{13}C NMR specrum δ 128.24 and 127.49, respectively), which is consistent with the chemical shifts of the C(5) atoms in 3-aminopyrazoles.[11]



It was found that 4-nitropyrazole (**25a**) is converted to 1,4-dinitropyrazole **26a** in high yield when treated with nitrogen(IV) oxide in the presence of ozonated oxygen (the so-called *Kyodai* nitration).[55]



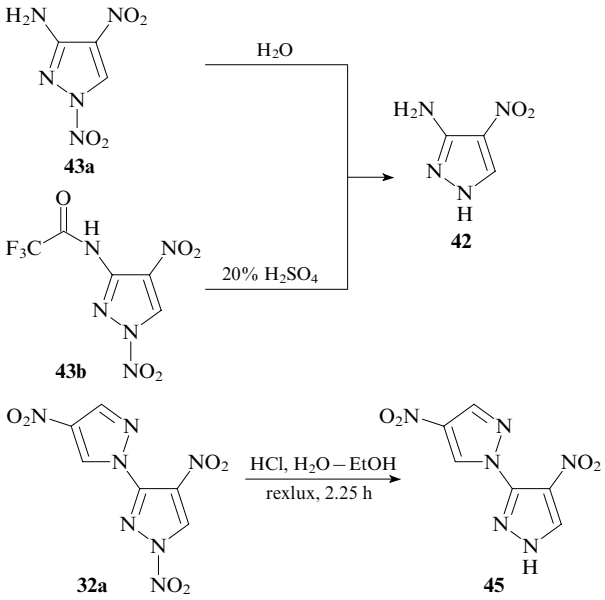
It was demonstrated[56] that nitrogen(V) oxide in the presence of faujasite nitrates both pyrazole (**37a**) and 1-nitropyrazole (**44**). This is the only instance of a direct nitration of 1-nitropyrazoles at a carbon atom of the heterocycle that is documented.



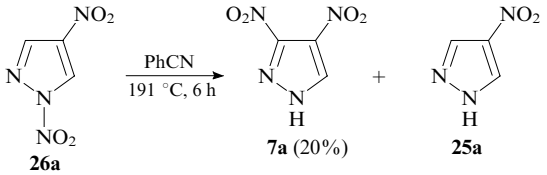
The nitration kinetics of pyrazole (**37a**) was investigated. It was establshed that the nitration reaction is first order with respect to pyrazole and does not depend on the N_2O_5 concentration. If faujasite F-720 (with the approximate composition $H_{12}Al_{12}Si_{180}O_{384}$) is employed as the catalyst, 1-nitropyrazole (**44**) is formed virtually immediately, it is then converted to 1,4-dinitropyrazole with an appreciable induction period. If faujasite F-780 (with the approximate composition $H_{4.2}Al_{4.2}Si_{187.6}O_{384}$) is the catalyst, the reaction rate is much lower (the activity of faujasite is proportional to the aluminium content): significant amounts of 1-nitropyrazole (**44**) are produced in 5 min, the formation of 1,4-dinitropyrazole has a long induction time (after 30 min, the yield of compound **26a** is 4.5%; after 1 h, it is 25%). If 1-nitropyrazole (**44**) is nitrated under the same conditions, there is no induction period, and if faujasite F-720 is the catalyst, a 90% yield of 1,4-dinitropyrazole (**26a**) is achieved already in 5 min.

2. Properties of 1,4-dinitropyrazoles

Many chemical reactions charateristic of *N*-nitropyrazoles, generally, also pertain to the 1,4-dinitro derivatives. Like the majority of *N*-nitropyrazoles, 1,4-dinitropyrazoles undergo denitration under acidic conditions. Thus compound **30** is hydrolytically unstable on storage in air,[39] pyrazoles **43a**,**b** are easily hydrolysed with water (the removal of the trifluoroacetyl group from the molecule **43b** requires an acid),[53] whereas the denitration of compound **32a** to bipyrazole **45** was carried out by its boiling in a solution of hydrogen chloride in aqueous ethanol.[41]

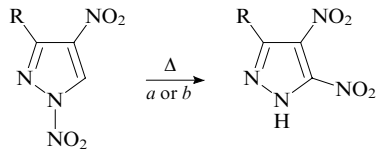


Like the majority of *N*-nitropyrazoles, 1,4-dinitro derivatives undergo thermal rearrangement into 3,4-dinitropyrazoles. The simplest 1,4-dinitropyrazole (**26a**), however, produces 3,4-dinitropyrazole (**7a**) only in low yield, the reaction is accompanied by the formation of a significant amount of a denitration product (**7a** : **25a** = 4 : 1).[15]



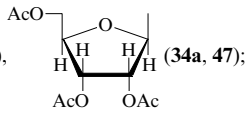
(5)

The presence of a substituent at the position 3 of pyrazole increases the yields of rearrangement products **46**, **47**.[15,42]



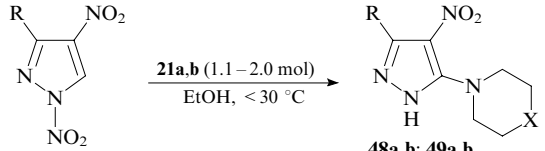
(6)

26d, **34a** **46** (80%), **47** (60%)

R = Ph (**26d**, **46**),  (**34a**, **47**);

(*a*) PhCN, 140 °C, 1.5 h (for **26b**); (*b*) PhOMe, 154 °C (for **34a**).

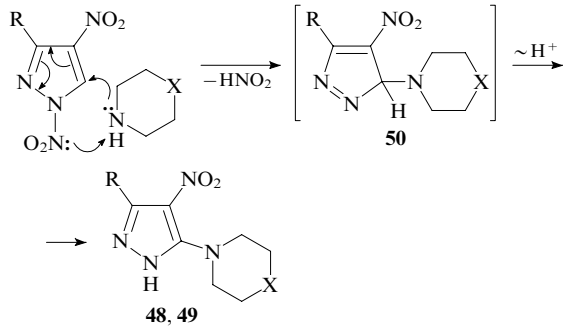
Nucleophilic *cine*-substitution of the *N*-nitro group in 1,4-dinitropyrazoles was discovered[31] in the studies of the reaction of 1,4-dinitropyrazoles **26a**,**b** with cyclic secondary amines **21a**,**b**. Unlike 1,3-dinitropyrazoles, which undergo denitration [see reaction (3)] when treated with the same amines, 1,4-dinitro derivatives give the corresponding NH-unsubstituted 3(5)-amino-4-nitropyrazoles **48**, **49**. The position 5 of the pyrazole ring of 3-methyl-1,4-dinitropyrazole (**26b**) was shown to be the site of an attack by a nucleophile in this reaction.



26a,**b** **48a**,**b**; **49a**,**b** (20% – 85%)

R = H (**26a**, **48a**, **49a**), Me (**26b**, **48b**, **49b**);
X = CH_2 (**21a**, **48a**,**b**), O (**21b**, **49a**,**b**).

A synchronous mechanism of this reaction with no formation of an intermediate anionic σ-complex is assumed. The produced 3*H*-pyrazoles **50** undergo rapid aromatisation to NH-pyrazoles.

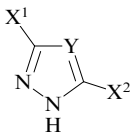


50

48, **49**

A semi-empirical calculation by the AM1-COSMO method[57] for the *cine*-substitution in 1,4- dinitropyrazoles **26a**,**b** in their reactions with CN^- also confirms the assumption on the absence of an anionic γ-complex. Presumably, fast aromatisation occurs through abstraction of a proton from the molecule of the intermediate 3*H*-pyrazole on treatment with an additional equivalent of the cyanide ion.

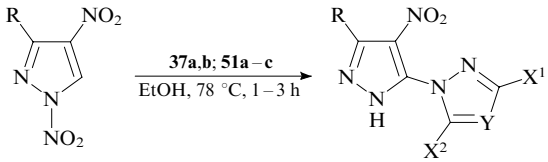
The use of azoles **37a**,**b** and **51a** – **g** as nucleophiles



51a – **g**

Compound **51**	X^1	X^2	Y
a	H	H	CEt
b	Ph	H	CH
c	Me	Me	CH
d	H	H	CCl
e	Me	H	CCl
f	Me	Me	CBr
g	H	H	N

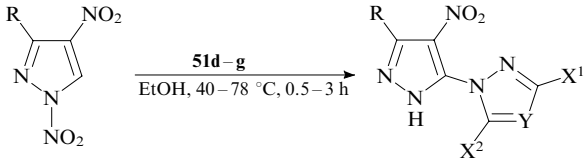
allowed an access to a wider panel of bipyrazoles **31**, **52** – **58**.[58] In the reactions with 3(5)-methylpyrazole (**37b**), mixtures of isomers (**52a**,**b**; **57a**,**b**) are obtained, the isomers with the Me group in the ring devoid of the NO_2 group occupying the position 3 (not 5), *i.e.*, **52a** and **57a**, predominate (4 : 1).



26a,**b** **31**, **52** – **58** (80% – 95%)

Compound	R	X^1	X^2	Y	Compound	R	X^1	X^2	Y
31	H	H	H	CH	**55**	H	Ph	H	CH
52a	H	Me	H	CH	**56**	Me	H	H	CH
52b	H	H	Me	CH	**57a**	Me	Me	H	CH
53	H	Me	Me	CH	**57b**	Me	H	Me	CH
54	H	H	H	CEt	**58**	Me	Me	Me	CH

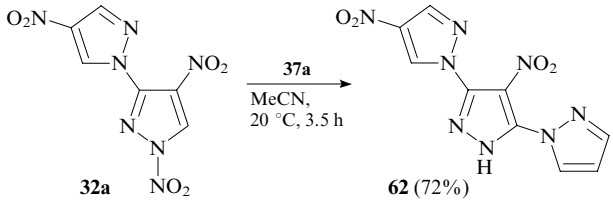
In an analogous manner, bipyrazole derivatives **59**, **60** and pyrazole **61** with a triazole substituent were synthesised.[59]



26a,**b** **59a**,**b**; **60a**,**b**; **61**

Compound	R	X^1	X^2	Y
59a	H	H	H	CCl
59b	Me	H	H	CCl
60a	H	Me	Me	CBr
60b	Me	Me	Me	CBr
61	Me	H	H	N

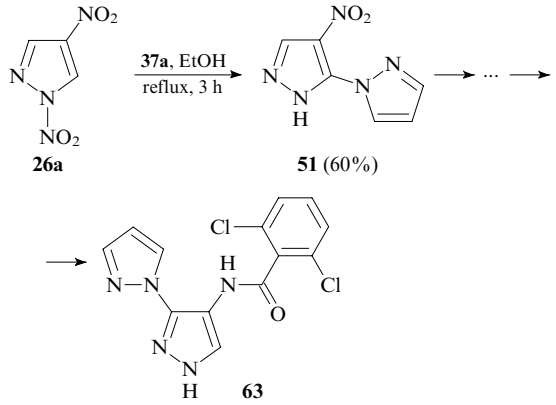
Synthesis of terpyrazole **62** is documented.[41]



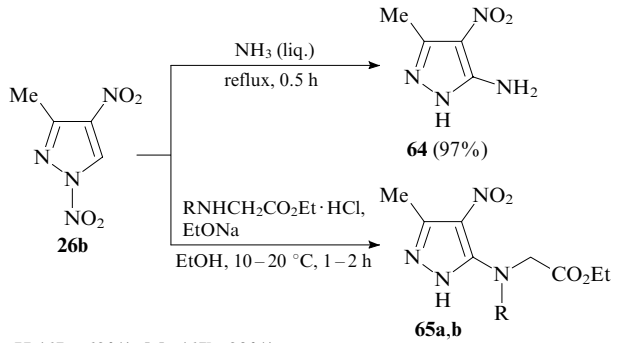
32a **62** (72%)

The treatment of trinitropyrazole with pyrazole (**37a**) yielded bipyrazole **24f** [see reaction (4)].[23,24]

cine-Substitution of an NO_2 group in dinitropyrazole **26a** was employed for the synthesis of *N*-(1,3′-bipyrazole-4′-yl)-2,6-dichlorobenzamide (**63**), an inhibitor of various kinases (CDK, GSK, Aurora kinase).[60] This compound is patented among other substances as a remedy that is efficacious in the treatment and prevention of asthma, diseases of the immune system and central nervous system, various inflammatory processes, *etc*. in the biochemistry of which the above-mentioned enzymes take part.

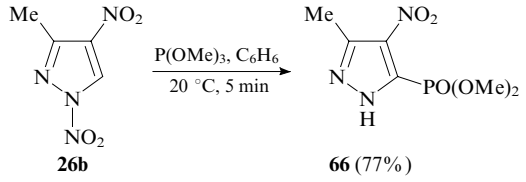


Other N-nucleophiles that are known to react in a *cine*-substitution fashion include ammonia, ethyl glycinate and ethyl sarcosinate[48] and the azide ion [see reaction (4)]. The reactions of dinitropyrazole **26b** with the three former of the abovementioned nucleophiles lead to products **64**, **65a**,**b**.

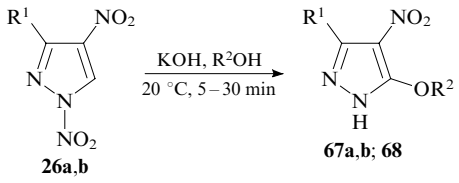


R = H (**65a**, 68%), Me (**65b**, 82%).

Reactions with P-nucleophiles can also result in the *cine*-substitution of the *N*-nitro group. Thus treatment of dinitropyrazole **26b** with trimethyl phosphite affords the corresponding dimethyl phosphonate **66**, the Arbuzov rearrangement product.[43]

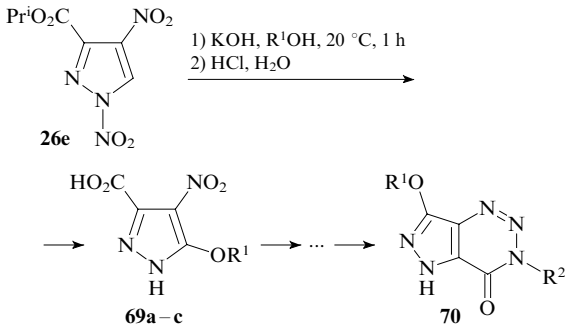


Treatment of dinitropyrazoles **26a**,**b** with alkoxides yields 3(5)-alkoxy-4-nitropyrazoles **67a**,**b** and **68**,[43,61,62] while trinitropyrazole **8a** gives dinitropyrazoles **24a**,**b** [see reaction (4)].[10,23,24]



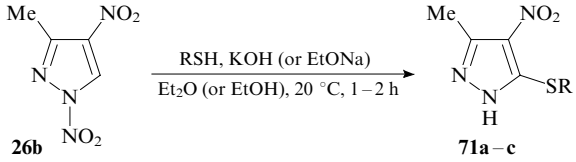
R^2 = Me: R^1 = H (**67a**, 61%), Me (**67b**, 92%);
R^1 = Me, R^2 = Et (**68**, 98%).

The nucleophilic *cine*-substitution of the $N-NO_2$ group in dinitropyrazole **26e** with O-nucleophiles was used[36] as the first step (the formation of nitropyrazoles **69a**–**c**) in the synthesis of pyrazolo[4,3-*d*]-1,2,3-triazin-4-(3*H*)-ones as potential biologically active compounds with the general formula **70**, structural analogues of pyrazolo[4,3-*d*]pyrimidines and natural purines.



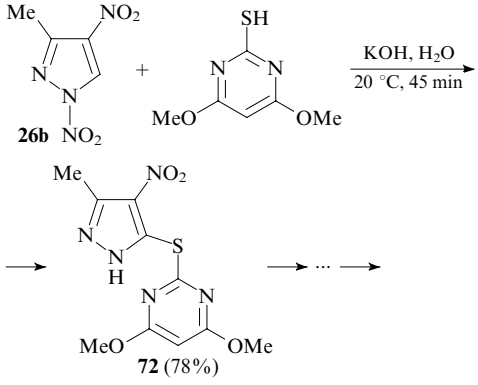
R^1 = Me (**69a**, 90%), $(CH_2)_2OMe$ (**69b**, 80%), Bn (**69c**, 60%);
R^2 = cyclo-C_5H_9, cyclo-C_3H_5, Bn, CHPhMe.

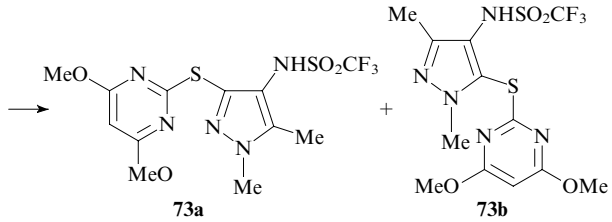
S-Nucleophiles (thiolate anions) also react in an analogous fashion.[43,48] For example, dinitropyrazole **26b** produced derivatives **71a**–**c**.



R = Et (**71a**, 97%), Ph (**71b**, 94%), CH_2CO_2Et (**71c**, 92%).

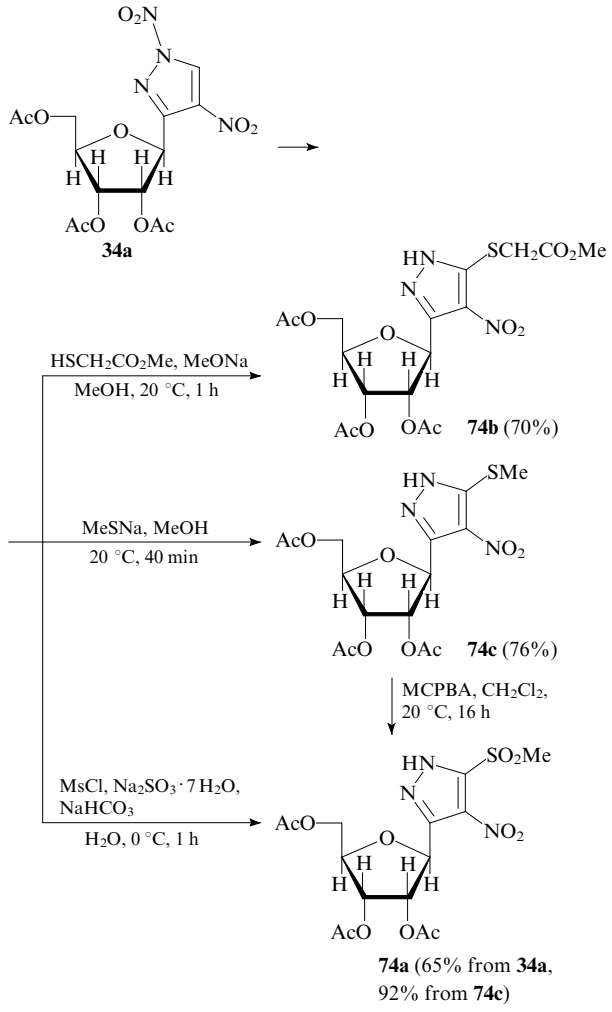
The *cine*-substitution of 4,6-dimethoxypyrimidine-2-thiolate for a nitro group in dinitropyrazole **26b** yielding nitropyrazole **72** was employed[63] for the synthesis of isomeric substituted pyrazoles **73a**,**b**. The latter were patented along with other compounds as herbicides effective against a wide range of broadleaved and herbaceous weeds and comparatively safe for cereal crops.





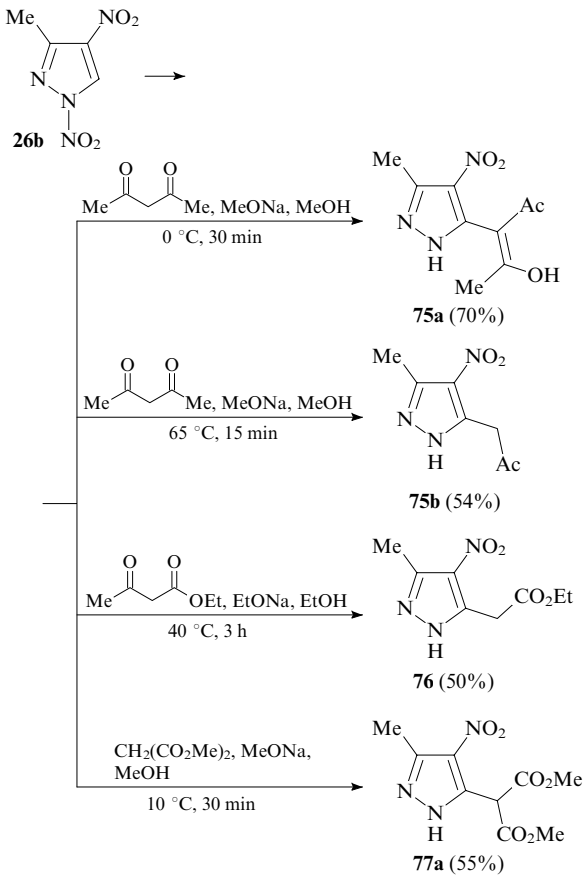
73a **73b**

Nucleophilic substitution in dinitropyrazole **34a** yielded [48] substituted nitropyrazoles **74a**,**b**, which in turn produced various sulfur-containing analogues of 4-carboxyimidazole nucleotides as potential inhibitors of the SAICAR-synthase. Compound **74a** can be obtained by two different methods: in one step or *via* sulfide **74c**.



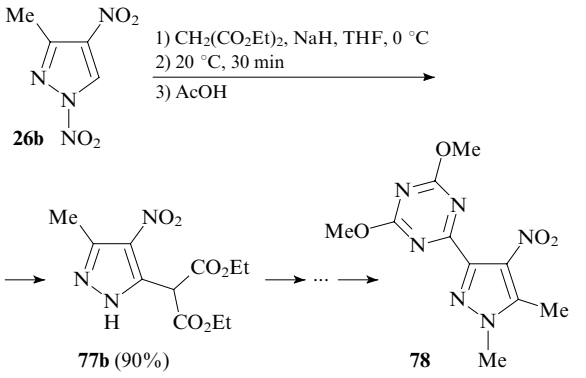
MCPBA is *m*-chloroperoxybenzoic acid.

A possibility of the use of C-nucleophiles (anions of various 1,3-dicarbonyl compounds) in the nucleophilic *cine*-substitution reaction of the *N*-nitro group in 1,4-dinitropyrazoles was demonstrated in the same study.[48] Thus compound **26b** reacts with the acetylacetone anion to give, depending on the reaction conditions, either nitropyrazole **75a** or nitropyrazole **75b**, which is the retro-Claisen condensation product of compound **75a**. Compound **76**, *i.e.*, an analogue of pyrazole **75b**, can be prepared by the reaction of dinitropyrazole **26b** with the ethyl acetoacetate anion, whereas the reaction with dimethyl malonate results in a 'normal' substitution product **77a**.



The possibility of the reaction of diethyl malonate with trinitropyrazole (**8a**) to form dinitropyrazole **24e** [reaction (4)] was demonstrated.[23, 24] It is of note that the nitromethane anion ($MeNO_2$, MeONa/MeOH) afforded only 3(5)-methyl-5(3)-methoxy-4-nitropyrazole (**67b**) [48] in 63% yield.

Compound **78** was synthesised [63] *via* derivative **77b**, which is formed by a *cine*-substitution of the nitro group in pyrazole **26b** with the diethyl malonate anion. Like its analogues **73a**,**b**, nitropyrazole **78** is patented as a herbicide.



Of all the C-nucleophiles that react with 1,4-dinitropyrazoles in a nucleophilic *cine*-substitution of the nitro group, the cyanide ion deserves special mention. Reactions of various dinitropyrazoles (**34a**,**b**; **36a**,**b**; **41a**–**d**) with potassium cyanide giving 4-nitropyrazole-3(5)-carbonitriles **79b**–**i** served as a key step in the synthesis of pyrazole-containing C-nucleoside antibiotics and their analogues (Table 2).

Table 2. Potential biologically active substances synthesised from substituted 4-nitropyrazoles **79b**–**i**.

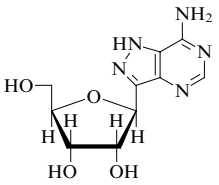
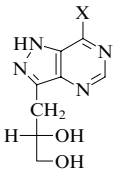
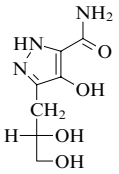
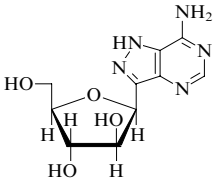
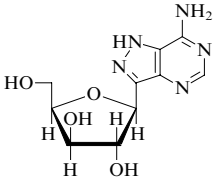
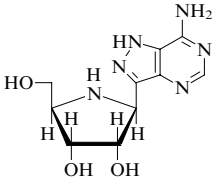
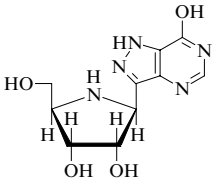
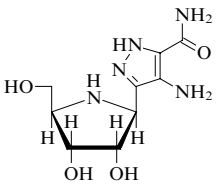
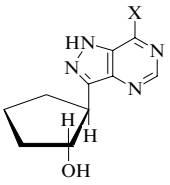
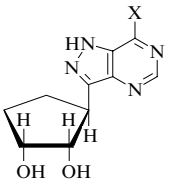
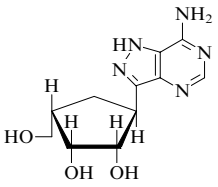
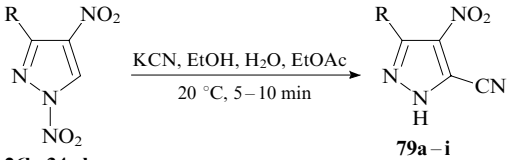
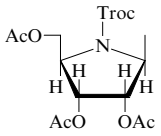
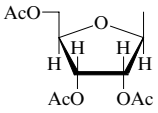
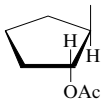
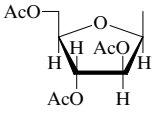
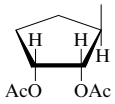
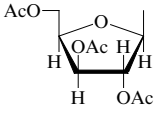
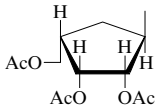
Precursor	Structure, name	Comment	Ref.
79b	 Formycin A	Formycin A is a C-nucleotide antibiotic, a natural isomer of adenosine, containing a pyrazole ring instead of the imidazole one. It possesses antiviral, antibacterial and antitumour activity	42, 43
79c		Formycin-type (A, X = NH_2; B, X = OH) analogues of (*S*)-DHPA [(*S*)-9-(2,3-dihydroxypropyl)adenine], an effective inhibitor of (*S*)-adenosine-L-homocysteine hydrolase, an analogue of the widely used drugs Acyclovir and Gancyclovir	44
79c		Pyrazofurin analogue of (*S*)-DHPA	44
79d	 Araformycin A	an analogue of Formycin A in which the D-ribofuranose ring is replaced by D-arabinofuranose	45
79e	 Xyloformycin A	an analogue of Formycin A in which the D-ribofuranose ring is replaced by D-xylofuranose	46
79f	 Azaformycin A	an analogue of the effective inhibitor of nucleoside hydrolases immucylline-A in which the pyrrole ring is replaced by the pyrazole ring	49
79f	 Azaformycin B	an analogue of immucylline-H in which the pyrrole ring is replaced by the pyrazole ring. (Immucylline-H is an exceedingly potent inhibitor of purine nucleoside phosphorylase and nucleoside hydrolases. In 2003, it was in clinical trials)	49
79f	 Azapyrazofurin	an analogue of the natural antibiotic Pyrazofurin in which the oxygen atom of the D-ribofuranose ring is replaced by an nitrogen atom and the 4-OH group in the pyrazole ring is replaced by an NH_2 group	49

Table 2 (continued).

Precursor	Structure, name	Comment	Ref.
79g		the simplest carbocyclic analogues of Formycin A (X = NH_2) and Formycin B (X = OH) in which the oxygen atom of the D-ribofuranose ring is replaced by a carbon atom and the 4-OH group and the 5-CH_2OH group are absent from the ring	50
79h		carbocyclic analogues of Formycin A (X = NH_2) and Formycin B (X = OH) in which the oxygen atom of the D-ribofuranose ring is replaced by a carbon atom and the 5-CH_2OH group is absent from the ring	51
79i		a carbocyclic analogue of Formycin A in which the oxygen atom of the D-ribofuranose ring is replaced by a carbon atom and the CH_2OH-group is in the epimeric position	52



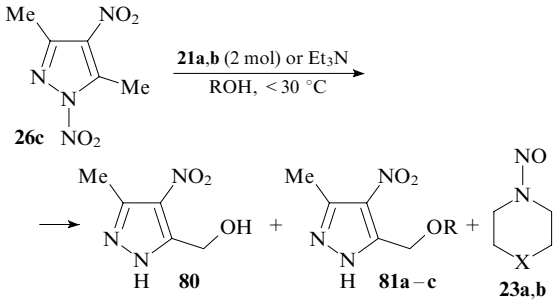
26b; **34a**,**b**; **36a**,**b**; **41a**–**d** → **79a**–**i**

Compound	R	Yield (%)	Compound	R	Yield (%)
79a	Me	85	**79f**		93
79b		89			
79c	see [a]	99	**79g**		68
79d		97	**79h**		90
79e		78	**79i**		90

[a] R = (*S*)-$CH_2CH(OAc)CH_2OAc$.

The reaction of trinitropyrazole (**8a**) with the cyanide ion was employed for the synthesis of 3,4-dinitropyrazole-5-carbonitrile **24c** [see reaction (4)].[23, 24]

Yet another nucleophilic substitution reaction of the *N*-nitro group in 1,4-dinitropyrazoles was found.[64] Thus treatment of 3,5-dimethyl-1,4-dinitropyrazole (**26c**) with secondary and tertiary amines (piperidine, morpholine, triethylamine) in an aliphatic alcohol (methanol, ethanol, propyl alcohol) results in 5(3)-hydroxymethyl (**80**) and 5(3)-alkoxymethyl (**81**) derivatives of 3(5)-methyl-4-nitropyrazole. Under the reaction conditions, secondary cyclic amines are converted to *N*-nitroso-compounds **23a**,**b** (Table 3).



(7)

26c → **80** + **81a**–**c** + **23a**,**b**

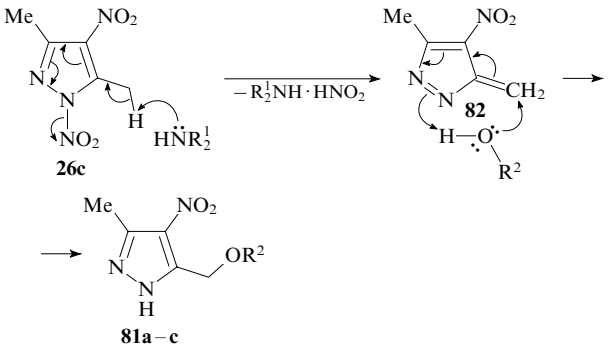
R = Me (**81a**), Et (**81b**), Pr^i (**81c**); X = O (**23a**), CH_2 (**23b**).

Table 3. Reactants and product yields in reaction (7).[64]

Amine	ROH	Yield (%)		
		23a,**b**	**80**	**81a**–**c**
	EtOH	74	81	18
	see [a]	45	45	
	Pr^iOH [b]	80	71	16
	EtOH	50	75	24
Et_3N	Pr^iOH		67	15
Et_3N	EtOH (anh.)		57	37
Et_3N	MeOH (anh.)		44	40

[a] In this case, the reaction occurs in the absence of ROH, the solvent is MeCN; [b] under reflux.

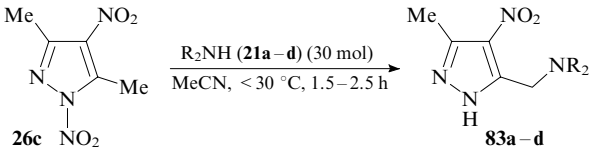
A reaction mechanism was suggested [64] that involved the formation of the reactive diazafulvene **82**.

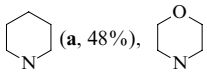


R^1 = Et; R^1-R^1 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$; R^2 = Me (**a**), Et (**b**), Pr^i (**c**).

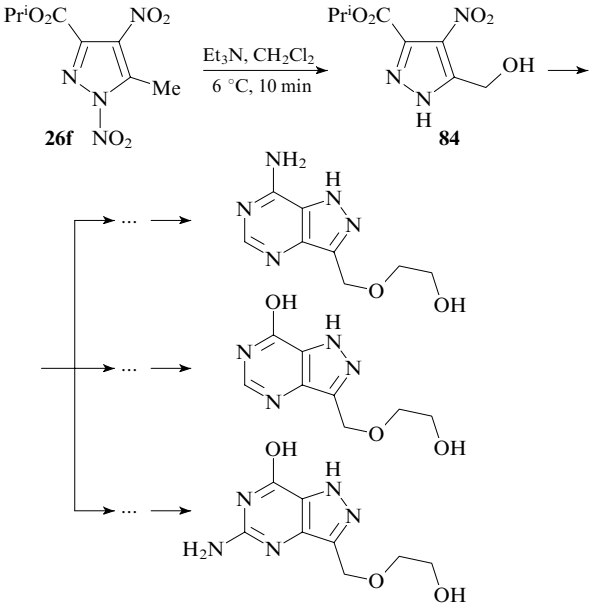
What is of special note is that, regardless of the solvent, the formation of alcohol **80** is always observed, presumably, as a result of the reaction of water with diazafulvene **82**. In anhydrous methanol or ethanol, however, alcohol **80** still persisted, which was rationalised as being formed upon aqueous work-up of the reaction mixture. In a later work,[65] it was supposed that water appears in the reaction mixture as a result of amine nitrosation.

With a great excess of an amine (30 equiv.), 3(5)-aminomethyl derivatives **83a**–**d** can also be prepared.[65]

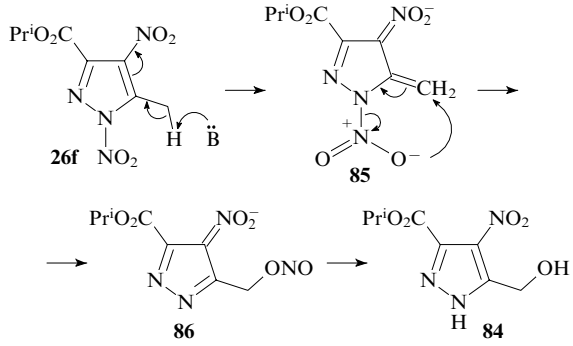


R_2N =  (**a**, 48%), (**b**, 77%), (**c**, 59%), Et_2N (**d**, 14%).

This reaction was employed for the conversion of the methyl group of pyrazole **26f** to the hydroxymethyl group of pyrazole **84** in one of steps of the synthesis of formycin analogues of acyclovir.[37]

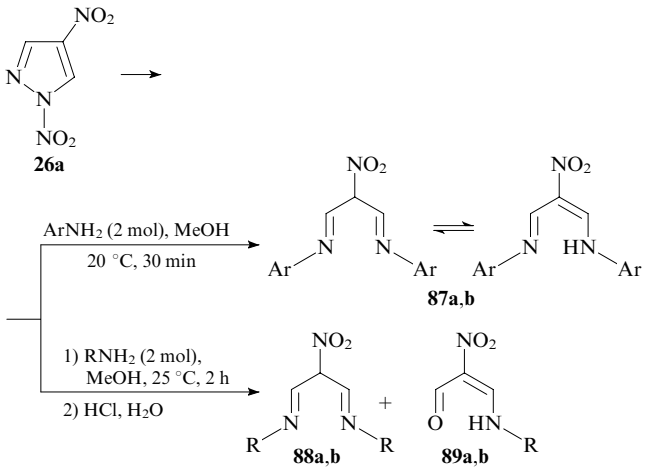


The authors of this investigation assume a somewhat different pathway of the reaction: the abstraction of a proton from dinitropyrazole **26f** is not followed by elimination of the NO_2 group to yield diazafulvene. Instead, the formation of a σ-complex **85** occurs where an intramolecular migration of the nitro group happens to produce nitrite ester **86**. Upon appropriate work-up, the latter is converted to the reaction product **84**. In favour of this mechanism is the fact that the addition of 2-mercaptoethanol to the reaction mixture does not lead to trapping of the corresponding diazafulvene.



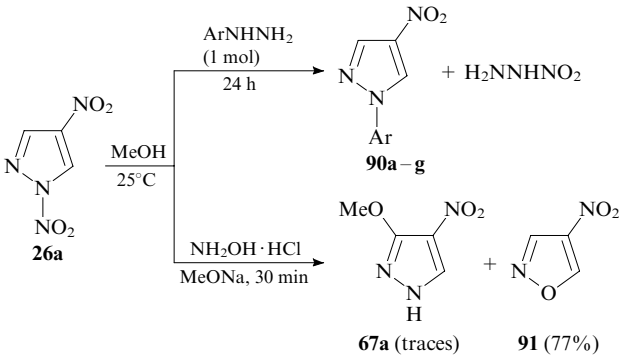
B is base.

Yet another unusual reaction in the 1,4-dinitropyrazole series was discovered fairly recently.[61] Treatment of dinitropyrazole **26a** with primary amines does not result in the *cine*-substitution products of the nitro group; instead, the pyrazole ring is opened. From aromatic amines, diimines **87a**,**b** are obtained, whereas from aliphatic amines, mixtures of diimines **88a**,**b** and acroleins **89a**,**b** are produced.



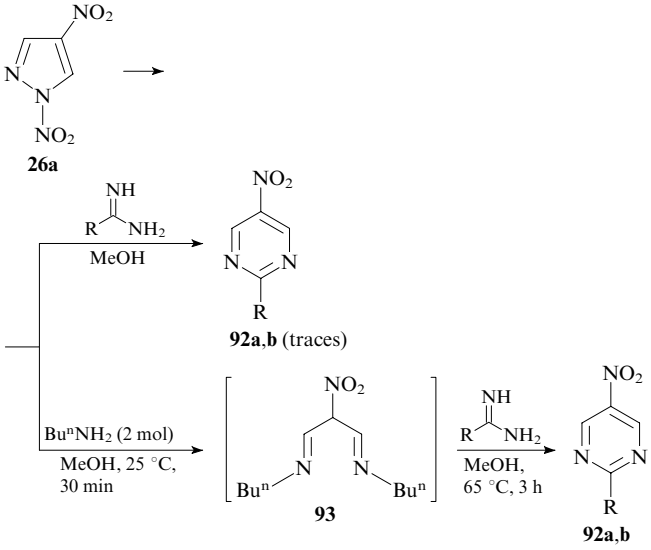
Ar = 4-MeC_6H_4 (**87a**, 54%), 4-$MeOC_6H_4$ (**87b**, 42%);
R = Cy (**88a**, 7%; **89a**), Bn (**88b**, 3%; **89b**).

The use of bisnucleophiles, for instance, arylhydrazines, in this reaction leads to the cyclisation of intermediate products. In this way, 1-aryl-4-nitropyrazoles **90a**–**g** can be synthesised in good yields. When hydoxylamine is used, 4-nitroisoxazole (**91**) is formed.



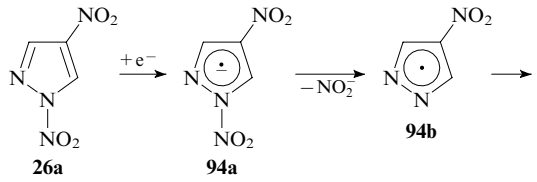
Compound **90**	Ar	Yield (%)	Compound **90**	Ar	Yield (%)
a	Ph	70	**e**	3-FC_6H_4	58
b	3-ClC_6H_4	79	**f**	4-FC_6H_4	76
c	4-ClC_6H_4	66	**g**	3,5-$F_2C_6H_3$	64
d	3,4-$Cl_2C_6H_3$	61			

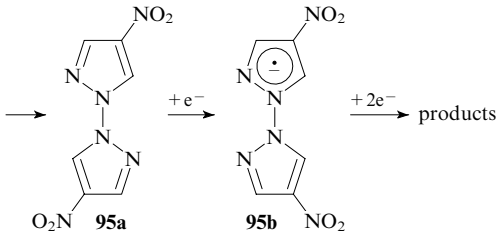
The re-cyclisation of dinitropyrazole **26a** to six-membered 5-nitropyrimidines **92a**,**b** does not occur on direct reaction with amidines. However, compounds **92a**,**b** can be prepared by sequential treatment of 1,4-dinitropyrazole with an aliphatic amine and the corresponding amidine. 5-Nitropyrimidines are obtained upon cyclisation of the intermediate diimine **93** and/or a substituted acrolein.



R = H (**92a**, 18%), Ph (**92b**, 31%).

In the electrochemical reduction of 1,4-dinitropyrazole (**26a**), five polarographic waves were observed with $E_{1/2} = -0.55$, -1.25, -1.7 ($NO_2^- + e^- \rightarrow {}^{\bullet}NO_2$), -2.20 and -2.75 V.[66] Taking into account data from EPR spectroscopy, a sequence of processes occuring upon the reduction of compound **26a** to form intermediates **94a**,**b** and **95a**,**b** was suggested.





It was shown[67] that despite a significant tendency of nitropyrazoles to denitration, gas chromatography (at 130–140 °C) can be used for isolation of dinitropyrazole **26c** from its mixtures with alkyl-, bromo-, nitro- and other dinitropyrazoles. At the same time 3-methyl-1,4-dinitropyrazole (**26b**) decomposes under chromatographic conditions.

Biological activity of nitropyrazoles **26a**–**c** is much akin to that of dinitropyrazoles **4a**,**c**,**d**.[21,35]

The potential usage of 1,4-dinitropyrazole (**26a**) for the suppression of ammonium nitrogen nitrification to nitrate ions in soil in order to prevent its fast removal from soil has been patented.[68]

The IR spectra of 1,4-dinitropyrazoles contain characteristic absorption bands at 1630–1680 cm^{-1} (anomalously low frequencies 1552 and 1575 cm^{-1} are reported[38,41] for compounds **29** and **32a,** respectively) and 1270–1290 cm^{-1} of the antisymmetric and symmetric vibrations of the NNO_2 group, and also absorption bands at 1510–1580 cm^{-1} (anomalously low frequencies 1552 and 1575 cm^{-1} are reported[45,46] for compounds **36a**,**b**, respectively) and 1315–1380 cm^{-1} corresponding to the antisymmetric and symmetric vibrations of the CNO_2 group(s).

The chemical shifts of H(3) and H(5) atoms in the ^{1}H NMR spectra of 1,4-dinitropyrazoles are in the ranges δ 8.12–8.21 and 9.00–9.91, respectively, depending on chemical environment of these atoms. The signals for the 3- and 5-Me-group protons in the ^{1}H NMR spectra of methyl-1,4-dinitropyrazoles are observed at δ 2.36–2.73 and 3.02–3.12 , respectively.

In the ^{13}C NMR spectra of 1,4-dinitropyrazoles, the signals for C(3), C(4) and C(5) atoms appear in the ranges δ 135.51–150.28, 126.48–137.09 and 124.38–142.21, respectively, depending on chemical environment of these atoms. The signals for the 3- and 5-Me group in the ^{13}C NMR spectra of methyl-1,4-dinitropyrazoles are observed in the ranges δ 13.50–14.02 and 12.97–13.15, respectively.

In the ^{15}N NMR spectra of 1,4-dinitropyrazoles, the chemical shifts of the N(1), N(2), NNO_2 and C(4)NO_2 nitrogen atoms fall into the ranges δ from -109.91 to -117.01; from -88.62 to -98.58; from -58.88 to -68.65 and from -18.91 to -30.76, respectively.

More complete information on the properties of 1,4-dinitropyrazoles is provided in Table 2 of the electronic supplement.

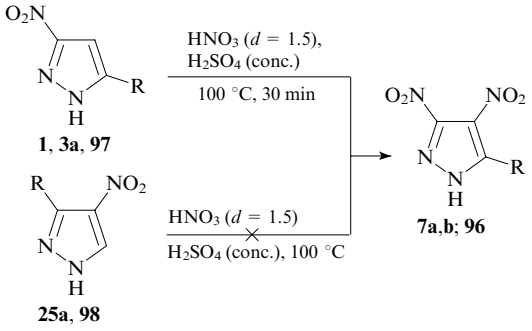
IV. 3,4-Dinitropyrazoles and 4,5-dinitropyrazoles

As has been mentioned earlier, NH-pyrazoles bearing two nitro groups at the 3,4- and 4,5-positions are tautomers, and in solutions, as a rule, exist as equilibrium mixtures. In addition, the number of known *N*-substituted 4,5-dinitropyrazoles is limited, which makes unreasonable their consideration in a separate section.

1. Synthesis of 3,4- and 4,5-dinitropyrazoles

The content of this section will be presented in the following sequence: first, methods of the preparation of 3,4- and 4,5-dinitropyrazoles by nitration are considered, then indirect methods of the introduction of nitro groups into a pyrazole ring are discussed and, finally, methods of the synthesis of known 3,4-dinitropyrazoles by functionalisation of compounds already containing a dinitropyrazole fragment are addressed. Such an arrangement allowed many transformations of 3,4-dinitropyrazoles that do not involve the ring nitro groups to be placed in the section covering the synthesis of these compounds rather than in the next section concerning their properties.

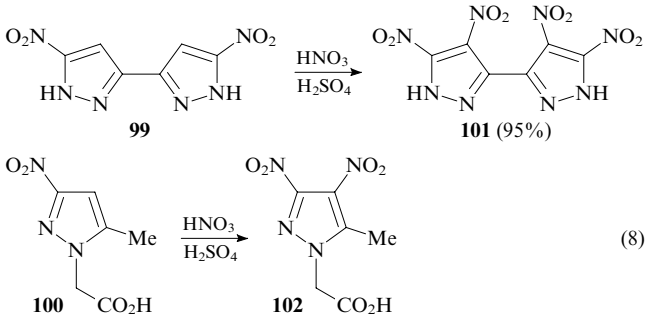
For the first time, a representative of the 3,4-dinitropyrazole series was obtained as early as 1935. Thus the synthesis of 3,4-dinitro-5-(3-pyridyl)pyrazole (**96**) by the nitration of 3-nitro-5-(3-pyridyl)pyrazole (**97**) (a by-product of the nicotine oxidation with nitric acid) with the nitrating mixture was reported.[69] At the same time, isomeric 4-nitro-3-(3-pyridyl)pyrazole (**98**) is not nitrated under these conditions (no dinitro compound **96** is formed). It was shown [15] that 3,4-dinitropyrazoles **7a**,**b** (and also **96**) can be prepared by nitration of 3(5)-nitropyrazoles **1** and **3a** with a nitric acid – sulfuric acid mixture. However, the nitration of 4-nitropyrazole **25a** (and also **98**) does not result in a 3,4-dinitro derivative.



1, **3a**, **97** **25a**, **98** **7a**,**b**; **96**

R = H (**1**; **7a**, 86%; **25a**), Me (**3a**; **7b**, 72%), 3-Py (**96**, ~100%; **97**; **98**); Py is pyridyl.

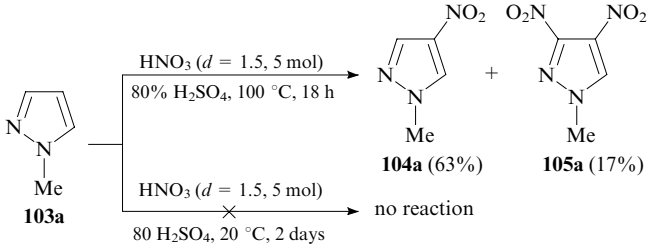
Similarly, it was found [10, 70, 71] that the nitration of bipyrazole **99** and pyrazolylacetic acid **100** with a nitric acid – sulfuric acid mixture led to the corresponding bipyrazole **101** and pyrazole **102** bearing nitro groups in positions 3 and 4.



99 **101** (95%) **100** **102** (8)

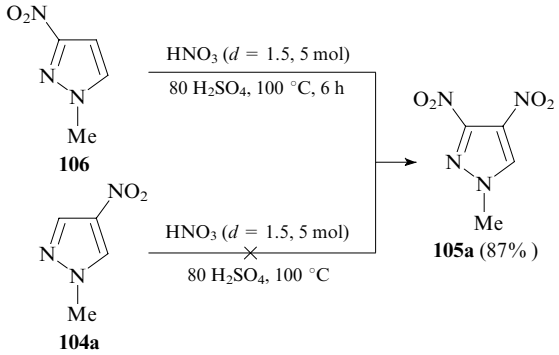
The structure of the potassium salt of compound **101** was determined by X-ray diffraction analysis [70] (see Fig. 1 of the electronic supplement). In the anion of pyrazole **101**, the dihedral angle between the planes of two pyrazole rings is 35.2°; the rotation angles of the nitro groups with respect to the planes of the pyrazole rings are 24.4° and 24.5° for 3-NO_2 and 28.3° and 36.3° for 4-NO_2 groups, which points to a sufficiently strong repulsion between nitro groups in positions 3 and 4.

It was established that 1-methylpyrazole (**103a**) is nitrated with nitric acid in 80% sulfuric acid at 100 °C to produce a mixture of 1-methyl-4-nitropyrazole (**104a**) and 1-methyl-3,4-dinitropyrazole (**105a**) in the ratio 3.8 : 1.[72] An increase in the nitration time did not result in an increase in the yield of product **105a**. This fact prompted the idea that the dinitro derivative is formed from the corresponding 3-nitropyrazole rather than the 4-isomer.



103a **104a** (63%) **105a** (17%)

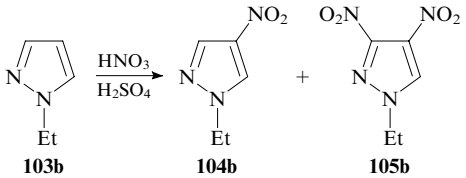
Indeed, 1-methyl-3-nitropyrazole (**106**) was identified in the reaction mixture as a transient species. Furthermore, a separate experiment demonstrated that 1-methyl-4-nitropyrazole (**104a**) is not nitrated under the conditions indicated, whereas 3-nitropyrazole **106** obtained by another method gives dinitropyrazole **105a** in the nitration. This fact proves that compound **105a** has the structure of 3,4-rather than the isomeric 4,5-dinitro derivative.



106 **104a** **105a** (87%)

Presumably, the intermediate formation of the 'abnormal' 3-nitration product can be rationalised by the [1,5]-sigmatropic shift of the NO_2 group in the transient 1-methyl-2-nitropyrazolium cation.

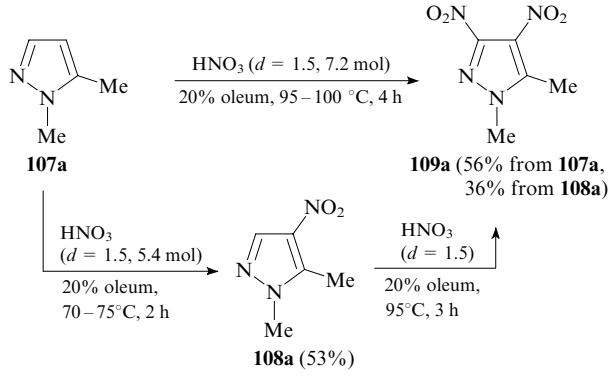
A similar picture was also observed [73] in the nitration of 1-ethylpyrazole (**103b**) under analogous conditions. In a mixture of mono- (**104b**) and dinitration (**105b**) products, the content of the latter is ~12 mol.%.



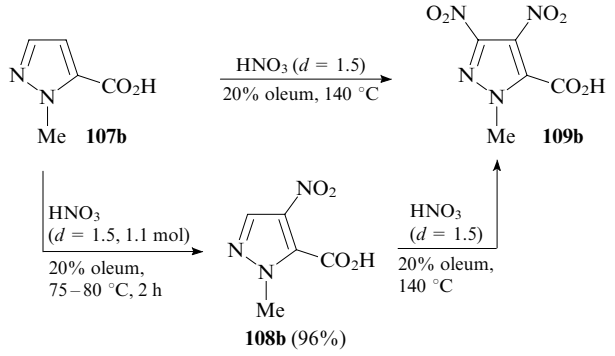
103b **104b** **105b**

The nitration of 1,5-dimethylpyrazole (**107a**) with nitric acid in 20% oleum has been studied.[74] It was established that the nitration at 70 – 75 °C leads to 1,5-dimethyl-4-nitropyrazole (**108a**). Under more drastic reaction conditions, 1,5-dimethyl-3,4-dinitropyrazole (**109a**) was the

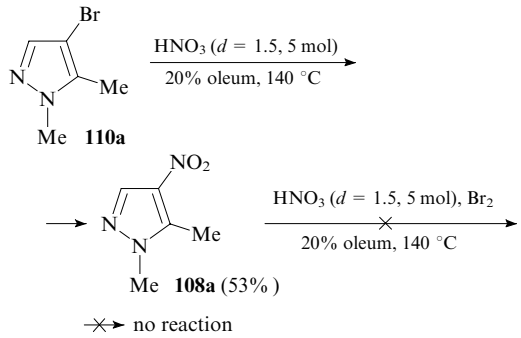
only product. This can also be obtained by the nitration of mononitro derivative **108a**. Thus, in this case, another sequence of the introduction of nitro groups into the pyrazole ring is observed as compared to methylpyrazole **103a**. It should be noted that no dinitro derivative is produced under analogous conditions from the isomeric 1,3-dimethylpyrazole.



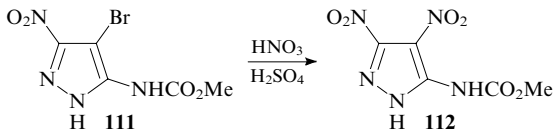
In an analogous manner, the nitration of 1-methylpyrazole-5-carboxylic acid (**107b**) occurs.[75,76] The only difference is that the introduction of the second nitro group into the pyrazole ring requires more drastic conditions (140 °C).



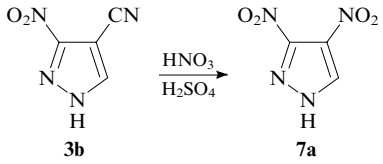
It should be noted that in the nitration of 1,5-dimethyl-4-bromopyrazole (**110a**) *ipso*-substitution of the bromine atom takes place to form nitropyrazole **108a**, which, however, is not nitrated further.[76] Presumably, the reason for such a behaviour of compound **108a** under the nitration conditions is the release of bromine-containing species ('Br^+'). Indeed, no nitration of this pyrazole in the presence of molecular bromine occurs.[76]



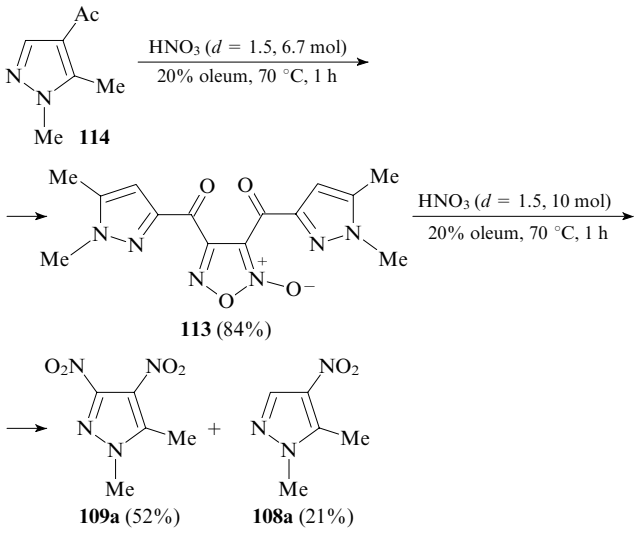
The *ipso*-nitration of methyl *N*-(4-bromo-3-nitropyrazol-5-yl)carbamate (**111**) was successfully applied[10] to the preparation of the corresponding dinitropyrazole **112**.



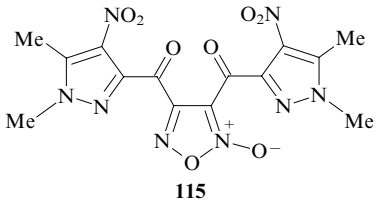
In some cases, *ipso*-nitration is an adverse side process. Thus 3,4-dinitropyrazole (**7a**) was isolated in an attempt[77] to nitrate 3(5)-nitropyrazole-4-carbonitrile (**3b**) to the corresponding 3,5-dinitropyrazole. This was explained by acid hydrolysis of the nitrile followed by nitrodecarboxylation.



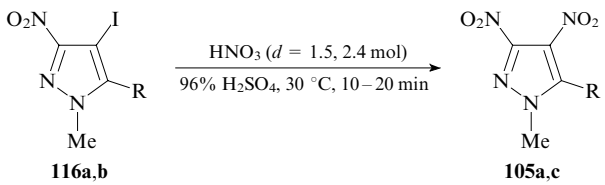
Yet another example of *ipso*-nitration is the formation of 4-nitro- and 3,4-dinitropyrazoles (**108a** and **109a**, respectively) from furoxan **113** with two pyrazolyl subsituents.[78] The latter is obtained from 4-acetylpyrazole **114** upon nitration in acetic anhydride.



Since at 70 °C the formation of dinitro derivative **109a** from mononitropyrazoles **108a** does not occur (see above), it was concluded that the nitration proceeded in part *via* compound **115**.



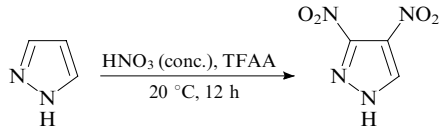
Dinitropyrazoles **105a**,**c** were obtained by the *ipso*-nitration of 4-iodopyrazoles **116a**,**b**.[79,80]



R = H (**116a**; **105a**, 88%), I (**116b**; **105c**, 94%).

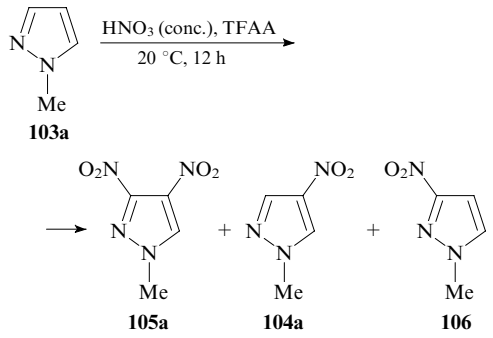
The nitration rates of compounds **116a**,**b** are appreciably higher than those for 1,3-dimethyl-4-nitro-5-R-pyrazoles (R = H, Me) despite the fact that the nitro group possesses great electron-withdrawing effect and, consequently, the nitration rate reduction should be observed in comparison with the corresponding methyl analogues. This is explained by the fact that, under the nitration conditions, compounds **116a**,**b** (contrary to Me-analogues) exist mainly in a non-protonated form, and the nitration rate of the non-protonated form of pyrazole, is obviously much higher. Control nitration experiments with acetyl nitrate (conditions in which Me-analogues are nitrated also as free bases) showed the reversed reactivities: methyl derivatives react in 10 min, whereas compounds **116a**,**b** remain unaffected during 24 h.

It was discovered that 3,4-dinitropyrazole (**7a**) is formed in moderate yield upon nitration of pyrazole (**37a**) with nitric acid in trifluoroacetic anhydride.[81]



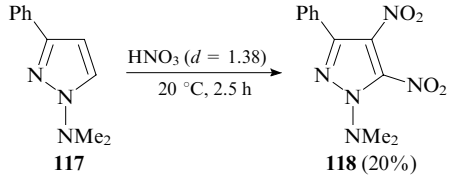
37a **7a** (41%)

The same research group described the nitration of 1-methylpyrazole (**103a**). An analysis of a mixture of nitration products by ^{1}H and ^{13}C NMR spectroscopy[82] with complete assignment of signals in the spectra showed that the ratio **105a** : **104a** : **106** was 15 : 50 : 35. However, in an earlier work[81] the same authors reported that only compound **106** is formed in 65% yield upon nitration of pyrazole **103a**.



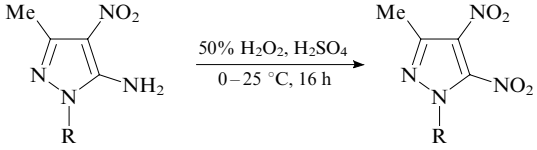
103a **105a** **104a** **106**

It was found[83] that 1-(dimethylamino)-3-phenylpyrazole (**117**) under exceptionally mild conditions is nitrated to yield dinitro derivative **118**. The nitration of compound **117** at the pyrazole ring was confirmed by the presence of a peak for the Ph group in the mass spectrum of product **118**.



117 **118** (20%)

The oxidation of 5-amino-4-nitropyrazoles **119a**–**c** produced[84] the corresponding dinitropyrazoles **120a**–**c** (compound **120a** was isolated as a potassium salt). The presence of a nitro group exactly in position 5 in compounds **120b**,**c** follows from the structures of aminopyrazoles **119b**,**c** for which the location of the amino group at the C(5) ring atom has been proved earlier.[85–87] Compounds **118** and **120b**,**c** are the only *N*-substituted 4,5-dinitropyrazoles known to date.

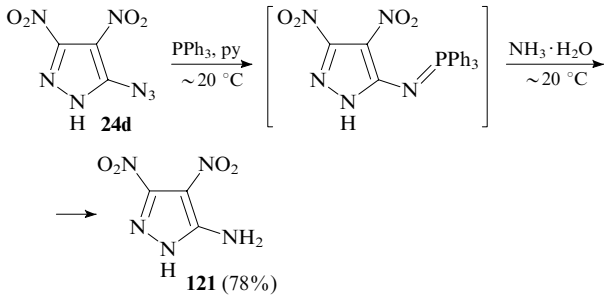


119a–**c** **120a**–**c**

R = H (**a**, 40%), Me (**b**, 81%), Ph (**c**, 52%).

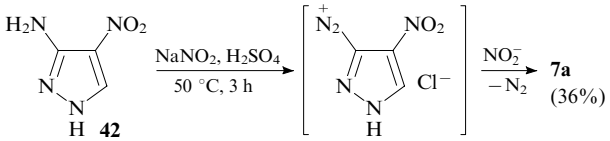
Some methods for the preparation of 3,4-dinitropyrazoles have already been mentioned. The thermal rearrangement of 1,4-dinitropyrazoles leads to 3,4-dinitropyrazoles [see reactions (5), (6)].[15,42] This reaction can serve as a good method for the preparative synthesis of 3(5),4-dinitro-5(3)-phenylpyrazole (**46**).

Yet another general method for the preparation of 3,4-dinitropyrazoles is the *cine*-substitution of the *N*-nitro group in trinitropyrazole **8a** on treatment with various nucleophiles [see reaction (4)].[10,23,24] However, it should be noted that 5-amino-3,4-dinitropyrazole (**121**) cannot be synthesised in this way. When pyrazole **8a** is treated with ammonia in various solvents (EtOH, MeOH, $CHCl_3$, CH_2Cl_2) in the temperature range from −30 to 20 °C, only resinification is observed. For the synthesis of compound **121,** azide **24d** was used[24] from which the target pyrazole could be obtained by sequential treatment with triphenylphosphine in pyridine (py) and aqueous ammonia.



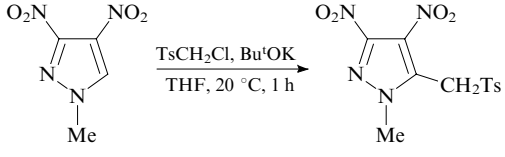
24d **121** (78%)

3,4-Dinitropyrazole (**7a**) was obtained by the diazotization of aminopyrazole **42** followed by a substitution of the nitro group for the diazo group when treated with an excess of sodium nitrite.[88]



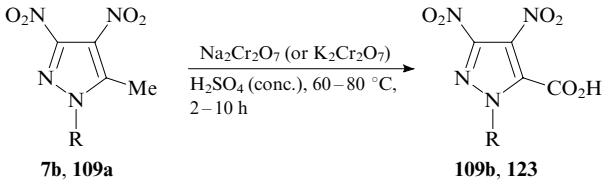
42 **7a** (36%)

1-Methyl-3,4-dinitro-5-(tosylmethyl)pyrazole (**122**) was synthesised[89] from compound **105a** by using vicarious nucleophilic substitution of a hydrogen atom in the position 5 of the pyrazole ring.



105a **122** (18%)

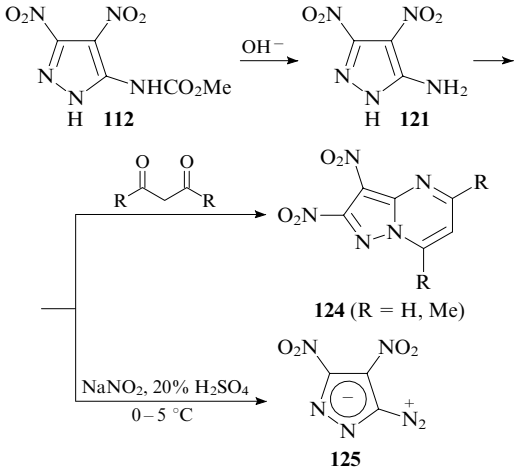
The oxidation of 3,4-dinitropyrazoles with potassium or sodium dichromate was employed [10, 90] for the preparation of 3,4-dinitropyrazole-5-carboxylic acid (**123**) and 1-methyl-3,4-dinitropyrazole-5-carboxylic acid (**109b**).



7b, **109a** **109b**, **123**

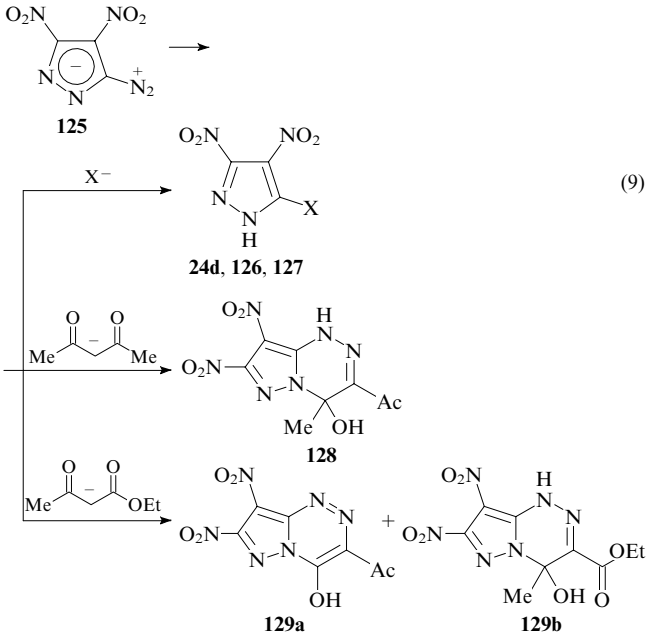
R = H (**7b**, **123**), Me (**109a**; **109b**, 41%).

Alkaline hydrolysis of carbamate **112** (which was obtained by the *ipso*-nitration of bromo derivative **111**, see above) is another way of the preparation of 5-amino-3,4-dinitropyrazole (**121**).[10] The latter when treated with 1,3-dicarbonyl compounds gives fused pyrazolo[1,5-*a*]pyrimidines **124**, while when treated with sodium nitrite in sulfuric acid it gives 5-diazo-3,4-dinitropyrazolate (an internal salt) (**125**).[10]



112 **121** **124** (R = H, Me) **125**

Various transformations of diazo compounds **125** have been studied.[10] Thus on treatment with azide, chloride and bromide ions a replacement of the diazo group occurs, and the corresponding 3,4-dinitropyrazoles **24d**, **126**, **127** are formed. The reactions of pyrazole **125** with anions of 1,3-dicarbonyl compounds lead to azo coupling products, where in the case of an asymmetric acetoacetic ester both possible products, *viz*., aromatic ketone **129a** and non-aromatic ethyl carboxylate **129b**, are produced.

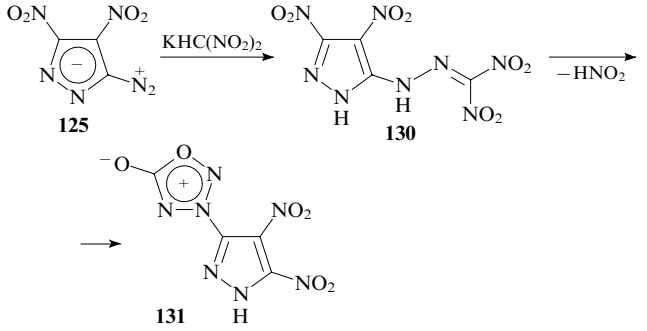


(9)

125 **24d**, **126**, **127** **128** **129a** **129b**

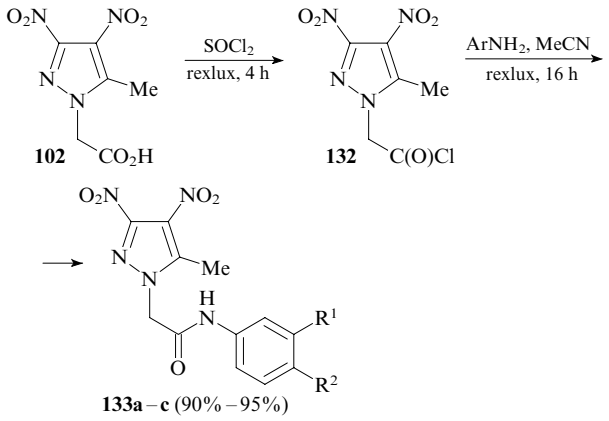
X = N_3 (**24d**), Cl (**126**), Br (**127**).

Diazopyrazole **125** when treated with potassium salt of dinitromethane yields (*via* intermediate compound **130**) derivative **131** (see Section V.1 for more details on the reaction mechanism).[39]



125 **130** **131**

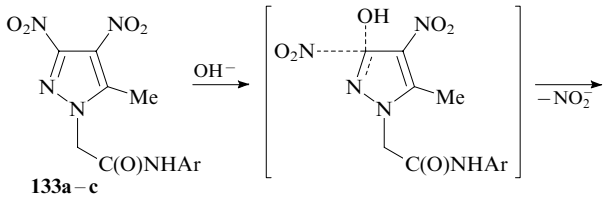
Classical chemical conversions of acid **102** [see reactions (8) and (10)] afforded, *via* intermediate pyrazolylacetyl chloride **132**, amides **133a–c**.[91]



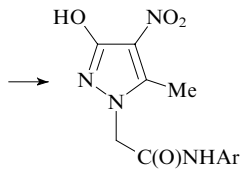
102 **132** **133a–c** (90%–95%)

Ar = 3-R^1-4-$R^2C_6H_3$; R^1 = H: R^2 = Me (**a**), OMe (**b**); $R^1 = R^2$ = OMe (**c**).

Hydrolysis of these amides with 0.1 M NaOH in 10% aqueous ethanol (amide concentrations 10^{-3}–10^{-4} mol litre^{-1}) in the 35–70 °C temperature range was studied by polarography and photometry.[91] All the studied compounds are hydrolysed to give a significant yield of the nitrite ion, which allows one to regard them as potential exogenous nitrogen(II) oxide sources. On the basis of certain activation parameters for the hydrolysis of compound **133b** ($\Delta G^{\neq} = 24.1 \pm 3.0$ kcal mol^{-1}, $\Delta H^{\neq} = 26.8 \pm 2.7$ kcal mol^{-1}, $\Delta S^{\neq} = -8.6 \pm 0.3$ cal mol^{-1} K^{-1}), it was assumed that the transition state is structurally closer to the product than to the initial nitropyrazole (this is

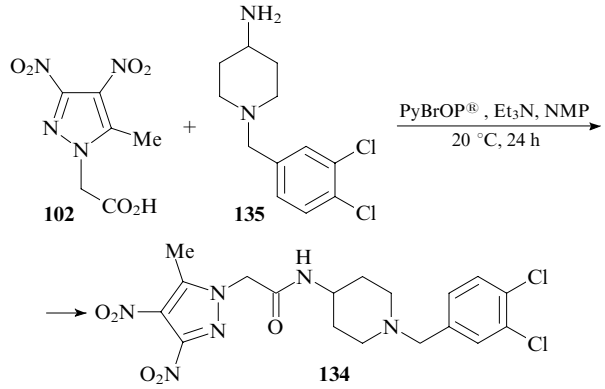


133a–c



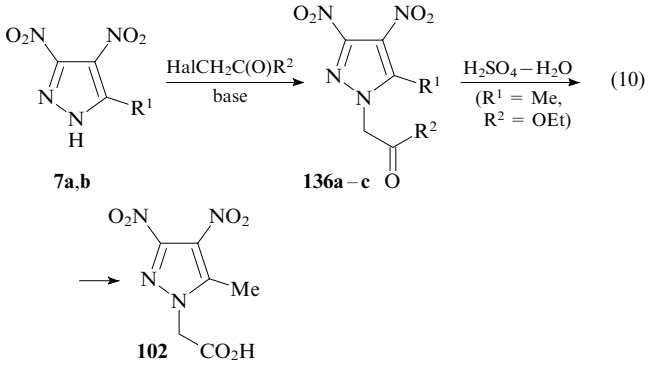
evidenced by a rather high $\Delta H^{\neq}$ value and a small negative $\Delta S^{\neq}$ value).

Amide **134** obtained [92] by the reaction of acid **102** with amine **135** in the presence of PyBroP® [bromotris(pyrrolidino)phosphonium hexafluorophosphate] and Et_3N acts as an antagonist of the CCR3 receptor and is patented along with other compounds as a drug against several diseases, in particular, asthma and rhinitis.



NMP is *N*-methylpyrrolidone.

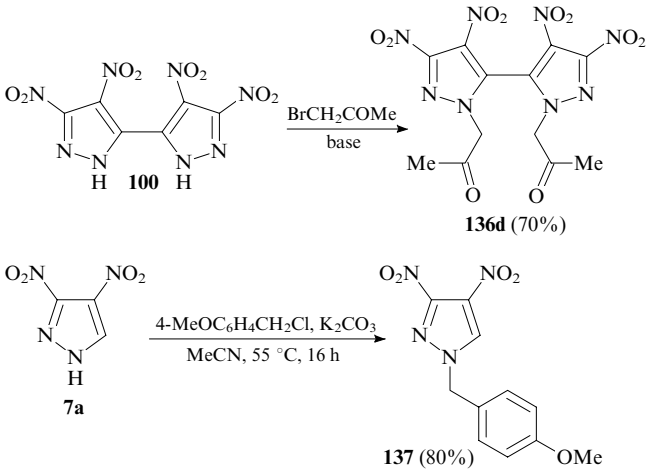
3,4-Dinitropyrazoles belong to comparatively strong NH-acids [93] and, when treated with bases, readily form salts (see Section IV.2 and Table 5 for details). In the presence of bases (an alkali, potash), 3,4-dinitropyrazoles are easily alkylated with various reagents, for example, bromoacetone,[10,40,71] ethyl chloroacetate,[94] methyl chloroacetate [10] and *p*-methoxybenzyl chloride,[61] being converted to derivatives **136a–d**, **137**, respectively. Hydrolysis of compound **136b** under very mild conditions results in acid **102**.



(10)

R^1 = H (**7a**), Me (**7b**).

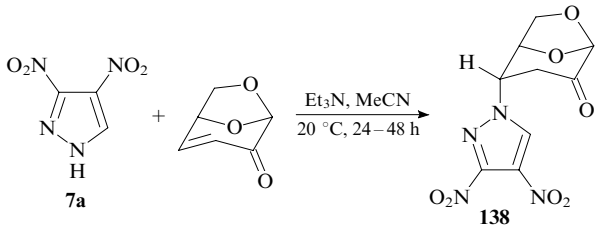
Compound **136**	R^1	R^2	Hal	Reaction conditions	Yield (%)
a	H	Me	Br	KOH, H_2O-Me_2CO, 20 °C, 20 h	52
b	Me	OEt	Cl	K_2CO_3, DMF, reflux, 5 h	–
c	Me	OMe	Cl	–	–



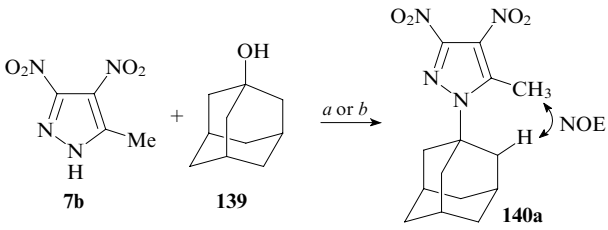
The location of the nitro group at the C(3) carbon atom was unambiguously determined [40] for compound **136a** using chemical shift values and the multiplicity of C(3) and C(5) carbon atom signals (δ 147.06, doublet, ^3J = 8.1 Hz and δ 135.04, doublet of triplets, ^1J = 204.4 Hz, ^3J = 3.2 Hz, respectively) in the ^{13}C NMR spectrum. As one can see, the direct coupling constant ^1J = 204.4 Hz and the coupling constant with the hydrogen atoms of the CH_2 group ^3J = 3.2 Hz are observed for one and the same carbon atom, which is possible only in the case of the 3,4-dinitro isomer.

The second-order rate constants were determined [95] for the alkylation reaction of the 3,4-dinitro pyrazole (**7a**) anion with benzyl chloride and ethyl 2-chloropropionate (ECP) in MeCN containing 0.1 mol litre^{-1} Bu_4NClO_4, at 22 °C: $\log k_{BnCl} = -2.11$, $\log k_{ECP} = -4.10$.

It was shown [96,97] that triethylamine-catalysed addition of dinitropyrazole **7a** to the conjugated double bond of levoglucosenone occurs regio- and stereoselectively to produce the only product **138**. Its structure was established by X-ray diffraction analysis (see Fig. 2 of the electronic supplement). The mutual arrangement of the NO_2 groups in the pyrazole ring follows also from the ^{13}C NMR spectrum (similarly to the spectrum of compound **136a**).



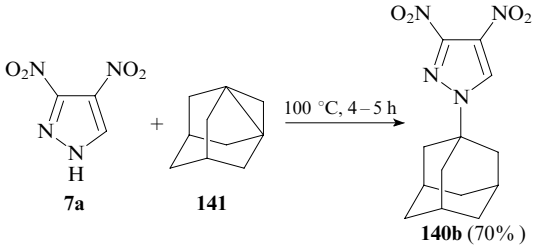
It was established [98] that an adamantyl substituent at the nitrogen atom can be introduced into dinitropyrazole **7b** on treatment with adamantan-1-ol (**139**) in either 82% sulfuric acid or a 4:1 (by mass) mixture H_3PO_4-AcOH. The



(*a*) 82% H_2SO_4, 20–22 °C, 72 h (25%);
(*b*) H_3PO_4-AcOH (4:1, by mass), 60 °C, 8 h (32%).

nuclear Overhauser effect (NOE) caused by interaction of the spatially adjacent protons of the methyl group and H(2) atom of the adamantyl substituent unambiguously proves the structure of compound **140a**.

A method of the introduction of an adamantyl substituent into 3,4-dinitropyrazole (**7a**) on treatment with dehydroadamantane (**141**) has been patented.[99] The orientation of the adamantylation with respect to the pyrazole ring was not considered.



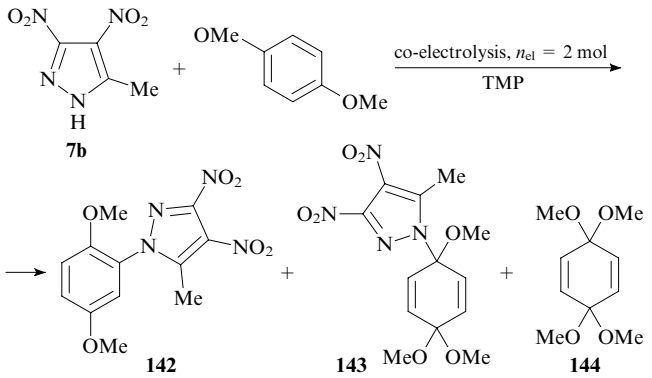
Co-electrolysis of dinitropyrazole **7b** and 1,4-dimethoxybenzene (DMB) in acetonitrile or methanol in an undivided cell in the presence of 2,4,6-trimethylpyridine (TMP) as a base was investigated.[100, 101] The major reaction product is compound **142**. However, depending on the electrolysis conditions and work-up of the reaction mixture, the formation of compounds **143** and **144** is possible (Table 4). The

Table 4. Electrolysis conditions for mixtures of compound **7b** and DMB and product yields.[100, 101]

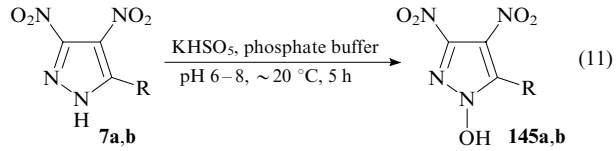
Ratio **7b** : DMB	Solvent	Ratio TMP : **7b**	Background electrolyte	Current yield **142** (%)
1.5	MeCN	0	Bu_4NClO_4	< 2
1.5	MeCN	0.5	Bu_4NClO_4	6
1.0	MeCN	0	$Bu_4N(pz)$[a]	6
1.5[b]	MeOH	0.5	Bu_4NClO_4	4
1.5[c]	MeOH	0.5	Bu_4NClO_4	16

[a] Hpz is **7b**; [b] after electrolysis, MeOH was evaporated *in vacuo* at 20–25 °C; in this case, 13% of compound **143** and < 2% of compound **144** were detected; [c] after evaporation of MeOH, the reaction mixture was heated at 110 °C for 5 h.

authors suggest an electrolysis mechanism and discuss it in detail, nevertheless, the orientation of the arylation with respect to the pyrazole ring is not considered in these studies.



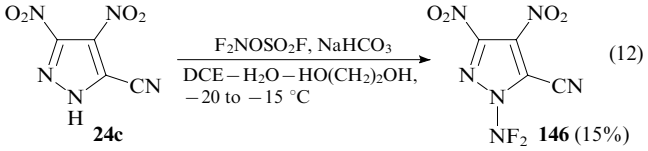
A method of the preparation of 1-hydroxy-3,4-dinitropyrazoles by oxidation of NH-pyrazoles **7a**,**b** with potassium peroxomonosulfate in a buffer solution has been developed.[102] No evidence is presented for the location of nitro groups in the position 3 of the ring for compounds **145a**,**b**. It should be noted that *N*-hydroxydinitropyrazoles are strong OH-acids: their pK_a values are several orders of magnitude higher than the corresponding values for the starting dinitropyrazoles **7a**,**b**.



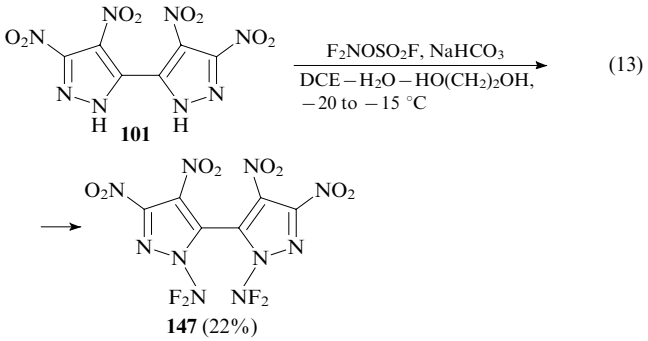
(11)

R = H (**a**, 48%), Me (**b**, 52%)

The preparation of difluoroaminodinitropyrazole **146** and -bipyrazole **147** by treatment of the corresponding NH-dinitropyrazoles **24c** and **101** with *O*-fluorosulfonyl-*N*,*N*-difluorohydroxylamine in an alkaline medium under conditions of phase-transfer catalysis (PTC) was reported.[103–105] It should be noted that the reagent employed is an ambident electrophile, and pyrazoles with a substantially lower acidity produce 1-fluorosulfonylpyrazoles rather than 1-difluoroaminopyrazoles.[106] Moreover, the pK_a values of azoles must not exceed 5. Thus 3,4-dinitropyrazole (**7a**) with pK_a is 5.48 does not react with *O*-fluorosulfonyl-*N*,*N*-difluorohydroxylamine.



(12)



(13)

DCE is 1,2-dichloroethane.

Compounds **146** and **147** are extremely impact sensitive (approximately like lead azide). This fact is, apparently, accounted for by low N–NF_2 bond energy, which is estimated as 26.8 kcal mol^{-1}.

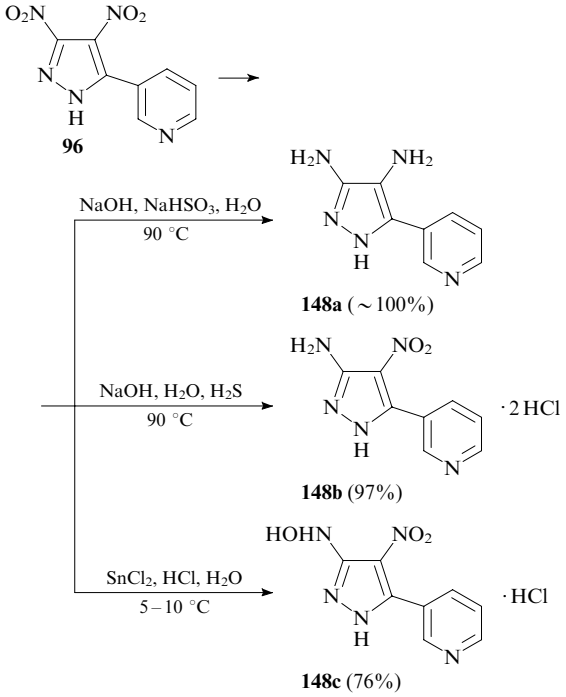
5,5′-Assembly of pyrazole rings in bipyrazole **147** was established[103, 105] by means of X-ray diffraction analysis (see Fig. 3 of the electronic supplement). The dihedral angle between two pyrazole ring planes is 60.6°, which seems to indicate the absence of conjugation between them (compare to an analogous value for the bipyrazole **101** anion, which is 35.2°); the rotation angles of the nitro groups with respect to the pyrazole ring planes are 19° and 86° for the 3-NO_2 groups (in the anion of compound **101** they are 24.4° and 24.5°), 36° and 12° for the 4-NO_2 groups (in the anion of compound **101** they are 28.3° and 36.3°). It should be noted that fluorine atoms in the NF_2 groups of compound **147** are non-equivalent, which is also manifested in the ^{19}F NMR

spectrum: signals (δ 107.35 and 111.46) appear as two doublets (^2J = 500 Hz). No evidence for the location of nitro groups in compound **146** is provided in the cited references.

The nitration of dinitropyrazoles **7a**,**b** resulting in trinitropyrazoles **8a**,**b** was mentioned in Section II.1 [reaction (1)].†

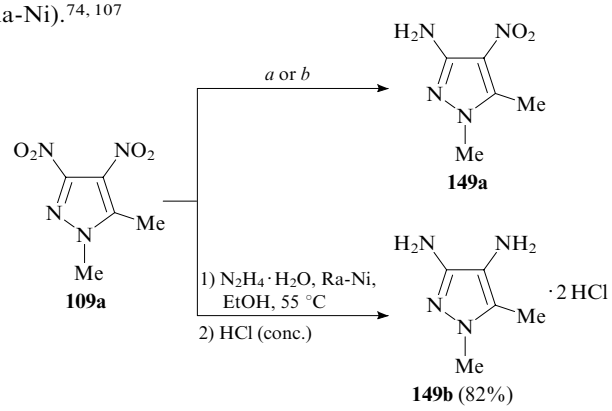
2. Properties of 3,4- and 4,5-dinitropyrazoles

Nitro groups in 3,4-dinitropyrazoles can be reduced by classical methods. Thus compound **96** being treated with sodium hydrogen sulfite yields diaminopyrazole **148a**.[69]



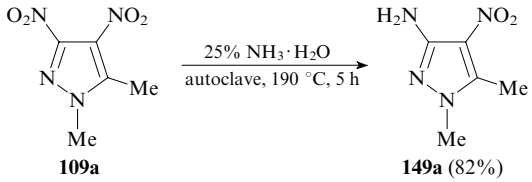
The use of an equivalent amount of the reductant allows the reduction of only one nitro group; in all the known instances, only the nitro group in the position 3 of the pyrazole ring is selectively reduced. Thus treatment of compound **96** with sodium hydrogen sulfide yields aminopyrazole **148b**. The position of the amino group was proved by deamination, which resulted in nitropyrazole **98** rather than **97**.[69] By using tin(II) chloride as the reductant, dinitropyrazole **96** was converted to the corresponding hydroxylamine **148c**.[69]

Similarly, the reduction of dinitropyrazole **109a** with sodium hydrogen sulfide or tin(II) chloride leads to aminopyrazole **149a**.[90] The position of the amino group in the molecule was proved by the fact that the characteristics of the obtained compound (melting point, ^{1}H NMR spectrum) were identical to those of 3-amino-1,5-dimethyl-4-nitropyrazole synthesised by the reaction of 3-bromo-1,5-dimethyl-4-nitropyrazole with ammonia where the position of the amino group is unambiguous. Diaminopyrazole **149b** is obtained from dinitropyrazole **109a** on treatment with hydrazine hydrate in the presence of the Raney nickel (Ra-Ni).[74, 107]

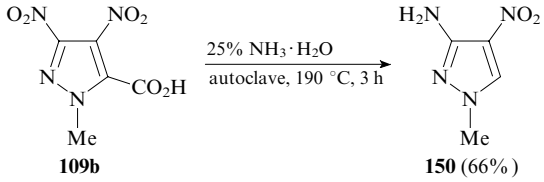


(*a*) NaHS, $MgSO_4$, H_2O, 80 °C, 30 min (66%);
(*b*) $SnCl_2$, HCl, AcOH, H_2O, reflux (56%).

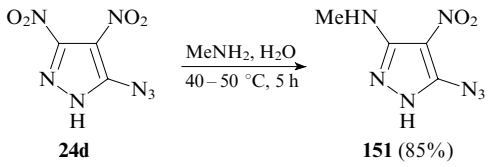
Aminopyrazole **149a** can be prepared from dinitropyrazole **109a** not only by reduction, but also by nucleophilic substitution. It was found[90] that the 3-NO_2 group in pyrazole **109a** is replaced by the NH_2 group on treatment with aqueous ammonia under drastic conditions (autoclave, 190 °C).[90]



An analogous conversion of compound **109b** is accompanied by decarboxylation and results in aminopyrazole **150**.[90]

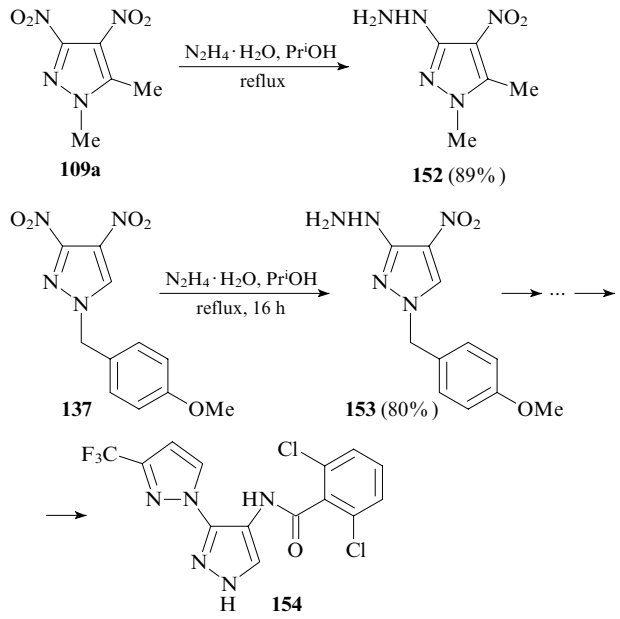


In contrast to compounds **109a**,**b**, dinitropyrazole **24d** replaces the 3-NO_2 group by methylamine under sufficiently mild conditions,[24] resulting in pyrazole **151**.

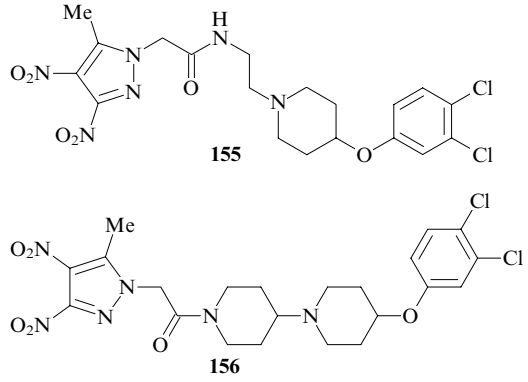


The nitro group in the 3 position can also be replaced by a hydrazine residue. Thus from compounds **109a** and **137** the corresponding products **152** (Ref. 108) and **153** (Ref. 60) were obtained. From the latter, compound **154** was synthesised in several steps. It is an inhibitor of various kinases (CDK, GSK, Aurora kinase) and is patented as an effective drug for treatment and prevention of diseases dependent on these enzymes.

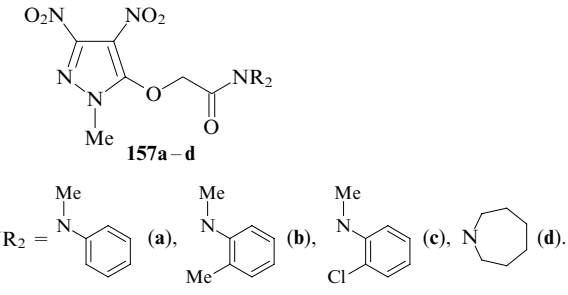
† After we had submitted the present review, we synthesised an isomer of trinitropyrazole **8a**, *viz*., previously unknown 3,4,5-trinitropyrazole, by the oxidation of 3(5)-amino-4,5(3)-dinitropyrazole (**121**) (m.p. = 182–184 °C; onset of decomposition at 252 °C). ^{13}C NMR spectrum (DMSO-d_6): δ 122.4 [C(4)], 147.1 [C(3), C(5)]; ^{14}N NMR spectrum (Me_2CO-d_6): δ −32.7 (all the NO_2 groups), −71.3 [N(2)], 7134.7 [N(1)].



Compounds **155** (Ref. 109) and **156** (Ref. 110) synthesised from acid **102** act as CCR3 receptor antagonists and were patented as drugs against a number of diseases, particularly, asthma and rhinitis.



Dinitropyrazoles **157a–d** were patented [111] as potent herbicides active against rice weeds, especially against the barnyard grass *Echinochloa crus-galli*; whereas rice plants are not affected by these compounds.



Dinitropyrazole **138** was patented [112] as a potential regulator of fat metabolism processes.

The well-known French company L'Oreal patented [113, 114] the possibility of the use of dinitropyrazoles **7a** and **102** in compositions for dyeing keratin fibres.

The research [94] indicates that compound **102** can restore the function of ischemia-damaged retina (experiments on rats). This suggests that 3,4-dinitropyrazoles like *N*-nitropyrazoles can act as exogenous sources of nitrogen(II) oxide.

As already noted above, 3,4-dinitropyrazoles act as comparatively strong NH-acids. The known pK_a values of 3,4-dinitropyrazoles are presented in Table. 5. Let us note that 3,4-dinitropyrazole (**7a**) has pK_a more than 2 orders of magnitude lower than 3,5-dinitropyrazole [pK_a = 3.14 (Ref. 93)]. Presumably, [93] this is associated with steric factors: in 3,4-dinitropyrazole, in contrast to the 3,5-isomer, both nitro groups cannot be co-planar with the pyrazole ring due to mutual repulsion, which results in a descrease in the delocalisation of the negative charge in the anion.

Table 5. The acidity constants of 3,4-dinitropyrazoles and bipyrazole **101**.

Compound	pK_a	pK_{BH^+}	Ref.
7a	5.48	−8.06	14, 93
7b	6.35	−8.1	93, 98
46	5.09	–	93
121	6.34	−7.12	10
101	1.80; 4.70	–	10
24c	4 (estimate)	–	103

Some 3,4-dinitropyrazoles belong to energetic substances, for example, the simplest unsubstituted 3,4-dinitropyrazole (**7a**), bipyrazole **101**, azasydnone **131** and difluoroamine derivative **147**. Selected experimental and calculated properties of these substances (density, heat of formation, heat of explosion, detonation rate, *etc*.) are documented.[39, 70, 104, 105]

3,4-Dinitropyrazole (**7a**) as one of the simplest representatives of energetic substances in the pyrazole series serves as a model compound for predicting physicochemical properties and validating authors' hypotheses.[115]

The electrochemical oxidation of the 3,4-dinitropyrazole (**7a**) anion in anhydrous acetonitrile was studied.[116] The determined half-wave potential value was $E_{1/2}$ = 1.85 V (*vs*. Ag reference electrode). The value 1.65 V was also reported.[95]

A convenient and fast polarographic method of the simultaneous determination of the content of nitropyrazoles in mixtures **7a** + **1** and **7a** + **105a** has been developed.[117, 118] (Model experiments were carried out with the equimolar mixtures at the 10^{-4} mol litre^{-1} pyrazole concentrations in a Britton–Robinson buffer solution at pH 11.6).

Experimental chemical shifts and coupling constants in the ^{1}H and ^{13}C NMR spectra of dinitropyrazole **105a** were compared with those calculated by various quantum chemical methods.[82] Satisfactory agreement of the parameters of the ^{1}H NMR spectra was obtained for all the calculation methods. For the ^{13}C NMR spectra, the best fit was observed in the case of calculations at the B3LYP/6-31 + G(d,p)//B3LYP/6-31G(d) level of theory.

Theoretical calculations of the activity of a wide range of $TpRe(CO)_2$ complexes [Tp is a tris(pyrazolyl)borate ligand] in the activation of a methane C–H-bond have been performed.[119] The calculated semiempirical electronic parameter (SEP) correlated with the vibration frequency ν_{CO} of the complexes proved to be the highest for the complex with the tris(3,4-dinitropyrazolyl)borate ligand. If only electronic factors are taken into account, of all compounds $TpRe(CO)_2$ examined this complex should possess the maximum catalytic activity in the reaction under consideration.

The IR spectra of 3(5),4-dinitropyrazoles contain characteristic absorption bands at 1505–1580 and

1325–1380 cm^{-1}, these frequencies corresponding to the antisymmetric and symmetric vibrations of the NO_2 groups.

The chemical shifts of H(5) in the ^1H NMR spectra of 3(5),4-dinitropyrazoles are in the range δ 8.20–9.08 depending on the chemical environment of these atoms. The signals for 3- and 5-Me group protons of methyl-3(5),4-dinitropyrazoles appear in the range δ 2.34–2.80, the signals for 1-Me groups are in the region δ 3.96–4.45.

The ^{13}C NMR spectra of *N*-substituted 3,4-dinitropyrazoles contain signals for the C(3), C(4) and C(5) atoms in the regions δ 141.6–148.3, 122.4–128.35 and 122.20–142.21, respectively, depending on the chemical environment of these atoms. The chemical shifts of the CNO_2, C(4) and CR atoms in *N*-unsubstituted 3(5),4-dinitropyrazoles are in the regions δ 147.9–152.0, 109.8–123.0 and 130.6–157.8, respectively. The signals for the 3- and 5-Me group carbon atoms of methyl-3(5),4-dinitropyrazoles are observed in the range δ 12.97–14.0 The signal for the 1-Me group carbon atom of compound **120b** appears at δ 39.9.

The ^{15}N NMR spectra of 3(5),4-dinitropyrazoles exhibit the signals for the N(1), N(2), C(3)NO_2 and C(4)NO_2 nitrogen atoms in the δ ranges from −117.01 to −210.37; from −78.10 to −108.32; from −23.20 to −31.02 and from −22.05 to −30.76, respectively.[24, 41, 102, 120, 121]

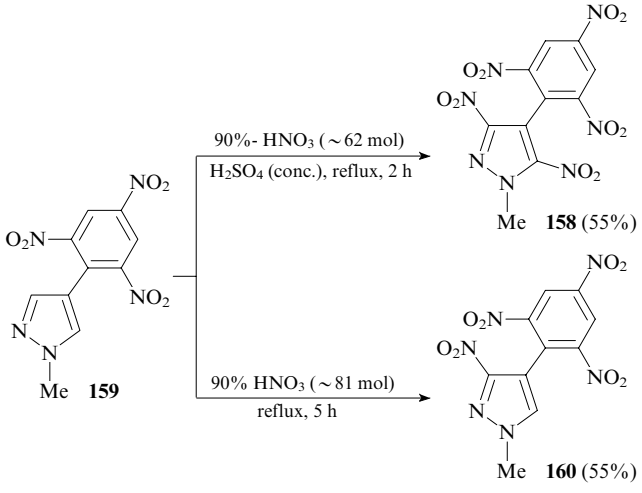
Data on the properties of 3,4-dinitropyrazoles are summarised in Table 3 of the electronic supplement.

V. 3,5-Dinitropyrazoles

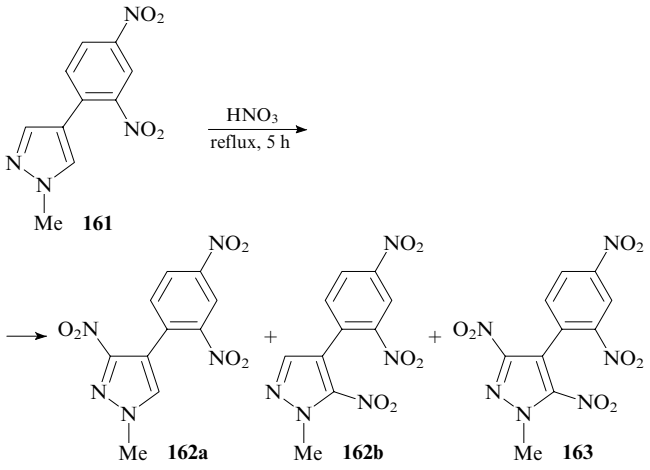
1. Synthesis of 3,5-dinitropyrazoles

The sequence of material presentation in this Section is analogous to that in Section IV.1.

The first 3,5-dinitropyrazole **158** described in the literature was synthesised[122] by the nitration of pyrazole **159** with a nitric acid–sulfuric acid mixture. If the nitration is carried out in the absence of sulfuric acid, 3-nitropyrazole **160** is obtained.



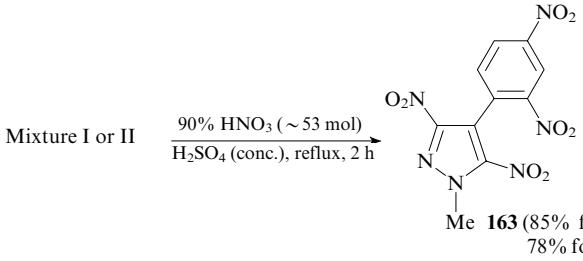
In the same study, the nitration of *N*-methylpyrazole **161** with nitric acid of different concentrations was examined. It was established that the nitration with 70% HNO_3 for 5 h does not lead to a complete conversion of the initial pyrazole, the products being 3- and 5-nitro isomers **162a**,**b**, respectively. The increase in the nitric acid concentration to 90% results in a full conversion of the starting pyrazole, and dinitropyrazole **163** appears among the reaction products.



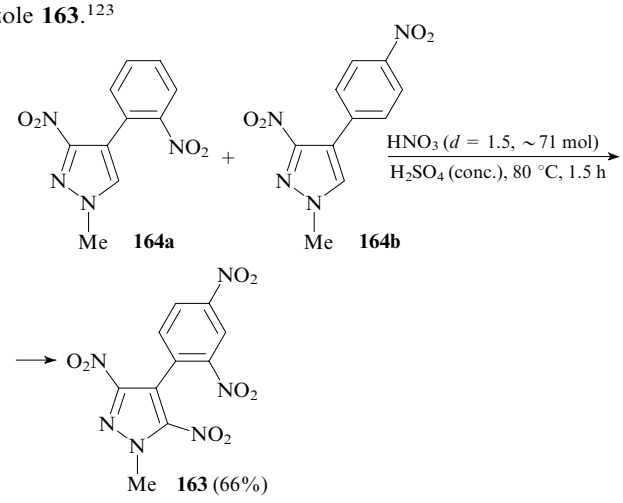
Mixture	$\omega(HNO_3)$ (%)[a]	Ratio HNO_3 : **161** (mol)	Content in the mixture (mol.%)			
			161	**162a**	**162b**	**163**
I	70	~370	59	24	17	0
II	90	~274	0	29	13	58

[a] ω is the mass concentration.

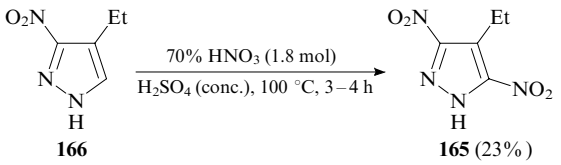
Both mixtures (I or II) can be subjected to further nitration using a nitric acid–sulfuric acid mixture,[122] resulting in dinitro derivative**163** in good yield.



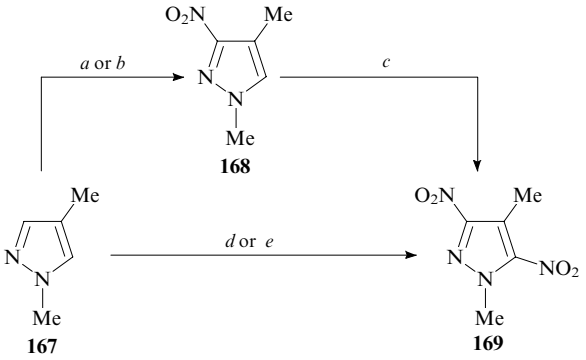
Analogously, it was demonstrated that the nitration of a mixture of isomeric nitropyrazoles **164a**,**b** (obtained by nitration of 1-methyl-4-phenylpyrazole with acetyl nitrate) with a nitric acid–sulfuric acid mixture leads to dinitropyrazole **163**.[123]



N-Unsubstituted 3,5-dinitropyrazole **165** can be synthesised by the nitration of 3(5)-nitropyrazole **166** with a nitric acid–sulfuric acid mixture.[15]



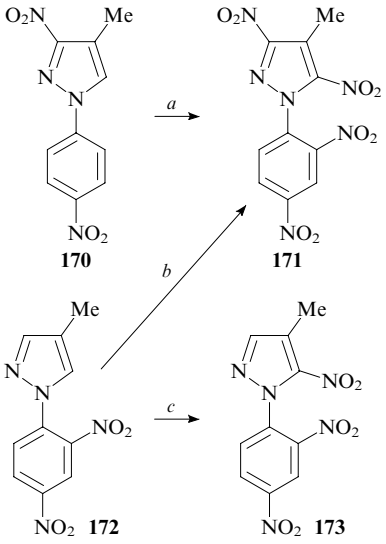
The kinetics of the nitration of 1,4-dimethylpyrazole (**167**) has been studied.[124] One-step nitration (like two-step nitration *via* the intermediate 3-nitropyrazole **168**) provides only an insignificant yield of dinitropyrazole **169** (conditions *a*–*d*). More recently, another research group developed [125,126] a preparative procedure for the synthesis of compound **169**, which allows one to increase its yield to 54% (conditions *e*).



(*a*) 70% HNO_3 (3.2 mol), Ac_2O, 0 °C, 5 h (yield 22%);
(*b*) HNO_3, H_2SO_4 (40%);
(*c*) 70% HNO_3 (~27.5 mol), 92% H_2SO_4 100 °C, 12 h (19%);
(*d*) 90% HNO_3 (~20.5 mol), H_2SO_4, reflux, 24 h (24%);
(*e*) HNO_3 (*d* = 1.5, ~4.6 mol), 92.5% H_2SO_4, 100 °C, 6 h (54%).

The molecular and crystal structure of dinitropyrazole **169** was studied [126,127] by X-ray diffraction (see. Fig. 4 of the electronic supplement). The pyrazole ring is planar; the torsional angles that characterise the rotations of the nitro groups with respect to the ring plane are small (1.36° for 3-NO_2 and 6.19° for 5-NO_2).

Pyrazole **170** produces dinitro derivative **171** also in low yield.[124] Recently, the latter was synthesised from



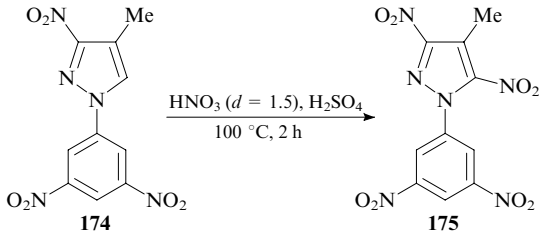
(*a*) 90% HNO_3 (~21 mol), 102% H_2SO_4, 120 °C, 24 h (29%);
(*b*) HNO_3 (*d* = 1.5, ~10 mol), 97.5% H_2SO_4, 100–105 °C, 3 h (64%);
(*c*) HNO_3 (*d* = 1.5, ~10 mol), 97.5% H_2SO_4, 30–40 °C, 10 min (77%).

methylpyrazole **172** (yield 64%). (For comparison, at low temperature pyrazole **172** yields 5-nitropyrazole **173**.[126,128])

The study of nitration kinetics of compounds **167**, **168** and **170** in sulfuric acid showed that all of them are nitrated as free bases as opposed to pyrazoles with the unsubstituted position 4, which undergo a nitration reaction as conjugated acids.[124] Presumably, the reactivity of the positions 3 and 4 of the pyrazole ring in free bases differs negligibly,‡ the distinction sharply increases for conjugated acids in which the position 3 is strongly deactivated due to the adjacent positively charged nitrogen atom; the same also concerns the position 5 of the pyrazole ring.

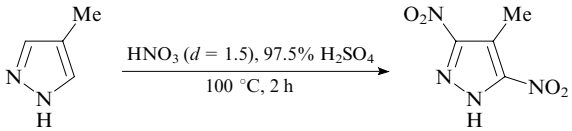
The structure of dinitropyrazole **171** was studied by X-ray diffraction analysis (see Fig. 5 of the electronic supplement).[126,128] One should note a considerable rotation of the benzene ring with respect to the pyrazole one [the angle between the corresponding planes is 65.5(3)°] and the rotation angles of the nitro groups with respect to the pyrazole ring are small [4.7(3)° for 3-NO_2 and 10.3(3)° for 5-NO_2].

The nitration of 3-nitropyrazole **174** with a nitric acid–sulfuric acid mixture gave 3,5-dinitropyrazole **175**.[126,129]



$\omega(H_2SO_4)$ (%)	Ratio HNO_3 : **174** (mol.)	Yield **175** (%)
96.5	5	46
96.5	2	79
98.5	5	74

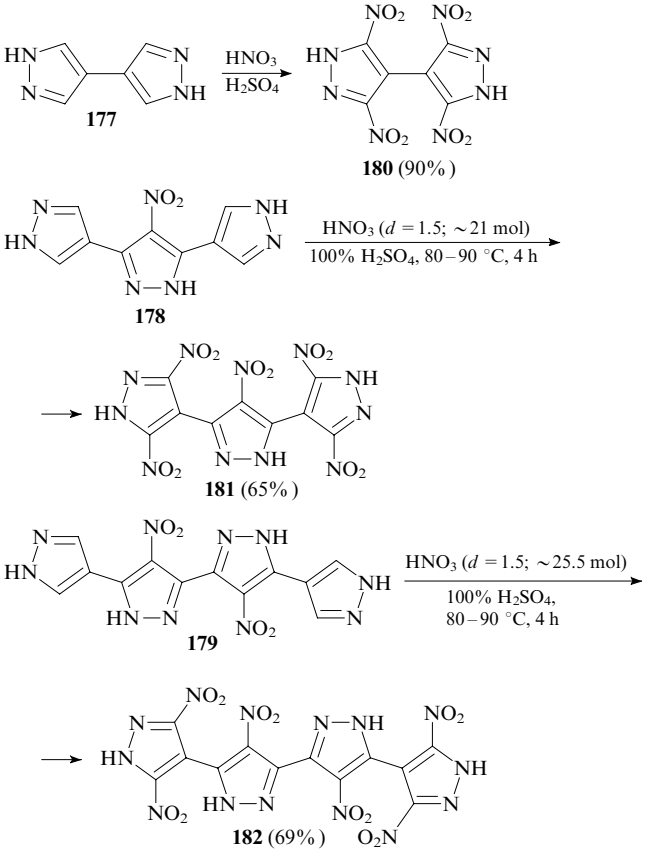
Unlike 1,4-dimethylpyrazole (**167**), *N*-unsubstituted 4-methylpyrazole is not nitrated to 3,5-dinitropyrazole **176** under the same conditions.[126,130] This fact is also confirmed by data from other studies.[122,123] It was noted [126,130] that in the synthesis of 3,5-dinitropyrazoles a critical factor is the amount of water in the reaction mixture: the preparation of the products in acceptable yields requires the use of highly concentrated nitric acid (d = 1.5 g cm^{-3}) and concentrated sulfuric acid (not less than 96%). The use of ordinary sulfuric acid (Russian federal standard 4204–77) results in low yields of nitration products. Using H_2SO_4 with 97.5% concentration allowed the synthesis of pyrazole **176** in good yield.[126,130]



It was shown [38,70,71] that the nitration of bi-, ter- and quaterpyrazoles (**177**–**179**) with a nitrating mixture leads to tetra-, penta- and hexanitro derivatives (**180**–**182,** respec-

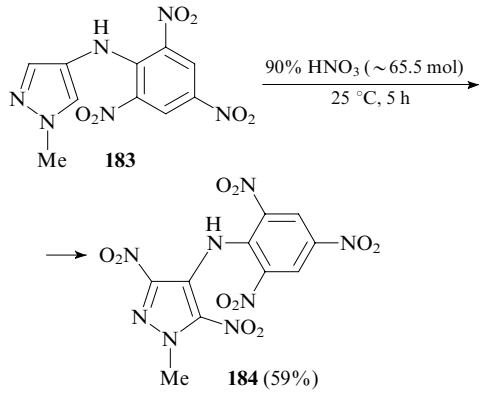
‡ This clears up the fact that the nitration of 1-methylpyrazole in 80% H_2SO_4 (the Hammett acidity function $H_0 \approx$ is 6.7) results in the nitration of both positions 3 and 4 (see Section IV.1).

tively). In a study [38] of nitration conditions it was established that depending on the reaction duration, the yields of compounds **181** and **182** first increase, and then descrease, there is an optimal time for each case. This reaction feature was related to the earlier discovered [131] ability of 5-nitropyrazoles to decompose under the nitration conditions.

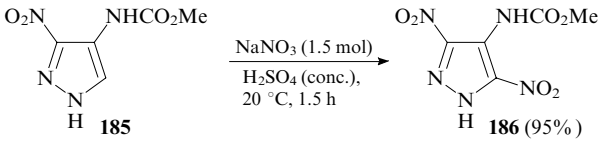


The structure of a monohydrate of compound **180** was determined by X-ray diffraction analysis (see. Fig. 6 of the electronic supplement).[70] The pyrazole rings are arranged virtually perpendicular to each other so that the strain created by nitro groups of the neighbouring rings is released; at the same time all four nitro groups are coplanar with the corresponding pyrazole rings.

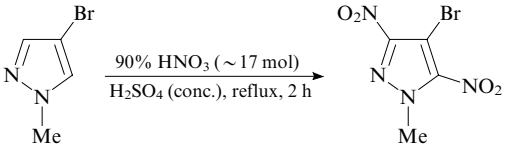
It was reported [132] that the nitration of amine **183** with a nitrating mixture under mild conditions resulted in 3,5-dinitropyrazole **184**.



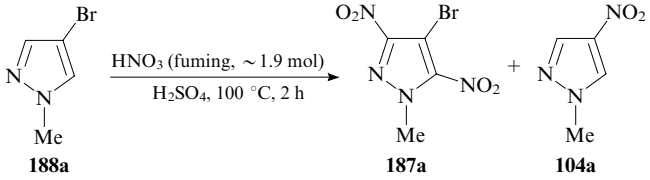
At room temperature, the nitration of 3-nitropyrazole **185** proceeds to dinitro derivative **186**.[77]



For the nitration of 4-halopyrazoles, the situation is more complex. Although the synthesis of 3,5-dinitropyrazole **187a** was described [132] as early as 1971, further studies indicated that the nitration conditions strongly affect the cource of the reaction.

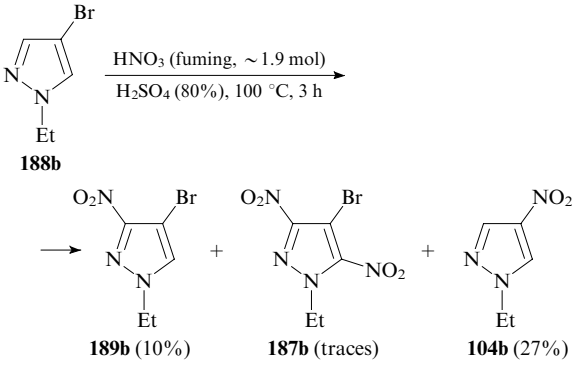


It was revealed [73] that in the nitration of 4-bromopyrazole **188a** with a nitric acid – sulfuric acid mixture, apart from dinitropyrazole **187a,** an *ipso*-substitution product of the bromine atom, *i.e.*, 4-nitropyrazole **104a**, is also formed. An increase in the concentration of sulfuric acid from 80% to 92%, as expected,[133] leads to a decrease in the proprotion of the *ipso*-nitration product.



$\omega(H_2SO_4)$ (%)	Ratio **187a** : **104a** (mol)	Yield (%)	
		187a	**104a**
80	1.4	24	17
92	3.0	–	–

It is of note that the nitration of 4-bromo-1-ethylpyrazole (**188b**) undertaken in the same study [73] under the same conditions led to a merely trace amount of 3,5-dinitropyrazole **187b**. The major reaction products were 4-bromo-3-nitropyrazole **189b** and 1-ethyl-4-nitropyrazole (**104b**) resulting from *ipso*-nitration.



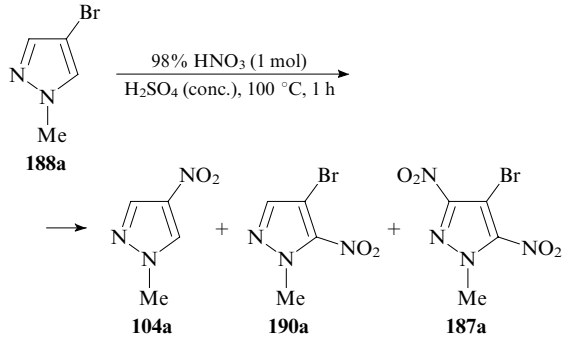
187b : **189b** : **104b** = 1 : 10.7 : 18.6

The dependence of nitration of 4-bromopyrazole **188a** with an equimolar amount of nitric acid in sufuric acid on the concentration of the latter was investigated [134] in detail. On nitration in 80% H_2SO_4 for 1 h, the formation of dinitropyrazole **187a** did not take place, the reaction products were 5-nitropyrazole **190a** and a nitrodebromination product **104a** (Table 6).

Table 6. The outcome of the nitration of pyrazole **188a** depending on the H_2SO_4 concentration.[134]

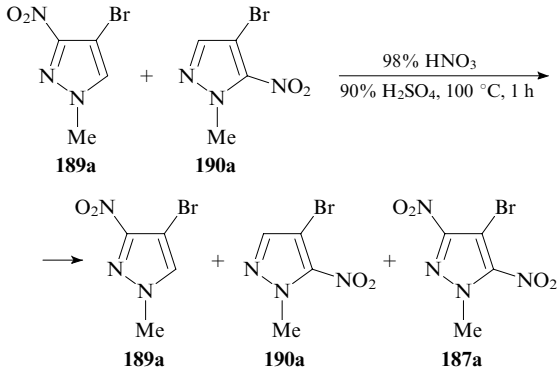
$\omega(H_2SO_4)$ (%)	Amount in the mixture (mol.%)				Ratio (**187a** + **190a**) : **104a**
	188a	**104a**	**190a**	**187a**	
80	40	50	10	0	1 : 5
90	10	40	40	10	5 : 4
102.5	18	10	54	18	7 : 1

An increase in the concentration of sufuric acid results, first, in a decrease in the proprotion of the *ipso*-nitration product and, second, in the appearance of dinitropyrazole **187a** among reaction products, which is formed, despite the use of the equimolar amount of HNO_3 relative to pyrazole **188a**. It should be noted that 4-bromo-1-methyl-3-nitropyrazole (**189a**) is not formed at any H_2SO_4 concentration.



A competitive nitration of a mixture of isomeric pyrazoles **189a** and **190a** with a deficiency of nitric acid at 100 °C for 1 h was carried out to ascertain the reaction route that leads to dinitropyrazole **187a**.[134] At the ratio **189a** : **190a** : HNO_3 = 1 : 1 : 1, 2/3 of pyrazole **189a** is consumed, while pyrazole **190a** does not react; at the ratio **189a** : **190a** : HNO_3 = 1 : 1 : 1.5, pyrazole **189a** is consumed completely and only 1/7 of pyrazole **190a**, *i.e.*, 3-nitro isomer **189a** in the nitration reaction reacts much faster than 5-nitro isomer **190a**. On this ground, a conclusion was drawn that the formation of bromodinitropyrazole **187a** in the nitration of **188a** occurs mainly from 3-nitro derivative **189a**.§

§ Such a conclusion, however, seems not quite correct. First, taking into account the data on higher activity of the position 5 of the pyrazole ring in the nitration reaction, it is reasonable to assume that pyrazole **188a** is also nitrated mainly in the position 5. Second, in 80% sulfuric acid, where no dinitropyrazole **187a** is formed, 3-nitro derivative **189a** is absent from the reaction mixture.



Ratio **189a** : **190a** : HNO_3 (mol.)	Ratio **189a** : **190a** : **187a** (mol.)
1 : 1 : 1	1 : 3 : 2
1 : 1 : 1.5	0 : 3 : 4

The nitration of 4-chloropyrazole **188c** was studied under the same conditions.[134] The difference in the behaviour of pyrazole **188c** and its analogue **188a** is, first, the absence of any nitrodechlorination and, second, the formation of a small amount (3%) of 3-nitro isomer in 90% and 102.5% H_2SO_4 (Table 7).

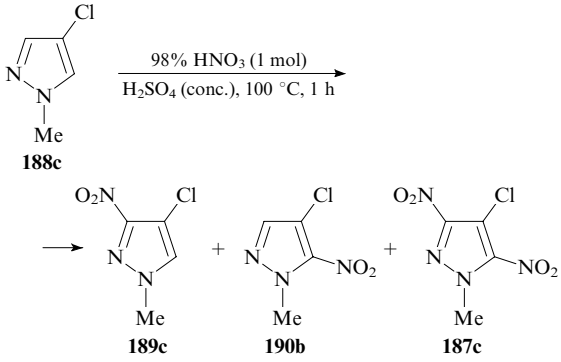
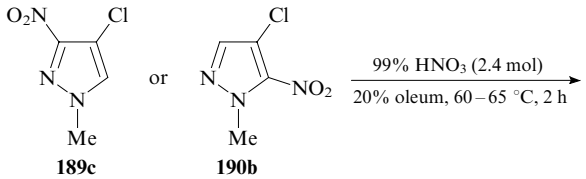
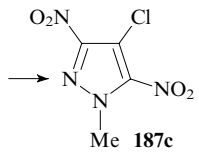


Table 7. The outcome of the nitration of pyrazole **188c** depending on the H_2SO_4 concentration.[134]

$\omega(H_2SO_4)$ (%)	Amount in the mixture (mol.%)			
	188c	**189c**	**190b**	**187c**
80	55	0	45	5
90	15	3	69	13
102.5	19	3	63	15

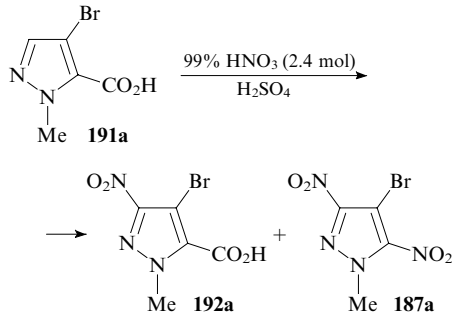
A preparative method of the synthesis of dinitro derivative **187c** from isomeric mononitro derivatives **189c** and **190b** is reported;[135] the yields are 78% and 65%, respectively.





187c

In the same study, the nitration of 4-halo-1-methylpyrazole-3- and -5-carboxylic acids was examined in detail. Thus acid **191a** being nitrated in 20% oleum at moderate temperatures yields a mixture of acid **192a** and its nitrodecarboxylation product, *i.e.*, dinitropyrazole **187a**. As the reaction temperature increases, the dinitropyrazole becomes the only product (Table 8).



191a **192a** **187a**

Table 8. The temperature dependence of the content of nitration products of pyrazole **191a** (in 20% oleum).[135]

Process conditions	Yields (%)	
	192a	**187a**
35–40 °C, 16 h	present (+**191a**)	15
60–65 °C, 2 h	43	51
65–70 °C, 4 h	0	68
70–75 °C, 2 h	0	69

The concentration of sulfuric acid also affects considerably the ratio of the reaction products.[76] The proportion of the dinitropyrazole is increased with an increase in the H_2SO_4 concentration, and in 100% acid, compound **192a** is absent from the reaction products (Table 9). Let us note that irrespective of the H_2SO_4 concentration, no nitrodebromination product was detected in the reaction mixture, though a bromine atom occupies the position 4 of the pyrazole ring.

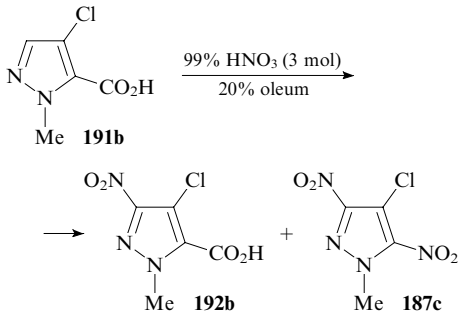
Table 9. The content of nitration products of pyrazole **191a** depending on the H_2SO_4 concentration (70 °C, 4 h).[76]

$\omega(H_2SO_4)$ (%)	Content in the mixture (mass %)	
	192a	**187a**
80	98	2
85	77	23
90	75	25
95	41	59
100	0	100

The nitration of carboxylic acid **191b** proceeds similarly.[135] A difference is that complete nitrodecarboxylation of product **192b** requires more drastic conditions (Table 10). Thus, bromodinitropyrazole **187a** becomes the only reaction product even at 65 °C, whereas chlorodinitropyrazole **187c** requires 85 °C. The use of an equimolar amount of nitric acid does not exclude the formation of dinitropyrazole **187c**, which points to a relatively high rate of the nitrodecarboxylation as compared to the rate of the 3-nitration of acid **191b**.

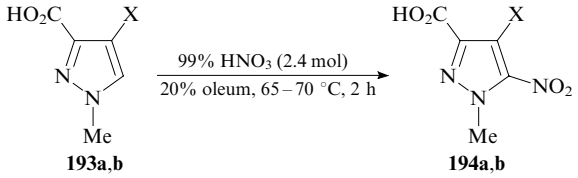
Table 10. The temperature dependence of the content of nitration products of pyazole **191b**.[135]

Nitration conditions	Amount in the mixture (mol.%)	
	192b	**187c**
60–65 °C, 2 h	58	42
65–70 °C, 4 h	37	63
70–75 °C, 4 h	28	72
70–75 °C, 5 h	15	85
80–85 °C, 6 h	0	100



191b **192b** **187c**

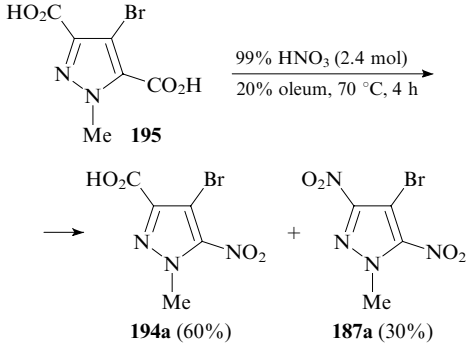
It should be noted that the isomers of acids **191a**,**b**, *i.e.*, 4-halo-3-carboxylic acids **193a**,**b**, give 5-nitro derivatives **194** under analogous conditions and do not yield nitrodecarboxylation products;[135] this also indicates a higher acivity of the position 5 as compared with the position 3 of the pyrazole ring in acidic nitration reactions.



193a,**b** **194a**,**b**

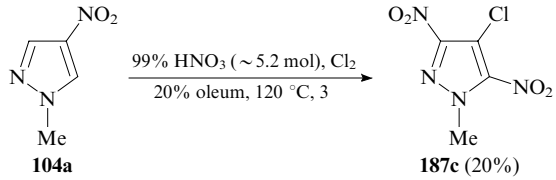
X = Br (**a**, 80%), Cl (**b**, 72%).

Higher acivity of the position 5 of the pyrazole ring was demonstrated[136] by the example of the nitrodecarboxylation of acid **195**. The reaction results in a mixture of compounds **194a** and **187a** in a ratio of 2 : 1.



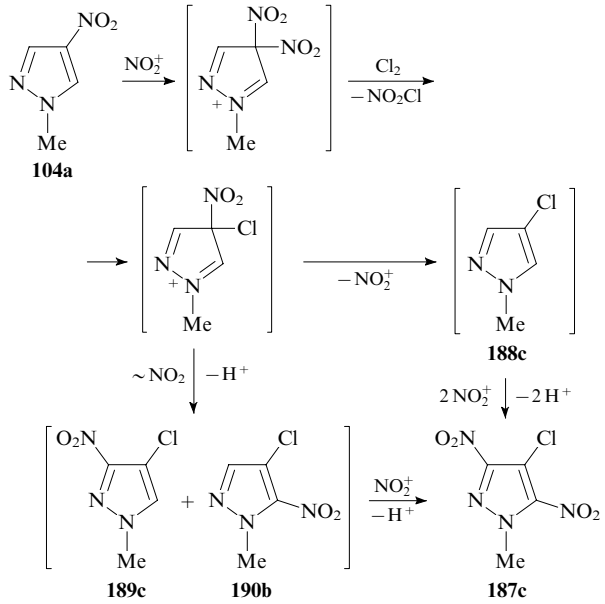
195 **194a** (60%) **187a** (30%)

3,5-Dinitropyrazole **187c** can be obtained from 4-nitropyrazole **104a** by nitration with simultaneous passage of gaseous chlorine through the reaction mixture.[137]



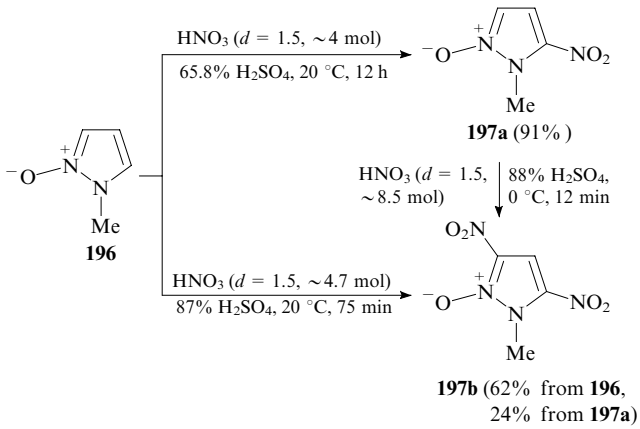
104a **187c** (20%)

The following mechanism of the formation of compound **187c** was suggested



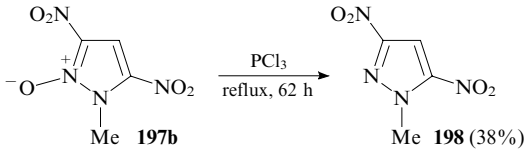
104a **188c** **189c** **190b** **187c**

Unlike pyrazoles with the unoccupied position 4 which is the reaction site of acidic niration in most cases, pyrazole *N*-oxides alter the course of nitration. Thus it was shown[138, 139] that pyrazole 2-oxide **196** produces 5-nitropyrazole 2-oxide **197a** upon nitration in 66% sulfuric acid. The nitration of compounds **196** and **197a** in a more concentrated H_2SO_4 (88%) results in 3,5-dinitropyrazole 2-oxide **197b**.



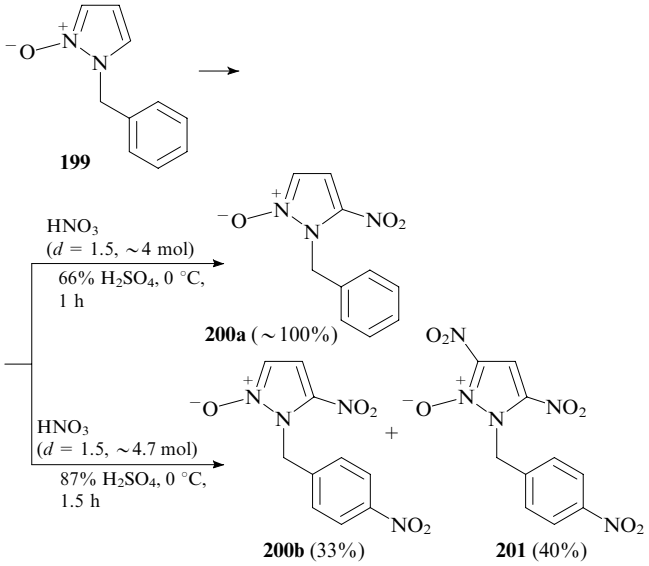
196 **197a** (91%) **197b** (62% from **196**, 24% from **197a**)

On treatment with phosphorus(III) chloride, *N*-oxide **197b** undergoes deoxygenation.[139] In this way, 4-unsubstituted dinitropyrazole **198** can be obtained.



197b **198** (38%)

Similarly, the nitration of pyrazole 2-oxide **199** was studied.[140] Depending on the acid concentration, either 5-nitropyrazole 2-oxide **200a**, or a mixture of 5-nitropyrazole 2-oxide **200b** with 3,5-dinitropyrazole 2-oxide **201** was obtained.

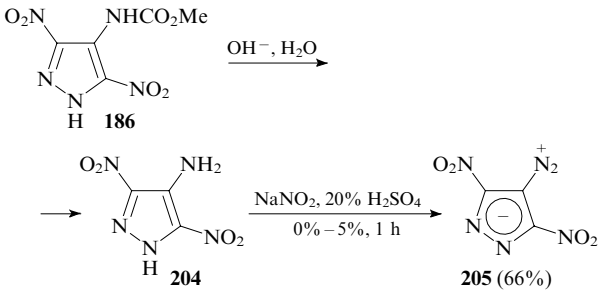


199 **200a** (~100%) **200b** (33%) **201** (40%)

The rearrangement of 1,3-dinitropyrazole (2), resulting in *N*-unsubstituted 3,5-dinitropyrazole (19), was already mentioned above [see Section II.2, reaction (2)].

From 3,5-dinitropyrazole **187a**, other 3,5-dinitropyrazoles can be derived. Thus it was found [132] that its reduction with sodium iodide in acetic acid leads to dinitropyrazole **198**, while reflux with copper in DMF (the Ullmann reaction) leads to tetranitrobipyrazole **202**. Heating of compound **187a** with amines in DMF or DMSO yields aminopyrazoles **203a–e** (in the case of ammonia, more drastic conditions are required) (Scheme 1).[132, 141]

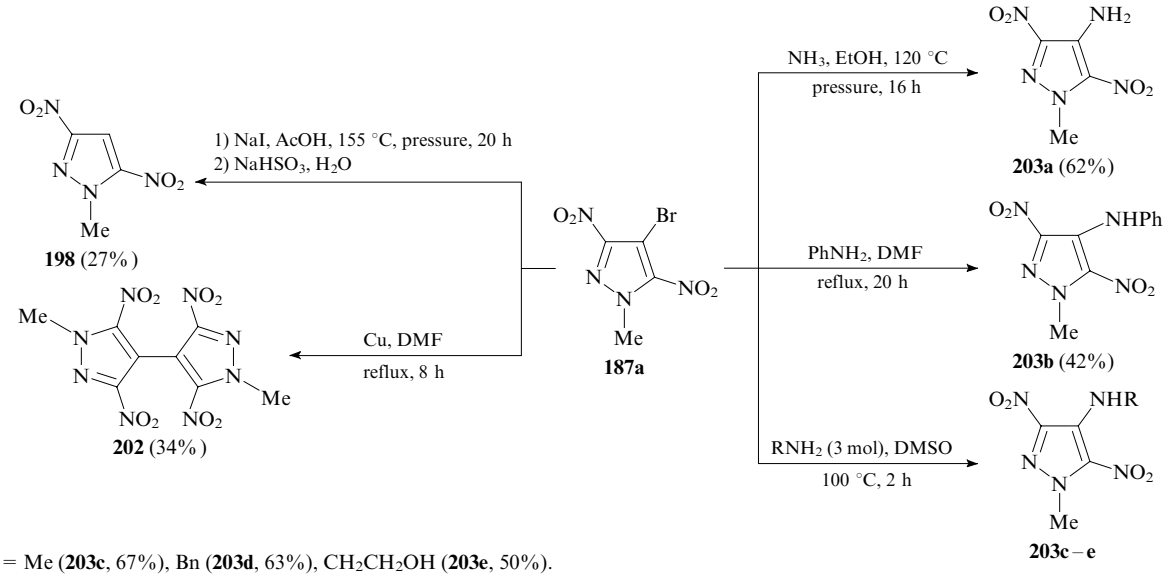
Alkaline hydrolysis of carbamate **186** affords aminopyrazole **204**,[142] diazotisation of which (occuring under standard conditions despite its low basicity) results in diazopyrazolate **205** existing, like its isomer **125**, as an internal salt.



186 **204** **205** (66%)

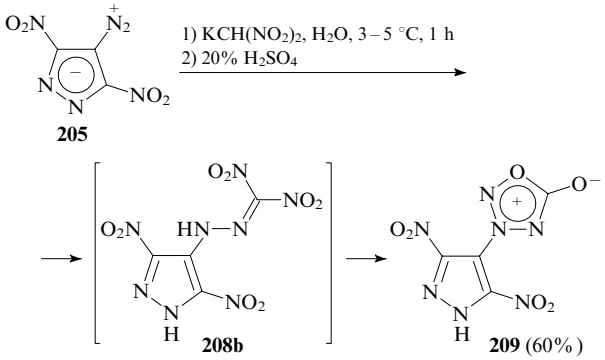
The chemical properties of compounds **205** and **125**, however, differ dramatically.[142] Thus when treated with azide and bromide ions and H_2O under acid catalysis, pyrazole **205** undergoes substitution of the NO_2 group in the position 3(5) (resulting in products **206a–c**), while

Scheme 1



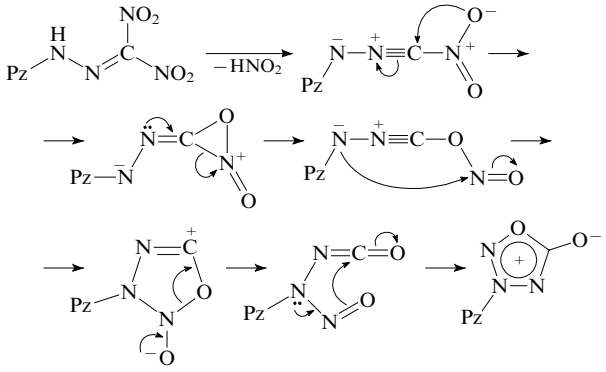
R = Me (**203c**, 67%), Bn (**203d**, 63%), CH_2CH_2OH (**203e**, 50%).

pyrazole **125** undergoes substitution of the diazo group. The reactions of compound **205** with acetylacetone- and nitroacetonitrile-derived anions lead to azo coupling products **207** and **208a**. For obvious steric reasons, the cyclisation of the product does not take place in contrast to an analogous reaction involving compound **125** [see reaction (9)] (Scheme 2).



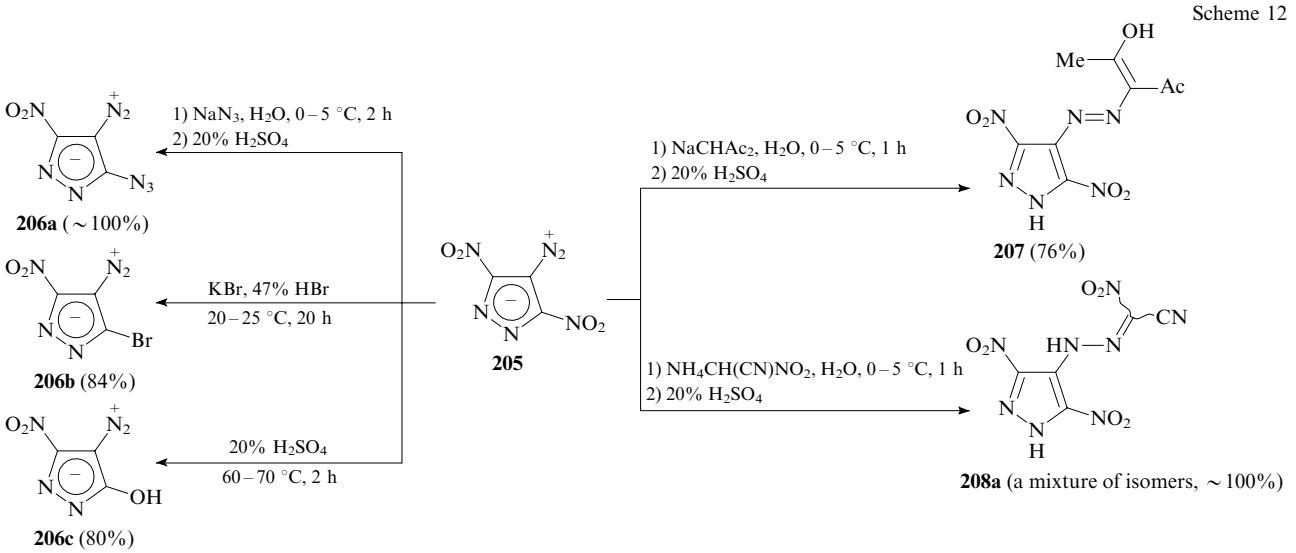
On treatment with dinitromethane potassium salt, diazopyrazole **205** gives an intermediate azo coupling product **208b**, which undergoes *in situ* transformation to azasydnone **209**,[143] an isomer of compound **131**.

The reaction mechanism based on literature analogies was suggested, which involves elimination of nitrous acid from compound **208b** followed by rearrangement of the nitro compound to the nitrite ester, migration of the nitroso group from the oxygen atom to the nitrogen atom and cyclization.

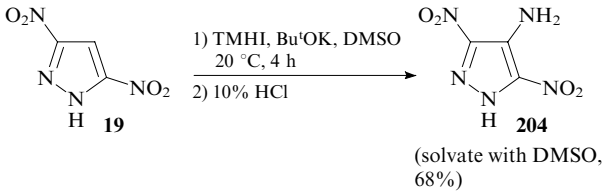


Pz is 3,5-dinitropyrazol-4-yl.

Scheme 12



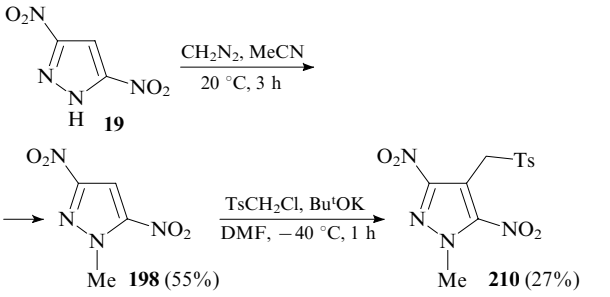
A method for the preparation of aminodinitropyrazole **204** by vicarious nucleophilic substitution of a hydrogen atom in unsubstituted dinitropyrazole **19** on treatment with trimethylhydrazonium iodide (TMHI) in the presence of potassium *tert*-butoxide has been developed.[140, 144]



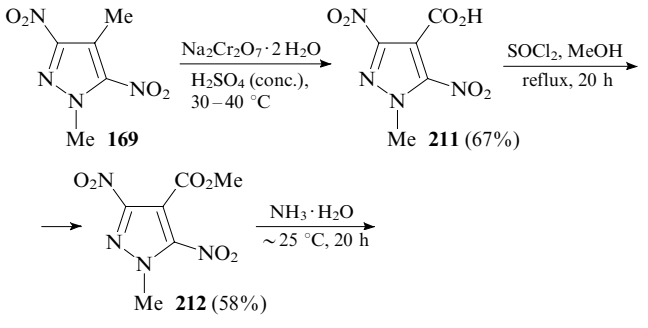
The structure of compound **204** (see Fig. 7 of the electronic supplement), and also of its solvate with DMSO was determined by X-ray diffraction analysis.[145] Both nitro groups are co-planar with the pyrazole ring.

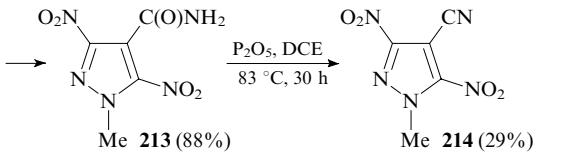
Generally speaking, the fact of a successful vicarious nucleophilic substitution in compound **19**, which is completely in an anionic form under such basic conditions, sets some wondering. Thus, this was explained[146] by a strong electron-withdrawing influence of two nitro groups. In a more recent investigation,[147] the reactivity of a large number of nitroazoles was found to correlate with spin density values in radical anions of these nitroazoles calculated by quantum chemical methods: only those azoles are reactive that produce radical anions with high values of spin density on the corresponding carbon atoms [for the 3,5-dinitropyrazole radical anion and radical dianion, the density values on the C(4) atom are +0.426 and +0.652, respectively].

On treatment with the chloromethyl tolyl sulfone anion, vicarious nucleophilic substitution of a hydrogen atom in dinitropyrazole **198** occurred;[89] the latter was obtained from compound **19** by methylation with diazomethane.



The syntheses of 3,5-dinitropyrazoles with different substituents in the position 4 of the pyrazole ring were described.[126, 127] The methyl group in the position 4 of dinitropyrazole **169** is readily oxidised with sodium dichromate to yield carboxylic acid **211**, from which derivatives **212**–**214** can be obtained by standard methods.





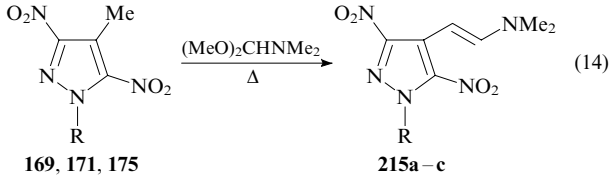
The molecular and crystal structure of nitrile **214** was studied by X-ray diffraction analysis (see Fig. 8 of the electronic supplement). The rotation angles of the nitro groups with respect to the pyrazole ring plane are small: 3.79° for 3-NO_2 and 2.69° for 5-NO_2.

Two nitro groups in the positions 3 and 5 of the pyrazole ring strongly activate the 4-methyl group. Thus 4-methyl-3,5-dinitropyrazoles undergo coupling reactions with dimethylformamide dimethyl acetal (Table 11).

Table 11. Conditions and product yields in reaction (14).

Compound **215**	Solvent	T/°C	Time/h	Yield (%)
a	DMF	~150	1	75
b	PhMe	~110	8	78
c	PhMe	~110	10	75

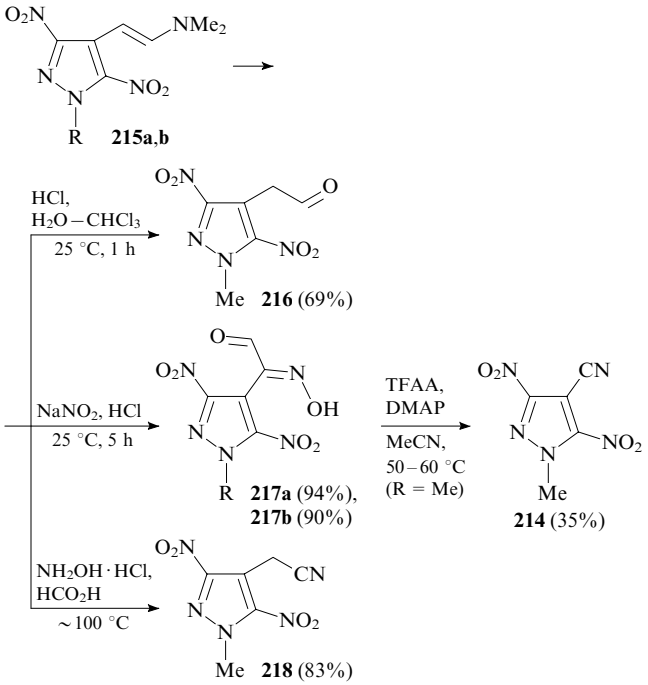
The reactivity of pyrazole **169** is similar to that of 2,4-dinitrotoluene.[125, 126] Dinitropyrazoles **171** and **175** bearing electron-withdrawing 2,4- (see Refs 126, 128) and 3,5-dinitrophenyl (DNP) substituents[126, 129] in the position 1 are even more reactive.



(14)

R = Me (**215a**), 2,4-DNP (**215b**), 3,5-DNP (**215c**).

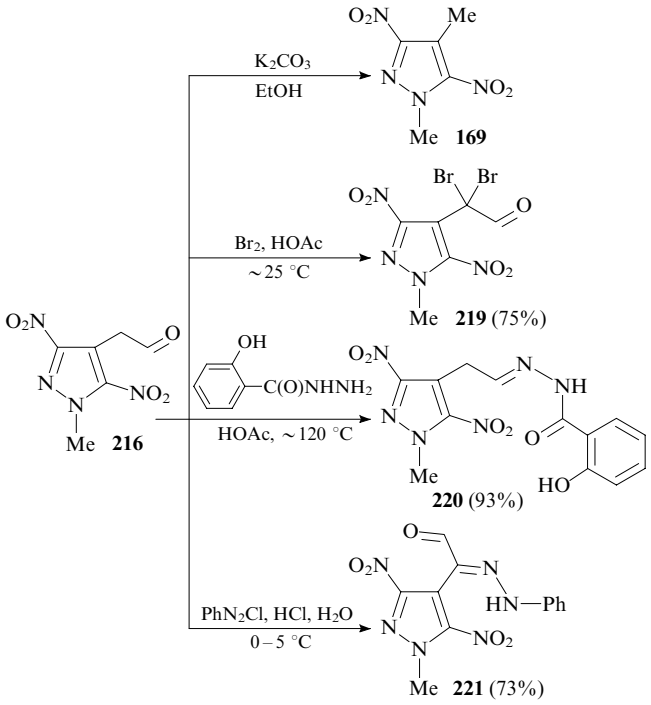
From enamines **215a**,**b**, diverse derivatives of the 3,5-dinitropyrazole series can be obtained. Thus upon acid



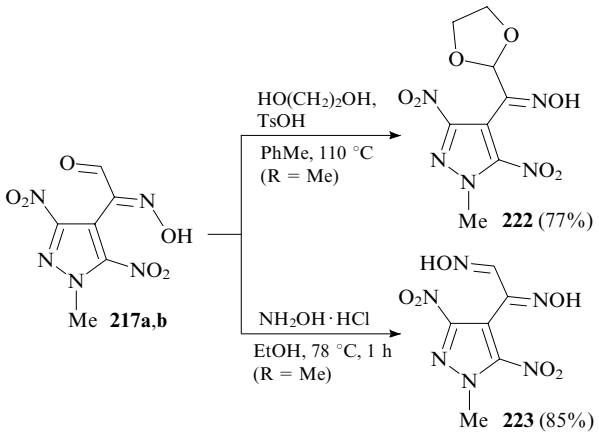
R = Me (**215a**, **217a**), 2,4-DNP (**215b**, **217b**).

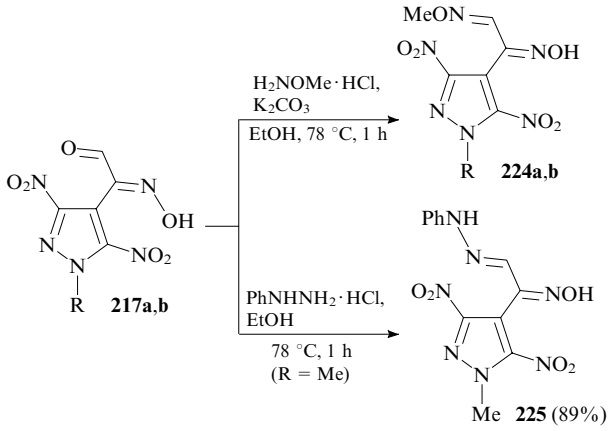
hydrolysis, compound **215a** yields aldehyde **216**; on treatment with $NaNO_2$ in concentrated HCl, enamines **215a**,**b** undergo hydrolysis and nitrosation *in situ* by nitrous acid to form aldehydes **217a**,**b**; upon reflux with $NH_2OH \cdot HCl$ in HCO_2H, enamine **215a** produces nitrile **218**.[125, 126, 128] Hydroxyimino aldehyde **217a** being treated with trifluoroacetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in MeCN yields nitrile **214**.[126, 127]

On treatment with potassium carbonate in alcohol, aldehyde **216** undergoes decarbonylation to produce dinitropyrazole **169**. The bromination of aldehyde **216** results in dibromo derivative **219**, the treatment with salicylohydrazide leads to hydrazono hydrazide **220**, while phenyldiazonium chloride results in hydrazono aldehyde **221**.[125, 126]



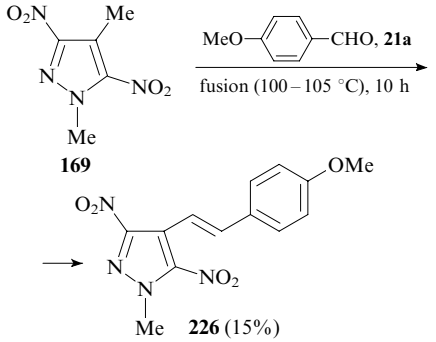
Different derivatives of aldehydes **217a**,**b** (compounds **222**–**225**) were prepared by reactions with ethylene glycol, hydroxylamine, *O*-methylhydroxylamine and phenylhydrazine.[125, 126, 128]



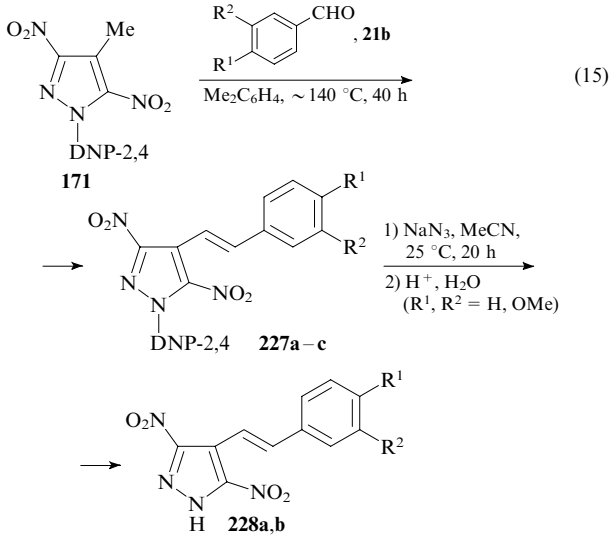


R = Me (**217a**; **224a**, 98%), 2,4-DNP (**217b**; **224b**, 92%).

The activating effect of two nitro groups is also manifested in the coupling of 4-methyl-3,5-dinitropyrazoles with aromatic aldehydes. Thus compound **169** reacts with anisaldehyde in the presence of piperidine (**21a**) under fairly drastic conditions (fusion of the reactants at ~100 °C), however, the product **226** is obtained in low yield.[126, 128]



Dinitropyrazole **171** with the electron-withdrawing 2,4-DNP group in the position 1 is able to undergo coupling with a wider range of aldehydes even on refluxing in xylene in the presence of morpholine (**21b**), the yields of products **227a**–**c** being higher than that of pyrazole **226**.[126, 128] Upon treatment of the coupling products **227a**,**b** with sodium azide, elimination of the 2,4-dinitrophenyl substituent

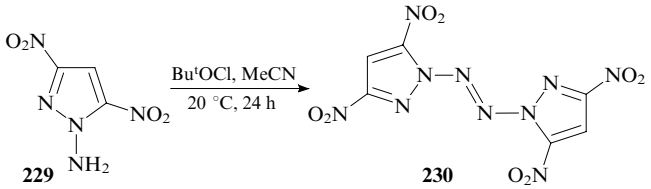


(15)

R^1 = OMe: R^2 = H (**227a**, 30%; **228a**, 96%),
OMe (**227b**, 38%; **228b**, 94%); R^1 = F, R^2 = H (**227c**, 32%).

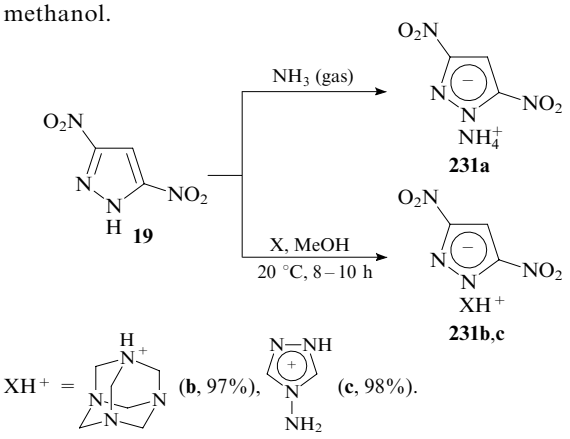
occurs. In this way, *N*-unsubstituted 3,5-dinitropyrazoles **228a**,**b** were obtained.[126, 128]

The oxidation of *N*-aminopyrazole **229** with *tert*-butyl hypochlorite results in *N*,*N*′-azobis(dinitropyrazole) **230**.[148]



229 **230**

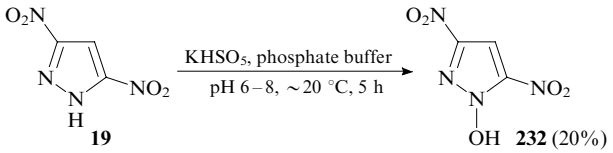
3,5-Dinitropyrazoles act as NH-acids (for details, see Section V.2) and produce salts when treated with bases. Quaternary ammonium salts of unsubstituted 3,5-dinitropyrazole (**19**) were proposed [149–152] as energetic compounds (see Section V.2). Ammonium salt **231a** can be prepared by passing gaseous ammonia through a solution of pyrazole **19** in ethanol or ether–ethanol.[149] Urotropinium [151] and 4-amino-1,2,4-triazolium [152] salts are obtained by the reaction of compound **19** with the corresponding base in methanol.



19 **231a** **231b**,**c**

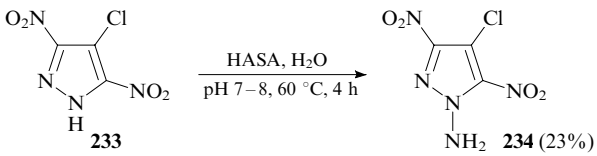
XH⁺ = (**b**, 97%), (**c**, 98%).

As in the case of 3,4-dinitropyrazoles [see Section IV.1, reaction (11)], 3,5-dinitropyrazole (**19**) being oxidised with potassium peroxymonosulfate in buffer solution with pH 6–8 yields 1-hydroxy-3,5-dinitropyrazole (**232**)[102] identified by ^{1}H NMR spectroscopy (not isolated in an individual state).



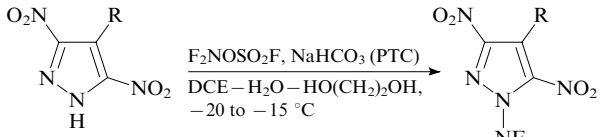
19 **232** (20%)

On treatment with hydroxylamine-*O*-sulfonic acid (HASA) at 60 °C in buffer solution, dinitropyrazole **233** gives the corresponding *N*-aminopyrazole **234**.[153, 154] The reaction should be carried out in the buffer solution, since hydrolysis of HASA proceeds at a comparable rate in parallel: as a result, in the absence of the buffer, the medium pH is reduced and the reaction stops.



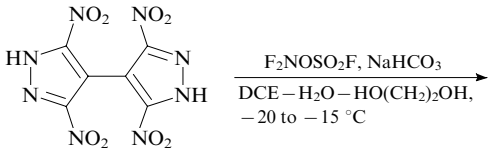
233 **234** (23%)

The reactions of 3,5-dinitropyrazoles **19**, **233**, **235** and bipyrazole **180** with *O*-fluorosulfonyl-*N*,*N*-difluorohydroxylamine in alkaline medium under conditions of phase-transfer catalysis are similar to the analogous reactions of 3,4-dinitropyrazoles [see Section IV.1, reactions (12), (13)] and result in the corresponding 1-difluoroaminopyrazoles **236a–c** and bipyrazole **236d** (only products **236c**,**d** were isolated in an individual state, while compounds **236a** and **236b** were characterised in solutions by ^{1}H NMR spectroscopy).[103–105]

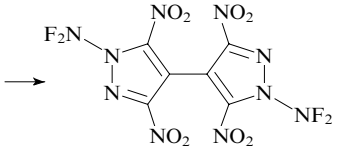


19, **233**, **235** **236a–c**

R = H (**19**; **236a**, 55%), Cl (**233**; **236b**, 5%), 2,4,6-$(O_2N)_3C_6H_2$ (**235**; **236c**, 80%).

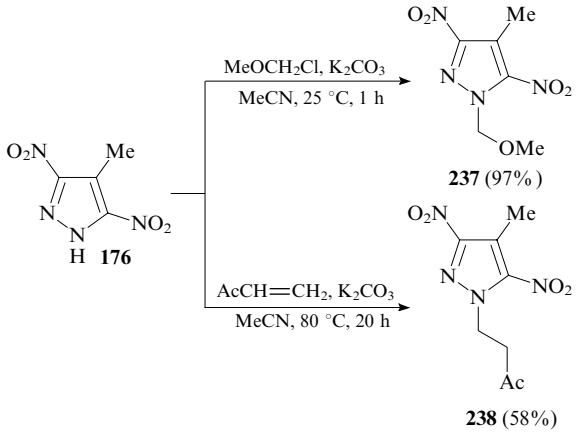


180



236d (11%)

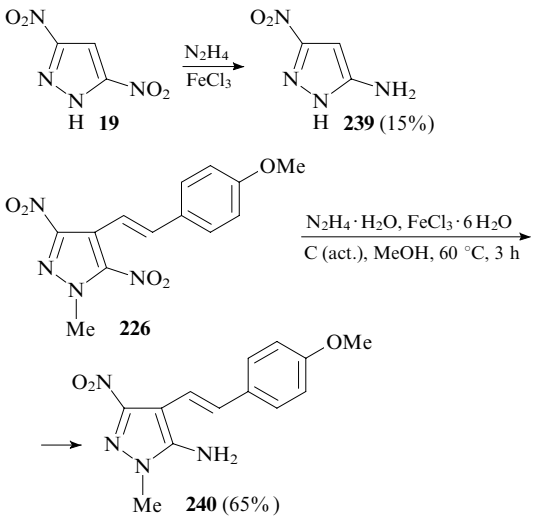
Dinitropyrazole **176** readily reacts with methoxymethyl chloride and methyl vinyl ketone in acetonitrile in the presence of potassium carbonate to yield the corresponding derivatives **237** and **238**.[126, 130]



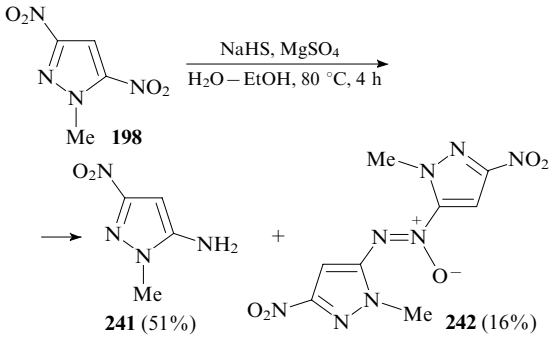
176 **237** (97%) **238** (58%)

2. Properties of 3,5-dinitropyrazoles

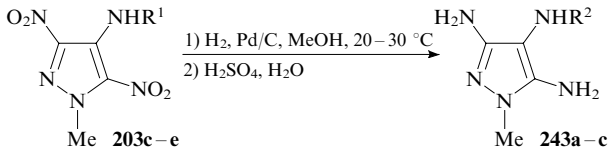
One or two nitro groups of 3,5-dinitropyrazoles can be reduced by classical methods. For example, reduction of dinitropyrazoles **19** and **226** with hydrazine in the presence of $FeCl_3$ produces amines **239** and **240**.[10, 126, 128] The location of the amino group in the products was determined by 2D NMR correlation methods (HMBC, HSQC).



It was established [155] that the reduction of dinitropyrazole **198** with sodium hydrogen sulfide yields a mixture of aminonitropyrazole **241** and azoxy derivative **242**. The site of the NO_2 group reduction (namely, the 5 position) was proved by the absence, from the mass spectra of products **241** and **242**, of ions with m/z $[M-17]^+$ characteristic of 5-nitropyrazoles.[156]



The hydrogenation of aminodinitropyrazoles **203c–e** on a palladium catalyst leads to the reduction of both nitro groups and formation of triaminonitropyrazoles **243a–c**.[141]

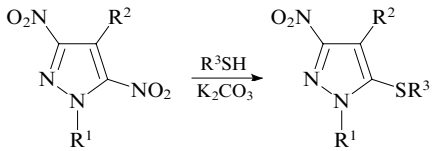


R^1 = Me (**203c**), Bn (**203d**), $(CH_2)_2OH$ (**203e**);
R^2 = Me (**243a**, 84%), H (**243b**, 89%), $(CH_2)_2OH$ (**243c**, 59%).

The triaminonitropyrazoles **243a–c** were patented [141] as active ingredient combinations for hair-dyeing agents.

On treatment with nucleophilic agents, 3,5-dinitropyrazoles in all known instances are subject to regioselective substitution of the 5-nitro group as determined by 2D NMR correlation spectroscopy (HMBC, HSQC, NOESY, ROESY).

The most reactive nucleophiles, *i.e.*, S-nucleophiles, react not only with compounds **175**, **213**, **226**, but even with dinitropyrazoles of low activity **169** and **237** (Table 12) to produce thiols **244–248**. 4-Substituents exhibiting $-M$-effect facilitate substantially the nucleophilic substitution. The substitution is also facilitated by a strongly electron-withdrawing substituent in the position 1.



(16)

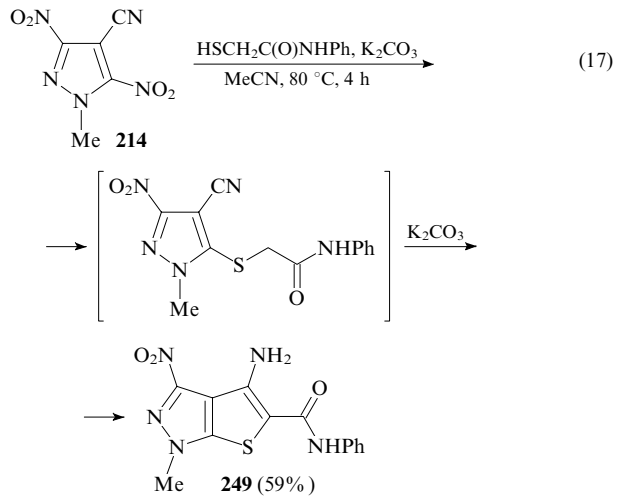
It is of note that the activity of the 5-NO_2 group in nucleophilic substitution reactions is higher than that of the nitro groups of the benzene ring in dinitropyrazole **175**: treatment with 1 equiv. of a nucleophile results exclusively in the substitution products of the 5-NO_2 group of the pyrazole ring (**245a**,**b**); an additional equivalent of the nucleophile leads to the substitution of an NO_2 group in the benzene ring.[126, 129]

In the case of 4-CN derivative **214**, the reaction with mercaptoacetanilide is accompanied by intramolecular cyclisation (the Thorpe–Ziegler reaction) to afford bicyclic product **249** (see Table. 12).

Table 12. Conditions and product yields in reactions (16) and (17).

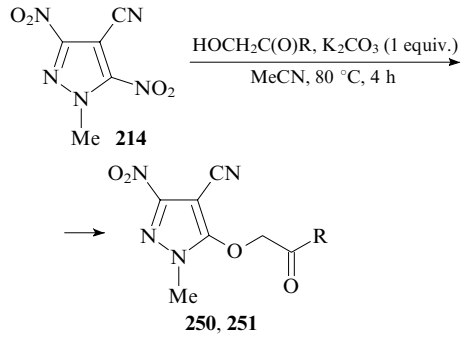
Starting compound	Product	R^1	R^2	R^3	Solvent	T/°C	Yield (%)	Ref.
169	**244**	Me	Me	$CH_2C(O)NHPh$	MeCN	80	28	126, 127
	244	Me	Me	$CH_2C(O)NHPh$	NMP	100	41	126, 127
175	**245a**	3,5-DNP	Me	$CH_2C(O)NHPh$	MeCN	~25	69	126, 129
	245b	3,5-DNP	Me	C_6H_4Cl-4	MeCN	80	70	126, 129
213	**246a**	Me	$C(O)NH_2$	Bn	DMF	~25	98	126, 127
	246b	Me	$C(O)NH_2$	CH_2CO_2Me	DMF	~25	55	126, 127
226	**247**	Me	$CH{=}CHC_6H_4OMe$-4	Bn	DMF	~25	58	126, 128
237	**248a**	$MeOCH_2$	Me	$CH_2C(O)NHPh$	MeCN	80	52	126, 130
	248b	$MeOCH_2$	Me	C_6H_4Me-4	MeCN	80	58	126, 130
214	**249** [a]	Me	CN	$CH_2C(O)NHPh$	MeCN	80	59	126, 127

[a] A product of substitution and cyclization *in situ*.

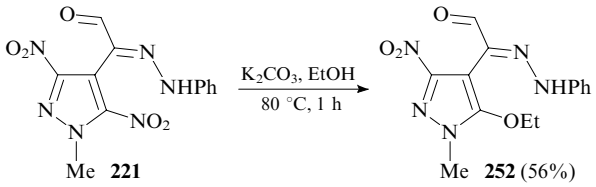


(17)

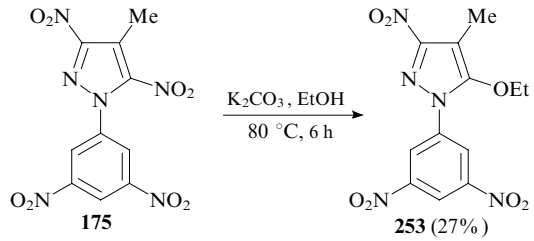
Less reactive *O*-nucleophiles does not react with dinitropyrazoles **169** and **237**; however, compounds bearing electron-withdrawing groups in the position 4 of the pyrazole ring react readily.[125–127] Thus dinitropyrazoles **214** and **221** give products **250**, **251** and **252** within 1 h in satisfactory yields.

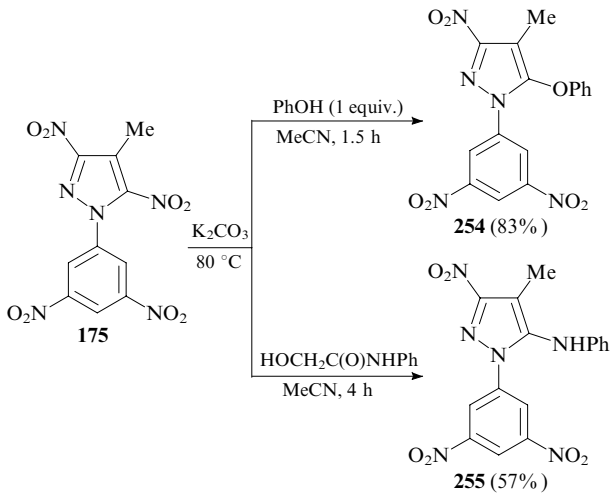


R = OEt (**250**, 72%), NHPh (**251**, 84%).

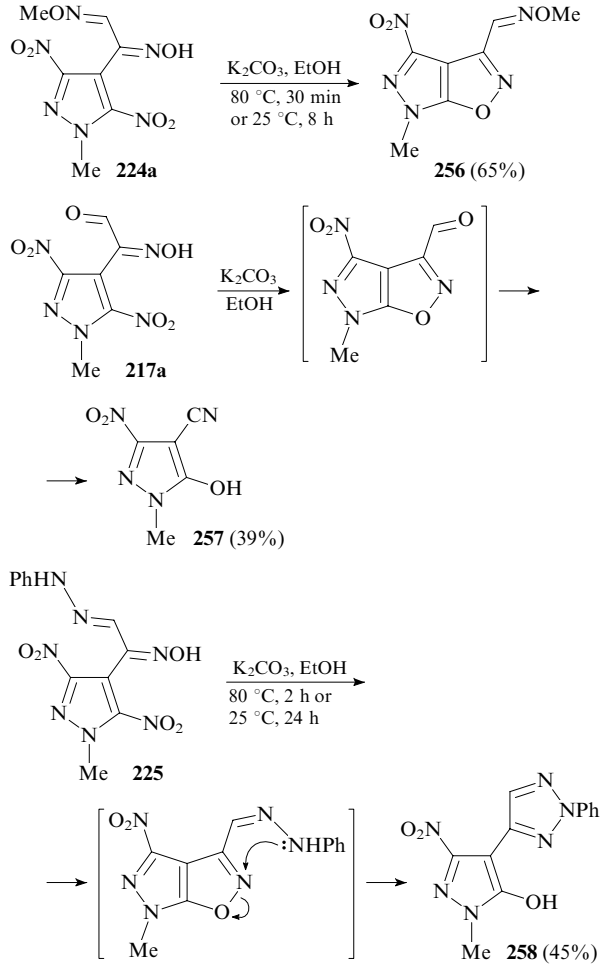


Dinitropyrazole **175** bearing a 3,5-DNP group in the position 1 also undergoes nucleophilic substitution reactions with *O*-nucleophiles. In this way, compounds **253** and **254** are obtained. Nevertheless, upon reaction with the glycolanilide anion, the 'normal' substitution product could not be isolated, instead, a product of the Smiles rearrangement, compound **255**, is formed.[126, 129]

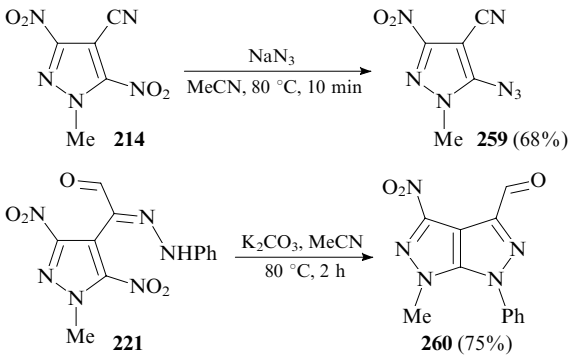




The NO_2 group in dinitropyrazoles **217a**, **224a**, **225** containing a 4-C=N(OH) group undergoes an intramolecular substitution on being treated with potassium carbonate to produce substituted pyrazolo[4,3-d]isoxazoles **256** or their transformations products **257**, **258**.[125, 126]

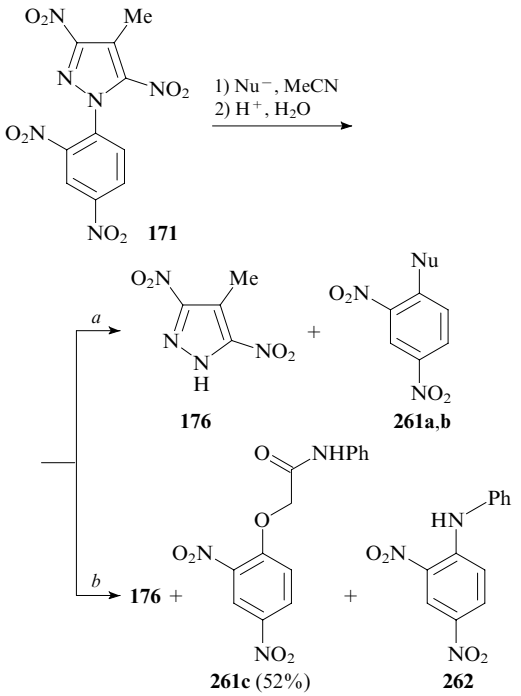


Two instances of the substitution of the 5-NO_2 group in 3,5-dinitropyrazoles upon treatment with N-nucleophiles are documented: the reaction of nitrile **214** with the azide ion resulting in azide **259** and the intramolecular cyclisation of dinitropyrazole **221** to give bicyclic compound **260**.[125–127]

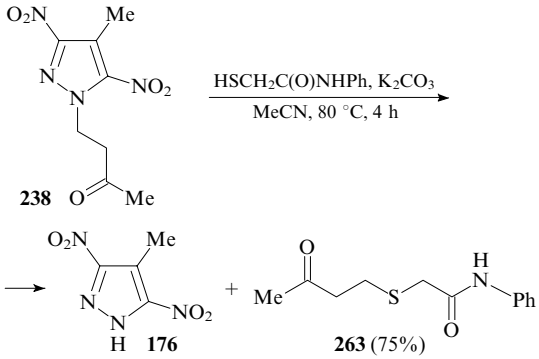


The reasons for such a great difference in the mobility of 3- and 5-NO_2 groups in *N*-substituted 3,5-dinitropyrazoles was studied[127] by quantum chemical methods using the model reaction of 1,4-dimethyl-3,5-dinitropyrazole (**169**) with the HS^- ion as a nucleophile. The calculation was performed by the density functional method (B3LYP) in the σ-31 + G* basis set with full geometry optimisation for two transition states corresponding to the nucleophilic substitution reactions of nitro groups in positions 3 and 5 of dinitropyrazole. It turned out that the free energy of activation of the nucleophilic substitution ($\Delta G^{\#}$) for the 5-NO_2 group in both gas phase and a highly polar solvent is lower than for the 3-NO_2 group by 9.4 and 7.9 kcal mol^{-1}, respectively, which corresponds to the 4 – 5 orders of magnitude difference in the nitro group substitution rates in the temperature range 20 – 100 °C. It is such a huge difference in the substitution rates that determines the regioselectivity of the nucleophilic substitution of 5-NO_2, *i.e.*, the formation of only one isomer of two is possible. It is believed that the substitution site is determined by an electrostatic factor [according to the calculation of the full Mulliken atomic charges, the charges on the C(5) and C(3) atoms in molecule 169 substantially differ and are equal to +0.569 and +0.457 *e*, respectively].

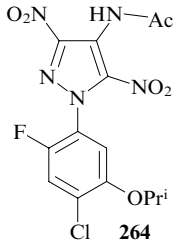
No 5-NO_2 substititution products are formed on treatment of dinitropyrazoles **171** and **238** with nucleophilic agents. Instead, elimination of the 1-substituent occurs to yield dinitropyrazole **176** and products **261** – **263** containing no pyrazole ring.[126, 128, 130] [The elimination of the 1-substituent in molecule **171** proceeds similarly to the reaction (15) involving nitropyrazoles **227a**,**b**.]



(*a*) Nu = N_3 (**261a**, 80%), $SCH_2C(O)NHPh$ (**261b**, 83%);
(*b*) Nu = $OCH_2C(O)NHPh$.



Dinitropyrazole **264** is patented[157] as a herbicide active against various weeds.



As already noted above, 3,5-dinitropyrazoles behave as NH-acids. The known pK_a values of 3,5-dinitropyrazoles are listed in Table 13.

Like dinitropyrazole **26c** (see above), dinitropyrazoles **169**, **187a** and **187b** can be isolated by gas chromatography at 130 – 140 °C.[67]

A method for the determination of ammonium salt **231a** on a milligram scale has been developed.[158] It is based on the potentiometric titration of aqueous solution of this salt with a solution of *N*-cetylpyridinium chloride (fluoroborate ion-selective electrode, the optimal pH value is 10.6).

The electrochemical oxidation of the 3,5-dinitropyrazole anion (**19**) in anhydrous acetonitrile was studied.[116] The determined half-wave potential was $E_{1/2}$ = 1.60 V (relative to the Ag-reference electrode).

A comparison with that for the 3,4-dinitropyrazole anion, $E_{1/2}$ = 1.85 V, shows that the 3,5-dinitropyrazole anion is oxidised more easily.

Some 3,5-dinitropyrazoles are energetic compounds. For example, an explosive mixture of ammonium salt of 3,5-dinitropyrazole (**231a**) with ammonium nitrate has been patented[149] (the addition of an appropriate amount of NH_4NO_3 allows one to increase the oxygen balance of the mixture and achieve the ratio O : C = 1 : 1 and higher). Other salts of 3,5-dinitropyrazole,[150] various mixtures of

Table 13. The acidity constants of 3,5-dinitropyrazoles and bipyrazole **180**.

Compound	pK_a	pK^+_{BH}	Ref.
19	3.14	–	93
165	3.80	–	93
204	3.42	–5.43	10, 137
180	1.79, 3.40	–	10

compound **230** (with ammonium nitrate, ammonium perchlorate and ammonium dinitramide) [148] were also patented as effective energetic materials. For selected experimental and calculated characteristics of 3,5-dinitropyrazoles as energetic compounds see Refs 39, 70, 104, 105 and 152.

Attempts were undertaken to predict the density and impact sensitivity of compounds **158**, **184** and **204** using different models.[159–162] The thermodynamic basicities of compounds **19** and **198** [163] were calculated and determined experimentally.

The IR-spectra of 3,5-dinitropyrazoles possess characteristic absorption bands at 1500–1590 and 1315–1375 cm^{-1} corresponding to antisymmetric and symmetric vibrations of NO_2 groups.

The ^1H NMR spectra of 3,5-dinitropyrazoles contain signals for the H(4) atoms in the range δ 7.64–8.09 (7.95–8.34 for 3,5-dinitropyrazole 2-oxide) depending on the chemical environment of these atoms. The protons of the 1- and 4-Me groups in the spectra of methyl-3,5-dinitropyrazoles resonate at δ 23–4.43 (4.03 for 1-methyl-3,5-dinitropyrazole 2-oxide **197b**) and 2.60–2.80, respectively.

In the ^{13}C NMR spectra of *N*-substituted 3,5-dinitropyrazoles, chemical shifts of the C(3), C(4) and C(5) atoms are observed in the ranges δ 150.34–155.19, 102.3–121.0 and 141.43–149.98, respectively, depending on the chemical environment of these atoms. *N*-Unsubstituted 3,5-dinitropyrazoles contain the signals for the C3(5) and C(4) atoms at δ 131.58–157.24 and 80.0–128.3, respectively. The signal for the 1-Me group carbon atom in the spectrum of compound **198** appears at δ 42.2.

In the ^{15}N NMR spectra of 3,5-dinitropyrazoles, the signals for the N(1) and N(2) nitrogen atoms appear in the ranges δ from −143.2 to −182.20 and from −69.53 to −113.5, respectively; the signals for the $C(3)NO_2$ and $C(5)NO_2$ nitro groups of *N*-substituted 3,5-dinitropyrazoles are in the ranges δ from −24.31 to −28.16 and from −29.26 to −32.40, respectively; the signal for $C(3)(5)NO_2$ in *N*-unsubstituted 3,5-dinitropyrazoles is in the range δ from −28.60 to −32.0.

Data on the properties of 3,5-dinitropyrazoles are summarised in Table 4 of the electronic supplement.

* * *

The material presented in this review demonstrates the significance of dinitropyrazoles in chemistry of heterocyclic compounds.

Dinitropyrazoles are prepared by such methods as direct nitration, thermal rearrangement of *N*-nitropyrazoles, oxidation of an amino group of the pyrazole ring, transformations of functional groups in side chains, *etc.*; in each particular case, the choice is governed by the pecularities of a desired product.

Among common properties of dinitropyrazoles, high activity of nitro groups in the positions 1 and 5 of the pyrazole ring should be distinguished. Of note is the different reactivities of non-equivalent nitro groups in dinitropyrazoles of all types, which opens up the possibility of directed functionalisation of the pyrazole ring.

Dinitropyrazoles possess high synthetic potential. Compounds that are either inavailable in other ways or obtained in low yields can be synthesised starting from dinitropyrazoles (including natural antibiotics and their analogues, bicyclic pyrazole-containing systems, pyrazole derivatives with a non-trivial combination of substituents, *etc.*). Besides, many dinitropyrazoles themselves possess a number of valuable properties and find practical applications as energetic materials, herbicides, insecticides, donors of nitrogen(II) oxide, and ingredients of dyeing mixtures.

Thus, further development of the chemistry of nitropyrazoles is of obvious interest from both scientific and practical viewpoints.

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