1,4-Dinitro-1*H*-imidazoles

Jerzy W. Suwiński

Centre of Polymer and Carbon Materials, Polish Academy of Sciences,
M. Curie-Skłodowskiej 34, Zabrze 41-819, Poland
E-mail: jsuwinski@cmpw-pan.edu.pl

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Abstract

The synthesis, properties, and reactions of 1,4-dinitro-1*H*-imidazoles as well as the hazards associated with working with them are comprehensively reviewed.

Keywords: Imidazoles, nitration, *cine* substitution, *ANRORC* reactions

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1. Introduction

Nitro- and polynitro-azoles are compounds showing high explosion performance and low sensitivity to impact.[1-3] They are also very valuable to the pharmaceutical chemistry as nitro-containing synthetic intermediates and drugs.[1,4-6] The potential use of dinitroimidazoles in preparations of new classes of high explosives and antimicrobial drugs has recently focused chemists' interests on 1,4-dinitro-1*H*-imidazole as the most convenient starting compound in the preparation of several useful products.

Among the theoretically possible *N.C*-dinitroimidazoles only seven compounds are known: 1,4-dinitro-1*H*-imidazole (**1**), its 2-methyl- (**2**), 5-methyl- (**3**), 2-isopropyl- (**4**), and 5-methoxycarbonyl- (**5**) derivatives. (Figure 1) Additionally, two isotopically modified analogues of compound **1**: 1,4-dinitro-1*H*-(2-^{2}H)imidazole (**1′**) and 1-(^{15}N)nitro-4-nitro-1*H*-imidazole (**1″**) have been described**.** Isomeric 1,2-dinitro-1*H*-imidazoles and 1,5-dinitro-1*H*-imidazoles remain unknown.

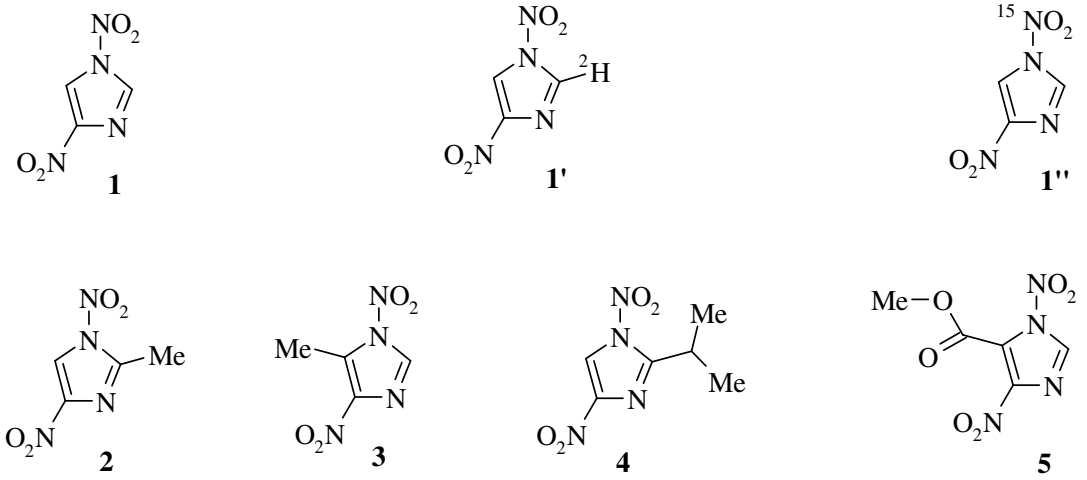


Figure 1. Known 1,4-dinitro-1*H*-imidazoles.

1,4-Dinitro-1*H*-imidazoles are potentially self-reacting explosive substances that are also harmful to mucosal linings and skin; one has to consider the risks associated with their synthesis and handling. Mixtures of nitric acid–acetic anhydride often used in synthesis of 1,4-dinitro-1*H*-imidazoles are also potentially explosive. Helal *et al.*[7] studied thermal and impact stability of dinitroimidazole **1**. Thermal stability analysis carried out by differential scanning calorimetry

indicated two very broad exothermic signals at 55-250 °C and 274-350 °C. Such result may suggest self-heating which without sufficient cooling can lead to explosion. In the accelerating rate calorimetry test, 2 g of dinitroimidazole **1** exploded violently. Thus, compound **1**, and probably at least some of its derivatives, based on the thermal testing, should be considered as self-reactive substances and stored in a freezer. On the other hand, compound **1** was not sensitive to impact.

Dinitroimidazole **1** is the most convenient starting material in the preparation of 2,4(5)-dinitro-1*H*-imidazole (**8**, Figure 2). It is well known that, under acidic conditions, imidazole and its derivatives cannot be nitrated in the position 2.[8] Thus, compound **8** can be synthesized either by nitration of nitroimidazole **6**, which is difficult to obtain and expensive, or by thermal rearrangement of the easily accessible compound **1**. The best way to obtain trinitroimidazole **10** and its alkyl derivatives, which are also of great interest as explosives, is the synthesis starting from compound **1**, its rearrangement and nitration of the resulting dinitroimidazole **8**. The need for compound **8** led to a series of attempts to improve the synthesis of its precursor **1** and to provide detailed studies on the thermal rearrangement of the latter compound. Not surprisingly, several patents have recently appeared in that domain.

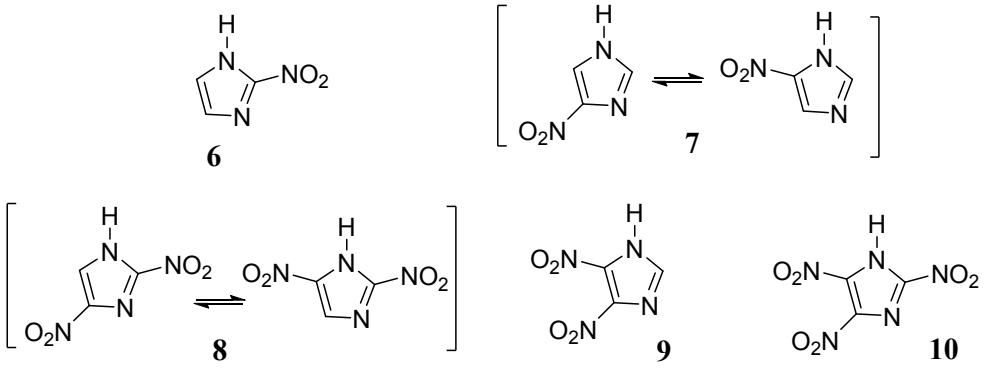


Figure 2. Simple *C*-nitro-, *C,C*-dinitro- and *C,C,C*-trinitroimidazoles.

No general reports on the synthesis, properties, or reactions of 1,4-dinitro-1*H*-imidazoles have yet been published. In contrast, 1,4-dinitro-1*H*-pyrazoles have recently been reviewed by Zaitsev *et al*.[11] Some scattered information on dinitroimidazoles **1–5** can be found in the general review on nitroazoles published by Larina and Lopyrev.[12] Over a dozen years ago, two reviews briefly reported on *cine* and *ANRORC* reactions of 1,4-dinitro-1*H*-imidazoles with nucleophiles.[13,14]

Compound **1** is a versatile reagent that can be applied not only to the preparation of dinitroimidazole **8**, as was mentioned earlier, but it is also a starting material for convenient syntheses of 5(4)-alkoxy-4(5)-nitro-1*H*-imidazoles (**11**), 5(4)-amino-4(5)-nitro-1*H*-imidazoles (**12**), and particularly of 1-alkyl-4-nitro-1*H*-imidazoles (**13**) and 1-aryl-4-nitro-1*H*-imidazoles (**14**) (Figure 3). Methyl derivatives **2** or **3** undergo similar transformations as dinitroimidazole **1**.

Reactions of 1,4-dinitro-1*H*-imidazoles described in this review and leading to other products, e.g., reactions of **1**-**3** with hydrazines, seem to be less important because until now they have not found a practical use.

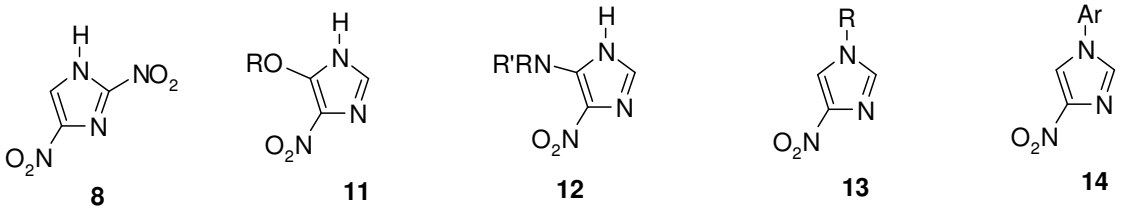


Figure 3. The most important types of product from 1,4-dinitro-1*H*-imidazole (**1**).

Dinitroimidazoles **1** and **8** are also starting materials in the preparation of some modern drugs. In 2000, Stover *et al*.[5] reported that compounds termed nitroimidazooxazines, e.g., PA-824 (**15**), had very high activity against known forms of tuberculosis (Figure 4).

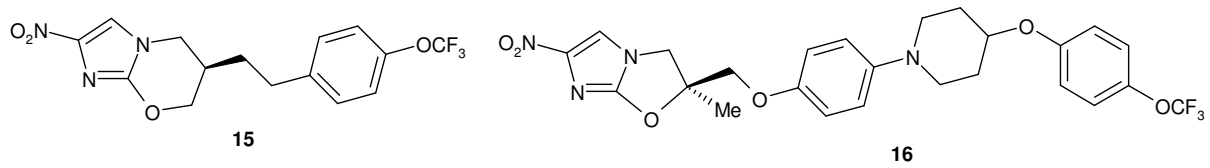


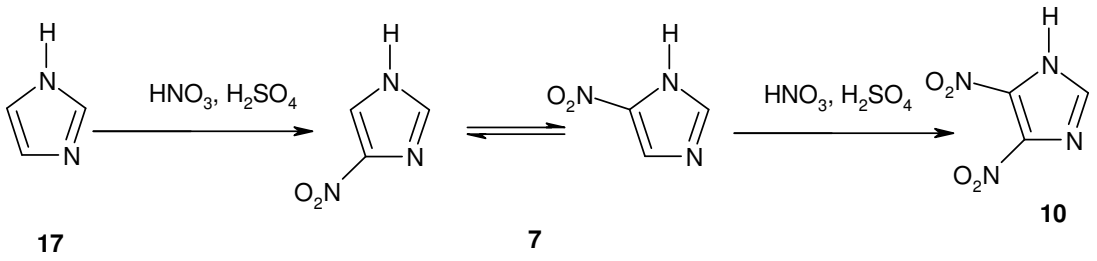
Figure 4. Structures of new anti-tuberculosis compounds PA-824 (**15**) and OPC-67683 (**16**).

That report gave rise to the synthesis and testing of a series of other nitroimidazooxazine and nitroimidazooxazole derivatives. Among them was the compound known by the acronym OPC-67683 (**16**, Fig. 3).[6] All of these compounds were synthesized from imidazole *via* compounds **7**, **1**, **8**, and then 2-chloro-4(5)-nitro-1*H*-imidazole followed by formation of 5- or 6-membered azaoxa rings. The *in vitro* intracellular anti-tubercular activity of OPC-67683 was better than that of isoniazid and as good as that of rifampin, the most effective antituberculosis drugs currently. Both nitrocompounds PA-824 and OPC-67683 were also active *in vivo* and are under currently undergoing further trials.[9] According to the Global Tuberculosis Report 2013, drug OPC-67683 is in phase III clinical trials.[10]

2. Synthesis of 1,4-Dinitro-1*H*-imidazoles

The direct nitration of imidazole (**17**) with acidic reagents is difficult due to its facile nitrogen protonation (pK_a ~ 7). Nitration of **17** by a nitric acid–sulfuric acid mixture proceeds in the 4- and 5-positions. Depending on conditions, it affords imidazole derivatives **7** and **9** containing one or two nitro groups respectively (Scheme 1). Under similar conditions, formation of 1-

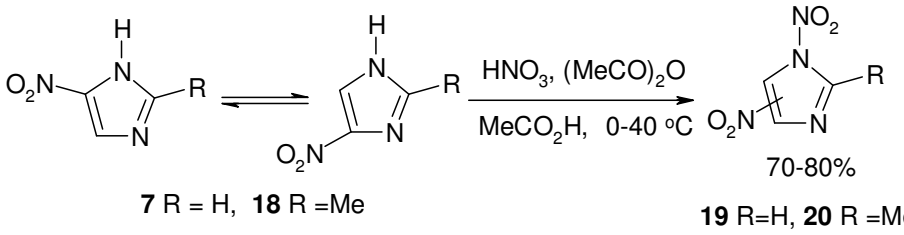
nitrated products was not observed. The amidine 2-position of the imidazole ring is inert to electrophiles.



Scheme 1. Nitration of imidazole in nitric acid - sulfuric acid mixtures.

2.1. Nitration of 4(5)-nitro-1*H*-imidazole in acetic anhydride–acetic acid mixtures

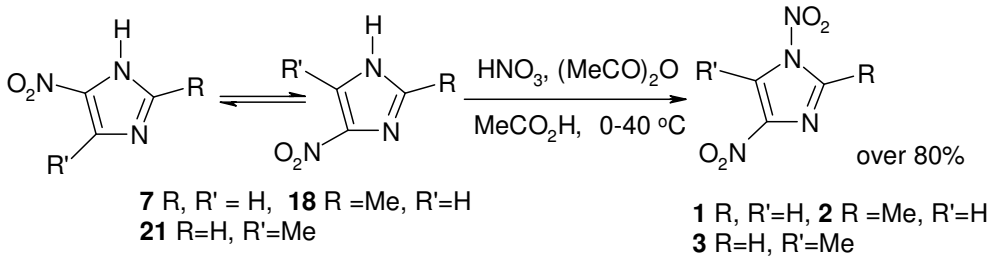
Dinitroimidazole **1** and its methyl derivative **2** were synthesized for the first time over 40 years ago by Novikov *et al*.[15] These workers showed that nitroimidazole **7** and its 2-methyl- derivative **18** on reaction with nitric acid in an acetic anhydride–acetic acid mixture afforded the respective *N*,*C*-dinitroimidazoles **19**, **20** in high yields (Scheme 2).



Scheme 2. Synthesis of dinitroimidazoles **1** and **2** by Novikov .

The positions of the *C*-nitro substituents in the products were uncertain then and the dinitro compounds were described as 1,4(5?)-dinitro- and 2-methyl-1,4(5?)-dinitro-imidazoles.[15] Novikov's procedure was suitable for the preparation of dinitroimidazoles at the ~1 g scale only. Later, Sundersam *et al*. used the same approach for the preparation of dinitroimidazole **1** on a larger scale and thermally converted product **1** into its isomer **8.** Compound **8** was then 1-methylated and treated with phosphorus(V) oxychloride to give 2-chloro-1-methyl-4-nitro-1*H*-imidazole. The latter compound is a convenient starting material for the synthesis of several biologically active compounds.[16] Novikov's method was modified by changing the proportions of reagents and the solvent for crystallization. The changes allowed the safe preparation of dinitroimidazoles **1** and **2** in amounts exceeding 10 g in one portion. Additionally, 5-methyl-1,4-dinitro-1*H*-imidazole (**3**) was obtained in a similar way from 5(4)-methyl-4(5)-nitro-1*H*-imidazole (**21**) (Scheme 3). Yields of dinitroimidazoles **1**–**3** exceeded 80%. It was noted that

products **1**–**3** could be safely crystallized from methanol to afford cubes that were much easier to handle than the long needles obtained from chlorohydrocarbons used previously.[18]



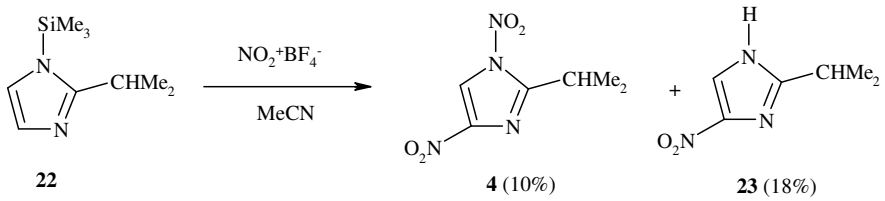
Scheme 3. Synthesis of dinitroimidazoles **1**-**3.**

Grimmett *et al*., probably being unaware of some earlier works, published syntheses of compounds **1–3** using concentrated nitric acid with acetic anhydride. The crystal and molecular structure of compound **1** was proved by X-ray crystallography.[19] Also methyl 1,4-dinitro-1*H*-imidazole-5-carboxylate (**5**) was prepared[20] using Novikov's method. Novikov's approach was applied to the syntheses of isotopically modified analogs **1′** and **1″** of compound **1**. 4-Nitro-1*H*-(2,5-$^{2}H_2$)imidazole was nitrated with nitric acid - acetic anhydride mixture under common conditions to yield 1,4-dinitro-1*H*-(2-^{2}H)imidazole (**1′**). An analogous approach was used for the preparation 1-(^{15}N)nitro-4-nitro-1*H*-imidazole (**1″**) from nitroimidazole **7** and a mixture of (^{15}N)nitric acid with acetic anhydride.[22] Using a similar procedure, Cho *et al*. achieved dinitroimidazole **1** in the highest yield (95%).[23] Song *et al*., from compound **1** *via* its isomer **8**, prepared new energetic salts based on 1-nitramino-2,4-dinitro-1*H*-imidazole. The structure of guanidinium 1-nitramino-2,4-dinitro-1*H*-imidazolate was confirmed by X-ray diffraction.[24] Wanner and Koomen prepared dinitroimidazole **1** and made use of it in a new synthesis of temozolomide.[25] Sakamoto *et al*. obtained an interesting biologically active spiroindoline class of compound containing arylnitroimidazole residues starting from dinitroimidazole **1**.[26] Therefore syntheses of dinitroimidazole **1** from imidazole or nitroimidazole **7** using Novikov's approach have been reported several times, often without or with only slight modifications, e.g., in refs 5 and 22-26. The production of 1,4-dinitro-1*H*-imidazole (**1**) was also described in patents or patent applications but a new approach was neither presented or claimed and so data from patents, apart from a few exceptions, are not reported here. Adoption of concentrated nitric acid–acetic anhydride mixtures for the preparation of nitric esters is not free from the risk of explosion. Side reactions (e.g., formation of tetranitromethane) can lead to the thermal decomposition of the system, especially under adiabatic conditions.[21] Nevertheless, no explosion has ever been reported in papers or patents in which Novikov's approach was applied.

2.2. Nitration of 2-isopropyl-1-trimethylsilyl-1*H*-imidazole by nitronium tetrafluoroborate

Nitration of 2-isopropyl-1*H*-imidazole under a variety of conditions was studied. Nitration in acetonitrile using nitronium tetrafluoroborate afforded only poor yield of 2-isopropyl-4(5)-nitro-

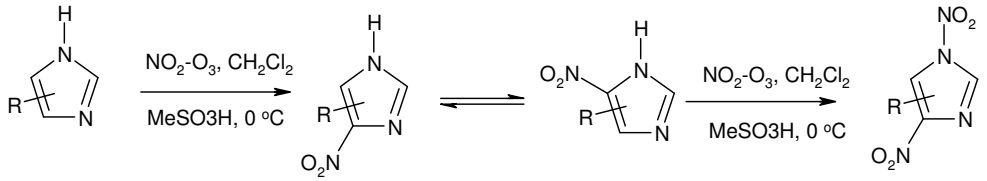
1*H*-imidazole. In contrast, the reaction of nitronium tetrafluoroborate with 2-isopropyl-1-trimethylsilyl-1*H*-imidazole (**22**), also conducted in acetonitrile (Scheme 4), gave a mixture of 2-isopropyl-4(5)-nitro-1*H*-imidazole (**23**, 18%) with dinitroimidazole (**4**, 10%). A structure of the dinitroimidazole was shown by X-ray crystallography to be 2-isopropyl-1,4-dinitro-1*H*-imidazole (**4**). Compound **4** was identical to the product obtained by nitration of 2-isopropyl-1*H*-imidazole using a mixture of concentrated nitric acid with acetic anhydride.[17]



Scheme 4. Synthesis of 2-isopropyl-1,4-dinitro-1*H*-imidazole (**4**).

2.3. Kyodai nitration of imidazole

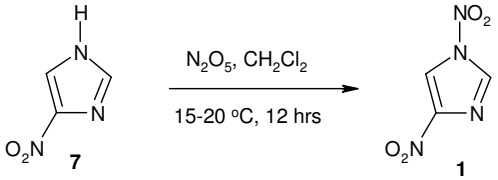
Compounds **1**–**3** were also obtained by Kyodai nitration of imidazole with nitrogen(IV) oxide and ozone in dichloromethane in the presence of methanesulfonic acid at 0 °C.[27] Kyodai nitration of imidazole under neutral condition gave poor yields of nitroimidazole **7**. A similar situation concerned nitration of *C*-methylimidazoles. The yields improved dramatically on addition of methanesulfonic acid. Nitroimidazole **7** was then converted under the same conditions but over a long period into product **1**. Therefore, Kyodai nitration of imidazole could be conducted in a one-pot procedure without separation of intermediate mononitroimidazoles **7, 17** or **21** (Scheme 5).[27] Nevertheless, the synthesis of dinitroimidazole **1** by Kyodai nitration cannot compete with Novikov's method.



Scheme 5. Kyodai nitration of imidazole and its *C*-methyl derivatives

2.4. "Green nitration" of 4(5)-nitro-1*H*-imidazole

Recently, Liu Hui-jun *et al*. have claimed the preparation of compound **1** by "green nitration" (Scheme 6). The authors treated nitroimidazole **7** in dichloromethane with 10% excess nitrogen(V) pentoxide for 12 hours at 15–20 °C to get the required dinitroazole **1** in 91% yield.[28]



Scheme 6. "Green nitration" of 4(5)-nitro-1*H*-imidazole.

3. Properties of 1,4-Dinitro-1*H*-imidazoles

3.1. Common physicochemical and spectroscopic properties

Some more common physicochemical and spectroscopic properties of dinitroimidazoles **1–5** found in the chemical literature are shown in Table 1.

Table 1. Physicochemical and spectroscopic properties of dinitroimidazoles **1**-**5**

Comp. No. Substituent	**1** -	**2** 2-Me	**3** 5-Me	**4** 2-(*i*-Pr)	**5** 5-CO_2Me
m. p. [°C] (solvent)	91,5-92.5 (CCl_4)[15]; 92-93 (MeOH)[18]	122-124 (CCl_4)[15]; 121-122 (MeOH)[18]	113-114 (MeOH)[18]	79-80 (ether-hexane)[17]	110-111 $CHCl_3$/hexane.[20]
^{1}H NMR	300 MHz, DMSO-d_6 2-H 8.97; 5-H 9.40 (2 × d, 1H, 1.5 Hz)[58]	300 MHz, DMSO-d_6 2-Me 2.67 (s, 3H); 5-H 9.26 (s, 1H)[58]	80 MHz, CD_3Cl 2-H 8.68 (s); 5-Me 2.92 (s, 3H)[18]		300 MHz, DMSO-d_6 CO_2Me 4.02 (3H, s); 2-H 9.15 (s)[20]
^{13}C NMR	(75.5 MHz) DMSO-d_6 2-C 132.6; 4-C 144.3; 5-C 115.9.[58]	75.5 MHz, DMSO-d_6 2-C 142.7; 4-C 141.4; 5-C 116.9; 2-Me 16.5.[58]	acetone-d_6 2-C 131.8 4-C 142.0 5-C 129.1 5-Me 11.6.[18]		
UV-VIS in MeOH	λ [nm] (log ε) 228 (4.13); 282 (3.76)[18]	λ [nm] (log ε) 230 (4.09); 296 (3.75)[18]	λ [nm] (log ε) 230 (4.08); 285 (3.7)[18]		
IR (KBr or Nujol) ν_{max} cm^{-1}	KBr: 1635, 1285.[19]				nujol: 1745 (C=O) 1640, 1270 (N-NO_2); 1580, 1335 (C-NO_2)[20]

Table 1. Continued

Comp. No.	**1**	**2**	**3**	**4**	**5**
Substituent	-	2-Me	5-Me	2-(*i*-Pr)	5-CO_2Me
	1,420 and 1.440 orthorhombic; P212121 *a* 5.853(3) *b* 9.591(8) *c* 10.392(5) Å V 583.4(7) $Å^3$, Z = 4 λ=0.71069 Å.[19]			1.426 and 1.436 monoclinic. P2,lc I = 15.488(5) *h* 6.072(3) *c* 10.030(5) Å β = 99.35(3) V = 930.7 $Å^3$ Z = 4 λ=1.5418 Å[17]	
MS: *m/z* 70 eV	158 (M^+), 46 (NO_2^+)˙, 30 ($NO^{+)}$.[18]	172 (M^+) 46 (NO_2^+), 30 ($NO^{+)}$.[18]	172 M^+ 46 NO_2^+, ($NO^{+)}$.[18]		

3.2. Potential explosive properties

Properties concerning thermal stability and potential explosive properties of dinitroimidazole **1** and other nitro derivatives of imidazole were calculated using quantum methods. These data will be presented in a separate part of this review. Experimental thermodynamic testing indicated that dinitroimidazole **1** was indeed a highly energetic substance with the potential for self-heating even at slightly elevated temperature that could lead to explosion. Reactions of **1** in solutions were of reduced risk.[29]

In the technical literature, the common acronym DNI is sometimes used for three isomeric dinitroimidazoles **1**, **8,** and **9**. 1,4-Dinitroimidazole (**1**) undergoes isomerization on heating to form 2,4(5)-dinitroimidazole (**8**). Transformation of compound **1** into the 4,5-dinitro-compound (**9**) is also possible. Comparisons of the 70 eV mass spectra of the three dinitroimidazoles **1**, **8** and **9** indicated the same *m/z* values; only their relative abundances were different.[30] Therefore data given for DNI thermal behavior often describe properties of compounds **8** and **9** rather than of isomer **1**. The sensitivity of DNI is very high compared to trinitrotoluene. Explosive velocity was 5300 m/s based on the given density. DNI exhibits an explosive force greater than triaminotrinitrobenzene or trinitrotoluene but lower than cyclotrimethylenetrinitramine or

cyclotetramethylenetetranitramine. DNI indicated high thermal sensitivity and impact insensitivity, yet it is a powerful high-performance explosive.

Yu and Bernstein studied the behavior of four multinitroimidazoles (**1**, **8,** and the 1-methyl derivatives of **8** and **10**) in excited upper vibronic states following absorption of single UV photons at 226, 236, and 248 nm. The experiments were conducted in nanosecond laser systems. The molecules decomposed into products through specific decomposition pathways, For compound **1** barriers for N1–NO_2 homolysis (34.5 kcal/mol) and nitro–nitrite isomerization N1–NO_2 (69.6 kcal/mol) or C4–NO_2 (61.0 kcal/mol).were calculated. Based on results of the calculations N–NO_2 homolysis should be the more favorable decomposition for dinitroimidazole **1** in the ground state. The reaction mechanism for decomposition of compound **1** following electronic excitation was also proposed. Then, the decomposition resulted in initial formation of an NO molecule.[31]

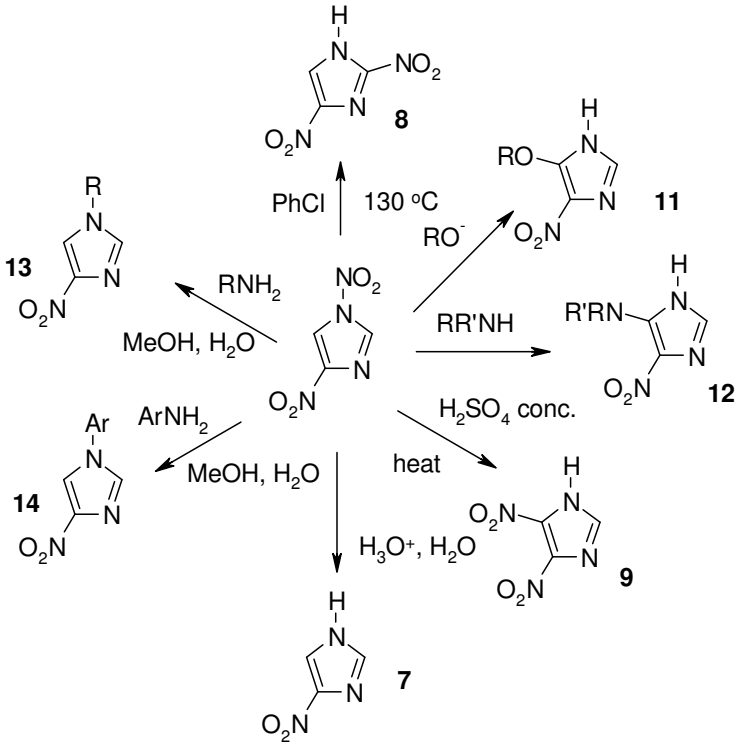
3.3. Harmfulness depending on the crystalline form

It must also be mentioned again that at least dinitroimidazoles **1–4** are seriously harmful to skin, irritate all mucous membranes and cause allergy problems. The substances are soluble in dichloroethane, chloroform, and benzene, only sparingly soluble in petroleum ether, and practically insoluble in water. They can be crystallized either from carbon tetrachloride, other halogenocarbohydrates, or from methanol. Compounds **1–3** crystallized from carbon tetrachloride forming colorless elongated needles. The needles easily cracked and dissipated. Crystallizing these substances from methanol afforded cubes that were much more convenient and safer for further work.[18]

4. Reactions of 1,4-Dinitro-1*H*-imidazoles

1,4-Dinitro-1*H*-imidazole (**1**) undergoes several transformations. Among these, three reactions gained much interest as useful alternatives to other known methods for the synthesis of the same or similar compounds. They were as follows: thermal rearrangement of dinitroimidazole **1** to its isomer **8;** *cine* nucleophilic substitution of compounds **1** (or **2**) with alkoxides and with 1*H*-azoles or secondary amines; and *ANRORC* reactions of dinitroimidazole **1** (or **2–3**) with aliphatic or aromatic primary aminocompounds (Scheme 7).

The thermal rearrangement of compound **1** to dinitroimidazole **8** can be conducted in inert organic solvents. The *cine* reactions afforded compounds 5(4)-alkoxy-4(5)-nitro-1*H*-imidazoles (**11)** or 5(4)-amino-4(5)-nitro-1*H*-imidazoles (**12)** respectively; *ANRORC* reactions led to the formation of 1-alkyl-4-nitro-1*H*-imidazoles (**13**) or 1-aryl-4-nitro-1*H*-imidazoles (**14**). The remaining processes were: disproportionation of dinitroimidazole **1** in hot concentrated sulfuric acid to mononitro- and dinitroimidazoles **7** and **10** as well as 1-denitration of the dinitrocompound **1** to nitrocompound **7** either in cold concentrated sulfuric acid or in dilute aqueous acids**.** Reactions of dinitroimidazole **1** with nucleophiles were often accompanied by 1-denitration of the starting imidazole.

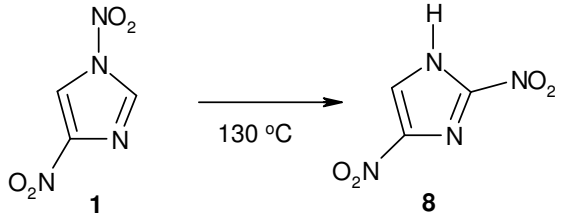


Scheme 7. More important transformations of dinitroimidazole **1.**

Dinitroimidazole **1** also reacted with unsubstituted, monosubstituted, and asymmetrically disubstituted hydrazines to give a variety of imidazole ring opening or ring transformation products. These latter reactions have little potential for synthesis of useful products.

4.1. Thermal rearrangement of dinitroimidazoles 1–3

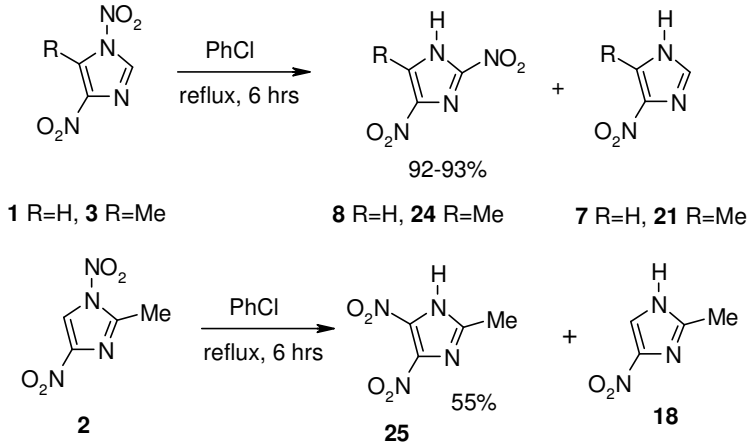
1,4-Dinitro-1*H*-imidazole (**1**) is a compound that is sensitive to heat, both in its solid state and in solution. The thermal rearrangement of dinitroimidazole **1** to 2,4(5)-dinitro-1*H*-imidazole (**8**) conducted in chlorobenzene at 130 °C (Scheme 8) was described for the first time by Sharnin *et al*. in a USSR patent.[32]



Scheme 8. Thermal rearrangement of dinitroimidazole **1** in boiling chlorobenzene.

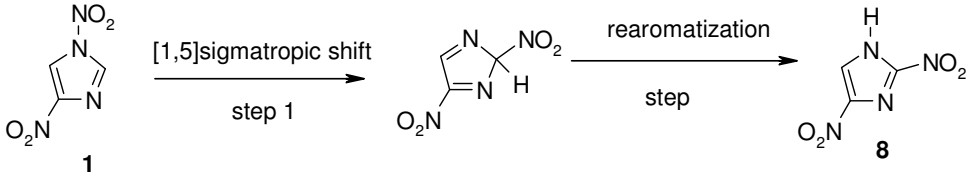
In the same patent, the conversion of dinitroimidazole **8** into 2-chloro-4(5)-nitro-1*H*-imidazole by treatment with phosphorus oxychloride was presented.[32]

Sudarsanan *et al*. obtained 2-chloro-4(5)-nitro-1*H*-imidazole from imidazole in four steps: *C*-nitration, *N*-nitration, thermal rearrangement, and conversion of the obtained dinitroimidazole **8** into chloronitroimidazole.[16] Some of Sharnin's reactions were repeated with dinitroimidazoles **1–3** by heating them in chlorobenzene at 120 °C for 5–8 hours, stirring until complete decay of the starting materials was achieved. The rearrangement of dinitroimidazole **1** afforded 2,4(5)-dinitro-1*H*-imidazole (**8**) in 92% yield. Compound **2** yielded 2-methyl-4,5-dinitro-1*H*-imidazole (**25**) in 55% yield together with a smaller amount of 2-methyl-4(5)-nitro-1*H*-imidazole (**18**). From dinitroimidazole **3**, its isomer, 5-methyl-2,4(5)-nitro-1*H*-imidazole (**24**), was prepared in 93% yield (Scheme 9). The structure of the latter product was proved by its conversion into the known 2-bromo-5(4)-methyl-4(5)-nitro-1*H*-imidazole. A mechanism of the rearrangement *via* intramolecular 1,5-sigmatropic shift was assumed but no evidence was given.[18] Three dinitroimidazoles obtained by thermal rearrangement of compounds **1–3** were also converted into their respective chloronitroimidazoles to search for new effective and nontoxic radiosensitizers of hypoxic tumor cells. Radiosensitizing efficiency of 2-chloro-4-nitro-1*H*-imidazoles on hypoxic cell proliferation *in vitro* and *in vivo* was studied but results were not promising enough to justify further tests.[33] According to Grimmett *et al*., dinitroimidazoles **1** and **2** when heated in solution at 100–140 ºC rearranged to afford *C,C*-dinitro isomers and some denitration products, while compound **3** failed to give identifiable products.[19] Bulusu *et al*.[22] studied in detail the thermal rearrangement of 1,4-dinitro-1*H*-imidazole (**1**) into 2,4(5)-dinitro-1*H*-imidazole (**8**). The reaction was carried out in chlorobenzene. at 115 °C for 15–20 hours. The post-reaction mixtures contained dinitroimidazole **8**, a small amount of nitroimidazole **7**, and trinitroimidazole **10** as by-products. Moisture and higher temperature increased their formation.



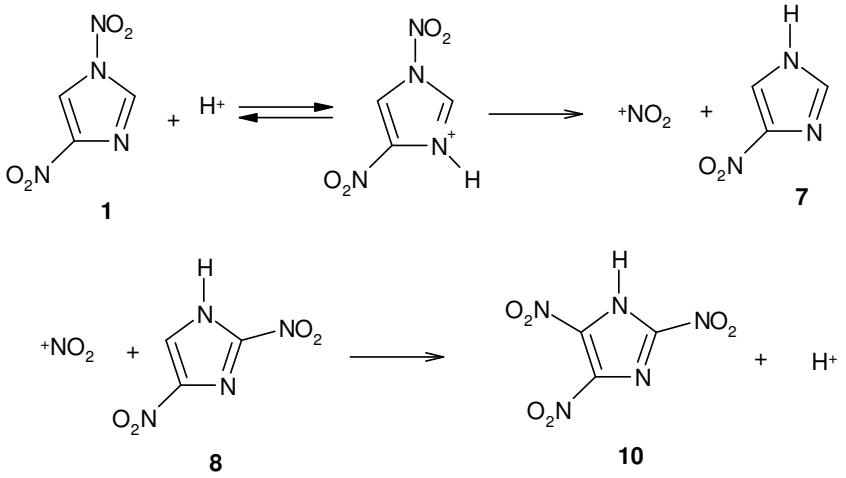
Scheme 9. Thermal rearrangement of dinitroimidazoles **1-3.**

The rearrangement was also carried out without a solvent. The reactions without solvent seemed to favor formation of by-products comparing to the conversion in solution. In differential scanning calorimetry experiments three signals were observed: an endotherm at 92 °C, corresponding to the melting point of dinitroimidazole **1,** then an exotherm at 115 °C related to the studied rearrangement, and finally an exotherm at 215 °C related to decomposition of dinitroimidazole **8**. In the mass spectrometry experiment, vapors of compound **1** were continuously analyzed from *m/z* 1 to 158. The thermal rearrangement of a mixture of isotopically modified dinitroimidazoles **1′** and **1″** was also studied by differential scanning calorimetry and mass spectrometric techniques No isotope exchange was found, proving the intramolecular course of the rearrangements. The proposed mechanism of rearrangement is depicted in Scheme 10.



Scheme 10. Mechanism of thermal rearrangement of dinitroimidazole **1.**

Formation of nitroimidazole 7 required water which probably came from adventitious moisture (Scheme 11), The nitronium cation forming in the hydrolysis could give trinitroimidazole **10**, as also shown in Scheme 11.

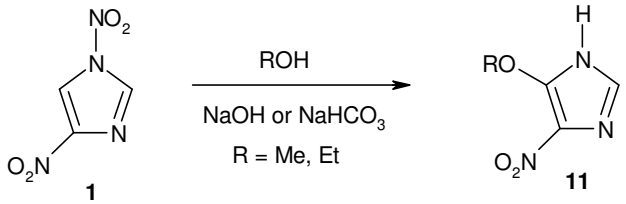


Scheme 11. Mechanism of the thermal formation of 4(5)-nitro-1*H*-imidazole (**7**) and 2,4,5-trinitro-1*H*-imidazole (**10**) from dinitroimidazole **8** in the thermal rearrangement of compound **1.**

The crystal structure of dinitroimidazole **8**, obtained by the thermal rearrangement of compound **1**, was studied by X-ray diffraction to verify the identity of product **8**. Some structural features of product **8** were compared with those of the starting material **1.**[34] Veretennikov and Pevzner, while looking for dinitroimidazole **8** as a useful material in the synthesis of 2,3-dihydro-6-nitroimidazo[2,1-*b*]oxazole analogs of antimycobacterial activity, investigated the microwave-assisted rearrangement of compound **1.**[35] A mechanism of the rearrangement was proposed based on mass spectrometry measurements and isotope labeling experiments. A few years later, Bhaumik and Akamanchi[36] also synthesized dinitroimidazole **8** as an important starting material for nitroimidazooxazole and nitroimidazooxazine types of anti-tubercular agents. The rearrangement of dinitroimidazole **1** was performed using microwave irradiation. Saikia *et al*.[37] reported a novel and rapid microwave-assisted method for the synthesis of some potential high explosives. In the course of investigations, the high temperature thermal rearrangement of dinitroimidazole **1** to dinitroimidazole **8** was also tested using microwave radiation as a heating source.[37] A patent concerning the synthesis of intermediates for insensitive melt-castable explosives provided a method for preparing dinitroimidazole **8** from nitroimidazole **7**, wherein separation of the intermediate dinitroimidazole **1** in powder form was avoided, so that it was possible to eliminate allergy problems in workers and to simplify the process, thereby improving its economy.[38]

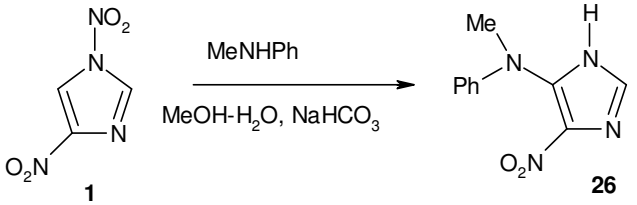
4.2. Nucleophilic c*ine*-substitution

Electron-deficient azole derivatives containing a nucleofugal group linked to the pyrrole-type nitrogen atom can be *cine* substituted. Such reactions are also known for some 1,4-dinitro-1*H*-imidazoles. As a result of the reaction, an entering group usually occupies the 5-position of the imidazole ring, although attack at the 2-position is also possible. The first report on the possibility of nucleophilic *cine*-substitution in 1,4-dinitro-1*H*-imidazoles was very brief.[39] The report noted the instability of **1** in water or methanol in the presence of alkalis and the formation of unstable 5(4)-hydroxy-4(5)-nitro-1*H*-imidazoles or stable 5(4)-alkoxy-4(5)-nitro-1*H*-imidazoles (**11**) respectively (Scheme 12). Under similar alkaline conditions, compound **2** reacted similarly, but dinitroimidazole **3** bearing a methyl group at C5 did not afford identified products.



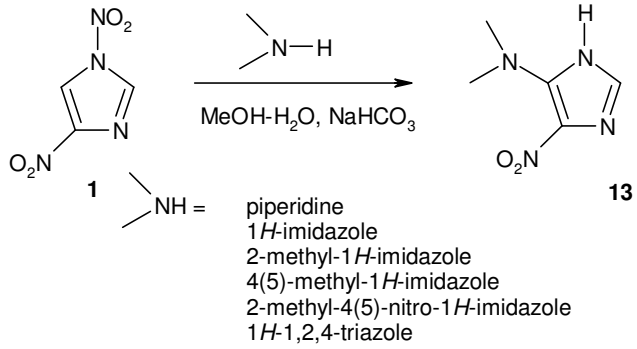
Scheme 12. *Cine* substitution of dinitroimidazole **1** with *O*-nucleophiles.

The kinetics of alkaline hydrolysis of compounds **1–3** was studied by UV spectroscopy at pH 8.46–10.78 of the aqueous solution. The order of hydrolysis rate constants measured as the decays of **1–3** across the whole range of pH was as follows: **3 < 2 < 1**; the products of the hydrolysis were not identified.[18] Later, the *cine* reaction became the subject of wider investigations. It was established that primary and secondary anilines reacted with compounds **1–3** in small volumes of aqueous methanol to afford colorful adducts that were not soluble in water. Solid adducts were not stable and decomposed to unidentified mixtures. In methanol and aqueous-methanol solution, adducts from dinitroimidazoles **1–3** and primary amines afforded 1-aryl-4-nitro-1*H*-imidazoles (**14**) in uncatalyzed *ANRORC* reactions.[40-41] Dinitroimidazole **1** reacting with *N*-methylaniline gave over 80% of 5(4)-[*N*-methyl-*N*-phenylamino]-4(5)-nitro-1*H*-imidazole (**26**, Scheme 13).[42] Compound **2** reacted in a similar way.



Scheme 13. *Cine* substitution of dinitroimidazole **1** with *N*-methylaniline.

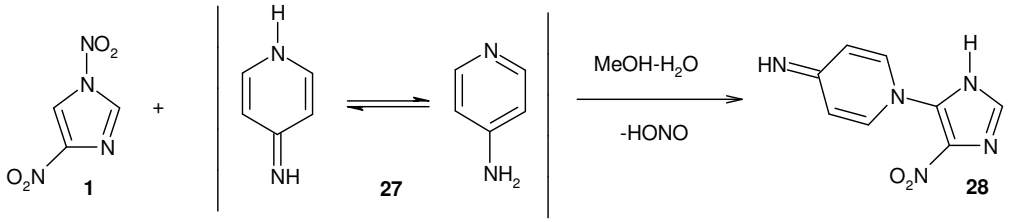
Compounds **1** and **2** with piperidine and with some 1*H*-azoles in the presence of a base also underwent *cine* nucleophilic substitution. The reaction with piperidine afforded the *cine* product in ~20% yield only. Yields of all obtained 5(4)-[azol-1-yl]-4(5)-nitro-1*H*-imidazoles exceeded 50% (Scheme 14).[43]



Scheme 14. *Cine*-substitution of dinitroimidazole **1** with piperidine and 1*H*-azoles.

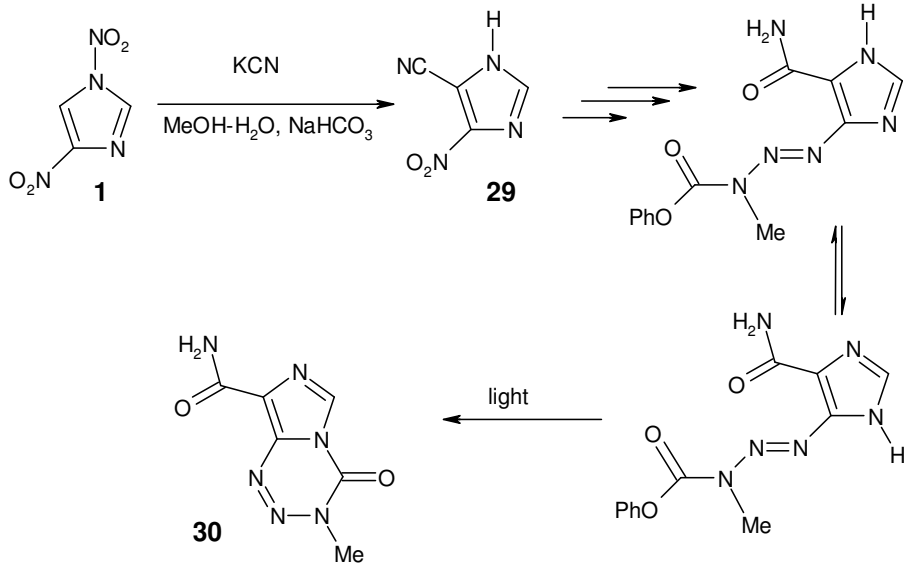
Interesting behavior was observed on treating dinitroimidazoles **1** or **2** with isomeric amino-pyridines. 2-Amino- and 3-aminopyridine behaved like primary anilines undergoing *ANRORC* transformations. In contrast, 4-aminopyridine (**27**) on reaction with **1** (or **2**) behaved similarly to 1*H*-azoles, giving nucleophilic *cine*-substitution product **28** (Scheme 15). The tautomeric

4-aminopyridine (**27**) is a stronger base (pK_a ~9.2) than its isomers and in the reaction probably played not only the role of a nucleophile but also of a base catalyzing the *cine* reaction.[44]



Scheme 15. *Cine* substitution reaction of compound **1** with 4-aminopyridine (**27**).

The reaction of dinitroimidazole **2** with the 1,8-diazabicyclo[5.4.0]undec-7-ene salts of 1*H*-azoles was studied in dimethylsulfoxide to avoid the alkaline hydrolysis of **2** in aqueous methanol. High yields of the expected products were obtained.[45] Substitution of dinitroimidazoles **1** and **2** could also be successfully performed with cyanide ions, which is the only known method for the preparation of 5(4)-cyano-4(5)-nitro-1*H*-imidazole (**29**).[46] That *cine* reaction has rather recently been applied in a new multistep synthesis of tomozolomide (**30**, Scheme 16).[25]



Scheme 16. Multistep synthesis of tomozolomide (**30**) from dinitroimidazole **1.**

Treatment of dinitroimidazole **1** with potassium (^{15}N)cyanide or potassium (^{13}C)cyanide in aqueous methanol in the presence of sodium bicarbonate afforded isotopically modified 5(4)-(^{15}N)cyano-4(5)-nitro-1*H*-imidazole and 5(4)-(^{13}C)cyano-4(5)-nitro-1*H*-imidazole respectively.[47] It was stressed that high yields of products from the *cine*-substitution of dinitroimidazoles **1** or **2**

with various nucleophiles could be obtained in aqueous methanol in the presence of sodium bicarbonate as a base.[40,47] Luo *et al.*, following procedures from ref. 47, used (^{15}N)cyanide, (^{13}C)cyanide and (^{15}N,^{13}C)cyanide anions as nucleophiles and prepared two known mono- and one new doubly-isotopically modified compound: 5(4)-(^{15}N,^{13}C)cyano-4(5)-nitro-1*H*-imidazole.[48] The products served as starting materials in syntheses of adenines. Two other compounds, the (1-^{15}N)adenine and (1-^{3}H)ribose, were also prepared. The compounds were then enzymatically coupled to isotopically modified ribosyl groups to give respectively substituted adenosines (**31**, Figure 5). The adenosines were used in the search for new drugs showing therapeutic effects against malaria.[48]

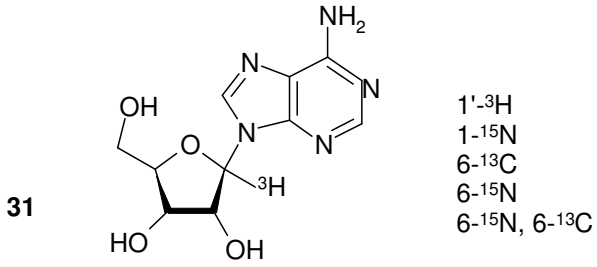
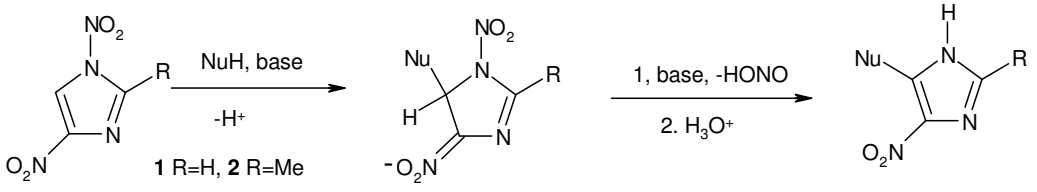


Figure 5. Isotopically modified adenosines **31.**

Compound **2** reacted with iodide or azide anions to form 2,2′-dimethyl-4,5′-dinitro-3′*H*-1,4′-biimidazole in low yields. The product was obtained probably by *cine* substitution of 1-nitro group with 2-methyl-4(5)-nitro-1*H*-imidazole anion, which must has been formed by 1-denitration of the starting dinitroimidazole **2**.

A comparison of the behavior of 1,4-dinitro-1*H*-imidazoles and 1,4-dinitro-1*H*-pyrazoles towards nucleophiles has been briefly discussed.[49] A mechanism for the *cine* substitution of dinitroimidazoles **1**, **2,** or **5** was not investigated in detail and certain aspects of the reaction remain rather unclear. Some mechanistic assumptions were made while discussing the *ANRORC* reaction mechanism of 1,4-dinitro-1*H*-imidazoles with amines. The postulated mechanism is shown in Scheme 17.[42]

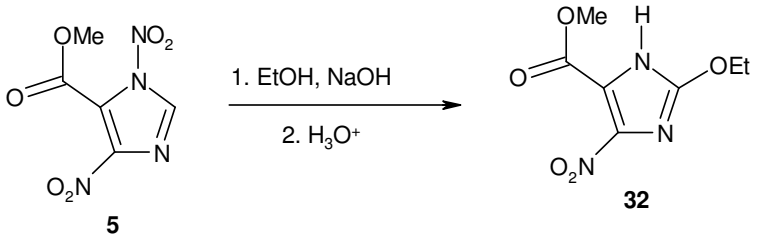


Scheme 17. Proposed mechanism of nucleophilic *cine* substitution of dinitroimidazoles **1-2.**

Analyzing together *ANRORC* and *cine* reactions of dinitroimidazoles **1** and **2**, one can exclude the mechanism of a *cine* reaction postulated by Habraken *et al.*[50] for nucleophilic *cine*

substitution of 1,4-dinitropyrazoles. Habraken assumed the reaction proceeded in two steps. Firstly, a nucleophile comes into the *ortho* position to the leaving group and cleaves the N–NO_2 bond, what resulted in the initial formation of a 3*H*-azole. Then the ultimate product is formed in a rapid 1,5-hydride shift of the hydrogen atom from C5 to N1. Other observed reactions of 1,4-dinitro-1*H*-pyrazoles with nucleophiles consisted of a ring transformation by arylhydrazines[49] or a displacement on the 1-nitro group by e.g., morpholine.[50-51]

The only known example of a nucleophilic attack on the 2-carbon in *cine* substitution of compounds **1**–**5** is ethanolysis (or methanolysis) of methyl-1,4-dinitro-1*H*-imidazole-5-carboxylate (**5**) under alkaline conditions at ambient temperature to afford compound **32** (Scheme 18).[20] In this case, *cine* substitution was accompanied by alkaline hydrolysis of the ester group either before or after the *cine* reaction.



Scheme 18. Cine nucleophilic substitution at C2 in compound **5**; synthesis of methyl 2-ethoxy-4(5)-nitro-1*H*-imidazole-5(4)-carboxylate (**32**).

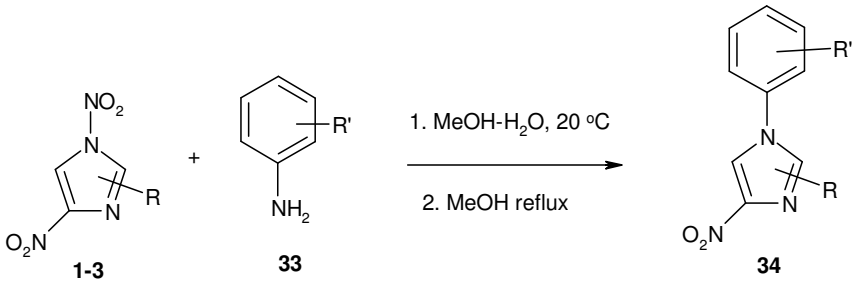
The *cine* reactions in 1,4-dinitro-1*H*-imidazoles probably preferentially begin with a nucleophilic attack on C5 or eventually on a substituent located there. A methyl group in the 5-position contains acidic protons. Basic hard nucleophiles, such as hydroxy or alkoxy anions, probably attack hydrogens of the methyl group and compound **3** decomposes then. If the position 5 is blocked by a substituent that does not react with bases, then nucleophiles can attack at C2. In the reaction of dinitroimidazole **5** with alkoxy anions, *cine* substitution at C2 was readily observed, probably following alkaline hydrolysis of the alkoxycarbonyl to carboxylate group. A direct attack of nucleophiles on the 1-nitro group cannot be excluded. Proof of this was obtained from the reaction of dinitroimidazole **2** with (^{15}N)ammonia.[52] Also, in several other reactions of dinitroimidazoles **1**–**3** with nucleophiles under alkaline or neutral conditions, 1-denitration was observed as a by-process. In reactions of 1,4-dinitro-1*H*-imidazoles with nucleophiles carried out in anhydrous acetonitrile or pyridine it was the only transformation noticed.

4.3. *ANRORC* reactions

A degenerate ring transformation (as observed in the reactions of dinitroimidazoles **1**–**3** with primary amino-compounds), considering the reaction mechanism, can be and is here called an *ANRORC* (Addition of a Nucleophile - Ring Opening - Ring Closure) reaction. The reaction is strictly regiospecific, affording only 1-substituted-4-nitro-1*H*-imidazoles. The scope of applic-

ability of the reaction is very wide. Dinitroimidazoles **1–3** react with aromatic and aliphatic amino-compounds of various structures and substituents to afford products **14** or **13** that are often difficult to prepare in another way. For example, the reaction with substituted anilines is the only simple, one-pot, efficient synthesis of 1-aryl-4-nitro-1*H*-imidazoles (**14**) not carrying very strong electron-withdrawing (*e.g.*, nitro) groups on the aryl substituent. To describe the *ANRORC* reaction, the following section is divided into three parts which differ in the type of starting amino compound (aromatic, aliphatic, sugar or nucleoside).

4.3.1. Reactions with aromatic primary amines. In contrast to secondary amines and 1*H*-azoles, neither aromatic nor aliphatic primary amines in reactions with dinitroimidazoles **1–3** afforded *cine* substitution products. The only exception was the reaction with 4-aminopyridine mentioned earlier (Section 4.2).[44] Instead, primary amines with 1,4-dinitro-1*H*-imidazoles formed the respective 1-alkyl- (**13**) or 1-aryl-4-nitro-1*H*-imidazoles (**14**). A new original approach to the synthesis of 4-nitro-1-phenyl-1*H*-imidazole and its substituted derivatives **34** in the reaction of dinitroimidazoles **1–3** with primary anilines **33** was patented and published.[53] (Scheme 19). The reaction was carried out in aqueous methanol and gave products in high yields irrespective of whether or not there was a methyl group at the imidazole ring. Anilines used in the reaction carried substituents such as chloro, methoxy, or methyl in *ortho, meta*, or *para* positions.



1 R=H, **2** R=2-Me, **3** R=4(5)-Me, R' = H, *o*-, *m*-, *p*-Cl, Me, MeO

Scheme 19. Synthesis of 4-nitro-1-phenyl-1*H*-imidazole and derivatives **34** in *ANRORC* reaction.

2-Amino- and 3-aminopyridines reacted with compounds **1** and **2** in the same manner as anilines to afford 1-(2 or 3-pyridyl)-4-nitro-1*H*-imidazoles in moderate to high yields.[44] An *ANRORC* mechanism for the reaction was proposed, although no details and no proof supporting the mechanism were given then. Effects of solvents on the reaction of dinitroimidazole **2** with *p*-toluidine, was studied in details.[42] In organic solvents containing 10 vol. % of water, an *ANRORC* product of type **14**: 2-methyl-1-(4′-methylphenyl)-4-nitro-1*H*-imidazole, was obtained. Dinitroimidazole **2** and *p*-toluidine (1:1) suspended in a small volume of aqueous methanol at 0–

5 °C reacted to yield a solid 1:1 adduct. The dried adduct, when dissolved in dry methanol, dimethyl sulfoxide, pyridine or acetonitrile at 25 °C, also gave the *ANRORC* product of type **14**. In anhydrous methanol or anhydrous dimethyl sulfoxide the same *ANRORC* transformation occurred with evolution of nitrous oxide. In contrast, 1-denitration of compound **2** was the only process observed in anhydrous acetonitrile and pyridine. Analyzing results of the above experiments the following conclusion can be drawn: the studied *ANRORC* reaction occurs *via* the ring opening adduct (**35**, Figure 6), a formation of which requires the presence of a solvent enabling a proton transfer. Recycling and rearomatization of the adduct can occur irrespective of an organic solvent type.

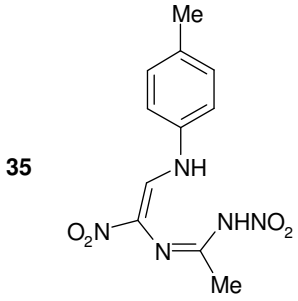
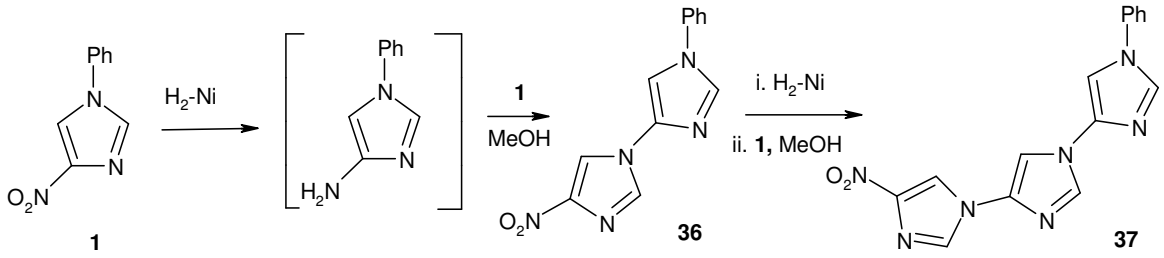


Figure 6. Proposed structure of *p*-toluidine-2-merhyl-1,4-dinitro-1*H*-imidazole adduct.

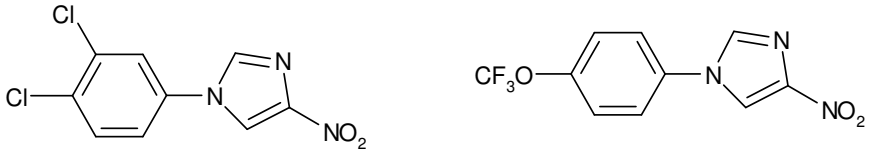
It is well known that free 1-alkyl(or aryl)-4-amino-1*H*-imidazoles are unstable but may be stabilized by, for example, acylation of the amino group. It was also shown that reduction of nitroimidazoles **14** could lead to the respective amino derivatives that were stable enough to react with dinitroimidazole **1** and afforded 1,4′-linked biimidazole **36** and triimidazole **37** (Scheme 20).[54]



Scheme 20. *ANRORC* synthesis of 1,4′-linked oligoimidazoles.

Arylnitroimidazoles **14** containing strong electron-withdrawing substituents such as a nitro group in the *ortho* or *para* position cannot be prepared by the *ANRORC* reaction. These compounds can be obtained by 1-arylation of nitroimidazole **7** salts. An example was shown by D'Auria *et al.*, who synthesized 1-(*p*-nitrophenyl)-4-nitro-1*H*-imidazole from nitroimidazole **7** and *p*-nitrofluorobenzene.[55] A series of compounds **14** containing electron-withdrawing

substituents was obtained either by an *ANRORC* reaction or by 1-arylation of nitro-1*H*-imidazoles. Products **14** from dinitroimidazole **2** and halogenoanilines indicated very promising activity in tuberculosis inhibition.[56] Several new 1-(halogenophenyl)-4-nitro-1*H*-imidazoles and 1-(dihalogenophenyl)-4-nitro-1*H*-imidazoles were prepared using the *ANRORC* approach.[57] The latter compounds and some other arylnitroimidazoles **14** were examined *in vitro* against human African trypanosomes. Two such compounds: 1-(3′,4′-dichlorophenyl)-4-nitro-1*H*-imidazole (**38**) and 4-nitro-1-(4′-trifluoromethoxyphenyl)-1*H*-imidazole (**39**) (Figure 7), showed very good antimicrobial activity and low cytotoxicity towards human cells.[58]



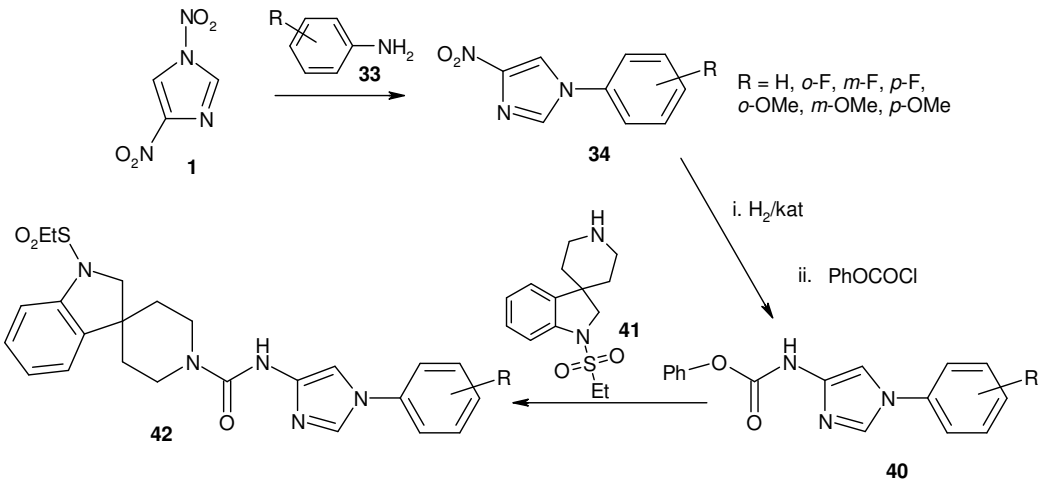
38 **39**

Figure 7. 1-Aryl-4-nitro-1*H*-imidazoles drugs for human African trypanosome treatment.

These two compounds **38** and **39**, which were in fact more promising than another nitroimidazole drug, Fexinidazole, currently in clinical trials, were additionally tested *in vivo* in mice. 4-Nitro-1-(4′-trifluoromethoxyphenyl)-1*H*-imidazole (**39**) was not only active but it did not show any mutagenicity, which is usually the main problem in the use of nitroimidazoles as drugs.[58]

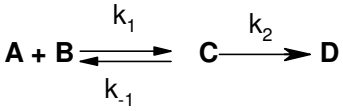
Neuropeptide Y is a factor stimulating the appetite. Neuropeptide Y5 receptor antagonists may bring considerable progress in the treatment of obesity. Sakamoto *et al.*[26] synthesized a series of spiroindoline derivatives and tested them as neuropeptide Y5 receptor antagonists. They studied the structure-activity-relationship of a spiroindoline class of compounds and identified them as effective in chronic obesity. Products were prepared from dinitroimidazole **1** and aniline, its fluoro- or methoxy- derivatives **33** in the *ANRORC* reaction to afford compounds **34** followed by reduction of 4-nitro- to amino-group. The unstable amino-derivatives were acylated in pyridine with phenyl chloroformate to give phenyl carbamates **40**, which without further purification were treated with 1-(ethylsulfonyl)-1,2-dihydrospiro[indole-3,4′-piperidine (**41**) to yield 1-(ethylsulfonyl)-*N*-(1-aryl-1*H*-imidazol-4-yl)-1,2-dihydro-1′*H*-spiro[indole-3,4′-piperidine]-1′-carboxamides (**42**) (Scheme 21). The best highly potent and orally available compound contained a 1-phenyl-1*H*-imidazole-4-amino substituent at the spiroindoline core.

Syntheses of *C*-nitro-*N*-phenylazoles were recently reviewed and a detailed procedure for preparation of 4-nitro-1-phenyl-1*H*-imidazole from dinitroimidazole **1** and aniline was given there.[59]



Scheme 21. Synthesis of neuropeptide Y5 receptor antagonists.

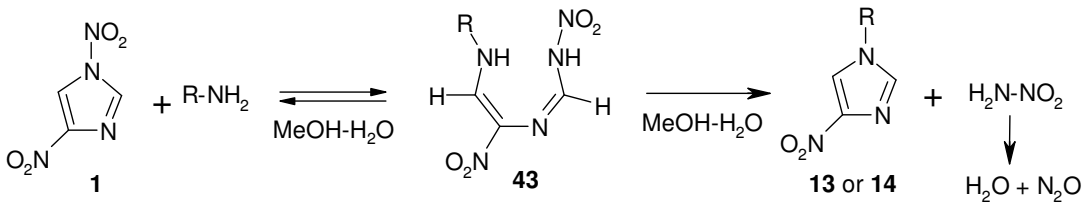
Llempen *et al.*[42] studied the kinetics of the reaction of compounds **1–3** with primary anilines, *N*-methylaniline, and *N,N*-dimethylaniline in water or aqueous methanol at 0–25 °C. In water at 0 °C, compounds **1–3** with equimolar amounts of aromatic amines formed water-insoluble colored adducts. Adducts of **1–3** with *N,N*-dimethylaniline when dissolved in methanol immediately dissociated to the starting materials. Adducts of dinitroimidazoles **1** or **2** with *N*-methylaniline or primary anilines in methanol solutions gave respective *cine* or *ANRORC* reaction products depending on the nature of the starting amine. Adduct of **3** with primary amines underwent the *ANRORC* reaction; the *cine* reaction with *N*-methylaniline was not observed. It was also found that the *cine* (in contrast to the *ANRORC*) reaction is catalyzed by bases. On the ground of numerical optimization of experimental kinetic data, the following simplified kinetic scheme for the reaction of **2** with primary anilines was proposed. Electron-withdrawing substituents in B diminished the rate constants k_1 and k_2 of C and D formation and only slightly affected the rate constant k_{-1}. The effect of the electron-donating group was the opposite. It was also shown that an adduct of **2** with aniline in aqueous methanol, decomposed with evolution of the respective volume of nitrous oxide. (Scheme 22).



where: **A** - dinitroimidazole **2**, **B** = aniline or its *C*-substituted derivative, **C** = intermediate adduct, **D** = product (1-aryl-2-methyl-4-nitro-1*H*-imidazole)

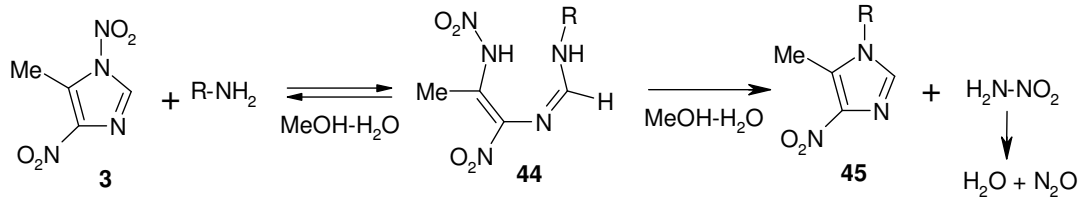
Scheme 22. The simplified kinetic scheme of the *ANRORC* mechanism.

Steps 1 and 2 from the simplified scheme of the *ANRORC* mechanism in the reaction of at least **1** and **2** with primary amines are probably the same regardless of a core linked to an amino group. The first step involves an attack by amine on atom C5 followed by N1–C5 bond break with the formation of an acyclic adduct **43**. The second step consists of an attack by the amino nitrogen atom from the adduct on C2 (numbered from the starting dinitroimidazole) and a ring closure followed by the elimination of the nitroamide molecule and aromatization to give new imidazole derivatives of type **13** or **14**. Ring opening is stabilized by a proton migration from the amine nitrogen atom to the ring N1 atom. The proton migration is a part of the slow crucial first step of the *ANRORC* reaction. The proposed mechanism of the *ANRORC* reaction shown in Scheme 23 is in conformity with all published experimental results.



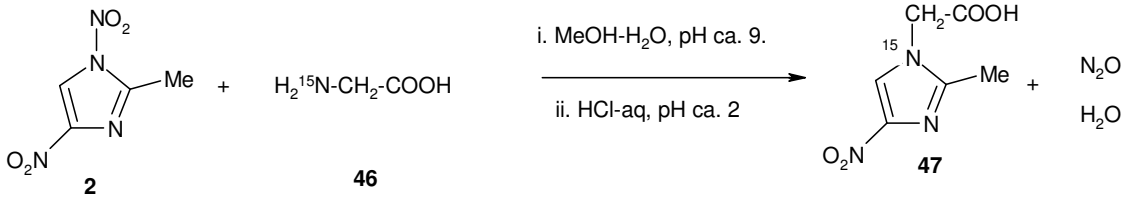
Scheme 23. Simplified mechanism of the *ANRORC* reaction of compound **1**.

Though none of the known results is inconsistent with the above postulated *ANRORC* mechanism, one important question remains unanswered. It concerns the behavior of dinitroimidazole **3** towards amines. It was shown that dinitroimidazole **3** with secondary amines did not undergo *cine* substitution but with primary amines it afforded products of the *ANRORC* reaction in high yields. Such results cannot exclude the *ANRORC* mechanism for dinitroimidazole **3** conversion into 5-methyl derivatives of **13** or **14** arising from an attack of the primary amine on C5 according to Scheme 23. Also an attack on C2 of the imidazole ring followed by C2–N1 breakage and a proton migration to N1 cannot be excluded. The forming acyclic adduct **44** would cyclize as a result of an attack by the secondary amine nitrogen atom, connected to atom C2, on atom C5 followed by elimination of nitramide (Scheme 24). It is interesting what experiment could resolve the remaining question concerning *ANRORC* mechanism of dinitroimidazole **3** with primary amines.



Scheme 24. Possible mechanism of *ANRORC* reaction of dinitroimidazole **3** with primary amines.

4.3.2. Reactions with compounds containing a primary amino group linked to an aliphatic carbon atom. The reaction of compound **2** with two enantiomers of alanine methyl ester afforded two practically pure methyl esters of (2*S* or 2*R*) 2-(2′-methyl-4′-nitro-1′*H*-imidazol-1′-yl)propanoic acids. That result indisputably showed that both the configuration of atom 2C and bond 2C–N in the starting alanine esters are preserved through the whole process, supporting an *ANRORC* mechanism.[60] Dinitroimidazole **2** treated with (^{15}N)glycine (**46**) yielded a product (Scheme 25) with a (^{15}N)nitrogen atom, namely [2-methyl-4-nitro-1*H*-(1-^{15}N)imidazole-1-yl]acetic acid (**47**). The structure of that product was established by spectroscopic and mass spectral analyses. Additionally, the authors postulated the evolution of nitrous oxide and water as by-products in the reaction.[61] The results of the two later experiments irrefutably proved an *ANRORC* mechanism of 1,4-dinitro-1*H*-imidazoles reactions with primary amino compounds into products of type **13**.



Scheme 25. Incorporation of (^{15}N)nitrogen atom into the imidazole ring.

A few years later, a conversion of 2-methyl-4(5)-nitro-1*H*-imidazole into isotopically modified 2-methyl-4(5)-nitro-1*H*-(1-^{15}N)imidazole in a four-stage process was published. Initially, [2-methyl-4-nitro-1*H*-(1-^{15}N)imidazol-1′-yl]acetic acid was obtained. The latter acid with bromine and phosphorus trichloride in anhydrous benzene formed a product that was subjected to hydrolysis to afford 2-methyl-4(5)-nitro-1*H*-(1-^{15}N)imidazole in 40% yield. Starting compound **2** was also treated with (^{15}N)ammonia to produce a mixture of isotopically modified and natural nitrous oxide. The latter result proved again that at least some nitrogen nucleophiles can attack not only the ring carbon atoms but also the exocyclic nitrogen atom of the 1-nitro group.[62] In order to find new effective nontoxic radiosensitizers of hypoxic tumor cells, a series of 4-nitro-1*H*-imidazoles with 1-substituents containing acid, ester, or phenol functions and eventually a 2-methyl group at the imidazole ring was prepared. The following types of compound were used as starting amino reagents: α-aminoacids, aminoalkanesulfonic acid, α-aminoacid esters, and dipeptides, as well as anilines substituted with carboxy, ester, hydroxyl, or sulfonic groups in the *ANRORC* reaction with dinitroimidazoles **1** and **2**. Unfortunately, besides some nitroimidazoles **14,** none of the synthesized compounds had properties suitable for application in cancer treatment. Enantiomers did not differ in radiosensitizing abilities or cytotoxicities.[63] In a search for a new efficient method for synthesis of chiral imidazole derivatives as purine precursors, the reactions of dinitroimidazoles **1** and **2** with chiral esters of α-aminoacids or chiral 3-amino-1,2-propandiols were successfully performed.[64] Wengel and

Walczak described a convenient synthesis of 1-(1′,3′-dihydroxy-2′-propyl)-4-nitro-1*H*-imidazoles in the reaction of dinitroimidazoles **1** and **2** with 2-amino-1,3-propandiole in a water–methanol solution.[65] Boncel *et al.* treated dinitroimidazole **1** with *beta*-alanine methyl ester and synthesized a compound identical to that obtained by the addition of nitroimidazole **7** to methyl acrylate.[66] Jaroshenko *et al.*, looking for a facile synthesis of fluorinated 1-desazapurines, prepared a series of 1-arylalkyl-4-nitro-1*H*-imidazoles **48**-**51** (Fig. 7) from dinitroimidazole **1** and benzylamines. The products were reduced to 4(5)-amino-1*H*-imidazoles and then used as starting materials in the syntheses of 1-desazapurines.[67]

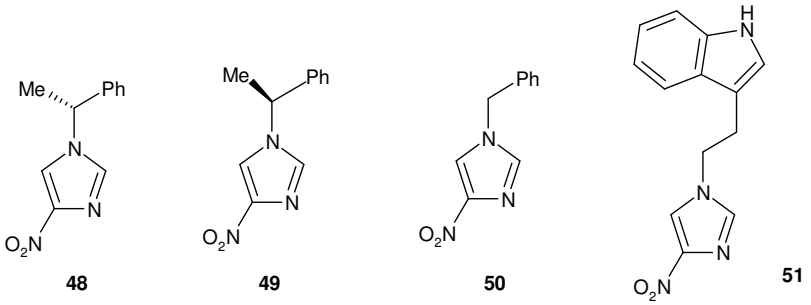
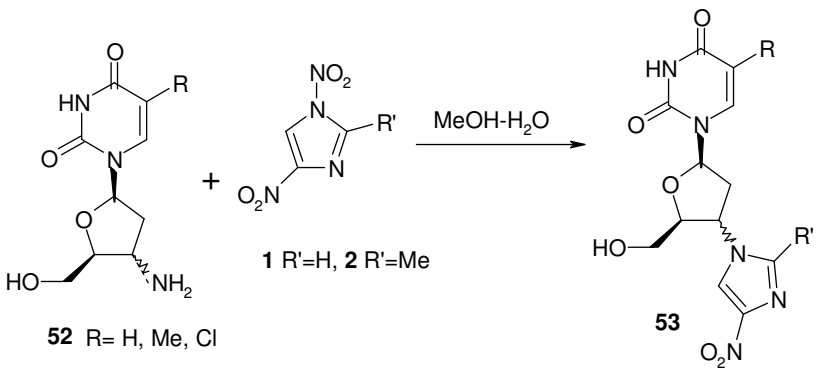


Figure 8. 1-Arylalkyl-4-nitro-1*H*-imidazoles prepared by *ANRORC* reaction of compound **1** with primary arylalkylamines.

1-Cycloalkyl-4-nitro-1*H*-imidazoles, obtained in an *ANRORC* reaction of dinitroimidazole **1** with 3-amino-1-benzyloxycyclobutane, were used in the synthesis of structurally novel kinase inhibitors containing a *cis*-1,3-disubstituted cyclobutane moiety.[7] Later, the same approach was applied to the synthesis of 4-acylamino derivatives of 1-cyclopentyl-1*H*-imidazole and 3-(1*H*-imidazol-1-yl)cyclobutanol. The treatment of dinitroimidazole **1** with the respective primary amines afforded nitroimidazoles of type **13**. These compounds were hydrogenated and gave unstable aminoimidazoles that were immediately acylated to afford the expected 1-substituted 4-acylamino-1*H*-imidazoles.[28]

4.3.3. Reactions with amino derivatives of sugars or nucleosides. Since the discovery of the *ANRORC* reaction of dinitroimidazoles **1–3** with amino-compounds, several syntheses or modifications of sugar derivatives or nucleosides by a replacement of the primary amino group with 4-nitroimidazol-1-yl substituent in the starting amino-compound have been published. Most of the modifications were performed in the course of a search for useful biologically active compounds. The reaction of dinitroimidazoles **1** or **2** with derivatives of 3′-aminouridine **52** gave their respective 3-(4′-nitro-1′*H*-imidazol-1′-yl)nucleosides **53**, being AZT analogs (Scheme 26).[68]

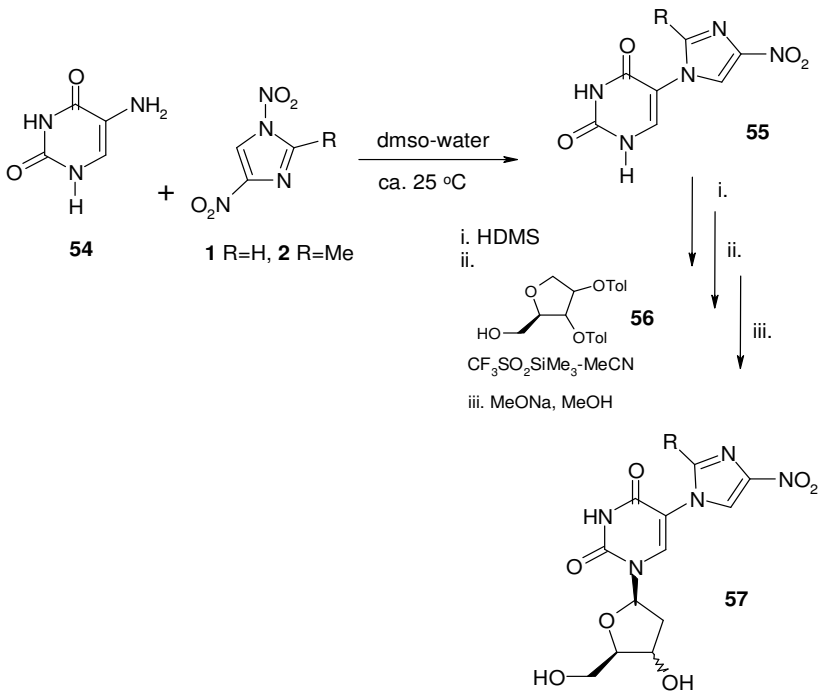


Scheme 26. Synthesis of AZT analogs by *ANRORC* reaction.

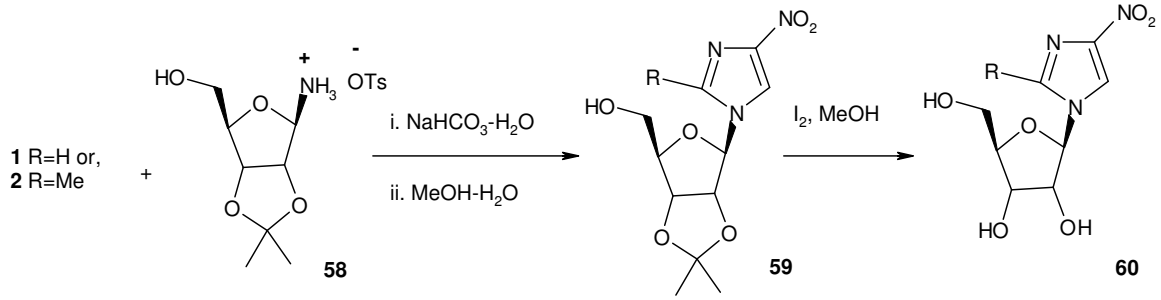
5-(4′-Nitro-1′*H*-imidazol-1′-yl)-2-deoxyuridines **57** were synthesized by the treatment of 5-(4′-nitro-1′*H*-imidazol-1′-yl)uracils **55** with 2-deoxy-3,5-di-*O*-*p*-toluolyl-α,β-D-*erythro*-pentafuranoside (**56**), following the reaction of dinitroimidazoles **1** and **2** with 5-aminouracil **54** in aqueous dimethyl sulfoxide (Scheme 27). Products of the reaction were tested against HIV.[69] 5-(4′-Nitro-1′*H*-imidazol-1′-yl)uracil (**54**) prepared in the *ANRORC* reaction was also 1-alkylated with methoxymethyloxirane to give the respective 5-substituted 1-(2′-hydroxy-3′-methoxypropyl)uracil. Its cytotoxicity against L1210 and macrophage RAW 264.7 cells *in vitro* was examined.[70] The *ANRORC* reaction of dinitroimidazole **2** with 1-amino-1-deoxy-D-glucopyranose was applied in a new approach to the synthesis of nucleosides. The obtained product was a mixture of two anomers that were separated as tetraacetyl derivatives following complete acetylation of the nucleoside anomers.[71] In a similar manner, the hitherto unknown 1-(2′-deoxy-2′-D-glucopyranosyl)-4-nitro-1*H*-imidazole was prepared.[72]

The reactions of dinitroimidazoles **1** and **2** with equimolar quantities of D-ribosylamine or 2,3-*O*-isopropylidene-D-ribofuranosylamine salt **58** in aqueous methanol at 20 °C yielded mixtures of two products. Only one of them contained both sugar and nitroimidazole fragments. The compounds were separated following peracetylation of the mixture to give the expected protected nitroimidazole nucleosides **59** and ribopyranose. Deprotection of nitroimidazole derivative gave the free nitroimidazole nucleosides **60** (Scheme 28).[73]

Experience gathered in the application of the *ANRORC* reaction in syntheses of nucleosides was expanded by Walczak *et al.* to acyclic nucleosides.[74] The *ANRORC* reaction of compounds **1** and **2** was applied for conversion of unprotected 2-amino-2-deoxy-D-hexopyranoses into 2-deoxy-2-(4′-nitro-1′*H*-imidazol-1′-yl)-D-hexopyranoses. The obtained mixtures of anomers were separated into pure products following acetylation.[75] A review by van der Plas appeared on degenerate ring transformation reactions[14] and was then cited by Hajos *et al.* in a review devoted to advances in ring transformation of five-membered heterocycles.[76]



Scheme 27. Multi-step synthesis of 5-(4′-nitro-1′*H*-imidazol-1′-yl)-2-deoxyuridines.



Scheme 28. Synthesis of nitroimidazole nucleosides.

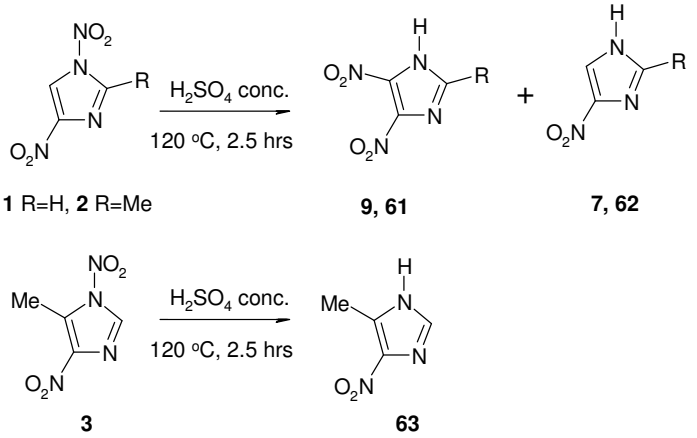
4.4. Disproportionation in hot sulfuric acid

The action of cold concentrated sulfuric acid on compounds **1–3** yielded the respective 4(5)-nitro-1*H*-imidazoles in very high yields,[18] but in hot concentrated sulfuric acid dinitroimidazoles **1–3** behaved in a different way.[15,18-19] Dinitroimidazole **1,** when heated in concentrated sulfuric acid at 120–125 °C for 2 hours, underwent rearrangement affording 50% crystalline 4,5-dinitro-1*H*-imidazole (**9**), which was identical to the compound prepared by direct exhaustive nitration of imidazole. The rearrangement of methyl derivative **2** under similar conditions for 4 hours gave 2-methyl-4,5-dinitro-1*H*-imidazole (**61**) in 40% yield.[15] Similar results were obtained while heating dinitroimidazoles **1** and **2** in concentrated sulfuric acid at 120 °C for around 2.5 hours. The 1-nitro group migrated to the 5-position of the imidazole ring, yielding over 30% of the

respective 4,5-dinitro-1*H*-imidazoles (**9**, **61**) together with the respective 1-denitration products (**7**, **62**) in 50% or 25% yields.[18] Compound **3** under similar conditions gave 5(4)-methyl-4(5)-nitro-1*H*-imidazole (**63**) in 60% yield as the only identified product (Scheme 29).

Grimmett *et al.*[19] reported similar results to those published earlier.[15, 18] Dinitroimidazoles **1** and **2,** when heated in solution at 100–140 ºC, rearranged to give *C*-nitro isomers and some 1-denitration products, but 5-methyl derivative **3** failed to give identifiable products.[19] Moderate or low yields of 4,5-dinitro-1*H*-imidazoles obtained by the disproportionation of compounds **1** and **2** in hot concentrated sulfuric acid and lack of rearrangement in the case of dinitroimidazole **3** demonstrated low synthetic usefulness of the reaction.

4,5-Dinitro-1*H*-imidazoles can be more easily prepared by direct acidic nitration of imidazoles. It is worth stressing again that in the experiments conducted in concentrated sulfuric acid over a range of temperatures from 0–140 °C, the introduction of a nitro group in the 2-position of the imidazole ring was never detected.



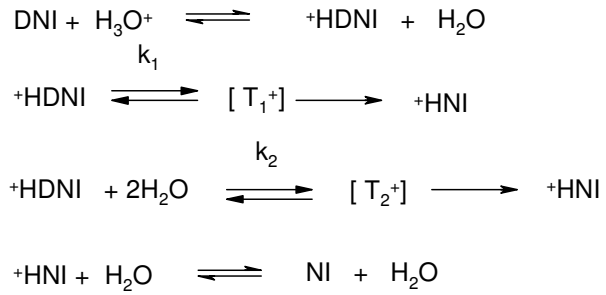
Scheme 29. Behavior of dinitroimidazoles **1-3** in hot concentrated sulfuric acid.

4.5. 1-Denitration of dinitroimidazoles 1–4

The action of cold concentrated sulfuric acid on compounds **1–3** led to a 1-nitro group splitting off from the imidazole ring with the formation of the respective 4(5)-nitro-1*H*-imidazoles.[15,18] Glass *et al.*[17] dissolved dinitroimidazole **4** in concentrated sulfuric acid and left it for 5 hours at room temperature. After cooling, neutralizing, and adjusting to pH 2, the resulting solution was extracted with chloroform and the layers were separated. Then the aqueous solution was adjusted to pH 5 and again extracted with chloroform. The combined chloroform extracts were concentrated to dryness to give 2-isopropyl-4(5)-nitro-1*H*-imidazole in 72% yield (Scheme 30).

Scheme 30. Behavior of 1,4-dinitro-1*H*-imidazoles in cold concentrated sulfuric acid.

Similar behavior of compounds **1–3** was observed while heating them under reflux in aqueous solutions of hydrochloric, phosphoric, or sulfuric acid. They yielded then the respective 4(5)-nitro-1*H*-imidazoles in 50–80% yields. No other organic species were detected in the post-reaction mixtures.[18] The kinetics of hydrolytic 1-denitration of dinitroimidazoles **1–3** in aqueous solutions of sulfuric acid at four concentrations (8.75, 18.00, 28.12, and 39.7%), at 25 °C and using an UV-visible spectrophotometric method was investigated in order to elucidate the mechanism of the reaction.[77] Under the conditions applied, the starting dinitroimidazoles exclusively afforded the respective 4(5)-nitro-1*H*-imidazoles. The products exhibited only single absorption maxima over 210 nm in the range 265–285 nm while starting compounds **1–3** show two maxima each at 225–230 nm and at 270–295 nm. Variations in absorption with progress of the reaction were used for determining kinetic data. Values of log k_Ψ (where k_Ψ is the pseudo-first order rate constant of the 1-denitration reaction expressed in sec^{-1}) were approximately linearly dependent on the Hammett acidity function H_o ($ArNH_2$) with slopes different from unity ($tg\alpha = -0.72$). The latter observation led to the conclusion that water was involved in a stage that limited the hydrolysis rate. Further analysis of the results indicated that two mechanisms of the hydrolysis with observed rate constants k_1 and k_2 operated in parallel as shown in Scheme 31.[76]



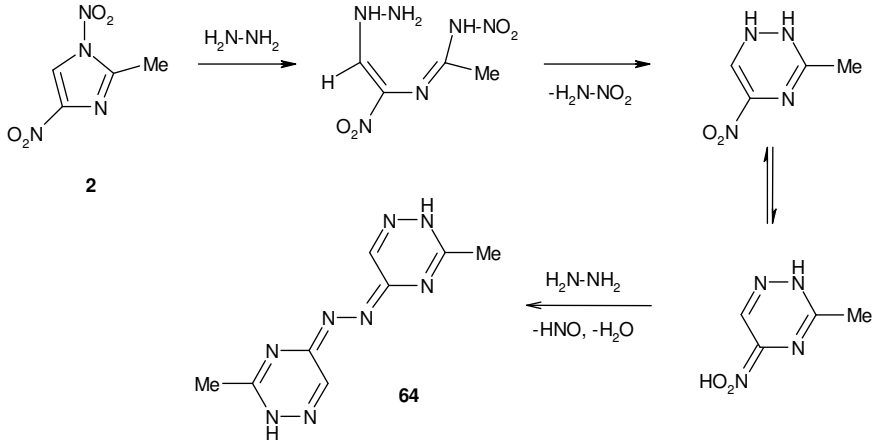
where: DNI means 1,4-dinitro-1*H*-imidazole, $^+$HDNI is protonated DNI, [T_1^+] the active complex of the first mechanism, NI is 4(5)-nitro-1*H*-imidazole, $^+$HNI is protonated NI, and [T_2^+] active complex in the second mechanism.

Scheme 31. Kinetics of acidic hydrolysis of 1,4-dinitro-1*H*-imidazole.

The second mechanism probably dominates. A formation of the four-centered active complex [T_2^+] was proposed. According to the proposal the active complex decomposed rapidly into nitroimidazole **7**, nitric(V) acid, and water.

4.6. Reactions with hydrazines

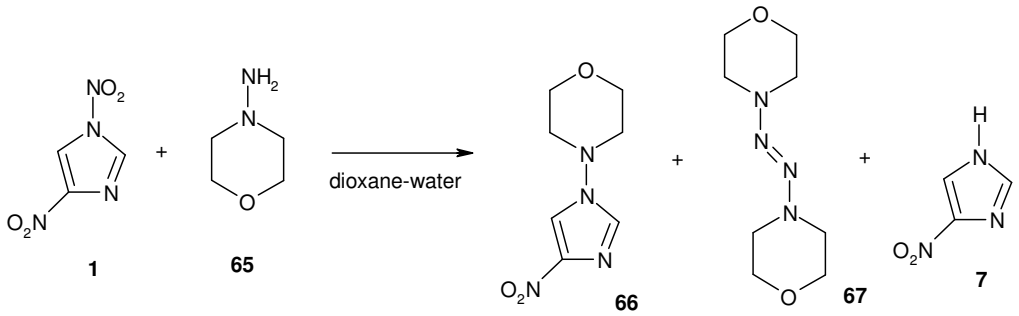
Attempts to prepare 1-amino-4-nitro-1*H*-imidazoles using an *ANRORC* reaction of dinitroimidazole **1**–**3** with hydrazines were undertaken, and rather unexpected outcomes of the reactions were observed.[78] Compound **2** reacting with hydrazine itself in water at pH 7.5–8.0 and 25 °C afforded a triazine derivative **64** in the imidazole ring expansion reaction. The structure of triazine **64** was determined by X-ray, and an *ANRORC* mechanism of the reaction was proposed (Scheme 32).



Scheme 32. Ring expansion in reaction of dinitroimidazole **2** with hydrazine.

Under similar conditions, dinitroimidazoles **1** and **3** were mainly 1-denitrated with the formation of the respective 4(5)-nitro-1*H*-imidazoles and with evolution of a gas containing nitrous oxide and nitrogen. The majority of the nitrous oxide probably came from the decomposition of unstable nitrohydrazide, which could be formed as the result of hydrazine attack on the 1-nitro group. Dinitroimidazoles **1–3** were also treated with monosubstituted hydrazines (phenylhydrazine, 1-hydroxyethylhydrazine, formylhydrazine, and *t*-butoxycarbonyl-hydrazine). In most of the experiments the starting dinitroimidazoles were only 1-denitrated. More interesting results were obtained from reactions of **1–3** with *t*-butoxycarbonylhydrazine carried out in aqueous dioxane. The reaction yielded di-(*t*-butoxycarbonylhydrazones) of glyoxal (65% from **1** and 48% from **2**) or of methylglyoxal (58% from **3**). A mechanism of these transformations was proposed (Scheme 33). The reactions of **1–3** with 1,1-disubstituted hydrazines (1,1-dimethylhydrazine, *N*-aminopiperidine, and *N*-aminomorpholine) yielded mixtures containing considerable quantities of 4(5)-nitro-1*H*-imidazoles. From the reaction of compound **1** with *N*-aminomorpholine (**65**), carried out in water at strictly controlled pH (7.5–8.0), two products besides nitroimidazole **7** were separated and analyzed. One of them was 1-(1′-

morpholino)-4-nitro-1*H*-imidazole (**66**), obviously the product of *ANRORC* reaction, while the other product was identified as azomorpholine (**67**) (Scheme 33).



Scheme 33. Reaction of dinitroimidazole **1** with *N*-aminomprpholine (**65**).

The mechanism of azomorpholine synthesis was proposed assuming an attack of *N*-aminomorpholine on the 1-nitro group with intermediate formation of *N*-(nitroamino)morpholine and its further reaction with the second molecule of the starting aminomorpholine.[78]

5. Theoretical Quantum Calculations of 1,4-Dinitro-1*H*-imidazole

Prediction of physicochemical properties of organic compounds, especially potentially explosive materials, is an essential step in designing new materials with improved property and performance. Impact sensitivity is one of the most important screening factors for novel high energy density materials. One way to estimate such property is use the General Interaction Properties Function developed by Politzer *et al.*[79] Recently, Rice and Hare[80] extended Politzer's scheme. They predicted impact sensitivities and thermal stabilities for thirtynine explosive molecules including 1,4-dinitro-1*H*-imidazole (**1**). Initially quantum calculations were performed at the B3LYP/6-31G* level and included geometry optimizations followed by normal mode analysis. Then the electron density and electrostatic potential of each molecule at its optimized geometry were evaluated. Parameters for five different model equations, being new quantitative structure-property relationships, were calculated using a set of 34 explosives for which experimental values of impact sensitivity were known. The calculated *h*50% value was defined as "the height from which 50% of the drops resulted in reaction of the sample". The results were often not reproducible; in some cases the tests gave widely varying *h*50% values. The predicted *h*50% values were calculated using all five models based on data derived from electrostatic potentials on the 0.001 au isosurface of electron density. Regression coefficients for models 1, 4 and 5 were as follows: 0.96, 0.97 and 0.95. The predicted *h*50% values for compound **1** (data are gathered in Table 2) varied from 80-32 cm for these three models.

Table 2. Experimental and predicted *h*50% values (cm) for 1,4-dinitro-1*H*-imidazole (**1**)

Exp.	V_{Mid}	$V^{-}/V^{av}/$	ν	Q	Q + ν
	Model 1	Model 2	Model 3	Model 4	Model 5
55	80(-25)	227(-172)	262(-207)	36(19)	38(17)

Model 1 was based on positive charge buildup over C-NO_2 bonds in an explosive substance.

$$h_{50\%} = y_0 + a\exp(-bV_{Mid}) + cV_{Mid} \quad (1)$$

with best-fit regression parameters: *a, b, c and* y_o. An average value of V_{Mid} was calculated according to equation 2.

$$V_{Mid} = \frac{1}{N}\sum_{i=1}^{N}\left(\frac{Q_c}{0.5R} + \frac{Q_N}{0.5R}\right) \quad (2)$$

in which the summation includes all C-N bonds in the molecule containing *N* of them. Q_c and Q_N are calculated atomic charges and *R* is the C-NO_2 bond length.

Models 2 and 3 were characterized by very low regression coefficients. Not surprisingly $h_{50\%}$ values calculated for compound **1** according to models 2 and 3 exceeded 220 cm, dramatically differing from the experimental value of 55 cm and therefore will not be presented here.

Model 4 assumed relations between $h_{50\%}$ and heat of detonation according to equation 3.

$$h_{50\%} = a_1 + a_2 exp\{-(a_3[Q - a_4])\} \quad (3)$$

where: a_1-a_4 are best-fit regression parameters and where *Q* is calculated from equation 4.

$$Q = H_d = \frac{-[\Delta H_f(Detonation\ products) - \Delta H_f(Explosive)]}{formula\ weight\ of\ explosive} \quad (4)$$

Model 5 (equation 5) uses an equation that incorporates the heat of detonation with the general interaction properties function balance parameter ν.

$$h_{50\%} = a_1 exp(a_2 v - a_3[Q - a_4]) \quad (5)$$

where: a_1-a_4 are best-fit regression parameters and v (balance parameter) is calculated according to equation 6.

$$v = \frac{\sigma_+^2\,\sigma_-^2}{[\sigma_{Tot}^2]^2} \quad (6)$$

where σ - calculated atomic and total charges.

By the presented calculations Rice and Hare proved that charges and electron densities surrounding explosive molecules could be useful in predicting degree of sensitivity of explosives to impact.

Attractive properties of 2,4(5)-1*H*-imidazole (**8**) readily available by from dinitroimidazole **1** prompted Su *et al.*[81] to theoretical quantum calculations of several data concerning not only compounds **1** and **8** but also other nitroimidazoles and their methyl derivatives. Dinitroimidazole **8** is much less sensitive to impact and is a *ca*. 60% stronger explosive material than 2,4,6-trinitrotoluene. The authors used density functional theory (DFT) approach to study the structure and thermochemistry properties of potential explosives. The calculated properties included: bond dissociation energies (BDE), heats of formation (HOF) and impact sensitivity values (h_{50}) for imidazole nitro derivatives including imidazoles **1**, **6**, **7**, **8**, **9** and **10**. All the calculations were carried out with the Gaussian 03 program package using the functionals B3LYP and B3P86 on 6-311G**level. For the compounds with known from literature bond parameters such as bond lengths and bond angles a very good agreement between experimental and calculated data was achieved. It was suggested earlier that the initial breakdown bond, for a number of energetic molecules including nitroimidazoles, was the bond R–NO_2. Thus, Su *et al.*, calculated the BDEs corresponding to homolytic C–NO_2 and N–NO_2 bond cleavage in the studied compounds. The calculated bond dissociation energies and heats of formations indisputably demonstrated that N-NO_2 bonds were weaker than C-NO_2 bonds and that *C,C*-dinitroimidazoles were more stable than *N,C*-dinitro isomers. Analysis of the results might also suggest that N–NO_2 as the weakest bond could be the "trigger linkage" in detonation of e.g., 1,4-dinitro-1*H*-imidazoles. Analysis of the calculation results revealed that the impact sensitivity h_{50} values depended on bond dissociation energies of the weakest bonds present in nitroimidazoles. This finding let Su *et al.* to predict h_{50} values of several nitroimidazoles and to prove that at least some of them with h_{50} larger than 60.0 cm, including nitroimidazole **2,** could be very useful potential explosive materials for some applications. The calculated data obtained for 1,4-dinitro-1*H*-imidazole (**1**) were as follows: N1-NO_2 BDE 34.5 kcal/mol, C4-NO_2 BDE 70 kcal/mol, the electronic energy calculated by B3LYP/6-311G** −635.34322, the electronic energy calculated by B3P86/6-311G** −636.76339, symmetry Cs, impact sensitivity *h*50 40 cm, HOF ΔH^0 calculated by B3LYP/6-311G** 55.3 kcal/mol and calculated by B3P86/6-311G**.55.4 kcal/mol. Quantitative structure-property relationship studies such as those presented by Rice and Hare[80] seem to provide the most efficient approaches in searching for new explosives. Kim *et al.*[82] followed Rice and Hare's approach based on the electrostatic potential calculations and introduced a new equation 7 for estimation of impact sensitivity values. They performed quantum calculations on B3LYP/6-31G(d) level, constructing an equation with five parameters where three of them were new. According to Kim *et al.*, equation 7 should allow prediction of impact sensitivities of several molecules including zwitterions. Results achieved for compounds **1** and **8** with the help of equation 7 are collected in Table 3.

$$h_{50\%} = a_1 + a_2(H) + a_3(HBD) + a_4(PSA) + a_5\sigma + a_6(\sigma_+^2) \quad (7)$$

where: *a1-a6* – best-fit regression parameters, *H* - number of hydrogen atoms, *HBD* - number of hydrogen bond donors, and *PSA* – polar surface area of the molecule, σ sum of the van der Waals molecular surface values, σ_+^2 is the variance of positive molecular surface. The regression coefficient was 0.97 and deviation of the predicted values from the experimental values was better than that from model 5.[79]

Table 3. Experimental and predicted $h_{50\%}$ values for compounds **1** and **8**

Compound No	Exp. $h_{50\%}$	Calc. $h_{50\%}$ Model 5	Calc. $h_{50\%}$ Model 7
1	55	38	36
8	105	41	18

Kim *et al.*, comparing impact sensitivity $h_{50\%}$values predicted from model 7 with those from model 5 for several high energy density materials, concluded that both density approaches and polar surface can lead to similar results. An advantage of the density approach lies in avoiding complex computation necessary in the polar surface approach. Unfortunately $h_{50\%}$values calculated for dinitroimidazoles **1** and **2** were far from the experimental data. It is clear that a further search for a computational model giving reliable results is still needed.

Conclusions

Though 1,4-dinitro-1*H*-imidazoles are very interesting compounds and have been known for over forty years their usefulness as starting materials in syntheses of valuable drugs and explosives has become obvious only recently. The reason for such situation can be derived from two facts: the title compounds are harmful and potentially explosive, and several earlier papers in the field were published in less available Polish and Russian journals. Furthermore, only a few derivatives (**2**–**5**) of the parent dinitroimidazole **1** are currently known. Therefore, the field is still open for the preparation of new 1,4-dinitro-1*H*-imidazoles and for their application to the syntheses of a variety of compounds with practical applications. Detailed theoretical quantum computational study of compound **1** and its derivatives, as well as their reactions, would be also rewarding.

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Author's Biography

Jerzy Wiktor Suwiński was born in 1939. He graduated from the Silesian University of Technology, Gliwice, Poland in 1961. He is PhD since 1968, is DSc since 1978, and is full professor since 1990. In 1973/74 he was a post-doc in the University of East Anglia with Prof. A. R. Katritzky. Between 1961 and 2012 he worked at the Silesian University of Technology and now he is professor at the Centre of Polymer and Carbon Materials of the Polish Academy of Sciences, Zabrze, Poland. The field of his scientific interests is the synthesis, physicochemical properties and reactivity of nitrogen-containing heterocycles.

