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Nucleophilic substitution reactions of 1-methyl-4,5-dinitroimidazole with aqueous ammonia or sodium azide

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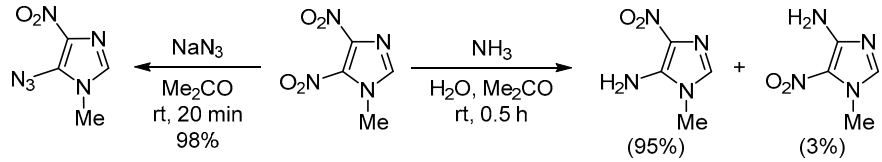
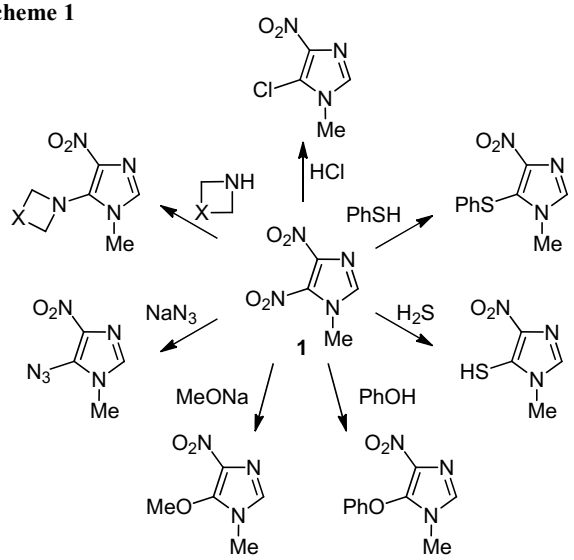


In this work, 5-amino-1-methyl-4-nitroimidazole was synthesized by amination reaction of 1-methyl-4,5-dinitroimidazole with aqueous ammonia in 95% yield. Meanwhile, one of its isomers, 4-amino-1-methyl-5-nitroimidazole as byproduct was obtained from the filtrate. Furthermore, nucleophilic substitution reaction of 1-methyl-4,5-dinitroimidazole with sodium azide gave 5-azido-1-methyl-4-nitroimidazole in 98% yield. The three compounds were characterized by IR, ^{1}H and ^{13}C NMR spectra, melting points, and elemental analysis. The structure of 4-amino-1-methyl-5-nitroimidazole was further confirmed by single crystal X-ray diffraction. These reactions indicate that the nitro group at position 5 of 1-methyl-4,5-dinitroimidazole is quite unstable, as well as partial substitution of nitro group at position 4 also occured in aqueous ammonia. Only one nitro group of the two is involved in nucleophilic substitution reaction in each case.

Keywords: 4-amino-1-methyl-5-nitroimidazole, 5-amino-1-methyl-4-nitroimidazole, 5-azido-1-methyl-4-nitroimidazole, 1-methyl-4,5-dinitroimidazole, nucleophilic substitution reaction.

Nitroimidazoles are widely used as antitumor, antibacterial, antifungal, antiviral drugs due to their biological activity.[1–4] Recently, polynitroimidazoles have become object of increased interest as energetic materials. Several nitro compounds with the imidazole moiety as the core have been reported as insensitive energetic materials.[5–12] It has been shown (Scheme 1) that when 1-methyl-4,5-dinitroimidazole (4,5-MDNI) (**1**) reacts with hydrochloric acid, chlorination occurs at position 5, thereby providing 5-chloro-1-methyl-4-nitroimidazole in 74% yield.[13] 4,5-MDNI (**1**) reacts with thiophenol, H_2S, phenol, sodium methylate, cyclic amine, or sodium azide, in all cases at position 5, and affords mercaptophenyl, mercapto, phenoxy, methoxy, cyclic amino, or azido derivatives, respectively (Scheme 1).[14–16] These reactions illustrate that the nitro group at position 5 is labile and hence susceptible to nucleophlic substitution reactions, whereas the nitro group at position 4 remains unaffected.

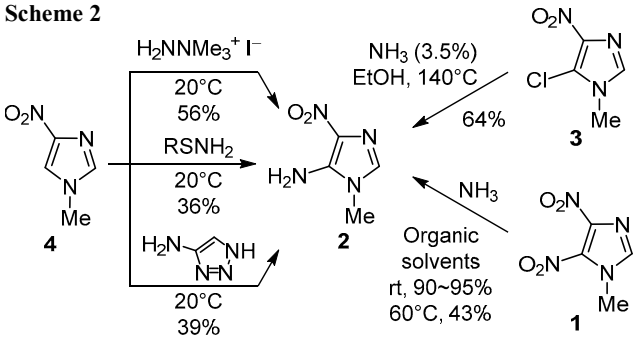
Scheme 1



5-Amino-1-methyl-4-nitroimidazole (**2**) as an intermediate compound has a wide range of applications. It not only displays solvatochromism, but also plays an important role as propellant with excellent detonation performance, high melting point, and low sensitivity. Therefore, it can be used for heat-resistant explosives. Three methods for the preparation of 5-amino-1-methyl-4-nitroimidazole (**2**) have

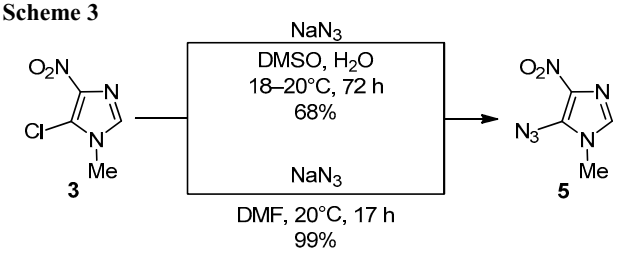
been reported (Scheme 2). In the first approach, 5-chloro-1-methyl-4-nitroimidazole (**3**) was heated with 3.5% alcoholic ammonia at 140°C.[17] The second method was amination reaction of 1-methyl-4-nitroimidazole (**4**) with trimethylhydrazinium iodide,[18] sulfenamide,[19] or 4-amino-1,2,3-triazole[20] to give product **2** at room temperature. Although the product obtained by the two methods had good purity, the reaction yield was relatively low and a long reaction time was necessary. Even more, the first method required high temperature, and the amination reagents of the second method were expensive. The third method, nucleophilic substitution reaction of 4,5-MDNI (**1**) with aqueous ammonia gave 5-amino-1-methyl-4-nitroimidazole (**2**) in high yield.[21,22] This method also has the advantages of low temperature, high purity, and low cost.

Scheme 2



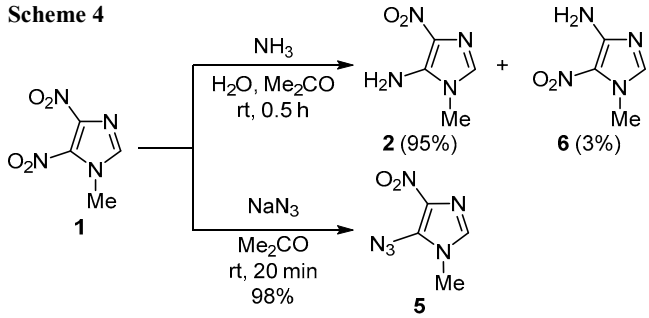
5-Azido-1-methyl-4-nitroimidazole (**5**) not only holds promise as a potential melt-casting explosive,[23] but also was used as a precursor to synthetic antiparasitic drugs.[16] Nucleophilic substitution reaction of 5-chloro-1-methyl-4-nitroimidazole (**3**) with sodium azide to give 5-azido-1-methyl-4-nitroimidazole (**5**) has been reported in two articles (Scheme 3).[23,24] The reported yield of product **5** was 68% with dimethyl sulfoxide and water as solvents at 18–20°C and 72 h reaction time.[23] However, when DMF was used as a solvent the yield of product **5** reached 99% at 20°C within 17 h.[24] In the first procedure, the lower yield could be due to the presence of water in the reaction system. Applying another method, 4,5-MDNI (**1**) was reacted with sodium azide in water to give 5-azido-1-methyl-4-nitroimidazole (**5**) in 99% yield at room temperature (Scheme 1).[16]

Scheme 3



In this paper, an improved synthetic method involving the direct amination of 4,5-MDNI (**1**) was used to synthesize 5-amino-1-methyl-4-nitroimidazole (**2**) with higher yield and higher purity at room temperature (Scheme 4). At the same time, the isomeric 4-amino-1-methyl-5-nitroimidazole (**6**) was obtained as byproduct by extracting the filtrate with ethyl acetate. During the experiment, we found that 5-amino-1-methyl-4-nitroimidazole (**2**) was soluble only in dimethylformamide and dimethyl sulfoxide (solubility 0.026 and 0.031 g/ml at 80°C, respectively) and insoluble in ethyl acetate. However, according to literature reports, it was extracted with ethyl acetate.[19,20] When we extracted the filtrate of the reaction mixture with ethyl acetate, the isomeric byproduct **6** was obtained. The structure of two compounds was confirmed by infrared spectroscopy, nuclear magnetic resonance spectroscopy, and elemental analysis, and the data are consistent with those reported before.[25] The structure of 4-amino-1-methyl-5-nitroimidazole (**6**) was further confirmed by single crystal diffraction analysis. The density of the electron cloud at the position C-5 is lower than at the position C-4 of the imidazole ring of 4,5-MDNI (**1**), which may explain why the nitro group is displaced more readily at C-5 than C-4 carbon atom.[15]

Scheme 4



Furthermore, 4,5-MDNI (**1**) was subjected to reaction with sodium azide in acetone under the ambient temperature. The reaction was very rapid and in 20 min 5-azido-1-methyl-4-nitroimidazole (**5**) was isolated as a pale-yellow solid in 98% yield (Scheme 4). When the filtrate was extracted with an organic solvent, such as dichloromethane, diethyl ether, ethyl acetate, or toluene, no other product was obtained. Unlike the nucleophilic substitution reaction with aqueous ammonia, when 4,5-MDNI (**1**) reacted with sodium azide the nitro group at the position C-4 was not replaced by an azide group, probably due to the lower basicity of azide ion in comparison with ammonia. Although this reaction has been performed in water,[16] we found that 4,5-MDNI (**1**) was not completely dissolved in water, and we chose acetone as the solvent.

The IR spectra of 5-amino-1-methyl-4-nitroimidazole (**2**) (Fig. 1*a*) and 4-amino-1-methyl-5-nitroimidazole (**6**) (Fig. 1*b*) show strong absorption peaks at 3444 (3456) and 1645 (1630) cm^{-1} (numbers in parentheses are for compound **6**), which can be assigned to the stretching and bending vibration of the NH_2 group, respectively. The stretching vibration absorption peak of =C–H fragment in the imidazole ring is observed at 3066 (3100) cm^{-1}. The bands at 1550 (1533) and 1325 (1304) cm^{-1} correspond to the asymmetric and symmetric stretching vibration movements of the C–NO_2 fragment, respectively. At 1409 (1404) cm^{-1}, there is the stretching vibration absorption peak of C=C bond of the imidazole ring. The band at 1373

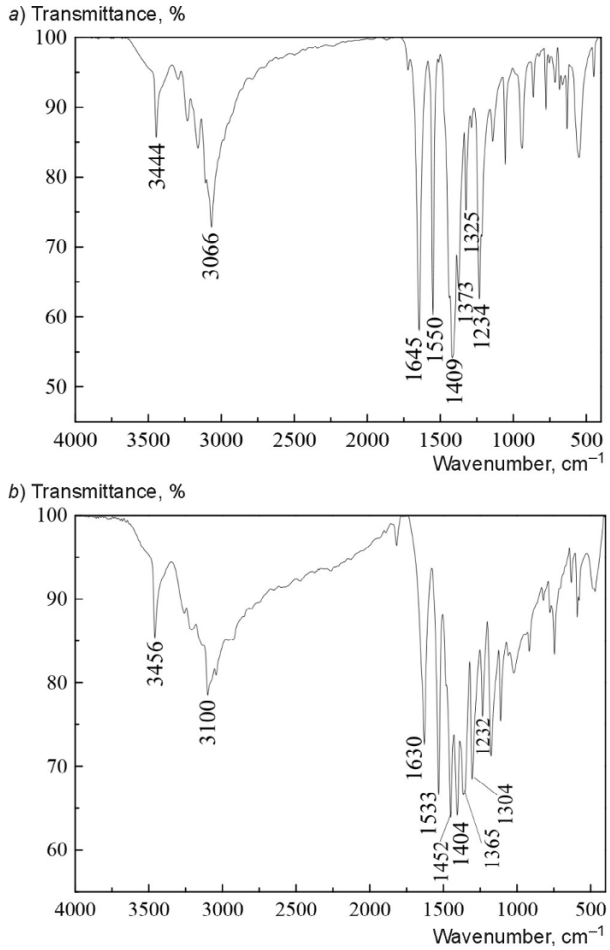


Figure 1. FT-IR spectra of *a*) 5-amino-1-methyl-4-nitromidazole (**2**) and *b*) 4-amino-1-methyl-5-nitroimidazole (**6**).

(1452 and 1365) cm^{-1} can be assigned to the bending vibration absorption of the methyl group. Finally, at 1234 (1232) cm^{-1} there is the stretching vibration absorption peak of the C–NH_2 bond. The differences in IR spectra of the two isomers may be due to the effect of the different positions of the amino and nitro substituents with respect to the imidazole ring.

4-Amino-1-methyl-5-nitroimidazole (**6**) crystallizes in the monoclinic crystal system with space group $P2_1/c$, and each elementary cell has eight molecules that form 4 pairs of nonequivalent molecules. The main crystallographic data are listed in Table 1S (Supplementary information file). The compound exhibits an unsymmetrical structure, as shown in Figure 2. The imidazole ring is almost planar with the dihedral angles 0.293° and 0.178° for the two molecules (Table 2S, Supplementary information file). The nitrogen atoms of the nitro groups and the amino groups, the hydrogen atoms of the amino groups, the oxygen atoms of the nitro groups, and the carbon atoms of the methyl groups are almost coplanar with the imidazole ring; for the respective torsion, see Table 3S (Supplementary information file). However, the hydrogen atoms of the methyl groups are rotated out of the plane.

The bond lengths of 4-amino-1-methyl-5-nitroimidazole (**6**) are shown in Table 4S (see Supplementary information file). The length of C–N and C–C bonds are shorter than the standard C–N (1.48 Å) and C–C (1.54 Å) single bonds, but longer than that of C=N (1.29 Å) and C=C (1.34 Å) double bonds. This may be illustrated by the resonance structure, as shown in Figure 3. This conjugative effect can also be found in the imidazole ring of 4,5-MDNI.[26]

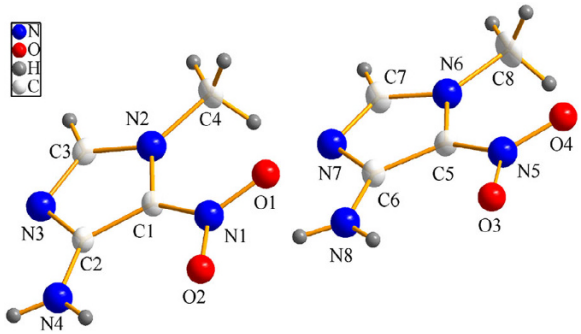


Figure 2. Molecular structure of 4-amino-1-methyl-5-nitroimidazole (**6**) according to X-ray diffraction analysis.

There are four different intermolecular hydrogen bonds in each unit cell of 4-amino-1-methyl-5-nitroimidazole, and each molecule of 4-amino-1-methyl-5-nitroimidazole (**6**) contains one intramolecular hydrogen bond (Fig. 4, Table 1). Except the hydrogen atoms of the methyl group, all atoms of the 4-amino-1-methyl-5-nitroimidazole molecule are coplanar, which may be due to intramolecular hydrogen bonds and conjugation effect.

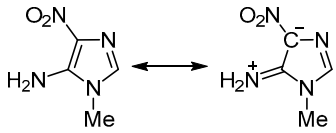


Figure 3. Resonance structures of 4-amino-1-methyl-5-nitroimidazole (**6**).

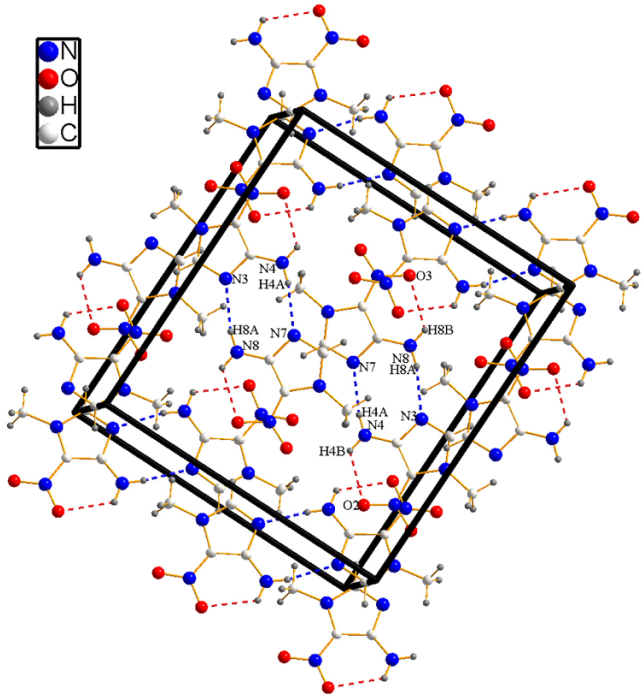


Figure 4. 2D chain of 4-amino-1-methyl-5-nitroimidazole (**6**) molecules in the elementary cell.

Table 1. Characteristics of hydrogen bonds in the crystal of 4-amino-1-methyl-5-nitroimidazole (**6**)

D–H…A	*d*(D–H), Å	*d*(H···A), Å	*d*(D···A), Å	∠(DHA), deg	Symmetry transformations
N(4)#20–H(4A)#21…N(7)#12	0.861	2.125	2.959	162.96	*x*, *y*, *z*
N(8)#8–H(8A)#9…N(3)#19	0.860	2.136	2.983	168.21	–*x*, 1 – *y*, –*z*
N(8)#8–H(8A)#9…N(3)#19	0.860	2.136	2.983	168.21	1 + *x*, *y*, 1 + *z*
N(4)#20–H(4A)#21…N(7)#12	0.861	2.125	2.959	162.96	1 – *x*, 1 – *y*, 1 – *z*
N(8)#8–H(8B)#10…O(3)#3	0.860	2.280	2.820	120.95	– *x*, 1 – *y*, –*z*
N(4)#20–H(4B)#22…O(2)#4	0.860	2.277	2.818	120.821	*x*, *y*, *z*

In summary, we have studied the nucleophilic substitution reactions of 1-methyl-4,5-dinitroimidazole with aqueous ammonia at room temperature, which produced 5-amino-1-methyl-4-nitroimidazole and the isomeric 4-amino-1-methyl-5-nitroimidazole as byproduct. The reaction of 1-methyl-4,5-dinitroimidazole with sodium azide in acetone at room temperature allowed to obtain 5-azido-1-methyl-4-nitroimidazole in high yield without side products. The structure of products of these reactions indicate that the nitro group at position 5 of the starting 1-methyl-4,5-dinitroimidazole is highly labile compared to position 4.

Experimental

IR spectra were recorded in KBr pellets on a Bruker Model Vertex 80 FTS spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Model AVANCE spectrometer (400 and 100 MHz, respectively). The solvent signals were used as internal reference (δ 2.50 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d_6; δ 2.05 and 29.8 ppm for ^{1}H and ^{13}C nuclei, respectively, in $(CD_3)_2CO$). Elemental analyses were performed on an Elementar Vario EL elemental analyzer. Melting points were determined using a Buchi Melting Point M-565 apparatus.

Acetone (AR, 99.5%) from XiLong Science Company was used as the reaction solvent.

4,5-MDNI (**1**) was prepared according to a published procedure.[27,28]

Caution: 4,5-MDNI is considered as dangerous and proper precaution should be taken in handling and storage.

5-Amino-1-methyl-4-nitroimidazole (2). 4,5-MDNI (**1**) (17.2 g, 0.1 mol) was dissolved in acetone (50 ml), and 25–28% aqueous ammonia (15 ml) was added slowly under stirring in a water bath to avoid a rise in temperature. The reaction mixture was stirred for 30 min at room temperature, during which the yellow precipitate was deposited which was filtered off and dried at 40°C. Yield 13.5 g (95%). Yellow powder. Mp 301.5–302.5°C (mp 301–303°C[13]). IR spectrum, ν, cm^{-1}: 3444 (–NH_2), 3066 (=C–H), 1645 (–NH_2), 1550 (C–NO_2), 1409 (C=C), 1373 (–CH_3), 1325 (C–NO_2), 1234 (C–NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.55 (2H, s, NH_2); 7.24 (1H, s, H-2); 3.43 (3H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 30.0 (CH_3); 126.7 (C-2); 133.9 (C-4); 141.6 (C-5). Found, %: C 33.68; H 4.32; N 39.24. $C_4H_6N_4O_2$. Calculated, %: C 33.81; H 4.26; N 39.42.

4-Amino-1-methyl-5-nitroimidazole (6). The filtrate of the above-mentioned reaction mixture was extracted with ethyl acetate (5×50 ml). The extracts were combined, washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Yield 0.42 g (3%). Pale-yellow powder. Mp 153.8–155.5°C (mp 157–160°C[25]). IR spectrum, ν, cm^{-1}: 3456 (–NH_2), 3100 (=C–H), 1630 (–NH_2), 1530 (C–NO_2), 1452 (–CH_3), 1404 (C=C), 1365 (–CH_3), 1304 (C–NO_2), 1232 (C–NH_2). ^{1}H NMR spectrum ($(CD_3)_2CO$), δ, ppm: 7.53 (1H, s, H-2); 6.74 (2H, s, NH_2); 3.88 (3H, s, CH_3). ^{13}C NMR spectrum ($(CD_3)_2CO$), δ, ppm: 35.8 (CH_3); 120.4 (C-5); 137.8 (C-2); 148.3 (C-4). Found, %: C 33.74; H 4.24; N 39.37. $C_4H_6N_4O_2$. Calculated, %: C 33.81; H 4.26; N 39.42.

5-Azido-1-methyl-4-nitroimidazole (5). A mixture of MDNI (**1**) (3.44 g, 0.02 mol), NaN_3 (1.95 g, 0.03 mol), and acetone (30 ml) was stirred at room temperature for 20 min. Then the precipitate that formed was filtered off, washed with water, and dried in vacuum. Yield 3.29 g (98%). Yellow powder. Mp 108.3–110°C (mp 108–110°C[16]). IR spectrum, ν, cm^{-1}: 2143 (–N_3), 1550 (C–NO_2), 1428 (–CH_3), 1410 (C=C), 1382 (C–NO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.61 (1H, s, H-2); 3.48 (3H, s, CH_3). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 30.8 (CH_3); 136.6 (C-2); 137.9 (C-5); 139.9 (C-4). Found, %: C 28.32; H 2.36; N 49.89. $C_4H_4N_6O_2$. Calculated, %: C 28.58; H 2.40; N 49.99.

X-ray structural investigation of 4-amino-1-methyl-5-nitroimidazole (6). Single crystals were grown from acetone solution by solvent evaporation method at ambient temperature. X-ray diffraction data were collected on an Agilent Xcalibur & Gemini diffractometer equipped with graphite monochromator; MoKα radiation (λ 0.07107 nm). The structure was solved by the direct methods (SHELXL-97 software)[29] and refined by the full-matrix-block least-squares method on F^2 with anisotropic thermal parameters for all non-hydrogen atoms (OLEX2 software).[30] The hydrogen atoms were added according to the theoretical models. The complete crystallographic data set was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1851350).

Supplementary information file containing crystallographic data of compound **6** is available at the journal website at http://link.springer.com/journal/10593.

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References

1. Breccia, A.; Cavalleri, B.; Adams, G. E. *Nitroimidazoles*: *Chemistry*, *Pharmacology and Clinical Applications*; Plenum Press: New York, 1982.
2. Nair, M. D.; Nagarajan, K. *Prog. Drug Res.* **1983**, *27*, 163.
3. Crozet, M. D.; Remusat, V.; Curti, C.; Vanelle, P. *Synth. Commun.* **2006**, *36*, 3639.
4. Larina, L.; Lopyrev, V. *Nitroazoles*: *Synthesis*, *Structure and Application*; Springer: New York, 2009.
5. Bulusu, S.; Damavarapu, R.; Autera, J. R.; Behrens, R.; Minier, L. M.; Villanueva, J.; Jayasuriya, K.; Axenrod, T. *J. Phys. Chem.* **1995**, *99*, 5009.
6. Rice, B. M.; Hare, J. J. *J. Phys. Chem. A* **2002**, *106*, 1770.
7. Cho, S. G.; Park, B. S. *J. Quantum Chem.* **1999**, *72*, 145.
8. Cho, J. R.; Kim, K. J.; Cho, S. G.; Kim, J. K. *J. Heterocycl. Chem.* **2002**, *39*, 141.
9. Novikov, S. S.; Khmel'nitskii, L. I.; Lebedev, O. V.; Sevast'yanova, V. V.; Epishina, L.V. *Chem. Heterocycl. Compd.* **1970**, *6*, 465. [*Khim. Geterotsikl. Soedin.* **1970**, 503.]
10. Novikov, S. S.; Khmel'nitskii, L. I.; Lebedev, O. V.; Epishina, L. V.; Sevost'yanova, V. V. *Chem. Heterocycl. Compd.* **1970**, *6*, 614. [*Khim. Geterotsikl. Soedin.* **1970**, 664.]
11. Katritzky, A. R.; Cundy, D. J.; Chen, J. *J. Energ. Mater.* **1993**, *11*, 345.
12. Gao, H. X.; Ye, C. F.; Gupta, O. D.; Xiao, J. C.; Hiskey, M. A.; Twamley, B.; Shreeve, J. M. *Chem.–Eur. J.* **2007**, *13*, 3853.
13. Suwinski, J.; Salwinska, E.; Watras, J.; Widel, M. *Polish J. Chem.* **1982**, *56*, 1261.
14. Koehler, H.; Dockner, T. US Patent 4900825.
15. Zaprutko, L.; Żwawiak, J.; Olender, D.; Gzella, A. *Heterocycles* **2012**, *85*, 2197.
16. Efimov, I.; Beliaev, N.; Beryozkina, T.; Slepukhin, P.; Bakulev, V. *Tetrahedron Lett.* **2016**, *57*, 1949.
17. Balaban, I. E. *J. Chem. Soc.* **1930**, 268.
18. Mąkosza, M.; Bialecki, M. *J. Org. Chem.* **1998**, *63*, 4878.
19. Vokin, A. I.; Shulunova, A. M.; Krivoruchka, I. G.; Krylova, O. V.; Lopyrev, V. A.; Turchaninov, V. K. *Russ. J. Gen. Chem.* **2002**, *72*, 449. [*Zh. Obshch. Khim.* **2002**, *72*, 483.]
20. Donskaya, O. V.; Elokhina, V. N.; Nakhmanovich, A. S.; Vakul'skaya, T. I.; Larina, L. I.; Vokin, A. I.; Albanov, A. I.; Lopyrev, V. A. *Tetrahedron Lett.* **2002**, *43*, 6613.
21. Koehler, H.; Dockner, T. EP Patent 0337255; *Chem. Abstr.* **1990**, *112*, 235295v.
22. Shen, F. F.; Lian, P. B.; Chen, L. Z.; Wang, J. L.; Cao, D. L. CN Patent 106995412.
23. Mukherjee, A.; Kumar, S.; Seth, M.; Bhadur, A. P. *Indian J. Chem.*, *Sect. B: Org. Chem. Incl. Med. Chem.* **1989**, *28*, 391.
24. Taher, A.; Eichenseher, S.; Slawin, A. M. Z.; Tennant, G.; Weaver, G. W. *J. Chem. Soc.*, *Perkin Trans. 1* **2002**, 1968.
25. Olender, D.; Żwawiak, J.; Zaprutko, L. *J. Heterocycl. Chem.* **2010**, *47*, 1049.
26. Li, Y.-X.; Wang, X.-J.; Wang, J.-L. *Acta Crystallogr.*, *Sect. E: Struct. Rep. Online* **2009**, *E65*, o3073.
27. Luo, J.; Liu, Y.-C.; Liu, Y.; Chai, T. *Chem. Heterocycl. Compd.* **2017**, *53*, 693. [*Khim. Geterotsikl. Soedin.* **2017**, *53*, 693.]
28. Cao, D. L.; Wang, X. J.; Yang, C. Y.; Song, L.; Han, H.; Zhou, J. F.; Chang, J. F. *Chin. J. Energ. Mater.* **2009**, *17*, 678.
29. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. A*: *Found. Crystallogr.* **2008**, *A64*, 112.
30. Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Crystallogr.* **2009**, *42*, 339.