# Nitration Studies on 2-Isopropylimidazole

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The nitration of 2-isopropylimidazole has been studied under a variety of conditions involving nitration of the unprotonated imidazole, the imidazole anion, or an imidazole radical. From the reaction of nitronium tetrafluoroborate with 1-trimethylsilyl-2-isopropylimidazole there was isolated a dinitro compound the structure of which was shown by X-ray crystallography to be 1,4-dinitro-2-isopropylimidazole.

On a étudié la nitration de 2-isopropylimidazole sous des conditions diverses y comprenant la nitration de l'imidazole non protoné, l'anion de l'imidazole ou un radical de l'imidazole. De la réaction entre le tétrafluoroborate de nitronium et le 1-triméthylsilyl-2-isopropylimidazole on a isolé un composé dinitro dont la structure s'est montrée d'être le 1,4-dinitro-2-isopropylimidazole avec l'aide de la cristallographie par rayons X.

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In the course of preparing the potent histomonostat (1, 2) and trichomonacide (3) 1-methyl-2-isopropyl-5-nitroimidazole,[2] we found it necessary to study alternate methods of nitrating the intermediate 2-isopropylimidazole, since the standard nitration procedure (4, 5) for 2-substituted imidazoles using a mixture of nitric and sulfuric acids gave only about 50% of the desired 2-isopropyl-4(5)-nitroimidazole. Nitration in the presence of mercuric chloride (6) gave slight improvement. Addition of sulfur trioxide to the nitrating mixture gave inferior results, in contrast to the improvement reported for the nitration of imidazole (7).

To augment these studies three alternate methods of nitrating 2-isopropylimidazole were attempted: (*a*) nitration of unprotonated imidazole derivative, (*b*) nitration of an imidazole anion, and (*c*) nitration of an imidazolium radical.

Katritzky and others (8, 9) have demonstrated that basic pyridines ($pK_a > +1$) are first protonated and then slowly nitrated, while weakly basic pyridines ($pK_a < -2.5$) undergo nitration under mild conditions as free bases. Thus, the difficulty in nitrating 2-substituted imidazoles with nitric–sulfuric acid mixtures might be ascribed to the fact that the protonated species is being nitrated (7).[3]

A procedure in which unprotonated basic nitrogen heterocycles may be nitrated was reported by Olah (11) who found that nitronium tetrafluoroborate nitrates aromatic compounds in solvents such as sulfolane and acetonitrile. However, a possible complicating feature when aromatic heterocycles are nitrated could be the occurrence of C or N nitration. Indeed, Olah and co-workers (12) found that nitronium tetrafluoroborate reacts with pyridine to form the *N*-nitro salt. Other pyridines and a quinoline have shown similar behavior (13).

Nitration of 2-isopropylimidazole with nitronium tetrafluoroborate gave crude 4(5)-nitro-2-isopropylimidazole in 49% yield (31% after recrystallization). Two reasonable mechanisms for this reaction are shown in Schemes 1 and 2.

These mechanisms suggest likely reasons for the low yield of **2**. The *N*-nitro intermediate (like *N*-nitropyridine) (12) may not undergo N to C rearrangement of the nitro group (14) or at least not completely. Ring opening of the *N*-nitro salt would also lead to reduced yields of **2**. Incidentally, a stable *N*-nitro salt could not be isolated from the reaction.

Another possible cause for the low yield of **2**, namely further reaction of this compound with nitronium tetrafluoroborate, is ruled out because **2** may be recovered in good yield after exposure to the nitration conditions.

Both Schemes 1 and 2 involve the formation of fluoroboric acid (or its salt with **2**). If 2-isopropylimidazole reacts with fluoroboric acid instead of nitronium tetrafluoroborate, the

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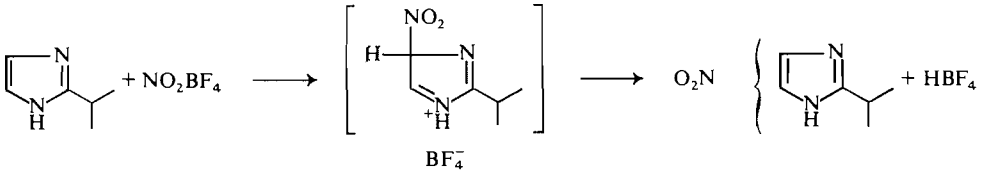
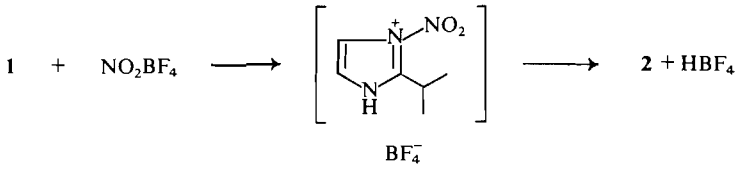
[3]The $pK_a$ in water of 2-ethylimidazole is 8 (10).

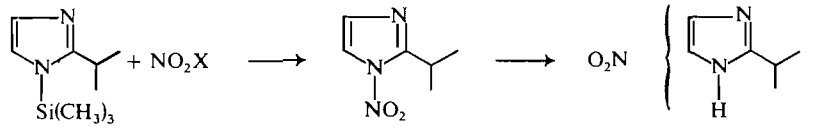


1 2

SCHEME 1

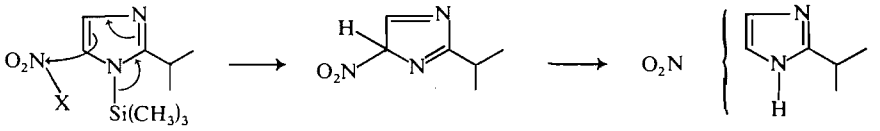


SCHEME 2



3 2

SCHEME 3



2

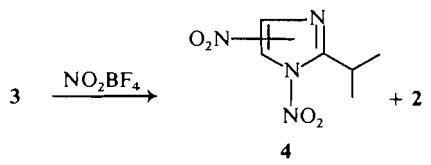
SCHEME 4

resulting salt might be stable to the reaction conditions. In this event, some 2-isopropylimidazole would be recovered on work-up, and this was indeed observed.

To avoid the formation of an unreactive 2-isopropylimidazolium salt in the nitration of 2-isopropylimidazole, a derivative which might undergo nitration without loss of a proton was investigated. 1-Trimethylsilyl-2-isopropylimidazole (**3**) might react with a $NO_2^+$ source according to Schemes 3 or 4. Scheme 3 is analogous to conversion of 1-trimethylsilylimidazole into 1-acetylimidazole (15), *N*,*N*′-thiocarbonyldiimidazole (16), and *N*,*N*′-imidazolesulfide (17) with acetyl chloride, thiophosgene, and sulfur dichloride, respectively. Scheme 4 is analogous to the formation of 1-acetyl-1,2,3-triazole from 2-trimethylsilyl-1,2,3-triazole and acetyl chloride (18). Unfortunately **2** was not obtained on treatment of 1-trimethylsilyl-2-isopropylimidazole with nitryl chloride.[4] The silyl compound **3**, however, afforded a mixture of **2** and a dinitro compound on reaction with nitronium tetrafluoroborate. The spectral data and elemental analysis for the dinitro compound are consistent with structure **4** (Scheme 5).

The u.v. or n.m.r. spectrum (20) of this compound does not unambiguously support one isomer (either **4***a* or **4***b*) over the other. Chemical support for the gross structure was obtained in two ways. Nitrolysis (21) of **4** in concentrated sulfuric acid gave **2**, and catalytic hydrogena-

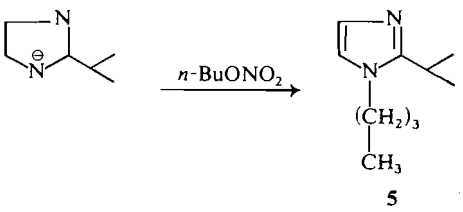
[4]Nitryl chloride, which may be in equilibrium with nitrogen dioxide and chlorine (19*a*, *b*) has been pictured as a source of free radicals (19*a*, *c*, *d*), chloronium ions (19*d*), and nitronium ions (19*c*).




4

**a** = 4-$NO_2$
**b** = 5-$NO_2$

SCHEME 5




5

SCHEME 6

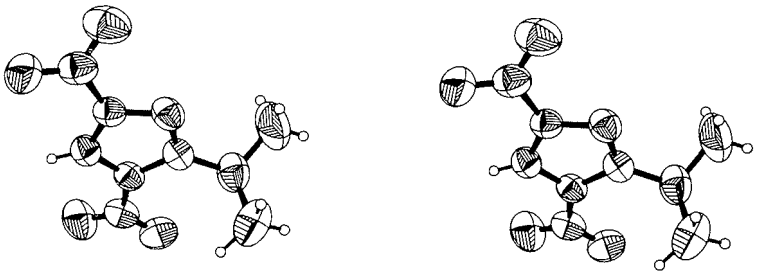


FIG. 1. Stereoscopic view of **4***a*.

tion in acetic anhydride (20*a*, 22) afforded a diacetate which was identical with that prepared by catalytic hydrogenation of **2** in acetic anhydride.

During the progress of this work a report appeared (23) which described the formation of 2-methyl-1 (4 or 5)-dinitroimidazole in high yield from the nitration of 2-methylimidazole with nitric acid in the presence of acetic anhydride. The exact position of the *C*-nitro group could not be determined. Application of these nitration conditions to **1** produced **4** in good yield. With sufficient material now easily available, crystals suitable for an X-ray analysis could be obtained, and the structure was shown to be 2-isopropyl-1,4-dinitroimidazole (**4***a*). (see Fig. 1).

Nitration of 2-isopropylimidazole anion (24) was then investigated. Sodium hydride converted 2-isopropylimidazole into the corresponding sodium salt, and the reaction of this salt with *n*-butyl nitrate in tetrahydrofuran gave only 1-*n*-butyl-2-isopropylimidazole (**5**) (Scheme 6).[5] This material was identical with the compound prepared from *n*-butyl iodide and the sodium salt of 2-isopropylimidazole.

[5]Solvolysis of nitrates has been shown to involve displacement on carbon, displacement on nitrogen, β-hydrogen elimination giving an olefin and α-hydrogen elimination giving a carbonyl compound (25).

For attempted nitration of an imidazole radical,[6] sodium 2-isopropylimidazole was reacted with tetranitromethane (28, 29), but no isolable **2** was formed. Also, decomposition of pernitrous acid (30) in the presence of 2-isopropylimidazole resulted only in the recovery of starting material.

## Experimental

All melting points were taken on a Thomas–Hoover capillary melting point apparatus, and are uncorrected. All elemental analyses were performed on samples which were recrystallized an additional time.

*Nitration of 2-Isopropylimidazole (1)*

*(A) Using Nitronium Tetrafluoroborate*

To a stirred slurry of nitronium tetrafluoroborate (32) (3.03 g, 0.022 mol) and dried, distilled acetonitrile (6 ml) cooled in an ice bath, a solution of 2-isopropylimidazole (2.02 g, 0.018 mol) in dried, distilled acetonitrile (30 ml) was added dropwise. Stirring and cooling were continued for 30 min after completion of the addition. The solution was then concentrated on a rotary evaporator and added to aqueous sodium bicarbonate solution without delay. The aqueous solution was extracted with chloroform and the extract dried (anhydrous $Na_2SO_4$) and concentrated to dryness, giving an orange–brown solid (1.38 g, 49%). This material was dissolved in benzene–chloroform, washed through an alumina (5 g) column, and recrystallized from water to give a total of 0.86 g (31%) of **2** in two crops, m.p. 182–183.5° (lit. (3, 31) m.p. 180°).

[6]Unfortunately, very little is known about the reactivity of imidazoles towards radicals (26, 27).

*(B) Using $HNO_3$–$Ac_2O$*

To a solution of 4.0 g of **1** in 115 ml of glacial acetic acid was added 26.4 ml of concentrated nitric acid and then 71.2 ml of acetic anhydride was added slowly over a period of 35–40 min while maintaining the temperature at 20–22°. After being stirred at this temperature for an additional hour, the mixture was added to 200 ml of water at 17–20°, stirred for 15 min, and extracted with methylene chloride. The extracts were washed with sodium bicarbonate solution, then with saturated salt solution, and dried over sodium sulfate. Evaporation of the solvent gave 2.8 g of crude **4***a*. Crystallization from ether–hexane gave 2.2 g (44%), m.p. 79–80°, identical (i.r., u.v., n.m.r.) with material obtained by nitration of **3** (see below).

*Nitration ($NO_2BF_4$) of 1-Trimethylsilyl-2-isopropylimidazole (**3**)*

A solution of 1-trimethylsilyl-2-isopropylimidazole (**3**) (prepared from 2-isopropylimidazole (1.00 g, 9.1 mmol) and hexamethyldisilazane (4.00 g, 31.0 mmol) in acetonitrile (10 ml)) was added dropwise to a stirred slurry of nitronium tetrafluoroborate (1.265 g, 9.5 mmol) and acetonitrile (5 ml) cooled in an ice bath. The solution was stirred for 30 min with ice cooling and benzene (2 ml) was added. It was concentrated on a rotary evaporator, neutralized with aqueous sodium bicarbonate, and extracted with chloroform. These extracts were dried ($Na_2SO_4$) and concentrated to an orange oil (1.07 g). A sample (150 mg) of this material was chromatographed on a layer of silica gel and eluted with a 4:5 acetone:cyclohexane mixture. Two bands separated from material at the origin and were extracted from the silica gel. Band 1 gave 25 mg of dinitro compound **4***a* (10%). Band 2 gave 36 mg of **2** (18%). Recrystallization of band 1 material from ether–hexane gave **4***a*, m.p. 76–77°.

Anal. Calcd. for $C_6H_8N_4O_4$: C, 36.00; H, 4.03; N, 27.99. Found: C, 35.78; H, 3.99; N, 27.71.

Recrystallization of band 2 material from acetonitrile gave **2**, m.p. 181–183°, identical (i.r., t.l.c., mixed m.p.) with an authentic sample.

*Sulfuric Acid Treatment of **4a***

A sample of **4***a* (41 mg, 0.26 mmol) was dissolved in concentrated sulfuric acid (8 drops). After standing 5 h at room temperature the solution was cooled, neutralized with aqueous sodium bicarbonate solution, and the p*H* adjusted to 2 with 1 *N* hydrochloric acid. This mixture was extracted with chloroform, the aqueous phase adjusted to p*H* 5 and again extracted with chloroform. The chloroform extracts were combined, dried ($Na_2SO_4$) and concentrated to dryness to give a solid (28.8 mg). This material was purified by t.l.c. to give a solid (28.5 mg, 72%) which was recrystallized from water to give 14 mg (36%) m.p. 181–182.5°, identical with **2** (mixed m.p., t.l.c., i.r.).

*Reaction of Sodium 2-Isopropylimidazole with n-Butyl Nitrate*

Sodium hydride (2.42 g, 54.5%) mineral oil dispersion, 0.055 mol) was added in small portions to a stirring solution of 2-isopropylimidazole (5.50 g, 0.050 mol) in anhydrous tetrahydrofuran (30 ml) under a nitrogen atmosphere. After stirring the reaction mixture for 2 h a solution of *n*-butyl nitrate (33) (5.95 g, 0.050 mol) in dry tetrahydrofuran (5 ml) was added dropwise and stirring was continued overnight. The reaction mixture was poured into water and the two phases separated. The aqueous solution was extracted with three 100 ml portions of chloroform. The water-insoluble phase was dissolved in chloroform and extracted with two 50 ml portions of dilute aqueous hydrochloric acid. The acidic aqueous solution was brought to p*H* 10 with concentrated ammonia and extracted with three 100 ml portions of chloroform. These chloroform extracts and those previously obtained were combined, dried ($Na_2SO_4$) and concentrated to a yellow oil which was distilled. A fraction distilling at 65–80° (1 mm) was collected (2.67 g, 32%). This material formed a picrate, m.p. 130.5–132°.

Anal. Calcd. for $C_{16}H_{21}N_5O_7$: C, 48.61; H, 5.32; N, 17.72. Found: C, 48.84; H, 5.49, N, 17.91.

*Reaction of Sodium 2-Isopropylimidazole with n-Butyl Iodide*

Sodium hydride (4.84 g, 54.5% mineral oil dispersion, 0.110 mol) was added portionwise to a stirred solution of 2-isopropylimidazole (11.0 g, 0.10 mol) in dry tetrahydrofuran (100 ml) under a nitrogen atmosphere. After stirring the reaction mixture for 3 h at room temperature, *n*-butyl iodide (18.0 g) was added dropwise. The reaction mixture was stirred overnight and then diluted with ether and filtered through Celite. The filtrate was concentrated to an oil. A sample of this oil was converted to a picrate, m.p. 131–132°, identical with material prepared from *n*-butyl nitrate.

Anal. Calcd. for $C_{16}H_{21}N_5O_7$: C, 48.61; H, 5.32; N, 17.72. Found: C, 48.58; H, 5.48; N, 17.89.

The remaining oil was distilled to give a fraction, b.p. 47–74° (0.7 mm); 8.7 g (52%).

*Crystallography*

The crystal data for **4***a* are:

$C_6H_8N_4O_4$ f.w. = 200.15

Monoclinic. $P2_1/c$, $a = 15.488(5)$, $b = 6.072(3)$, $c = 10.030(5)$ Å, $\beta = 99.35(3)°$, $V = 930.7$ Å$^3$, $\rho_o = 1.34(3)$, $Z = 4$, $\rho_c = 1.428$ g cm$^{-3}$ (21 °C, CuK$\alpha$, $\lambda = 1.5418$ Å).

The intensity data were measured on a Hilger–Watts model Y290 four circle diffractometer by a moving crystal-moving detector method. Nickel filtered CuK$\alpha$ radiation and pulse height discrimination were used. Of the 1749 accessible reflections in the unique quadrant ($2\theta < 140°$), 1000 had intensities significantly greater than background. The crystal was approximately $0.05 \times 0.2 \times 0.5$ mm.

The structure was solved by straightforward application of the symbolic addition method (34). All of the heavier atoms were located from the first *E*-map except for the three isopropyl carbon atoms, which were found in the subsequent electron density map. The hydrogen atoms were located from a difference Fourier calculated after refinement of the heavier atoms. Full matrix least squares refinement was continued with isotropic temperature factors for the hydrogens and anisotropic temperature factors for the other atoms until the shifts in all parameters were less than 1/6 of their respective standard deviations. A difference Fourier based on the final parameters has no features greater than 0.1 *e* Å$^{-3}$ in magnitude. The final $R = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.044$ for the 1000 observed data.

The function minimized in the least squares refinement was $\Sigma w||F_o|-|F_c||^2$ where $w = 1/(3.2 + |F_o| + 0.019|F_o|^2)$ for the observed data and $w = 0$ for the unobserved data.

TABLE 1. Final parameters (e.s.d.'s) × $10^4$
T.F. (iso) = $\exp[-B\sin^2\theta/\lambda^2]$
T.F. (aniso) = $\exp[-(h^2\beta11 + k^2\beta22 + l^2\beta33 + \beta hk\beta12 + 2hl\beta13 + 2k\beta23)]$

| Atom | $x$ | $y$ | $z$ | $B \times 10$ or $\beta11$ | $\beta22$ | $\beta33$ | $\beta12$ | $\beta13$ | $\beta23$ |
|---|---|---|---|---|---|---|---|---|---|
| N(1) | 1783(2) | −6310(4) | −1661(3) | 53(1) | 280(8) | 109(3) | −14(3) | 12(1) | −21(4) |
| C(2) | 2573(2) | −5168(6) | −1459(3) | 52(2) | 355(11) | 119(4) | −17(3) | 13(2) | 4(5) |
| N(3) | 2476(2) | −3370(4) | −787(3) | 56(1) | 339(9) | 127(4) | −24(3) | 18(2) | −26(4) |
| C(4) | 1632(2) | −3396(5) | −556(3) | 55(1) | 282(9) | 101(4) | 1(3) | 14(2) | 6(4) |
| C(5) | 1180(2) | −5172(6) | −1079(3) | 48(1) | 344(10) | 109(4) | −8(3) | 8(2) | 19(5) |
| N(2) | 1558(2) | −8288(5) | −2402(3) | 74(2) | 337(10) | 116(4) | −18(4) | 9(2) | −11(4) |
| O(1) | 2142(2) | −9246(4) | −2800(3) | 91(2) | 384(9) | 153(4) | 23(3) | 12(2) | −52(4) |
| O(2) | 0801(2) | −8788(5) | −2557(3) | 75(2) | 566(12) | 214(5) | −75(4) | 12(2) | −104(6) |
| N(4) | 1302(2) | −1676(5) | 205(3) | 77(2) | 315(9) | 112(4) | 12(3) | 23(2) | 21(4) |
| O(3) | 1755(2) | −25(5) | 464(3) | 106(2) | 363(8) | 154(4) | −25(3) | 34(2) | −49(4) |
| O(4) | 591(2) | −1944(5) | 539(3) | 80(2) | 464(10) | 207(4) | 33(3) | 61(2) | 28(5) |
| C(6) | 3410(3) | −5904(8) | −1887(5) | 61(2) | 532(17) | 171(6) | −15(5) | 37(3) | −46(9) |
| C(7) | 3956(6) | −3887(16) | −2109(13) | 77(3) | 790(35) | 377(17) | −54(10) | 92(7) | −22(23) |
| C(8) | 3868(4) | −7530(14) | −820(8) | 68(3) | 727(29) | 274(11) | 60(8) | 27(5) | −20(14) |
| H(5) | 630(30) | −5620(70) | −1100(40) | 66(10) | | | | | |
| H(6) | 3280(30) | −6630(70) | −2700(50) | 72(11) | | | | | |
| H(7)A | 4440(50) | −4260(110) | −2230(70) | 117(19) | | | | | |
| H(7)B | 3690(50) | −2980(140) | −2710(80) | 143(35) | | | | | |
| H(7)C | 4090(40) | −3000(100) | −1290(60) | 105(21) | | | | | |
| H(8)A | 4020(40) | −6450(110) | −90(60) | 119(21) | | | | | |
| H(8)B | 4340(50) | −7900(100) | −1170(60) | 119(19) | | | | | |
| H(8)C | 3430(50) | −8810(110) | −750(70) | 134(22) | | | | | |

TABLE 2. Bond lengths (Å) in **4***a* with standard deviations in parentheses

| Bond | Length | Bond | Length |
|---|---|---|---|
| N(1)—C(2) | 1.392(4) | N(2)—O(2) | 1.195(4) |
| C(2)—N(3) | 1.305(4) | C(4)—N(4) | 1.435(4) |
| N(3)—C(4) | 1.365(4) | N(4)—O(3) | 1.227(4) |
| C(4)—C(5) | 1.344(5) | N(4)—O(4) | 1.214(4) |
| C(5)—N(1) | 1.367(4) | C(2)—C(6) | 1.497(5) |
| N(1)—N(2) | 1.426(4) | C(6)—C(7) | 1.526(8) |
| N(2)—O(1) | 1.198(4) | C(7)—C(8) | 1.542(8) |

TABLE 3. Bond angles (degrees) in **4***a* with standard deviations in parentheses

| Bond | Angle |
|---|---|
| C(5)—N(1)—C(2) | 109.4(3) |
| N(1)—C(2)—N(3) | 108.6(3) |
| C(2)—N(3)—C(4) | 105.8(3) |
| N(3)—C(4)—C(5) | 113.3(3) |
| C(4)—C(5)—N(1) | 103.0(3) |
| N(2)—N(1)—C(2) | 129.1(3) |
| N(2)—N(1)—C(5) | 121.4(3) |
| O(1)—N(2)—O(2) | 127.7(3) |
| O(1)—N(2)—N(1) | 116.6(3) |
| O(2)—N(2)—N(1) | 115.7(3) |
| N(4)—C(4)—N(3) | 121.0(3) |
| N(4)—C(4)—C(5) | 125.8(3) |
| O(3)—N(4)—O(4) | 124.4(3) |
| O(3)—N(4)—C(4) | 117.8(3) |
| O(4)—N(4)—C(4) | 117.8(3) |
| C(6)—C(2)—N(1) | 126.2(3) |
| C(6)—C(2)—N(3) | 125.2(3) |
| C(7)—C(6)—C(8) | 114.3(7) |
| C(7)—C(6)—C(2) | 109.2(5) |
| C(8)—C(6)—C(2) | 108.4(5) |

The refinement calculations were made with a local modification of the program ORFLS (35). Standard atomic scattering curves were used for O, C, N (36), and H (37).

The final atomic parameters and their estimated standard deviations are listed in Table 1. Tables 2 and 3 contain the bond lengths and bond angles for the non-hydrogen atoms. A table of the final $F_o$ and $F_c$ values has been placed in the Depository for Unpublished Data.[7]

The imidazole ring is planar to within ±0.005 Å. The 1-nitro nitrogen (N(2) is displaced 0.07 Å from the plane of the ring while N(4) and C(6) lie 0.04 and 0.06 Å, respectively, out of the plane on the opposite side from N(2). The nitro groups are both twisted slightly from the plane of the imidazole ring. The dihedral angles between the plane of the ring and the 1-nitro (N(2), O(1), O(2)) and 4-nitro (N(4), O(3), O(4)) groups are 7.3 and 10.0°, respectively.

[7]These data are available upon request from the Depository for Unpublished Data, National Science Library, National Research Council of Canada, Ottawa K1A 0S2, Canada.

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