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Original article

Synthesis and anti-tuberculosis activity of *N*-aryl-*C*-nitroazoles

Krzysztof Walczak, Andrzej Gondela, Jerzy Suwiński *

Department of Organic Chemistry, Biochemistry and Biotechnology, Silesian University of Technology, Krzywoustego 4, 44-100 Gliwice, Poland

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Abstract

Twelve *N*-aryl derivatives of 4-nitroimidazole, 2-methyl-4-nitroimidazole, 4-nitropyrazole or 3-nitro-1,2,4-triazole have been synthesized either by a degenerated ring transformation reaction of 1,4-dinitroimidazoles with 4-substituted anilines or by a condensation of fluoronitrobenzenes with salts prepared from *C*-nitro-1*H*-azoles and 1,8-diazabicyclo[5.4.0]-7-undecene. The Tuberculosis Antimicrobial Acquisition and Coordinating Facility has provided anti-mycobacterial data concerning inhibition activity of 12 compounds.

Keywords: Arylnitroazoles; Synthesis; Tuberculosis inhibition

1. Introduction

The recent substantial increase in tuberculosis incidence throughout the world is caused, in many cases, by the drug-resistant *Mycobacterium tuberculosis*. The anti-tubercular strategies based on isoniazid, pyrazin amide, ethambutol, rifampicin and streptomycin are very often insufficient [1]. This is the major problem in curing tuberculosis in HIV-infected patients what causes an urgent need for new active agents. A special interest has been focussed on five membered heterocyclic compounds used very often in the pharmacological and medicinal applications. The anti-tuberculosis activity of pyrrole [2–4], oxadiazole [5], imidazole [6,7], triazole [8–11] and other heterocyclic systems [12–14] derivatives has been reported. Several of the tested derivatives have shown promising properties. Nevertheless, none of the compounds screened as *Mycobacterium tuberculosis* inhibitors belonged to *N*-aryl-*C*-nitroazoles, thus to a group of compounds synthesized and screened during this work.

2. Chemistry

For a long time *N*-aryl derivatives of *C*-nitro-1*H*-azoles have been scarcely known due to serious limitations of methods potentially useful in the compounds preparation. The first approach involved nitration of 1-arylazoles. Carbon atoms of azole rings are less susceptible to electrophiles than those of benzene. Thus, during nitration of 1-phenylazoles, nitronium cation is attacking preferably benzene to azole's rings [15]. The second approach involved nucleophilic substitution of chlorine or fluorine atom in benzene derivatives by nitroazoles. Low nucleophilicity of *C*-nitro-1*H*-azoles and poor solubility of their Na or K-salts limited the latter method to the syntheses of *N*-(2,4-dinitro- or 4-nitrophenyl)-*C*-nitroazoles. Additionally, yields of the obtained products, at least according to known procedures, are low and purification of the derivatives is troublesome [16,17]. We have elaborated general methods for the preparation of 1-aryl-4-nitroimidazoles [18,19] and of 1-aryl-4-nitropyrazoles [20]. Both methods involve degenerated ring transformation (*anrorc*) in reactions of 1,4-dinitroimidazoles or 1,4-dinitropyrazoles with anilines or phenylhydrazines, respectively. A detailed *anrorc* mechanism of the formation of 1-substituted 4-nitroimidazoles has been established [18,19,21]. The method can be successfully applied to the synthesis of 1-aryl-4-nitroazoles containing electron-donating or relatively week electron-withdrawing substitu-

* Corresponding author. Tel.: +48-32-2371839; fax: +48-32-2371549.
E-mail address: suwinski@polsl.gliwice.pl (J. Suwiński).

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ents like OH, OR, R, Cl, Br, COOR etc in aryl group [18,20]. The reactions occur under very mild conditions in aqueous methanol and usually at ambient temperature affording 1-aryl-4-nitroazoles in high yields [18,20]. Very weak nucleophiles (e.g. 2,4-dinitroaniline or 2,4-dinitrophenylhydrazine) do not react with 1,4-dinitroazoles.

In order to introduce 2,4-dinitrophenyl or 4-nitrophenyl substituent on the pyrrole type nitrogen atom in *C*-nitro-1*H*-azoles we used a reaction of 1-fluoro-2,4-dinitro- or 1-fluoro-4-nitrobenzene accordingly with nitroazole-1,8-diazabicyclo[5.4.0]-7-undecenium salts [22,23]. This method, being a modification of a known approach [16], provided the desired pure derivatives in high yields.

3. Biological tests

Biological primary in vitro tests against *Mycobacterium tuberculosis* H_{37}Rv (ATCC 27294) for 12 *N*-aryl-*C*-nitroazoles at concentrations of 6.25 μg/ml were carried out in Southern Research Institute in BACTEC 12 B medium, using a broth micro dilution assay, the Micro plate Alamar Blue Assay (MABA). Data from the primary assay (level 1) revealed four active compounds (effecting >90% inhibition). Afterwards they have been tested in minimum inhibitory concentration (MIC) assay (level 2). Three of them, namely **3c, 8e** and **g** were also tested at level 2 in cytotoxicity (IC_{50}) assays. MIC and IC_{50} values for those three 1-aryl-nitroazoles to VERO cell line in culture media were determined and selectivity indexes (SI = MIC/IC_{50}) were calculated. The Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) provided all biological data through a research and development contract with the US National Institute of Allergy and Infectious Diseases.

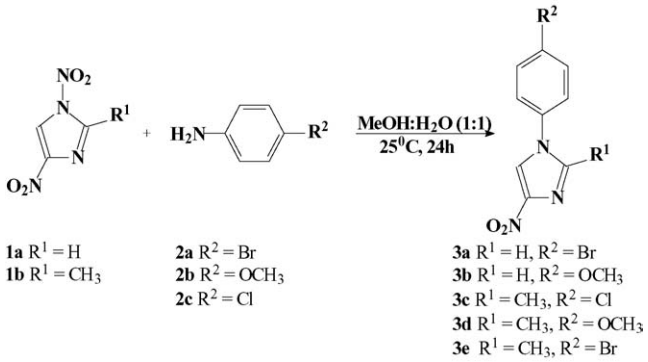
4. Results and discussion

Five 1-aryl-4-nitroimidazoles were obtained by the *anrorc* reaction. Treatment of 1,4-dinitroimidazole **(1a)** with 4-bromoaniline (**2a**) or 4-methoxyaniline (**2b**) in aqueous methanol at 25 °C for 24 h afforded 1-(4-bromophenyl)-4-nitroimidazole (**3a**) and 1-(4-methoxyphenyl)-4-nitroimidazole (**3b**), respectively. A similar treatment of 2-methyl-1,4-dinitroimidazole (**1b**) with **2a,b** or 4-chloroaniline (**2c**) gave appropriate 1-(4-substituted)-2-methyl-4-nitroimidazoles (Scheme 1). After a single crystallization analytically pure products were obtained in yields exceeding 75%.

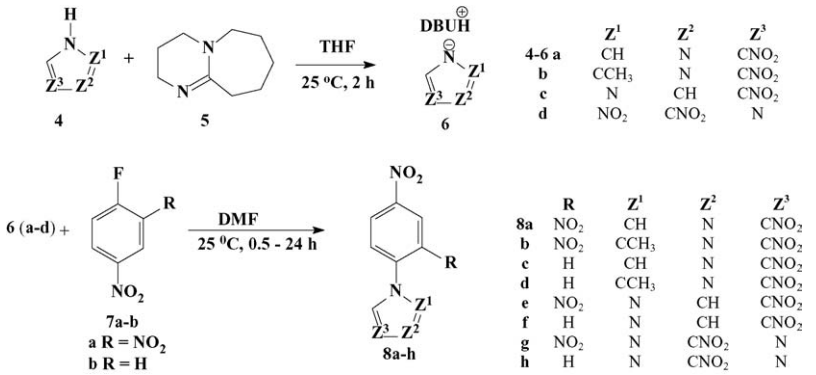
Eight 2,4-dinitrophenyl- or 4-nitrophenyl derivatives of 4-nitroimidazole (**4a–b**), 4-nitropyrazole (**4c**) and of 3-nitro-1,2,4-triazole (**4d**) were obtained by a two-step synthesis. At first suspensions of **4a–d** in tetrahydrofuran were treated with equimolar amounts of 1,8-diazabicyclo[5.4.0]-7-undecene (**5**) at about 25 °C for 2 h. On cooling the reaction mixtures deposited solids of the forming salts **6**. The salts were collected, rinsed with *n*-pentane and dried to give **6a–d**, ready for the use in a next step.

Dry salts **6a–d** were dissolved in dimethylformamide and treated with fluoronitrobenzenes **7a–b** at 25 °C for 24 h. The reaction mixtures on dilution with icy water deposited gummy solids, which were crystallized to afford pure products **8a–h** (Scheme 2). All the obtained compounds were characterized by sharp melting points, correct elemental analyses, ^{1}H NMR and ^{13}C NMR spectra.

Anti-mycobacterial data concerning 12 *N*-aryl-*C*-nitroazoles tested as inhibitors against *Mycobacterium tuberculosis* are collected in Table 1. In the primary assay four compounds shown distinctive activity. Among 1-aryl-4-nitroimidazoles without nitro groups at 1-aryl substituent only 1-(4-chlorophenyl-2-methyl-4-nitroimidazole (**3c**)



Scheme 1.



Scheme 2.

Table 1
Tuberculosis inhibition test (Alamar) preliminary results

Compound No.	Azole	Azole ring substituents	Benzene ring substituents	MIC [a] (μg/ml)	Inhibition (%) and activity
3a	Imidazole	4-NO_2	4-Br	>6.25	76
3b	Imidazole	4-NO_2	4-CH_3O	>6.25	0
8c	Imidazole	4-NO_2	4-NO_2	>6.25	0
3c	Imidazole	2-CH_3	4-Cl	<6.25	99
		4-NO_2			+
3d	Imidazole	2-CH_3	4-CH_3O	>6.25	0
		4-NO_2			–
3e	Imidazole	2-CH_3	4-Br	>6.25	85
		4–NO_2			
8b	Imidazole	2-CH_3	2,4-diNO_2	<6.25	91
		4-NO_2			+
8d	Imidazole	2-CH_3	4-NO_2	>6.25	83
		4-NO_2			–
8e	Pyrazole	4-NO_2	2,4-diNO_2	<6.25	96
					+
8f	Pyrazole	4-NO_2	4-NO_2	>6.25	11
					–
8g	1,2,4-Triazole	3-NO_2	2,4-diNO_2	<6.25	99
					+
8h	1,2,4-Triazole	3-NO_2	4-NO_2	>6.25	7
					–

[a] MIC at a single concentration 6.25 μg/ml (by MABA in BACTEC 12B medium against *Mycobacterium tuberculosis* $H_{37}Rv$); inhibition over 90% indicates activity designated by +.

demonstrated sufficient activity (99% of inhibition at 6.25 μg/ml), others derivatives were considered as inactive though bromo derivatives **3a** and **3e** were characterized by 76% and 85% inhibition, respectively.

Three *N*-(2,4-dinitrophenyl)-*C*-nitroazole derivatives (**8b,e** and **g**) proved to be active in the primary screen with inhibition over 90%. In contrast to that four tested *N*-(4-nitrophenyl)-*C*-nitroazoles (**8c,d,f** and **h**) shown inhibition ranging only from 83% for **8d** (2-methyl-4-nitroimidazole derivative) to 0% for a similar compound **8c** lacking 2-methyl group at imidazole ring. Thus, inhibition activity of **8b,e** and **g** can rather be attributed to the 2,4-dinitrophenyl fragment than to *C*-nitroazolyl ones, (Table 1) [11].

It is not easy to draw further conclusions concerning structure–inhibition activity relationship basing on the obtained results. Nevertheless, it seems clear that electron-donating substituent on 1-nitrogen atom in *C*-nitroimidazoles diminishes inhibition activity of the compounds. Surprisingly, it also appears that 2-methyl-4-nitroimidazoles are more active than 4-nitroimidazoles. These assumptions can be supported by results of the similar tests on a series of *N*-alkyl-*C*-nitroimidazoles (containing additional substituents in the *N*-alkyl chain) among which unfortunately none demonstrated inhibition activity over 20%.[1]

More promising tuberculosis inhibitors **3c, 8e** and **g** were tested at level 2 in MIC and cytotoxicity assays. Important results of those assays are disclosed in Table 2 together with the data for control drugs INH and RMP. Discouraging low solubility of *N*-(2,4-dinitrophenyl)-*C*-nitroazoles **8e** and **g** restrained their further screening.

Table 2
Tuberculosis inhibition activity and cytotoxicity assays summary [a] concerning compounds **3c, 8e** and **g**

Compound	MIC assay (level 2) and cytotoxicity assay			
	Inhib. (%)	MIC (μg/ml)	IC_{50} (μg/ml)	SI
3c	99	0.39	>62.5	>160
8e	96	6.25	0.40	0.06
8g	99	6.25	0.39	0.06
INH	>99	<0.05	>1 000	>40 000
RMP	>99	<0.125	>100	>800

[a] Inhib.—inhibition; MIC—minimum inhibitory concentration (generally MIC <1 μg/ml is an excellent lead); IC_{50}—toxicity to a VERO cell line; SI—selectivity index defined as the ratio of IC_{50} to MIC (it should be >10 for further testing).

5. Conclusions

None of the tested compounds demonstrated tuberculosis inhibition activity and cytotoxicity results better or at least similar to the control drugs isoniazid (INH) and rifampicin (RMP). Microphage assay (level 3) probably will not be carried out even with 1-(4-chlorophenyl)-2-metyhyl-4-nitroimidazole (**3c**). Nevertheless, the results obtained with the latter compound has encouraged us to the preparation of other *N*-aryl-*C*-nitroazoles particularly containing *N*-(halophenyl)- and *N*-(dihalophenyl) substituents, which can bring more promising results. Syntheses and tuberculosis inhibition activity of these new compounds will be published in due time.

[1] Examples: 1-(2-Hydroxy-3-methoxypropyl)-2-methyl-4-nitro-*1H*-imidazole and (*R*)-(+)-1-(2,3-dihydroxypropyl)-2-methyl-4-nitro-*1H*-imidazole exhibit inhibition of 2% and 16%, respectively.

6. Experimental

Melting points are uncorrected. Elemental analyses were performed on Perkin-Elmer 240C apparatus and were correct within acceptable errors. ^{1}H and ^{13}C spectra were recorded on a Varian (300 and 75.5 MHz) spectrometer in DMSO-d_6 solutions with TMS as an internal standard.

Dinitroimidazoles **1a–b** were prepared as described by us elsewhere [24]. 4-Nitropyrazole was prepared according to the reported procedure [25]. 3-Nitro-1,2,4-triazole and other starting reagents and solvents were purchased form Aldrich.

*6.1. A general procedure for the synthesis of arylimidazoles (**3a–e**)*

A solution of dinitroimidazole (**1a** or **1b**, 5 mmol) and amine (**2a–c**, 5 mmol) in aqueous methanol (10 ml, 1:9) was stirred in a closed vessel at 25 °C for 24 h and then poured into cold water. The precipitated solids were separated and crystallized from methanol or acetone to yield pure products **3a–e**.

*6.1.1. 1-(4-Bromophenyl)-4-nitro-1*H*-imidazole (**3a**)*

Yield 92%, m.p. 213–214 °C. ^{1}H NMR: δ (ppm): 8.99 (d, 1H, J = 1.5 Hz, H-5imid), 8.47 (d, 1H, J = 1.5 Hz, H-2imid), 7.76 (m, 4H, C_6H_4); ^{13}C NMR: δ (ppm): 148.12, 135.42, 134.69, 132.65, 123.20, 122.94, 121.26, 119.43. Anal.: $C_9H_6BrN_3O_2$.

*6.1.2. 1-(4-Methoxyphenyl)-4-nitro-1*H*-imidazole (**3b**)*

Yield 90%, m.p. 189–190 °C. ^{1}H NMR: δ (ppm): 8.91 (d, 1H, J = 1.5 Hz, H-5imid), 8.37 (d, 1H, J = 1.5 Hz, H-2imid), 7.72 (dd, 2H, J = 2.1 Hz, 6.8 Hz, H-3, H-5), 7.12 (2H, J = 2.1 Hz, 6.8 Hz, H-2, H-6), 3.83 (s, 3H, OCH_3); ^{13}C NMR: δ (ppm): 159.25, 147.87, 135.65, 128.69, 122.96 (2C), 119.90, 114.93 (2C), 55.60 (OCH_3). Anal.: $C_{10}H_9N_3O_3$.

*6.1.3. 1-(4-Chlorophenyl)-2-methyl-4-nitro-1*H*-imidazole (**3c**)*

Yield 84%, m.p. 107–108 °C. ^{1}H NMR: δ (ppm): 8.59 (s, 1H, H-5imid), 7.72–7.66 (m, 4H, Ar), 2.32(s, 3H, CH_3); ^{13}C NMR: δ (ppm): 146.17, 144.80, 134.57, 134.12, 129.66 (2C), 127.75 (2C), 122.64, 119.02, 13.41 (CH_3). Anal.: $C_{10}H_8ClN_3O_2$.

*6.1.4. 1-(4-Methoxyphenyl)-2-methyl-4-nitro-1*H*-imidazole (**3d**)*

Yield 92%, m.p. 124–125 °C. ^{1}H NMR: δ (ppm): 8.50 (s, 1H, H-5imid), 7.54 (d, 2H, J = 9.0 Hz, H-3, H-5), 7.11 (d, 2H, J = 9.0 Hz, H-2, H-6), 3.84 (s, 3H, OCH_3), 2.28 (s, 3H, CH_3); ^{13}C NMR: δ (ppm): 159.73, 145.95, 144.98, 128.52, 127.16 (2C), 122.79, 114.70 (2C), 55.56 (OCH_3), 13.30 (CH_3). Anal.: $C_{11}H_{11}N_3O_3$.

*6.1.5. 1-(4-Bromophenyl)-2-methyl-4-nitro-1*H*-imidazole (**3e**)*

Yield 89%, m.p. 124–125 °C. ^{1}H NMR: δ (ppm): 8.59 (s, 1H, H-5imid), 7.80 (d, 2H, J = 8.7 Hz, H-3, H-5), 7.60 (d, 2H, J = 8.7 Hz, H-2, H-6), 2.33 (s, 3H, CH_3); ^{13}C NMR: δ (ppm): 146.17, 144.74, 134.98, 132.60 (2C), 127.98 (2C), 122.62, 122.56, 13.41 (CH_3). Anal.: $C_{10}H_8BrN_3O_2$.

6.2. A general procedure for preparation of C*-nitroazole-DBU salts **6a–d***

1,8-Diazabicyclo[5.4.0]-7-undecene (5, 10 mmol) was added dropwise into a stirred solution of *C*-nitroazole (**4a–d**, 10 mmol) in tetrahydrofuran (5 ml) at 25 °C. Ten minutes later the resulting mixture (containing already some precipitations) was cooled down to circa –10 °C and left at this temperature for 1 h. The precipitations were collected, washed with cold *n*-pentane (10 ml) and dried in vacuum desiccator over solid sodium hydroxide.

*6.2.1. (4-Nitropyrazole)-DBU salt (**6c**)*

Yield 94%, m.p. 114–115 °C. It was analysed and used without further purification. Anal.: $C_{12}H_{19}N_5O_2$.

*6.2.2. (3-Nitro-1,2,4-triazole)-DBU salt (**6d**)*

Yield 77%, m.p. 143–144 °C. Anal.: $C_{11}H_{18}N_6O_2$.

*6.2.3. (*C*-Nitro-NH-azoles)-DBU salts **6a–b***

They had properties as described by us earlier (**6a**: m.p. 75–76 °C, lit. [23] 74–75 °C; **6b**: m.p. 102–103 °C, lit. [22] 103–104 °C).

6.3. A general procedure for the preparation of N*-aryl-*C*-nitroazoles **8a–g***

To nitroazole-DBU salt (**6a–d**, 10 mmol), dissolved in dimethylformamide (7 ml), fluoronitroarene (**7a–b**, 10 mmol) in dimethylformamide (3 ml) was added. Samples of the resulting solution, stirred at ambient temperature, were analysed from time to time by TLC. When a reaction was completed (30 min to 24 h—the times of a decay of the starting material spots on TLC plate), the reaction mixture was poured onto ice–water mixture (50 g: 50 ml). The precipitations were collected, crystallized from ethyl acetate–methanol (1:3) mixture and dried on air. Crude gummy 1-(2,4-dinitrophenyl)-4-nitropyrazole (**8e**) before crystallization was dissolved in ethyl acetate. The latter solution was dried over magnesium sulphate; then the solvent was removed and the residue crystallized as usual. Yields and properties of crystallized products **8a–g** are given below.

*6.3.1. 1-(2,4-Dinitrophenyl)-4-nitro-1*H*-imidazole (**8a**)*

Yield 80%; m.p. 153–154 °C, (154–156 °C dec. [17]) ^{1}H NMR: δ (ppm): 9.09 (d, 1H, J = 2.7 Hz, H-3), 8.88 (d, 1H, J = 1.5 Hz, H-5imid), 8.79 (dd, 1H, J = 2.7 Hz, 8.7 Hz, H-5), 8.28 (d, 1H, J = 1.5 Hz, H-2 imid), 8.19 (d, 1H, J = 8.7 Hz, H-6). ^{13}C NMR: δ (ppm): 147.95, 147.81, 137.78, 133.52, 131.60. 129.26, 122.61, 121.44. Anal.: $C_9H_5N_5O_6$.

*6.3.2. 1-(2,4-Dinitrophenyl)-2-methyl-4-nitro-1*H-*imidazole (**8b**)*

Yield 83%, m.p. 191–192 °C (194–196 °C [17]); ^{1}H NMR: δ (ppm): 9.03 (d, 1H, J = 2.4 Hz, H-6), 8.80 (dd, 1H, J = 2.4 Hz, 8.7 Hz, H-5), 8.66 (s, 1H, H-5imid), 8.23 (d, 1H, J = 8.7 Hz, H-3), 2.41(s, 3H, Me). ^{13}C NMR: δ (ppm): 148.33, 146.71, 145.70, 144.99, 133.30, 132.72, 129.49, 122.98, 121.52. Anal.: $C_{10}H_7N_5O_6$ (C, H, N,O).

*6.3.3. 1-(4-Nitrophenyl)-4-nitro-1*H-*imidazole (**8c**)*

Yield 77%; m.p. 190–191 °C (188–190 °C dec. [17]). ^{1}H NMR: δ (ppm): 9.18 (d, 1H, J = 1.5 Hz, H-5imid), 8.66 (d, 1H, J = 1.5 Hz, H-2), 8.43 (dd, 2H, J = 2.1 Hz, 9.0 Hz, H-3, H-5), 8.14 (dd, 2H, J = 2.1 Hz, 9.0 Hz, H-2, H-6). ^{13}C NMR: δ (ppm): 148.43, 146.58, 140.14, 135.84, 125.29, 121.90, 119.56. Anal.: $C_9H_6N_4O_4$ (C, H, N, O).

*6.3.4. 2-methyl-4-nitro-1-(4-nitrophenyl)-1*H-*imidazole (**8d**)*

Yield 80%, m.p. 186–187 °C, (lit. 185–187 °C dec. [17]). ^{1}H NMR: δ (ppm): 8.69 (s, 1H, H-5imid), 8.45 (2H, dd, J = 2.1 Hz, 6.6 Hz, H-2, H-6), 7.94 (dd, 2H, J = 2.1 Hz, 6.6 Hz, H-3, H-5), 2.40 (s, 3H, Me). ^{13}C NMR: δ (ppm): 147.40, 146.41, 144.67, 140.71, 127.10, 124.90, 122.31, 13.59. Anal.: $C_{10}H_8N_4O_4$.

*6.3.5. 1-(2,4-Dinitrophenyl)-4-nitro-1*H-*pyrazole (**8e**)*

Yield 63%; m.p. 162–163 °C, (lit. 160 °C [16]). ^{1}H NMR: δ (ppm): 9.74 (s, 1H, H-5pyr), 8.94 (d, 1H, J = 2.4 Hz, H-3), 8.74 (dd, 1H, J = 2.4 Hz, 8.7 Hz, H-5), 8.66 (s, 1H, H-3pyr), 8.28 (d, 1H, J = 8.7 Hz, H-6). ^{13}C NMR: δ (ppm): 147.09, 143.37, 138.38, 137.41, 134.91, 132.10, 128.41, 127.84, 121.32. Anal.: $C_9H_5N_5O_6$ (C, H, N).

*6.3.6. 4-Nitro-1-(4-nitrophenyl)-1*H-*pyrazole (**8f**)*

Yield 90%, m.p. 162–163 °C. ^{1}H NMR: δ (ppm): 9.86 (s, 1H, H-5pyr), 8.64 (s, 1H, H-3pyr), 8,41 (d, 2H, J = 8,4 Hz, H-2, H-6), 8.24 (d, 2H, J = 8.4 Hz, H-3, H-5). ^{13}C NMR: δ (ppm): 146.29, 142.62, 137.89, 137.54, 129.26, 125.31. 119.97. Anal.: $C_9H_6N_4O_4$.

*6.3.7. 1-(2,4-Dinitrophenyl)-3-nitro-1*H-*[1,2,4]-triazole (**8g**)*

Yield 75%, m.p. 103–104 °C (98–100 °C [16]). ^{1}H NMR: δ (ppm): 9.55 (s, 1H, H-5triazole), 9.02(d, 1H, J = 2.4 Hz, H-3), 8.33(dd, 1H, J = 2.4 Hz, 8.7 Hz, H-5), 8.34(d, 1H, J = 8.7 Hz, H-6). ^{13}C NMR: δ (ppm): 162.97, 148.52, 148.12, 143.17, 132.32, 129.78, 129.08, 121.53. Anal.: $C_8H_4N_6O_6$.

*6.3.8. 3-Nitro-1-(4-nitrophenyl)-1*H-*[1,2,4]-triazole (**8h**)*

Yield 34%, m.p. 200–201 °C dec. ^{1}H NMR: δ (ppm): 9.78 (s, 1H, H-5), 8.51(d, 2H, J = 9.0 Hz, H-2, H-6), 8.25 (d, 2H, J = 9.0 Hz, H-3, H-5). ^{13}C NMR: δ (ppm): 147.21, 145.95, 140.11, 125.58, 121.02, tiazole C-3 not observed.

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