HETEROCYCLES, Vol. 85, No. 9, 2012, pp. 2197 - 2211. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 6th May, 2012, Accepted, 2nd July, 2012, Published online, 9th July, 2012
DOI: 10.3987/COM-12-12502

REGIOSELECTIVE NITRO GROUP SUBSTITUTION. SYNTHESIS OF ISOMERIC 4-AMINO-5-NITRO- AND 5-AMINO-4-NITROIMIDAZOLES

Lucjusz Zaprutko,* Justyna Żwawiak, Dorota Olender, and Andrzej Gzella

Department of Organic Chemistry, Pharmaceutical Faculty, Poznan University of Medical Sciences, 60-780 Poznan, Grunwaldzka 6, Poland

Abstract – On the basis of the reactions between 4,5-dinitroimidazole derivatives (1-methyl-4,5-dinitroimidazole, 1,2-dimethyl-4,5-dinitroimidazole and ethyl 2-(4,5-dinitroimidazol-1-yl)acetate) and cyclic amines (morpholine, piperidine or pyrrolidine) in mild conditions (THF or ethanolic solution), the order of nitro group substitution has been discovered for the first time. The influence of the solvent, steric effects and possibility of hydrogen bonds formation on the reaction direction has been discussed. Also, the way of formation of diamino-substitution product and interesting isomerization process is presented.

INTRODUCTION

Nitro-bearing imidazoles show a wide spectrum of pharmacological activity. The compounds with a nitro group at position 5 are usually more active than the corresponding 4-nitro-derivatives. On the other hand, 4-nitroimidazoles show less toxicity than 5-nitro-derivatives. These effects are particularly pronounced for 2,4- and 2,5-dinitroimidazoles. Introduction of an electron accepting substituent at position 5 in the 4-nitroimidazole ring causes increase in cytotoxic and radiosensibiliting activity.[1] These compounds are essential especially in the treatment of diseases caused by bacteria and protozoa. The best known – Metronidazole, is effective against *Bacteroides, Fusobacterium, Megasphaera, Clostridium,* sometimes *Peptococcus* and *Helicobacter pylorii*. Tinidazole was found to be active against *Gardnella vaginalis, Propionibacterium, Eubacterium, Campylobacter, Actinomyces* and *Spirochetes*. Nimorazole and ornidazole have demonstrated activity against trichomoniasis.[1-4] Besides, nitroimidazoles are good radiation enhancers of hypoxic cells. From among nitroazoles, Misonidazole seems to be the best known

radiosensitizer.[5] Moreover, some bicyclic nitroimidazooxazoles show considerable activity against tuberculosis.[6,7]

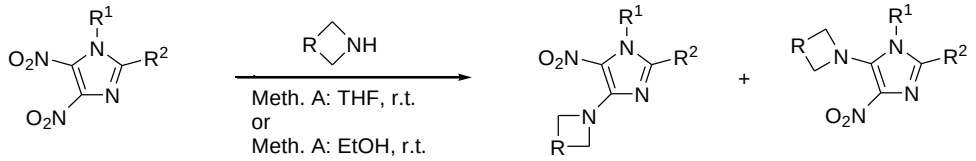
A number of azole derivatives with a nitro and amino group in the same molecule are known to show antifungal,[8] anti-HIV[9] and antioxidant activity.[10] One of the methods of obtaining aminonitroimidazoles is the substitution of one nitro group with amine in 4,5-dinitroimidazoles. Some examples of these reactions have been described earlier,[11-14] but in each of these cases only respective 5-amino-4-nitroimidazole derivatives were obtained. The substitution of *C*-4 nitro group with amines in some 4,5-dinitroimidazole derivatives leading to the respective 4-amino-5-nitroimidazole derivatives has also been described.[15-17]

There have been some reports on simultaneous substitution of both the nitro groups with amines.[15,16] Suwinski *et al.*[11] as well as Koehler and Dockner[12] reported that the treatment of 1-methyl- or 1,2-dimethyl-4,5-dinitroimidazole (**1, 5**) with amines in water or alcoholic (mainly ethanolic) solutions, with or without addition of the base, led to the nucleophilic substitution of C(5) nitro group. According to these methods only respective 5-amino-4-nitroimidazoles can be obtained.

In continuation of our earlier studies on nitroimidazoles,[16] in this paper it is shown that the nucleophilic substitution of nitro group takes place both in positions 4 and 5 as result of the treatment of 1-methyl-4,5-dinitroimidazole (**1**), 1,2-dimethyl-4,5-dinitroimidazole (**5**), as well as ethyl 2-(4,5-dinitroimidazol-1-yl)-acetate (**9**) with cyclic amines, especially with morpholine, piperidine or pyrrolidine in THF solution (method A) or in ethanolic solution (method B). The influence of the solvent, steric effects and possibility of hydrogen bond formation on the reaction direction is being discussed. For the first time, the order of nitro groups substitution in N-alkyl-4,5-dinitroimidazoles has been determined. What is more, interesting observations of isomers transformation has been made. It is proved that the isomeric 4-amino-5-nitro- and 5-amino-4-nitroimidazole derivatives can be distinguished on the basis of the ^{1}H-NMR spectral analysis of the substrates and reaction products. Moreover, the order of nitro group substitution is discovered and a mechanism of formation of diamino-substitution product manners is presented.

RESULTS AND DISCUSSION

The target compounds were synthesized by the procedure illustrated in Scheme 1. These reactions were carried out most effectively only in some selected solvents such as THF (method A) or ethanol (method B). The use of other reaction media e.g. methylene chloride, acetonitrile, DMF or DMSO caused formation of complex mixtures from which it was difficult to isolate stable single products in pure state. However, the presence of desired compounds in comparable concentrations in these mixtures was confirmed by TLC as well as spectroscopic methods.



1, 5, 9, 13 **2a, 3a, 4a, 6a, 7a, 8a, 10a, 11a, 12a** **2b, 3b, 4b, 6b, 7b, 8b, 10b, 11b, 12b**

Compd. No.	R^1	R^2	R
1	Me	-H	-----
2a, 2b	Me	-H	$-CH_2-O-CH_2-$
3a, 3b	Me	-H	$-CH_2-CH_2-CH_2-$
4a, 4b	Me	-H	$-CH_2-CH_2-$
5	Me	Me	-----
6a, 6b	Me	Me	$-CH_2-O-CH_2-$
7a, 7b	Me	Me	$-CH_2-CH_2-CH_2-$
8a, 8b	Me	Me	$-CH_2-CH_2-$
9	$-CH_2CO_2Et$	-H	-----
10a, 10b	$-CH_2CO_2Et$	-H	$-CH_2-O-CH_2-$
11a, 11b	$-CH_2CO_2Et$	-H	$-CH_2-CH_2-CH_2-$
12a, 12b	$-CH_2CO_2Et$	-H	$-CH_2-CH_2-$
13	$-CH_2CO_2Et$	Me	-----

Scheme 1. Synthesis of 4-amino-5-nitroimidazoles and 5-amino-4-nitroimidazoles in the nitro group substitution reaction.

The appropriate 4,5–dinitroimidazole derivatives **1**, **5**, **9**, and **13** were treated with morpholine, piperidine or pyrrolidine in THF solution, at room temperature and at the 1:2 molar ratio. In these conditions the respective 4-amino-5-nitroimidazoles **2a**, **3a**, **4a**, **6a**, **10a**, **11a** and **12a** (Scheme 1) were formed as major products, which could be isolated in crystalline form. Most of them were obtained with a satisfactory yield not less than 70%. The only exceptions were the piperidine derivatives **3a** (yield 46%) and **11a** (yield 42%). The attempts of obtaining of the compounds with methyl groups at 1 and 2 position and with piperidine or pyrrolidine group connected with C(4) atom (**7a**, **8a**) in the state enabling full characterisation were not successful. These compounds were partially decomposed during isolation and purification processes, but the presence of the expected products in the mixtures formed was confirmed

by TLC and ^{1}H NMR methods. The TLC plate shows an intensive yellow spot with R_f higher than for the opposite isomer. The proton magnetic resonance spectrum reveals a distinct signal at δ = 3.83 ppm, near the signal at δ = 3.45 ppm, which are characteristic of *N*-methyl groups in the differently substituted nitroimidazole ring. The isomeric 5-amino-4-nitroimidazole derivatives **2b**, **3b**, **4b**, **6b**, **7b**, **8b**, **10b**, **11b** and **12b** in these conditions were formed in the yield below 10%.

We have found that a substituent with significant steric and electronic effect at the N-1 position of imidazole ring affects the reactivity of the nitro group in the nucleophilic substitution reactions. The ester group in compounds **13** and **9** prevents or obstructs separation of products. Only in compounds **9**, it is possible to isolate 5-nitro isomers labelled with a letter **a**. The **b** type isomer was formed in small amounts but it can be detected only by ^{1}H NMR spectroscopy.

The nitro group bonded to C(4) atom of the imidazole ring seems to be privileged in the substitution reactions in aprotic solvents (e.g. THF) because of the steric effects. Besides, it is expected that in the formed sigma-complex, dihedral angle between C(5) nitro group and imidazole ring will be significantly diminished because of nitro group participation in conjugated 4-amino-5-nitroimidazole system. It causes significant shortening of exocyclic C(5)-NO_2 bond. This effect is observed in different 4-amino-5-nitroimidazoles with refcodes: ELUBIW, QIKDUJ, QIKFAR, SATBIZ, SATQIO, WOCWAM, WOCWAM01 deposited in CSD data base, Cambridge, version 5.32.[18] In the found seven structures, C(5) nitro group is approximately placed in the imidazole ring plane, and mean bond distance between C(5) and NO_2 group is 1.391(6) Å. It is shorter by 13σ than normal single Csp^2 – NO_2 bond distance (1.468(1) Å).[19]

Besides, a stabilization of C(5) nitro group is possible through the intramolecular hydrogen bond between the oxygen atom of that group and the hydrogen atom of amine.

If ethanol is used as solvent instead of THF and the remaining reaction conditions are similar to those given above, the products of treatment on **1**, **5** and **9** with morpholine, piperidine or pyrrolidine are again a mixture of both isomeric 4-amino-5-nitro- and 5-amino-4-nitroimidazole derivatives. But then the yields of 5-amino-4-nitroimidazole **2b** – **4b** and **6b** – **8b** are three to five times higher than reaction was run in THF. In contrast the yields of 4-amino-5-nitroimidazoles **2a – 4a** and **6a** are significantly decreased (Table 1). The isomeric ratios of the reaction products **10a** and **10b**, i.e. compounds with ester group at N(1) atom, are in both methods comparable and independent of the nature of solvent used. This ratio was found on the basis of ^{1}H NMR signals intensity. In spite of much effort, the attempts to isolate the 5-amino-4-nitroimidazole derivatives **10b – 12b** failed, though they were visible on TLC plates. This failure was probably due to unstability of these compounds. The majority of aminonitroimidazole derivatives isolated in pure form undergo decomposition process when stored for a few months.

Table 1. Amino-nitroimidazoles synthesized by a nitro group substitution with cyclic amine in dinitroimidazoles.

No.	Appearance Solvent for crystallization	Mp (°C) Lit. mp. (°C)[a]	Time (h)	Yield (%) in method A	Yield (%) in method B	Formula, Molecular mass	Analysis, calcd./found C(%)	H(%)	N(%)
2a	yellow needles cyclohexane	132-134 ---	24	72	18	$C_8H_{12}N_4O_3$ 212.21	45.28 45.55	5.70 5.88	26.40 26.13
2b	pale yellow prisms EtOAc	220-221 114-115[5]	24	9	34	$C_8H_{12}N_4O_3$ 212.21	45.28 45.50	5.70 5.80	26.40 26.04
3a	yellow needles *n*-hexane	75-76 71-72[5]	2	46	32	$C_9H_{14}N_4O_2$ 210.24	51.41 51.60	6.71 6.78	26.65 26.54
3b	pale yellow plates *n*-hexane + EtOAc (2:1)	180-182 184-185[5]	2	8	38	$C_9H_{14}N_4O_2$ 210.24	51.41 51.57	6.71 6.80	26.65 26.49
4a	orange plates *n*-hexane	105-106 ---	2	70	33	$C_8H_{12}N_4O_2$ 196.21	48.96 49.05	6.18 6.29	28.56 28.45
4b	yellow plates CCl_4	89-90 90-91[5]	2	9	39	$C_8H_{12}N_4O_2$ 196.21	48.96 49.12	6.18 6.36	28.56 28.37
6a	yellow plates *n*-hexane + EtOAc (2:1)	130-131 ---	24	70	35	$C_9H_{14}N_4O_3$ 226.24	47.78 47.98	6.24 6.48	24.76 24.77
6b	pale yellow plates *n*-hexane + EtOAc (2:1)	158-159 140-141[5]	24	3	16	$C_9H_{14}N_4O_3$ 226.24	47.78 48.00	6.24 6.50	24.76 24.46
7a	*unstable dark yellow oil*		2			$C_{10}H_{16}N_4O_2$ 224.26			

7b	yellow prisms *n*-hexane + EtOAc (2:1)	172-174 166-167[5]	2	6	21	$C_{10}H_{16}N_4O_2$ 224.26	53.56 53.80	7.19 7.22	24.98 24.79
8a	*unstable dark yellow oil*		2			$C_9H_{14}N_4O_2$ 210.24			
8b	yellow plates CCl_4	87-88 85-86[5]	2	7	15	$C_9H_{14}N_4O_2$ 210.24	51.41 52.29	6.71 6.88	26.65 26.52
10a	yellow needles aqua	112-114 ---	1	72	73	$C_{11}H_{16}N_4O_5$ 284.27	46.55 46.48	5.56 5.67	19.88 19.71
10b	*not isolated identified with ^1H NMR only*	xxx	1	7	6	$C_{11}H_{16}N_4O_5$ 284.27	xxx	xxx	xxx
11a	orange needles diluted EtOH	79-81 ---	1	42	43	$C_{12}H_{18}N_4O_4$ 282.30	51.28 51.06	6.35 6.43	19.77 19.85
11b	*not isolated identified with ^1H NMR only*	xxx	1	4	4	$C_{12}H_{18}N_4O_4$ 282.30	xxx	xxx	xxx
12a	yellow needles diluted EtOH	97-98 ---	1	79	77	$C_{11}H_{16}N_4O_4$ 268.27	49.27 49.25	6.22 6.01	21.20 20.88
12b	*not isolated identified with ^1H NMR only*	xxx	1	7	7	$C_{11}H_{16}N_4O_4$ 268.27	xxx	xxx	xxx

In alcoholic, and especially in ethanolic solutions, the C(4) nitro group of 4,5-dinitro-compounds **1** and **5** with relatively small substituent at N(1) position easily interacted with the solvent with formation of intermolecular hydrogen bonds –N=O···HO–C_2H_5. Probably for this reason, substitution reactivity of C(4) nitro group is slightly reduced in comparison with that of the same group in C(5) position, which becomes more preferable and susceptible to substitution in these conditions. The possibility of C(5) nitro group

substitution in dinitroimidazole derivatives with a bulkier group at N(1) atom, e.g. in compounds **9** and **13**, is essentially decreased. The ability of this group to form hydrogen bonds significantly influences its substitution possibility. In this situation, the intramolecular hydrogen bonds –N=O···H–CH= between oxygen atom of nitro group and hydrogen atom of C(6) methylene fragment are formed. This hydrogen atom C(6)-H6B is activated by carbonyl group from neighbouring ester moiety in the chain. Presence of the weak hydrogen bond in **9** was established with X-ray diffraction methods. The molecular structures of compounds **9** and **7b** and the atom-labelling schemes are illustrated in Figures 1 and 2, respectively. Results of the X-ray analysis of **9** show that the C4- and C5-nitro groups are significantly twisted out of the imidazole plane, the dihedral angles between the appropriate planes being 27.14(11) and 36.00(13)° (Figure 1). Besides, the exocyclic C4–N12 [1.4453(13) Å] and C5–N15 [1.4524(15) Å] are similar and only slightly shortened with respect to the normal length of the Csp^2–NO_2 bond of 1.468(1) Å [18]. These observations are in consistence with that reported for 3-chloro-1-(4,5-dinitroimidazol-1-yl)propan-2-ol.[15] It should be noticed that in this compound both nitro groups are exchanged for a piperidine or morpholine residues.

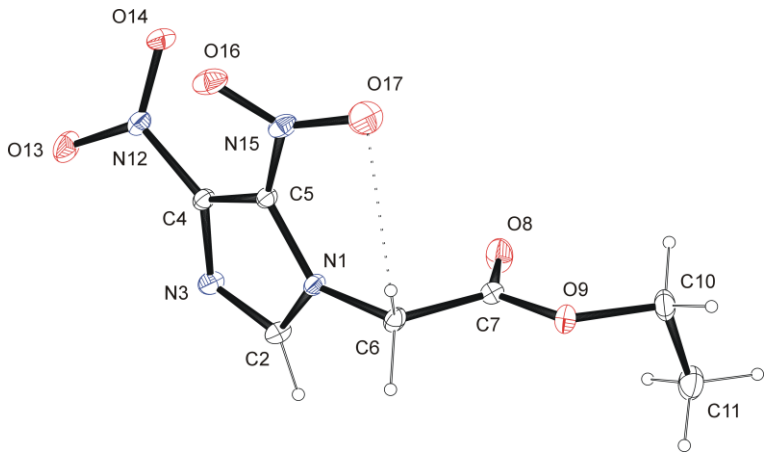


Figure 1. A perspective view of the molecule of **9**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

In compound **7b**, the nitro group and the piperidine moiety are connected with C4 and C5 atoms, respectively. The two substituents subtent very different interplanar angles of 6.90(6)° (nitro group) and 63.51(7)° (mean plane of the piperidine residue) to the imidazole ring (Figure 2).

The nitro group takes part in the conjugation system of the imidazole ring. In consequence, the bond distance C4–N8 [1.4201(18) Å] is significantly shorter (about 23 δ) than the normal single Csp^2–NO_2

bond and the nitro group shows an extraordinary stability on treatment with piperidine and morpholine.[15,16]

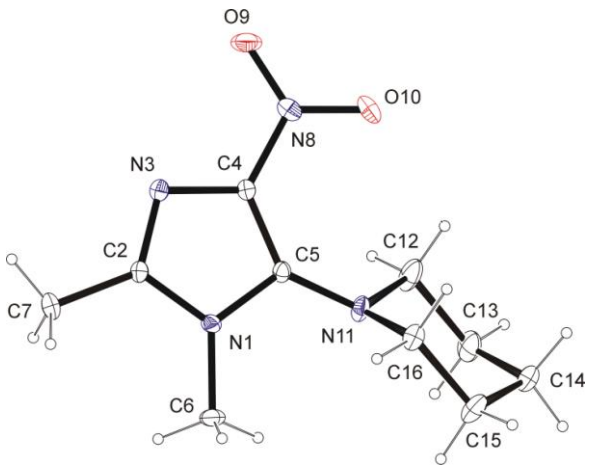


Figure 2. A view of the molecule of **7b**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are depicted as spheres of arbitrary radii.

For confirmation of the positions of nitro group and substituted amino group in compounds obtained from dinitroimidazoles, their basic properties were compared with appropriate literature data for amino-nitroimidazoles obtained from respective halonitroimidazoles with the known earlier determined structure. Synthesis of 5-amino-4-nitroimidazoles **2b – 4b** and **6b – 8b** from appropriate 5-bromo- or 5-iodo-4-nitroimidazole was described also by Kulkarni *et al.*[20] The conformity of melting points proves the location of amino group at position C(5) in the imidazole derivatives **3b, 4b, 7b** and **8b**. The compounds of 5-aminoimidazole **2b** and **6b** are the exceptions (see Table 1). It is doubtlessly possible to distinguish 5-amino-4-nitroimidazoles **2b – 4b**, **6b – 8b** and **10b – 12b** from 4-amino-5-nitroimidazoles **2a – 4a, 6a – 8a** and **10a – 12a** on the basis of their ^{1}H NMR spectra analysis. The signal assigned to hydrogen atoms of methyl or methylene aliphatic substituent directly bonded with N(1) atom of the imidazole ring, therefore present in direct vicinity of substituent at C(5) imidazole atom, is used to distinguish these two isomeric kinds of compounds. According to the data in Table 2, the substitution of C(4) nitro group in dinitroimidazoles of with amines causes a very narrow (0.01-0.14 ppm) diamagnetic shift, but substitution of C(5) nitro group causes a significantly greater (0.35-0.46 ppm) diamagnetic shift of proton signals assigned to N(1)-CH_3 or N(1)-CH_2 – group. This difference in the position of these signals to enables a simple distinction of the isomers obtained.

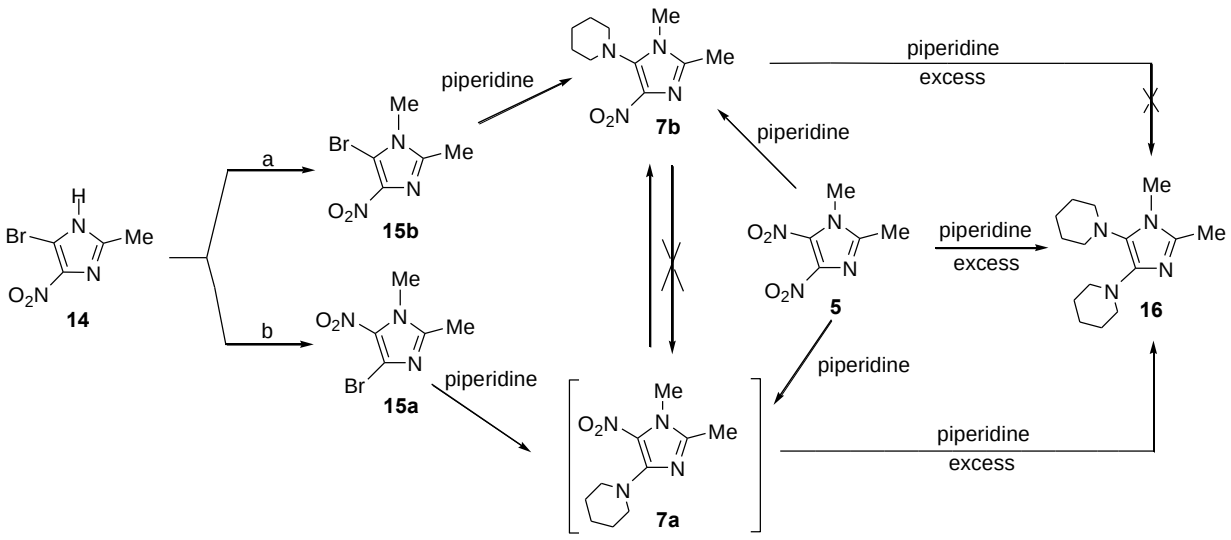
Table 2. Differentiated magnetic shifts of 4-amino-5-nitro- and 5-amino-4-nitroimidazole derivatives[a].

Compd. No		Magnetic shift of protons N-CH_2- [ppm]	Diamagnetic shift relatively to respective dinitrocompound [ppm]
1		*4.01*	---
2	**a**	3.94	0.07
	b	3.61	0.40
3	**a**	3.92	0.09
	b	3.56	0.45
4	**a**	3.90	0.11
	b	3.58	0.43
5		*3.86*	---
6	**a**	3.85	0.01
	b	3.51	0.35
7	**a**	3.83	0.03
	b	3.45	0.41
8	**a**	3.83	0.03
	b	3.46	0.40
9		*5.08*	---
10	**a**	4.97	0.11
	b	4.62	0.46
11	**a**	4.95	0.13
	b	4.64	0.44
12	**a**	4.94	0.14
	b	4.64	0.44

[a] ^{1}H NMR chemical shifts for compounds **10b** – **12b** were determined from spectra recorded for crude reaction mixtures containing both isomers

The isomers of aminonitroimidazoles with a nitro group in the C(5) position were found less stable than the other isomers. Therefore, an attempt was made to synthesize this type of compound according to the synthetic method for **7a**. We had to use the method described by Kulkarni[20] based on the treatment of piperidine on 4-bromo-1,2-dimethyl-5-nitroimidazole (**15a**) because compound **7a** was not isolated in

pure state. It was proved that the known methods of syntheses of **15a**[15] and **7a**[20] are not fully reproducible. We succeeded to develop a very selective methylation method of 4(5)-bromo-2-methyl-5(4)-nitroimidazole to **15a.** If diazomethane is used instead of dimethyl sulphate,[21] the yield of **15a** is 70% but the isomeric 5-bromo-1,2-dimethyl-4-nitroimidazole **15b** is formed with the yield of about 3% only. Compound **7a** in the form yellow needles should be obtained with a melting point at 107 – 108 °C through excess of piperidine treatment on **15a** in the reaction conditions described in.[21] In the same conditions we obtained only a colorless product with melting point 109 – 111 °C not identical with **7a**, but having the structure of 1,2-dimethyl-4,5-dipiperidineimidazole **16**. The same compound was obtained with the use of **5** as a substrate instead of **15a** and at least fivefold excess of piperidine. Compound **7b**, which is a 4-nitro-5-piperidine- derivative, isomeric to compound **7a**, is obtainable with use of an appropriate halonitroimidazole, i.e. 5-bromo-1,2-dimethyl-4-nitroimidazole **15b** by substitution of bromine atom as well as using of respective dinitroimidazole derivative **5**. The latter reaction gives a mixture of isomers **7a** and **7b**. Only 4-nitro-isomer **7b** could be isolated by a chromatographic method. Attempts at **7a** isomer isolation led to its systematic conversion into the more stable isomer **7b**. However, the treatment of the crude compound **7a** with piperidine in at least double excess led to formation of 4,5-dipiperidine derivative **16**. In compound **7b** it is not possible to substitute the C(4) nitro group with piperidine in any reaction conditions used for compound **16** synthesis. Similar isomerization of 4-bromo-2-methyl-5-nitro-1-phenacylimidazoles into 5-bromo-2-methyl-4-nitro-1-phenacylimidazoles upon heating under reflux was described by Sobiak.[22] Isomerization of **7a** into **7b** proceeding probably according to the same reaction mechanism. The reaction in the reverse direction from **7b** to **7a** is impossible (Scheme 2).



Scheme 2. Synthesis of piperidine-nitroimidazoles in the bromine or nitro group substitution reaction.[a]

[a] Reagents and conditions: (a) Me_2SO_4, NaOH, 60 °C; (b) Me_2SO_4, 30 °C or CH_2N_2.

CONCLUSION

In conclusion, we have developed a synthetic approach to formation of isomeric substitution products amino-nitroimidazoles. The substituent at the N-1 position of the imidazole ring was found to influence the reactivity of the nitro group in nucleophilic substitution reactions. Moreover, the nitro group connected with C(4) atom of the imidazole ring was found privileged in the substitution reactions in aprotic solvents (e.g. THF) because of the steric effect.

EXPERIMENTAL

The substrates were obtained according to literature methods[23,24] and **14** was obtained by the alkaline bromination of a commercial 2-methyl-4-nitroimidazole. Reactions of dinitroimidazoles with amines were performed with use of two methods (A and B). Progress of the reaction was monitored by TLC method on plates covered with Kieselgel 60, which were developed with a mixture of *n*-hexane and EtOAc (2:1). The spots were observed in the UV-light (254 nm) as well as in the daylight without additional visualisation or after I_2 vapour action. The products were purified by flash column chromatography on neutral alumina I° acc. Brockmann. Melting points were determined on a Boetius apparatus and are uncorrected. IR spectra were recorded in KBr tablets (0.5%) using a Carl Zeiss Jena Specord 71-IR apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions using a Varian Gemini 300VT (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm relative to *TMS* as internal standard. The mass spectrum of **16** was obtained on a Jeol JMS D-100 instrument. Elemental analyses for C, H and N contents were performed on the Elementar Vario EL III apparatus.

Crystal structures of 1,2-dimethylo-4-nitro-5-piperidineimidazole **7b** and ethyl 2-(4,5-dinitroimidazol-1-yl)acetate **9** were determined by the X-ray diffraction studies. The diffraction intensity data for crystals **7b** and **9** were collected at 130(2) K with an Oxford Diffraction Xcalibur A diffractometer processed with the Oxford Diffraction CrysAlis Pro Software.[25] Intensity data collection employed the ω- scans with graphite monochromatized Mo $K\alpha$ radiation. Both structures were solved by direct methods and refined by full matrix least-squares on F^2 (SHELXS-97 and SHELXL-97).[26]

General procedures for the reactions of *N*-substituted 4,5-dinitroimidazole derivatives 1, 5 and 9 with cyclic amines.

Method A (in THF solution). Into a solution of appropriate dinitroimidazole derivative (2.5 mmol, **1** – 0.43 g, **5** – 0.47 g, **9** – 0.61 g or **13** – 0.64 g) in THF (5.0 mL), a solution of a respective cyclic amine (5.0 mmol; 0.44 mL morpholine or 0.49 mL piperidine or 0.42 mL pyrrolidine) also in THF (5.0 mL), was added dropwise. The mixture was stirred at room temperature until the spot of the substrate on TLC plate disappeared. The times are given in Table 1. Subsequently Al_2O_3 (4.0 g) was added and the solvent was

evaporated at a slightly increased temperature. The residue was dried in vacuum. Then it was purified by chromatographic technique on the Al_2O_3 (30.0 g) column with a mixture of *n*-hexane and EtOAc (2:1). The volumes of fractions were determined on the basis of TLC control and maintained in the range of 70 and 200 mL. The 4-amino-5-nitroimidazoles, i.e. compounds labelled with a letter **a**, were isolated from the second fraction, but the isomeric 5-amino-4-nitroimidazoles, labelled with a letter **b**, were isolated from the fourth fraction. Compounds **10b**, **11b** and **12b** were not isolated but were identified in the fourth fraction, as well as in the mother liquors after crystallization of compounds **10a**, **11a** and **12a**.

Method B (in ethanolic solution). The reactions were performed in the same way as in the method A, with the only difference in the use of EtOH as a solvent instead of THF. After the specified reaction times the reaction mixtures were diluted with water (80 mL) and extracted many times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated at only slightly increased temperature, to a volume of about 10 mL. Subsequently Al_2O_3 (4.0 g) was added and the isolation of products was performed in the same manner as in method A.

Alternatively, it is possible to change a chromatographic eluent after isolation of the first isomer. The mixture of n-hexane and EtOAc (2:1) can be replaced by this ester alone. In this way the volume of the fraction with the second isomer can be significantly decreased.

In methods A or B the pure products or their mixtures were isolated as presented in Table 1.

Methylation of 4(5)-bromo-2-methyl-5(4)-nitroimidazole (14) with diazomethane: An excess of diazomethane ethereal solution was added dropwise into a suspension of 4(5)-bromo-2-methyl-5(4)-nitroimidazole (**14**) (4.12 g, 20.0 mmol) in Et_2O (200 mL). The reaction mixture was left standing for about 6 h at room temperature, during which the substrate was almost completely dissolved. The filtered ethereal solution was concentrated and the solid residue was chromatographed on basic alumina with the use of a mixture of *n*-hexane and EtOAc (2:1) as a developing solvent. The second fraction contained 3.02 g (68.6%) of 4-bromo-1,2-dimethyl-5-nitroimidazole (**15a**) but from the fourth fraction 0.13 g (2.9%) of 5-bromo-1,2-dimethyl-4-nitroimidazole (**15b**) was obtained. The products were recrystallized from diluted EtOH.

4-Bromo-1,2-dimethyl-5-nitroimidazole (15a). This compound was obtained as light cream prisms, mp 112-113 °C (lit.[20]: 107-108 °C, lit.[21]: 108-109 °C). IR (KBr, cm^{-1}): 2920 (C-CH_3), 2800 (N-CH_3), 1560, 1310 (NO_2); ^{1}H NMR ($CDCl_3$, δ ppm): 3.92 (s, 3H, N-CH_3), 2.50 (s, 3H, 2-CH_3).

5-Bromo-1,2-dimethyl-4-nitroimidazole (15b). This compound was obtained as light greenish-yellow small prisms, mp 163-165 °C (lit.[20]: 158-159 °C, lit.[21]: 161-162 °C). IR (KBr, cm^{-1}): 2925 (C-CH_3), 2810 (N-CH_3), 1540, 1320 (NO_2); ^{1}H NMR ($CDCl_3$, δ ppm): 3.67 (s, 3H, N-CH_3), 2.50 (s, 3H, 2-CH_3).

The same compounds can be obtained with use of dimethyl sulfate in basic conditions, but in this manner

there are formed in the reversed ratio.[5,6]

Reactions of 4(5)-bromo-5(4)-nitroderivatives of 1,2-dimethylimidazole (15a and 15b) with piperidine.

Reaction of 5-bromo-1,2-dimethyl-4-nitroimidazole (15b) with piperidine. Into a solution of 5-bromo-1,2-dimethyl-4-nitroimidazole (**15b**) (0.70 g, 3.0 mmol) in EtOH (20 mL), a solution of piperidine (1.47 mL, 15.0 mmol) in EtOH (20 mL) was added successively and intensely orange mixture was heated under reflux for 4 h. After cooling, water (200 mL) was added and the mixture obtained was extracted many times with CH_2Cl_2. Organic layer was dried with $MgSO_4$ and concentrated. The oily residue was crystallized with use of EtOH and water (1:3) mixture. The amount of 0.60 g (84%) of yellow needles of 1,2-dimethyl-4-nitro-5-piperidineimidazole (**7b**) with mp 166-167 °C was obtained. Subsequent recrystallization from n-hexane and EtOAc (2:1) mixture gave yellow prisms with mp 172-174 °C, which means that the product was the same as that obtained from 1,2-dimethyl-4,5-dinitroimidazole (**5**). **(7b)** IR (KBr, cm^{-1}): 2925 (C-CH_3), 2810 (N-CH_3), 1540, 1320 (NO_2).

Reaction of 4-bromo-1,2-dimethyl-5-nitroimidazole (15a) with piperidine. Into a solution of 4-bromo-1,2-dimethyl-5-nitroimidazole (**15a**) (0.70 g, 3.0 mmol) in EtOH (20 mL), a solution of piperidine (1.47 mL, 15.0 mmol) in EtOH (20 mL) was added successively and intensive orange mixture obtained was heated under reflux for 4 h. Then nearly whole solvent was removed in distillation. The brown, thick residue was extracted three times with small quantities of Et_2O. Ethereal solution was concentrated and light brown oily substance was crystallized from a mixture of EtOH and water (1:1) with charcoal. There was obtained 0.32 g of 1,2-dimethyl-4,5-dipiperidineimidazole (**16**) (yield 39%) as fine white needles, mp 109-111 °C, R_f = 0.67 (on Al_2O_3, in 2:1 mixture of *n*-hexane and ethyl acetate); IR (KBr, cm^{-1}): 2925 (C-CH_3), 2810 (N-CH_3); ^{1}H NMR ($CDCl_3$, δ ppm): 2.25 (s, 3H, 2-CH_3), 3.28 (s, 3H, N-CH_3), 1.51 (m, 4H), 1.61 (m, 8H), 2.93 (m, 8H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.89, 28.43, 24.26 and 24.34, 26.75, 26.95, 52.91, 53.86, 123.12, 126.36, 152.53; Ms *m/z* (% relative intensity): 262 (100), 219 (13), 205 (28), 193 (15), 191 (11), 69 (11); Anal. Calcd for $C_{15}H_{26}N_4$: C, 68.66; H, 9.99; N, 21.35. Found: C, 68.40; H, 10.03; N, 21.17.

The same product was obtained in the reaction of 1,2-dimethyl-4,5-dinitroimidazole (**5**) with fivefold excess of piperidine in boiling ethanolic solution. The yields of the products from these above two syntheses were comparable.

SUPPORTING INFORMATION

The supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre (CCDC), 12 Union ROAD, Cambridge CB2 1EZ (UK), Tel.: (+44) 1223/336-408, Fax: (+44)

1223/336-033, E-mail: deposit@ccdc.cam.ac.uk, World Wide Web: http://www.ccdc.cam.ac.uk (deposition No. for **7b**: CCDC 836419, for **9**: CCDC 836418).

REFERENCES

1. J. H. Boyer, 'Nitroazoles', VCH Publishers Inc., Florida, 1986, pp. 165–166.
2. A. Mital, *Sci. Pharm.*, 2009, **77**, 497.
3. H. A. Allimony, H. A. Saad, and F. A. Mariah, *Indian J. Chem. Sec. B*, 1999, **38**, 445.
4. W. Raether and H. Hanel, *Parasitol. Res.*, 2003, **90**, Suppl. 1, 19.
5. C. D. Freeman, N. E. Klutman, and K. C. Lamp, *Drugs*, 1997, **54**, 679.
6. E. B. Clifton, H. I. M. Boshoff, and C. S. Dowd, *Curr. Pharm. Design*, 2004, **10**, 3239.
7. M. Adib, E. Sheibani, M. Mostofi, K. Ghanbary, and H. R. Bijanzadeh, *Tetrahedron*, 2006, **62**, 3435.
8. V. A. Makarov, O. B. Riabova, V. G. Granik, V. M. Dahse, A. Stelzner, P. Wutzler, and M. Schmidtke, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 37.
9. N. Al-Masoudi, Y. Al-Soud, E. De Clercq, and C. Pannecouque, *Antiviral Chem. Chemother.*, 2007, **18**, 191.
10. D. Olender, J. Żwawiak, V. Lukianchuk, R. Lesyk, A. Kropacz, A. Fojutowski, and L. Zaprutko, *Eur. J. Med. Chem.*, 2009, **44**, 645.
11. J. Suwiński, W. Król, and C. Pacocha, Zeszyty Naukowe Politechniki Śląskiej, Seria: Chemia, 1985, **111**, 13.
12. H. Koehler and T. Dockner, BASF AG, European Patent EP 0,337, 255, A1, 1989 (*Chem. Abstr.*, 1990, 112, 235295v).
13. V. S. Mokrushin, N. A. Belyaev, M. Y. Kolobov, and A. N. Fedotov, *Chem. Heterocycl. Compd.*, 1983, **19**, 650.
14. O. S. El'tsov and V. S. Mokrushin, *Chem. Heterocycl. Compd.*, 2002, **38**, 1331.
15. A. Gzella, U. Wrzeciono, and W. Pöppel, *Acta Cryst. C*, 1999, *C***55**, 1562.
16. A. Gzella, U. Wrzeciono, and W. Pöppel, *Acta Cryst. C*, 2000, *C***56**, 1161.
17. L. Zaprutko, D. Olender, and A. Gzella, *Monatsch. Chem.*, 2003, **134**, 1145.
18. F. H. Allen, *Acta Cryst.*, 2002, **B58**, 380.
19. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1–19.
20. S. Kulkarni, M. R. Grimmett, L. R. Hanton, and J. Simpson, *Austral. J. Chem.*, 1987, **40**, 1399 and papers cited herein.
21. V. Šunjić, T. Fajdiga, M. Japelj, and P. Rems, *J. Heterocycl. Chem.*, 1969, **6**, 53.

22. S. Sobiak, *J. Pract. Chemie,* 1999, **341**, 179.
23. S. S. Novikov, L. I. Khmel'nitskii, O. V. Lebedev, V. V. Sevost'yanova, and L. V. Epishina, *Chem. Heterocycl. Compd.*, 1970, **6**, 465.
24. L. Zaprutko, U. Wrzeciono, M. Gajdziński, M. Bartkowiak, K. Lutomski, W. Michalska, and K. Pietkiewicz, *Pharmazie,* 1982, **47**, 258.
25. Oxford Diffraction 2010; CrysAlis PRO Software. Oxford Diffraction Ltd.: Yarnton, Oxfordshire, England.
26. G. M. Sheldrick, SHELXS-97 and SHELXL-97. Release 97-2, University of Göttingen, Germany, 2008.