Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2021, **31**, 555–557

Mendeleev Communications

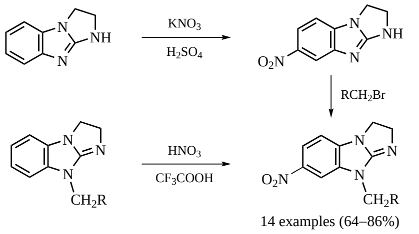
Nitration of 2,3-dihydroimidazo[1,2-*a*]benzimidazole and its N^9-substituted derivatives

Vadim S. Sochnev,[a] Tatyana A. Kuz'menko,[a] Anatolii S. Morkovnik,*[a]
Lyudmila N. Divaeva,[a] Anastasia S. Podobina,[a] Alexander A. Zubenko,[b]
Pavel B. Chepurnoy,[a] Gennadii S. Borodkin[a] and Alexander I. Klimenko[b]

[a] *Institute of Physical and Organic Chemistry, Southern Federal University, 344090 Rostov-on-Don, Russian Federation. E-mail: asmorkovnik@sfedu.ru*
[b] *North-Caucasian Zonal Research Veterinary Institute, 346406 Novocherkassk, Russian Federation*

DOI: 10.1016/j.mencom.2021.07.040

7-Nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazole and its N^9-substituted derivatives can be conveniently synthesized by nitration of the corresponding tricyclic precursors with a nitrating mixture or with the HNO_3/CF_3COOH system. This reaction occurs fairly smoothly and with good regioselectivity.



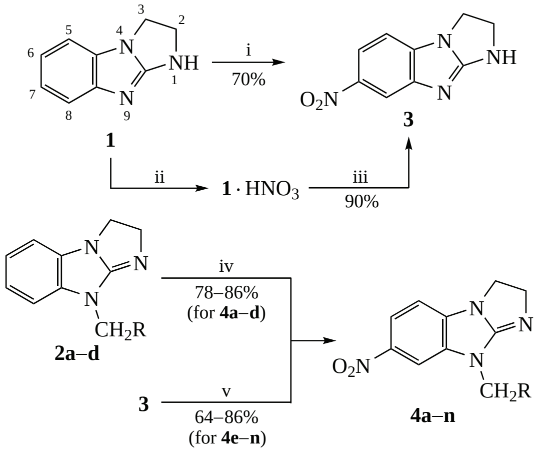
Keywords: 7-nitro-2,3-dihydroimidazo[1,2-*a*]benzimidazoles, imidazo[1,2-*a*]benzimidazoles, nitration, ^{15}N NMR, quantum chemical calculations, anti-infective activity.

The development of the chemistry of 2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazole **1** is largely stimulated by the high and diverse pharmacological activity of its derivatives.[1–10] To date, a preparative procedure for the synthesis of compound **1** from benzimidazole-2-sulfonic acid has been developed.[11,12] Compound **1** that exists as the 1*H*-tautomer[13] is successfully alkylated under neutral conditions to give various N^9-derivatives.[1,2,4,14] 9-(2-Dialkylaminoethyl)-substituted compounds of this series that are of particular interest for biological screening are synthesized in good yields by a different protocol, namely, by cyclization of 2-amino-1-(2-dialkylaminoethyl)benzimidazoles with 1,2-dibromoethane.[3,15,16] Clinical trials of one representative of these 9-substituted compounds, 9-(2-diethylaminoethyl)-2,3-dihydroimidazo[1,2-*a*]benzimidazole (diabenol) as the antidiabetic drug demonstrated a number of important pharmacological effects, for example, on the glucose and glycated hemoglobin levels, thrombogenic potential, hemorheology improvement, insulin production, and decreasing the insulin resistance.[3,17]

2,3-Dihydroimidazo[1,2-*a*]benzimidazoles containing substituents at the benzene ring are much less available. They were synthesized in a multistage manner in low overall yields from the corresponding *o*-nitroanilines.[5,13]

In this work, we studied whether compound **1** and some of its 9-alkylated derivatives **2a–d** could undergo direct nitration. In fact, treatment of a solution of dihydro imidazobenzimidazole **1** in conc. H_2SO_4 with an equimolar amount of KNO_3 at –5 °C resulted in nitro derivative **3** in 70% yield (Scheme 1). The yield of compound **3** can be improved to 90% if the hydronitrate of base **1**, which is formed on treatment of its solution in acetone with nitric acid to reach pH value of 1, is added to conc. H_2SO_4.[†] Previously, 7-nitro derivative **3** with the similar melting point was obtained from 2,4-dinitrochlorobenzene.[13]

Position 7 of the nitro group in structure **3** was confirmed by NMR spectroscopy and quantum chemical studies. The characteristics of the ^{1}H NMR spectrum of compound **3** allow us to exclude the substitution at positions 5 and 8 in the tricyclic ring system. In the ^{15}N–^{1}H HMBC spectrum, the $^{15}N^9$ nucleus forms a single cross-peak (184.78; 8.02 ppm), obviously with the C^8H proton that is nearest to it. In the ^{1}H NMR spectrum, this



a R = H
b R = Et_2NCH_2
c R = morpholinomethyl
d R = piperidinomethyl
e R = 4-$Bu^tC_6H_4$
f R = 4-ClC_6H_4
g R = 4-$F_3CC_6H_4$
h R = $PhOCH_2$
i R = 4-$MeOC_6H_4OCH_2$
j R = 4-$ClC_6H_4OCH_2$
k R = PhC(O)
l R = 3,4-$(MeO)_2C_6H_3C(O)$
m R = 4-$FC_6H_4C(O)$
n R = 4-$ClC_6H_4C(O)$

Scheme 1 *Reagents and conditions*: i, KNO_3/H_2SO_4, –5 °C; ii, HNO_3, Me_2CO; iii, H_2SO_4, –5 °C; iv, CF_3COOH, HNO_3, 30–35 °C, 2–3 h; v, RCH_2Br, DMF, reflux, 6 h.

proton resonates as a doublet with *J* 2.1 Hz, which is possible only if the nitro group is located at position 7 (for details, see Online Supplementary Materials).

According to the DFT quantum chemical calculations (B3LYP/6-311G**), in the protonated form of substrate **1**, which in fact undergoes nitration, the bond of the N^4 atom with the benzene ring (1.402 Å) is shorter than that of the N^9 atom (1.418 Å). This indicates a higher electron donating ability and a stronger conjugation of the N^4 atom, which is responsible for the transfer of π-electron density to the C^7 atom, as compared to the N^9 atom, which has a similar effect on the C^6 atom. As a result, the C^7 atom makes a larger contribution to the HOMO with this shape than the C^6 atom does. Moreover, a larger negative Mulliken charge is localized on the C^7 atom (–0.128 for C^7 and –0.121 for C^6). Thus, position 7 in protonated molecule **1** is the most sensitive to electrophilic attack, both in the case of orbital control and charge control of the reaction.

To additionally confirm the structure of compound **3**, the chemical shifts for ^{1}H, ^{13}C and ^{15}N nuclei in the 6- and 7-nitro derivatives of **1** were calculated using the SOS DFPT IGLO method (B3LYP/6-311G**//PW91-PW91/IGLO-II).[18] In this case, we considered only the most stable 1*H*-tautomeric forms of these compounds, which are more favorable by 5.4 and 6.5 kcal mol^{-1}, respectively, in the gas phase than the 9*H*-tautomeric forms. In polar media, due to the higher polarity of 1*H*-forms, the difference in the energies of the tautomers would obviously be even more significant. It was found that the $\delta_{C(8a)}$ value is the diagnostic parameter that makes it possible to distinguish between 6- and 7-substituted structures. Its experimental value (148.70 ppm) is in good agreement with the calculated one for the 7-nitro derivative (146.41 ppm) but not for its 6-nitro isomer (156.77 ppm).

Nitration of 9-methyl-2,3-dihydroimidazobenzimidazole **2a**[2] in trifluoroacetic acid solution with two equivalents of nitric acid (*d* 1.39) at 30–35 °C also gives 7-nitro derivative **4a** in 86% yield. Nitration nearly does not occur with one equivalent of nitric acid, apparently, due to the reagent consumption for the protonation of the starting material. Under the same conditions but with three equivalents of nitric acid, dialkylaminoethyl derivatives **2b–d** are also successfully nitrated to afford 7-nitro substituted compounds **4b–d**, diabenol 7-nitro derivative **4b** in particular, in 78–86% yields.[‡] Since compounds **2b–d** (especially **2b**) are low-melting,[2,3] it is more convenient to perform the reaction with their dihydronitrates obtained preliminarily using as little as one equivalent of nitric acid.

The position of the nitro group in structures **4a–d** was determined by NMR spectroscopy. According to the appearance of the ^{1}H NMR spectra, the substituent in these compounds could in principle be located at positions 6 or 7. In the HMBC ^{15}N–^{1}H spectrum of nitro derivative **4c**, the $^{15}N^9$ nucleus gives two cross peaks with benzene ring protons. Since one of them that has chemical shifts of 102.26, 7.67 ppm is significantly (almost 3.5-fold) more intense than the other one, it can be confidently attributed to the H^8 proton, which is the closest to the $^{15}N^9$ nucleus. This proton manifests itself as a doublet with *J* 2.2 Hz in the ^{1}H NMR spectrum, which implies that the nitro group is located at position 7 in this case.

This nitration direction of 9-substituted compounds **2a–d** is also confirmed by quantum chemical calculation data for the protonated form of model 9-methyl derivative **2a** showing that the electron density on the HOMO is again substantially higher at position 7 than on the C^6 atom, and of course, on the C^5 and C^8 atoms (see Online Supplementary Materials).

Though compound **3** contains a strong electron-withdrawing nitro group, its NH moiety can be readily alkylated with benzyl, 2-aryloxyethyl and phenacyl bromides to give the corresponding N^9-substituted derivatives **4e–n** (see Scheme 1).

Preliminary screening of the anti-infective activity of the nitro derivatives of dihydroimidazo[1,2-*a*]benzimidazole showed that compounds **4** had pronounced protistocidal activity against *Colpoda steinii amoebae*: they surpassed the reference drug Toltrazuril in this respect (**4e**,**f**,**h–j**) or were not inferior to it (**4h**; see Online Supplementary Materials).

This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation within the framework of State Assignment (SFedU, no. FENW-2020-0031, 0852-2020-0031) and was performed using the equipment of the Center for Collective Use ‘Molecular Spectroscopy’ of the Southern Federal University.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.07.040.

References

1 V. A. Anisimova, I. E. Tolpygin, A. A. Spasov, V. A. Kosolapov, A. V. Stepanov and A. F. Kucheryavenko, *Pharm. Chem. J.*, 2006, **40**, 261 [*Khim. Farm. Zh.*, 2006, **40** (5), 27].

2 V. A. Anisimova, M. V. Levchenko, G. V. Kovalev, A. A. Spasov, G. P. Dudchenko, S. G. Antonyan, N. V. Bessudnova and R. E. Libinzon, *Pharm. Chem. J.*, 1987, **21**, 201 (*Khim. Farm. Zh.*, 1987, **21**, 313).

3 V. A. Anisimova, M. I. Balabolkin, G. P. Vdovina, I. I. Dedov, V. I. Minkin, V. I. Petrov and A. A. Spasov, *Patent RU 2386634 C2*, 2010.

4 A. A. Spasov, V. A. Anisimova, V. I. Petrov, A. F. Kucheryavenko, I. E. Tolpygin and V. I. Minkin, *Patent RU 2453312 C1*, 2012.

5 L. Dubua, Ya. Evanno, L. Even, K. Jill, A. Malaida, D. Mashnik and N. Rakotoarisoa, *Patent EA 014450 B1*, 2010.

6 V. A. Anisimova, M. V. Levchenko, T. B. Korochina, A. A. Spasov, S. G. Kovalev and G. P. Dudchenko, *Patent EP 571253 A1*, 1993.

7 V. A. Anisimova, A. A. Spasov, V. A. Kosolapov, I. E. Tolpygin, E. V. Tibir’kova, O. A. Salaznikova, V. A. Kuznetsova, N. A. Gurova, K. V. Lenskaya, D. S. Yakovlev, D. V. Mal’tsev, N. A. Kolobrodova, T. M. Mitina and O. Yu. Grechko, *Pharm. Chem. J.*, 2013, **46**, 647 [*Khim. Farm. Zh.*, 2012, **46** (11), 15].

8 S. Oh, S. Kim, S. Kong, G. Yang, N. Lee, D. Han, J. Goo, J. L. Siqueira-Neto, L. H. Freitas-Junior and R. Song, *Eur. J. Med. Chem.*, 2014, **84**, 395.

9 K. M. Khan, Z. Shah, V. U. Ahmad, N. Ambreen, M. Khan, M. Taha, F. Rahim, S. Noreen, S. Perveen, M. I. Choudhary and W. Voelter, *Bioorg. Med. Chem.*, 2012, **20**, 1521.

[†] *7-Nitro-2,3-dihydro-1*H*-imidazo[1,2-*a*]benzimidazole* **3**. A solution of dihydroimidazobenzimidazole **1** (1.59 g, 10 mmol) in acetone (25 ml) was treated with 65% HNO_3 to reach pH value of 1. After 0.5 h, the resulting precipitate was filtered off and washed with acetone. The yield of salt **1** · HNO_3 was 2.2 g (98%), mp 214–215 °C (EtOH). Found (%): C, 48.5; H, 4.7; N, 25.3. Calc. for $C_9H_{10}N_4O_3$ (%): C, 48.7; H, 4.9; N, 25.5. The resulting hydronitrate was added in portions to stirred conc. H_2SO_4 (16 ml) cooled to −5 °C, and this was kept for 0.5 h at that temperature. The mixture was then poured onto ice and alkalinized with conc. NH_4OH. The thus precipitated nitro derivative **3** was filtered off and washed with water. Yield 1.8 g (90%), yellow crystals, mp 261–263 °C (EtOH) (lit.[13] mp 262–263 °C).

[‡] *7-Nitro-9-(RCH_2)-2,3-dihydroimidazo[1,2-*a*]benzimidazoles* **4a**–**d**. Nitric acid (*d* 1.39, 1.4 ml, 20 mmol for **2a**; 2.1 ml, 30 mmol for **2b**–**d**) was added to a stirred solution of the corresponding 9-alkylated substrate **2a**–**d** (10 mmol) in trifluoroacetic acid (10 ml), and the mixture was stirred at 30−35 °C for 2.5–3 h (TLC monitoring). The resulting reaction solution was poured onto ice and alkalinized with conc. NH_4OH to pH 9–10. In the case of compound **4a**, a bright yellow precipitate formed, which was filtered off and washed with water. Compounds **4b**–**d** were extracted with $CHCl_3$ (3 × 20 ml), the solvent was distilled off, and the residue was chromatographed on a column with Al_2O_3 (12 × 3 cm, $CHCl_3$ as the eluent). The fractions with R_f 0.5 (**4a**) and 0.4 (**4b**–**d**) were collected.

The detailed characteristics of nitro derivatives **3** and **4a**–**n** are given in Online Supplementary Materials.

10 O. N. Zhukovskaya, A. A. Spasov, D. A. Babkov and A. S. Morkovnik, *Patent RU 2650877 C1*, 2018.

11 V. A. Anisimova, M. V. Levchenko, Yu. V. Koschienko and A. F. Pozharskiy, *Patent SU 952847*, 1982.

12 A. M. Simonov and V. N. Komissarov, *Chem. Heterocycl. Compd*., 1975, **11**, 723 (*Khim. Geterotsikl. Soedin*., 1975, 826).

13 R. J. North and A. R. Day, *J. Heterocycl. Chem*., 1969, **6**, 655.

14 V. A. Anisimova, I. E. Tolpygin and O. I. Askalepova, *Chem. Heterocycl. Compd*., 2014, **49**, 1748 (*Khim. Geterotsikl. Soedin.*, 2013, 1887).

15 L. N. Divaeva, T. A. Kuzmenko, A. S. Morkovnik and V. N. Komissarov, *Chem. Heterocycl. Compd*., 2006, **42**, 463 (*Khim. Geterotsikl. Soedin.*, 2006, 528).

16 Y. A. Kikugawa, *Synthesis*, 1981, 124.

17 (*a*) G. V. Kovalev, A. A. Spasov, V. A. Anisimova, G. P. Vdovina, S. G. Kovalev, M. I. Balabolkin, G. G. Mamaeva, G. P. Dudchenko and M. V. Levchenko, *Patent RU 2061481 C1*, 1996; (*b*) V. M. Kreminskaya and N. N. Zolotov, *Patent RU 2485952 C2*, 2013.

18 V. G. Malkin, O. L. Malkina, M. E. Casida and D. R. Salahub, *J. Am. Chem. Soc*., 1994, **116**, 5898.

Received: 4th January 2021; Com. 21/6412