Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2023, **33**, 650–652

Mendeleev Communications

Regioselective synthesis of 2-(1*H*-benzimidazol-1-yl)-5-nitro- and 2-(5-nitro-1*H*-benzimidazol-1-yl)anilines

Roman S. Begunov,*[a] Anna V. Chetvertakova[a] and Margarita E. Neganova[b,c]

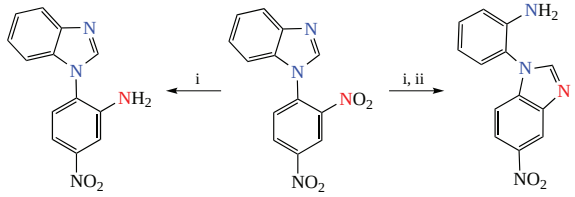
[a] *P. G. Demidov Yaroslavl State University, 150003 Yaroslavl, Russian Federation. E-mail: begunov@bio.uniyar.ac.ru*

[b] *Institute of Physiologically Active Compounds, Federal Research Center of Problems of Chemical Physics and Medicinal Chemistry, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation*

[c] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119334 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2023.09.020

The efficiency of two strategies for the synthesis of *N*-(2-aminophenyl)-5-nitrobenzimidazole derivatives was studied. The promising route involves the stages of 1-(2,4-dinitrophenyl)-1*H*-benzimidazole monoreduction at 2-positioned nitro group and tandem conversion involving recyclization of the intermediate *N*-(2-amino-4-nitrophenyl)-5-nitrobenzimidazole.



i, $TiCl_3$, 31% HCl, 30 °C, 5 min; ii, Pr^iOH, 80 °C, 4 h

Keywords: nitroanilines, benzimidazole derivatives, regioselective reduction, recyclization–isomerization, titanium trichloride.

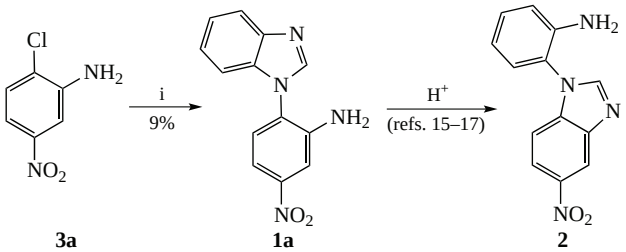
N-(2-Aminoaryl)benzimidazoles are used in the syntheses of practically important fused derivatives with a nodal nitrogen atom containing five-, six-, or seven-membered azaheterocycles annulated to an imidazole unit (see Online Supplementary Materials, Scheme S1).[1–4] Such polyfused compounds are of interest for development of new drugs and compounds for biomedical studies.[5–14] Imidazo[2,1-*a*]benzimidazole derivatives are potential inhibitors of p53 protein that acts as a suppressor of malignant tumor formation[5] and corticotropin-releasing factor 1 receptor antagonists.[6] Benzimidazo[1,2-*a*]quinoxalines and similar compounds are used to develop highly efficient anticancer drugs with insignificant side effects.[2,7,8] Benzimidazo-fused benzodiazepines and their isomers also play an important role in pharmaceutics[9–12] while some of them are considered promising biomacromolecule markers owing to their intense fluorescence.[4]

Due to the high practical importance of these biologically active fused heterocycles, there is a need for new *N*-(2-aminoaryl)-benzimidazoles. A literature survey showed that *N*-arylbenzimidazole nitro amino derivatives have not previously been used as substrates, although the presence of a nitro group in the resulting polycyclic polyazaheterocycle offers ample opportunities for its further functionalization. Therefore, an efficient method for the synthesis of two *N*-(2-aminoaryl)-benzimidazole nitro derivatives not previously reported, namely, 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline **1a** and 2-(5-nitro-1*H*-benzimidazol-1-yl)aniline **2**, was developed in this work.

Of the many possible strategies for their synthesis, two approaches seemed to be the rational. The first one (Scheme 1) involved the reaction of 2-chloro-5-nitroaniline **3a** with 1*H*-benzimidazole followed by isomerization of the resulting 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline **1a** in the acid-catalyzed recyclization discovered in our previous studies.[15–17] However, due to low reactivity of 2-chloro-5-nitroaniline **3a** in the S_NAr reaction with benzimidazole (K_2CO_3, DMF, 140 °C, 10 h) the NMR yield of product **1a** was as low as 9%.

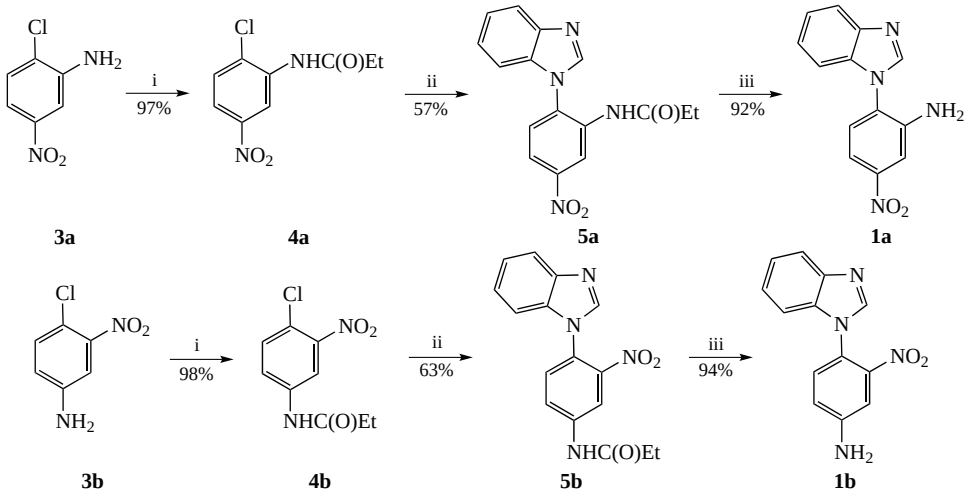
Obviously, activation of substrate **3a** was required, namely, by acylation of the amino group (Scheme 2), similar to that employed earlier in the synthesis of 4-(3-amino-4-nitrophenoxy)benzoic acid.[18] The corresponding substitution product **5a** was obtained by an S_NAr reaction in 57% yield. Its carboxamide function was hydrolyzed in 50% H_2SO_4 at 40 °C for 1.5 h to afford the desired compound **1a** in 92% yield (51% for two steps). The similar synthesis of isomeric 4-(1*H*-benzimidazol-1-yl)-3-nitroaniline **1b** was also performed; the sample **1b** was necessary for identification of monoreduction products in further investigations. The structures of compounds **1a**,**b** were identified by ^1H and ^{13}C NMR spectroscopy and by ESI-HRMS. The proton signals were assigned using 2D NOESY ^1H–^1H spectroscopy (for details, see Online Supplementary Materials).

The second pathway to compounds **1a** and **2** also involved two steps (Scheme 3). For this purpose, 2,4-dinitrochlorobenzene **6** was reacted with benzimidazole to obtain 1-(2,4-dinitrophenyl)-1*H*-benzimidazole **7** in 97% yield. To prepare nitroaniline **1a** from dinitroarene **7**, the selective reduction of the *ortho*-positioned nitro group should be accomplished. For this end, the

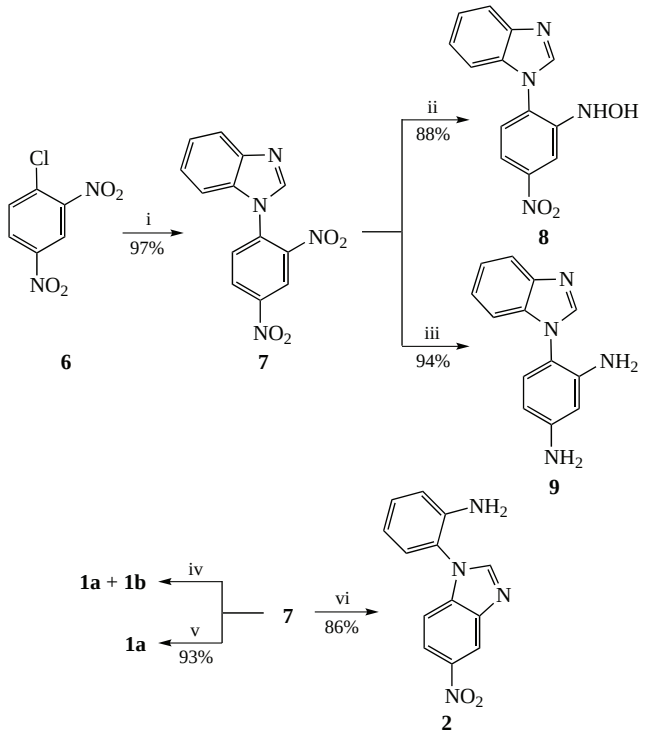


3a **1a** **2**

Scheme 1 *Reagents and conditions*: i, benzimidazole, K_2CO_3, DMF, 140 °C, 10 h.



Scheme 2 *Reagents and conditions*: i, $(EtCO)_2O$, DMF, 90 °C, 1 h; ii, benzimidazole, DMF, K_2CO_3, 120 °C, 8.5 h; iii, 50% H_2SO_4, 40 °C, 1.5 h.



Scheme 3 *Reagents and conditions*: i, benzimidazole, K_2CO_3, DMF, 100 °C, 1 h; ii, $SnCl_2{\cdot}H_2O$ (3 equiv.), Pr^iOH, 4% HCl, 50 °C, 20 min; iii, $TiCl_3$ (13 equiv.), HCl, 50 °C, 10 min; iv, $TiCl_3$ (6.1 equiv.), Pr^iOH + 4% HCl, 40 °C, 5 min; v, $TiCl_3$ (6.1 equiv.), 31% HCl, 30 °C, 5 min; vi, $TiCl_3$ (6.1 equiv.), 31% HCl, 30 °C, 5 min, then 70% Pr^iOH, 80 °C, 4 h.

effect of various factors, *viz*., the nature of the reducing agent, HCl concentration and reaction temperature, on the selectivity of the monoreduction process was studied.

In fact, reduction of **7** with 3 equiv. $SnCl_2$ in a dilute HCl/H_2O/Pr^iOH mixture at 50 °C for 20 min gave a product of incomplete reduction, namely, nitro hydroxylamine **8** (see Scheme 3). If the concentration of hydrochloric acid was increased to 18% and the temperature was raised to 70 °C, after 30 min the transformation of the nitro group into amine group did not occur, either. The appearance of the *ortho*-amino product **1a** was observed only when a mixture of Pr^iOH with 24% or 36% HCl was used. However, this reaction was not clean and delivered amino **1a**,**b** and diamino **9** products along with hydroxylamine **8**. Reduction in hydrochloric acid at 50–70 °C without isopropanol favored an increase in the amount of these impurities.

Ultimately, we turned our attention to titanium trichloride as the reducing agent. With excess $TiCl_3$ (6.1 equiv.), diamine **9** was formed (see Scheme 3). The optimization for mono-reduction into **1a** was performed in the temperature range of 30–80 °C; the pH of the medium and the nature of the solvent were also varied (Table 1). The solution of the reducing agent in hydrochloric acid (50 ml) was prepared by adding water or hydrochloric acid to 15% $TiCl_3$ solution in 10% HCl. Dinitro compound **7** was dissolved in Pr^iOH (50 ml) or hydrochloric acid with the required concentration. The substrate and the reducing agent were added simultaneously.

In fact, the reduction of dinitro substrate **7** both in the acid water–alcohol medium (see Table 1, entries 1–4) or in hydrochloric acid of various concentration (entries 5–8) at 80 °C gave in general three nitro amino products. As the concentration of HCl in the reaction mixture increased, the amount of product **1b** of the *para*-nitro group monoreduction decreased. At the same time, the content of isomer **2** first increased and then decreased. Nitro amine **2**, a product of the recyclization, was missing if the reduction was performed at 40 °C (entries 9–12). Like in the series of experiments 1–8, the selectivity toward nitroaniline **1a** increased with raising proton-donor properties of the medium. Lowering the temperature to 30 °C (entries 13, 14) and gradual feeding of the reducing agent (entry 14) made it possible to obtain compound **1a** in a yield of 93% with a minimum amount

Table 1 Optimization of reduction of 1-(2,4-dinitrophenyl)benzimidazole **7** (C = 35 mmol dm^{-3}) with $TiCl_3$.

Entry	Solvent	T/°C	Total yield (%)	**1a**/**1b**/**2** ratio[a,b]
1	Pr^iOH + 4% HCl	80	94	1.00 : 0.95 : 0.22
2	Pr^iOH + 9% HCl	80	96	1.00 : 0.88 : 0.39
3	Pr^iOH + 18% HCl	80	97	1.00 : 0.75 : 0.84
4	Pr^iOH + 27% HCl	80	95	1.00 : 0.41 : 0.26
5	4% HCl	80	95	1.00 : 0.68 : 0.54
6	9% HCl	80	97	1.00 : 0.59 : 0.62
7	18% HCl	80	98	1.00 : 0.55 : 0.51
8	31% HCl	80	96	1.00 : 0.31 : 0.19
9	Pr^iOH + 4% HCl	40	94	1.00 : 0.86 : 0
10	Pr^iOH + 18% HCl	40	96	1.00 : 0.58 : 0
11	Pr^iOH + 27% HCl	40	96	1.00 : 0.22 : 0
12	31% HCl	40	97	1.00 : 0.09 : 0
13	31% HCl	30	98	1.00 : 0.06 : 0
14[c]	31% HCl	30	97	1.00 : traces : 0

[a] Diamine **9** was missing in all experiments. [b] From ^{1}H NMR. [c] The reducing agent was added over a period of 5 min.

of impurities. Such a regioselectivity in monoreduction of **7** may be explained by the existence of a dinitro amine substrate in the strong acidic medium in the form of hydrochloric salt. The presence of a positively charged substituent at the *ortho*-position to the nitro group in 1-amino-2,4-dinitrobenzenes favors its reduction before the other group.[19–21]

The highest fraction of nitro amine **2** was formed in experiment 3 (see Table 1) at 80 °C in a mixture of Pr^{i}OH and 18% HCl. On the other hand, the synthesis of the *ortho*-amino derivative **1a** from which isomer **2** to be further produced required a low temperature and a stronger protogenic environment. Therefore, to obtain compound **2** in individual form, the reduction of **7** was carried out in 31% HCl at 30 °C (see Scheme 3, procedure vi) followed by addition of 70% aqueous Pr^{i}OH solution and heating at 80 °C for 4 h. The target recyclization product **2** was thus obtained in 86% yield.

In conclusion, the efficiency of two promising strategies for the synthesis of 2-(1*H*-benzimidazol-1-yl)-5-nitroaniline **1a** and 2-(5-nitro-1*H*-benzimidazol-1-yl)aniline **2** was compared. The regularities of the monoreduction of *N*-(2,4-dinitrophenyl)-benzimidazole **7** and recyclization of nitroaniline **1a** were established while implementing one of these approaches. Based on these studies, efficient protocols for the synthesis of *N*-(2-aminophenyl)benzimidazole nitro derivatives were developed. These compounds can be used to obtain new biologically active fused benzimidazole derivatives with a nodal nitrogen atom.

This study was supported by YarSU Development Program until 2030, project no. GM-2023-1.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.020.

References

1 P. Subramanian and K. P. Kaliappan, *Eur. J. Org. Chem.*, 2014, 5986.
2 R. Singh, R. Kumar, M. Pandrala, P. Kaur, S. Gupta, D. Tailor, S. V. Malhotra and D. B. Salunke, *Arch. Pharm.*, 2021, **354**, 2000393.
3 W. Chen, Y. Du, M. Wang, Y. Fang, W. Yu and J. Chang, *Org. Chem. Front.*, 2020, **7**, 3705.
4 S. Mitra, N. Chattopadhyay and P. Chattopadhyay, *RSC Adv.*, 2013, **3**, 1862.
5 M. S. Christodoulou, F. Colombo, D. Passarella, G. Ieronimo, V. Zuco, M. De Cesare and F. Zunino, *Bioorg. Med. Chem.*, 2011, **19**, 1649.
6 X. Han, S. S. Pin, K. Burris, L. K. Fung, S. Huang, M. T. Taber, J. Zhang and G. M. Dubowchik, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4029.
7 Z. Zghaib, J.-F. Guichou, J. Vappiani, N. Bec, K. Hadj-Kaddour, L.-A. Vincent, S. Paniagua-Gayraud, C. Larroque, G. Moarbess, P. Cuq, I. Kassab, C. Deleuze-Masquéfa, M. Diab-Assaf and P.-A. Bonnet, *Bioorg. Med. Chem.*, 2016, **24**, 2433.
8 J. Saliba, C. Deleuze-Masquéfa, A. Iskandarani, R. El Eit, R. Hmadi, F.-X. Mahon, A. Bazarbachi, P.-A. Bonnet and R. Nasr, *Anti-Cancer Drugs*, 2014, **25**, 624.
9 M. J. Kukla, H. J. Breslin, R. Pauwels, C. L. Fedde, M. Miranda, M. K. Scott, R. G. Sherrill, A. Raeymaekers, J. Van Gelder, K. Andries, M. A. C. Janssen, E. De Clerq and P. A. J. Janssen, *J. Med. Chem.*, 1991, **34**, 746.
10 M. J. Kukla, H. J. Breslin, C. J. Diamond, P. P. Grous, C. Y. Ho, M. Miranda, J. D. Rodgers, R. G. Sherrill, E. de Clercq, R. Pauwels, K. Andries, L. Moens, M. A. C. Janssen and P. A. Janssen, *J. Med. Chem.*, 1991, **34**, 3187.
11 H. J. Breslin, M. J. Kukla, D. W. Ludovici, R. Mohrbacher, W. Ho, M. Miranda, J. D. Rodgers, T. K. Hitchens, G. Leo, D. A. Gautier, C. Y. Ho, M. K. Scott, E. de Clercq, R. Pauwels, K. Andries, M. A. C. Janssen and P. A. Janssen, *J. Med. Chem.*, 1995, **38**, 771.
12 W. Ho, M. J. Kukla, H. J. Breslin, D. W. Ludovici, P. P. Grous, C. J. Diamond, M. Miranda, J. D. Rodgers, C. Y. Ho, E. De Clercq, R. Pauwels, K. Andries, M. A. C. Janssen and P. A. J. Janssen, *J. Med. Chem.*, 1995, **38**, 794.
13 R. S. Begunov, Yu. R. Aleksandrova, E. Yu. Yandulova, N. S. Nikolaeva and M. E. Neganova, *Mendeleev Commun.*, 2023, **33**, 237.
14 V. S. Sochnev, T. A. Kuz'menko, A. S. Morkovnik, L. N. Divaeva, A. S. Podobina, A. A. Zubenko, P. B. Chepurnoy, G. S. Borodkin and A. I. Klimenko, *Mendeleev Commun.*, 2021, **31**, 555.
15 R. S. Begunov, T. V. Shebunina, Yu. S. Yakovleva and S. I. Firgang, *Mendeleev Commun.*, 2013, **23**, 354.
16 R. S. Begunov, T. V. Shebunina, V. A. Buzina, A. N. Fakhrutdinov and A. S. Shashkov, *Russ. Chem. Bull.*, 2016, **65**, 822.
17 R. S. Begunov, A. N. Fakhrutdinov and A. A. Sokolov, *ChemistrySelect*, 2020, **5**, 3544.
18 A. Y. Leikin, A. L. Rusanov, R. S. Begunov and A. I. Fomenkov, *Polym. Sci., Ser. C*, 2009, **51**, 12 (*Vysokomol. Soedin., Ser. C*, 2009, **51**, 1264).
19 I. I. Bilkis, S. I. Uskov, V. S. Galdilov and V. D. Shteingarts, *Zh. Org. Khim.*, 1986, **22**, 1247 (in Russian).
20 S. I. Uskov, I. I. Bilkis and V. D. Shteingarts, *Russ. J. Org. Chem.*, 1991, **27**, 31 (*Zh. Org. Khim.*, 1991, **27**, 36).
21 R. S. Begunov and G. A. Ryzvanovich, *Chem. Heterocycl. Compd.*, 2004, **40**, 1224 (*Khim. Geterotsikl. Soedin.*, 2004, **40**, 1407).

Received: 3rd June 2023; Com. 23/7151