Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2021, **31**, 821–823

Mendeleev Communications

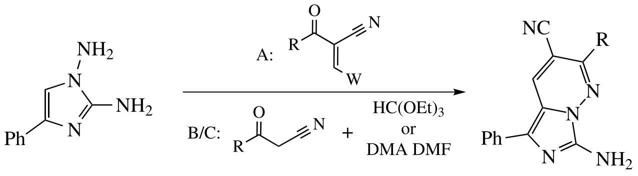
Regioselective synthesis of novel imidazo[1,5-*b*]pyridazine derivatives from diaminoimidazoles and α-acylacrylonitriles

Dmitriy Yu. Vandyshev,*[a] Evgeniya A. Kosheleva,[a] Vladimir A. Polikarchuk,[a] Daria A. Mangusheva,[a] Gleb L. Denisov[b] and Khidmet S. Shikhaliev[a]

[a] *Voronezh State University, 394018 Voronezh, Russian Federation. E-mail: vandyshev@cs.vsu.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2021.11.017

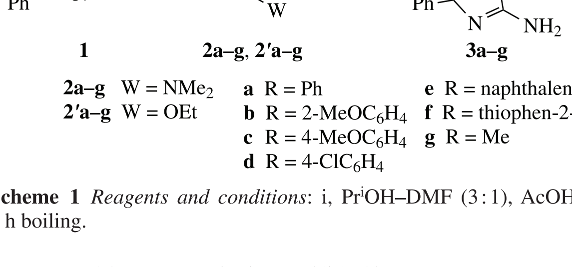
The heterocyclization of 1,2-diamino-4*H*-phenylimidazole with α-acylacrylonitriles affords cleanly 7-amino-2-R-5-phenylimidazo[1,5-*b*]pyridazine-3-carbonitriles. The strating α-acylacrylonitriles can be generated *in situ* from 3-oxo-3-(het)arylpropanenitriles and triethylorthoformate or dimethylformamide dimethyl acetal, and the products can be prepared in one pot.



Keywords: imidazo[1,5-*b*]pyridazine, 1,2-diamino-4*H*-phenylimidazole, nitrogen heterocycles, regioselectivity, multicomponent reactions.

The imidazole system and its benzo-, azolo-, and azino-annealed derivatives are parts of a large number of bioactive compounds,[1–4] including naturally occurring ones.[1] Synthetic organic and medicinal chemistry have recently been focusing on 1,2-diaminoimidazoles not substituted at the position 4. The molecule represents a chemotype of polynucleophilic N-heterocycles with high synthetic potential due to the presence of two amino functions, an active endocyclic nitrogen atom, and the highly reactive centre C^5. The most common area which is utilized in the chemistry of diaminoimidazoles is the preparation of imidazo[1,5-*b*]pyridazine systems, which are widely used for the production of medicinal products[5–16] and as ligand-forming agents.[17] However, the key issue in the preparation of imidazopyridazines and diaminoimidazoles is the regioselectivity of the used reactions.[18–24]

The paper considers the specifics of the reaction of 1,2-diamino-4-phenylimidazole in two-component and three-component heterocyclizations with 3-oxo-3-R-propanenitriles, including regioselectivity of the investigated reactions. Following the analysis of works,[18–24] MeOH, Pr^{i}OH, DMF, AcOH, and their mixtures were tested in the search for initial conditions of the reaction. We found that the reaction between 1,2-diaminoimidazole **1** and α-dimethylaminomethylidene β-oxo nitriles **2a**–**g**, as well as their ethoxymethylidene analogues, proceeds most smoothly in a 3 : 1 Pr^{i}OH/DMF mixture containing 1–2 drops of AcOH (Scheme 1). The maximum yield when using **2a**–**f** was obtained after 2 h of boiling. In case of 2-dimethylaminomethylidene-3-oxobutanolnitrile **2g** in which the (het)aryl fragment is replaced by a methyl group, the reaction proceeded significantly faster (40 min).



1 **2a–g**, **2′a–g** **3a–g**

2a–g W = NMe$_2$ **a** R = Ph **e** R = naphthalen-2-yl
2′a–g W = OEt **b** R = 2-MeOC$_6$H$_4$ **f** R = thiophen-2-yl
c R = 4-MeOC$_6$H$_4$ **g** R = Me
d R = 4-ClC$_6$H$_4$

Scheme 1 *Reagents and conditions*: i, Pr^{i}OH–DMF (3 : 1), AcOH (cat.), 2 h boiling.

It should be noted that moving from dimethylamino derivatives **2a**–**g** to their ethoxymethylidene analogues (for example, **2′a**, **2′c**, **2′g**) provided the same products with comparable yields. The structure of the isolated compounds was proved using X-ray structural analysis for compound **3a**,† and it was established that the very 7-amino-2-(het)aryl- and 7-amino-2-methyl-5-phenylimiazo[1,5-*b*]pyridazine-3-carbonitriles **3a**–**f** and **3g**, respectively, were formed in the course of the studied cascade reaction (Figure 1) rather than other possible isomers (for more discussion, see Online Supplementary Materials).

---

† *Crystal data for* **3a**. $C_{19}H_{13}N_5$ ($M = 311.34$), triclinic, space group $P\bar{1}$, at 296 K: $a = 4.9675(3)$, $b = 11.6255(6)$ and $c = 14.6955(8)$ Å, $\alpha = 92.858(3)°$, $\beta = 95.807(3)°$, $\gamma = 99.509(3)°$, $V = 830.79(8)$ Å^3, $Z = 2$, $d_{\text{calc}} = 1.245$ g cm^{-3}, μ(MoKα) = 0.78 cm^{-1}, $F(000) = 324$. Intensities of 25584 reflections were measured with a Bruker D8 Quest CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta < 56°$], and 4016 independent reflections ($R_{\text{int}} = 0.1585$) were used in the further refinement. Using Olex2,[25] the structure was solved with the ShelXT[26] structure solution program using Intrinsic Phasing and refined with the XL[27] refinement package using Least Squares minimization. Hydrogen atoms of NH$_2$ group were located from difference Fourier synthesis, positions of others were calculated, and they all were refined in the isotropic approximation using the riding model. The refinement converged to $wR_2 = 0.1630$ and GOF = 0.957 for all the independent reflections [$R_1 = 0.0561$ was calculated against F for 2037 observed reflections with $I > 2\sigma(I)$].

CCDC 2087764 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

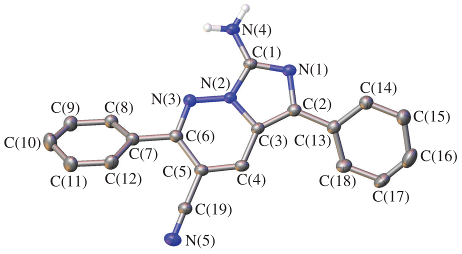
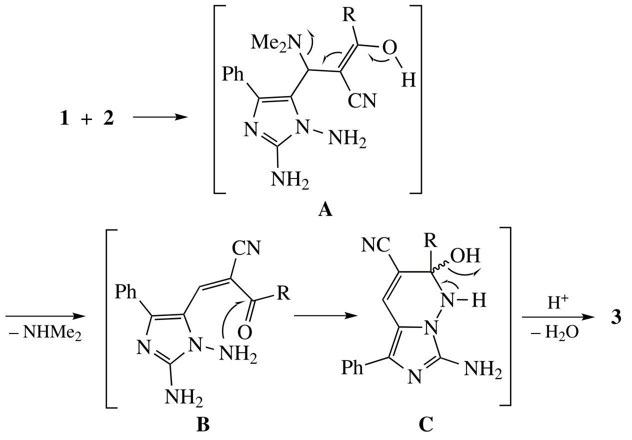


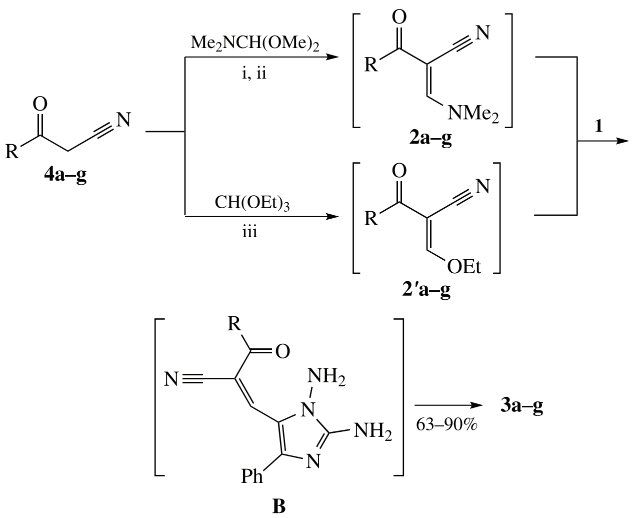
Figure 1 General view of compound **3a** in representation of atoms *via* thermal ellipsoids ($p = 30\%$). Hydrogen atoms except those of the NH_2 group as well as minor components of the disordered phenyl groups are not shown.



Scheme 2

Based on the obtained results, we have proposed the following mechanism for this transformation (Scheme 2). We assume that the process mostly occurs under thermodynamic control and results in the formation of a more stable (due to steric hindrance) regioisomer **3**. This was confirmed by the fact that replacement of the aryl group by less bulky methyl one (R = Me, reactants **2g** and **2′g**) significantly decreased the reaction time. At the first stage, intermediate **A** being the product of the classical Michael reaction, cleaves off the dimethylamine molecule and transforms into intermediate **B**. At the last stage, an acid-catalyzed nucleophilic attack of the N^1 amino group on the carbonyl group occurs followed by the dehydration and formation of the final product **3a** (see Scheme 2, for more discussion, see Online Supplementary Materials).

Imidazopyridazines **3a**–**g** can also be obtained by three-component reactions between 3-oxo-3-R-propanenitriles **4a**–**g** and triethyl orthoformate or dimethylformamide dimethylacetal (Scheme 3). The conditions of the process are absolutely identical to the two-component processes. It should be noted that the yields of products of multicomponent reactions differ slightly from those of two-component reactions. Considering the obtained results, we can assume that multicomponent reactions include the stage of the formation of enamine(ethoxy)-methylidene derivative **2**, whose reaction with diaminoimidazole results in the formation of adduct **B** (see also Scheme 2). The intramolecular condensation of the latter results in the formation of the final products – imidazo[1,5-*b*]pyridazine **3a**–**g**.



Scheme 3 *Reagents and conditions*: i, **4**, $Me_2NCH(OMe)_2$, DMF, room temperature, 6 h (**2a**–**g** are formed); ii, **1**, Pr^iOH, AcOH (cat.), 2 h; iii, **1** + **4**, $CH(OEt)_3$, Pr^iOH–DMF (3 : 1), AcOH (cat.), 2 h boiling.

To sum up, the two-component and three-component reactions of 1,2-diamino-4-phenylimidazole with β-oxo nitriles proceed regioselectively when boiled in a mixture of isopropyl alcohol and DMF in the presence of catalytic amounts of acetic acid for 60–120 min to produce 7-amino-2-R-5-phenylimidazo[1,5-*b*]-pyridazine-3-carbonitriles.

The study received financial support from the Ministry of Science and Higher Education of the Russian Federation within the framework of State Contract with universities regarding scientific research in 2020–2022 (grant no. FZGU-2020-0044). X-ray diffraction data were collected with the financial support from the Ministry of Science and Higher Education of the Russian Federation using the equipment of Center for molecular composition studies of INEOS RAS.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.11.017.

References

1 A. Hollis and Z. Ahmed, *N. Engl. J. Med.*, 2013, **369**, 2474.
2 R. V. Shingalapur, K. M. Hosamani and R. S. Keri, *Eur. J. Med. Chem.*, 2009, **44**, 4244.
3 C. Congiu, M. T. Cocco and V. Onnis, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 989.
4 M. Tonelli, M. Simone, B. Tasso, F. Novelli and V. Boido, *Bioorg. Med. Chem.*, 2010, **18**, 2937.
5 W.-S. Huang, C. A. Metcalf, R. Sundaramoorthi, Y. Wang, D. Zou, R. M. Thomas, X. Zhu, L. Cai, D. Wen, S. Liu, J. Romero, J. Qi, I. Chen, G. Banda, S. P. Lentini, S. Das, Q. Xu, J. Keats, F. Wang, S. Wardwell, Y. Ning, J. T. Snodgrass, M. I. Broudy, K. Russian, T. Zhou, L. Commodore, N. I. Narasimhan, Q. K. Mohemmad, J. Iuliucci, V. M. Rivera, D. C. Dalgarno, T. K. Sawyer, T. Clackson and W. C. Shakespeare, *J. Med. Chem.*, 2010, **53**, 4701.
6 E. A. Peterson, A. A. Boezio, P. S. Andrewa, C. M. Boezio, T. L. Bush, A. C. Cheng, D. Choquette, J. R. Coats, A. E. Colletti, K. W. Copeland, M. DuPont, R. Graceffa, B. Grubinska, J. L. Kim, R. T. Lewis, J. Liu, E. L. Mullady, M. H. Potashman, K. Romero, P. L. Shaffer, M. K. Stanton, J. C. Stellwagen, Y. Teffera, S. Yi, T. Cai and D. S. La, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4967.
7 G. D. Miller, D. W. Woessner, M. J. Sirch and C. S. Lim, *Mol. Pharmaceutics*, 2013, **10**, 3475.
8 J. M. Foulks, K. J. Carpenter, B. Luo, Y. Xu, A. Senina, R. Nix, A. Chan, A. Clifford, M. Wilkes, D. Vollmer, B. Brenning, S. Merx, S. Lai, M. V. McCullar, K.-K. Ho, D. J. Albertson, L. T. Call, J. J. Bearss, S. Tripp, T. Liu, B. J. Stephens, A. Mollard, S. L. Warner, D. J. Bearss and S. B. Kanner, *Neoplasia*, 2014, **16**, 403.
9 R. Benfang and R. Jiannifu, *Patent CN 110396089*, 2019.
10 D. C. D'Amico, B. J. Herberich, C. L. M. Jackson, L. H. Pettus, A. Tasker, H.-L. Wang, B. Wu and R. Wurz, *Patent WO 2012/148775*, 2012.
11 S. Moreau, P. Coudert, C. Rubat, D. Vallee-Goyet, D. Gardette, J. C. Gramain and J. Couquelet, *Bioorg. Med. Chem.*, 1998, **6**, 983.
12 M. G. Rimoli, E. Russo, M. Cataldi, R. Citraro, P. Ambrosino, D. Melisi, A. Curcio, S. De Lucia, P. Patrignani, G. De Sarro and E. Abignente, *Neuropharmacology*, 2009, **56**, 637.
13 T. M. Chapman, S. A. Osborne, N. Bouloc, J. M. Large, C. Wallace, K. Birchall, K. H. Ansell, H. M. Jones, D. Taylor, B. Clough, J. L. Green and A. A. Holder, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3064.

14 L. R. Roberts, P. A. Bradley, M. E. Bunnage, K. S. England, D. Fairman, Y. M. Fobian, D. N. A. Fox, G. E. Gymer, S. E. Heasley, J. Molette, G. L. Smith, M. A. Schmidt, M. A. Tones and K. N. Dack, *Bioorg. Med. Chem. Lett*., 2011, **21**, 6515.

15 M. Follmann, J. Ackerstaff, G. Redlich, F. Wunder, D. Lang, A. Kern, P. Fey, N. Griebenow, W. Kroh, E.-M. Becker-Pelster, A. Kretschmer, V. Geiss, V. Li, A. Straub, J. Mittendorf, R. Jautelat, H. Schirok, K.-H. Schlemmer, K. Lustig, M. Gerisch, A. Knorr, H. Tinel, T. Mondritzki, H. Trübel, P. Sandner and J.-P. Stasch, *J. Med. Chem*., 2017, **60**, 5146.

16 P. G. Sergeev and V. G. Nenajdenko, *Russ. Chem. Rev.*, 2020, **89**, 393.

17 S. Ruch, T. Irrgang and R. Kempe, *Chem. – Eur. J.*, 2014, **20**, 13279.

18 V. V. Lipson, N. V. Svetlichnaya, M. G. Shirobokov, V. I. Musatov, O. V. Shishkin and S. V. Shishkina, *Russ. J. Org. Chem*., 2012, **48**, 273 (*Zh. Org. Khim*., 2012, **48**, 281).

19 V. V. Lipson, N. V. Svetlichnaya, S. V. Shishkina and O. V. Shishkin, *Mendeleev Commun*., 2008, **18**, 141.

20 D. Yu. Vandyshev, Kh. S. Shikhaliyev, A. Yu. Potapov and M. Yu. Krysin, *Chem. Heterocycl. Compd*., 2014, **50**, 1316 (*Khim. Geterotsikl. Soedin*., 2014, 1428).

21 D. Yu. Vandyshev, Kh. S. Shikhaliyev, A. Yu. Potapov and M. Yu. Krysin, *Chem. Heterocycl. Compd*., 2015, **51**, 829 (*Khim. Geterotsikl. Soedin*., 2015, 829).

22 D. Yu. Vandyshev, Kh. S. Shikhaliev, A. Yu. Potapov, M. Yu. Krysin, F. I. Zubkov and L. V. Sapronova, *Beilstein J. Org. Chem*., 2017, **13**, 2561.

23 D. Yu. Vandyshev, Kh. S. Shikhaliyev, A. Yu. Potapov and M. Yu. Krysin, *Chem. Heterocycl. Compd*., 2015, **51**, 573 (*Khim. Geterotsikl. Soedin*., 2015, 573).

24 R. Brückner, J.-P. Lavergne and P. Viallefont, *Liebigs Ann. Chem*., 1979, 639.

25 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr*., 2009, **42**, 339.

26 G. M. Sheldrick, *Acta Crystallogr*., 2015, **A71**, 3.

27 G. M. Sheldrick, *Acta Crystallogr*., 2008, **A64**, 112.

Received: 7th June 2021; Com. 21/6580