Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2022, **32**, 795–797

Mendeleev Communications

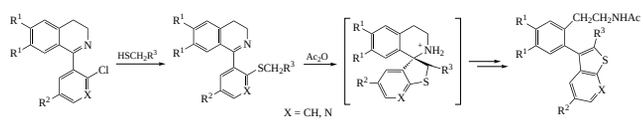
Novel recyclization of 3,4-dihydroisoquinolines as an efficient route to a new type of heteroarylated derivatives of β-arylethylamines

Vadim S. Sochnev,[a] Anatolii S. Morkovnik,*[a] Alexander A. Zubenko,[b] Lyudmila N. Divaeva,[a] Oleg P. Demidov,[c] Tatyana N. Gribanova,[a] Leonid N. Fetisov,[b] Viktorya V. Chekrysheva,[b] Kristina N. Kononenko,[b] Marya A. Bodryakova,[b] Alexander I. Klimenko,[b] Gennadii S. Borodkin[a] and Igor A. Estrin[d]

[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*
[c] *North-Caucasus Federal University, 355009 Stavropol, Russian Federation*
[d] *Rostov State Transport University, 344038 Rostov-on-Don, Russian Federation*

DOI: 10.1016/j.mencom.2022.11.029

A new recyclization of 3,4-dihydroisoquinolines is a convenient route to derivatives of new β-(*o*-benzothienylaryl)- and β-(*o*-thieno[2,3-*b*]pyridinylaryl)-containing ethylamines. These compounds look promising monoaminergic agents.



Keywords: 3,4-dihydroisoquinolines, β-arylethylamines, recyclization, heterocyclization, *o*-benzothienylarenes, *o*-thieno[2,3-*b*]pyridinylarenes.

Derivatives of β-aryl- and β-heteroaryl-containing ethylamines that are structural analogues of biogenic amines are interesting as potential monoaminergic agents with diverse biological activity, such as psychotropic or even, which seems somewhat unexpected at first glance, antitumor action.[1] Compounds of this series with different lengths and/or compositions of the noncyclic linker usually underlie the structure of clinically employed synthetic monoaminergic agents (see, for example, data on serotoninergic agents[2]). Most commonly, agents of this kind do not contain phenolic hydroxy groups, and this fact may prevent their undesirable ROS-generating activity that is possible for biogenic amines.[3] A particularly interesting type of β-aryl(heteroaryl)ethylamines are their heteroaryl derivatives, primarily those where the heteroaryl group is bound to an aromatic (heteroaromatic) part of the basic scaffold. This makes them looking like hetero analogues of a very important biphenyl scaffold encountered in bioactive compounds.[4]

Previously, we suggested an efficient and a rather general approach to one of the varieties of such amines, namely, those in which the heteroaryl and aminoethyl groups are adjacent to each other. Its specific feature is that it employs reaction sequences that involve some preliminary transformations to form key structures with suitable reactivity, such as derivatives of fused heterocyclic systems, and their recyclization. The common feature of such recyclizations is that both heteroaryl and aminoethyl groups in the molecules are formed at once. Groups of the first type are formed from the structural elements of the heterocyclic ring that is opened, its functional or other reactive group; as a rule, the reagent that induces recyclization is also involved. Groups of the second type are formed from elements of the heterocyclic ring when its opening also results in the formation (from the rest of the original cyclic system) of the (hetero)arene moiety of the basic scaffold. In this type of recyclizations, the main problem is that a specific type of recyclization is required for each new type of heterocyclic ring of the heteroaryl group, or rather, the hetero-ring of this group through which it is bound to the main scaffold.

Still, since a number of new recyclizations of this kind were identified in the series of functionalized 3,4-dihydroisoquinolines, 3,4-dihydrocarbolines, 3,4-dihydronaphtho[2,1-*f*]isoquinolinines,

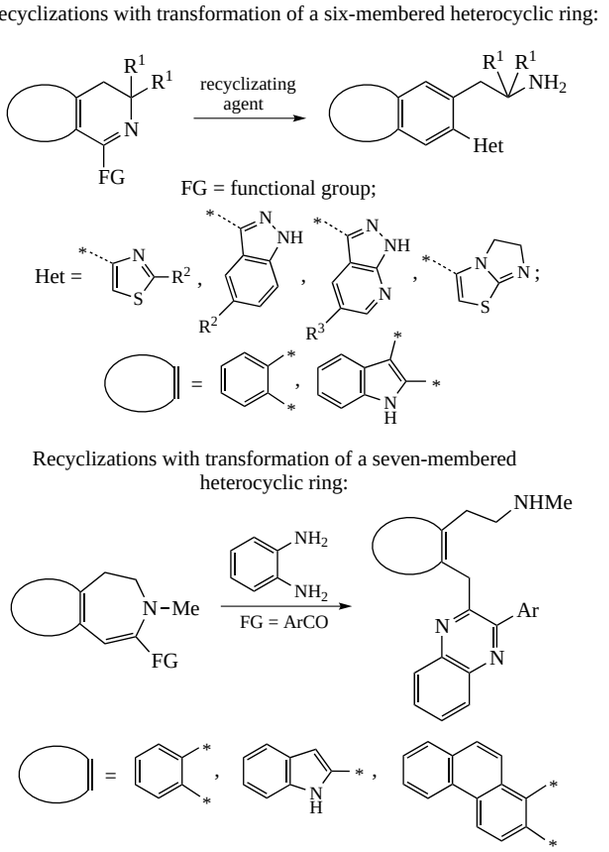
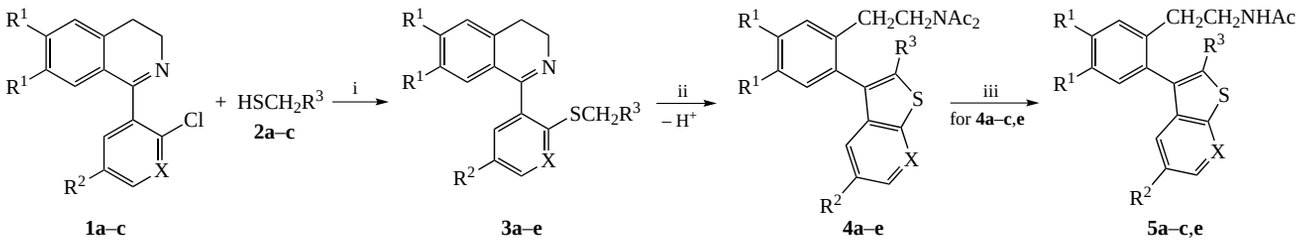


Figure 1 New recyclizations providing β-[*o*-(hetero)arylaryl]ethylamines.



1a–c **3a–e** **4a–e** **5a–c,e**

4b, 97%
4c, 69%
4d, 69%

5a, 76%
5b, 65%
5c, 54%
5e, 66%

1 R^1 = H, R^2 = NO_2, X = CH (**a**); R^1 = OMe, R^2 = NO_2, X = CH (**b**); R^1 = OMe, R^2 = H, X = N (**c**)
2 R^3 = benzimidazol-2-yl (**a**), COOEt (**b**), $CONH_2$ (**c**)
3 R^1 = H, R^2 = NO_2, R^3 = benzimidazol-2-yl, X = CH (**a**); R^1 = OMe, R^2 = NO_2, X = CH, R^3 = COOEt (**b**), benzimidazol-2-yl (**c**), $CONH_2$ (**d**); R^1 = OMe, R^2 = H, R^3 = benzimidazol-2-yl, X = N (**e**)
4 R^1 = H, R^2 = NO_2, X = CH, R^3 = benzimidazol-2-yl (**a**); R^1 = OMe, R^2 = NO_2, X = CH, R^3 = COOEt (**b**), benzimidazol-2-yl (**c**), CN (**d**); R^1 = OMe, R^2 = H, X = N, R^3 = benzimidazol-2-yl (**e**)
5 R^1 = H, R^2 = NO_2, X = CH, R^3 = benzimidazol-2-yl (**a**); R^1 = OMe, R^2 = NO_2, X = CH, R^3 = COOEt (**b**), benzimidazol-2-yl (**c**); R^1 = OMe, R^2 = H, X = N, R^3 = benzimidazol-2-yl (**e**)

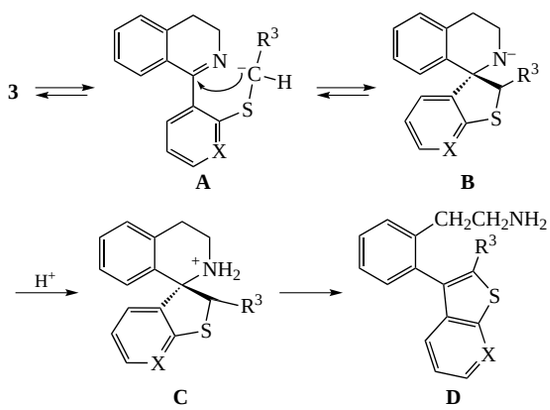
Scheme 1 *Reagents and conditions*: i, NaH, DMF (for **2b**, **2e**), 24 h, 25 °C (for **2b**), 3 h, 110–115 °C (for **2e**); EtONa–EtOH, reflux 0.5 or 4 h (for **2a**, **2c**, **2d**); ii, Ac_2O, reflux; iii, $NH_2NH_2 \cdot H_2O$, EtOH, 24 h, 20–25 °C. Compounds **3c**,**e** and **4a**,**e** were used in the reactions without purification.

fused dihydroazepines with [*d*]-annulated benzene, indole or phenanthrene moiety, it became possible to apply the synthetic strategy under consideration to obtain heteroarylated β-aryl-, β-phenanthrylethylamines and tryptamines with a few types of heteroaryl groups (Figure 1).[5] No doubt, this approach can be extended to other types of cyclic systems, heterocycles that undergo recyclization in these systems, and types of heteroarylating groups that are built.

This work shows how it can be implemented to obtain derivatives of new β-(*o*-heteroarylaryl)ethylamines containing bicyclic heteroaryl groups at the *ortho*-position, namely, benzothienyl and thieno[2,3-*b*]pyridinyl groups, bound to the neurotropic scaffold through a thiophene ring. For this purpose, we employed a new recyclization that we have discovered and report below, in a series of 1-aryl- and 1-(2-pyridyl)-3,4-dihydroisoquinolines. The preliminary pre-recyclization transformation providing sulfide functionalization of such isoquinolines required for the reaction to occur was implemented as the synthesis of methylene-active dihydroisoquinoline sulfides of type **3** by the reaction of 1-*o*-chloroaryl- or 1-(2-chloropyridyl)-3,4-dihydroisoquinolines **1** with methylene-active thiols **2** (Scheme 1).

The efficiency of the suggested general scheme was demonstrated using the example of dihydroisoquinolines **1a–c** and the corresponding sulfides **3a–e**. Compounds **3a–e** on not too long (2–8 h) boiling in Ac_2O that catalyzes this reaction undergo isomerization-type recyclization complicated by *N*-acylation to give *N*,*N*-diacetyl derivatives of *o*-benzothienyl- and *o*-thieno[2,3-*b*]pyridinyl-containing β-arylethylamines **4a–e** in 66–97% yields (see Scheme 1 and Online Supplementary Materials for experimental details). In the case of compound **3d**, the reaction is accompanied by dehydration of the amido group, so nitrile **4d** is formed instead of the corresponding amide.

The likely recyclization pathway (Scheme 2) reflects the non-typical character of the reaction, namely, opening of the reactive hetero-ring occurs only after a new hetero-ring, in this case thiophene, is formed. The reaction involves spiro-cyclization of the *C*-anion of substrate **A** into the isomeric spiro-*N*-anion **B**, followed by opening of the six-membered hetero-ring resulting in cleavage of the spiro-cyclic structure, most likely in its cationic spiro-form **C**. This scheme is supported by the fact that structures **A**, **B** and **C** are the minima on the potential energy surfaces of the corresponding systems, as shown by calculations using DFT method [B3LYP/6-311+(d,p)] for $R^1 = R^2 = H$ and $R^3 = CN$, while the seemingly most problematic conversion **A** → **B** occurs rather readily *via* transition state **TS** (Figure 2, see also Online



A **B** **C** **D**

Scheme 2

Supplementary Materials). It is characterized by the energy barrier $E^{\neq}$ = 16.4 kcal mol^{-1}, while the overall reaction has moderately unfavorable thermodynamics (ΔE = +14.8 kcal mol^{-1}), which is not an impassable factor, given that the recyclization in general is clearly almost irreversible.

Compounds **4** are capable of monodeacylation with hydrazine hydrate that readily occurs at room temperature. This method was utilized to convert diacetyl derivatives **4a–c**,**e** to the corresponding monoacetyl ones **5a–c**,**e** in 54–76% yields (see Scheme 1).

The structures of the resulting sulfides and products of their recyclization and subsequent deacylation were confirmed by ^{1}H, ^{13}C NMR spectroscopy and high resolution mass-spectrometry, along with results of single-crystal X-ray spectroscopic studies

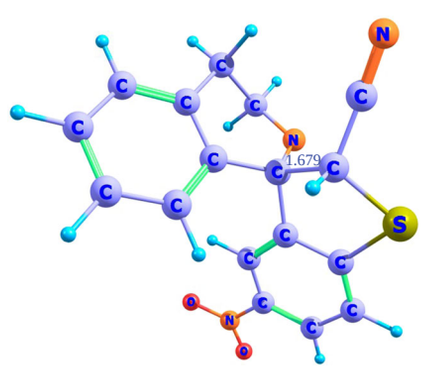


Figure 2 Structure of transition state **TS** for the spiro-cyclization of *C*-anion **A** to spiro-*N*-anion **B** with $R^1 = R^2 = H$, $R^3 = CN$; B3LYP/6-311+G(d,p).

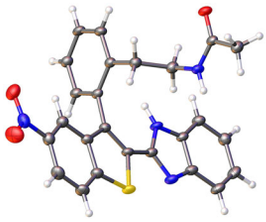


Figure 3 Molecular structure of one of the atropoisomers of compound **5c** according to single-crystal X-ray spectroscopy data.

of bi-heteroaryl derivative **5c** (Figure 3). Compound **5c** in the solid phase exists as a mixture of two atropoisomers with respect to the aryl–heteroaryl bond, and a pair of these isomers builds an elementary crystal cell.†

An important advantage of the reaction described herein is that it allows synthesizing pharmacophore-saturated structures of heteroarylated β-arylethylamines with a heteroaryl group of bi-heteroaryl type or with a bifunctionalized, and thus easily transformable in terms of available substituents, benzothiophene bicycle. Structures of this kind should be useful agents in the search for selective monoaminergic agents.[12]

In summary, we suggested a convenient route to a new type of heteroaryl derivatives of β-arylethylamines that are potential monoaminergic agents comprising 3-benzothienyl or thieno[2,3-*b*]pyridin-3-yl groups at the *ortho*-position.

This study was financially supported by the Russian Foundation for Basic Research (grant no. 20-03-00657). The starting compounds were synthesized at the North Caucasian Zonal Research Veterinary Institute (Program for fundamental studies of State Academies of Sciences for 2013–2022; project no. 0710-2019-0044). Quantum-chemical calculations and interpretation of reaction mechanisms were performed at the Southern Federal University (State assignment in the field of scientific activity, Southern Federal University, 2020, project FENW-2020-0031, 0852-2020-0031).

† *Crystal data for* **5c**. $C_{25}H_{20}N_4O_3S$ (M = 456.51 g mol^{-1}), monoclinic, space group $P2_1/c$ (no. 14), a = 10.0803(2), b = 15.0856(4) and c = 14.3380(4) Å, β = 106.089(3)°, V = 2094.94(10) Å^3, Z = 4, T = 100.15 K, μ(CuKα) = 1.687 mm^{-1}, d_{calc} = 1.447 g cm^{-3}, 21849 reflections measured (8.692 ⩽ 2θ ⩽ 156.252°), 4365 unique (R_{int} = 0.0665, R_{sigma} = 0.0410) which were used in all calculations. The final R_1 was 0.0508 [$I > 2\sigma(I)$] and wR_2 was 0.1549 (all data).

The experimental data for structure **5c** were obtained on an Agilent SuperNova diffractometer using a microfocus X-ray source with a copper anode and an Atlas S2 two-dimensional CCD detector. The reflections were collected, unit cell parameters determined and refined using the specialized CrysAlisPro 1.171.38.41 software suite (Rigaku Oxford Diffraction, 2015).[8] The structures were solved using the ShelXT program (Sheldrick, 2015)[9] and refined with the ShelXL program (Sheldrick, 2015).[10] Molecular graphics and presentation of structures for publication were performed with the Olex^2 ver. 1.5 software suite.[11]

CCDC 2161739 (crystal from acetonitrile) 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.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.11.029.

References

1 (*a*) A. Rosas-Cruz, N. Salinas-Jazmín and M. A. Velasco-Velázquez, *Technol. Cancer Res. Treat.*, 2021, 15330338211027913; (*b*) M. S. I. Roney and S.-K. Park, *Arch. Pharmacal Res.*, 2018, **41**, 384; (*c*) J. S. Weissenrieder, J. D. Neighbors, R. B. Mailman and R. J. Hohl, *J. Pharmacol. Exp. Ther.*, 2019, **370**, 111; (*d*) J.-K. Lee, D.-H. Nam and J. Lee, *Oncol. Lett.*, 2016, **11**, 1281.
2 S. L. Kitson, *Curr. Pharm. Des.*, 2007 **13**, 2621.
3 N. Genet, M. Billaud, R. Rossignol, M. Dubois, J. Gillibert-Duplantier, B. E. Isakson, R. Marthan, J.-P. Savineau and C. Guibert, *Front. Physiol.*, 2017, **8**, 76.
4 B. Zdrazil and R. Guha, *J. Med. Chem.*, 2018, **61**, 4688.
5 (*a*) A. A. Zubenko, A. S. Morkovnik, L. N. Divaeva, O. P. Demidov, V. G. Kartsev, V. S. Sochnev, A. I. Klimenko, N. M. Dobaeva, G. S. Borodkin, A. N. Bodryakov, M. A. Bodryakova and L. N. Fetisov, *Mendeleev Commun.*, 2021, **31**, 125; (*b*) A. A. Zubenko, A. S. Morkovnik, L. N. Divaeva, O. P. Demidov, V. S. Sochnev, I. G. Borodkina, Yu. D. Drobin and A. A. Spasov, *Mendeleev Commun.*, 2020, **30**, 28; (*c*) A. A. Zubenko, A. S. Morkovnik, L. N. Divaeva, V. S. Sochnev, O. P. Demidov, A. I. Klimenko, L. N. Fetisov, A. N. Bodryakov, M. A. Bodryakova and G. S. Borodkin, *Mendeleev Commun.*, 2022, **32**, 265; (*d*) A. A. Zubenko, A. S. Morkovnik, L. N. Divaeva, V. S. Sochnev, O. P. Demidov, A. N. Bodryakov, L. N. Fetisov, K. N. Kononenko, M. A. Bodryakova and A. I. Klimenko, *Russ. J. Gen. Chem.*, 2021, **91**, 792 (*Zh. Obshch. Khim.*, 2021, **91**, 703).
6 E. Suna and P. Trapencieris, *Chem. Heterocycl. Compd.*, 2000, **36**, 287.
7 C.-Y. Kuo, M.-J. Wu and Y.-H. Kuo, *Eur. J. Med. Chem.*, 2006, **41**, 940.
8 *CrysAlisPro Software System, version 1.171.38.41*, Rigaku Oxford Diffraction, Oxford, 2015.
9 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **A71**, 3.
10 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3.
11 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. J. Puschmann, *Appl. Crystallogr.*, 2009, **42**, 339.
12 D. Kułaga, A. K. Drabczyk, G. Satał, G. Latacz, K. Rózga, D. Plażuk and J. Jaskowska, *Eur. J. Med. Chem.*, 2022, **227**, 113931.

Received: 31st March 2022; Com. 22/6854