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New type of recyclization in 3,4-dihydroisoquinolines in the synthesis of β-(*o*-indazolylaryl)ethylamines and their 7-azaindazolyl analogues

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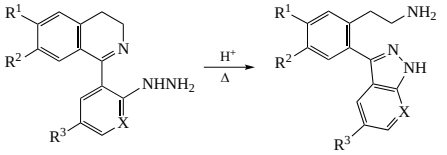
1-(2-Hydrazinoaryl)-3,4-dihydroisoquinolines and their hydrazinopyridyl analogues undergo recyclization affording novel (7-aza)indazolyl-β-arylethylamines. The products are expected to possess neurotropic activities.



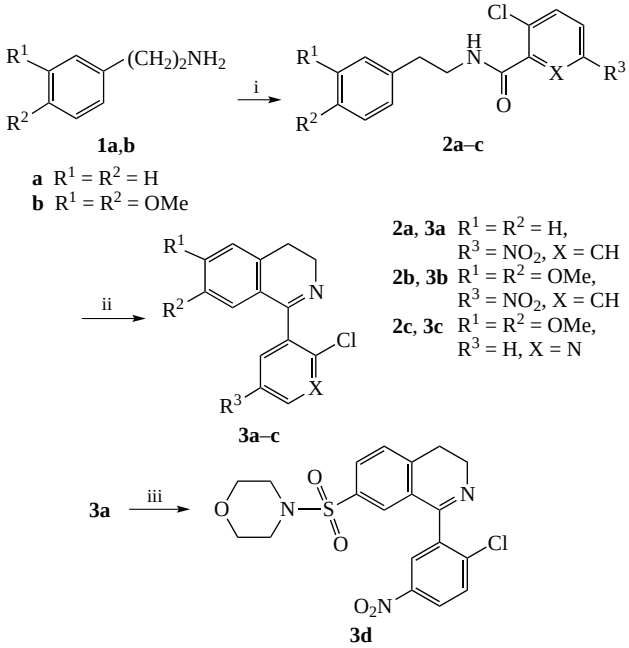
Keywords: 1-(2-hydrazinoaryl)-3,4-dihydroisoquinolines, isoquinolines, β-phenylethylamines, recyclization, indazoles, 7-azaindazoles.

Indazoles belonging to the class of privileged scaffolds[1] and analogous azaindazoles exhibit diverse biological activities.[2–17] For this reason, the chemistry of indazoles is of great interest. New synthetic approaches to indazoles are based mainly on various cyclization reactions.[18] On the other hand, recyclization reactions also have considerable potential in this regard.

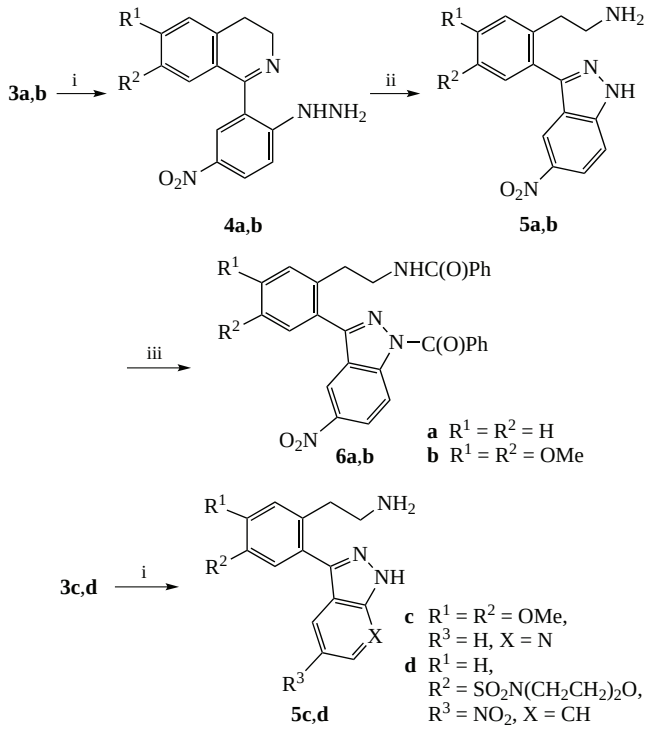
This work reports that new 1-(2-hydrazinoaryl)-3,4-dihydroisoquinolines and their 2-hydrazino-3-pyridyl analogues undergo recyclization into the corresponding novel 3-arylindazoles and 3-aryl-7-azaindazoles equipped with β-aminoethyl substituent at the *ortho*-position of the aryl group. Due to the structural relationship with neurotransmitters and neuromodulators[19] of the β-arylethylamine structure, such compounds may be regarded as potential neurotropic agents and starting compounds for various further chemical transformations. The principal difference between the reaction in question and the previously reported recyclizations of 1-chloromethyl-3,4-dihydroisoquinolines[20] and acyl derivatives of hydrogenated [*d*]-fused tetrahydroazepines[21,22] (also resulting in *ortho*-hetarylated β-arylethylamines) relates to the nature of the reaction centre in the substituent. These differences correspond to both the nature of the side reaction center, which is of nucleophilic rather than electrophilic nature in this reaction, and the participation or non-participation of atoms of a foreign reagent in building the new hetero-ring, the nature of heteroaryl groups formed in the reaction, and the type of their binding to the *ortho*-position of the aryl group.

The starting hydrazino derivatives were obtained from β-arylethylamines **1a**,**b** by the reaction sequence involving their *N*-acylation with the corresponding (hetero)aroyl chlorides followed by the Bischler–Napieralsky cyclization of the resulting monoacyl derivatives **2a**–**c** to give 1-[2-chloroaryl(pyridyl)]-3,4-dihydroisoquinolines **3a**–**c** (Scheme 1). Yet another similar chloro derivative, sulfamide **3d**, was obtained by sulfonation of the benzene ring of compound **3a**.

The reaction of chloro derivatives **3a**,**b** with hydrazine was carried out by refluxing in 2-methoxyethanol for 0.5–1 h to afford individual hydrazino derivatives **4a**,**b** (Scheme 2). Subsequent recyclization of these compounds was performed in the presence of conc. HCl by refluxing in the same solvent for 8 and 20 h, respectively, to give hydrochlorides of 2-(indazolylaryl)-ethylamines **5a**,**b** in 62 and 95% yields. In this case, the acid is necessary to convert the substrate into its N^2-protonated form **A** (Figure 1) in which the hydrogenated pyridinium ring manifests enhanced electrophilicity. In the case of chloro derivatives **3c**,**d**, the nucleophilic exchange and recyclization stages were carried out in a one-pot mode, and the application of HCl additive was not necessary (see Scheme 2). The yields of (aza)indazolyl



Scheme 1 *Reagents and conditions*: i, 2-Cl-5-$O_2NC_6H_3C(O)Cl$ (for **2a**,**b**) or 2-chloronicotinoyl chloride (for **2c**), K_2CO_3, H_2O, 0–5 °C; ii, $POCl_3$, 105–110 °C; iii, $ClSO_3H$, 130–135 °C, then morpholine, DMF, 20–25 °C.



Scheme 2 *Reagents and conditions*: i, $NH_2NH_2{\cdot}H_2O$, $MeO(CH_2)_2OH$, reflux, 0.5–1 h (for **3a**,**b**) or 4–5 h (for **3c**,**d**); ii, NH_2NH_2, $MeO(CH_2)_2OH$, HCl, reflux, 8–20 h; iii, PhC(O)Cl, pyridine, 20–25 °C.

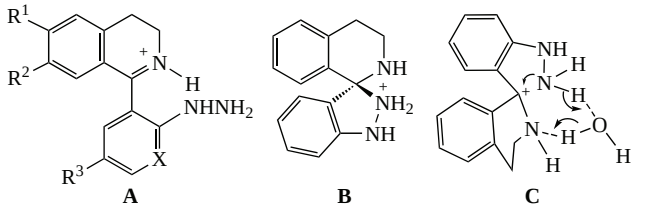


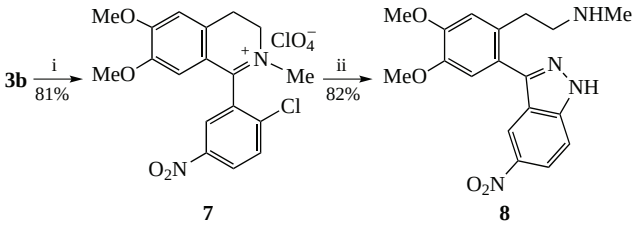
Figure 1 Structures of the protonated form of hydrazines (**A**), the simplest spiro form (**B**), and the possible transition state of concerted recyclization with catalysis by a water molecule (**C**).

β-arylethylamines **5c**,**d** amounted to 77 and 42%, respectively, with respect to the chloro derivatives used for the reaction. These transformations should be regarded as spontaneous reactions in view of the fact that they do not require any additional reagent to build the new hetero ring. Undoubtedly, this recyclization can also be used for the synthesis of structural analogues of compounds **5** built on the basis of [*d*]-fused pyrazoles of other types. When compounds **5a**,**b** were treated with benzoyl chloride, the acylation occurred at both primary amine group and indazole NH moiety to give dibenzoyl derivatives **6a**,**b** (see Scheme 2).

Apparently, the driving force of the recyclization of compounds **4** is the intramolecular nucleophilic attack of the hydrazine group at the electrophilic site of the protonated hetero ring of structure **A** (see Figure 1), as well as the significantly higher thermodynamic stability of the protonated recyclization products compared to the protonated substrates (the difference in the total energies of the simplest protonated structures **5a** and **4a** calculated by the DFT (B3LYP/6-31G**) method without correction for ZPE is –16.9 kcal mol^{-1}). In terms of the mechanism, this recyclization somewhat resembles the cyclization of *o*-acylfluorobenzenes with hydrazine[23] and recyclization of 5-polyfluoroaryl-1,2,4-oxadiazoles with methylhydrazine into fluorinated indazoles.[24] However, despite the higher electrophilicity of protonated forms **A**, the indicated nucleophilic attack itself is insufficiently favorable energetically for the formation of a C–N bond thus leading to spirocyclic intermediates of type **B**. This is indicated by the results of calculations for structure **B** which does not satisfy the energy minimum (*cf.* ref. 25 with similar data for hydrazine-induced oxadiazole–indazole recyclization). Moreover, it can hardly correspond to the sufficiently low lying transition state of concerted recyclization since it requires an energetically unfavorable accompanying proton transfer from the hydrazino group to the N^2 ring atom, which implies the formation of an additional, highly sterically hindered four-membered cyclic reaction node. However, such concerted process with simultaneous proton transfer can be efficiently catalyzed by molecules of proton-donor solvents, for example, water, by incorporation of its OH group in the cyclic proton-transfer reaction node that becomes weakly sterically hindered. The efficiency of this kind of catalysis was demonstrated, for example, for the sulfoxidation of sulfides with H_2O_2 (see, *e.g.*, ref. 26 and the references therein). As applied to the recyclization of hydrazines **4**, such catalysis by a water molecule implies the reaction *via* transition states of type **C** (see Figure 1).

The important role of cationic form **A** in the recyclization of hydrazino derivatives **4** is confirmed by the two next facts. (1) The ability of N^2-quaternized substrates to undergo similar recyclization was exemplified for quaternary salt **7** (Scheme 3), which additionally provides an easy access to *N*-alkyl analogues of compounds **5**, such as amine **8**. (2) As mentioned above, hydrazines **4a**,**b** are unable to undergo recyclization in the absence of highly acidic promoters.

The structures of compounds **5**, **6** and **8** were confirmed by NMR spectroscopy (see Online Supplementary Materials), as well as by single-crystal X-ray diffraction data for hydroperchlorate of amine **5c** (Figure 2).[†] As it follows from these data, the crystal structure of this salt is stabilized by intramolecular N(1)···HN(4) (2.09 Å) and intermolecular N(4)H···O(5) (2.09 Å) hydrogen bonds whose role is not so significant in solution. At least, the chemical shift of ammonium group protons (8.19 ppm) in a solution of compound **5c** in



Scheme 3 *Reagents and conditions*: i, Me_2SO_4, 125 °C, EtOH, then 60% $HClO_4$; ii, $NH_2NH_2{\cdot}H_2O$, $MeO(CH_2)_2OH$, reflux.

[†] *Crystal data for* **5c**·$HClO_4$. $C_{16}H_{19}ClN_4O_6$ (M = 398.80 g mol^{-1}), triclinic, space group $P\bar{1}$ (no. 2) at 293 K: a = 9.5028(3), b = 9.8960(3) and c = 10.6677(4) Å, α = 82.837(3)°, β = 63.674(3)°, γ = 89.785(3)°, V = 890.63(6) Å^3, Z = 2, μ(CuKα) = 2.292 mm^{-1}, d_{calc} = 1.487 g cm^{-3}, 9923 reflections measured (9.022° ⩽ 2θ ⩽ 152.478°), 3612 unique (R_{int} = 0.0157, R_{sigma} = 0.0159) which were used in all calculations. The final R_1 was 0.0366 [$I > 2\sigma(I)$] and wR_2 was 0.1036 (all data).

Experimental data for structure **5c**·$HClO_4$ were obtained with 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).[27] The structures were solved using the ShelXT program (Sheldrick, 2015)[28] and refined with the ShelXL program (Sheldrick, 2015).[29] Molecular graphics and presentation of structures for publication were performed with the Olex^2 ver. 1.2.10 software suite.[30]

CCDC 2047116 (crystal from methanol) 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.

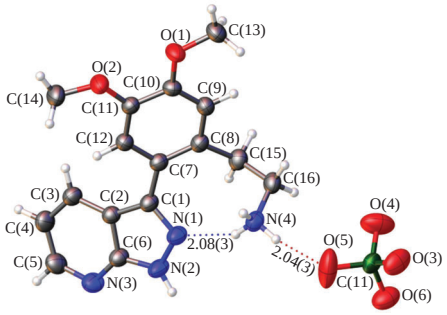


Figure 2 Molecular structure of hydroperchlorate **5c** showing the displacement ellipsoids drawn at the 50% probability level**.**

DMSO-d_6 indicates that a significant intramolecular hydrogen bond does not exist under these conditions.

The recyclization of hydrazino derivatives **4** was studied and the structure of *o*-(7-azaindazolyl)-β-arylethylamine **5c** was determined at the Southern Federal University (SFedU) and the North Caucasian Zonal Research Veterinary Institute (SKZNIVI) with financial support from the Russian Foundation for Basic Research (grant no. 20-03-00657). Compounds **2b**, **3a**,**b**,**d** and **4a**,**b** were synthesized at SKZNIVI with financial support from the program for fundamental scientific studies of State academies of sciences for 2013–2021 (no. 0710-2019-0044). NMR spectrometers of the Center for Molecular Spectroscopy of the Southern Federal University (Rostov-on-Don) and single-crystal X-ray diffraction equipment of the North Caucasus Federal University (Stavropol) were used.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.03.038.

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