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Mendeleev Commun., 2020, **30**, 28–30

Mendeleev Communications

New route to bioactive 2-(hetero)arylethylamines *via* nucleophilic ring opening in fused 7-acyl-2,3-dihydroazepines

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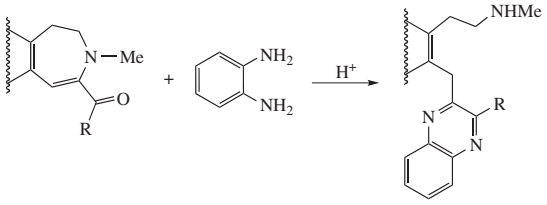
DOI: 10.1016/j.mencom.2020.01.009

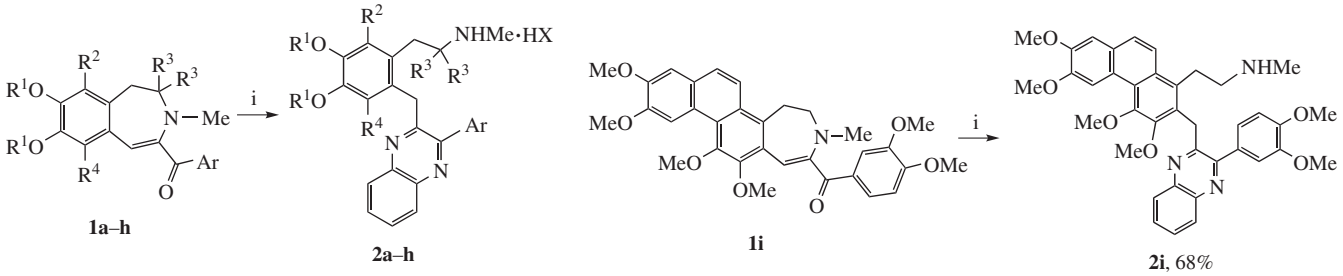
Nucleophilic heterocyclic ring opening in fused 7-acyl-1,2-dihydroazepines with *o*-phenylenediamine affords β-(hetero)arylethylamines.



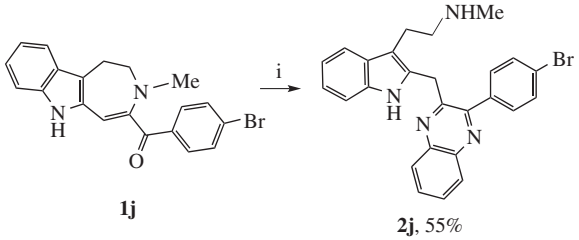
Keywords: fused dihydroazepines, azepine–pyrazine recyclization, β-aryl(heteroaryl)ethylamines, bioactive amines, ring opening reactions.

β-(Hetero)arylethylamines with rather simple structures act as neurotransmitters, neuromodulators and hormones (adrenaline, norepinephrine, dopamine, serotonin, melatonin, *etc*.) that are of importance for the central and peripheral nervous systems.[1–6] Their derivatives with more complex structures are interesting objects for the creation of neurotropic and other types of drugs.[7]

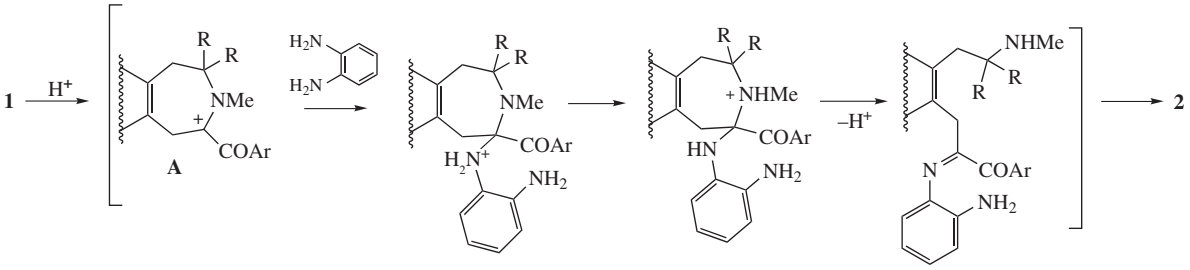
An important synthetic access to β-(hetero)arylethylamines involves the nucleophilic opening of the heterocyclic ring in nitrogen-containing heterocycles with formation of the β-aminoethyl group, for example, in 3,4-dihydroisoquinolinium quaternary salts.[8–12] If a suitable additional reagent is used, these reactions can proceed further, in particular, with recyclization involving the formed β-aminoethyl group. We employed this principle in the synthesis of fused 7-(hetero)aroyl-1,2-dihydroazepines **1** from 3,4-dihydroisoquinolinium salts with participation of acylmethyl halides.[13]



a R^1 = Me, R^2 = R^3 = R^4 = H, Ar = Ph, HX = HBr, 89%
b R^1 = Me, R^2 = R^3 = R^4 = H, Ar = 4-$O_2NC_6H_4$, HX = $H_2C_2O_4$, 72%
c R^1 = Me, R^2 = R^3 = R^4 = H, Ar = 4-BrC_6H_4, HX = HBr, 90%
d R^1 = Me, R^2 = R^3 = R^4 = H, Ar = 3,4-$Cl_2C_6H_3$, no HX, 62%
e R^1 = R^3 = Me, R^2 = R^4 = H, Ar = 3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-6-yl, HX = HCl, 71%
f R^1 = R^3 = Me, R^2 = R^4 = H, Ar = 4-BrC_6H_4, no HX, 65%
g R^1 + R^1 = CH_2, R^2 = R^3 = H, R^4 = OMe, Ar = 4-BrC_6H_4, HX = HBr, 92%
h R^1 + R^1 = CH_2, R^2 = Br, R^3 = H, R^4 = OMe, Ar = 4-$H_2NC_6H_4$, HX = HCl, 92%



Scheme 1 *Reagents and conditions*: i, *o*-$(H_2N)_2C_6H_4$, EtOH, conc. HCl, reflux, then workup.



Scheme 2

When evaluating the synthetic potential of keto azepines **1** (Scheme 1), we assumed that like their non-functionalized dihydroazepine analogues, they could also be used for the similar synthesis of various β-(hetero)arylethylamines. Unlike the case of 3,4-dihydroisoquinoline substrates, the opening of dihydroazepine ring should be catalyzed by acids due to the possibility of C-protonation with formation of carbocations that could add nucleophiles. As bielectrophiles, keto derivatives **1** and their carbocationic forms **A** (Scheme 2) should form promising β-(hetero)arylethylamines of complex structures upon reactions with binucleophiles.

Here we describe the reactions between keto derivatives **1a–j** belonging to different dihydroazepine systems and *o*-phenylenediamine as a typical N,N-binucleophile (see Scheme 1). The reaction was carried out in an alcohol–hydrochloric acid solution (20.0 : 3.3, v/v) with an equimolar substrate/reactant ratio under reflux.

In fact, the nucleophilic cleavage of the seven-membered ring in azepine ketones **1** did occur. Moreover, due to the presence of two electrophilic centers in the substrates, the open forms underwent further cyclization to afford pyrazine heterocycle. Products **2a–j** of this azepine–pyrazine recyclization are representatives of previously unknown (quinoxalin-2-yl)methyl derivatives of bioactive β-(hetero)arylethylamines (see Scheme 1),[†] and more generally, of virtually unexplored heteroarylmethyl-β-(hetero)-arylethylamines with similar structures, of which only four analogues with (indazol-1-yl)methyl substituents have been described.[14] The use of substrates with various cyclic systems afforded quinoxalylmethyl-substituted β-arylethylamines with monocyclic or fused aryl groups, as well as their tryptamine analogues. Apparently, the method can be expanded for the synthesis of other derivatives based on heterocyclic non-indole systems. In combination with the pyridine–azepine recyclization,[13(c),15] the reaction under consideration can be used successfully for structural modification of cotarnine and glaucine with their conversion into arylethylamine derivatives. Indeed, the synthesis of amines **2g–i** clearly demonstrates this possibility.

The most likely route of the keto azepine recyclization includes direct opening of the heterocyclic ring in intermediate **A** by the amino group of the reactant involving intermediate N,N-prototropy (see Scheme 2). Alternatively, ketimine containing an additional free primary amino group can be formed at first (not shown).

Note that N-protonation might be an alternative pathway of acid activation of substrates **1** without the formation of carbocationic intermediates. However, judging by the data of a DFT quantum chemical study (B3LYP/6-31**, see Online Supplementary Materials), this route is non-competitive due to poor electrophilicity of N-protonated form of substrate, which is indicated by very high energies of transition states of its ring opening.

The highest yields (up to 92%) were achieved in cases of benz[*d*]azepine and [1,3]dioxolo[4,5-*h*]benz[*d*]azepines **1a–g** and were somewhat lower for substrates of other types.

The structure of quinoxalylmethyl derivatives **2a–j** was confirmed by elemental analysis, 1D (^{1}H and ^{13}C) and 2D (COSY ^{1}H–^{1}H, HSQC ^{13}C–^{1}H and HMBC ^{13}C–^{1}H and ^{15}N–^{1}H) NMR spectroscopy (see Online Supplementary Materials). In the ^{1}H NMR spectra (600 MHz) of compounds **2a–j**, one two-proton and two one-proton multiplets in the δ 7.65–7.99 (H-6,7), 7.69–8.05 (H-8), and 8.04–8.12 (H-5) regions correspond to the benzene ring protons in the quinoxaline system; the 2-CH_2 group appears as singlet or two doublets at 4.29–4.70 ppm; the ethylene bridge, if presents, gives two distorted triplets of methylene protons at δ 2.48–3.11 and 2.60–3.30, and the *N*-methyl group resonates as singlet in the 2.14–2.55 ppm region.

The structure of amine **2g** was also confirmed by a single-crystal X-ray diffraction study (Figure 1).[‡]

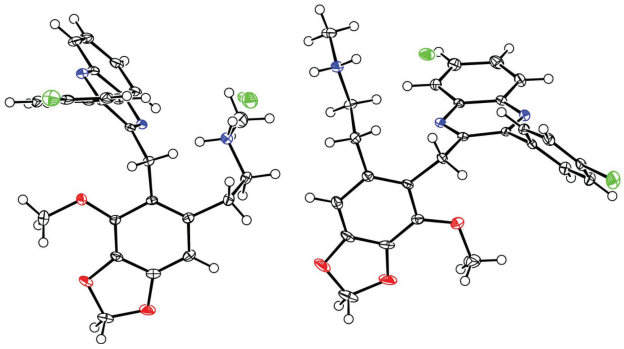


Figure 1 Molecular structure of compound **2g** according to XRD data. The ellipsoids are drawn at the 50% probability level.

[†] *General procedure for the synthesis of amines* **2a–j**. A mixture of the corresponding azepine **1** (0.01 mol), *o*-phenylenediamine (0.01 mol), ethanol (20 ml) and conc. HCl (3.3 ml, 0.04 mol) was refluxed for 2 h and poured into a solution of K_2CO_3 (5.5 g, 0.04 mol) in water (60 ml), extracted with chloroform (3×15 ml), dried with anhydrous Na_2CO_3 and evaporated to dryness *in vacuo* at 50–60 °C. Compounds **2d**,**f**,**i**,**j** were preliminarily purified by column chromatography (Al_2O_3, $CHCl_3$), while amines **2a–c**,**e**,**g**,**h** were purified by conversion to salts on treatment with the corresponding acids in EtOH. The final purification of the basic or salt amine forms was carried out by recrystallization from suitable solvents.

[‡] *Crystal data for* **2g**. Crystals of $C_{26}H_{25}Br_2N_3O_3$ (M = 587.29) are triclinic, space group $P\bar{1}$ (no. 2): a = 8.7525(1), b = 16.5910(3) and c = 19.9431(4) Å, α = 70.140(2)°, β = 78.5970(10)°, γ = 87.9010(10)°, V = 2668.53(8) Å^3, Z = 2, d_{calc} = 1.462 g cm^{-3}, μ(MoKα) = 4.105 mm^{-1}, F(000) = 1184.0. X-ray structural studies were performed on an Agilent SuperNova diffractometer using microfocus X-ray source with copper anode [CuKα (λ = 1.54184)] and Atlas S2 CCD detector at 100 K. 56701 reflections were measured and 11116 independent reflections (R_{int} = 0.0543, R_σ = 0.0329) were used in a further refinement. The final R_1 was 0.0352 [$I > 2\sigma(I)$] and wR_2 was 0.0916 (all data). The structures were solved with ShelXT[16] program using Intrinsic Phasing and refined with the ShelXL[16] refinement package using Least Squares minimisation.

CCDC 1897576 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.

In summary, fused 7-acyl-2,3-dihydroazepines being sensitive to nucleophilic attack were found to be suitable for the synthesis of β-(hetero)arylethylamines containing (quinoxalin-2-yl) methyl substituent, which are hardly available by other methods. The compounds obtained look promising due to the privileged character of the quinoxaline scaffold[7,17] and its presence in some important natural compounds.[18,19]

The preparation of this publication and its supporting materials, discussion of the reaction mechanism, examination of the structure of the compounds **2** by spectral methods, synthesis of compounds **2d,e** and quantum chemical calculations were carried out at the Southern Federal University with support by the Ministry of Science and Higher Education of the Russian Federation (project no. 4.5821.2017/8.9). The synthesis of compounds **2a–c,f–j** and discussion of their structures were performed at the North-Caucasian Zonal Research Veterinary Institute under the Program for Basic Research of the State Academies of Sciences for 2013-2020 (subject no. 0710-2019-0044). To prove the structure of the compounds obtained, we used the equipment 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).

Online Supplementary Materials

Supplementary data associated with this paper can be found in the online version at doi: 10.1016/j.mencom.2020.01.009.

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Received: 3rd June 2019; Com. 19/5940