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Thiourea assisted recyclization of 1-(chloromethyl)dihydroisoquinolines: a convenient route to β-(*o*-thiazolylaryl)ethylamines

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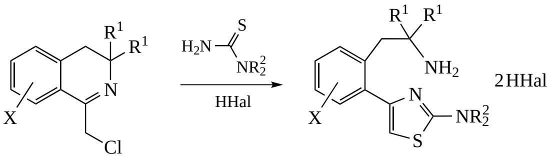
1-Chloromethyl-3,4-dihydroisoquinolines upon treatment with thioureas under acidic conditions undergo recyclization to afford new β-[*o*-(thiazol-4-yl)aryl]ethylamines.



13 examples

Keywords: 1-chloromethyl-3,4-dihydroisoquinolines, isoquinolines, recyclization, thiazoles, 2-arylethylamines, thioureas.

In recent years, synthetic and semi-synthetic analogues of natural products,[1–3] the so-called pseudo-natural products (PNPs),[4] have attracted attention in the field of biologically oriented synthesis.[5] This is due to the concept that natural compounds 'have been optimized in a very long natural selection process for optimal interactions with biological macromolecules'.[6]

Among the interesting types of PNPs, there are structural analogues of the neuroamines of the β-(hetero)arylethylamine series which play a crucial role as neurotransmitters, neurohormones and trace amine neuromodulators.[7,8] Neurospecific β-(hetero)arylethylamine scaffold is presented in antidepressants venlafaxine, desvenlafaxine and oxitriptan, adrenergic receptor agonists ephedrine and ritodrine, anxiolytic with CNS depressant activity phenybut, muscarinic receptor blocker darifenacin, vasoconstrictors levomethamphetamine and levonordefrin, hormone antagonist cetrorelix.[9]

The simplest β-(hetero)arylethylamines are known to possess serious unwanted side effects on the central nervous system;[10] hence, in drug design it seems reasonable to incorporate such a moiety into more complex structures. Various heteroaryl analogues of β-arylethylamines, in particular, with a heteroaryl or heteroaryl-containing substituent in aryl group are of considerable interest. Of the latter, the most studied are *meta*- and *para*-heteroarylated structures,[11–13] although their *ortho*-heteroarylated analogues are also documented.

β-(*o*-Heteroarylaryl)ethylamines were obtained mostly from β-(*o*-haloaryl)ethylamines by the Suzuki reaction.[14–18] Cross-coupling of β-arylethylamines with heteroarenes,[19] nucleophilic exchange of tosyloxy group in β-(*o*-heteroarylaryl)ethyl tosylates for an amino group,[20] reduction of *o*-heteroarylbenzyl-containing carboxamides or cyanides,[21] closure of the heterocyclic ring at the *ortho*-positioned substituent of the corresponding β-arylethylamine derivatives[22] as well as reduction of *o*-heteroaryl-ω-nitrostyrenes[23] were also reported.

In our opinion, a promising synthetic approach to β-(*o*-heteroarylaryl)ethylamines is the use of two-step reaction sequence including nucleophilic, β-aminoethyl-releasing, heterocyclic ring opening in fused ring systems, and subsequent heterocyclization of thus formed *ortho*-substituted β-(hetero)-arylethylamines as *ortho*-heteroaryl-building process occurring with participation of the non-aminic functional group. A very attractive one-pot version of such a sequence can be possible if heterocyclic substrates and heterocycle-opening reagents have two reaction centers capable of pairwise interaction. In this way, both processes are combined into one recyclization reaction.

As substrates for such recyclizations, compounds with optimally annulated hydrogenated pyridine or azepine rings are of significant interest. As applied to azepine structures,[24] in the reaction of d-annulated 7-acyl-2,3-dihydroazepines[25] with *o*-phenylenediamine, the formation of β-[*o*-(2-quinoxalylmethyl)aryl]ethylamines occurred.

The present study shows that this general approach can be extended to fused pyridine derivatives, namely, 1-chloromethyl-3,4-dihydroisoquinolines **1a**–**c** (Schemes 1 and 2). These isoquinolines under the action of thioureas or their analogues **2a**–**j** in boiling alcohols in the presence of HCl or HBr undergo effective recyclization into compounds **3a**–**m**, representatives of earlier unknown β-[*o*-(thiazol-4-yl)aryl]ethylamines, with the yields varying from moderate to excellent.†

The structure of the obtained compounds **3a**–**m** was confirmed by NMR spectroscopy and HRMS spectrometry. The case of

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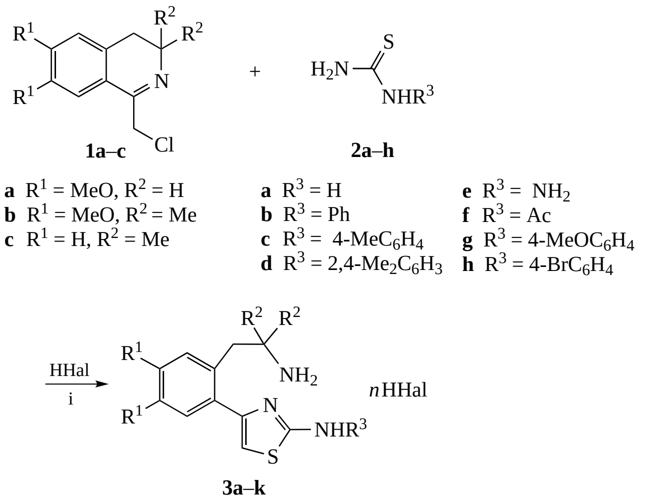
† *General procedure for the synthesis of compounds* **3**. A solution of dihydroisoquinoline **1** (5 mmol), thiourea or thiosemicarbazide **2** (5 mmol) and conc. HCl or HBr (10 mmol) in PrOH, EtOH or $MeOCH_2CH_2OH$ was refluxed for the specified time and cooled. The formed precipitate was filtered off, washed with propanol (3 × 8 ml) and recrystallized from the appropriate solvent (for more detail, see Schemes 1 and 2 and Online Supplementary Materials).

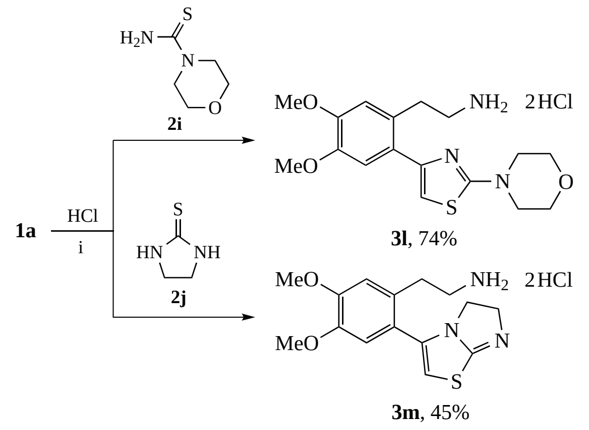


a R^1 = MeO, R^2 = H
b R^1 = MeO, R^2 = Me
c R^1 = H, R^2 = Me

a R^3 = H
b R^3 = Ph
c R^3 = 4-MeC_6H_4
d R^3 = 2,4-$Me_2C_6H_3$
e R^3 = NH_2
f R^3 = Ac
g R^3 = 4-$MeOC_6H_4$
h R^3 = 4-BrC_6H_4

a R^1 = MeO, R^2 = R^3 = H, Hal = Cl, 92%
b R^1 = MeO, R^2 = H, R^3 = Ph, Hal = Cl, 67%
c R^1 = MeO, R^2 = H, R^3 = 4-MeC_6H_4, Hal = Br, 33%
d R^1 = MeO, R^2 = H, R^3 = 2,4-$Me_2C_6H_3$, Hal = Br, 95%
e R^1 = MeO, R^2 = H, R^3 = NH_2, Hal = Cl, 82%
f R^1 = MeO, R^2 = Me, R^3 = H, Hal = Cl, 63%
g R^1 = MeO, R^2 = Me, R^3 = Ac, Hal = Cl, 42%
h R^1 = MeO, R^2 = Me, R^3 = Ph, Hal = Cl, 76%
i R^1 = MeO, R^2 = Me, R^3 = 4-$MeOC_6H_4$, Hal = Br, 95%
j R^1 = MeO, R^2 = Me, R^3 = 4-BrC_6H_4, Hal = Cl, 48%
k R^1 = R^3 = H, R^2 = Me, Hal = Cl, 63%
n = 2 (for **3g** n = 1)

Scheme 1 *Reagents and conditions*: i, HHal (2 equiv.), PrOH (EtOH for **3b**), reflux, 1 h (0.3 h for **3a**, 2 h for **3b**).



Scheme 2 *Reagents and conditions*: i, HCl (2 equiv.), PrOH (for **3l**), reflux 1 h, $MeO(CH_2)_2OH$ (for **3m**), reflux, 3 h.

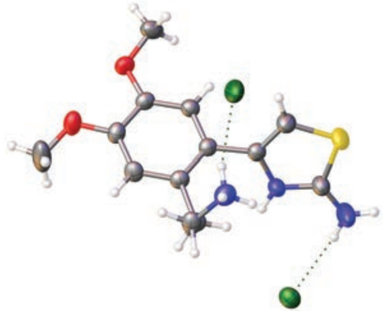
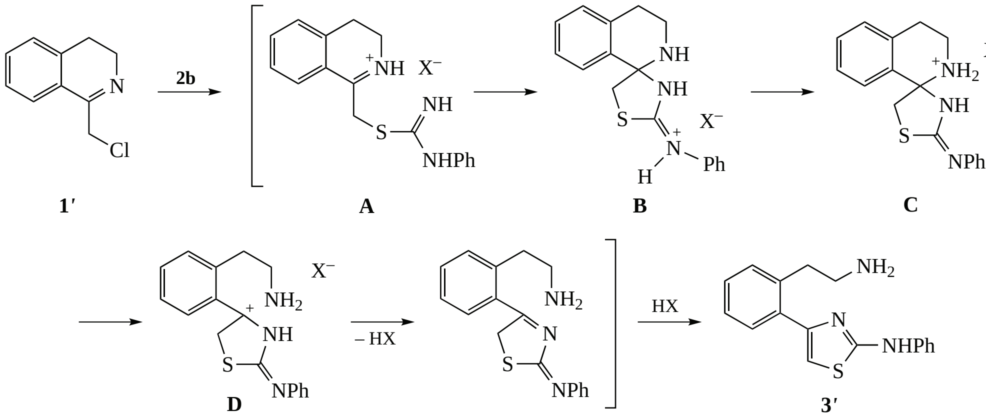


Figure 1 Molecular structure of bis-hydrochloride **3a** (displacement ellipsoids are drawn at the 50% probability level).

compound **3a** was ultimately established by single crystal X-ray diffraction study[‡] (Figure 1, see also Online Supplementary Materials).

According to data of DFT (BHHLYP/6-311G**) calculations for the model system containing 3,4-dihydro-1-chloromethylisoquinoline **1′** and compound **2b** (Scheme 3), the reaction has a rather unusual mechanism when the ring-closure precedes the ring-opening step (usually similar transformations occur in the reverse order). The driving forces of two these processes are the intramolecular N-nucleophilic attack in the intermediate of type **A**, and the sharp weakening of N(1)–C(2) bond in tautomer **C** of spiro precursor **B**. The final stages of the reaction are deprotonation of the open chain structure **D** and the C → N prototropic isomerization giving final structure **3′** (see Scheme 3). According to these data, the transformations $\mathbf{A}^+ \rightarrow \mathbf{B}^+$ and $\mathbf{C}^+ \rightarrow \mathbf{D}^+$ have low-barrier transition states TS1 and TS2 with $\Delta G^{\neq}_{calc}$ 5.5 and 3.5 kcal mol^{-1}, respectively (see Online Supplementary Materials).



Scheme 3

[‡] *Crystal data for* **3a**. $C_{13}H_{19}Cl_2N_3O_2S$ (M = 352.27), monoclinic, space group $P2_1/n$ (no. 14), at 293 K: a = 14.1345(2), b = 8.83290(10) and c = 14.4961(2) Å, β = 110.176(2)°, V = 1698.76(4) Å^3, Z = 4, μ(Cu$K\alpha$) = 4.652 mm^{-1}, d_{calc} = 1.377 g cm^{-3}, 19797 reflections measured (7.534° ⩽ 2θ ⩽ 152.368°), 3551 unique (R_{int} = 0.0497, R_σ = 0.0315) which were used in all calculations. The final R_1 was 0.0401 [$I > 2\sigma(I)$] and wR_2 was 0.1122 (all data).

The data were obtained on an Agilent SuperNova diffractometer using a microfocus X-ray source with 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).[26] The structures were solved using the ShelXT program[27] and refined with the ShelXL program.[28] Molecular graphics and presentation of structures for publication were performed with the Olex^2 ver 1.2.10 software suite.[29]

CCDC 2031011 [crystal from mixed solvents (1 : 1 methanol/n-propanol)] 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.

Note that analogous but free radical transformations are also possible.[30] However, the high substrate dependence of free radical transformations makes their widespread use problematic.

It should be noted that the thiazole scaffold which presents in arylethylamines **3** is considered as privileged and itself attracts considerable attention in the design of new drugs (see, for example ref. 31).

In conclusion, the proposed synthetic approach can be effectively used for the preparation of both *o*-heteroarylmethyl-[24] and β-(*o*-heteroarylaryl)ethylamines. It seems very likely that β-[*o*-(thiazol-4-yl)-heteroaryl]ethylamines can be obtained in a similar way.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.01.040.

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