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Synthesis of new physiologically active (2-oxoimidazolidin-5-yl)indoles

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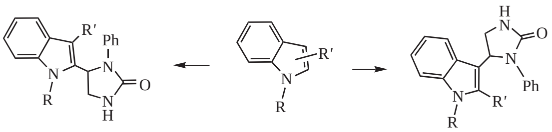
Boron trifluoride-catalyzed amidoalkylation of indole derivatives with 5-hydroxy-1-phenylimidozolidin-2-one affords new biheterocycles with a direct C–C bond. Among them, 3- or 2-(2-oxoimidazolidin-5-yl)indoles manifest anti-inflammatory activity with relatively low toxicity.



2 examples

6 examples

Keywords: amidoalkylation, biheterocycles, 3- or 2-(2-oxoimidazolidin-5-yl)indoles, anti-inflammatory activity, indoles, imidazolylindoles.

Heterocyclic compounds containing a 2- or 3-substituted indole moiety are the most widespread constituents of natural and synthetic bioactive molecules.[1] In most cases, the biological activity of a compound is directly related to the presence of an indole core[2] in the molecule. Nowadays, the therapeutic potential of indole pharmaceuticals (Indomethacin, Roxindole, Indalpine, Delavirdine, Perindopril, Ondansetron, Sumatriptan, Tadalafil, Fluvastatin, *etc*.) has been exhausted. Therefore, a search for new analogues is underway, and their efficiency as anti-inflammatory,[3] anti-HIV,[4] antituberculous,[5] anti-malarial[6] and anticonvulsant drugs[7] is being estimated. In addition, indole-containing compounds with antidiabetic,[8] antimicrobial,[9] antitumor,[10,11] antifungal,[12,13] anti-dyslipidemic[14] and other valuable properties are known. However, the potential of indole-based small molecules as anti-inflammatory agents has been studied rather poorly.

In turn, incorporation of a heterocyclic moiety into the indole molecule may be promising in terms of adjusting the existing biological activity, improving the pharmacological properties and finding its new types, as well as creating new drugs.[14–17] Incorporating an additional heterocycle into bioactive molecules can affect their pK_a, construct conformational hindrance, vary the hydrophilic-hydrophobic balance or increase lipophilicity. Moreover, these parameters can be modulated both separately and in various combinations.[18] Substituted imidazolylindoles also exhibit a wide range of physiological activity, in particular, as C protein kinase inhibitors.[19] Two heterocyclic moieties, imidazolidin-2-one and indole, are combined in Sertindole, an antipsychotic drug used in the treatment of schizophrenia.[20] Thus, incorporation of an additional heterocyclic core allows one to obtain compounds that are superior in activity to the currently used drugs.[21]

However, this approach is still not widely used to obtain biheterocycles in which two heterocyclic moieties are directly bound by a carbon–carbon bond, and which belong to new pharmacologically oriented heterocyclic ensembles. At the same time, in terms of anti-inflammatory drug design based on 2- or 3-substituted indoles, direct incorporation of the imidazolidin-2-one group into this heterocyclic scaffold to give 2- or 3-(2-oxoimidazolidin-5-yl)indoles can ensure its interaction with the hydrophobic pockets of the target protein, in particular, due to acceptors and hydrogen bond donors in functional derivatives at positions 1 and 5.

The purpose of this work was to synthesize such new 3- or 2-(2-oxoimidazolidin-5-yl)indoles **1** and **2**, respectively, using amidoalkylation reaction with 5-hydroxy-1-phenylimidazolidin-2-one **3** as the key reactant (Scheme 1). The possibility of using available 5-hydroxyimidazolidin-2-ones as amidoalkylating agents for the preparation of biheterocyclic compounds was not studied to date. One of the probable reasons is that their hydroxy group is eliminated rather readily under acid and alkaline catalysis conditions. Compound **3** was obtained by chemoselective reduction[22] of the amide moiety of the corresponding hydantoin derivative (see Scheme 1).

The next amidoalkylation step (see Scheme 1) was carried out under Lewis acid catalysis. Performing the reaction in THF in the presence of catalytic amounts of boron trifluoride etherate provided satisfactory results to afford desired biheterocycles **1a**–**f** and **2a**,**b** in 11–32% yields.

Comparative analysis of isomeric amidoalkylation products, namely, **1b** *vs.* **2a** and **1e** *vs.* **2b**, showed that such isomers had different physicochemical properties and their ^{1}H NMR spectra were different.[†] The aliphatic parts of these spectra retain the

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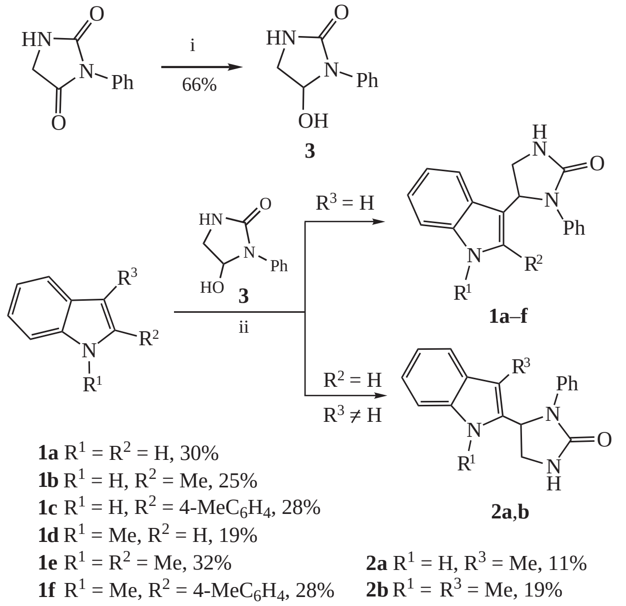
[†] For details, see Online Supplementary Materials.

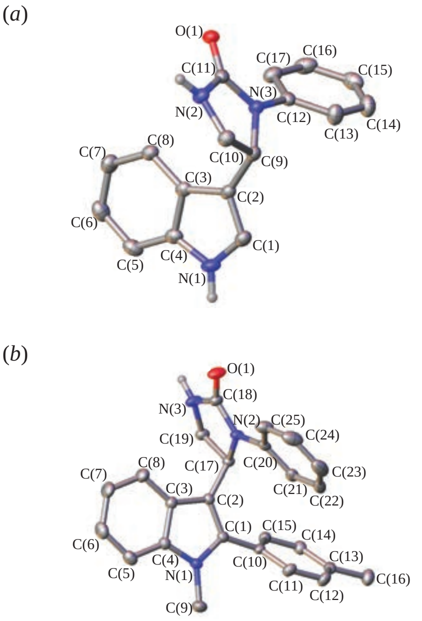


1a $R^1 = R^2 = H$, 30%
1b $R^1 = H$, $R^2 = Me$, 25%
1c $R^1 = H$, $R^2 = 4\text{-}MeC_6H_4$, 28%
1d $R^1 = Me$, $R^2 = H$, 19%
1e $R^1 = R^2 = Me$, 32%
1f $R^1 = Me$, $R^2 = 4\text{-}MeC_6H_4$, 28%
2a $R^1 = H$, $R^3 = Me$, 11%
2b $R^1 = R^3 = Me$, 19%

Scheme 1 *Reagents and conditions*: i, $LiAlH_4$, THF, 20 °C; ii, $BF_3{\cdot}Et_2O$, THF, 20 °C.

proton signals for 1-phenylimidazolidin-2-one moieties, as well as signals for substituents at the indole component. In the spectra of compounds obtained from N-unsubstituted indoles **1a–c** and **2a**, a broadened NH signal is observed at δ 10.87–11.32 for compounds **1a–c** (DMSO-d_6) and δ 8.46 for **2a** ($CDCl_3$), which allows us to rule out the assumption about the attack at position 1 of the indole. The spectra of all compounds **1**, unlike those of the starting indoles, contain no signal for the H-3 proton of the indole core. The total set of spectral data suggests that under these conditions, the amidoalkylation occurs at position 3 if it is not occupied. No products of amidoalkylation at positions 1 and 5 of indoles are formed even if strong agents such as sulfuric and trifluoroacetic acids are used as the catalysts. However, their use causes strong resinification of the reaction mixture. Raising the reaction temperature also favours resinification. Importantly, under the acid catalysis, the hydroxy group in 5-hydroxyimidazolidin-2-one is readily eliminated to produce the corresponding imidazol-2-one. We succeeded somehow in reducing this effect by application of boron trifluoride etherate in catalytic amounts at 20 °C. Solving the problem of obtaining the target compounds in high yield will be the subject of our further work.

The structure of compounds **1a** and **1f** was unambiguously confirmed by their X-ray single-crystal diffraction analysis (Figure 1).[‡]


(*a*)

(*b*)

Figure 1 Molecular structures of compounds (*a*) **1a** and (*b*) **1f** with atoms given as thermal ellipsoids at 50% probability level. Second symmetry-independent molecule in **1a** and the solvate methanol molecule in **1f** together with hydrogen atoms (except for those of NH groups) are omitted for clarity.

Under the indicated conditions, no Wagner–Meerwein double rearrangement products were found that would be characteristic of indole derivatives in an acidic environment and indolylpyrazolidines present in the reaction mixtures.

A characteristic feature of our approach to the synthesis of biheterocyclic compounds in which two heterocyclic moieties are directly bound by a carbon–carbon bond is the ease of replacement of the hydroxy group in an α-hydroxy alkanamide by C-nucleophilic indole moieties. It is worth noting that the well-known examples of the amidoalkylation of indoles are generally limited to simple alkylating agents.[23,24] A few imidazolylindole derivatives that can be considered as structural analogous of compounds **1** were described in a patent,[21] but these compounds contained an aromatic imidazolone moiety instead of an imidazolidinone one and were obtained by multi-stage synthesis with intramolecular condensation as the last stage. Similar compounds were obtained[25] as side products of the reaction between 4,5-dimethoxyimidazolidin-2-one and indolylmagnesium bromide in the presence of a Lewis acid to give 4,5-bis(indol-3-yl)imidazolidin-2-one.

[‡] Crystals of compounds **1a** and **1f** were grown after distillation by multiple cycles of cooling and heating.

Crystal data for **1a**. $C_{17}H_{15}N_3O$, $M = 277.32$, monoclinic, space group $C2/c$, 120 K: $a = 31.1999(15)$, $b = 9.6008(5)$ and $c = 18.1218(9)$ Å, $\beta = 90.234(2)°$, $Z = 16$ ($Z' = 2$), $V = 5428.2(5)$ Å^3, $d_{calc} = 1.357$ g cm^{-3}, $F(000) = 2336$. Colourless prism-shaped single crystal with dimensions 0.15×0.2×0.25 mm was selected and intensities of 38005 reflections were measured using a Bruker APEX2 DUO CCD diffractometer (ω and φ scans, sealed tube, λ[Cu-Kα] = 1.54178 Å, $\mu = 0.696$ mm^{-1}, $2\theta_{max} = 136.04°$). After merging of equivalents and absorption correction, 4890 independent reflections ($R_{int} = 0.0214$) were used for the structure solution and refinement. Final R factors: $R_1 = 0.0304$ [4661 reflections with $I > 2\sigma(I)$], $wR_2 = 0.0803$ (all reflections), GOF = 1.032.

Crystal data for **1f**·MeOH. $C_{26}H_{27}N_3O_2$, $M = 413.50$, triclinic, space group $P\bar{1}$, 120 K: $a = 10.3813(13)$, $b = 10.4643(14)$ and $c = 10.9767(14)$ Å, $\alpha = 69.775(3)°$, $\beta = 77.091(3)°$, $\gamma = 88.883(3)°$, $Z = 2$ ($Z' = 1$), $V = 1088.5(2)$ Å^3, $d_{calc} = 1.262$ g cm^{-3}, $F(000) = 440$. Colourless prism-shaped single crystal with dimensions 0.15×0.2×0.25 mm was selected and intensities of 15081 reflections were measured using a Bruker APEX2 DUO CCD diffractometer (ω and φ scans, sealed tube, λ[Mo-Kα] = 0.71073 Å, $\mu = 0.0.081$ mm^{-1}, $2\theta_{max} = 58°$). After merging of equivalents and absorption correction, 5778 independent reflections ($R_{int} = 0.0657$) were used for the structure solution and refinement. Final R factors: $R_1 = 0.0687$ [3342 reflections with $I > 2\sigma(I)$], $wR_2 = 0.1887$ (all reflections), GOF = 1.024.

Using Olex2,[26] the structures were solved with the ShelXT structure solution program[27] using Intrinsic Phasing and refined against F^2 with the SHELXTL PLUS 5.0 refinement package[28] using full-matrix least-squares technique. The positions of hydrogen atoms of NH groups in both compounds and those of solvent molecule in **1f** were found in difference Fourier synthesis. Positions of other hydrogen atoms were calculated, and they all were refined in isotropic approximation in riding model. Molecular graphics were drawn using Olex2 program.

CCDC 1979556 and 1979557 contain 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.

Tests on cells of mouse microglia of the BV-2 line (CVCL_0182) and human neuroblastoma of the SH-SY5Y line (ATCCCRL-2266) showed that biheterocycles **1a**–**f** manifested cytotoxicity and an anti-inflammatory effect. The results of determining the toxicity of the compounds on SH-SY5Y human neuroblastoma cells (incubation for 24 h), MTT test, mean ± standard deviation ($N = 3$) revealed that compounds **1a**–**f** manifested toxicity toward these cells (see Online Supplementary Materials). Compounds **1a**–**c** showed no toxic effect up to a concentration of 100 μM. The cytotoxicity of compounds **1e**, **1d** and **1f** in the concentration range from 10 to 100 μM was found to be EC_{50} = 147 ± 10, 95 ± 5 and 57 ± 5 μM, respectively (mean ± standard deviation within experiments). Low cytotoxicity toward the BV-2 line was also found. The results on mouse BV-2 line microglia cells (24 h), MTT test, mean±standard deviation (3 experiments) show that only compound **1f** has significant toxicity in the concentration range of 10–100 μM, EC_{50} = 19 ± 3 μM. Compounds **1a** and **1c** were found to be nontoxic. Compounds **1e**, **1d** and **1b** caused the death of 20 to 40% cells at a concentration of 100 μM.

Under conditions of inflammatory response induction by bacterial lipopolysaccharide on the BV-2 mouse microglia cell line, all the compounds exhibited anti-inflammatory activity. The highest effect was shown by **1e** and **1d** that provided suppression of the response by up to 50% in the concentration range from 0.1 to 10 μM. However, complete suppression of the inflammatory response by any of the compounds in a nontoxic concentration range was not observed.

In conclusion, we have found that the use of 5-hydroxy-1-phenylimidozolidin-2-one as an amidoalkylating agent for a number substituted indoles allows one to obtain biheterocyclic compounds with a direct C–C bond. Some of the synthesized derivatives possess anti-inflammatory activity and relatively low toxicity.

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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.2020.05.029.

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