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β-Carbolines as intermediates in indirect heteroarylation of tryptamines exemplified by the synthesis of 2-pyrazolyltryptamines

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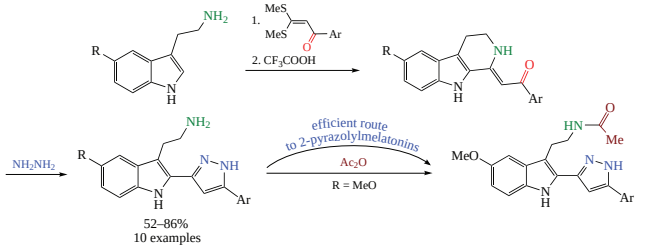
A cyclization–recyclization pathway for indirect 2-heteroarylation of tryptamines has been suggested by the example of introducing the pyrazolyl moiety. The process involves the intermediate cyclization of tryptamines into push–pull type β-carboline semi-products. The relative stability of the tautomeric forms of 2-pyrazolyltryptamines has been estimated using the DFT method.

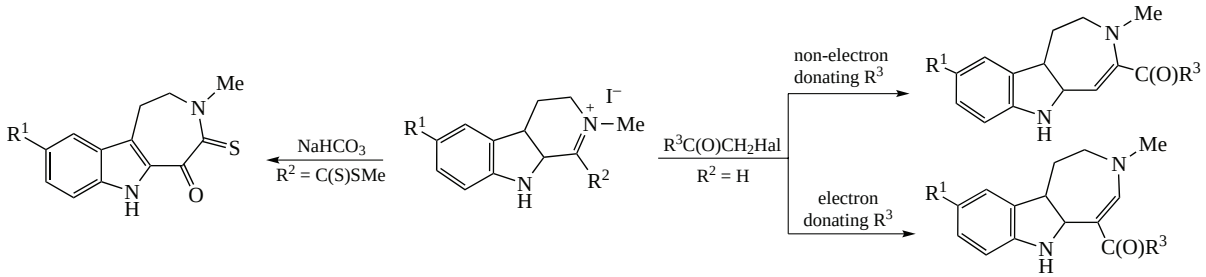


Keywords: tryptamines, 1-aroylmethylidene-1,2,3,4-tetrahydro-β-carbolines, β-carbolines, recyclization, 2-(pyrazol-3-yl)tryptamine, 2-(pyrazol-3-yl)-*O*-methylserotonins, pyrazolylmelatonins, quantum chemical calculations.

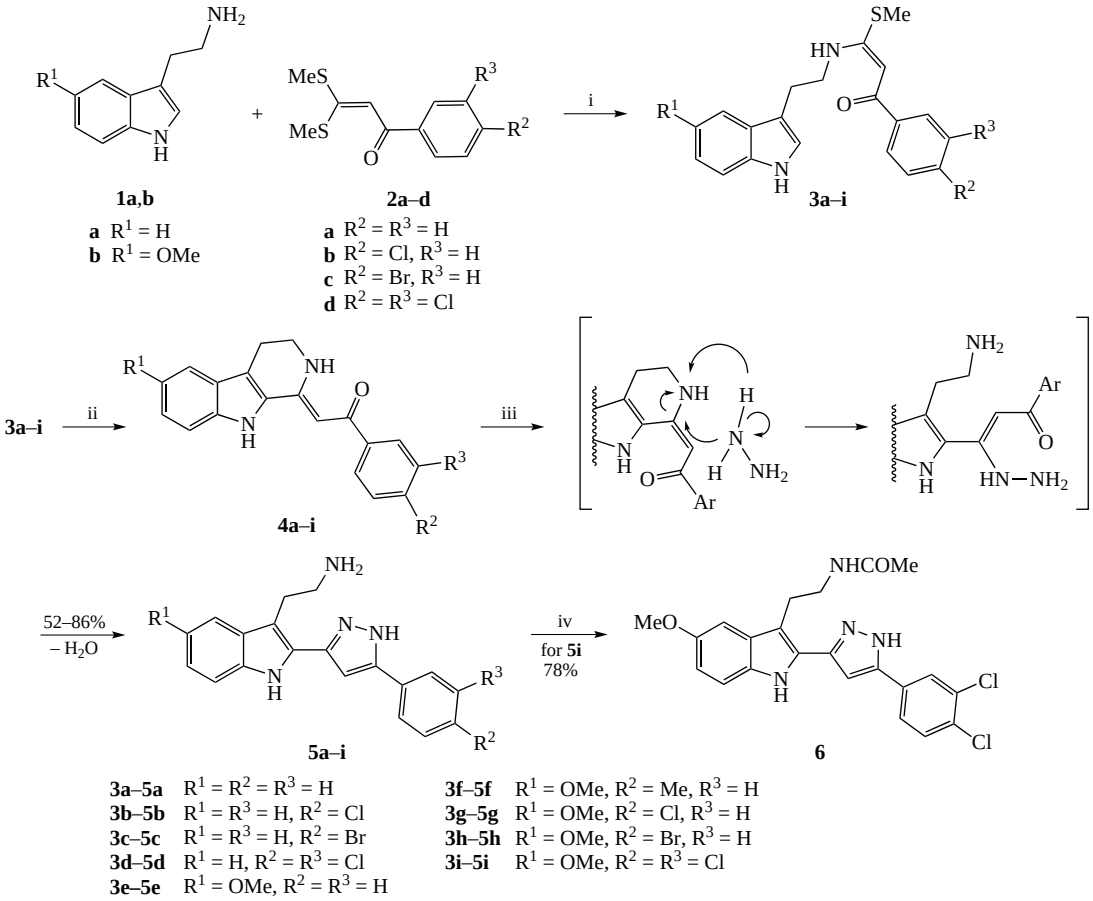
β-Carbolines possess diverse biological activity[1–3] and play important role in plant metabolism. They can be also interesting as synthons for obraining derivatives of other cyclic systems with a smaller or larger number (dimension) of fused rings.[4–6] Essentially electrophilic 3,4-dihydro-β-carbolines are susceptible for nucleophilic opening of the hydrogenated pyridine ring, which provides some potential for various kinds of recyclizations, for example, of the particularly attractive ANRORC-type ones.

Two of such recyclizations involving quaternary salts of 3,4-dihydro-β-carbolines with expansion of the six-membered hetero ring to a seven-membered one were suggested as efficient methods for the synthesis of novel 4- and 5-(hetero)aroyl derivatives as well as oxothioxo derivatives of 1,2-dihydro-azepino[4,5-*b*]indoles (Scheme 1).[4,5,7,8] In these transformations, the indole bicycle and the 2-aminoethyl group of the opened tryptamine form participate in building the new heterocyclic ring. An alternative recyclization route is also possible, when a new hetero ring is constructed from the 2-positioned acyl group of the open form and the proper reagent thus leading to 2-heteroaryltryptamines.

The present work demonstrates the possibility of these types of recyclizations as well as their use as a key step in the indirect heteroarylation of tryptamines at position 2. It also describes the transformation of simplest tryptamines **1a,b** (that are alkaloids[9–11] and important endobiotics[12]) into 2-pyrazolyltryptamines representing a new structural variant of indole-pyrazole hybrids.[13] The initial step of pyrazolylation (Scheme 2) is the well-known[6,14] and readily occurring two-step cyclization of tryptamines involving *N*-substitution of the methylthio group in *S*,*S*-dimethylacetals of *C*-acylketenes **2a–d** by the action of these amines and actual cyclization of the substitution products **3a–i** into push–pull type carbolines[15] **4a–i**. To convert these carbolines into pyrazolyl derivatives of tryptamines, we used the recyclization discovered in this work, which is new for the β-carboline series and follows the alternative route with participation of hydrazine. The products are the representatives of new 2-[pyrazol-3(5)-yl]-tryptamines **5a–i** and, in particular, 2-(pyrazol-3-yl)-*O*-methylserotonins **5e–i**. The reaction occurs by refluxing (6 h) carbolines with a small excess of hydrazine hydrate in *n*-propanol (see Scheme 2). The yields of compounds **5a–e**,**g–i** are 69–86%, whereas in the case of compound **5f** the yield is significantly



Scheme 1



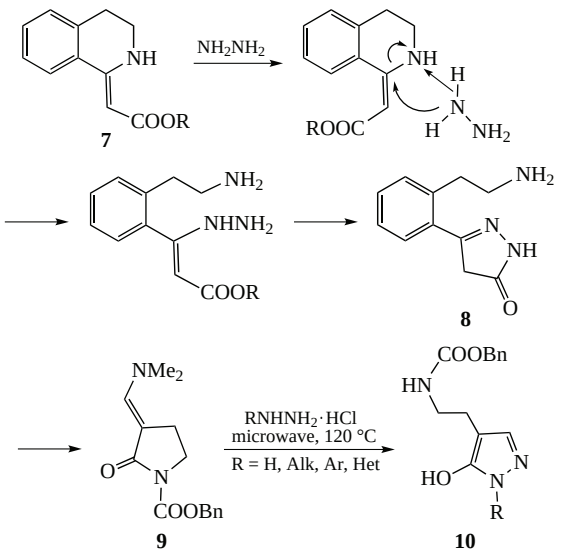
Scheme 2 *Reagents and conditions*: i, see refs. 14, 15; ii, CF_3COOH, 40–45 °C, 3 h, 20–55 °C, 24 h; iii, NH_2NH_2, PrOH, 6 h; iv, Ac_2O, 50–60 °C, 10 min.

lower, 52%. This may be due to a decrease in electrophilicity of CO group of substrate **4f** due to the hyperconjugation +M-effect of the *para*-positioned CH_3 group. One of the *O*-methylserotonins thus obtained, **5i**, was converted into the corresponding 2-(pyrazol-3-yl)melatonin **6** as an example.

Like the recyclization of 1-(alkoxycarbonyl)methylidene-3,4-dihydroisoquinolines of type **7** to β-[*o*-(oxopyrazolyl)phenyl]-ethylamines of type **8** that we reported recently[16] (Scheme 3), the reaction outlined in Scheme 2 is most likely to begin with the cleavage of the hydrogenated pyridine ring by the nucleophilic substitution mechanism of the hydrazino-deamination reaction type. There is also a certain analogy with another recyclization, but in the monocyclic series, namely, that of pyrroles **9** to *N*-benzyloxycarbonyl-2-(pyrazol-4-yl)ethylamines **10**.[17]

The structures of compounds **5** and **6** were confirmed by ^1H, ^{13}C NMR and HRMS methods. Quantum chemical calculations for the simplest pyrazolyltryptamine **5a** (DFT, B3LYP/6-311G**, see Online Supplementary Materials) show that of its two pyrazole tautomers, the 3-aryl-5-indolyl one is noticeably more stable. Both tautomers have two conformers each, and all the four tautomer-conformer forms have considerable π-conjugation, judging by the relatively small dihedral angles ϕ between the planes of the two heteroarene systems and the pyrazole and benzene rings (within ~7 to 35°). An argument in favor of this can be provided by the calculated data for biphenyl, in which, with ϕ = 38°, a fairly significant conjugation of the two rings is still preserved with a stabilization energy of about 10 kcal mol^{-1}.[18] The total E_{tot}^{calc} energies of the 3-aryl-5-indolyl tautomer conformers have values of –953.9016596 (the conformer with the smallest ϕ angles) and –953.8971979 atomic units; the corresponding E_{tot}^{calc} values for the 5-aryl-3-indolyl tautomer are –953.8973086 and –953.8972140 atomic units. Thus, the difference in the energies of the most stable conformers of the two tautomeric forms is 2.7 kcal mol^{-1}.

Prediction of the biological activity of pyrazolylmelatonin **6** and its analog containing no chlorine atoms using the PASS program[19] shows that such compounds should primarily be ligands for various kinds of kinases, for example, inhibitors of platelet-derived growth factor receptor tyrosine kinase (PDGF-R). They may also be of interest as possible agents for the treatment of CNS diseases, as well as cystic fibrosis – by modulating the activity of the transmembrane regulator of cystic fibrosis.



Scheme 3

In summary, using pyrazolylation as an example, the feasibility of indirect 2-heteroarylation of tryptamines by the cyclization–recyclization scheme, with intermediate formation of push–pull β-carboline structures, was herein demonstrated.

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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.2023.09.018.

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