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HETEROCYCLES IN FOCUS

Synthesis of pyrazino[1,2-*a*]indoles and indolo-[1,2-*a*]quinoxalines (microreview)

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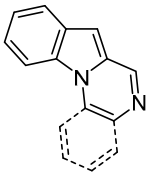
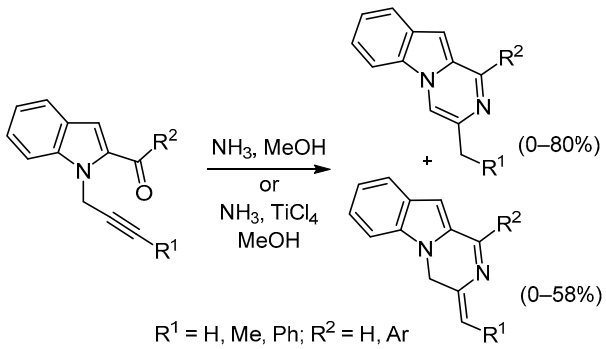


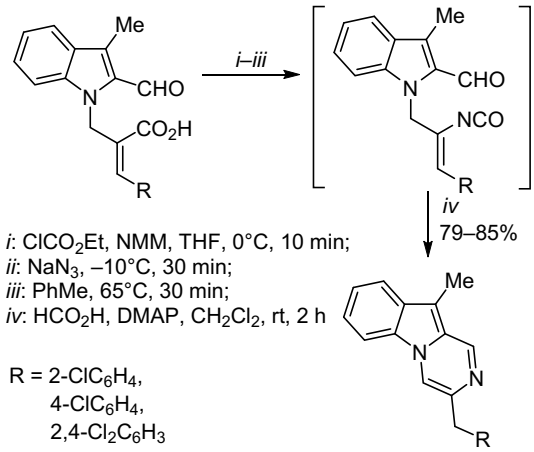
The review is dedicated to the methods of synthesis of pyrazino[1,2-*a*]indoles and indolo[1,2-*a*]-quinoxalines. The primary approach to the synthesis of these heterocyclic systems is the annulation of a pyrazine ring to a functionalized indole ring by means of condensation of carbonyl compounds, radical reactions catalyzed by transition metals, as well as hypervalent iodine compounds.

Synthesis of pyrazino[1,2-*a*]indoles

N-Propargyl-substituted indoles containing a carbonyl group at the C-2 atom may be converted into pyrazino[1,2-*a*]-indoles by ammonia. Isomeric aromatic dihydropyrazino-indoles may form as a result of the reaction. The conditions for selective formation of pyrazinoindole were found by researchers as well as shown by them that the use of different Lewis acids accelerates the reaction and increases product yields.[1]



An interesting method for the synthesis of pyrazinoindoles is based on the Curtius rearrangement.[2] The resulting isocyanate is hydrolyzed to an amino functionality followed by intramolecular cyclization *in situ* to the corresponding pyrazine ring.



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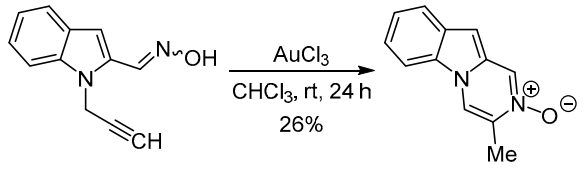
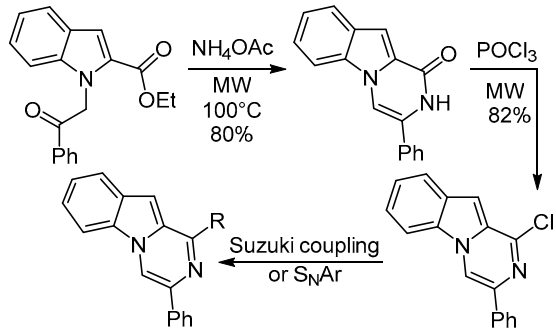
Synthesis of pyrazino[1,2-*a*]indoles (continued)

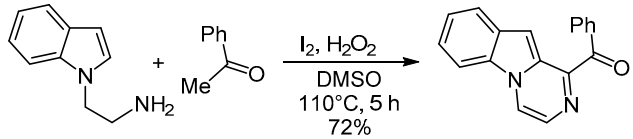
Heating ethyl 1-(2-oxo-2-phenylethyl)-1*H*-indole-2-carboxylate in ammonium acetate using microwave irradiation results in the formation of 4-oxopyrazine derivative, treating of which with phosphorus oxychloride yields chloro-substituted pyrazinoindole. The synthetic potential of this compound was demonstrated in nucleophilic aromatic substitution reactions and Suzuki cross-coupling reactions in the synthesis of 1-substituted 3-phenylpyrazino[1,2-*a*]indoles.[3]

Cyclization of the oxime of propargyl-substituted indole-2-carbaldehyde at the alkynyl group by the action of $AuCl_3$ gives pyrazinoindole *N*-oxide in 26% yield.[4]



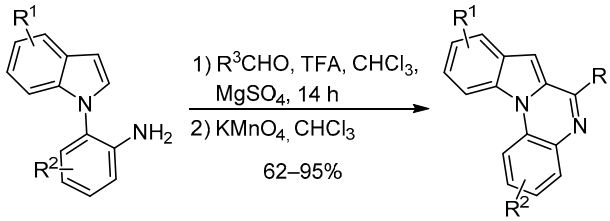


1-Benzoylpyrazino[1,2-*a*]indole can be obtained by iodine-promoted C–H-coupling reaction of indole-1-ethanamine and acetophenone.[5]



Synthesis of indolo[1,2-*a*]quinoxalines

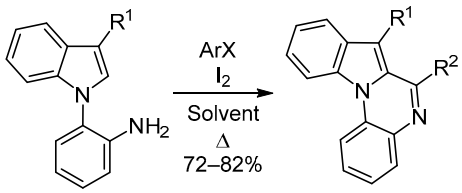
Synthesis *via* the Pictet-Spengler reaction. Modifications of the Pictet-Spengler reaction are widely used in the synthesis of indolo[1,2-*a*]quinoxalines. Substituted 2-(indol-1-yl)anilines and aromatic aldehydes are used as the starting materials. Cyclization may be carried out in the presence of trifluoroacetic acid,[6,7] cyanuric acid,[8] *para*-dodecylbenzenesulfonic acid,[9] as well as in the presence of catalytic amounts of $FeCl_3$,[10] $AlCl_3$.[11] The resulting dihydroindolo[1,2-*a*]quinoxaline is oxidized by the



R^1 = H, OMe, OBn, Br; R^2 = H, Me, Br, F, Het;
R^3 = Ar, Het

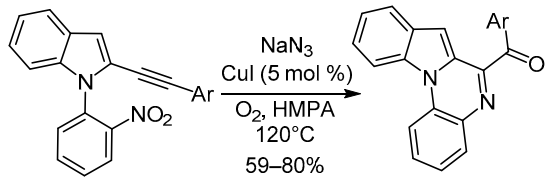
Another method based on reduction of the nitro group followed by intramolecular cyclization at the ester group has also found use.[13]

Oxidative cyclization. 2-(Indol-1-yl)anilines can also be converted into indolo[1,2-*a*]quinoxalines in a reaction with aryl methyl ketones[14] or with benzylamines[15] in the presence of oxidants such as molecular iodine or O_2 in DMSO.

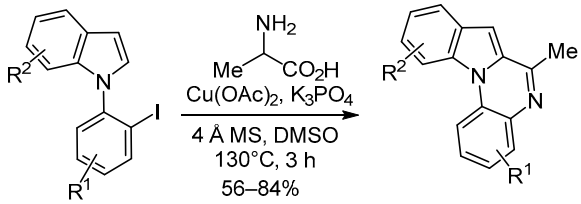


X = COMe, CH_2NH_2;
R^1 = H, Me; R^2 = COAr, Ar

Metal-catalyzed reactions. The reaction sequence of nucleophilic substitution of the nitro group and [2+3] cycloaddition catalyzed by copper(I) provides a route to aroyl-substituted indoloquinoxalines.[16]

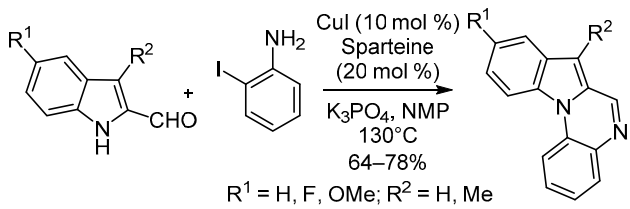


An interesting domino synthesis of indoloquinoxalines is based on a copper-catalyzed reaction of *N*-(2-iodophenyl)-indoles with amino acids. It is assumed that the reaction begins with the Ullmann amino acid arylation followed by decarboxylation and electrophilic attack at position 2 of the indole ring; the final product forms *via* aerobic oxidation.[17]



R^1 = H, 4-Me; R^2 = H, 3-Me, 6-Cl

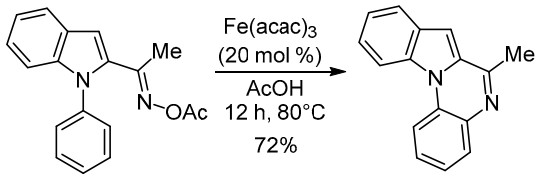
Another copper-catalyzed process involves the use of indole-2-carbaldehydes and *o*-iodoaniline. The use of sparteine as a ligand proved advantageous because substantially increased the product yield.[18]



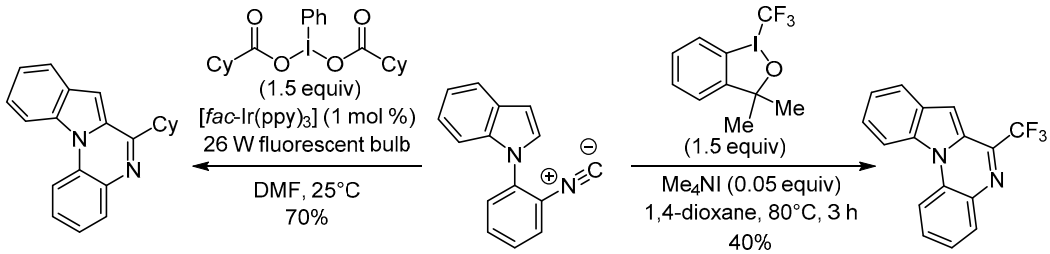
R^1 = H, F, OMe; R^2 = H, Me

Synthesis of indolo[1,2-*a*]quinoxalines (continued)

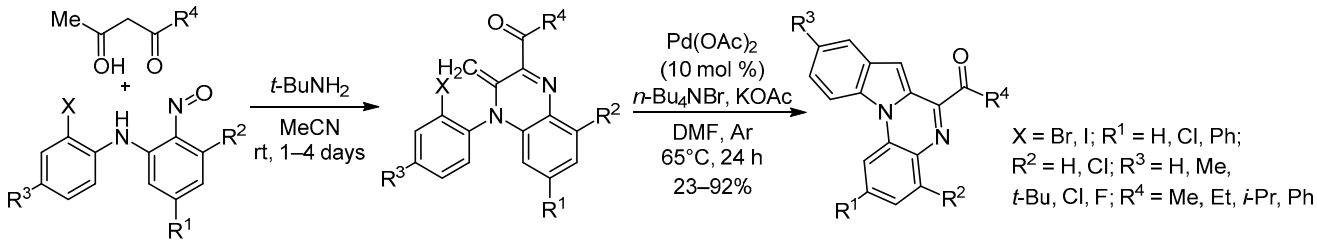
It has been found that 1-(*N*-phenylindol-2-yl)ethanone *O*-acetyl oxime participates in an intramolecular C(sp^2)–N cross-coupling reaction upon heating in acetic acid in the presence of iron acetylacetonate (III).[19]



Hypervalent iodine in the synthesis of indolo[1,2-*a*]-quinoxalines. Indoloquinoxalines can be obtained *via* intramolecular photo-induced radical cyclization of isonitriles initiated by visible light in the presence of an iridium photocatalyst. The authors have investigated various derivatives of hypervalent iodine and the effect of substituents on the product of this photocatalyzed reaction.[20] It was later shown that the radical cyclization using Togni reagent II led to similar cyclization with the formation of trifluoromethyl-substituted indoloquinoxalines.[21] In this case, tetramethylammonium iodide served as the radical initiator.



Condensation of nitroso-substituted anilines. The only example of constructing indoloquinoxaline by creating the pyrrole ring is the condensation of 1,3-dicarbonyl compounds with nitroso-substituted anilines in the presence of *tert*-butylamine. The process initially leads to the formation quinoxaline ring, with the indole moiety forming in the intramolecular Heck reaction.[22]



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